

Metabolic syndrome and heart failure: data from the FADOI CONFINE study

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ABSTRACT

Approximately 20%-30% of the population in industrialized countries suffers from metabolic syndrome (MetS), a condition that may double the risk of diabetes mellitus and heart diseases in the normal population. Both MetS *per se* and its components increase the risk of atherosclerosis and acute coronary artery disease and heart failure (HF). We reviewed the data from a recent survey of patients admitted to Italian internal medicine wards due to chronic heart failure to ascertain the prevalence and the relationships between MetS and HF in *real life* patients. Our data shows that some risk factors for this syndrome (above all obesity) reflect a sort of Janus phenomenon in that they are well-recognized risk factors for HF in young people, but they lose their unfavorable predictive value in elderly patients with HF.

Introduction

Metabolic syndrome (MetS) describes the clustering of various metabolic components, including dysglycemia (glucose intolerance/diabetes mellitus), hypertension, elevated triglyceride levels, low high-density lipoprotein cholesterol levels and obesity.^{1,2}

A close relationship has been repeatedly demonstrated between the individual components of MetS and/or MetS as a whole and an increased risk of atherosclerotic diseases. A poor outcome has also been described after acute coronary syndrome³ and, more recently, in MetS with congestive heart failure.⁴⁻⁸ However the prevalence and clinical significance of MetS in chronic heart failure (CHF) still remain to be fully elucidated.

The aging of the population, the decreased mortality from coronary heart disease over the past few decades, the growing number of treatment options for HF and its comorbidities have led to an increased prevalence of heart failure (HF) with quite different characteristics compared with those of the patients randomized for the clinical trials.⁹⁻¹¹ Then we have investigated the relationship between MetS and HF reported in the CONFINE (Comorbidities and Outcome in Internal Medicine units) study¹² to define its prevalence and clinical significance in *real world* patients.

Materials and Methods

The CONFINE study is a multi-centric longitudinal observational study, performed according to the spot analysis method. It was conducted in 91 internal medicine units evenly distributed throughout Italy, which enrolled a total of 1411 patients with HF present in the wards in 5 well-defined days (index days) in 2006-2007 according to the European Society of Cardiology (ESC) 2005 guidelines without any exclusion criteria.¹³

The patients were divided into 2 groups, with MetS or without MetS (No-MetS), according to the most widely accepted definition from the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) (Table 1).¹⁴

Baseline demographic data (age, sex, height, body weight, and waist), CHF New York Heart Association (NYHA) class and etiology, blood pressure, pulse rate, laboratory parameters, medications, including angiotensin-converting enzyme inhibitors (ACEI), an-

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giotensin-receptor blockers (ARB), β -blockers were collected from the medical records. The left ventricular ejection fraction (LVEF) was measured by echocardiography.

The following comorbidities were evaluated: i) chronic renal failure, stratified by creatinine clearance calculated according to Cockcroft Gould; ii) previously diagnosed diabetes mellitus, specific therapy or blood glucose levels above 126 mg/dL; iii) hypertension with stages of severity, according to the European Society of Hypertension (ESH)-ESC guidelines,¹⁵ previously diagnosed chronic obstructive pulmonary disease or specific therapy; iv) chronic inflammatory diseases (rheumatoid arthritis, ulcerative colitis, Crohn's disease, etc.); v) dementia evaluated on the basis of the Pfeiffer test;¹⁶ vi) anemia defined according to World Health Organization (WHO) criteria;¹⁷ vii) cerebrovascular disease according to a history of stroke or transient ischemic attack; viii) disability tested according to the Barthel index score.¹⁸

In adults, overweight was defined as a body mass index (BMI) of 25 to 29.9 kg/m², and obesity was defined as a BMI of 30 kg/m² or higher.

Statistical analysis

Data was stratified according to MetS status. The prevalence of MetS was determined by dividing the number of patients positive for MetS (≥ 3 of the NCEP-ATP III criteria) by the total number of patients in the CONFINE study. Continuous variables are expressed as mean \pm SEM (standard error mean). Comparisons between 2 groups with and without Mets were performed with unpaired T-test for continuous variables and X-test for categorical variables.

$P < 0.05$ was considered to be statistically significant.

Results

In the CONFINE study, 515 subjects met the NCEP III criteria of MetS (284 F), mean age was a lit-

tle younger than No-MetS (F 80.12 \pm 7.9 and M 75.08 \pm 9.4) (Table 1), less than 5% of patients fulfilled the five inclusion criteria.

The characteristics of MetS and No-MetS subjects are reported in Table 2.

The characteristics by gender of MetS and No-MetS subjects are reported in Table 3. Females are older than males in both groups (79.9 \pm 7.6 vs 75.1 \pm 8.8 for Mets patients, $P < 0.001$, and 81.2 \pm 9.2 vs 77.4 \pm 10.5 in No-Mets patients).

Systolic function (LVEF) is similar in both sexes, but in women LVEF $> 50\%$ is prevalent (61.4% vs 38.6; P : not significant).

The therapy administered on admission is summarized in Table 4.

It should be noticed that the prevalence of ARBs and β blockers and, marginally, of ACEI, diuretics and Ca-channel blockers differ between the two groups, given the higher prevalence of hypertension in the MetS subgroup.

Comorbidities

Comorbidities were evaluated in the two groups. Some differ by gender and some are part of the inclusion criteria for MetS. Values on admission and at discharge are reported in Table 5.

Subjects with no cognitive defects were more numerous in the MetS group, moderate to severe dementia was significantly higher in males and females of the No-MetS group on admission (5.5% vs 4.2%; $P < 0.05$ and 15.1% vs 9.1%; $P < 0.05$ respectively) and at discharge (7.4% vs 4.9%; $P < 0.05$ and 12.8% vs 8.5%; $P < 0.05$ respectively).

Anemia was more present among women both at admission and at discharge in both groups.

Sixty patient died at the hospital, 12 in the MetS group and 48 in the No-MetS with a statistically significant difference ($X^2 = 6.6$; $P < 0.01$). The outcome variables are reported in Table 6.

Blood pressure, weight, BMI (all inclusive criteria

Table 1. Definition of metabolic syndrome in National Cholesterol Education Program (NCEP).

Risk factor	Defining level
Abdominal obesity (waist circumference)	
Men	> 102 cm (> 40 in)
Women	> 88 cm (> 35 in)
Triglycerides	≥ 150 mg/dL
High-density lipoprotein cholesterol	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	$\geq 130 / \geq 85$ mmHg
Fasting glucose	≥ 110 mg/dL*

Three out of the 5 criteria need to be met to have a positive diagnosis, which now has an International Classification of Disease (ICD) code (277.7). *The fasting glucose cut-off point has recently changed to 100 mg/dL.

in MetS) were higher in the MetS group, heart rate was faster in the MetS group, hemoglobin and creatinine were not statistically different.

Discussion and Conclusions

Metabolic syndrome is a risk factor for HF. It is independently associated with the incidence of HF in subjects with a past history of coronary heart disease.¹⁹ Moreover, according to ATP-III criteria with BMI replaced by waist circumference, it has shown to be a significant, independent predictor of subsequent HF, even after adjusting for coronary heart disease.⁸

The association of MetS and each of its components with the incidence of HF is well-known and it has been postulated that HF risk may not be associated with MetS *per se*, but rather with its individual risk factors. The strongest independent predictors of HF are insulin resistance or an equivalent factor (like abdominal adiposity).²⁰

A recent report has investigated the prevalence of

MetS in Japanese patients with HF²¹ and the relationship of MetS or its components with the phenotype and etiology of HF, but MetS criteria were defined as the presence of 2 or more abnormalities in addition to a waist circumference of >85 cm in males and >90 cm according to the new definition by the *ad hoc* Japanese Committee. However these criteria do not match the NCEP III criteria and are related to an Asian population, taking into account that MetS criteria are known to differ according to ethnic groups.²²

The prevalence of MetS in adult Italian subjects (≥ 20 years) ranges between 22% and 28%, but in subjects over 50 years it ranges from 30% in males to 40% in females. In females over 60 years of age the prevalence is even higher than in males. In the Veneto region MetS may be encountered in 57% of women aged 65-84 years *versus* 27% of age-matched men.²³ However, to our knowledge, the prevalence of MetS in HF has not yet been described in the Italian population.

Our data shows that patients with HF admitted to Italian hospitals may have MetS in nearly one third of

Table 2. Characteristics of subjects with or without metabolic syndromes.

	CONFINE (n=1411)	MetS (N=515)	No-MetS (N=896)	P
Mean age (year \pm SD)	78.72 \pm 9.55	77.8 \pm 8.5	79.2 \pm 10.0	0.007
Fasting glucose (mg/dL \pm SD)	136.8 \pm 70.0	147.9 \pm 82.0	130.5 \pm 61.2	0.001
Waist circumference (cm \pm SD)	94.5 \pm 15.0	99.9 \pm 14.8	88.0 \pm 12.5	0.001
Smoker*	23.6%	23.5%	23.7%	0.05
BMI ^o	27.1 \pm 5.3	28.3 \pm 5.4	26.2 \pm 5.1	0.001
Cholesterol (mg/dL \pm SD)	153.1 \pm 52.6	156.1 \pm 56.4	150.8 \pm 49.6	0.0064
HDL cholesterol (mg/dL \pm SD) [#]	43.3 \pm 21.4	38.0 \pm 13.9	48.7 \pm 25.7	0.001
Triglycerides (mg/dL \pm SD)	96.6 \pm 48.3	113.0 \pm 59.0	84.3 \pm 33.5	0.001
NYHA on admission	3.15 \pm 0.76	3.14 \pm 0.74	3.16 \pm 0.77	0.64
NYHA at discharge	2.25 \pm 0.74	2.17 \pm 0.74	2.30 \pm 0.75	0.038
NYHA III, IV on admission (%)	81.7%	81.6%	81.7%	0.9
NYHA III, IV at discharge (%) [§]	30.4%	27.4%	32.1%	0.1
LVEF (%) [^]	43.1 \pm 12.3	43.9 \pm 11.9	42.4 \pm 12.6	0.2
% of LVEF > or =50% on admission	33.8%	34.6%	33.2%	0.8
% of LVEF > or =30% on admission	18.3%	14.7%	21.7%	0.2
Vital signs				
SBP	140.8 \pm 26.8	151.3 \pm 24.1	134.9 \pm 26.5	0.001
DBP	81.3 \pm 13.1	85.9 \pm 12.3	78.6 \pm 13.7	0.001
Heart rate (beat/min)	91.4 \pm 21.6	93.8 \pm 21.5	90.0 \pm 21.6	0.001

CONFINE, Comorbidities and Outcome in patients with chronic heart Failure: a study in Internal Medicine units; MetS, metabolic syndrome; No-MetS, without metabolic syndrome; SD, standard deviation; BMI, body mass index; HDL, high-density lipoprotein; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure. *n=313 smokers, 99 former smoker (quitted from more than 6 months) n=1330 NYHA class registered on admission (MetS=487, No-MetS=843); ^on=590 data sheets; [#]n=728 data sheets; [^]n=1174 NYHA class registered at discharge (MetS=437, No-MetS=737); [§]n=827 echocardiogram performed.

the whole population. The subjects with MetS have a quite different phenotype. In fact they are younger than their No-MetS counterparts and, as expected, females are older than males with a mean difference of two years. Apart from inclusion criteria, which obviously

demonstrate a remarkable statistically significant difference from other patients with HF, these patients show also a faster heart rate (93.8±21.9 vs 90.0 vs±21.3), taking into account that the heart rate is a well-known independent risk factor for HF and its outcome.²⁴

Table 3. Clinical and laboratory characteristics in subjects with or without metabolic syndromes (number of patients in brackets).

	Male			Female		
	MetS (N=231)	No-MetS (N=330)	P	MetS (N=284)	No-MetS (N=407)	P
Mean age (year±SD)	75.1±8.8	77.4±10.5	0.0046	79.9±7.6	81.2±9.2	0.008
Fasting blood glucose on admission	139.9±69.8	129.11±60.3	0.001	154.3±90.1	132.0±64.5	0.001
Cholesterol (mg/dL±SD)	152.4±47.9	147.5±46.0	0.197	159.0±62.4	154.4±53.7	0.22
Cholesterol HDL (mg/dL±SD) (747)	34.9±11.9	46.1±21.4	0.001	40.1±14.9	52.3±30.6	0.001
Triglycerides on admission (mg/dL±SD) (947)	115.7±52.9	86.1±35.1	0.001	110.4±63.6	82.1±31.7	0.001
Waist circumference cm (598)	104.68±13.7	91.0±11.2	0.001	96.2±14.5	84.0±13.13	0.001
BMI (1108)	28.5±5.2	26.2±4.6	0.001	28.12±4.6	26.1±5.6	0.001
NYHA on admission (1330)	3.1±0.7	3.1±0.8	0.87	3.1±0.8	3.2±0.7	0.32
NYHA at discharge (1174)	2.1±0.8	2.3±0.8	0.019	2.2±0.7	2.3±0.7	0.047
NYHA III-IV(%) on admission	83.5%	80.6%	0.02	80.1%	84.3%	0.07
SBP	151.6±24.9	134.5±23.2	0.001	150.8±23.5	135.6±25.9	0.001
DBP	86.5±12.62	78.73±13.5	0.001	85.3±12.1	78.7±12.9	0.001
Heart rate (beat/min)	93.7±21.5	89.6±21.4	0.022	93.96±22.0	90.3±21.3	0.028
LVEF (%)	42.5±10.8	41.8±12.3	0.4	45.15±12.9	43.6±12.7	0.14
% LVEF >=50% on admission*	38.6%	49.5%	0.28	61.4%	50.5%	0.9

MetS, metabolic syndrome; No-MetS, without metabolic syndrome; SD, standard deviation; HDL, high-density lipoprotein; BMI, body mass index; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction. *Number of LVEF > or =50% was 203 of 827 echocardiography performed.

Table 4. Therapy in subjects with or without metabolic syndromes.

	Total% (N=1411)	MetS% (N=507)	No-MetS% (N=894)	P (χ^2)*
Allopurinol	16.0	15.3	16.3	0.64
ARBs alone	14.6	18.9	12.2	0.001
ACEI	51.9	53.4	51.0	0.37
ACEI+ARBS ^o	66.5	72.3	63.3	0.01
Acetylsalicylic acid	34.2	36.6	32.7	0.13
β blockers	23.8	28.9	22.0	0.001
Ca-channel blockers	13.9	16.2	12.6	0.06
Digitalis	30.4	32.2	29.3	0.77
Diuretics (oral)	46.5	43.2	51.6	0.06
Spironolactone	20.9	20.1	21.3	0.58
Warfarin	23.0	23.8	22.4	0.70

MetS, metabolic syndrome; No-MetS, without metabolic syndrome; ARBs, angiotensin-receptor blockers; ACEI, angiotensin-converting enzyme inhibitors. * χ^2 between MetS and No-MetS subjects; ^oACEI+ARBS means the use of one or both drugs (the use of both drugs is really minimal) which inhibit the renin-angiotensin-aldosterone system.

On admission NYHA class III-IV and marked depressed or preserved systolic function are similar. Taking into account that these baseline values on admission for HF may be considered the same in the two groups, how can we justify the lower hospital mortality of the MetS subjects? These patients are more hypertensive, have higher blood glucose levels on admission, have a faster heart rate, which are all well-known significant risk factors²⁵ for adverse cardiovascular events, yet they die less than their counterparts. Actually our data shows that MetS patients with HF have a younger age; also considering that the difference of mean age is about two years in both sexes. Since HF has an age-dependent prognosis,²⁶ this outcome obviously mirrors this variable.

It is well-known that each component of the MetS and MetS itself is positively correlated to cognitive defects.²⁷⁻³⁰ In our study dementia is less represented in the MetS subjects. It has been recently reported that MetS measured in late life is not associated with a risk

of dementia and after age 75 MetS patients may even have lower risk of dementia.^{31,32} In other words, cognitive defects are age-related, but in MetS patients their prevalence seems to be less evident. Therefore considering that dementia is a risk factor for a negative HF outcome (as we have previously shown in the whole population of the CONFINE study), but it is less prevalent in MetS subjects, we may justify the better outcome of the patients in our study.

This may also be due to a more extensive use of ARBs and β blockers (and marginally of diuretics and Ca channel blockers) in the MetS group, taking into account that these drugs are used to treat hypertension, which is one of the components of MetS. More specifically β blockers, the cornerstone of heart failure treatment, are more used on admission in the MetS subjects than in No-MetS group. In our opinion higher blood pressure in MetS subjects, reducing the chance of hypotension, makes it much easier and safer to prescribe β blockers.

Table 5. Comorbidities in subjects with or without metabolic syndromes.

	MetS			No-MetS		
	Admission (N=514)	Discharge (N=463)	P	Admission (N=922)	Discharge (N=823)	P
GFR*						
Normal	56.8	57.4	ns	55.2	58	ns
61-89	16.7	19.2	ns	14.4	14.7	ns
31-60	19.4	17.5	ns	18	16.1	ns
0-30	6.4	5.4	ns	12	10.5	ns
Dialysis	0.1	0.1	ns	0.3	0.5	ns
Diabetes	39.2	37.3	ns	28.7	27	ns
Hypertension^o						
No	20.6	37.3	0.001	52.1	60.8	0.001
Mild	40.6	51.6	0.001	31	30.5	ns
Moderate	31.5	10.8	0.001	18.1	8.2	0.001
Severe	7.2	0.1	0.001	4.4	0.3	0.001
COPD	25.1	25.2	ns	27.6	26.9	ns
Dementia						
No	82.1	82.5	0.9	76.4	76.6	0.9
Mild (3-4)	10.9	10.6	0.9	12.1	13.4	0.5
Moderate (5-6)	4.6	4.7	0.9	7.3	6.7	0.6
Severe > or =7	2.3	2.1	0.9	4.1	3.4	0.01
Chronic disease[#]	7.2	7.1	0.9	7.6	7.5	0.9
Cachexia[§]	4.8	4.3	ns	7.8	7.3	ns
Anemia[^]	40.4	36.9	0.01	40.5	37.2	0.01

MetS, metabolic syndrome; No-MetS, without metabolic syndrome; GFR, glomerular filtration rate; ns, not significant; COPD, chronic obstructive pulmonary disease. *GFR according to the Cockcroft Gould formula; ^oESH-ESC criteria: mild=140/85-159/99; moderate=160/100-179/109; severe > or =180/100; [#]Include rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis and chronic hepatitis or cirrhosis; [§]BMI<18.5; [^]according WHO criteria.

Table 6. Outcome variables in subjects with or without metabolic syndromes.

	Deceased (N=60)			Not deceased (N=1351)		
	MetS (N=12)	No-MetS (N=48)	P	MetS (N=503)	No-MetS (N=848)	P
NYHA class on admission	4.00±0.00	3.39±0.64	0.005	3.11±0.74	3.15±0.71	0.3
Weight	88.2±29.7	72.55±18.4	0.05	78.2±18.5	74.5±18.4	0.005
BMI*	27.1±5.3	24.2±5.3	0.16	28.3±5.4	26.2±5.8	0.001
LVEF°	31.8±7.5	35.5±16.5	0.4	44.3±11.8	42.6±12.5	0.17
LVEF>50%	0	0	0	35.6%	33.4%	
LVEF<30%	50%	50%	0	13.5%	20.1%	
SBP	141.7±15.6	124.7±30.7	0.07	151.5±24.2	135.4±24.1	0.001
DBP	83.7±8.8	71.3±13.4	0.005	85.9±12.4	79.0±13.0	0.001
Heart rate	101.0±28.5	93.3±27.5	0.4	93.6±21.7	89.8±21.0	0.001
Hemoglobin (g/dL)	11.4±2.3	11.4±2.5	0.08	12.0±2.9	12.2±3.1	0.5
Creatinine (mg/mL)	1.49±0.74	1.96±1.01	0.11	1.48±1.00	1.47±0.92	0.8

MetS, metabolic syndrome; No-MetS, without metabolic syndrome; NYHA, New York Heart Association; BMI, body mass index; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure. *1107 data sheets; °N=405 echocardiography on admission.

Consequently hypertension, a significant risk factor for HF, may be paradoxically and indirectly a *protective* risk factor for HF in MetS patients: i) because they must be treated with drugs which lower blood pressure; ii) because among these drugs, the most widely used are β blockers and ARBs that are the cornerstone of HF treatment; and iii) because hypertension makes the prescription of these agents safer.

We have not taken into account the effects of the lipid lowering therapy (statins) that is now considered useful in countering risk factors for HF,³³ since we had not enough data to perform a statistical analysis.

Therefore taking into account that the NYHA class is a continuous variable and that the value of NYHA class on admission in both groups is the same: i) if the mean NYHA class at discharge was better in MetS subjects compared with No-MetS (do they respond better to treatment?); and ii) if the mean LVEF value on admission in MetS subjects deceased was lower than in their counterparts, then may we argue that a negative prognosis in MetS subjects is associated with a more impaired cardiovascular function?

In other words may the paradox of obesity and MetS³⁴⁻³⁷ be confirmed?

From our data we may suggest that the interaction between MetS and obesity reflects a sort of double-faced Janus phenomenon. They are well-recognized risk factors for HF³⁸ in young people, but the older the age, the more they lose their dangerous potential so much so that in elderly patients with HF they even become predictive of a positive outcome.

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