



Clinical burden and predictors of non-cardiovascular mortality and morbidity in advanced heart failure

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Clinical burden and predictors of non-cardiovascular mortality and morbidity in advanced heart failure

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KEYWORDS:

advanced heart failure;
non-cardiovascular
comorbidity;
mortality;
morbidity;
non-cardiovascular
events

BACKGROUND: The changing demographic of heart failure (HF) increases the exposure to non-cardiovascular (non-CV) events. We investigated the distribution of non-CV mortality/morbidity and the characteristics associated with higher risk of non-CV events in patients with advanced HF.

METHODS: Patients from the HELP-HF registry were stratified according to the number of 2018 HFA-ESC criteria for advanced HF. Endpoints were non-CV mortality and non-CV hospitalization. Competing risk analyses were performed assessing the association between HFA-ESC criteria and study outcomes and the additional predictors of non-CV endpoints.

RESULTS: One thousand one hundred and forty-nine patients were included (median age 77 years-IQR 69–83). At 6, 12, 18 and 22 months, cumulative incidence of CV vs non-CV mortality was 13% vs 5%, 17% vs 8%, 20% vs 12%, 23% vs 12%, and of CV vs non-CV hospitalization was 26% vs 11%, 38% vs 17%, 45% vs 20%, 50% vs 21%. HFA-ESC criteria were associated with increasing adjusted risk of CV death, whereas no association was observed for CV hospitalization, non-CV death and non-CV

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hospitalization. Predictors of non-CV death were age, chronic obstructive pulmonary disease, dementia, preserved ejection fraction, > 1 HF hospitalization and hemoglobin.

CONCLUSIONS: Patients with advanced HF are exposed to high, even though not predominant, burden of non-CV outcomes. HFA-ESC criteria aid to stratify the risk of CV death, but are not associated with lower competing risk of non-CV outcomes. Alternative factors can be useful to define the patients with advanced HF at risk of non-CV events in order to better select patients for treatments specifically reducing CV risk.

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Heart failure (HF) is a global pandemic with an increasing prevalence and a prognosis that remains poor despite the continuous advances in pharmacological and non-pharmacological treatments.^{1–3} With the growing complexity and the progressive aging of the HF population, a rising exposure to cardiovascular (CV) and non-CV events not directly explained by HF is observed in patients with HF.^{4,5} Only 30% and 50% of 30-day re-admissions after diagnosis of HF are indeed due to HF and CV causes, respectively, with the other half related to non-CV causes.^{5,6} The high impact of non-CV events has a major role in human and financial resources allocation, as these patients are less likely to benefit from interventions aimed at improving cardiac function. This may be critical in patients with advanced HF who may need high intensity therapies, such as mechanical circulatory support. Advanced HF represents the final stage of the syndrome in which patients experience refractory symptoms, multiple HF re-admissions and poor survival.⁷ The prompt identification of these patients allows a timely referral for advanced organ-replacement therapies (i.e. heart transplant [HT] or mechanical circulatory support), if indicated, or, alternatively, a destination to palliative and end of life care.⁸ Recently, the ability of the 2018 HFA-ESC definition of advanced HF to identify patients at increased risk of mortality and HF hospitalization in a real-world scenario has been demonstrated.⁹ However, patients with advanced HF are often elderly and with multiple comorbidities in contemporary care, so that prediction of CV versus non-CV causes of their poor outcomes may help to better select treatment and resources allocation. In the present study, we sought to define the proportional distribution of non-CV mortality and morbidity outcomes and to identify the characteristics associated with higher risk of non-CV events in patients with criteria of advanced HF included in the HELP-HF (Assessment of the I Need Help markers in Heart failure) Registry, a multicenter registry from four Italian high-volume, tertiary care, centers.⁹

Methods

Study population

The observational, retrospective, multicenter HELP-HF registry has been previously described.⁹ Briefly, it included all consecutive patients who were hospitalized for acute HF or were evaluated as

outpatients for chronic HF at four Italian high-volume centers between January 1, 2020 and November 30, 2021, and presenting ≥ 1 “I NEED HELP” high-risk marker.³ Details on the 2018 updated Heart Failure Association-European Society of Cardiology (HFA-ESC) criteria for advanced HF were collected and a patient fulfilled the definition of advanced HF if all four criteria were met.⁷ Institutional review board approval was waived for this registry because of its retrospective design with collection of anonymized data and without any study-specific intervention. The study complies with the ISHLT Ethics statement. All included inpatients and outpatients were managed and treated according to current HF guidelines and as per local clinical practice.³ Additional data on medical history, clinical presentation, echocardiography and laboratory findings and medical therapy were recorded.

Study endpoints

The primary study endpoints were 1-year CV and non-CV mortality. 1-year CV and non-CV hospitalizations were assessed as secondary endpoints. Outcome information was obtained from official medical reports, direct telephone contact with patients, their families or general practitioners. CV vs non-CV causes of death/hospitalization were assessed by the local investigators at the participating centers.

Statistical analysis

Continuous variables were reported as mean (standard deviation) or median (interquartile range [IQR]), whereas categorical variables were reported as counts (percentages).

Cumulative incidence of the study endpoints was evaluated in the total cohort and according to the number of fulfilled 2018 HFA-ESC advanced HF criteria using the cause-specific hazard method to account for the competing risk of mortality/hospitalization for the alternative cause (i.e. CV mortality and CV hospitalization when assessing the non-CV endpoints, and non-CV mortality and non-CV hospitalization when assessing the CV endpoints) and was plotted using the cumulative incidence function. For all endpoints, follow-up was evaluated at the date of the event or the last available follow-up. The association between the number of fulfilled 2018 HFA-ESC advanced HF criteria and the outcomes of interest (i.e. CV mortality, CV hospitalization, non-CV mortality and non-CV hospitalization) was investigated by fitting unadjusted and adjusted cause-specific Cox proportional hazards regression analyses. Covariates selected for the multivariable Cox regression models included variables validated in the outcome model of the first HELP-HF registry report and variables with potential impact on non-CV mortality and hospitalization and were marked with “a” in Table 1.⁹ Additional predictors of non-

Table 1 Main Characteristics of the HELP-HF Cohort

	Overall (n = 1149)
Age (years) ^a	77 (69–83)
Male sex ^a	773 (67)
BMI (kg/m ²)	26 (23–29)
<i>HF phenotype^a</i>	
HFrEF	699 (61)
HFmrEF	122 (11)
HFpEF	328 (29)
LVEF	35 (25–50)
RV dysfunction	482 (43)
Moderate-severe MR	683 (61)
Moderate-severe TR	585 (53)
New-onset HF ^a	187 (16)
Time since HF diagnosis (months)	30 (3–84)
HF hospitalization(s) during last year ^a	
1	284 (25)
> 1	131 (11)
NYHA class III–IV ^a	738 (64)
Inpatient ^a	777 (68)
<i>Number of HFA/ESC 2018 criteria</i>	
0	240 (21)
1	273 (24)
2	228 (20)
3	215 (19)
4	193 (17)
<i>Comorbidities and frailty</i>	
Hypertension ^a	817 (71)
Dyslipidaemia	609 (53)
Diabetes ^a	447 (39)
History of AF ^a	641 (56)
CAD	504 (44)
Prior myocardial infarction	380 (33)
Prior PCI	336 (29)
Prior CABG	171 (15)
Prior valve surgery	139 (12)
Prior percutaneous valve intervention	
TAVR	28 (2)
Mitral TEER	49 (4)
Known cardiomyopathy	291 (25)
Prior myocarditis	22 (2)
Peripheral artery disease ^a	205 (18)
Prior stroke or TIA ^a	173 (15)
COPD ^a	266 (23)
Chronic kidney disease ^a	650 (57)
Dialysis	28 (2)
History of cancer	276 (24)
Cardiac cachexia	42 (4)
MCI or dementia ^a	157 (14)
Depression ^a	107 (9)
ADL or IADL impairment ^a	339 (31)
Balance disorders ^a	391 (36)
Mild	274 (25)
Falls	117 (11)
Living alone	305 (27)
<i>Cardiac implantable electronic devices^a</i>	
Pacemaker	167 (14)
ICD	183 (16)
CRT	183 (16)
<i>Clinical presentation</i>	
Cardiogenic shock	153 (13)

Table 1 (Continued)

	Overall (n = 1149)
Acute pulmonary edema	153 (13)
Rales > 1/3 lung fields	490 (43)
Peripheral edema	673 (59)
Systolic blood pressure (mmHg) ^a	120 (105–140)
Heart rate (bpm) ^a	75 (64–89)
IV loop diuretics ^a	778 (68)
Use of inotropes/vasopressors	277 (24)
Need of temporary MCS	
IABP	40 (3)
Impella	5 (0.4)
VA-ECMO	3 (0.3)
Need of mechanical ventilation	
Non-invasive	159 (14)
Invasive	35 (3)
Need of CRRT/ultrafiltration	45 (4)
Need of ICU admission	253 (22)
INTERMACS profile 1–3	104 (9)
ACC/AHA stage D	185 (16)
<i>Laboratory</i>	
Creatinine (mg/dl)	1.48 (1.08–2.07)
eGFR (ml/min/1.73 m ²) ^a	42 (27–61)
Urea (mg/dl)	69 (47–109)
Hemoglobin (g/dl) ^a	12.0 (10.6–13.5)
Sodium (mmol/l)	140 (137–142)
Potassium (mmol/l)	4.2 (3.9–4.6)
NTproBNP (pg/ml)	5254 (2541–12421)
Total bilirubin (mg/dl)	0.87 (0.58–1.30)
<i>Medical therapy for HF (at inclusion)</i>	
Beta-blockers	882 (77)
Dose ≥50% target dose	438 (38)
ACEi/ARB/ARNI	585 (51.0)
Dose ≥50% target dose	262 (22.9)
MRA	630 (54.9)
Dose ≥50% target dose	596 (52.0)
Loop diuretic daily dose (mg)	50 (25–125)

ACC, American College of Cardiology; ACEi, angiotensin-converting enzyme inhibitor; ADL, activities of daily living; AF, atrial fibrillation; AHA, American Heart Association; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRRT, continuous renal replacement therapy; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IABP, intra-aortic balloon pump; IADL, instrumental activities of daily living; ICD, implantable cardioverter-defibrillator; ICU, intensive care unit; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IV, intravenous; LVEF, left ventricular ejection fraction; MCI, mild cognitive impairment; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; RV, right ventricle; TAVR, transcatheter aortic valve replacement; TEER, transcatheter edge-to-edge repair; TIA, transient ischemic attack; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Data are presented as n (%), mean ± standard deviation and median (interquartile range).

^aVariables included in multivariable Cox regression model.

CV mortality and non-CV hospitalization were selected via stepwise forward approach (Akaike information criterion) among variables included in the model, and their interaction with 2018 HFA-ESC advanced HF criteria was also explored. The proportional hazards assumption was verified by assessment of the Schoenfeld residuals. P values < 0.05 were considered statistically significant. Statistical analyses were performed using R statistical package 4.1.3 (R Foundation, Wien, Austria), with libraries “survival”, “cmprsk”, “ggplot2”.

Results

Study population and outcomes

A total of 1149 patients (68% inpatients) were included. [Table 1](#) summarizes the main characteristics of the overall population. Median age was 77 years (IQR 69–83), 33% were females, 61% had HF with reduced ejection fraction (HFrEF), 11% HF with mildly reduced EF and 28% HF with preserved EF (HFpEF).³ A total of 193 patients (16.8%) fulfilled all four 2018 HFA-ESC advanced HF criteria, 215 patients (18.7%) had three criteria, 228 (19.8%) had two criteria, 273 (23.8%) had one criterion and 240 (20.9%) patients had no criteria. Prevalence of main CV and non-CV comorbidities was high: 71% had hypertension, 39% diabetes, 18% peripheral artery disease, 56% history of atrial fibrillation, 57% chronic kidney disease, 24% history of cancer, 14% dementia and 9% depressive disorders, 36% reported balance disorders (mild or falls) in the last 12 months.

Over a median follow-up of 8.5 months (IQR 3.5–12.8), 265 patients (23%) died (81 non-CV deaths, 31% of total deaths) and 590 (51%) were hospitalized (179 non-CV hospitalizations, 30% of total hospitalizations). As shown in [Figure 1](#), cumulative incidence of CV vs non-CV mortality at 6, 12, 18 and 22 months was 13% vs 5%, 17% vs 8%, 20% vs 12%, 23% vs 12%, and cumulative incidence of CV vs non-CV hospitalization at 6, 12, 18 and 22 months was 26% vs 11%, 38% vs 17%, 45% vs 20%, 50% vs 21%.

Association between 2018 HFA-ESC criteria and type of outcome

[Figure 2](#) shows the cumulative incidence of CV vs non-CV mortality (panel A) and of CV vs non-CV hospitalization (panel B) according to the number of fulfilled 2018 HFA-ESC advanced HF criteria. As the number of 2018 HFA-ESC advanced HF criteria increased, the cumulative incidence of both CV mortality and CV hospitalization increased, whereas the cumulative incidence of non-CV mortality and non-CV hospitalization remained stable up to three 2018 HFA-ESC advanced HF criteria and decreased when all the four criteria were fulfilled.

At unadjusted analysis, the risk of CV death increased with increasing number of 2018 HFA-ESC advanced HF criteria, with p value < 0.05 for ≥ 2 associated criteria ([Supplementary Figure 1](#)). No association was found between the number of associated 2018 HFA-ESC advanced

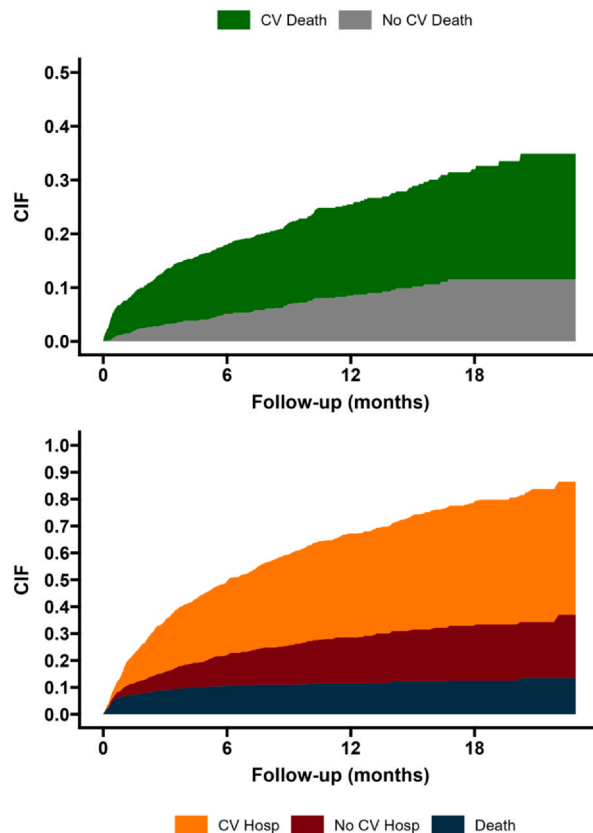


Figure 1 Cumulative incidence of cardiovascular vs non-cardiovascular death (upper panel) and of cardiovascular vs non-cardiovascular hospitalization (lower panel). CV, cardiovascular; Hosp, hospitalization.

HF criteria and the risk of non-CV death, whereas the risk of CV hospitalization was increased with ≥ 3 associated criteria and a lower risk of non-CV hospitalization was observed with 4 associated criteria ([Supplementary Figure 1](#)). After multiple adjustments, the increasing risk of CV death associated with higher number of 2018 HFA-ESC advanced HF criteria was confirmed (HR 2.22, 95%CI 1.07–4.60, $p=0.032$ for 2 vs 0 criteria, HR 2.10, 95% CI 1.02–4.30, $p=0.044$ for 3 vs 0 criteria, HR 3.66, 95% CI 1.79–7.48, $p < 0.001$ for 4 vs 0 criteria) ([Figure 3](#) and [Graphical Abstract](#)). No association with the number of 2018 HFA-ESC advanced HF criteria was instead observed with the risk of non-CV death, CV hospitalization and non-CV hospitalization ([Figure 3](#) and [Graphical Abstract](#)).

Characteristics associated with the risk of non-cardiovascular outcome

Variables associated with the risk of non-CV death and non-CV hospitalization are shown in [Table 2](#) ([Graphical Abstract](#)). Specifically, age at baseline, chronic obstructive pulmonary disease (COPD) and dementia showed an association with higher risk of non-CV death, whereas > 1 HF hospitalization in the last year, hemoglobin and HFpEF phenotype were associated with lower risk of non-CV death. Variables associated with higher risk of non-CV hospitalization were depression, balance disorders (falls)

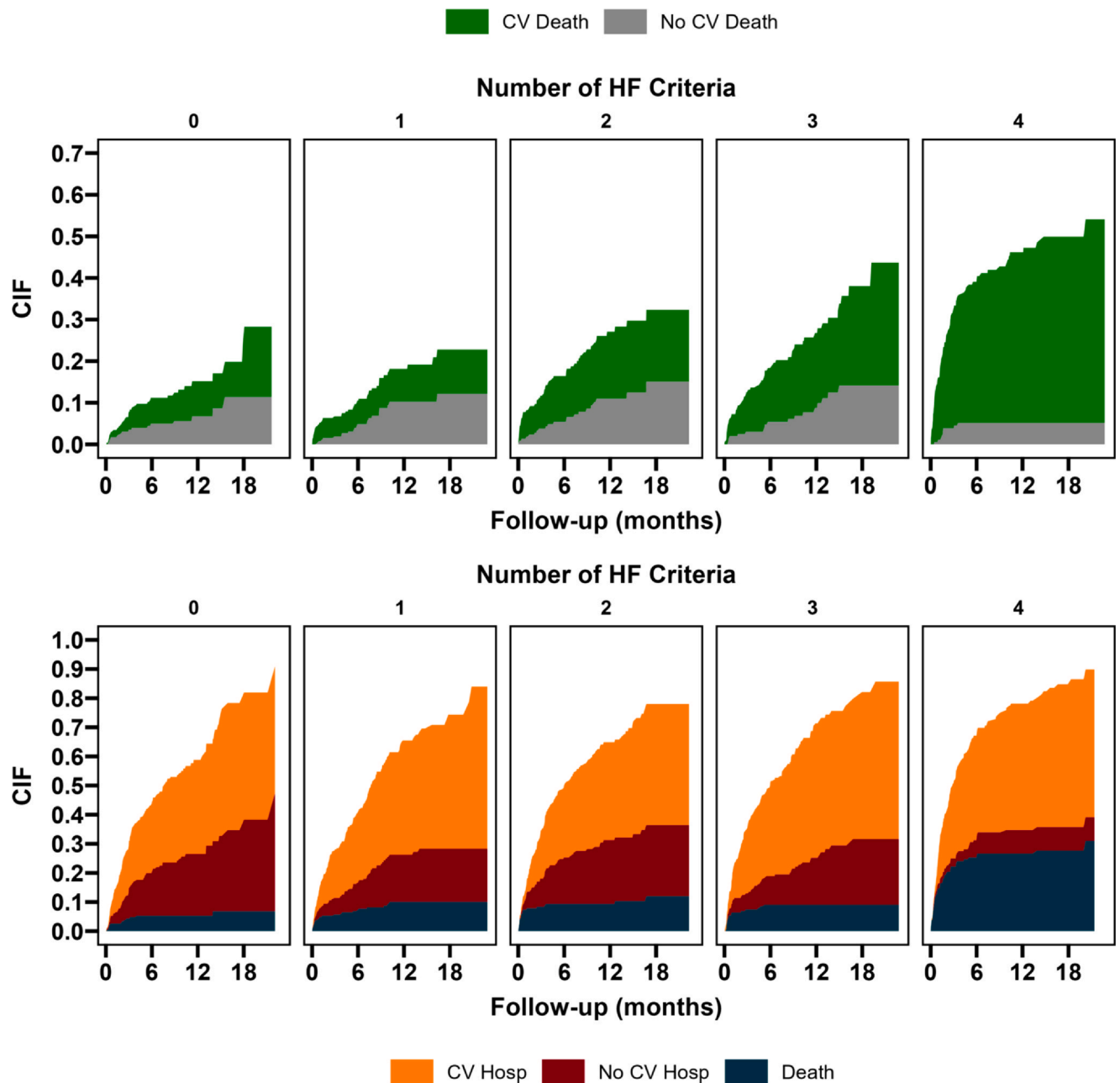


Figure 2 Cumulative incidence of cardiovascular vs non-cardiovascular death (upper panels) and of cardiovascular vs non-cardiovascular hospitalization (bottom panels) stratified by the number of fulfilled HFA/ESC 2018 criteria for advanced HF. CV, cardiovascular; HF, heart failure; HFA-ESC, Heart Failure Association of the European Society of Cardiology; Hosp, hospitalization. *Cumulative incidence reported in main text.*

and peripheral artery disease, whereas hemoglobin, > 1 HF hospitalization in the last year, dose of loop diuretics, use of mineralocorticoid receptor antagonists and female sex demonstrated an association with lower risk of non-CV hospitalization. No interaction was observed between these predictors and 2018 HFA-ESC advanced HF criteria.

Discussion

The recent updated definition of advanced HF based on the criteria proposed in the 2018 HFA-ESC position statement aimed to define a subset of patients at very high risk of

clinical events that are supposed to be mediated by HF.⁷ The real-world HELP-HF registry consistently reported > 30% 90-day mortality and about 45% 90-day mortality or HF hospitalization.⁹ However, with the changing demographic of the general HF population, non-CV causes account for a progressively larger proportion of the overall mortality/morbidity, but the impact of non-CV events in patients with advanced HF was unknown. In the present study, we focused on the proportional distribution of non-CV vs CV outcomes in a real-world cohort of high-risk patients with HF. The main findings are that (1) CV and non-CV comorbidities, as well as frailty indicators, are frequent in contemporary patients with HF and high-risk

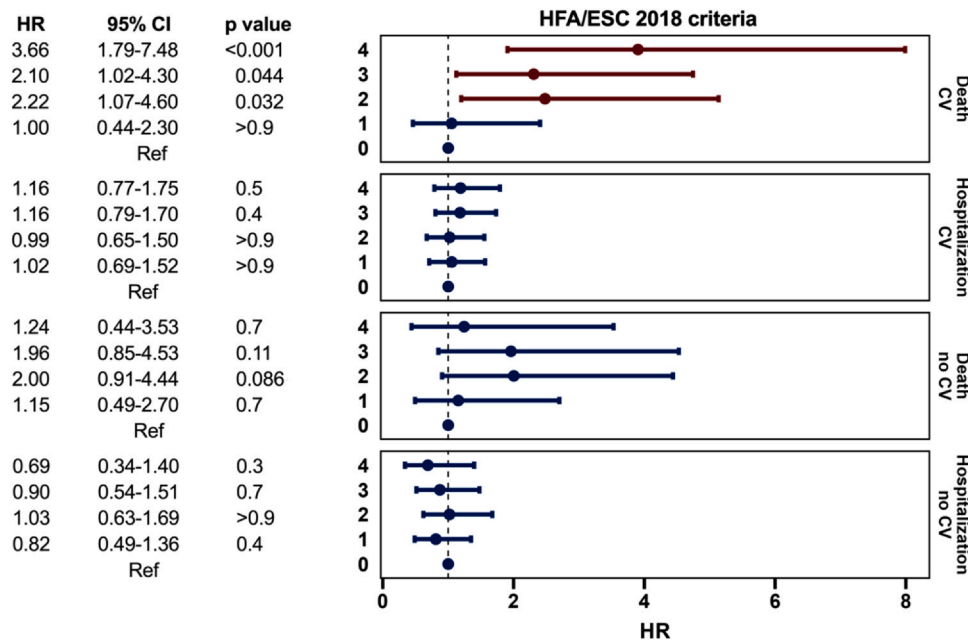


Figure 3 Adjusted association between HFA/ESC 2018 advanced heart failure criteria and outcomes. CI, confidence interval; CV, cardiovascular; HFA/ESC, Heart Failure Association/European Society of Cardiology; HR, hazard ratio.

Table 2 Variables Associated with the Risk of non-CV Events at Multivariate Cause-specific Cox Model

	Non-CV mortality		Non-CV hospitalization	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (for 1 year increase)	1.05 (1.02–1.09)	0.002		
Sex (female vs male)			0.64 (0.42–0.96)	0.031
Number HF hospitalizations last 12 years				
1 vs 0	0.62 (0.29–1.32)	0.200	0.80 (0.46–1.41)	0.400
> 1 vs 0	0.17 (0.04–0.73)	0.016	0.27 (0.09–0.87)	0.028
COPD	1.86 (1.09–3.19)	0.024		
Peripheral artery disease			1.72 (1.11–2.69)	0.016
Dementia	1.76 (1.10–2.79)	0.016		
Hemoglobin (g/dl)	0.85 (0.75–0.98)	0.020	0.82 (0.75–0.89)	< 0.001
HF phenotype				
HFmrEF vs HFrEF	0.92 (0.43–1.97)	0.800		
HFpEF vs HFrEF	0.40 (0.20–0.79)	0.009		
Depression			2.01 (1.15–3.54)	0.014
Balance disorders				
Mild vs none			1.42 (0.93–2.16)	0.10
Falls vs none			2.17 (1.31–3.60)	0.003
Loop diuretics daily dose (for 25 mg increase)			0.95 (0.93–0.997)	0.035
MRAs			0.59 (0.41–0.85)	0.004

COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; MRAs, mineralocorticoid receptor antagonists.

criteria, generating additional complexity in the management of the later stages of HF; (2) even though in our high-risk cohort the majority of mortality and morbidity outcomes had CV causes, the overall rate of non-CV events was significant attesting the changing characteristics of these patients; (3) 2018 HFA-ESC advanced HF criteria were associated with higher risk of CV mortality, but did not contribute to stratify patients at lower risk of non-CV events; (4) we identified other predictors of the risk of non-

CV death and hospitalization which could aid the risk stratification process in advanced HF.

Comorbidities and frailty in the current high-risk population with HF

The amount of CV and non-CV comorbidities in the HF populations is growing overtime. In the most recent reports, ~80% of patients with HF have ≥3 coexisting

comorbidities^{1,5,10} and this higher complexity has massive implications in terms of prognosis and costs for the healthcare systems.^{11–13} Another aspect that drew increasing attention is frailty, in particular with the progressive aging of the HF population. The coexistence of frailty in patients with HF complicates their overall care, negatively influences the titration of treatments and is a marker of poor prognosis.^{14,15} The presence of non-CV comorbidities is in contrast with the ideal outline of patients with advanced HF who need aggressive therapeutic interventions aimed at HF alone. In the 2022 report from the International Society for Heart and Lung Transplantation, median age of HT recipients was 57 years, 20% had diabetes and less had other concomitant comorbidities, and <20% of patients implanted with left ventricular assist device (LVAD) were >70 years old.^{16,17} Moreover, comorbidities and frailty negatively impact on the outcome of HT and LVAD recipients or even may be contraindications to either of them.¹⁸ The current scenario of advanced HF appears instead different. Median age of our high-risk HF cohort was 77 years, ~40% had diabetes, >50% had CKD and >20% had COPD and previous cancer. Also, cognitive disorders and other indicators of frailty such as balance disorders and impairment in daily life activities were highly prevalent. A similar profile has been observed in the Olmsted County population when 2018 HFA-ESC advanced HF criteria were applied, confirming the overall complexity of these patients and the considerable need of resources for their management.¹⁹

Distribution of cardiovascular vs non-cardiovascular events and impact of advanced heart failure criteria

The evolving landscape of the HF population induced intense changes in the risk profile of affected individuals. The known high burden of HF-related mortality and morbidity has to be coupled with an increasing risk of non-CV outcomes. For instance, patients with HF spent 3-fold longer time in hospital for non-CV reasons compared to non-HF patients and non-CV causes are the most frequent reasons for early readmission after HF diagnosis.^{5,6,20} The overall prevalence of advanced HF in the HF community is 10–15%.^{19,21} This is the condition at the highest risk of HF-related events, leading to consider the non-CV risk as secondary. Available data mainly reported on the risk of overall or CV mortality and CV or HF hospitalizations, while the competing risk of dying or being hospitalized for non-CV reasons remained unknown. In the Olmsted County population, one-half of patients with advanced HF died within 12 months and 25% survived >2 years.¹⁹ In the first report from the HELP-HF registry, 23% of patients died and 27% were hospitalized for HF during 260 days median follow-up. The 1-year rate of all-cause mortality (46.5% vs 21.5%) and of HF hospitalization (39.5% vs 26.9%) was higher in the 193 (16.8%) patients with all 4 HFA-ESC advanced HF criteria.⁹ In this study, by separating CV vs non-CV causes of mortality and hospitalizations, we have

demonstrated that in high-risk patients with HF one-third of deaths and 40% of hospitalizations occurred for non-CV causes. Although the proportions are lower compared to the global HF community,^{5,6} the total burden is very high given the overall absolute risk of mortality and morbidity of this subset of patients.

As expected, the proportion of CV events increased with higher number of 2018 HFA-ESC advanced HF criteria, whereas the cumulative incidence of non-CV outcomes decreased only when all 4 criteria were fulfilled. Accordingly, we have observed a significant association between the number of HFA-ESC advanced HF criteria and the risk of CV death (with ≥ 2 criteria) and CV hospitalization (with ≥ 3 criteria). However, after adjustment for multiple covariates with impact on both the CV and the non-CV risk, HFA-ESC advanced HF criteria remained associated with the risk of CV death, but not with the risk of CV hospitalization. This might appear in contradiction with the recent data from the HELP-HF registry, which demonstrated higher risk of HF hospitalizations associated with HFA-ESC advanced HF criteria, and could be explained by the influence of other covariates included in the model on the risk of other non-HF related CV events and by the potential influence of social status (i.e. living alone vs with family/caregiver). On the other hand, the progressive increase in risk of CV outcomes determined by the number of fulfilled criteria was not paired with a lower competing risk of non-CV events, attesting the necessity of associating alternative strategies for the prediction of the non-CV risk in order to support the overall care of these patients, from the referral to advanced HF therapies to the need of palliative care.^{22,23}

Other indicators for the stratification of non-cardiovascular risk

The identification of patients at risk of non-CV events in the later stages of HF has important implications in the overall management, since it may guide the selection and the timing for referral to advanced HF treatments (i.e. HT and or LVAD) or, alternatively, the choice of a more conservative approach, which includes end-of-life care and avoiding futile advanced medical therapy. In randomized controlled trials on HF, HF hospitalizations are classically a primary measure of outcome and reducing the risk of HF hospitalization is a main focus for cardiologists in clinical practice. However, contemporary patients with HF are exposed to a dramatic burden of non-CV events which account for >50% of the readmissions to the hospital and are a major determinant of their high overall mortality.^{5,6} In HFrEF, emerging evidence also suggests the need to consider risk of non-CV death for the selection of candidates for primary prevention implantable cardioverter defibrillator.²⁴ In our study age, COPD and dementia were associated with higher risk of non-CV death, attesting the difficult management of older and multimorbid patients with HF. In particular for age, its predictive association was independent from non-CV comorbidities and frailty markers, suggesting that in older patients a very careful and selective approach by clinicians to the candidacy to advanced HF treatments is

important. The association of hemoglobin values with the lower risk of both non-CV mortality and hospitalization confirms the negative prognostic impact of anemia in patients with HF and especially the relation with non-CV events.²⁵ The inverse relation with the number of previous HF hospitalization is consistent with the exponential increase in risk of re-admission due to HF for patients discharged from a HF hospitalization.²⁶ The lower risk of non-CV death observed for HFpEF is explained by the lower overall mortality risk (i.e. all-cause, CV and non-CV) we have observed in HFpEF patients enrolled in this cohort. Other variables were associated with higher risk of non-CV hospitalization that included markers of frailty such as cognitive and balance disorders, which can predispose to non-CV admissions since they are frequently associated with multiple comorbidities and may also expose to drugs adverse reactions or trauma.¹⁴ Higher dose of loop diuretics was associated with lower risk of non-CV hospitalization and this might be related with more severe HF and, thus, higher competing risk of HF-related outcomes. Use of mineralocorticoid receptor antagonists might be a surrogate of better global patient condition, since their use in HF is associated with younger age, better renal function, and better treatment optimization.²⁷ Finally, the lower competing risk of non-CV hospitalization observed in high-risk HF females probably deserves dedicated investigation, since in former studies the association between sex and non-CV hospitalization was neutral.²⁸ In this study, it might be partially related to a lower or delayed access to care, which has been reported in females vs males with HF.²⁹ No interactions were found between the predictors of non-CV death and hospitalization and the number of 2018 HFA-ESC advanced HF criteria, thus their predictive effect was consistent across the overall profile of high-risk patients with HF.

Limitations

As all the observational studies on registries, this study suffers from the common bias due to its retrospective design. Furthermore, the clinical events were not externally adjudicated. Although multicentric, this study enrolled patients from a single country, thus our findings might not be applicable to other geographical areas. The relatively short period of inclusion limited the follow-up duration. Since non-CV events were the main focus of the study, we did not specifically assess the risk of all-cause mortality and of HF hospitalization, which have been already described.⁹ We cannot exclude that behind the predictive association of older age with non-CV mortality and morbidity other factors typical of older individuals, such as non-CV comorbidities and frailty might have a role. However, our analysis was adjusted for most of the non-CV comorbidities and of the frailty markers (i.e. balance disorders, cognitive impairment, impairment in daily life activities). In the multivariable analysis, covariates previously validated in the HELP-HF registry and others with potential impact on the risk of CV and non-CV prognosis were included.⁹ However, we cannot exclude a bias related to residual confounders. The present study was conducted during the major phase of the COVID-19 pandemic in Italy, and this

might have influenced the observed ratio between CV and non-CV mortality as well as the rate of HF hospitalization since access of patients to the hospital and referral from secondary centers were decreased during the pandemic.³⁰ In our cohort, 18 out of 81 non-CV death were recorded as due to COVID-19. Finally, the limited sample size has lowered the power of our analyses, and for this reason we applied a stepwise forward approach for the selection of predictors if non-CV events predictors (see statistical methods). Further dedicated studies are needed to validate our findings.

Conclusions

Although patients with advanced HF are predominantly exposed to CV mortality and morbidity events, the burden of non-CV outcomes is high, particularly considering the high absolute risk characterizing these patients. The 2018 HFA-ESC criteria aid to stratify the risk of CV death, but are not associated with lower competing risk of non-CV outcomes. Alternative risk predictors can be useful to define the non-CV risk in patients with advanced HF in order to guide the selection and the timing of advanced HF-specific treatments, to optimize financial and human resource allocation, to define the pathways for end-of-life care and, in conclusion, to minimize futility.

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Appendix A. Supporting material

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.healun.2023.11.006](https://doi.org/10.1016/j.healun.2023.11.006).

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