

# Body Mass Index, Cardiac Reverse Remodeling, and Outcomes with Cardiac Resynchronization Therapy in Heart Failure: Insights from Two-Dimensional Speckle-Tracking Echocardiography

Ting-Yu Lan, Xin Sun, Hao Wang

Department of Echocardiography, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100037, People's Republic of China

Correspondence: Hao Wang, Department of Echocardiography, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 167 Beilishi Road, Beijing, 100037, People's Republic of China, Tel +86 18611323100, Email haowangdrwh@163.com

**Objective:** This study aimed to evaluate the effects of cardiac resynchronization therapy (CRT) on cardiac reverse remodeling and long-term clinical outcomes in individuals with advanced heart failure, stratified by body mass index (BMI), using two-dimensional speckle-tracking echocardiography.

**Methods:** In this retrospective, single-center study, a cohort of 141 patients with heart failure who underwent CRT implantation between 2008 and 2014 was categorized into 4 BMI groups. Clinical and echocardiographic parameters were assessed at baseline and six months post-therapy. Strain analyses of the left atrium and left ventricle were performed using EchoPAC, and long-term clinical outcomes were recorded.

**Results:** Participants classified as overweight (BMI 24–28 kg/m<sup>2</sup>) or obese (BMI ≥ 28 kg/m<sup>2</sup>) demonstrated greater improvements in clinical status and echocardiographic strain measures ( $p < 0.05$ ), along with higher CRT response rates compared to those classified as underweight (BMI < 18.5 kg/m<sup>2</sup>) or normal weight (BMI 18.5–24 kg/m<sup>2</sup>). Additionally, patients who were overweight and obese exhibited more favorable long-term outcomes. Left atrial conduit strain (LAScd) emerged as an independent predictor of CRT response and prognosis.

**Conclusion:** CRT was associated with greater clinical and echocardiographic benefits in patients with higher BMI, and LAScd was identified as a key predictor of therapeutic response and long-term prognosis.

**Keywords:** body mass indices, cardiac resynchronization therapy, left atrial conduit strain, obese, obesity paradox, overweight, two-dimensional speckle-tracking echocardiography

## Introduction

Heart failure (HF) is a major global health concern, contributing to substantial morbidity, mortality, reduced quality of life, and increased healthcare expenditures. Cardiac resynchronization therapy (CRT) has demonstrated efficacy in patients with HF characterized by reduced left ventricular ejection fraction (LVEF) and wide QRS complexes on electrocardiography.<sup>1,2</sup> However, a considerable proportion (30–40%) of patients undergoing conventional CRT do not exhibit a positive therapeutic response, with non-responsiveness attributed to multiple factors.<sup>3–5</sup> Despite advancements in CRT, the underlying mechanisms responsible for non-response remain inadequately understood.

Recent studies have revealed that while obesity is a recognized risk factor for HF, paradoxically, patients who are overweight or obese have been associated with improved prognosis and survival rates in HF.<sup>6,7</sup> The authenticity of the “obesity-survival paradox” in heart failure is uncertain, possibly due to methodological issues like reverse causation and confounding factors. The mechanisms behind this paradox are unclear, but possible explanations include earlier symptom

onset, better medication access and tolerance, higher cardioprotective adipokines, increased anti-inflammatory lipoproteins, and greater weight reserves mitigating cardio-metabolic changes and cardiac cachexia.<sup>6</sup> Furthermore, an elevated body mass index (BMI) has been independently correlated with favorable clinical outcomes among those receiving CRT.<sup>8–10</sup> Given the high prevalence of obesity among patients newly diagnosed with HF and the increasing use of CRT in this population, it is essential to evaluate the impact of BMI on CRT responsiveness.<sup>11</sup>

CRT is designed to correct intraventricular dyssynchrony, and echocardiography plays a key role in predicting therapeutic responses.<sup>12</sup> Advanced imaging modalities, such as speckle-tracking echocardiography (STE) facilitate a more precise and comprehensive assessment of myocardial function. STE, which relies on the tracking and quantification of myocardial deformation, enables the accurate evaluation of myocardial mechanics.<sup>13</sup> This technique serves as an additional tool for identifying patients who are more likely to derive therapeutic benefit from CRT.<sup>14</sup> Differences in strain patterns between responders and non-responders, particularly across various BMI categories, may yield crucial mechanistic insights into how substrate properties, potentially influenced by BMI, affect the electromechanical response to CRT.

While previous studies<sup>8–10</sup> have primarily focused on correlating BMI with clinical endpoints, they often lacked a detailed assessment of myocardial mechanics through advanced techniques such as 2D-STE, particularly in a BMI-stratified context. This limitation hinders the comprehensive understanding of the relationship between BMI and myocardial function. 2D-STE offers sensitive and quantitative measures of myocardial deformation (strain) that can reveal impairments prior to any noticeable changes in ejection fraction or conventional echocardiographic parameters. Our study uniquely employs this technology specifically within pre-defined BMI strata.

The aim of this study was to evaluate the role of two-dimensional speckle-tracking echocardiography (2D-STE) in assessing the influence of BMI on cardiac reverse remodeling and long-term outcomes following CRT in patients with HF.

## Methods

### Study Population

A retrospective analysis was conducted on 151 patients who underwent CRT at Fuwai Hospital between January 2008 and July 2014. Eligibility criteria included an LVEF of <35%, a QRS duration of  $\geq 120$  ms, and New York Heart Association (NYHA) functional class II–IV despite receiving at least two months of optimized medical therapy. Exclusion criteria were LVEF  $\geq 35\%$ , QRS duration < 120 ms, persistent atrial fibrillation, and alternating bundle branch block morphologies. All patients had undergone at least three months of optimal medical therapy prior to the CRT procedure. Ischemic cardiomyopathy was diagnosed based on findings from coronary angiography or documented myocardial infarction. The study protocol was approved by the Ethics Committee of Fuwai Hospital, and written informed consent was obtained from all participants. Clinical and echocardiographic assessments were performed at baseline and repeated after six months.

### Pacemaker Implantation

Biventricular pacemaker implantation was performed under local anesthesia. Lead placement was achieved through the cephalic or subclavian veins. The right atrial and ventricular leads were positioned using a conventional approach, while the left ventricular lead was placed in the lateral coronary vein. If this placement was not feasible, the posterolateral or anterior vein was used as an alternative.

### Definitions and Follow-Up

BMI was calculated as weight divided by height squared and recorded at baseline. Patients were categorized as underweight, normal weight, overweight, or obese based on the definitions established by the Chinese Obesity Working Group: < 18.5 kg/m<sup>2</sup>, 18.5–24 kg/m<sup>2</sup>, 24–28 kg/m<sup>2</sup>, and  $\geq 28$  kg/m<sup>2</sup>, respectively.<sup>15</sup>

Patients were assessed in-clinic at 1, 3, 6, and 12 months post-CRT implantation, then biannually. Telephone interviews supplemented in-person visits. Clinical and echocardiographic evaluations were conducted six months after device implantation. Endpoint adjudication was performed by two independent cardiologists blinded to 2D-STE data.

Clinical events, including cardiac death and hospitalization for HF, were identified through clinical interviews or telephone follow-ups. CRT response was defined as a  $\geq 15\%$  relative reduction in left ventricular end-systolic volume (LVESV) on echocardiographic assessment post-implantation.<sup>16</sup> Non-responders included patients who died, underwent heart transplantation, or required hospitalization for HF within six months.

The primary endpoints were all-cause mortality and hospitalization due to decompensated HF, excluding events related to inappropriate therapies for atrial tachyarrhythmia, lead fractures, or oversensing. Data from the initial evaluation, including laboratory results, medication use, echocardiographic parameters, and demographic data, were retrospectively retrieved from electronic medical records. Long-term follow-up was conducted through telephone interviews or chart reviews after device implantation.

## Echocardiographic Examinations

**Standard Measurements:** Prior to the retrospective analysis, echocardiographic images in DICOM format were analyzed offline using EchoPAC 204 (GE Healthcare, Norway). All measurements were conducted in accordance with the guidelines of the American Society of Echocardiography and included standard echocardiographic parameters.<sup>17</sup>

## Speckle Tracking Imaging

**Left ventricular layer-specific strain:** Left ventricular layer-specific strain analysis was conducted by marking end-diastole at the maximum R wave on the electrocardiogram and end-systole at the point of aortic valve closure. Using the “2D-strain” mode, analysis was conducted in the three-chamber, two-chamber, and four-chamber views. The myocardial region of interest was delineated by tracing both sides of the mitral annulus and the apical endocardium, ensuring that the width of the selected myocardial region corresponded to myocardial thickness from the endocardium to the epicardium. Upon verification, the software automatically calculated the global longitudinal strain (LVGLS) of the left ventricle, along with layer-specific strain values for the endocardial, midmyocardial, and epicardial layers. A similar approach was used for circumferential strain analysis using the parasternal short-axis view at the basal, midpapillary, and apical levels (Figures 1A-B).

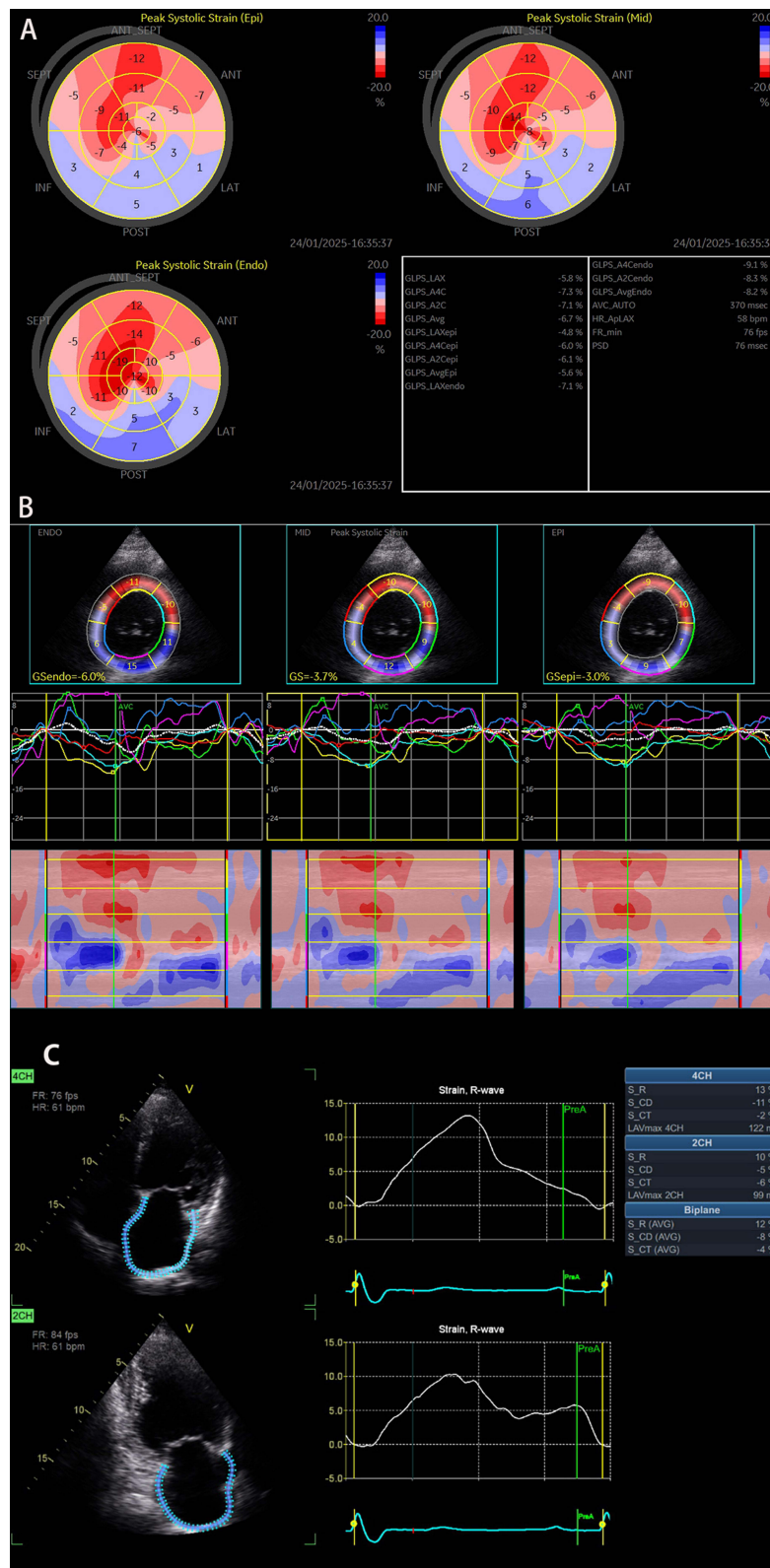
**Left atrial strain:** For left atrial strain analysis, the AFI LA mode was selected. Sampling points were placed at both sides of the mitral annulus and at the superior aspect of the left atrium in the four-chamber view, ensuring exclusion of the pulmonary vein inlet. The software automatically generated the region of interest. Left atrial reservoir strain (LASr), LAScd, and left atrial systolic strain (LASct) were measured in both the four-chamber and two-chamber views. The software then computed the mean values of each left atrial strain parameter across both sections (Figure 1C). The offline quantitative analysis, including speckle tracking, was performed by blinded assessors and to clarify the blinding status during image acquisition.

## Inter- and Intra-Observer Variability

To evaluate the reproducibility of the 2D-STE strain measurements, a cohort of 32 participants from each group was selected for both intra-observer and inter-observer variability analysis. The same observer assessed intra-observer agreement by measuring identical echocardiographic images at an average interval of two weeks. Inter-observer agreement was determined by comparing the initial observer’s measurements with those obtained by a second, blinded observer.

## Statistical Analysis

Continuous variables were expressed as the mean  $\pm$  standard deviation (SD), while categorical variables were reported as absolute numbers or percentages. Data analysis was conducted using SPSS 29.0 software along with SPSSAU (<https://spssau.com/index.html>). The normality of the data was rigorously evaluated utilizing the Kolmogorov–Smirnov test. The Homogeneity of Variance was thoroughly examined using Levene’s test. Normally distributed data were meticulously compared employing one-way ANOVA with Bonferroni correction alongside the Kruskal–Wallis *H*-test. The chi-squared test or Fisher’s exact test was applied for the comparison of dichotomous variables.



**Figure 1** Left ventricular layer-specific strain and left atrial strain analysis. **(A)** Left ventricular longitudinal strain, **(B)** left ventricular circumferential strain, and **(C)** left atrial strain.

Changes in echocardiographic parameters between baseline and the six-month follow-up were assessed using the paired *t*-test. Kaplan-Meier survival curves were generated to evaluate time-to-event outcomes and were compared using the Log rank test. The annual event rate was calculated by dividing the number of adverse clinical events by the average follow-up duration in years. Logistic regression analysis was performed to determine the association between baseline parameters and CRT response. Additionally, Cox regression and stepwise regression analyses were conducted to assess the relationship between baseline parameters and clinical outcomes. The covariates included for adjustment in multivariate models comprised age, gender, ischemic cardiomyopathy, LVEF, and MR severity. Variables with a *p*-value < 0.05 in the univariate analysis were incorporated into a multivariate stepwise regression model to identify independent predictors. Both interobserver and intraobserver variability were evaluated using intraclass correlation coefficients (ICCs). A significance threshold of *p* < 0.05 was applied for all statistical analyses.

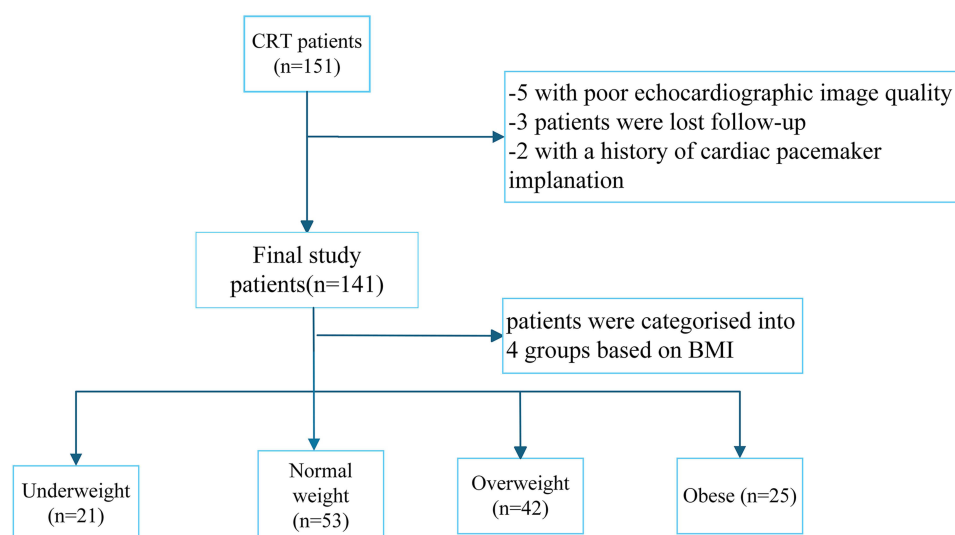
## Results

### The Clinical and Demographic Characteristics of the Study Population

The study initially enrolled 151 patients, of whom 10 were excluded for various reasons, resulting in a final cohort of 141 patients (Figure 2). The clinical characteristics of patients across the four BMI categories are summarized in Table 1. The mean BMI was  $24.1 \pm 5.7$  kg/m<sup>2</sup>, with values ranging from 14.7 kg/m<sup>2</sup> to 39.2 kg/m<sup>2</sup>. Based on BMI at admission, 21 individuals (15%) were categorized as underweight, 53 (37%) as normal weight, 42 (30%) as overweight, and 25 (18%) as obese.

The mean age of the patients was  $61.2 \pm 11.1$  years, with men comprising 58% of the study population. Significant differences were observed among the BMI groups in terms of body surface area (BSA) and plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. Beta-blocker use was more prevalent among individuals in the obese category compared to other groups. Notably, NT-proBNP levels were higher in those classified as underweight or normal weight.

These findings provide valuable insights into the relationship between BMI and clinical characteristics in patients undergoing CRT. The observed differences in NT-proBNP levels and medication usage across BMI categories may have implications for personalized treatment strategies. Further investigation is warranted to explore these associations in greater detail.



**Figure 2** Flowchart depicting the study population. Patients were categorized as underweight, normal weight, overweight, or obese based on the definitions established by the Chinese Obesity Working Group: < 18.5 kg/m<sup>2</sup>, 18.5–24 kg/m<sup>2</sup>, 24–28 kg/m<sup>2</sup>, and ≥ 28 kg/m<sup>2</sup>, respectively.

**Table 1** General Characteristics of Study Population

Demographics	All (n=141)	Underweight (n=21)	Normal (n=53)	Overweight (n=42)	Obese (n=25)
Age (year)	61.2± 11.1	63.2±10.9	60.2±10.5	59.1±12.7	58.6±13.6
Gender (male %)	82(58%)	14(67%)	35(66%)	18(43%)	15(60%)
BSA (m <sup>2</sup> )*	1.74±0.19	1.62±0.11	1.70±0.15	1.78±0.23	1.84±0.16
Heart rate (beats/minutes)	68.2±7.07	67.7±7.31	68.7±6.90	65.2±8.47	71.5±5.96
SBP, mmHg	112±12.9	113±10.8	110±13.5	115±10.1	109±15.7
DBP, mmHg	67.4±9.50	67.1±7.40	66.9±10.2	70.5±8.40	65.8±12.4
QRS interval (s)*	172.9± 69.7	161.5± 79.6	165.9± 73.3	179.8±58.4	180.1±54.7
NYHA class					
II	28(20%)	4(19%)	10(19%)	6(14%)	8(32%)
III	58(41%)	10(48%)	22(42%)	19(45%)	7(28%)
IV	55(39%)	7(33%)	21(39%)	17(41%)	10(40%)
Ischaemic aetiology (%)	40(28%)	2(10%)	13(25%)	17(40%)	8(32%)
Medications (n %)					
ACEI (%)	85(60%)	14(67%)	32(60%)	23(55%)	16(64%)
Diuretics (%)	87(62%)	11(52%)	35(66%)	24(57%)	17(68%)
Beta-blockers (%)*	62(44%)	10(48%)	24(45%)	12(29%)	16(64%)
Statin (%)	35(25%)	7(33%)	15(28%)	5(12%)	8(32%)
Laboratory results					
Serum creatinine (mg/dl)	1.2±0.7	1.3±0.8	1.1±0.5	1.2±0.4	1.1±0.8
BUN (mmol/L)	8.7±3.5	8.9±3.1	8.3±3.8	7.9±4.5	9.0±2.8
NT-proBNP (pmol/L)*	2035.8±1387.6	2889.3±1458.7	2365.1±1163.5	1896.41±1557.9	1465.5±953.4

**Notes:** The categorical data are presented as number (%), and consecutive data are expressed as the mean±standard deviation. \* $p < 0.05$  for trend.

**Abbreviations:** ACEI, angiotensin-converting enzyme inhibitor; BSA, body surface area; BUN, blood urea nitrogen; DBP, diastolic blood pressure; SBP, systolic blood pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA class, New York Heart Association functional class.

## Improved Cardiac Function Associated with Higher BMI and Reverse Remodeling

After six months of CRT, a positive response was observed in 62% of the study population. A significant difference in response rates was identified among the BMI categories. Patients classified as overweight or obese demonstrated higher response rates (78% and 80%, respectively) compared to those classified as underweight or normal weight (43% and 47%, respectively). Statistical analysis revealed significant differences in response rates between overweight and normal weight patients ( $p = 0.03$ ), overweight and underweight patients ( $p = 0.01$ ), obese and normal weight patients ( $p = 0.01$ ), and obese and underweight patients ( $p = 0.002$ ). These findings indicate that BMI influences CRT outcomes.

Data presented in Table 2 indicate a clear association between BMI and improvements in cardiac function over a six-month period. Greater reductions in left ventricular end-diastolic volume and LVESV, along with enhanced ejection fraction, were observed in overweight and obese patients compared to those classified as underweight or normal weight. Furthermore, the incidence of severe mitral regurgitation at six months post-CRT was lower in the overweight and obese groups compared to the underweight and normal weight groups ( $p = 0.002$ ).

Analysis of speckle-tracking echocardiographic parameters demonstrated a significant improvement in LVGLS following CRT in overweight and obese patients compared to those classified as underweight or normal weight ( $p = 0.04$ ). Additionally, baseline assessments revealed that overweight and obese individuals exhibited higher values of LASr, LAScd, and LASct compared to their underweight and normal weight counterparts (overall  $p = 0.007$ ,  $p = 0.02$ , and  $p = 0.03$ , respectively). However, patients in the underweight and normal weight categories did not demonstrate greater post-CRT improvements in these parameters. No significant differences were observed in the remaining echocardiographic measures between the groups. These findings underscore the potential influence of BMI on cardiac function following CRT.

**Table 2** Standard Echocardiography Measurements and Speckle Tracking Echocardiographic Parameters

Parameter	Underweight (n=21)		Normal (n=53)		Overweight (n=42)		Obese (n=25)	
	Baseline	6 Months	Baseline	6 Months	Baseline	6 Months	Baseline	6 Months
LVEDV (mL)* <sup>&amp;</sup>	181.4±52.4	163.0±24.3	193.7±20.6	175.6±22.7	172.5± 27.3 <sup>a</sup>	153.9±26.8 <sup>a</sup>	163.3±28.6 <sup>b</sup>	146.7±20.2 <sup>b</sup>
LVESV (mL)* <sup>&amp;</sup>	134.2±27.4	114.5±28.5	144.2±25.7	123.7±28.8	126.8±24.5 <sup>a</sup>	105.3±26.9 <sup>a</sup>	118.6±18.1 <sup>b</sup>	98.6±20.7 <sup>b</sup>
LVEF (%) <sup>&amp;</sup>	25.7 ±2.3	30.2±3.7	25.3±2.0	29.7±3.0	26.5±2.4	31.5±4.5	27.1±2.6	32.8±3.8
LAVI (mL/m <sup>2</sup> )*	44.1±10.6	45.2±2.85	43.8±6.21	40.6±7.42	43.0±7.53	39.6±6.41	42.3±7.90	39.5±8.03
E/A	1.6±1.07	1.8±0.92	1.6±0.67	1.3±0.98	1.47±1.05	1.17±1.06	1.26± 0.75	0.88 ± 0.59
E/e'	11.3±9.2	13.8±8.7	11.6±12.1	12.3±8.7	14.5±5.83	10.1±5.50	14.3 ±3.3	11.4±3.3
E (m/s)	81.2 ±38.1	80.5 ±40.8	75.8±36.7	69.7±55.3	77.5±24.4	68.3±23.4	75.6±91.3	63.2±22.6
e' (cm/s)	7.40 ±1.26	6.70±6.90	6.20±3.20	6.50±3.17	7.4 ±1.26	6.7±6.9	6.20±2.10	6.70± 1.30
DT (ms)	215.2±45.3	287.1±67.4	203.1 ±121.9	183.4 ±141.8	212.2±35.0	187.5±29.4	239.2 ± 39.2	196.5±27.9
Severe MR (%) <sup>&amp;</sup>	10(47%)	8(38%)	22(42%)	19(36%)	18(43%) <sup>a</sup>	8(19%) <sup>a</sup>	9(36%) <sup>b</sup>	2(8%) <sup>b</sup>
LV GLS endo (%)	-7.4±2.3	-8.3±2.9	-7.7±2.5	-8.2±2.9	-7.6±2.1	-9.5±3.5	-8.1±2.3	-8.9±3.9
LV GLS mid (%)	-6.0±2.5	-7.0±2.8	-7.0±2.7	-8.4±3.4	-6.4±2.3	-8.3±2.5	-6.6±2.4	-7.4±4.7
LV GLS epi (%)	-4.9±2.1	-5.9±2.8	-5.9±2.4	7.4±3.3	-5.4±2.5	-7.2±2.6	-5.8±2.0	-6.4±4.4
LVGLS (%) <sup>&amp;</sup>	-6.2±2.2	-7.1±2.8	-7.1±2.7	-8.5±3.4	-6.5±2.0 <sup>a</sup>	-10.3±13.5 <sup>a</sup>	-6.9±2.2 <sup>b</sup>	-8.3±2.4 <sup>b</sup>
LV GCS endo (%)	-6.2±1.3	-6.6±1.2	-6.3±1.9	-6.9±1.7	-6.2±2.1	-6.5±1.6	-7.0±1.6	-7.5±1.4
LV GCS mid (%)	-5.1±1.2	-5.4±1.1	-4.9±1.7	-5.7±1.5	-5.2±2.1	-5.6±1.5	-5.9±1.6	-6.4±1.4
LV GCS epi (%)	-3.8±1.1	-4.3±1.0	-4.1±1.9	-4.5±1.5	-4.3±2.2	-4.5±1.8	-5.1±1.5	-4.3±2.5
LVGCS (%)	-5.0±1.0	-5.5±2.3	-5.1±1.8	-5.7±2.5	-5.2±2.1	-5.4±2.6	-5.9±1.6	-6.4±1.8
LASr (%) <sup>&amp;</sup>	16.9±2.9	17.8±4.8	17.8±3.9	18.6±5.8	19.7±3.5 <sup>a</sup>	21.8±4.9 <sup>a</sup>	19.8±3.5 <sup>b</sup>	21.5±5.1 <sup>b</sup>
LAScd (%) <sup>&amp;</sup>	-10.6±2.4	-11.1±3.4	-11.3±2.5	-11.6±3.6	-12.2±2.3 <sup>a</sup>	-13.7±3.1 <sup>a</sup>	-12.4±2.2 <sup>b</sup>	-13.6±3.4 <sup>b</sup>
LASct (%) <sup>*</sup>	-6.5±1.5	-6.7±1.7	-6.6±1.9	-7.0±2.3	-7.5±1.7	-7.7±3.3	-7.4±1.6	-7.9±1.9

**Notes:** \*: comparison between groups at baseline levels  $p < 0.05$ , <sup>&</sup>: comparison between the groups after 6 months  $p < 0.05$ , a: overweight group baseline levels and within-group comparisons at 6 months  $p < 0.05$ , b: obese group baseline levels and within-group comparisons at 6 months  $p < 0.05$ .

**Abbreviations:** LVEDV, left ventricle end-diastolic volume; LVESV, left ventricle end-systolic volume; LVEF, left ventricle ejection fraction; LAVI, left atrial volume index; E, the peak early diastolic velocity; A, the peak atrial contraction velocity; e', Early diastolic peak velocity of the mitral ring; DT, deceleration time; MR, mitral valve regurgitation; LV GLS<sub>endo</sub>, left ventricle longitudinal strain of endocardial; LV GLS<sub>mid</sub>, left ventricle longitudinal strain of midmyocardial; LV GLS<sub>epi</sub>, left ventricle longitudinal strain of epicardial; LV GLS, left ventricle longitudinal strain; LV GCS<sub>endo</sub>, left ventricle circumferential strain of endocardial; LV GCS<sub>mid</sub>, left ventricle circumferential strain of midmyocardial; LV GCS<sub>epi</sub>, left ventricle circumferential strain of epicardial; LV GCS, left ventricle circumferential strain; LASr, the left atrial reservoir strain; LAScd, the left atrial conduit strain; LASct, left atrial systolic strain.

A comprehensive evaluation of baseline parameters was conducted using both univariate and multivariate analyses to determine their predictive value for a favorable CRT response (Table 3). The results indicate that a higher BMI, beta-blocker use, and specific LAScd levels were associated with an increased likelihood of a positive CRT response, emphasizing the relevance of these factors in clinical decision-making.

## Cardiac Reverse Remodeling and Long-Term Outcome

Over a mean follow-up duration of  $29.8 \pm 19.7$  months, 23 out of 141 patients (16.3%) experienced mortality, predominantly due to HF or sudden cardiac events. Additionally, 41 patients (28.3%) required hospitalization due to worsening HF. Notably, all-cause mortality was highest among those classified as underweight (33.3%), compared to patients with who were normal weight (20.8%), overweight (7.1%), and obesity (8%). The observed differences in mortality rates across BMI categories were statistically significant ( $p = 0.031$ ).

Univariate analysis demonstrated that patients who were overweight or obese exhibited the highest event-free survival rates compared to those classified as normal weight or underweight (Figure 3). This trend was observed across various clinical outcomes, including all-cause mortality and hospitalization for decompensated HF. Further analysis using Cox and stepwise regression models indicated that a higher BMI was associated with a reduced risk of adverse clinical events ( $p < 0.001$ , Table 4). In contrast, the presence of NYHA class III–IV symptoms, beta-blocker use, and LAScd values demonstrated a significant association with adverse clinical outcomes ( $p = 0.015$ ,

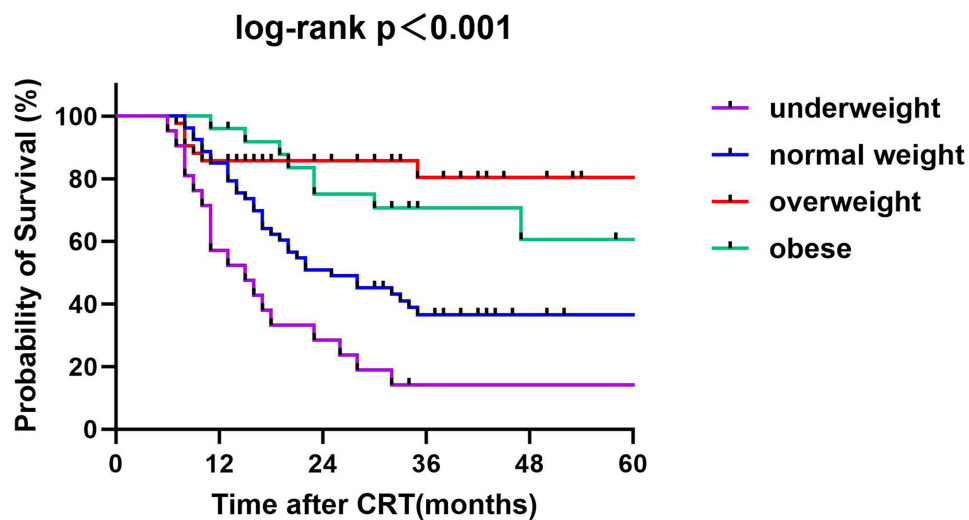
**Table 3** Uni- and Multivariate Predictors of Response to CRT by Logistic Regression Analysis

Variable	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Male gender	0.72(0.36–1.45)	0.36		
QRS duration	1.05(0.94–1.31)	0.02		
NHYA class (III-IV)	1.82(0.79–4.21)	0.16		
BMI>24kg/m <sup>2</sup>	4.5(2.11–9.38)	<0.001	0.07(0.04–0.13)	0.003
Beta-blockers (%)	35.8(10.3–124.8)	0.06	0.15(0.08–0.21)	0.001
LAVI (mL/m <sup>2</sup> )	0.98(0.93–1.02)	0.31		
LVEDV (mL)	0.92(0.89–0.94)	<0.001		
LVESV (mL)	0.89(0.86–0.92)	<0.001		
LVEF (%)	1.37(1.16–1.62)	0.001		
LASr (%)	31.6(3.3–297.7)	0.03		
LAScd (%)	0.25(0.16–0.40)	<0.001	0.09(0.02–0.37)	0.001
LASct (%)	0.07(0.03–0.19)	<0.001		

$p = 0.016$ , and  $p < 0.001$ , respectively). These findings underscore the multifaceted relationship between BMI, pharmacological management, and clinical outcomes in patients with HF.

## Reproducibility

The reliability and reproducibility of strain measurements using 2D-STE were assessed by calculating ICCs for inter- and intra-observer variability. The intraclass correlation coefficient (ICC) for LVGLS is 0.82, the ICC for left ventricular global circumferential strain (LVGCS) is 0.84, the ICC for LASr is 0.85, the ICC for LAScd is 0.88, and the ICC for LASct is 0.83.



**Figure 3** Kaplan-Meier survival curves depicting long-term survival among different BMI groups.

**Table 4** Uni- and Multivariate Predictors of Clinical Events (Death and/or HF Hospitalization) by Cox and Stepwise Regression Analysis

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Male gender	1.33 (0.82–2.16)	0.25		
NHYA class (III-IV)	2.51(1.31–4.81)	0.01	0.21(0.04–0.37)	0.015
BMI>24kg/m <sup>2</sup>	0.32(0.19–0.55)	<0.001	–0.30 (–0.45- –0.15)	<0.001
Beta-blockers (%)	1.02(0.63–1.63)	0.95	0.20(0.04–0.37)	0.016
LAVI (mL/m <sup>2</sup> )	1.03(0.99–1.06)	0.16		
LVEDVI (mL)	1.02(1.01–1.03)	<0.001		
LVESV (mL)	1.03(1.01–1.04)	<0.001		
LVEF (%)	0.92(0.83–1.01)	0.09		
Relative change in LV GLS	1.13(1.03–1.24)	0.010		
LASr (%)	0.86 (0.81–0.92)	<0.001		
LAScd (%)	1.24(1.12–1.37)	<0.001	0.07 (0.04–0.11)	<0.001
LASct (%)	1.27(1.10–1.46)	0.001		
Change in LASr	0.47(0.29–0.75)	0.002		
Change in LAScd	1.17(1.09–1.25)	<0.001		
Change in LASct	1.07 (1.00–1.15)	0.04		

## Discussion

According to a study examining patients undergoing CRT, an unexpected phenomenon referred to as the “obesity paradox” was identified. It was found that those classified as overweight or obese exhibited higher response rates and more favorable clinical outcomes compared to patients with normal weight or underweight status. Furthermore, LAScd emerged as a significant predictor of CRT response and positive prognosis.

## BMI and CRT

BMI serves as a valuable tool for estimating body composition and identifying patients who are overweight or obese. Although BMI levels in China are generally lower than in western countries, it is important to consider the recommended classifications for this population. Therefore, we used the native recommended classification for BMI.<sup>15</sup>

The focus of this study was on 141 participants with HF, nearly half (67) were classified as overweight or obese based on their BMI. According to the research, a significant association between baseline BMI and treatment response is present. Patients who were underweight or of normal weight showed lower response rates compared to those classified as overweight or obese. Additionally, baseline BMI was found to be a strong predictor of response to CRT in further analysis. These results highlight the importance of evaluating BMI when considering CRT for patients with HF to improve treatment outcomes. Interestingly, according to the study being overweight or obese did not increase the risk of adverse events, contrary to common belief. Patients with higher BMI levels showed better cardiac function and improved survival rates compared to those with normal or underweight statuses in advanced HF cases undergoing CRT. Considering these findings, we propose that BMI should be evaluated among eligible candidates for CRT to enhance response rates. Patients with low BMI may experience sarcopenia or malnutrition; therefore, we recommend a comprehensive nutritional assessment and muscle strength testing prior to CRT implantation. Additionally, providing preoperative nutritional support in high-risk patients may improve postoperative outcomes.

This observation supports the phenomenon commonly known as the obesity paradox.<sup>6–10</sup> Obesity significantly increases the risk of heart failure (HF).<sup>6</sup> In this study, the higher BMI group did not experience worse outcomes and even showed trends towards better results, aligning with the “obesity paradox”. This phenomenon suggests that greater fat reserves may provide energy during high metabolic demands like HF and may be linked to a favorable neurohormonal environment.<sup>8</sup> Additionally, obese patients may seek treatment sooner due to earlier symptoms and may respond better to certain HF medications.<sup>9,10</sup> However, the “obesity paradox” is complex and influenced by various confounding factors,

and this observational study has limitations in establishing causality. In the management of heart failure (HF), obesity should not be regarded as a protective factor at the expense of weight management. Instead, a more nuanced assessment of patients' body composition, metabolic status, and functional reserve is warranted. Future risk stratification and treatment strategies may necessitate the incorporation of metabolic health indicators beyond body mass index (BMI). Understanding paradoxical mechanisms can aid in identifying which obese HF patients might benefit from specific interventions. Overall, these findings highlight the complex relationship between BMI, treatment response, and outcomes in patients with HF undergoing CRT. By understanding the influence of BMI on therapeutic effectiveness, healthcare providers can more effectively tailor treatment strategies to optimize patient care and improve overall prognosis.

## 2D-STE and CRT

Cardiac imaging plays a key role in identifying patients with HF who may benefit from CRT, a treatment aimed at restoring coordinated cardiac function. Although other researchers have explored the relationship between cardiac imaging and CRT outcomes, definitive conclusions remain inconclusive.<sup>1,13,14</sup> Current clinical guidelines primarily consider clinical status, QRS duration, and LVEF as the primary determinants for CRT eligibility, while the assessment of cardiac asynchrony through additional imaging modalities is not regarded as a crucial factor in the decision-making process.<sup>14</sup> Recent advancements in imaging technology, particularly 2D-STE, have significantly improved the ability to detect and quantify myocardial functional changes through strain and strain rate analysis. According to the research, baseline strain variability is a reliable predictor of CRT response.<sup>18,19</sup> In this study, patients classified as overweight or obese exhibited a significant improvement in LV GLS following six months of CRT compared to those classified as underweight or normal weight ( $p = 0.04$ ). These findings emphasize the relevance of STE in evaluating CRT effectiveness, as LV GLS parameters serve as valuable predictors of treatment response. The results highlight the potential use of STE in optimizing CRT assessment and individualizing treatment strategies.

## The Role of LA Strain in Patients Receiving CRT

The impact of CRT on LA remodeling represents a key area of investigation, though much of the existing research has primarily focused on LV remodeling. In HF, progressive LA dysfunction leads to a decline in LA compliance, resulting in increased LA pressure and elevated hemodynamic stress on the pulmonary circulation.<sup>20</sup> This process contributes to the development of postcapillary pulmonary hypertension and pulmonary vascular remodeling. Additionally, adverse LA remodeling is associated with an increased risk of atrial fibrillation, a condition that significantly heightens the likelihood of cardiovascular events.

Traditionally, LA remodeling has been characterized based on changes in LA volume, with limited emphasis on LA functional assessment. However, emerging evidence indicates that CRT may induce LA reverse remodeling, a phenomenon linked to improved cardiovascular outcomes.<sup>21</sup> The beneficial effects of CRT on LA remodeling are likely mediated through its role in reversing maladaptive remodeling by improving LV geometry, reducing mitral regurgitation, decreasing LV mass, enhancing diastolic function, and lowering LV filling pressures.<sup>22</sup> Some studies have proposed that monitoring changes in LASr before and after the CRT procedure may provide valuable insights into the beneficial effects of CRT.<sup>20-22</sup>

Recent findings indicate that baseline values of LASr, LAScd, and LASct were significantly higher in patients classified as overweight or obese ( $p = 0.007$ ,  $p = 0.02$ , and  $p = 0.03$ , respectively) and demonstrated greater improvements following CRT. In contrast to previous research, from the present study, we discovered LAScd as a strong independent predictor of both CRT response and favorable clinical prognosis.

Functional mitral regurgitation is frequently observed in patients with HF and reduced LVEF and is primarily attributed to progressive cardiac remodeling, which leads to papillary muscle displacement and annular dilation.<sup>20</sup> LAScd occurs during early diastole, when the LA functions as a conduit for the rapid transfer of stored blood into the LV. This strain serves as an indicator of the capacity of the LA for efficient emptying. In the presence of mitral regurgitation, a portion of systolic blood regurgitates into the LA, leading to a substantial increase in atrial volume load. Consequently, during the conduit phase, the presence of regurgitant blood imposes additional resistance, impairing the ability of the LA to transfer blood into the LV and resulting in a reduction in conduit-phase strain. To compensate, the LA

increases contractility in an effort to maintain normal cardiac output, thereby partially masking the decline in conduit-phase strain. However, over time, this compensatory mechanism becomes insufficient, further exacerbating LA dysfunction. Additionally, impaired LA conduit-phase strain contributes to worsening mitral regurgitation.

In this study, the likelihood of severe mitral regurgitation was significantly reduced following CRT among patients classified as overweight and obese (from 43% to 19% and 36% to 8%, respectively; overall  $p < 0.05$ ). A reduction in conduit-phase strain reflects a diminished ability of the LA to effectively empty blood into the LV. As a functional measure, LA strain serves as an important metric for evaluating the effects of CRT. When CRT is successful, ventricular systolic synchrony is improved, thereby reducing the hemodynamic burden on the LA. Accordingly, LA strain, particularly LAScd, was identified as a strong predictor of CRT response and long-term clinical outcomes. Improvements in LA strain post-CRT likely reflect reductions in hemodynamic stress and enhanced ventricular synchrony, both of which contribute to improved cardiovascular outcomes. Notably, LAScd is a negative value, and its correlation with prognosis indicates that a lower absolute value is indicative of worse clinical outcomes, highlighting the significance of monitoring LA strain in CRT assessment.

In conclusion, while previous research has primarily focused on LV remodeling in patients with HF undergoing CRT, recent evidence underscores the substantial impact of CRT on LA remodeling. By improving ventricular synchrony and reducing hemodynamic burden on the LA, CRT promotes LA reverse remodeling and enhances cardiovascular outcomes. LAScd emerges as a key predictor of CRT response and long-term prognosis, reinforcing the importance of LA strain assessment in evaluating CRT efficacy. Further research is warranted to elucidate the mechanisms underlying the beneficial effects of CRT on LA remodeling and its implications for HF management.

## Study Limitations

The limitations of this study are primarily related to its retrospective, observational design. Conducted at a single center with a relatively small sample size, the study is subject to potential selection bias. The sample size was constrained by the number of eligible CRT recipients meeting strict inclusion criteria during the study period. As a retrospective analysis concentrating on long-term outcomes for patients with successful implantation, this study was unable to include cases where implantation attempts were unsuccessful. Additionally, patients with inadequate image quality were excluded from strain analysis, which may have restricted the generalizability of the findings.

Another limitation is the use of diagnostic criteria specifically designed for Chinese populations, without accounting for additional anthropometric factors such as waist circumference, which may influence the assessment of obesity-related outcomes. While BMI at CRT implantation was meticulously documented, longitudinal changes in BMI during follow-up were not systematically analyzed. This static assessment may obscure the influence of weight trajectories on CRT outcomes. Future studies should incorporate serial measurements of BMI, ideally combined with body composition analysis, to elucidate the dynamic interplay between nutritional status evolution and CRT response. Although we adjusted for major comorbidities (specifically ischemic etiology) in our multivariate models, detailed data regarding specific medications and adherence metrics were unavailable. This limitation hinders our ability to determine whether different BMI groups received equitable guideline-directed therapy. Nonetheless, protocol-defined drug optimization was conducted quarterly at our center throughout the study period, thereby minimizing significant deviations. Furthermore, variations in strain measurements across different vendors of 2D-STE equipment pose challenges for direct comparisons between ultrasound platforms.

Despite these limitations, the study offers valuable insights into the relationship between obesity and cardiac function in Chinese populations, highlighting the need for further research to validate these findings in larger, multi-center groups with diverse populations.

## Conclusion

This study identified the presence of the “obesity paradox” in patients undergoing CRT. The findings indicate that patients classified as overweight or obese exhibit higher response rates and more favorable long-term prognoses compared to patients with normal weight or underweight status. Specifically, a higher BMI and absolute LAScd values were associated with improved clinical outcomes. Together, these findings indicate that Body Mass Index (BMI) should

be considered during routine pre-Cardiac Resynchronization Therapy (CRT) implant assessments, and that patients with normal weight, particularly those who are underweight, should be closely monitored following CRT implantation. Left Atrial Strain (LAScd) emerges as a significant predictor of CRT response and long-term prognosis, underscoring the importance of assessing left atrial strain in evaluating CRT efficacy. The observational, single-center design inherently restricts causal inference and generalizability. Moreover, we acknowledge that the relatively small sample size, particularly within the underweight BMI subgroup, limited the capacity for robust subgroup analyses. Furthermore, although we identified an association between the obesity paradox, LAScd, and CRT response/outcomes, this observation necessitates validation through larger, prospective multi-center studies. Future research should also endeavor to establish definitive cut-off values for LAScd in predicting CRT response and prognosis.

## Abbreviations

2D-STE, two-dimensional speckle-tracking echocardiography; CRT, cardiac resynchronization therapy; BMI, body mass indices; LA, left atrium; LV, left ventricle; LAScd, left atrial conduit strain; HF, heart failure; LVEF, left ventricle ejection fraction; ECG, electrocardiogram; STE, speckle tracking echocardiography; NYHA, New York Heart Association; LVESV, left ventricle end-systolic volume; LV GLS, left ventricle global longitudinal strain; LV GCS, left ventricle global circumferential strain; LASr, left atrial reservoir strain; LASct, the left atrial systolic strain; SD, standard deviation; ANOVA, one-way analysis of variance; BSA, body surface area; NT-proBNP, plasma N-terminal pro-brain natriuretic peptide; LVEDV, left ventricle end-diastolic volume; EF, ejection fraction MR, mitral regurgitation.

## Data Sharing Statement

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of Fuwai Hospital. This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

## Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## Disclosure

The authors declare that they have no conflicts of interest regarding this work.

## References

1. Aalen JM, Donal E, Larsen CK, et al. Imaging predictors of response to cardiac resynchronization therapy: left ventricular work asymmetry by echocardiography and septal viability by cardiac magnetic resonance. *Eur Heart J*. 2020;41(39):3813–3823. PMID: 32918449; PMCID: PMC7599033. doi:10.1093/eurheartj/ehaa603
2. Beela AS, Manetti CA, Prinzen FW, Delhaas T, Herbots L, Lumens J. The mechanistic interaction between mechanical dyssynchrony and filling pressure in cardiac resynchronisation therapy candidates. *Eur Heart J Cardiovasc Imaging*. 2025;26(3):424–434. PMID: 39513574; PMCID: PMC11879185. doi:10.1093/ehjci/jeae286
3. Chen X, Jin Q, Qiu Z, et al. Outcomes of upgrading to LBBP in CRT nonresponders: a prospective, multicenter, nonrandomized, case-control study. *JACC Clin Electrophysiol*. 2024;10(1):108–120. Epub 2023 Nov 8. PMID: 37943191. doi:10.1016/j.jacep.2023.08.031
4. Leclercq C, Burri H, Curnis A, et al. Cardiac resynchronization therapy non-responder to responder conversion rate in the more response to cardiac resynchronization therapy with MultiPoint Pacing (MORE-CRT MPP) study: results from Phase I. *Eur Heart J*. 2019;40(35):2979–2987. PMID: 30859220. doi:10.1093/eurheartj/ehz109
5. Leclercq C, Burri H, Delnoy PP, et al. Cardiac resynchronization therapy non-responder to responder conversion rate in the MORE-CRT MPP trial. *Europace*. 2023;25(10):euad294. PMID: 37776313; PMCID: PMC10561537. doi:10.1093/europace/euad294
6. Fu K, Dong Y, Wang Z, et al. The role of body composition in left ventricular remodeling, reverse remodeling, and clinical outcomes for heart failure with mildly reduced ejection fraction: more knowledge to the “obesity paradox”. *Cardiovasc Diabetol*. 2024;23(1):334. PMID: 39261931; PMCID: PMC11391770. doi:10.1186/s12933-024-02430-9
7. Butt JH, Thune JJ, Nielsen JC, et al. Anthropometric measures and long-term mortality in non-ischaemic heart failure with reduced ejection fraction: questioning the obesity paradox. *Eur J Heart Fail*. 2024;45(16). Epub ahead of print. PMID: 39155576. doi:10.1002/ejhf.3424
8. Merkel ED, Behon A, Masszi R, et al. Obesity paradox in patients with reduced ejection fraction eligible for device implantation - an observational study. *ESC Heart Fail*. 2024;11(6):3616–3625. Epub 2024 Jul 19. PMID: 39031161; PMCID: PMC11631315. doi:10.1002/ehf2.14961

9. Yanagisawa S, Inden Y, Shimano M, et al. Impact of cardiac resynchronization therapy-defibrillator implantation on the association between body mass index and prognosis in patients with heart failure. *J Interv Card Electrophysiol.* 2015;43(3):269–277. Epub 2015 May 24. PMID: 26003807. doi:10.1007/s10840-015-0015-3
10. Papageorgiou N, Briasoulis A, Barra S, et al. Long-term impact of body mass index on survival of patients undergoing cardiac resynchronization therapy: a multi-centre study. *Am J Cardiol.* 2021;153:79–85. Epub 2021 Jun 25. PMID: 34183146. doi:10.1016/j.amjcard.2021.05.024
11. Cox B, Luyten LJ, Dockx Y, et al. Association between maternal prepregnancy body mass index and anthropometric parameters, blood pressure, and retinal microvasculature in children age 4 to 6 years. *JAMA Network Open.* 2020;3(5):e204662. PMID: 32396192; PMCID: PMC7218490. doi:10.1001/jamanetworkopen.2020.4662
12. Sperlongano S, Benfari G, Ilardi F, et al; Echocardiography Working Group of the Italian Society of Cardiology. Role of speckle tracking echocardiography beyond current guidelines in cardiac resynchronization therapy. *Int J Cardiol.* 2024;402:131885. Epub 2024 Feb 20. PMID: 38382847. doi:10.1016/j.ijcard.2024.131885
13. Taha K, Bourfiss M, Te Riele ASJM, et al. A head-to-head comparison of speckle tracking echocardiography and feature tracking cardiovascular magnetic resonance imaging in right ventricular deformation. *Eur Heart J Cardiovasc Imaging.* 2021;22(8):950–958. PMID: 32462176; PMCID: PMC8291671. doi:10.1093/ehjci/jeaa088
14. Stefanidis A, Korlou P, Margos P, et al. The implementation of speckle tracking echocardiography for cardiac resynchronization therapy optimisation. A rotational myocardial mechanics interpretation. *Echo Res Pract.* 2024;11(1):28. PMID: 39617943; PMCID: PMC11610125. doi:10.1186/s44156-024-00062-z
15. Song Z, Gao M, Lv J, et al; China Kadoorie Biobank (CKB) Collaborative Group. Metabolically healthy obesity, transition to unhealthy phenotypes, and type 2 diabetes in 0.5 million Chinese adults: the China Kadoorie Biobank. *Eur J Endocrinol.* 2022;186(2):233–244. PMID: 34874895; PMCID: PMC8789025. doi:10.1530/EJE-21-0743
16. Chung ES, Leon AR, Tavazzi L, et al. Results of the predictors of response to CRT (PROSPECT) trial. *Circulation.* 2008;117(20):2608–2616. Epub 2008 May 5. PMID: 18458170. doi:10.1161/CIRCULATIONAHA.107.743120
17. Mitchell C, Rahko PS, Blauwet LA, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr.* 2019;32(1):1–64. Epub 2018 Oct 1. PMID: 30282592. doi:10.1016/j.echo.2018.06.004
18. Antoniou N, Kalaitzoglou M, Tsigkriki L, et al. Speckle tracking echocardiography in patients with non-ischemic dilated cardiomyopathy who undergo cardiac resynchronization therapy: a narrative review. *Diagnostics.* 2024;14(11):1178. PMID: 38893704; PMCID: PMC11171556. doi:10.3390/diagnostics14111178
19. Mele D, Toselli T, Capasso F, et al. Comparison of myocardial deformation and velocity dyssynchrony for identification of responders to cardiac resynchronization therapy. *Eur J Heart Fail.* 2009;11(4):391–399. Epub 2009 Mar 3. PMID: 19261620. doi:10.1093/eurjhf/hfp032
20. Stassen J, Galloo X, Hirasawa K, et al. Interaction between secondary mitral regurgitation and left atrial function and their prognostic implications after cardiac resynchronization therapy. *Eur Heart J Cardiovasc Imaging.* 2023;24(4):532–541. PMID: 35900222; PMCID: PMC10029846. doi:10.1093/ehjci/jeac149
21. Inciardi RM, Bonelli A, Biering-Sorensen T, et al. Left atrial disease and left atrial reverse remodelling across different stages of heart failure development and progression: a new target for prevention and treatment. *Eur J Heart Fail.* 2022;24(6):959–975. Epub 2022 Jun 6. PMID: 35598167; PMCID: PMC9542359. doi:10.1002/ejhf.2562
22. Bouwmeester S, Mast TP, Keulards DCJ, et al. Left atrial reverse remodeling predicts long-term survival after cardiac resynchronization therapy. *J Echocardiogr.* 2022;20(2):115–123. Epub 2021 Nov 25. PMID: 34822132. doi:10.1007/s12574-021-00559-0

Journal of Multidisciplinary Healthcare

Publish your work in this journal

The Journal of Multidisciplinary Healthcare is an international, peer-reviewed open-access journal that aims to represent and publish research in healthcare areas delivered by practitioners of different disciplines. This includes studies and reviews conducted by multidisciplinary teams as well as research which evaluates the results or conduct of such teams or healthcare processes in general. The journal covers a very wide range of areas and welcomes submissions from practitioners at all levels, from all over the world. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/journal-of-multidisciplinary-healthcare-journal>

**Dovepress**  
Taylor & Francis Group