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Review

The Role of Pulmonary Rehabilitation in Lung Transplantation for Cystic Fibrosis

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Abstract

Cystic fibrosis (CF) is a genetic disorder that significantly impacts respiratory function, leading to progressive lung damage and ultimately respiratory failure. Lung transplantation (LTx) is a critical intervention for CF patients with end-stage lung disease, offering improved survival and quality of life. Pulmonary rehabilitation (PR) plays a pivotal role both preoperatively and postoperatively in optimizing outcomes for LTx candidates and recipients. Pre-transplant PR interventions, including exercise programs, airway clearance techniques, and psychological support, enhance functional capacity and prepare patients for surgery. These interventions improve survival rates and long-term quality of life by addressing modifiable risk factors and boosting physical and mental resilience. Post-transplant, PR is essential in managing chest hygiene, preventing complications related to immobilization, and supporting recovery. Integrating individualized rehabilitation strategies, including home-based programs and virtual support, has shown promise in optimizing rehabilitation efforts, mainly when in-person sessions are not feasible. This review highlights the importance of early identification of transplant candidates, the benefits of pre-transplant rehabilitation in improving functional outcomes, and the critical role of PR in post-transplant care for CF patients. Continued

research is necessary to refine PR protocols and ensure optimal care for CF patients throughout their transplant journey.

Keywords
Cistic fibrosis; lung transplantation; pulmonary rehabilitation

1. Introduction

Cystic fibrosis (CF) is a genetic disorder that arises from the dysfunction of chloride channels, resulting in thick, sticky secretions primarily impacting the respiratory system. These secretions predispose the lungs to chronic infections, persistent inflammation, and progressive structural damage, ultimately leading to respiratory failure [1]. Over time, this cycle reduces pulmonary function, exercise capacity, and quality of life. Pulmonary rehabilitation (PR) has become a cornerstone in managing these symptoms, enhancing physical capacity, and slowing disease progression, particularly in advanced stages [2].

Lung transplantation (LTx) is a vital therapeutic option for patients with CF who reach end-stage lung disease. The criteria for deciding on lung transplantation in patients diagnosed with cystic fibrosis [3] are summarized in Table 1. Median survival for people with CF who have had a transplant has improved. According to the 2019 International Society for Heart and Lung Transplantation Registry report, the median survival for adults transplanted between 1992 and 2017 is 9.9 years. This means that half of the individuals transplanted between 1992 and 2017 were alive 9.9 years after the transplant [4].

Table 1 Criteria considered when deciding on lung transplantation in patients diagnosed with cystic fibrosis.

Timing of Referral
Referral for lung transplantation should occur for an individual with CF meeting any of the following criteria despite optimal medical management including a trial of elexacaftor/tezacaftor/ivacaftor if eligible: FEV_1 <30% predicted in adults (or <40% predicted in children) FEV_1 <40% predicted in adults (or <50% predicted in children) and any of the following: ○ Six-minute walk distance <400 meters ○ $PaCO_2$ >50 mmHg ○ Hypoxemia at rest or with exertion ○ Pulmonary hypertension (PA systolic pressure >50 mmHg on echocardiogram or evidence of right ventricular dysfunction) ○ Worsening nutritional status despite supplementation ○ 2 exacerbations per year requiring intravenous antibiotics ○ Massive hemoptysis (>240 mL) requiring bronchial artery embolization ○ Pneumothorax

FEV_1 <50% predicted and rapidly declining based on pulmonary function testing or progressive symptoms
Any exacerbation requiring positive pressure ventilation
Timing of Listing
Listing for lung transplantation should occur for an individual with CF meeting any of the above referral criteria in combination with any of the following:
FEV_1 <25% predicted
Rapid decline in lung function or progressive symptoms (>30% relative decline in FEV_1 over 12 months)
Frequent hospitalization, particularly if >28 days hospitalized in the preceding year
Any exacerbation requiring mechanical ventilation
Chronic respiratory failure with hypoxemia or hypercapnia, particularly for those with increasing oxygen requirements or needing long-term non-invasive ventilation therapy
Pulmonary hypertension (Pulmonary arterial systolic pressure >50 mmHg on echocardiogram or evidence of right ventricular dysfunction)
Worsening nutritional status, particularly with BMI <18 kg/m^2 despite nutritional interventions
Recurrent massive hemoptysis despite bronchial artery embolization
World Health Organization functional class IV

Abreventions: BMI: body mass index; FEV1: Forced expiratory volume in one second; PA: Pulmonary Artery.

Lung transplantation offers the potential to dramatically improve survival and quality of life by replacing severely damaged lungs with healthy donor organs [1]. However, this procedure involves significant risks, making careful assessment of each patient's clinical status, potential for post-transplant recovery, and long-term prognosis essential. Pre-transplant optimization through PR plays a pivotal role by enhancing physical fitness, addressing nutritional deficiencies, and bolstering psychological resilience to prepare patients for the demands of surgery and recovery [5].

Candidate selection for LTx in CF entails a rigorous multidisciplinary evaluation to ensure that those most likely to benefit are prioritized [6]. According to updated standards by the European Cystic Fibrosis Society, early identification of patients who might require transplantation is crucial. The guidelines provide evidence-based strategies for managing CF, focusing on early intervention, comprehensive care, and multidisciplinary approaches. Key recommendations include addressing modifiable risk factors, optimizing nutrition, preventing infections, and maintaining lung function to delay disease progression and improve transplant outcomes [7]. One study explores the decision-making process for selecting LTx recipients and examines factors such as overall health, disease progression, comorbidities, and performance status in determining eligibility for transplantation. The study emphasizes the critical importance of timely referral to transplant centers and a multidisciplinary approach to improving patient outcomes. It highlights the value of addressing preventable factors through PR, weight management, and smoking cessation interventions to enhance patient eligibility for LTx [8].

2. Pre-Transplant Pulmonary Rehabilitation

Functional status at the time of lung transplant listing plays a crucial role in predicting outcomes for individuals with CF. Research indicates that poor functional status at the time of waitlist placement is strongly associated with worse pretransplant outcomes, which can significantly affect overall survival and post-transplant quality of life [9]. One study highlights the substantial impact of functional impairments, particularly among pediatric patients. Using the Lansky Play Performance Scale, the study found that children with severely impaired functional status faced significantly higher risks of adverse pre-transplant outcomes, including removal from the waitlist due to deterioration or death. This underscores the importance of pre-transplant interventions, such as PR, to mitigate modifiable risk factors and enhance readiness for transplantation [9].

Pulmonary rehabilitation has proven to be an essential strategy for improving pretransplant functional status in CF patients. Tailored rehabilitation programs focusing on enhancing exercise capacity, optimizing respiratory health, and bolstering psychological resilience can improve patients' readiness for transplantation [10, 11]. Early PR interventions may also improve post-transplant recovery by building physical and mental reserves [12]. The adoption of PR as a pre-transplant intervention not only increases survival probabilities but also improves long-term quality of life by addressing the factors essential for successful transplantation and recovery [5].

2.1 Benefits of Pre-Transplant Rehabilitation in Patients with CF

Pre-transplant rehabilitation is gaining recognition as a crucial strategy in the management of CF patients, especially for those awaiting LTx. Numerous studies have demonstrated the significant advantages of pre-transplant rehabilitation in improving lung function, exercise capacity, and quality of life for these individuals. Research indicates that combining structured exercise, airway clearance techniques, and psychological support can enhance respiratory health and overall well-being, even during advanced stages of CF [13].

Another study explored foundational principles of rehabilitation and reactivation for individuals with respiratory conditions. It focused on personalized rehabilitation programs to enhance lung function, alleviate symptoms, and improve physical performance. The study investigated various rehabilitation strategies, including exercise training, breathing techniques, and multidisciplinary care approaches. Results demonstrated reductions in hospital admissions, improved quality of life, and long-term benefits for patients with chronic respiratory diseases. The findings emphasized the importance of a comprehensive assessment before rehabilitation and the integration of PR into standard care practices to optimize functional outcomes for chronic respiratory conditions, including CF and COPD [14].

A review provided a thorough analysis of PR for CF, highlighting its role in managing respiratory symptoms and improving health outcomes. It emphasized combining exercise training, airway clearance techniques, and education as part of an effective PR program. While PR was shown to improve exercise capacity, lung function, and quality of life—even in advanced stages of CF—challenges were noted, such as variability in program designs and the need for more individualized approaches. Accessibility and adherence to PR programs were also identified as barriers, suggesting the necessity of further research to optimize protocols and assess long-term effects on CF care [15]. Another study examined the short-term effects of physical exercise and physiotherapy on key respiratory health metrics such as sputum expectoration, oxygen saturation, and lung function in

young CF patients. Results showed that specific combinations of exercise and physiotherapy were effective in improving sputum clearance and oxygen levels, demonstrating the value of integrating physical activity with traditional CF treatments. However, the study emphasized the importance of personalized approaches, as the effectiveness of different combinations varied from patient to patient. These findings suggest that individualized rehabilitation strategies may yield better outcomes than standardized treatment plans for optimal respiratory health [16]. Finally, a study investigated the impact of airway clearance physiotherapy on health-related quality of life (HRQoL) in CF patients. It found consistent airway clearance physiotherapy significantly improved HRQoL, particularly regarding respiratory symptoms and physical functioning. While the study affirmed the value of regular physiotherapy in managing chronic respiratory issues in CF, it recommended further research to evaluate the long-term effects of various physiotherapy regimens to optimize treatment protocols [17].

Pulmonary rehabilitation plays a crucial role in the care of patients with cystic fibrosis, not only during their medical treatment but also in the preoperative period if surgery is considered, as well as in the early and late postoperative phases. Alternative methods beyond traditional approaches should also be considered when necessary to ensure patients have access to PR. A pilot study examined the feasibility of a home-based PR program for CF patients awaiting LTx. Results showed that the home-based program, which included personalized exercise routines and telemedicine feedback, led to higher completion rates and smaller declines in the 6-minute walk test, making it a viable and safe option, mainly when in-person rehabilitation is not feasible [18]. An interactive analysis study conducted in 2021 used qualitative methods to explore the rehabilitation experiences of CF patients and healthcare professionals. Semi-structured interviews with five patients and six healthcare providers revealed key themes such as the physical and psychological benefits of structured exercise, barriers specific to CF, the importance of supportive relationships, and preferences for hybrid rehabilitation models combining in-person and virtual sessions. While remote support was adequate, the study highlighted the need for enhancements in virtual platforms and evidence-based approaches tailored to CF rehabilitation, suggesting hybrid models as a promising solution for better outcomes [19].

3. Individualized Rehabilitation Programs in CF

In cystic fibrosis patients, PR before LTx typically falls into two key areas: airway clearance techniques and exercise. Although studies utilizing alternative therapy methods such as self-hypnosis, sophrology, relaxation, and holistic gymnastics can be found, their application remains relatively uncommon [20].

3.1 Airway Clearance Techniques

Strategies to improve compliance with airway clearance and exercise regimens in cystic fibrosis patients are key elements of PR programs. Research has shown that personalized interventions particularly those incorporating active participation and motivational techniques are the most effective in increasing adherence. Furthermore, combining educational support with practical assistance has a positive impact on both motivation and compliance. However, further research is required to identify the most effective strategies for different CF populations [21].

The clinical practice guidelines for physiotherapy in CF patients recommend various airway clearance techniques, including Active Cycle of Breathing Techniques (ACBT), Positive Expiratory Pressure (PEP) therapy, and autogenic drainage (AD), either independently or in combination, depending on individual patient needs. These techniques aim to improve airway clearance, with structured exercise programs also playing an essential role in CF management. Exercise programs help reduce sputum impedance, improve lung function, and enhance overall fitness, which is necessary for maintaining health in CF patients [22]. Research has shown that ACBT significantly improves sputum clearance and lung function, with results comparable to standard airway clearance techniques. However, more extensive studies with extended follow-up periods must assess its long-term effects.

Positive Expiratory Pressure therapy has improved airway clearance and lung function, though evidence regarding its impact on quality of life remains mixed. Additionally, the use of oscillating devices has been found to improve airway clearance and pulmonary function in CF patients, but again, the long-term benefits require more robust studies [23]. Elexacaftor-lumacaftor-ivacaftor therapy has led to a reduction in the time spent on daily respiratory physiotherapies, such as aerosol therapy and airway clearance treatments (ACTs), although these tasks remain time-consuming. Despite this reduction, a small percentage of patients discontinued using the PEP mask, suggesting that respiratory care remains challenging even with new treatment options [24]. Studies exploring the short-term effects of PEP masks on ventilation inhomogeneity in CF children have shown that PEP therapy did not significantly improve ventilation efficiency, suggesting that short-term studies may not be the best method for evaluating the effectiveness of airway clearance techniques. Further research is needed to fully understand the benefits and optimal use of airway clearance methods, including PEP therapy and oscillating devices [25]. The study in the Cochrane Database of Systematic Reviews evaluated the effectiveness of PEP therapy for airway clearance in CF patients. The analysis found that PEP therapy improved airway clearance and overall lung function, though the effects on quality of life were mixed. While it is considered a practical part of a comprehensive airway clearance strategy, the study highlighted the need for more high-quality research to confirm the long-term benefits and optimal use of PEP therapy in CF treatment [26]. Another review found that PEP therapy showed a significant reduction in respiratory exacerbations compared to other techniques, mainly when used with a mask. It also suggested improvements in forced expiratory volume (FEV_1), though the evidence on long-term benefits was mixed. The authors concluded that while PEP therapy could be beneficial, more high-quality, long-term studies are needed to determine the optimal use and full scope of benefits of PEP therapy for CF patients [27].

Some studies have focused on the potential of structured exercise as an airway clearance technique in CF, exploring whether it could reduce reliance on traditional methods like conventional chest physiotherapy (CPT). The results suggest that exercise can not only improve physical fitness but also help with airway clearance, offering a sustainable option for managing CF. Combining exercise with other ACTs is emphasized, with both interventions contributing to improved lung function, physical capacity, and quality of life. Additionally, pilot studies on home-based PR programs, utilizing telemedicine, have shown positive results, highlighting their feasibility and safety, particularly when in-person rehabilitation is not an option [28, 29]. In a systematic review, the effectiveness of ACTs was compared to the absence of ACTs for CF patients. The findings demonstrated that ACTs significantly improved lung function, reduced pulmonary exacerbations, and enhanced respiratory health. Despite these benefits, the review highlighted that the

effectiveness of specific ACTs could vary across patients, suggesting a need for further research to identify the most effective techniques for individual CF patients [30]. Another review compared exercise to traditional airway clearance methods. It found that exercise and ACTs positively impacted lung function, exercise capacity, and quality of life in CF patients. Exercise may provide additional benefits, such as improving cardiovascular fitness and muscle strength, which are crucial for overall health. The study indicated that combining exercise with ACTs could give the best outcomes for CF patients [13].

3.2 Physical Activity and Exercise

Exercise is crucial in managing CF, offering multiple benefits such as improving lung function, aerobic capacity, muscle strength, and overall quality of life. Regular physical activity enhances respiratory muscle function, which can aid in sputum clearance, thereby improving respiratory health. Furthermore, exercise is an integral part of comprehensive care for CF patients, helping manage complications like malnutrition and reduced physical endurance. Exercise regimens should be tailored to the individual based on their physical condition and clinical status, with further research needed to establish the most effective exercise protocols for different stages of the disease [31].

The extracorporeal life support (ECLS) serves as a bridge to lung transplantation. It increases the patient's comfort in physiotherapy sessions by reducing mechanical ventilation usage rates [32]. The International Society for Heart and Lung Transplantation (ISHLT) consensus statement on the perioperative use of ECLS in lung transplantation emphasizes the critical role of multidisciplinary team collaboration in optimizing outcomes during preoperative, intraoperative and postoperative care. It highlights that cannulation strategies and the integration of ECLS should be individualized, considering patient-specific factors and procedural complexities [33]. While rehabilitation on ECMO remains rare in the cystic fibrosis population, the use of ECLS, particularly extracorporeal membrane oxygenation (ECMO), has shown promise in enhancing hemodynamic stability and facilitating lung-protective strategies during and after transplantation. Incorporating these principles into the rehabilitation process, as well as leveraging insights from existing postoperative ECMO rehabilitation literature, can provide a comprehensive framework for managing this unique patient cohort. One study reported that of 6 LTx candidates diagnosed with CF who underwent ECMO, 1 underwent surgery, 1 recovered from acute respiratory failure, and 4 died despite ECMO. The study attributes patient losses to the inability to find the donor in time [34]. In another study, the safety of mobilization was reported in 37 pre-TX cases in which femoral cannulation was used [35]. In another study in which the data of 511 cases were examined retrospectively, it was reported that a higher intensity of early mobilization could be achieved when ECMO was applied [36].

For CF patients who undergo LTx, exercise also proves beneficial, though there is limited research on its impact on transplant recipients. Exercise helps improve physical performance, which is crucial for survival and health after an LTx, suggesting a need for more studies in this area [37]. Recent trials have also examined whether aerobic exercise could be a viable alternative to CPT. These studies assess pulmonary function, functional capacity, and quality of life in CF patients, with findings potentially guiding clinical decisions on treatment options, in addition to traditional aerobic and strength training exercises, various other exercise disciplines are also utilized in CF rehabilitation.

Nordic walking, a low-impact exercise, has shown promise in improving walking distance, exercise capacity, and overall physical performance in patients awaiting LTx. It provides stability, particularly for patients with balance or fatigue [38].

Inspiratory muscle training is used in rehabilitation to exercise respiratory muscles in various conditions associated with limited ventilatory reserve. Inspiratory muscle training is easy to perform and can be done at home without specific supervision (in adults) before or after an LTx. Nevertheless, additional rigorous investigations should aim to replicate the positive effects [39]. Research also explored the relationship between expiratory muscle strength and exercise tolerance in CF adults. The study found that patients with stronger expiratory muscles had better exercise performance, suggesting that improving expiratory muscle strength may enhance functional outcomes [40]. Additionally, inspiratory muscle training was shown to significantly improve pulmonary function, postural stability, and overall functional capacity in children with CF, supporting its potential as an adjunct to standard CF treatments [41].

4. Post-Transplant Pulmonary Rehabilitation

The importance of PR in managing CF patients after LTx is significant. The approaches used in this period include general PR and chest physiotherapy strategies, but there is no specialized protocol for CF. What distinguishes CF patients from other groups is the systemic nature of the disease and the continuation of problems in other exocrine glands, which affect different body systems [42]. Post-lung transplant physiotherapy begins in intensive care and continues when the patient transitions to the clinical ward. The primary focus in the early stages is maintaining and ensuring chest hygiene and preventing complications related to immobilization [43].

The number of studies on post-transplant PR in CF patients is very limited. One such study investigated the self-reported engagement of children and adolescents with cystic fibrosis in daily activities following bilateral LTx. Over the first 18 months post-transplant, participants and their parents reported stable quality of life scores. However, the types of activities causing difficulty shifted. Initially, challenges were related to self-care and family engagement, but later, community participation and independence became more prominent. This highlights the importance of occupational therapy in post-transplant care [44]. The other study assessed the impact of an early rehabilitation program for adult CF patients during hospitalization. Patients in the intervention group, who participated in supervised physical training for 14 days, showed significant improvements in muscle strength and quality of life compared to controls. However, no significant differences were found in lung function or the 6-minute walk distance between the two groups. This suggests that while physical training enhances overall well-being, it may not lead to significant improvements in specific respiratory metrics [37].

5. Complication Management Following Lung Transplantation

Complications following LTx in CF patients can significantly impact long-term health outcomes. One of the primary concerns is the risk of acute rejection, which remains a significant challenge, particularly in the early post-transplant period. Studies emphasize the importance of continuous monitoring for signs of rejection, infection, and chronic lung allograft dysfunction, which can result in the gradual decline of lung function over time. These complications often require tailored interventions, including the adjustment of immunosuppressive medications and the

implementation of specific antimicrobial therapies to manage infections effectively [45]. Additionally, managing comorbidities such as diabetes, osteoporosis, and musculoskeletal issues becomes crucial in improving the overall quality of life, and preventing further complications in transplant recipients of rehabilitation in preventing or managing these complications is pivotal [46].

The study outlines models of post-transplant care for individuals with CF, focusing on best practices for managing patients after LTx. The paper emphasizes the critical importance of personalized, multidisciplinary care teams in optimizing post-transplant outcomes. These teams should include pulmonologists, surgeons, rehabilitation specialists, and mental health professionals to address the complex medical and psychosocial needs of CF patients post-transplant. Key considerations include long-term monitoring for complications such as rejection, infection, and organ dysfunction, as well as interventions to improve lung function and quality of life. The study stresses the importance of ongoing PR, patient education, and mental health support, recognizing the significant challenges patients face following transplantation. Furthermore, the study highlights the role of structured follow-up care and the need for continued research to refine care models that enhance survival and quality of life for CF transplant recipients. The authors also advocate for improved patient engagement and empowerment through comprehensive care plans that involve patients in their post-transplant journey, ensuring they are well-prepared for both the physical and emotional challenges that follow lung transplantation [47].

A study examined the outcomes of LTx in CF patients, specifically focusing on those undergoing a second lung transplant. It evaluated survival rates, complications, and general prognosis for patients undergoing re-transplantation, investigating factors that influence the success of such procedures. The study highlighted the critical role of post-transplant management and follow-up in influencing long-term survival. Early intervention and personalized treatment approaches for assessing eligibility for a second transplant were also emphasized as crucial for better outcomes. These findings contribute to refining strategies for optimizing second transplant procedures [48].

5.1 Future Implementation in the Daily Practice and/or Limitations

Despite the established benefits of PR in CF patients undergoing LTx, several challenges and limitations hinder its widespread adoption in clinical practice. One key issue is the variability in PR program availability, standardization, and accessibility, particularly for patients in regions with limited specialized CF care centers. Additionally, adherence to PR remains a concern, as factors such as disease burden, frequent hospitalizations, and logistical barriers may reduce patient participation. Integrating telerehabilitation and home-based exercise programs has shown promise in improving accessibility and compliance. Still, further research is needed to optimize these approaches and validate their long-term efficacy. Another limitation is the lack of large-scale, randomized, controlled trials assessing the impact of pre- and post-transplant rehabilitation on long-term transplant outcomes, survival rates, and quality of life. Moreover, while advancements in CF treatments, such as modulator therapies, have altered disease progression, their implications on PR needs and transplant candidacy require further exploration. Future efforts should focus on developing personalized rehabilitation protocols, enhancing multidisciplinary collaboration, and leveraging technology to improve patient engagement and long-term adherence to PR interventions. Addressing these challenges will be crucial in refining PR strategies and ensuring optimal outcomes for CF patients before and after LTx.

6. Conclusion

Preoperative and postoperative PR play a crucial role for LTx candidates and recipients with cystic fibrosis. Preoperative rehabilitation enhances patients' functional capacity, enabling them to achieve an optimal physical condition for surgery, significantly improving surgical outcomes. In the postoperative phase, rehabilitation interventions focused on chest hygiene and preventing complications related to immobilization are essential in supporting recovery.

Author Contributions

The author did all the research work for this study.

Competing Interests

The authors report there are no competing interests to declare.

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