Frailty Is Common in Heart Transplant Candidates But Is Not Associated With Clinical Events and Is Reversible After Heart Transplantation

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Assessment of frailty before heart transplant (HT) is recommended but is not standard in most HT protocols. Our objective was to evaluate frailty at inclusion in HT list and during follow-up and to assess the influence of baseline frailty on prognosis. A prospective multicenter study in all adults included in the nonurgent HT waiting list. Frailty was defined as Fried's frailty phenotype score ≥3. Mean follow-up was 25.9 ± 1.2 months. Of 99 patients (mean age 54.8 [43.1 to 62.5] years, 70 men [70.7%]), 28 were frail (28.3%). A total of 85 patients received HT after 0.5 ± 0.01 years. Waiting time was shorter in frail patients (0.6 years [0.3 to 0.8] vs 0.2 years [0.1 to 0.4], p = 0.001) because of an increase in priority. Baseline frailty was not associated with overall mortality, (hazard ratio 0.99 [95% confidence interval 0.41 to 2.37, p = 0.98]). A total of 16 transplant recipients died (18.8%). Of the remaining 69 HT recipients, 65 underwent frailty evaluation during follow-up. Patients without baseline frailty (n = 49) did not develop it after HT. Of 16 patients with baseline frailty, only 2 were still frail at the end of follow-up. Frailty is common in HT candidates but is reversible in most cases after HT and is not associated with post-transplant mortality. Our results suggest that frailty should not be considered an exclusion criterion for HT. **(Am J Cardiol 2023;205:28−34)**

Keywords: frailty, heart transplantation, mortality, reversible

Frailty, defined as vulnerability to stressors, is common in patients with heart failure (HF), affecting 10% of older people (≥65 years) and as many as 54% of those with HF.[1,2] Most studies agree on its prognostic value and its association with hospitalizations and higher mortality.[3] Previous studies suggest that frailty is common in heart transplant (HT) candidates and might influence post-transplant mortality.[4,5] A recent consensus recommends assessing frailty when listing patients for HT, suggesting the use of a modified version of Fried's frailty phenotype (FFP),[6] although this scale, was initially developed for elderly populations (≥65 years old) and its use in younger populations is still uncertain.[7] Our aim was to evaluate frailty at inclusion in HT list and during follow-up and to assess the influence of frailty on prognosis following the international recommendations previously mentioned.

Methods

The design, protocol, and baseline characteristics of the Frailty Evaluation after List Inclusion, Characteristics, and Influence on Transplantation And Results (FELICITAR) study have been previously published.[8,9] In summary, FELICITAR is a prospective observational consecutive multicenter registry of adults listed for elective or emergency list 1 HT, excluding bedridden patients and emergency list 0 (when listing inclusion). The organ allocation system in Spain when listing was as follows: Elective list: patients who were not on emergency list 0 or 1. Emergency list 1: Regional preference. Patients on normofunctional medium-term and long-term ventricular assist devices (VADs) or patients with a VAD that was dysfunctional owing to line infection, digestive bleeding,

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or severe right ventricular failure. It also included patients with protein-losing enteropathy because of a dysfunctional Fontan connection. Emergency list 0: National preference. This included patients with short-term VAD, extracorporeal membrane oxygenation (ECMO) without multiorgan failure and patients with medium-term and long-term VAD that was dysfunctional owing to mechanical impairment or thromboembolism.[10] The primary end point was all-cause mortality 1 year after HT. Secondary end points included inhospital outcomes (need of reintubation, intensive care unit stay, hospital stay, primary graft failure, infection, cytomegalovirus (CMV) infection and rejection) and other 1-year post-transplant outcomes (infection, C cytomegalovirus infection, rejection, readmissions). We evaluated patients at inclusion, every 3 months until HT and 3, 6, and 12 months after HT. Frailty was present with FFP ≥3. We also assessed depression with Patient Health Questionnaire (depression if Patient Health Questionnaire 9 ≥5), cognitive impairment with Montreal Cognitive Assessment (cognitive impairment if Montreal Cognitive Assessment ≤26), quality of life with Minnesota Living with Heart Failure Questionnaire, (scoring from zero to 105 being 0: no limitation; 105:maximum limitation) and Barthel's index for activities of daily living (<40 severe functional disability, 40 to 60 moderate functional disability, >60 mild or no functional disability). We defined 2 variables according to frailty and event prediction: baseline frailty, and pretransplant frailty (the last frailty measurement before transplant). Median time between baseline and pretransplant frailty was 3 months (25 percentile 0 months, 75 percentile 6 months), mean 3.8 ± 4.9 months. Post-transplant frailty was defined as 12-, 6-, or 3-month post-transplant frailty (the latest available).

The study was conducted in accordance with the World Medical Association Declaration of Helsinki and approved by the Ethics Committee of Gregorio Marañón General Hospital, Madrid, Spain. All patients provided informed consent.

To compare the differences in binary variables, we used the chi-square test with the Fischer correction when necessary. For continuous variables, we assessed normality using the Kolmogorov-Smirnov test. Waiting time, length of stay, intubation hours, and intensive care unit days were not normal variables and are expressed as median (quartile 1 to quartile 3) and compared with the Mann−Whitney *U*. Normal quantitative variables are expressed as mean ± SD and were compared with the Student's *t* test. Events while waiting and after HT are presented using Kaplan−Meier curves. We analyzed univariate mortality using the log-rank test. Multivariable Cox regression analyses (backward selection) were performed to determine mortality predictors and to assess the independent association of frailty with mortality. All variables with p <0.10 in univariate analyses were included in multivariable analyses. Statistical analysis was performed with SPSS, version 22.0 (IBM, Armonk, New York).

Results

Of 99 patients (mean age 54.8 years, 70 men [70.7%]), 28 were frail (28.3%). Compared with nonfrail patients, frail patients had lower Barthel's index, more advanced heart disease (hospitalized when listed and higher wedge pulmonary pressure), higher rates of depression, and worse quality of life (Table 1).

Table 1
Baseline characteristics according to the presence of frailty

	Frail (n=28)	Non-frail (n=71)	p
Demographics			
Not hospitalized (at home)	12 (42.9)	46 (64.8)	**0.046**
Sex (female)	11 (39.3)	18 (25.4)	0.170
Age	49.3±15.4	52±13.5	0.399
Body mass index (kg/m2)	23±3.8	25.7±4.2	**0.005**
Brachial circumference (cm)	25.5±4.1	27.8±4.4	**0.024**
Charlson comorbidity index	2±1	2.1±1	0.740
Baseline situation			
Number of drugs taken by the patient	8.2±3.2	9.1±3.2	0.234
VAD	2 (7.1)	4 (5.6)	0.777
Days in intensive care unit (1 year before)	3.9±7.6	3.4±12.4	0.873
Barthel scale	94.6±9.6	99±3.9	**0.027**
Heart failure etiology			
Ischemic	2(7.1)	21 (29.6)	0.052
Dilated (non-ischemic)	8 (28.6)	18 (25.4)	
Others	18 (64.3)	32 (45.1)	
Hemodynamic and analytic values			
Right atrial pressure (mmHg)	11.7±6.4	9.1±6.3	0.083
Wedge pulmonary pressure (mmHg)	21.9±8.3	17.1±8.1	**0.012**
Hb (g/L)	12.3±2.4	13.9±2	**0.001**
eGFR (ml/min/1,73m^2)	63.8±23.4	62.4±25.6	0.794
Nt-proBNP (pg/mL)	6557.8±8828.6	3871.7±5077.9	0.140
Albumin	4±0.6	4.1±0.5	0.224
Bilirrubin	1±0.8	1.1±0.8	0.465
Geriatric syndromes			
FFP score	3.5±0.7	0.8±0.7	**<0.001**
SPPB score	7.1±2.7	10±1.8	**<0.001**
Grip (kg)	20.5±9.4	30±9.8	**<0.001**
PHQ9 score	9.4±6.2	6±6.1	**0.014**
Depression	22 (75.9)	33 (47.8)	**0.011**
MoCA score	25±4.4	25.1±4.2	0.860
MLHFQ score	59.4±21.1	46.1±24.6	**0.016**

eGFR = estimated glomerular filtration rate; FFP = Fried frailty phenotype; Hb = hemoglobin; MoCA = Montreal Cognitive Assessment; MLHFQ = Minnesota Living with Heart Failure Questionnaire; PHQ9 = Patient Health Questionnaire; SPPB = Short Physical Performance Battery; VAD = ventricular assist device.

A total of 85 patients received HT. Mean time on waiting list was 0.5 ± 0.01 years, with a minimum of 9 days and maximum of 1.7 years (median 0.5 years). Waiting time was longer in nonfrail patients than in frail patients (0.6 years [0.3 to 0.8] vs 0.2 years [0.1 to 0.4], p = 0.001). Compared with nonfrail patients, frail patients increased their priority status while waiting more frequently (6-month priority increase 50.0% vs 9.6% years p <0.001) (Figure 1). Nine patients died before HT and 4 were delisted (Figure 2). Mortality on the waiting list was independently associated with pulmonary wedge pressure: hazard ratio (HR) 1.07, 95% confidence interval (CI) 1 to 1.14, p = 0.04 but not with baseline frailty (HR 1.22, 95% CI 0.24 to 6.33, p = 0.81) or baseline grip strength (HR 1.01, 95% CI 0.95 to 1.08, p = 0.682). A total of 56 patients had ≥1 follow-up

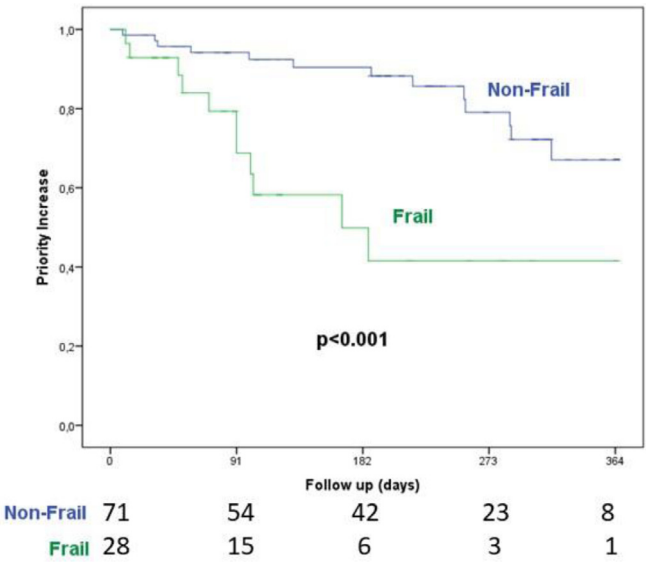

Figure 1. Kaplan–Meier curves for priority increase in waiting list according to the presence of baseline frailty.

visits before HT, 10 of them did rehabilitation, none of them were frail.

Fifteen patients were transplanted in emergency list 0 (national priority). Four with ECMO, 2 with Impella, 4 with short-term mechanical assist device, 3 with dysfunctional long-term VAD, and 2 were prioritized for hypersensitization (one with a long-term VAD). Frail patients were transplanted more frequently in emergency list 0 than nonfrail patients (32% vs 11.7%, p = 0.033). There were no relevant differences between frail and nonfrail regarding being transplanted with ECMO/Impella short VAD, or inotropes (Table 2).

Baseline frailty was associated with reintubation rate (frailty 5 [20.8%] vs no frailty 3 [5.2%], p = 0.003). Rehabilitation efforts were also similar in frail and nonfrail patients. The other inhospital and 1-year outcomes were similar in patients with and without baseline frailty (Tables 3 and 4). All-cause mortality was similar between baseline-frail and nonfrail patients (Figure 3) (actuarial mortality 25% vs 25.4%, p = 0.979) and baseline frailty was not an independent predictor of mortality (HR 0.99, 95% CI 0.41 to 2.37, p = 0.98). Pretransplant frailty was not a predictor of mortality either (HR 0.91, 95% CI 0.29 to 2.82, p = 0.87) (Figure 3). Baseline grip strength neither influenced 1-year mortality (HR 0.99, 95% CI 0.94 to 1.04, p = 0.6) nor actuarial mortality (HR 1, 95% CI 0.96 to 1.03, p = 0.78).

Frailty evolution is shown in Figure 4. A total of 16 transplant recipients died. Of the remaining 69 HT recipients, 65 underwent frailty evaluation during follow-up. Patients without baseline frailty (n = 49) did not develop it

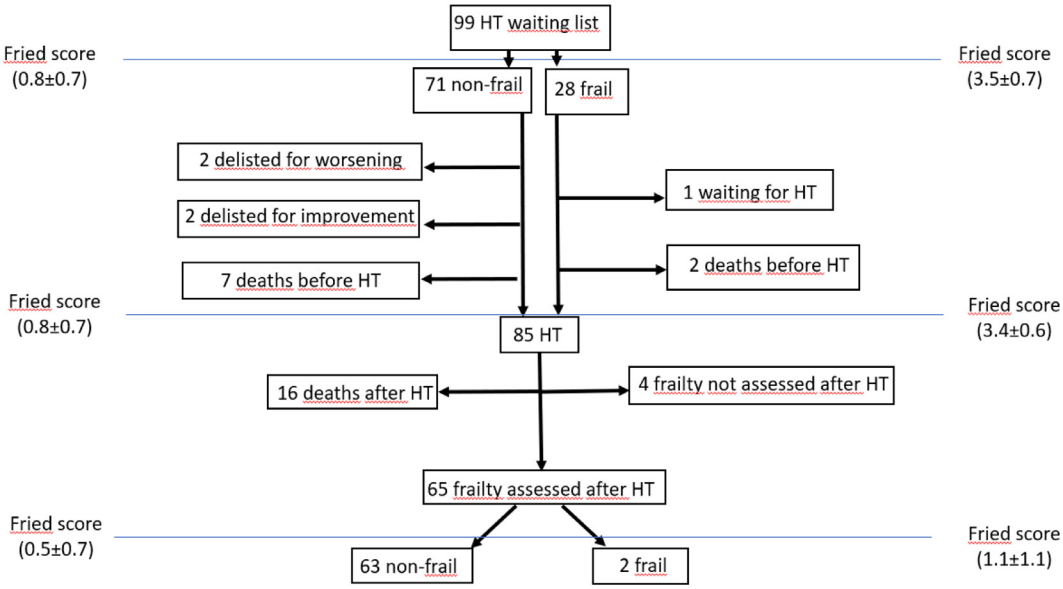

Figure 2. Flow chart according to the presence of baseline frailty.

Table 2
Clinical events according to the presence of baseline frailty: Severity at the time of transplantation

	Frail at inclusion (25)	Non-frail at inclusion (60)	P
Time on waiting list (days)	91 (42-156)	202 (105-307)	**0.001**
Iv inotropes	9/25 (36%)	18/60 (30%)	0.588
ECMO/Impella/Levitronix	5/25 (20%)	5/60 (8.3%)	0.150
Emergency list 0* **(at transplantation)**	8/25 (32%)	7/60 (11.7%)	**0.033**

ECMO = extracorporeal membrane oxygenation; iv = intravenous.
* Emergency list 0: National preference. This included patients with short-term ventricular assist devices, ECMO without multiorgan failure, and patients with medium- and long-term VAD that was dysfunctional owing to mechanical impairment or thromboembolism. Sometimes an exception could be requested for certain clinical situations such as sensitization.

Table 3
Clinical events according to the presence of baseline frailty: In-hospital outcomes

	Frail at inclusion (25)	Non-frail at inclusion (60)	P
Need of reintubation	5/24 (20.8%)	3/58 (5.2%)	**0.03**
ICU stay (days)	8 (5-18.5)	7 (5 -10)	0.466
Hospital stay (days)	22 (17-34)	22 (16-36)	0.996
Rehabilitation	17/25 (68%)	37/59 (62.7%)	0.644
Primary graft failure	7/25 (28%)	9/59 (15.3%)	0.174
Infection	9/24 (37.5 %)	18/59 (30.5 %)	0.538
Cytomegalovirus infection	5/24 (20.8 %)	6/58 (10.3%)	0.205
Rejection	4/24 (16.7 %)	6/58 (10.3%)	0.468

ICU = intensive care unit.

Table 4
Clinical events according to the presence of baseline frailty: 1-year post-transplant outcomes

	Frail at inclusión (25)	Non-frail at inclusión (60)	P
Death	5/25 (20%)	11/60 (18.3%)	0.858
Readmissions	12/18 (66.7%)	32/53 (60.4%)	0.635
Infection	14/25 (56%)	31/60 (51.7%)	0.715
Cytomegalovirus infection	9/25 (36%)	22/60 (36.7%)	0.954
Rejection	5/25 (20%)	13/60 (21.7%)	0.864

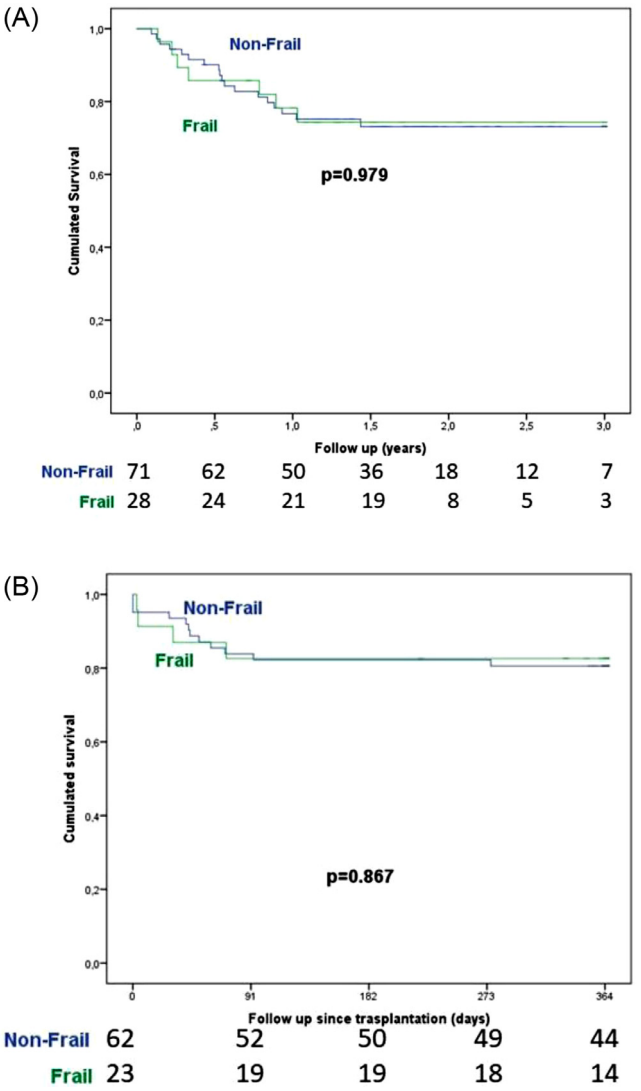

Figure 3. (*A*) Kaplan−Meier curves for the cumulative survival during follow-up. (*B*) Kaplan−Meier curves for 1-year post-transplant survival according to pretransplant frailty.

after HT. Of 16 patients with baseline frailty, 2 were still frail at the end of follow-up. In a similar way to the improvement in frailty, patients improved their grip strength (p = 0.024). However, this improvement did not

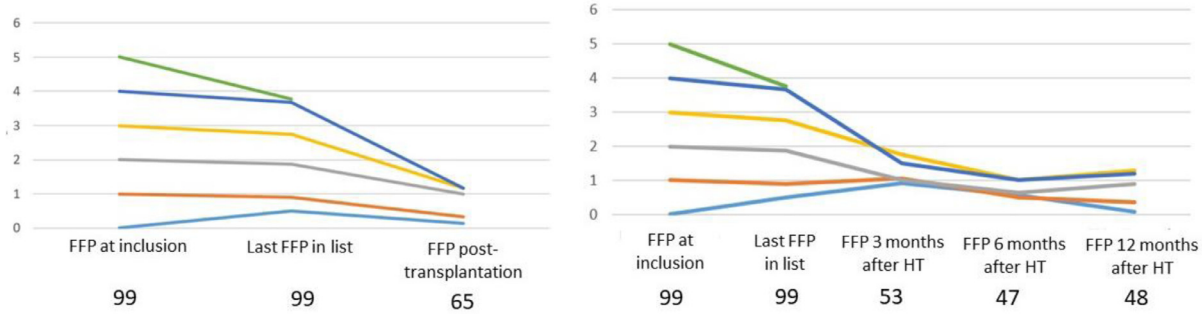

Figure 4. Frailty evolution assessed by FFP before and after heart transplantation. Each line represents the different scores of FFP at inclusion and the evolution of those patients score during follow-up (mean FFP).

reach statistical significance for each of the groups, although there was a tendency in the frail group.

Discussion

Our study shows that frailty is common in HT candidates. Frail patients wait less for HT, increase their priority more frequently, and are more frequently transplanted in national emergency. This unintentional prioritization probably led to similar survival than nonfrail patients. Also, frailty is reversible after transplant.

Although frailty has traditionally been considered a geriatric syndrome, young patients (<65 years) can develop frailty because of accelerated aging and co-morbidity.[11] In this context, frailty might be reversible.[12] In addition, younger populations with end-stage heart disease may also develop frailty. Jha et al[4] reported 33% of frail patients in an Australian population with advanced HF. A more recent analysis of the same cohort reported a 31% of frail 6 months before HT.[5] Our results are consistent with this high prevalence of frailty in the relatively young population of HT recipients.

Few data are available regarding the influence of frailty on HT outcomes. A summary of the published studies can be listed in Table 5. In the Australian cohort,[4,5,13] the authors found lower overall survival in frail patients compared with nonfrail patients, and longer hospital stays. On the contrary, we report similar overall and post-transplant survival in frail and nonfrail patients, and we did not find differences inhospital stays. These discrepancies could be because of some modifications in the physical definition of frailty and, also, because of a different proportion of

Table 5
Summary of studies assessing frailty influence on heart transplant outcomes

First author name, year	N	Type of study	Frailty measurement	%Frailty	Time from frailty assessment to HT	Influence on outcomes
Jha,2016*	120 advanced HF 46 HT recipients	Single-center Prospective	Modified FFP	33% (baseline)	○ No data	○ Overall 337 days mortality: 41% frail vs. 21 % non-frail ○ Post-transplant survival: 52% frail vs. 100% non-frail, (non-significant difference).
Macdonald, 2021*	140 HT recipients	Single-center Prospective	Modified FFP + MoCA	31% (prior to HT)	○ Frail patients: 3.1±2.1 months ○ Non-frail patients: 3.3±1.9 months	○ Post-transplant mortality: 26% frail vs. 5% non-frail
Seese,2021	36,790 HT recipients	Retrospective	Multidomain approach			○ Frail patients higher rates of mortality
	Varughese,2021	113 advanced HF 48 HT listed 32 HT recipients	Single-center Retrospective	Multidomain approach		○ Frailty tended to be associated with increased probability of death
Aili, 2022*	343 advanced HF 208 HT listed 152 HT recipients	Single-center Prospective	Modified FFP Modified FFP + MoCA	28% 38%	○ Median time: 5 months (2-9 months) (in both groups, frail and non-frail)	○ Frail patients higher rates of mortality
Lee, 2022	44 advanced HF 25 HT listed 14 HT recipients	Single-center Prospective	SPPB FFP FRS		○ No data	○ Frailty associated with overall mortality
FELICITAR	99 HT listed 85 HT recipients	Multi-center Prospective	FFP	% (baseline)	○ Frail patients: 3.03 (1.4-5.2) months ○ Non-frail patients: 6.73 (3.5-10.2) months	○ Overall mortality: 25% frail vs. 25.4 % non-frail, non.significant difference. ○ Post-transplant mortality: 20% frail vs. 18.3% non-frail, non. significant difference

* Australian cohort. Jha, Macdonald and Aili published results from the same cohort of patients in different timing.

HF = heart failure; HT = heart transplantation; FELICITAR = Frailty Evaluation after List Inclusion, Characteristics, and Influence on Transplantation And Results; FFP = Fried frailty phenotype; FRS = Frailty Risk Score; ICU = intensive care unit; MoCA = Montreal Cognitive Assessment; SPPB = Short Physical Performance Battery.

transplanted patients (only 35% of Australian patients were finally transplanted vs 86% in our cohort).[4] Moreover, in our cohort there are differences in waiting time between frail and nonfrail patients. We found that frail patients waited less for HT than nonfrail patients, increased their priority more frequently, and were more commonly transplanted in national emergency priority. This unintentional prioritization is probably because of a more advanced cardiac disease represented by cardiac cachexia with lower body mass index and brachial circumference than nonfrail patients.[14] These patients would suffer adverse events while waiting and, subsequently, transplanted before because of deterioration. This prioritization implies an increase in the risk of reintubation, but it does not increase long-term mortality. Our data suggest that HT reverses frailty, suggesting that frailty assessed by FFP in this young population mainly represents "cardiac" frailty. Thus, a sicker population requires closer follow-up and earlier transplantation.

Other studies showed adverse post-transplant outcomes using a multidomain approach to assess frailty.[15,16] However, we believe that including multimorbidity, dependency, and age to assess frailty is not representative of frailty as an independent clinical entity, but of the global assessment that is usually carried out before HT.[15,16]

In patients who underwent left VAD (LVAD), frailty has been associated with adverse outcomes. A handgrip strength <25% of body weight increases postoperative complication rates and mortality after LVAD implantation.[17] A meta-analysis of 13 studies including 3,435 patients who underwent LVAD showed that frailty was a predictor of longer intubation, hospital stay, and long-term mortality.[18]

Frailty considered as a physical phenotype is a dynamic entity.[19] Thus, frailty could be reversible or lead to disability (irreversible) when no restorative action is performed.[20,21] In patients listed for HT restorative interventions before HT are known as "prehabilitation"[22] and in HT recipients may improve post-transplant outcomes.[23] Also, frailty could be reversible with cardiac therapies and the improvement in the underlying heart disease. Our FELICITAR cohort represents a young population with this phenotype, and we report an 88% of frailty reversion 1-year after HT that could be influenced both by a pretransplant improvement and by HT. We have not shown that prehabilitation has an influence on our results. However, the lack of data on post-transplant rehabilitation limits these conclusions. Previous HF studies found frailty reversion with LVAD[17,24–26] and sacubitril-valsartan.[27] In patients who underwent LVAD or HT a significant improvement in frailty score postintervention has been described.[25]

FELICITAR is the first prospective study that suggests that there is no association between frailty and prognosis after HT. However, our study has some limitations, because of its descriptive nature, operator/observer-dependent biases, some subjective items of FFP, and lack of data on post-transplant rehabilitation. In addition, our sample size might not be large enough to find some relevant differences in outcomes between frail and nonfrail patients. Our younger frail cohort may also represent a more resilient population and there could be doubts about the suitability of FFP in this population. However, the choice of the FFP was made in accordance with international recommendations and we believe that our data reinforce the idea that this scale allows detection of "cardiac" frailty and, thus, severity in this population. This would reinforce the idea of different subgroups of frail patients.[28]

In conclusion, frailty is common in HT candidates but is reversible in most patients after HT and is not associated with 1-year mortality. This could be because of a shorter time in waiting list because of unintentional prioritization. Frailty alone should not be considered an exclusion criterion for HT.

Declaration of Competing Interest

The authors have no competing interests to declare.

Acknowledgment

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