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Frailty Measures in Patients Listed for Lung Transplantation

Elyn Montgomery, RN, MCN,[1] Phillip J. Newton, RN, PhD,[2] Sungwon Chang, PhD,[1] Wenbo Peng, PhD,[1] Sunita R. Jha, PhD,[1,3] Kay Wilhelm, MBBS, MD, FRANZCP,[3-5] Peter S. Macdonald, MD, PhD,[4] Monique Malouf, MBBS, FRACP[4]

[1] Faculty of Health, University of Technology Sydney, Sydney, Australia.

[2] School of Nursing and Midwifery, Western Sydney University, Sydney, Australia.

[3] School of Medicine, University of Notre Dame, Sydney, Australia.

[4] Heart and Lung Transplant Program, St Vincent's Hospital, Sydney, Australia.

[5] Consultation Liaison Psychiatry, St Vincent's Hospital, Sydney, Australia.

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Authorship

E.M.: Participated in research design, writing of the paper, performance of the research and data analysis.

P.J.N.: Participated in research design, writing of the paper and data analysis.

S.C.: Participated in writing of the paper and data analysis.

W.P.: Participated in writing of the paper and data analysis.

S.R.J.: Participated in writing of the paper and performance of the research.

K.W.: Participated in research design, writing of the paper and data analysis.

P.S.M.: Participated in research design, writing of the paper and data analysis.

M.M.: Participated in research design, writing of the paper and data analysis.

Corresponding author: Ms. Elyn Montgomery Faculty of Health University of Technology Sydney PO Box 123 Broadway, NSW, Australia 2007 Telephone: +61 2 9514 5050 Email: elyn.montgomery@uts.edu.au

Abbreviations

BMI	Body mass index
CI	Confidence interval
CogF	Cognitive frailty
ComF	Combined frailty
DepF	Depressive frailty
DLCO	Diffusing capacity of the lung for carbon monoxide
DMI-10	Depression in Medical Illness assessment
eGFR	Estimated glomerular filtration rate
FEV_1	Forced expiratory volume in 1 second
FFP	Fried Frailty Phenotype
FVC	Forced vital capacity
HREC	Human Research Ethics Committee
ICU	Intensive care unit
IRR	Incidence rate ratio
ISHLT	International society for heart and lung transplantation
LOS	Length of stay
MCI	Mild cognitive impairment
mFFP	Modified Fried Frailty Phenotype
MOCA	Montreal Cognitive Assessment
PaO_2	Arterial partial pressure of oxygen
PF	Physical frailty

ROC	Receiver operating characteristic
SHARE FI	Survey of Health, Ageing, and Retirement in Europe Frailty Instrument
SMW	6-minute walk distance

Abstract

Background

The study aimed to determine whether the addition of cognitive impairment, depression, or both, to the assessment of physical frailty (PF) is associated with the risk of lung transplant (LTX) waitlist mortality.

Methods

Since March 2013, all patients referred for LTX evaluation underwent PF assessment. Cognition was assessed using the Montreal Cognitive Assessment and depression assessed using the Depression in Medical Illness questionnaire. We assessed the association of 4 composite frailty measures: PF ≥3 of 5 = frail, cognitive frailty (CogF ≥ 3 of 6 = frail), depressive frailty (DepF ≥ 3 of 6 = frail), and combined frailty (ComF ≥ 3 of 7 = frail) with waitlist mortality.

Results

The prevalence of PF was 78 (22%), CogF 100 (28%), DepF 105 (29%), and ComF 124 (34%). Waitlist survival in the non-PF group was 94% ± 2% versus 71% ± 7% in the PF group ($p < 0.001$). Cox proportional hazards regression analysis demonstrated that PF (Adjusted HR, 4.88; 95% CI, 2.06 - 11.56), mild cognitive impairment (Adjusted HR, 3.03; 95% CI, 1.05 - 8.78) and hypoalbuminemia (Adjusted HR, 0.89; 95% CI, 0.82 - 0.97) were independent predictors of waitlist mortality. There was no significant difference in the area under the curve of the 4 frailty measures.

Conclusions

The addition of cognitive function and depression variables to the PF assessment increased the number of patients classified as frail. However, the addition of these variables, does not strengthen the association with LTX waitlist mortality compared to the PF measure.

Background

Frailty is a clinically recognized syndrome of decreased physiologic reserve characterized by vulnerability to adverse health outcomes,[1] including increased disability and death in numerous chronic disease populations.[2-4]

Frailty is common in LTX candidates and associated with delisting and death on the waitlist.[2] We have previously reported that frailty is prevalent in patients referred for lung or heart transplantation and demonstrated that frailty is associated with increased mortality on the waitlist and following transplantation.[4,5] Frailty is recognized as an important consideration in the evaluation of LTX candidates. The International Society of Heart and Lung Transplantation (ISHLT) recognize low physiologic reserve in association with increasing age as a contraindication to LTX.[6] A recent survey by the American Society of Transplantation of specialists across the solid organ transplant specialties demonstrated that 93% of respondents believed that frailty assessment should be incorporated into the selection process of transplant candidates.[7]

Pretransplant frailty assessment may improve risk stratification and refine candidate selection.[2] However, there is not yet consensus on the most appropriate frailty measure in the field of LTX. Fried's frailty phenotype (FFP) is the most widely studied measure[1] and most frequently used assessment of physical frailty in LTX candidates. The FFP measures declining physiologic reserve across the following 5 domains: exhaustion, weakness, slowness, physical inactivity and weight loss.

As knowledge in application of frailty measures in LTX candidates progresses, it is important to ensure that the frailty domains being measured are associated with the biological processes underlying advanced lung disease.[7] The role of decreased cognitive performance and depression in frail patients is increasingly being considered in the definition of frailty for clinical and research purposes[8-12] and the omission of cognition and mood assessment tools is

recognized as a limitation to the FFP.[7] A recent report on frailty in solid organ transplantation recognized additional factors may contribute to frailty in transplant candidates and suggested the MOCA be used to assess cognition in the evaluation of frailty in LTX candidates.[7]

The aim of this study was to identify whether the inclusion of cognitive and depressive domains to the assessment of physical frailty is associated with the risk of LTX waitlist mortality.

Materials and Methods

The St Vincent's Hospital Research Ethics Committee reviewed and approved this study (HREC Reference number LNR/13/SVH/ 21). Informed consent was obtained from all patients for their data to be entered prospectively into a dedicated database for subsequent analysis.

Study population

The study population was derived from 529 consecutive patients with advanced lung failure who underwent LTX evaluation at our center between 1 March 2013 and 30 August 2019. Those excluded were the 33 patients who did not undergo frailty assessment in their LTX evaluation and those assessed as unsuitable for LTX (69 patients were medically unsuitable, 11 patients died during LTX evaluation, 22 declined LTX, 14 that had their listing delayed, and 5 patients who were still undergoing evaluation). Of the 375 patients who were listed for LTX, 12 patients on extracorporeal membrane oxygenation prior to LTX were excluded. The remaining 363 were included in the study cohort. Of these, 299 received a transplant within 12-months following frailty assessment (Figure 1).

Measures of frailty

Physical frailty

Physical frailty was assessed using a modified version of the FFP to categorize patients as frail or nonfrail. Details of the modified assessment tool have previously been published[5,13]

and are outlined in Table 1. The FFP assesses the following 5 physical domains: exhaustion, grip strength, gait speed, unintended weight loss and physical activity. The Survey of Health, Ageing, and Retirement in Europe Frailty Instrument (SHARE FI) is a well validated frailty measure.[14] Due to concern that weight loss may be masked in patients treated with steroids or with fluid retention secondary to right heart failure complicating their lung disease, we adopted the SHARE FI modification by replacing unintentional weight loss with loss of appetite over the 3-months prior to assessment.[14] The Minnesota Leisure Time Activity Questionnaire was replaced with frequency of activities requiring a low or moderate level of energy based on the SHARE FI.[14] Gait speed was timed over 5 meters. Our modifications to the FFP allowed a rapid assessment that can be easily administered by various members of the multidisciplinary team.[14] Patients were assessed as frail if ≥ 3 domains of the modified FFP (mFFP) were present.

Cognitive frailty

The Montreal Cognitive Assessment (MOCA) was used to assess current cognitive function across a number of domains (language, visuospatial abilities, abstract thinking, memory and recall), with a score < 26/30 classified as cognitive impairment.[15] Those assessed as cognitively impaired with a mFFP score of ≥ 2 points were classified as frail[8] (Table 1).

Depressive frailty

The Depression in the Medically Ill (DMI-10) questionnaire was designed to assess depression with medical illness, as most common depression measures have items like loss of appetite and poor concentration which overlap with physical symptoms.[16,17] A score of ≥ 9/30 was classified as a likely case of clinical depression. Those assessed as depressed with a mFFP score of ≥ 2 points were classified as frail (Table 1).

Combined frailty

A composite 7-item measure was assessed, which included the mFFP with both depression and cognitive impairment. A score ≥ 3 of 7 was classified as frail, and < 3 as nonfrail. Table 1 outlines how each of the 7 domains were measured.

Assessment of lung disease severity

Markers of lung disease severity were obtained as part of routine pre-LTX evaluation. These prognostic markers included PaO_2 levels, FEV_1, FEV_1 % predicted, FVC, FVC % predicted, DLCO, DLCO % predicted, and 6-minute walk distance. Biochemical parameters were obtained including blood hemoglobin level, serum creatinine, serum albumin, serum bilirubin, presence of anemia (Male: hemoglobin <130 g/L; Female: hemoglobin <115 g/L), presence of hypoalbuminemia (serum albumin <33 g/L [albumin reference interval up to 2/9/18 was 36–52g/L. Following introduction of BCP assay method on 2/9/18, new reference interval is 33–48g/L]), estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease formula. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2).

Outcome measures

LTX waitlist survival was determined from date of frailty assessment up to 12-months post frailty assessment. We were concerned that frailty status in patients on the waitlist may vary over time. To ensure frailty status was accurately classified, waitlist survival analyses were limited to 12-months postfrailty assessment.

Twelve-month post-LTX survival, post-LTX intubation time, days in intensive care unit (ICU), and hospital length of stay (LOS) were recorded for all patients that underwent LTX during the study period.

Statistical analysis

Descriptive statistics were calculated for all variables. The 4 frailty measures were used to determine the number of patients in the nonfrail and frail categories for the total study population. A receiver operating characteristics (ROC) curve analysis was applied to establish the optimal cutoff point for each frailty measure. The optimal cutoffs are the point on the ROC curve closest to (0,1).[18]

The association between the frailty category and age, gender, diagnostic category, cognitive impairment, depression, markers of lung disease severity, hematologic, and biochemical parameters, and the association between pre-LTX cognitive impairment and depression were made using unpaired t-tests or Mann Whitney U tests for continuous variables and Chi-square tests or, where appropriate, Fisher's exact test for categorical variables. Baseline characteristics are presented as mean ± SD or median and interquartile range for continuous variables and frequency (percent) for categorical variables.

For comparison of outcomes, waitlist survival time was defined as the time between the date of frailty assessment and the date of death or censoring (12-months post frailty assessment or date of delisting or date of transplant). Twelve-month post-LTX survival was defined as the time between the date of LTX and the date of death or 12-months post-LTX. A negative binomial regression model was used to compare post-LTX intubation time, ICU LOS, hospital LOS stratified by pre-LTX frailty status, cognitive function and depression adjusting for age and gender. The negative binomial model is a common method used for count data where the Poisson regression model does not explain all the variance. No patients were lost to follow-up.

Kaplan-Meier cumulative survival curves were generated for each frailty measure and the log-rank test was used to compare waitlist survival time and post-LTX survival time between nonfrail and frail groups. Cox proportional hazards models were used to assess the impact of

the 4 frailty measures on waitlist survival after adjusting for selected covariates: age, gender, FEV_1 % predicted, serum albumin, and serum hemoglobin. To understand the individual association of the cognitive function and depression deficits with waitlist mortality MOCA category and DMI-10 category were added to the survival model that included PF. The impact of the 4 frailty measures on post-LTX survival was assessed adjusting for age, gender, post-LTX intubation time, ICU LOS, and hospital LOS. MOCA category and DMI-10 category were added to the post-LTX survival model that included PF. Covariates were selected for inclusion in the models guided by clinical expertise aided with statistical judgement to ensure a parsimonious list would be included. *P*-values of < 0.05 were considered statistically significant.

The ROC curve was applied to examine the overall classification accuracy of the 4 frailty measures. The area under the ROC curve (AUC) and 95% confidence intervals (CI) were also calculated. A larger AUC indicates a better overall diagnostic accuracy. A value of ≥ 0.7 was considered acceptable discrimination.[19] The PF measure was applied as a "gold standard". The difference of the AUC of PF ROC curve was compared against CogF, DepF, and ComF measures using the DeLong method.[20]

All data analyses were conducted using IBM SPSS, Version 26 (IBM. Corp. Armonk, NY).

Results

Prevalence of frailty

Frailty was assessed in 363 patients (209 male and 154 females; median age 55 (41, 61) years, range 16-71 years) listed for LTX. Of these, 299 underwent LTX, 33 remained on the waitlist, 26 died on the waitlist, and 5 were delisted. The underlying causes of lung failure were interstitial lung disease 130 (36%), chronic obstructive pulmonary disease 108 (29%), cystic fibrosis 61 (17%), pulmonary arterial hypertension 8 (2%), chronic lung allograft dysfunction 19 (5%), congenital heart disease 12 (4%), and other lung diseases 25 (7%).

Baseline characteristics stratified by physical frailty status are outlined in Table 2. From the 363 LTX candidates who underwent frailty assessment the prevalence of PF was 78 (22%), CogF 100 (28%), DepF 105 (29%), and ComF 124 (34%). Regardless of frailty measure, the optimal cut-off was 3. PF was associated with cognitive impairment when assessed as a categorical variable and depression when assessed as a continuous and categorical variable. Physical frailty was more common in those that died on the waitlist (54%) than those that underwent LTX (19%) or remained on the waitlist (19%).

Regardless of the frailty measure used, frailty was associated with FVC, FVC % predicted, low creatinine, hypoalbuminemia (as a continuous and categorical variable) and anemia (as a continuous and categorical variable). Frailty was independent of age, FEV_1, FEV_1 % predicted, SMW, and PaO_2 (Table 2).

Frailty measures and LTX waitlist survival

The median duration of follow-up for the 363 patients was 195 (100, 365) days. Twenty-six patients died ≤12-months post frailty assessment. The addition of cognitive function and depression variables to the PF assessment increased the number of patients who were classified as frail (PF 78 (22%), CogF 100 (28%), DepF 105 (29%), and ComF 124 (34%)). Kaplan-Meier survival curves stratified by frailty status for the 4 frailty measures are shown in Figure 2. Regardless of the frailty measure used, waitlist survival was significantly lower in the frail group ($p < 0.05$).

Univariate analysis showed significant differences in waitlist survival time between frail and nonfrail patients for all 4 frailty measures. The significance persisted even after adjusting for covariates including age, gender, FEV_1% predicted, serum albumin, and serum hemoglobin (Table 3). When assessing the individual association of the cognitive function and depression deficits mild cognitive impairment (MCI) (MOCA < 26/30) was an independent predictor of waitlist mortality (Adjusted HR, 3.03; 95% CI, 1.05 - 8.78).

When assessed as a continuous and categorical variable hypoalbuminemia was associated with all 4 frailty measures ($p < 0.05$). After adjusting for age, gender, FEV_1% predicted, PF, MOCA category, DMI-10 category, and serum hemoglobin, each g/L decrease in serum albumin increased the risk of waitlist mortality by 0.1 (Serum albumin g/L: Adjusted HR, 0.9; 95% CI, 0.82 - 0.97, p=0.01).

Frailty and LTX outcomes

Two hundred and ninety-nine patients (180 male and 119 females; median age 56 (42,61), range 16-71) underwent LTX ≤ 12-months post frailty assessment. Median time to transplant was 179 (96, 327) days. By PF 56 (19%), CogF 75 (25%), DepF 77 (26%), and ComF 95 (32%) were classified as frail pre-LTX. Thirty-three (11%) patients died up to 12-months following LTX. Kaplan-Meier 12-month post-LTX survival curves stratified by frailty status for the 4 frailty measures are shown in Figure S1 http://links.lww.com/TP/C237 . Regardless of the frailty measure used, 12-month post-LTX survival was similar in the nonfrail group versus the frail group (p= NS). When adjusted for age, gender, post-LTX intubation time, ICU LOS, and hospital LOS frailty was not associated with post-transplant mortality (Table S1 http://links.lww.com/TP/C237). Age (Adjusted HR, 1.04; 95% CI, 1.01 - 1.08, p=0.02) and ICU LOS (Adjusted HR, 1.03; 95% CI, 1.01 - 1.05, p=0.04) were independent predictors of post-LTX mortality. When assessing the independent association of pre-LTX cognitive function and depression deficits there was no statistically significant association with post-LTX mortality. When assessed using CogF, intubation time (Adjusted incidence rate ratio (IRR) 1.7; 95% CI, 1.3 - 2.4) and ICU LOS (Adjusted IRR 1.5; 95% CI,1.2 - 1.9) were significantly longer in the frail group versus the nonfrail group, with similar results using ComF for intubation time (Adjusted IRR 1.6; 95% CI, 1.2 - 2.1) and ICU LOS (Adjusted IRR 1.4; 95% CI, 1.1 - 1.8) (Table 4).

Seventy-seven (26%) patients were classified as cognitively impaired pre-LTX. After adjusting for age, gender, and PF, MCI was associated with increased intubation time, ICU LOS, and hospital LOS following LTX (Table 4). Seventy-nine (26%) patients were classified as depressed pre-LTX. Depression was not associated with increased intubation time, ICU LOS, or hospital LOS (Table 4).

Association of the 4 frailty measures with the risk of LTX waitlist mortality

There was no significant difference in the AUC of the 4 frailty measures. The ROC curves of the 4 frailty measures are shown in Figure 3. PF had the largest AUC with 0.72 (95% CI: 0.62, 0.83). The differences of AUC between PF and CogF and the difference between PF and DepF were not significant indicating PF, CogF, and DepF had similar overall classification accuracy. ComF with 0.68 (95% CI: 0.57, 0.78) had the smallest AUC among the frailty measures demonstrating the lowest overall classification accuracy.

Discussion

The major findings of our study are firstly, that frailty defined using PF, CogF, DepF, or ComF is common in patients listed for LTX. We have previously reported a PF prevalence of 24% in a cohort of patients undergoing LTX evaluation and 16%, as assessed pre-LTX, in a cohort of LTX recipients.[5,13] In our present study the prevalence of PF was 22%, CogF 28%, DepF 29%, and ComF 34% in patients on the LTX waitlist. Secondly, PF, low serum albumin, and MCI are independently associated with waitlist mortality. Thirdly, all 4 frailty measures reach the same estimate of risk with no statistically significant difference in association with LTX waitlist mortality. Previous studies have reported that physical frailty is prevalent in LTX candidates, associated with an increased risk of delisting or death in LTX candidates, and decreased survival following LTX.[2,21,22] To our knowledge, this is the first study to assess the addition of cognitive function and depressive domains to the assessment of physical frailty with the risk of mortality in patients listed for LTX.

Frailty measures have traditionally assessed physical domains.[1] However, more recently frailty has been described as a multidimensional syndrome, considering cognitive and mood domains.[23] We have previously reported that cognitive frailty is prevalent and associated with increased pretransplant mortality in patients referred for heart transplantation.[8,12] We hypothesized we would see similar results in those listed for LTX. In our cohort the addition of the cognitive function and depression variables to the PF measure did not strengthen the association with LTX waitlist mortality. In fact, the ComF measure weakened the association with waitlist mortality. We believe the 4 frailty measures converged on similar estimates of risk due to the commonality of the physical domains across the measures and the association with waitlist mortality is primarily driven by the PF measure.

The MOCA has been shown to identify MCI and found to be a better discriminator than the Mini-Mental State Examination.[24] This is important as patients over the age of 60 are more frequently being referred for LTX evaluation. We hypothesized that the addition of cognitive impairment to 2 or more physical domains of the frailty phenotype would be associated with the risk of waitlist mortality based on our previous results in the heart transplant population.[8,12] In our cohort, the addition of the cognitive function variable to the frailty measures demonstrated a similar association with waitlist mortality which we believe is primarily driven by the PF measures. However, MCI (MOCA <26) was associated with waitlist mortality (Adjusted HR, 3.03; 95% CI, 1.05 - 8.78). This is important as appropriate interventions differ. Following LTX, CogF was associated with increased intubation time (Adjusted IRR 1.7; 95% CI, 1.3 - 2.4) and ICU LOS (Adjusted IRR 1.5; 95% CI, 1.2 - 1.9). PF was not associated with worse post-LTX outcomes. Importantly, pre-LTX MCI (MOCA <26) was associated with worse post-LTX outcomes including increased intubation time, ICU LOS, and hospital LOS. This may be the result of an increased rate and severity of postoperative delirium which has been associated with preexisting cognitive impairment in

previous studies.[25,26] We believe that cognitive assessment is clinically important and should be included in the evaluation of LTX candidates.

Hypoalbuminemia has been shown to be associated with increased LTX waitlist mortality, post-LTX mortality and postoperative complications.[27-29] Our results demonstrate that hypoalbuminemia is associated with frailty, regardless of the measure, and is an independent predictor of waitlist mortality. Consultation with a nutrition specialist and consideration of nutritional supplementation has been recommended as a potential intervention to address frailty in LTX candidates and is a part of routine evaluation for LTX at our centre.[7] Further studies are needed to assess the effect of hypoalbuminemia on frailty measures and the benefit of nutritional intervention in the management of frailty and hypoalbuminemia in LTX candidates.

In our study pretransplant frailty status was not associated with posttransplant survival. We have previously reported similar findings in a cohort of patients with ILD.[5] Similarly, Rozenberg and colleagues reported that frail LTX candidates saw greater improvements following LTX than their nonfrail counterparts and that frailty was not associated with 1-year mortality.[30] We believe that if frail patients are prioritized on the waitlist and transplanted early, they may achieve similar post-LTX survival outcomes to their nonfrail counterparts. However, this should be carefully considered in older, frail LTX candidates given our results demonstrated age is associated with post-LTX mortality (Adjusted HR, 1.04; 95% CI, 1.01 - 1.08).

Our findings that the addition of cognitive function and depression variables to the PF assessment increased the number of patients who were classified as frail and that there was no difference between the 4 frailty measures and the risk of LTX waitlist mortality may inform future studies on the most appropriate frailty measure in LTX.

Limitations

Our study was a single-center, retrospective design. As such, direct inferences must be interpreted in the context of our study population. The study used a modified physical frailty measure which is not LTX specific. The modified tool has been validated in patients undergoing heart transplant evaluation,[31] but not yet in a population of LTX candidates. As our unit evaluates patients for both heart and lung transplant, the tool is simple to administer and clinically feasible for our population. The combination of measures used to assess physical frailty, cognitive impairment, and depression have not been validated as a whole but have been validated separately. Although we found no statistically significant difference between the 4 frailty measures, the PF, CogF, and DepF measures demonstrated acceptable discrimination.

Conclusion

The addition of cognitive function and depression variables to the PF assessment increased the number of patients who were classified as frail. However, the addition of these variables did not strengthen the association with LTX waitlist mortality compared to the PF measure. Further research is needed to determine the most suitable frailty measure in LTX and appropriate interventions that may decrease the risks associated with frailty.

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Figure legend

Figure 1. Diagram of study population. ECMO, extracorporeal membrane oxygenation; LTX, lung transplant.

Figure 2. LTX waitlist survival stratified by frailty status according to the 4 frailty measures (A–D). Patients have been censored at the time of LTX. LTX, lung transplant.

Figure 3. Areas under ROC curves for the 4 frailty measure (n=363): ability to identify risk of lung transplant waitlist mortality. AUC, area under the curve; CI, confidence interval; CogF, cognitive frailty; ComF, combined frailty; DepF, depressive frailty; PF, physical frailty; ROC, receiver operating characteristic.

Table 1. The 5 domains of the modified Fried Frailty Phenotype and the additional domains of cognition and mood were assigned 1 point if present or 0 if absent with frailty scores ≥3 considered frail and scores 0–2 considered nonfrail.

Domain	Scoring criteria	Frailty measure
Exhaustion	"In the last week, did you feel on at least 3 days, that everything you did was an effort?" and "In the last week, did you feel on at least 3 days, that you could not get going?" a response of "yes" to either question met the criteria for exhaustion	
Grip Strength	Grip strength was considered weak if the average of 3 consecutive attempts on the left and right hand fell below 2 standard deviations of sex and age adjusted normative values	
Mobility	Walking speed was considered slow if the average of 3 attempts took 6 seconds or more to complete 5 meters	
Appetite	"Have you, in the last 3 months, been eating more/less than usual?" A response of "less" was classified as poor appetite	
Physical activity	"How often do you engage in activities that require a low or moderate level of energy, such as gardening, cleaning the car or going for a walk?" A response of "1 to 3 times a month or hardly ever" was classified as physical inactivity	Physical frailty: /5
MOCA	Abnormal MOCA score < 26	Cognitive frailty: /6
DMI-10	Abnormal DMI-10 score ≥ 9	Depressive frailty: /6
		Combined frailty: /7

MOCA: Montreal cognitive assessment; DMI-10: Depression in Medical Illness (10-item version).

Table 2. Baseline demographics stratified by physical frailty status.

	Physical frailty		
	Nonfrail (n = 285)	Frail (n = 78)	*P*
Age, median (IQR), y	56 (42–62)	54 (37–61)	0.19
Male gender, n (%)	171 (60%)	38 (49%)	0.07
Diagnostic category, n (%)			0.002
ILD	96 (34%)	34 (44%)	
COPD	94 (33%)	14 (18%)	
CF	51 (18%)	10 (13%)	
PAH	7 (2%)	1 (1%)	
Other	17 (6%)	8 (10%)	
CLAD	9 (3%)	10 (13%)	
CHD	11 (4%)	1 (1%)	
BMI, mean ± SD, kg/m^2	24.1 ± 5.0	23.0 ± 5.2	0.09
FEV_1, median (IQR)	1.0 (0.7–1.7)	1.0 (0.6–1.6)	0.39
FEV_1 % predicted, median (IQR)	34 (25–54)	33 (24–56)	0.91
FVC, mean ± SD	2.5 ± 0.8	2.0 ± 0.8	<0.001
FVC % predicted, mean ± SD	67 ± 20	57 ± 18	<0.001
DLCO, median (IQR)	8.1 (5.9–11.6)	7.1 (5.3–10.3)	0.18
DLCO % predicted, median (IQR)	28 (22–41)	28 (21–41)	0.62
PaO_2, mean ± SD, mmHg	63.0 ± 11.3	62.2 ± 11.9	0.61
SMW, mean ± SD, m	333 ± 121	306 ± 131	0.19
Serum creatinine, median (IQR), µmol/L	74 (62–88)	66 (55–79)	0.01
eGFR < 60ml/min per m^2, n (%)	24 (8%)	5 (6%)	0.56
Serum bilirubin, median (IQR), µmol/L	8 (5–12)	6 (4–9)	0.002
Serum albumin, mean ± SD, g/L	43 ± 5	39 ± 6	<0.001
Hypoalbuminemia < 33g/L, n (%)	15 (5%)	13 (17%)	<0.001
Serum hemoglobin, mean ± SD, g/L	143 ± 17	134 ± 19	<0.001
Anemia, male < 130g/L; female <115g/L; n (%)	24 (8%)	16 (21%)	0.003
Exhaustion, n (%)	79 (28%)	60 (77%)	<0.001
Weak grip strength, n (%)	68 (24%)	53 (68%)	<0.001
Slow walk speed, n (%)	23 (8%)	45 (55%)	<0.001
Reduced appetite, n (%)	64 (23%)	55 (71%)	<0.001
Physical inactivity, n (%)	37 (13%)	57 (73%)	<0.001
MOCA score, n (%)	27 (26,29)	27 (24,29)	0.23
Abnormal MOCA < 26, n (%)	67 (23%)	28 (36%)	0.03
DMI score, n (%)	4 (2–8)	9 (3–14)	<0.001
Abnormal DMI ≥ 9, n (%)	62 (22%)	39 (51%)	<0.001

BMI, body mass index; CF, cystic fibrosis; CHD, congenital heart disease; CLAD, chronic lung allograft dysfunction; COPD, chronic obstructive pulmonary disease;

DLCO, diffusing capacity of the lung for carbon monoxide; DMI, Depression in Medical Illness assessment; eGFR, estimated glomerular filtration rate; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ILD, interstitial lung disease; IQR, interquartile range; MOCA, Montreal Cognitive Assessment; PAH, pulmonary arterial hypertension; PaO_2, arterial partial pressure of oxygen; SMW, 6-minute walk distance.

Table 3. Cox proportional hazards regression analysis for lung transplant waitlist survival: unadjusted and adjusted hazard ratios for the 4 frailty measures.

Frailty measure	Unadjusted hazard ratio (95% confidence interval)	Adjusted hazard ratio (95% confidence interval)
Physical frailty	5.06 (2.34–10.95)	[a]4.88 (2.06–11.56)
Cognitive frailty	3.43 (1.58–7.41)	[b]2.88 (1.28–6.50)
Depressive frailty	4.37 (1.98–9.63)	[b]3.66 (1.58–8.47)
Combined frailty	3.30 (1.50–7.26)	[b]2.76 (1.22–6.24)

[a]Adjusted for age, gender, FEV_1% predicted, cognitive function, depression, serum albumin, and serum hemoglobin.

[b]Adjusted for age, gender, FEV_1% predicted, serum albumin, and serum hemoglobin.

Table 4. Comparison of post–lung transplant clinical characteristics stratified by pre–lung transplant frailty status, cognitive function, and depression.

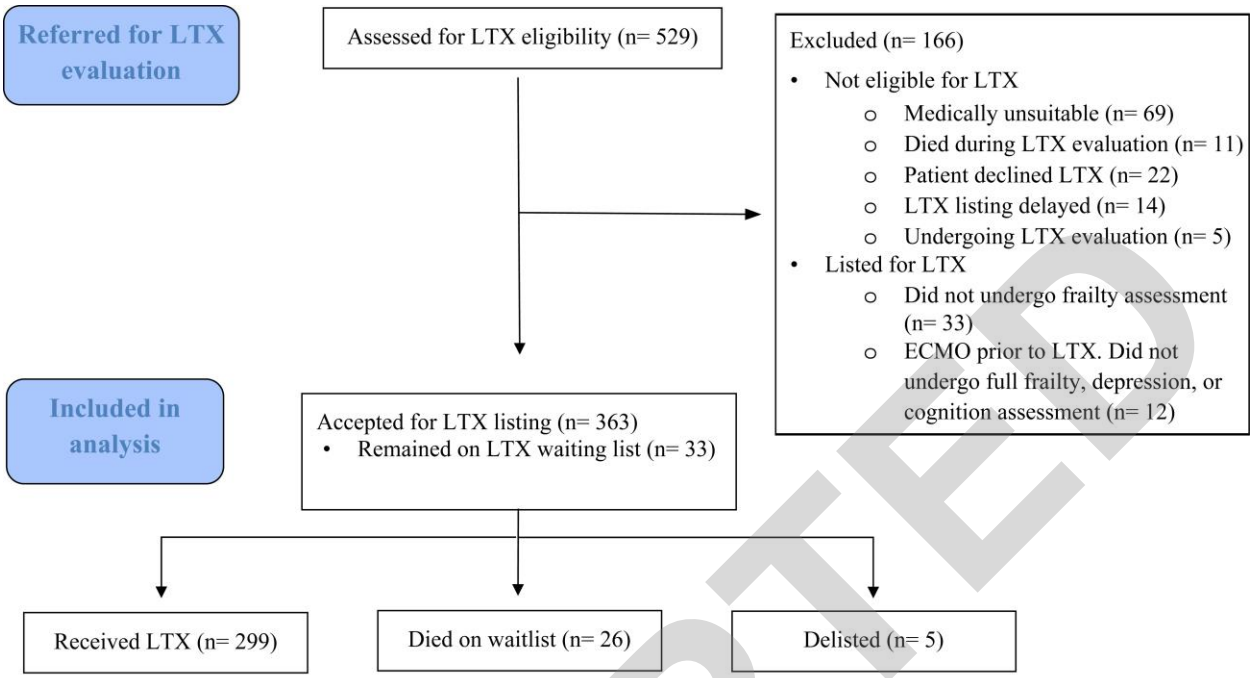
	PF		CogF		DepF		ComF		MOCA category		DMI-10 category	
	Nonfrail (n = 243)	Frail (n = 56)	Nonfrail (n = 224)	Frail (n = 75)	Nonfrail (n = 222)	Frail (n = 77)	Nonfrail (n = 204)	Frail (n = 95)	No cognitive impairment (n = 222)	Cognitive impairment (n = 77)	Not depressed (n = 220)	Depressed (n = 79)
Intubation time, h	Ref	1.3 (0.9–1.8)	Ref	[a]1.7 (1.3–2.4)	Ref	1.3 (0.9–1.7)	Ref	[a]1.6 (1.2–2.1)	Ref	[a]2.3 (1.7–3.1)	Ref	0.7 (0.5–1.0)
ICU LOS, d	Ref	1.3 (0.9–1.4)	Ref	[a]1.5 (1.2–1.9)	Ref	1.3 (0.9–1.6)	Ref	[a]1.4 (1.1–1.8)	Ref	[a]1.8 (1.5–2.3)	Ref	1.0 (0.8–1.2)
Hospital LOS, d	Ref	1.1 (0.9–1.4)	Ref	1.2 (1.0–1.5)	Ref	1.1 (0.9–1.4)	Ref	1.2 (1.0–1.5)	Ref	[a]1.3 (1.1–1.5)	Ref	1.0 (0.9–1.2)

Data expressed as incidence rate ratio (95% confidence interval). A negative binomial regression model was used with age and gender as covariates.

[a]Indicates a statistically significant result.

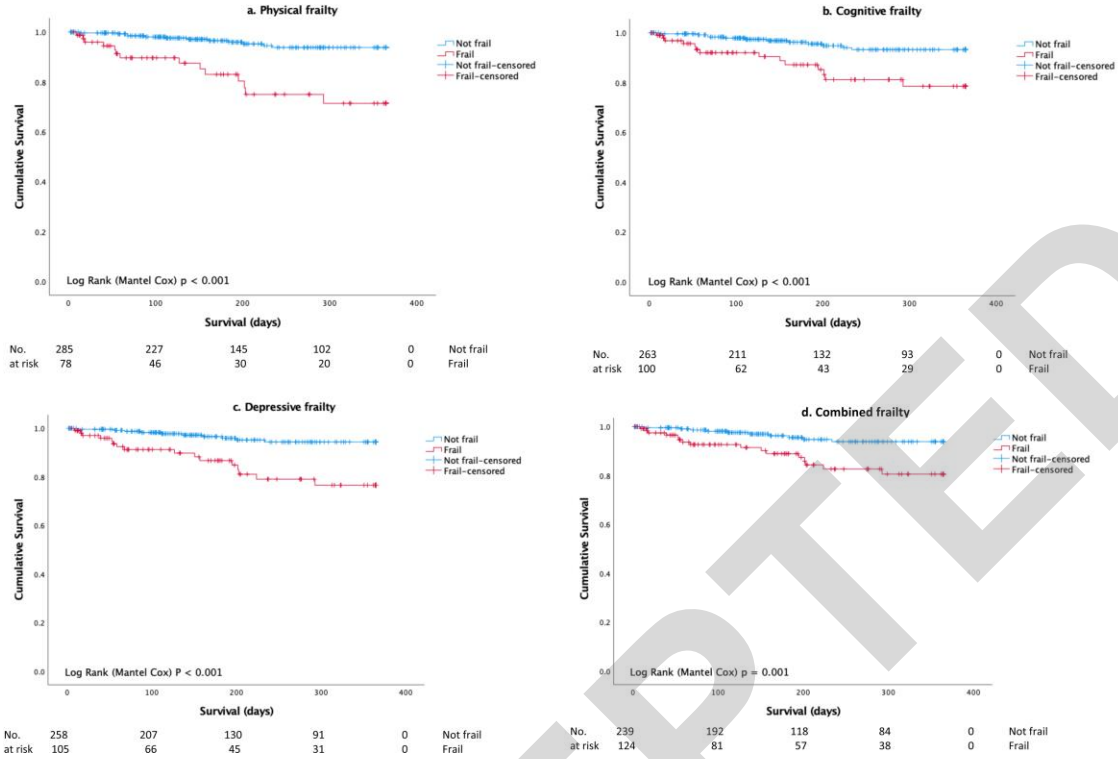
CogF, cognitive frailty; ComF, combined frailty; DepF, depressive frailty; DMI-10, Depression in the Medically Ill questionnaire; ICU, intensive care unit; LOS, length of stay; MOCA, Montreal Cognitive Assessment; PF, physical frailty.

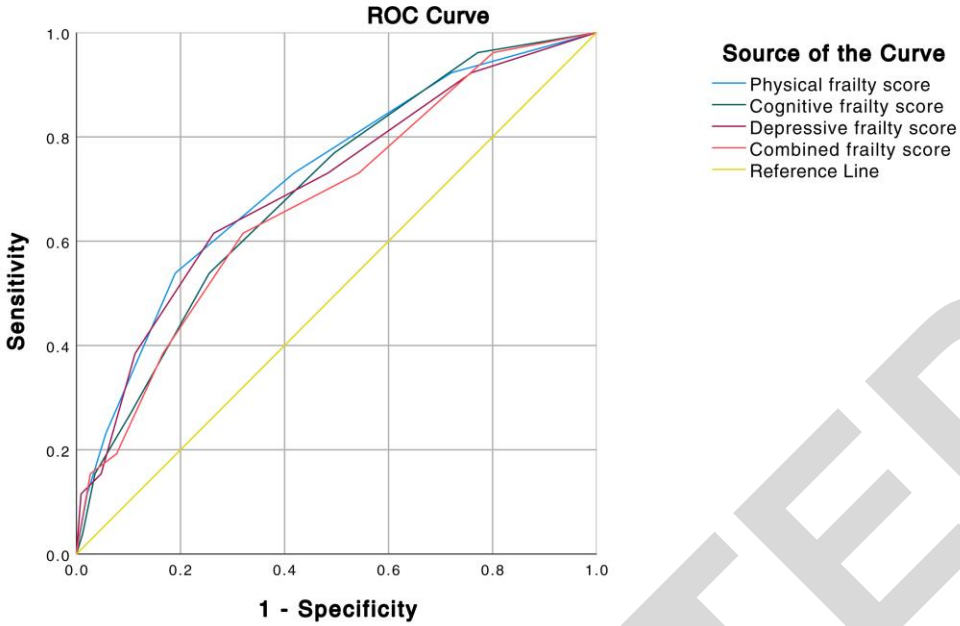
Figure 1



LTX: lung transplant; ECMO: extracorporeal membrane oxygenation

Figure 2: LTX waitlist survival stratified by frailty status according to the four frailty measures. Patients have been censored at the time of LTX.





Frailty Measure	AUC	95% CI	p-value*
PF	0.72	(0.62, 0.83)	Ref
CogF	0.70	(0.60, 0.80)	0.33
DepF	0.71	(0.60, 0.82)	0.42
ComF	0.68	(0.57, 0.78)	0.03

*p-value has been adjusted for the multiple testings.