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RESEARCH ARTICLE

Frailty according to the 2019 HFA-ESC definition in patients at risk for advanced heart failure: Insights from the HELP-HF registry

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Aims Frailty is highly prevalent in patients with heart failure (HF), but a concordant definition of this condition is lacking. The Heart Failure Association of the European Society of Cardiology (HFA-ESC) proposed in 2019 a new multi-domain definition of frailty, but it has never been validated.

Methods and results Patients from the HELP-HF registry were stratified according to the number of HFA-ESC frailty domains fulfilled and to the cumulative deficits frailty index (FI) quintiles. Prevalence of frailty and of each domain was reported, as well as the rate of the composite of all-cause death and HF hospitalization, its single components, and cardiovascular death in each group and quintile. Among 854 included patients, 37 (4.3%), 206 (24.1%), 365 (42.8%), 217 (25.4%), and 29 (3.4%) patients fulfilled zero, one, two, three, or four domains, respectively, while 179 patients had a FI < 0.21 and were considered not frail. The 1-year risk of adverse events increased proportionally to the number of domains fulfilled (for each criterion increase, all-cause death or HF hospitalization: hazard ratio [HR] 1.43, 95% confidence interval [CI] 1.27–1.62; all-cause death: HR 1.72, 95% CI 1.46–2.02, HF hospitalizations: subHR 1.21, 95% CI 1.04–1.31; cardiovascular death: HR 1.77, 95% CI 1.45–2.15). Consistent results were found stratifying the cohort for FI quintiles. The FI as a continuous variable demonstrated higher discriminative ability than the number of domains fulfilled (area under the curve = 0.68 vs. 0.64, $p = 0.004$).

Conclusion Frailty in patients at risk for advanced HF, assessed via a multi-domain approach and the FI, is highly prevalent and identifies those at increased risk of adverse events. The FI was found to be slightly more effective in identifying patients at increased risk of mortality.

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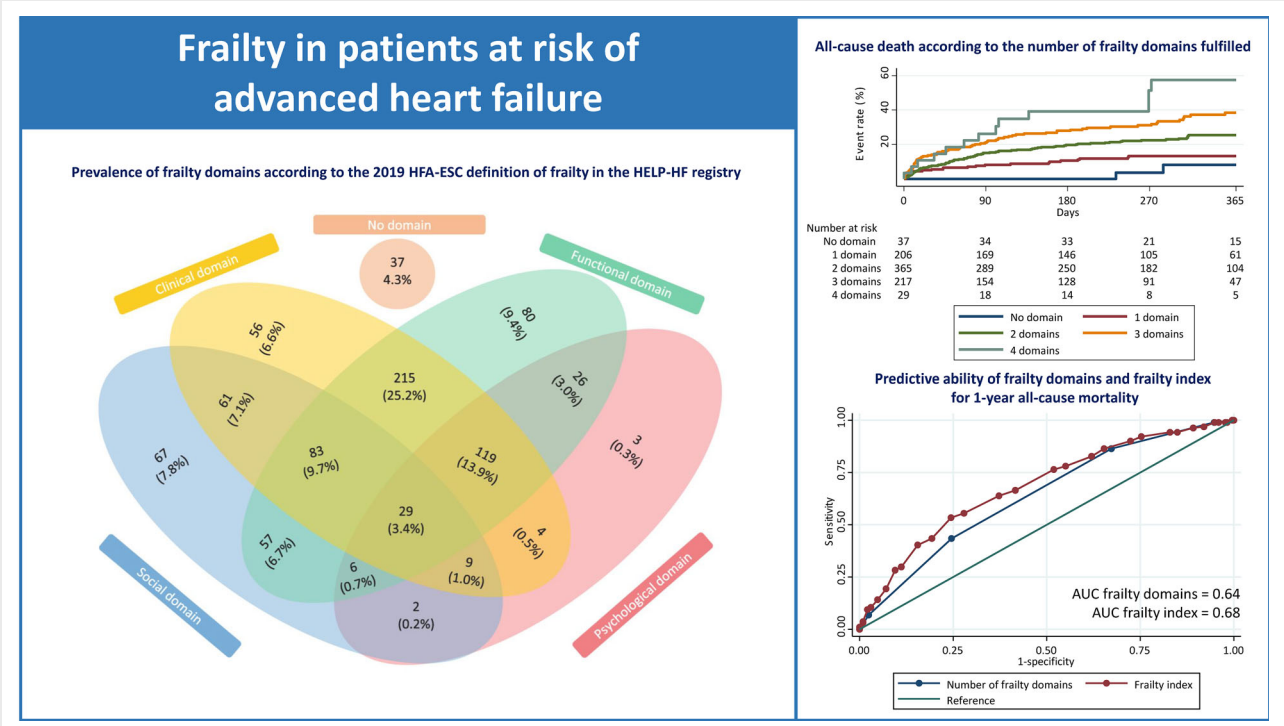
Graphical Abstract



Frailty in patients at risk of advanced heart failure. AUC, area under the curve; HFA-ESC, Heart Failure Association of the European Society of Cardiology.

Keywords Advanced heart failure • Frailty • Frailty index • Heart failure

Introduction

Frailty is a clinical condition that affects up to 45% of people living with heart failure (HF) and that further worsens their prognosis.[1] Despite rising evidence on the importance of frailty evaluation, no validated instrument to identify such syndrome exists, thus preventing a standardized assessment of its prevalence and prognostic impact. Most definitions derive from two models: the cumulative deficit[2] and the physical frailty model.[3] The former relies on the creation of a complex frailty index (FI), resulting from the addition of multiple individual deficiencies and conditions, and evaluates frailty as the ratio between patient's deficits and the total number of deficits considered; the latter is based on the assessment of physical domains (i.e. unintentional weight loss, exhaustion, reduced handgrip strength, slow walking speed, and low physical activity) and frailty is defined when at least three of them are present. However, both models are limited in their routine use by complexity in assessment, high risk of misclassification, need for a more holistic approach, or by being time-consuming.[4] Therefore, in 2019 the Heart Failure Association of the European Society of Cardiology (HFA-ESC) proposed a new consensus definition of frailty and a frailty score based on four domains: clinical, psycho-cognitive, functional, and social domains.[5] Each of them is identified by simple information, easy to assess during patients' interview.[4] The 2019 HFA-ESC definition describes frailty as a multidimensional dynamic state, independent of age, which makes the individual with HF more vulnerable to the effect of stressors.[4] However, such score and the additive effect of the four domains have never been evaluated in a cohort of HF patients. The present study aims to address such issue, by analysing the prevalence of each domain and to assess their individual and additive impact on prognosis in a cohort of patients at risk for advanced HF; moreover, we aim to compare it with a cumulative deficits-based FI.

Methods

The HELP-HF registry

The design of the HELP-HF registry has been previously described.[6] Briefly, it is an observational, retrospective, multicentre registry including consecutive HF patients who were hospitalized for acute HF or evaluated as outpatients for chronic HF at four Italian high-volume

centres between January 2020 and November 2021. Included patients presented at least one 'I NEED HELP' high-risk marker[7,8]; de-identified individual patient data on medical history, clinical presentation, echocardiography and laboratory findings, guideline-directed medical therapy (GDMT) and clinical outcomes were collected. Congestion and perfusion status at clinical presentation were described according to available guidelines and position statements. The American Heart Association/American College of Cardiology HF stage and the INTERMACS class were reported, based on previous definitions.[9,10] Follow-up was performed by means of medical record or telephone contact. 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.

HFA-ESC frailty definition

The four domains involved in the HFA-ESC frailty definition are: (1) clinical domain, which takes into account the number and type of comorbidities, weight loss and/or falls; (2) psycho-cognitive domain, assessing cognitive impairment, dementia and/or depression; (3) functional domain, evaluating impairment in (instrumental) activities of daily living, mobility and/or balance; (4) social domain, taking into account social support, institutionalization and/or the lack of support.

Study population

In the present analysis, data regarding the 2019 HFA-ESC frailty domains were collected and patients without available data regarding at least one component for each domain were excluded. The variables included in each definition were reported by the investigators. Comorbidities to be included in the clinical domain were selected among those known to impact on the prognosis of HF patients.[11] Patients were stratified into five groups according to the number of domains fulfilled (no domain; one domain; two domains; three domains; four domains). We used a standard procedure to construct a FI using the deficit accumulation approach[12]: 30 different items covering demographic and laboratory data, vital signs and comorbidities were considered (online supplementary *Table S1*) and to each of them a score ranging from 0 (not present) to 1 (present at the greatest severity) was assigned. The FI was calculated by dividing the sum of the variables by the total number of variables measured: the FI ranged from 0 to 1, with higher values identifying frailer patients. A standard cut-off of <0.21 was used to define patients as not frail[13,14]; patients were also divided into quintiles according to the calculated FI. Patients were also stratified into three groups, based on the concordance between the frailty domain group and the FI quintile (Group 1, frailty domain group = FI quintile; Group 2, frailty domain group > FI quintile; Group 3, frailty domain group < FI quintile).

Study objectives and endpoints

The aim of this study was (i) to report the prevalence of frailty as defined by the 2019 HFA-ESC consensus document and of each of the four frailty domains included in the definition, (ii) to compare this method of frailty assessment to that obtained through the calculated FI, focusing on the reclassification of frailty severity, and (iii) to identify the impact of frailty, of each domain, and of the FI, on the composite of all-cause death and HF hospitalization, its single components, and of cardiovascular (CV) death at 1 year.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range) and were compared with the ANOVA test or the Kruskal–Wallis test, based on their distribution. Normal distribution was checked for all variables using the Shapiro–Wilk test. Categorical variables are presented as numbers and percentages and were compared with the χ^2 or Fisher's exact test, as appropriate. Clinical endpoints were analysed using the Kaplan–Meier method and compared between groups using the log-rank test. For all endpoints, follow-up was evaluated at the date of the event or the last available follow-up, which was censored at 1 year. Cox proportional hazards regression analysis was also performed to assess the prognostic impact of frailty and its domains on all-cause mortality, CV mortality and the composite of HF hospitalization and all-cause mortality; the occurrence of first HF hospitalization was evaluated using the Fine–Gray hazard method to account for the competing risk of mortality and was plotted using the cumulative incidence function. We performed a multivariable Cox regression analysis testing the impact of each domain on clinical outcome: each individual domain was adjusted for the other domains. After multivariable analysis, a formal test of equality (Wald test) of the obtained adjusted hazard ratios (HRs) was performed, thus evaluating whether each HR (for a specific criterion) was significantly different as compared to any other HR. An overall *p*-value reflecting global differences across all the adjusted HRs was also calculated for all endpoints. We also performed multivariable analyses adjusting for GDMT prescription, as well as for covariates with univariable $p < 0.10$ and other selected covariates considered to be relevant according to the investigators' judgment (e.g., age and sex).[6,15] The use of sodium–glucose cotransporter 2 inhibitors was not included in the multivariable model, as these drugs were still not recommended during the study period.[16] Results of the Cox regression analyses are reported as HR and 95% confidence interval (CI). Results of the Fine–Gray models are reported as subhazard ratio (SHR) with 95% CI. The comparison between frailty domain performance and FI in predicting outcomes was analysed by patient reclassification into three groups, as well as by plotting receiver operating characteristic (ROC) curves for the primary outcome from logistic regression analysis and comparing them via a non-parametric approach. This analysis was performed considering logistic regression models since advanced therapies for HF must be considered only in patients with life expectancy of at least 1 year with good quality of life, not considering the timing of events within 1 year, making more appropriate the use of logistic regression in this setting. The Youden index to identify the best cut-off point to optimize sensitivity and specificity for the FI was also calculated. All reported *p*-values are two-sided, and a $p < 0.05$ was considered statistically significant. Statistical analyses were performed using STATA version 17.0 (Stata Corp., College Station, TX, USA).

Results

2019 HFA-ESC frailty definition

As reported in *Table 1*, among 854 included patients, 37 (4.3%) fulfilled no frailty domain, whereas 206 (24.1%), 365 (42.8%), 217 (25.4%) patients fulfilled one, two or three frailty domains, respectively, while 29 patients (3.4%) fulfilled the definition of all four frailty domains. The clinical domain was fulfilled by 576 (67.4%) patients, 198 (23.2%) patients satisfied the criteria for the psycho-cognitive one, whereas 615 (72%) and 314 (36.8%) fulfilled the functional and social domains, respectively. The

Table 1 Baseline characteristics according to the number of frailty domains fulfilled

Variable	Not frail	1 domain	2 domains	3 domains	4 domains	*p*-value
Patients, *n* (%)	37 (4.3)	206 (24.1)	365 (42.8)	217 (25.4)	29 (3.4)	–
Age (years)	70.3 (12.2)	71.6 (13.3)	75.4 (10.7)	78 (10.8)	79.1 (7.5)	<0.001
Female sex, *n* (%)	10 (27)	56 (27.2)	115 (31.5)	91 (41.9)	12 (41.38)	0.001
BMI (kg/m^2)	24.2 (21.8–25.7)	26.4 (23.1–29.4)	26 (22.9–29.9)	25.3 (22.7–29.4)	25.2 (22.9–31.1)	0.46
NYHA class III–IV, *n* (%)	10 (27)	111 (53.9)	263 (72.1)	163 (75.1)	20 (69)	<0.001
>1 HF hospitalization in the last year, *n* (%)	8 (21.6)	38 (18.5)	110 (30.1)	77 (35.5)	3 (10.3)	0.009
Previous MI, *n* (%)	6 (16.2)	41 (19.9)	153 (41.9)	83 (38.3)	8 (27.6)	<0.001
Hypertension, *n* (%)	14 (37.8)	124 (60.2)	274 (75.1)	177 (81.6)	24 (82.76)	<0.001
Diabetes, *n* (%)	5 (13.5)	47 (22.8)	161 (44.1)	115 (53)	13 (44.8)	<0.001
COPD, *n* (%)	3 (8.1)	30 (14.6)	96 (26.3)	65 (29.9)	9 (31)	<0.001
LVEF (%)	35 (24–50)	30 (23–45)	38 (23–50)	40 (26–55)	32 (21–40)	0.002
SBP (mmHg)	120 (100–140)	120 (110–140)	120 (110–140)	120 (105–140)	121 (103.5–132.5)	0.92
HR (bpm)	70 (60–86)	80 (70–94)	72 (64–87)	75 (64–90)	74 (65–90)	0.060
Potassium (mmol/L)	4.1 (3.7–4.7)	4.2 (3.8–4.5)	4.2 (3.8–4.6)	4.1 (3.7–4.6)	4.2 (3.7–4.6)	0.67
eGFR (mmol/L)	57.6 (40.3–74.3)	52.3 (31.1–68.3)	36.5 (25–55)	34.7 (24.3–50.8)	40.2 (21.2–62.6)	<0.001
Haemoglobin (g/dl)	13.3 (11.9–14.2)	12.7 (11.3–14.5)	11.9 (10.5–13.2)	11.6 (10.2–12.7)	11 (9.9–13)	<0.001
ACEi/ARB/ARNI[a], *n* (%)	11 (29.7)	46 (22.3)	73 (20.0)	49 (22.7)	7 (24.1)	0.69
Beta-blocker[a], *n* (%)	12 (32.4)	87 (42.2)	152 (41.8)	64 (29.5)	7 (24.1)	0.010
MRA[a], *n* (%)	17 (45.9)	114 (55.3)	193 (53.0)	103 (47.7)	14 (48.3)	0.50
Loop diuretics[b], mg	25 (0–50)	50 (20–100)	50 (20–125)	55 (25–125)	62.5 (40–150)	<0.001

Data are reported as mean (standard deviation) or median (interquartile range), unless otherwise indicated.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure.
[a]For patients receiving guideline-directed medical therapy, *n* (%) refer to those receiving at least 50% of the optimal recommended dose.
[b]For loop diuretics, mg of furosemide equivalents are displayed.

number of frailty domains fulfilled was associated with increased comorbidity burden, reduced estimated glomerular filtration rate and worse functional status, as shown by higher prevalence of New York Heart Association class III/IV at presentation in patients with at least 1 domain fulfilled ($p < 0.001$). Beta-blockers at a dose >50% of target dose were less frequently prescribed in patients with more frailty domains, whereas renin–angiotensin–aldosterone system inhibitors and mineralocorticoid receptor antagonists where similarly given in all patients; frailer patients were also treated with higher home loop diuretic dose.

Frailty index

The constructed FI was normally distributed (online supplementary *Figure S1*) and 179 patients presented a FI < 0.21. After dividing patients into quintiles, the population was stratified as follows: Q1: FI < 0.21, $n = 179$; Q2: FI 0.21–0.29, $n = 185$; Q3: FI 0.30–0.34, $n = 199$; Q4: FI 0.35–0.4, $n = 160$; and Q5: FI ≥ 0.41, $n = 131$.

Patient reclassification

As depicted in *Figure 1*, 260 patients (30.4%) were in a FI quintile higher than the respective group based on the number of frailty domains fulfilled, 348 (40.8%) were in a lower quintile and 246 patients in the same group as defined by FI quintiles and the number of frailty domains fulfilled.

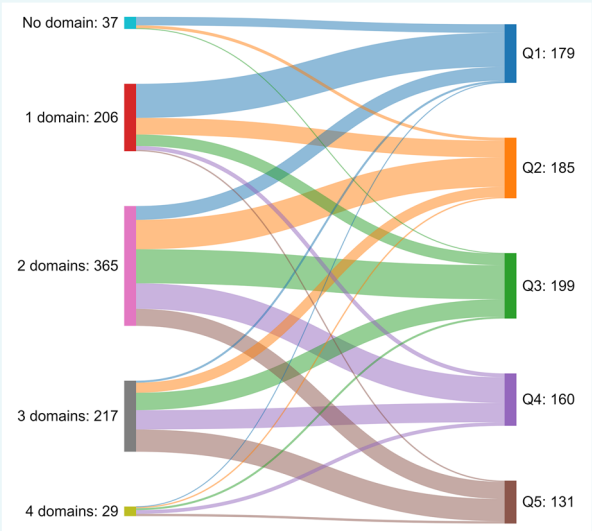


Figure 1 Patient reclassification from groups based on frailty domains to frailty index quintiles. Sankey diagram showing patient reclassification from the number of frailty domains fulfilled to the frailty quintile, based on the calculated frailty index. Q1–5, quintiles 1–5.

Clinical outcomes according to the frailty domains

An increasing number of frailty domains was associated, for each domain increase, with a higher risk of 1-year all-cause death or HF hospitalization (HR 1.43, 95% CI 1.27–1.62, $p < 0.001$) as well as of all-cause death (HR 1.72, 95% CI 1.46–2.02, $p < 0.001$), CV death (HR 1.77, 95% CI 1.45–2.15, $p < 0.001$) and HF hospitalizations (SHR 1.21, 95% CI 1.04–1.31 $p = 0.012$) (*Figure 2* and online supplementary *Figure S2*). Consistent results were found after adjusting for GDMT prescription (online supplementary *Table S2*) or other known modifiers, except for HF hospitalizations ($p = 0.073$) (online supplementary *Table S3*). When analysing domains as ordinal variables, significant differences compared with patients with no domain fulfilled were found starting from those fulfilling two domains, except for the risk of HF hospitalizations, which was significantly higher only in patients with three domains, and of CV death, which was found to be increased in those fulfilling three and four domains (*Table 2*).

The prognostic impact of each domain is reported in *Table 3*; consistent results were found at multivariable analysis (online supplementary *Table S4*). A significant difference was observed across all the adjusted HRs exclusively for all-cause death ($p = 0.026$); individual comparisons between adjusted HR are reported in online supplementary *Tables S5–S8*.

Clinical outcomes according to frailty index

When assessing FI quintiles, frailer patients demonstrated, for each quintile increase, an increased risk of 1-year all-cause death or HF hospitalization (HR 1.38, 95% CI 1.27–1.49, $p < 0.001$), as well as of all-cause death (HR 1.52, 95% CI 1.36–1.70, $p < 0.001$), CV death (HR 1.55, 95% CI 1.36–1.78, $p < 0.001$), and HF hospitalization (HR 1.22, 95% CI 1.10–1.36, $p < 0.001$) (*Figure 2* and online supplementary *Figure S2*). When analysing quintiles as ordinal variable, significant differences were found starting from Q3, except for HF hospitalizations which were higher only in Q3 and Q5 patients with respect to patients in Q1 (*Table 2*). Consistent results were found when assessing FI as a continuous variable (online supplementary *Table S9*).

All-cause mortality according to frailty index quintiles and frailty domains

Once comparing frailty domains to FI quintiles, patients in Group 2 (frailty domain group > FI quintile) had a risk of all-cause death

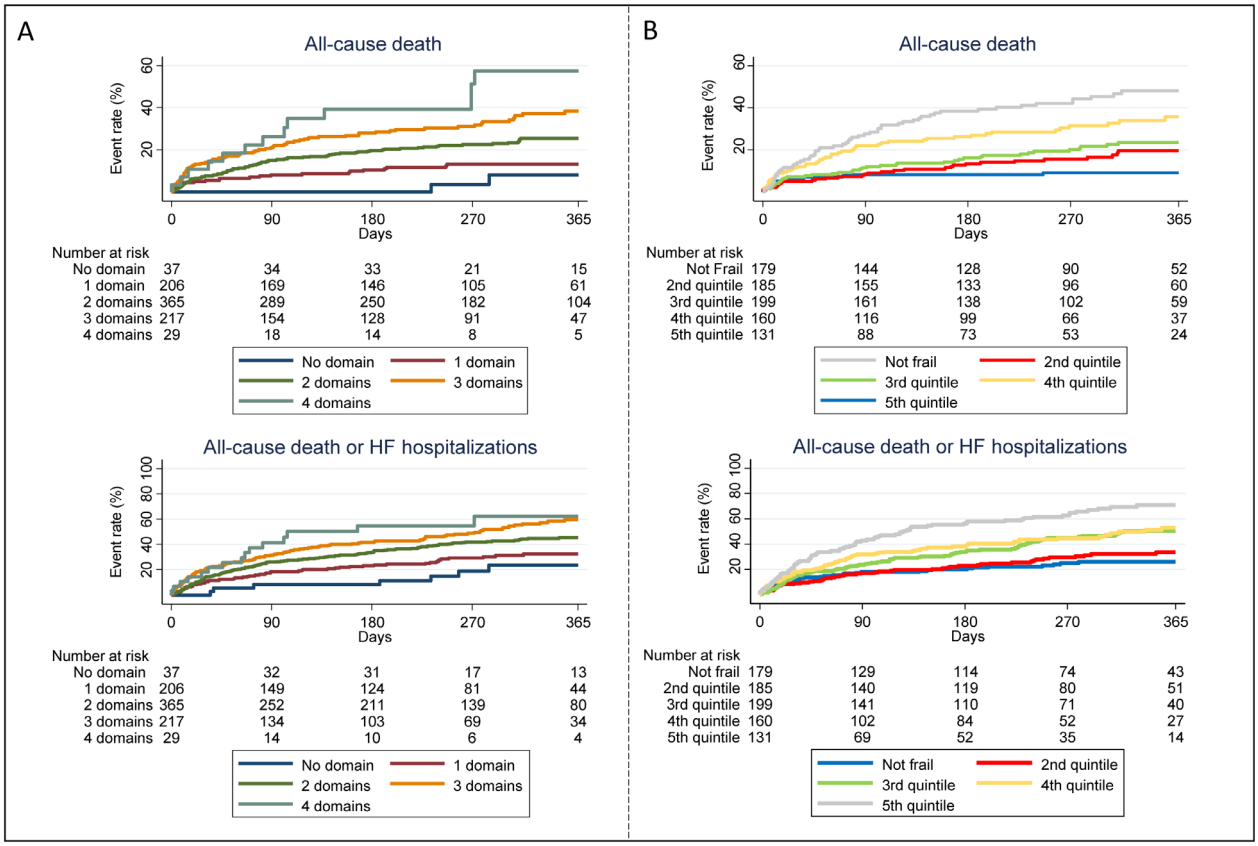


Figure 2 Clinical outcomes stratified by (*A*) the number of frailty domains fulfilled or (*B*) frailty quintiles (*B*). (*A*) Kaplan–Meier curves showing the impact of the number of frailty domains on all-cause death and the composite of all-cause death or heart failure (HF) hospitalizations. (*B*) Kaplan–Meier curves showing the impact of frailty quintiles on all-cause death and the composite of all-cause death or HF hospitalizations.

Table 2 Impact of the number of frailty domains and frailty quintiles on clinical outcomes

Subgroup	All-cause death		CV death		First HFH		All-cause death or HFH	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	SHR (95% CI)	*p*-value	HR (95% CI)	*p*-value
No domain	**ref**	–	ref	–	ref	–	ref	–
One domain	2.39 (0.56–10.12)	0.24	1.59 (0.36–6.90)	0.54	1.51 (0.60–3.82)	0.38	1.68 (0.77–3.69)	0.19
Two domains	4.65 (1.15–18.95)	0.032	3.10 (0.76–12.72)	0.12	1.94 (0.79–4.75)	0.15	2.57 (1.2–5.48)	0.015
Three domains	7.47 (1.83–30.46)	0.005	5.68 (1.38–23.31)	0.02	2.36 (0.95–5.84)	0.06	3.58 (1.67–7.69)	<0.001
Four domains	11.63 (2.62–51.55)	<0.001	7.85 (1.70–36.37)	0.008	1.87 (0.56–6.23)	0.31	4.36 (1.78–10.7)	<0.001
Q1	ref	–	ref	–	ref	–	ref	–
Q2	1.88 (1.01–3.49)	0.05	1.37 (0.68–2.78)	0.38	1.01 (0.61–1.67)	0.97	1.21 (0.80–1.82)	0.37
Q3	2.36 (1.30–4.26)	0.005	1.56 (0.79–3.08)	0.20	1.74 (1.11–2.72)	0.015	2.00 (1.37–2.91)	<0.001
Q4	3.93 (2.20–7.01)	<0.001	3.50 (1.86–6.57)	<0.001	1.21 (0.74–2.00)	0.45	2.21 (1.50–3.26)	<0.001
Q5	5.83 (3.30–10.30)	<0.001	5.02 (2.70–9.34)	<0.001	2.40 (1.50–3.83)	<0.001	3.61 (2.48–5.27)	<0.001

CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalization; HR, hazard ratio; Q1–5, quintiles 1–5; SHR, subhazard ratio.

Table 3 Impact of each frailty domain on clinical outcomes at univariable analysis

Frailty domain	All-cause death		CV death		First HFH		All-cause death or HFH	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	SHR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Clinical domain	1.72 (1.22–2.42)	0.002	1.79 (1.19–2.70)	0.005	1.38 (1.00–1.91)	0.05	1.49 (1.16–1.92)	0.002
Functional domain	3.09 (1.98–4.81)	<0.001	3.49 (2.01–6.07)	<0.001	1.39 (0.99–1.95)	0.06	1.93 (1.45–2.55)	<0.001
Social domain	0.94 (0.69–1.27)	0.67	1.02 (0.72–1.46)	0.9	1.10 (0.82–1.47)	0.52	1.01 (0.80–1.26)	0.96
Psycho-cognitive domain	2.12 (1.58–2.84)	<0.001	1.98 (1.39–2.82)	<0.001	1.04 (0.75–1.44)	0.82	1.55 (1.22–1.96)	<0.001

CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalization; HR, hazard ratio; SHR, subhazard ratio.

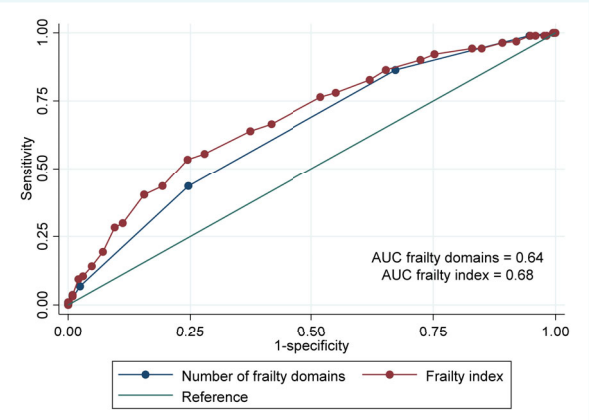


Figure 3 Receiver-operating characteristic (ROC) curve comparison for frailty domains versus frailty index with respect to all-cause death. ROC curves demonstrating the performance of the frailty index and the number of frailty domains to predict all-cause death. AUC, area under the curve.

similar to those in Group 1 (frailty domain group = FI quintile, HR 0.82, 95% CI 0.56–1.20), whereas patients in Group 3 (frailty domain group < FI quintile) had a higher risk compared with Group 1 (HR 1.72, 95% CI 1.21–2.44). The improved predictive ability of FI compared with the number of frailty domains fulfilled with respect to all-cause mortality was also supported by plotting ROC curves for both models (area under the curve (AUC) for frailty domains = 0.64, 95% CI 0.60–0.68 vs. AUC FI = 0.68, 95% CI 0.64–0.73, $p = 0.004$) (*Figure 3*). The optimal cut-off point to maximize sensitivity and specificity for the FI was 0.37.

Discussion

The importance of frailty assessment in HF patients has been investigated by multiple studies.[12,14] A recent systematic review evaluating the relationship between frailty and adverse outcomes in patients with HF reported that, among the 20 included studies, frail patients presented an increased risk of mortality (HR 1.59, 95% CI 1.39–1.82) and HF hospitalization (HR 1.31, 95% CI 1.21–1.42).[17] However, included studies assessed frailty via heterogeneous methods, mostly based on the cumulative deficit approach or the physical frailty model, the former being hard to apply in clinical practice and the latter being focused only on a small portion of the clinical characteristics of these patients.[4] Such limits are widely known: another meta-analysis reported a high heterogeneity ($I^2 = 98.26\%$) when assessing the prevalence of frailty in patients with HF.[1] Therefore, both approaches might impair a reliable evaluation of the prevalence and prognostic impact of such condition.

In our study, we proposed an alternative approach to frailty evaluation[4]; to our knowledge, this is the first study evaluating the use of the 2019 HFA-ESC definition of frailty, which was proposed

to be easier to implement in every day clinical practice and to incorporate more domains than a classical FI.

Our analysis confirmed the high prevalence of frailty in patients with HF, specifically addressing those at risk for advanced HF (i.e., presenting at least one 'I NEED HELP' marker). More than 95% of patients in our cohort had at least one frailty criterion and approximately two thirds fulfilled two or more frailty domains. About 5% of included patients satisfied all four criteria of the 2019 HFA-ESC definition of frailty (*Graphical Abstract*). The most common domains were the clinical and functional ones. As expected, patients fulfilling the definition of more frailty domains had progressively greater prevalence of comorbidities, older age, and female sex, and lower estimated glomerular filtration rate and serum haemoglobin. These findings are in line with those reported in a similar subanalysis from the TOPCAT trial, which, however, used a cumulative deficit approach to assess frailty.[14] Therefore, we also constructed a cumulative deficit FI which identified ~80% of patients as 'frail' by applying the frequently used cut-off of 0.21. With respect to previous studies, the percentage of patients deemed to be frail in our analysis is higher, a difference possibly related to the inclusion of stable outpatients in those studies, which typically excluded patients with advanced HF.[12,18] Therefore, comparison with the results from these studies should be cautiously interpreted, not only due to differences in patient phenotype and inclusion criteria, but also to the number and type of variables included in the FI calculation.

In our study, both approaches to frailty identification allowed to detect patients at increased risk of adverse outcomes. In particular, the cumulative number of frailty domains, as well as the stratification of the FI in quintiles, were associated with a progressive increase in the risk of adverse events. In the setting of patients at risk for advanced HF, our findings corroborate available evidence on the prognostic impact of frailty. Indeed, the results from our study stress the recognition of frailty as a fundamental step for an accurate risk stratification of patients with HF, as the high number of comorbidities and the impaired functional capacity typical of these patients make them more vulnerable, reduce daily autonomy and their resistance to stressors.[19] Not surprisingly, frailty contributes to adverse short- and long-term outcomes both in patients managed medically and in relation to interventional procedures, due to an increased risk of complications and limited benefit,[20] and its prognostic role appears to be independent of specific HF risk scores.[21–23] Frailty assessment is particularly relevant in patients with advanced HF, for whom most of the limited therapeutic options involve costly interventional procedures such as mitral valve edge-to-edge repair and surgical procedures such as left ventricular assist device implantation. Indeed, worse outcomes have been reported in frail patients undergoing both mitral valve edge-to-edge repair and left ventricular assist device implantation.[24–26] It should be stressed that frailty recognition is important not only to avoid potentially futile interventions, but also because frailty can be managed, and consequently procedural risks reduced and short- and long-term outcomes improved.[27]

Of interest, rates of GDMT prescription, except for beta-blockers, were similar among multiple degrees of frailty, suggesting comparable treatment intensity in our cohort, and did not modify the effect of frailty on the risk of adverse events (online supplementary *Table S2*). Nevertheless, prescription and up-titration of GDMT remained limited in a significant proportion of patients, with a potential role of clinical inertia also in this cohort.[28]

The exclusion of 295 out of 1149 patients (25.7%) from the entire HELP-HF registry due to missing information in at least one of the domains might question the easiness of introducing such method, but such limitation should be ascribed to the retrospective nature of our study. Better granularity may be obtained via a direct and prospective assessment of frailty domains, as proposed by the HFA-ESC consensus,[4] thus facilitating frailty identification in daily clinical practice, where the application of a FI is surely less immediate. In addition, such limitation may have also underestimated the ability of frailty domains to predict adverse prognosis in our population, especially when considering the social domain. Nonetheless, frailty domains showed a suboptimal accuracy in all-cause death prediction and performed significantly worse than the FI. However, FIs vary among studies, due to differences in the variables included, whereas the implementation of a frailty assessment based on four standardized domains might allow to identify in a more reproducible way patients at increased risk. As an example, our FI was calculated considering different features with respect to the index developed by Sanders *et al.*[14] and the prognostic impact of a high comorbidity burden might be enhanced by such approach, while it is probably underestimated when using frailty domains. Based on such consideration, the cut-off of FI = 0.37 to optimally identify patients at increased risk of death, found in our cohort, should only be considered as hypothesis-generating.

Moreover, it is debatable to consider as frail a patient only if all frailty domains are present: considering the definition of frailty as a condition involving multiple functional units of an individual[4,5] and based on the worse outcomes observed in our population in patients who fulfilled the definition of more than one domain, we suggest considering as frail those patients fulfilling at least two of the HFA-ESC domains. By such an approach, the use of frailty domains might also help to overcome the limitations related to the physical frailty model, since the latter does not provide a holistic approach to frailty assessment and has been questioned in HF due to possible floor effect.[4] As regards to the social domain, we do not suggest to omit it from the four items to be evaluated, given its relevance in the holistic evaluation of the patient, the easiness of prospectively assess this domain and the recognized impact of having a caregiver,[29] despite the limited prognostic impact shown in our cohort. In line with this finding, the recently published consensus statement by the International Society for Heart and Lung Transplantation does not mention the social domain among the features to be considered when assessing and managing frailty in advanced HF.[30] In addition, in the HFA-ESC position paper on frailty in patients with HF,[4] the authors did not specify whether a specific cut-off for the number of comorbidities to be included in the clinical domain exists; therefore, we dichotomized patients according to the median number of relevant comorbidities, but, despite demonstrating a promising potential, this new method still requires extensive validation. The main limitations of our study are related to its retrospective observational nature, which limited the assessment of frailty domains

and the number of variables to be included in the FI. Moreover, no external outcome adjudication was performed. In addition, our sample size may have limited the power to detect significant differences in the risk of clinical outcome, especially for the smallest subgroups, as well as the conduction of further sub-analysis.

In conclusion, in our contemporary, real-word, multicentre cohort of patients with HF and at least one high-risk 'I NEED HELP' marker, frailty assessment via the 2019 HFA-ESC frailty domains confirmed frailty as a highly prevalent condiamong patients with HF and identified those at increased risk of adverse events. Similar findings were obtained using a FI, despite the latter being more effective in predicting the risk of mortality. Prospective studies are needed to better and directly define the impact of such domains on patients' prognosis.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: M.P. received personal fees from Abbott Vascular, AstraZeneca, Boehringer Ingelheim and Vifor Pharma. D.S. reports personal fees from Novartis, Merck, GSK, Novo Nordisk, Janssen, outside the submitted work. M. Merlo reports personal fees from Pfizer, Novartis, Novo Nordisk and Vifor pharma, outside of the present work. G.S. reports consulting fees from Novartis, Impulse Dynamics and Biotronik, and speaker and honoraria from Novartis, Bayer, AstraZeneca, Boston Scientific, Vifor Pharma, Menarini and Akcea Therapeutics, outside the submitted work. M. Metra received personal consulting honoraria of minimal amount from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Edwards Therapeutics, Roche Diagnostics for participation in advisory board meetings and executive committees of clinical trials. All other authors have nothing to disclose.

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