

Does Body Mass Index Influence Mortality in Patients With Heart Failure?

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Introduction and objectives. Obesity is an independent risk factor for congestive heart failure. Paradoxically, improved survival has been observed in obese heart failure patients. The objective of this study was to analyze the relationship between body mass index (BMI) and the 2-year mortality rate in outpatients with heart failure of different etiologies who were attending a heart failure unit.

Methods. Baseline BMI and survival status at 2-year follow-up were recorded in 501 patients (73% men, median age 68 years). Heart failure etiology was mainly ischemic heart disease, present in 59%. The patients' median ejection fraction was 30%. They were divided into four groups according to BMI: low weight (<20.5), normal weight (20.5 to <25.5), overweight (25.5 to <30), and obese (≥ 30).

Results. The mortality rate at 2 years differed significantly ($P < .001$) between the groups: 46.7% for low-weight patients, 27.8% for normal-weight patients, 18.7% for overweight patients, and 16% for obese patients. After adjusting for age, sex, heart failure etiology, functional class, ejection fraction, hypertension, diabetes, estimated creatinine clearance rate, plasma hemoglobin level, and treatment received, BMI remained an independent predictor of reduced mortality at 2 years (odds ratio=0.92 [0.88–0.97]).

Conclusions. A high BMI has been associated with lower all-cause mortality rates at 2-year follow-up. Our findings in a broad population of patients with heart failure of different etiologies further confirm the existence of a paradoxical relationship between obesity and heart failure outcome.

Key words: Heart failure. Obesity. Body mass index. Survival. Prognosis.

¿El índice de masa corporal influye en la mortalidad de los pacientes con insuficiencia cardíaca?

Introducción y objetivos. La obesidad es un factor de riesgo independiente de que se desarrolle insuficiencia cardíaca. Paradójicamente, se ha observado una mayor supervivencia en los pacientes obesos con insuficiencia cardíaca. El objetivo del estudio es analizar la relación entre el índice de masa corporal (IMC) y la mortalidad a 2 años en una población ambulatoria de pacientes con insuficiencia cardíaca de diferentes etiologías en una unidad especializada.

Métodos. Se analizó el índice de masa corporal en la primera visita y la supervivencia a 2 años en 501 pacientes (el 73% varones; mediana de edad, 68 años). La principal etiología de la insuficiencia cardíaca fue la cardiopatía isquémica (59%). La fracción de eyección media fue del 30%. Los pacientes fueron clasificados en función de su índice de masa corporal en 4 grupos: bajo peso (IMC < 20,5), peso normal (IMC de 20,5 a < 25,5), sobrepeso (IMC de 25,5 a < 30) y obesidad (IMC ≥ 30).

Resultados. La mortalidad a 2 años difirió significativamente ($p < 0,001$) entre los distintos grupos: bajo peso, 46,7%; peso normal, 27,8%; sobrepeso, 18,7%, y obesidad, 16%. Tras ajustar por edad, sexo, etiología, clase funcional, fracción de eyección, hipertensión, diabetes, aclaramiento de creatinina estimado, hemoglobina plasmática y los tratamientos realizados, el IMC permaneció como predictor independiente de mortalidad a 2 años (odds ratio = 0,92 [0,88-0,97]).

Conclusiones. Un mayor IMC tiene relación con menor mortalidad por todas las causas a los 2 años de seguimiento. Nuestros resultados contribuyen a confirmar, en una población general con insuficiencia cardíaca de diferentes etiologías, la relación paradójica entre la obesidad y el pronóstico de la insuficiencia cardíaca.

Palabras clave: Insuficiencia cardíaca. Obesidad. Índice de masa corporal. Supervivencia. Pronóstico.

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INTRODUCTION

Changes in diet and a steady, widespread increase in sedentarism have led to a rise in the incidence and prevalence of obesity in the general population.¹ The impact has been most marked in the United States,²

ABBREVIATIONS

BMI: body mass index
 LVEF: left ventricular ejection fraction
 MLWHFQ: Minnesota Living With Heart Failure Questionnaire
 NYHA: New York Heart Association
 SEEDO: Spanish Society for the Study of Obesity (*Sociedad Española para el Estudio de la Obesidad*)

although Europe has also been affected by the epidemic. According to a registry maintained by the Spanish Society for the Study of Obesity (SEEDO),³ the prevalence of obesity (body mass index [BMI] ≥ 30) in the general population of Spain was 14.5% between 1999 and 2000, with a higher prevalence in women and older people. Prevalence rates were as high as 20%-30% in those aged 55 years or over. Obesity has been identified as an independent risk factor for heart failure,^{4,6} which is not always related to the course of the ischemic heart disease.⁴ The association between obesity and heart failure derives from several factors,⁷ among them an increased incidence of high blood pressure in obese patients, higher levels of insulin resistance⁸ or the so-called metabolic syndrome X,⁴ and different pathophysiological mechanisms^{7,9,10} such as the increase in telediastolic left ventricular end diastolic pressure, an increase which does not always lead to the development of systolic dysfunction.¹¹ In spite of being recognized as risk factors for heart failure and leading to a poorer prognosis in patients with cardiovascular disease,¹² obesity, or overweight in heart failure patients have been linked to a lower mortality rate once the disease is present. Several publications have referred to this paradoxical relationship and it has been suggested that we need to better understand its complexities, particularly given the clinical and economic impact of the 2 conditions.^{13,14}

The aim of this study was to analyze the relationship between BMI and mortality over a 2 year period in ambulatory patients with heart failure attending a heart failure unit; to ascertain whether this relationship was affected by ventricular function, and; to determine whether BMI affects quality of life in these patients, as the literature is not conclusive in this regard.

METHODS

Of the 508 patients admitted to the unit between August 2001 and December 2004, data on BMI at the first visit and vital status after 2 years of follow-up were available for 501 patients. Patients had been sent primarily from cardiology and internal medicine services as well as, to a lesser degree, from emergency departments or cardiologists in our hospital's reference area. The criterion

for admission to the unit was having heart failure as the main diagnosis.

Demographic, clinical, echocardiographic, and analytical data were collected, and BMI was calculated from weight and height measurements taken at the first visit to the unit. BMI was calculated by dividing weight (in kilograms) by height (in meters) squared. The relationship between BMI and survival at 2 years was analyzed for 4 patient subgroups, categorized according to their BMI and based on the World Health Organization (WHO) 1999 criteria (Technical Report Series, n.º 854; Geneva: 1999): low weight (BMI < 20.5), normal weight (BMI 20.5 to < 25.5), overweight (BMI from 25.5 to < 30), and obese (BMI ≥ 30).

Statistical analyses were carried out using the SPSS® 11.0 statistical package for Windows. Due to a non-normal distribution, the association between BMI (treated as a continuous variable) and mortality at 2 years was analyzed using the Kruskal-Wallis test. Logistic regression was used to calculate odds ratios (OR). In a multivariate logistic regression analysis, mortality at 2 years was the dependent variable and independent variables were BMI (treated as a continuous variable), age, sex, NYHA functional class, left ventricular ejection fraction (LVEF), heart failure etiology, presence of diabetes and high blood pressure, estimated creatinine clearance rate, plasma hemoglobin level, and treatment (beta-blockers, angiotensin converting enzyme [ACE] inhibitors or angiotensin II receptor antagonists [ARA-II], loop diuretics, spironolactone, digoxin, and statins). The conditional backward stepwise method was used.

The relationship between the different groups categorized by BMI and mortality at 2 years was analyzed using the χ^2 test (linear by linear association for the combined analysis of the 4 groups) or Fisher's test, depending on the number of patients. Between-group comparisons were performed using the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables, after determining that they were not normally distributed.

Kaplan-Meier survival curves were obtained for the different BMI subgroups.

The relationship between BMI and mortality was also analyzed taking into account whether patients had a LVEF $< 40\%$ or $\geq 40\%$.

Patient quality of life was evaluated using the Minnesota Living with Heart Failure Questionnaire¹⁵ (MLWHFQ) during the first visit to the unit (501 patients) and after 2 years of follow-up (312 patients). The MLWHFQ has been used previously in Spain¹⁶ and consists of 21 questions designed to determine the extent to which heart failure affects the physical, psychological, and socioeconomic aspects of patients' lives. The questions refer to the signs and symptoms of heart failure, social relationships, physical and sexual activity, work, and emotions. Response options for all questions are on a

TABLE 1. Demographic and Clinical Characteristics

Patients, n	501
Men:women	364:137
Age, median (interval), years	68 (31-91)
Etiology, n (%)	
Ischemic heart disease	295 (58.9)
Dilated cardiomyopathy	51 (10.2)
Hypertensive heart disease	53 (10.6)
Alcoholic heart disease	28 (5.6)
Toxic heart disease	8 (1.6)
Valvulopathy	33 (6.6)
Others	33 (6.6)
Time of evolution, median (interval), months	21 (0-288)
NYHA functional class, n (%)	
I	19 (3.8)
II	253 (50.5)
III	211 (42.1)
IV	18 (3.6)
LVEF, median (interval)	30 (5-81)
LVEF <40%, n (%)	375 (74.9)
LVEF ≥40%, n (%)	126 (25.1)
Diabetes, n (%)	201 (40.1)
HBP, n (%)	278 (55.5)
BMI, n (%)	
<20.5 (low weight)	30 (6)
20.5 to <25.5 (normal weight)	144 (28.7)
25.5 to <30 (overweight)	171 (34.1)
≥30 (obese)	156 (31.1)

LVEF indicates left ventricular ejection fraction; HBP, high blood pressure; BMI, body mass index; NYHA, New York Heart Association.

scale from 0 (no problems) to 5 (many problems). A higher score represents worse quality of life.

The study was performed in compliance with the Law on the Protection of Personal Data and in accordance with the Helsinki Declaration of the World Medical Association.

RESULTS

Patient demographic characteristics and distribution by groups according to BMI are shown in Table 1. Tables 2 and 3 show the clinical characteristics of the patients and the treatments they received. Mortality after 2 years of follow-up was 22.1%. BMI treated as a continuous variable was significantly associated with mortality ($P<.001$): a higher BMI was associated with lower mortality (OR=0.91 [0.87-0.96]). After adjusting for age, sex, etiology, NYHA functional class, LVEF, high blood pressure, diabetes, estimated creatinine clearance rate, plasma hemoglobin level, and the type of treatment received, BMI was still an independent predictor of mortality (OR=0.92 [0.88-0.97]) (Table 4). For every 1 point increase in BMI, risk of death decreased by 8%. Figure 1 shows mortality at 2 years for the different groups classified according to BMI; it is particularly notable that mortality increases with a lower BMI.

The between-group differences observed were statistically significant when the 4 groups were analyzed

TABLE 2. Clinical Characteristics According to Body Mass Index

	Low Weight (n=30)	Normal Weight (n=144)	Overweight (n=171)	Obese (n=156)	P
Age, median (interval), years	71 (33-85)	70 (31-86)	69 (35-91)	64 (35-87)	<.001
Men, %	80	75.7	74.9	66	NS
Ischemic etiology, %	26.7	65.9	60.2	57	<.001
Diabetes, %	23.3	37.5	38	48.7	.01
HBP, %	20	56.9	49.1	67.3	<.001
LVEF, median (interval), %	28.5 (11-70)	30 (8-76)	31 (5-77)	34 (11-81)	NS
Class III-IV, %	63.3	45.8	41.1	47.4	NS
CCr, median (interval), mL/min	35.8 (16-78)	44.5 (6-125)	52.5 (10-144)	65.9 (11-372)	<.001
Plasma Hb, mean (SD), g/dL	12.5 (1.9)	12.6 (1.7)	13 (1.7)	13.2 (1.8)	.008

CCr indicates estimated creatinine clearance rate; SD, standard deviation; LVEF, left ventricular ejection fraction; Hb, hemoglobin; HBP, high blood pressure.

TABLE 3. Treatment According to Body Mass Index

	Low Weight (n=30)	Normal Weight (n=144)	Overweight (n=171)	Obese (n=156)	P
Beta-blockers	46.6	65.9	73.1	76.2	.005
ACE inhibitors or ARA-II	83.3	85.4	85.3	85.6	NS
Spironolactone	43.3	26.3	31.5	37.1	NS
Digoxin	53.3	24.3	25.7	23.1	.006
Statins	26.6	53.4	61.4	58.3	.004
Loop diuretics	100	72.9	84.7	72.7	.002

ARA-II indicates angiotension II receptor antagonists; ACE, angiotensin converting enzyme. Values expressed as percentages.

TABLE 4. Multivariate Logistic Regression Analysis (Conditional Backward Stepwise)

Variables Retained In the Model	OR	95% CI
Age	1.04	1.01-1.06
LVEF	0.98	0.96-0.99
NYHA functional class	2.02	1.32-3.08
Diabetes	2.17	1.31-3.61
BMI	0.92	0.88-0.97
Beta-blockers	0.43	0.25-0.74
Statins	0.46	0.27-0.77
ACE inhibitors or ARA-II	0.47	0.25-0.87

ARA-II indicates angiotension II receptor antagonists; LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme; BMI, body mass index; NYHA, New York Heart Association.

Variables introduced which were not retained in the final model: sex, etiology, high blood pressure, diuretics, digoxin, spironolactone, estimated creatinine clearance rate, plasma hemoglobin level.

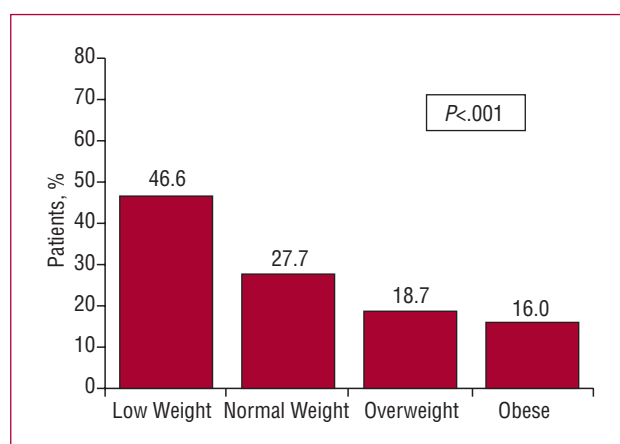


Figure 1. Mortality after 2 years of follow-up in the different groups defined by body mass index. Statistical significance of the χ^2 test (linear by linear association) for the combined analysis of the 4 groups.

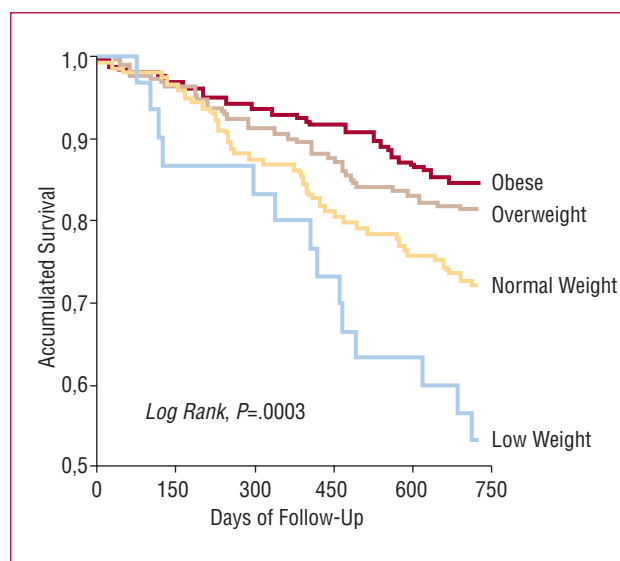


Figure 2. Kaplan-Meier survival curves for the different groups defined by body mass index.

together (linear by linear association, $P < .001$), as well as when the normal weight group was compared with the other groups, except in the case of the overweight group. In the latter case, statistical significance was almost reached for the difference in mortality (low weight, $P = .04$; obesity, $P = .01$; overweight, $P = .05$). Figure 2 shows the accumulated survival curves. Of the 156 obese patients, 30 had a BMI > 40 , which is classified by morbid obesity by the WHO guidelines. In this series, none of the morbidly obese patients died.

Table 5 shows the causes of death in each of the groups studied. Although the proportion of cases of sudden death was higher in the obese group and non-cardiovascular mortality was higher in the low weight group, the differences were not statistically significant.

Given the differences in the literature regarding the impact of LVEF on the association between BMI and survival,¹⁷ we divided patients into those with LVEF $< 40\%$ and $\geq 40\%$. Mortality at 2 years for the different groups classified according to BMI and LVEF is shown in Figure 3. Although mortality was higher in low weight patients in both LVEF groups (41.6% of patients with LVEF $< 40\%$ and 66.6% of those with LVEF $\geq 40\%$), the differences with respect to the normal weight patients were not statistically significant, probably due to the small number of patients. The difference was statistically significant, in both groups, in relation to overweight and obese patients. On the other hand, overweight patients showed a tendency to lower mortality than normal weight patients in both LVEF groups, though the differences were not statistically significant. The difference in mortality between normal weight and obese patients was confined to those with LVEF $< 40\%$ (13.6% and 28.4%; $P = .006$).

The scores on the MLWHFQ questionnaire at the baseline visit are shown in Figure 4; low weight patients had the highest score and therefore the poorest quality of life. There were no statistically significant differences between the normal weight, overweight, and obese patients, although the latter showed a certain tendency towards higher scores (worse quality of life). At the 2 year visit ($n = 312$), patients in all groups except the low weight group had better quality of life scores than at baseline (Figure 5). The MLWHFQ scores for each group are shown in Figure 6 as a function of the patient's situation after 2 years; in all of the groups, patients who died during follow-up had worse quality of life scores at baseline, although the differences were not statistically significant in the overweight group.

DISCUSSION

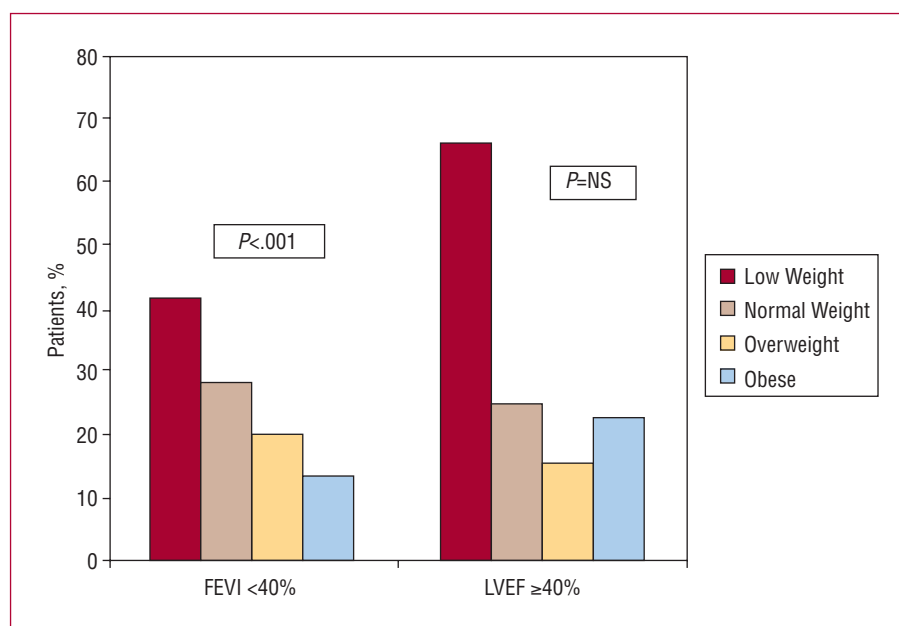
In some patients with chronic illnesses such as end-stage kidney failure or terminal cancer, as well as in some older patients in general, it has been found that obesity is paradoxically associated with an improved prognosis.¹⁸⁻²⁰

TABLE 5. Causes of Death

Cause of Death	Low Weight (n=14)	Normal Weight (n=40)	Overweight (n=32)	Obesity (n=25)	P
Unknown	0 (0%)	3 (7.5%)	2 (6.3%)	3 (12%)	NS
Heart failure	5 (35.7%)	13 (32.5%)	11 (34.3%)	9 (36%)	
Sudden death	3 (21.4%)	7 (17.5%)	5 (15.6%)	9 (36%)	
AMI	0 (0%)	2 (5%)	3 (9.4%)	0 (0%)	
Stroke	0 (0%)	1 (2.5%)	0 (0%)	0 (0%)	
Other cardiovascular causes	0 (0%)	1 (2.5%)	2 (6.3%)	1 (4%)	
Procedures	0 (0%)	2 (5%)	0 (0%)	0 (0%)	
Non-cardiovascular	6 (42.9%)	11 (27.5%)	9 (28.1%)	3 (12%)	

AMI indicates acute myocardial infarction.

Figure 3. Mortality after 2 years of follow-up as a function of the left ventricular ejection fraction (LVEF) in the different groups defined by body mass index. Statistical significance of the χ^2 test (linear by linear association) for the combined analysis of the four groups.



It has also been observed during follow-up after myocardial infarction that obese patients have a similar prognosis to normal weight patients²¹ and the same phenomenon has been observed in patients with heart failure. Previously published studies,²²⁻²⁴ such as the DIG study,^{23,24} have analyzed the relationship between BMI and mortality in patients with stable chronic heart failure. The DIG study included over 7000 patients and showed that mortality was higher in patients with normal weight (BMI ≥ 18.5 to <25) than in those with overweight (BMI ≥ 25 to <30), and higher in the latter than in obese patients (BMI ≥ 30). All of the groups had similar clinical and demographic characteristics. Analysis of 5010 patients in the Valsartan Heart Failure Trial²⁵ found that the lowest mortality rates occurred in obese patients (BMI >30) and that the risk of death from heart failure in low weight patients was 4 times that in obese patients. Normal weight, overweight, and obese groups all had a lower mortality risk than the low weight group, independently of ventricular function, symptoms, and treatment with beta-

blockers, among other factors. In our 2 year follow-up study carried out in ambulatory heart failure patients, we observed that mortality increased as BMI decreased. The obese patients included differed significantly in certain aspects from other groups in that they were younger, received more beta blockers, and there were higher proportions of women, hypertensive, and diabetic patients (Table 2). The multivariate analysis included all of these factors, however, and BMI continued to show a statistically significant relationship with mortality after 2 years. After adjusting for other variables, the risk of all-cause mortality decreased by 8% for each 1 point increase in BMI. In the Val-HeFT²⁵ study, the decrease was 4% for each one point gain in BMI. The relationship between BMI and mortality has also been observed in hospitalized heart failure patients.²⁶

Some studies have indicated that the relation between BMI and mortality might be U shaped in heart failure patients. If that were the case, mortality rates in patients with the lowest (patients with cachexia) and highest

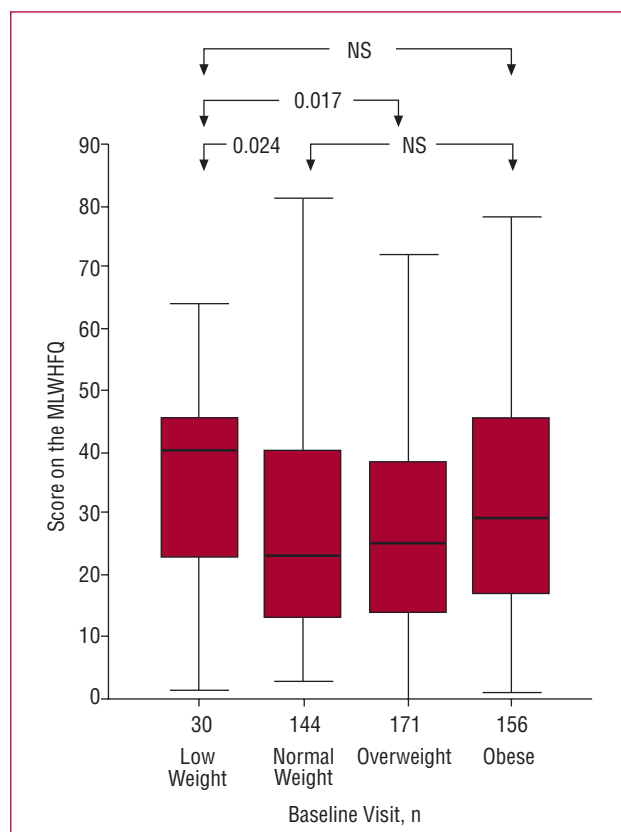


Figure 4. Scores on the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) at the baseline visit in the different study groups defined by BMI (n=501). NS indicates non-significant.

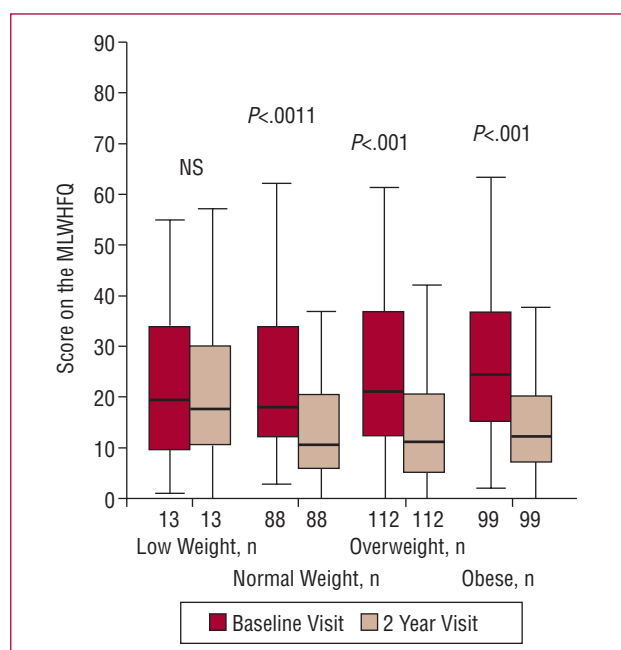


Figure 5. Comparison of baseline and 2 year follow-up (n=312) scores on the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) in the different study groups defined by BMI. NS indicates non-significant.

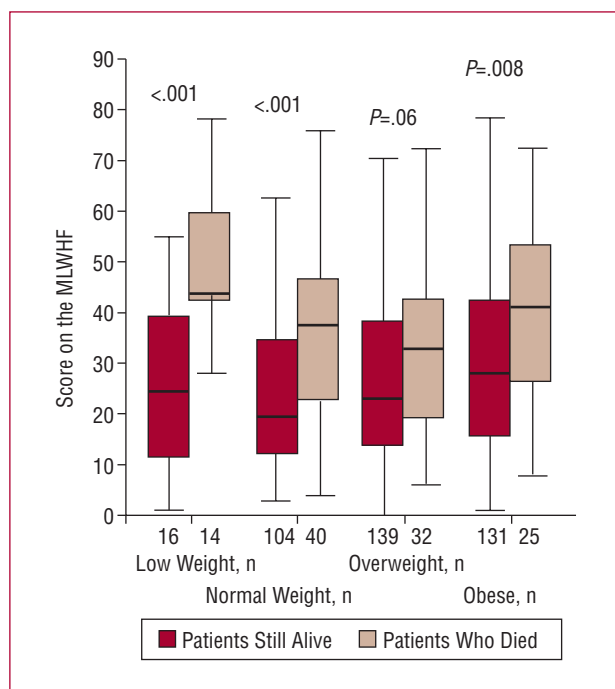


Figure 6. Comparison of baseline scores on the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) in the different study groups defined by BMI and as a function of their clinical situation after 2 years of follow-up.

(morbidly obese patients) BMI values would be higher than those in normal weight, overweight, and moderately obese patients.²⁷ After 2 years, we did not observe such a U-curve. Mortality in the obese patients was lower than in the other groups, including the overweight group, and none of the morbidly obese patients (BMI >40) in our series died. It has been suggested that this U shaped mortality curve might be more evident in heart failure patients with a depressed systolic function. In the study by Gustafsson et al,¹⁷ which analyzed hospitalized patients with heart failure, mortality was higher in obese patients with heart failure and depressed systolic function than in normal weight patients, in contrast to those with heart failure and normal systolic function. We also analyzed patients according to their LVEF (<40% and ≥40%) and found that the obese patients with a significantly better prognosis than normal weight patients were those with depressed systolic function. We did not observe a U shaped mortality curve in patients with depressed LVEF, which confirms the paradoxical relationship between mortality and obesity in these heart failure patients. In patients with LVEF ≥40%, mortality was similar in obese and normal weight patients.

Several publications^{1,6,28} have reported the existence of a relationship between obesity and sudden death. In our study, the proportion of patients who suffered sudden death was higher among obese patients than in the other groups, although the differences were not statistically significant. In contrast to other series,²⁵ we found that

mortality due to progression of heart failure was similar across all groups. On the other hand, a tendency towards higher non-cardiovascular mortality was observed in the low weight patients.

The influence of obesity on patients' health status also warrants study. Conard et al¹⁴ showed that the paradoxical increase in survival in obese heart failure patients was not accompanied by better self-perceived health status measured using a quality of life questionnaire. Patient perceptions had not improved when the instrument was re-administered 1 year later. Evangelista et al²⁹ also found that obese patients with heart failure had poorer scores on quality of life questionnaires as well as symptoms of depression, thereby adding a new twist to this already complex relationship, as the association between a poorer prognosis and poorer baseline quality of life in heart failure patients is well established.³⁰ We analyzed quality of life using the MLWHFQ questionnaire and, although we observed a certain tendency towards a poorer quality of life in obese patients in comparison to normal weight patients, the differences were not statistically significant. In contrast to the study by Conard et al,¹⁴ obese patients in our study did report some improvement in quality of life after 2 years: the improvement was similar to that seen in the other groups, as shown in Figure 5. Furthermore, obese patients with poorer quality of life at baseline also had a poorer prognosis, as can be seen in Figure 6. This was also true of the other groups in the study.

In spite of all that has been said about the paradoxical relationship between obesity and mortality in heart failure patients, factors such as the impact of loss to follow-up of morbidly obese patients with heart failure might cast doubt on the extent of any true causality in the relationship.³¹ Whatever the case, and despite the fact that different hypotheses have been put forward to explain the relationship,^{18,27,32} all of the data published to date point to the need for further studies to help understand the details of the association. Although there is clearly a need to modify the classic primary risk factors in heart failure patients, the attitude to obesity in these patients is not so well-established.

Limitations

The study has limitations which are inherent to all retrospective studies. Likewise, the BMI is an indirect measure which does not discriminate between bodily composition in regard to different types of tissue, although it is a more comfortable way of estimating patients' body fat composition than other more precise measures. BMI may have been overestimated in some patients, however, as the reference weight in the first visit could be greater than the true or "dry" weight which would be reached once treatment for heart failure was optimized.

The low weight group had substantially fewer patients than the other groups and differed on some clinical

parameters, a fact which should be taken into account when evaluating the results, even though a multivariate analysis was carried out.

A considerable part of the mortality was due to non-cardiovascular causes, particularly in the low weight group, which may limit comparability between our results and those of previous studies.

Although the sample included here was drawn from a general population with heart failure attending a single multidisciplinary heart failure unit in a tertiary hospital, they were nevertheless selected from the total population of heart failure patients. The majority came from the cardiology service and their heart failure was predominantly due to ischemic heart disease. It was also a relatively young population with a low proportion of women. The results may therefore not be generalizable to the population of heart failure patients as a whole.

CONCLUSIONS

A higher BMI was associated with lower all-cause mortality after 2 years of follow-up. These results confirm, in a general population with heart failure of different etiologies, the paradoxical relationship between obesity and the prognosis for heart failure. In contrast with other studies, we did not observe a U curve for mortality in these patients. The protective effects of a certain degree of overweight or obesity appear to be particularly noticeable in patients with systolic dysfunction.

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