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HF progression among outpatients with HF in a community setting☆

Annamaria Iorio [a,b], Federico Rea [c,d,*], Giulia Barbati [e,c], Arjuna Scagnetto [e], Elena Peruzzi [f], Agnese Garavaglia [f], Giovanni Corrao [c,d], Gianfranco Sinagra [b], Andrea Di Lenarda [g]

[a] Cardiology Unit, Papa Giovanni XXIII Hospital Bergamo, Italy
[b] Cardiovascular Department, University Hospital and Health Services, Trieste, Italy
[c] National Centre for Healthcare Research & Pharmacoepidemiology, at the University of Milano-Bicocca, Milan, Italy
[d] Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milano, Italy
[e] Biostatistics Unit, Department of Medical Sciences, University of Trieste, Trieste, Italy
[f] Novartis Farma, Italy
[g] Cardiovascular Center, University Hospital and Health Services, Trieste, Italy

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ABSTRACT

Background: Incidence and prognostic impact of heart failure (HF) progression has been not well addressed.
Methods: From 2009 until 2015, consecutive ambulatory HF patients were recruited. HF progression was defined by the presence of at least two of the following criteria: step up of ≥1 New York Heart Association (NYHA) class; decrease LVEF ≥ 10 points; association of diuretics or increase ≥ 50% of furosemide dosage, or HF hospitalization.
Results: 2528 met study criteria (mean age 76; 42% women). Of these, 48% had ischemic heart disease, 18% patients with LVEF ≤ 35%. During a median follow-up of 2.4 years, overall mortality was 31% (95% CI: 29%–33%), whereas rate of HF progression or death was 57% (95% CI: 55%–59%). The 4-year incidence of HF progression was 39% (95% CI: 37%–41%) whereas the competing mortality rate was 18% (95% CI: 16%–19%). Rates of HF progression and death were higher in HF patients with LVEF ≤ 35% vs >35% (HF progression: 42% vs 38%, $p = 0.012$; death as a competing risk: 22% vs 17%, $p = 0.002$). HF progression identified HF patients with a worse survival (HR = 3.16, 95% CI: 2.75–3.72). In cause-specific Cox models, age, previous HF hospitalization, chronic obstructive pulmonary disease, chronic kidney disease, anemia, sex, LVEF ≤ 35% emerged as prognostic factors of HF progression.
Conclusions: Among outpatients with HF, at 4 years 39% presented a HF progression, while 18% died before any sign of HF progression. This trend was higher in patients with LVEF ≤ 35%. These findings may have implications for healthcare planning and resource allocation.

1. Introduction

Heart failure (HF) is a major and growing public health issue, characterized by steep morbidity and mortality rates, and high costs [1]. The prevalence of HF is estimated to be 38 million people worldwide, a trend that is increasing, due to an aging population [1]. Despite the advances in the understanding of the pathophysiology of chronic HF and the improvements in its therapy, HF mortality and morbidity rates remain high [2,3].

A substantial proportion of this poor outcome appears to be mainly related to HF progression [3,4]. Several studies describe the variables used to identify HF patients at high mortality risk [5,6], however there is still inadequate information available about HF patients with an increased risk of disease progression. Indeed, one relevant gap is represented by the lack of data on the rates and risk factors for HF progression among patients with stable HF. This information would be important for the HF referral centers, in particular for an optimal management of the healthcare resources. In addition, a better characterization of the prognostic factors of worsening HF may help to prevent death from progressive HF, and facilitate the identification of the best strategies for these patients. In this regard, a characterization is of more specific interest if it considers patients with left ventricular ejection fraction (LVEF) ≤ 35%, a subset of the HF population which is often eligible for advanced HF therapies and in which disease-modifying drugs have been tested, showing to be effective.

Therefore, the aim of this study was to estimate the rate of HF progression in HF patients receiving outpatient care, and to evaluate risk

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* Corresponding author at: Dipartimento di Statistica e Metodi Quantitativi, Sezione di Biostatistica, Epidemiologia e Sanità Pubblica, Università degli Studi di Milano-Bicocca, Via Bicocca degli Arcimboldi, 8, Edificio U7, 20126 Milano, Italy.
E-mail address: f.rea@campus.unimib.it (F. Rea).

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factors associated with HF progression. We also investigated the trend of HF progression according to LVEF, taking into account death as a competing risk.

2. Methods

2.1. Study setting

Between November 2009 and December 2015, consecutive HF patients who attended the Outpatient Clinics of the Cardiovascular Center and Cardiovascular Department of Trieste (northeast of Italy) were enrolled. This public health system area is largely inclusive (87.1% of all cardiovascular outpatient clinical evaluations), thus facilitating a population-based cardiovascular research.

The index visit was considered to be the first evaluation with HF diagnosis and an available LVEF echocardiographic evaluation linked to the visit, and a coded value of NYHA class. The pre-period study window ranged from 2004 to 2009, in order to retrieve all the hospitalizations during the five years preceding the index visit for each member of the study cohort. The patients were followed at Cardiovascular Center of Trieste that indeed is a dedicated HF clinical center. The end of the follow-up was set for December 31, 2016.

2.2. Data sources

To select patients and clinical variables, coding data derived from the *E*-chart of Outpatient Clinic (Cardionet®) were utilized. The E-Chart includes medical information collected by cardiologists during their routine clinical practice, including patients' history, cardiovascular diagnosis and comorbidities in coded form, laboratory tests, procedures, and drugs prescriptions, sorted by means of electronic indexes. The *E*-Chart also allows the access to folders which include clinic consultations, emergency department visits, other instrumental procedures – or laboratory analyses – and hospitalizations. Medical records are routinely reviewed by clinicians during each clinical evaluation, in order to update medical history, diagnostic procedures, and treatment. Additionally, the *E*-Chart is included into a regional Data Warehouse that contains other databases, such as the Registry of Births and Deaths, Hospital Discharge, the District Healthcare Services (intermediate and home care), Public Laboratories and Public Drug Distribution System. This integrated database established the Observatory of Cardiovascular Disease. Using this integrated database, we were able to enhance the data of the *E*-chart with the discharge codes of previous hospitalizations (within the prior 5 years), based on the standard nomenclature of the International Classification of Diseases-Ninth Revision (ICD-9CM), available laboratory data, interventional procedures, and treatments purchased in affiliated pharmacies. Specifically, in order to link HF patients to their ECG and Echo values, as well as laboratory parameters, the following temporal rule was adopted: if a procedure or laboratory exam had been recorded exactly on the same day of the visit, it was linked (note: 86% and 30% of the ECG and ECHO values, respectively, were recorded in the same day of the visit); otherwise, a previous procedure or laboratory exam was searched in the system with a maximum time interval of 6 months before the visit or – last option – within 3 months after the visit (note: this last occurrence happened only in 3% and 6% of the visits, respectively). To minimize the intra-observer variability, all echocardiographic examinations are performed by board-certified cardiologists with >10 years of clinical experience in performing and interpreting echocardiographic examinations based on a pre-defined protocol for the performance of echocardiographic exam, its storage, review and measurement. Specifically, inter- and intra-observer variability of echocardiographic measurements were assessed by randomly selecting a sample of 26 patients (three different operators, double evaluation each). This allowed to achieve 80% power to detect an intra-class correlation coefficient (ICC) of 0.8 under the null hypothesis of ICC = 0.60, by using an F-test at a significance level of 0.05. The intra-observer variability was evaluated by computing ICC between repeated measures of the same operator. For all echocardiographic parameters, the ICC for inter-observer reproducibility were ≥0.80, whereas ICC for intra-observer reproducibility were ≥0.90 (all $p < 0.001$). Based on ICD-9CM codes of previous hospitalizations, integrated with diagnoses and laboratory values at the index visit, the Charlson Comorbidity Index was calculated [7,8]; in addition, some of the non-cardiac comorbidities not included in the Charlson Comorbidity Index were also considered, based on their important prognostic role in patients with HF [9]. Paroxysmal, persistent or permanent type of atrial fibrillation was considered together if documented in the history or at enrolment ECG. Body mass index was calculated as the height-to-weight ratio (kg/m^2), and obesity was defined as a body mass index ≥ 30 kg/m^2. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg and/or a diastolic blood pressure ≥ 90 mm Hg at the time of enrolment, and/or as a history of hypertension [9]. Renal failure was defined as an estimated glomerular filtration rate < 60 mL/min/1.73 m^2, calculated using the CKD-EPI formula [10]. Anemia was defined according to World Health Organization criteria (Hb < 8.1 mmol/L in men and 7.5 mmol/L in women) [11]. With regard to the pharmacological therapy, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and or beta-blockers and mineralocorticoid receptor antagonists were considered evidence-based drugs. Adherence to the prescribed evidence-based HF therapy (i.e. angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and or beta-blockers, and/or MRAs) was evaluated during the entire follow-up. Patients were considered adherent if they observed at least 75% of their treatment schedule with all the evidence-based drugs prescribed by the cardiologist at the index visit (and updated at subsequent visits). The institutional ethical board approved the study, and an informed consent was obtained, in line with the hospital administration policies of the institutional review board.

2.3. Study population

All HF consecutive patients included in the E-Chart were recruited. For the identification of the HF patients, the following steps were taken. First, a search in the electronic medical records, using appropriate keywords (Heart Failure, Chronic Heart Failure, Systolic Heart Failure, Diastolic Heart Failure) to select patients with HF-related clinical findings. In order to avoid any diagnostic underestimation, data from the medical E-chart were combined with the discharge codes of any previous hospital access (based on the standard nomenclature of the ICD-9 CM) and/or interventional procedures for HF patients (i.e. ICD implantation). Subsequently, prospective cases were manually reviewed by clinicians, to validate the diagnosis of HF using the criteria established in 2012 by the European Cardiology Society, and confirmed by their most recent guidelines of 2016 [12,13]. Patients were divided into two groups, according to LVEF (LVEF > 35% and LVEF ≤ 35%). HF patients without any simultaneously available value of LVEF or NYHA class, as measured within the enrollment period considered, were excluded from the analysis.

2.4. Definition of HF progression

HF progression was defined as a hospital admission for HF or a clinical worsening due to the presence of at least two of the following criteria compared to the levels observed at the index visit: (i) a ≥1 increase in NYHA class; (ii) a ≥10 points decrease in LVEF; (iii) a ≥50% (and in any case > 25 mg) increase in furosemide dosage or a new combination of diuretics (thiazides + furosemide), whatever came first. Clinical HF progression was defined considering only the clinical criteria (i.e. excluding HF hospitalization).

2.5. Endpoints

The primary endpoint was the HF progression in a time-to-event analysis, accounting for the competing risk of death from any cause. The secondary endpoint was the composite endpoint of death and HF progression.

2.6. Statistical analysis

Descriptive statistics for all baseline variables were produced for the total population and were compared between groups, stratified by LVEF categories at the index visit and by HF progression during follow-up. Summary statistics of the clinical and instrumental variables at the index visit were expressed as median (interquartile range, IQR), or counts and percentage, as appropriate. Comparisons between groups for continuous variables were performed with the Mann-Whitney test, according to the parameter distribution. The Chi-square or Fisher exact test was calculated for categorical variables. Cumulative incidence curves for the composite end-point of HF progression or death were estimated with the Kaplan-Meier method, stratified by LVEF groups and compared by means of the Log-Rank test. Cumulative incidence curves for the primary end-point of HF progression were estimated using the competing risk approach, considering all-cause death as a competing risk, both for the total population and for groups stratified by LVEF. Appropriate K-sample tests for comparing the cumulative incidence of a competing risk were calculated, in order to identify any differences among the groups [14]. For the primary endpoint of HF progression, univariable and multivariable cause-specific Cox regression models were estimated for the total population under study, censoring all-cause deaths. Univariable and multivariable standard Cox regression models were also estimated for the composite endpoint. For each candidate predictor at the index visit, unadjusted Hazard Ratios (HR) were calculated, and multivariable models were produced, based on the list of parameters significant at univariable analysis and clinically relevant, identifying the subgroup of independent predictors in a full-model approach. The proportional hazard assumption for the time-fixed covariates was tested by means of Schoenfeld residuals [15]. A time-dependent variable was also included in both the cause-specific and the standard Cox model, since compliance with the HF therapy ("Patient adherence") changed during the follow-up. As a supplementary analysis, the impact of developing clinical HF progression (i.e. not considering HF hospitalization) on the risk of death during the follow-up was also evaluated, in a time-dependent Cox model. The "extended" Kaplan-Meier approach was used to depict the effect of the time-dependent clinical HF progression on death [16].

3. Results

A total of 3424 consecutive subjects were identified as HF patients. Of these, 896 (26%) were excluded because the LVEF value or the NYHA class were not available. Hence, a total of 2528 (74%) patients met the selection criteria of the study. Patients excluded from the analysis because of missing LVEF values or NYHA class were much older (median age 82), predominantly females and lower rate of ischemic heart disease (Supplementary Table 1).

The clinical characteristics of the whole selected HF population, as well as those of the groups sorted by HF progression, are shown in Table 1. Overall, the median age was 76, 42% were female, and a significant background prevalence of ischemic heart disease, hypertension and history of atrial fibrillation.

Table 1
Clinical characteristics of the whole HF population as well as according to HF progression.

Variable	Study cohort (2528)	HF progression		p Value
		No (1487, 59%)	Yes (1041, 41%)	
Age, median (IQR), years	76 (70–82)	76 (69–82)	76 (70–82)	0.406
Gender, male, n. (%)	1470 (58)	836 (56)	634 (61)	0.019
NYHA III-IV, n. (%)	338 (13)	226 (15)	112 (11)	0.001
Body mass index, median (IQR), kg\m^2	26 (24–30)	26 (24–30)	26 (24–30)	0.653
Body mass index < 20, median (IQR), kg\m^2	133 (5)	78 (5)	55 (5)	0.656
20 ≤ Body mass index ≤ 25, median (IQR), kg\m^2	832 (33)	500 (34)	332 (32)	
Body mass index > 25, median (IQR), kg\m^2	1563 (62)	909 (61)	654 (63)	
Systolic blood pressure, median (IQR), mm Hg	130 (120–145)	130 (120–145)	130 (120–145)	0.970
Heart Rate, median (IQR), beats/min	71 (63–81)	71 (64–82)	70 (62–80)	0.128
Heart Rate < 70 bpm, n. (%)	1049 (41)	605 (41)	444 (43)	0.331
Left ventricular ejection fraction, median (IQR), %	54 (40–63)	54 (41–63)	53 (39–63)	0.321
eGFR, median (IQR), mL/min/1.73 m^2	62 (45–77)	62 (45–79)	60 (43–76)	0.035
eGFR < 30 mL/min/1.73 m^2, n. (%)	213 (10)	126 (10)	87 (9)	0.037
Sodium, median (IQR), mmol/L	140 (137–141)	140 (137–141)	140 (137–142)	0.101
Potassium, median (IQR), mmol/L	4.2 (3.6–4.6)	4.2 (3.6–4.6)	4.2 (3.6–4.6)	0.517
Haemoglobin, median (IQR), mmol/L	8.0 (7.1–8.8)	8.0 (7.2–8.9)	7.9 (7.1–8.8)	0.113
Total cholesterol, median (IQR), mmol/L	4.1 (3.1–5.1)	4.1 (3.1–5.1)	4.1 (3.2–5.0)	0.922
LDL cholesterol, median (IQR), mmol/L	2.5 (1.9–3.3)	2.6 (2.0–3.3)	2.5 (1.9–3.1)	0.005
Ischemic disease, n. (%)	1209 (48)	658 (44)	551 (53)	<0.001
Atrial Fibrillation, n. (%)	1341 (53)	762 (51)	579 (56)	0.030
Hypertension, n. (%)	2026 (80)	1173 (79)	853 (82)	0.058
Obesity, n. (%)	587 (23)	344 (23)	243 (23)	0.902
Diabetes Mellitus, n. (%)	975 (39)	530 (36)	445 (43)	<0.001
Peripheral vascular disease, n. (%)	674 (27)	363 (24)	311 (30)	0.002
Chronic Kidney disease, n. (%)	1317 (52)	702 (47)	615 (59)	<0.001
COPD, n. (%)	846 (34)	449 (30)	397 (38)	<0.001
Anemia, n. (%)	981 (39)	532 (36)	449 (43)	<0.001
Liver Disease, n. (%)	123 (5)	66 (4)	57 (5)	0.233
Cancer, n. (%)	353 (14)	203 (14)	150 (14)	0.589
Dementia, n. (%)	37 (2)	23 (2)	14 (1)	0.677
Rheumatological disorder, n. (%)	117 (5)	58 (4)	59 (6)	0.037
Peptic ulcer disease, n. (%)	82 (3)	42 (3)	40 (4)	0.155
Cerebrovascular accident, n. (%)	375 (15)	196 (13)	179 (17)	0.005
Charlson Index ≥ 3, n. (%)	1940 (77)	1071 (72)	869 (83)	<0.001
Previous HF hospitalization, n. (%)	847 (33)	452 (30)	395 (38)	<0.001
ICD	125 (5)	68 (5)	57 (5)	0.303
CRT	38 (2)	22 (1)	16 (2)	0.907
Number of cardiovascular drugs ≥ 5, n. (%)	987 (39)	545 (37)	442 (42)	0.003
Number of drugs ≥ 5, n. (%)	1682 (69)	939 (66)	743 (74)	<0.001

AF: Atrial Fibrillation; COPD: Chronic Obstructive Pulmonary Disease; CRT: Cardiac Resynchronization Therapy; eGFR: estimated Glomerular Filtration Rate; HF: Heart Failure; ICD: Implantable Cardioverter Defibrillator; IQR: Interquartile Range; LDL: Low Density Lipoprotein; NYHA: New York Heart Association.

Significant differences between patients with HF progression and their counterparts were observed, with respect to demographics, cardiac comorbidities, aetiology and pharmacological treatment. Patients with HF progression were more often males, with a lower mean of LVEF, but a higher prevalence of atrial fibrillation in the history and ischemic heart disease, along with a higher burden of non-cardiac comorbidities and previous HF hospitalizations. Consistently with the higher rates of cardiac and non-cardiac comorbidities, patients with HF progression had a higher number of prescriptions of cardiovascular and non-cardiovascular drugs.

HF hospitalization was the most common predefined HF progression criterion: 65% of patients who experienced HF progression was hospitalized for HF, whereas 28%, 25% and 11% had a worsening of the NYHA class, the need to increase diuretic, decrease of LVEF value, respectively (note: the sum of these figures was not limited to 100% because two criteria were needed to defined the progression).

A comparison between LVEF groups (LVEF > 35% vs LVEF ≤ 35%) revealed that patients with LVEF ≤ 35% were younger, with a higher prevalence of males, more advanced HF symptoms and ischemic heart disease (Supplementary Table 2). In addition, these patients were more likely to have at least one previous HF hospitalization and a higher number of CV pharmacological prescriptions. Conversely, non-cardiac comorbidities had a similar prevalence between the two groups, with the exception of renal disease, which was more frequent in patients with LVEF ≤ 35%. Patients with LVEF ≤ 35% had a worse prognosis, with a higher risk for all-cause mortality and significantly higher rates of HF hospitalization, but a lower rates of non-cardiovascular hospitalization.

The median follow-up was 2.4 years. More than 40% of patients had at least 3 years of follow-up, and 79% at least 1 year of follow-up.

After accounting for competing mortality, the 4-year incidence of HF progression (primary endpoint) was 39% (95% CI: 37% to 41%), whereas clinical HF progression was 18% (95% CI: 16% to 19%). Of note, 18% (95% CI: 16% to 19%) of patients died before progressing to HF (competing mortality rate) (Fig. 1 panel A).

The incidence rates of HF progression and death were significantly higher in HF patients with LVEF ≤ 35% than those patients with LVEF > 35% (HF progression: 42% vs 38%, respectively, $p = 0.012$; death: 22% vs 17%, respectively, $p = 0.002$) (Fig. 1 panel B).

This trend was considerable high at early follow-up term, particularly in those patients with LVEF ≤ 35% (1-year HF progression: 20%; death: 11%).

Overall, there was a higher rate of HF progression at 4-year in older patients (age > 75) than in younger counterpart (age ≤ 75) (42% vs 36%, $p < 0.001$), mainly due to hospitalization (39% vs 27%, $p < 0.001$).

The 4-year rate of the composite endpoint of HF progression or death (secondary endpoint) was 57% (95% CI: 55% to 59%) (Fig. 2 panel A). This rate was confirmed to be higher in patients with LVEF ≤ 35% than patients with LVEF > 35% (65% vs 55%, respectively, $p < 0.001$) (Fig. 2 panel B). When mortality was evaluated as a global non-competing event (i.e. considering all deaths before or after HF progression), the rate was 31%

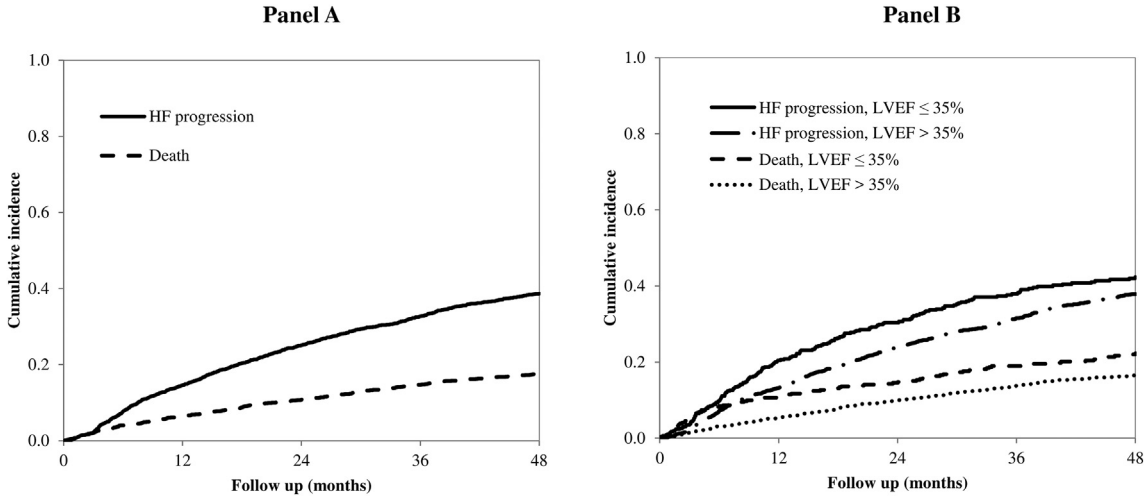

Fig. 1. Cumulative incidence of HF progression and mortality as a competing event among the whole cohort (Panel A) as well as according to LVEF (Panel B). HF: Heart failure; LVEF: Left ventricular ejection fraction.

(95% CI: 29% to 33%) in the overall population, and 40% (95% CI: 35% to 45%) vs 29% (95% CI: 27% to 31%) in the LVEF ≤ 35% and LVEF > 35% groups, respectively.

Again, the rate of composite events was notably high at 1-year (21%), particularly in those patients with LVEF ≤ 35% (31%).

3.1. HF progression and mortality

Overall, patients developing HF progression showed a worse survival (HR = 3.16; 95%, CI 2.75–3.62) (Fig. S1). Of note, also HF patients showing a "clinical" HF progression (excluding HF hospitalization) maintained a higher risk of death (HR = 1.94, 95% CI: 1.65–2.28). This latter trend occur similarly in patients with LVEF ≤ 35% (HR = 1.95, 95% CI, 1.36–2.78) and those patients with LVEF > 35% (HR = 1.93, 95% CI: 1.62–2.31) (Fig. S2). Additionally, we performed analysis according to HF types (HF with reduced ejection fraction (HFrEF) LVEF ≤ 50% vs HF with preserved ejection fraction (HFpEF); LVEF > 50%). Again, HF progression identify a poor prognosis irrespective from LVEF-HF type (HFrEF: HR = 3.22; 95%, CI 2.62–3.97 vs HFpEF: HR = 3.10; 95%, CI 2.59–3.72; p for interaction: 0.497) (Fig. S3).

3.2. Predictors of HF progression

In the Cox model for HF progression – including the clinical characteristics emerged from the univariable analysis – age, previous HF hospitalization, COPD, CKD, anemia, male gender, LVEF ≤ 35% emerged as independent prognostic risk factors (Table 2).

Interestingly, the same variables were confirmed to be independent risk factors for the composite endpoint with the addition of BMI < 20 kg\m^2 that showed an increased risk compared with those with 20 ≤ BMI ≤ 25 kg\m^2. Remarkably, patient adherence emerged as an independent protective factor for the composite endpoint (Table 2).

4. Discussion

Several studies have reported risk factors of mortality in ambulatory patients with HF [9,17–19]. Instead, we provided data for disease progression among this subset of patients. Although established arbitrarily, the criteria of HF progression – defined by a functional worsening of the NYHA class and the LVEF value, the need to increase the dose of the diuretic or HF hospitalizations – appeared to be a reliable tool to identify HF patients with a high probability of a poor prognosis. This may not surprise, since in HF patients these individual factors showed to be independently related to a poor prognosis. However, for the first time our findings highlight that the combination of these factors may be an effective tool to identify the progressive HF process.

Herein, a large, contemporary, community-based HF population was brought together. Interestingly, but not unexpectedly, our study cohort showed demographic and clinical differences compared to previous HF populations derived from trials and registry studies, whereas our findings are similar with previous epidemiological studies considering unselected HF populations [9,18,20–22]. In line with these studies, our population included elderly patients, a high proportion of females and a wide range of comorbidities.

In this clinical scenario, it was observed that, at 4 years of follow-up, 39% of outpatients with HF presented HF progression, despite receiving specialized and optimized care in an HF center, within a dedicated HF program and a structured follow-up. In line with previous observations [23–25] HF hospitalizations were common with a significant impact on adverse prognosis. Even though HF hospitalization presented an high contribution for identifying of HF progression, we found that the clinical HF progression was also common (18%), and it was associated with an increased risk of subsequent death. Hence, these data underline that focusing only on HF hospitalizations, we can underestimate the frequency of worsening and may fail to recognize other manifestations of worsening that may lead to adverse outcome in HF setting.

These findings are relevant to both clinical practice and the conduct of future clinical trials in HF. From a clinical practice perspective, our data may contribute to inform healthcare professionals as to which patients are most at risk of developing progression disease, thereby leading to a recommendation to intensify follow-up and tailor effective interventions in this subset of patients. On the other hand, in an era of uncertainty about how assessing the best goals of treatment in clinical trials for HF patients [26], our findings may support the use of the expanded composite end-point. Beyond HF hospitalization alone, the inclusion of episodes of outpatient intensification of diuretic therapy, worsening of clinical symptoms and reduced LVEF, in a composite outcome would increase the power to discriminate treatment effectiveness. In this sense, our data also reinforce the hypothesis supported by Okumura et al. [27] that in ambulatory setting the use of the expanded composite endpoint may have the potential to reduce sample size and duration of follow-up. In establishing the frequency and prognostic importance of the episodes of worsening in setting of outpatients with HF, Okumara et al. demonstrated that inclusion of episodes of outpatient intensification of therapy and treatment in emergency department added a modest but important number of events. Importantly, the authors recognized the need of expanded composite outcome that might be of use as an end point in future clinical trials, in subset of outpatients.

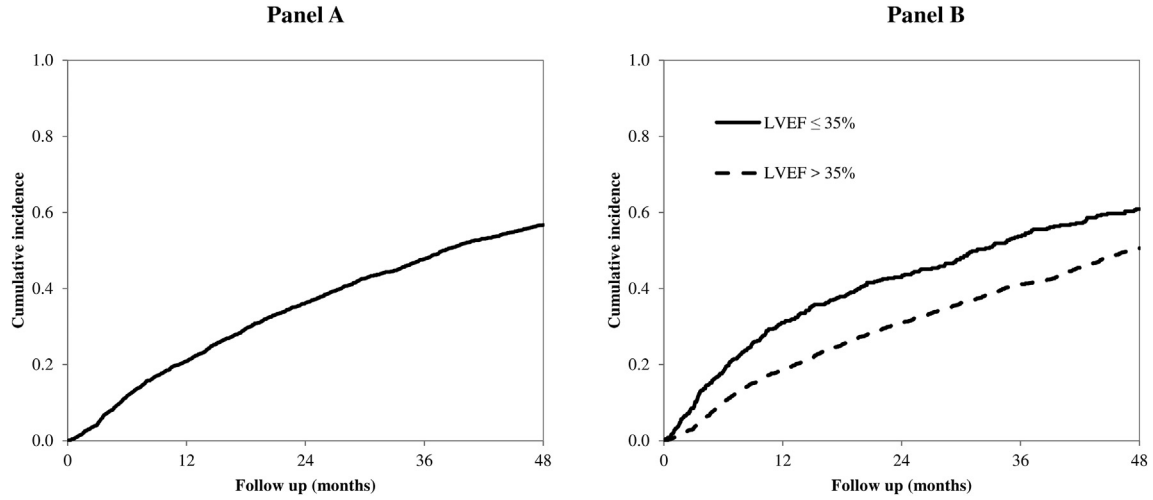

Fig. 2. Cumulative incidence of the composite endpoint of HF progression or death among the whole cohort (Panel A) as well as according to LVEF (Panel B). LVEF: Left ventricular ejection fraction.

Overall, our data confirm the gruesome fact that HF remains a disease with a severe prognosis also in stable HF outpatients. Particularly, a rate of all-cause mortality was high with mortality rate of 31% within 4-year and 8% within 1-year. These rates are higher than in the ESC HF Long-Term Registry [28], in which the 1-year all-cause mortality rate was 6.9%. Intriguingly, in the present HF population, within 4-years 18% of mortality occurred before HF progression. The high risk in this subgroup may be attributable in part to sudden cardiac death. Anyway, these observations highlight the need to improve risk stratification and treat intensively in HF patients before HF progression.

4.1. HF progression in patients with severely reduced LVEF

It is also worth noting that, in the cohort analyzed, patient with LVEF ≤ 35% had a worse prognosis with respect to their HF counterparts, thereby highlighting the still great importance of a further optimization of the evidence-based treatment in this HF setting, despite the significant progress made over the past 20 years [29]. Although it is not fully understood why some patients who had a period of stable HF enter in a progressive process of disease decline, the higher incidence of HF progression in this subset of patients may suggest that the neurohumoral mechanisms continue to play a critical role in mediating this decline [30]. In this sense, new agents capable of providing a more complete modulation of the neurohumoral dysfunction will be an important tool to slow the disease progression [31].

We are unaware of any other large study that assessed HF progression and compared the behavior between LVEF groups. Indeed, Kalogeropoulus et al. [3] estimated the rate of progression to Stage D among Stage C outpatients with reduced LVEF over 3 years of follow-up. They found that 12.2% of patients progressed to Stage D, with 25.1% of patients who had either progressed to Stage D or died. Although the authors identified with specific criteria the progression of HF patients, that study focused only on HF patients progressing to an advanced status. Our study, on the contrary, assessed the HF progression irrespective of any HF clinical status at baseline. Specifically, our data indicate that HF patients with clinical HF progression may have a poor survival prognosis, regardless of the HF status. In addition, unlike the data reported by Kalogeropoulus et al., the current analysis refers to a real-world setting, wherein patients are more representative of the typical patients seen in daily practice.

Table 2
Multivariable cause-specific Cox Model on the HF progression and composite outcome.

HF progression				
Parameter	HR	95% CI		p Value
Age	1.019	1.010	1.027	<0. 001
Sex (Male)	1.261	1.091	1.456	0.002
Previous HF hospitalization	1.302	1.125	1.507	<0.001
Chronic obstructive pulmonary disease	1.249	1.077	1.449	0.003
Chronic Kidney disease	1.288	1.111	1.492	0.001
Anemia	1.343	1.166	1.546	<0.001
Left ventricular ejection fraction ≤ 35%	1.318	1.107	1.568	0.002
Composite outcome (HF progression or death)				
Parameter	HR	95% CI		p value
Patient-adherence	0.823	0.729	0.929	0.002
Age	1.037	1.030	1.043	<0.001
Sex (Male)	1.351	1.213	1.505	<0.001
Body mass index, kg/m^2 < 20	1.306	1.051	1.624	0.016
20 ≤ Body mass index, kg/m^2 ≤ 25	Ref.			
Body mass index, kg/m^2 > 25	0.922	0.825	1.031	0.153
Previous HF hospitalization	1.279	1.148	1.425	<0.001
Chronic obstructive pulmonary disease	1.302	1.171	1.447	<0.001
Diabetes Mellitus	1.183	1.064	1.316	0.002
Chronic Kidney disease	1.217	1.093	1.356	0.004
Anemia	1.301	1.171	1.445	<0.001
Left ventricular ejection fraction ≤ 35%	1.340	1.178	1.525	<0.001

HR: Hazard Ratio; CI: Confidence Interval; HF: Heart Failure.

4.2. Predictors of HF progression

After years of focus on risk factor-related mortality in HF, an important gap emerged, due to the lack of identification of the risk factors for HF progression. In this sense, a deeper knowledge of the risk factors for disease progression would be an important support when communicating the prognosis to HF patients. Furthermore, a deeper understanding of the risk factor-related HF progression could have strong implications with regard to disease management programs, quality improvement initiatives. Among the estimated pool of known risk factors in HF patients, COPD, CKD, and anemia emerged as independent risk factors for progressive HF. The stimulating observation that the extracardiac disease predicts HF progression probably originates from the influence this condition has on the HF pathophysiology. Although the mechanisms by which these extracardiac conditions predict HF progression are not known, the published evidence about the impact of non-cardiac comorbidities on the adverse outcomes in the HF population [9,21,22,32,33] makes the correlation between these extracardiac conditions and progressive HF plausible. In addition, LVEF ≤ 35% was confirmed as an important prognostic risk factor for the progression of the disease, highlighting the need to intensify the research efforts, in

order to improve the outcomes for this subset of patients. These risk factors were confirmed as predictors also for competing mortality. Interestingly, adherence to therapy turned out to have a protective effect only when including mortality in the endpoint. This finding may be subject to several interpretations; however, the absence of a prognostic significance of the adherence to therapy with regard to HF progression might emphasize the important need to intensify HF treatment in order to control HF progression. However, the adherence to therapy emerged as independent protective factor for composite end-point. This trend was in agreement with previous observations where a poor adherence in HF setting was associated with a worse prognosis [34]. Also, lower BMI values increased the risk as reported in previous investigations [35].

4.3. Limitations

Although the criteria of HF clinical progression were established arbitrarily, disease progression is a continuous, therefore any threshold is also inherently arbitrary. However, the proposed criteria of HF progression seemed to be a reliable tool to identify HF patients at high risk, even though the specific incidence of disease progression may vary and be subject to a referral bias due to our clinical practices. The lack in our study of a systematic evaluation of natriuretic peptides in stable patients has prevented the possibility of using significant changes of BNP/NTproBNP values (i.e. increase ≥ 50%) to confirm worsening of NYHA class. Thus, our definition needs to be confirmed and implemented in other HF populations. Ongoing, among the criteria of HF progression, we also included HF hospitalizations. Although hospitalization may appear as a very soft criterion and often the true presence of HF may be difficult, hospitalizations for HF represent an adverse event in HF patients, being a major event considered in clinical HF trials. Indeed, HF progression criteria including or not HF hospitalization identified in any case patients with a worse prognosis, thus indicating that our proposed criteria represent a reliable tool to identify HF patients with a high probability of a poor prognosis.

All patients of this analysis were white, which prevents the application of these data to other racial groups.

The identification of chronic conditions was done mainly through a review of ICD-9CM codes, and coding procedures may differ across geographic regions and hospital systems. However, ICD-9CM codes were confirmed by chart review, as well as by specific instrumental, laboratory and pharmaceutical data for chronic diseases. Although this integrated method for the identification of non-cardiac comorbidities tries to minimize any potential underestimation, relying on a physician's diagnosis in itself always poses a risk of misclassification and underdiagnosis.

Another limitation is the absence of a direct comparison between HF with borderline or mid-range ejection fraction (HFmrEF) and the other HF-LVEF types (HFrEF and HFpEF). Although this topic is fascinating, our aim was to go beyond any previously published result which compared HF patients with respect to the cutoff LVEF ≤ 35%.

Although the method used to identify HF patients minimizes the risk of underestimation, the diagnosis of HF with preserved ejection fraction is obviously more challenging than that of HFrEF, and could be easily more influenced by mistakes, due to the lack of systematic natriuretic peptide evaluation and standardized and universally accepted diagnostic criteria. In addition, 896 patients (25%) were excluded from the study cohort because the LVEF value and the NYHA class had not been simultaneously documented, leading to a potential bias; the fact that this is a real representation of the population variability clinical picture must be taken into account.

5. Conclusions

We reported the incidence of HF progression in a contemporary community chronic HF population which is representative of the patients observed in a real-world setting. We observed a significant incidence of HF progression, with a higher disease progression among patients with LVEF ≤ 35%. We also identified the factors which increase the risk of disease progression and mortality, thereby refining the risk stratification of HF patients.

Although our estimates need confirmation, these data are important for the scientific community and the healthcare system, since they show that HF remains a condition with high morbidity and mortality rates, despite a clinically stable condition of chronic HF and the improvements in its therapy. Hence, our findings may help identify the patients in need of an aggressive medical treatment or complex therapeutic regimes.

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Conflict of interest

Peruzzi and Garavaglia are employed at Novartis Pharma Italy at the time of submission. Other authors declare that they have no conflict of interest to disclose.

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