OPEN

The Relationship Between Rehabilitation and Frailty in Advanced Heart or Lung Disease

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Background. Frailty increases morbidity and mortality in patients with advanced heart and lung disease. Emerging evidence shows that postoperative cardiac or pulmonary rehabilitation can improve the frailty status of these patients. The aim of this hypothesis-generating study was to test the relationship between prehabilitation and frailty in patients with advanced heart or lung disease referred for heart and lung transplantation. **Methods.** The study was a retrospective audit of consecutive patients with advanced heart or lung disease referred for transplant assessment between January 2021 and December 2022. Frailty scores were recorded using Fried's frailty phenotype (range, 0–5), and rehabilitation status of patients at the time of frailty assessment was recorded. **Results.** Of 286 patients, 124 patients had advanced heart disease (mean age 53 ± 12 y; 82% men) and 162 patients had advanced lung disease (mean age 55 ± 12 y; 43% men). Sixty-nine (24%) patients were robust (score 0), 156 (55%) were prefrail (score, 1–2), and 61 (21%) were frail (score, 3–5). Eighty-two (29%) patients participated in hospital-based rehabilitation, 72 (25%) in home-based rehabilitation, and 132 (46%) in no rehabilitation. Frailty scores were significantly lower in patients participating in hospital-based or home-based rehabilitation compared with patients not participating in rehabilitation (0.8 ± 1.0 versus 0.8 ± 0.9 versus 2.3 ± 1.2, $P < 0.0001$). **Conclusions.** This study shows that patients participating in cardiac or pulmonary rehabilitation are less frail compared with patients not participating in rehabilitation. These findings suggest that prehabilitation could be beneficial for patients awaiting heart or lung transplantation.

(*Transplantation Direct* 2024;10: e1606; doi: 10.1097/TXD.0000000000001606.)

Frailty is a term used to describe a multidimensional syndrome in which a patient's physiological reserve is decreased, affecting multiple organs, and putting them in a state of increased vulnerability to stressors.[1] Frailty is known to increase the risk of adverse events, such as falls, disability, hospitalization, and mortality.[2,3] Frailty increases with age and is more prevalent in older people.[4] Although older patients are more vulnerable to frailty, younger patients with heart or lung failure are also vulnerable to disease-related frailty, that is, organ-failure-related frailty.[5,6] Ultimately, these high levels of frailty have led to screening to be implemented into clinical practice for risk management. This is an emerging point of focus for the perioperative clinician in charge of heart or lung transplant patients as they have a high incidence of frailty because of end-stage cardiopulmonary failure.[5,7,8]

Frail heart failure patients have a higher mortality rate than nonfrail patients both before and after heart transplantation.[9-11] Similarly, lung transplant patients with frailty were found to have increased postoperative morbidity and mortality,[12] and 1-y actuarial survival rates were lower in frail patients compared with their nonfrail counterparts.[12]

Received 23 December 2023.
Accepted 15 January 2024.

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V.D. conducted the analysis under the supervision of M.M. and P.S.M. and wrote the first draft. R.P., L.H., and S.T. conducted the frailty assessments and documented patient involvement in rehabilitation. M.W., L.E.S., L.H., P.B., K.D., and A.H. all provided critical review of the article. M.M. and P.S.M. conceived the study and oversaw the analysis and writing of the article. All authors have approved of the final version.
P.S.M. has received research grant funding from Amgen and Novartis paid to his institution and consultancy fees from Astra-Zeneca, Boehringer-Ingelheim, and Novartis for work unrelated to this submission. The other authors declare no conflicts of interest.
Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

ISSN: 2373-8731
DOI: 10.1097/TXD.0000000000001606

Despite the high morbidity and mortality rates associated with frailty, several studies have provided encouraging evidence that the frailty phenotype can be reversed in patients after a heart or lung transplant. One study observed that 12 of 13 heart transplant recipients successfully reversed their frailty posttransplant through rehabilitation.[13] Another study revealed that 17 of 18 lung transplant recipients were recategorized as nonfrail from frail following rehabilitation posttransplant.[14]

These studies successfully showed reversibility in frailty following heart or lung transplantation using rehabilitation. This led us and others to explore the possibility that prehabilitation can be used to reverse frailty or lower frailty scores in patients before their operation to reduce operative and postoperative risks. Prehabilitation is a novel concept where rehabilitation is started during the preoperative period as well as managing any other risk factors that the patient may have before the surgery.[13] Some prospective studies have provided preliminary evidence that frailty scores and physical performance can be improved through rehabilitation in patients with advanced heart and lung disease.[15-21]

The aim of this study was to identify whether advanced heart or lung disease patients participating in a hospital-based rehabilitation program or a home-based structured exercise program at the time of their frailty assessment had lower frailty scores compared with patients who are not under any type of rehabilitation program.

MATERIALS AND METHODS

Study Design

The study was a retrospective audit of patient data stored in the Cardiopulmonary Research (CPR) database at St Vincent's Hospital in Sydney. All patients who are referred for heart or lung transplantation undergo an assessment by a multidisciplinary team. This team consists of transplant physicians and surgeons, transplant nurse coordinators, physiotherapists, dieticians, occupational therapists, and medical social workers. Routine assessments for heart and lung transplantation include frailty assessment, cognitive assessment, and depression assessment, which were conducted by the occupational therapist. The occupational therapist confirmed whether the advanced heart and lung disease patients were participating in any hospital-based rehabilitation program, home-based structured exercise program, or neither at the time of their frailty assessment. The results of the frailty assessment, cognitive and depression assessment, and participation in hospital-based rehabilitation, home-based structured exercise program, or neither of all the patients were entered into the CPR database in the Heart-Lung clinic. The Human Research Ethics Committee approved the study protocol at St Vincent's Hospital Sydney. The study's Human Research Ethics Committee reference number is 2023/ETH01371. The study complied with the International Society for Heart Lung Transplantation ethics statement.

Study Population

The study reviewed CPR database records of 328 consecutive patients between January 1, 2021, and December 31, 2022. Of these patients, 18 were excluded due to having had previous heart or lung transplants, and a further 16 were excluded due to previous ventricular assist device implants. Finally, 8 more patients were excluded due to missing rehabilitation statistics, leaving the total study population of 286: 124 patients with advanced heart disease and 162 patients with advanced lung disease (Figure 1).

Outcome Measures

Frailty was determined using the modified Fried's frailty phenotype instrument. The 5 domains used for the assessment tool are outlined in Table 1 and have previously been described in detail.[9,10] Each domain of the instrument has a possible score of 0 or 1. The categorization of the scoring was done such that patients with a score of 0 were considered nonfrail or robust, patients with a score of 1 to 2 were prefrail, and patients with a score of 3 to 5 were categorized as frail.

Cognitive impairment in patients was assessed using the Montreal Cognitive Assessment (MOCA), where scores <26 were considered cognitive impairment.[22] The depression assessment was done using the 10-item Depression in Medical Illness (DMI-10) questionnaire where patients having the score >9 were considered as depressed.[23]

The hemoglobin levels and albumin levels were also measured in grams per liter, and the status of whether patients were inpatients or outpatients at the time of frailty assessment was also noted.

Statistical Analysis

All continuous variables from the analyses are presented as mean values and SDs. All categorical data are presented as a proportion of the overall study population. Chi-square tests were used for all categorical data, whereas unpaired *t* tests were used for independent, continuous variables. Frailty category and rehabilitation status for heart and lung patients were tested using 2 × 3 contingency tables. In the combined analysis for frailty status and rehabilitation status age, MOCA score, DMI score, hemoglobin, and albumin were all tested using analysis of variance, whereas sex was tested using a contingency test. All the statistical analyses were performed with IBM SPSS Statistics software (version 26).The *P* value for statistical significance has been defined as a *P* value of <0.05.

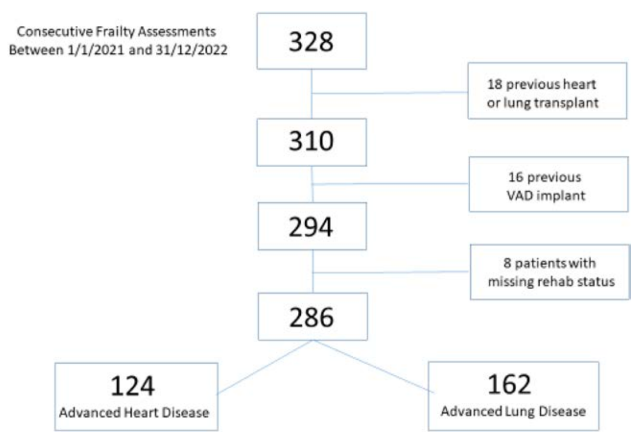

FIGURE 1. Consort diagram depicting the total study population including the number of patients who were excluded and their reason for exclusion.

TABLE 1.

Modified FFP instrument including the 5 domains of physical frailty

Domain	Measurement	Result
Exhaustion	In the past month have you felt more exhausted than usual: Yes—most of the time No—none of the time/rarely	A response of "yes" met the criterion for exhaustion
Grip strength	Jamar Dynamometer	Weak if the average of 3 consecutive attempts on the left and right hand fell <2 SDs of sex- and age-adjusted normative values
Mobility	5 m gait speed test	Slow if the average of 3 attempts took ≥6 s to complete 5 m
Unintentional weight loss	In the last 6 mo, have you lost >5 kg of dry weight without trying?	A response of Yes met the criterion for unintentional weight loss
Physical activity	How often do you do physical exercise? Less than once per week/hardly ever once per week or more	A response of "less than once per week or hardly ever" was classified as physical inactivity

FFP, Fried's frailty phenotype.

RESULTS

Study Population Characteristics

The study population consisted of 162 patients with advanced lung disease (mean age 55 ± 12 y; 43% men) and 124 patients with advanced heart disease patients (mean age 53 ± 12 y; 82% men). The distribution of diagnoses in the heart and lung population is depicted in Figure 2, with dilated cardiomyopathy being the most common diagnosis in the heart population, whereas interstitial lung disease was the most common diagnosis in the lung population.

Prevalence of Frailty

A combined analysis of heart and lung patients regarding frailty status revealed that frailty was independent of age as depicted in Table 2. A higher proportion of men were in the frail and prefrail groups (72% and 61%, respectively) compared with the robust group (49%; $P = 0.028$; frail versus prefrail versus robust). Frailty was associated with a lower MOCA score in the frail and prefrail groups compared with the robust group ($P < 0.005$). Frailty was associated with a higher DMI score and lower hemoglobin and albumin levels in the frail group as compared with the prefrail and robust groups ($P < 0.0001$). Applying the Bonferroni Correction, frailty was independent of age and sex, whereas a lower MOCA score, higher DMI score, and lower hemoglobin and albumin levels were statistically associated with frailty.

As shown in **Table S1** (**SDC,** http://links.lww.com/TXD/A634), which only contains results from advanced heart disease patients, frailty was independent of age, sex, and MOCA score and was associated with a higher DMI score (frail versus prefrail versus robust, $P = 0.033$) and lower hemoglobin and albumin levels (frail versus prefrail versus robust, $P < 0.0001$). Following the application of the Bonferroni Correction, frailty was statistically associated with lower hemoglobin and albumin levels and independent of the other domains.

As shown in **Table S2** (**SDC,** http://links.lww.com/TXD/A634), which contains results from advanced lung disease patients only, frailty was independent of age, sex, and hemoglobin level. Frailty was associated with a lower MOCA score ($P = 0.013$), a higher DMI score ($P = 0.0002$), and lower albumin level ($P = 0.027$). Following Bonferroni Correction, frailty was independent of age, sex, MOCA score, hemoglobin level, and albumin level and is only statistically associated with a higher DMI score (frail versus prefrail versus robust).

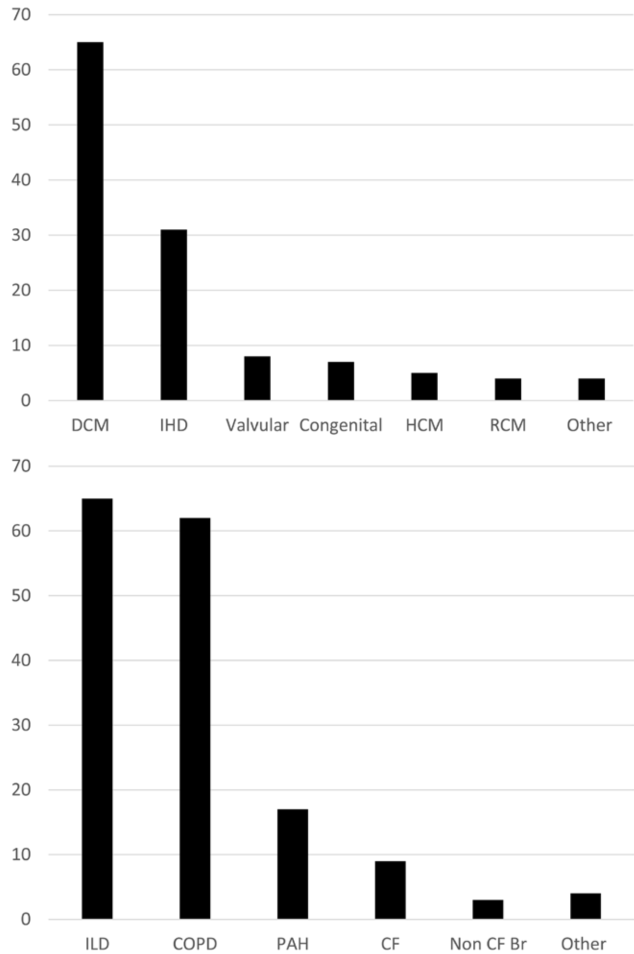

FIGURE 2. Distribution of diagnoses among the study population patients. The x-axis in both panels depicts the different diagnoses of patients in the study. The y-axis in both figures depicts the number of cases for each condition. The upper panel depicts the distribution of diagnoses in the advanced heart disease population from a total of 124 patients. The lower panel depicts the distribution of diagnoses in the advanced lung disease population from a total of 162 patients. CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; IHD, ischemic heart disease; ILD, interstitial lung disease; non-CF Br, non-CF bronchiectasis; PAH, pulmonary arterial hypertension; RCM, restrictive cardiomyopathy; VHD, valvular heart disease.

Rehabilitation Status at the Time of Frailty Assessment

At the time of frailty assessment, it was recorded whether patients were participating in hospital-based rehabilitation,

TABLE 2.

Baseline characteristics of the total study population defined by frailty status

Frailty status	Robust (N = 69)	Prefrail (N = 156)	Frail (N = 61)	*P*
Age, y	54 ± 12	53 ± 13	55 ± 10	NS
Sex (M:F)	34:35	95:61	44:17	0.028
% Male	49%	61%	72%	
MOCA (–/30)	27 ± 2	26 ± 3	26 ± 3	<0.005
DMI (–/30)	6 ± 5	8 ± 7	11 ± 8	<0.0001
Hemoglobin, g/L	142 ± 19	145 ± 20	126 ± 23	<0.0001
Albumin, g/L	39 ± 4	39 ± 5	35 ± 5	<0.0001

Continuous data presented as mean ± standard deviation. Categorical data presented as number and percentage.
DMI, Depression in Medical Illness Questionnaire; M:F, male:female; MOCA, Montreal Cognitive Assessment; NS, not significant.

a home-based structured exercise program, or neither. One hundred thirty-two patients (46% of the cohort) underwent no rehabilitation. Of the remaining patients, 82 were participating in a hospital-based rehabilitation program, whereas 72 were participating in a home-based structured exercise program. A higher proportion of patients with advanced lung disease were participating in some form of rehabilitation compared with the advanced heart disease population.

Combined analysis (Table 3) of heart and lung patients revealed that MOCA score, DMI score, and hemoglobin levels were independent of rehabilitation status. Patients who were participating in hospital-based or home-based rehabilitation had significantly lower frailty scores compared with patients who were participating in no rehabilitation (0.8 ± 1.0, 0.9 ± 1.0, and 2.3 ± 1.2, respectively; $P < 0.0001$). In terms of the frailty category, a higher proportion of hospital-based and home-based rehabilitation patients were categorized as robust, whereas a higher proportion of patients undergoing no rehabilitation were frail ($P < 0.0001$). Serum albumin levels were significantly lower in the no rehabilitation group as opposed to hospital-based and home-based rehabilitation groups ($P < 0.0001$).

Separate analysis of the heart patients (Table 4) and lung patients (Table 5) revealed similar findings to those observed in the combined analysis.

Frailty Status and Effect of Being an Inpatient or Outpatient

Eighty-five patients were inpatients at the time of their frailty assessment. Table 6 compares their baseline characteristics and frailty scores with those of the outpatient cohort. Inpatients were more commonly men with advanced heart disease. Hemoglobin and albumin scores were significantly lower in inpatients than in outpatients ($P < 0.0001$). Frailty scores were significantly higher in inpatients compared with outpatients (2.4 ± 1.6 versus 1.2 ± 1.2, $P < 0.0001$). When looking at the frailty category, a higher proportion of inpatients than outpatients were categorized as frail, whereas more outpatients were robust compared with inpatients ($P < 0.0001$). Nonetheless, patients who were participating in hospital-based or home-based rehabilitation at the time of hospital admission had significantly lower frailty scores than patients who were not participating in any form of rehabilitation: 1.7 ± 1.4 versus 1.1 ± 0.7 versus 2.7 ± 1.1, respectively, $P < 0.0001$). Only 2 of 22 (9%) inpatients who were participating in either hospital-based or home-based rehabilitation were classified as frail compared with 35 of 63 (56%) inpatients who were not ($P < 0.0001$).

DISCUSSION

Three key findings stood out from this study. First, patients with advanced heart or lung disease who participated in hospital-based and home-based rehabilitation had significantly lower frailty scores than patients who did not participate in any rehabilitation program. This was a consistent finding across both patient cohorts. These results align with earlier studies testing the effect of structured exercise training programs in heart failure patients.[24-26] These studies have also reported that participating in center or home-based training significantly reduces frailty scores. Similarly, studies testing the relationship between frailty and rehabilitation in patients with chronic lung diseases have revealed that rehabilitation improved frailty markers in patients along with an overall favorable outcome in frailty scores of patients.[27,28]

TABLE 3.

Impact of rehabilitation status on selected characteristics of the total study population

Rehabilitation status	Hospital-based (N = 82)	Home-based (N = 71)	None (N = 133)	*P*
Heart/lung (%)	9/73 (7/45)	34/37 (28/23)	81/52 (65/32)	<0.0001
Frailty score (–/5)	0.8 ± 1.0	0.8 ± 0.9	2.3 ± 1.2	<0.0001
Frailty category (%)	35/42/5	29/40/2	5/74/54	
Robust/prefrail/frail	(43/51/6)	(41/56/3)	4/56/40	<0.0001
MOCA (–/30)	26 ± 3	27 ± 3	26 ± 3	NS
DMI (–/30)	9 ± 7	7 ± 5	9 ± 7	NS
Hemoglobin, g/L	142 ± 20	144 ± 18	137 ± 25	0.062
Albumin, g/L	39 ± 4	39 ± 4	36 ± 6	<0.0001

Continuous data presented as mean ± standard deviation. Categorical data presented as number with percentage in brackets.
DMI, Depression in Medical Illness Questionnaire; MOCA, Montreal Cognitive Assessment; NS, not significant.

TABLE 4.
Impact of rehabilitation status on the advanced heart disease study population

Rehabilitation status	Hospital-based (N = 9)	Home-based (N = 34)	None (N = 81)	*P*
Age, y	50 ± 14	56 ± 10	52 ± 12	NS
Sex (M:F)	7:2	27:7	68:13	NS
Frailty score (–/5)	1.2 ± 1.1	0.8 ± 0.7	2.3 ± 1.2	<0.0001
Frailty category (%) Robust/prefrail/frail	3/5/1 (30/60/10)	12/22/0 (35/65/0)	4/42/35 (5/52/43)	0.0001
MOCA (–/30)	27 ± 3	26 ± 3	26 ± 3	NS
DMI (–/30)	7 ± 9	6 ± 5	8 ± 7	NS
Hemoglobin, g/L	136 ± 15	142 ± 16	134 ± 25	NS
Albumin, g/L	38 ± 4	40 ± 5	36 ± 6	0.0052
Inpatient/outpatient (%)	3/6 (33/67)	11/23 (33/67)	52/29 (64/36)	<0.0001

Continuous data presented as mean ± standard deviation. Categorical data presented as number with percentage in brackets.
DMI, Depression in Medical Illness Questionnaire; M:F, male:female; MOCA, Montreal Cognitive Assessment; NS, not significant.

TABLE 5.
Impact of rehabilitation status on the advanced lung disease study population

Rehabilitation status	Hospital-based (N = 73)	Home-based (N = 37)	None (N = 52)	*P*
Age, y	56 ± 10	52 ± 15	55 ± 12	NS
Sex (M:F)	25:48	20:17	26:26	NS
Frailty score (–/5)	0.8 ± 1.0	0.8 ± 0.9	2.2 ± 1.2	<0.0001
Frailty category (%) Robust/prefrail/frail	32/37/4 (44/51/5)	17/18/2 (46/49/5)	1/32/19 (2/65/33)	<0.0001
MOCA (–/30)	26 ± 3	27 ± 2	26 ± 3	NS
DMI (–/30)	9 ± 7	7 ± 6	9 ± 7	NS
Hemoglobin, g/L	143 ± 20	147 ± 19	142 ± 23	NS
Albumin, g/L	40 ± 4	39 ± 4	37 ± 5	0.0072
Inpatient/outpatient (%)	7/66 (10/90)	1/36 (3/97)	11/41 (21/79)	0.021

Continuous data presented as mean ± standard deviation. Categorical data presented as number with percentage in brackets.
DMI, Depression in Medical Illness Questionnaire; M:F, male:female; MOCA, Montreal Cognitive Assessment; NS, not significant.

TABLE 6.
Patient demographic and frailty status based on hospital admission status

	Inpatient at frailty assessment (N = 85)	Outpatient at frailty assessment (N = 201)	*P*
Age, y	53 ± 12	55 ± 12	NS
Sex (M:F)	73:12	100:101	<0.0001
Heart/lung	66:19	58:143	<0.0001
Frailty score (–/5)	2.4 ± 1.6	1.2 ± 1.2	<0.0001
Frailty category (%)	5/43/37	62/113/26	
Robust/prefrail/frail	6/51/43	31/56/13	<0.0001
MOCA (–/30)	26 ± 3	26 ± 3	NS
DMI (–/30)	8 ± 7	8 ± 7	NS
Hemoglobin, g/L	133 ± 24	144 ± 20	<0.0001
Albumin, g/L	35 ± 5	39 ± 4	<0.0001

Continuous data presented as mean ± standard deviation. Categorical data presented as number with percentage in brackets.
DMI, Depression in Medical Illness Questionnaire; M:F, male:female; MOCA, Montreal Cognitive Assessment; NS, not significant.

The second important finding is that there is no apparent benefit in undertaking one type of rehabilitation program more than the other, that is, hospital-based rehabilitation is not more beneficial and effective than home-based structured exercise programs or vice versa. This result aligns with previous studies that have suggested that hospital-based and home-based rehabilitation programs have similar beneficial effects on heart and lung disease patients.[29-31] Our study combined data from both heart and lung disease patients and used frailty scores for comparison, whereas previous studies have used different indicators (such as gait, peak oxygen consumption, and chronic respiratory questionnaire dyspnea subscale score) to identify the end result. This finding suggests that rehabilitation helps prevention frailty or stops or reverse the development of frailty. Alternatively, the lower frailty scores could be due to more frail people being less likely to participate in rehabilitation programs. We think that the former is the more likely explanation as previous studies have revealed that reversibility and prevention of frailty are possible.[13,14,24] These studies revealed that frailty scores of patients undergoing rehabilitation after heart or lung transplantation improved significantly. However, to further confirm this hypothesis, future research in the form of a longitudinal study following up on patients enrolled in a rehabilitation program with baseline and repeat frailty assessment would be needed.

The third important result from this study is that inpatients have significantly higher frailty scores and a higher prevalence of frailty than outpatients. This is not surprising because inpatients are more likely to have a more severe clinical status and/or require more surveillance compared with outpatients who are usually in a stable condition and considered well enough to be managed at home.[32] Moreover, increased frailty is associated with an increased risk of morbidity, mortality, and hospitalization (or nursing home admission).[9,33,34] Nonetheless, it is noteworthy that inpatients who were participating in rehabilitation before their hospital admission had significantly lower frailty scores and lower prevalence of frailty compared with inpatients who were not.

Clinical and Research Implications

This study highlights the potential benefits of implementing rehabilitation during the preoperative period, rather than just postoperatively, to reduce frailty scores in patients with advanced heart or lung disease. Our findings align with the emerging concept of prehabilitation, which suggests that preparing for surgery by exercising can lead to faster recovery of function and a reduced rate of postoperative complications.[21,35,36] Research has shown that the preoperative period is when patients are most receptive to interventions and motivated to change but lack the needed confidence, making it the most appropriate time to teach and instill behavioral changes.[37,38]

Preliminary evidence has already emerged supporting the effects and benefits of prehabilitation in cardiac and lung surgery patients. In a systematic review and meta-analysis of prehabilitation before cardiac surgery, Steinmetz et al[20] reported an improvement in the 6-min walk distance, reduced length of hospital stay, and decreased risk of atrial fibrillation in patients who participated in prehabilitation as opposed to those who did not. Similarly, studies conducted on lung disease patients by Goldsmith et al and Boujibar et al revealed that patients who underwent prehabilitation had improved frailty and dyspnea scores and fewer postoperative complications compared with patients who did not undergo prehabilitation.[16,17] However, the studies in the systematic review were all reported to have a high risk of performance bias,[20] whereas the study by Boujibar et al[16] was a small clinical trial of 38 patients. In another systematic review, Pesce de Souza et al[39] examined the impact of exercise training for patients awaiting solid organ transplantation. They identified 23 articles: 7 in heart, 10 in lung, 2 in kidney, and 4 in liver transplant candidates. Although patient acceptance ranged from 16% to 100% across the studies, the median acceptance was high at 97%. Although endpoints differed between studies, most reported improvements in exercise tolerance and none reported any adverse events related to exercise. Clinical trials with larger sample sizes and lesser risk of bias are now required to confirm these results regarding the effects and benefits of prehabilitation.

Strengths and Limitations

The major limitations of this study was its retrospective single-center design and relatively small study population. In addition, participation in hospital-based rehabilitation or a structured home-based exercise program was based on self-reporting by the patients. There is likely to be a "self-selection" bias in that less symptomatic patients and those with better social support and easier access to healthcare are more likely to participate in rehabilitation programs. Additionally, being a cross-sectional study, it is difficult to determine whether the relationship between rehabilitation and frailty is causal or coincidental. Although our study is hypothesis-generating rather than hypothesis-proving, it provides strong evidence to support the conduct of a longitudinal study to investigate the role of prehabilitation in preventing or reversing frailty in patients with advanced heart or lung disease. Although hospital-based rehabilitation has the advantage of providing direct observation and supervision of patients, hospital-based programs often have limited capacity both in terms of patient volume and duration. In addition, hospital-based rehabilitation is impractical for many patients who live in rural and remote locations.

Given our observation that frailty scores were similar for patients undertaking home-based compared with hospital-based rehabilitation, we think that home-based rehabilitation has the potential to benefit a larger proportion of patients. With the increasing utilization of mobile health applications to support patient care in their home environment, we further think that an application-supported exercise and nutritional support program could be applied to patients with advanced heart or lung disease who are being assessed for advanced therapies. In an 8-wk pilot study, Singer et al[40] reported high patient acceptance and trends to improve frailty scores in 13 lung transplant candidates who received a home-based, mobile health supported prehabilitation program. Larger studies targeting prefrail or frail patients undertaking a home-based prehabilitation program are now warranted. These studies should be conducted for a minimum of 3 mo with endpoints that include patient acceptance, activity tracking, and repeat frailty assessment.[41]

CONCLUSION

Frailty is associated with increased morbidity and mortality in heart and lung disease patients. This study tested the relationship between frailty and rehabilitation in patients with advanced heart or lung disease who were being assessed for heart or lung transplantation. The key finding was that patients undergoing hospital-based rehabilitation or a home-based exercise program were significantly less frail than patients undergoing no rehabilitation. These findings suggest that having patients participate in rehabilitation preoperatively, otherwise known as prehabilitation, will be beneficial for them. In the future, prospectively designed longitudinal studies and clinical trials should be conducted to further support this hypothesis.

ACKNOWLEDGMENTS

The authors acknowledge the contribution of Mr Christopher Bragg, for his work as the database manager in maintaining the Cardiopulmonary Research database.

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