OPEN

Relationship of Exercise Capacity, Physical Function, and Frailty Measures With Clinical Outcomes and Healthcare Utilization in Lung Transplantation: A Scoping Review

Nicholas Bourgeois, MSc,[1,2] Shirin M. Shallwani, MSc,[3] Fahad S. Al-Huda, MA (Cantab),[4] Sunita Mathur, PhD,[5,6] Charles Poirier, MD,[1] and Tania Janaudis-Ferreira, PhD[2,6,7,8]

Background. Measures of exercise capacity, frailty, and physical function are commonly used in lung transplant candidates and recipients to evaluate their physical limitations and the effects of exercise training and to select candidates for transplantation. It is unclear how these measures are related to clinical outcomes and healthcare utilization before and after lung transplantation. The purpose of this scoping review was to describe how measures of exercise capacity, physical function, and frailty are related to pre- and posttransplant outcomes. **Methods.** We considered studies of any design that included performance-based tests of exercise capacity, physical function, and frailty in adult lung transplant candidates or recipients. Outcomes of interest were clinical outcomes (eg, mortality, quality of life) and healthcare utilization. **Results.** Seventy-two articles met the inclusion criteria. The 6-min walk test (6MWT) was shown to be related to mortality on the waiting list with different distance values as cutoffs points. There were inconsistent results regarding the relationship of the 6MWT with other clinical outcomes. Few studies have examined the relationship between the cardiopulmonary exercise test or the short physical performance battery and clinical outcomes, although some studies have shown relationship with survival posttransplant and quality of life. Few studies examined the relationship between the tests of interest and healthcare utilization, and the results were inconsistent. **Conclusions.** Except for the relationship between the 6MWT and mortality on the waiting list, there is limited evidence regarding the relationship of performance-based measures of exercise capacity, frailty, and physical function with clinical outcomes or healthcare utilization.

(*Transplantation Direct* 2022;8: e1385; doi: 10.1097/TXD.0000000000001385).

INTRODUCTION

Every year, close to 100 800 solid organ transplants are performed worldwide, of which around 4000 to 4500 are lung transplants.[1,2] Individuals with advanced lung disease frequently experience severe dyspnea, decreased exercise capacity, muscle weakness, and frailty, which impact their capacity to perform activities of daily living and participate in social and work activities.[3,4] The mechanisms underlying

Received 25 July 2022.

Accepted 10 August 2022.

[1] Lung Transplant Program, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada.

[2] School of Physical and Occupational Therapy, McGill University, Montreal, QC, Canada.

[3] School of Rehabilitation Sciences, University of Ottawa, Ottawa, ON, Canada.

[4] Faculty of Biology Medicine and Health, School of Medicine, The University of Manchester, Manchester, United Kingdom.

[5] School of Rehabilitation Therapy, Queen's University, Kingston, ON, Canada.

[6] Canadian Donation and Transplantation Research Program, Edmonton, AB, Canada.

[7] Centre for Outcomes Research and Evaluation (CORE), Research Institute of the McGill University Health Centre, Montreal, QC, Canada.

[8] Translational Research in Respiratory Diseases Program, Research Institute of the McGill University Health Centre, Montreal, QC, Canada.

No specific funding was received to create this work. N.B. has received a fellowship scholarship from the Centre Hospitalier de l'Université de Montréal.

The authors declare no conflicts of interest.

N.B., S.M.S., S.M., C.P., and T.J.-F. contributed to developing the research questions and design. N.B. executed the initial database search and conducted the literature review. N.B. and S.M.S. performed the screening of the abstracts and full texts. N.B., S.M.S., and F.S.A.-H. conducted the extraction of the data. N.B., S.M.S., S.M., C.P., and T.J.-F. contributed to the draft of the article, provided critical feedback on the article, and approved the final version.

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).

Correspondence: Tania Janaudis-Ferreira, PhD, Centre for Outcomes Research and Evaluation (CORE), Research Institute of the McGill University Health Centre, 5252 de Maisonneuve Blvd. W, Room # 3E01, Montreal, QC H4A 3J1, Canada. (tania.janaudis-ferreira@mcgill.ca).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001385

reduced exercise capacity and physical function limitations are multifactorial, including alterations in lung mechanics and gas exchange, cardiovascular limitations, peripheral muscle dysfunction, deconditioning, malnutrition, fatigue, and anemia.[5-10] Improvements posttransplant in physical capacity are observed mainly because of improved organ function and reduction of disease symptoms.[7] However, exercise capacity is still impaired in transplant recipients with 40% to 70% of age-predicted values.[7,11,12] Myopathy from immunosuppressive medication, reduced proportion of type I muscle fibers, reduced mitochondrial oxidative capacity, muscle atrophy, low physical activity levels, primary graft dysfunction, infections, and healthcare utilization outcomes such as prolonged intensive care unit (ICU) or hospital stay are factors that contribute to physical limitations in the post–lung transplantation period.[7,9,11]

The 6-min walk test (6MWT) is widely used to assess functional status of lung transplant patients and is part of the evaluation criteria for transplantation.[13] However, it has recently been suggested that including assessment of physical function and physical frailty in the evaluation for lung transplantation may improve risk stratification and evaluation of prognosis.[14,15] In clinical settings, a combination of aerobic capacity, muscle function, mobility, and physical activity testing can be used in lung transplant candidates and recipients to evaluate their physical limitations pre- and posttransplant, select candidates for transplantation, and evaluate the effects of exercise training.[5]

As indicated in a recent international consensus document, poor physical functional status is considered as an absolute contraindication for lung transplantation.[16] Therefore, it is important to understand how physical function is related to outcomes pre- and posttransplant to ensure that clinical decisions for transplant candidacy are being made on the basis of current evidence. To our knowledge, there are no reviews exploring the relationship between functional measures of exercise capacity, physical function, and frailty with outcomes before and after lung transplantation. This topic was identified as a research priority in a 2014 expert meeting on exercise in transplantation.[9]

Therefore, the research question for this scoping review is to describe what is known about the relationship of performance-based tests of exercise capacity, physical function, and frailty with clinical outcomes and healthcare utilization in lung transplantation. The findings of this scoping review will inform clinicians and researchers about the available measures of functional status in lung transplantation, as well as guide them on the prioritization and assessment for eligibility of lung transplant candidates and on the optimization of the management of lung transplant recipients.

MATERIALS AND METHODS

This review was guided by the methodological framework proposed by Arksey and O'Malley.[17] The general purpose of scoping reviews is to identify and map the current literature on a topic by identifying key concepts and sources of evidence that can inform practice in the field.[18] The reporting of this review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Extension for Scoping Reviews[19] and by the PRISMA Extension for Reporting Literature Searches.[20]

Search Strategy

In collaboration with the research team and a librarian, the main author (N.B.) performed an electronic literature search of MEDLINE (Ovid) from inception until June 2021. The search strategy used in MEDLINE was then adapted for Embase (Ovid) and CINAHL (see Strategy S1, SDC, http://links.lww.com/TXD/A454, for search terms used in MEDLINE). There were no time limits or language restriction on the search. The results from the 3 databases were then combined, and duplicates were removed using EndNote 20 (EndNote, Clarivate Analytics, Boston, MA).

Inclusion Criteria

We included studies that examined, as primary or secondary objective, the relationship of exercise capacity, physical function, or frailty performance-based tests with clinical outcomes pre– and post–lung transplantation and healthcare utilization. We considered studies that included adult lung transplant candidates (referred or waitlisted) with any lung disease or lung transplant recipients. We also included studies that analyzed separately a subgroup of transplant candidates and studies with chronic lung disease patients where at least 80% of them were referred or underwent an eligibility assessment for transplant. We considered retrospective or prospective studies, cohort studies, case-control studies, natural events studies, time series, randomized controlled trials, and sequential or cross-over designs, as well as congress or conference abstracts and theses.

The performance-based measures of interest were functional exercise capacity measures defined as field walking-based tests (eg, 6MWT or endurance shuttle walk test) or lab-based tests (eg, cardiopulmonary exercise test [CPET]), physical function, and frailty measures. We used the International Classification of Functioning, Disability, and Health[21] to determine the type of physical function tests we would include. We considered tests that used performance-based mobility as a construct (eg, sitting, standing, maintaining a standing position, walking short distances, and walking long distances), such as gait speed over 4 m (4MGS), sit-to-stand (STS) tests, the short physical performance battery (SPPB), or Timed Up and Go.[5,21] The SPPB is a physical performance test that measures lower extremity function, but it has also been considered as a surrogate of physical frailty.[22,23] As we were interested in performance-based measures, frailty was defined only by the SPPB.

The clinical outcomes of interest were mortality on the waiting list, hospitalization during the waiting time, survival or mortality posttransplant, chronic lung allograft dysfunction (CLAD), and quality of life (QOL) pre- or posttransplant. For healthcare utilization posttransplant, outcomes of interest were hospital length of stay (LOS), ICU LOS, time on mechanical ventilation, discharge destination, and rehospitalization posttransplant.

We excluded studies that (1) considered pediatric patients or heart-lung transplant patients; (2) only examined the effects of pulmonary rehabilitation in lung transplant candidates or recipients; (3) included pure measures of balance, measures of frailty evaluated through a questionnaire or index (eg, Clinical Frailty Scale, Fried Frailty Index), index measures that included the 6MWT (eg, Lung Allocation Score), or physical activity measures (eg, accelerometry); and (4) examined the psychometric properties of a measure. Finally, we excluded articles in languages other than English, French, Portuguese, Spanish, or Swedish and records of reviews, case studies, editorials, and commentaries.

Screening Process, Data Extraction, and Data Synthesis

The Rayyan Web Application[24] was used for the screening process. Two authors (N.B. and S.M.S.) screened the titles and abstracts in the first round of review and then screened full texts in the second round. All disagreements were resolved without the need to consult a third reviewer. One author (N.B.) performed the data extraction, and 2 authors (S.M.S. and F.S.A.) verified the extracted data. Information about study characteristics (design, type of article, country), population, performance-based measures used, relationship with outcomes of interest (if studied and the absence or presence of a significant relationship), main findings, conclusions, and limitations were retrieved. If the information was not clear or the full text was not available, one attempt was made to contact the corresponding author via email. The data were synthesized separately for lung transplant candidates and lung transplant recipients. If a study included lung transplant recipients, but the data of the physical tests were collected retrospectively and therefore performed pretransplant, this information will be mentioned in the results section of lung transplant recipients. As this is a scoping review, which included studies of different designs where methodological and statistical approaches were used, a meta-analysis was not conducted.

RESULTS

Literature Search and Characteristics of Included Studies

The numbers of records identified through the electronic databases and of included and excluded studies are shown in the PRISMA flow diagram (Figure 1). Eighty records (72 unique studies) that provided data from over 45 000 participants met our inclusion criteria. Forty-two studies included lung transplant candidates and 30 with lung transplant recipients. Table 1 presents the characteristics of the studies included in the review. Most studies came from North America, were published in the last 10 y, and were in English, except for 1 study in Spanish. Many studies were retrospective cohort studies (47 studies). In studies that included lung transplant candidates, chronic obstructive pulmonary disease (COPD) was the most common diagnosis (13 158 patients in 16 studies), and idiopathic interstitial pneumonia was the most frequently studied population (26 studies). In studies that included lung transplant recipients, restrictive lung disease was the most common pretransplant diagnosis (6907 patients in 37 studies) , and idiopathic interstitial pneumonias was also the most frequently studied population (16 studies). The 6MWT was the most common included measure (58 studies), followed by the SPPB (12 studies). One study included measures of physical function (5-time STS [5STS] and 4MGS). The statistical analysis used in the studies to determine the presence of relationship was the time-to-event regression analysis (Cox regression model, Kaplan-Meier survival curve) in 44 studies, followed by linear or logistic regression analysis (16 studies), correlations (7 studies), and between-groups analysis (5 studies).

Relationship With Clinical Outcomes in Lung Transplant Candidates

A summary of the relationship of measures of exercise capacity, frailty, and physical function with clinical outcomes in studies that included lung transplant candidates is shown in Figure 2. Exercise capacity measures were the most common measure in the included studies. Twenty-six studies examined the relationship of the 6MWT with mortality or survival on the waiting list.[25-50] Of those, 20 studies showed a significant relationship with mortality on the waiting list, with the vast majority (14 studies) using a hazard ratio to calculate mortality risk with the 6MWT distance (6MWD).[25-44] Seven studies examined the relationship of the 6MWT with mortality or survival posttransplant,[14,27,30,47,51-53] with 3 studies showing that a lower 6MWD is associated with this outcome.[27,51,52] Five studies examined the relationship of the 6MWT with QOL,[46,54-57] with 3 studies showing some relationship with QOL pretransplant.[46,55,56] One study[26] examined and showed a relationship between the 6MWT and delisting of transplant candidates. More information about the direction of these relationships is presented in Table S1 (SDC, http://links.lww.com/TXD/A454).

Three articles examined the relationship of the CPET with mortality or survival on the waiting list with all of them showing a statistically significant relationship.[29,31,58] There were no studies that examined the relationship between the CPET and the other outcomes. Only 1 study examined the relationship of the endurance shuttle walk test with mortality or survival on the waiting list, with no significant relationship found.[49] The relationship between SPPB and clinical outcomes was examined in 6 studies.[10,14,59-62] One study showed a significant relationship of the SPPB with mortality on the waiting list and with delisting pretransplant,[59] 2 studies with pretransplant QOL,[10,61] and 1 study with posttransplant QOL.[62] Physical function measures (eg, 5STS, 4MGS) were only used in 1 study that showed no relationship with mortality posttransplant.[14] More information about the direction of these relationships is presented in Tables S2 and S3 (SDC, http://links.lww.com/TXD/A454). There were no studies that examined the relationship of exercise capacity, physical function, or frailty performance-based measures with CLAD development posttransplant.

Relationship With Healthcare Utilization in Lung Transplant Candidates

The relationship of performance-based measures of exercise capacity, physical function, and frailty with healthcare utilization in lung transplant candidates was studied in 8 studies.[10,14,45,51,53,60,63,64] Five studies examined the relationship of the 6MWT with hospital LOS[14,51,53,63,64] and 3 studies with ICU LOS.[51,63,65] Of those, 2 studies showed a significant relationship of a higher 6MWD with hospital LOS[51,64] and 1 with ICU LOS,[51] using similar cutoffs of 346[51] and 350 m[64] for the 6MWD. Three studies examined the relationship between the SPPB and hospital LOS[10,14,60] and 2 studies with ICU LOS.[14,60] Of those, only 1 study showed a significant relationship and hospital LOS.[14] One study[14] examined the relationship of the 5STS and 4MGS with hospital and ICU LOS with no significant relationship shown. Three studies examined the relationship of the 6MWT with time on mechanical ventilation,[14,45,63] and of those, only 1 study showed a significant relationship.[14] Mayer et al[14] also examined the relationship of SPPB, 5STS, and 4MGS with time on mechanical ventilation but showed no significant relationship. The relationship between the SPPB and discharge destination was examined by Wickerson et al,[60] but no significant

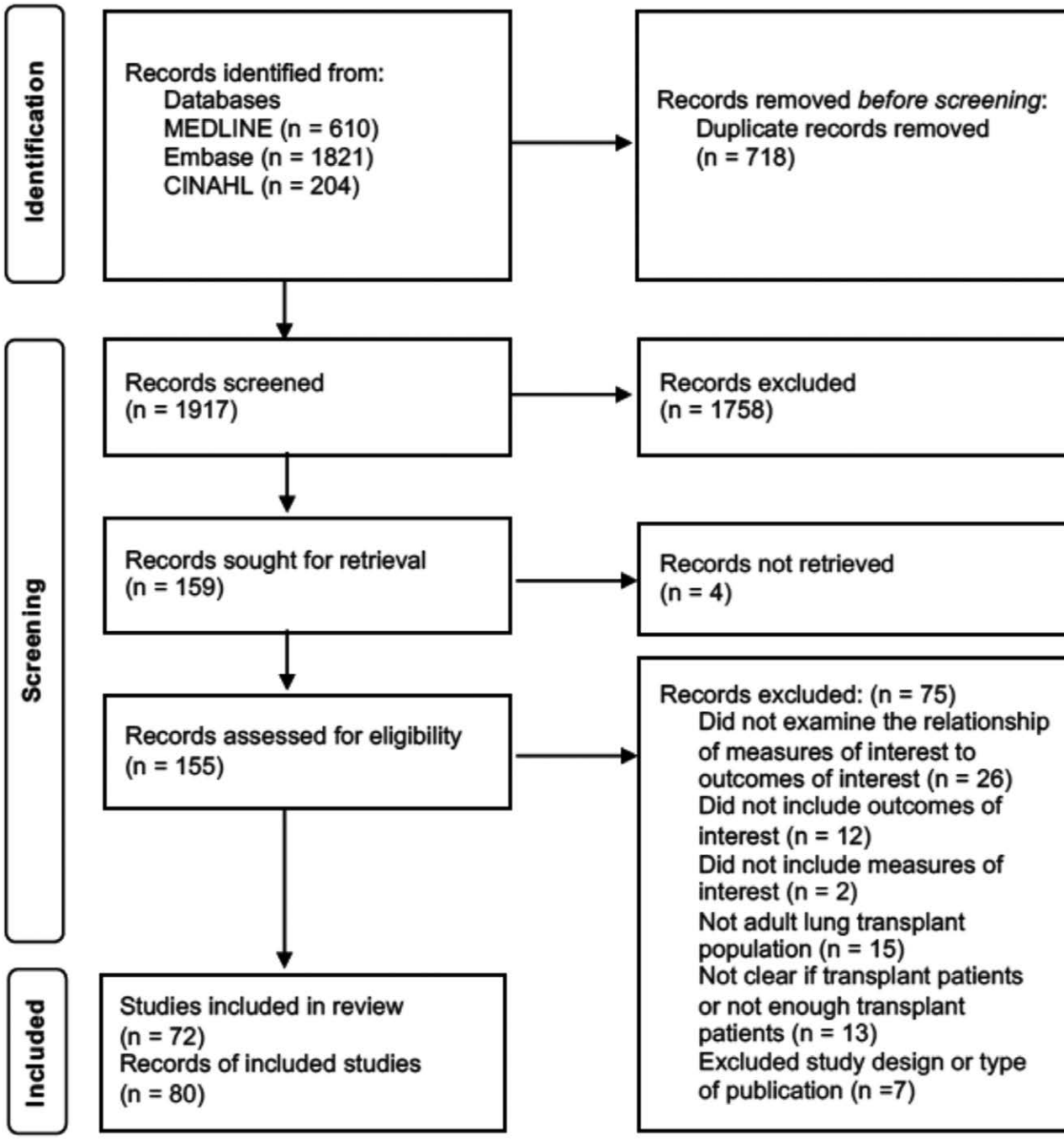


FIGURE 1. PRISMA flow chart of the database search to final inclusion of studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

relationship was shown. Bauldoff et al[53] examined the relationship between 6MWT and rehospitalization posttransplant and have found that patients achieving a 6MWD <244 m had a higher percentage of in-hospital days in the first year posttransplant. Finally, no studies have examined the relationship of the tests of interest and the number of hospitalizations during the waiting period. A summary of the number of studies that included lung transplant candidates and examined the relationship of measures of exercise capacity, frailty, and physical function with healthcare utilization is shown in Figure 3. More information about the direction of the relationship is presented in Table S4 (SDC, http://links.lww.com/TXD/A454).

Relationship With Clinical Outcomes in Lung Transplant Recipients

A summary of the relationship of measures of exercise capacity, frailty, and physical function with clinical outcomes in studies that included lung transplant recipients is shown in Figure 4. Fourteen studies examined the relationship of pretransplant 6MWT with mortality posttransplant.[66-79] Of those, 7 studies showed a significant relationship with mortality posttransplant.[66-72] Three studies examined the relationship of posttransplant 6MWT with mortality or survival posttransplant[68,80,81] with 2 studies showing a significant relationship with this outcome.[68,80] The relationship of the CPET with

TABLE 1.

Characteristics of the included studies

	Lung transplant candidates (n = 42)	Lung transplant recipients (n = 30)
Type of records, n		
Full-text articles	31[a]	21
Conference abstracts	10	9
Thesis	1	0
Study design, n		
Retrospective cohort study	29	18
Prospective cohort study	11	10
Cross-sectional study	2	2
Year of publication, n		
1990–2000	2	0
2001–2010	10	6
2011–2015	11	7
2016–2021	19	17
Continent/region, n		
North America	25	18
South America	1	1
Europe	7	10
Asia	5	1
Oceania	4	0
Diagnosis (number of patients/number of studies)		
Restrictive		
IIP (IPF, PPFE, NSIP, COP)	2047/26	1147/16
Autoimmune	97/7	33/1
Hypersensitivity pneumonitis	23/7	31/1
Sarcoidosis	71/6	33/3
Other (LAM, histiocytosis)	10/4	244/7
Not specified	6531/10	5419/9
Obstructive		
COPD/emphysema	13158/16	450/13
Alpha-1 antitrypsin	56/4	22/3
Cystic fibrosis	1891/16	1451/14
Bronchiectasis	56/3	8/2
Bronchiolitis obliterans syndrome	22/1	1/1
Not specified	4317/1	3617/5
Pulmonary vascular disease	662/10	367/9
Retransplant	7/1	5/2
Not specified/not mentioned	2724/15	982/15
Tests included in studies, n		
6MWT	36	22
SPPB	6	6
CPET	3	2
ESWT	1	0
5STS	1	0
4MGS	1	0

[a]One article was a research correspondence.

4MGS, 4-m gait speed; 5STS, 5 times sit-to-stand; 6MWT, 6-min walk test; COP, cryptogenic organizing pneumonia; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise test; ESWT, endurance shuttle walk test; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; LAM, lymphangioleiomyomatosis; NSIP, nonspecific interstitial pneumonia; PPFE, pleuroparenchymal fibroelastosis; SPPB, short physical performance battery.

mortality posttransplant was examined in 2 studies,[82,83] in which both have shown a significant relationship. Three studies examined the relationship between SPPB and mortality posttransplant; in 1 study, the test was done pretransplant[84] and in 2 studies posttransplant.[85,86] All these studies showed a significant relationship with this outcome.

One study examined the relationship of pretransplant 6MWT with QOL posttransplant with no significant relationship shown.[87] Two studies examined the relationship of the posttransplant 6MWT with QOL posttransplant.[88,89] Ihle et al[88] have shown a relationship with a better QOL for double-lung transplant than single-lung transplant recipients, and Gerbase et al[89] have only shown a relationship with bilateral transplantation. Three studies examined the relationship between SPPB and QOL posttransplant; in 1 study, the test was done pretransplant[90] and in 2 studies posttransplant,[85,90] in which all of them have shown a significant relationship with this outcome.

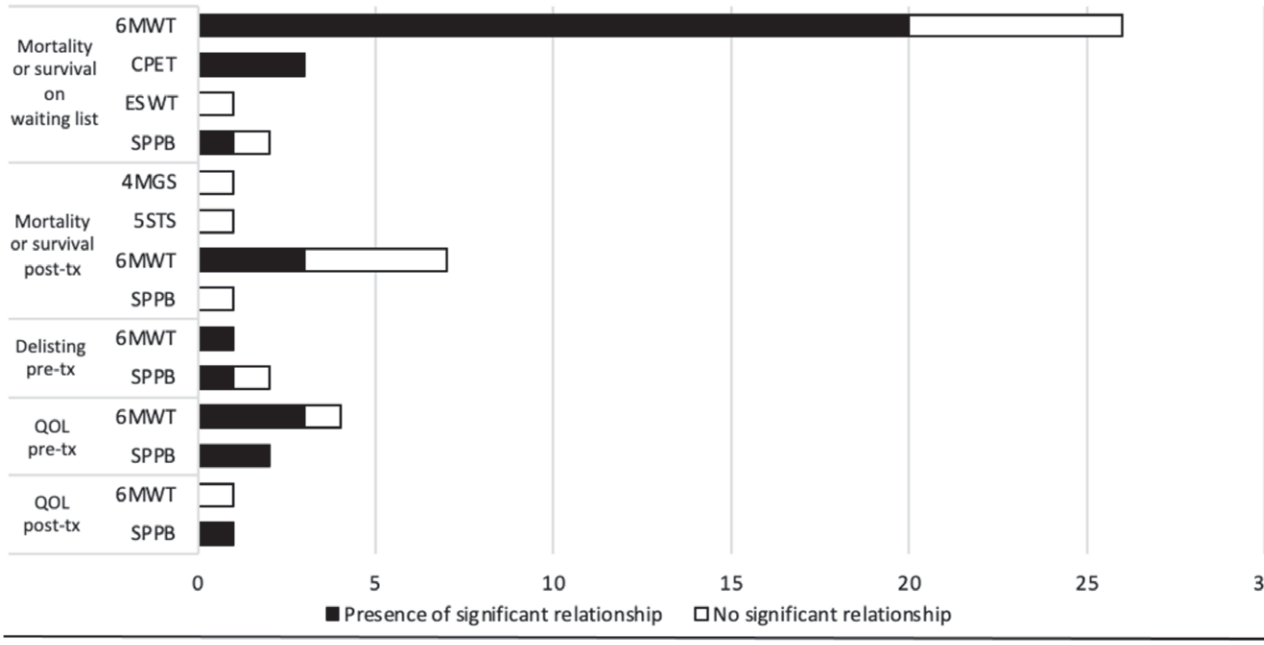
Three studies examined the relationship of pretransplant 6MWT with CLAD development, and none of them have shown a relationship.[68,78,91] Three studies examined the relationship of posttransplant 6MWT with CLAD development.[68,92,93] Of those, 2 studies showed a significant relationship with the outcome.[92,93] Maheshwari et al[94] have shown a significant relationship between posttransplant SPPB and CLAD development. More information about the direction of these relationships is presented in Table S5 (SDC, http://links.lww.com/TXD/A454). There were no studies that examined the relationship of pretransplant CPET or any physical function measures with clinical outcomes.

Relationship With Healthcare Utilization in Lung Transplant Recipients

Healthcare utilization in lung transplant recipients was mentioned in only 4 studies.[67,73,87,95] Figure 5 presents a summary of the relationship of measures of exercise capacity, frailty, and physical function and healthcare utilization in studies that included lung transplant recipients. Two studies examined the relationship between the pretransplant 6MWT and hospital LOS.[67,73] Of those, 1 study showed a significant relationship with hospital LOS.[67] The relationship between pretransplant 6MWT and discharge destination was examined in 2 studies, with none of them showing a relationship.[73,87] Halpern et al[73] have shown no relationship between the pretransplant 6MWT and rehospitalization after the transplant. On the contrary, Courtwright et al[95] have shown a significant relationship between the posttransplant SPPB and rehospitalization. More information about the direction of these relationships is presented in Table S6 (SDC, http://links.lww.com/TXD/A454). There were no studies that examined the relationship of physical function tests or CPET with healthcare utilization. There were no studies that examined the relationship of the measures of interest and ICU LOS or time on mechanical ventilation posttransplant.

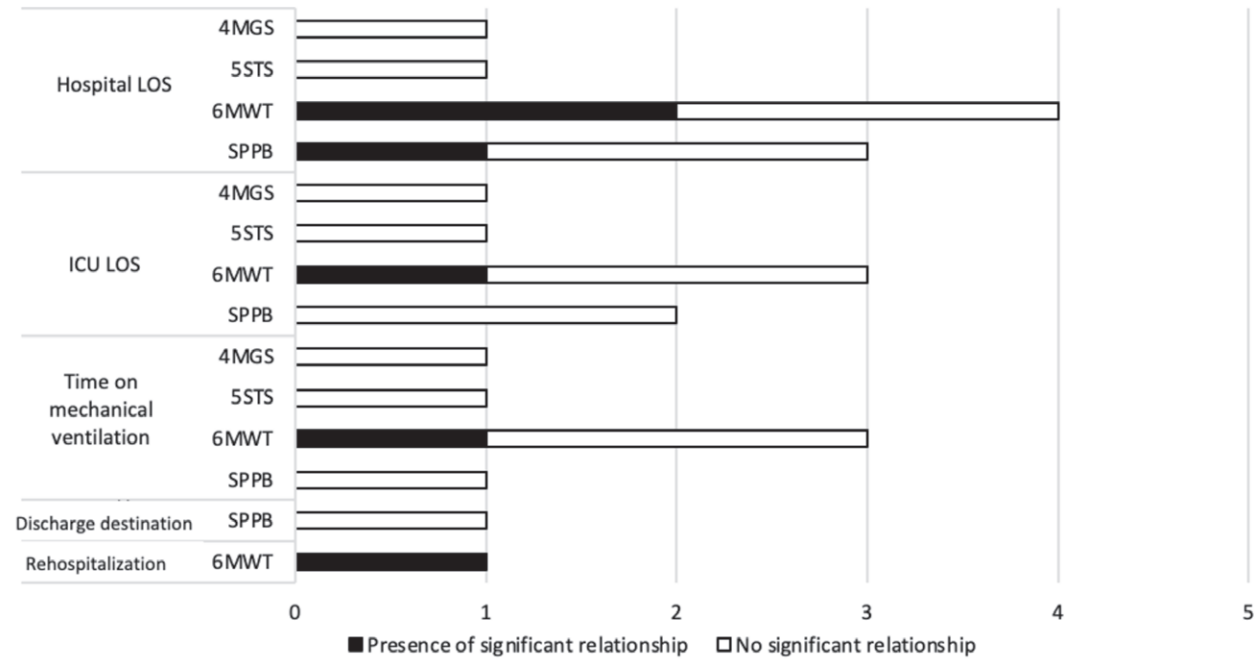
6MWT and Mortality on the Waiting List

The relationship of the 6MWT to mortality or survival on the waiting list in lung transplant candidates has been well studied (26 studies; Figure 1). A description of the 20 studies that have demonstrated a relationship between the 6MWD and mortality on the waiting list is presented in Table 2. The walked distance cutoffs used for mortality analyses ranged from 46 to 470 m. Studies that calculated a hazard ratio (HR) for mortality with 6MWD reported an HR between 1.79 and 5.1 (Table 2). One study[43] reported an HR of 0.77 per 61-m increment and 1 study[35] an HR of 0.97 per 10-m increase. These 20 studies included patients who had mostly interstitial



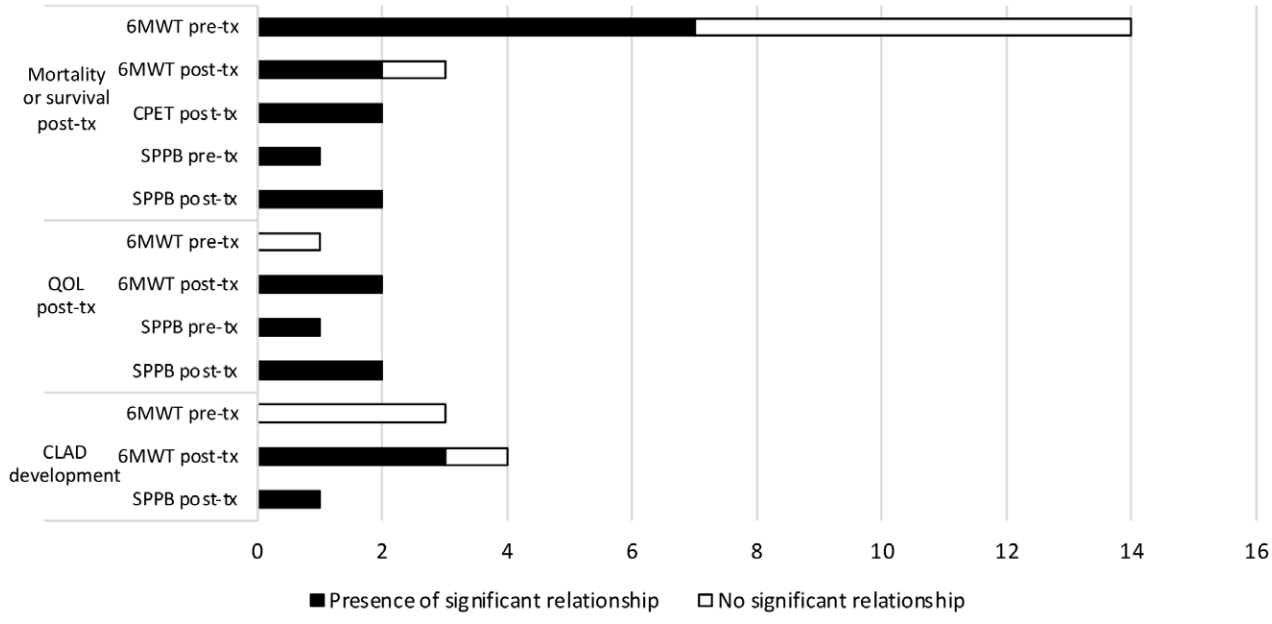
6MWT: six-minute walk test; CPET: cardiopulmonary exercise test; ESWT: endurance shuttle walk test; SPPB: short physical performance battery; 5STS; five times sit-to-stand; 4MGS: four-meter gait speed; QOL: Quality of life; tx: transplant
Note: all significant relationships indicated associations between higher performance-based test measures and improved clinical outcomes (i.e. decreased mortality, increased survival, better QOL, reduced healthcare utilization)

FIGURE 2. Number of studies with lung transplant candidates examining the relationship with clinical outcomes. Note: All significant relationships indicated associations between higher performance-based test measures and improved clinical outcomes (ie, decreased mortality, increased survival, better QOL, reduced healthcare utilization). 4MGS, 4-m gait speed; 5STS, 5 times sit-to-stand; 6MWT, 6-min walk test; CPET, cardiopulmonary exercise test; ESWT, endurance shuttle walk test; QOL, quality of life; SPPB, short physical performance battery; tx, transplant.



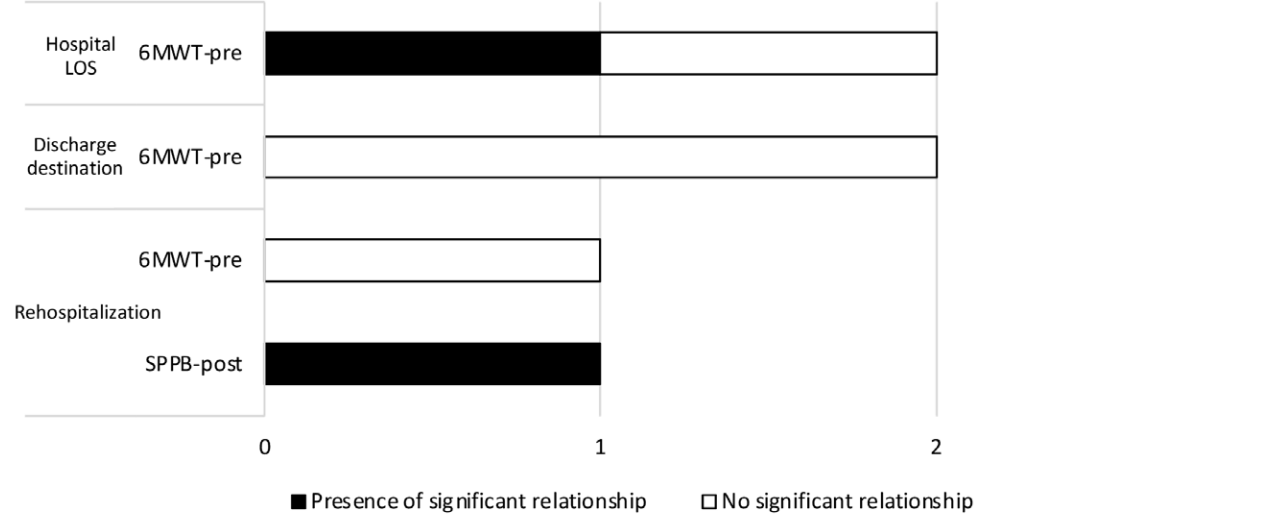
6MWT: six-minute walk test; CPET: cardiopulmonary exercise test; ESWT: endurance shuttle walk test; SPPB: short physical performance battery; 5STS; five times sit-to-stand; 4MGS: four-meter gait speed; LOS: Length of stay; ICU: Intensive Care Unit
Note: all significant relationships indicated associations between higher performance-basedtest measures and improved clinical outcomes (i.e. decreased mortality, increased survival, better QOL, reduced healthcare utilization)

FIGURE 3. Number of studies with lung transplant candidates examining the relationship with healthcare utilization. Note: All significant relationships indicated associations between higher performance-based test measures and improved clinical outcomes (ie, decreased mortality, increased survival, better quality of life, reduced healthcare utilization). 4MGS, 4-m gait speed; 5STS, 5 times sit-to-stand; 6MWT, 6-min walk test; ICU, intensive care unit; LOS, length of stay; SPPB, short physical performance battery.



6MWT: six-minute walk test; CPET: cardiopulmonary exercise test; SPPB: short physical performance battery; QOL: Quality of life; tx: transplant; CLAD: Chronic Lung Allograft Dysfunction

FIGURE 4. Number of studies with lung transplant recipients that have shown a relationship with clinical outcomes. 6MWT, 6-min walk test; CLAD, chronic lung allograft dysfunction; CPET, cardiopulmonary exercise test; QOL, quality of life; SPPB, short physical performance battery; tx, transplant.



6MWT: six-minute walk test; SPPB: short physical performance battery; LOS: Length of stay

FIGURE 5. Number of studies with lung transplant recipients that have shown a relationship with healthcare utilization outcomes. 6MWT, 6-min walk test; LOS, length of stay; SPPB, short physical performance battery.

lung diseases (n = 16), but studies also included patients with COPD (n = 7), cystic fibrosis (n = 5), or pulmonary arterial hypertension (n = 3).

DISCUSSION

This study reviewed information about the relationship of performance-based tests of exercise capacity, physical function, and frailty with clinical outcomes and healthcare utilization in lung transplantation. Most of the evidence in the literature lies in the relationship between the 6MWT and mortality on the waiting list. The studies showed that functional exercise capacity measured by the 6MWT is inversely related to mortality on the waiting list in lung transplant candidates. Few studies included other measures of exercise capacity (eg, CPET) or physical function and frailty measures, and therefore, the relationship of these tests with clinical outcomes is unclear. A limited number of studies examined the relationship of the tests of interest with healthcare utilization, and the results were inconsistent.

TABLE 2.

Cutoffs used for the 6MWD in relationship with mortality or survival during transplantation waiting time

First author, year	Lung diseases	Distance, m	Analysis 6MWD	Main findings
Thabut, 2008[30]	COPD	46	Continuous	*Parameters associated with survival*: Age, alpha 1-antitrypsin deficiency, functional status, oxygen requirement, *6MWD*, continuous mechanical ventilation, FEV_1, systolic pulmonary artery pressure, and BMI. *HR mortality*: 6MWD <150 ft HR = 1.79 (1.46-2.20)
Lotshaw, 2006[41]	–	46	–	6MWD of 46 m had a high specificity to predict death, but poor sensitivity *Likelihood ratios to predict survival (sensitivity/specificity)*: 6MWD of 46 m = 5 (0.05/0.99) 6MWD of 152 m = 2.3 (0.33/0.86) 6MWD of 305 m = 4.9 (0.83/0.29)
Castleberry, 2017[43]	COPD-ILD-CF-PAH	168–198	Per 61-m increment	Discrimination distance for 30-d mortality: 168 m 6-mo mortality: 198 m *HR mortality*: 6MWD per 61 m increment HR = 0.77 (0.75-0.79)
Timofte, 2020[32]	COPD-ILD-CF-PAH	200	Continuous	Distance walked and percent of predicted distance were associated inversely with mortality *HR mortality*: 6MWD <200 m HR = 2.1 (1.1-4.0) 6MWD <45% of predicted walk distance HR = 2.7 (1.2-5.7)
Lederer, 2006[39]	IPF	207	Continuous	Patients with a lower 6MWD had an increased mortality rate Cutoff with 74% sensitivity and 73% specificity for death within 6 mo *HR mortality*: 6MWD <207 m HR = 5.1 (3.0-8.8)
Timofte, 2016[25]	COPD	229	Continuous	Lower median survival days for patients with 6MWD <750 ft and low FVC (<50%) *HR mortality*: 6MWD <229 m + FVC <50% HR = 3.07 (2.31-4.07)
Ikezoe, 2017[35]	ILD	250	Per 10-m increment	*Associations with mortality*: BMI, % predicted FVC, % predicted DLCO, *6MWD*, oxygen flow ≥2 L/min at 6MWT, GAP stage III *Cutoff at 250 m*: Patients with a 6MWD <250 m had significantly shorter survival times than those with a 6MWD ≥250 m *HR mortality*: 6MWD Per 10 m increment HR = 0.97 (0.95-0.99)
Oshima, 2019[33]	ILD	250	Continuous	*Parameters associated with survival*: TTR (serum transthyretin) and 6MWD *Hazard ratio mortality*: 6MWD <207 m HR = 5.1 (3.0-8.8)
Martinu, 2008[27]	COPD-ILD-CF	274	Per 152-m increment	*HR mortality*: 6MWD per 152 m increment HR = 0.57 (0.43-0.77)
Tuppin, 2008[34]	COPD-ILD-CF	315	Continuous	Protective effect for each 1-m increase in walk distance *Risk ratio mortality*: 6MWD for each 1-m increase RR = 0.994 (0.990-0.997)
Kawut, 2005[31]	ILD	350	Continuous	*Parameters associated with survival*: Ethnicity, lower DLCO% predicted, pulmonary hypertension, and 6MWD Oxygen saturation, peak VO_2/kg, and peak oxygen pulse during CPET *HR mortality*: 6MWD <350 m HR = 4.6 (1.5-14.2)
Jastrzebski, 2005[36]	ILD	350	–	*Parameters associated with survival*: patient with left ventricular ejection fraction >50% and 6MWD >350 m

Continued next page

TABLE 2. (Continued)

Cutoffs used for the 6MWD in relationship with mortality or survival during transplantation waiting time

First author, year	Lung diseases	Distance, m	Analysis 6MWD	Main findings
Ochman, 2020[37]	IPF	350	–	*Risk of death*: 10× more for 6MWD ≤72 m vs 6MWD >350 m 3× more for 6MWD of 253–350 m vs 6MWD >350 m
Kadikar, 1997[42]	COPD-ILD-CF-PAH	400	–	Increased risk of death for patients with 6MWD ≤400 m
Leuchte, 2015[38]	IPF	470	Continuous	*Parameters associated with survival*: 6MWD and daily activity class (AC>II) *HR mortality*: 6MWD <470 m HR = 1.8 (1.1-4.0)
Zhu, 2021[26]	ILD	NM	Per 50-m decrease	*Predictors of mortality*: Blood group O vs A, shorter height, need for hospitalization at listing, and reduced 6MWD *HR mortality*: 6MWD per 50 m decrease HR = 1.28 (1.10-1.49)
Yu, 2018[28]	IPF	NM	Continuous	*Predictors of mortality*: Serum carcinoembryonic antigen, LAS, and 6MWD *HR mortality*: 6MWD (m) HR = 0.992 (0.987-0.998)
Layton, 2017[29]	ILD	NM	Continuous	*Parameters associated with survival*: All CPET parameters and 6MWD *Risk of mortality*: ↑ 1 m in 6MWD is reducing the risk by 1%
Higo, 2017[44]	ILD	NM	Continuous	*Early death group vs long wait group*: 6MWD: 119 ± 118 vs 200 ± 91 m (P = 0.04)
Klooster, 2015[40]	IPF	NM	Continuous	*Parameters associated with survival:* Use of supplemental oxygen and 6MWD *HR mortality*: 6MWD (m) HR = 0.996 (0.994-0.999)

6MWD, 6-min walk distance; BMI, body mass index; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; D_{LCO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in the first second; FVC, functional vital capacity; GAP, gender-age-physiology index; HR, hazard ratio; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LAS, lung allocation score; NM, not mentioned; PAH, pulmonary arterial hypertension.

The large number of studies including the 6MWT as a measure of functional exercise capacity in lung transplant candidates was expected because this test has been recommended as part of the selection process for lung transplantation by the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation since 2006.[96] The inverse relationship between the 6MWT and mortality has also been observed in other populations such as liver transplant candidates[97] and individuals with chronic kidney disease.[98] The 6MWT has been shown to be correlated with lung function and disease severity in different lung diseases,[99-102] but it actually evaluates the global response of all body systems (eg, pulmonary, cardiovascular, circulatory, musculoskeletal, metabolic) involved during exercise or activities of daily living.[103] For this reason, the 6MWT is an important test to be included in the listing criterion for lung transplantation.

Functional exercise capacity measured by the 6MWT has been shown to improve after a pulmonary rehabilitation program in lung transplant candidates.[104-106] The average increase in 6MWT distance in these studies has shown an increase of 58,[104] 72,[105] and 62 m,[106] which are all greater than the minimal important difference of 30 m for the 6MWT in chronic respiratory disease.[107] It remains to be studied whether an improvement in 6MWT during the waitlist time can impact mortality during this period.[1,7] In addition, as many different 6MWD cutoffs were used for the 6MWT to examine the relationship of this test with waitlist mortality, more research is needed to define specific cutoffs points to help with risk stratification in this population.

Although our review identified a limited number of studies that have shown a relationship of the CPET with clinical outcomes or healthcare utilization, this relationship has been studied in other populations. The CPET has been shown to be related to survival in COPD,[108,109] in primary pulmonary hypertension,[110] and in cystic fibrosis.[111] It is considered a gold-standard test for detecting adverse events such as cardiovascular events in heart failure patients[112] and for differential diagnosis of cardiovascular or respiratory diseases.[113] The CPET is recommended by the International Society of Heart and Lung Transplant for assessment for heart transplantation,[114] and it has been shown to be related to mortality and increased hospitalization time in end-stage liver disease,[97] as well as to survival in individuals with chronic kidney disease.[98] As the predictive value of CPET in lung transplantation is unclear and considering that the CPET is not a simple test to conduct, more research is needed to justify the utilization of the CPET over the 6MWT in addition to that of detecting adverse events during exercise.

Our findings revealed that some studies have shown a significant relationship between the SPPB and clinical outcomes; however, the conclusion about these relationships is unclear because of the limited number of studies. This may be explained by the fact that we only included performance-based tests of frailty, excluding studies with other measures of frailty such as the Fried Frailty Index and Cumulative Deficits Frailty Index. Another explanation could be that, although the importance of frailty in transplantation has grown recently, the assessment of frailty is not being performed routinely pre- or posttransplant in the clinics or research studies. One recent narrative review[115] presented information on the relationship of the SPPB, Fried Frailty Phenotype, and Cumulative Deficits Frailty Index with pre- and posttransplant outcomes in lung transplantation. The authors concluded that frailty was associated with a poorer health-related QOL, pretransplant delisting, and pre- and posttransplant mortality.[115] Aligned with these findings, our review identified some relationship of the SPPB with survival posttransplant and QOL but only in a limited number of studies. In other solid organ transplant groups, frailty, measured by the SPPB and Fried Frailty Index, has been shown to be related to waitlist mortality in liver[116] and lung[117] transplant candidates and to post–kidney transplant mortality.[118] Nevertheless, further investigation is needed in lung transplant patients to determine the relationship between frailty measures and clinical outcomes.

We found only 1 study (single center with 25 subjects) that included physical function tests (5STS and 4MGS). This study did not show a relationship of these tests with survival posttransplant or healthcare utilization (hospital LOS, ICU LOS, or time on mechanical ventilation). Physical function measures have been shown to be associated with clinical outcomes and healthcare utilization in populations that may be listed for transplant.[119-122] A recent systematic review[119] examined the prognostic value of measures of physical function and muscle strength in relation to exacerbations, hospitalizations, and mortality in individuals with COPD. The review included 7 articles and revealed that the 1-min STS, 5STS, and Timed Up and Go have shown some relationship with survival.[119] The 1-min STS test has been recently used as an alternative exercise capacity test for the 6MWT in chronic lung diseases[120,121] including lung transplant candidates and recipients[123,124] and was shown to be associated with mortality at 5 y in COPD.[122] Other studies have shown that gait speed was associated with delisting in liver transplant candidates[97] and with mortality in individuals with chronic kidney disease.[98] These physical function tests are more feasible to be performed in clinical practice,[125] as well as remotely.[126] The evidence for the relationship between physical function measures and clinical outcomes in lung transplant patients is limited; however, given the simplicity and practicality of these tests and the emerging evidence in terms of validity in lung transplant patients, these tests may be used more often in the future, and consequently, more evidence in terms of relationship with clinical outcomes may become available.

There was only a limited number of studies examining healthcare utilization outcomes and the performance-based tests of interest. Surprisingly, no study has examined the relationship between performance-based tests done after the surgery in lung transplant recipients and discharge destination. A possible explanation could be that some performance-based tests are difficult to be executed in the acute phase posttransplantation because of the presence of equipment on the patient, such as mechanical ventilation or chest tubes and instability postsurgery. As lung transplantation surgery is expensive,[127] reducing the duration of the hospitalization is of interest to reduce healthcare costs. Unfortunately, we have found a very limited number of studies that included hospital or ICU LOS as outcomes. The most studied relationship was between the 6MWT and hospital LOS; however, the results were inconsistent among the 4 studies included in our review. Interestingly, Li et al[128] have shown that the 6MWD before transplant was related to a shorter hospital LOS but was not included in this review because they included heart-lung transplant candidates in their analysis. Still, more research on this relationship is needed because it was only examined in a limited number of studies.

The scoping review design allows a comprehensive, broad review of the literature and the identification of research gaps.[129] The strength of this review is that it is the first to compile the evidence regarding performance-based tests of exercise capacity, physical function, and frailty used in lung transplantation in relation to important outcomes such as mortality, survival, QOL, and hospital LOS. It also raises the awareness on the utility of these tests in lung transplantation. As the decision of listing a patient for lung transplantation is influenced by risk factors for poor posttransplant outcomes such as functional status,[16] there is a need to know which tests could be used to assess these patients that could possibly influence the outcomes of transplantation. Our goal was to inform clinicians and researchers about the relationship between functional status measures and outcomes in lung transplantation, which may guide them on the assessment of lung transplant candidates, and management of lung transplant recipients. This review revealed that, apart from the 6MWT, there is not enough evidence on the other performance-based tests of interest to suggest their use to predict outcomes. Additionally, this review showed the existing gaps in the literature regarding the use of different measures in lung transplantation, which can inform future research. A summary of recommendations for clinical practice and research is summarized in Table 3.

This review has some limitations. Because this is a scoping review with the goal of providing an overview of the evidence for the relationships of measures with outcomes, the methodological quality and appropriateness of the statistical analysis of the included studies were not assessed. This is not mandatory for a scoping review[129]; however, it can still affect our conclusions because some methodological flaws could influence results of the included studies. In addition, because of the nature of a scoping review, there was methodological and statistical analysis heterogeneity in the included studies, and therefore, a meta-analysis was not conducted. Another limitation of our review is the limited number of studies related to all performance-based tests except for the 6MWT. This limited us from drawing more robust conclusions about the relationship of these tests with outcomes. In addition, we had to exclude studies that combined the results of lung transplant patients with other types of diagnoses such as heart-lung transplantation or chronic lung diseases. Nevertheless, this scoping review is a mapping of the literature and provides important information such as the most common tests used in research and the number of published studies in this field, as

TABLE 3.

Summary of the recommendations for clinical practice and research

Main findings	Recommendations for clinical practice	Recommendations for research
Most of the studies included the 6MWT. 6MWT is inversely related to mortality on the waiting list in lung transplant candidates. Many different 6MWD cutoffs were used for the 6MWT to examine the relationship of this test with waitlist mortality.	The 6MWT has been recommended as part of selection process for lung transplantation by the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. The 6MWT evaluates the global response of all body systems and should be used in clinical practice.	It remains to be studied whether an improvement in 6MWT during the waitlist time can impact mortality during this period. More research is needed to define specific cutoffs points to help with risk stratification in this population.
There was a limited number of studies that have shown a relationship between the CPET and clinical outcomes or healthcare utilization.	To date, there is no evidence that the CPET should be routinely used in the selection process of lung transplantation or posttransplant.	As the predictive value of CPET in lung transplant is unclear and considering that the CPET is not a simple test to conduct, more research would be needed to justify the utilization of the CPET over the 6MWT.
There was a limited number of studies that have shown a relationship of the SPPB and clinical outcomes.	The SPPB is a relatively simple test to be conducted and is considered a surrogate measure for frailty. Considering the recent clinical importance of frailty, we recommend including it in clinical practice.	Further investigation is needed in lung transplant patients to determine the relationship of frailty measures and clinical outcomes.
Only 1 study included physical function tests (5STS and 4MGS), which did not show a relationship between these tests and survival posttransplant or healthcare utilization.	Physical function measures have been shown to be associated with outcomes and healthcare utilization in populations that may be listed for transplant (eg, COPD and ILD). The 1-min STS test has been recently used as an alternative exercise capacity test for the 6MWT in chronic lung diseases including lung transplant candidates and recipients. These physical function tests are more feasible to be performed in clinical practice and remotely and may be considered in clinical practice for transplant patients.	More research is needed to establish the relationship of physical function tests and clinical outcomes and healthcare utilization.
There was a limited number of studies examining healthcare utilization outcomes and the performance-based tests of interest.	As lung transplantation surgery is expensive, reducing the duration of hospitalization is of interest to reduce healthcare costs. To date, there is no evidence that improving physical function of lung transplant candidates or recipients will reduce healthcare utilization.	More research is needed to determine the association between performance-based tests and healthcare utilization such as hospital length of stay or rehospitalization in lung transplantation.

4MGS, 4-m gait speed test; 5STS, 5 times sit-to-stand test; 6MWD, 6-min walk distance; 6MWT, 6-min walk test; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise test; ILD, interstitial lung disease; SPPB, short physical performance battery.

well as the available evidence for the relationships of the tests of interest with clinical outcomes and healthcare utilization.

CONCLUSION

The majority of the studies that have examined the relationship between the 6MWT and mortality on the lung transplant waiting list have shown a significant association with mortality using different 6MWD values as cutoffs. To date, there is insufficient evidence regarding the relationship between other tests and clinical outcomes. It remains unclear if performance-based tests of exercise capacity, physical function, and frailty could be associated with outcomes such as hospital LOS or number of hospitalizations. Further evidence on relationships of physical function tests (eg, SPPB, STS tests) with outcomes would help clinicians make better decisions on the selection of lung transplant candidates and management of lung transplant recipients.

REFERENCES

1. Pesce de Souza F, Massierer D, Anand Raje U, et al. Exercise interventions in solid organ transplant candidates: a systematic review. *Clin Transplant*. 2020;34:e13900.
2. Chambers DC, Cherikh WS, Harhay MO, et al; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart And Lung Transplantation: thirty-sixth adult lung and heart-lung transplantation report—2019; focus theme: donor and recipient size match. *J Heart Lung Transplant*. 2019;38:1042–1055.
3. Johnson JL, Campbell AC, Bowers M, et al. Understanding the social consequences of chronic obstructive pulmonary disease: the effects of stigma and gender. *Proc Am Thorac Soc*. 2007;4:680–682.
4. Spruit MA, Singh SJ, Garvey C, et al; ATS/ERS Task Force on Pulmonary Rehabilitation. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188:e13–e64.
5. Wickerson L, Rozenberg D, Janaudis-Ferreira T, et al. Physical rehabilitation for lung transplant candidates and recipients: an evidence-informed clinical approach. *World J Transplant*. 2016;6:517–531.
6. Langer D. Rehabilitation in patients before and after lung transplantation. *Respiration*. 2015;89:353–362.
7. Janaudis-Ferreira T, Mathur S, Deliva R, et al. Exercise for solid organ transplant candidates and recipients: a joint position statement of the Canadian society of transplantation and CAN-RESTORE. *Transplantation*. 2019;103:e220–e238.
8. Martelli V, Mathur S, Wickerson L, et al. Impaired cardiac autonomic response in lung transplant patients: a retrospective cohort study. *Clin Transplant*. 2019;33:e13612.
9. Mathur S, Janaudis-Ferreira T, Wickerson L, et al. Meeting report: consensus recommendations for a research agenda in exercise in solid organ transplantation. *Am J Transplant*. 2014;14:2235–2245.
10. Rozenberg D, Singer LG, Herridge M, et al. Evaluation of skeletal muscle function in lung transplant candidates. *Transplantation*. 2017;101:2183–2191.
11. Walsh JR, Chambers DC, Davis RJ, et al. Impaired exercise capacity after lung transplantation is related to delayed recovery of muscle strength. *Clin Transplant*. 2013;27:E504–E511.
12. Didsbury M, McGee RG, Tong A, et al. Exercise training in solid organ transplant recipients: a systematic review and meta-analysis. *Transplantation*. 2013;95:679–687.
13. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from

the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2015;34:1–15.
14. Mayer KP, Henning AN, Gaines KM, et al. Physical function measured prior to lung transplantation is associated with posttransplant patient outcomes. *Transplant Proc*. 2021;53:288–295.
15. Kobashigawa J, Dadhania D, Bhorade S, et al. Report from the American Society of Transplantation on frailty in solid organ transplantation. *Am J Transplant*. 2019;19:984–994.
16. Leard LE, Holm AM, Valapour M, et al. Consensus document for the selection of lung transplant candidates: an update from the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2021;40:1349–1379.
17. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol*. 2005;8:19–32.
18. Munn Z, Peters MDJ, Stern C, et al. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol*. 2018;18:143.
19. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. 2018;169:467–473.
20. Rethlefsen ML, Kirtley S, Waffenschmidt S, et al; PRISMA-S Group. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. *Syst Rev*. 2021;10:39.
21. World Health Organization. International Classification of Functioning, Disability and Health (ICF). Available at https://icd.who.int/dev11/l-icf/en. Accessed January 8, 2022.
22. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;49:M85–M94.
23. Pritchard JM, Kennedy CC, Karampatos S, et al. Measuring frailty in clinical practice: a comparison of physical frailty assessment methods in a geriatric out-patient clinic. *BMC Geriatr*. 2017;17:264.
24. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan—a web and mobile app for systematic reviews. *Syst Rev*. 2016;5:210.
25. Timofte I, Terrin M, Wijesinha M, et al. 6 minute walk test and FVC analysis: a new method to prioritize organ allocation for patients with COPD. *Am J Transplant*. 2016;16:597.
26. Zhu MZL, Levvey BJ, McGiffin DC, et al. An intention-to-treat view of lung transplantation for interstitial lung disease: successful strategies to minimize waiting list and posttransplant mortality. *Transplantation*. 2022;106:188–199.
27. Martinu T, Babyak MA, O'Connell CF, et al; INSPIRE Investigators. Baseline 6-min walk distance predicts survival in lung transplant candidates. *Am J Transplant*. 2008;8:1498–1505.
28. Yu WS, Lee JG, Paik HC, et al. Carcinoembryonic antigen predicts waitlist mortality in lung transplant candidates with idiopathic pulmonary fibrosis. *Eur J Cardiothorac Surg*. 2018;54:847–852.
29. Layton AM, Armstrong HF, Kim HP, et al. Cardiopulmonary exercise factors predict survival in patients with advanced interstitial lung disease referred for lung transplantation. *Respir Med*. 2017;126:59–67.
30. Thabut G, Ravaud P, Christie JD, et al. Determinants of the survival benefit of lung transplantation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2008;177:1156–1163.
31. Kawut SM, O'Shea MK, Bartels MN, et al. Exercise testing determines survival in patients with diffuse parenchymal lung disease evaluated for lung transplantation. *Respir Med*. 2005;99:1431–1439.
32. Timofte I, Tonelli A, Diaz-Abad M, et al. Gait-speed and oxygen flow during six-minute walk test predicts mortality in patients with advanced lung disease. *Monaldi Arch Chest Dis*. 2020;90:66–72.
33. Oshima A, Nishimura A, Chen-Yoshikawa TF, et al. Nutrition-related factors associated with waiting list mortality in patients with interstitial lung disease: a retrospective cohort study. *Clin Transplant*. 2019;33:e13566.
34. Tuppin MP, Paratz JD, Chang AT, et al. Predictive utility of the 6-minute walk distance on survival in patients awaiting lung transplantation. *J Heart Lung Transplant*. 2008;27:729–734.
35. Ikezoe K, Handa T, Tanizawa K, et al. Prognostic factors and outcomes in Japanese lung transplant candidates with interstitial lung disease. *PLoS One*. 2017;12:e0183171.
36. Jastrzebski D, Kozielski J, Nowak J, et al. Prognostic risk factors in patients with interstitial lung disease referred for lung transplantation. *J Physiol Pharmacol*. 2005;56 Suppl 4:107–113.
37. Ochman M, Urlik M, Tatoj Z, et al. Retrospective cohort study of patients qualified for lung transplantation due to idiopathic pulmonary fibrosis—single-centre experience. *Arch Med Sci*. 2020;16:621–626.
38. Leuchte HH, Mernitz P, Baezner C, et al. Self-report daily life activity as a prognostic marker of idiopathic pulmonary fibrosis. *Respiration*. 2015;90:460–467.
39. Lederer DJ, Arcasoy SM, Wilt JS, et al. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2006;174:659–664.
40. ten Klooster L, Nossent GD, Kwakkel-van Erp JM, et al. Ten-year survival in patients with idiopathic pulmonary fibrosis after lung transplantation. *Lung*. 2015;193:919–926.
41. Lotshaw A, Coleman A, Luthye B, et al. The predictive value of the six-minute walk test and lung transplant survival. *Cardiopulm Phys Ther J*. 2006;17:143.
42. Kadikar A, Maurer J, Kesten S. The six-minute walk test: a guide to assessment for lung transplantation. *J Heart Lung Transplant*. 1997;16:313–319.
43. Castleberry A, Mulvihill MS, Yerokun BA, et al. The utility of 6-minute walk distance in predicting waitlist mortality for lung transplant candidates. *J Heart Lung Transplant*. 2017;36:780–786.
44. Higo H, Kurosaki T, Ichihara E, et al. Clinical characteristics of Japanese candidates for lung transplant for interstitial lung disease and risk factors for early death while on the waiting list. *Respir Investig*. 2017;55:264–269.
45. Walsh JR, Chambers DC, Yerkovich ST, et al. Low levels of physical activity predict worse survival to lung transplantation and poor early post-operative outcomes. *J Heart Lung Transplant*. 2016;35:1041–1043.
46. Chen F, Oga T, Yamada T, et al. Lung allocation score and health-related quality of life in Japanese candidates for lung transplantation. *Interact Cardiovasc Thorac Surg*. 2015;21:28–33.
47. Stavem K, Bjørtuft Ø, Borgan Ø, et al. Lung transplantation in patients with chronic obstructive pulmonary disease in a national cohort is without obvious survival benefit. *J Heart Lung Transplant*. 2006;25:75–84.
48. Bennett D, Fossi A, Bargagli E, et al. Mortality on the waiting list for lung transplantation in patients with idiopathic pulmonary fibrosis: a single-centre experience. *Lung*. 2015;193:677–681.
49. Ketchell RI, Roughton M, Agent P, et al. Predicting survival in end-stage cystic fibrosis. *Respir Med*. 2009;103:1441–1447.
50. Lotshaw AM, Luedtke-Hoffmann K, Bourdeau N, et al. Walk speed trends in patients with end-stage lung disease awaiting and after lung transplantation. *J Heart Lung Transplant*. 2012;31:S81.
51. Sterrenberg S, Kuttykrishnan S, Zadworny M, et al. Pre-transplant 6-minute walk test predicts early post-operative ambulation and outcomes after lung transplantation. Presented at Western Regional Meeting Abstracts. *J Invest Med*. 2014;62:144–285.
52. Lotshaw AM, Meyer DM, Thompson M, et al. Six-minute walk test as an indicator of lung transplant survival at 1 year. *J Heart Lung Transplant*. 2009;28:S168.
53. Bauldoff GS, Van Berkel V, Fox M, et al. Pulmonary rehabilitation in lung transplant candidates: impact on post-transplant inpatient utilization and mortality. *Am J Respir Crit Care Med*. 2017;195:A2694.
54. Singer JP, Katz PP, Soong A, et al. Effect of lung transplantation on health-related quality of life in the era of the lung allocation score: a U.S. prospective cohort study. *Am J Transplant*. 2017;17:1334–1345.
55. Verma G, Marras T, Chowdhury N, et al. Health-related quality of life and 6 min walk distance in patients with idiopathic pulmonary fibrosis. *Can Respir J*. 2011;18:283–287.
56. Feltrim MI, Rozanski A, Oliveira C, et al. Quality of life in patients awaiting lung transplantation and the correlation of functional capacity. *Eur Respir J*. 2012;40:P1190.
57. Burns HK. *Physiologic and psychosocial attributes of quality of life in lung transplant candidates.* [dissertation]. University of Pittsburgh; 1993. Available at https://www.proquest.com/docview/304075047. Accessed June 22, 2021.
58. Armstrong HF, Basner RC, Lederer DJ, et al. Cardiopulmonary exercise testing helps predict one-year transplant-free survival in patients with interstitial lung disease. *Am J Respir Crit Care Med*. 2015;191:A2241.
59. Singer JP, Diamond JM, Gries CJ, et al. Frailty phenotypes, disability, and outcomes in adult candidates for lung transplantation. *Am J Respir Crit Care Med*. 2015;192:1325–1334.
60. Wickerson L, Rozenberg D, Gottesman C, et al. Pre-transplant short physical performance battery: response to pre-habilitation and relationship to pre- and early post-lung-transplant outcomes. *Clin Transplant*. 2020;34:e14095.
61. Singer JP, Katz PP, Dean MY, et al. Frailty is common in lung transplant candidates and associated with poorer health-related quality of life. *J Heart Lung Transplant*. 2013;32:S43.

62. Perez AA, Hays SR, Soong A, et al. Improvements in frailty contribute to substantial improvements in quality of life after lung transplantation in patients with cystic fibrosis. *Pediatr Pulmonol*. 2020;55:1406–1413.
63. Massierer D, Bourgeois N, Räkel A, et al. Changes in 6-minute walking distance in lung transplant candidates while participating in a home-based pre-habilitation program—a retrospective chart review. *Clin Transplant*. 2020;34:e14045.
64. Jackson F, Painter L, Fontanilla IS, et al. Frailty: does it predict length of stay in hospital post lung transplant. *J Heart Lung Transplant*. 2018;37:S121–S122.
65. Florian J, Watte G, Teixeira PJZ, et al. Pulmonary rehabilitation improves survival in patients with idiopathic pulmonary fibrosis undergoing lung transplantation. *Sci Rep*. 2019;9:9347.
66. Kampschulte E, Benazzo A, Boehm P, et al. 6MWT as useful predictor for long term survival after lung transplantation in patients with ILD. *Eur Respir J*. 2020;56:1944.
67. Smith PJ, Snyder LD, Palmer SM, et al. Depression, social support, and clinical outcomes following lung transplantation: a single-center cohort study. *Transpl Int*. 2018;31:495–502.
68. Smith PJ, Byrd R, Lusby M, et al. Depressive symptoms, exercise capacity, and clinical outcomes after lung transplantation. *Psychosom Med*. 2018;80:403–409.
69. Chaikriangkrai K, Jhun HY, Graviss EA, et al. Overweight-mortality paradox and impact of six-minute walk distance in lung transplantation. *Ann Thorac Med*. 2015;10:169–175.
70. Caires NP, Silva SC, Caldeira V, et al. Preoperative six-minute-walk test in lung transplantation: survival predictor. *Eur Respir J*. 2017;50:PA1549.
71. Machuca TN, Schio SM, Camargo SM, et al. Prognostic factors in lung transplantation: the Santa Casa de Porto Alegre experience. *Transplantation*. 2011;91:1297–1303.
72. Castleberry AW, Englum BR, Snyder LD, et al. The utility of preoperative six-minute-walk distance in lung transplantation. *Am J Respir Crit Care Med*. 2015;192:843–852.
73. Halpern AL, Boshier PR, White AM, et al. A comparison of frailty measures at listing to predict outcomes after lung transplantation. *Ann Thorac Surg*. 2020;109:233–240.
74. Khawar MU, Yazdani D, Zhu Z, et al. Clinical outcomes and survival following lung transplantation in patients with lymphangioleiomyomatosis. *J Heart Lung Transplant*. 2019;38:949–955.
75. Wajda N, Zhu Z, Jandarov R, et al. Clinical outcomes and survival following lung transplantation in patients with pulmonary Langerhans cell histiocytosis. *Respirology*. 2020;25:644–650.
76. González Castro A, Suberviola Cañas B, Quesada Suescun A, et al. Evaluation of the pre-operative exercise capacity as survival marker in the lung transplant recipients [in Spainish]. *Med Intensiva*. 2008;32:65–70.
77. Amor MS, Rosengarten D, Shitenberg D, et al. Lung transplantation in idiopathic pulmonary fibrosis: risk factors and outcome. *Isr Med Assoc J*. 2020;22:741–746.
78. Bode H, Verleden SE, Wuyts WA, et al. Outcome of lung transplantation in non-idiopathic pulmonary fibrosis interstitial lung disease. *Clin Transplant*. 2019;33:e13661.
79. Seoane L, Alex S, Pirtle C, et al. Utility of the 6-minute walk test following lung transplantation. *Ochsner J*. 2010;10:227–230.
80. Nathan SD, Shlobin OA, Reese E, et al. Prognostic value of the 6min walk test in bronchiolitis obliterans syndrome. *Respir Med*. 2009;103:1816–1821.
81. Ebenbichler GR, Habenicht R, Kienbacher T. The six minutes walk test in lung transplant recipients: reliability, concurrent and predictive validity. *PM R*. 2020;12:S22–S23.
82. Armstrong HF, Garber CE, Bartels MN. Exercise testing parameters associated with post lung transplant mortality. *Respir Physiol Neurobiol*. 2012;181:118–122.
83. Armstrong HF, Bartels MN. Post lung transplant exercise testing and mortality. *J Heart Lung Transplant*. 2011;30:S150.
84. Singer JP, Diamond JM, Anderson MR, et al. Frailty phenotypes and mortality after lung transplantation: a prospective cohort study. *Am J Transplant*. 2018;18:1995–2004.
85. Venado A, Kolaitis NA, Huang CY, et al. Frailty after lung transplantation is associated with impaired health-related quality of life and mortality. *Thorax*. 2020;75:669–678.
86. Venado A, McCulloch C, Greenland JR, et al. Frailty trajectories in adult lung transplantation: a cohort study. *J Heart Lung Transplant*. 2019;38:699–707.
87. Rozenberg D, Mathur S, Tomlinson G, et al. Clinical implications of prestransplant skeletal muscle mass, strength, and exercise capacity on functional recovery in lung transplant recipients after 7 or more days of mechanical ventilation. *Chest*. 2017;152:A1106.
88. Ihle F, Hatz R, Czerner S, et al. Determinants of quality of life after lung transplantation. *Open Transplant J*. 2015;8:1–7.
89. Gerbase MW, Spiliopoulos A, Rochat T, et al. Health-related quality of life following single or bilateral lung transplantation: a 7-year comparison to functional outcome. *Chest*. 2005;128:1371–1378.
90. Kolaitis NA, Soong A, Gao Y, et al. Frailty is associated with greater impairments in health-related quality of life after lung transplantation than before. *J Heart Lung Transplant*. 2019;38:S226–S227.
91. Gerbase MW, Soccal PM, Spiliopoulos A, et al. Long-term health-related quality of life and walking capacity of lung recipients with and without bronchiolitis obliterans syndrome. *J Heart Lung Transplant*. 2008;27:898–904.
92. Ihle F, Neurohr C, Huppmann P, et al. Health related quality of life and exercise capacity in lung transplant recipients with and without bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med*. 2011;183:A4664.
93. Brugière O, Pessione F, Thabut G, et al. Bronchiolitis obliterans syndrome after single-lung transplantation: impact of time to onset on functional pattern and survival. *Chest*. 2002;121:1883–1889.
94. Maheshwari J, Greenland J, Gao Y, et al. Frailty is associated with subsequent development of chronic lung allograft dysfunction following lung transplantation. *J Heart Lung Transplant*. 2021;40:S301–S302.
95. Courtwright AM, Zaleski D, Gardo L, et al. Causes, preventability, and cost of unplanned rehospitalizations within 30 days of discharge after lung transplantation. *Transplantation.* 2018;102:838–844.
96. Orens JB, Estenne M, Arcasoy S, et al; Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2006;25:745–755.
97. Williams FR, Milliken D, Lai JC, et al. Assessment of the frail patient with end-stage liver disease: a practical overview of sarcopenia, physical function, and disability. *Hepatol Commun*. 2021;5:923–937.
98. Painter P, Roshanravan B. The association of physical activity and physical function with clinical outcomes in adults with chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2013;22:615–623.
99. Lancaster LH. Utility of the six-minute walk test in patients with idiopathic pulmonary fibrosis. *Multidiscip Respir Med*. 2018;13:45.
100. Martin C, Chapron J, Hubert D, et al. Prognostic value of six minute walk test in cystic fibrosis adults. *Respir Med*. 2013;107:1881–1887.
101. Zeng GS, Chen LC, Fan HZ, et al. The relationship between steps of 6MWT and COPD severity: a cross-sectional study. *Int J Chron Obstruct Pulmon Dis*. 2019;14:141–148.
102. Villalba WO, Sampaio-Barros PD, Pereira MC, et al. Six-minute walk test for the evaluation of pulmonary disease severity in scleroderma patients. *Chest*. 2007;131:217–222.
103. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166:111–117.
104. da Fontoura FF, Berton DC, Watte G, et al. Pulmonary rehabilitation in patients with advanced idiopathic pulmonary fibrosis referred for lung transplantation. *J Cardiopulm Rehabil Prev*. 2018;38:131–134.
105. Florian J, Rubin A, Mattiello R, et al. Impact of pulmonary rehabilitation on quality of life and functional capacity in patients on waiting lists for lung transplantation. *J Bras Pneumol*. 2013;39:349–356.
106. Jastrzebski D, Ochman M, Ziora D, et al. Pulmonary rehabilitation in patients referred for lung transplantation. *Adv Exp Med Biol*. 2013;755:19–25.
107. Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. *Eur Respir J*. 2014;44:1447–1478.
108. Hiraga T, Maekura R, Okuda Y, et al. Prognostic predictors for survival in patients with COPD using cardiopulmonary exercise testing lung physiology and prognosis in COPD. *Clin Physiol Funct Imaging*. 2003;23:324–331.
109. Oga T, Nishimura K, Tsukino M, et al. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med*. 2003;167:544–549.

110. Wensel R, Opitz CF, Anker SD, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. *Circulation*. 2002;106:319–324.
111. Moorcroft AJ, Dodd ME, Webb AK. Exercise testing and prognosis in adult cystic fibrosis. *Thorax*. 1997;52:291–293.
112. Cahalin LP, Chase P, Arena R, et al. A meta-analysis of the prognostic significance of cardiopulmonary exercise testing in patients with heart failure. *Heart Fail Rev*. 2013;18:79–94.
113. Riebe D, Ehrman JK, Liguori G, et al; American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. 10th ed. Wolters Kluwer; 2018.
114. Mehra MR, Canter CE, Hannan MM, et al; International Society for Heart Lung Transplantation (ISHLT) Infectious Diseases, Pediatric and Heart Failure and Transplantation Councils. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant*. 2016;35:1–23.
115. Varughese R, Rozenberg D, Singer LG. An update on frailty in lung transplantation. *Curr Opin Organ Transplant*. 2020;25:274–279.
116. Lai JC, Feng S, Terrault NA, et al. Frailty predicts waitlist mortality in liver transplant candidates. *Am J Transplant*. 2014;14:1870–1879.
117. Montgomery E, Macdonald PS, Newton PJ, et al. Frailty as a predictor of mortality in patients with interstitial lung disease referred for lung transplantation. *Transplantation*. 2020;104:864–872.
118. Nastasi AJ, McAdams-DeMarco MA, Schrack J, et al. Pre-kidney transplant lower extremity impairment and post-kidney transplant mortality. *Am J Transplant*. 2018;18:189–196.
119. Massierer D, Alsowayan W, Lima VP, et al. Prognostic value of simple measures of physical function and muscle strength in COPD: a systematic review. *Respir Med*. 2020;161:105856.
120. Reychler G, Boucard E, Peran L, et al. One minute sit-to-stand test is an alternative to 6MWT to measure functional exercise performance in COPD patients. *Clin Respir J*. 2018;12:1247–1256.
121 Briand J, Behal H, Chenivesse C, et al. The 1-minute sit-to-stand test to detect exercise-induced oxygen desaturation in patients with interstitial lung disease. *Ther Adv Respir Dis*. 2018;12:1753466618793028.
122. Crook S, Frei A, Ter Riet G, et al. Prediction of long-term clinical outcomes using simple functional exercise performance tests in patients with COPD: a 5-year prospective cohort study. *Respir Res.* 2017;18:112.
123. Tarrant BJ, Robinson R, Le Maitre C, et al. The utility of the sit-to-stand test for inpatients in the acute hospital setting after lung transplantation. *Phys Ther*. 2020;100:1217–1228.
124. Kohlbrenner D, Benden C, Radtke T. The 1-minute sit-to-stand test in lung transplant candidates: an alternative to the 6-minute walk test. *Respir Care*. 2020;65:437–443.
125. Benton MJ, Alexander JL. Validation of functional fitness tests as surrogates for strength measurement in frail, older adults with chronic obstructive pulmonary disease. *Am J Phys Med Rehabil*. 2009;88:579–583.
126. Holland AE, Malaguti C, Hoffman M, et al. Home-based or remote exercise testing in chronic respiratory disease, during the COVID-19 pandemic and beyond: a rapid review. *Chron Respir Dis*. 2020;17:1479973120952418.
127. Gross CR, Raghu G. The cost of lung transplantation and the quality of life post-transplant. *Clin Chest Med*. 1997;18:391–403.
128. Li M, Mathur S, Chowdhury NA, et al. Pulmonary rehabilitation in lung transplant candidates. *J Heart Lung Transplant*. 2013;32:626–632.
129. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci*. 2010;5:69.