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Gender Differences in Heart Failure: Findings from Italian Internal Medicine Wards

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Abstract: Background and aim: Literature evidence shows that about one half of patients with heart failure (HF) are females. However, they are poorly represented in clinical trials. Therefore, this syndrome remains still understood and its burden underestimated in female sex. The aim of our study was to compare demography, etiology, clinical patterns, outcome, co-morbidity, disability and cognitive performance between females and males in a cohort of patients with HF. Materials and methods: We analyzed data of the Confine Study, a recently real world survey performed in Italian Internal Medicine wards. We compared clinical and instrumental characteristics between males and females. Results: Females with HF were significantly older than men. Hypertensive and valvular etiologies were significantly more prevalent in females whereas ischemic and dilatative were in males. Neither clinical aspects, with the exception of atrial fibrillation, nor echocardiographic aspects were more frequent in females. According to international guidelines on topic, both sexes received under-treatment, but this one was more evident in females. Females presented more frequently cognitive impairment and functional disability than males. Conclusion: Female sex is under-represented in clinical trials on HF. Our study may provide a contribute on this topic.

Keywords: Heart Failure, Gender, Therapy, Symptoms, Diagnosis, Epidemiology, Internal Medicine

1. Introduction

Heart failure (HF) prevalence increased steadily over the last decades. Aging population, advancements in the treatment of coronary heart disease and intensive control of blood hypertension proved a consequent rise in the number of hospital admissions for HF exacerbations.

Large population-based studies identify key sex-based differences in HF incidence and prevalence. In the Framingham Heart HF incidence increased by approximately 5% in women in the 1990s compared with the 1970s (1). In the Olmsted County Study, no significant increase in HF incidence was seen in men but a significant 10% increase in women since 1979 (2). Despite the overall incidence of HF remains approximately 25% lower in women compared with men, women account for 50-55% of the prevalent HF cases because of their greater life expectancy. Therefore, women represent a growing proportion of the heart failure epidemic. Around 35% of cardiovascular (CVD) mortality in women is due to HF (3). However, women are yet understudied and represented in clinical trials, sometimes inadequately powered to detect a benefit of HF therapy. So, HF remains a poorly recognized and poorly understood syndrome in women (4,5).

Literature evidence shows that women with HF are more likely to be older, hypertensive, have less ischemic heart disease and may have more preserved systolic function when compared with their male counterparts (6,7). However, literature lacks on HF in women in the *"real world"*. Previous studies have shown that the patients admitted in Internal Medicine (IM) wards are strictly similar to that of the real world. In fact, in this setting the patients are older,

have multiple co-morbidity and the majority of them are women (8). Therefore, the aim of our study was to analyse gender related differences in HF with respect to the demographics, underlying etiology, outcome, prevalence of co-morbidity, functional disability and cognitive performance status in Internal Medicine wards.

2. Materials and Methods

The CONFINE Study (**C**omorbidities and **O**utcome i**N** patients with chronic heart **F**ailure: a study in **I**nter**N**al m**E**dicine units in Italy) is an observational, multicenters study performed in 91 Internal Medicine wards representative of the Italian setting and associated to the Scientific Society FADOI (Italian Federation of the Associations of Hospital Internists). General results of the CONFINE Study were previously published (9).

The patient were recruited according to a spot analysis method as elsewhere stated (9). All patients with HF according to the European Society of Cardiology (ESC) guidelines (10) admitted or already present in the ward in the index day where enrolled in the study, without any exclusion criteria.

The patients were divided by gender and the following data relative to index day, day of hospitalization and day of discharge were collected: age, gender, blood pressure, heart rate, NYHA class, body mass index (BMI), 12-leads ECG records, etiology of heart failure, co-morbidities (see below), laboratory findings, pharmacological treatment with particular reference to cardiovascular therapy.

Trans-thoracic echocardiogram was performed only in some selected centers according to instrument availability.

The following comorbidities were systematically recorded:

- chronic obstructive pulmonary disease (COPD): defined on the clinical ground or specific therapy
- diabetes: defined as previous diagnosis, or specific therapy, or blood glucose greater than 126 mg/dl
- blood hypertension: defined according to the Guidelines issued by International Society of Hypertension (ISH)-ESC (11) or specific therapy.
- anemia: defined according to the World Health Organization (WHO) definition (12)
- renal failure: glomerular filtration rate (GFR) was calculated according to the Cockroft-Gault formula
- chronic inflammatory diseases (e.g. Rheumatoid arthritis, systemic lupus erythematous, ulcerative colitis, Crohn disease)
- cognitive impairment/dementia: evaluated on the basis of the Pfeiffer test (13)
- cerebrovascular disease: patient's history of stroke or transient ischemic attack

Functional disability was evaluated by the Barthel Index (14); quality of life was assessed by administering the Minnesota Living with Heart Failure (MLWHF) Questionnaire (15).

Poor outcome was defined as in hospital all cause mortality or worsening of clinical conditions that required transfer to Intensive Care Unit.

3. Ethical Approval

The study was approved by the local ethic committees of the Centers participating to the CONFINE Study. Written informed consent for data handling was also obtained by the patients.

4. Statistics

The data were analysed by calculating averages (Mean $\pm$ SD) of continuous variables or percentages for not-continuous ones. In some cases, it was applied a transformation in not-continuous variable in order to define a clinical severity (mild, moderate and severe) score. Numeric variables were compared by Student t test for paired data and discrete variables were summarized by frequency percent and compared by the chi-square test to find significant differences between males and females. A p value $< 0,05$ was considered statistically significant. Statistical analyses were carried out using SAS software (version 9.1, SAS Institute Cary, NC, USA).

5. Results

5.1. Patients Population

In the CONFINE Study 1430 patients were recruited. In the whole cohort, genders were equally represented (M 48%, F 52%). The mean age of female was statistically higher (80,7 ± 8,7 versus 76,6 ± 10 years, $p<0.001$). 56,9% of females were 80 years old or older compared with 36% of males ($p<0.001$). Underweight and severe obesity were significantly more represented in females. Blood glucose, total cholesterol, HDL cholesterol were statistically higher in females, whereas uric acid was in males. No differences were found for the mean systolic and diastolic blood pressure and for the other laboratory parameters analyzed. The Tab.I summarizes the general characteristics of patients according to sex.

Table I. *General characteristic of patients according to sex.*

	Male N=693	**Female N=737**	**P**
Age (mean $\pm$ SD)	76,6 $\pm$ 10,0	80,7$\pm$ 8,7	0,001
$\leq$ 40	0,3%	0,2%	0,001
41-60	4,4%	1,9%	0,001
61-70	12,8%	6,2%	0,001
71-80	35,1%	26,5%	0,001

	Male N=693	Female N=737	P
81-90	29,4%	46,2%	0,001
>90	6,6%	10,7%	0,008
BMI (mean ± SD)	27,4 ± 7,0 N=555	27,0 ± 5,7 N= 531	ns
Underweight (≤18,5)	1,3%	3,7%	0,01
Normal (18,5-24,9)	33,8%	37,4%	ns
Overweight (25-29,9)	44,8%	33,3%	0,001
Obese (≥30,0)	17,6%	24,6%	0,005
Vital signs			
SBP (mean ± SD- mmHg)	140,2 ± 27,6	141,6 ± 26,0	ns
DBP (mean ± SD –mmHg)	81,3 ± 13,7	81,3 ± 13,0	ns
Heart rate (mean ± SD-beats/min)	90,1± 21,5	91,7 ± 21,8	ns
TSH (mean ± SD-mU/L-n=525)	4,3 ± 15,9	3,4 ± 11,7	ns
Creatinine (mean ± SD-mg/dL)	1,48 ± 0,9	1,53 ± 0,9	ns.
BUN (mean ± SD mg/dL)	64,4 ± 49,8	62,8 ± 43,41	ns
Blood (glucose mean ± SD mg/dL)	132,7 ± 63,8 628	140,9 ± 75,4 687	0,03
Total cholesterol (mean ± SD mg/Dl)	149,33 ± 46,7 465	156,5 ± 58,0 454	0,04
HDL cholesterol (mean ± SD mg/dL)	41,3 ± 18,8 366	45,3 ± 32,7 367	0,01
Tryglicerides (mean ± SD mg/dL)	97,6± 45,2 465	98,42 ± 51,3 473	0,8
Uric acid (mean ± SD mg/dL)	7,8 ± 4,8	7,1 ± 2,7	0,002

Legend: Data are expressed by mean ± SD or percentage. BMI= Body Mass Index; SBP= Systolic blood pressure; DBP= Diastolic blood pressure; BUN= Blood urea nitrogen, TSH=thyroid stimulating hormone; HDL=high density lipoprotein

5.2. HF Characteristics

Around 40% of men and 35% of women were admitted with a " de novo " diagnosis of HF; most of them were in NYHA Class III-IV with no differences by gender. Hypertensive and valvular etiologies were significantly more prevalent in females, whereas ischemic and dilatative heart etiologies were significantly higher in males (see Tab. II).

Table II. *HF characteristic according to sex.*

	Male	Female	P (X2 Yates)
NYHA Class (%)	Number (N)= 636	N= 679	
I	1,5	2,5	0.3
II	16,8	14,8	0,4
III	47,6	44,5	0,3
IV	33,9	38,1	0,1
Underlying cause of heart failure (%)			
Hypertensive heart disease	39	46,5	0,001
Ischemic heart disease	46	37,5	0,001
Valvular heart disease	15,6	26,0	0,001
Dilatative Heart disease	21,9	14,1	0,002
Congenital heart disease	0,2	0,9	ns
Other	12,5	15,4	ns
Risk factors for clinical deterioration (%)	N=692	N=736	
Hypertension	28,1	31,6	0,1
Arrhytmias	27,6	29,3	0,5
Anaemia	18,9	22,4	0,3
Poor compliance to therapy	16,2	14,1	0,3
Thyreotoxicosis	1,3	1,9	0,4
Pulmonary embolism	0,8	0,1	0,7
Signs and symptoms (%)	N=688	N= 731	
Exertion dyspnea	86,3	85,2	0,6
Lung crepitations	78,9	78,4	0,9
Ankle edema	71,8	66,5	0,03

	Male	Female	P (X2 Yates)
Night cough	51,6	49,6	0,5
Neck vein distension	53,3	47,8	0,04
Hepatomegaly	50,6	36,6	0,001
Pleural effusion	35,9	36,9	0,7
Acute pulmonary edema	23,2	25,6	0,3
12-leads ECG records at hospital admission (%)	N=680	N=723	
Sinus rhythm	51,8	45,2	0,01
Atrial fibrillation	38,5	46,2	0,004
Pacemaker rhythm	11,9	8,2	0,03
Left bundle branch block	15,8	14,4	0,01
Right bundle branch block	14,8	10,5	0,5
Left ventricular hypertrophy	24,7	26,9	0,2
Echocardiography at hospital admission	N= 197	N= 206	
Left ventricle Ejection Fraction (LVEF)	42,1 $\pm$ 11,7	44,4 $\pm$ 12,7	0,008
LVEF >50%	35,5 %	31,5 %	ns
LVEF <30%	15,7 %	20,8 %	ns

No difference was noted for risk factors of clinical deterioration. None sign or symptom was significantly more frequent in females. The prevailing phenotype was the congestive syndrome for both sexes. At hospital admission trans-thoracic echocardiography showed an average left ventricular ejection fraction (LVEF) higher in women, but significant difference was not found for LVEF <30% or LVEF> 50% according to sex. Myocardial infarction was present in 4,4% in men and 5,4% in women: this difference was not statistically significant (p=0,4).

5.3. Co-morbidity

The average number of co-morbidities was significantly higher in females (3,4 vs 3,2 ; p<0,01). Women showed significantly more prevalence of mild hypertension, severe renal failure (GFR<30ml/min), metabolic syndrome and cognitive impairment but lower prevalence of COPD. The other differences were not statistically significant (see Tab. III).

Table III. *Prevalence of co-morbidity according to sex*

	Male N=690	Female N=731	
GFR*	%	%	P
Normal	53,4	58,1	0,05
61-89	16,3	13,8	ns
31-60	20,8	16,4	0,05
0-30	8,6	11,4	0,05
Dialysis	0,5	0,1	ns
Diabetes	32,7	32,6	ns
Hypertension			
No	39,1	35,2	ns
Mild	33,3	35,7	0,01
Moderate	22,1	23,6	ns
Severe	5,3	5,3	ns
COPD	32,8%	21,0%	0,001
Cachexia ^	6,6%	6,8%	ns
Dementia	18%	24,7%	0,01
Anemia °	41,3%	42,6%	ns
Metabolic syndrome §	45,5%	55,5%	0,01
Chronic disease§§	7,1%	7,8%	ns

Legend: GFR=glomerular filtration rate; COPD=chronic obstructive pulmonary disease
* according to the Cockroft-Gault formula
^ BMI< 18,5
° according to the WHO criteria
§ minimum 3 NCEPIII criteria to meet the diagnosis of metabolic syndrome
§§ include Rheumatoid Arthritis, Systemic Lupus erythematous, Crohn disease, Ulcerative colitis and Chronic Hepatitis or Cirrhosis

5.4. Treatment

The prevalence of cardiovascular therapy at the hospital admission and discharge is reported in Tab. IV. The dose of each pharmacological class was impossible to report from the data sheets. At hospital discharge ACE inhibitors and/or ARBS, beta blockers and anti-aldosterone agents were more prescribed compared with hospital admission for both sexes. Females were significantly more treated with digoxin and less with aspirin than their male counterpart at hospital discharge. None significant difference was registered in the intravenous administration of diuretics (furosemide), nitrates, inhotropic agents such as dobutamine and antiarrhythmics such as amiodarone at hospital admission for acute or decompensated HF (Tab. V). In the subgroup of patients with atrial fibrillation (N=601, 42%), the prescription of aspirin (ASA) and vitamin K antagonists (VKAs) increased at hospital discharge. However, none statistically significant difference between sexes was found (Tab. VI).

Table IV. *Use of cardiovascular drugs according to sex.*

	Hospital admission (%)			**Hospital discharge (%)**		
	Male N=672	**Female N = 715**	**P**	**Male N=581**	**Female N=640**	**P**
ACE-inhibitors	52,6	51,2	0,59	47,3	45,6	0,55
Allopurinol	18,7	13,7	0,05	24,9	20,3	0,05
ARBs	13	16	0,13	32,1	32,2	0,9
Aspirin	37,6	31,2	0,001	42,6	33,4	0,001
Beta blockers	23,6	23,7	0,9	31,6	30,4	0,6
Calcium-channel blockers	12	15,8	0,05	13,7	15,4	0,4
Digoxin	26	30,3	0,1	25,4	37,2	0,001
Furosemide (oral)	47,3	45,6	0,53	80,3	81,6	0,6
Anti-aldosterone agents	21	20,6	0,9	29,5	34,5	0,05
Warfarin	22,4	23,6	ns	24,7	25,6	ns

*N=number of data sheets available; for 14 subjects gender was not reported

Table V. *Intravenous pharmacological treatment according to sex at hospital admission*

Drugs by i.v.route at hospital admission (%)	**Males (N=652)**	**Females (N=699)**	**p (X^2) test**
Diuretics	61,8	63,6	0,51
Nitrates	17,3	16,3	0,09
Dobutamine	1,5	0,7	0,2
Amiodarone	3,9	2,5	0,2

Table VI. *Antithrombotic treatment in patients with atrial fibrillation and heart failure according to sex*

	Hospital admission			**Hospital discharge**		
	M	**F**	**P (X^2 test**	**M**	**F**	**P (X^2 test**
Vitamin K anatagonists (%)	36,3	40,0	0,4	43,2	42,0	0,9
Antiplatelet drugs (%)	28,4	26,6	0,68	35	31,5	0,67

5.5. Functional Status and Quality of Life

Barthel Index Score (BIS) was tested at index day and at hospital discharge to ascertain whether hospitalization may impair self autonomy. A severely impaired functional status (BIS ≤ 30) was registered in 17,6% of males and in 27,6% of females (p<0,01). For each activity performing BIS the average score was higher in men than in women both at the index day and at the discharge, which means that females have less self autonomy for each activity. Females showed a remarkable higher prevalence of permanent bed rest (12,3% vs 17,4%) and urinary incontinence (12,0% vs 18,2%) than males. In hospital staying worsened significantly disability in both sexes.

The average score in the Minnesota Living with Heart Failure Questionnaire was similar in both sexes (M=58,5 $\pm$ 35,8 vs 60,5 $\pm$ 31,9, ns). Only the answers to the questions n° 10 (*Making your sexual activities more difficult?*) and n° 21 (*Making you feel depressed ?*) showed a statistically significant difference between sexes (p<=0,01). Both for men and women the most troublesome concerns with HF were hospitalization (more than 60%), shortness of breath (more than 55%) and loss of energy (53-56%) (See Tab. VIII).

Table VII. *The Barthel Index distribution according to sex*

	Male			Female		
	Index day N=512	**Discharge N=461**	**P**	**Index day N=559**	**Discharge N=515**	**P**
Barthel Index Score	64,7 ± 30,7	72,21± 28,8	0,001	53,9 ± 31,4	61,46± 31,7	0,001
Activity						
Feeling (0-10)	7,9 ± 2,9	8,4 ± 2,8	0,005	6,9 ± 3,4	7,5 ± 3,2	0,005
Bathing (0-5)	2,5 ± 2,5	2,8 ± 2,5	0,01	1,7 ± 2,4	2,1 ± 2,5	0,001
Grooming (0-5)	3,1 ± 2,4	3,4 ± 2,3	0,01	2,5 ± 2,5	3,0 ± 2,4	0,001
Dressing (0-10)	5,8 ± 3,7	6,5 ± 3,6	0,005	4,6 ± 3,7	5,4 ± 3,7	0,001
Bowels (0-10)	8,3± 3,1	8,4± 3,0	ns	7,4 ± 3,6	7,7± 3,5	ns
Bladder (0-10)	7,5 ± 3,5	7,7 ± 3,6	ns	6,4 ± 4,1	7,0 ± 4,0	0,05
Toilet use (0-10)	6,1 ± 4,0	6,8 ± 3,9	0,001	4,6 ± 3,9	5,6 ± 3,9	0,001
Transfer (bed to chair and back) (0-15)	9,1± 5,3	10,4 + 5,0	0,001	7,5 ± 5,2	8,7 ± 5,3	0,001
Mobility (on level surfaces) (0-15)	9,8± 5,3	10,9+ 5,0	0,001	8,0 ± 5,6	9,1 ± 5,5	0,001
Stairs (0-10)	5,0 ± 4,0	5,9± 3,9	0,001	3,8 ± 3,8	4,7 ± 3,9	0,001

Legend: in brackets the score grading for each item (total 0-100). Total score and every activity (mean ± SD) were compared with values of index day. N= number of data sheets recorded

Table VIII. *The Minnesota Living with Heart Failure Questionnaire distribution according to sex.*

Did your HF prevented you from living as you wanted during the last two months		**SCORE**							
		Mean ± SD	**Mean ± SD**	**0 – 1 (%)**		**2 – 3 (%)**		**4 – 5 (%)**	
		M	**F**	**M**	**F**	**M**	**F**	**M**	**F**
1	Causing swelling in your ankles, legs?	2,5 ± 1,6	2,5 ± 1,7	28,1	29,6	41,8	41,2	30	29,1
2	Making you sit or lie down to rest during the day?	2,9 ± 1,4	2,9± 1,5	16,9	17,6	43,5	42,1	39,5	40,2
3	Making you walking about or climbing stairs difficult?	3,4± 1,5	3,4 ± 1,6	12	13,6	34,4	29,6	49,2	56,3
4	Making your working around the house yard difficult?	3,1 ± 1,6	3,3± 1,6	17,7	15,5	34,6	30,8	47,5	53,6
5	Making your going places away from home difficult?	2,9 ± 1,8	3,0± 1,8	25,3	21,8	31,2	30,3	41,2	47,9
6	Making your sleeping well at night difficult?	2,9 ± 1,5	3,1 ± 1,5	19,8	17,6	38,9	37,3	41,2	45,1
7	Making your sleeping to or doing things with your friend or family difficult?	2,6 ± 1,7	2,6 ± 1,7	26,4	27,2	39,5	36	33,4	36,7
8	Making your working to earn a living difficult?	1,8 ± 1,8	2,0 ± 1,9	50,3	46,9	25,1	23,1	24,5	29,8
9	Making your recreational past times, sports or hobbies difficult?	2,3 ± 1,7	2,4 ± 1,8	36,6	35,4	32,9	31,2	30	14,2
10	Making your sexual activities more difficult?	1,9 ± 2,1	1,5 ± 2,1	55.7	64,5	13,7	10,5	30,6	24,9
11	Making you eat less of the foods you like ?	2,2 ± 1,6	2,4 ± 1,6	33,8	30,6	42,7	43,6	23,4	25,6
12	Making you short of breath?	3,5 ± 1,4	3,5 ± 1,4	9,3	11,6	34,6	20,2	56	58
13	Making you tired, fatigued or low on energy?	3,4 ± 1,4	3,4 ± 1,5	10,7	13,2	34,8	29,8	53,9	56,8
14	Making you stay in a	3,5 ± 1,0	3,6 ± 1,5	11,6	12,2	26,4	20,1	61,5	63,7

Did your HF prevented you from living as you wanted during the last two months		SCORE							
		Mean ± SD	Mean ± SD	0 – 1 (%)		2 – 3 (%)		4 – 5 (%)	
		M	F	M	F	M	F	M	F
	hospital ?								
15	Costing you money for medical care?	3,5 ± 1,7	3,6 ± 1,8	46,7	44,8	32,3	30,1	20,9	25,1
16	Giving you side effects from medications?	1,6 ± 1,5	1,6 ± 1,6	50,7	50,3	35,3	34,3	12,6	13,4
17	Making you feel you are a burden to your family or friends?	2,2± 1,6	2,4± 1,8	38,2	35,4	34	29,8	27,6	34,6
18	Making you feel a loss of self-control in your life?	2,4 ± 1,0	2,5± 1,7	32,1	30,8	37,6	34,8	30,2	34,3
18	Making you feel a loss of self-control in your life?	2,4 ± 1,0	2,5± 1,7	32,1	30,8	37,6	34,8	30,2	34,3
19	Making you worry?	2,7± 1,6	3,0 ± 1,6	23,2	20,1	35,9	34,3	40,8	45,6
20	Making it difficult for you to concentrate or remember things?	2,4 ± 1,6	2,6± 1,7	33,1	28,9	35	36	31,7	35
21	Making you feel depressed ?	2,4 ± 1,6	2,7 ± 1,7	32,7	27,2	49,8	35,4	27,9	36,5

Legend: M=Male; F=Female. Mean ± SD for each single item with score percentage are reported. Males number=476, Females number=528.

5.6. Cognitive Deficit/Dementia

The Short portable mental status questionnaire (Pfeiffer test) corrected by education was performed in 1021 subjects; data at the index day and at the discharge are reported in Tab. IX. We found a higher severe to moderate cognitive defect (8-10 versus 5-7 scores) in females compared to males at the index day and hospital discharge. Hospitalization worsened cognitive ability and remarkably increased the cognitive impairment at hospital discharge in both sexes.

Table IX. *Pfeiffer test distribution according to sex*

	Male N=478			Female N=533		
	Index day	Discharge	P	Index day	Discharge	P
Pfeiffer test (mean ± SD)	2,57 ± 3,07	2,15 ± 3,12	0,05	3,46 ± 3,42	2,96 ± 3,34	0,05
0-2 (%) - normal	58,6	66,6	0,08	47,8	54,7	0,04
3- 4 (%) - mild	14,9	12,3	0,22	16	14,5	0,59
5-7 (%) - moderate	16,2	12,3	0,04	20,9	17,9	0,28
8-10 (%) - severe	9,2	8,8	0,89	15,2	9,2	0,27

Legend: N= number of patients

Table X. *NYHA Class at hospital discharge*

NYHA (%)	Males	Females	P (X2 test)
I	12,6	9,7	0,1
II	58,4	58,1	0,9
III	21,5	25,2	0,09
IV	7,4	6,2	0,3

5.7. Outcome

Mean length of hospital stay was similar in both sexes. None significant difference was noticed between sex in NYHA class at hospital discharge. NYHA improved during hospitalization, classes I-II rising from less than 20% at hospital admission to around 70% at hospital discharge (Tab. X). In hospital mortality was 4,4% (60 patients, 24 males and 36 females, p=ns).

6. Discussion

HF is a worldwide epidemic health problem, burdening for a high percentage of resources of healthcare systems. Therefore, the knowledge of characteristics of patients with HF is of utmost importance. Our study provide information about HF in patients admitted in Italian Internal Medicine

wards. Our study demonstrates that HF population admitted in Internal Medicine wards is extremely old, mean age being around 80 years. Females result significantly older than males. The distribution of age by using deciles underlines that female sex prevails in the extreme age of life: in fact more than 10% are 90 years old and older.

In our population, arterial blood hypertension represent the most prevalent HF etiology in females, confirming the results of a pooled analysis of five large clinical trials which demonstrated that 60% of females versus 43% of males with HF had non ischemic etiology (16). To now, arterial blood hypertension has a great population-attributable cardiovascular risk percentage in both sexes, and it is associated with more incident HF in females (17). It has been demonstrated that arterial blood hypertension increases the risk of HF by threefold in females compared to twofold in males (18).

It has been demonstrated that females with HF are more symptomatic at presentation (16,19). In our study, despite we found that congestive syndrome represents the most prevalent phenotype, we did not find difference in clinical presentation between sexes.

HF with preserved LVEF is reported to represent the most frequent HF pattern in females (20-22). We confirmed this finding, however it should be remarked that our cohort of patients is older compared to those previously reported and quite similar to those of other surveys in identical settings in Italy (8,23). The advanced age of our cohort may blunt the gender differences of LVEF reported in the literature.

Isolate HF was found to be present only in less than 10% of our cohort. In fact, both sexes showed at least one or two co-morbidities. A lot of co-morbidities should be taken in special consideration due to their severe burden on HF outcome. Chronic kidney disease (CKD) is common in HF failure, and shares many risk factors with HF such as age, arterial blood hypertension, diabetes, and coronary artery disease. Over one half of all HF patients may have moderate to severe CKD. A reduction of glomerular filtration goes on pari-passu the growing age of population and this is more evident in females (24). A study of about 120,000 contemporary acute hospitalized HF patients from the ADHERE registry indicates that CKD, defined as GFR <60 ml/min/1.73m^2, was present in 64% of patients. Remarkably, in this study 44%, 13% and 7% of patients had stage 3, 4 and 5 CKD, respectively (24). Mean age of patients and impaired renal function were strictly related. Most HF patients with CKD were females (54%, 58% and 54% respectively for stage 3, 4 and 5), while the majority of patients with stage 1 and 2 kidney function were males (57% and 53, respectively)(24). Our study confirmed these findings, demonstrating a higher prevalence of mild renal failure in males compared with females who presented a higher percentage of moderate (stage 3).

In our study, COPD is less represented in females as elsewhere reported (25).

No gender differences in the prevalence of diabetes, regardless of the HF etiology has been reported; the prevalence ranged between 10 and 35%, with higher percentages recorded in the studies enrolling patients with worse HF (26,27).The prevalence of diabetes is near 10% higher in females with ischemic etiology of HF , while there was no difference in prevalence among females without ischemic HF when compared with males (16), our findings being in agreement with the abovementioned results.

Even if in absence of diabetes, obesity is a risk factor for HF. It has been estimated that the population-attributable risk percentage of HF due to overweight was 14% in females and 9% in males, while the corresponding percentages due to obesity were 14% in females and 11% in males (28). Metabolic syndrome too may play a role in favouring HF (29-32). This was confirmed in our study where BMI > 30 and metabolic syndrome prevailed in females, as previously demonstrated (33).

National Heart Failure Project and the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE-HF) trials found that older females with HF were less likely to receive guideline-recommended treatments compared with males (34). Females seem to be less likely to receive β-blockers than males as confirmed by CHARM study (35-36). Moreover, despite the relatively small number of females participating in each study, pooled data from the MERIT-HF, CIBIS-II and COPERNICUS trials yielded a mortality benefit with β-blockers in females similar to that recorded in males (37-39).

Our study confirms that beta blockers are still underused in clinical practice, however in our population none difference in beta blockers prescription was noted. In our study advanced age and co-morbidity seem to influence the beta blockers prescription more than gender.

Females seem to receive less ACE inhibitors than males (35). Nevertheless ACE inhibitors have shown to confer benefit on survival to males with HF and reduced LVE, to date strong literature evidence has not available for females, being demonstrated a not significant 15% reduction in all cause mortality by using ACE-inhibitors in females (40). A 12 years follow up of SOLV trial found a not significant survival benefit for females who were randomized to enalapril (41). A meta-analysis of major clinical trials concluded that only females with symptomatic LV systolic dysfunction may benefit by the use of ACE inhibitors, whereas females without symptomatic LV systolic dysfunction may have no benefits (42). Head-to-head comparisons of losartan and captopril in elderly patients with LVEF less than 40% found no benefit of losartan over captopril, an effect that was similar according to gender (43). More recently, a population based study confirmed that no difference was evident in the effectiveness of angiotensin receptor-blockers and angiotensin converting enzyme inhibitors in patients with congestive HF, however females treated by using ARS seemed to have better outcome than those on ACE inhibitors (44).

Overall, treatment by using RAAS inhibitors, with exception of spironolactone, was prescribed in both genders

in around 75% of our patients, showing a significant increasing from hospital admission to hospital discharge. Instead, treatment by using spironolactone increased at hospital discharge only in females.

It has been demonstrated that digoxin seem to have none effect on mortality and decreased hospitalizations for HF (45). In females treated by using digoxin, it has been demonstrated a significant increased risk for all-cause mortality and a trend toward more hospital admissions (46). A *post hoc* analyses of our data showed that females had a higher serum digoxin concentration raising the hypothesis that this may contribute to the increased mortality among females (47).

In our study, digoxin was prescribed much more as expected according to the most recent guidelines. It was prescribed significantly more in females than in males at the hospital discharge and this finding may be explained only in part related to a higher prevalence of atrial fibrillation in females. This finding should be taken in account from internists caring patients with HF.

Although a retrospective analysis of the SOLVD trial showed that females with HF had an increased risk of thromboembolic events compared with males, cardioembolic prevention by using anticoagulants or antiplatet drugs seem to be prescribed less than males (48). Our study seems to confirm literature evidence: despite prescription of vitamin K antagonists and antiplatelet drugs increased from admission to hospital discharge, it remains underused (49).

HF is a troublesome syndrome, burdening on quality of life much more than other chronic diseases, such as arthritis and COPD (50). Impairment seems to be mainly related to intolerance to exercise, distress proved by symptoms, impaired role functioning in marital and family relationships, diminished job functioning, and reduced social support. (51-53). Females have significantly worse general life satisfaction, physical function, and social and general health scores than males but none difference in current life situation or emotional distress (54).

In our study we have registered that both males and females with HF show a poor quality of life and confirmed that females feel more depressed than males and fear for loss of energy to work, walk, climb and they have growing feeling to be a burden for the family. We found that the scoring in Minnesota Living with Heart Failure Questionnaire was higher than that elsewhere reported in NYHA class I-III (55-57). It could be due to high prevalence of patients in NYHA Class III-IV at hospital admission owing the acute worsening of HF. Therefore, it is not surprising that the most troublesome problem for these patients, irrespective of gender, was the fear to be hospitalized.

In our study, functional disability worsened during hospitalization in both genders but much more in females than males. Noteworthy, severe disability (Barthel Index < 30) was present in near 30% of females and 20% of males. This is a real problem for HF management, thereby we suggest that functional disability should be enclosed routinely at hospital discharge, taking into account that severe disability seems to be a powerful marker of negative outcome (9).

Cognitive performance status resulted different in females who showed more severe functional impairment compared to males and this was much more evident at hospital admission. During hospitalization Pfeiffer grading score improved in both sexes. This fact could be due to HF which per se may contribute to impair cognitive status, suggesting that an appropriate HF treatment could reduce cognitive defects, as elsewhere reported (58,59).

Most epidemiological studies found that females have better survival after the onset of HF, mortality risk being approximately 15-20% less than males, but data of in hospital mortality in females lack. Much recently, in a large multicenter registry enrolling over than 50,000 patients, it was demonstrated that despite differences in baseline characteristics, females and males have similar in-hospital mortality, irrespective from LVEF (60). Our findings confirmed these data, length of hospital stay and in hospital mortality being similar in both sexes. However, it should be remarked that females were discharged more compromised, being NYHA class IV more prevalent in females at hospital discharge.

In conclusion, HF is a pandemic diseases burdened by high mortality, morbidity and healthcare costs. Gender medicine is emerging as one of the main sub-specialty for healthcare professionals. Our study may contribute to understanding the difference between sexes in HF.

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