8-11-2015

Association Between Preoperative Pulmonary Rehabilitation And Postoperative Hospital Outcomes

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ABSTRACT

SHENEE' K. LAURENCE
ASSOCIATION BETWEEN PREOPERATIVE PULMONARY REHABILITATION AND POSTOPERATIVE HOSPITAL OUTCOMES
(Under the direction of SHANTA R. DUBE)

INTRODUCTION: Preoperative pulmonary rehabilitation (PPR) is an emerging therapy for transplant candidates who are awaiting surgery. Research indicates that PPR training has benefits for improving exercise tolerance, but little researcher exists on the association between PPR on post-transplant hospital outcomes.

METHODS: The study was a non-probability cross-sectional analysis performed on data for post-transplant recipients who received either a single or bilateral lung transplant from February 8, 2007 to July 8, 2014. The study sample consisted of 207 transplant recipients. Analyses of the associations between independent variables: preoperative pulmonary rehabilitation and six-minute walk distance (6MWD) and covariates were performed by logistic regression analysis to examine the following outcomes: length of stay, hospital readmissions in the first 90 days post-transplant, and the number of hospital readmissions in the first 90 days.

RESULTS: Transplant recipients who participated in preoperative pulmonary rehabilitation had 1.77 times greater odds of being readmitted in the first 90 days post-transplant compared to recipients who did not participated in preoperative pulmonary rehabilitation. Transplant recipients whose 6MWD was greater than 207 meters and who participated in preoperative pulmonary rehabilitation had 4.99 times greater odds of length of staying 12 days or less post-transplant surgery compared to transplant recipients whose walk distance was less than 207 meters and who did not participate in preoperative pulmonary rehabilitation.

CONCLUSION: Pulmonary rehabilitation is an important part of the lung transplant. The results of this study indicate the importance of preoperative lung transplant on post-transplant outcomes for transplant recipients.

INDEX WORDS: preoperative pulmonary rehabilitation, six-minute walk distance, length of stay, lung transplant

ASSOCIATION BETWEEN PREOPERATIVE PULMONARY REHABILITATION AND POSTOPERATIVE HOSPITAL OUTCOMES

by

Shenee' K. Laurence

B.S.N, GEORGIA STATE UNIVERSITY

A Thesis Submitted to the Graduate Faculty
of Georgia State University in Partial Fulfillment
of the
Requirements for the Degree

MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA
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ASSOCIATION BETWEEN PREOPERATIVE PULMONARY REHABILITATION AND HOSPITAL READMISSIONS IN THE FIRST 90 DAYS AFTER LUNG TRANSPLANTATION SURGERY

by

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DEDICATION

For my family and friends who have always given me unconditional love and support.

ACKNOWLEDGEMENTS

My utmost respect and gratitude go to my advisor, Dr. Shanta Dube, who has been a constant source of inspiration throughout my thesis experience here at Georgia State University. Thank you for your valuable insight and wisdom that you were always willing to convey and your encouragement that kept me going. Thanks also go to my graduate thesis committee for their efforts, advice, and guidance, Dr. David Neujahr, Dr. Remzi Bag, and Melissa Nelson. To the members of the McKelvey Lung Transplant Team thank you for training me in the ways of pre and post lung transplant, being an extra pair of helping hands when needed, for covering my patient load when I had to leave for class early and listening to all of my ideas whether they were insane or not. Life-long friends can be few and far in between, but thank you Krystal, Kadija, and Frita for being people that I can rely on, trust, and confide in. And last, but definitely not least, thank you to my family who has always been there to encourage me to push through the hard times, give exaltations during the good, and remind me to always believe in myself and God. Your love has been a true blessing. Mom, Dad, and Shaquala you let me find my own way while still being there to give advice or a helping hand when I struggled. And thank you especially to my husband, Kensley. Thank you for helping me when I hit rock bottom and wanted to quit. Thank you for being that voice to remind me that with the Lord on my side all things are possible. Thank you for putting aside your business aspirations to support me unconditionally and providing the tough love I needed to make it to this point in graduate school. I love you and thank you for your encouragement.

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ABSTRACT PRESENTATIONS

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Paper presented at the American College of Gastroenterology Annual Scientific Meeting and Postgraduate Course Conference in Philadelphia, PA

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CHAPTER I.

INTRODUCTION

Based on the most up to date data published in February of this year by the Organ Procurement and Transplant Network website there are currently 1,644 lung transplant candidates on the national waiting list. In the state of Georgia, there are 28 lung transplant candidates on the waiting list. The average wait time on the national wait list for a lung transplant is a year to two years. In Georgia, the average wait time is six months to less than a year. This extended time spent on the waiting list for a lung transplant could be detrimental to a waitlisted candidate for two reason. The transplant's disease progression could deteriorate to the point where the candidate becomes too ill for transplant surgery. The other reason is due to their exercise intolerance and their inability to participate in daily exercise; they become too deconditioned to have lung transplant surgery. These reasons explain the important role preoperative pulmonary rehabilitation plays for waitlisted transplant candidates. Pulmonary rehabilitation maintains endurance, strength, and overall good health, which is why participation in preoperative pulmonary rehabilitation is an important part of the pre-transplant process. There is evidence that pulmonary rehabilitation can stabilize, and potentially reverse many systemic manifestations of the disease processes. Pulmonary rehabilitation helps with advanced lung disease management and improvements in quality of life (Yusen et al., 2010).

Since the middle of the 20th century, pulmonary rehabilitation and its components have been used by clinicians. During this time, the use of pulmonary rehabilitation was based on expert opinion from trial and error. The first randomized clinical trial of pulmonary rehabilitation occurred in 1991, with a small group of 19 recipients diagnosed with chronic obstructive pulmonary disease (COPD). The aim of the study was to see if recipients experienced marked improvement with higher or lower levels of exercise training which using a cycle ergometer. Results of the study showed higher levels of training correlated to better outcomes. In 1994, the first study related the effects of pulmonary rehabilitation and dyspnea demonstrated that pulmonary rehabilitation can decrease ventilatory demand and reduction in post- exercise dyspnea. In 1996, the first large randomized control trial of 119 recipients diagnosed with COPD, received treatment at a comprehensive outpatient pulmonary (which included education and exercise training). The results of the program showed improvements, but a decline in the improvements after 18 months. Over the next 11 years, pulmonary rehabilitation would reach

several milestones. In 2007, the American College of Chest Physicians (ACCP) and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) documented very strong evidence supporting the effectiveness of upper and lower extremities in exercise training. They also recorded improvements in dyspnea and quality of life. The ACCP and AACVPR summarized the current evidence-based guidelines for pulmonary rehabilitation. In 2008, pulmonary rehabilitation became the most effective therapy in increasing exercise capacity of COPD recipients and was added to the current treatment algorithm for COPD by the Global Initiative for Obstructive Lung Disease (GOLD). Pulmonary rehabilitation became a covered benefit for selected aspects of COPD under the Centers for Medicare and Medicaid (CMS) in January 2010 (Nici & Zuwallack, 2011).

Statement of the Problem

Due to the exercise intolerance caused by to physiology changes of end-stage lung disease, many recipients are often much more deconditioned than recipients without end-stage lung diseases prior to lung transplantation surgery. A person's pre-transplant physical activity status is contributory to their post-transplant physical function. Limited physical activity prior to a major surgery such as lung transplantation, increases an individual's morbidity and mortality during their hospital stay.

Purpose of the Study

There are numerous studies on the benefits of pulmonary rehabilitation after lung transplantation, but few studies exist on the benefits pre-transplant. This retrospective study determines if there is an association between participation in preoperative pulmonary rehabilitation and hospital outcomes. The next chapter will the review the current literature on preoperative pulmonary rehabilitation in non-restrictive and restrictive lung diseases and the benefits of preoperative pulmonary rehabilitation for waitlisted lung transplant candidates.

Research Questions:

The researcher sets out to understand the impact of preoperative pulmonary rehabilitation on the number of hospital readmissions in the first 90 days post-transplant. Specifically, the research will determine the relationship of preoperative pulmonary rehabilitation and 6MWD on hospital outcomes.

Research Question 1: Do lung transplant recipients who engaged in preoperative pulmonary rehabilitation differ on post-operative hospital readmissions compared to those who did not engage in preoperative pulmonary rehabilitation?

$H_0$1: Lung transplant recipients who engaged in preoperative pulmonary rehabilitation will have an equal odds of being readmitted post 90 days compared to lung transplant recipients who did not engage in preoperative pulmonary rehabilitation.

$H_0$2: Lung transplant recipients who engaged in preoperative pulmonary rehabilitation will have an equal odds of having < 2 readmissions when compared to lung transplant recipients who did not engage in preoperative pulmonary rehabilitation.

Research Question 2: Do lung transplant recipients who engaged in 6MWD differ on hospital length of stay post-surgery compared to those who did not engage in a 6MWD?

$H_0$1: Lung transplant recipients who engaged in 6MWD will have an equal odds of having ≤ 12 day stay compared to lung transplant recipients who did not engage in 6MWD.

Exploratory Research Question 3: Do lung transplant recipients who did not engage in both preoperative pulmonary rehabilitation and 6MWD differ on hospital admissions from those who engaged in at least one or both of the preoperative behaviors?

CHAPTER II

LITERATURE REVIEW

A literature review was conducted to examine the body of literature that was relevant to the research question: Does preoperative pulmonary rehabilitation among lung transplant recipients result in reduced hospital readmissions in the first 90 days after lung transplant surgery? Prior to selecting the research articles, the researcher reviewed the definition of *pulmonary rehabilitation* to ensure the literature review captured the broad definitions of pulmonary rehabilitation and how preoperative pulmonary rehabilitation is beneficial.

A literature search was performed using the following databases: PubMed, PubFacts, Google, and ERIC. The following search terms were used to conduct literature review: *definition of pulmonary rehabilitation, home-based pulmonary rehabilitation, outpatient pulmonary rehabilitation, preoperative rehabilitation and transplant candidates, benefits of pulmonary rehabilitation and the following diseases: COPD, Cystic Fibrosis, Idiopathic Pulmonary Fibrosis, Pulmonary Hypertension, Bronchiectasis, Pulmonary Fibrosis, and Sarcoidosis, exercise testing determines survival, and 6 MWD prognostic factor and survival in transplant recipients.* This literature review's organized in the following thematic format (a) definitions of pulmonary rehabilitation, (b) pulmonary rehabilitation settings, (c) general benefits of preoperative pulmonary rehabilitation for COPD and non-COPD diseases; (d) benefits of preoperative pulmonary prior to lung transplant surgery; and (e) 6MWD as determinants of survival for transplant candidates.

Definitions of Pulmonary Rehabilitation

In 2006, the American Thoracic Society (ATS) and European Respiratory Society (ERS) adopted a new definition of pulmonary rehabilitation. They defined pulmonary rehabilitation as: *"Pulmonary rehabilitation is an evidence-based, multidisciplinary and comprehensive intervention for recipients with chronic lung disorders who are symptomatic and have some disability. Pulmonary rehabilitation is aimed to decrease symptoms, optimize functional state, increase participation, and reduce health-care costs through stabilizing or reversing systemic manifestations of the disease"* (Nici et al., 2006). The ATS and ERS' broader definition of pulmonary rehabilitation is a strategic patient-centered intervention plan where the goal is the

lifelong management of patient's chronic respiratory symptoms. The patient-centered intervention plan should be a dynamic multidisciplinary collaboration among the patient, family, and healthcare workers. The aim of the intervention program is to address both the primary and secondary deteriorations of the recipients' disease process.

Pulmonary rehabilitation programs, as described by Troosters, Grosselink, Janssens, and Decramer (2010), are exercise training intervention programs with a multidisciplinary approach. A simpler is definition is an exercise program used to reverse the systemic skeletal muscle dysfunction in respiratory diseases. The aim of the pulmonary rehabilitation program should be to increase ventilatory efficiency, reduced dyspnea, and increased exercise capacity and to be performed at a minimum of 3 times per a week for at least eight weeks.

Nici & Zuwallack, (2011) define pulmonary rehabilitation as comprehensive interventions for recipients with chronic advanced respiratory disease. These are recipients who are symptomatic and have experience decreased daily life activities. Pulmonary rehabilitation interventions would reduce symptoms, improve functional status, increase participation and reduce healthcare costs.

With the advances in the understanding of the science and processes of pulmonary rehabilitation, in 2013 the ATS and ERS decided to update the definition of pulmonary rehabilitation. The first definition of pulmonary rehabilitation created seven years prior was an evidence-based, multidisciplinary approach for treating advanced chronic respiratory diseases with the focus on stabilizing the disease reversing and systemic manifestations. The ATS and ERS gained a more comprehensive understanding of the parts of pulmonary rehabilitation combined with years of clinical experience and expert opinion. With this newfound understanding, the ATS and ERS revised the definition of pulmonary rehabilitation interdisciplinary intervention for recipients with any respiratory disease that included focus on behavior modifications. The ATS and ERS' new adopted definition stated: *"Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors."* (Martijn et al., 2013).

The new ATS and ETS' definition of pulmonary rehabilitation is a more individualized patient-centered intervention. The main components of the pulmonary program: exercise training, self-management education, and behavioral modification remain the same as the pulmonary rehabilitation program defined in 2006. The format of the pulmonary rehabilitation programs may vary. Similarly, the indication for pulmonary rehabilitation no longer is restrained to recipients suffering from COPD but to recipients who illustrate symptoms of shortness of breath at a regular pace on level ground while on optimum therapy. Pulmonary rehabilitation should be individualized including age specific, cultural sensitive, and both patient and family involvement (Al Moamary, Aloniny, & Al-Hajjaj, 2014). The team involved should include interdisciplinary team members (i.e. physicians, respiratory therapists, nurse, social workers, or occupational therapists). The focus of the interventions should be unique to the needs of the recipients, based on initial, current and ongoing assessments. The interventions should be in direct correlation with the patient's disease severity, complexity, and comorbidities (Martijn, 2013).

The use of the term 'intervention' for pulmonary rehabilitation has the implied meaning that pulmonary rehabilitation is to be prescribed as a treatment plan. Troosters, Gosselink, Janssens & Decramer (2010), state there are reported extensive benefits of pulmonary rehabilitation in stable lung disease recipients. However in recipients with milder disease there is limited efficacy of pulmonary rehabilitation due to limited substantial evidence. This is evident in a trial conducted in recipients with a forced expiratory volume less than 60% in one second only showed modest improvements after pulmonary rehabilitation.

Contrarily, Martijn et al. shows with more clinically expert based data pulmonary rehabilitation can be integrated throughout the clinical course of a patient's disease; therefore it can be initiated at any stage of the disease. Pulmonary rehabilitation can be recommended during periods of clinical stability or directly after an exacerbation. The goal of pulmonary rehabilitation is to minimize symptom burden and maximize exercise performance. While promoting autonomy pulmonary rehabilitation, increasing participation in activities of daily living, quality of life, and enhancing long-term health changing behavior (2014).

Complementary to this, Troosters, Hornikx, Demeyer, Camillo, Janssens (2014), agree there are recipients who should be prescribed pulmonary rehabilitation without hesitation. Recipients who have recently been admitted to the hospital with acute COPD exacerbations and

recipients with severe dyspnea in whom all pharmacologic options have been exhausted. The potential beneficial gains of pulmonary rehabilitation for these two group of recipients is essential for their lung function.

Pulmonary Rehabilitation: Hospital-based and Home-based Pulmonary Rehabilitation

Traditionally, pulmonary rehabilitation programs were performed in hospital-based facilities. In the early 1990s, home-based pulmonary rehabilitation programs became popular options for recipients. The current trend is hospital-based pulmonary rehabilitation programs. Inpatient pulmonary programs are thought to be the optimal pulmonary rehabilitations setting for lung transplant recipients to receive pulmonary rehabilitation in terms of setting, supervision, complexity, and duration. As the burden of end-stage lung disease continues increases and rising healthcare costs perhaps a way to increase the number of transplant recipients in pulmonary rehabilitations is to approve home-based programs. There naturally will be challenges in the funding and management of home based programs, but the pros of home-based pulmonary programs far outweigh the cons.

A group of researchers have completed studies analyzing the efficacy of home-based pulmonary rehabilitation programs compared to hospital-based programs (Mathis et al., 2008; Mendes de Oliveira et al., 2008).

Malthis et al. (2008) completed a study of 252 recipients who after a 4-week education program took part in home-based rehabilitation or hospital-based rehabilitation for eight weeks. The transplant recipients were followed for 40-weeks to complete a one year study. The results of the study showed improved cycling endurance time at three months, both groups associated with statistically and clinically significant improvement in health status. Overall at three months and one year both rehabilitation strategies, home-based and hospital-based, had similar efficacy in 6MWD, endurance time, and improvements in dyspnea. The clinical trial provides evidence that using self-monitored home-based pulmonary rehabilitation may be a viable option for recipients.

The results of the randomized controlled prospective study by Merdes de Oliveira et al. revealed the clinical benefits (6MWD) achieved in the clinical setting were not significantly greater than those achieved in the self-monitored home modality. The results of this study also revealed another positive aspect the retention rate of participation. The dropout rate was notably less in the at home group than in the hospital-based group. The researchers feel the positive

results of this study demonstrate home-based pulmonary rehabilitation is logistically easier and will have greater patient adherence due to non-necessity of transportation to specialized clinics (2010).

The benefits of home-based pulmonary rehabilitation were shown to extend to recipients with restrictive lung diseases in a study conducted by Kapaya, Takahaskhi, Sugawara, Kasai, Kiyokawa, and Shioya (2009). The study was a multidisciplinary home-based program. The home-based program included: exercise training with upper and lower limb exercises, respiratory muscles stretching calisthenics, level walking for at least 15 minutes inspiratory and expiratory muscles forces and a 45 minute education class. The results of the study showed that PR for restrictive lung diseases has the same effects as recipients with COPD if the severity of the disease was similar. The restrictive lung disease group had increases in six-minute walk distance, exercise intolerance, and quality of life.

Conversely, Elliott et al., (2011) tested the effect of home-based program on the recovery of lung transplant recipients. The study was an individualized eight week home-based physical rehabilitation program. The program was conducted through a multi-center randomized controlled trial to assess the physical function of pulmonary rehabilitation on recipients who survived a critical illness. The results of the study revealed the home-based rehabilitation both groups did have improvements in physical endurance. The researchers contribute the lack of a significant improvement due to lack of compliance since sessions were unsupervised, and training intensity was not adequate.

For most of the comparison research on hospital-based versus home-based pulmonary rehabilitation; there is evidence of results showing the efficacy of home-based programs if recipients are well selected and supervision is provided.

Respiratory Illnesses Potentially Requiring Lung Transplantation

Chronic obstructive pulmonary disease (COPD) is a type of lung disease where airflow is chronically obstructed. This obstructed airflow interferes and prohibits normal breathing; COPD is not fully reversible and is the third leading cause of death in United States. The prevalence of COPD among adults in the United States varies considerably by state and region. The prevalence of COPD is less than 4% in Washington and Minnesota compared to greater than 9% in Alabama and Kentucky. The area in the United States with the highest COPD prevalence cluster is along the Ohio and lower Mississippi Rivers. There has been declined in the

number of deaths related to COPD in men (10.6 per 100,000 between 1999 and 2010). Unfortunately, there has been no significant change in death rate had occurred in women. The prevalence rates for women were 35.3 per 100,000 in 1999 and 36.4 per 100,000 in 2010 ("COPD among Georgia Adults", n.d.).

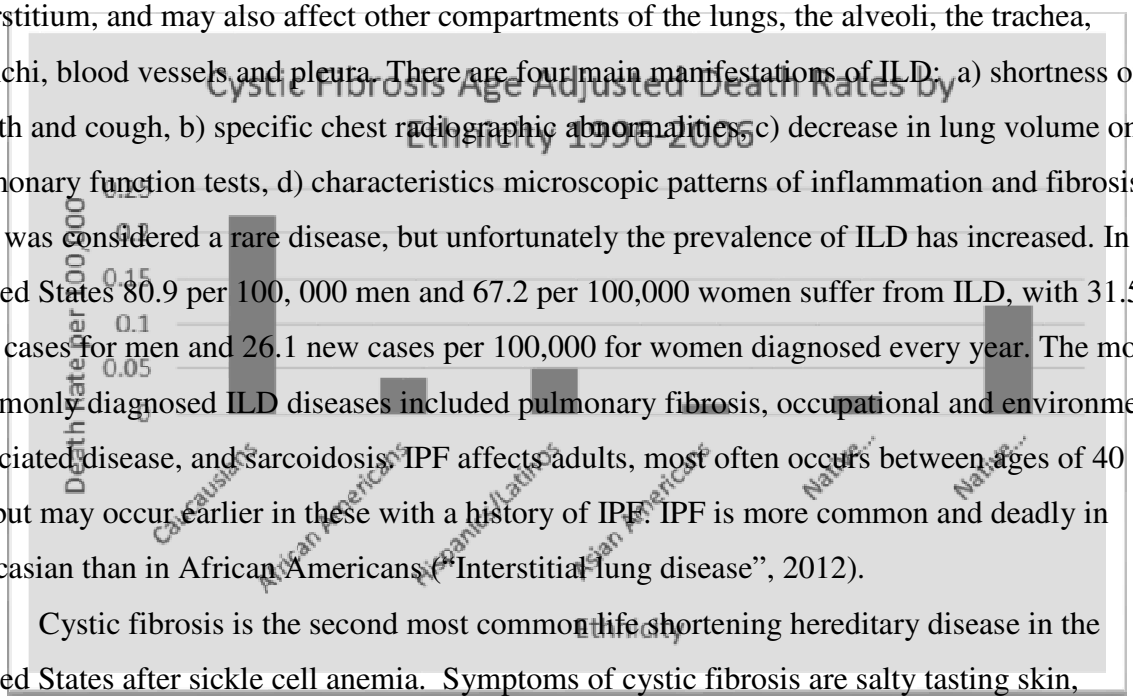
Individuals in the state of Georgia with COPD are more likely to be Caucasian, age 55 years or older, female, unable to work and have less than a high school diploma. A current household income of less than $25,000 are divorced, separated or widowed and have a history of smoking or asthma (http://www.cdc.gov/copd/data.htm). The demographics of Georgians with COPD are summarized in the table below.

Table 1.1 Demographics of Georgia Adults with COPD (data obtained from 2011 BRFSS)

Characteristics	Percentage %
Age Group (Years)	
18-44	3.8
45-54	7.4
55-64	11.5
65-74	13.7
>75	12.4
Race/Ethnicity	
White	8.3
Black	5.4
Hispanic	0
Other	7.8
Gender	
Male	5.6
Female	8.2
Employment Status	
Employed	2.7
Unemployed	8.5
Homemaker/Student	4
Retired	11.8
Unable to work	29
Education	
Less than high school diploma or GED	14.7
High school diploma or GED	7.2
At least some College	4.3
Income	
<$25,000	12.3
$25,000-$49,999	5.7
$50,000-$74,999	3.6
>$75,000	2.1
Marital Status	
Married	6
Divorced/Widowed/Separated	13.8
Never Married	3.6
Member of Unmarried Couple	0
Smoking Status	
Current Smoker	14.2
Former Smoker	9.2
Never Smoked	3.4
Ever had Asthma	
Yes	25.3
No	4

Interstitial lung diseases (ILD) this is a broad term that describes a collection of over 200 chronic lung diseases. These respiratory diseases are grouped together based on how the affect

the respiratory system-lack of these diseases affect the tissue space around alveoli (air sacs), the interstitium, and may also affect other compartments of the lungs, the alveoli, the trachea, bronchi, blood vessels and pleura. There are four main manifestations of ILD: a) shortness of breath and cough, b) specific chest radiographic abnormalities, c) decrease in lung volume on pulmonary function tests, d) characteristics microscopic patterns of inflammation and fibrosis. ILD was considered a rare disease, but unfortunately the prevalence of ILD has increased. In the United States 80.9 per 100, 000 men and 67.2 per 100,000 women suffer from ILD, with 31.5 new cases for men and 26.1 new cases per 100,000 for women diagnosed every year. The most commonly diagnosed ILD diseases included pulmonary fibrosis, occupational and environmental associated disease, and sarcoidosis. IPF affects adults, most often occurs between ages of 40 and 70, but may occur earlier in these with a history of IPF. IPF is more common and deadly in Caucasian than in African Americans ("Interstitial lung disease", 2012).



Cystic fibrosis is the second most common life shortening hereditary disease in the United States after sickle cell anemia. Symptoms of cystic fibrosis are salty tasting skin, wheezing or shortness of breath, persistent cough and excessive mucus, frequent lung infections (pneumonia and bronchitis), frequent sinus infections, nasal polyps, poor weight gain and growth, fouls-smelling greasy stools, and broadening of fingertips and toes. In the United States there are approximately 30,000 Americans diagnosed with CF and 1,000 new cases are diagnosed yearly. Cystic fibrosis equally affects males and females, while it does occur in nearly every race, Caucasians of Northern European descent are more often diagnosed with cystic fibrosis, with every 1 in 2500 Caucasian births being affected. The median age survival for a person with cystic fibrosis without a lung transplant is 37.4 years; the age adjusted death rate is higher for Caucasians (0.22 per 100,000) than other racial and ethnic groups ("Cystic Fibrosis, n.d).

Table 1 Cystic Fibrosis Age Adjusted Death Rates

Bronchiectasis (non-cystic fibrosis) is a chronic condition characterized by irreversible widening of the medium sized airways with inflammation, chronic bacterial infection and destruction of the bronchial walls. The characteristic features are abnormally dilated thick-walled bronchi that are inflamed and chronically infected by bacteria. The symptoms of non-CF bronchiectasis vary from person to person; some recipients have no symptoms at all, some recipients have symptoms only during exacerbations, and other recipients have experience symptoms daily. The clinical manifestations of non-CF bronchiectasis are persistent cough with daily micropurulent sputum production (lasting months to years), recurrent pulmonary infections resulting in airway damage which may produce streaked sputum and hemoptysis, dyspnea, wheezing, pleuritic chest pain, and adventitious breath sounds (crackles, wheezing, or rhonchi) [Neves, Guerra, Ponce, Miranda, and Vouga, 2011].

In analysis of US health plan claims for over 46 healthcare plans in 2009, Dwibedi, Joish, Spilsbury-Cantalupo, Operschall and Luong (2012), found the prevalence of non-CF bronchiectasis increased with increasing age; prevalence was lowest among individuals younger than 18 years of age (4.48 per 100,00) and highest among individuals 75 years of age and older (378.74 per 100,000). In terms of gender differences non-CF bronchiectasis was more prevalent among women. Dwibedhi et al. also noted regional variations across nine census regions with Middle Atlantic Regions having the highest prevalence at 57.29 per 100,000 and west North

Central regions having the lowest prevalence of non-CF bronchiectasis at 28.60 per 100,000 (2012).

In another study of US Medicare data, the 8 year period of prevalence of non-CF prevalence increased by 8.7% per year of life. The report also suggested in terms of ethnicity there is a higher prevalence among Asians compared to African Americans and European-Americans ("Bronchiectasis", 2012).

Pulmonary hypertension is a respiratory illness which there is high blood pressure in the lung arteries; the arteries narrow and decreases blood flow. Over time the arteries stiffen and become blocked – this narrowing of the pulmonary arteries over times causes stress on the heart and leads to the enlarge heart and heat failure. The symptoms of pulmonary hypertension during the initial stage of the disease are common to many other medical conditions: difficulty breathing, fatigue, shortness of breath. As the disease progresses the symptoms become more severe: dizziness, chest pain, ankle swelling, and palpitations.

Due to lack of specific ICD-9 codes for the conditions of pulmonary hypertension and risk of misdiagnosis; the exact prevalence of PH is largely unknown. Kirson et al analyzed private insurance claims and Medicare database claims from 1999 to 2007. The results of the data analysis revealed the prevalence rates of PH increases with age and are higher among women. The data analysis also showed the estimated US prevalence of PH is higher than existing estimates (Kirson, Birnbaum,Ivanova, Waldmen, Joish, and Williamson, 2011).

As the above diseases progress and become more debilitating, lung transplantation is the therapeutic measure for recipients with end-stage lung diseases who have exhausted all other available treatments without improvements. In order to become a transplant recipients there are certain criteria candidates have to meet prior to transplantation. While the requirements vary from transplant center these are the generally agreed upon criteria:

- End-stage lung disease
- Has exhausted other available therapies without success
- No other compounding comorbidities involving heart, kidney, liver
- No HIV, untreated Hepatitis, cancers
- Not currently using/abusing alcohol, smoking, drug abuse
- Acceptable BMI (usually above the range of malnourished and below the range of obese)

- Age
- Acceptable psychological profile
- Adequate social support
- Financial able to pay for expenses post-transplant
- Able to comply with post-transplant regimen.
- Acceptable results from extensive medical tests which evaluate their overall health status and suitability for transplant surgery

Once a person is accepted as by a transplant center, they are added to recipient waiting list and assigned a lung allocation score (LAS). The LAS takes into account various measures of the patient's health. The LAS system allocates donated lungs according to the immediacy of need rather than how long a patient has been on the transplant list.

The following table is information from UNOS database illustrating the number of lung transplants completed from January 1, 1998 to November 30, 2014.

Table 1.2 Number of Lung Transplants performed from January 1, 1999 to November 30, 2014

	COPD	Cystic Fibrosis	Non-CF Bronchiectasis	Pulmonary Hypertension	ILD	Total
Caucasian						
Male	**3941**	**1834**	**173**	**232**	**4516**	**10696**
Female	**4180**	**1612**	**202**	**489**	**1656**	**8139**
Caucasian Total						***18835***
African American						
Male	**219**	**17**	**23**	**11**	**258**	**528**
Female	**240**	**21**	**9**	**56**	**266**	**592**
African American Total						***1120***
Hispanic						
Male	**63**	**47**	**19**	**19**	**391**	**539**
Female	**43**	**45**	**35**	**40**	**217**	**380**
Hispanic Total						***919***
Unknown						
Male	**0**	**1**	**0**	**0**	**1**	**2**
Female	**1**	**0**	**1**	**0**	**1**	**3**
Unknown Total						***5***
Asian						
Male	**14**	**1**	**9**	**3**	**98**	**125**
Female	**8**	**0**	**9**	**15**	**42**	**74**
Asian Total						***199***
American Indian/Alaskan Native						
Male	**5**	**3**	**2**	**7**	**14**	**31**
Female	**10**	**2**	**1**	**4**	**14**	**31**
American Indian/Alaskan Native Total						***62***
Pacific Islander						
Male	**0**	**0**	**1**	**2**	**6**	**9**
Female	**1**	**0**	**1**	**2**	**2**	**6**
Pacific Islander Total						***15***
Multi-Racial						
Male	**4**	**0**	**2**	**1**	**7**	**14**
Female	**12**	**2**	**1**	**1**	**9**	**25**
Multi-Racial Total						***39***
Total	**8741 (31.6 %)**	**3585 (13.0%)**	**488 (1.8%)**	**875 (3.2%)**	**7498 (27.1%)**	**21187 (76.7%)**

on Adults Living in the United States

Physiology of Exercise Intolerance in Obstructive and Restrictive Respiratory Diseases

There is a direct association between obstructive respiratory diseases, such as COPD and ventilatory constraints, abnormal pulmonary gas exchange, peripheral muscle dysfunction, cardiac dysfunction, and limitations due to lower limb and respiratory muscle dysfunction. Each of these processes alone or a combination of can lead to exercise intolerance.

Ventilatory limitations. Spruitt et al. describe the ventilatory limitations (constraints) requirements experienced by recipients diagnosed with COPD are due to increase work of breathing, increased dead space ventilation, impaired gas exchange and increased ventilatory demand as a consequence of deconditioning and peripheral muscle dysfunction. The

increase in demand causes a limit in the maximum ventilation during exercise resulting in two respiratory symptoms of COPD: expiratory airflow obstruction and hyperinflation. Expiratory airflow obstruction and hyperinflation lead to further increased work of breathing, increased load and mechanical constraints on the respiratory muscles-this leads to an increasing intensified sense of dyspnea (2013).

Gas exchange limitation. Pulmonary ventilation increases as a direct result of hypoxia. Hypoxia causes an increase in pulmonary ventilation by changing peripheral chemoreceptor outputs and indirectly stimulating lactic acid production. This process causes a set of change reactions: lactic academia occurs as a result of anaerobic metabolism by the muscles during higher intensity exercise; leads to failure of the muscle tasks and thus increases pulmonary ventilation. Lactic acid buffering results in an increase in carbon dioxide production and acidosis stimulating the carotid bodies (Martijn et al., 2013).

Cardiac limitations. Chronic respiratory disease also affect the cardiovascular system in numerous ways: the main way is an increase in the right ventricular afterload. The consequences of overloaded right ventricular may lead to right ventricular hypertrophy and failure which can cause compromise left ventricular filling by producing septal shifts, which further decreases the hearts ability to meet exercise demands leading to tachyarrhythmias or right atrial pressure (Martijn, 2012).

Limitations due to lower limb and respiratory muscle dysfunction. The peripheral muscle dysfunction experienced in recipients with COPD is caused by single or multifactorial causes: inactivity induced deconditioning, systemic inflammation, oxidative stress, smoking, blood gases disturbances, nutritional imbalances, abnormally low hormone levels, aging, or prolonged corticosteroid use. Other factors leading to skeletal muscle dysfunction is the increased ventilatory requirements recipients with COPD experience with any given exercise work rate, which causes an increasing burden on the respiratory muscles (Martijn et al., 2012).

In order to adapt to chronic overload the diaphragm of individuals with COPD have greater resistance to fatigue; the inspiratory muscles are capable of generating more pressure than non COPD individuals. While this resistance to fatigue may be seen as an advantage it actual causes recipients with COPD to experience static and dynamic hyperinflation, which places their muscles at a mechanical disadvantage. Even with the adaptation in their diaphragm

individuals with COPD still experience both inspiratory muscle strength and inspiratory muscle endurance weakness, which causes reduced exercise performance (Martijn, 2013).

Research has shown the physiology effects of exercise intolerance of restrictive lung disease are similar to the symptoms of obstructive respiratory disorders. These restrictive lung conditions are, but not limited to, interstitial lung disease, non-cystic fibrosis bronchiectasis, and pulmonary arterial hypertension.

Exercise intolerance is a key feature in restrictive lung disorders and characteristic symptoms are dyspnea on exertion or hypoxemia. Exercise intolerance in restrictive respiratory diseases are caused by many of the same mechanisms as obstructive respiratory diseases: impaired gas exchange, circulatory limitations, altered respiratory mechanisms, abnormalities in muscle oxygen extraction and utilization, abnormal breathing patterns, and dynamic hypoinflation during exertion (Markovitz and Cooper, 2010).

Benefits of Pulmonary Rehabilitation on Exercise Intolerance and Prior To Lung Transplant Surgery

Literature Review of the Benefits of PR for Obstructive Respiratory Diseases				
Author/title	**Study Aim**	**Sample**	**Results**	**Implications for practice, research, theory**
Pulmonary rehabilitation improves cardiovascular response to exercise in COPD. **Ramponi et al.**		27 recipients diagnosed with COPD who participated in 9 week pulmonary rehabilitation program	transplant recipients experienced enhanced ventilatory capacity while exercising which lead to an enhancement in their breathing patterns. This enhancement in their breathing pattern was associated with reduced with dynamic hyperinflation and also improved exercise intolerance	
Benefits of pulmonary rehabilitation in patients with COPD and normal exercise capacity. **Lan et al.**	The effects of PR in patients with normal exercise capacity on health-related quality of life and exercise capacity.	Twenty-six subjects with COPD and normal exercise capacity were studied. All subjects participated in 12-week, 2 sessions per week, hospital-based, out-patient PR. Baseline and post-PR status were evaluated by spirometry, the St George's Respiratory Questionnaire, cardiopulmonary exercise test, respiratory muscle strength, and dyspnea scores.	revealed two positive effects of pulmonary rehabilitation on ventilatory limitations: improved the exercise capacity and level of exertional dyspnea. The scores of dyspnea at the end of the exercise pre-pulmonary rehabilitation was 5.7. The scores of dyspnea decreased by 0.9 points post-pulmonary rehabilitation. The scores of the level of exertional dyspnea post pulmonary rehabilitation were nearly that of healthy subjects.	
Exercise dyspnea in patients with COPD **Stendardi, Binazzi, and Scano**	Review of exercise dyspnea in COPD	None	Despite the unaltered ventilatory equivalents for carbon dioxide, pulmonary rehabilitation produces less Borg per unit of change in ventilation; which results in improved mechanical efficiency. To summarize the effects of pulmonary rehabilitation has on gas exchange exercise training reduces dyspnea by reducing the inspiratory effort, end-expiratory-lung-volume and respiratory rate. The end effect is a reduction in the respiratory effect to concurrent volume	

Literature Review of the Benefits of PR for Obstructive Respiratory Diseases				
Author/title	**Study Aim**	**Sample**	**Results**	**Implications for practice, research, theory**
Severe exercise-induced hypoxemia. **Garvey, Tiep, Barnett, Carter, Hart and Casaburi**	Review of severe exercise-induced hypoxemia	None	Recommended oxygen saturation should be the center of monitoring of a pulmonary rehabilitation program to improve hypoxia experienced by recipients suffering from COPD. Contrary to other studies which have recommended high intensity workouts, Garvey et al are recommending low intensity exercise in initial states of exercise, until clinical baselines are defined such as dyspnea levels, oxygen saturation, and heart rate.	
Pulmonary rehabilitation improves heart rate variability at peak exercise,exercise capacity and health-related quality of life in chronic obstructivepulmonary disease. **Cheng, Wu, Yang, Huang C., Huang H., Chu W., and Lan C**	Evaluate the effects pulmonary rehabilitation has on the impaired cardiac autonomic modulation in recipients with COPD which causes depressed heart rate variability.	Sixty-four patients with COPD participated in a 12-week, 2 sessions-per-week, hospital-based PR program. Baseline and post-PR status were evaluated by spirometry, HRV, health-related quality of life (HRQL, St. George's Respiratory Questionnaire, SGRQ), cardiopulmonary exercise test, respiratory muscle strength, and dyspnea Borg's scale.	Despite the unaltered ventilatory equivalents for carbon dioxide, pulmonary rehabilitation produces less Borg per unit of change in ventilation; which results in improved mechanical efficiency. To summarize the effects of pulmonary rehabilitation has on gas exchange exercise training reduces dyspnea by reducing the inspiratory effort, end-expiratory-lung-volume and respiratory rate. The end effect is a reduction in the respiratory effect to concurrent volume	The results of the study showed a significant improvement in autonomic modulation at peak exercise after pulmonary rehabilitation. The improvements in autonomic modulation not only occurred at peak exercise but also during periods of rest. The authors contribute the reason for the marked improvement in autonomic modulation is related to exercise training re-establishes exercise tolerance, decreases ischemic metabolites during exercise and further reduces sympathetic activity. In conclusion pulmonary rehabilitation decreased parasympathetic activity and increased sympathetic activity, improved the balance between parasympathetic and sympathetic activities, and improved heart rate variability.
Impact of resistance training in chronic obstructive pulmonary disease patients during periods of acute exacerbation **Borges, RC and Carvalho, CR**	To evaluate the effects of whole-body resistance training on exercise capacity, health-related quality of life (HRQOL), and muscle strength in patients hospitalized for exacerbation of chronic obstructive pulmonary disease	Patients (N=46) were randomized to either a control group (CG) or training group (TG), and 29 patients completed the study	Increases muscle strength and improves exercise capacity in recipients with COPD. The researchers believe the peak improvement in muscle strength was directly related to an improvement in neurologic adaptation.	The researchers concluded that pulmonary rehabilitation can be a useful intervention to reduce or prevent decreases in muscle strength during hospitalizations

Literature Review of the Benefits of PR for Obstructive Respiratory Diseases				
Predictors of benefit following pulmonary re habilitation for interstit iallung disease **Holland et al**	evaluate the impact of pulmonary rehabilitation on the severity of ILD	prospective study of 44 subjects with ILD	The results of the study showed improvement in functional exercise capacity for people with IPF. The differences in the improvement in the functional exercise capacity of individuals with IPF compared with individuals with COPD is the improvements were related to markers of disease severity and prognosis. The highest peak of improvements were seen when the disease was at its mildest. ILD is one of the least commonly referred disease processes for pulmonary rehabilitation because many physicians feel the benefits are unproven.	The results of this study prove the benefits of pulmonary rehabilitation for IPF are greater when delivered early in the course of the disease, but regardless of disease severity individuals with ILD are still likely to achieve sustained improvements in dyspnea and quality of life

Literature Review of the Benefits of PR for Restrictive Lung Diseases				
Author/title	**Study Aim**	**Sample**	**Results**	**Implications for practice, research, theory**
Respiratory muscle function in patients with cystic fibrosis. **Dassios, Katelri Doudounakis and Dimitriou**	the beneficial role of exercise in maintain their health and to see the effects of regular exercise on the respiratory muscle function indices	44 cystic fibrosis recipients	The results of the study indicate that exercise training is beneficial for individuals with cystic fibrosis. Exercise training leads to strengthening of the respiratory muscles which will aid in maintaining ventilatory balance.	The results of the study indicate that exercise training is beneficial for individuals with cystic fibrosis. Exercise training leads to strengthening of the respiratory muscles which will aid in maintaining ventilatory balance
Exercise programme in recipients with cystic fibrosis: A randomized controlled trial **Rovedder et al.**	randomized controlled study of 46 transplant recipients with a pre-transplant diagnosis of COPD demonstrated participation in resistance training as part of pulmonary rehabilitation program	clinical trial of adults with CF, who participated in home-based pulmonary rehabilitation program with aerobic training and muscle strength training	did not show any positive effects in muscle strength of the lower limbs or aerobic condition. Rovedder et al. (2014) explain the lack of gain in muscle strength as a result of the difference in the size of the muscle groups exercised. Another reason for no effect in muscle strength was the study time may have been too short for effects of training to be seen. To explain no improvement in the aerobic condition of recipients who participated in pulmonary rehabilitation, Rovedder et al (2014) contributed this to the recipients' combination of previous illness and lack of physical activity which would contribute to low tolerance to exercise and limited gain in fitness	The results of this study are an outlier as many of the present CF studies have shown several benefits of pulmonary rehabilitation including an increase in muscle mass, muscle strength, body weight, and a decrease in residual volume which attributes to great flexibility and thoracic mobility
Safety and efficacy of exercise training in various forms of Pulmonary hypertension. **Grunig et al., 2012**	The efficacy and safety of respiratory and exercise training in recipients diagnosed with pulmonary hypertension	183 patients with PH (pulmonary arterialhypertension (PAH), chronic thromboembolic PH and PH due to respiratory or left heart diseases received exercise training in hospital for 3 weeks and continued at home.	The results of the study showed that exercise training can improve the quality of life, peak oxygen consumption, exercise capacity, oxygen pulse even in recipients who are classified in WHO functional class IV (individuals who are unable to carry out any physical activity without symptoms; these recipients typically display symptoms of fatigue even at rest and discomfort is increased with activity). However, PH is different than other non-COPD diseases in response to pulmonary rehabilitation. The effects of exercise training is independent on the etiology of PH	

Literature Review of the Benefits of Pulmonary Rehabilitation Prior to Lung Transplant				
Author/title	**Study Aim**	**Sample**	**Results**	**Implications for practice, research, theory**
Pulmonary rehabilitation in lung transplant candidates **Li, Mathur, Chowdury, Helen, and Singer**	randomized controlled study of 46 transplant recipients with a pre-transplant diagnosis of COPD demonstrated participation in resistance training as part of pulmonary rehabilitation program	a retrospective cohort study of recipients 18 years of age and older who have received a single, double, or heart-lung transplant between January 2004 and June 2009 at Toronto General. The recipients had to have pre-transplant exercise data available. The recipients participated in pulmonary rehabilitation during the entire waiting period three times a week for 1.5 to 2 hour sessions.	The results of the study did not show an improvement in the recipients 6MWD after participating in pulmonary rehabilitation, but the recipients were able to maintain pre transplant 6MWD. Li et al. results revealed the greater the final 6MWD prior to transplant was associated with a shorter hospital length of stay.	
Effects of pulmonary rehabilitation in bronchiectasis: A retrospective study **Ong, Lee, Hill, Holland & Denehy**	evaluate the impact of pulmonary rehabilitation on the severity of ILD	111 recipients, diagnosed with bronchiectasis who participated in a retrospectively study, demonstrated individuals with bronchiectasis achieve improvements in exercise capacity and quality of life after participating in a 6 week to 8 week outpatient pulmonary program	The effects of pulmonary rehabilitation were able to be maintained for 12 months post pulmonary rehabilitation. The results of this study also provide support that individuals with bronchiectasis do not have a significantly different response to pulmonary rehabilitation than recipients with COPD, which is useful information for physicians who have concerns of referring recipients with bronchiectasis for pulmonary rehabilitation	
A pilot study of pulmonary rehabilitation and chest physiotherapy versus chest physiotherapy alone in bronchiectasis **Mandal et al.**	The aim of our study was to assess the efficacy of pulmonary rehabilitation in addition to regular chest physiotherapy in non cystic fibrosis bronchiectasis.	Thirty patients with clinically significant bronchiectasis and limited exercise tolerance were randomized into either the control or intervention group.	a pilot comparison study in bronchiectasis recipients who received chest physiotherapy versus bronchiectasis recipients who received chest physiotherapy (CP) and pulmonary rehabilitation found adding pulmonary rehabilitation to CP led to significant improvements in exercise capacity compared to recipients who received CP alone	The improvements in exercise capacity was maintained for 12 weeks after the intervention ended

6-minute Walk Distance (6MWD) as Determinant of Survival in Transplant Candidates

Exercise testing has become a convenient method of evaluating respiratory function; the six-minute walk distance is one way to measure this. The six-minute walk has proven to be reproducible and is tolerated by recipients with various disease severities. The six-minute walk test evaluates the distance a person can walk on a flat, rigid surface in six-minutes; the purpose of the test is to determine exercise tolerance and oxygen saturation during submaximal exercise (Morales-Blanhir, 2011).

A study population of 376 recipients with diverse native diseases listed for lung transplantation who were prospectively followed from the time of listing onward. The results of the study found a relationship between baseline 6MWD and patient mortality (after variable adjustment). The results indicated that in a 28 month follow up period for every 500 foot increments in baseline 6MWD there was greater than 50% reduction in mortality-this trend was seen across all diseases categories and through transplantation. The researchers found that the baseline 6MWD is predictive of survival regardless of transplant status (Martinu, 2008).

In another retrospective cohort study, 51 recipients who were diagnosed with ILD analyzed if the 6MWD is associated with survival in recipients with ILD referred for lung transplantation. The results of the study did show that oxygen saturation and 6MWD are associated with the risks of death in recipients with IlD who were evaluated for lung transplantation. Oxygen desaturation with exercise is one of the common respiratory issues of ILD; researchers of the study found that lower oxygen saturation during exercise or recovery was associated with an increased risk of death. To conclude the results of this study found excellent sensitivity and specificity of oxygen saturation <95% with unloaded exercise and 6MWD < 350m for prediction of death on the list for recipients with ILD for a patient with oxygen saturation of <95% there was a 75% chance of dying on the list (Kawut, 2005).

For lung transplant candidates the 6MWD has shown high sensitivity as a predictor of mortality. Among recipients on the waiting list for transplantation on a 6MWD of less than 300m was associated with much earlier mortality. The 6MWD is a useful tool that represents an accurate and efficient method of quantifying exercise tolerance.

Kenn et al. (2014) conducted a retrospective clinical pre-analysis and post-analysis of lung transplant candidates in pulmonary rehab. The aim of their study was to see how effective PR was in not only in recipients with COPD but in recipients with other lung diseases waiting for

transplant. The results of their study showed short-term comprehensive PR can significantly improve exercise capacity. The data of this study showed two other positive effects of PR: 1) candidates with greater exercise capacity prior to lung transplant showed favorable post-transplant outcomes, 2) candidates, both with COPD and restrictive lung diseases, showed an increase in 6MWD. These two important positive effects support that PR is beneficial for candidates pre-transplant and will results in better post-transplant outcomes for the patient.

CHAPTER III

Methods

Introduction

The study contained several variables related to post-transplant outcomes. In order to appropriately consider all factors believed to affect transplant recipient's post-transplant hospital outcomes and to determine the variables to be used in the study, we conducted through extensive research literature and looked for variables that clearly demonstrated risk or protective properties that could potential affect the hospital outcomes of transplant recipients. Institutional Review Boards at Georgia State University and Emory University approved the study as exempted research.

Study Design and Sample

The study is a non-probability sample of lung transplant recipients who underwent surgery from February 8, 2007 to July 8, 2014. The information from the data set was obtained from a secondary data source, the data warehouse at Emory University Transplant Center. Subjects were recipients with diverse end-stage lung disease processes.

During this period the total number of recipients was 214; seven transplant recipients were excluded due to death immediately after transplant while in the hospital. Thus, the sample size for this study is 207 transplant recipients with a 5.0% margin of error and a 95% confidence interval.

Measures

The instruments used to collect data on transplant recipients was the data warehouse at Emory University Hospital and chart abstraction. Pre-transplant and post-transplant coordinators and other healthcare disciplines update and enter the transplant recipient's data in the data warehouse during the pre and post-transplant phase of care. Chart abstraction was used to collected limited data information on the transplant recipients' participation in preoperative pulmonary rehabilitation and six-minute walk distance.

Data Analysis Overview

Independent Variables

Three independent variables were tested in this study: 1) pulmonary rehabilitation, 2) six-minute walk distance, and 3) total number of preoperative behaviors.

Preoperative Pulmonary Rehabilitation

Preoperative pulmonary rehabilitation was defined as a dichotomous variable: participation and no participation. Participation in pulmonary rehabilitation was based on the guidelines of the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) [American Association of Cardiovascular…2004]. Participation in preoperative pulmonary rehabilitation including participating in one of the three following levels of rehabilitation:

- Inpatient pulmonary rehabilitation must have: a) attended 3-5 preoperative pulmonary sessions a week, b) for 30 to 90 minutes a session and c) for at least 4 weeks, and d) within 6 months of transplant.
- Transplant recipients who participated in home pulmonary rehabilitation must have attended one inpatient session (which will provide home pulmonary instructions tailored to disease severity and patient tolerance) and a) work-out 3-5 sessions a week, b) for 30 to 90 minutes, c) for at least 4 weeks, and d) within 6 months of transplant.
- Transplant recipients with decline in pulmonary function must have participated in preoperative pulmonary rehabilitation interval training: a) 10-30 minutes sessions with breaks as needed, b) 5 to 7 days a week, c) for at least 4 weeks and d) within 6 months of transplant.

Inpatient and home preoperative rehabilitation must have been performed on a stationary bike where resistance can be changed and distance measured, treadmill or surface track. Upper arm exercises should have been performed on an arm ergometry, with light weights or Therabands. In order to decrease a possible bias towards the null, preoperative pulmonary rehabilitation inclusion was not limited to recipients who completed pulmonary programs. Recipients with any participation in pulmonary rehabilitation were considered as engaging in preoperative pulmonary rehabilitation. Lung transplant recipients who did not engage in preoperative pulmonary rehabilitation were the referent group.

Six-Minute Walk Distance (6MWD)

The 6MWD is an index used to determine the transplant recipient's ability to perform daily life activities. The 6MWD measures the distance a transplant candidate can walk within a 6-minute time limit; the distance is measured in feet (ft.) or meters (m). A study by Duke University researchers found for every 50 meter increased in walk distance over 207 meters

during 6MWD there was an increase in survival. There was approximately a 1.5 greater relative risk of survival for lung transplant recipients who walked greater than 207 meters compared to those who walked less than 207 meters (Martinu, Babyak, and Palmer, 2008). Based on the results of the Duke University study, 6MWD was dichotomized into two categories. The first category was transplant recipients who walked 207 meters and more in their last preoperative 6MWD. The second category were transplant recipients who walked less than 207 meters in their last preoperative 6MWD. The referent group was lung transplant recipients who walked less than 207 meters during their last preoperative 6MWD.

Total Number of Preoperative Behaviors

The remaining variable is a created by two combined variable. Preoperative pulmonary rehabilitation and 6MWD to create a new variable. The variable is an exploratory variable with three categorical levels. The first level is no participation in preoperative pulmonary rehabilitation and 6MWD less than 207 meters. The second level is participation in preoperative pulmonary rehabilitation or 6MWD greater than or equal to 207 meters. The third level is participation in preoperative pulmonary rehabilitation and greater than or equal to 207 meters.

Dependent Variables

Transplant recipients readmitted in the first 90 days post-transplant were defined as a "yes". Recipients not admitted in the first 90 days post-transplant were defined as a "no". The number of readmissions was dichotomized to two levels: less than two readmissions or greater than two admissions in the first 90 days post-transplant. Dichotomization of this variable was based on a study conducted by Vigneswaran et al. (2010). The study results showed early admissions in the first 90 days post-transplant are an early predictor of recipient survival following isolated lung transplantation. The results indicated the 90-day conditional survival at one, three, and five years for those patients readmitted within 90 days were 76%, 59%, and 52%, respectively. For patients not readmitted the values were respectively 93%, 80%, and 76%.

The variable length of stay was dichotomized as 12 days and less and greater than 12 days based on clinical knowledge as transplant practitioner and univariate statistics from the current data. The results of PROC UNIVARIATE for the length of stay the mode was 14 days and the 25% quantile was 12 days.

Further support for this dichotomization is based on clinical observations where the average length of stay for transplant recipients is 7-14 days. The goal of the transplant team is to

discharge safely and efficiently the new transplant recipients once they are stable to decrease the risk of hospital acquired infection. Transplant recipients are typically discharged home 14 days post-transplant. Further support for this dichotomization is based on clinical observations where the average length of stay for transplant recipients is 7-14 days.

Other transplant recipients' characteristics were gender (male/female), racial ethnicity (Caucasian, African American, other), age (less than 20, 20-44, 45-54, 55 and older), and pre-transplant diagnosis body mass index (underweight, normal, overweight, obese). Transplant recipients' clinical data were pre-transplant diagnosis (chronic obstructive pulmonary disease [COPD]), idiopathic pulmonary fibrosis [IPF], sarcoidosis, cystic fibrosis, other end-stage lung diseases), and lung laterality (single or double lung).

All analyses were conducted using Statistical Analysis System (SAS) 9.3 software. SAS survey procedures were employed to account for complex study design. Descriptive statistics was obtained, to summarize, the distribution of study variables. The chi-square (X^2) statistic was used to compare the differences in the distribution of participation of recipients who participated in preoperative pulmonary rehabilitation within each recipient characteristic. The column percent used in the two-way table was used to analyze the differences in within each category. For example to analyze males who participated in preoperative pulmonary rehabilitation compared to males who did not participate in preoperative pulmonary rehabilitation.

Logistic regression calculates the probability or success over the probability of failure, the results of the analysis are in the form of an odd ratio. The dependent variable in the logistic regression is usually dichotomous. The independent or predictor variables in the logistic regression can take any form. Logistic regression makes no assumption about the distribution of the independent variables. The independent variables do not have to be normally distributed, linearly related or of equal variance within each group. The goal of logistic regression is to predict the category of outcome for individual cases using the most parsimonious model correctly.

Logistic regression was used to examine the association between dependent variables, 6MWD and preoperative pulmonary rehabilitation and independent variables. For all statistical analyses, a level of $\alpha = 0.05$ was used for significance testing.

CHAPTER IV

Results

Sample Demographics

The final analytic data consisted of 207 lung transplant recipients, 128 recipients who participated in preoperative pulmonary rehabilitation and 79 who did not participate in preoperative pulmonary rehabilitation.

The recipients ranged in age from 16 to 73 years with a mean age 55.10 years (SD=11.91) and a mean BMI of 25 (SD=4.48) for the study population. The largest transplant recipient age group for both men and women were adults age 55 and older. As shown in Table 4.1 adults age 55 and older were more likely to participate in preoperative pulmonary rehabilitation compared other age groups ($p<0.05$).

A stratified analysis of Africans Americans participation in preoperative pulmonary rehabilitation, age, and gender was performed. African American males who were 55 years of age and older were 1.54 more times likely not to participate in preoperative pulmonary rehabilitation compared to African American females ($p<0.05$).

Cystic Fibrosis and other (BOOP, Apha-1) pre-transplant diagnosis have the highest percent of recipients who did not participate in preoperative pulmonary rehabilitation. A stratified analysis of preoperative pulmonary rehabilitation and gender while controlling for pre-transplant diagnosis was completed. The results of the analysis revealed females diagnosed with cystic fibrosis were 1.12 times more likely not to participate in pulmonary rehabilitation compared to males diagnosed with cystic fibrosis. However, males with other pre-transplant diagnoses were 1.32 times more likely not to participate in preoperative pulmonary rehabilitation compared to females diagnosed with other pre-transplant diagnoses.

Table 4.1 Transplant Recipients Pre-Transplant Demographics Characteristics and Clinical Data

	Pre-Op Rehab	No Pre-Op Rehab	P-value
	N = 128	N= 79	
Gender			**0.0550**
Male	56.25	69.62	
Female	43.75	30.38	
Ethnic Race			**0.1573**
Caucasian	81.25	70.89	
African American	15.63	26.58	
Other	3.13	2.53	
Age			**0.0037**
Less than 20	0	3.80	
20-44	10.94	20.25	
45-54	11.72	20.25	
55-older	77.34	55.70	
Pre transplant Diagnosis			**0.0003**
COPD	36.72	20.25	
IPF	43.75	44.30	
Sarcoidosis	6.25	2.53	
Bronchiectasis	3.91	0.00	
Cystic Fibrosis	3.13	12.66	
Other	6.25	20.25	
Pre-transplant BMI			**0.5655**
Underweight	6.25	8.86	
Normal	38.28	41.77	
Overweight	42.19	41.77	
Obese	13.28	7.59	
6MWD			**0.0240**
Less than 207 meters	17.32	31.08	
207 meters and more	82.68	68.92	
Laterality			**0.6548**
Single lung transplant	24.22	21.52	
Bilateral lung transplant	75.78	78.48	
Smoking History			**0.1081**
Former Smoker	54.43	65.63	
Never Smoked	45.57	34.38	

+ Numeric values in table are column percentages from Chi-square data analysis

Table 4.2 Descriptive Summary Statistics for Pre-Transplant Recipients

Variables	Count	Mean	Standard Deviation
Age	207	55.09662	11.9127222
Pre-transplant BMI	207	25.0	4.47693294
Six-minute Walk Distance	201	271.1940	90.14725527

Bivariate Logistic Regression

Research Question 1: Do lung transplant recipients who engaged in preoperative pulmonary rehabilitation differ on post-operative hospital readmissions compared to those who did not engage in preoperative pulmonary rehabilitation?

$H_0$1: Lung transplant recipients who engaged in preoperative pulmonary rehabilitation will have an equal odds of being readmitted post 90 days compared to lung transplant recipients who did not engage in preoperative pulmonary rehabilitation.

Table 4.3 shows regressions coefficients with an odds ratio and significance level at α=0.05. The results indicates that the odds of being admitted post 90 days is greater for those who engage in preoperative rehabilitation compared to those who did not engage in preoperative pulmonary rehabilitation. Transplant recipients who engaged in preoperative pulmonary rehabilitation were 1.77 times more likely to be readmitted within the first 90 days compared to transplant recipients who did not engage in preoperative pulmonary rehabilitation. The null hypothesis was rejected.

Table 4.3 Summary of Logistic Regressions Analysis of the Association of the Effect of Preoperative Pulmonary Rehabilitation on Transplant Recipients Readmissions in the First 90 Days Post-transplant

	Readmission in First 90 Days Post Transplant		
Parameter	Estimate	Odds Ratio	P-value
Intercept	-0.0253		
Did not participate in preoperative pulmonary rehabilitation		1.00 (Referent group)	
Participated in preoperative pulmonary rehabilitation		1.77+	0.0497

$H_0$2: Lung transplant recipients who engaged in preoperative pulmonary rehabilitation will have an equal odds of having < 2 readmissions when compared to lung transplant recipients who did not engage in preoperative pulmonary rehabilitation.

Estimates in Table 4.4,indicate that there is no difference in lung transplant recipients who engaged in preoperative pulmonary rehabilitation when compared to lung transplant recipients who did not engage in preoperative pulmonary rehabilitation in odds of having <2 admissions. Therefore we fail to reject the null hypothesis.

Table 4.4 Summary of Logistic Regressions Analysis of the Association of the Effect of Preoperative Pulmonary Rehabilitation on the Number of Post-transplant Readmissions

	Number of Post-Transplant Readmissions		
Parameter	Estimate	Odds Ratio	P-value
Intercept	1.2204		
Did not participate in preoperative pulmonary rehabilitation		1.00 (Referent group)	
Participated in preoperative pulmonary rehabilitation		0.65	0.1893

Research Question 2: Do lung transplant recipients who engaged in 6MWD differ on hospital length of stay post-surgery compared to those who did not engage in a 6MWD?

$H_0$1: Lung transplant recipients who engaged in 6MWD will have an equal odds of having ≤ 12 day stay compared to lung transplant recipients who did not engage in 6MWD.

For research question two we reject the null hypothesis that transplant recipients who engaged in 6MWD of 207 meters or more do not differ from transplant recipients who walked less than 207 meters on hospital length of stay post-surgery. Transplant recipients who engaged in a 6MWD of 207 meters or more were 4.99 times more likely to be discharged from the hospital in less than 12 days post-transplant surgery compared to transplant recipients with a 6MWD of less than 207 meters.

Table 4.5 Summary of Logistic Regression Analysis of the Association of Effect of Transplant Recipients last Pre-Transplant Six-minute Walk Distance on Length of Stay in the Hospital after Transplant Surgery

Length of Stay in Hospital After Transplant Surgery			
Parameter	Estimate	Odds Ratio	P-value
Intercept	-2.6391		
Walked less than 207 meters		1.00 (Referent group)	
Walked 207 meters and more		4.99+	0.0101
+ 6 observations were deleted due to missing values for the response			

Exploratory Research Question 3: Do lung transplant recipients who did not engage in both preoperative pulmonary rehabilitation and SMWD differ on hospital admissions from those who engaged in at least one or both of the preoperative behaviors?

There were three outcomes examined in this research question. The first outcome examined transplant recipients who engaged in preoperative pulmonary rehabilitation or engaged in a SWMD greater than or equal to 207 meters. The second outcome examined transplant recipients who engaged in preoperative pulmonary rehabilitation and engaged in a SMWD was greater than or equal to 207 meters. The third outcome, the referent group, examined transplant recipients who did not engage in preoperative pulmonary rehabilitation and engaged in SMWD less than 207 meters.

Table 4.6, we reject the null hypothesis. Lung transplant recipients who did not engage in both preoperative pulmonary rehabilitation and 6MWD do not differ on hospital admissions from those who engaged in at least one or both of the preoperative behaviors.

Transplant recipients who participated in preoperative pulmonary rehabilitation or whose 6MWD was greater than or equal to 207 meters have 3.10 times of odds of being readmitted in the first 90 days post-transplant compared to transplant recipients who did not participate in preoperative rehabilitation and SMWD less than 207 meters.

Transplant recipients who participated in both preoperative pulmonary rehabilitation and whose 6MWD was greater than or equal to 207 meters have 3.72 times the odds of being readmitted in the first 90 days post-transplant compared to transplant recipients who did not participate in preoperative rehabilitation and SMWD less than 2-7 meters.

Table 4.6 Summary of Logistic Regressions Analysis of the Association of the Effect of Variable Total Number of Preoperative Behaviors Rehabilitation on Transplant Recipients Readmissions in the First 90 Days Post-transplant

Readmission in First 90 Days Post-Transplant			
Parameter	Estimate	Odds Ratio	P-value
Intercept	-0.6286		
Did not participation in preoperative pulmonary rehabilitation and SWMD less than 207 meters		1.00 Referent group	
Participated in preoperative pulmonary rehabilitation or SMWD was greater than or equal to 207 meters		3.10	0.0159
Participated in preoperative pulmonary rehabilitation and SMWD was greater than or equal to 207 meters		3.72	0.0037

There is no difference in the number of post-transplant readmissions in the first 90 days post-transplant between those who participated in preoperative pulmonary rehabilitation or whose 6MWD was greater than or equal to 207 meters compared to those who did not participate in pulmonary rehabilitation and whose SMWD was less than 207 meters (Table 4.7); we fail to reject the null hypothesis.

Table 4.7 we fail to reject the null hypothesis. There is no difference in the number of post-transplant readmissions in the first 90 days between those who participated in preoperative pulmonary rehabilitation and whose 6MWD was greater than or equal to 207 meters compared to those who did not participate in pulmonary rehabilitation and whose SMWD was less than 207 meters.

Table 4.7 Summary of Logistic Regressions Analysis of the Association of the Effect of Variable Total number of preoperative behaviors on the Number of Post-transplant Readmissions in the first 90 days

Number of Post-Transplant Readmissions in First 90 Days			
Parameter	Estimate	Odds Ratio	P-value
Intercept	1.5581		
Did not participation in preoperative pulmonary rehabilitation and SWMD less than 207 meters		1.00 Referent group	
Participated in preoperative pulmonary rehabilitation or SMWD was greater than or equal to 207 meters		0.55	0.2809
Participated in preoperative pulmonary rehabilitation and SMWD was greater than or equal to 207 meters		0.50	0.1916

In Table 4.8, we fail to reject the null hypothesis; there is no difference between recipients who participated in preoperative pulmonary rehabilitation or who 6MWD was greater

than or equal to 207 meters compare to transplant recipients who did not participate in preoperative pulmonary rehabilitation or complete a 6MWD.

However, transplant recipients who participated in preoperative pulmonary rehabilitation and whose 6MWD was greater than or equal to 207 meters had 2.34 times the odd of having a length of stay of 12 days or less after transplant surgery, so we reject the null hypothesis.

Table 4.8 Summary of Logistic Regression Analysis of the Association of the Variable Total number of preoperative behaviors on Length of Stay in the Hospital after Transplant Surgery

Length of Stay in the Hospital After Transplant		
Parameter	Odds Ratio	P-value
Did not participation in preoperative pulmonary rehabilitation or complete a 6MWD	1.00 Referent group	
Participated in preoperative pulmonary rehabilitation or SMWD was greater than or equal to 207 meters	1.82	0.1202
Participated in preoperative pulmonary rehabilitation and SMWD was greater than or equal to 207 meters	2.34	0.0222

Chapter V
Discussion and Conclusion

The findings of the study did and did not support the study's original research questions and hypotheses.

The first research question related to the association between participation in preoperative pulmonary rehabilitation and readmissions in the first 90 days post-transplant yield unusual findings. The results of regressions analysis showed a significant association between recipients' who participated in preoperative pulmonary rehabilitation and readmission in the first 90 days post-transplant.

The second research question's focus was on the association between preoperative pulmonary rehabilitation and number of hospital admissions in the first 90 days post-transplant. As with the results showed recipients who participated in preoperative pulmonary rehabilitation were more likely to have more than two hospital readmissions compared to those who did not participate in preoperative pulmonary rehabilitation. The results of this association were not statistically significant.

The next research question focused on recipients 6MWD and length of stay in the hospital. The results show an association between recipients' who participate in preoperative pulmonary rehabilitation or whose 6MWD was greater than or equal to 207 meters and recipients who participated in pulmonary rehabilitation and whose 6MWD was greater than 207 meters found that there was an association of readmission in the first 90 days post-transplant.

The number of preoperative behaviors research questions results was a summary of all previous behaviors tested in other research questions. The results of this research question yielded unexpected results. Recipients who participated in preoperative pulmonary rehabilitation and/or had a 6MWD greater than or equal to 207 meters were more likely to be admitted in the first 90 days post-transplant.

Preoperative pulmonary rehabilitation is believed to be beneficial or have an almost "protective" effect post-transplant. Conversely, the results showed transplant recipients who participated in pulmonary rehabilitation and/or had a 6MWD greater than or equal to 207 meters were readmitted in the first 90 days. We assessed the other baseline covariates for potential answers to why this association may have occurred, but further analysis of the covariates did not

present additional findings. We do, however, have a theory and plausible explanation for the observed observations.

Based on standard clinical practice and observations at Emory University, plausible explanations for these findings are as follows. It is possible that transplant recipients who remain actively engaged while waitlisted tend to be more proactive in their post-transplant care. Observations of these patients indicate that they are more likely to contact the transplant team when they have a medical concern or issue. Since the greatest risk of mortality for transplant recipients is the first year post-transplant, the Emory transplant team is aggressive in ensuring recipients are healthy and very cautious when recipients show signs of illness. When the proactive transplant recipient who is less than 90 days post-transplant calls with a medical illness, the transplant teams will more than likely admit the transplant recipient. These explanations are based upon experiences of the researchers and therefore to substantiate and test this theory. A study is needed with larger sample size to understand the results better.

There was an association between a recipient's 6MWD (greater than or equal to 207 meters) and length of stay of 12 days or less. The results of logistic regression analysis among recipients' who participate in preoperative pulmonary rehabilitation or whose 6MWD greater than or equal to 207 meters and recipients who participated in pulmonary rehabilitation and whose 6MWD was greater than 207 meters found that there was an association of readmission in the first 90 days post-transplant. Participation in preoperative pulmonary rehabilitation and 6MWD of greater than or equal to 207 meters was associated with a length of stay of 12 days or less in the hospital after transplant surgery. This finding supports the data of previous research studies of the importance of pulmonary rehabilitation of increasing 6MWD. This finding also illustrates the importance of both participation in preoperative pulmonary rehabilitation and 6MWD on transplant recipients outcomes.

Some results in the present study were not statistically significance, however may have practical significance on recipient outcomes. Recipients who participated in preoperative pulmonary rehabilitation or whose 6MWD was greater than or equal to 207 meters were 1.82 times more likely to be discharged in 12 days or less than those who did not participate in preoperative pulmonary rehabilitation or complete a 6MWD. Though this finding was not statistically significant, it is possible that is still has relevance, and further test with larger sample size is needed.

The outcomes were assessed for potential confounding. There was an association between age and length of stay after transplant. When logistic regression was used to adjust for confounding, the odds ratio increased from 4.99 to 5.10, and the p-value changed from 0.0101 to 0.0093.Since the adjusted odds ratio differed from the crudes odd ratio by less than 10%, there was no confounding by the covariate age. No further confounding was found between outcomes and other covariates.

There are a very limited number of studies to which the findings in this study could be compared. Research studies on the outcomes of preoperative pulmonary rehabilitation are focused on the physiological outcomes mainly in non-transplant recipients. Rochester (2008) physiological benefits of preoperative rehabilitation in the post-transplant phase. Rochester states preoperative pulmonary rehabilitation will reduce minute ventilation at comparable workloads, restore normal or near-normal lung function and gas exchange and elimination of substantial ventilatory limitation to exercise. Improvement in these respiratory physiological functions may enable the lung transplant recipient to exercise at higher intensities and achieve greater gains in aerobic and exercise fitness. Rochester also states it is not known whether preoperative pulmonary rehabilitation increases survival to surgery, increases a recipients' tolerance of surgery, reduces post-surgical complications or improves post-surgical outcomes.

Six-minute walk distance (6MWD) research studies aims are to assess the benefits of interventions on the increase or decrease in 6MWD. Other studies on 6MWD focus on 6MWD predicting survival or indicating transplant candidates prognosis. Martinu et al. conducted an extensive large prospective two-center study. The cohort for the study was patients listed for lung transplantation. The researchers used Cox proportional hazard model to determine the importance of 6MWD in predicting the candidates' survival. The results of the study revealed a 50% decrease in mortality for every 500 feet (152.4m) increase in 6MWD.

Strengths

The strengths of the study are the finding of the importance of 6MWD of the hospital outcomes. The finding supports the importance of recipients participation in preoperative pulmonary rehabilitation to achieve better postsurgical outcomes.

Limitations

The lack of associations in the number of readmissions may have been due to smaller sample size and insufficient power in the study design to detect differences at the $p<.05$ level. . The total sample size was only 207 transplant recipients. The male Caucasian population was the largest population in the study compared to females and other ethnic races.

The referent group used in the study was not a true control group. In healthcare, it is unethical to withhold a treatment that may be beneficial for a patient, so the referent group used was transplant recipients who decided not to participate in preoperative pulmonary rehabilitation. The data collected on transplant recipients' participation in preoperative pulmonary rehabilitation was obtained by chart abstraction. The transplant recipients' participation in preoperative rehabilitation was verified by only one person. In order to decrease potential misclassification, the recipients' participation in pre-operative rehabilitation should be verified by someone else. Six values for recipients 6MWD were missing. The values were unable to be located during chart abstraction. The six missing values did not affect the normality of 6MWD variable. When assessed for skewness, 6MWD was normal (not skewed to the left or the right).

Future Study

Studies are needed that explain the benefits of preoperative pulmonary rehabilitation on post-transplant outcomes. Previous research studies regarding preoperative pulmonary rehabilitation primarily focused on the psychological benefits of preoperative pulmonary rehabilitation. Research needs to be done to show the effects of pre-operative pulmonary rehabilitation on decreasing surgical complications, surgical outcomes, and hospital outcomes (i.e. time on the mechanical ventilator and number of admissions). This study could be used as a baseline for future studies. The next study to assess the benefits of preoperative pulmonary rehabilitation on post-transplant outcomes would ideally be a prospective study design. A prospective cohort study with a larger sample size that would occur in transplant center where preoperative pulmonary rehabilitation was still optional. The researchers would follow the transplant recipients from the time they are listed for lung transplant until they are one year post-transplant. The researchers would compare the hospital outcomes investigated in this study at three months, six months, nine months, and one year post-transplant. A study structured with four follow up periods would provide the transplant research community with data on the

importance of preoperative pulmonary rehabilitation on hospital outcomes during the first year post-transplant when the chance of survival is low.

Conclusion

In the first year post-transplant 78% of the patients survive. There are general risk for any major surgery including lung transplant. There are increased risk of pulmonary postoperative complications for the following risk factors: upper abdominal and thoracic surgery, surgery greater than 3 hours, underlying chronic pulmonary disease, and history of smoking, age greater than 60, obesity, and poor exercise tolerance. Transplant candidates recipients have at least 5 to 7 of the risk factors listed which puts them at a high risk for pulmonary postoperative complications. Based on this list of risk factors it is vital transplant recipients have an understanding of the importance perioperative pulmonary rehabilitation plays in their post-transplant hospital outcomes.

The present analysis examined the relationship between preoperative rehabilitation, 6MWD and hospital outcomes among transplant recipients. The association between 6MWD and length of stay has beneficial outcomes for the recipient and healthcare. Recipients with a 6MWD greater than or equal to 207 meters and who participated in preoperative pulmonary rehabilitation had a decreased length of stay in the hospital. The average cost per day for an inpatient stay in the state of Georgia averages $1605 per a day. The average length of stay for transplant recipients averages 7 to 14 days after transplant. A transplant recipient who participated in pre-operative pulmonary rehabilitation and whose 6MWD was greater than or equal to 207 meters length of stay was less than or equal to 12 days. This averages about $3210 less in hospital costs. This study supports previous literature on the importance of pulmonary rehabilitation, but also suggests the relationship between pulmonary rehabilitation and readmissions is complex.

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