

## FEATURED PAPERS

# The impact of frailty on mortality after heart transplantation



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**KEYWORDS:**

frailty;  
cognitive impairment;  
heart transplantation;  
mortality;  
duration of  
hospitalization

**BACKGROUND:** Frailty is prevalent in the patients with advanced heart failure; however, its impact on clinical outcomes after heart transplantation (HTx) is unclear. The aim of this study was to assess the impact of pre-transplant frailty on mortality and the duration of hospitalization after HTx.

**METHODS:** We retrospectively reviewed the post-transplant outcomes of 140 patients with advanced heart failure who had undergone frailty assessment within the 6-month interval before HTx: 43 of them were frail (F) and 97 were non-frail (NF).

**RESULTS:** Post-transplant survival rates for the NF cohort at 1 and 12 months were 97% (93–100) and 95% (91–99) (95% CI), respectively. In contrast, post-transplant survival rates for the F cohort at the same time points were 86% (76–96) and 74% (60–84) ( $p < 0.0008$  vs NF cohort), respectively. The Cox proportional hazards regression analysis demonstrated that pre-transplant frailty was an independent predictor of post-transplant mortality with a hazard ratio of 3.8 (95% CI: 1.4–10.5). Intensive care unit and hospital length of stay were 2 and 7 days longer in the F cohort (both  $p < 0.05$ ), respectively, than in the NF cohort.

**CONCLUSIONS:** Frailty within 6 months before HTx is independently associated with increased mortality and prolonged hospitalization after transplantation. Future research should focus on the development of strategies to mitigate the adverse effects of pre-transplant frailty.

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The prevalence of heart failure and resulting hospitalizations are increasing in the Western society.<sup>1</sup> Heart transplantation (HTx) remains the treatment of choice for selected patients with advanced heart failure who are resistant to other treatment options.<sup>2</sup> The aim of HTx is to reduce disability, improve quality of life, and extend the survival of patients with advanced heart failure who otherwise have a poor prognosis. HTx is a major surgical procedure that carries a substantial operative mortality risk.<sup>3</sup> Advanced age and frailty are recognized risk factors for adverse outcomes such as death and prolonged hospitalization after a wide range of surgical procedures.<sup>4</sup> Pre-transplant frailty has been associated with an increased mortality after kidney and lung transplantation<sup>5,6</sup>; however, there are little published data on the impact of frailty on survival after HTx.<sup>7</sup> It is a current International Society for Heart and Lung Transplantation's recommendation that all patients referred for heart transplant should undergo an assessment of frailty.<sup>2</sup> We have previously reported that frailty is prevalent in the patients with advanced heart failure and is an independent risk factor for pre-transplant mortality in these patients.<sup>7,8</sup> Furthermore, frailty has been observed in all adult age groups and across all body mass index categories in the patients with advanced heart failure.

We have also reported that frailty is largely reversible in the majority of patients who undergo bridge-to-transplant (BTT) ventricular assist device (VAD) implantation or HTx<sup>9</sup>; however, our previous reports included only a few patients to assess the impact of frailty on survival after these major surgical interventions. Hence, the primary aim of this study was to assess the impact of pre-transplant frailty on mortality after HTx. The secondary aim of the study was to assess the impact of pre-transplant frailty on the duration of hospitalization after HTx.

## Methods

We conducted a retrospective review of post-transplant outcomes in 140 heart transplant recipients who had undergone frailty assessment

within the 6-month period before HTx. Baseline demographic data and post-transplant outcome data were obtained with informed consent and entered prospectively into a dedicated database. The study was approved by the St Vincent's Hospital Research Ethics Committee (Reference Number 2019/ETH03097).

## Study population

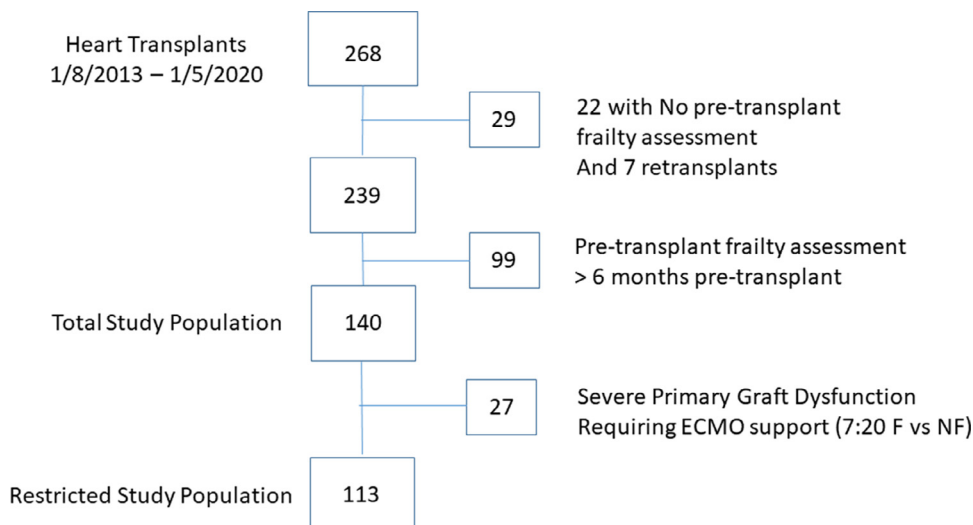
The study population was derived from 268 consecutive heart transplant recipients who underwent HTx at our institution between August 1, 2013 and April 30, 2020. We excluded 6 patients who underwent heart retransplantation and another 23 who did not undergo frailty assessment before transplantation. Of the remaining 239 patients, 99 underwent frailty assessment more than 6 months before HTx and 140 underwent frailty assessment within the 6 months before HTx (Figure 1).

## Frailty assessment

We used a modified version of the Fried Frailty Phenotype (FFP) as described previously.<sup>7,8</sup> The FFP assesses 5 physical domains: fatigue, grip strength, gait speed, unintended weight loss, and physical activity. Gait speed was timed over 5 meters. Subjects who were unable to complete the walk were scored 1 point. The first modification was to replace the unintended weight loss with the loss of appetite over the 3 months before assessment as we were concerned that weight loss may be masked by fluid retention. The second modification was to incorporate cognitive impairment as another domain. Cognition was measured using the Montreal Cognitive Assessment (MOCA) tool.<sup>10</sup> Patients who achieved a MOCA score of less than 26 out of 30 were defined as cognitively impaired and were scored 1 point on the frailty instrument. Patients who scored  $\geq 3$  points from the 6 domains were classified as frail (F).<sup>7,8</sup>

## Baseline recipient characteristics

Baseline demographic data recorded at the time of frailty assessment and a part of routine heart transplant assessment included recipient age and gender, underlying cause of heart failure, heart failure phenotype (heart failure with reduced ejection fraction or heart failure with preserved ejection fraction), echocardiographic



**Figure 1** Flowchart shows how the study population was derived from all the patients who underwent HTx between August 2013 and May 2020 at our institution. ECMO, extracorporeal membrane oxygenation; F, frail; HTx, heart transplantation; NF, non-frail.

parameters, right heart catheter measurements, and hematologic and biochemical data (including renal and liver function). We also recorded the data of patients who were managed with mechanical circulatory support before transplantation. The patients also underwent depression assessment using the Depression in Medical Illness-10 Questionnaire as described previously.<sup>7,8</sup>

## Baseline donor characteristics

Donor information included donor age and gender, cause of death, deceased donation pathway (donation after brain death or donation after circulatory death [DCD]), and mode of retrieval (static cold storage vs normothermic machine perfusion). Donors were also classified as standard criteria or marginal based on the following characteristics: donor age > 50 years, donor ischemic time > 6 hours, and donor left ventricular ejection fraction < 45% at the time of retrieval or DCD pathway to donation.

## Statistical analyses

All analyses reported in the Results section were based on the frailty definition that incorporated cognitive assessment. Selected baseline characteristics based on physical frailty alone are presented in [Supplementary Table S1](#) available online at [www.jhltonline.org](http://www.jhltonline.org), and post-transplant survival stratified by physical frailty is shown in [Supplementary Figure S1](#) online. Baseline characteristics are presented as mean  $\pm$  SD for continuous variables and as frequency (%) for categorical variables. Baseline recipient and donor characteristics were compared between F and non-frail (NF) patients using unpaired *t*-tests for continuous variables and chi-square tests for categorical variables. Post-transplant survival was measured using Kaplan–Meier cumulative survival curves, and the log-rank test was used to compare the survival rates between the F and NF groups. Post-transplant survival was expressed as percentage (95% CI). The Cox proportional hazards model was used to assess the impact of cognitive frailty on post-transplant survival after adjusting for selected covariates. Post-transplant durations of intubation, intensive care unit (ICU) stay, and hospital stay were compared using Mann–Whitney *U* tests for non-parametric data. A *p*-value less than 0.05 was considered significant.

## Results

### Prevalence of frailty

The prevalence of frailty among all 239 patients who underwent frailty assessment before HTx was 24%. Comparing those who underwent frailty assessment more than 6 months before transplantation with those who were assessed < 6 months before transplantation, the prevalence of frailty was significantly higher in those assessed within 6 months of transplantation (31% vs 14%, *p* < 0.01). In addition, VAD support was significantly less (26% vs 40%, *p* < 0.05). Other baseline characteristics, including age, gender, and body mass index, were similar between those assessed less than and more than 6 months after transplantation (see [Supplementary Table S2](#) online).

Subsequent analyses were limited to the cohort that underwent frailty assessment < 6 months before HTx: 43 of the 140 heart transplant recipients (31%) were classified as F. The mean time between frailty assessment and HTx was

$3.1 \pm 2.1$  months in the F cohort and  $3.3 \pm 1.9$  months in the NF cohort. [Table 1](#) summarizes the baseline recipient characteristics stratified by the recipient frailty status. Compared with the NF cohort, a higher proportion of the F cohort were females and had heart failure with preserved ejection fraction. F patients also had significantly higher right atrial and pulmonary artery wedge pressure and lower cardiac index at the time of frailty assessment. Serum bilirubin levels were also higher in the F cohort. [Table 2](#) summarizes the baseline donor characteristics stratified by recipient frailty status. The only significant difference was the higher proportion of female donors transplanted into F recipients. A total of 41% of the donors were classified as marginal including 24 DCD donors. There was a non-significant trend toward an increased utilization of marginal donors in NF recipients.

### Post-transplant survival

Post-transplant 1-, 2-, and 5-year survival rates for the total cohort were  $88 \pm 3\%$ ,  $87 \pm 3\%$ , and  $82 \pm 4\%$ , respectively. Kaplan–Meier survival curves stratified by frailty status are shown in [Figure 2a](#). Post-transplant survival was significantly lower in the F cohort than in the NF cohort (*p* = 0.0008, log-rank test). The survival curves separated early in the first month after transplantation and continued to diverge over the first year after transplantation. Post-transplant survival rates for the NF cohort at 1 and 12 months were 97% (93–100) and 95% (91–99), respectively. In contrast, post-transplant survival rates for the F cohort at the same time points were 86% (76–96) and 74% (60–84), respectively.

A total of 27 recipients (19%) experienced severe primary graft dysfunction and required extracorporeal membrane oxygenation support in the immediate post-transplant period. Of these 27 recipients, 7 (16%) were F and 20 (21%) were NF (*p* = non-significant, F vs NF). In total, 9 of the 27 patients with severe primary graft dysfunction died: 4 of 7 F patients and 5 of 20 NF patients (*p* = non-significant). [Figure 2b](#) shows the post-transplant survival stratified by frailty status after the exclusion of 27 patients who experienced severe primary graft dysfunction. Post-transplant survival remained significantly poorer in the F cohort than in the NF cohort. [Table 3](#) shows the causes of death stratified by frailty status.

A total of 37 heart transplant recipients were on VAD support before transplantation. All 37 had undergone frailty assessment before VAD implantation and again before HTx. [Figure 3](#) shows the trajectory of frailty from before VAD implantation to before heart transplantation. In total, 9 of 15 F patients became NF after VAD implantation. Conversely, 4 of 22 patients who were NF became F after VAD implantation. [Figure 4](#) shows the Kaplan–Meier survival curves after HTx for VAD-supported patients stratified by the frailty status before HTx. Post-transplant survival was significantly lower in the F cohort than in the NF cohort.

[Table 4](#) shows the results of univariate analyses of the impact of selected baseline variables on post-transplant

**Table 1** Recipients' Baseline Characteristics Stratified by Frailty Status

Frailty status, recipients' characteristics	Total, N = 140	NF, n = 97 (69%)	F, n = 43 (31%)	p-value
Age, years	53 ± 13	54 ± 13	51 ± 14	NS
Gender, n (%)				<0.005
Male	91 (65)	71 (73)	20 (47)	
Female	49 (35)	26 (27)	23 (53)	
BMI, kg/m <sup>2</sup>	26 ± 5	26 ± 5	26 ± 6	NS
Heart failure duration, years	4.7 ± 5.8	4.1 ± 5.9	5.9 ± 7.1	NS
LVEDD, mm	64 ± 13	65 ± 12	61 ± 14	NS
LVEF, %	28 ± 15	26 ± 13	31 ± 18	<0.05
HFREF, n (%)	120 (86)	88 (91)	32 (74)	<0.05
VAD support before HTx, n (%)				NS
LVAD	33 (24)	25 (26)	8 (19)	
BVAD	4 (3)	2 (1)	2 (5)	
MRAP, mm Hg	15 ± 7	14 ± 6	17 ± 7	<0.005
MPAWP, mm Hg	24 ± 8	23 ± 8	26 ± 7	<0.05
MPAP, mm Hg	34 ± 10	33 ± 9	36 ± 11	NS
Cardiac index, liter/min/m <sup>2</sup>	2 ± 0.6	2.1 ± 0.5	1.8 ± 0.7	<0.05
PVRi dynes × sec/cm <sup>5</sup> /m <sup>2</sup>	415 ± 220	408 ± 229	430 ± 198	NS
Serum creatinine, μmol/liter	111 ± 45	113 ± 48	108 ± 48	NS
eGFR, liter/min/1.73 m <sup>2</sup>	64 ± 20	64 ± 19	63 ± 22	NS
Serum bilirubin, μmol/liter	24 ± 17	21 ± 14	29 ± 22	<0.01
Serum albumin, g/liter	40 ± 6	40 ± 6	39 ± 5	NS
Hypoalbuminemia, n (%)	26 (19)	17 (18)	9 (21)	NS
Hemoglobin, g/liter	136 ± 18	132 ± 18	129 ± 17	NS
Anemia, n (%)	45 (32)	31 (32)	14 (33)	NS
MOCA score	26 ± 3	26 ± 3	24 ± 4	<0.005
Abnormal MOCA, n (%)	58 (41)	31 (32)	27 (63)	<0.001
DMI-10 score	6 ± 6	5 ± 5	7 ± 6	NS
Abnormal DMI-10, n (%)	37 (26)	22 (13)	16 (37)	NS

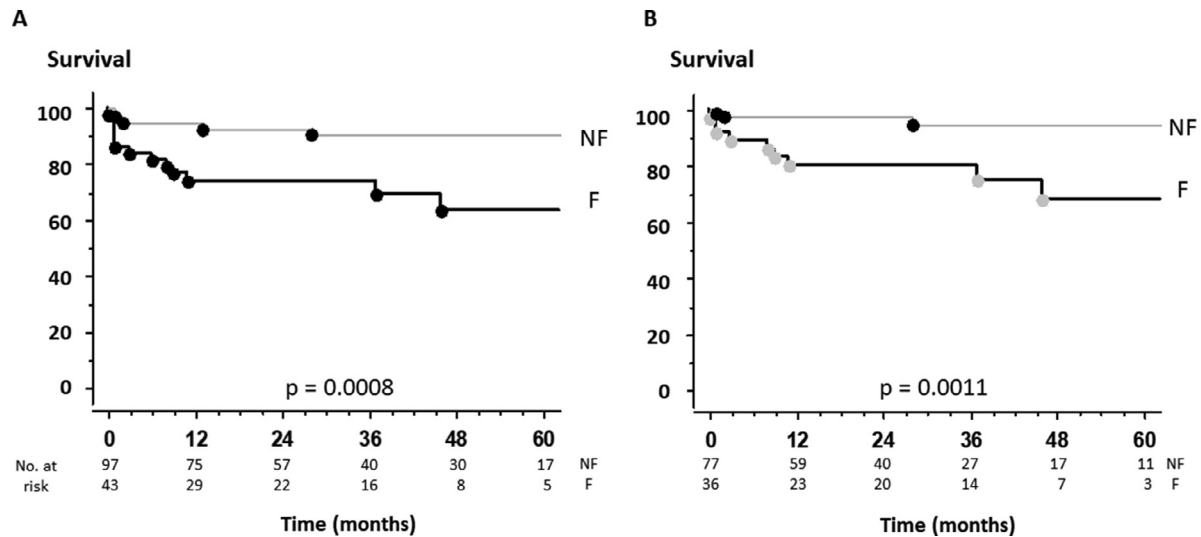
Abbreviations: BMI, body mass index; BVAD, biventricular assist device; DMI, Depression in Medical Illness; eGFR, estimated glomerular filtration rate; F, frail; HFREF, heart failure with reduced ejection fraction; HTx, heart transplantation; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MOCA, Montreal Cognitive Assessment; MPAP, mean pulmonary artery pressure; MPAWP, mean pulmonary artery wedge pressure; MRAP, mean right atrial pressure; NF, non-frail; NS, non-significant; PVRi, pulmonary vascular resistance index; VAD, ventricular assist device.

**Table 2** Donor Characteristics Stratified by Recipient Frailty Status

Recipient status, donor characteristics	Total, N = 140	NF, n = 97 (69%)	F, n = 43 (31%)	p-value
Age, years	36 ± 12	37 ± 12	36 ± 12	NS
Gender, n (%)				<0.05
Male	99 (71)	75 (77)	24 (56)	
Female	41 (29)	22 (23)	19 (44)	
D/R gender match, n (%)				NS
Matched	125 (89)	88 (91)	37 (86)	
Mismatched <sup>a</sup>	15 (11)	9 (9)	6 (14)	
Donation pathway, n (%)				NS
DBD	116 (83)	77 (79)	39 (91)	
DCD	24 (17)	20 (21)	4 (9)	
Cause of death, n (%)				NS
Hypoxic brain injury	52 (37)	35 (36)	17 (40)	
Traumatic brain injury	39 (29)	28 (29)	11 (26)	
Spontaneous ICH/CVA	41 (29)	28 (29)	13 (30)	
Other	8 (6)	4 (4)	4 (9)	
Ischemic time (DBD)	224 ± 73	221 ± 77	231 ± 66	NS
Marginal category, n (%)	58 (41)	46 (47)	12 (28)	NS
NMP use, n (%)	26 (19)	21 (22)	5 (12)	NS

Abbreviations: CVA, cerebrovascular accident; D/R, donor/recipient; DBD, donation after brain death; DCD, donation after circulatory death; ICH, intracranial hemorrhage; F, frail; NMP, normothermic machine perfusion; NF, non-frail; NS, non-significant.

<sup>a</sup>Includes 4 female donor/male recipient transplants: 3 in the NF cohort and 1 in the F cohort. All 4 recipients remain long-term survivors.



**Figure 2** Kaplan–Meier post-transplant survival curves stratified by pre-transplant frailty status. (a) The survival rates of all 140 patients who underwent frailty assessment within the 6-month period before transplantation. (b) The survival rates of the same population after the exclusion of 27 patients (7 F and 20 NF) who experienced severe primary graft dysfunction that required ECMO support. Dots denote the times of uncensored events (deaths). ECMO, extracorporeal membrane oxygenation; F, frail; NF, non-frail; No., number.

**Table 3** Causes of Death after HTx Stratified by Frailty Status

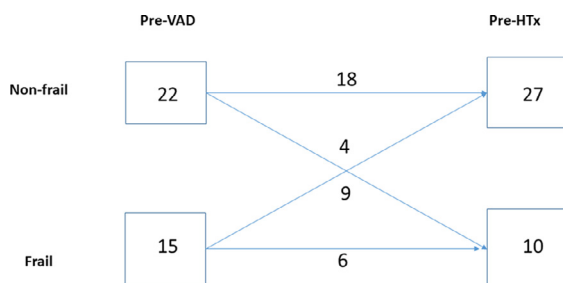
Cause of death	F (n = 43)	NF (n = 97)
Primary graft failure	4	5
Multiorgan failure	1	1
Cerebrovascular accident	2	0
Infection	2	1
Acute rejection	2	0
Cardiac allograft vasculopathy	2	1
Total	13	8

Abbreviation: F, frail; HTx, heart transplantation; NF, non-frail.

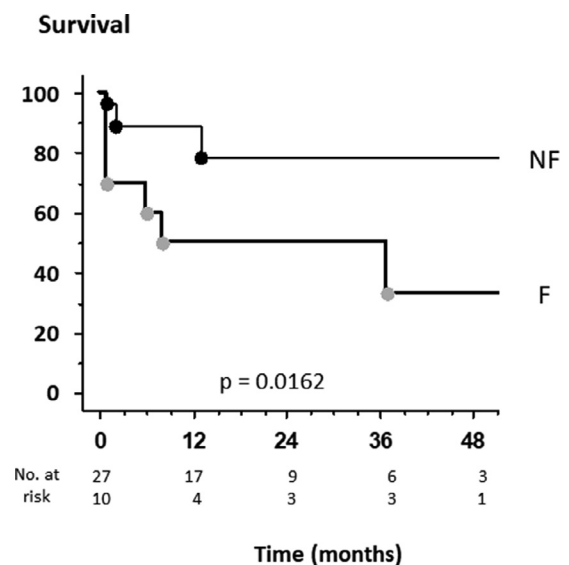
### Post-transplant duration of hospitalization

The impact of frailty on the duration of hospitalization was assessed after excluding the 27 patients with severe primary graft failure. [Table 6](#) shows the effects of pre-transplant frailty on the duration of intubation, ICU length of stay (LOS), and hospital stay after transplantation. The median duration of intubation was 19 hours in the NF group as compared with 40 hours in the F group ( $p = 0.15$ ). The median ICU LOS was 2 days longer in the F cohort ( $p < 0.01$  vs NF cohort) and the median hospital stay was 1 week longer in the F cohort ( $p < 0.05$  vs NF cohort).

survival. We then selected the significant univariate predictors of survival for inclusion in a Cox proportional hazards regression analysis of post-transplant survival. [Table 5](#) shows the results of this analysis. The only 2 independent predictors of reduced survival after HTx were frailty with a hazard ratio of 3.8 (95% CI: 1.4–10.5,  $p = 0.010$ ) and severe primary graft dysfunction with a hazard ratio of 3.2 (95% CI: 1.2–8.1,  $p = 0.016$ ).



**Figure 3** Change in the frailty status of 37 patients who underwent frailty assessment before VAD implantation and then again within 6 months before HTx. HTx, heart transplantation; VAD, ventricular assist device.



**Figure 4** Post-transplant Kaplan–Meier survival curves of VAD-supported patients stratified by pre-transplant frailty status. Dots denote the times of uncensored events (deaths). F, frail; NF, non-frail; No., number; VAD, ventricular assist device.



**Table 4** Univariate Significance of Selected Covariates for Post-Transplant Survival

Covariate	p-value
Age > 60 years	0.3282
Female gender	0.1024
Reduced grip strength (> 2 SDs below age- and gender-matched normative value)	0.0353 <sup>a</sup>
Reduced cognition (MOCA < 26)	0.2680
Depression (DMI ≥ 9)	0.5067
Renal impairment (eGFR < 60 liter/min/1.73 m <sup>2</sup> )	0.3661
Anemia	0.0119 <sup>a</sup>
Hypoalbuminemia	0.0037 <sup>a</sup>
Right heart failure (RAP > 10 mm Hg)	0.6388
VAD implantation	0.0008 <sup>a</sup>
Frailty	0.0008 <sup>a</sup>
Severe PGF requiring ECMO	0.0032 <sup>a</sup>

Abbreviations: DMI, Depression in Medical Illness; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; MOCA, Montreal Cognitive Assessment; PGF, primary graft failure; RAP, right atrial pressure; VAD, ventricular assist device.

All covariates were expressed as categorical variables with the cut-points for each variable as indicated in the Table.

<sup>a</sup>Significant p-value.

**Table 5** Cox Proportional Hazards Regression Analysis for Selected Covariates

Covariate	Hazard ratio	95% CI	p-value
Frailty	3.8	1.4–10.5	0.0103
Severe PGF	3.2	1.2–8.1	0.0160
Pre-Tx VAD	2.5	0.9–6.5	0.0669
Hypoalbuminemia	2.4	0.9–6.2	0.0782
Anemia	2.1	0.8–5.4	0.1296
Reduced grip strength	1.3	0.5–3.7	0.6235

Abbreviations: PGF, primary graft failure; Tx, Transplant; VAD, ventricular assist device.

**Table 6** The Effects of Pre-Transplant Frailty on the Post-Transplant Duration of Intubation, ICU LOS, and Hospital LOS

Time interval	Total (N = 113)	F (n = 36)	NF (n = 77)
Intubation time (hours)	20 (13–60)	40 (13–72)	19 (13–42)
ICU LOS (days)	4 (3–7)	6 (3–8)	4 <sup>a</sup> (3–7)
Hospital LOS (days)	20 (14–30)	25 (15–44)	18 <sup>b</sup> (13–29)

Abbreviations: F, frail; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; NF, non-frail.

Data expressed as median and IQR.

<sup>a</sup>p < 0.01 vs NF.

<sup>b</sup>p < 0.05 vs NF.

## Discussion

The major findings of this study were that the presence of frailty within 6 months before HTx was associated with significantly increased mortality and duration of hospitalization after

transplantation. Previous studies have reported that pre-transplant frailty is associated with increased morbidity after kidney and liver transplantation<sup>11–13</sup> and increased mortality after kidney and lung transplantation.<sup>5,6</sup> This study demonstrates a similar adverse effect of pre-transplant frailty on clinical outcomes after HTx.

We used a modification of the FFP, that has been the most commonly used frailty instrument in the studies of patients with heart failure<sup>14,15</sup> and was recently recommended for frailty studies of ambulant patients with heart failure who were being assessed for advanced heart failure therapies.<sup>16</sup> We also incorporated cognitive impairment in the frailty assessment<sup>7</sup> because this modification identifies an additional proportion of patients (about 10%) with similar pre-transplant mortality to those with physical frailty. Cognitive impairment has also been shown to identify individuals at an increased risk of post-operative delirium, stroke, and mortality.<sup>17–20</sup> We previously reported<sup>7</sup> and more recently validated (manuscript under review) that frailty as measured using our modified FFP instrument is present in approximately 33% of patients with advanced heart failure referred to our transplant program and that it is associated with an increased pre-transplant mortality. In this study, we found that the increased mortality risk associated with frailty is also observed after HTx, is of similar magnitude to the increased mortality risk observed before transplantation, and is independent of other recognized risk factors for 1-year mortality, including primary graft failure.

The substantial increase in post-transplant mortality observed in the patients with frailty raises the question of whether F patients should be accepted for HTx. Although frailty was first described in community-dwelling geriatric populations,<sup>21,22</sup> it is now recognized that frailty may also occur in association with multiple chronic disease states including heart failure.<sup>23</sup> Age-related and disease-related frailty are both proinflammatory states that have overlapping features including fatigue and reduced exercise performance.<sup>24</sup> We have previously reported that frailty is partially or fully reversible in the majority of patients after BTT VAD implantation and HTx.<sup>9</sup> Based on this experience and our understanding that frailty is largely the result of the underlying disease process in patients with advanced heart failure who are referred for HTx, we believe that younger F patients should still be considered for HTx. Assessing the suitability of older F patients with heart failure for HTx is more challenging. Older patients with heart failure often have multiple comorbidities that along with increased age may contribute to the frailty phenotype.<sup>25</sup> Such patients are less likely to demonstrate the reversibility of their frailty after major surgical intervention.<sup>25</sup> Maurer et al<sup>26</sup> reported that less than 50% of F elderly destination VAD recipients with a mean age of 71 years became NF after VAD implantation.

The knowledge that frailty is associated with increased post-transplant mortality and yet is potentially reversible after BTT VAD implantation or HTx raises 2 further questions. Is there a role for pre-habilitation to try and reverse the frailty phenotype before surgery? Second, should F patients be considered for BTT VAD implantation before

HTx as a bridge to candidacy? Pre-habilitation is an attractive concept and has been widely used to prepare patients, including the F elderly, for major surgical interventions in the hope that it will reduce postoperative complications, LOS, mortality, and healthcare costs. A systematic review of exercise pre-habilitation in the patients awaiting solid organ transplantation identified 23 studies.<sup>27</sup> Patient acceptance ranged from 16% to 100%. None of the studies reported any serious adverse effects of pre-habilitation, suggesting that this is a safe intervention even in those with advanced heart failure. Most reported improvements in exercise measures and 2 studies reported improved mental composite scores after the intervention; however, the impacts of pre-habilitation on post-transplant outcomes are still unclear. Although the majority of these studies included patients awaiting HTx or lung transplantation, only 1 study assessed frailty before and after the intervention.<sup>28</sup> This non-randomized pilot study in patients awaiting lung transplantation reported strong trends toward improved frailty scores after an 8-week home-based exercise and nutrition intervention program. More recently, Gimeno-Santos et al<sup>29</sup> reported the results of a similar non-randomized pilot study in which they showed that a multimodal pre-habilitation program improved exercise performance in the patients awaiting HTx; however, the frailty status was not assessed in that trial. So far, there have been no studies that have assessed the impact of pre-habilitation in the F heart transplant candidates on post-transplant outcomes.

VAD implantation is not limited by device availability and it provides the opportunity for post-VAD rehabilitation to reverse the frailty phenotype before listing for HTx.<sup>9,30</sup> Our experience with the VAD-supported heart transplant recipients in this study highlights the dynamic nature of frailty. Although the majority of F patients improved their frailty status after VAD implantation, 4 of 22 patients who were NF before VAD implantation subsequently developed frailty. All 4 patients had experienced major complications after VAD implantation. Although the number of patients was small, the post-transplant mortality of VAD-supported patients who were F before transplantation was high and significantly worse than for NF patients. The clinical implications of these findings are that VAD-supported patients who are NF or who become NF after VAD implantation are the suitable candidates for HTx. Conversely, patients who remain or become F after VAD implantation may face an unacceptable risk from HTx. A further clinical implication of our findings is that repeat assessment to detect changes in the frailty status will be important in identifying those patients who improve or worsen their frailty status in response to interventions such as pre-habilitation or VAD implantation. The optimal interval between assessments may vary depending on the intervention and baseline frailty status. However, based on our previous experience, we believe that a minimum of 3 months after intervention would be needed to determine the reversal or partial reversal of frailty.<sup>9</sup>

Our findings in relation to the impact of frailty on the duration of post-operative hospitalization is consistent with

the findings reported by Robinson et al<sup>31</sup> regarding the impact of cognitive frailty on the duration of post-operative hospitalization for subjects aged over 50 years undergoing major thoracic, abdominal, or vascular surgery with planned ICU admission. In that study, pre-operative cognitive impairment was the single strongest predictor of post-operative delirium and increased hospitalization. Although we did not formally assess post-operative delirium in our cohort, we hypothesize that this is likely to be a major factor contributing to the prolonged ICU and hospital stay observed in our F patients. A prospective study with systematic delirium assessment will be needed to test this hypothesis.

## Study limitations

Our study was a single-center retrospective analysis with a limited sample size. Nonetheless, frailty was assessed prospectively with the findings entered into a dedicated database. We excluded heart transplant recipients whose frailty assessment was performed more than 6 months before the date of HTx owing to the concern that their frailty status may have altered over that period. Among the 99 patients excluded for this reason, VAD support was more common and frailty was less prevalent. We and others have previously reported the reversal of the frailty phenotype<sup>9,30</sup> and improvement in the MOCA scores<sup>32</sup> after VAD support. This observation may explain the lower prevalence of frailty in this cohort. Finally, there is clearly a survival bias for the VAD-supported cohort that subsequently underwent HTx as patients who died during VAD support were excluded from the analysis.

## Conclusions

Frailty within 6 months of HTx is independently associated with increased mortality and prolonged hospitalization after transplantation. Future research should focus on the development of strategies to mitigate the adverse effects of pre-transplant frailty, who is likely to benefit from these strategies, and should focus on how to broach these issues with patients and their families.

## Disclosure statement

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## Supplementary data

Supplementary data associated with this article can be found in the online version at [www.jhltonline.org/](http://www.jhltonline.org/).

## Supplementary materials

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