Results of an observational retrospective multicenter study: "Campania INternal medicine - the Clinical INternist for heart failure"

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ABSTRACT

Introduction. The Campania population is characterized by a high incidence and prevalence of heart failure (HF). The aim of this study is to describe the clinical epidemiology, comorbidities, and treatments in HF patients admitted to Internal Medicine Wards (IMW) in Campania. Materials and Methods. It is a retrospective, regional, multicentric, observational study including patients admitted to 15 IMW in Campania, with an HF diagnosis, over a period of three consecutive months. Results. We identified 427 patients, stratified by ejection fraction (EF) category (127 EF≤40%; 216 EF 41-49%; 84 EF≥50%). In comparison with HFpEF subjects, patients with HFrEF were younger (74 years *vs*. 9 years), more commonly male (67% *vs*. 32%), and more likely to have an ischaemic aetiology (45% *vs*. 25%). The most used drugs at the time of hospitalization and after were Diuretics (80.3/93.5%), BBs (69.6/92.6%), and Statins (52.1/63.7%), with statistically significant pre-/post- differences (P≤0.05). Conclusions. EF is more likely to be non-preserved in younger males and in patients with CAD etiology. Hospitalization influences in a statistically significant way the change or adjustment of therapy for almost all drugs.

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Introduction

Heart failure (HF) is a common chronic medical problem associated with considerable morbidity and mortality. Its incidence and prevalence are increasing worldwide, due to the aging of the population, the improvement of medical treatments, and improved survival after diagnosis.[1-3]

The incidence of HF in Europe is about 3/1000 peo-

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ple per year (all age groups) and about 5/1000 person-years in adults. Its prevalence is about 1-2% in adults and increases with age: around 1% in the ones aged <55 years and >10% in the ones aged 70 years or over.[4]

In Italy, the mean annual incidence of HF per 1000 person-years is 1.99, and the prevalence per 1000 people is 17.0.[5] HF management is often complicated by the complex context of multimorbidity and geriatric syndromes which amplifies the personal and societal impact of the disease. HF hospitalizations represent 1% to 2% of all hospital admissions and are associated with the highest 30-day readmission rate (about 20-50%).[6]

In Europe, the number of discharges from hospitalization for HF per million people is 2671 [interquartile range (IQR) 1771-4317], while in Italy, it is 2770.[5]

HF management is not solely under the care of cardiologists but is also handled by non-cardiologists, mainly internists.[7] Several studies report that HF patients, older, with multiple co-morbidities, and at high risk for readmission are admitted to internal medicine departments.[8-11]

The aim of this study is to describe the clinical epidemiology, comorbidities, and treatment patterns in HF patients admitted to Internal Medicine Wards (IMW) in the Campania region, stratified by the left ventricular ejection fraction (LVEF) category according to the 2016 ESC guidelines. Further, this study is meant to serve as a resource for the development of a strategic approach to the prevention and treatment of HF.[12]

Materials and Methods

"Campania INternal medicine - the Clinical INternist for HF" is a retrospective, regional, multicentric, observational study including patients admitted to 15 IMW in Campania, with an HF diagnosis, over a period of three consecutive months, between January 2020 and January 2022.

Patients were divided into three subgroups according to the 2016 ESC guidelines: heart failure with reduced ejection fraction (HFrEF) (HFrEF≤40%), mildly reduced EF (HFmrEF 41-49%), and preserved EF (HFpEF≥50%).

We analyzed demographic data, hospitalization diagnosis, heart rate and rhythm, blood pressure, aetiology of HF, NYHA class, some echocardiography parameters, thoracic ultrasound, previous hospitalization, some laboratory parameters, length of hospitalization, re-admissions, and therapy. The following comorbidities were systematically recorded: i) chronic obstructive pulmonary disease (COPD), identified on the basis of clinical data or specific therapy; ii) diabetes, identified on the basis of previous diagnosis, or specific therapy, or blood fasting glucose >126 mg/dL; iii) systemic hypertension, identified according to the European Society of Hypertension/European Society of Cardiology guidelines; iv) anemia, identified according to the World Health Organization (WHO) definition; v) renal insufficiency, identified on the basis of glomerular filtration rate, according to the MDRD formula; vi) cancer; vii) cerebrovascular disease, identified on the basis of a history of stroke or transient ischemic attack; viii) liver cirrhosis.

Inclusion criteria

All inpatients with HF at the time of admission were enrolled in the study.

Eligible patients were either those suffering from known chronic heart failure but hospitalized for a different acute illness or those hospitalized for acute heart failure.

There were no specific exclusion criteria other than age, which was required to be higher than 18 years.

An echocardiography assessment of LVEF was necessary at enrolment.

The study was approved by the Ethics Committees of the coordinator center. It was conducted in accordance with current regulations and the Helsinki Declaration.

Participating centres

Patients were enrolled at hospitals in the following centers of the Campania region: Naples, Salerno, Cava de' Tirreni (SA), Avellino, Caserta, Marcianise (CE), Aversa (CE), Pozzuoli (NA), Sorrento (NA), Mercato San Severino (SA).

Statistical analysis

Sample size

The sample size was calculated assuming that 50% of patients had an EF between 40% and 50%, a confidence interval of 95%, a maximum error of 5%, and a design effect of two, for a total of a minimum of 385 participants.

Statistical analysis

Statistical analysis was carried out in multiple steps. First, descriptive analysis was performed, and frequencies and percentages were reported for each characteristic of the sample. Then, a bivariate analysis was carried out using the t-test and chi-square test to evaluate the association between potential causal variables and each outcome of interest. Then, to account for the two-stage cluster sampling, a logistic regression model was estimated by using a Generalized Estimation Equation analysis to investigate independent characteristics associated with the following outcome of interest: EF on admission to the hospital.

Baseline continuous variables were reported as the mean ± standard deviation or as the median and IQR,

as appropriate. Categorical variables were reported as percentages.

A univariate analysis was conducted using the chi-square test between the EF outcomes, which were divided into 3 categories based on the EFs (EF≤40%, EF 41-49%, EF≥50%), and the pooled variables (personal data and anamnestic data) to identify the main risk factors associated with having a preserved EF.

All variables that were statistically significant at the entry in univariate analysis by the EF group (P<0.05) and variables considered to be of relevant clinical interest as fixed covariates were included in the multivariate analysis, which was performed with the logistic regression test, with the same outcome to quantify the risk of having a more or less conserved EF and to exclude confounding bias of the variables associated in a statistically significant way to the univariate that was chosen for the model creation.

All analysis was performed using the Stata version 16 statistical software.

Results

We identified 427 patients, stratified by EF category (127 EF≤40%; 216 EF 41-49%; 84 EF≥50%), diagnosed with HF, consecutively admitted to 15 IMWs in a period of three months; mean age 78.5 years; 210 (49.2%) females (F), 217 (50.8%) males (M); 49.3% patients had atrial fibrillation. High blood pressure was the most frequent cause of HF (55.5%); the prevalence of ischaemic HF was higher in M (39.1% *vs*. 19.3%, P<0.001); 49.2% of patients had had at least one hospitalization in the previous year, while 16.4% of patients had been hospitalized over the previous 30 days.

Hypertension was the most frequently associated disease with HF (88.8%). Other significant comorbidities were chronic renal failure (62.5%), diabetes (48.0%), COPD (46.0%), and cerebral vascular disease (27.7%). The mean duration of the hospitalization was 10.7 days.

The clinical, aetiological, and comorbidity features in patients with HF stratified for EF are shown in Table 1. An univariate analysis was conducted using the chi-square test between the EF outcomes, which were divided into 3 categories based on the EFs (EF≤40%, EF 41-49%, EF≥50%), and the pooled variables (personal data and anamnestic data) to identify the main risk factors associated with a more or less preserved EF, and the variables associated in a statistically significant way with the outcome resulted to be: age (P<0.001), sex (P<0.001), NYHA class (P=0.006), previous hospitalization in the last year (P=0.011), dyslipidemia (P=0.03), liver disease (P=0.02), ischaemic heart disease (P<0.001), hypertensive aetiology (associated with a more preserved EF) (P<0.001), coronary artery disease (CAD) aetiology (associated with a less preserved EF) (P<0.001), increased atrial volumes (P=0.012), increased ventricular volumes (P<0.048), taking oxygen therapy (P=0.02), taking Angiotensin Receptor Blockers (ARBs) (P<0.001), taking B-Blockers (BBs) (P=0.007), taking Calcium Channel Blockers (CCBs) (P<0.001) taking Direct Oral Anti-Coagulants (DOACs) (P=0.05), taking Statins (P<0.001) (Table 1).

A multivariate analysis was then performed with the logistic regression test to quantify the risk of having a more or less conserved EF and to exclude confounding bias of the variables associated in a statistically significant way with the univariate that was chosen for model creation; this analysis showed that the variables that increased the risk were: patients' age, a continuous variable (OR ± SE: 1.03±0.1 CI: 1-1.06), female sex (2.7±0.6; 1.7-4.1); Hypertensive aetiology (3.2±1.15; 1.6-6.5), CAD aetiology (0.4 ± 0.17; 0.1-0.9), increased atrial volumes (0.1±0.08; 0.04-0.4), taking CCBs (4.9±2.2; 2.1-11). Table 2 presents a multivariate logistic regression model showing associations between independent variables and a preserved EF.

Pharmacological therapy of HF patients at admission and at discharge according to the EF category is presented in Table 3 and in Figure 1. The most used drugs at the time of hospitalization and after were diuretics (80.3/93.5%), BBs (69.6/92.6%), and Statins (52.1/63.7%) with statistically significant pre-/post- differences (P≤0.05). As for therapy with Sacubitril/Valsartan (S/V), there are statistically significant differences both between the pre-/post- groups (3.6/18.8%) and among the patients belonging to the same EF category. At admission, there was no statistically significant difference between the use of this drug and EF, while a difference was found after discharge. S/V was used more in the group with EF<40% than in the other two groups (60.6%; P<0.001).

Discussion

The "Campania INternal medicine - the Clinical INternist for HF study" provides a contemporary regional database of HF patients, stratified by LVEF category, as suggested by the 2016 ESC guidelines. Left ventricular EF remains the major parameter for diagnosis, phenotyping, prognosis, and treatment decisions in HF patients.[13]

With the 2016 ESC HF guidelines, a separate entity, HF with mid-range EF (HFmrEF; defined as EF 40-49%), was introduced with the aim of fostering research in this EF range, which had been less investigated than HF with reduced EF (HFrEF; EF≤40%) and preserved EF (HFpEF; EF≥50%). According to contemporary trials, HFmrEF is an intermediate HF type between HF with preserved EF (HFpEF) and HF with reduced EF (HFrEF). The prevalence of HFmrEF within all HF patients is estimated to be 10-25%.[13]

Table 1. Baseline characteristics in chronic heart failure patients stratified by ejection fraction.

Variable	All (427)	EF≤40% (127)	EF 41-49% (216)	EF≥50%(84)	P-value
Age mean±SD	78.5±10	74.45±10.5	79.6±10	79.1±9.5	<0.001
Age >75	71.6%	59.8%	77.8%	73.8%	<0.001
Gender female	49.2%	32.3%	48.15%	67.85%	<0.001
Heart Rate (HR)	88.3±17.5	88.7±16.6	89.44±17.9	90.25±17.75	0.5
HR≥70	94.5%	93.4%	94.2%	97%	0.6
HR at discharge mean ± SD	74.3±10.2	72.8±7	76.2±11	71.4±11.2	0.7
HR at discharge ≥ 70	80.1%	78%	82.9%	76.2%	0.3
NYHA III/IV	73.1%	19.2%	27.62%	63.41%	0.006
Hospitalization last 30 days	16.4%	15.87%	17.8%	13.41%	0.6
Hospitalization last 1 year	49.2%	55.1%	51.2%	34.6%	0.011
Hypertension	88.8%	84.25%	91.20	89.29	0.1
Atrial Fibrillation	49%	44%	52.8%	47%	0.26
Kidney failure	62.5%	64.8%	60.7%	63.7%	0.7
Diabetes	48.05%	47%	47%	52.44%	0.6
COPD	46%	39.8%	48.6%	48.1%	0.28
Cognitive Impairment	33%	28.4%	37%	29%	0.2
Active cancer	9.6%	9.7%	8.2%	13.2%	0.4
Previous stroke	23.7%	27%	24.3%	17.3%	0.3
Dyslipidemia	43.8%	50%	44.7%	31.6%	0.03
Liver Disease	9.4%	9.65%	6.34%	17.33%	0.02
CAD	42.25%	60%	35.44%	32.43%	<0.001
Anemia	67.2%	66.1%	65.6%	73.2%	0.4
Iron Deficiency	45.6%	53.5%	44.2%	41%	0.2
Hypertensive aetiology	55.5%	33%	64.7%	67.1%	<0.001
CAD aetiology	29.9%	45.45%	22.55%	24.66%	<0.001
Increased Ventricular Volumes	87.9%	91.9%	88.3%	80.2%	0.048
Increased Atrial Volumes	81.2%	89.4%	79.2%	73.7%	0.012
ICD or PM	22.7%	51%	11%	13.1%	<0.001

EF, ejection fraction; SD, standard deviation; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; ICD, implantable cardioverter-defibrillator; PM, pacemaker.

Table 2 . Multivariate logistic regression model showing associations between independent variables and a preserved ejection fraction.

Ejection fraction category	O.R. ± SE	P (95% Conf Interval)
Log-likelihood = -133.59423 , χ103,88 (18 dF) P<0,001		
Age	1.03 ±0.1	0.02 (1-1.06)
Female sex	2.7±0.6	0.005 (1.7-4.1)
Hypertensive etiology	3.2±1.15	0.001 (1.6-6.5)
CAD etiology	0.4±0.17	0.03 (0.1-0.9)
Increased atrial volumes	0.1±0.08	0.001 (0.04-0.4)
CCBs therapy	4.9±2.2	<0.001 (2.1-11)

O.R., odds ratio; SE, standard error; CAD, coronary artery disease; CCBs, calcium channel blockers.

An important finding of our study is that HF patients stratified by EF categories represent different phenotypes in terms of clinical presentation, aetiology, and pharmacotherapies.

Patients with HFpEF represent ≈ 20% (19.7%) of all cases, the ones with HFrEF ≈ 30% (29.7%), and the ones with HFmrEF ≈ 50% (50.6%). These regional epidemiological observations contrast with the ones from other studies in hospitalized patients, which report about 50% of patients having HFrEF and 50% having HFpEF/HFmrEF.

An important consideration lies in the imprecision

Table 3. Pharmacological treatments administered in heart failure patients at admission (ante) and at discharge (post) according to ejection fraction.

Variabile (OBS)	All (427) (%)		EF≤40% (127) (%)		EF 41-49% (216) (%)		EF≥50% (84) (%)		P-value	
	Ante	Post	Ante	Post	Ante	Post	Ante	Post	Pre	Post
Oxygen therapy	57.4	39.9	52.2	39.6	63.8	36	47.1	53.45	0.02	0,06
Diuretics	80.3	93.5	79.6	92.8	81.1	94,1	78.9	93.1	0.9	0.9
ACE inhibitors	48.95	44.5	58.6	29.2	45.3	49.2	44.3	53.9	0.5	0.002
ARBs	31.58	23.4	18.3	9.2	35.5	32.3	41.2	19.3	<0.001	<0.001
BBs	69.6	92.6	78.9	95.2	67.15	92.8	59.7	88.1	0.007	0.218
MRAs	24	47	29.5	56.5	21.4	45.7	23.4	35.5	0.2	0.03
Digoxin	10.9	7.1	14.3	6.4%	9.6	8.6	9.5	3.3	0.4	0.7
Ivabradine	4.1	9.5	5.7	14%	4	7.7	2	8.2	0.4	0.23
S/V	3.6	18.8	6.7	60.6%	3	2.2	0	0	0.6	<0.001
CCB	28.3	36.4	14.1	16%	32.2	46.7	32.2	37.1	<0.001	<0.001
Nitrates	10.8	7.7	15.1	7.4%	8.6	7.7	10.8	8.2	0.2	0.9
Warfarin	13.7	2	13.8	2.1%	15.5	2.7	7.8	0	0.3	0.4
DOACs	22.9	36.5	22.4	36.7%	19.4	34.4	33.8	41.8	0.05	0.5
LMWHs	14.6	14.2	20	10%	13.1	13.7	10.6	21.3	0.2	0.15
Anti-platelets	50.6	43.1	57.3	52.5%	51.5	41.5	36.8	32.8	0.04	0.04
Statins	52.1	63.7	58.4	71.6%	53.2	67.6	37.9	39.3	<0.001	<0.001

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BBs, B-Blockers; MRAs, mineralocorticoid receptor antagonists; S/V, sacubitril/valsartan; CCB, calcium channel blockers; DOACs, direct oral anti-coagulants; LMWHs, low-molecular-weight heparins.

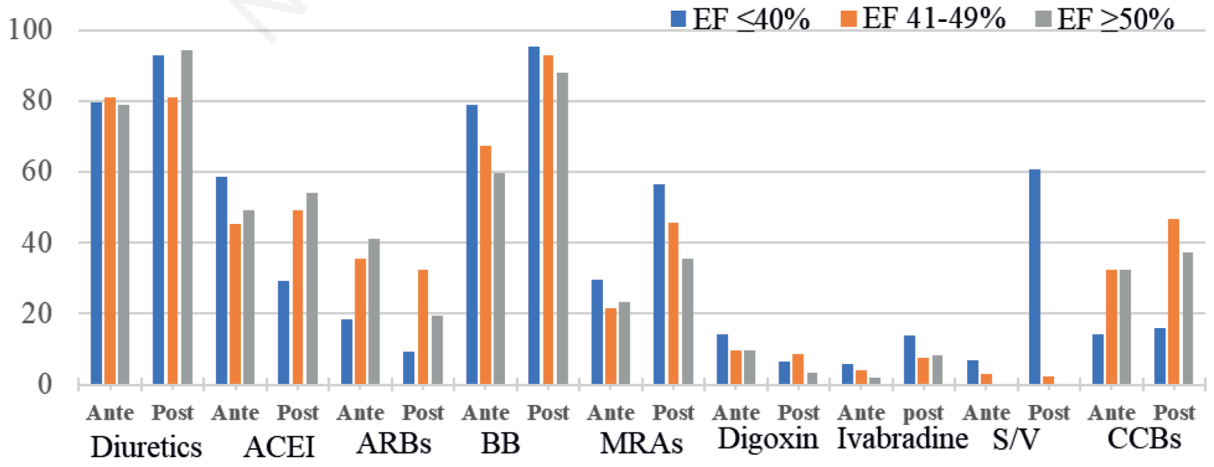

Figure 1. Pharmacological treatments administered in HF pts at admission et at discharge according to the EF category. ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BB, beta-blockers; MRAs, mineralocorticoid receptor antagonists, S/V, sacubitril/valsartan, CCBs, calcium channel blockers.

of EF measurements and their variability over time.[14]

Intra-observer and inter-observer variability of standard echocardiographic left ventricular EF assessment is reported to be 8-21% and 6-13%, respectively.[15]

In a systematic review of the reliability of EF measurement by echocardiography, this technique may be adequate to establish that EF is clearly abnormal (<30%) or normal (>50%), while between 30% and 50% it is imprecise.[16]

Furthermore, since HF patients admitted to IMW, and eligible for this study, are hospitalized both for non-cardiovascular causes and for cardiovascular causes, and the ones with HF-related hospitalizations are older and less cooperative, accurate identification of EF is difficult.

In our study, the assessment of LVEF could not be standardized and, therefore, might be subject to different assessments among different operators, which may result in the misclassification of some patients.

Patients with HFmrEF share features with both HFrEF patients, such as a higher prevalence of men and anemia, and HFpEF patients, such as their age, and hypertensive aetiology.

As in other studies, our patients with HFrEF are typically younger than patients with HFpEF. Men are more likely to have HFrEF, while women have typical HF with preserved EF, which is also consistent with previous studies.[17-20] An ischaemic aetiology is more commonly reported in HFrEF than in HFpEF, whereas hypertension, diabetes, and atrial fibrillation (AF) are more prevalent in HFpEF.

Our results were compared with those of the 2017 ESC Heart Failure Long-Term Registry,[21] a prospective, observational study, collecting epidemiological information in HF outpatients, stratified by LVEF. Compared with our patients, the ones enrolled in ESC Registry were younger (mean age 64.8±13.3 *vs*. 78.5±10), mainly males (71.8% *vs*. 50.8%), few in NYHA class III/IV (26% *vs*. 73.1%) with ischaemic heart disease as main aetiology (42.9% *vs*. 29.9%). Moreover, in ESC Registry, 59.8% of HF patients were classified as having HFrEF (*vs*. 29.7%), 24.2% as having HFmrEF (*vs*. 50.6%), and 16% as having HFpEF (*vs*. 19.7%).

This comparison demonstrates significant differences in the epidemiological characteristics of HF patients admitted to IMW and Cardiology Department. As well as other studies,[22-25] this confirms that HF patients cared for by cardiologists are younger and with a higher prevalence of coronary artery disease and decreased left ventricular function, while the opposite is seen in most patients admitted to IMW, as demonstrated by our study.

Furthermore, the results on the whole population of this study, regardless of EF category, were compared with other Italian studies on patients with HF, hospitalized in IMW: the TEMISTOCLE study, an observational study on 2127 patients with HF admitted in 417 cardiology and internal medicine hospital units;[8] the FASHION study, a prospective multicentric study about HF in Campania IMW;[11] the CONFINE study about comorbidities and outcomes in patients with chronic HF in internal medicine units;[9] and the SMIT study a prospective multicentric study about HF in Toscana IMW.[10]

The CIN CIN study confirms that the Campania population is elderly (mean age 78.5±10 *vs*. 77±10 - TEMISTOCLE; 82.5±8.9 - SMIT; 77.3±10 - FASHION; 78.7±9.6- CONFINE), characterized by a high incidence and prevalence of HF. It is due to the large percentage of subjects at high cardiovascular risk.[26]

Our patients were symptomatic. 73.1% of all patients are III/IV NYHA class (*vs*. 55.5% - FASHION; 81.7% - CONFINE; 83.3% - SMIT). The first comorbidity turned out to be high blood pressure, with a higher percentage than in the other studies (88.8% *vs*. 62.8% - CONFINE; 72.6% - SMIT; 76.9% - FASHION), followed by renal failure, present in 62.5% (a higher percentage than in the TEMISTOCLE study - 7.2%; in CONFINE - 44.2%; and in FASHION - 35.7%; but not in SMIT - 78.9%). The number of comorbidities in the same patients was very high (>4 in 64.9%), much higher than SMIT (≥4 comorbidities in 40.6%) and CONFINE (≥4 in 8.8%). The prevalence of AF was 49% (*vs*. 45.3% - TEMISTOCLE; 42.7% - CONFINE; 47% - SMIT). About 50% of all patients with HF had been hospitalized at least once in the last year (*vs*. 39.7% - FASHION; 42.8% - TEMISTOCLE; 50.7% - SMIT).

Clinical causes for previous hospitalizations are not known, but they are indicative of a fragile population. However, it is now known that after the initial diagnosis, HF patients are hospitalized about once a year.[27]

Readmissions are often due to reasons other than HF, reflecting the high comorbidity burden in these patients.[28]

Among any possible disease, HF is associated with the highest 30-day readmission rate (about 20-25%).[6]

Our retrospective study shows that 16.4% of all patients were hospitalized in the last 30 days and that hospitalization for patients with HF is a critical event that may become a clinical opportunity to improve the management of HF, including adherence to guideline-based medical therapy.

The collected data suggest that hospitalization influences in a statistically significant way the change or adjustment of therapy for almost all drugs, such as S/V, DOACs, BBs, and Angiotensin-converting-enzyme inhibitor (ACEI), in patients with HF and confirm, as suggested by the 2016 ESC guidelines, that LVEF has an essential role in guiding the therapy of HF patients.

In our study, the most used drugs at the time of hos-

pitalization and after were found to be diuretics (80.3/93.5%) and BBs (69.6/92.6%).

There is an evident increase in the use of BBs in all patients with HF (69.6%, *vs*. 31.1% - CONFINE; 51.7% - SMIT; 7.3% -TEMISTOCLE; and 52.3% - FASHION), as well as an increase in the percentage of S/V utilization between admission (6.7%) and discharge from the department (60.1%) in HFrEF patients, according to the 2016 ESC guidelines. Compared to the FADOI FASHION, an observational study about HF, conducted in 2014 in 23 departments of Internal Medicine in Campania, and the AGISCO STUDY,[29] another observational FADOI study, conducted in June 2016 in 29 departments of Campania Internal Medicine, which confirmed a non-optimal adherence to the HF guidelines, the present study indicates a great improvement for HF therapy standards, including BBs, ACEI/ARBs and diuretics, and a sufficient intake of other life-saving therapies, such as S/V, especially for patients with HFrEF.

Conclusions

HF patients stratified by different categories of EF, with reduced EF (HFrEF; EF≤40%), mildly reduced EF (HFmrEF; EF 41-49%), and preserved EF (HFpEF; EF≥50%), represent different phenotypes in terms of demography, clinical presentation, and aetiology.

Our data provide us with the features of patients with HF in Campania, helping us in their effective management.

As reported in previous studies, our analysis shows that the advanced age and the comorbidities characterize the patients with HF admitted to Internal Medicine and out-of-hospital drug prescriptions are only partially compliant with the standards outlined by current guidelines.

Multivariate analysis shows that EF is more likely to be non-preserved in younger, male patients, in patients with CAD aetiology, and in the ones with increased atrial volumes. Instead, patients who, on entry, presented a hypertensive aetiology were mostly female, older, and were taking CCBs, and were found to be up to five times more likely to have a preserved EF.

The collected data suggest that hospitalization influences in a statistically significant way the change or adjustment of therapy for almost all drugs; for some drugs, such as S/V, DOACs, BBs, and ACEI, the change of therapy is associated with the EF Group.

Limitation

Since it was a retrospective study, mortality for all causes could not be assessed.

The use of SGLT2 inhibitors (glifozins) was not evaluated because enrolment for this study began before the 2021 ESC Guidelines publication.

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