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Patterns of comorbidities differentially impact on in-hospital outcomes in heart failure patients

Veronica Murru^{1,3}, Elena Belfiori^{1,3}, Alessandro Sestu^{1,3}, Andrea Casanova¹, Carla Serra² and Angelo Scuteri^{1,2*} 

Abstract

Background Cardiac and non-cardiac comorbidities are highly prevalent in patients with heart failure (HF). The aim of the present study was to describe their selective impact on in-hospital outcomes (length of hospitalization and mortality) of HF patients hospitalized in an Internal Medicine Unit.

Methods Between January 2017 and December 2022, 12,435 (6146 F, 6289 M) inpatients were hospitalized in our Internal Medicine Unit. HF was defined according to the International Statistical Classification of Diseases and Related Health Problems (ICD) version 9 codes 428, 402.01, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93. Patients were classified by burden of overall, cardiac, and of non-cardiac comorbidities (0, 1, 2, 3+). Multivariable regression models were used to assess associations between comorbidity burden and length of stay (linear regression) or in-hospital mortality (logistic regression).

Results HF patients (1481, or 11.9% of all hospitalizations during the observation period) had on average comorbidity count of 1.6. An increasing number of comorbidities was associated with longer duration of hospitalization and mortality. Non-cardiac, but not cardiac, comorbidities were associated with significantly higher length of stay (beta coefficient 2.86 ± 0.27) and in-hospital mortality (OR 1.90, 95% confidence interval (CI) 1.60–2.23; $p < 0.0001$).

Conclusions Cardiac and non-cardiac comorbidities differentially impact on in-hospital outcomes of older HF patients hospitalized in an Internal Medicine unit. Their more precise management will allow a reduction of avoidable hospitalization in HF patients.

Keywords Heart failure, Hospitalization, Comorbidities, Length of stay

Introduction

Heart failure (HF), whose prevalence increases with age [1], has reached epidemic proportions, resulting in a major contributor to population health. [2]. HF epidemic also represents a challenge to healthcare sustainability because of its impact on healthcare expenditure. While patients enrolled in clinical trials and in several HF registries are mainly hospitalized and followed up in Cardiology Units [3], an increasing number of HF patients are being admitted to Internal Medicine and Geriatric Units due to the HF epidemic, advanced age, and non-cardiac comorbidities [4].

*Correspondence:

Angelo Scuteri
angelo.scuteri@unica.it

¹ Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

² Internal Medicine Unit – University Hospital Monserrato - Azienda Ospedaliero-Universitaria di Cagliari – Cagliari, Cagliari, Italy

³ Post Graduate, Medical School of Internal Medicine, University of Cagliari, Cagliari, Italy



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All these considerations taken together, the number of HF patients with multiple comorbidities is increasing, with more than 25% of patients presenting ≥ 3 comorbidities [5]. Comorbidity impacts on therapeutic plans and patient's prognosis, but also on outcomes: patterns of symptoms, rate of progression, response to treatment as well as complications, hospital readmissions, and health care use [6]. Recurrent hospitalization in HF patients represents a change in the trajectory of the disease and its progression, and a major contributor to HF costs. Hospitalization also represents an outcome of HF care. In fact, it reflects the complex interplay between quality and continuity of care, the underlying cardiac function, and patient multimorbidity.

In recognition of the relevance of comorbidities in HF patients, the Charlson's Comorbidity Index (CCI) is widely used and is often considered the gold standard for assessing comorbidities in clinical research [7]. With the growing knowledge about the role of comorbidities in the management and prognosis of patients, two limitations of the CCI should be acknowledged and overcome: 1) the CCI was developed to predict mortality, and not "softer" outcomes [7]; 2) though the 19 conditions contributing to the CCI do not have all the same weight, the CCI score provides an overall burden of comorbidity, with no insight on differential impact of selected conditions on health care indicators and/or patient's quality of life.

The purpose of the present study was to describe the prevalence of comorbidities in HF patients hospitalized in an Internal Medicine ward and their impact on in-hospital outcomes (mortality, length of stay).

The underlying hypothesis is that cardiac and non-cardiac comorbidities differentially impact on in-hospital outcomes of older HF patients.

Methods

Study design and data collection

A retrospective observational study based on administrative sources was conducted. We used data from Hospital Discharge Record (SDO) of patients admitted to the Internal Medicine Unit of University Hospital "Duilio Casula" in Cagliari (Italy) between January 1 st, 2017, and December 31 st, 2022.

The SDO system records one primary and up to five secondary diagnoses, with the primary goal of defining a diagnostic-related group (DRG). DRG identifies the payment/reimbursement the Hospital receives for each hospitalization. The primary diagnosis is the main reason for a patient's hospital admission, while a secondary diagnosis refers to any additional health condition that coexists with the primary diagnosis at the time of admission and that may contribute to render a DRG a "complicated

DRG" (with the relative higher payment/reimbursement than a not-complicated DRG).

Although "International Statistical Classification of Diseases and Related Health Problems" (ICD) version 10 was released on October 1, 2015, the Sardinia Region continues to adopt the Ninth Edition code for identifying primary and secondary diagnoses.

With these premises in mind, ICD codes were used to define HF and to identify most common comorbidities. The ICD codes used to identify HF and the most prevalent cardiac and non-cardiac comorbidities are listed in Supplementary Table 1.

Limitations deriving from such approach are presented in the [Discussion](#) section.

HF was further classified as whether it was the primary diagnosis (HFp) (people hospitalized because of an acute episode of HF decompensation) or a secondary diagnosis (HFs) (people hospitalized with HF).

Four cardiac (atrial fibrillation, hypertension, diabetes mellitus, coronary artery disease—CHD) and five non-cardiac (respiratory failure and pneumonia, kidney disease, *anaemia*, sepsis, dementia) comorbidities were included in the analysis.

In-hospital outcomes: Length of stay and mortality

Length of stay (days) was calculated from SDO. Furthermore, we identified patients who died during their hospitalization.

Statistical analysis

Data were analysed with Statistical Package for the Social Sciences SPSS® 20.0 (IBM Corp., Armonk, NY).

Categorical variables were presented as frequencies and percentages, while continuous variables as means with standard deviations.

Differences in mean values between groups were compared by Wilcoxon rank-sum test or Mann–Whitney U test non-parametric Wilcoxon test.

We assessed the association between comorbidities and duration of hospitalization (length of stay) via a multivariable regression analysis model.

Multivariate logistic regression was used to assess the association between comorbidities and in-hospital mortality. Zero non-cardiac comorbidities also served as the reference group for these analyses.

All statistical tests were two-sided. *P*-values < 0.05 were considered significant.

Results

Cohort characteristics

Over the six-year observation time, a total of 12,435 hospitalizations (6146 female, 6289 male) occurred in the Internal Medicine Unit. Of those, 1481 (or 11.9%)

patients presented a diagnosis of HF. Their mean age was 82.3 ± 9.3 years. More specifically, 610 patients (41.2% of those with HF) had HFp and 871 (58.8%) had HFs.

Patients with zero comorbidities included 27.2% of hospitalized patients without HF, followed by 37.5% with one comorbidity, 23.7% with two comorbidities, 9.0% with three comorbidities, and 2.6% with four or more comorbidities. The corresponding picture for HF patients was 13.7% with zero comorbidities, followed by 35.5% with one comorbidity, 30.0% with two comorbidities, 15.4% with three comorbidities, and 5.4% with four or more comorbidities (Fig. 1).

A greater prevalence of multiple comorbidities was observed in patients with HFs as compared to those with HFp: for example, 25.8% of HFs patients had three or more comorbidities as compared to 13.7% of HFp patients (Fig. 1).

Occurrence of cardiac and non-cardiac comorbidity

HF hospitalized patients with zero cardiac comorbidities were 55.2%, followed by 31.7% with one cardiac comorbidity, 10.9% with two cardiac comorbidities, and 2.2% with three or more cardiac comorbidities (Fig. 2).

The corresponding picture for non-cardiac comorbidities was 23.4% with zero non-cardiac comorbidities, followed by 44.1% with one non-cardiac comorbidity, 20.6% with two non-cardiac comorbidities, and 5.9% with three or more non-cardiac comorbidities (Fig. 2).

Patients with HFp had more cardiac comorbidities than those with HFs, who had at least one non-cardiac comorbidity in 84.7% of cases as compared to 50.3% in HFp.

Atrial fibrillation was the most prevalent cardiac comorbidity (25.6%) in HF patients, followed by hypertension (17.0%), diabetes mellitus (9.9%), and prevalent

coronary heart disease (7.9%) (Table 1). Respiratory failure and pneumonia were the most prevalent non-cardiac comorbidity within HF population (38.9%), followed by kidney disease (27.9%), anemia (15.5%), sepsis (8.7%), and dementia (4.7%) (Table 1).

Atrial fibrillation was more common in HFp (31.0% versus 21.7%), while respiratory failure or pneumonia (55.0% versus 15.9%) and sepsis (14.0% versus 1.2%) were more common in HFs.

The burden of cardiac and non-cardiac comorbidities on length of stay

The number of comorbidities was associated with the in-hospital length of stay. As illustrated in Fig. 3, the average length of stay progressively increased in association with the number of comorbidities from 7.6 ± 0.5 days in subjects with no comorbidity to 13.9 ± 1.5 days in subjects with 4+ comorbidities ($p < 0.0001$).

Interestingly, the length of stay was greater in HFs than in HFp patients, at any level of comorbidity.

Multiple regression analyses, controlling for age and sex, confirmed this observation (number of comorbidities: beta coefficient 1.41 ± 0.22 , $p < 0.0001$). It is noteworthy that, after controlling for age and sex, only non-cardiac comorbidities remained significantly associated with an increased duration of hospitalization (number of non-cardiac comorbidity: beta coefficient 2.86 ± 0.27 , $p < 0.0001$).

The burden of cardiac and non-cardiac comorbidities on in-hospital mortality

No significant linear correlation was found between in-hospital mortality and length of stay. Rather, the association between in-hospital mortality and length of stay showed

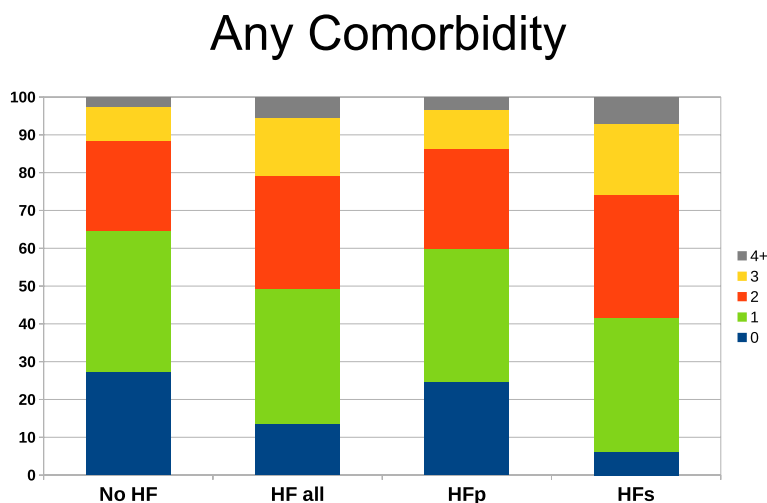


Fig. 1 Distribution of overall comorbidities in hospitalized patients with or without HF (left columns), and because of HFp or with HFs (right columns)

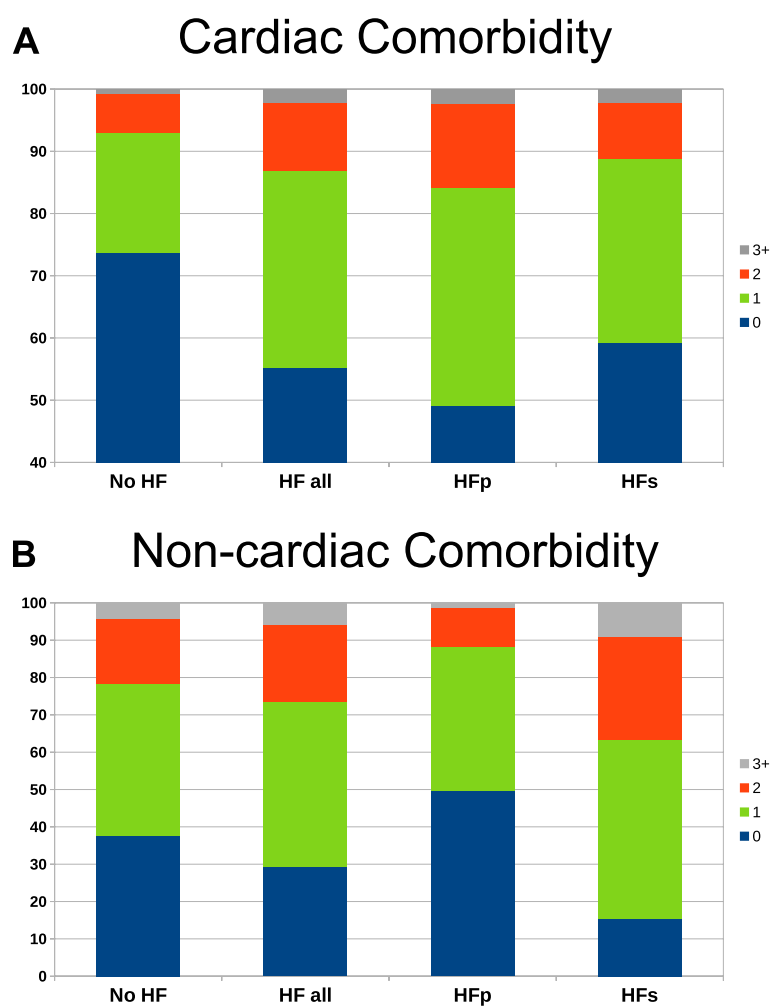


Fig. 2 Distribution of the number of cardiac (top panel) and non-cardiac (bottom panel) comorbidities

Table 1 Prevalence of specific cardiac and non-cardiac comorbidities in the study population

	No HF	HF all	<i>p</i> value	HFp	HFp	<i>p</i> value
Cardiac						
Atrial fibrillation	6.6	25.6	0.000	31.5	21.7	0.000
Hypertension	14.0	17.0	0.002	17.9	16.3	0.429
Diabetes Mellitus	10.5	9.9	0.505	10.3	9.5	0.665
CHD	3.0	7.9	0.000	9.7	6.5	0.027
Non-cardiac						
Respiratory Failure + Pneumonia	21.3	38.9	0.000	15.9	54.9	0.000
Kidney Disease	12.8	27.9	0.000	25.3	29.7	0.058
Anemia	18.3	15.6	0.010	13.0	17.4	0.022
Sepsis	10.4	8.7	0.043	1.2	14.0	0.000
Dementia	4.7	4.7	0.992	4.7	4.7	0.916

CHD Coronary Heart Disease

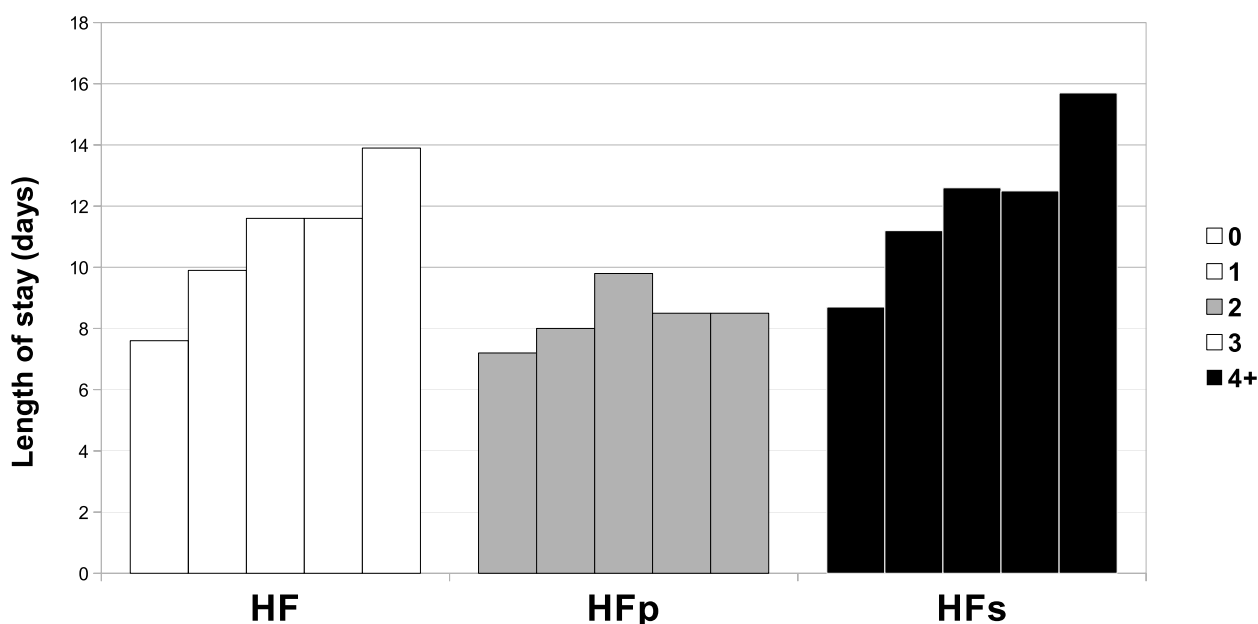


Fig. 3 Association between the number of comorbidities and the length of stay in hospital in HF patients

a tendency toward a J-shaped relationship (Supplemental Fig. 1) – possibly reflecting early death upon admission.

In-hospital mortality was associated with the number of comorbidities: it was 4.4% in HF patients with zero comorbidities, increased to 13.7% in HF patients with one comorbidity, 18.9% with two comorbidities, 21.5% with three comorbidities, and 23.8% with four or more comorbidities (Fig. 4). In-hospital mortality was similar in HFcs and in HFp patients if they presented zero or one comorbidity; it was dramatically greater in HFcs than in HFp patients with two or more comorbidities (Fig. 4).

Multivariable logistic regression analyses, controlling for age, sex, and length of stay, revealed that the number of comorbidities is associated with significantly greater odds of in-hospital mortality (adjusted OR 1.42, 95% CI 1.25–1.62; $p < 0.0001$). The impact of comorbidity on in-hospital mortality appeared attributable to non-cardiac (adjusted OR 1.90, 95% CI 1.60–2.23; $p < 0.0001$) but not to cardiac comorbidity in HF patients (adjusted OR 0.97, 95% CI 0.80–1.18; $p = 0.76$).

Having two comorbidities was associated with six-fold higher odds of in-hospital mortality; the odds did not further increase with a greater number of comorbidities. Of note, as illustrated in Table 2, the increase in the number of non-cardiac—but not in the number of cardiac—comorbidities resulted in greater mortality in HF patients.

Discussion

The main findings of the present study were as follows: (i) HF represents a common condition (12%) in patients hospitalized in Internal Medicine wards; (ii) only 44% of

HF patients are hospitalized because of acute decompensation; (iii) in HF patients, the prevalence of 0, 1, 2, 3, ≥ 4 comorbidities was 13.7%, 35.5%, 30.0%, 15.4%, and 5.4%, respectively; (iv) non-cardiac comorbidities were associated with longer duration of hospitalization and with higher rates of in-hospital mortality.

HF prevalence is increasing, both in the general population and among hospitalized patients, as a facet of improved survival after acute coronary syndrome [2, 8]. Consequently, older subjects present a greater prevalence of HF (7%–11%) than the younger population [1, 2]. Despite the advent of new guideline-recommended treatments for HF, known to reduce hospitalization, mortality from HF has increased in the USA in the last decade [9].

Although most studies describe HF patients admitted to and followed by Cardiology units, in the real-world a considerable proportion of HF patients are admitted to and followed up by Internal Medicine and Geriatrics units [3]. Additionally, a growing older population of HF patients faces multimorbidity, which also exposes them to potentially inappropriate medical prescription [10]. We observed that multiple comorbidities are far more common in HF than in non-HF patients (twice concerning the presence of ≥ 3 comorbidities). The presence of ≥ 2 non-cardiac comorbidities is two-fold more common than the presence of ≥ 2 cardiac comorbidities in older HF patients. Non-cardiac comorbidities have been associated with a greater risk of hospitalization in chronic HF patients with reduced ejection fraction [11, 12] as well as with increased mortality [13, 14]. Our study adds to these observations that non-cardiac

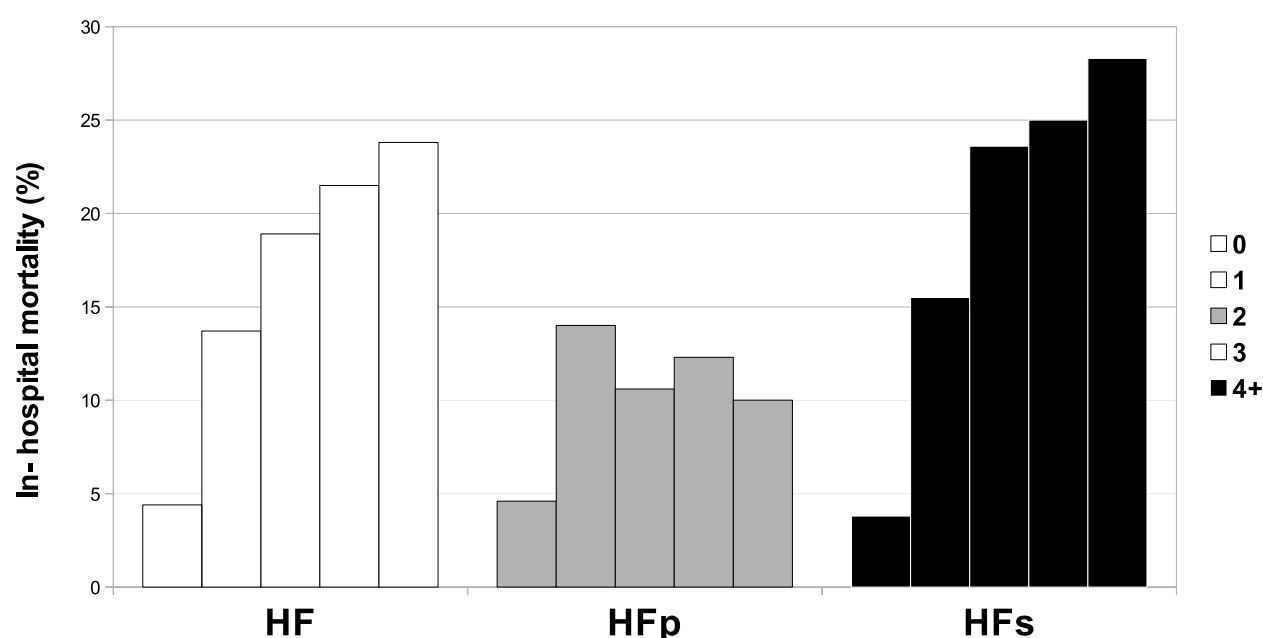


Fig. 4 Association between the number of comorbidities and in-hospital mortality in HF patients

Table 2 Odds of in-hospital mortality with increasing number of overall, cardiac, and non-cardiac comorbidities in HF patients

Comorbidity (n)	Overall		Cardiac		Non-cardiac	
	OR	95% CI	OR	95% CI	OR	95% CI
0 (ref)	--		--		--	
1	2.87	(1.19–6.96)	0.97	(0.71–1.33)	2.36	(1.53–3.64)
2	6.04	(2.58–14.15)	0.68	(0.48–1.16)	3.93	(2.46–6.23)
3+	6.21	(2.56–14.96)	0.61	(0.21–1.80)	7.58	(4.25–13.54)
	$P < 0.0001$		$P = 0.44$		$P < 0.0001$	

– but not cardiac—comorbidities were associated with twofold greater odds of in-hospital mortality and longer hospitalization.

Characterizing co-morbidity with high prevalence in hospitalized HF patients and elucidating their selective impact on in-hospital outcome may improve risk stratification of HF patients, showing potential treatments and interventions and better understanding of underlying mechanisms [15, 16]. All together, these findings underline once more that about half of hospitalizations occur in *patients with HF* rather than *because of HF*, i.e. because of acute HF decompensation. Of note, at any level of comorbidity the length of stay was greater in HFcs than in HFp patients. Factors underlying this observation have not been adequately characterized. It is likely that non-cardiac comorbidities impact on optimal innovative medication titration) [17, 18] and lead to a greater occurrence of side effects concerning the quality of life of older HF patients (particularly hypotension,

and medication-medication or medication-disease interactions) [19].

Novel risk stratification algorithms and multidisciplinary models of care will improve the management of older HF patients with cardiac and non-cardiac comorbidities.

The impact of comorbidities on HF patients is such that ESC 2021 Guidelines encompassed a large section on both cardiac and non-cardiac comorbidities, highlighting their prevalence and their impact on specific dilemmas in the treatment [20]. Additionally, ESC Guidelines foster the assessment of frailty in patients with HF. Comprehensive multidimensional assessment exploring the four domains of clinical, psycho-cognitive, functional, and social is promoted to postpone functional decline and reduce hospitalization in older HF patients [21]. A similar recommendation had also been proposed by the American Heart Association [22] and the American College of Cardiology [23].

Limitations and strengths

The potential limitations of this study merit consideration. First, it is a retrospective study including patients admitted to internal medicine units, which introduces a selection bias. Second, Sardinia Region still adopts ICD-9 codes to code primary and secondary diagnoses. This might have resulted in different estimates of HF cases if ICD-10 codes—released on October 1, 2015 – had been adopted. However, the aim of the present study was certainly not to provide an exact estimate of HF hospitalization rate. Rather, it was to highlight patterns of comorbidities in HF patients hospitalized in an Internal Medicine Unit.

A potential additional limitation was the method of comorbidity identification. Hospital Discharge Records allow for the identification of comorbidities that impact healthcare resource utilization during hospitalization. However, this approach is less accurate in detecting cardiovascular disorders common in HF patients, such as mitral or aortic valvular diseases and atrial flutter. In fact, the reported occurrence of atrial fibrillation or hypertension is much lower than commonly reported in HF patients from registries and/or clinical trials. Last but not least, the use of so called “administrative data” does not allow access to clinical profiles of included patients (ejection fraction category, treatment and its adherence to Guidelines, severity of comorbidities).

The present study has a major strength: it reports data from hospitalized HF patients in an Internal Medicine Unit. They constitute a growing proportion of HF patients, often older and more complex as compared to HF patients admitted to Cardiology Units [24] commonly included in current registries.

Conclusions

The present study recalls attention to the role of non-cardiac comorbidities in predicting in-hospital outcome in HF patients admitted to an internal medicine unit – where HF is present in 11% of hospitalized patients.

Since the hospital admission of these very old HF patients with several non-cardiac comorbidities will continue to increase, it is imperative that we optimize the management of non-cardiovascular conditions to improve outcomes and reduce early in-hospital mortality – accomplishing the recommendation of ESC Guidelines “In addition to optimizing medical and device therapies for HF, attention should also be given to how HF care is delivered”, i.e. implementing the models of care and disseminating a multidisciplinary management of older HF patients.

Improved management of HF patients in the pre-discharge and early post-discharge phase after hospitalization will be critical to reduce the burden of

re-hospitalization and increase the time spent at home [21].

Future studies are encouraged to adopt a multidisciplinary approach to the growing older HF patients, which will simplify the identification of more risky phenotypes and the early identification of preventable factors precipitating hospitalization.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12877-025-06002-8>.

Supplementary Material 1.

Supplementary Material 2.

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None.

Authors' contributions

Conceptualization, AScuteri Methodology, VM, EB, AS, CS, AScuteri Data Curation, AC Formal Analysis, EB, AScuteri Writing – Original Draft Preparation, VM, AScuteri Writing – Review & Editing, VM, EB, AS, AC.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of University Hospital of Cagliari (Azienda Ospedaliera Universitaria Cagliari) (PROT. NP/2023/949 on March 1 st, 2023). The IRB waived the need for participant consent, consistent with national regulations deeming it unnecessary.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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