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Review

Frailty as a Prognostic Indicator in Lung Transplantation: A Comprehensive Analysis

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Abstract: Introduction: Frailty is a complex pathobiological process characterized by diminished physiological reserve and increased vulnerability to stressors, which has been associated with unfavorable outcomes before and after lung transplantation. Methods: We undertook an extensive narrative review, encompassing a thorough exploration of original papers, observational studies, case reports, and meta-analyses published between 1990 and July 2023, in various databases, including PubMed, Embase, Cochrane Library, Wiley Online Library databases, and Google Scholar. The search terms [frailty] AND [lung transplant] were utilized. Additionally, the reference lists of retrieved articles were examined. Inclusion criteria comprised studies written in English and involving human subjects. The identified studies were categorized into pre-transplant and post-transplant populations, and the measurement tools used to assess frailty were analyzed, along with the clinical implications reported in the studies. Results: From 1 January 1990 to 1 July 2023, a total of 10 studies on frailty and lung transplantation were identified through online sources and bibliographic searches, involving a total of 2759 patients. Among these studies, six focused on the pre-transplant population, while four examined the post-transplant population. The Fried Frailty Phenotype (FFP) and the Short Physical Performance Battery (SPPB) were the most employed tools for measuring frailty. A table presents additional frailty assessment instruments and the clinical implications described in the studies. Conclusions: Frailty is prevalent both in patients with end-stage respiratory diseases awaiting lung transplantation and in postoperative lung transplant recipients. Most transplant centers recognize the value of assessing frailty in the evaluation of potential candidates for lung transplantation. Frailty has been shown to impact mortality on the waitlist and in the post-transplant period. However, the most effective methods for measuring frailty in lung transplant candidates and recipients have yet to be determined. Strategies to reverse frailty are available and show promising results on outcomes.

Keywords: sarcopenia; transplantation; waitlist mortality; lung transplant; frailty score

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1. Introduction

Frailty is a multifaceted clinical syndrome associated with age, characterized by an imbalance in energy, sarcopenia, and diminished strength and exercise capacity. It results in heightened susceptibility to sudden and disproportionate functional decline following stressors, leading to impaired function and negative health consequences [1]. Frailty exists on a continuum, ranging from fitness to frailty, and can fluctuate over time [2]. Importantly, frailty has the potential for reversibility [3,4]. Although the precise underlying pathobiological mechanisms remain largely unknown, frailty stems from cumulative declines across various physiological systems. It affects a significant proportion of adults with advanced lung disease (up to 28%) and, in particular, interstitial lung disease (up to 50%) [5,6].

Two extensive cohort studies, the Longitudinal Aging Study Amsterdam (LASA) [7] and the InCHIANTI study [8], have demonstrated the natural progression of frailty. They revealed that exhaustion is typically the initial physical component of frailty to manifest, followed by slower gait speed, reduced physical activity, and weakness [2,9]. Weight loss tends to occur at a later stage compared to the other physical components of frailty [2].

With the rapid expansion of the aging population, the number of older adults with frailty is increasing, placing greater demands on healthcare systems (including transplant centers) worldwide. Lung transplant candidates who exhibit frailty face elevated risks of adverse health outcomes. Consequently, effective strategies to manage frailty in these individuals are crucial. In this review, we provide a comprehensive summary of existing studies investigating frailty in both lung transplant candidates and recipients.

2. Methods

We conducted a narrative review by means of a comprehensive search of original papers, observational studies, case reports, and meta-analyses published between 1990 and July 2023 in various databases, including PubMed, Embase, Cochrane Library, Wiley Online Library databases, and Google Scholar. The search terms [frailty] AND [lung transplant] were utilized.

Additionally, the reference lists of retrieved articles were examined. Inclusion criteria comprised studies written in English and involving human subjects.

The identified studies were categorized into pre-transplant and post-transplant populations, and the measurement tools used to assess frailty were analyzed, along with the clinical implications reported in the studies.

3. Results

From 1 January 1990 to 1 July 2023, a total of 10 studies on frailty and lung transplantation were identified through online sources and bibliographic searches, involving a total of 2759 patients. Among these studies, six focused on the pre-transplant population, while four examined the post-transplant population. The Fried Frailty Phenotype (FFP) and the Short Physical Performance Battery (SPPB) were the most employed tools for measuring frailty. Table 1 presents additional frailty assessment instruments and the clinical implications described in the studies.

Table 1. Clinical implications of the different available frailty assessment tools in lung transplantation.

Author (Date), Number of Patients	Number of Patients	Patient Population	Frailty Tool	Clinical Implications in Lung Transplantation
Baldwin (2017) [10]	N = 373, Frailty N = 79 (21%, DASI)	Pre-LTx	DASI MLTA FFP	DASI (simple 12-item questionnaire) improves predictive value of frailty in lung transplant candidates, compared to MLTA
Singer (2015) [5]	N = 395 (N = 354 FFP, N = 262 SPPB) Frailty N = 99 (28%, FFP) Frailty N = 26 (10%, SPPB)	Pre-LTx	FFP SPPB	Frailty is independently associated with • greater disability • increased risk of delisting • death on the waitlist
Layton (2017) [11]	N = 68 Frailty N = 8 (12%, FFP)	Pre-Tx	FFP	Frailty contributes to • reduced exercise maximal capacity, independent of respiratory disease severity and respiratory diagnosis
Wilson (2016) [12]	N = 144 Frailty N = 46 (32%, FI)	Pre-Tx	FI	Pre-transplant frailty is independently associated with • decreased survival after lung transplant
Venado (2019) [13]	N = 244 (SPPB) N = 162 (FFP) Frail N = 55 (23%, SPPB) Frail N = 69 (43%)	Pre-Tx	FFP SPPB	Pre-transplant frailty: • improved in many patients after lung transplant • remained stable after improvement • should not be an absolute contraindication to transplantation

Table 1. *Cont.*

Author (Date), Number of Patients	Number of Patients	Patient Population	Frailty Tool	Clinical Implications in Lung Transplantation
Anderson (2019) [14]	N = 253 Frail N = 116 (46%)	Pre-Tx	FFP	Strong relationship between visceral adipose tissue area (VAT), measured on bioelectrical impedance assay (BIA), and frailty • both low and high VAT are associated with an increased risk of frailty
Montgomery (2020) [15]	N = 166 Frail N = 27 (16%)	Post-Tx	mFFP	Physical frailty was largely reversible following lung transplantation
Courtwright (2019) [16]	N = 111 Frail N = 60 (54%)	Post-Tx	SPPB	Frailty at discharge after lung transplantation was common (more than half of the lung transplant recipients affected) and was associated with • female sex • pre-frailty at listing for lung transplant • acute kidney injury post-transplant • longer intensive care unit stay • most frail patients improved and became non-frail after intensive outpatient physiotherapy treatment
Singer (2018) [17]	N = 318 (SPPB) N = 299 (FFP) Frail N = 65 (20%, SPPB) Frail N = 100 (33%, FFP)	Post-Tx	SPPB FFP	Frailty measured by SPPB was associated with both 1- and 4-year mortality risk Frail patients had an absolute increase of 12.5% in the risk of death within the first year post-transplant Frailty measured by FFP was associated with increased risk of death within the first postoperative year but not over a longer follow-up Preoperative frailty was associated with an increased risk of death after lung transplantation
Montgomery (2022) [18]	N = 363 Frailty N = 78 (22%, PF)	Post-Tx	Combined PF, MCA, DMI	Presence of physical frailty is common (22%) in the pre-Tx population Physical frailty, low serum albumin, and mild cognitive impairment are independently associated with waitlist mortality Cognitive function and depressive domains can be added to the assessment of physical frailty

Abbreviations: CSHA CFS = Canadian Study of Health and Aging Clinical Frailty Scale; DASI = Duke Activity Status Index; DMI = Depression in Medical Illness; FFP = Fried Frailty Phenotype; FI = Frailty Index; LOS = length of stay; mFFP = modified Fried Frailty Phenotype, MCA = Montreal Cognitive Assessment; MLTA = Minnesota Leisure Time Physical Activity; PF = physical frailty; Post-LTx = post-lung-transplant candidates; Pre-LTx = pre-lung-transplant candidates; SPPB = Short Physical Performance Battery.

4. Discussion

In the analysis of frailty assessments for lung transplant candidates and recipients, the most studied assessment tools are the FFP and SPPB, both of which are reliable and validated tools with predictive value in transplant recipients.

The prevalence of frailty varied between 10% and 54% based on the study and frailty assessment tool used. In lung transplant candidates, frailty was independently associated with higher disability, an increased risk of delisting, and greater mortality on the waitlist. Additionally, pre-transplant frailty was linked to decreased survival following lung transplantation.

It is crucial to note that frailty alone should not be considered a contraindication for lung transplantation, as many patients experienced improvements in frailty after the procedure, with stability maintained post-improvement. While the International Society for Heart and Lung Transplantation (ISHLT) consensus document highlights high and low body mass index (BMI) as risk factors, a more effective parameter could be the measurement of the visceral adipose tissue area (VAT) using bioelectrical impedance, which revealed that both high and low VAT were associated with an increased risk of frailty [14,19].

Findings from studies involving post-transplant patients indicated a high prevalence of frailty after lung transplantation. Frailty observed at discharge following lung transplantation was linked to complications such as acute kidney injury and a longer stay in the intensive care unit [16].

Both pre- and postoperative frailty were associated with an elevated risk of mortality. Other risk factors included low serum albumin, mild cognitive impairment, and depression. Many authors emphasize the potential reversibility of frailty through intensive physiotherapy and dietary interventions. Figure 1 provides a comprehensive overview of the various facets of frailty.

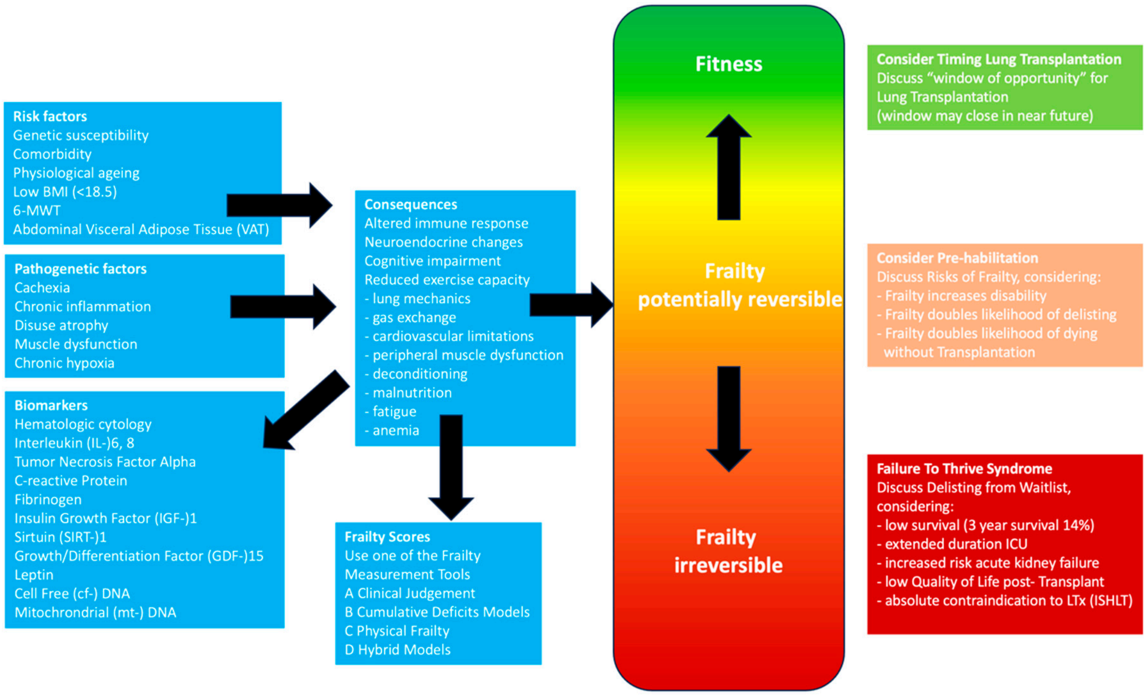

Figure 1. Multifaceted Aspects of Frailty in Lung Transplantation.

4.1. Epidemiology of Frailty

The prevalence of frailty varies depending on the population and the specific tool used to assess frailty. According to the Friend Frailty Phenotype (FFP), in the United States, the frailty prevalence ranges from 7 to 12% among community-dwelling older adults aged ≥65 years [1].

The prevalence of frailty in general increases with age, starting from 3.9% in the age group of 65–74 years and rising to 25% in individuals aged 85 years and older, with a higher percentage observed among women compared to men [1].

In the context of solid organ transplant recipients, the percentage of frailty varies widely, ranging from 2.7% to 100% [20]. In our study, focusing on lung transplant cohorts, we observed a range of 10% to 54% in terms of frailty prevalence, as previously mentioned.

4.2. Measurement Tools in Frailty

Table 2 presents various approaches used for assessing frailty in solid organ transplant candidates [20]. However, there is currently no consensus or widely accepted standardized frailty tool specifically designed for this population [20]. Several methods are employed to evaluate frailty. The first approach involves clinical judgement, often referred to as the “eyeball test”. Another method is the use of cumulative deficits models, such as the Frailty

Index, which quantifies a range of health-related deficits or impairments to determine an individual's frailty level. Physical frailty models, including the Fried Frailty Phenotype (FFP), Short Physical Performance Battery (SPPB), and others, offer an alternative approach by assessing an individual's physical capabilities and functioning, including muscle strength, gait speed, balance, and overall physical performance. In addition, hybrid models of frailty have emerged, combining multiple indicators or approaches to provide a comprehensive assessment. These hybrid models may incorporate elements from clinical judgement, cumulative deficits models, and physical frailty models, along with considerations of cognitive function, psychosocial aspects, and comorbidities.

Table 2. Frailty measurement tools.

Measuring Frailty	
Clinical judgement	• The "Eyeball Test"
Cumulative deficits models	• Frailty Index (FI) by Mitnitski, using the Canadian Study of Health and Aging (CSHA) [21] • Cumulative Deficits Frailty Index [22]
Physical frailty	• Fried Frailty Phenotype (FFP), using data from the Cardiovascular Health Study [4] • Short Physical Performance Battery (SPPB) • Predictive chart-based evaluation of lung transplant candidates [23] • and many others
Hybrid models	• A combination of some of the above-mentioned assessments

The Frailty Index (FI) is calculated by dividing the number of deficits present by the total number of deficits assessed, providing a measure of an individual's frailty level. A Frailty Index score below 0.25 indicates a non-frail state, while a score above 0.25 indicates frailty.

In the field of lung transplantation, there are specific frailty measures designed for lung transplant candidates or both lung and other solid organ transplant candidates [5,10–16,18,24–30]. One such measure is the Lung Transplant Frailty Scale (LT-FS), which was developed based on a study involving 342 lung transplant candidates [31]. However, we perceive the LT-FS to be relatively complex to administer due to the requirements for specific devices and the inclusion of laboratory parameters not routinely measured in standard clinical transplant practice. In contrast, the Cumulative Deficits Frailty Index utilizes only elements from routine transplant candidacy evaluation without additional testing, making it easier to perform as all parameters have generally been assessed and are known [22]. These variables encompass various aspects, including comorbidities, laboratory measurements, body mass index (BMI), and hospitalizations. The Cumulative Deficits Frailty Index has demonstrated the ability to predict outcomes for solid organ transplant candidates [22]. It has been shown that pre-transplant frailty is associated with reduced survival after lung transplantation. The Cumulative Deficits Frailty Index, based on a retrospective chart review of 815 heart, kidney, liver, and lung patients from a single center in Toronto, has been associated with an increased risk of discharge to rehabilitation after transplantation, death/delisting before transplantation, and death after transplantation. Among patients undergoing lung transplantation, the presence of pre-existing frailty was linked to a higher risk of mortality, even after accounting for age, sex, and receiving bilateral lung transplantation [12]. This study also observed a substantial prevalence of frailty of 45.1% (46 out of 102).

The Frailty Risk Score (FRS) is another scoring system, derived from a retrospective chart review of 84 lung transplant recipients from a single center (UCLA) [23]. It is important to note that most patients in this study underwent single lung transplantation, and none of them had undergone previous transplantation. The age of the included patients ranged from 42 to 77 years at the time of evaluation [23]. The authors found that the FRS could be efficiently calculated using electronic medical record notes collected during the initial evaluation for lung transplantation. Interestingly, this study, as well as previous studies utilizing different frailty assessment methods in lung transplant recipients, did not observe a significant correlation between frailty and age [5,23,29].

4.3. Pathogenesis

Frailty is a complex and multifactorial process characterized by dysregulation in multiple physiological systems, resulting in altered immune response, neuroendocrine changes, and cognitive impairment [32]. While frailty shares similarities with aging, it differs in its inability to maintain homeostasis. The development of frailty is influenced by genetic susceptibility, comorbidities, physiological aging, and environmental factors [32].

Biomarkers have been proposed as potential indicators for frailty. Sarcopenia, the loss of skeletal muscle mass and function, is often considered a biological component of physical frailty and is associated with adverse health outcomes [33]. Measurement of the psoas muscle (lean psoas area) via computed tomography scans can be used to assess the severity of sarcopenia and has been found to be significantly associated with postoperative outcomes in lung transplant recipients. Larger core muscle size is correlated with fewer days on mechanical ventilation, reduced tracheostomy requirements, and shorter stays in the intensive care unit after lung transplantation [34]. Interestingly, sarcopenia can be present both in patients with normal weight and in overweight patients, as approximately one-third of normal-weight individuals and one-fourth of overweight individuals exhibit low lean psoas area [34]. Both sarcopenia and frailty share common underlying mechanisms, including physical inactivity, nutritional deficiencies, chronic inflammation, immune senescence, and neuroendocrine dysregulation [35]. Further research is needed to establish standardized definitions and criteria for sarcopenia, determine optimal measurement methods, and evaluate the prognosis of frailty in the presence or absence of coexisting sarcopenia [32].

4.4. Exercise Capacity in Frailty

Reduced exercise capacity and limitations in physical function can be attributed to various factors, including changes in lung mechanics and gas exchange, cardiovascular limitations, peripheral muscle dysfunction, deconditioning, malnutrition fatigue, and anemia [36].

Although lung transplantation can lead to improvements in physical capacity by enhancing organ function and alleviating disease symptoms, transplant recipients still experience impaired exercise capacity, typically achieving only 40–70% of age-predicted values [36–39]. The International Society for Heart and Lung Transplantation (ISHLT) consensus document for the selection of lung transplant candidates emphasizes that individuals with limited functional status and poor potential for post-transplant rehabilitation are considered absolute contraindications for lung transplantation [19]. This highlights the importance of understanding the relationship between physical function and outcomes both before and after lung transplantation. However, surprisingly, there is a lack of studies investigating the correlation between exercise capacity and outcomes in the context of lung transplantation [36].

Except for the association between the 6-minute walk test (6 MWT) and mortality while awaiting lung transplantation, there is insufficient evidence regarding the relationship between performance-based measures of exercise capacity, frailty, physical function, and clinical outcomes or health care utilization [36].

In a comprehensive study conducted by Singer et al., involving 395 subjects, it was observed that frailty had a stronger association with exercise capacity and grip strength compared to lung function [5]. Furthermore, Layton's findings indicated that frailty significantly contributed to the decline in exercise capacity among lung transplant candidates, regardless of the severity of their lung disease [11].

This suggests that frailty is also a significant non-pulmonary consequence of advanced lung disease. Cachexia, chronic inflammation, disuse atrophy, muscle dysfunction, and chronic hypoxia are proposed as the underlying mechanisms contributing to frailty in these candidates, suggesting that frailty exists independently of comorbidity and disability.

The 6-minute walk test (6-MWT) was commonly utilized in most studies and exhibited an inverse relationship with mortality on the waiting list for lung transplantation. The Pulmonary Scientific Council of the ISHLT has recommended the inclusion of the 6-MWT in the selection process for lung transplantation, as it assesses the overall response of all body systems and should be incorporated into clinical practice [36].

4.5. Laboratory Markers in Frailty

Singer et al. conducted a study that revealed elevated levels of plasma IL-6, tumor necrosis factor receptor I, and leptin in frail individuals [5]. Venado et al. demonstrated an improvement in frailty following lung transplantation and attributed this improvement to a reduction in systemic inflammation after the surgery [13]. Elevated serum biomarker levels, such as those of interleukin (IL)-6, IL-8, tumor necrosis factor-alpha (which is associated with altered intercellular communication), C-reactive protein, and fibrinogen, showed improvement after lung transplantation [13].

The cessation of inactivity, chronic hypoxia, and cigarette smoking, all of which are inducers of myostatin, contributed to the improvement in frailty after lung transplantation [13]. Additionally, the absence of hospitalizations for pulmonary exacerbations and the discontinuation of corticosteroid treatment after transplantation also played a role in reducing frailty. Other biomarkers linked to frailty, including Insulin-like Growth Factor (IGF)-1 and Sirtuin (SIRT)-1, which are associated with deregulated nutrient sensing, and Growth/Differentiation Factor (GDF)-15, highlight the importance of inflammation and nutrient sensing in frailty [40]. Leptin, a cytokine produced by adipose tissue, has been associated with the risk of primary graft dysfunction (PGD) [41].

An interesting new biomarker under investigation is cell-free DNA (cf-DNA), which is released into the circulation following tissue damage or cellular stress. Levels of cf-DNA have been shown to correlate with frailty, reflecting the extent of damage and inflammation [42].

Similarly, mitochondrial DNA (mt-DNA) has also been identified as a biomarker for frailty [42]. In the context of transplantation, donor-derived cf-DNA may be used as a biomarker for acute allograft dysfunction [43].

4.6. Other Risk Factors in Frail Lung Transplant Candidates

Additional indicators of physical frailty include having a body mass index (BMI) below 18.5 kg/m^2 and measuring the 6-minute walk distance (as discussed before).

However, using a low BMI alone as a measure of muscle wasting is inadequate, and neither the 6-minute walk distance nor the BMI can accurately predict mortality [12]. A significant finding by Anderson et al. was the relationship between frailty and visceral adipose tissue (VAT) [14]. This relationship was found to be non-linear, highlighting the limitations of solely focusing on obesity as measured by BMI. The BMI does not provide information about the distribution of adipose tissue or muscle mass in the body. It is important to note that obesity, as indicated by BMI, is associated with an increased risk of primary graft dysfunction (PGD) and death after lung transplantation [14,41]. Conversely, a low amount of VAT is also linked to frailty. This relationship can be attributed to protein-energy wasting and the absence of energy reserves in the body [14].

4.7. Prognosis and Postoperative Complications

In a study by Singer et al., it was found that the presence of frailty was linked to increased disability and nearly doubled the likelihood of being delisted or dying without receiving a lung transplantation [5].

Wilson demonstrated that pre-transplant frailty had an independent correlation with lower survival rates following lung transplantation [12]. Frail patients had estimated survival rates of 71.7% at 1 year and 14.3% at 3 years, in comparison to 92.9% and 66.1% for non-frail patients, respectively. This increased risk of death remained significant even after adjusting for factors such as age, sex, and bilateral lung transplantation.

In Courtwright's study, it was discovered that out of the patients who underwent lung transplantation, 60 individuals (54.1%) were identified as frail [16]. The study further revealed that the presence of frailty during discharge after lung transplantation was linked to pre-existing frailty at the time of being listed for the procedure. Additionally, it was associated with the occurrence of acute kidney failure following the transplantation, and an extended duration of stay in the intensive care unit.

4.8. Frailty: Reason for Delisting and a Contraindication to Lung Transplantation?

Frail individuals who are considered as potential candidates for lung transplantation face a substantial risk of experiencing various adverse health outcomes. Therefore, understanding the concept of frailty plays a vital role in enabling informed decision-making regarding the potential risks and benefits associated with lung transplantation. This understanding goes beyond the traditional evaluation of commonly assessed biomarkers and requires active involvement from both the potential lung transplant candidates and their healthcare providers within the lung transplant team.

In the initial year following lung transplantation, a significant number of patients encounter complications that can result in disability and a decline in their overall quality of life. The increasing prevalence of post-transplant morbidity further contributes to this burden.

Montgomery et al. conducted research on the impact of lung transplantation on postoperative frailty among lung transplant recipients [15]. Their study revealed that physical frailty can be significantly reversed after lung transplantation, emphasizing the importance of recognizing frailty as a dynamic condition rather than a permanent state [15]. However, it is noteworthy that the study by Montgomery et al. included a substantial proportion of cystic fibrosis patients, who traditionally are evaluated for lung transplantation at a younger age [15]. The landscape of cystic fibrosis treatment has experienced significant changes in recent years due to the introduction of highly effective modulator therapies. As a result, the findings of the study may not be directly applicable or comparable to the current practices and outcomes observed in transplant centers today.

One study investigated a group of 35 postoperative lung transplant recipients, who were identified as frail at discharge, participated in an outpatient physiotherapy program, and showed striking outcomes [16]. These individuals exhibited a significant median improvement in the Short Physical Performance Battery (SPPB), and an impressive 85.7% of them transitioned from a frail state to a non-frail state within a median period of 6 weeks [16].

4.9. Management of Frailty

Although identifying individuals requiring additional support based on the presence of frailty may seem like an ideal approach, there is currently insufficient substantial evidence to support this strategy [2,32]. Moreover, there is a scarcity of research on the most effective tools for detecting frailty. Due to the limited availability of concrete evidence for interventions, practical approaches to addressing frailty in everyday clinical practice include physical therapy, pulmonary rehabilitation, nutritional supplementation, and interventions by social workers or psychologists [2,32].

5. Conclusions

In the context of lung transplantation, there are several noteworthy frailty aspects to consider. Firstly, it is frequently observed that candidates for lung transplant exhibit phenotypic frailty. This indicates that a considerable number of individuals being considered for transplant may have frailty-related concerns that require attention. Secondly, studies have demonstrated that higher cumulative deficits, which reflect overall health impairment, are independently associated with lower survival rates following lung transplantation. This underscores the significance of evaluating the cumulative health status of candidates when assessing their suitability for transplantation. The assessment of frailty prior to transplantation holds promise in enhancing risk stratification and fine-tuning candidate selection [32]. Additionally, the process of selecting lung transplant candidates is significantly impacted by the need to establish the validity of frailty measures. It is crucial to demonstrate that these measures have a robust and independent association with post-transplant outcomes, ensuring that candidate selection decisions are based on reliable and predictive criteria. Lastly, there is a need for further research into potential interventions that aim to reverse or alleviate frailty among candidates for lung transplantation. There are promising areas of study that deserve attention, such as pulmonary rehabilitation programs that aim to enhance respiratory function and overall physical conditioning. Additionally, exploring strategies for nutritional supplementation holds potential in improving outcomes and addressing frailty among individuals undergoing lung transplantation. While these interventions hold the potential to enhance the overall health outcomes of lung transplant candidates, further research is needed to determine their effectiveness and optimal implementation. Taking into account these key considerations, it is clear that understanding and addressing frailty among lung transplant candidates is vital for optimizing the selection process, choosing appropriate measures to address frailty pre-transplant, and improving post-transplant outcomes. More research and exploration of potential interventions are necessary to advance the management of frailty in this specific solid organ transplant population.

6. Outlook

Future research should focus on comparing different frailty assessment tools to determine their impact on patient outcomes while on the waiting list. It is also important to investigate whether interventions that improve pre-transplant frailty also lead to better waitlist outcomes and improved post-transplant outcomes. Further understanding of the prognostic value of frailty in the peri-transplant period is needed as well. Additionally, there is an urgent need for trials evaluating the effectiveness of nutritional supplementation through various methods such as oral, enteral, or total parenteral nutrition. The development of novel measures of frailty, including new imaging techniques and body composition analysis like VAS, should be explored. Furthermore, the investigation of potential new biomarkers, such as cf-DNA or mt-DNA, holds promise in identifying and measuring frailty at a more molecular level.

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