Metabolic Syndrome Increases Mortality in Heart Failure

Address for correspondence:
Leonardo Tamariz, MD, MPH
University of Miami
Humana Health Services
Research Center
Miami, FL 33136
ltamariz@med.miami.edu

Leonardo Tamariz, MD, MPH; Benjamin Hassan, MD; Ana Palacio, MD, MPH;
Lee Arcement, MD, MPH; Ron Horswell, PhD; Kathy Hebert, MD, MMM, MPH
Department of Medicine, Miller School of Medicine at the University of Miami (Tamariz, Hassan, Palacio, Hebert), Miami, Florida; University of Miami-Humana Health Services Research Center, Miami, Florida (Tamariz, Palacio); Veterans Affairs Medical Center, Miami, Florida (Tamariz, Palacio); Leonard J. Chabert Medical Center, Houma, Louisiana (Arcement); Pennington Biomedical Research Center, Baton Rouge, Louisiana, (Horswell)

ABSTRACT

Background: Metabolic syndrome (MetS) is a risk factor for diabetes, cardiovascular disease, and heart failure, but little is known about the impact of MetS in patients who already have heart failure (HF).
Hypothesis: MetS increases mortality in HF.
Methods: We performed an analysis in 865 indigent HF patients enrolled in a HF disease management program at the Chabert Medical Center in Louisiana. All subjects were classified as having MetS if they met three or more of the National Cholesterol Education Program criteria. Mortality was defined using the Social Security Death Index. We calculated the relative hazard (RH) of death for those patients with and without MetS.
Results: The prevalence of MetS was 40% (95% confidence interval [CI]: 37–43). These subjects had similar ages (54.3±13.4 vs 55.7±12.8 years), more likely to be female (43% vs 33%), had similar baseline ejection fraction (31.4±9.7 vs 30.0±11.0), and New York Heart Association (NYHA) classification (2.20±0.9 vs 2.15±0.9). After 2.6±2.2 years of follow-up 24% of the MetS group died compared to 16% in the non-MetS group ($p < 0.01$). The RH of death for the MetS group was 1.5 (95% CI: 1.1–2.1) when compared to the non-MetS group after adjustment demographics, use of angiotensin-converting enzyme (ACE) inhibitor and β-blocker, hematocrit, creatinine, educational level, and baseline ejection fraction.
Conclusions: The prevalence of MetS is high in indigent HF patients, and it increases the risk of death. Physicians treating patients with HF need to address the current MetS epidemic in HF.

Introduction

Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors with independent risk of diabetes, cardiovascular disease (CVD), heart failure, and both cardiovascular and all-cause mortality in a wide variety of populations.[1,2] The prevalence of MetS worldwide has reached pandemic proportions.[3–5]

Heart failure (HF)[1] is a major health problem with an attributable burden of morbidity and mortality.[6] MetS increases the risk of HF,[7] but the mechanism is complex and involves hypertensive and/or diabetic microvascular ischemia leading to maladaptive subclinical cardiac structural changes.[8–10]

Recently, some effort has been focused on assessing the impact of MetS on mortality in those with established cardiovascular disease. It has been shown that MetS increases mortality in subjects with acute myocardial infarction (MI), previous MI, and in or after coronary artery bypass grafting surgery (CABG).[11–14] However, little is known about the impact of the presence of MetS has on mortality in HF. The aim of this study is to determine the prevalence of MetS in indigent patients with HF and to determine whether the presence or absence of MetS is associated with an increase in mortality.

Methods

Setting and Study Population

A prospective cohort of 865 consecutive indigent HF patients with left ventricular ejection fraction (LVEF) less than 40% were enrolled in a HF disease management (HFDM) program in a rural South Louisiana public hospital, Chabert Medical Center, between August 1999 and October 2003. This center serves a patient population that is largely indigent; >55% of total encounters involve patients who are below 200% of the federal poverty level and/or are uninsured. This study was approved by the Ochsner Institutional Review Board.

A simple, structured treatment protocol was used to decrease practice variation and improve guideline adherence. Each patient viewed a 12-minute video on HF. Patients were taught how self-titration of oral diuretics for a >2 lb weight gain. Patients eligible for angiotensin-converting enzyme (ACE) inhibitors and β-blockers were instructed on the use of these medications and titrated to the maximum dose tolerated. To improve compliance with their prescribed regimens, patients were screened by the social worker to determine eligibility for medication assistance programs sponsored by pharmaceutical companies.

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Metabolic Syndrome

MetS was defined according to the updated criteria from the Third Adult Treatment Panel Report of the National Cholesterol Education Program (NCEP-ATP III), which requires the presence of ≥3 of the following: elevated triglyceride (TG) level ≥150 mg/dL, reduced high-density lipoprotein cholesterol (HDL-c) (men <40 and women <50 mg/dL), elevated fasting glucose ≥100 mg/dL or previously diagnosed diabetes, elevated blood pressure (BP; systolic BP ≥130 mm Hg and/or diastolic BP ≥85 mm Hg or on antihypertensive medication or large waist circumference (>102 cm in men and >88 cm in women).[15] MetS status was evaluated at the initial visit.

Framingham Risk Score

The Framingham risk equation was computed as a 10 y probability of having a major coronary event. Patients were classified into 10-year risk groups: <20% and >20% probability of having a cardiovascular event.[16]

Mortality

Mortality information was obtained through the Social Security Death Index. The last update was done at the end of 2006. Survival times were calculated from the date of the first visit to the HFDM program to the date of death or last visit.

Echocardiographic Parameters

All patients had an echocardiogram performed in the left lateral decubitus position. Ejection fraction (EF) was determined from multiple views, including parasternal, short axis, long axis, and 2-chamber views using the "eye-ball" method. The presence or absence of diastolic dysfunction was also ascertained.

Statistical Analysis

The data were stratified according to MetS status. Continuous variables were evaluated using t test and categorical variables using X2. Prevalence of the MetS was determined by dividing the number of patients positive for the MetS (≥3 of the NCEP-ATP III criteria) by the total number of patients in the HFDM program. The 95% confidence interval (CI) was calculated assuming a binomial distribution.

We also assessed the individual contributions of each component to the risk of mortality and used standardized coefficients to facilitate comparisons. The standardization was done by dividing the mean of each component with the corresponding standard deviation. Logistic regression was used to calculate the odds ratio (OR) with its corresponding 95% CI of mortality for each predictor adjusted for demographics, ejection fraction, and use of mortality reducing HF medications.

Mortality rates and incidence per 1000 person-years are reported and the p value calculated using a log-rank statistic. Kaplan-Meier curves present the unadjusted survival rates. The proportionality of events was evaluated using Schoenfeld residuals. Cox proportional models were used to calculate the relative hazard (RH) of death by MetS status. The RH was adjusted to demographics, use of ACE inhibitor and β-blocker, hematocrit, creatinine, educational level, and baseline ejection fraction.

To test the hypothesis that MetS increases the risk of death irrespective of the Framingham risk score we introduced this variable into the final model and if the hazard ratio of the variable MetS continued to be significant our hypothesis was proven.

Results

Prevalence of Metabolic Syndrome and Baseline Characteristics

The prevalence of MetS was 40% (95% CI: 37–43). Selected baseline characteristics of the entire sample are shown by MetS status in Table 1. Subjects with MetS were more likely to be female and less likely to be African American. No differences were found regarding age and ischemic cardiomyopathy.

Echocardiographic and Clinical Parameters

Table 2 shows the echocardiographic and clinical features by MetS status. A slightly higher percentage of advanced diastolic HF (30% vs 23%, $p = 0.07$) was observed among patients without MetS compared patients with MetS.

Risk of Death

Table 3 shows the unadjusted mortality rates by MetS status. After a mean follow-up of 2.6±2.2 years, more patients in the MetS group died than in the non-MetS group (24% and 16%, respectively, $p < 0.01$). Figure 1 shows the Kaplan-Meier curve by MetS status. Mortality was similar up to 4 years of follow-up ($p = 0.71$); after 4 years the difference in mortality was significant ($p = 0.04$).

The RH of death for the MetS (versus non-MetS) group was 1.5 (95% CI: 1.1–2.1) after adjustment for demographics, use of ACE inhibitor and β-blocker, hematocrit, creatinine, educational level, and baseline ejection fraction.

Predictors of Death Related to Metabolic Syndrome

Table 4 shows the adjusted relative hazard of mortality for each standardized component of MetS. The OR of death for glucose was 1.25; 95% CI (1.05–1.50), and HDL-c was 0.67; 95% CI (0.51–0.89). Figure 2 shows the risk of death by MetS status and high risk Framingham score. Patients with MetS died more often regardless of the Framingham risk score ($p = 0.015$). Patients with MetS and diabetes (RH: 1.79; 95% CI: 1.09–2.91) died more often than those with MetS and without diabetes (RH: 1.42; 95% CI: 0.84–2.39).

Table 1. Baseline Characteristics of HFDM Patients by Metabolic Syndrome Status

Characteristic	Metabolic Syndrome Present	Metabolic Syndrome Absent	*p* value
Number	349	516	
Age (years)	54.3±13.4	55.7±12.8	0.11
Female gender (%)	43	33	<0.01
Ischemic cardiomyopathy (%)	36	34	0.54
African-American (%)	30	44	<0.01
Waist circumference	44.6±6.2	39.4±6.9	<0.01
Glucose (mg/dl)	148.7±66.6	120.4±50.9	<0.01
HDL (mg/dl)	39.8±111.1	49.9±18.9	<0.01
Triglycerides (mg/dl)	184.8±9.2	98.2±54.4	<0.01
Systolic blood pressure (mm Hg)	135.5±24.0	126.2±23.3	<0.01
Diastolic blood pressure (mm Hg)	79.2±16.1	73.4±14.8	<0.01
ACE inhibitor use, %	94	92	0.25
β-blocker use, %	97	94	0.04
Digoxin use, %	10	8	0.89
Angiotensin receptor blocker use, %	5	3	0.12

Abbreviations: ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein; HFDM, heart failure disease management.

Table 2. Changes in Echocardiographic and Clinical Heart Failure Parameters by Metabolic Syndrome Status

Echocardiogram	Metabolic Syndrome Present	Metabolic Syndrome Absent	*p* value
Ejection fraction	31.4±9.7	30.0±11.0	0.07
Advanced diastolic dysfunction	23	30	0.07
NYHA	2.20±0.9	2.15± 0.9	0.51

Abbreviation: NYHA, New York Heart Association.

Table 3. Crude Mortality Rates and per 1,000 Person-Years by Metabolic Syndrome Status

Event rate	Metabolic Syndrome Present	Metabolic Syndrome Absent	*p* value
Number (%)	82 (24)	84 (16)	<0.01
Rate per 1,000 person-years	93	72	<0.01

Discussion

MetS is highly prevalent in indigent HF patients and is associated with an increased risk of death in these patients after adjustment for demographics, use of ACE inhibitors and β-blockers, hematocrit, creatinine, educational level, and baseline ejection fraction.

Several studies have reported on the prevalence of MetS. The only population-based study in the United States using the NCEP-ATP III classification population (NHANES) reported a prevalence of 35%.[5] High prevalence of MetS has also been reported in selected populations, such as post-MI (46%)[14,16] or primary prevention populations.[17] Outside the US, the prevalence of MetS ranges from 15% to 38%.[18] We found a higher prevalence of MetS than previous US reports and also evaluated the impact of MetS on mortality in patients with HF from an indigent HFDM population.

Prospective cohorts[6,11,12,19–22] and a meta-analysis of those studies[2] found a clear association between mortality and MetS. Those studies included patients with post-MI, post-coronary artery bypass grafts, and nondiabetics. Our study follows the same trend in a different population with HF that is certainly subject to the same increase in cardiovascular risk profile as previously studied populations.

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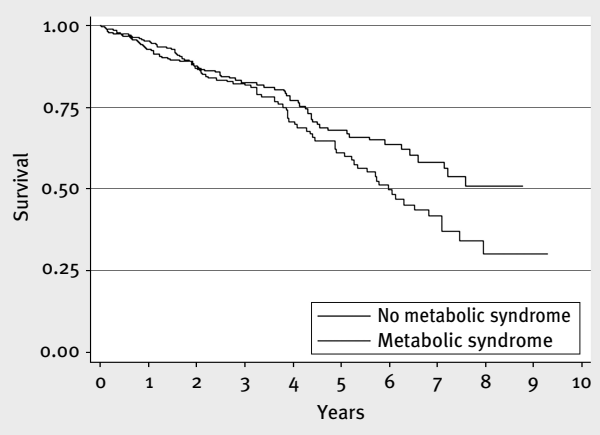

Figure 1. Survival by metabolic syndrome.

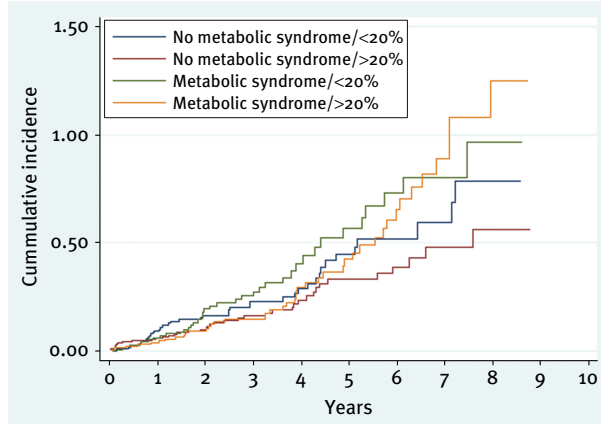

Figure 2. Incidence of death by metabolic syndrome and Framingham risk.

Table 4. Predictors of Death for Each Standardized Component of the Metabolic Syndrome

Standardized Characteristic	OR (95% CI)*	*p* value
Glucose	1.25 (1.05–1.50)	0.01
Waist circumference	1.19 (0.30–4.68)	0.79
HDL-c	0.67 (0.51–0.89)	<0.01
Triglycerides	1.14 (0.94–1.38)	0.18
Systolic blood pressure	0.93 (0.76–1.15)	0.53
Diastolic blood pressure	0.85 (0.69–1.06)	0.16

*Adjusted for age, gender, ischemic cardiomyoapthy, ejection fraction, ACE inhibitor use, and β-blocker use. Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio.

Sympathetic activation is 1 possible mechanism, which characterizes both HF[23–25] and MetS[26,27] and could potentially explain the excess mortality in patients with both syndromes. This theory is supported by the recent publication by Grassi et al that showed MetS potentiates the sympathetic activation in HF.[28] In some studies, which included patients after a MI delayed onset of the mortality effects (after 2 years), it has been observed,[13,21,22] while other studies report mortality effects before 2 years.[12,16] Similar to our results, de Simone et al found a higher risk of death according to diabetic status.[21] These results indicate that the effect of MetS on mortality varies by population. Among the components of MetS, glucose, and low HDL-c were identified as the main determinants influencing mortality risk. This increased mortality risk was irrespective of the Framingham risk score. Other studies have also identified HDL-C, elevated triglycerides, and blood pressure as predictors of major coronary events.[16,17]

Limitations include the use of a single center site of indigent HF patients and may not generalize to the entire HF population. The components of MetS were only measured at baseline, and therefore no changes over time could be examined.

In conclusion, MetS is highly prevalent in indigent patients with HF and it is associated with an increase in risk of death.

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