Skeletal Muscle Dysfunction in Lung Transplant Patients

by

Dmitry Rozenberg

A thesis submitted in conformity with the requirements
for the degree of Doctor in Philosophy

Institute of Medical Science
University of Toronto

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ABSTRACT:

Lung transplantation improves health-related quality of life (HRQL), daily function and survival for individuals with advanced lung disease. However, lung transplantation is now offered to older and more complex patients who are at a higher risk of skeletal muscle dysfunction; the implications of which remain uncertain. The overall objective was to assess how elements of muscle dysfunction (mass, strength and function) are associated with pre- and post-transplant physical function, HRQL, and clinical outcomes. We hypothesized that pre-transplant skeletal muscle dysfunction would be associated with impairments in pre-transplant HRQL, activities of daily-living (ADL), six-minute walk distance (6MWD), and worse post-transplant functional recovery with increased pre- and post-transplant mortality. Three studies targeting the pre- and post-transplant periods were undertaken. In study 1, a novel method of muscle mass quantification using computed tomography (CT) was retrospectively evaluated in 527 lung transplant candidates. CT muscle cross-sectional area in transplant candidates was 10% lower than age and sex-matched controls and independently associated with 6MWD, strength training volumes and post-transplant hospital length of stay (LOS), but no association was observed with pre- or post-transplant mortality. In study 2, muscle mass assessed with bio-electrical impedance, quadriceps strength, and function (Short Physical Performance Battery, SPPB) were prospectively evaluated in 50 lung transplant candidates. Quadriceps strength and SPPB were associated with pre-transplant HRQL, ADL, and 6MWD. Number of muscle deficits (mass,
strength and/or function) was directly correlated with post-transplant hospital LOS, but not with delisting/mortality or post-transplant 6MWD. In study 3, the impact of pre-transplant skeletal muscle mass and function on post-transplant functional independence, HRQL, and 6MWD was evaluated in a select group of lung transplant recipients with prolonged mechanical ventilation (≥7 days). Age and intensive care unit (ICU) LOS were the only determinants of early post-transplant functional recovery, highlighting the importance of ICU-acquired morbidity. In summary, these studies demonstrate that skeletal muscle function is an important marker of pre-transplant daily function and predicts post-transplant hospital LOS, but is not a significant predictor of post-transplant function or mortality. Future studies should examine whether targeted rehabilitation strategies in the pre-transplant period may improve daily function and early post-transplant outcomes.
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STATEMENT OF CONTRIBUTIONS:

This thesis is presented in manuscript format and consists of six chapters. Chapter 1 is a summary of the main problem and a review of the literature. My previously published systematic review on this topic was utilized to help guide the literature review, overall objective and hypothesis for this thesis. Chapter 2 provides a detailed framework of the thesis objectives and hypotheses. Chapters 3 to 5 comprise three separate manuscripts of original investigation, two of which have been published. Chapter 6 provides an overall discussion for the thesis and outlines future research directions arising from this work.

Summary of Contributions Related to Thesis:


Contributions:

Contributed to conception and design (DR, LG.S, SM), selection of articles (DR, LW, SM), analysis or interpretation of data (DR, LW, LG.S, SM), drafted the article (DR) and revised the article critically for important intellectual content (DR, LW, LG.S, SM).


Contributions:

DR, LG.S, MH, RG, and SM made substantial contributions to the conception and design of the work. DR wrote the first draft of the manuscript and SM, MH, RG, HS, NA.C, PM, and LG.S revised the manuscript for important intellectual content. All authors made substantial contributions to the analysis or interpretation of data.

**Contributions:**
DR, LG.S, MH, RG, LW, NA.C and SM made substantial contributions to the conception and design of the work. DR wrote the first draft of the manuscript and LG.S, MH, RG, LW, NA.C, and SM revised the manuscript for important intellectual content. All authors made substantial contributions to the analysis or interpretation of data.


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ABBREVIATIONS:

ADL = Activities of Daily Living
BIA = Bio-electrical Impedance
BMI = Body Mass Index
CI = Confidence Interval
COPD = Chronic Obstructive Pulmonary Disease
CSA = Cross-sectional Area
CT = Computed Tomography
D-XA = Dual Energy X-ray Absorptiometry
ECLS = Extra-corporeal Life Support
ECMO = Extra-corporeal Membrane Oxygenation
FIM = Functional Independence Measure
FFM = Fat free mass
FFMI = Fat-free mass index
HRQL = Health-related Quality of Life
ICU = Intensive Care Unit
ICUAW = Intensive Care Unit Acquired Weakness
ILD = Interstitial Lung Disease
LAS = Lung Allocation Score
LCADL = London Chest Activity of Daily Living
MIP = Maximal Inspiratory Pressure
MEP = Maximal Expiratory Pressure
MRC = Medical Research Council
MV = Mechanical Ventilation
PASE = Physical Activity Scale for the Elderly
PCS  =  Physical Component Score
PGD  =  Primary Graft Dysfunction
SD   =  Standard Deviation
SE   =  Standard Error
SF-36 = Short-Form 36
SPPB = Short Physical Performance Battery
6MWD = Six-minute Walk Distance
6MWT = Six-Minute Walk Test
SGRQ = St. George's Respiratory Questionnaire
CHAPTER 1

Literature Review and Introduction

1.0 Statement of the Problem

Chronic lung disease is a significant problem world-wide. It is estimated that hundreds of millions of people are living with significant respiratory symptoms and approximately four million people die from their chronic lung disease each year.\textsuperscript{1} Globally, chronic obstructive pulmonary disease (COPD) is projected to be the third leading cause of morbidity and mortality by 2020.\textsuperscript{2} Similarly, interstitial lung disease (ILD) is one of the most common conditions referred for lung transplantation.\textsuperscript{3,4} Pulmonary arterial hypertension,\textsuperscript{5} cystic fibrosis,\textsuperscript{6} and bronchiectasis\textsuperscript{7} also account for a significant degree of morbidity and mortality. For many of these chronic lung diseases, lung transplantation remains the only life-saving treatment strategy.\textsuperscript{8}

Chronic lung disease is generally associated with a number of co-morbidities that can lead to increased morbidity and mortality.\textsuperscript{9-11} A common extra-pulmonary manifestation of chronic lung disease is skeletal muscle dysfunction.\textsuperscript{12,13} Skeletal muscle dysfunction is an encompassing term that refers to the structural and functional changes observed in skeletal muscles.\textsuperscript{14} The evaluation of skeletal muscle dysfunction can span the spectrum from alterations in bioenergetics, contractility and structural integrity at the muscle fiber level to non-invasive measures of muscle mass, strength and performance of functional activities.\textsuperscript{14,15} To date, the majority of research in the area of skeletal muscle dysfunction in chronic lung disease has focused on patients with COPD, but there is increasing recognition of the importance of this extra-parenchymal manifestation in other disease states such as ILD,\textsuperscript{12} pulmonary hypertension,\textsuperscript{16} cystic fibrosis,\textsuperscript{17} bronchiectasis\textsuperscript{18} and pre- and post-thoracic surgery, including lung transplantation.\textsuperscript{19}
Skeletal muscle dysfunction is prevalent in advanced lung disease. In COPD patients, elements of skeletal muscle dysfunction including impaired muscle mass, strength, and physical performance have been described. Decreased skeletal muscle strength has been observed in other chronic respiratory conditions such as pulmonary fibrosis and cystic fibrosis. In COPD, skeletal muscle dysfunction has been associated with reduced physical activity, exercise capacity, health-related quality of life (HRQL), hospital length of stay and survival. Important contributing factors to skeletal muscle dysfunction include physical inactivity, deconditioning, hypoxemia, malnutrition, and use of corticosteroids. In other chronic lung disease states, less is known about the clinical implications of skeletal muscle dysfunction.

Lung transplantation is a life-saving procedure for many individuals with advanced lung disease. These patients undergo a comprehensive, multi-disciplinary evaluation of their medical and psycho-social issues to determine their risks and benefits with lung transplantation. Based on the international guidelines for selection of lung transplant candidates, physical deconditioning is often emphasized as an absolute contraindication for surgery. Routine physical measures in the pre-transplant period include assessment of body mass index (BMI), six-minute walk distance (6MWD), pulmonary function and oxygen requirements. It is well-established that exercise capacity pre-transplant is associated with increased pre and post-transplant mortality. Similarly, lung transplant candidates who are underweight (BMI < 18.5 kg/m²) or obese (BMI ≥ 30 kg/m²) have been observed to have increased morbidity and mortality in the post-transplant period.

Skeletal muscle mass and strength are significantly impaired in the pre- and post-transplant period. However, the clinical implications of skeletal muscle dysfunction (muscle mass, strength and function) have not been well described in lung transplantation with respect to its association with HRQL, exercise capacity, activities of daily living (ADL), and pre- and post-
transplant clinical outcomes. A better understanding of skeletal muscle dysfunction and its implications in the pre- and post-transplant period could potentially help with candidate selection and rehabilitation strategies.

This thesis aims to characterize individual elements of skeletal muscle dysfunction (muscle mass, strength and physical performance) in lung transplant candidates and assess their association with pre- and post-transplant physical function, HRQL, and clinical outcomes. We hypothesized that skeletal muscle dysfunction will independently be associated with pre-transplant physical function and HRQL and with early post-transplant outcomes. This will be evaluated through three complementary studies in lung transplant candidates and recipients from a single transplant center. A detailed thesis framework is provided in Chapter 2.

The present introductory chapter will be comprised of five main sections. Section 1 will review the current state of lung transplantation worldwide and outcomes commonly measured in lung transplantation. Section 2 will outline the pathogenesis, diagnosis, and clinical implications of skeletal muscle dysfunction in chronic lung disease, lung transplant candidates and recipients. Section 3 will highlight the prognostic utility of pre-operative measures such as aerobic capacity and physical performance tests with major surgery and solid-organ transplantation. Section 4 will outline the implications of prolonged mechanical ventilation, critical care and hospital length of stay in patients undergoing major surgical procedures with a focus on lung transplantation. Section 5 will review the rehabilitation strategies utilized in the post-transplant period in lung transplant recipients.

1.1 Overview of Lung Transplantation

Lung transplantation is a life-saving procedure for many patients with advanced lung disease. There have been many medical and surgical advances over the last 30 years since the first successful lung transplantation, with significant improvement in survival. The number of lung
transplants performed annually continues to grow internationally. The latest report from the International Society of Heart and Lung Transplant (ISHLT) Registry reported close to 4000 adult lung transplants performed in 2014 compared to approximately 2100 transplants in 2004. Based on the ISHLT registry data, the median survival after lung transplantation was 5.7 years. In addition to survival, lung transplantation confers a significant benefit with respect to HRQL and functional capacity.

The selection of lung transplant candidates has evolved over time to include patients who are older, have increased co-morbidities, and potentially greater functional limitations. Based on the recent ISHLT guidelines for selection of lung transplant candidates, a number of relative contraindications were updated but the selection criteria remains fairly broad with the greatest emphasis placed on potential life years gained. Generally, a comprehensive risk assessment is recommended that includes medical comorbidities, functional status, psychosocial elements and life expectancy with transplant. The ISHLT guidelines recommend consideration of transplant for severe lung disease when medical therapy is ineffective, mortality without transplantation is greater than 50% at two years, there is a reasonable chance of survival beyond 90 days with transplant (> 80%), there is appropriate psychosocial support, and absence of significant extra-parenchymal comorbidity that would limit five year survival post-transplant.

With improvement in survival, lung transplantation is no longer restricted to the youngest and fittest patients. The median age of transplant recipients has gradually increased from 43 to 56 years from 1990 to 2011. Furthermore, the adoption of the Lung Allocation Score (LAS) in the United States and Europe, which prioritizes patients with a high expected pre-transplant mortality, has increased the average age and complexity of transplant recipients. As a result of surgical advances, extra-corporeal membrane oxygenation (ECMO) is also gaining recognition as a potential viable option for critically ill lung transplant candidates.
provides both cardiac and respiratory support through an external circuit to support patients with cardiac or respiratory failure. Early outcomes with ECMO were generally poor with about 40% one year survival, partly attributed to immobilization leading to critical care myopathy. In the last several years, the outcomes with awake ECMO strategies that allow mobilization due to reduced sedation have been favorable with one year survival being greater than 80%. Thus, critically ill patients admitted to the ICU are more likely to be prioritized for lung transplantation, but are at greater risk of pre-transplant mortality and post-transplant morbidity and mortality.

The sections that follow in this chapter describe the survival benefit of lung transplantation and several prognostic factors. A detailed overview of the benefits in HRQL, ADL, exercise capacity and physical activity will be summarized. The relationship between these functional measures and skeletal muscle will be highlighted.

### 1.1.2 Survival with Lung Transplantation:

Survival in the first-year post-transplant has significantly improved over the last era compared to eras preceding 2000, with unadjusted survival in the first year post-transplant being 80%. In the early post-transplant period, infection is the leading cause of morbidity and mortality in lung transplant recipients. Infection can occur as a primary process or in association with surgical complications (i.e. bleeding, airway complications) or primary graft dysfunction.

Beyond the first year, chronic allograft dysfunction is a significant risk factor for respiratory infections and mortality. The risk of developing chronic allograft dysfunction is high with the incidence approaching about 50 percent at 5 years after lung transplantation. Chronic allograft dysfunction is also associated with significant functional decline and impairments in HRQL. Unfortunately, there are no available treatment strategies for chronic allograft dysfunction and this remains a major hurdle limiting long-term survival.
1.1.3 Risk Factors Associated with Lung Transplant Mortality

Recipient characteristics such as age, lung diagnosis, body composition, and disease severity have been described to be important determinants of mortality as described below.\textsuperscript{25,46}

Age:
Lung transplant candidates over the age of 65 years have usually been thought of as having a relative contraindication for lung transplantation. Nevertheless, the number of lung transplant recipients older than 65 years old has increased significantly in the United States approaching about one third of recipients.\textsuperscript{47} Worldwide, a similar proportion of older lung transplant recipients has been observed with about 40 percent being older than 60 years of age.\textsuperscript{30,48} At our center, the proportion of older lung transplant recipients in 2016 was comparable to international data with 61/142 (43\%) being 60 years or older (Toronto Lung Transplant Clinical Database). The unadjusted five-year survival based on the ISHLT registry (1990-2011) for those over the age of 65 years old was 38\%, 46\% for those between 60-65 years old, and 52\% to 57\% across three age categories (50-59, 35-49 and 18-34 years old, respectively).\textsuperscript{30} However, it is important to highlight that these survival differences were not adjusted for type of transplant, era or transplant indication, which are important contributing factors. It is not surprising that older recipients have a shorter actuarial survival than younger patients, but the shorter survival in older recipients is not solely attributable to actuarial differences.\textsuperscript{49} Genao et al. recently demonstrated that the functional trajectory of older lung transplant recipients (≥ 65 years) compared to younger recipients was similar in the first 5 years post-transplant, potentially supporting the benefit of transplantation in older patients.\textsuperscript{50} Furthermore, our group has shown that lung transplant recipients derive a significant HRQL benefit with transplantation, which does not differ significantly for older recipients.\textsuperscript{26}
**Diagnosis:**

The most common indications for adult lung transplantation continue to evolve given worldwide changes in lung allocation practices that have increased the proportion of ILD candidates.\(^8\) This trend can be attributed to more liberal criteria which accepts older lung transplant candidates and the widespread adoption of allocation systems that prioritize transplantation based on disease severity, which favors ILD.\(^8\) Presently, ILD (28%) remains the second most common indication for lung transplantation after COPD (36%) reported to the ISHLT registry.\(^25\) Other common indications for lung transplantation include cystic fibrosis (16%) and pulmonary arterial hypertension (4%). Lung transplant recipients with COPD are known to have the best one-year survival compared to other diagnoses such as ILD and pulmonary arterial hypertension that have the lowest one-year survival.\(^25\) ILD has also been associated with the lowest 10-year survival with long term survival greatest for patients with pulmonary arterial hypertension and cystic fibrosis. Unfortunately, ILD and in particular idiopathic pulmonary fibrosis, is associated with the worst prognosis among the common indications for lung transplantation.\(^8\)

**Body Composition:**

The association between pre-transplant BMI and post-transplant outcomes has been investigated in several studies. A number of single center studies have shown that pre-transplant obesity (BMI ≥ 30 kg/m\(^2\)) was associated with increased morbidity and mortality post-transplantation.\(^51\)\(^-\)\(^53\) However, no association between increased BMI (30-34.9 kg/m\(^2\)) and one year mortality was observed in over 9000 lung transplant candidates who underwent lung transplantation in the United States from 2005-2011, suggesting that it might not be the best marker of body composition.\(^54\) Thus, the updated ISHLT guidelines recommend that obesity (BMI ≥ 30 kg/m\(^2\)) be considered a relative contraindication for transplantation.\(^8\) Similarly, the role of low BMI (< 18.5 kg/m\(^2\)) and risk of mortality has been conflicting with
studies showing increased risk\textsuperscript{53,54} whereas other studies did not find a significant relationship.\textsuperscript{53,55} In a recent systematic review and meta-analysis of 13 studies, 7 of which were included in the meta-analysis, there was an increased risk of mortality in lung transplant candidates who were underweight (BMI < 18.5 kg/m\textsuperscript{2}; RR: 1.36 95\% CI 1.11-1.66) or obese (BMI $\geq$ 30 kg/m\textsuperscript{2}; RR: 1.90 95\% CI 1.45-2.56).\textsuperscript{24}

A potential reason for the variability in results with BMI and transplant outcomes is the fact that BMI is a poor measure of body composition. Body mass index has been shown to misclassify greater than one-third of healthy adults as non-obese when in fact their adipose levels were significantly increased with gold standard tests of body composition such as Dual-energy X-ray Absorptiometry (D-XA).\textsuperscript{56} Similarly in lung transplant candidates, Singer et al. observed that BMI had a very poor sensitivity in discriminating clinically important adipose tissues levels and sarcopenia (i.e. low muscle mass) measured with D-XA.\textsuperscript{54} Taken together, these results suggest that BMI is helpful clinically but needs to be interpreted with caution given the unmeasured loss of skeletal muscle mass and potential for increased visceral fat distribution, which has been shown to be an important predictor of mortality in the general population and in other solid organ transplant recipients.\textsuperscript{57,58}

**Lung Allocation Score and Canadian Listing Status:**

One system that has been adopted in the United States and Europe is the lung allocation score (LAS).\textsuperscript{59} The LAS is calculated using statistical modeling to estimate the risk of one year mortality on the transplant list and the survival benefit with transplantation.\textsuperscript{60} A number of demographic, physiological and clinical parameters are included: such as age, BMI, diagnosis, presence of diabetes, pulmonary function, pulmonary pressures, 6MWD, oxygen requirements, renal function and need for mechanical ventilation (MV) pre-transplant.\textsuperscript{60} A score from 0 to 100 is derived based on statistical modeling and higher scores represent increased transplant urgency and greater likelihood that a patient would derive early survival
benefit from lung transplantation. Since the implementation of the LAS in the United States, there has been a significant reduction in waitlist mortality, increased number of transplants, and a higher proportion of transplants performed for older recipients and those with ILD. Since the implementation of the LAS in the United States, there has been a significant reduction in waitlist mortality, increased number of transplants, and a higher proportion of transplants performed for older recipients and those with ILD.31

In Canada, we utilize the listing transplant urgency which consists of two statuses: Status 1 (stable), and 2 (deteriorating). Our program has added a “Rapidly Deteriorating” status to indicate patients with a very high mortality risk pre-transplant. The Canadian listing urgency status is a subjective determination of disease severity predictive of waiting list survival. Whereas both the Canadian listing and the LAS attempt to balance the need for lung transplantation and ability to survive the procedure, neither system considers important patient reported outcomes such as HRQL or ADL in the pre-transplant period. In fact, the LAS has been observed to be poorly associated with HRQL in a cohort of lung transplant candidates in Japan and in our own patients. This is an important consideration as many candidates undergo lung transplantation to derive benefits in HRQL and physical function, not solely survival.

1.1.4 Health Related Quality of Life:

Health related quality of life is significantly improved with lung transplantation compared to pre-transplant values. A number of generic and disease specific instruments have been utilized in lung transplantation to study HRQL. The Short-Form 36 (SF-36) is the most commonly used generic HRQL instrument in lung transplantation. It comprises eight health domains and two summary scores, physical and mental component scores (PCS and MCS), with higher scores denoting better HRQL. Each domain and summary score ranges from 0 to 100 with a standard deviation of 10, and a population normative score of 50, for the most recent version of the SF-36 (version 2). A 5-point difference in the PCS or MCS is considered clinically significant. The most common respiratory-specific HRQL instrument is
the St. George's Respiratory Questionnaire (SGRQ). The SGRQ was originally developed to be used in COPD patients, but has been expanded to other respiratory disease states. The SGRQ consists of three domains (symptoms, activity and impacts) and total score. The SGRQ has a range of scores from 0 to 100 with higher scores signifying worse HRQL. A minimally important difference for the SGRQ has been described as 4 points.

Health-related quality of life is significantly impaired in lung transplant candidates on both generic and disease specific instruments and declines during the waitlist period. In a prospective cohort study from our center of 430 lung transplant candidates, the mean SF-36 PCS score steadily declined leading up to transplant by about 15 points over a three year period from a baseline score of 40 points. Similarly, the mean SGRQ total score was 45 at initial assessment with greater impairments at the time closest to transplant (about a 20-point worsening). Furthermore, HRQL impairments tend to be more pronounced in the physical function domains compared to those of mental health pre-transplant.

Lung transplant recipients experience significant improvements in the physical function, physical role and general health domains in the first 6 months post-transplant with less improvement observed beyond six-months. The improvements observed at 6 months post-transplant were greater than 20 points in physical functioning and general health domains. There is limited improvement in the mental HRQL domains with transplant given the possibility of a ceiling effect, as these values have been comparable to population normative values pre-transplant. With lung transplantation, there are also large and significant improvements in the respiratory specific HRQL measures. Kugler et al. observed a significant gradual improvement (ranging from 15-26 on the total SGRQ domain) first-year post-transplant. Similarly, Singer et al from our center observed a dramatic improvement in the SGRQ total domain of 47 points in a mixed model adjusted for age, sex, diagnosis and time post-transplant.
Several predictors of post-transplant HRQL have been described. The large observational study (n=430) from our center demonstrated no clinically significant associations between HRQL and age at the time of lung transplantation; however, ILD patients were noted to derive less HRQL benefit than cystic fibrosis patients.26 With respect to gender differences, women have been described to have less HRQL benefit with transplantation possibly due to increased post-operative symptoms, but this has only been observed in a few studies.83,84 Other predictors of post-transplant HRQL include chronic allograft dysfunction, side-effects of immuno-suppression, and pain.44,45,85

### 1.1.5 Functional Outcomes

**Activities of Daily Living:**

Patients with advanced lung disease have decreased ability to perform ADL, which are essential for every day well-being and independence.86 Activities of daily living can be captured with the use of questionnaires, which provide information on the current functional level.87 They can be characterized into three main categories based on the description by De Vriendt et al.88 Basic ADL include behaviours such as bathing, dressing and self-grooming. Instrumental ADL include daily tasks such as various house chores, shopping and financial responsibilities. Advanced ADL are more complex activities that are often driven by personal cultural experiences and motivation, but go beyond activities required for personal independence such as working and hobbies.88,89

The primary limitation in carrying out ADL in chronic lung disease is dyspnea and individuals with advanced disease often decrease their ADL and/or require assistance from a caregiver. The degree of disability experienced by those living with advanced lung disease is not well captured by measures of pulmonary function, thus standardized disability questionnaires can be very helpful in assessing disease impact.90,91 The inability to perform ADL due to dyspnea
can often impair self-efficacy and HRQL. More importantly, limitations in ADL have been associated with increased mortality in COPD.

In lung transplant candidates, participation in ADL has not been well characterized. In a study by Muller et al, the London Chest Activity of Daily Living (LCADL) scale was utilized in lung transplant candidates. This scale assesses the impact of dyspnea on carrying out ADL in four domains: self-care, house-hold activities, physical and leisure activity. Scores on the LCADL were associated with exercise capacity pre-transplant, with the majority reporting their ADL limitations due to dyspnea. Singer et al. recently established a 15-item Lung Transplant Valued Life Activities disability scale that has been shown to be valid and responsive to change. These two scales are promising in the field of lung transplantation as previous assessments of disability were quite limited focusing mainly on basic ADL or whether someone was employed. To our knowledge, an assessment of ADL in the early (< 3 months) or late post-transplant period has not been previously described and could help provide greater insight into associations with HRQL and function.

The importance of independence with basic functioning in the pre-transplant period was highlighted in a study of over 7800 lung transplant candidates utilizing data from the United Network for Organ Sharing database. Greater pre-operative functional independence measured by Karnofsky Performance Status Score was associated with lower mortality at one year. Only about 12% required no assistance, whereas the remaining lung transplant candidates required complete (30%) or partial assistance (58%) pre-operatively. In addition to pre-transplant functional independence, other factors such as older age (> 60 years), pre-transplant ICU admission with requirement for ECMO or mechanical ventilation were associated with an increased one year mortality. Despite the case complexity in transplant recipients, the Karnofsky Performance Score has been shown to be an independent predictor of outcomes in solid-organ abdominal transplantation and lung re-transplantation.
**Exercise Capacity:**

The 6MWT is a sub-maximal exercise test which is the most common functional assessment of exercise capacity in advanced lung disease and lung transplant candidates.\(^{102}\) It was originally developed to be used in COPD patients, but has been applied broadly in other chronic respiratory conditions. The 6MWT has been shown to be a good marker of disease severity, functional impairment, and aerobic capacity in lung transplant candidates,\(^{103}\) but has some limitations given the variability observed between tests due to learning effects.\(^{104}\) However, other field walking tests such as incremental and endurance shuttle walk tests, which are externally paced might be more sensitive to assess effects of interventions such as exercise training\(^{105,106}\) or bronchodilator therapy.\(^{107}\) Furthermore, shuttle walk tests are less vulnerable to testing variation (e.g. site or operator).\(^{102}\) However, the 6MWT is commonly used in lung transplantation given its established prognostic value and incorporation into the LAS.\(^{23,108}\)

Most lung transplant candidates achieve less than 400 meters on the 6MWT with a distance of 45-55% predicted.\(^{22,109}\) In the largest study to-date of over 9500 lung transplant candidates, the median 6MWD was 240 m IQR [137-330].\(^{23}\) The 6MWD has been observed to be relatively preserved during the pre-transplant period (decline of 15 meters) in a select group of lung transplant candidates from our center participating in outpatient pulmonary rehabilitation with available rehabilitation data.\(^{110}\)

Low 6MWD has been shown to be associated with pre-transplant delisting, mortality\(^{22,111}\) and post-transplant outcomes such as hospital length of stay\(^{110}\) and survival.\(^{23,112}\) A low 6MWD in the pre-transplant period has also been associated with increased risk of discharge to inpatient rehabilitation post-transplant.\(^{113}\) Castleberry et al. demonstrated in over 9500 lung transplant candidates that higher pre-transplant 6MWD was associated with higher peri-operative (30 and 90 day) and one-year survival post-transplant.\(^{23}\) The results from their
study indicate that 6MWD is best incorporated as a continuous variable given no clear
dichotomous cut-offs for survival. The 6MWT provides a global assessment of physical
fitness, which has been described to be an important marker in predicting the physiological
stress response with surgery.\textsuperscript{114,115}

In the post-transplant period, exercise capacity improves to 65-85% of predicted 6MWD within
3 to 4 months post-transplant.\textsuperscript{116,117} Ventilatory limitation is generally not a concern in lung
transplant recipients in the post-transplant period in the absence of complications such as
infection or chronic rejection.\textsuperscript{118} With cardiopulmonary exercise testing, most lung transplant
recipients have oxygen saturations above 90% on room air\textsuperscript{119,120} and the majority report
significant leg fatigue as opposed to dyspnea, as a major factor in stopping their exercise
test.\textsuperscript{121} Recovery in quadriceps strength has been implicated as a key contributor to the post-
transplant walk distance achieved.\textsuperscript{116,122} Thus, skeletal muscle dysfunction plays a critical role
in the exercise limitations observed post-transplant.\textsuperscript{27,121}

**Physical Activity:**

Evaluation of physical activity in the pre-transplant period provides another avenue for
functional assessment. Physical activity levels can be evaluated using questionnaires,
pedometers or accelerometers.\textsuperscript{123} An assessment of physical activity in lung transplant
candidates can also assist with physical activity counselling and establishment of pulmonary
rehabilitation goals.

Lung transplant candidates have been observed to have reduced physical activity levels.\textsuperscript{124,125}
A study from our center showed that lung transplant candidates with ILD had significantly
reduced daily step counts, which were higher on their rehabilitation days.\textsuperscript{125} However, even
on rehabilitation days, the daily step count of 3780 ± 2196 was significantly lower than the
average daily step count of 9500 and 8400 steps per day achieved by healthy Canadian men
and women, respectively.\textsuperscript{126} Similarly, Langer et al demonstrated in 96 lung transplant candidates with COPD and ILD that they were significantly inactive with a total of 2928 ± 1796 steps achieved.\textsuperscript{124} Furthermore, they observed that lung transplant candidates had a lower time walking daily by 23% compared to non-listed COPD patients at their center despite being 12 years younger.\textsuperscript{124} Patients with COPD actually have the lowest daily physically activity levels (5319 steps) compared to other cardiopulmonary populations such as patients with heart failure (7464 steps).\textsuperscript{127}

Based on accelerometer data, Langer et al. also observed that their group of lung transplant candidates spent only about 5% of their waking hours walking (34 ± 19 minutes) with the rest of the time standing (26%) or sitting/lying down (69%).\textsuperscript{124} In comparison, the amount of time spent in sedentary activity (less than 2 metabolic equivalents) for the general North American population has been variable, ranging from 50-69%.\textsuperscript{126,128} Thus, lung transplant candidates spend more time in sedentary activity; however, it is important to highlight that the general North American population is quite sedentary with only 15% achieving the recommended targets of 150 minutes of moderate-vigorous intensity activity per week.\textsuperscript{128}

Physical activity levels have been characterized using the Physical Activity Questionnaire in the Elderly (PASE), which is a validated 12-item self-administered questionnaire measuring the amount of physical activity in the previous one week in those over the age of 65.\textsuperscript{129} Unfortunately, there is no readily available physical activity questionnaire that has routinely been used in advanced lung disease; however, the PASE has been previously validated in COPD patients using accelerometers to predict severe levels of physical inactivity.\textsuperscript{130} From our center, Mendes et al observed that self-reported PASE scores were significantly lower in ILD transplant candidates compared to healthy age and sex matched controls (81 ± 50 vs. 178 ± 120, \(p=0.03\)),\textsuperscript{131} and in fact the levels in these transplant candidates were noted to be comparable to frail community dwelling elderly patients.\textsuperscript{132}
Physical activity levels generally improve post-transplant beyond the first three months; however, are still reduced at the one year mark post-transplant compared to healthy controls. Daily step count and time spent in moderate intensity activity was found to be reduced by 42% and 66%, respectively, compared to controls at the one year mark post-transplant. Physical activity levels one year post-transplant have been shown to be closely associated with exercise capacity, quadriceps strength and HRQL. Rehabilitation in the first 3 months post-transplant has been demonstrated to lead to sustained improvement in physical activity levels in lung transplant recipients at one year post-transplant. However, physical activity levels beyond the first year post-transplant have not been described.

**Skeletal Muscle Dysfunction**

Individual elements of skeletal muscle dysfunction such as muscle mass, strength, and physical performance have been described in lung transplant patients using various non-invasive modalities. Reduced skeletal muscle mass and lower extremity strength are commonly observed in the pre-transplant period with persistence of skeletal muscle dysfunction up to five years post-transplant. Kyle et al. noted in 37 lung transplant patients that low fat-free mass with bio-electrical impedance (BIA) was observed in two-thirds of transplant candidates and seen in one-third of patients two years post-transplant. Similarly, quadriceps strength was impaired in the pre-transplant period (mean range 49-86%) with persistence of quadriceps weakness beyond three-months post-transplant (58-101%) based on a systematic review of 18 lung transplant studies. Bossenbroek et al. demonstrated that the sit-to-stand test, predominantly an assessment of lower extremity strength, was noted to be significantly lower in candidates compared to lung transplant recipients on average 5-years post-transplant (7.7 ± 2.5 versus 10 ± 4.4 repetitions in 30 seconds). Even though there was significant recovery in lower extremity strength and function with the sit-to-stand test, these values were still lower than healthy adults.
One important element of muscle function is endurance, which is the ability of the muscle to sustain repeated contractions. There is evidence in COPD patients that the aerobic profile is significantly impaired with reduction in the size of oxidative muscle fibers (type 1), oxidative enzyme concentration, mitochondrial and capillary density. These changes in the aerobic profile of muscle can contribute to impaired muscle endurance and activity tolerance, as observed in COPD. Lands et al. observed in 19 lung transplant recipients low exercise performance with cycling about 18 months post lung transplantation, partly attributed to reduced leg muscle work capacity (i.e. endurance), independent of any ventilatory or cardiac limitations.

Individual elements of skeletal muscle dysfunction have been shown to be closely associated with physical activity levels and exercise capacity in lung transplant candidates and recipients. Quadriceps strength has moderate correlation with daily steps in lung transplant candidates and recipients (r=0.51-0.66). Quadriceps strength has also been shown to correlate with post-transplant 6MWD (r=0.41) and with peak oxygen uptake (r=0.71) in transplant recipients. In lung transplant candidates, performance on the sit-to-stand test correlated with physical activity levels characterized by daily steps (r=0.45). Thus, skeletal muscle dysfunction has important systemic consequences on physical activity levels and exercise capacity in the pre- and post-transplant periods.

The effects of skeletal muscle dysfunction on patient reported outcomes such as HRQL and ADL in the pre- and post-transplant periods have not been investigated to-date. Skeletal muscle evaluation may provide an additional assessment of daily function which may help elucidate the limitations experienced by lung transplant candidates and recipients. This is an important area of investigation in lung transplant candidates and recipients as skeletal muscle function may prove to be modifiable with exercise training, ultimately affecting HRQL, daily function and transplant outcomes.
1.2: Evaluation of Skeletal Muscle Dysfunction in Chronic Lung Disease and Lung Transplant Patients

Skeletal muscle dysfunction is multi-factorial with several factors described in chronic lung disease and lung transplant recipients. A common contributing factor to skeletal muscle dysfunction in chronic respiratory disease is muscle disuse (i.e. deconditioning) due to physical inactivity. However, there are a myriad of additional factors that need to be considered, including factors common to transplant recipients such as ongoing use of corticosteroids, calcineurin inhibitors, inflammation and oxidative stress.

These factors can affect both the structure and function of skeletal muscle in chronic lung disease and transplant recipients with changes in muscle fiber atrophy and fiber type shift, and through changes in blood vessel capillarization, mitochondrial function and bioenergetics as described in further detail below. Unlike chronic lung disease, the mechanisms underlying skeletal muscle dysfunction in lung transplant recipients have not been well characterized, as highlighted below.

This section presents an overview of the generic and disease specific factors (i.e. those that are related to chronic lung disease and transplant recipients) that may contribute to skeletal muscle dysfunction, summarized in Table 1-1. A discussion that follows reviews non-invasive measurements of skeletal muscle mass, strength and function in chronic lung disease and lung transplantation, including their clinical implications.

1.2.1: Generic and Disease Specific Factors Related to Skeletal Muscle Dysfunction in Chronic Lung Disease and Transplant Recipients

Aging:

Age is known to be a significant factor associated with a decline in skeletal muscle mass and function. Aging is associated with the loss of motor neurons, especially the larger motor units with the higher recruitment thresholds resulting in denervation, and as a consequence
leading to muscle fiber loss, atrophy, and function.\textsuperscript{152,153} The cross-sectional area (CSA) of both type I (oxidative) and type II (glycolytic) fibers has been shown to be reduced in the elderly compared to younger adults; however, the atrophy of fast twitch, glycolytic fibers appears to be preferentially affected with aging.\textsuperscript{154,155} Furthermore, the capacity for motor neurons to reinnervate neighbouring muscle fibers is also significantly impaired with aging.\textsuperscript{156}

Rosenberg was the first to coin the term sarcopenia in 1989, mainly describing age-related muscle mass loss.\textsuperscript{157} However, a recent consensus from the European Working Group on Sarcopenia in the Elderly proposed that the definition of sarcopenia capture loss of strength or physical function in addition to muscle mass loss.\textsuperscript{158} Unfortunately, to-date there has been no well-established definition of sarcopenia in chronic lung disease; however, it is believed that chronic lung disease accentuates many of the processes related to the development of sarcopenia.\textsuperscript{159-161} Given that the age of lung transplant candidates continues to increase, sarcopenia is certainly an important consideration both in the pre- and post-transplant period.

**Muscle Disuse and Physical Inactivity:**

Muscle disuse has been described as an important contributing factor for skeletal muscle dysfunction. Disuse has been associated with muscle atrophy, weakness, decreased muscle fiber cross-sectional area (CSA) and loss of oxidative muscle fibers (Type I) with a preferential shift towards fast twitch muscle fibers (Type II).\textsuperscript{14,162} These changes in turn contribute to loss of muscular endurance and activity tolerance, where the muscle energy requirements are quickly depleted even at low exercise intensities.\textsuperscript{141,163} Muscle disuse is associated with similar limb muscle changes as seen in COPD patients, which is in contrast to what is observed with aging where there is a preferential loss of type II muscle fibers.\textsuperscript{14,164}

Prolonged periods of bed rest from hospitalization can lead to accelerated losses in muscle mass, strength and physical function.\textsuperscript{165} Loss of muscle mass due to inactivity tends to affect
the lower extremities and is more rapid in the early days of inactivity. Kortebein et al observed that the loss of lower extremity muscle mass was more pronounced in older healthy adults than younger patients after 10 days of bed rest. Similarly, Kortebein et al demonstrated in healthy older adults that 10 days of bed rest with a stable diet resulted in reductions in knee extensor strength (-13%), leg power (-14%), and aerobic capacity (-12%). de Boer et al. observed that the lower extremity muscles affected with bedrest were primarily the anti-gravity muscles (quadriceps and calf muscles) compared to the non-antigravity muscles (hamstrings and tibialis anterior). This highlights the importance of muscle loading with everyday activity and the preferential loss of muscle in specific muscle groups.

In chronic respiratory disease, physical inactivity is established to be an important contributing factor for skeletal muscle dysfunction. Physical inactivity has been observed even in mild COPD and is associated with impairments in quadriceps muscle size. In lung transplant candidates with ILD, daily step count had moderate correlation with quadriceps strength. Similarly, Mendes et al. observed significant muscle atrophy and weakness of the lower limb muscles compared to the upper extremity muscles in lung transplant candidates with ILD who had low self-reported physical activity levels, providing indirect evidence of a pattern of weakness associated with muscle disuse. In the post-transplant period, physical activity levels remain reduced in the first-year post-transplant and quadriceps strength has been observed to parallel the increase in physical activity levels.

**Smoking:**

A number of mechanisms have been proposed for the effects of cigarette smoking on skeletal muscle dysfunction, specifically affecting muscle atrophy. Some of the mechanisms include: oxidative stress, decreased protein synthesis, and inflammation. Immunological factors have also been suggested to be responsible for the persistence of the noxious
stimulus from smoking, which could have effects on skeletal muscle with inflammatory cytokines reaching the muscle via the circulation.\textsuperscript{177-179} In lung transplant candidates, the persistence of the immunological stimulus is probably less of a concern given most lung transplant programs require smoking cessation for a minimum of 6 months duration, consistent with our program requirements.

**Inflammation and Oxidative Stress:**

Systemic inflammation can lead to activation of cytokines which are responsible for local muscle protein degradation or activation of proteolytic pathways.\textsuperscript{180-182} As described in several reviews, cytokines can induce muscle atrophy through transcriptional activities via several mechanisms including the ubiquitin-proteasome system, autophagy-lysosome system, and apoptosis.\textsuperscript{183,184} In particular, tumor-necrosis factor alpha and interleukin-1 have been shown to stimulate muscle specific proteins of the ubiquitin-proteasome system, which can impact muscle catabolism and impair muscle contraction.\textsuperscript{185,186}

Oxidative stress is another contributing factor that has been described to be related to inflammation in chronic diseases such as COPD.\textsuperscript{187} Oxidative stress can induce a rise in inflammatory cytokines, which could lead to some of the adverse effects on skeletal muscle atrophy described above.\textsuperscript{187} Skeletal limb muscles have been observed to have a greater degree of oxidative stress compared to the respiratory muscles in animal models.\textsuperscript{188,189} Oxidative stress is postulated as a contributing factor for muscle protein dysregulation required for muscle structure and function, which in turn can lead to impairments in muscle protein regeneration.\textsuperscript{190} In lung transplant recipients, the ability to combat oxidative stress has been shown to be compromised up to one year post-transplant with low levels of anti-oxidant markers observed in serum and bronchoalveolar lavage fluid in 19 transplant recipients.\textsuperscript{191} However, the direct effects of oxidative stress on skeletal muscle has not been described in lung transplant recipients.
Generalized inflammation and oxidative stress can also have a significant effect on mitochondrial density and bio-genesis,\textsuperscript{192} which have been associated with muscle atrophy, weakness and loss of muscle endurance in patients with advanced lung disease and survivors of critical illness. In COPD patients, mitochondrial density and biogenesis were significantly reduced in the vastus lateralis muscles compared to healthy controls.\textsuperscript{148,193} Similarly, mitochondrial function (ability to synthesize adenosine triphosphate, the energy currency of the cell) was 50% lower in patients with ICU acquired weakness after two weeks of mechanical ventilation compared to controls undergoing hip replacement surgery.\textsuperscript{194} Similarly, lung transplant recipients have been shown to have a lower number of oxidative muscle fibers (type 1) and decreased oxidative enzyme activity.\textsuperscript{149} In the post-transplant period, mitochondrial function of skeletal muscle may be affected to a greater degree given the chronic exposure to calcineurin inhibitors, which are known to hinder mitochondrial biogenesis.\textsuperscript{195}

**Respiratory Failure:**

Hypoxemia and hypercapnea have been observed in a number of chronic respiratory conditions to contribute to skeletal muscle dysfunction, specifically reduced muscle strength and endurance.\textsuperscript{196,197} Hypoxemia can affect energy storage, protein synthesis and impaired muscle contractility.\textsuperscript{198-200} Hypercapnea through skeletal muscle acidosis can lead to impairments in skeletal muscle protein synthesis in vitro, which could impair muscle size.\textsuperscript{201} In lung transplant recipients, the effects of hypoxemia and hypercapnea on skeletal muscle function have not been previously assessed and might be more applicable in transplant candidates. Lung transplant recipients are generally not limited from a ventilatory stand-point in the absence of acute or chronic allograft dysfunction.\textsuperscript{118}

**Nutritional Abnormalities:**

Nutritional status can have a significant impact on skeletal muscle dysfunction. Malnutrition
has been associated with reduced muscle mass, lower proportion of oxidative muscle fibers, and reduced physical function.\textsuperscript{202,203} The potential mechanism responsible for these changes involve an imbalance between dietary intake (e.g. macro-nutrients like protein) and energy expenditure (increased due to respiratory effort and systemic inflammation).\textsuperscript{190,204}

In lung transplant candidates, malnutrition has been observed in about 10% of patients based on pre-operative nutritional variables such as low BMI < 18.5 kg/m\textsuperscript{2}, albumin, total protein, immunoglobulins and total lymphocyte count.\textsuperscript{205} Malnourished lung transplant candidates demonstrated worse one year survival post-transplant and increased risk for post-operative infections.\textsuperscript{205}

**Corticosteroids and Immuno-Suppressive Medications**

Corticosteroids are required for management of exacerbations and as part of maintenance therapy in many inflammatory respiratory conditions, and are a mainstay of immunosuppressive therapy post-transplant. Corticosteroids contribute to increased muscular protein breakdown, which is supported by increased myostatin levels and reduced anabolic hormones such as insulin-like growth factor 1 levels.\textsuperscript{206,207} Chronic corticosteroid use has been observed to be associated with quadriceps muscle weakness in ILD patients, and muscle strength had an inverse relationship with the total dose of corticosteroids received.\textsuperscript{208} A similar association between average daily dose of corticosteroids and quadriceps strength was observed in cystic fibrosis patients.\textsuperscript{209} In the peri-operative post-transplant setting, Nava et al demonstrated that 5 days of treatment with high dose corticosteroids for acute rejection in lung transplant recipients was associated with generalized muscle weakness (respiratory and quadriceps) in 45% of patients, which took up to 2 months to recover from.\textsuperscript{210}

In addition to corticosteroids, lung transplant recipients are exposed to calcineurin inhibitors which are believed to impair skeletal muscle function. Calcineurin inhibitors impair the ability
of blood vessels supplying muscle fibers to dilate thus reducing oxygen delivery to the exercising muscle.\textsuperscript{211,212} In addition, calcineurin inhibitors have been shown to significantly reduce mitochondrial oxidative capacity in animal studies.\textsuperscript{213} Taken together, calcineurin inhibitors and corticosteroids are thought to have a significant effect on skeletal muscle function in lung transplant patients. In other solid organ transplant recipients such as cardiac, renal and liver, immunosuppressive medications have been implicated as a contributor to skeletal muscle dysfunction, given a similar pattern of peripheral exercise limitation as seen in lung transplant recipients.\textsuperscript{214-216}

\textbf{Table 1-1:} Comparison of Factors Related to Skeletal Muscle Dysfunction in Chronic Lung Disease and Lung Transplant Recipients

<table>
<thead>
<tr>
<th>Factors</th>
<th>Chronic Lung Disease</th>
<th>Lung Transplant Recipients</th>
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<tbody>
<tr>
<td>Aging</td>
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<td>(152,153)</td>
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<tr>
<td>Physical Inactivity</td>
<td>(131,162)</td>
<td>(117,133)</td>
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<td>Smoking</td>
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<td>Inflammation</td>
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<td>Oxidative Stress</td>
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<tr>
<td>Calcineurin Inhibitors</td>
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\textbf{Note:} Reference examples are provided in brackets.
1.2.2 Rationale for Measuring Muscle Mass, Strength and Function

Whereas the original definition of sarcopenia (i.e. loss of muscle mass) was meant to be applied to the elderly, loss of muscle mass can occur with disuse, inflammation and malnutrition; risk factors common to chronic lung disease as outlined above. These risk factors could lead to alterations in protein synthesis, proteolysis, and impairments in neuromuscular functioning. The European Working Group on Sarcopenia in Older People (EWGSOP) defines sarcopenia as low muscle mass and one of low muscle function (strength or performance).

It was originally thought that skeletal muscle mass explained the loss of strength in older adults. However, longitudinal studies have demonstrated that muscle mass and strength are not necessarily concordant. A large prospective study in community dwelling elderly (Health, Aging and Body Composition study) demonstrated that the decrease in quadriceps muscle strength was significantly more rapid than muscle mass, suggesting that the decline in muscle mass and strength can take on different trajectories. Similarly, in studies of muscle disuse from bedrest or in survivors of critical illness the relationship of muscle mass with strength was modest suggesting a more complex relationship between the two measures. In fact, neurologic function and the intrinsic force-generating properties of skeletal muscle have been proposed as significant contributing factors to muscle weakness, which can have a differential effect with aging and in chronic disease. Thus, Clark and Manini coined the termed dynapenia referring to the age-related loss of muscle strength and power, independent of muscle mass. They proposed that loss of muscle strength and mass should be evaluated independently and sarcopenia be reserved to describe the age-related loss of muscle mass. With aging, loss of muscle strength has been shown to be a stronger prognostic marker for disability and death than loss of muscle mass.
In chronic lung disease, there is no agreed upon definition of skeletal muscle dysfunction and it is not known which elements of muscle dysfunction (muscle mass, strength and function) are most closely associated with physical function, HRQL and clinical outcomes. In a large cohort of COPD patients, Jones et al. observed sarcopenia using the EWGSOP definition in 15% of participants; however, quadriceps weakness was present in more than half of these patients. This study illustrates a similar pattern of discordance of skeletal muscle mass and strength in chronic lung disease as seen in community dwelling older adults, raising the question of which skeletal muscle measures are most informative clinically.

A wide range of tools are available to measure skeletal muscle mass, strength and physical performance. Some modalities are better suited for research compared to the clinical setting. The availability, cost, and ease of measurement will often dictate use of these instruments. The next three sections will review the wide range of modalities available for measurement of skeletal muscle mass, strength and function and more importantly outline the skeletal muscle impairments in chronic lung disease and lung transplant patients. The available measurement modalities are outlined in Figure 1-1.

**Figure 1-1:** Skeletal Muscle Mass, Strength and Physical Performance Measures
1.2.3 Muscle Mass Measurements:

Muscle atrophy is recognized as an important extra-pulmonary manifestation of chronic lung disease associated with physical disability,\textsuperscript{224} quality of life\textsuperscript{225} and mortality.\textsuperscript{226} A number of anthropometric measurements and non-invasive modalities have been utilized to characterize muscle mass, which include imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound (US), along with other modalities such as bio-electrical impedance (BIA) and Dual-energy X-ray absorptiometry (D-XA).\textsuperscript{227,228} The advantages and disadvantages of each technique are summarized below.

Anthropometric Measures:

Anthropometric measurements such as mid-arm circumference\textsuperscript{229} and sum of skin folds\textsuperscript{230} have been applied as estimates of fat-free mass using regression equations developed in healthy populations; however, their predictive capabilities are inferior to non-invasive modalities such as MRI\textsuperscript{231} and they have not been validated in lung transplant patients. Furthermore, sarcopenia consensus guidelines in the elderly recommend against the use of anthropometric measurements for estimation of fat-free mass given age-related changes in tissue adiposity and skin elasticity, which can yield mixed results.\textsuperscript{158} Body mass index has been the most common anthropometric measurement utilized in lung transplantation and adopted by ISHLT guidelines. However, BMI is a relatively poor measure of low muscle mass when compared to traditional measures such as D-XA. Singer et al. observed in a sub-cohort of 142 lung transplant candidates with available D-XA, only 5% were observed to have low BMI (< 18.5 kg/m\textsuperscript{2}), whereas 46% were characterized as sarcopenic.\textsuperscript{54}

Computed Tomography:

Computed tomography was one of the first imaging modalities that allowed whole-body and regional quantification of skeletal muscle size.\textsuperscript{228} The analysis can be performed manually or
in a semi-automated manner with a number of software programs such as MATLAB, NIH ImageJ or Slice-O-Matic that can identify linear attenuation coefficients, which correspond to different body tissues.\textsuperscript{232,233} Skeletal muscle has a pre-defined coefficient of attenuation (-29 to 150 Hounsfield units), which allows it to be differentiated from fat tissue (-30 to -190 Hounsfield units) using the specialized software. Computed tomography is able to provide quantification of intermuscular adipose tissue, which allows one to assess the amount of muscle fat infiltration, which is associated with physical function.\textsuperscript{234} Computed tomography has been applied across several disease states to characterize the trunk and limb muscles.

Computed tomography CSA from abdominal CT scans at the third lumbar vertebral level (psoas, paraspinous or thigh muscles) has generally been used, as it has been shown to approximate whole body skeletal muscle mass in healthy populations.\textsuperscript{235} Morphometric techniques with abdominal CT have been well described in major surgery and liver transplantation,\textsuperscript{236-238} but the application of CT for quantification of trunk muscle mass has only recently been undertaken in chronic respiratory disease. Abdominal CT scans have been utilized in lung transplant candidates as a measure of sarcopenia\textsuperscript{239,240} and the use of thoracic CT scans has recently been described in non-listed COPD and lung transplant patients using various protocols.\textsuperscript{241-244} Skeletal muscle mass has been quantified using the level of the aortic arch\textsuperscript{241,242}, twelfth thoracic vertebral level\textsuperscript{243} and in one study using the level of the carina.\textsuperscript{244} This is promising as thoracic CT scans are readily available in lung transplant candidates, but have not been routinely utilized for estimation of skeletal muscle mass.

Computed tomography has generally been applied in chronic respiratory disease for assessment of peripheral muscles. The most common CT protocol used is that of Bernard et al. where muscle CSA is measured halfway between pubic symphysis and inferior femoral condyle.\textsuperscript{245} With CT, a number of studies have demonstrated significant quadriceps muscle atrophy of the lower extremity in COPD, cystic fibrosis and pulmonary arterial hypertension
compared to controls, ranging from 6-39%.\textsuperscript{180,246-248} In lung transplant recipients, Pinet et al. demonstrated that CSA of the quadriceps measured with CT was reduced by 30% in 12 cystic fibrosis patients post-transplant (median 48 months) compared to healthy age-matched controls.\textsuperscript{144}

**Magnetic Resonance Imaging:**

Magnetic resonance imaging is often regarded as the gold standard for assessment of peripheral muscle size.\textsuperscript{249} It is able to provide detailed information on muscle size and composition of the peripheral muscles. In addition, a single cross-sectional MRI slice at the third lumbar vertebral level has been shown to have strong correlation with whole body skeletal muscle mass volume assessed with MRI, suggesting a single slice estimate can potentially be used.\textsuperscript{250} However, MRI is significantly more costly than other modalities (i.e. CT, ultrasound), time consuming and requires additional expertise for analysis.\textsuperscript{228} It also has several contraindications requiring exclusion of patients with pacemakers, defibrillators, intracranial metallic clips or previous exposure to metallic bodies in the eye.\textsuperscript{251} Thus, MRI has generally been reserved for assessment of peripheral muscle when detailed structural information and composition has been required.

In chronic lung disease, MRI has been used to assess lower extremity muscle size in several studies. COPD patients had approximately 20-25% lower quadriceps CSA and volume compared to healthy controls.\textsuperscript{231,252,253} In lung transplant recipients, muscle size with MRI was shown to be similar to COPD patients who had not undergone transplantation.\textsuperscript{254} Based on a systematic review, there have been no other studies in lung transplant candidates or recipients that have utilized MRI as an imaging modality for assessment of muscle size.\textsuperscript{21}

**Ultrasound:**

Ultrasound has been used in patients with chronic respiratory disease to assess peripheral
skeletal muscle size and quality.\textsuperscript{131,255} Ultrasound is relatively inexpensive, portable, has no radiation exposure and is relatively easy to perform in the clinical and laboratory setting.\textsuperscript{256} One limitation of ultrasound is the small field of view which limits the imaging to smaller muscles, such as the rectus femoris of the quadriceps. However, muscle size of the limbs from ultrasound has been shown to correlate closely with CT\textsuperscript{257} and MRI\textsuperscript{258} in COPD patients and healthy individuals, respectively.

In COPD, quadriceps muscle atrophy has commonly been observed with ultrasound with values generally 17-25% lower than that of healthy controls.\textsuperscript{172,257,259} A study from our center by Mendes et al. demonstrated that lung transplant candidates with ILD had significant quadriceps atrophy with ultrasound, with accompanying loss in strength of the knee extensors, but no difference in size of the biceps muscles observed.\textsuperscript{131} Ultrasound has not been studied in the post-transplant setting as an assessment of lower extremity atrophy, but holds a great deal of promise given its portability and potential for clinical application in the critical care and inpatient settings.\textsuperscript{256}

**Bioelectrical Impedance Analysis:**

Bio-electrical impedance is one of the older forms of body composition assessment and was developed in the 1950-1960s by Hoffer, Nyboer and Thomasset.\textsuperscript{260,261,262} It allows quantification of fat-free mass and fat percentage for the entire body based on conductivity of current (i.e. flow of energy). Bio-electrical impedance utilizes the differential conductivity of tissues to differentiate highly conductive tissues (i.e. skeletal muscle) versus low-conductance tissues such as fat and bone.\textsuperscript{260} As with other imaging modalities, BIA is also able to provide muscle quality assessments using phase angle, which is the ratio of resistance (energy dissipation) and reactance (energy storage).\textsuperscript{263} Phase angle assesses cellular integrity, which carries prognostic information in chronic disease.\textsuperscript{263} Bio-electrical impedance is commonly
used today in assessment of body composition as it is readily available, inexpensive, and results require limited analysis.

In advanced lung disease and lung transplantation, low fat free mass has been observed with BIA.\textsuperscript{21,264} Fat-free mass is known to be reduced in the pre- and post-transplant periods.\textsuperscript{135,265} Kyle et al. demonstrated in 37 lung transplant candidates that low fat-free mass index was prevalent in the pre-transplant period in two-thirds of patients compared to 5\% of healthy controls.\textsuperscript{135} Even though fat-free mass improved post-transplant, one-third of patients were observed to have persistence of low fat-free mass index two years post-transplant.\textsuperscript{135}

**Dual-energy X-ray Absorptiometry:**

Dual-energy x-ray absorptiometry is commonly utilized for assessment of skeletal muscle mass and body composition. It has relatively low radiation exposure, modest cost, and is able to characterize lean muscle mass, bone and fat tissue systemically and for various body compartments.\textsuperscript{266,267} Given that the majority of lean soft tissue is found in the arms and legs, the appendicular skeletal muscle mass is often used as a surrogate measure of skeletal muscle mass.\textsuperscript{266} One drawback of D-XA measurement is its inability to characterize muscle quality (i.e. fat infiltration), which the other imaging modalities are able to capture. The other limitation is the lack of portability which makes it hard to apply clinically or in large population studies.

In COPD patients, sarcopenia was present in 36/91 (40\%) participants with low muscle mass, defined using normative values for skeletal muscle index from D-XA (appendicular lean mass/height\textsuperscript{2}). Low muscle mass was strongly associated with the prognostic BODE Index (score encompassing body mass index, airflow obstruction, dyspnea, and exercise capacity), independent of age, sex, smoking status, and disease severity.\textsuperscript{268} In lung transplant
candidates, Singer et al. demonstrated the presence of sarcopenia with D-XA in 65/142 (46%) patients was more commonly seen in those with low or normal weight (BMI < 25 kg/m²).  

**Clinical Importance of Skeletal Muscle Mass**

Irrespective of the modality utilized, the clinical implications of low skeletal muscle mass have been described predominantly for people with COPD. Systemic measures of low muscle mass with BIA and quadriceps atrophy have been observed to be associated with increased mortality in patients with COPD independent of lung function. The association between weight loss and reduced survival in COPD, cystic fibrosis and chronic heart failure have been well described; however, anthropometric measures such as BMI are unable to assess the importance of the various body composition compartments (i.e. muscle mass versus fat). Skeletal muscle mass is known to be affected to a greater degree than fat tissue in chronic respiratory disease. The pathogenesis of muscle mass loss is thought to be related to increased protein catabolism, systemic inflammation, malnutrition, and chronic inactivity. Loss of muscle mass can lead to increased risk of infection and difficulty coping with major stressors such as critical illness. Skeletal muscle also constitutes the largest insulin sensitive tissue in the body and is critical in regulating metabolism and body composition. Thus, a more comprehensive evaluation of body composition and assessment of skeletal muscle mass could potentially help predict pre- and post-transplant outcomes.

The choice of imaging modality depends on the level of tissue differentiation required (muscle versus fat), availability, cost, clinical setting, technical expertise and exposure to radiation or other contraindications. Bio-electrical impedance analysis offers a validated measure of fat-free mass quantification that is portable, reproducible and inexpensive. Alternative methods for determining muscle mass such as D-XA or muscle size using CT or MRI have been used primarily in research settings given the higher cost, difficulty with equipment access, and
concerns regarding radiation exposure with D-XA and CT. However, retrospective analysis of thoracic CT scans, which are generally obtained for routine care, can provide a novel and practical opportunity to quantify skeletal muscle mass in advanced lung disease and transplantation with no added cost or radiation exposure.

1.2.4 Peripheral and Respiratory Muscle Strength Measurements

Muscle strength is the ability of the muscle to generate maximal force, which is often evaluated in the clinical and research setting. A number of methods to assess muscle strength in advanced lung disease have been utilized such as manual muscle testing, hand-held dynamometers, and computerized dynamometers. In the research setting, computerized dynamometers have been the most common modality used in chronic lung disease and lung transplantation given their reliability, accuracy and safety. However, there are several limitations with computerized dynamometers such as their higher costs, limited accessibility, training requirements, and time required for testing. Thus, a hand-held dynamometer might be a good alternative for measuring muscle strength clinically where time and availability are limited but greater caution should be taken when testing large muscle groups (i.e. knee extension) given the mechanical difficulty of testing and poor reliability. Similarly, non-volitional methods such as muscle or nerve stimulation have been used in an attempt to remove the motivational component of voluntary muscle strength tests. However, non-volitional methods have not commonly been utilized due to some of the expertise required and discomfort with electrical nerve stimulation, especially if repeated measures are required. Over the last few years, novel techniques have been applied such as magnetic stimulation of skeletal muscles which is relatively painless but requires additional technical expertise. Thus, a number of techniques can be utilized in the clinical and research settings to evaluate muscle strength. Standardized evaluation of muscle strength
allows identification of muscle weakness and prescription of resistance training in chronic respiratory disease.

The majority of studies in advanced lung disease have examined strength in the lower extremity using volitional tests demonstrating a reduction of 20 to 30% in quadriceps strength compared to healthy controls.\textsuperscript{131,285-287} A similar pattern has been observed with non-volitional tests such as magnetic femoral nerve stimulation.\textsuperscript{288,289} Given the quadriceps is one of the major muscles involved with daily activity (i.e. walking, sit-to-stand) and is easily accessible, it has been the focus of investigation in chronic respiratory disease.

The natural history of lower extremity muscle weakness in chronic respiratory disease is not entirely clear but there is some suggestion that lower extremity weakness could have a gradual decline accelerated by exacerbations.\textsuperscript{290} In one study, COPD patients were noted to have an accelerated decline of about 4% over one year, whereas a lower annual decline of 1-2% in quadriceps strength was observed in another cohort of COPD patients, similar to what is generally seen in a healthy elderly population.\textsuperscript{285,173}

In lung transplantation, the quadriceps muscle has been the muscle most studied. Based on our systematic review of 18 studies of lung transplant candidates and recipients, quadriceps muscle strength in the pre-transplant period was significantly reduced (mean range of 49-86% of predicted values), with a further reduction in the immediate post-transplant period (51-72%), and with gradual improvement beyond 3-months post-transplant (58-101%).\textsuperscript{21} Generally, lower extremity muscles have been shown to be weaker than the upper extremity muscles. In the pre-transplant period, hand-grip force is generally greater than 80% predicted and preserved throughout the post-transplant period.\textsuperscript{116,117,124} With hand-held dynamometry, both biceps and triceps strength was greater than 80% in the pre- and post-transplant periods.\textsuperscript{143,291} The preservation of upper extremity strength could be partly explained by the fact that upper
extremity muscles are often involved in maintaining essential activities of daily living such as self-care (i.e. brushing teeth, combing hair), where as physical activities that rely on lower extremity muscles such as walking are often reduced. 

**Clinical Implications of Peripheral Muscle Strength:**

As in the general population, quadriceps muscle strength has been shown to be an important independent predictor of survival in COPD. Swallow et al. demonstrated that quadriceps muscle weakness was predictive of mortality in COPD patients, independent of age, BMI, whole body fat-free mass index, and lung function. The prognostic implications of lower extremity skeletal muscle dysfunction are further supported by findings by Marquis et al who demonstrated that quadriceps muscle atrophy was associated with increased mortality in COPD patients, independent of BMI. However, it remains unclear to what extent skeletal muscle weakness is a systemic process or one that is confined to the lower extremities in patients with chronic lung disease. Systemic factors outlined above such as inflammation, hypoxemia, and nutrition may have an influence on local muscle factors (i.e. contractile properties, blood flow) that can lead to muscle atrophy and weakness. These systemic factors might be important mediators of clinical outcomes such as survival.

In lung transplantation, the association of pre-transplant skeletal muscle strength with post-transplant outcomes remains unknown to-date and is an important area of research. In the post-transplant period, Maury et al. observed that quadriceps weakness post-transplant was associated with longer ICU length of stay, and quadriceps strength in the first three months post-transplant was lower than pre-transplant values. The mechanisms underlying post-transplant muscle weakness are not well understood and include elements of acute-deconditioning and immuno-suppressive medications, but the contribution of other factors such as oxidative stress, inflammation, and malnutrition have not been explored.
**Respiratory Muscle Strength:**

Maximal respiratory pressures are often reduced in patients with COPD despite a training-like effect from increased ventilatory load that makes these muscles more resistant to fatigue.\textsuperscript{295,296} However, resistive loading of the diaphragm muscles has been shown to actually accentuate diaphragm injury, through disruption of myofibrillar structure.\textsuperscript{297} Dysfunction of the respiratory muscles may worsen the chronic ventilatory failure observed in COPD patients and has been shown to be a risk factor for hospital readmissions.\textsuperscript{298} In turn, acute respiratory exacerbations can further impair respiratory muscle function.\textsuperscript{299} Lung volume changes (i.e. dynamic hyperinflation) during respiratory exacerbations can create a mechanical disadvantage for the diaphragm, rib cage and intercostal muscles potentially imposing further functional deterioration.\textsuperscript{299} In addition to respiratory exacerbations, other key contributing factors for respiratory muscle dysfunction include age and nutritional abnormalities.\textsuperscript{296,300}

To-date, respiratory muscle strength in lung transplant candidates or recipients in the early post-transplant period has not been studied. Pinet et al compared diaphragmatic thickness and non-volitional force measures in 12 lung transplant recipients, on average 48 months post-transplant (range 8-95 months), to 12 matched healthy controls.\textsuperscript{301} They observed that diaphragm muscles had preserved strength and thickness compared to controls, but respiratory muscle strength in the early post-transplant period was not assessed. Respiratory muscle structure and function in the peri-operative transplant period is an important area of future investigation given that respiratory muscle strength, if impaired, can potentially be amenable to inspiratory muscle training. In a recent systematic review and meta-analysis of eight studies, inspiratory muscle training pre-operatively was shown to be associated with a lower risk of combined pulmonary complications (RR: 0.48, 95% CI: 0.26 to 0.89) following open cardiac, thoracic and upper abdominal surgery.\textsuperscript{302} Furthermore, pre-operative
inspiratory muscle training significantly improved respiratory muscle strength in the early post-operative period.\textsuperscript{302}

\textbf{1.2.5 Assessment of Physical Performance:}

A number of physical performance tests have been used in advanced lung disease that allow for characterization of mobility, balance and physical function. The most common lower limb performance tests utilized in advanced lung disease have included gait speed, sit-to-stand, and the short-physical performance battery (SPPB).\textsuperscript{303} These simple performance based functional tests may be more informative with respect to skeletal muscle function than an assessment of exercise capacity using the six-minute walk test (6MWT). The 6MWT is affected by multiple factors such as cardio-pulmonary limitations, dyspnea and fatigue, which makes it hard to isolate lower extremity performance.\textsuperscript{102} Thus, functional tests can provide information that is more specific to muscle function, which can assist with exercise prescription, outcome assessment and mobility aid recommendations.

\textbf{Gait Speed:}

The most common gait speed assessment in COPD patients has been the 4 meter gait speed.\textsuperscript{303} The 4 meter gait speed assessment has been shown to be a valid and reliable measure in advanced lung disease. It correlates with measures of exercise capacity (6MWT),\textsuperscript{304,305} HRQL as assessed by the SGRQ,\textsuperscript{304} and physical activity levels.\textsuperscript{305} There have been a number of variations to the gait speed assessment which have included various course durations (i.e. 10 meters)\textsuperscript{306} and various protocols (i.e. standing or walking start), which could influence maximal gait speed achieved.\textsuperscript{303}

\textbf{Sit-to-Stand Test:}

This assessment can be performed in several ways to assess number of repetitions in a
specific period of time (i.e. 30 or 60 seconds) or time period it takes to perform a certain number of repetitions (i.e. five repetitions). In patients with advanced lung disease, the time taken to perform five repetitions on the sit-to-stand test is commonly utilized. It has been shown to be valid, reproducible and responsive with pulmonary rehabilitation. In one study, the one minute sit-to-stand test was observed to be a strong predictor of two year mortality in COPD patients.

**Timed Up and Go Test:**
The test can be performed in a clinical setting and individuals are instructed to rise from a chair, walk 3 meters, and return to the chair to sit down. The Timed Up and Go Test is able to assess risk of falling and functional disabilities. The Timed Up and Go Test has been described as a predictor of HRQL at one year follow-up in COPD patients. It has been shown to be reliable with very good reproducibility. However, its performance characteristics require further study in advanced lung disease, as evaluation has taken place at both usual and fast speeds.

**Short-Physical Performance Battery:**
The SPPB is a functional assessment of balance (tandem standing), five repetitions of the sit-to-stand test and 4-meter gait speed, which has been utilized in community dwelling elderly and populations with advanced lung disease. Each of these three measures is scored from 0 to 4, with a total score out of 12. The SPPB is easy to perform, it has good validity and reliability, and requires less than five minutes to complete. The SPPB has been shown to be associated with exercise capacity (6MWD), quadriceps strength and future disability at two year follow-up in COPD.

**Physical Performance Tests in Lung Transplantation:**
In lung transplant candidates, there have only been a few studies utilizing physical
performance tests. In a systematic review of 18 studies, only two studies utilized the sit-to-stand test to assess physical function in lung transplant candidates. Recently, Mendes et al. demonstrated that the Timed Up and Go Test was significantly reduced in lung transplant candidates with ILD compared to controls. In addition, the SPPB has been used as a marker of physical frailty and shown to be associated with disability and pre-transplant delisting and mortality. To our knowledge, the association of these physical performance tests with HRQL, ADL and post-transplant outcomes have not been previously described in lung transplantation.

**Functional Independence Measure:**

The functional independence measure (FIM) is an 18-item questionnaire that assesses the level of assistance required by the patient. It has been applied in rehabilitation across a diverse group of patients including critical care survivors and lung transplant recipients. The FIM consists of 2 main domains: motor (13 items; self-care, sphincter control, mobility, and locomotion) and cognitive (5 items; communication and social cognition) with each item given a score from 1 to 7. The total 18 items range from 18 to 126 with higher scores signifying greater functional independence. Scores less than 40 reflect total assistance, whereas a score of 50 represents moderate level of assistance. An accepted minimally clinically important difference for the total FIM score is 20 and previous reports have attempted to establish specific cut-offs for the minimally important difference in stroke survivors: 22 and 17 points for the total FIM and motor domain, respectively. The motor domain of the total FIM has been observed to be responsive to change in lung transplant recipients undergoing inpatient rehabilitation. The FIM has been utilized at our center as a research tool in ICU patients, some of whom had lung transplants. It provides a comprehensive assessment of functioning, along with limitations in ADL, which is not always practical to capture through physical assessment.
In summary, this section described the most common modalities utilized to evaluate skeletal muscle mass, strength and function in advanced lung disease and lung transplant patients. The next section will address the prognostic implications of these measurements and physical fitness with major surgery and solid-organ transplantation, with a focus on lung transplantation.

1.3: Importance of Physical Fitness with Major Surgery and Solid-organ Transplantation

Thoracic-abdominal surgery and solid organ transplantation are major surgical procedures that can result in increased peri-operative complications such as significant physical deconditioning, prolonged hospital length of stay, and increased mortality compared to intermediate or low risk surgery.³²³,³²⁴ A number of factors such as general anaesthesia, prolonged surgical time, hemodynamic instability, high-dose corticosteroids in transplant recipients and blood loss predispose patients to higher risk of peri-operative complications with these procedures.³²⁵,³²⁶ A better understanding of patient risk factors for the upcoming surgery could help inform patients, their families and the medical team of potential peri-operative and long-term outcomes, which may help with transplant consent discussions. To-date, risk stratification with major surgical procedures has often been a subjective assessment of patient physiologic reserve, often described as the "eye-ball" test in surgery.³²⁷ However, more robust and repeatable pre-operative assessments of physiologic reserve could help inform rehabilitation strategies pre-operatively that could lead to improved outcomes.

The following section reviews pre-operative physiological risk factors with major surgery and solid organ transplantation, with a focus on lung transplantation. A discussion of pre-operative exercise training follows.
1.3.1 Physiological Stress Response with Major Surgery:

Physical fitness prior to thoraco-abdominal surgery has been associated with post-operative outcomes. Surgery is a physical stressor and the recovery post-surgery often involves periods of bed-rest and immobility. Periods of inactivity post-operatively have been related to muscle atrophy, weakness, and pulmonary complications.\textsuperscript{328} In patients undergoing lung resection, low pre-surgical aerobic capacity has been associated with post-operative complications such as pneumonia, respiratory failure, and increased mortality.\textsuperscript{329,330} Similarly, Szekely et al demonstrated that COPD patients with a 6MWD of less than 200 meters were more likely to have a prolonged hospitalization (> 3 weeks) after lung volume reduction surgery.\textsuperscript{331} In patients undergoing major abdominal oncological surgery, pre-operative self-reported physical activity levels and measurements of physical fitness were associated with post-operative length of stay and mortality.\textsuperscript{332} Thus, across a number of patient populations and surgical interventions, pre-operative physical fitness and conditioning is often associated with post-operative function, cardio-pulmonary complications, and hospital length of stay.

Functional decline with major surgery is multi-factorial. Surgery can lead to prolonged periods of bedrest, which can result in increased physical deconditioning. The physiological stress response from surgery can also act as a catabolic stimulus, hindering peripheral and diaphragm muscle function, through increased protein breakdown.\textsuperscript{333} Furthermore, surgical procedures near the diaphragm can induce respiratory muscular impairment through several pathophysiological mechanisms including direct distortion of the respiratory muscles, alteration in the thoraco-abdominal mechanics, and phrenic nerve reflex inhibition.\textsuperscript{334} Welvaart et al. demonstrated that patients undergoing a thoracotomy for a tumor in the right lung were noted to have significant reductions in diaphragm force generation (about 35%) and this force loss was more prominent in the fast twitch (type II) fibers after only 2 hours of
surgery. In addition to post-operative inactivity, the surgical stress response has been observed to induce an increased inflammatory response (higher interleukin-6 levels), which have been associated with reduced muscle endurance and self-reported fatigue levels, more pronounced in older adults. Thus, many peri-operative factors such as surgical stress, inflammation, muscle catabolism and physical inactivity can have significant effects on peripheral and respiratory muscle function.

Most healthy individuals can respond appropriately to surgical stress and restore physiological balance in the post-operative period. However, patients with chronic disease and poor physical function pre-operatively have a harder time restoring this balance, which could hinder post-operative recovery and lead to increased health care utilization. Thus, the ability to identify pre-operative indicators of physical function such as skeletal muscle mass, strength and physical performance can potentially help with prognostication, as described in the next section.

### 1.3.2 Skeletal Muscle Strength and Physical Performance with Major Surgery and Solid-Organ Transplantation:

There have only been a few studies that have assessed the clinical implications of functional deficits (muscle strength and physical performance) in the pre-operative period. Afilalo et al, demonstrated in elderly cardiovascular patients over the age of 70 years old that slow gait speed over 5 meters was associated with the primary composite end point of in-hospital post-operative mortality and major morbidity with cardiac surgery. Robinson et al. demonstrated in patients over 65 years old undergoing colorectal and cardiac surgical procedures that greater time required to complete the Timed Up and Go Test was associated with increased post-operative complications such as requirement for discharge to another institution, 30-day hospital readmission, and one year mortality. Irrespective of the procedure, the Timed Up
and Go Test had better performance operating characteristics than the standard surgical risk
calculators. Similarly, a history of one or more falls in the previous 6 months was
associated with lower likelihood of being discharged home, and an increased chance for 30-
day readmission to hospital with colorectal and cardiac surgical procedures in older adults.

Functional assessments before major surgery have been mainly limited to the lower extremity
such as assessment of gait speed, Timed Up and Go Test, and falls history. Another
limitation is that pre-operative skeletal muscle function has been mainly assessed in the
elderly patient population.

In one study of 292 liver transplant candidates, the association of CT-based measures of
sarcopenia and functional measures was evaluated. Hand-grip strength and SPPB were
associated with pre-transplant mortality, whereas this relationship was not observed with
skeletal muscle mass quantified with abdominal CT. This highlights the prognostic
implications of functional deficits (muscle strength and physical performance) in the pre-
operative period, which have not been a major focus of investigation to-date in lung
transplantation.

In lung transplantation, a few studies have looked at pre-transplant functional status indirectly
to assess post-transplant outcomes. Grimm et al utilized the United Network for Organ
Sharing dataset to demonstrate that pre-operative performance status using the Karnofsky
Performance Status had a significant association with one year mortality post-transplant in
over 7800 lung transplant recipients. Wilson et al. assessed the impact of frailty, as a
marker of decreased physiologic reserve in 144 lung transplant candidates. A higher score on
the frailty deficit index was associated with increased one year mortality, but no association
was seen with ICU or hospital length of stay. To-date, associations between pre-transplant
muscle function (strength and performance) and post-transplant outcomes have not been
studied in lung transplant candidates, and may provide an objective measure of physiologic reserve in this patient population.\textsuperscript{21}

**1.3.3 Skeletal Muscle Mass with Major Surgery and Solid Organ Transplantation:**

As a measure of sarcopenia (low muscle mass), the evaluation of total psoas muscle cross-sectional area with CT morphometric techniques has been studied across several major surgical procedures pre-operatively, as a means of risk stratification. With major elective general or vascular surgery, lower psoas muscle size was associated with increased risk of complications and one year mortality.\textsuperscript{344} A similar association with core muscle size was seen with abdominal aortic repair and aortic valve replacement.\textsuperscript{238,345}

In solid-organ transplantation, sarcopenia (low muscle mass) has been associated with increased risk of morbidity and mortality post-transplant.\textsuperscript{28,277,344} Most of the literature on sarcopenia in transplantation has come from liver transplant candidates with a few studies from other solid organ transplants.\textsuperscript{277} Furthermore, sarcopenia has been defined by various methodologies across the different organ groups.

**Liver:**

The importance of muscle mass was first demonstrated in liver transplantation by Englesbe et al. who showed that total psoas muscle area on abdominal CT scan was associated with post-transplant mortality.\textsuperscript{236} In a similar study, pre-transplant sarcopenia was associated with a significantly increased risk of serious post-transplant infections and mortality among 207 liver transplant recipients based on total psoas muscle area.\textsuperscript{346} Montano-Loza et al demonstrated that sarcopenia was also associated with waitlist mortality in liver transplant candidates.\textsuperscript{347} In a recent systemic review and meta-analysis of 19 studies in liver transplantation, low skeletal muscle mass with abdominal CT was prevalent and ranged from 22 to 70% given various cut-
However, irrespective of the definition, sarcopenia was associated with increased risk of post-transplant infection and mortality in the pooled analysis.\textsuperscript{348}

**Renal:**

Low muscle mass pre-transplant was associated with worse outcomes in renal transplant recipients. Muscle mass was calculated from a formula utilizing pre-transplant serum creatinine in a large cohort of patients on dialysis awaiting transplantation. Low muscle mass was associated with increased mortality post-transplant and a 2.2 fold increased risk of renal graft loss.\textsuperscript{349} In a large observational study of over 14,500 renal transplant candidates, Molznar et al observed there was increased mortality on the waiting list with lower muscle mass, as measured by serum creatinine.\textsuperscript{350} In chronic kidney disease, the convention of protein-energy wasting is often used as proposed by the International Society of Renal Nutrition and Metabolism which requires 3 out of 4 criteria (serum chemistry, body mass index, muscle mass, and dietary intake).\textsuperscript{351} Muscle mass comprises one of four criteria and is defined by reduced mid-arm muscle circumference or creatinine levels.\textsuperscript{351} However, this concept has been mainly limited to end-stage renal disease and not applied in other chronic disease states.

**Cardiac:**

No studies to-date have examined the clinical implications of muscle wasting in cardiac transplantation.\textsuperscript{277} However, the role of sarcopenia has been described in patients undergoing aortic valve replacements. Low skeletal muscle cross-sectional area derived from abdominal CT images at the third lumbar level was associated with longer hospital length of stay in patients undergoing trans-catheter aortic valve replacements and was more prognostic than functional measures (hand-grip strength and 5-meter gait speed).\textsuperscript{352} Similarly, Paknikar et al.
demonstrated that low psoas muscle size on abdominal CT was associated with increased early morbidity, health-care utilization and decreased two-year survival in a large cohort of patients undergoing open and trans-catheter aortic valve replacements.345

Lung:

In lung transplantation, quantification of muscle mass using abdominal CT scans at the third lumbar vertebral level has recently been described, similar to the approach utilized in liver transplant candidates. Muscle CSA in lung transplantation has been associated with post-transplant outcomes such as ICU and hospital length of stay.239,240 However, the majority of lung transplant programs including our center, perform mainly thoracic CT scans limiting the applicability of abdominal CT scans. The clinical implications of muscle CSA from chest CT has been recently described in one study of lung transplant candidates.244 Surprisingly, they observed an increased one year mortality in the quartile with the highest muscle CSA, but this analysis did not adjust for older age or higher proportion of ILD patients in this quartile. Thus, the prognostic utility of skeletal muscle mass using thoracic CT in lung transplantation remains poorly defined and its association with pre-transplant delisting, mortality and functional outcomes has not been previously described.

Skeletal muscle mass in the pre-transplant period is emerging as an important risk factor in solid-organ transplantation.277 Even though a number of techniques have been utilized in solid-organ transplantation with varying cut-offs to define sarcopenia, there is clear evidence that low muscle mass is a common problem and could provide prognostic value.

The clinical implications of muscle functional deficits, in addition to skeletal muscle mass, require further investigation. It also remains unclear whether the prognostic implications of skeletal muscle mass apply equally across the various surgical interventions.
1.3.4 Pre-Operative Exercise Training with Major Surgery and Solid-Organ Transplantation

Exercise Training prior to Major Surgery

Exercise training has been shown to be beneficial in improving cardio-pulmonary and musculoskeletal fitness across many chronic disease states, which are important markers of peri-operative morbidity and mortality, as described above.\(^\text{353}^\) Thus, pre-habilitation (aerobic, strength and respiratory muscle training) has been utilized pre-operatively in preparation for cardio-thoracic and abdominal surgical procedures.\(^\text{354-356}^\) In patients undergoing cardiac surgery, an inpatient cardio-pulmonary rehab program pre- and post-operatively has been shown to be associated with shorter hospital length of stay and reduced post-operative cardio-pulmonary complications (pleural effusions, atelectasis, pneumonia and arrhythmias).\(^\text{357}^\) In a study by Arthur et al of low risk cardiac patients awaiting elective coronary artery bypass surgery, exercise training (aerobic and strength) combined with education resulted in a shorter ICU and hospital length of stay compared to the usual care group encouraged to remain physically active.\(^\text{358}^\) Furthermore, exercise training improved HRQL in this group of patients, which was maintained for up to 6 months post-operatively. In patients awaiting lung resection for malignancy, pre-operative aerobic exercise training has been associated with increased aerobic capacity\(^\text{355,359}^\) and lower post-operative complications.\(^\text{329,330,360}^\) In patients undergoing colorectal surgery, both pre-rehabilitation programs (stationary cycling plus resistance training or walking recommendations and breathing exercises) resulted in significant increases in 6MWD pre-operatively, and those with improvement in their functional capacity demonstrated a faster recovery post-operatively in their functional capacity.\(^\text{361}^\) Thus, exercise training prior to major surgery has been shown to have a positive effect on cardio-pulmonary fitness and peri-operative morbidity, but the effects on mortality require further study.\(^\text{362,363}^\)
Pre-Operative Exercise Training in Solid-Organ Transplantation:

In a recent systematic review of exercise training in solid-organ transplant candidates, only 11 studies including heart (n=6) and lung transplant (n=5) candidates were identified with no studies in liver and renal transplant candidates. Adherence to rehabilitation was observed to be very good in cardiac and lung transplant candidates, ranging from 82.5% to 100%. Exercise training was well tolerated in this group of patients with no serious adverse events, but it was difficult to ascertain the safety profile of exercise training due to the lack of reported data. Mild side-effects such as myalgias, fatigue, pre-syncope and palpitations have been previously described to affect fewer than 5% of training participants with advanced cardio-pulmonary disease.

There have been several studies in lung transplant candidates examining the benefits of exercise training pre-transplant. In a small pilot study of 9 lung transplant candidates, lung transplant patients were randomized to a 6-week rehabilitation program comprising of education versus education plus exercise. In both groups, the walk distance and Quality of Well-being scores increased with completion of the 6 week program but no difference was seen between groups in this small group of patients. Florian et al. demonstrated that a multi-disciplinary program consisting of 36 sessions pre-transplant had a significant effect on exercise capacity and HRQL pre-transplant. Similarly, in 60 lung transplant candidates with COPD, 6MWD was shown to have mild improvement (about 35 meters) in both the continuous and interval training groups. Jastrzebski et al. examined the benefits of a 12 week Nordic walking program in lung transplant candidates demonstrating improvements in 6MWD and HRQL, without any adverse events. At our center, Li et al retrospectively examined 345 lung transplant candidates over a five year period and found that pre-transplant exercise capacity and muscle training volumes were preserved over a median duration of six months, whereas HRQL scores declined. It is possible that the decline seen in HRQL with pulmonary
rehabilitation compared to other rehabilitation programs in the present study may be related to disease severity and longer wait-time to transplantation (median of 6 months), compared to other standard 12 week rehabilitation programs.\textsuperscript{371,372} Despite the decline in HRQL, lung transplant candidates with a greater 6MWD pre-transplant had a shorter hospital length of stay post-transplant.\textsuperscript{110} To date, the benefits of pre-transplant rehabilitation on post-transplant functional recovery, HRQL, and clinical outcomes (ICU, hospital length of stay, and discharge disposition) have not been evaluated.

At our center, pre-transplant outpatient pulmonary rehabilitation is standard of care with all patients exercising three times per week for the entire time they are on the lung transplant waiting listing. This is fairly unique among the solid organ transplant programs in Canada.\textsuperscript{373} Lung transplant candidates perform stretching, aerobic and resistance training with each session lasting about 90 minutes in duration. Patients participate in the program until transplantation and all exercise sessions are supervised by a physical therapist. The training intensity is determined by the physical therapist and progressed accordingly based on rate of perceived exertion, exercise capacity, heart rate and oxygen requirements. A more detailed description of the Toronto Lung Transplant Rehabilitation program has been previously published.\textsuperscript{374} Patients that are too ill to participate in pulmonary rehabilitation due to admission to the hospital ward or ICU, participate in some form of rehabilitation guided by the inpatient physical therapists. Stretching exercises, limited resistance and aerobic training are incorporated into a daily routine as per patient tolerance.\textsuperscript{374}

1.4: Implications of Prolonged Mechanical Ventilation, Critical Care and Hospital Length of Stay

Lung transplant recipients are routinely admitted to the ICU post-transplant; however, the post-operative period can be associated with several complications that can prolong ICU and
hospital length of stay. The typical range for ICU and hospital length of stay in lung transplant recipients at our center has been 4-5 and 18-23 median days, respectively.\textsuperscript{109,110,113} Primary graft dysfunction (PGD) is one of the leading causes of early morbidity and mortality in lung transplant recipients.\textsuperscript{375,376} Infections, acute rejection, and non-pulmonary events such as arrhythmias and delirium may also complicate the post-operative period.\textsuperscript{377} Treatment for PGD is largely supportive with low volume mechanical ventilation for prevention of barotrauma and application of extra-corporeal membrane oxygenation for refractory hypoxemia.\textsuperscript{378} Unfortunately, PGD can also lead to a protracted course of mechanical ventilation or extra-corporeal life support, which can potentially result in a number of extra-pulmonary complications as seen with other ICU survivors.\textsuperscript{379}

1.4.1 Intensive Care Unit Length of Stay and Clinical Implications

Prolonged mechanical ventilation has been associated with poor functional outcomes and increased health-care costs. A single center study by Unroe et al. of 126 medical and surgical patients showed that 3 weeks of mechanical ventilation was associated with an overall one-year mortality rate of 44\%, with only 9\% being functionally independent.\textsuperscript{380} Similarly, the one-year mortality post-ICU was 48\% in a multi-centered study of patients receiving 21 days of mechanical ventilation.\textsuperscript{381} Herridge et al. demonstrated in a large, prospective multi-center study that patients experienced significant morbidity and mortality after 7 or more days of mechanical ventilation.\textsuperscript{319} Age and ICU length of stay were significant prognostic markers of functional recovery and one year mortality in this group of patients. Younger patients (< 42 years old) and those that had an ICU length of stay of less than 2 weeks had the best functional outcomes. More importantly, early functional recovery as measured by the 7-day functional independence measure was an independent predictor of one-year mortality. Thus,
poor functional outcomes can result even after as little as 7 days of mechanical ventilation in a medical and surgical ICU setting.

Patients that sustain a prolonged ICU course are susceptible to ICU acquired weakness (ICUAW), which is characterized by clinically detected weakness in the setting of critical illness when no other plausible etiology is identified. Factors associated with ICUAW include multi-organ dysfunction, sepsis, prolonged period of mechanical ventilation or immobilization. At least one quarter of patients are observed to have ICUAW after 5-7 days of mechanical ventilation. In those ventilated for ≥ 10 days, ICUAW was seen in as many as two-thirds of patients. ICUAW is a major determinant of functional impairment and health care utilization. In non-transplant populations with acute lung injury, prolonged mechanical ventilation (≥ 7 days) has been shown to be associated with impairments in physical function and HRQL that persisted up to 5 years, despite complete normalization of their lung function.

Transplantation adds an extra level of complexity to the continuum of skeletal muscle dysfunction given the interplay between pre-transplant factors related to chronic disease (e.g. deteriorating clinical status) and post-transplant factors (e.g. reduced mobility or activity from prolonged ICU stay, ongoing immune-suppression). Thus, skeletal muscle dysfunction in the pre-transplant period may be an even greater concern in lung transplant recipients with complex peri-operative courses due to factors such as PGD, infection, systemic organ failure, and bleeding. This can potentially result in prolonged ICU length of stay and higher rates of ICUAW.

Even though it has not been well described in lung transplant recipients, prolonged mechanical ventilation may lead to other significant extra-pulmonary manifestations such as cognitive impairment and psychological sequelae (i.e. depression). Cognitive impairment
(global cognition and executive function) is an important manifestation of ICU survivors and has been seen across ICU etiologies.\textsuperscript{391} In survivors of acute respiratory distress syndrome, cognitive impairments were observed in 70-100\% of patients at hospital discharge and 46-80\% at one year.\textsuperscript{392} In lung transplant recipients, Smith and colleagues observed that 57\% of participants had persistent cognitive impairment at three months post-transplant, with cognitive performance worse in those experiencing delirium during hospitalization post-transplant.\textsuperscript{393} In addition, psychological distress can result from numerous stressors surrounding a complex ICU stay post-transplant given the underlying muscle weakness, cognitive impairments, and potential strain on the caregiver.\textsuperscript{394,395} These factors may result in increased health-care utilization and increased re-admission rates as seen in other ICU populations,\textsuperscript{319,396} which may have significant effects on functional recovery and morbidity in lung transplant recipients.

1.4.2 Functional Status Prior to ICU Admission

There have only been a few studies that looked at the importance of functional trajectories prior to ICU admission, as most studies enrolled patients at the time of their ICU admission. In a unique study by Ferrante et al utilizing a longitudinal database of community dwelling elderly patients, those with higher levels of disability on 13 basic, instrumental, and mobility activities prior to their ICU admission experienced significantly worse outcomes post-ICU discharge.\textsuperscript{397} Pre-ICU functional trajectory groups with mild-moderate and severe disability had double (HR: 2.41 95\% CI 1.29-4.50) and triple (HR: 3.84 95\% 1.84-8.03) the rates of one-year mortality post ICU discharge, respectively. Similarly, Lone et al. demonstrated in a large representative national database of 7656 ICU admitted patients across the United States in 2005, the number of previous hospital admissions (RR: 1.05 95\% 1.04 – 1.05) and comorbidities (RR (≥ 1 score on the Charlson index): 1.39 95\% 1.29 -1.51) were independent
predictors of subsequent hospital admission over the next five years, whereas acute illness severity or organ support (e.g. dialysis) at the time of ICU admission were not predictive of subsequent health-care utilization. These studies illustrate the important impact of pre-ICU comorbidities and functional independence on health-care utilization, morbidity, and mortality post critical illness.

1.4.3 Peri-operative ICU Management

Mechanical Ventilation or Extra-Corporeal Life Support Pre-Transplant

Lung transplant candidates admitted to the ICU pre-transplant are at increased risk of complications such as prolonged ICU stays pre- and post-transplant, increased risk of infections, malnutrition, and skeletal muscle impairments. Even short periods of immobilization of one week in the ICU have been shown to be associated with significant early and rapid muscle atrophy, associated with decreased protein synthesis and significant ICU acquired weakness, which can result in significant morbidity and mortality. Thus, lung transplant patients requiring traditional non-ambulatory mechanical ventilation pre-transplant are at risk of critical care myopathy and have a significantly lower one year survival compared to those transplanted without any form of bridging life support.

In the last several years, ECMO has been applied with minimal sedation which allows awake patients to participate in physical activity and rehabilitation. The outcomes with awake ECMO strategies compared to traditional non-ambulatory mechanical ventilation strategies have been favorable. Feuhner et al demonstrated that survival at 6 months post-transplant in the ECMO group (n=26) was 80% compared to 50% in the mechanically ventilated, non-ambulatory historical control group (n=34). Furthermore, lung transplant patients requiring ECMO pre-transplant compared to mechanically ventilated patients had a shorter period of post-transplant mechanical ventilation (14 vs. 37 median days, p=0.04) and a trend towards
shorter hospital length of stay (38 vs. 67 median days, p=0.06). Similarly, Nosotti et al. demonstrated in 11 patients a significant survival benefit at one year post-transplant in patients bridged with ECMO (87.5%) compared to invasive mechanical ventilation (50%).

Early ambulation of critically ill patients on ECMO has been undertaken by several centers including our own, but most of the evidence for long term functional benefits with early rehabilitation in the ICU comes from patients on mechanical ventilation as described below. Even though the number of transplants bridged with ECMO has been small, ECMO is emerging as a viable option for bridging critically ill, appropriately selected lung transplant candidates to transplantation. This selection is critical given some of the potential physical and cognitive morbidity that may result on ECMO with increased risk of bleeding, infection, or renal failure and less common complications such as limb ischemia, stroke and air emboli.

Early Mobility During and After Mechanical Ventilation

In the critical care setting, early rehabilitation of mechanically ventilated patients has been shown to be safe and effective. Early activity in the ICU setting has been associated with reduced ICU and hospital length of stay and reduction in readmission rates and mortality in the first year post ICU. Similarly, the functional status is significantly improved at the time of hospital discharge in those undergoing physical and occupational therapy early on during their ICU admission. Burtin et al. demonstrated in a clinical trial of 90 critically ill survivors that early exercise training (starting from day 5) was associated with improved 6MWD, quadriceps strength and SF-36 Physical Functioning at hospital discharge compared to the control group. With respect to exercise intensity, one well randomized controlled trial demonstrated that physical function at 6 months post-ICU discharge was improved with both intensive and standard physical therapy programs, but the benefit of a more intensive physical therapy program was not observed. It is possible that the lack of benefit with the more
intensive physical therapy program may be related to the increased heterogeneity seen in critical care populations with varying ages, comorbidities, and ICU durations. Thus, the optimal rehabilitation program in the ICU and post-ICU discharge remains unclear and may need to be tailored to the individual patient given the varying case complexity of critical care survivors.

Despite good evidence for physical therapy in the ICU setting, there is significant variability in mobility practices internationally for mechanically ventilated patients. In a large cohort of ICU patients in Scotland and Australia, early mobilization was not commonly utilized (Scotland: 41% vs. Australia: 16%). Several barriers were identified which included sedation, mechanical ventilation and physiological instability. In another prospective, multi-centered study across 12 ICUs in New Zealand and Australia of 194 patients, no mobilization was observed in more than 80% of potential episodes for early mobility. More than half of these patients went on to develop ICUAW, which was associated with increased mortality in the first three months post ICU discharge. In North America, there was also significant heterogeneity in the type and frequency of physiotherapy provided to ICU patients based on the hospital and clinical scenario.

**Rehabilitation in the Intensive Care Unit for Lung Transplant Recipients**

As with other critical care populations, early rehabilitation can help with functional capacity, muscle strength and discharge from the critical care unit. In a study by Maury et al., the deterioration in quadriceps muscle strength from pre-transplant levels was observed to be related to ICU length of stay. The recovery in muscle strength in lung transplant recipients is multi-factorial with significant contributing factors including high dose of immunosuppression, prolonged bed rest, and impairments in oxidative capacity.
Physical rehabilitation in the ICU setting should be started as early as possible focusing on sitting and early mobilization. The same principles apply in lung transplantation as in other critical care patients, in-order to offset the early onset of skeletal muscle wasting and weakness. At our center, critical care patients participate in an early mobility program with close supervision and tailored progression from the physical therapist. The program progresses from passive and active bed exercises, transferring from bed to chair, standing or marching on the spot, and ambulating with high wheeled walker up to 200 m. These set of exercises can be performed in the ICU setting in patients on mechanical ventilation and extra-corporeal life support, with appropriate modifications. There is good evidence to support the safety and feasibility of early rehabilitation in critically ill patients. Furthermore, there is significant benefit with respect to lower extremity strength, quality of life, decreased ICU and hospital length of stay, and significant cost-savings, but these have not been assessed in lung transplant recipients.

1.5: Recovery Beyond Hospital Admission in Lung Transplant Recipients

1.5.1 Out-Patient Rehabilitation:

The benefits of outpatient pulmonary rehabilitation beyond the immediate post-transplant period have been described in several studies to-date. Langer et al. had examined 12 weeks of supervised lower limb resistance and endurance training (three times per week) initiated after hospital discharge compared to routine physical activity education. Six-minute walk distance, quadriceps strength, physical activity levels and SF-36 physical functioning domain were significantly increased after 12 weeks of exercise with differences between the two groups persisting up to 12 months. Similarly, Maury et al. had previously demonstrated in an observational study that three months of pulmonary rehabilitation post-transplant was
associated with improvements in exercise capacity (140 ± 91 m) and quadriceps strength (35 ± 48%), but quadriceps strength still remained below pre-transplant levels at three months post-transplant. Munro et al observed a similar pattern of improvement in exercise capacity, lung function and all domains of the SF-36 in the first 3 months post-transplant with a standard outpatient pulmonary rehabilitation program. However, the effects of the two observational studies need to be interpreted with caution given the natural improvement observed in the functional measures in the first year post-transplant. With the post-transplant rehabilitation studies to-date, lung transplant recipients with complicated courses post-transplant (i.e. prolonged periods of mechanical ventilation) were generally excluded from these studies.

At our center, lung transplant recipients participate in outpatient pulmonary rehabilitation for 12-weeks post-transplant. The program is similar to the pre-transplant phase with stretching, aerobic and resistance exercises performed three times weekly. The focus on improving ambulation, exercise capacity and recovery of muscle strength and function are given during this rehabilitation phase.

1.5.2 Inpatient Rehabilitation Post-Transplant:

Whereas outpatient pulmonary rehabilitation is generally standard of care across most Canadian lung transplant centers, some patients require an inpatient rehabilitation program due to physical deconditioning resulting from a prolonged hospital stay. A number of medical complications can arise such as major bleeding, pulmonary infections, PGD, hemodynamic instability and requirement for hemodialysis, which can prolong discharge from the critical care unit and hospital. At our center, lung transplant recipients that do not meet functional requirements for a safe discharge home based on a multi-disciplinary assessment are referred to an inpatient rehabilitation program. We have recently demonstrated that in addition to
total hospital length of stay, other independent predictors of discharge to inpatient rehabilitation were age, last 6MWD pre-transplant and requirement for mechanical ventilation pre-transplant.\textsuperscript{113}

Inpatient rehabilitation programs for lung transplant recipients have been shown to be effective allowing low intensity resistance, aerobic and balance training in a closely supervised environment.\textsuperscript{320,421} The most common benefits with inpatient rehabilitation have been in the physical domains noted on the functional independence measure associated with bathing, dressing, walking, stair climbing and ability to perform transfers, which are affected to a greater degree by proximal muscle weakness.\textsuperscript{421} Lung transplant recipients demonstrated similar gains in FIM per day with rehabilitation similar to the benefits observed in other forms of inpatient rehabilitation programs such as stroke.\textsuperscript{422} Thus, inpatient rehabilitation programs allow for earlier discharge from acute care hospital beds and earlier functional recovery.\textsuperscript{320,421} However, close medical monitoring is required for this patient population given the risk of infection and graft rejection that might warrant transfer back to the acute care facility.\textsuperscript{320,421}

1.6: Summary

Lung transplantation is a life-saving therapy for patients with end-stage lung disease. Current evidence demonstrates that skeletal muscle dysfunction is prevalent in advanced lung disease and lung transplant candidates. There are a number of generic and disease specific factors that contribute to impairments in skeletal muscle mass, strength and function, which can be characterized using several non-invasive modalities. However, the clinical implications of skeletal muscle impairments (muscle mass, strength and function) with respect to pre-transplant exercise capacity, ADL and HRQL have not been well described. Furthermore, the association of pre-operative skeletal muscle function with post-transplant functional recovery and clinical outcomes remains unknown, especially in patients with a complicated course.
post-transplant. Thus, utilization of readily available non-invasive measures to characterize skeletal muscle dysfunction will provide an opportunity to better understand the importance of pre-operative skeletal muscle mass, strength and physical function throughout the transplant process.

A better understanding of the nature, prevalence and clinical implications of muscle dysfunction could potentially lead to more informed transplant listing criteria and improved clinical outcomes pre- and post-transplant. It can also help with targeted exercise training to improve skeletal muscle health and potentially patient reported outcomes such as HRQL and ADL. A comprehensive understanding of skeletal muscle dysfunction can be applied to other high-risk populations such as the elderly, other solid organ transplant candidates, and those with prolonged hospital or ICU stays.
CHAPTER 2

Thesis Overview:

The proposed doctoral work provides an opportunity to better understand the manifestations of skeletal muscle dysfunction and the clinical implications of muscle dysfunction in lung transplant patients. Given the lack of agreement as to which definition of skeletal muscle dysfunction should be utilized in chronic disease, the present doctoral work will examine individual elements of skeletal muscle dysfunction (muscle mass, strength and physical performance) and the combination of these parameters to improve our understanding of the relationship between these measures. This will be accomplished through three complementary studies, with different lung transplant cohorts, targeting both the pre- and post-transplant periods, Figure 2-1.

2.1 Overall Aim and Hypothesis:

Overall Aim:
To characterize individual elements of skeletal muscle function (muscle mass, strength and physical performance) in lung transplant candidates and assess their association with pre- and post-transplant physical function, HRQL, and clinical outcomes.

Overall Hypothesis:
Skeletal muscle mass, strength and physical performance will be independently associated with pre-transplant physical function and HRQL. Pre-operative skeletal muscle dysfunction will help inform post-transplant functional recovery, HRQL, and clinical outcomes in the early post-transplant period.
2.2 Study Aims and Hypotheses:

**Study # 1 (Chapter 3)**

Study one will retrospectively assess the utility of using thoracic computed tomography (CT) scans in 527 lung transplant candidates (November 2003 to May 2009), as a measure of skeletal muscle mass, with a subset of patients having HRQL and pulmonary rehabilitation measures.

**Aims:**

1A) Compare thoracic muscle CSA in lung transplant candidates and controls.

1B) Assess the associations of thoracic muscle CSA with exercise capacity, muscle training volumes, HRQL, pre- and post-transplant clinical outcomes.

**Hypotheses:**

1A) Lung transplant candidates will have lower muscle CSA than healthy controls.
1B) Low thoracic muscle CSA will be associated with reduced exercise capacity, HRQL, lower muscle training volumes, longer hospital length of stay and increased peri-operative mortality post-transplant.

Study # 2 (Chapter 4):

Study two is a prospective cohort study evaluating muscle mass, strength and physical performance in 50 adult lung transplant candidates participating in pulmonary rehabilitation.

Aims:

2A) Characterize the distribution of skeletal muscle deficits (low muscle mass, strength and physical performance) in lung transplant candidates.

2B) Assess the association of skeletal muscle deficits with pre-transplant exercise capacity, activities of daily living and HRQL.

2C) As a secondary aim, assess the association between skeletal muscle deficits and pre- and early post-transplant clinical outcomes.

Hypotheses:

2A) Lung transplant candidates will have significant overlap in skeletal muscle deficits with impairments seen predominantly in lower extremity strength and physical performance.

2B) Quadriceps strength and physical performance will be associated with exercise capacity, activities of daily living and HRQL pre-transplant.

2C) The combination of all three skeletal muscle deficits will be associated with increased hospital length of stay and pre- and early post-transplant mortality.

Study # 3 (Chapter 5):

Study three will evaluate skeletal muscle dysfunction in the pre- transplant period in a group of lung transplant recipients who are at high risk for long-term skeletal muscle dysfunction.

This will be a sub-analysis of a large prospective cohort study (RECOVER), which assessed exercise capacity, HRQL, physical function and clinical outcomes up to 2 years post-ICU, in
survivors who required mechanical ventilation for at least 7 days. For all 80 lung transplant recipients in this cohort, we will retrospectively collect rehabilitation data pertaining to pre-transplant muscle mass, strength and exercise capacity to assess their clinical implications on post-transplant outcomes three-months post-ICU discharge.

**Aims:**

3A) To assess the association of pre-transplant skeletal muscle mass, strength and exercise capacity on functional independence 7-days post ICU discharge in lung transplant recipients with prolonged mechanical ventilation (≥ 7 days).

3B) To evaluate the impact of pre-transplant muscle mass, strength and exercise capacity on early post-transplant functional independence, exercise capacity (6MWD), HRQL (SF-36 PCS), and discharge disposition at 3 months post-ICU discharge.

**Hypotheses:**

3A) Pre-transplant functional deficits (muscle strength and exercise capacity) will be independently associated with impaired functional independence at 7 days post-ICU discharge.

3B) Pre-transplant functional deficits (muscle strength and exercise capacity) will be associated with functional independence, HRQL and the change in exercise capacity from pre-transplant values three months post-ICU discharge. Skeletal muscle mass and exercise capacity will be important mediators of discharge disposition.
CHAPTER 3:

3.0 Thoracic Muscle Cross-Sectional Area is Associated with Hospital Length of Stay Post Lung Transplantation

3.1 Abstract:

**Background/Objectives:** Low muscle mass is common in lung transplant candidates, however, the clinical implications have not been well described. The study aims were to compare skeletal muscle mass in lung transplant candidates with controls using thoracic muscle cross-sectional area (CSA) from computed tomography and assess the association with pre- and post-transplant clinical outcomes.

**Methods:** This was a retrospective, single centre cohort study of 527 lung transplant candidates (median age: 55 IQR [42-62] years; 54% male). Thoracic muscle CSA was compared to an age-and sex-matched control group. Associations between muscle CSA and pre-transplant six-minute walk distance (6MWD), health-related quality of life (HRQL), delisting/mortality, and post-transplant hospital outcomes and one-year mortality were evaluated using multivariable regression analysis.

**Results:** Muscle CSA for lung transplant candidates was about 10% lower than controls (n=38). Muscle CSA was associated with pre-transplant 6MWD, but not HRQL, delisting or pre- or post-transplant mortality. Muscle CSA (per 10 cm$^2$ difference) was associated with shorter hospital stay [0.7 median days 95% CI (0.2-1.3), p=0.04], but did not predict discharge to inpatient rehabilitation [OR: 0.85 95% (CI 0.71 to 1.02), p=0.07] after adjustment for age, sex, diagnosis, height-squared and 6MWD.
Conclusion: Thoracic muscle CSA is a simple, readily available estimate of skeletal muscle mass in lung transplant candidates predictive of hospital length of stay, but further study is needed to evaluate the relative contribution of muscle mass versus functional deficits (strength and performance) in predicting post-transplant outcomes.
3.2 Introduction:

Lung transplantation provides a significant benefit with respect to HRQL, exercise capacity, and survival in people with advanced lung disease. However, optimal selection of lung transplant candidates remains of critical priority given the morbidity and mortality associated with transplantation. One fifth of lung transplant candidates die or are de-listed prior to receiving a transplant and the mortality rate post-transplant is almost 20% in the first year. Despite improvements in medical management and surgical techniques, there is a growing need for novel assessments of physical function and body composition that could aid with risk stratification and management in this population.

Sarcopenia, defined as age-related loss of muscle mass and function, is related to increased physical disability, impairments in HRQL and death in older adults and is accelerated in chronic disease states. Low muscle mass has been independently associated with reduced post-transplant survival in liver and renal transplant recipients. In lung transplant patients, low muscle mass has been observed to be prevalent using bio-electrical impedance (BIA), however, measures of muscle mass have not been routinely utilized for prognostication in lung transplantation.

A simple, readily available measure of muscle mass is needed in lung transplantation. A practical method for quantifying segmental muscle mass is computed tomography (CT), which is considered a gold-standard for muscle size measurement. Muscle CSA taken from a single axial slice from abdominal CT has been shown to be a good marker of total body skeletal mass. In those undergoing major abdominal surgeries, low psoas muscle size from abdominal CT has been associated with increased post-operative complications, health-care costs and increased mortality. In a recent systematic review of 19 studies in liver transplantation, low skeletal muscle mass (i.e. sarcopenia) quantified with abdominal CT was
observed to be prevalent (range 22-70%) and associated with waiting list and post-transplant mortality. Similarly, in lung transplant patients muscle CSA from abdominal CT has been associated with post-transplant outcomes such as intensive care unit (ICU) and hospital length of stay. In COPD patients, muscle CSA from chest CT has been associated with disease severity, exercise capacity, and mortality. We have recently shown that measures of thoracic muscle CSA from a single axial slice of the chest correlated well with accepted measures of muscle mass and were reproducible in lung transplant candidates. Chest CT muscle CSA could prove to be a valuable marker in risk stratification given the availability of chest CT in clinical practice. To our knowledge, the clinical implications of muscle CSA with respect to pre-transplant de-listing/mortality, HRQL, and strength training volumes have not been previously described. Furthermore, the incremental utility of muscle CSA to predict post-transplant outcomes compared to established parameters such as the 6MWD remains unknown.

The aims of this study were to compare thoracic muscle CSA in lung transplant candidates with controls and to assess the associations of thoracic muscle CSA with six-minute walk distance (6MWD), strength training volumes, HRQL, pre- and post-transplant clinical outcomes. The secondary aim was to evaluate the prognostic utility of muscle CSA as an adjunct to pre-transplant 6MWD in predicting early post-transplant outcomes. We hypothesized that muscle CSA would be significantly reduced in lung transplant candidates and independently associated with functional capacity, pre-transplant de-listing/death, and early post-transplant outcomes, independent of 6MWD.

3.3 Methods:

3.3.1 Study Design and Participants:
This was a retrospective cohort study of adult lung transplant candidates (age ≥ 18 years)
listed at University Health Network between November 1, 2003 and May 30, 2009. This period was chosen due to an available set of exercise data from a prior study.\textsuperscript{110} For inclusion in the current study, patients had to have a chest CT within 3 months of transplant listing. Lung transplant patients who were listed for a re-transplant during the study period were excluded. Research ethics approval was obtained from University Health Network (REB # 13-6430-BE) and University of Toronto (REB # 30785).

The control group was comprised of 38 participants matched for age (≥ 50 years old) and sex who underwent lung cancer screening with low dose CT, as part of a research study at University Health Network.\textsuperscript{430} All participants had at least a 10 pack-year smoking history, had generally good health, and no history of malignancy. The sample size was determined based on the assumption that thoracic CSA would be 20% lower for lung transplant candidates than controls (effect size=1.0, n=17 for each sex). Previous studies have demonstrated that peripheral measures of muscle mass (i.e. quadriceps CSA) were about 20% lower in COPD patients compared with controls.\textsuperscript{245,257}

3.3.2 Muscle Cross-Sectional Area Assessment:

Thoracic CT (1-5 mm slices) were acquired on a Toshiba Aquillion scanner as part of routine clinical evaluation for lung transplantation. The CT scan utilized for analysis was within three months of transplant listing. Muscle CSA of the pectoralis major and minor, intercostals, serratus anterior, paraspinal and latissimus dorsi muscles was quantified from CT using Slice-O-matic software (Version 5.0, Tomovision, Montreal, Canada, Slice-O-Matic), Hounsfield unit ranges of -29 to 150, Figure 3-1.\textsuperscript{431,432} The average of three slices, one at the carina level and one slice above and below, were used to quantify muscle CSA. The same technique was applied to the control group using low dose thoracic CT images (1-1.25 mm slices).
We have previously demonstrated that thoracic muscle CSA from a single axial CT slice correlates strongly with thoracic muscle volume ($r=0.89-0.91$, $p < 0.001$) and has excellent inter-rater reliability. The inter-rater reliability for this study was re-assessed in the first twenty subjects, between two observers (D.R and P.M) at the carinal level, (ICC $=0.998$, 95% CI $0.995$ to $0.999$). Given the high ICC values, muscle CSA for the remaining subjects was assessed by one observer (D.R).

The construct validity of thoracic muscle CSA was also assessed using a separate lung transplant cohort ($n=50$) from our center described in Chapter 4. Thoracic muscle CSA had a strong association with fat-free mass index from BIA ($r=0.71$, $p < 0.0001$), Appendix-Figure 1A.

**Figure 3-1:** Representation of Cross-sectional Muscle Area using Slice-O-Matic Software

**Thoracic Muscles:** Orange = Pectoralis; Green = Intercostal Muscles; Red = Para-Spinal Muscles; Blue = Serratus Anterior and Latissimus Dorsi Muscles

### 3.3.3 Clinical Variables:

The following variables were abstracted from the medical records and Toronto Lung Transplant clinical database at the time of transplant listing: Age (years), sex, anthropometric
measurements (weight (kg), height (cm), and body mass index (kg/m^2)), diagnostic indication for transplant, daily corticosteroid use, albumin (g/L), and need for bridging to lung transplantation with mechanical ventilation or extra-corporeal life support. The listing urgency status (Status 1, 2 and Rapidly deteriorating) was assessed at the time of transplant listing, which is a subjective determination of disease severity predictive of waiting list survival.61

Exercise capacity was evaluated using the 6MWD (meters), which was routinely performed within 4 weeks of transplant listing by a physical therapist as per American Thoracic Society guidelines104,433 and reported as percent predicted.434 All lung transplant candidates at our centre participate in a mandatory pulmonary rehabilitation program three times per week, which is initiated at the time of listing and is ongoing for the waitlist duration.110,125 As a surrogate of muscle strength, biceps and quadriceps strength training volumes at the start of pulmonary rehabilitation (end of first week) were calculated from training logs on a subset of patients as follows: [# repetitions * weight (pounds) * # sets].110 Training volumes were calculated at the start of rehabilitation to reduce the influence of any training effect with rehabilitation.

Short-Form 36 (SF-36) and St. George’s Respiratory Questionnaire (SGRQ) were available in a subset of patients within three months of transplant listing from a completed prospective study on HRQL.26 We included the SF-36 physical function domain, SF-36 physical component score, and the activity domain of the SGRQ given their associations with physical activity in lung transplant patients.109,117

Pre-transplant clinical outcomes assessed were medical delisting or death. We treated these two as a composite outcome and patients were medically delisted if they were too ill to derive benefit from lung transplantation. Post-transplant outcomes included: days of mechanical ventilation, ICU days, hospital length of stay, mortality in hospital and at one year, and
development of grade 3 primary graft dysfunction (PGD) at 72 hours as per International Society of Heart-Lung Transplant consensus definition (PaO2/FiO2 ratio of < 200 mmHg or requirement for extra-corporeal membrane oxygenation or nitric oxide). Grade 3 PGD was specifically evaluated as it is associated with post-transplant mortality. Discharge disposition (home versus inpatient rehabilitation) was also documented. The standard practice at our center is for lung transplant recipients to participate in an outpatient rehabilitation program for at least 3-months post-transplant; however, recipients that are unable to meet functional requirements for safe discharge home are referred to an inpatient rehabilitation program. Pre- and post-transplant outcomes were abstracted from the Toronto Lung Transplant clinical database.

3.3.4 Statistical Analysis:

Analysis was performed using Graph-Pad Prism (Version 7.0) and R (Version 3.32). Continuous variables are described using mean ± standard deviation or median [interquartile range 25-75%] with categorical variables described using frequencies. Visual inspection of scatter plots, Kolmogorov-Smirnov and Pearson omnibus normality tests were used to assess the distribution of data. Muscle CSA of lung transplant candidates aged 50-69 years versus controls in the same age group were compared using an unpaired t-test with Welch’s correction, stratified by sex.

Bivariate and multivariable associations between muscle CSA and 6MWD, strength training volumes, HRQL, and pre-transplant medical delisting/death and post-transplant outcomes were assessed using linear and logistic regression analyses. Covariates were selected based on previously described associations with muscle mass (age, sex, height-squared (m²) and diagnosis) with additional clinically relevant co-variates outlined in the results section. Logistic regression analyses examined the association of muscle CSA with development of grade 3 PGD at 72 hours and mortality on the post-transplant admission and at one year. After
exclusion of patients who died during the hospitalization post-transplant, multivariable quantile regression was used to assess the relationship of pre-transplant muscle CSA with median time-based post-transplant outcomes (days of mechanical ventilation, ICU and hospital length of stay). Discharge disposition (home versus inpatient rehabilitation) was assessed using logistic regression. Pre-transplant 6MWD was included in post-transplant multivariable regression models to assess the incremental utility of muscle CSA in prediction of early post-transplant outcomes.

We performed model diagnostics examining plots of residuals to ensure assumptions of independence, normality and constant variation of errors were met. A p value of < 0.05 was considered significant for all analyses.

3.4 Results:

3.4.1 Participants:

There were 527 lung transplant candidates included in the study, Figure 3-2. Baseline characteristics are described in Table 3-1. The mean muscle CSA for the lung transplant cohort was 94 ± 25 cm². Greater muscle CSA was associated with male sex, greater body mass index, height, and a diagnosis of interstitial lung disease (ILD) or cystic fibrosis (CF), Table 3-1. Muscle CSA was not associated with age, daily prednisone use, albumin levels, or listing status (Table 3-1).
Figure 3-2: Flow Diagram of Lung Transplant Candidates Included in the Study
### Table 3-1: Patient Characteristics and Associations with Muscle Cross-sectional Area

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cohort Summary (n=527)</th>
<th>Bivariate: Mean Difference in muscle CSA</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>55 IQR [42-62]</td>
<td>-1.17 (-2.72 to 0.37)</td>
<td>0.14</td>
</tr>
<tr>
<td>Male Sex</td>
<td>283 (54%)</td>
<td>33.4 (30.1 to 36.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ILD</td>
<td>225 (43%)</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>COPD</td>
<td>123 (23%)</td>
<td>-18.7 (-24.0 to -13.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CF</td>
<td>98 (19%)</td>
<td>-0.95 (-6.7 to 4.8)</td>
<td>0.74</td>
</tr>
<tr>
<td>PAH</td>
<td>21 (4%)</td>
<td>-12.3 (-23.1 to -1.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Other</td>
<td>60 (11%)</td>
<td>-14.9 (-21.8 to -8.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body Mass Index (per kg/m²), n=521</td>
<td>24.0 ± 4.4</td>
<td>1.77 (1.29 to 2.24)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI Categories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal Weight: 18.5-24.9</td>
<td>223 (43%)</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Underweight: BMI &lt; 18.5</td>
<td>68 (13%)</td>
<td>-4.2 (-10.8 to 2.4)</td>
<td>0.28</td>
</tr>
<tr>
<td>Overweight: 25.0-29.9</td>
<td>188 (36%)</td>
<td>9.9 (5.2 to 14.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Obese: ≥ 30.0</td>
<td>42 (8%)</td>
<td>22.3 (14.3 to 30.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (per cm), n=527</td>
<td>168 ± 10</td>
<td>1.45 (1.27 to 1.64)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Albumin (per 1 g/L), n=472</td>
<td>39 ± 6</td>
<td>0.06 (-0.33 to 0.45)</td>
<td>0.76</td>
</tr>
<tr>
<td>Daily Prednisone Use</td>
<td>192 (36%)</td>
<td>-2.1 (-6.6 to 2.4)</td>
<td>0.36</td>
</tr>
<tr>
<td>Transplant Listing Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One (standard priority)</td>
<td>260 (49%)</td>
<td>Reference</td>
<td>-</td>
</tr>
<tr>
<td>Two (high priority)</td>
<td>229 (44%)</td>
<td>2.8 (-1.7 to 7.3)</td>
<td>0.23</td>
</tr>
<tr>
<td>Rapidly Deteriorating</td>
<td>38 (7%)</td>
<td>4.7 (-4.0 to 13.3)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Data are presented as n (%), mean ± SD, or median [25-75% interquartile range].

**Abbreviations:** BMI = Body Mass Index; CSA = Cross-sectional area; COPD = Chronic Obstructive Pulmonary Disease; CF = Cystic Fibrosis; ILD = Interstitial Lung Disease; PAH = Pulmonary Arterial Hypertension.

### 3.4.2 Muscle CSA in Lung Transplant Candidates and Healthy Controls

When stratified by sex and age (50-69 years), lung transplant candidates had 10% lower muscle CSA than controls with no significant difference in BMI (Figure 3). Muscle CSA was as follows: [Males: Lung Transplant (n=183): 106 ± 20 vs. Controls (n=19) 117 ± 12 cm², p=0.002 and Females: Lung Transplant (n=131): 72 ± 15 vs. Controls (n=19): 80 ± 8 cm², p=0.001].
Figure 3-3A – Male Lung Transplant Candidates vs. Controls (Ages 50-69 years):
Age (Lung Transplant: 60.0 ± 5.1 vs. Controls 59.6 ± 5.4 years, p=0.78); BMI (Lung Transplant: 25.4 ± 4.0 kg/m² vs. Controls: 25.7 ± 2.5 kg/m², p=0.67).

Figure 3-3B - Female Lung Transplant Candidates vs. Controls (Ages 50-69 years):
Age (Lung Transplant: 59.7 ± 5.1 vs. Controls: 59.5 ± 5.3 years, p=0.89); BMI (Lung Transplant: 24.5 ± 4.1 kg/m² vs. Controls: 26.1 ± 3.8 kg/m², p=0.11)

Abbreviations: LTx = Lung Transplant; mCSA = Muscle Cross-Sectional Area
3.4.3 Six-Minute Walk Distance, Strength Training Volumes, and Quality of Life:

The lung transplant candidates had low 6MWD (46 ± 17 % predicted) and HRQL (SF-36 PCS: 27 ± 8 and SGRQ Activity Domain: 92 [79-92]). Six-minute walk distance, strength training volumes and HRQL were associated with muscle CSA in the bivariate analysis (Table 3-2). This relationship remained significant for 6MWD and strength training volumes when adjusted for age, sex, height-squared and diagnosis, Table 3-2. For instance, for every 10 cm² increase in muscle CSA, 6MWD increased by 9.3 m 95% CI (3.7-14.9), p= 0.001, R²=0.23. The strength of the association with muscle CSA was stronger for biceps training volumes than quadriceps (R² 0.21 vs. 0.10) after adjustment. There was no independent relationship observed between available HRQL measures and muscle CSA after adjustment for covariates (Table 3-2). Lung transplant candidates with available HRQL data (n=400) compared to those without (n=127) had greater 6MWD and were more likely to be transplanted with no difference in muscle CSA or demographics observed between the two groups (Table 3-3).

3.4.4 Pre-transplant Clinical Outcomes:

Of the 527 lung transplant candidates, n= 15 (3%) were medically delisted, n=67 (13 %) died, and n=14 (3 %) taken off the transplant list due to clinical improvement with the remainder being transplanted. There was no relationship observed between muscle CSA and medical delisting or death (Table 3-2).
**Table 3-2:** Associations between Thoracic Muscle Cross-sectional Area and Exercise Capacity, Strength Training Volumes, Quality of Life, and Pre-transplant Outcomes

<table>
<thead>
<tr>
<th>Outcome Parameters</th>
<th>Cohort Summary</th>
<th><strong>Bivariate:</strong> Mean Difference for every 10 cm² in mCSA (95% CI)</th>
<th>p value</th>
<th><strong>†Multivariate:</strong> Mean Difference for every 10 cm² in mCSA (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Six-minute walk distance (m), n=499</td>
<td>312 ± 123</td>
<td>10.9 (6.7 to 15.1)</td>
<td>&lt; 0.001</td>
<td>9.3 (3.7 to 14.9)</td>
<td>0.001</td>
</tr>
<tr>
<td><em>Biceps Training volume (reps</em>lbs), n=258</td>
<td>40 IQR [30-60]</td>
<td>5.7 (4.1 to 7.2)</td>
<td>&lt; 0.001</td>
<td>4.6 (2.4 to 6.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>*Quadriceps Training volume (reps *lbs), n=252</td>
<td>30 IQR [20-45]</td>
<td>3.0 (1.8 to 4.3)</td>
<td>&lt; 0.001</td>
<td>2.3 (0.4 to 4.2)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Quality of Life (n=400)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-Form 36 Physical Function Domain</td>
<td>15 IQR [10-32.5]</td>
<td>1.3 (0.6 to 2.0)</td>
<td>0.001</td>
<td>0.55 (-0.4 to 1.5)</td>
<td>0.26</td>
</tr>
<tr>
<td>Short-Form 36 Physical Component Score</td>
<td>27 ± 8</td>
<td>0.5 (0.2 to 0.8)</td>
<td>0.003</td>
<td>0.3 (-0.1 to 0.8)</td>
<td>0.17</td>
</tr>
<tr>
<td>SGRQ Activity Domain</td>
<td>92 IQR [79-92]</td>
<td>-0.8 (-1.3 to -0.3)</td>
<td>0.003</td>
<td>-0.14 (-0.9 to 0.6)</td>
<td>0.69</td>
</tr>
<tr>
<td>**** Clinical Outcomes (n=513)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delisting/Mortality vs. Transplanted</td>
<td>82 (16%) vs. 431 (84%)</td>
<td>0.91 (0.80 to 1.01)</td>
<td>0.08</td>
<td>0.96 (0.78 to 1.11)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, median [25-75% interquartile range], or mean difference (95% confidence interval).

*Biceps and Quadriceps training volumes taken at initiation of rehabilitation.

** Excluded due to Medical Improvement Pre-Transplant (n=14).

† Multivariate Mean Difference for mCSA for Physical Function and Quality of Life Outcomes:
Adjusted for Age, Sex, Height (m²) and Diagnosis.

‡ Multivariate Odds Ratio for mCSA for Delisting/Mortality vs. Transplanted:
Adjusted for Age, Sex, Height (m²), Diagnosis, and Program Transplant Listing Status

**Abbreviations:** CI: Confidence Interval; mCSA = Muscle Cross-sectional area; SGRQ = St. George’s Respiratory Questionnaire; OR = Odds Ratio
### Table 3-3: Characteristics of Subjects by Availability of Health-related Quality of Life Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Available HRQL (n=400)</th>
<th>No Available HRQL (n=127)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Median [IQR] years</td>
<td>55 IQR [43-62]</td>
<td>53 [40-62]</td>
<td>0.36</td>
</tr>
<tr>
<td>Male Sex</td>
<td>217 (54%)</td>
<td>66 (52%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial Lung Disease</td>
<td>170 (42.5%)</td>
<td>55 (43%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>102 (25.5%)</td>
<td>21 (17%)</td>
<td></td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>68 (17%)</td>
<td>30 (24%)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Arterial Hypertension</td>
<td>17 (4%)</td>
<td>4 (3%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>43 (11%)</td>
<td>17 (13%)</td>
<td></td>
</tr>
<tr>
<td>Muscle Cross-sectional Area (cm²)</td>
<td>94 ± 25</td>
<td>93 ± 26</td>
<td>0.57</td>
</tr>
<tr>
<td>Six-minute Walk Distance (m) (n=398/101)</td>
<td>322 ± 118</td>
<td>271 ± 133</td>
<td>0.01</td>
</tr>
<tr>
<td>Transplanted (n=431)</td>
<td>337 (84%)</td>
<td>94 (74%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Delisted/Died (n=82)</td>
<td>54 (14%)</td>
<td>28 (22%)</td>
<td></td>
</tr>
<tr>
<td>Medically Improved (n=14)</td>
<td>9 (2%)</td>
<td>5 (4%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or median [25-75% interquartile range].

**Abbreviations**: HRQL = Health-related Quality of Life

### 3.4.5 Post-transplant Clinical Outcomes:

A total of 431/527 (82%) were transplanted with the majority receiving a double lung transplantation 359 (83%). Twenty-seven of 431 (6%) lung transplant recipients required bridging with mechanical ventilation (n=19, 4%) or extra-corporeal life support (n=8, 2%) with a median duration of 10 IQR [7-24] days in the ICU pre-transplant. No difference in muscle CSA [-5.8 cm² (-12.9 to 1.3), p=0.11)] was observed in those requiring bridging to transplantation compared to those transplanted without bridging, adjusted for age, sex, height-squared and diagnosis.

389 (90%) transplant recipients survived to hospital discharge with causes for in-hospital mortality outlined in Figure 3-2. There was no observable difference in muscle CSA for hospital discharge versus death for every 10 cm², controlling for age, sex, height-squared and diagnosis [OR: 1.13 95% (0.94-1.36), p=0.20]. Hospital mortality was increased in 51 lung transplant...
recipients (12%) who developed grade 3 PGD [OR=4.8 95% (2.3-9.8, p < 0.001)], but no independent association was observed between pre-transplant muscle CSA and development of Grade 3 PGD [adjusted OR=0.91 95% (0.77-1.08, p=0.27) for every 10 cm²].

Of those surviving to hospital discharge, the adjusted OR of being discharged to inpatient rehab versus home was 17% lower for every 10 cm² increase in muscle CSA, **Table 3-4**. Muscle CSA was no longer independently associated with discharge to inpatient rehabilitation when pre-transplant 6MWD was incorporated into the model (**Table 3-4**) with 6MWD associated with a reduced risk of being discharged to inpatient rehabilitation [OR = 0.74 95% CI (0.56-0.97, p=0.03, n=372), for every 100 m increase. None of the other covariates (age, sex or height-squared) were independently associated with discharge disposition except for a diagnosis of COPD or CF, relative to ILD, who were less likely to be discharged to inpatient rehabilitation (p=0.002).

After excluding patients who died during the transplant hospital admission, the median length of stay in the intensive care unit (ICU) and hospital was 4 days IQR [2-11] and 20 days IQR [14-35], respectively. Muscle CSA was independently associated with shorter hospital length of stay [0.7 median days 95% (0.2 - 1.3), p=0.04] per 10 cm² muscle CSA], even after adjustment for pre-transplant 6MWD [-1.3 median days 95% (-2.8 to -0.2, p=0.045, n=372) per 100 m increase], **Table 3-4**. None of the other covariates were independently associated with hospital length of stay. No independent relationship was observed between muscle CSA and mechanical ventilation or ICU days post-transplant, **Table 3-4**.

A total of n=75 (17%) recipients died within one-year post-transplant. There was no independent association found between muscle CSA and one-year all-cause mortality [OR=0.92 95% CI (0.80-1.06, p=0.26) for every 10 cm²], adjusted for age, sex, height-squared and diagnosis.
**Table 3-4:** Associations Between Muscle Cross-sectional Area and Post-Transplant Outcomes

<table>
<thead>
<tr>
<th><em>Outcomes</em></th>
<th>Transplanted Cohort Summary (n=389)</th>
<th>Bivariate: Median Difference 10 cm² in mCSA (95% CI)</th>
<th>p</th>
<th>** Model 1: Median Difference 10 cm² in mCSA (95% CI) Multivariate</th>
<th>p</th>
<th>† Model 2: Median Difference 10 cm² in mCSA (95% CI) Multivariate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of Mechanical Ventilation (n=385)</td>
<td>2 IQR [1-6]</td>
<td>-0.1 (-0.14 to 0.1)</td>
<td>0.10</td>
<td>0 (-0.14 to 0)</td>
<td>1.0</td>
<td>0 (-0.18 to 0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Days of Intensive Care</td>
<td>4 IQR [2-11]</td>
<td>0 (-0.3 to 0.1)</td>
<td>1.0</td>
<td>-0.1 (-0.3 to 0.1)</td>
<td>0.40</td>
<td>-0.1 (-0.3 to 0.1)</td>
<td>0.49</td>
</tr>
<tr>
<td>Hospital Length of Stay</td>
<td>20 IQR [14-35]</td>
<td>-0.8 (-1.4 to -0.1)</td>
<td>0.01</td>
<td>-0.9 (-1.4 to -0.4)</td>
<td>0.01</td>
<td>-0.7 (-1.3 to -0.2)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Bivariate:</strong> OR for every 10 cm² in mCSA (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>** Model 1:** OR for every 10 cm² in mCSA (95% CI) Multivariate</td>
<td></td>
<td>** Model 2:** OR for every 10 cm² in mCSA (95% CI) Multivariate</td>
<td></td>
</tr>
<tr>
<td>Discharge Disposition</td>
<td></td>
<td></td>
<td></td>
<td>** Model 1:** OR for every 10 cm² in mCSA (95% CI) Multivariate</td>
<td></td>
<td>** Model 2:** OR for every 10 cm² in mCSA (95% CI) Multivariate</td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>321 (83%)</td>
<td>Rehab: Home 0.92 (0.83 to 1.02)</td>
<td>0.11</td>
<td>Rehab: Home 0.83 (0.70 to 0.98)</td>
<td>0.03</td>
<td>Rehab: Home 0.85 (0.71 to 1.02)</td>
<td>0.07</td>
</tr>
<tr>
<td>Inpatient Rehab</td>
<td>68 (17%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as n (%), median [25-75% interquartile range], or median difference (95% confidence interval).

*Outcomes on n=389 recipients; excluded those that died post-transplant in hospital.

**Multivariate Median Difference for mCSA on Days of Mechanical Ventilation, Intensive Care, and Hospital Length of Stay AND Multivariate Odds Ratio for mCSA on Discharge Disposition**

**Model 1:** Adjusted for Age, Sex, Height (m²) and Diagnosis.

† Model 2: Adjusted for Age, Sex, Height (m²), Diagnosis and Six-minute Walk Distance (n=372).

**Abbreviations:** CI: Confidence Interval; mCSA = muscle cross-sectional area; OR = Odds Ratio
3.5 Discussion:

This is the first study to provide evidence that muscle CSA was significantly reduced in lung transplant candidates compared to a control group. Muscle CSA was independently associated with 6MWD, strength training volumes, and post-transplant hospital length of stay. This technique of measuring muscle CSA provides a valid surrogate for muscle mass with no added cost or radiation exposure.241,437

Lung transplant candidates on average had a 10% lower thoracic CSA compared to age and sex matched healthy controls. This difference is comparable to lung transplant studies using bio-electrical impedance to characterize fat free mass.426 Sarcopenia, specifically low muscle mass, has been described to be an important measure since it is a marker of increased catabolic state and limited protein reserve, which is essential during periods of stress such as major surgery, hospitalization or critical illness.438 In the present study, lower muscle CSA was independently associated with greater hospital length of stay. These findings are consistent with previous reports in patient populations undergoing major surgical procedures such as general surgery, liver and renal transplantation where core muscle size from abdominal CT was associated with longer hospital stay, higher rates of infection, and increased rates of post-transplant mortality.236,344,348,349,439 In lung transplantation, pre-transplant abdominal muscle CSA has been shown to be associated with ICU240 and hospital length of stay.239 Kelm et al. observed that muscle CSA was associated with three-year survival in a selected sample of 36 lung transplant recipients with available abdominal CT scans.239 This is in contrast to the present study and that of Weig et al. where muscle CSA was not related with hospital or one year mortality.240 Thus, the relationship between muscle mass and post-transplant mortality requires further study in lung transplantation.
We observed that muscle CSA was closely associated with 6MWD and accounted for 23% of the variation in 6MWD after adjustment for confounders. This is consistent with previously described relationships between 6MWD and measures of muscle mass assessed with bio-electrical impedance and quadriceps CSA. Six-minute walk distance is commonly utilized by pulmonary rehabilitation programs as an assessment of cardiopulmonary fitness. However, the effect of exercise training on body composition parameters such as muscle mass is rarely evaluated due to practical limitations. There is evidence from COPD patients that loss of lean muscle mass, irrespective of body weight, has significant implications on exercise capacity and muscle strength. Thus, characterization of muscle CSA from available CT scans could potentially be used as a surrogate measure of muscle mass in the evaluation of patients for pulmonary rehabilitation.

Thoracic muscle CSA was also associated with biceps and quadriceps strength training volumes. The close relationship between muscle size and strength has been mainly described for the limb muscles in chronic lung disease. However, there is growing evidence that limb muscle size is related to trunk muscle CSA. In the present study, a stronger association between thoracic muscle CSA and biceps training volumes was observed compared to quadriceps volumes, which could partly be explained by the proximity of the upper limb (shoulder) muscles captured on the axial CT slices with the present technique. The differing relationship could also be due to the fact that upper limb and core muscles might be less prone to disuse related muscle atrophy than quadriceps muscles.

We hypothesized that greater muscle CSA, a surrogate marker of muscle mass and therefore overall physical fitness, would be associated with improved HRQL. Studies in patients with moderate COPD have described the relationship between muscle mass and HRQL to be mediated through levels of dyspnea and physical activity. However, we did not observe an independent association between muscle CSA and HRQL physical domains. This could
possibly be explained by the fact that this relationship is mainly mediated by daily activity levels, one of the main determinants of HRQL in lung transplant candidates.\textsuperscript{124,125} It is also possible that those patients without available HRQL might have demonstrated a differing relationship with muscle CSA, as this group was observed to have a lower exercise capacity and higher likelihood of medical delisting or mortality pre-transplant.

Measurement of thoracic muscle CSA as a marker of muscle mass is an attractive method given that sarcopenia is being recognized as an important prognostic and modifiable determinant in advanced lung disease.\textsuperscript{28,159} However, thoracic muscle CSA might be better incorporated as part of sarcopenia evaluation that includes both muscle mass and functional deficits (muscle strength and physical function)\textsuperscript{158} given increasing evidence demonstrating that these functional deficits have important clinical implications in advanced lung disease. Quadriceps strength has been shown to be a significant predictor of mortality in COPD patients.\textsuperscript{294} Low physical function assessed with the Short Physical Performance Battery has been associated with pre-transplant delisting and mortality.\textsuperscript{318} In the present study, we compared the utility of skeletal muscle mass to the 6MWT which is the most common measure of cardiorespiratory fitness in advanced lung disease\textsuperscript{102} and has been shown to be a strong prognostic marker of post-transplant outcomes.\textsuperscript{23,110} Skeletal muscle mass and 6MWD were both independently associated with hospital length of stay; however, 6MWD was a stronger predictor of discharge disposition. This is not entirely surprising as the 6MWT captures limitations in the cardio-respiratory and musculo-skeletal systems, whereas skeletal muscle mass characterizes only one element of the sarcopenia definition.\textsuperscript{158} We propose that a comprehensive pre-transplant assessment of muscle mass, strength, functional performance, and exercise capacity could provide further prognostic information in those recipients who are more likely to sustain a longer hospital course and require discharge to inpatient rehabilitation. Given the complex interaction between muscle mass, strength and physical function,\textsuperscript{223,425} future
studies exploring the prognostic implications of all three impairments as complementary measures to 6MWD in lung transplantation are needed.

It is important to acknowledge several limitations in the present study. This was a single, centre retrospective study with muscle CSA measured at the time of transplant listing. Muscle size could potentially change while on the transplant list; however, previous studies using BIA have described no significant change in muscle mass in the pre-transplant period.\textsuperscript{135} It also remains unknown whether thoracic muscle CSA would change during an ICU admission pre-transplant; a setting where the measurement of skeletal muscle mass remains a logistical challenge.\textsuperscript{450} Secondly, our control group was obtained from a cohort undergoing lung cancer screening who were \( \geq 50 \) years old and had at least a 10 pack-year smoking history. One can argue whether this is an appropriate control group; however, the muscle CSA difference would likely be even greater compared to control subjects without a history of smoking as it is known to be a risk factor for muscle atrophy.\textsuperscript{451,452} It is also important to acknowledge that most cystic fibrosis patients were not age-matched with this older control group. In addition, it is unknown whether severe lung disease alters the geometry of the thoracic cavity, which could lead to differences in thoracic muscle CSA attributable to variation in the distribution of the thoracic muscles rather than muscle atrophy.\textsuperscript{241,243} However, in a previous study we observed that a single thoracic axial CT slice was closely associated with thoracic muscle volume obtained from several slices in lung transplant candidates.\textsuperscript{429} Furthermore, we did not observe an association between muscle CSA and transplant listing urgency. Unfortunately, we are unable to comment on the relationship between muscle CSA and Lung Allocation Score from the present study. Finally, all lung transplant patients at our center participate in a structured rehabilitation program, which could have an impact on the pre- and post-transplant clinical outcomes.
3.6 Conclusion:

In summary, thoracic muscle CSA can be applied as a novel, simple measure of skeletal muscle mass and is independently associated with six-minute walk distance, strength training volumes and post-transplant hospital length of stay. Further study is needed to assess the contribution of functional deficits (strength and physical performance) in addition to muscle mass in the evaluation of lung transplant candidates.
4.0 Evaluation of Skeletal Muscle Function in Lung Transplant Candidates

4.1 Abstract:

**Background/Objectives:** Lung transplantation is offered to older and more complex patients who may be at higher risk of skeletal muscle dysfunction, but the clinical implications of this remain uncertain. The study aims were to characterize deficits in skeletal muscle mass, strength and physical performance and examine the associations of these deficits with clinical outcomes.

**Methods:** Fifty lung transplant candidates (58% male, 59 ± 9 years) were prospectively evaluated for skeletal muscle deficits: muscle mass using bio-electrical impedance, quadriceps, respiratory muscle and handgrip strength, and physical performance with the Short Physical Performance Battery. Comparisons between number of muscle deficits (low muscle mass, quadriceps strength and physical performance) and six-minute walk distance (6MWD), London Chest Activity of Daily Living Questionnaire (LCADL), and quality of life were assessed using one-way ANOVA. Associations with pre- and post-transplant delisting/mortality, hospital duration, and three-month post-transplant 6MWD were evaluated using Fisher’s exact test and Spearman correlation.

**Results:** Deficits in quadriceps strength (n=27) and physical performance (n=24) were more common than muscle mass (n=8). Lung transplant candidates with two or three muscle deficits (42%) compared to those without any deficits (26%) had worse 6MWD=-109 m, 95%CI (-175 to -43), LCADL=18, 95%CI (7-30), and St. George’s Activity Domain=12, 95%CI...
Number of muscle deficits was associated with post-transplant hospital stay ($r=0.34$, $p=0.04$), but not with delisting/mortality or post-transplant 6MWD.

**Conclusion:** Deficits in quadriceps muscle strength and physical performance are common in lung transplant candidates and further research is needed to assess whether modifying muscle function pre-transplant can lead to improved clinical outcomes.

**Contents of this chapter have been published in Transplantation:**


**Please go the journal’s website to read the contents of Chapter 4.**

CHAPTER 5

5.0 Clinical Implications of Pre-Transplant Skeletal Muscle Mass, Strength and Exercise Capacity on Functional Recovery in Lung Transplant Recipients after 7 or More Days of Mechanical Ventilation

5.1 Abstract:

Background/Objectives: Lung transplant patients are at risk of peri-operative complications that can result in a prolonged course of mechanical ventilation (MV). Unlike other intensive care unit (ICU) patients, all lung transplant recipients undergo rehabilitation prior to their transplant and ICU stay with the goal of optimizing functional recovery after transplantation. We hypothesized that greater pre-transplant skeletal muscle mass, strength and exercise capacity would be associated with better post-transplant functional recovery in lung transplant recipients requiring at least 7 days of MV.

Methods: Single center analysis of lung transplant recipients who required ≥ 7 days of MV peri-operatively and participated in a prospective cohort study (RECOVER) evaluating post-ICU recovery. Pre-transplant skeletal muscle mass (using thoracic computed tomography cross-sectional area), strength (captured with muscle training volumes) and exercise capacity (6MWD) were evaluated retrospectively. Post-transplant outcomes included the Functional Independence Measure motor subscale (motor FIM, primary outcome at 7 days post-ICU) and secondary outcomes included the Short-Form 36 Physical Component Score (SF-36 PCS), change in 6MWD with transplant, and discharge disposition at 3 months post-ICU. Pre-transplant predictors of recovery (age, sex, ICU length of stay (LOS), muscle mass, strength and 6MWD) were assessed using multivariable regression.
**Results:** 80 lung transplant recipients (48% male; median age 57 IQR [44-64]) were included. 72 (90%) recipients survived to ICU discharge with a total median ICU LOS of 24 IQR [17-36] days. At 7-days post-ICU, these participants required maximal-total assistance (motor FIM; 33 (SD) ± 19), with age being the only independent predictor (β= -5.2 ± 1.7, per 10 years). At three-months post-ICU, lung transplant recipients had persistent functional limitations: motor FIM (80 ± 17, minimal assistance), low 6MWD (63 ± 23 % predicted), SF-36 PCS (35 ± 10) and high rates of discharge to inpatient rehabilitation (43%) versus home. At three-months post-ICU, younger age and shorter ICU length of stay were the only independent predictors of better post-transplant motor FIM, greater SF-36 PCS, and a higher likelihood of being discharged home, whereas pre-transplant muscle mass, strength, and 6MWD were not significant.

**Conclusions:** In a select group of lung transplant recipients surviving 7 or more days of MV, age and ICU LOS were significant determinants of early functional recovery and discharge disposition. The lack of association between pre-transplant skeletal muscle function and post-transplant outcomes highlights the importance of ICU acquired morbidity in this group of patients. These findings may help facilitate discharge planning and discussions between the health care team, patients, and their families about the clinical implications of ≥ 7 days of MV peri-operatively.
5.2 Introduction:

Lung transplantation is offered to older and more medically complex patients that may have an increased risk for a prolonged intensive care unit (ICU) and hospital course post-transplant. Critical illness can result in significant skeletal muscle atrophy and functional loss, which can occur early in the first week of ICU. Furthermore, prolonged periods of immobility after lung or heart-lung transplantation can result in deconditioning, which is known to be associated with delayed functional recovery. Several studies have shown that physical conditioning pre-operatively may mitigate the physical stress involved with major surgery and critical illness.

Early post-operative complications in lung transplant recipients such as primary graft dysfunction (PGD), infection, systemic organ failure, and bleeding may result in a prolonged course of mechanical ventilation (MV) and ICU stay. Prolonged MV is not uncommon in lung transplant recipients, especially in the 10-30% recipients experiencing PGD, and could potentially lead to an accelerated decline in physical function in the early post-transplant period. A greater number of lung transplant recipients are also supported with MV or extra-corporeal life support (ECLS) while awaiting transplantation, which may further contribute to ICU-acquired weakness (ICUAW). The RECOVER program group has shown that medical and surgical ICU survivors (excluding lung transplant recipients) who required at least 7 days of MV had significantly increased morbidity and mortality based on risk strata determined by age and ICU length of stay (LOS) and these predicted functional independence at one week through one year after ICU discharge. In patients with acute lung injury, muscle weakness is common after a prolonged ICU admission (≥ 7 days) and is associated with long-term impairments in physical function and health-related quality of life (HRQL). These studies suggest that
early physical limitations from prolonged MV and immobilization may result in significant long-term functional disability.

Unlike other critically ill patients with an unpredictable admission to the ICU, lung transplant candidates generally perform pre-transplant pulmonary rehabilitation prior to their ICU admission. We know that pulmonary rehabilitation helps preserve exercise capacity in lung transplant candidates, even in the setting of progressive decline in lung function, and a greater exercise capacity pre-transplant is associated with a shorter LOS post-transplant and a higher likelihood of being discharged home. Low skeletal muscle mass (i.e. sarcopenia) pre-transplant and lower extremity weakness post-transplant have been independently associated with increased hospital length of stay and mortality after lung transplantation. However, no studies to date have assessed whether pre-transplant skeletal muscle parameters and exercise capacity are associated with early post-transplant functional recovery in lung transplant recipients, especially in those with prolonged periods of MV. We chose to investigate early post-transplant outcomes (< 3 months post-ICU discharge) given evidence from the RECOVER cohort and in lung transplant recipients that long-term outcomes were influenced by early post-operative events.

The objectives of this study were to assess the association of pre-transplant skeletal muscle mass, strength and exercise capacity with post-transplant Functional Independence Measure motor subscale (primary outcome at 7 days post-ICU discharge) and secondary measures including HRQL (Short-Form 36 Physical Component Score), change in 6MWD with transplantation, discharge disposition, and mortality at 3 months post-ICU in lung transplant recipients with ≥ 7 days of MV. We hypothesized that greater pre-transplant skeletal muscle mass, strength and exercise capacity would be associated with better early post-transplant functional recovery, greater HRQL, and a higher likelihood of being discharged home.
5.3 Methods:

5.3.1 Study Design and Participants:

This was an analysis of adult lung transplant recipients who participated in the RECOVER Program study at the University Health Network (UHN) between October 1, 2009 to December 31, 2014, (NCT 00896220). Participants were included if they required a minimum of 7 consecutive days of MV pre- or post-transplant during the index transplant admission, Figure 1. Research ethics approval was obtained from UHN (REB #15-8858 BE) and University of Toronto (REB #31637).

All lung transplant candidates were enrolled in an outpatient pulmonary rehabilitation program comprised of stretching, aerobic and resistance training three times per week for the entire waiting period, as previously described. Patients who were too ill to participate in outpatient pulmonary rehabilitation (i.e. admitted to hospital or ICU) underwent an inpatient rehabilitation program supervised by a physical therapist, if admitted at UHN. Corridor ambulation, bedside cycling, and resistance exercises were continued as tolerated for ward patients and early mobilization was undertaken for ICU patients.

5.3.2 Pre-transplant Muscle Mass, Strength and Functional Capacity

Muscle Mass:
Thoracic muscle cross-sectional area (CSA) of the pectoralis major and minor, inter-costals, latissimus dorsi and para-spinal muscles was quantified from computed tomography (CT) scans, which were performed as part of routine clinical care. Muscle CSA was measured at two time points pre-transplant: within 3 months of transplant listing and the last available assessment pre-transplant. Muscle CSA was manually segmented using Slice-O-Matic software (Tomovision, Montreal, Canada) with the Hounsfield unit ranges of -29 to 150, as
previously described.\textsuperscript{429} We have previously shown that CT muscle CSA has excellent intra and inter-reliability\textsuperscript{429} and is a good surrogate marker of fat-free mass index assessed with bio-electrical impedance (r=0.71, p < 0.0001) in lung transplant candidates, Appendix 1- Figure 3-1A.

Muscle Strength:
The sum of biceps and quadriceps training volumes (number of repetitions multiplied by weight lifted in pounds) were obtained from review of pre-transplant pulmonary rehabilitation records and served as surrogate measures of upper and lower limb muscle strength.\textsuperscript{110} In the cohort of 50 lung transplant candidates described in Chapter 4, we observed moderate correlations between biceps training volumes and hand-grip strength (r=0.68 p < 0.001) and quadriceps training volumes and quadriceps peak torque (r=0.49, p<0.001), Appendix 1, Figure 5-1A and 5-2A). These correlations suggest that muscle training volumes may serve as indirect measures of upper and lower limb strength. The biceps and quadriceps training volumes were abstracted within four weeks of rehabilitation initiation and from the last available assessment pre-transplant. Patients who were unable to perform resistance exercises against a training load were assigned a score of zero.

Functional Capacity:
Functional capacity was assessed by a physical therapist or their assistant using the six minute walk test (6MWT) in accordance with the American Thoracic Society (ATS) Guidelines.\textsuperscript{104,433} The 6MWT is repeated every three months as part of routine care at our centre. The six-minute walk distance (6MWD) from the time of listing and the last available assessment before transplantation were abstracted from the patient chart and requirement for supplemental oxygen and walking aid during the 6MWT were also noted.

5.3.3 Pre-Transplant Clinical Parameters:
The following information was abstracted from the pre-transplant medical records: age, sex, indication for transplant, body mass index, transplant listing urgency (Status 1, 2 and Rapidly Deteriorating), requirement for hospital admission or ICU pre-transplant (including MV or ECLS), daily corticosteroid use and median dose. Lung allocation score was calculated pre-transplant using the United Network for Organ Sharing calculator.47,59

5.3.4 Peri-operative and Post-Transplant Outcomes:

The severity of illness was characterized by the Acute Physiology, Age and Chronic Health Evaluation II score461 ascertained within 24 hours of ICU admission. The Multiple Organ Dysfunction Score462 was calculated daily for the first week and the Multiple Organ Dysfunction Score at day 7 was reported as it coincided with the minimum duration of MV required for this study. Requirement for extracorporeal membrane oxygenation (ECMO), tracheostomy and renal replacement therapy during the ICU stay were reported. Grade 3 PGD at 72 hours as per International Society of Heart-Lung Transplant consensus definition (PaO₂/FiO₂ ratio of < 200 mmHg or requirement for ECMO or nitric oxide) was evaluated.435

The primary outcome measure was the motor subscale of the functional independence measure (FIM) at 7-days post ICU discharge.321 The FIM consists of 2 main subscales: motor (4 categories including self-care, sphincter control, transfers and locomotion consisting of 13 items) and cognitive (2 categories: communication and social cognition with 5 items) with each item given a score from 1 (total assistance) to 7 (complete independence).321 The motor subscale (maximal score of 91) was used in the RECOVER program in a diverse group of medical and surgical ICU patients319 and observed to be responsive to change in lung transplant recipients undergoing inpatient rehabilitation.320,421

Six-minute walk distance at three months post-ICU discharge was assessed in accordance with the ATS Guidelines as part of routine clinical care and obtained from chart review.104,433 The
absolute change in 6MWD (meters) from pre-transplant to post-transplant values was calculated. The change in 6MWD was chosen as it has been shown to be associated with the recovery in quadriceps strength from pre-transplant baseline values, independent of graft function.\textsuperscript{122}

Health-related quality of life at 3 months post-ICU was evaluated with the Short-Form 36 (SF-36). The SF-36 has been shown to be reliable, valid, and responsive in advanced lung disease and after transplantation.\textsuperscript{26,76,463} The physical component score (PCS) was the primary HRQL measure and has a minimal clinically important difference reported to be $\geq 4$ units.\textsuperscript{464}

The Medical Research Council (MRC) score at 3 months post-ICU discharge was used to evaluate strength. Six muscle groups were tested bilaterally (upper and lower body), each scored 0 to 5 for a maximal score of 60.\textsuperscript{465} A total score of less than 48 out of 60 has been shown to represent significant generalized muscle weakness and has been used as a criterion to diagnose ICU acquired weakness (ICUAW).\textsuperscript{465} Even though this composite MRC score of $< 48/60$ (80\%) is arbitrary, it has been shown to have excellent inter-rater reliability post-ICU discharge in medical and surgical patients.\textsuperscript{466,467}

Other outcomes assessed were pre- and post-transplant days of MV and ICU, post-transplant hospital length of stay, discharge disposition (home or inpatient rehabilitation), mortality in hospital and at 90 days post-ICU.

5.3.5 Statistical Analysis:

Analysis was performed using Graph-Pad Prism (Version 7.0) and R (Version. 3.32). Continuous variables are described using mean $\pm$ standard deviation or median [interquartile range 25-75\%] with categorical variables described using frequencies. Visual inspection of
scatter plots, Kolmogorov-Smirnov and Pearson omnibus normality tests were used to assess the distribution of data.

Transplant listing measures and the last available thoracic muscle CSA, training volumes, and 6MWD before transplantation were compared using paired t-tests. Multi-variable linear-regression models assessed the association between the predictor variables age, sex, total ICU length of stay (sum of pre- and post-transplant ICU days), last available muscle CSA, training volumes, and 6MWD pre-transplant with the outcome variables: 7-day post-ICU motor FIM (primary outcome) and secondary outcomes motor FIM, SF-36 PCS and change in 6MWD at three-months post ICU. After excluding participants who died in ICU or hospital post-transplant, the same independent co-variates were used to evaluate the association with discharge disposition and mortality using logistic regression.

We performed model diagnostics examining plots of residuals to ensure assumptions of independence, normality and constant variation of errors were met. A p value of < 0.05 was considered significant for all analyses.

5.4 Results:

5.4.1 Pre-Transplant:

Eighty lung transplant recipients were included from the RECOVER Program study. The lung transplant cohort comprised of 38 males (48%) with a median age of 57 IQR [44-64] years. Baseline characteristics are shown in Table 5-1. The most common indications for transplantation were interstitial lung disease (51%) and chronic obstructive pulmonary disease (16%). The median lung allocation score was 38 [35-44] and 21 (27%) patients were admitted to hospital or ICU pre-transplant. The median days in the ICU pre-transplant for the 15 lung transplant candidates bridged to transplantation was 12 IQR [10-15] days.
Figure 5-1: Flow Diagram of Study Participants
Table 5-1: Baseline Characteristics at Transplant (n=80)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Median IQR (years)</td>
<td>57 IQR [44-64]</td>
</tr>
<tr>
<td>Males (n, %)</td>
<td>38 (48%)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>24.2 ± 4.8</td>
</tr>
<tr>
<td><strong>Diagnosis:</strong></td>
<td></td>
</tr>
<tr>
<td>Interstitial Lung Disease</td>
<td>41 (51%)</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>13 (16%)</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Pulmonary Arterial Hypertension</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>*Other</td>
<td>11 (14%)</td>
</tr>
<tr>
<td>Oral Corticosteroid therapy (n, median dose, mg)</td>
<td>41, 15 mg IQR [10-22.5]</td>
</tr>
<tr>
<td><strong>Inpatient Prior to Transplant (n=21)</strong></td>
<td></td>
</tr>
<tr>
<td>Hospital Ward</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>ICU (ECLS/Mechanical Ventilation)</td>
<td>15 (19%)</td>
</tr>
<tr>
<td><strong>Lung Allocation Score</strong></td>
<td></td>
</tr>
<tr>
<td>Time of Transplant</td>
<td>38 [35-44]</td>
</tr>
<tr>
<td><strong>Type of Transplant</strong></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Double</td>
<td>72 (90%)</td>
</tr>
<tr>
<td><strong>APACHE II Score, Median IQR</strong></td>
<td>22 IQR [19-26]</td>
</tr>
</tbody>
</table>

*Other: Includes re-transplants (n=5, 6%)

**Abbreviations:** APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; ICU = Intensive Care Unit; ECLS = Extra-corporeal Life Support

Most lung transplant recipients (85%) participated in an outpatient pulmonary rehabilitation program pre-transplant, on average attending 43 IQR [11-108] sessions with a median wait time for transplant of 107 [33-251] days. Lung transplant candidates demonstrated small but significant increases in their muscle training volumes during rehabilitation despite a decrease in their 6MWD, Table 5-2. There was no significant change observed in muscle CSA pre-transplant. Most lung transplant candidates required a high level of oxygen supplementation for exertion (Table 5-2) and fifty percent (40/80) used a walker or cane.
Table 5-2: Muscle CSA, Training Volumes, Exercise Capacity and Oxygen Requirements at Listing and Before Transplantation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Listing</th>
<th>Before Transplantation</th>
<th>Change during pre-transplant period Mean Difference (95% CI)</th>
<th>* p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic Muscle CSA (cm²)</td>
<td>92 ± 24 (n=80)</td>
<td>86 ± 22 (n=34)</td>
<td>-2 (-5 to 0.4), n=34</td>
<td>0.09</td>
</tr>
<tr>
<td>** Biceps Training Volumes (lbs*reps)</td>
<td>45 ± 31 (n=69)</td>
<td>54 ± 47 (n=71)</td>
<td>11 (4 - 18), n=69</td>
<td>0.002</td>
</tr>
<tr>
<td>** Quadriceps Training Volumes (lbs*reps)</td>
<td>29 ± 18 (n=69)</td>
<td>38 ± 31 (n=71)</td>
<td>10 (4 - 15), n=69</td>
<td>0.001</td>
</tr>
<tr>
<td>** Biceps and Quadriceps Training Volumes (lbs*reps)</td>
<td>73 ± 46 (n=69)</td>
<td>92 ± 75 (n=71)</td>
<td>21 (10 to 32), n=69</td>
<td>0.001</td>
</tr>
<tr>
<td>Six-minute Walk Distance (meters)</td>
<td>307 ± 110 (n=80)</td>
<td>266 ± 117 (n=55)</td>
<td>-43 (-67 to -19), n=55</td>
<td>0.001</td>
</tr>
<tr>
<td>** Oxygen Supplementation (FIO₂):**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (0.21)</td>
<td>Frequency (%), n=80</td>
<td>Frequency (%), n=55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3L/min (0.24-0.30)</td>
<td>12 (15%)</td>
<td>4 (7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-6L/min (0.33-0.39)</td>
<td>18 (23%)</td>
<td>6 (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-10L/min (0.45-0.51)</td>
<td>33 (42%)</td>
<td>19 (35%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venturi (0.50)/Oxymask (10-15L/min)</td>
<td>4 (5%)</td>
<td>6 (11%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-rebreather (10-15L/min)</td>
<td>8 (10%)</td>
<td>10 (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean FIO₂</td>
<td>0.38 ± 0.19</td>
<td>0.50 ± 0.26</td>
<td>0.13 (0.07-0.18), n=55</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD, or mean (95% CI), and n (%).

*Paired student t-test used to compare listing to last available measure before transplantation.

**Patients unable to perform strength training exercises with weights were assigned a score of zero for their muscle training volumes.

† Oxygen Supplementation during Six-minute Walk Test

** Abbreviations: CI = Confidence Interval; CSA = Cross-sectional Area; FIO₂ = Inspired Fraction of Oxygen
At the time of transplant, 59 (74%) were participating in an outpatient pulmonary rehabilitation program. There were no significant differences between the outpatient and inpatient rehabilitation groups with respect to thoracic muscle CSA (88 ± 23 vs. 97 ± 25 cm², p=0.18) or 6MWD (291 ± 108 vs. 246 ± 148 meters, p=0.21) based on the last assessment pre-transplant. Muscle training volumes were significantly greater in those participating in the outpatient compared to inpatient rehabilitation programs (114 ± 67 vs. 28 ± 62 reps*lbs, n=53/18, p < 0.001).

5.4.2 Post-Transplant:

Intensive Care Unit Course:
Of the 80 lung transplant recipients requiring ≥ 7 days of MV, 23 (29%) developed Grade 3 PGD and 12 (15%) required ECMO support post-operatively. Seventy-two (90%) recipients survived to ICU discharge with a total median ICU LOS of 24 IQR [17-36] days and total MV duration of 21 IQR [12-31] days. The median Multiple Organ Dysfunction Score at 7 days of MV was 7 IQR [5-7], with 16 (22%) requiring renal replacement therapy and 57 (79%) receiving tracheostomy.

Functional Recovery at Seven Days Post Intensive Care Unit Discharge
The mean score for the motor FIM was 33 ± 19 representing moderate to total assistance at 7-days post ICU discharge. 21 of 53 (40%) were unable to walk to perform the 6MWT. Older age (for every 10 years) was the only independent covariate associated with a 5-point decrease in the motor FIM as shown in Table 5-3. The last available thoracic muscle CSA, muscle training volumes, and 6MWD were not associated with the 7-day post ICU motor FIM.

Outcomes up to Three Months Post Intensive Care Unit Discharge
A total of 67 lung transplant recipients were discharged from hospital with 29 (43%)
transferred to inpatient rehabilitation and 38 (57%) discharged home. The median hospital
LOS was 58 IQR [38-83] days for this group of patients. Older age and ICU LOS were the
only two significant co-variates associated with discharge to inpatient rehabilitation, Table 5-4.

At three-months post-ICU discharge, there was significant improvement in the motor domain
of the FIM with the total score of 80 ± 17. Age at transplant and post-transplant ICU LOS
were the only significant determinants of FIM at three months with no association observed
between pre-transplant muscle CSA, muscle training volumes, or 6MWD, Table 5-3.
Approximately one-third (10/33) of lung transplant recipients had muscle weakness defined as
a total MRC strength score of < 48/60.

Table 5-3: Multivariate Association with Pre-Transplant Predictors and Motor
Functional Independence Measure at 7 and 90 days Post-ICU.

<table>
<thead>
<tr>
<th>Multivariate Parameters</th>
<th>Mean Effect ± SE on 7-Day Motor FIM (n=54)</th>
<th>Mean Effect ± SE on 3 Month Motor FIM (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10 years</td>
<td>-5.2 ± 1.7 *</td>
<td>-3.1 ± 0.8 *</td>
</tr>
<tr>
<td>Male Sex</td>
<td>3.3 ± 6.9</td>
<td>-0.3 ± 3.4</td>
</tr>
<tr>
<td>ICU LOS, per 10 days</td>
<td>-1.7 ± 0.8</td>
<td>-2.2 ± 0.4 *</td>
</tr>
<tr>
<td>Muscle CSA (10 cm²)</td>
<td>-0.2 ± 1.4</td>
<td>0.1 ± 0.7</td>
</tr>
<tr>
<td>Muscle TrainingVolumes</td>
<td>-0.03 ± 0.4</td>
<td>0.1 ± 0.2</td>
</tr>
<tr>
<td>(per 10 lbs*reps)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWD (per 100 m)</td>
<td>-0.1 ± 2.5</td>
<td>0.8 ± 1.1</td>
</tr>
<tr>
<td>Adjusted R²</td>
<td>0.10</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Data presented as mean effect ± standard error. * p value < 0.05

Abbreviations: CSA = Cross-sectional Area; FIM = Functional Independence Measure;
ICU = Intensive Care Unit; LOS = Length of Stay; SD = Standard Deviation; SE= Standard Error;
6MWD = Six-minute walk distance
**Table 5-4:** Multivariate Association with Pre-Transplant Predictors and Post-Transplant Discharge Disposition (Inpatient Rehabilitation vs. Home).

<table>
<thead>
<tr>
<th>Multivariate Parameters</th>
<th>Rehab: Home (n=61) OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10 years</td>
<td>1.70 (1.03 – 2.82)</td>
<td>0.04</td>
</tr>
<tr>
<td>Male Sex</td>
<td>1.27 (0.24 – 6.77)</td>
<td>0.78</td>
</tr>
<tr>
<td>ICU LOS, per 10 days</td>
<td>1.49 (1.06 – 2.10)</td>
<td>0.02</td>
</tr>
<tr>
<td>Muscle CSA (10 cm²)</td>
<td>0.94 (0.66 – 1.33)</td>
<td>0.72</td>
</tr>
<tr>
<td>Muscle Training Volumes (per 10 lbs*reps)</td>
<td>0.98 (0.90 – 1.07)</td>
<td>0.65</td>
</tr>
<tr>
<td>6MWD (per 100 m)</td>
<td>1.25 (0.76 – 2.07)</td>
<td>0.38</td>
</tr>
<tr>
<td>C-statistic</td>
<td>0.74</td>
<td>-</td>
</tr>
</tbody>
</table>

Data presented as odds ratio (95% confidence interval).

**Abbreviations:** CI = Confidence Interval; CSA = Cross-sectional Area; ICU = Intensive Care Unit; LAS = Lung Allocation Score; LOS = Length of Stay; OR = Odds Ratio; 6MWD = Six-minute walk distance

Exercise capacity was low at 3 months post-ICU discharge, 360 ± 134 meters (63 ± 23 % predicted, n=53). A high proportion of participants used a walker or cane (22/53, 42%) to perform the 6MWT, but only 4/53 (8%) required supplemental oxygen. In a multivariate analysis, the last 6MWD pre-transplant (per 100 meters) was inversely associated with the change from pre-transplant to post-transplant 6MWD (β = -81 meters, SE ± 14.9, p < 0.001, n=48). Other significant independent covariates of 6MWD change from pre-transplant values were age (for every 10 years, β = -36 meters, SE ± 13, p = 0.01) and ICU LOS (every 10 days, β = -26 meters, SE ± 12, p = 0.03) with muscle CSA, training volumes and sex not significant in the multivariate analysis.

The mean SF-36 PCS at 3 months post-ICU was 35 ± 10 (mean population score 50). Age (for every 10 years, β = -2.9, SE ± 1.2, p = 0.02, n=30) and ICU LOS (for every 10 days, β = -1.0, SE ± 0.48, p= 0.02, n=30) were independently associated with SF-36 PCS. None of the
other pre-transplant covariates (muscle CSA, training volumes, and 6MWD) were associated with HRQL.

The overall mortality at three months post-ICU discharge was 13 (16%) with causes outlined in Figure 5-1. No identifiable pre-transplant factors were found to be associated with post-transplant mortality, Table 5-5.

Table 5-5: Bivariate Association with Pre-Transplant Risk Factors and Post-Transplant Mortality Three Months Post-ICU Discharge (n=80)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Bivariate Association with Mortality OR (95 % CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10 years</td>
<td>0.91 (0.60 – 1.36)</td>
<td>0.63</td>
</tr>
<tr>
<td>Male Sex</td>
<td>1.97 (0.58 – 6.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Hospital or ICU Admission Pre-Transplant</td>
<td>1.99 (0.57 – 7.0)</td>
<td>0.28</td>
</tr>
<tr>
<td>Lung Allocation Score</td>
<td>1.0 (0.70 – 1.42)</td>
<td>1.0</td>
</tr>
<tr>
<td>Muscle CSA (10 cm²)</td>
<td>1.07 (0.83 – 1.37)</td>
<td>0.62</td>
</tr>
<tr>
<td>Muscle Training Volumes (per 10 lbs*reps), n=71</td>
<td>0.98 (0.90 – 1.08)</td>
<td>0.76</td>
</tr>
<tr>
<td>6MWD (per 100 m)</td>
<td>1.32 (0.79 – 2.21)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Data presented as odds ratio (95% confidence interval).

**Abbreviations:** CSA = Cross-sectional Area; ICU = Intensive Care Unit; LAS = Lung Allocation Score; LOS = Length of Stay; 6MWD = Six-minute walk distance.

5.5 Discussion:

The present study is the first to assess the implications of pre-transplant skeletal muscle parameters and exercise capacity on post-transplant functional outcomes in lung transplant recipients surviving at least 7 days of MV and critical illness. Lung transplant recipients discharged from the ICU had early impairments in functional recovery, HRQL, exercise capacity and an increased proportion required discharge to inpatient rehabilitation. Older age and ICU LOS were independent predictors of early post-transplant functional recovery, where as no association with pre-transplant muscle CSA, muscle training volumes, and exercise capacity was observed.
The finding that older age is associated with worse early functional recovery in the present cohort of lung transplant recipients is consistent with the results of the multi-center RECOVER study. In medical and surgical ICU survivors with at least 7 days of MV, age and ICU LOS determined risk stratification groupings and one year mortality independent of ICU admitting diagnosis or illness severity. Older age is particularly relevant in the current era given the growing number of older lung transplant recipients, with over one-third being over the age of 65 years old. Whereas older patients have been shown to have reduced post-transplant survival, Genao et al. demonstrated that the functional trajectory of older lung transplant recipients (≥ 65 years) compared to younger recipients was similar post-transplant. Similarly, lung transplantation was shown to confer HRQL benefits beyond the first 3 months post-transplant that were not significantly different in older recipients. This contrasts with the present study that had demonstrated older age to have an inverse association with FIM, HRQL, and exercise capacity in the first 3 months post-ICU discharge, highlighting the importance of age as an important physiological marker in those sustaining a prolonged course of MV. Older age is a risk factor for ICUAW and development of geriatric syndromes (i.e. delirium, falls) which could potentially hinder recovery in functional independence and exercise capacity in those experiencing complications post-transplant.

ICU LOS was an important predictor of functional independence, HRQL and exercise capacity in the present cohort of lung transplant recipients. Prolonged periods of bedrest and critical illness can lead to significant muscle atrophy and ICUAW, resulting in decreased functional mobility. Maury et al previously demonstrated that longer duration spent in the ICU was associated with a moderate reduction in quadriceps muscle strength in lung transplant recipients who had a median ICU stay of 6 days. In addition to prolonged immobility, other risk factors for skeletal muscle dysfunction in lung transplant recipients include hypoxemia, infection, and high dose corticosteroid use which can all lead to
increased incidence of ICUAW. In addition to corticosteroid therapy, all lung transplant recipients at our center are started on calcineurin inhibitors post-transplant which may influence skeletal muscle recovery. However, a significant risk factor for early functional impairments remains prolonged ICU duration with two weeks described as a risk factor for development of critical illness neuropathy or myopathy. This is certainly an important consideration in our cohort of lung transplant recipients who had a median ICU stay of 24 days.

The lung transplant recipients at 7 days post-ICU discharge had a mean motor FIM score of 33 ± 19, which represents total dependence on activities of daily living such as bathing, dressing, transferring and walking. Forty percent of patients were unable to walk without physical assistance at 7 days post-ICU discharge and therefore unable to perform the 6MWT. As in the RECOVER study, we observed a gradient of disability measured with the motor FIM that was associated with age and ICU LOS but independent of pre-transplant skeletal muscle mass, strength or exercise capacity further highlighting the importance of ICU acquired morbidity in this cohort of patients. Given the marked physical limitations observed 7-days post ICU discharge, it is not entirely surprising that the hospital length of stay and discharge rates to inpatient rehabilitation were nearly 2.5 times of those described for our program previously (usual median hospital stay of 22 days and discharge rates to inpatient rehabilitation of 17%). We have previously shown that hospital LOS was an independent predictor of discharge disposition as prolonged periods of bedrest and critical illness could lead to further deconditioning and muscle atrophy through proteolysis. In the present study, we observed that total ICU LOS was independently associated with discharge to inpatient rehabilitation. Thus, transfer to a rehabilitation facility may be considered earlier in the hospital course as it has been shown to be safe and associated with significant functional recovery post-transplant. This information is critical as it can help guide discussions pre-
transplant with respect to discharge planning and assist with rehabilitation decisions in the event of a protracted ICU course post-transplant.

Despite moderate-severe limitations within 7-days of ICU discharge, lung transplant recipients demonstrated significant functional gains at 3 months post-ICU discharge requiring minimal assistance (motor FIM score of 80), which was comparable to the non-transplant RECOVER cohort. However, there was a significant degree of heterogeneity among this group of lung transplant recipients with approximately one third having generalized muscle weakness with a total MRC score < 48/60. This was not necessarily reflected by the 6MWD which was reduced at around 63% predicted, but comparable to the non-transplant RECOVER cohort and to other cohorts of lung transplant recipients at three months post-transplant. This highlights the limitation of the 6MWT which is the most commonly used functional exercise measure; however, is not able to specifically isolate muscular function and weakness. The improvement in functional capacity at three months post-ICU is most likely a result of significant alleviation of ventilatory limitation with transplantation, but persistent limitations in exercise capacity have been shown to be related to musculoskeletal impairments. Other clinical assessments of muscular function such as the Short-Physical Performance Battery (SPPB) could help identify musculoskeletal and mobility impairments pre- and post-transplant and serve as potential targets for rehabilitation.

We hypothesized that greater pre-transplant skeletal muscle mass, strength and exercise capacity would be associated with better post-transplant functional recovery in lung transplant recipients requiring ≥ 7 days of MV. In lung transplant recipients with a standard duration of MV (usually < 72 hours post-transplant), greater skeletal muscle mass and exercise capacity have been previously shown to be associated with reduced hospital length of stay, lower likelihood of being discharged to inpatient rehabilitation and reduced mortality in lung transplant recipients. The lack of association with pre-transplant skeletal muscle function
and post-transplant outcomes may be related to the high degree of case complexity observed in these patients sustaining ≥ 7 days of MV. This was a cohort with declining pre-transplant exercise capacity, a high proportion requiring bridging to transplantation, and post-transplant had complications associated with high rates needing dialysis and tracheostomy. Furthermore, the resulting case complexity in this lung transplant cohort was only partly explained by Grade 3 PGD, which was observed in only one-third of the lung transplant recipients. Other important sequela post ICU that need to be considered are cognitive impairment and depression, which have been shown to be associated with physical function post-transplant and also with short and long term functional outcomes in a broad group of ICU survivors. Thus, the contribution of pre-transplant skeletal muscle function comprises one of many elements of post-transplant functional recovery in a group with a high degree of case complexity.

Our study has several limitations. First, skeletal muscle dysfunction in the pre-transplant period was obtained from chart records using muscle training volumes, which did not allow us to capture direct strength measures or physical performance, which may have been more prognostic of post-transplant outcomes. We also used an estimate of whole body muscle mass from thoracic CT, which was preserved in the pre-transplant period despite a significant decline in functional capacity. It is possible that thoracic CT is not as sensitive as limb muscle atrophy, which is known to be an important prognostic marker in advanced lung disease. We were also unable to comment on the influence of respiratory muscle dysfunction (i.e. diaphragm atrophy and strength), which could have influenced some of the functional and clinical outcomes in this group of patients, as previously described in non-transplant ICU survivors. Furthermore, a large proportion of ICU survivors had missed outcome assessments at three months due to medical illness or admission to inpatient rehabilitation at other facilities. Bias in demographic characteristics and functional recovery may exist in those
who had missed evaluations. We chose the time-frame of up to three months post-ICU for evaluation of post-transplant outcomes based on the RECOVER study which demonstrated that early post-transplant outcomes were associated with long-term morbidity and mortality. However, it is important to highlight that muscle strength, exercise capacity and self-reported physical function have been shown to have ongoing improvement up to one year post-transplant. The association with pre-transplant skeletal muscle function may have been different if assessments were taken at later time points post-transplant. Furthermore, lung transplant recipients participate in rehabilitation up to three-months post-transplant in both outpatient and inpatient programs as deemed appropriate by the transplant team. This certainly could have had a differential effect on the three-month functional independence, HRQL and exercise capacity in this group of patients. In addition, muscle strength measures with the MRC scale were only performed at three months post-ICU discharge. Thus, we are unable to comment on the relative contribution of ICU acquired weakness versus pre-transplant skeletal muscle weakness in these patients. Furthermore, given the limitations of sample size, we grouped the ICU LOS of the fifteen patients bridged to lung transplantation with the rest of the transplant cohort, which may have underestimated the negative consequences of pre-transplant ICU admission on post-transplant functional recovery. Lastly, it is important to highlight the findings in this study apply to a select group of patients with a prolonged ICU LOS and not to the entire pool of lung transplant recipients, most of whom do not require ≥ 7 days of MV.

5.6 Conclusion:

Lung transplant recipients with a minimum of 7 days MV experienced significant morbidity and impairments in early functional recovery resulting in a high proportion being discharged to inpatient rehabilitation. Older age and prolonged ICU LOS were significant predictors of early functional disability. Other pre-transplant factors such as skeletal muscle mass, training
volumes, and exercise capacity were not associated with post-transplant outcomes highlighting the importance of ICU acquired morbidity in this group of patients. The findings from this study could help facilitate advance care discussions among clinicians, patients and their caregivers about the clinical implications of prolonged peri-operative MV. Future investigations should aim to explore the implications of other pre-transplant markers such as direct measures of peripheral muscle size and strength, functional capacity decline, and ECLS support on post-transplant outcomes in recipients with complex peri-operative courses.
CHAPTER 6

6.0 Discussion:

6.1 Overview of Findings:

The findings from the three studies comprising this thesis highlight the importance of skeletal muscle mass, strength and function on pre- and early post-transplant clinical outcomes in three distinct, but complementary lung transplant cohorts from a single large lung transplant center. The novel findings in this thesis are:

Chapter 3 (Study 1):

1) Thoracic muscle cross-sectional area (CSA), a novel surrogate marker of whole body muscle mass was reduced in lung transplant candidates compared to controls.
2) Thoracic muscle CSA was independently associated with pre-transplant exercise capacity, strength training volumes, but not health-related quality of life (HRQL).
3) Thoracic muscle CSA was independently associated with hospital length of stay post-transplant, but not pre- or post-transplant mortality.

Chapter 4 (Study 2):

1) Skeletal muscle deficits (muscle mass, strength and physical function) were common in the pre-transplant period and characterized mainly by reductions in quadriceps strength and physical performance.
2) A greater number of skeletal muscle deficits was associated with lower exercise capacity, greater impairments in activities of daily living (ADL), lower HRQL, and longer post-transplant hospital length of stay.
Chapter 5 (Study 3):

1) Lung transplant recipients who required seven or more days of mechanical ventilation had significant impairments in functional recovery, HRQL, exercise capacity, and high rates of discharge to inpatient rehabilitation.

2) Older age and intensive care unit (ICU) duration were the strongest predictors of early post-transplant functional recovery, whereas no association was observed for pre-transplant thoracic muscle CSA, strength training volumes, or exercise capacity.

The findings in the present thesis highlight that evaluation of skeletal muscle dysfunction pre-transplant was most informative in understanding the daily functional and exercise limitations experienced by lung transplant candidates. Future studies should examine whether targeted rehabilitation strategies in the pre-transplant period may improve daily function and early post-transplant outcomes.

6.2: Assessment of Skeletal Muscle Dysfunction in Lung Transplant Candidates

In the present doctoral work, we began with the framework of sarcopenia (decreased muscle mass and low peripheral muscle strength or physical function defined using the consensus definition). Sarcopenia defined using the consensus definition has been shown to be associated with an increased risk of adverse outcomes such as physical disability, poor HRQL and death in community dwelling elderly. However in patients with advanced lung disease, individual skeletal muscle impairments such as low quadriceps strength, mid-thigh cross-sectional area, and fat free mass have been observed to be associated with increased morbidity and mortality. Similarly, in liver and renal transplant candidates low skeletal muscle mass has been related to increased post-transplant mortality. Individual measures of sarcopenia (muscle mass, strength and function) have generally been evaluated
in lung transplant candidates, but their clinical implications not previously assessed. Therefore, we placed equal emphasis on all three measures due to the lack of agreement as to which elements of muscle dysfunction were most relevant in chronic disease and transplant candidates. We focused on the associations between individual elements of muscle dysfunction pre-transplant and clinically relevant outcomes such as exercise capacity, physical function, HRQL and pre- and post-transplant clinical outcomes. The individual measures of skeletal muscle dysfunction are discussed below.

**Muscle Mass Assessments:**

Skeletal muscle mass was assessed using two modalities in the present thesis. Whole body fat free mass was evaluated using bio-electrical impedance (BIA), which is an accurate and valid technique that has been utilized in advanced lung disease and lung transplant candidates. Whole body muscle mass was estimated using muscle CSA from thoracic computed tomography (CT) in Chapters 3 and 5. Although thoracic muscle CSA is not the standard method of skeletal muscle mass assessment, we demonstrated for the first time that thoracic muscle CSA had a strong association with fat free mass index (obtained using BIA) in 50 lung transplant candidates. Lung transplant candidates were also noted to have lower thoracic muscle CSA by 10% compared to control subjects, which is consistent with the difference in fat free mass observed with BIA, further supporting the construct validity of this measure. Unlike recently applied muscle CSA techniques using abdominal CT measures, we used thoracic CT scans as they are readily available in all lung transplant candidates without any additional cost or radiation exposure. The anatomical landmark for thoracic CSA was the carina, which was chosen given the ease of clinical identification, and previous evidence from our group demonstrating that any representative CSA slice in the mid thoracic levels was closely associated with thoracic muscle volume. Thus, as recommended by the sarcopenia consensus guidelines for assessment of whole body muscle
mass, we estimated skeletal muscle mass using two validated measures in lung transplant candidates.

In Chapter 4, whole body muscle mass was observed to be relatively preserved in the majority of lung transplant candidates, whereas impairments in lower extremity strength and physical performance were more common. A similar pattern was recently observed in over 500 stable outpatients with moderate to severe COPD (not listed for transplant) who had a high prevalence of quadriceps weakness (57%), but less than 10% of these patients had concomitant low muscle mass with BIA before initiation of pulmonary rehabilitation. In community dwelling older adults, the loss of lower extremity strength has been shown to occur more rapidly than the accompanying loss of quadriceps muscle mass with aging. Several factors have been proposed that can contribute to the differential loss of muscle function relative to muscle mass including reduction in intrinsic force generating properties, muscle quality (i.e. fat infiltration), and neuromuscular changes in voluntary control. Thus, as observed in Chapter 4, functional deficits (reduced strength and physical performance, also referred to as dynapenia) might be more informative with respect to physical disability in advanced lung disease and may be more predictive of post-transplant outcomes compared to whole body muscle mass measures.

It is important to highlight that the present thesis does not allow us to comment on site specific muscle atrophy in lung transplant candidates. In previous work, our lab has previously demonstrated moderate to strong associations between thoracic muscle CSA and both quadriceps muscle thickness and rectus femoris CSA assessed with B-mode ultrasound. It is possible that estimates of whole body muscle mass might underestimate regional changes in limb muscle atrophy observed in lung transplant candidates, as lower extremity muscles have been shown to have increased vulnerability for muscle atrophy compared to other muscle groups. Measurement of localized muscle atrophy (i.e. quadriceps CSA) has
important functional consequences given the moderate-strong association between quadriceps muscle size, strength and physical performance.\textsuperscript{172,257} Furthermore, regional muscle measurements with non-invasive imaging modalities (computed tomography, magnetic resonance imaging, or ultrasound) may also be used to evaluate muscle quality (i.e. fat infiltration), which has been shown to be an important mediator of physical function and disability, independent of muscle size.\textsuperscript{483} Thus, the consensus definition of sarcopenia proposed in community dwelling elderly which presently integrates whole-body muscle mass,\textsuperscript{158} might not be as applicable in chronic lung disease, given evidence for preferential lower extremity muscle atrophy, weakness, and functional deficits compared to loss of whole body muscle mass.

**Muscle Strength Assessments:**

Skeletal muscle strength was assessed using various methods in the three studies: computerized dynamometer (Biodex; gold standard tool), hand-held and hand grip dynamometers, and muscle training volumes obtained from exercise training logs, all of which have been previously utilized at our center.\textsuperscript{110,125,131} Whereas computerized dynamometers are considered the gold standard and the most common tool used in the research setting to evaluate peripheral muscle strength, their utilization in the clinical setting has been limited due to higher cost, accessibility, training and time required for testing.\textsuperscript{252} Hand-held dynamometers offer a good alternative in the clinical setting for assessment of muscle strength given their portability, low cost and ability to evaluate any peripheral muscle group. However, hand-held dynamometers have their limitations, especially when testing larger muscle groups such as knee extensors given their lower accuracy and reliability, as stronger individuals can potentially break the opposing force of the tester.\textsuperscript{280,281} In the cohort of lung transplant candidates described in Chapter 4, we observed that there was moderate agreement between traditional measures of hand-grip strength and quadriceps strength
isometric peak torque) from Biodex with biceps and quadriceps muscle training volumes obtained from pulmonary rehabilitation, respectively. This is promising as upper and lower extremity muscle training volumes are routinely used at our center for resistance training in pulmonary rehabilitation and offer a potential surrogate measure of muscle strength that may be utilized clinically, when standard strength testing is not feasible in a busy clinical setting. However, there are a few limitations that arise when using training volumes to estimate muscle strength given patients are not usually trained to their peak muscle capacity and the resistance exercises are generally progressed by a specific incremental load.

The pattern of muscle weakness with predominance of lower extremity dysfunction (quadriceps weakness and low score on the SPPB) compared to upper extremity weakness (hand-grip strength), as observed in Chapter 4, is in keeping with general disuse and deconditioning. Quadriceps weakness (greater than one standard deviation) was seen in over half of the lung transplant candidates compared to low hand-grip strength seen in about one-third of candidates. In Chapters 3 and 5, strength training volumes of the biceps were generally about 30% greater than the quadriceps training volumes. This pattern has been previously described in advanced lung disease patients given the relative preservation of upper extremity strength with greater reliance on these muscles to carry out ADL (i.e. food preparation and self-care), whereas tasks such as daily walking that rely on muscles of the lower extremities are often reduced in the pre-transplant period. Even though quadriceps strength was more commonly reduced and had a stronger association with HRQL and ADL than hand grip strength, we are unable to comment on the contribution of the proximal muscles of the shoulder girdle (i.e. trapezius, deltoids). More importantly, the proximal upper extremity muscles have been observed to be weaker than the distal muscles in COPD, which could have had a differential effect on HRQL and ADL. Also, future assessment of upper extremity endurance, which has been shown to correlate with proximal
upper extremity exercise capacity, strength and performance of ADL,131,484 might provide additional insight into the daily functional limitations experienced by lung transplant candidates.

**Assessment of Lower Extremity Function**

In Chapter 4, we observed significant impairments in the total score of the SPPB in lung transplant candidates within 4 weeks of transplant listing. We used a cut-off score of less than 10 points (out of 12) which has previously been shown to be associated with muscle atrophy and lower extremity dysfunction in COPD.485 We observed that 48% of lung transplant candidates had low scores on the SPPB, which was consistent with the proportion observed in another study from our center examining skeletal muscle dysfunction in twenty-six transplant candidates with ILD.131 The impairments in SPPB were predominantly in gait speed and the sit-to-stand test with only a few patients demonstrating impairments in balance (tandem stance). Singer et al. in a large cohort of lung transplant candidates (n=262) observed a similar pattern in SPPB scores, with balance instability observed in only 8% of participants.318 In addition to preservation of balance, we observed a low percentage of self-reported falls (12%) in the previous year in our lung transplant cohort. This contrasts with findings in COPD where 46% of patients had a self-reported fall in the preceding year and standard balance screening tests could discriminate fallers from non-fallers.312 There are several possibilities for the decreased prevalence of falls observed in our lung transplant cohort. First, the low prevalence of balance instability and falls observed could be due to the highly-selected nature of lung transplant candidates, as compared to the larger population of patients with advanced lung disease. Second, the prevalence of self-reported falls may have been lower in our cohort of lung transplant candidates in Chapter 4, given the high proportion of ILD participants. Individuals with ILD may have fewer balance deficits than people with COPD given differences in co-morbidities and corticosteroid use, which are known to affect balance.486 However,
further verification of falls risk in non-COPD patients is needed given the high morbidity associated with falling in community dwelling elderly.487,488

**Pre-transplant Exercise Capacity: Six-minute Walk Test**

The 6MWD is one of the most important known predictors of pre- and post-transplant mortality and is commonly utilized as a measure of exercise capacity in lung transplantation.22,23,104 However, the 6MWT is unable to isolate the contribution of peripheral limitations (i.e. muscle) to exercise from central limitations (ventilatory or cardiovascular).104 In Chapter 4, we observed low to moderate correlations between 6MWD and quadriceps strength or SPPB, respectively. The lower associations in our cohort could be related to disease severity, highlighting the greater contribution of ventilatory limitations to exercise capacity in lung transplant candidates compared to non-listed COPD and ILD patients. In our cohort, the FEV1 for obstructive lung disease was 21 ± 7 % and the FVC for restrictive lung disease was 46 ± 16 %. Gosselink et al. in their cohort of non-transplant COPD patients (FEV1 43 ± 19 %) observed a moderate association (r=0.63) between quadriceps force and 6MWD.489 Similarly, Nishiyama et al. noted that quadriceps force was associated with aerobic capacity (r=0.62) in a group of mild IPF patients with a FVC (77 ± 17 %).20 Our findings are in line with Singer et al. who observed a moderate association between SPPB and 6MWD (r=-0.54), where as no significant association was observed by Van der Woude et al. between quadriceps strength and 6MWD (r-value not reported) in their cohort of lung transplant candidates.291,318 Thus, it is important to recognize that the contribution of lower extremity muscle strength to exercise capacity will vary depending on disease severity and population studied. Furthermore, physical performance tests that integrate balance and lower extremity strength are potentially more informative than exercise capacity in highlighting the daily functional limitations experienced by community dwelling elderly 490 and those with advanced lung disease.303 Future investigations are needed to understand the contribution of lower
extremity endurance (i.e. leg fatigue) to daily function, as endurance has been described to be an important factor limiting functional capacity, especially in the presence of hypoxemia.\textsuperscript{197}

**Assessment of Patient Reported Outcomes Pre-Transplant:**

We used standard, validated measures of HRQL evaluation (Short Form-36 and St. George’s Respiratory Questionnaire) and ADL (London Chest Questionnaire) in lung transplant candidates.\textsuperscript{26,95} The degree of impairment in HRQL measures was consistent with other studies from our center that had assessed HRQL in stable outpatients.\textsuperscript{109} We observed that functional deficits (strength and physical performance) had moderate associations with HRQL and ADL (Chapter 4), whereas no independent association was observed with muscle mass (Chapters 3 and 4). This is in keeping with the literature as the degree of disability experienced by those living with advanced lung disease is not captured well with static measures such as lung function, and functional measures (strength and performance) are potentially more informative in understanding limitations in daily function.\textsuperscript{90,91}

We suspect the lack of association between skeletal muscle mass and HRQL in the present thesis could be related to the fact that we utilized a measure of whole body muscle mass in both studies. The association between muscle mass and HRQL would likely have been stronger if lower extremity muscle size was assessed, as quadriceps size provides a better reflection of physical activity levels.\textsuperscript{172} Physical activity has been shown to be a strong determinant of HRQL in lung transplant candidates.\textsuperscript{109,124} The lack of association between skeletal muscle mass and HRQL could also be due to the fact that HRQL measurements were obtained from stable outpatients participating in pulmonary rehabilitation. Mostert et al. observed that the loss of fat free mass in COPD patients had a stronger relationship with the St. George’s Respiratory questionnaire and functional measures than muscle mass evaluated at a single time point. Loss of fat-free mass is more likely to be seen in patients requiring hospitalization or those unable to participate in pulmonary rehabilitation.\textsuperscript{445} Thus, it is possible
the relationship in Chapter 3 between skeletal muscle mass and HRQL could have been stronger in those unable to complete HRQL assessments, as those without these assessments were observed to have lower exercise capacity and were more likely to be delisted or die pre-transplant.

Whereas we observed a moderate association with functional muscle deficits and pre-transplant HRQL and ADL in Chapter 4, no association was seen in Chapters 4 and 5 between skeletal muscle dysfunction and Lung Allocation score (LAS). It is important to highlight that the LAS was designed to optimize survival over the first-year post-transplant, but does not factor elements such as skeletal muscle dysfunction, HRQL, ADL and post-transplant function.32 The significant differences in HRQL and ADL across skeletal muscle deficits (Chapter 4) suggests that skeletal muscle dysfunction provides greater insight into pre-transplant HRQL and disability, which are not captured with the LAS.61,62 A better understanding of the physical factors that influence daily function could help inform the optimal timing of transplant listing as many candidates pursue transplantation to derive benefit in HRQL and ADL, not just survival.

6.3: Determinants of Skeletal Muscle Dysfunction in Lung Transplant Candidates

There are multiple factors which can contribute to skeletal muscle dysfunction in people with advanced lung disease such as hypoxemia, malnutrition, physical inactivity/disuse, corticosteroids, and systemic inflammation.12,14 The lung transplant candidates in all three studies had multiple factors which could have contributed to skeletal muscle dysfunction as outlined in the conceptual framework in Figure 6-1. Most study participants (> 90%) were using long-term oxygen therapy for exertion and about one third were taking daily oral corticosteroids. In addition, unintentional weight loss ≥ 10 pounds in the year prior was observed in about one quarter of our study participants in Chapter 4, which could be related to
imbalance of protein synthesis and degradation pathways as previously described in cardiopulmonary disease. We can infer from Chapters 4 and 5 that one contributing factor for skeletal muscle dysfunction was muscle disuse, given a higher proportion of transplant candidates with preferential weakness of the lower extremity muscles relative to the upper extremities. In addition, a large proportion of patients in Chapter 4 had low self-reported physical activity levels, as previously described in lung transplant candidates. Unfortunately, given the cross-sectional nature of the thesis studies we are unable to comment on the direct contribution of each of these factors, but several key associations are highlighted below.

**Figure 6-1:** Conceptual Framework of Factors Affecting Skeletal Muscle Mass, Strength and Function. **Legend:** Studies assessing risk factors outlined in brackets. Study 1 = Chapter 3, Study 2 = Chapter 4, and Study 3 = Chapter 5.
Malnutrition/Weight Loss:

In Chapter 4, we noted that COPD patients were more likely to have unintentional weight loss in the year preceding transplant listing compared to ILD patients, and the weight loss was associated with reduced skeletal muscle mass assessed with BIA. In chapter 3, lung transplant candidates with COPD were also observed to have lower skeletal muscle mass compared to ILD patients based on thoracic muscle CSA, independent of age and sex. It is possible that disease duration could have had an influence on muscle mass, as ILD patients are generally referred for lung transplantation earlier in their disease course, which could mitigate some of the muscle mass loss with respiratory exacerbations, disease progression and corticosteroid therapy. The lower skeletal muscle mass observed in COPD patients is an important consideration as it is a marker of increased catabolic state and reduced protein reserve, which is essential during periods of major surgery such as transplantation and critical illness. In addition, weight loss has been shown to affect diaphragm bulk which could have significant effects on respiratory muscle function in the post-transplant period.

Hypoxemia:

Most study participants (> 90%) required long-term oxygen therapy for exertion at the time of transplant listing. There was a progressive increase in oxygen requirements while on the lung transplant list as observed in Chapter 5 and consistent with previous work from our center. Even though we are unable to comment on the direct effect of hypoxemia on skeletal muscle dysfunction, chronic hypoxia is known to have a significant effect on skeletal muscle mass in humans. Chronic respiratory disease patients with low arterial oxygen levels have been shown to have significantly reduced body weight and muscle mass. This muscle atrophy is thought to be mediated through hypoxemia induced oxidative stress and inflammation. In addition, chronic hypoxemia can result in decreased muscle strength and endurance, with a shift towards type II (fast-twitch fibers).
Corticosteroids:

We did not observe an association between elements of skeletal muscle dysfunction and corticosteroid use in any of the three studies assessing thoracic muscle CSA or peripheral muscles. This contrasts with previous reports in COPD and ILD that have described steroid myopathy as a significant contributor to hand-grip strength and quadriceps weakness.\textsuperscript{208,498,499} However, there are several important differences that should be highlighted. First, the cross-sectional nature of the studies did not allow us to capture the cumulative dose of corticosteroids in the preceding six months, which was the main determinant assessed in previous studies.\textsuperscript{498,499} Secondly, the pattern of steroid use in lung transplant candidates may be different from non-listed patients given that prescribers might be more conscientious of the metabolic consequences such as weight gain, osteoporosis and diabetes in transplant candidates.\textsuperscript{500,501} Thirdly, the pattern of steroid use in Chapter 4 assessing peripheral muscles may have been different in this recent ILD predominant cohort given the known harmful effects of chronic prednisone therapy in IPF patients.\textsuperscript{502} Finally, we had assessed the impact of corticosteroids on thoracic muscle CSA in two out of the three studies, which potentially would be less affected than the peripheral muscles.\textsuperscript{503}

One important question that remains unanswered in advanced lung disease is to what extent skeletal muscle dysfunction is a result of years of muscle disuse and physical inactivity versus an underlying myopathy from multiple factors such as hypoxemia, corticosteroids, malnutrition and inflammation. To try to differentiate disuse versus myopathy, it will be important to match patients with chronic lung disease and controls with a similar level of physical activity followed longitudinally for several years. This is an ongoing challenge in many other chronic disease states as well, including congestive
heart failure and diabetes, given the significant overlap in musculoskeletal risk factors.504,505

6.4: Association of Skeletal Muscle Dysfunction with Post-transplant Outcomes

Given the established impairments in skeletal muscle function in the pre-transplant period,21 the prognostic utility of pre-transplant muscle mass, strength and function in predicting clinically important post-transplant outcomes was evaluated in this thesis.

Hospital Length of Stay:

Pre-transplant thoracic muscle CSA and total number of skeletal muscle deficits were associated with post-transplant hospital length of stay in Chapters 3 and 4, where as no association with pre-transplant muscle mass and function was observed in Chapter 5 in a group of lung transplant patients with a prolonged course of MV (≥ 7 days). The findings in Chapters 3 and 4 are consistent with previous studies that have demonstrated that better physical function and conditioning prior to surgery hastens hospital recovery.332,506,507 We have also previously shown that pulmonary rehabilitation pre-transplant generally preserves exercise capacity (6MWD), and a greater 6MWD pre-transplant was associated with reduced post-transplant hospital length of stay.110 This faster recovery potentially allows for early participation in supervised rehabilitation post-transplant and reduces the negative consequences of bed-rest that could result in significant deconditioning.508,509 To our knowledge, Chapter 5 is the first study to demonstrate that any pre-transplant conditioning achieved with rehabilitation was significantly mitigated by 7 or more days of MV. However, it is important to highlight in this study a high proportion (26%) of lung transplant candidates were admitted to hospital or ICU pre-transplant, which could have certainly limited some of the musculoskeletal gains which occurred with pre-transplant pulmonary rehabilitation. In fact, this group of patients showed less increase in their muscle training volumes and had a
significant decrease in their exercise capacity pre-transplant compared to patients with standard peri-operative courses at our center.\textsuperscript{110}

**Discharge Disposition:**

Lung transplant recipients with a prolonged hospital length of stay had high rates of discharge to inpatient rehabilitation compared to discharge home. In fact, discharge to inpatient rehabilitation was independently associated with total peri-operative ICU length of stay in Chapter 5, which may help with earlier discharge planning. A long stay in the critical care unit and hospital can result in decreased functional capacity, mobility, and skeletal muscle dysfunction, which in turn can lead to prolonged hospitalization and increased rehabilitation requirements.\textsuperscript{510} In a previous study from our center by Tang M et al, total hospital length of stay was found to be an independent predictor of discharge disposition.\textsuperscript{113} This is consistent with the findings in the present thesis illustrating lung transplant recipients with a prolonged hospitalization (median stay of 58 days) had higher rates of discharge to inpatient rehabilitation (43%), than the discharge rates observed in Chapters 3 and 4 (11-17%) with typical post-transplant hospital stays (median range; 20-23 days). The standard practice at our center is for lung transplant recipients to participate in outpatient rehabilitation for at least 3-months post-transplant; however, recipients that are unable to meet functional requirements for safe discharge home are referred to an inpatient rehabilitation program. The decision to discharge patients to inpatient rehabilitation is complex and could potentially be initiated early in the post-transplant period. There are multiple factors that need to be considered in the post-transplant period that could necessitate discharge to inpatient rehabilitation such as medical requirements (i.e. dialysis), ability to exercise, motivation, social circumstances, and transplant team perception.\textsuperscript{374} In addition, early discharge to inpatient rehabilitation is a promising cost-saving strategy as it optimizes functional recovery and reduces the number of days that lung transplant recipients occupy acute care hospital beds.\textsuperscript{520} Inpatient rehabilitation
focuses on increasing functional independence through low intensity resistance, balance and aerobic training that is more individualized and progressed more gradually than the outpatient program, which is a feasible option for patients with low baseline function at the time of hospital discharge.374

**Functional Independence Post-transplant:**

The Functional Independence Measure (FIM) applied in the early post-transplant period provides a multi-dimensional patient centered approach to evaluating the level of assistance required for performance of ADL.321 The FIM has been previously applied across several medical and surgical disease states, including cardio-pulmonary transplantation.319,421 Lung transplant recipients with a prolonged course of MV (Chapter 5) were observed to have severe limitations in the motor FIM at 7-days post ICU discharge, representing maximal to total assistance. The greatest limitations were with toileting, transfers, dressing and locomotion. Importantly, 40% of lung transplant recipients were unable to walk at 7 days post-ICU discharge and therefore unable to perform the 6MWT. This highlights the utility of the FIM measure over the 6MWT in the early post-transplant period. By three months post-ICU discharge, lung transplant recipients demonstrated significant functional gains demonstrating moderate independence with the FIM. The recovery in physical function observed in lung transplant recipients at 7 days and 3 months post-ICU discharge was comparable to the main multi-center RECOVER cohort with mixed diagnoses.319 In chapter 5, age and ICU length of stay were consistently shown to be the two most important determinants of functional recovery, independent of pre-transplant skeletal muscle mass, strength training volumes, and exercise capacity. Furthermore, these results in lung transplant recipients are consistent with previous findings demonstrating that functional recovery post-ICU is independent of admitting disease severity, medical or surgical intervention.319
Improvement in Functional Capacity Post-Transplant:

Exercise capacity at three-months post-transplant improved by 96 meters in Chapter 4 and by 104 m in Chapter 5. This is comparable to other observational studies demonstrating increases in 6MWD ranging from 92 to 152 meters, primarily due to alleviation of ventilatory limitations with transplantation.\textsuperscript{116,122,420} The variability in recovery in 6MWD with transplantation could possibly be attributed to multiple factors such as ICU and hospital length of stay, demographics (age and diagnosis), and differences in rehabilitation practices across studies. Despite a prolonged ICU course, the patient cohort studied in Chapter 5 showed an improvement in exercise capacity at 3 months post-ICU that was comparable to cohorts with a more typical course post-transplant as observed in the literature and Chapter 4.\textsuperscript{116,122,420} This indicates there is rehabilitation potential with respect to functional capacity in lung transplant recipients experiencing a complex post-operative course.

In Chapter 5, lung transplant recipients with lower pre-transplant exercise capacity demonstrated a greater potential for improvement in their exercise capacity post-transplant despite a complicated hospital course. A similar relationship was observed by Walsh et al. where post-transplant exercise capacity was inversely associated with pre-transplant 6MWD and quadriceps muscle strength recovery was a stronger determinant of exercise capacity than graft function up to 26 weeks post-transplant.\textsuperscript{122} Similarly, Wickerson et al. noted that lower pre-transplant 6MWD was associated with a greater improvement in daily physical activity levels three-months post-transplant independent of lung function.\textsuperscript{109} These studies demonstrate that lung transplant recipients with lower pre-transplant exercise capacity have a greater potential to improve their post-transplant functional capacity as a result of significant alleviation of ventilatory limitation with transplantation, but limitations in exercise capacity persist mainly due to musculoskeletal impairments.\textsuperscript{122} In Chapter 5, exercise capacity at 3 months post-ICU was reduced at 63% predicted with approximately one-third of lung
transplant recipients (10/33) having generalized muscle weakness based on the Medical Research Council scale. It is important to highlight that recovery in exercise capacity post-transplant is complex and multiple other factors need to be considered such as muscle endurance, oxidative capacity, and the use of walking aids, which could have a significant contribution on walk distance.

**Health-Related Quality of Life after Lung Transplantation:**

Self-perceived physical function in the post-transplant period was captured with the SF-36 Physical Component Score (PCS). We observed that the post-transplant SF-36 PCS (35 ± 10) at three months post-ICU discharge remained below population normative values (score of 50), but was comparable to the HRQL observed in other studies of lung transplant recipients and other critically ill patients (RECOVER). In fact, age and ICU length of stay were the only significant determinants of post-transplant HRQL, independent of pre-transplant skeletal muscle mass, strength training volumes or exercise capacity. As in the larger RECOVER cohort, the SF-36 PCS had a moderate to strong association with the motor FIM at three-months post ICU discharge, highlighting the importance of post-transplant function on HRQL physical domains after transplant. Wickerson et al. in an observational cohort study at our centre observed that increased physical activity levels paralleled the improvement in HRQL up to 6 months post-transplant. In addition to increasing functional independence and physical activity levels, the improvement in HRQL in the early post-transplant period is multi-factorial with other contributing factors including alleviation of ventilatory limitations, liberation from oxygen therapy, improvement in post-operative pain and potentially rehabilitation.

It is difficult to separate the effect of rehabilitation from the natural recovery of HRQL in lung transplant recipients, as all lung transplant patients at our center undergo post-transplant
rehabilitation. However, Langer et al in a randomized control trial demonstrated no difference in any of the SF-36 domains after 3 months of outpatient rehabilitation compared to the control group (encouraged to be physically active) after hospital discharge.\textsuperscript{117} It is possible that the lack of a difference in HRQL observed in their study could be related to the significant immediate improvement in HRQL with transplantation. The effect of post-transplant rehabilitation on HRQL might be more pronounced in lung transplant recipients with a complex hospital course; however, a randomized clinical trial to assess this would not be ethical given the known positive benefits of rehabilitation in this group of patients.

**Post-transplant Mortality:**

In this thesis, the association of skeletal muscle dysfunction with standard peri-operative and early post-transplant outcomes, including mortality was evaluated. We chose to investigate early post-transplant outcomes given previous studies demonstrating that long-term outcomes were significantly influenced by early post-operative events in lung transplant recipients.\textsuperscript{51,457,460} Similarly, in the general medical and surgical ICU setting, functional independence at 7 days post-ICU discharge was prognostic of one year mortality.\textsuperscript{319}

We hypothesized that low skeletal muscle mass would be associated with increased morbidity and mortality post-transplant given that skeletal muscle mass is an important marker of physiologic and protein reserve, which is essential during periods of critical illness and major surgery such as transplantation.\textsuperscript{438} However, we observed no association between pre-transplant skeletal muscle mass and peri-operative hospital and one-year mortality (Chapter 3). Similarly, no association was observed between skeletal muscle deficits and early post-transplant mortality (3 months) in Chapters 4 and 5, but it is important to highlight that we were not statistically powered for this analysis in the latter two studies. To our knowledge, there have been a total of three studies recently published in lung transplant candidates that examined the association between skeletal muscle mass and post-transplant mortality. Kelm
et al. demonstrated that low pre-transplant abdominal muscle CSA was associated with one and three-year survival in a select group of lung transplant candidates (n=36) mainly with COPD.\textsuperscript{239} This is in contrast with the findings in Chapter 3 and those of Weig et al. who found no association between low skeletal muscle mass and post-transplant mortality in hospital and at one year.\textsuperscript{240} Interestingly, Lee et al. utilizing a similar technique as our group for quantifying thoracic muscle CSA at the carina observed that lung transplant candidates in the largest muscle CSA quartile had the lowest one year survival, however, their analysis was not adjusted for older age or higher proportion of ILD patients which could have biased their results.\textsuperscript{244} Thus, the differences between the studies could be related to measurement techniques, thresholds used to define sarcopenia, rehabilitation practices, and transplant indication, as ILD patients are known to have the worst post-transplant survival compared to other diagnostic groups.\textsuperscript{423} It is also possible that measurement of whole body muscle mass might not be an ideal prognostic marker of mortality in this group of patients given that selection of lung transplant candidates is dependent on their body weight and nutritional status. Thus, evaluation of muscle atrophy of the lower extremities might prove to be more prognostic in future investigations given increased vulnerability for regional, lower limb muscle atrophy compared to whole body muscle mass measurements in chronic lung disease.\textsuperscript{245,513}

The peri-operative hospital mortality rate was similar across all three studies in this thesis ranging from 10-16\%, with the greatest mortality observed in lung transplant recipients with prolonged mechanical ventilation (Chapter 5). Given that primary graft dysfunction (PGD) is one of the most common causes of peri-operative mortality in lung transplant recipients and associated with body composition,\textsuperscript{376,514} we evaluated the association of PGD with skeletal muscle mass. In Chapters 3 and 5, we did not observe an association between skeletal muscle mass and development of PGD. This is interesting as increased pre-transplant BMI has been described as an important determinant of PGD, which lends further support that
perhaps increased adipose tissue is a stronger contributor to development of PGD than muscle mass in lung transplant recipients, and could be mediated through higher plasma leptin levels. Furthermore, a similar relationship between adiposity and delayed graft function and graft survival has been observed in renal transplant recipients. Whereas we did not assess tissue adiposity in the present work, future studies exploring the mechanisms underlying changes in skeletal muscle mass and adipose tissue could help advance our understanding of the risks associated with obesity and PGD in lung transplant recipients.

6.5: Clinical Implications of Skeletal Muscle Function Assessment

The present thesis examined several measures of skeletal muscle dysfunction (muscle mass, strength and function) individually and in combination. We observed that whole body muscle mass assessed with thoracic muscle CSA was independently associated with post-transplant hospital length of stay, but not with pre-transplant HRQL. Similarly, the total number of skeletal muscle deficits pre-transplant (muscle mass, strength or low physical performance) was associated with post-transplant hospital length of stay, but functional deficits (strength and performance) were more informative of patient reported outcomes and exercise capacity pre-transplant. It is important to highlight that the skeletal muscle measures in the present thesis did not predict functional recovery or mortality post-transplant.

The utility of these non-invasive muscle measures is gaining recognition in lung transplantation, as they have recently been shown to be good prognostic markers of pre- and post-transplant morbidity and mortality in several studies, although outcomes have been variable across studies and measurement modalities. It is possible the variability observed with transplant outcomes could be related to the phenotypic heterogeneity of skeletal muscle dysfunction in lung transplant candidates and recipients. Skeletal muscle dysfunction might prove to be more informative in transplant recipients with typical peri-
operative ICU courses than those with complex and prolonged ICU stays who may have a high degree of ICUAW and functional disability, not necessarily predicted by pre-transplant skeletal muscle dysfunction as observed in Chapter 5.

As evidence in the field emerges, standardization of muscle measurement techniques and establishment of valid cut-offs for low muscle mass and function could potentially assist with transplant candidacy evaluation and prognostication. It is possible that lung transplant candidates who have lower muscle mass, strength and physical function could benefit from lung transplant prioritization as individual elements of skeletal muscle dysfunction have been shown to be amenable to rehabilitation.159 Interestingly, lung transplant recipients in Chapter 5 who had skeletal muscle impairments pre-transplant demonstrated functional improvements post-transplant even in the setting of a complex peri-operative course demonstrating rehabilitation potential. A better understanding of risk factors (i.e. malnutrition, physical inactivity, corticosteroids) and heterogeneity in skeletal muscle dysfunction (muscle mass, strength and function) could help guide rehabilitation strategies and inform the degree of reversibility in the pre- and post-transplant periods.

6.6 Limitations

Several limitations should be considered when interpreting the findings of this thesis. First, the studies in the present work did not capture individuals who were assessed for lung transplantation and deemed unsuitable for transplant listing. Patients with advanced lung disease declined for transplant listing could have been sicker and have a greater prevalence of skeletal muscle dysfunction than those who were listed. Thus, this could have underestimated the effect of skeletal muscle dysfunction on HRQL and functional outcomes in patients with advanced lung disease. Secondly, the cross-sectional study design of two of the studies limits our ability to comment on the influence of risk factors or the natural progression
of skeletal muscle dysfunction in patients with advanced lung disease. Whereas we considered common factors affecting muscle such as age, sex, diagnosis, body stature, and corticosteroid use, skeletal muscle function could be influenced by other determinants pre- and post-transplant such as respiratory exacerbations, comorbidities, nutritional status and physical activity levels which were not assessed across all studies.\textsuperscript{12,517} Thirdly, there were some limitations with our muscle mass and strength measures that need to be highlighted.

We evaluated whole body muscle mass using BIA or estimated muscle mass using thoracic muscle CSA and thus are unable to comment on regional atrophy (such as that of the lower limb muscles) or muscle composition, which could certainly have had a differential effect on HRQL and ADL measures. Furthermore, we used non-invasive, volitional measures of skeletal muscle function (muscle strength and physical performance) in the present thesis. Volitional measures are influenced by factors such as neuromuscular factors (e.g. central activation), motivation and cooperation, which may underestimate the actual contractile capacity of the muscle despite standardization of strength measurement techniques.

Furthermore, volitional measures do not allow for isolation of the central (i.e. motor cortex, nerve conduction) from peripheral factors (i.e. neuro-muscular junction and muscle fibers) associated with muscle force contraction. It is also important to highlight that muscle strength was the predominant functional deficit assessed as we did not capture muscle endurance or lower extremity muscle power, which have been shown to be stronger prognostic markers of mobility and disability in older adults compared to muscle strength.\textsuperscript{518-520}

Another important limitation is that the patient cohorts studied in all three studies were drawn from a single, large tertiary center. The Toronto Lung Transplant program requires all lung transplant candidates to participate in a standard pulmonary rehabilitation program while awaiting lung transplantation. Certainly, the clinical implications of pre-transplant skeletal muscle dysfunction could be very different at other transplant centers without a mandatory
pulmonary rehabilitation program or in centers with smaller transplant volumes. The present thesis also did not assess certain environmental and patient factors that could have had an influence on hospital length of stay and discharge disposition, such as caregiver support. Even though all lung transplant candidates in our program are required to have a pre-arranged support person with appropriate living arrangements, factors such as availability of inpatient rehabilitation beds, relocation distance, caregiver support, and neuropsychological sequelae post-transplant could have had an influential effect on discharge disposition. Furthermore, all ICU and hospital ward patients post-transplant participate in a mobility program and perform light exercises as prescribed and supervised by a physiotherapist. However, the recovery during the peri-operative period and discharge disposition could be affected by participation in hospital rehabilitation. Thus, future prospective studies should aim to record these environmental and patient factors to assess their influence on discharge disposition.

6.7: Conclusion:

This thesis provides new evidence highlighting the clinical implications of skeletal muscle dysfunction in lung transplant patients. Skeletal muscle dysfunction in lung transplant candidates was associated with HRQL, ADL, and exercise capacity and associated with post-transplant hospital length of stay. In a select group of lung transplant recipients who required ≥ 7 days of MV, age and ICU duration were the only significant determinants of post-transplant functional outcomes and this highlights the importance of ICU acquired morbidity in these patients. Given the changing demographics with lung transplant candidates being older and presenting with greater complexity, the findings of this thesis may help facilitate discussion and informed consent among patients, families, and the health-care team about potential outcomes peri-operatively. Future work will need to help clarify whether targeted
rehabilitation strategies in the pre-transplant period may improve daily function and early post-transplant outcomes.

6.8 Future Directions:

There are several areas of future investigation that arise from this work on skeletal muscle dysfunction in lung transplant candidates. Future studies will need to focus on non-listed chronic lung disease patients both in the inpatient and outpatient settings, across various disease states, given the phenotypic heterogeneity in skeletal muscle dysfunction observed in the present thesis. The ability to capture patients earlier in their disease course even prior to transplant listing and ability to monitor the change in skeletal muscle mass, strength and function across various disease states could provide a better understanding of certain skeletal muscle determinants (i.e. corticosteroids, hypoxemia, malnutrition). To-date, it remains unclear whether changes in skeletal muscle mass and function (strength and physical performance) occur rapidly with exacerbations, if the decline is step-wise over time or if individuals with chronic respiratory disease actually have an accelerated decline in lower extremity muscle strength above the 1-2% per year experienced by the aging population. Thus, future studies should aim to study a number of chronic lung disease cohorts over longer periods of follow-up, which could help understand the change in skeletal muscle structure and function over time with respiratory exacerbations and between disease states.

Future investigations should aim to characterize muscle specific atrophy and composition, as whole-body measures could underestimate the presence of muscle atrophy, particularly of the lower extremity muscles. One promising modality is B-mode ultrasound, which offers a portable, reliable, low-cost imaging modality that can be utilized across a variety of clinical settings including hospitalized and critically ill patients. In addition to skeletal muscle atrophy, it is possible to assess muscle quality (i.e. fibrous or muscle fat infiltration) with
ultrasound using echo intensity.\textsuperscript{524,525} Future studies could focus on whether low muscle quality is more predictive of clinical outcomes than muscle atrophy or weakness in advanced lung disease and lung transplant candidates.

In the present thesis, we observed relative preservation of respiratory muscle strength in the majority of lung transplant candidates using traditional, volitional measures (i.e. maximal inspiratory and expiratory pressures). We suspect that non-volitional measures of diaphragm function might be a more sensitive marker of respiratory muscle dysfunction in advanced lung disease. Future study could utilize non-volitional measures such as B-mode ultrasound to assess diaphragm thickness and inspiratory capacity from measures of diaphragm thickening in patients admitted with an exacerbation.\textsuperscript{526} The hypothesis is that high inspiratory effort during an exacerbation can result in diaphragm injury and dysfunction. To-date, the association of diaphragm dysfunction with HRQL, exercise capacity, duration of hospitalization, rates of respiratory failure and mortality have not been previously described in advanced lung disease or transplant patients, and could prove to be an important prognostic marker. Also, evaluation of inspiratory muscle training in lung transplant candidates with respiratory muscle dysfunction may prove to be beneficial, especially in those experiencing a complex peri-operative ICU course.

Given the increasing prevalence of obesity in pulmonary disease,\textsuperscript{527} characterization of body composition beyond traditional anthropometric measures such as BMI will be important, as BMI is a poor surrogate marker for skeletal muscle mass and adiposity. Patients with sarcopenia (low muscle mass) and obesity can present a phenotype that is associated with greater inflammation and increased physical disability.\textsuperscript{528} Body composition assessment can help with prognostication in COPD and ILD.\textsuperscript{529,530} Similarly, increased levels of adiposity in lung transplant recipients have been linked with higher rates of PGD and mortality.\textsuperscript{460} Presently, body composition is evaluated clinically using D-XA or BIA, which allow systemic
and segmental characterization of fat free mass and tissue adiposity but is not always practical in the clinical setting. One promising modality that can be applied in future studies is the use of thoracic CT, which in addition to estimates of skeletal muscle mass can allow for characterization of adiposity levels. The application of thoracic CT for body composition assessment is promising given its readily availability in patients with advanced lung disease, but CT requires further validation in representative cohorts.

From the present thesis, low skeletal muscle mass was observed to be associated with unintentional weight loss in the preceding year. Adequate nutritional support is required in chronic respiratory disease for preservation of body weight, muscle mass, respiratory and limb muscle strength. Unfortunately, most of the literature on nutritional supplementation comes from COPD where supplementation is effective when combined with exercise training in patients with low body weight. However, the effects of nutritional supplementation on patients with ILD remains unclear. Also, the benefits of dietary modification on skeletal muscle function in patients with normal weight or those with sarcopenic obesity have not been well established, and is an important area of future investigation given the increasing prevalence of obesity in advanced lung disease. Future studies should explore the application of novel modalities such as phase angle with bioelectrical impedance and automated, self-administered 24-hour dietary recalls, which can provide additional insight into nutritional status pre- and post-transplant in a variety of clinical settings.

Recently, the construct of frailty which encompasses an individual’s ability to deal with physiological stressors has been shown to be predictive of pre-transplant delisting/mortality and post-transplant survival. Frailty allows for a holistic assessment of the individual taking into account psycho-social, cognitive and physical factors which have been shown to be intertwined and may be protective against functional impairments post-transplant. It is possible that the prognostic utility of frailty measures might be improved with incorporation of
musculoskeletal measures, which have been demonstrated to be amenable to rehabilitation and may prove to be objective measures of functional gain.\textsuperscript{159} If frailty and skeletal muscle measures are going to be routinely applied in the clinical setting for transplant candidacy evaluation, factors such as time, feasibility, and costs associated with these functional measures will need to be evaluated in future studies.

The extent that muscle mass, strength and function are modifiable with exercise training in the pre- and post-transplant period is an important area of future investigation. Skeletal muscle dysfunction is known to be present in the pre-transplant period with limitations persisting post-transplant.\textsuperscript{21} In fact, quadriceps strength has been observed to be lower than pre-transplant values in the early post-transplant period even after exercise training suggesting that lower extremity weakness and function is not solely related to acute muscle deconditioning from hospitalization.\textsuperscript{116} However, factors in the post-transplant period hindering recovery of skeletal muscle function have not been well described. The role of chronic corticosteroids and calcineurin inhibitors on skeletal muscle mass, composition (i.e. fat infiltration)\textsuperscript{539} and oxidative capacity\textsuperscript{540} may help inform some of the underlying mechanisms of skeletal muscle dysfunction post-transplant. Fat infiltration and oxidative capacity can be evaluated using non-invasive imaging modalities (ultrasound, CT, or MRI)\textsuperscript{255,539,541} and near-infrared spectroscopy,\textsuperscript{542} respectively. It is possible that a subset of lung transplant recipients who sustain periods of critical illness with hospitalizations along their journey to transplantation could have difficulty with muscle anabolism and not necessarily proteolysis, as shown in non-transplant critical care survivors.\textsuperscript{219} This could account for some of the phenotypic heterogeneity observed in skeletal muscle function pre- and post-transplant,\textsuperscript{21} but future studies utilizing molecular analysis of atrophy and hypertrophy pathways may be informative.

The findings in the present thesis were limited to the pre-transplant period and early post-transplant period within the first three-months post-transplant. Future investigations should
aim to further understand the implications of declining pre-transplant functional capacity and peri-operative ICU support on skeletal muscle function beyond the early post-transplant period. Given the ongoing exposure to immunosuppression, infection and chronic rejection, progressive skeletal muscle impairments may play a significant role in the post-transplant period and can have a significant effect on ADL, HRQL, functional capacity, and metabolic consequences such as diabetes and hypertension. Future studies should assess whether educational strategies targeting an active, healthy lifestyle pertaining to nutrition and physical activity will allow lung transplant recipients to derive a greater and sustained HRQL and functional benefit with transplantation.
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173


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Figure 3-1A: Thoracic Muscle Cross-Sectional Area vs. Whole Body Muscle Mass with Bio-electrical Impedance

Abbreviations: CSA= Cross-Sectional Area
Chapter 4:

**Table 4-1A: Daily Corticosteroid Use and Skeletal Muscle Mass and Strength Differences**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Daily Oral Corticosteroids (n=18)</th>
<th>No Daily Use (n=32)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 ± 11</td>
<td>61 ± 8</td>
<td>0.18</td>
</tr>
<tr>
<td>Male Sex</td>
<td>11 (61%)</td>
<td>18 (56%)</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>Diagnosis:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial Lung Disease</td>
<td>16 (89%)</td>
<td>16 (50%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Chronic Obstructive Lung Disease</td>
<td>1 (5.5%)</td>
<td>11 (34%)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>0 %</td>
<td>4 (13%)</td>
<td></td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>1 (5.5%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Fat-Free Mass Index (kg/m²)</td>
<td>18.4 ± 2.7</td>
<td>18.2 ± 2.8</td>
<td>0.80</td>
</tr>
<tr>
<td>Hand-Grip Strength (% Predicted)</td>
<td>87 ± 19</td>
<td>88 ± 19</td>
<td>0.99</td>
</tr>
<tr>
<td>Quadriceps Strength (% Predicted)</td>
<td>82 ± 19</td>
<td>77 ± 20</td>
<td>0.36</td>
</tr>
<tr>
<td>Maximal Inspiratory Pressure (%)</td>
<td>101 ± 34</td>
<td>101 ± 39</td>
<td>0.99</td>
</tr>
<tr>
<td>Maximal Expiratory Pressure (%)</td>
<td>131 ± 46</td>
<td>131 ± 46</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Results presented as mean ± SD and Proportion, n (%).
Chapter 5:

Figure 5-1A: Biceps Training Volumes in Pulmonary Rehabilitation vs Hand-Grip Strength (n=49) at 4 weeks after transplant listing.

Abbreviations: lbs = Pounds; Reps = Repetitions

Figure 5-2A: Quadriceps Training Volumes in Pulmonary Rehabilitation vs Quadriceps Strength from Biodex (n=49) at 4 weeks after transplant listing.

Abbreviations: lbs = Pounds; Reps = Repetitions
APPENDIX 2: Ethics Approval Letters for Studies 1 to 3
Notification of REB Continued Approval

Date: July 28th, 2016
To: Dr. Lianne Singer
    Room 134, Floor 11, PMB, New Clinical Services Building, Toronto General Hospital, 585 University Avenue, Toronto, Ontario, Canada, M5G 2N2

Re: 13-6430-BE
    Retrospective Review of Frailty in Advanced Lung Disease

REB Review Type: Expedited
REB Initial Approval Date: July 30th, 2013
REB Annual Approval Date: July 30th, 2016
REB Expiry Date: July 30th, 2017

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada. The approval and the views of the REB have been documented in writing.

Best wishes on the successful completion of your project.

Sincerely,

[Signature]

Lisungu Chieza, MSc., CCRA
Research Ethics Coordinator

For: Alan Barolet, MD PhD FRCPC
Co-Chair, University Health Network Research Ethics Board
Dear Dr. Lianne Singer, Dr. Sunita Mathur and Dr. Dmitry Rozenberg,

Re: Administrative Approval of your research protocol entitled, "Retrospective review of frailty in advanced lung disease"

We are writing to advise you that the Office of Research Ethics (ORE) has granted administrative approval to the above-named research protocol. The level of approval is based on the following role(s) of the University of Toronto (University), as you have identified with your submission and administered under the terms and conditions of the affiliation agreement between the University and the associated TAHSN hospital:

- Graduate Student research - hospital-based only
- Storage or analysis of De-identified Personal Information (data)

This approval does not substitute for ethics approval, which has been obtained from your hospital Research Ethics Board (REB). Please note that you do not need to submit Annual Renewals, Study Completion Reports or Amendments to the ORE unless the involvement of the University changes so that ethics review is required. Please contact the ORE to determine whether a particular change to the University's involvement requires ethics review.

Best wishes for the successful completion of your research.

Yours sincerely,

[Signature]

Dario Kuzmanovic
REB Manager
NOTIFICATION OF REB RENEWAL APPROVAL

Date: February 10, 2017

To: Lianne G Singer
Room 134; Floor 11, Room 134, PMB, New Clinical Services Building; Toronto General Hospital; 585 University Avenue, M5G 2N2; Toronto, Ontario, Canada

Re: 13-6696
Evaluation of Frailty and Sarcopenia in Advanced Lung Disease

REB Review Type: Delegated
REB Initial Approval Date: February 21, 2014
REB Renewal Approval Effective Date: February 21, 2017
Lapse In REB Approval: N/A
REB Expiry Date: February 21, 2018

The University Health Network Research Ethics Board has reviewed and approved the Renewal (13-6696.4) for the above mentioned study.

Best wishes on the successful completion of your project.

Sincerely,
Svetlana Tzvetkova
Ethics Coordinator, University Health Network Research Ethics Board

For: Alan Barolet
Co-Chair, University Health Network Research Ethics Board

The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada.
March 13, 2017

Dear Dr. Mathur and Dr. Dmitry Rozenberg,

Re: Your research protocol entitled, “Evaluation of frailty and sarcopenia in advanced lung disease”

ETHICS APPROVAL

Original Approval Date: March 24, 2014
Expiry Date: March 23, 2018
Continuing Review Level: 1
Renewal: Data Analysis Only

We are writing to advise you that you have been granted annual renewal of ethics approval to the above-referenced research protocol through the Research Ethics Board (REB) delegated process. Please note that all protocols involving ongoing data collection or interaction with human participants are subject to re-evaluation after 5 years. Ongoing research under this protocol must be renewed prior to the expiry date.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events should be reported to the Research Oversight and Compliance - Human Research Ethics Program as soon as possible. If your research is funded by a third party, please contact the assigned Research Funding Officer in Research Services to ensure that your funds are released.

Please ensure that you submit an Ethics Renewal Form or a Study Completion/Closure Report 15 to 30 days prior to the expiry date of your protocol. Note that ethics renewals for studies cannot be accepted more than 30 days prior to the date of expiry as per our guidelines.

Please note, all approved research studies are eligible for a routine Post-Approval Review (PAR) site visit. If chosen, you will receive a notification letter from our office. For information on PAR, please see http://www.research.utoronto.ca/wp-content/uploads/documents/2014/09/PAR-Program-Description-1.pdf.

Best wishes for the successful completion of your research.

Yours sincerely,

Elizabeth Peter, Ph.D.
REB Chair
**NOTIFICATION OF REB RENEWAL APPROVAL**

**Date:** March 13, 2017  
**To:** Lianne G Singer  
Room 134; Floor 11, Room 134, PMB, New Clinical Services Building; Toronto General Hospital; 585 University Avenue, M5G 2N2; Toronto, Ontario, Canada  
**Re:** 15-8858  
Clinical Implications of Sarcopenia in Lung Transplant Patients

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<th>REB Review Type:</th>
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<td>REB Initial Approval Date:</td>
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<tr>
<td>REB Expiry Date:</td>
<td>March 26, 2018</td>
</tr>
</tbody>
</table>

The University Health Network Research Ethics Board has reviewed and approved the Renewal (15-8858.3) for the above mentioned study.

Best wishes on the successful completion of your project.

Sincerely,  
**Marina Mikhail**  
Ethics Coordinator, University Health Network Research Ethics Board

For: Alan Barolet  
Co-Chair, University Health Network Research Ethics Board

*The UHN Research Ethics Board operates in compliance with the Tri-Council Policy Statement; ICH Guideline for Good Clinical Practice E6(R1); Ontario Personal Health Information Protection Act (2004); Part C Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations and the Medical Devices Regulations of Health Canada.*
Dear Dr. Lianne Singer, Dr. Sunita Mathur and Dr. Dmitry Rozenberg,

Re: Administrative Approval of your research protocol entitled, "Clinical implications of sarcopenia in lung transplant patients"

We are writing to advise you that the Office of Research Ethics (ORE) has granted administrative approval to the above-named research protocol. The level of approval is based on the following role(s) of the University of Toronto (University), as you have identified with your submission and administered under the terms and conditions of the affiliation agreement between the University and the associated TAHSN hospital:

- Graduate Student research - hospital-based only
- Storage or analysis of De-identified Personal Information (data)

This approval does not substitute for ethics approval, which has been obtained from your hospital Research Ethics Board (REB). Please note that you do not need to submit Annual Renewals, Study Completion Reports or Amendments to the ORE unless the involvement of the University changes so that ethics review is required. Please contact the ORE to determine whether a particular change to the University's involvement requires ethics review.

Best wishes for the successful completion of your research.

Yours sincerely,

Dario Kuzmanovic
REB Manager
APPENDIX 3: Consent Form for Study 2 (Chapter 4)
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Title: Evaluation of Frailty and Sarcopenia in Advanced Lung Disease

Investigator: Dr. Lianne Singer, MD

Phone Number: 416-340-4800 ext. 4996

Co-Investigators: Dr. Sunita Mathur, PT, PhD
Lisa Wickerson, BSc (PT), MSc
Dr. Dmitry Rozenberg, MD

Funder: Ontario Thoracic Society

Introduction

You are being asked to take part in a research study. Please read this explanation about the study and its risks and benefits before you decide if you would like to take part. You should take as much time as you need to make your decision. You should ask the study doctor or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish. Participation in this study is voluntary.

Background and Purpose

You have been asked to take part in this research study because you have been placed on the lung transplant waiting list at the University Health Network (UHN). While we know that lung transplant outcomes are often dependent on factors like age and make-up (fat and muscle), it is unclear whether there are other processes such as frailty – in other words, the ability of the body to withstand physical stress that may play a key role.

Some of the factors that may tell us that a person can withstand a physical stress, such as surgery are the amount of muscle the person has, their physical strength and their ability to walk or balance. These factors tend to be decreased in people with advanced lung disease. However, the effect of muscular health and ability to tolerate physical stress on quality of life, health care use, and transplant outcomes has not been previously studied in patients awaiting lung transplantation. This study will give us a preliminary assessment of the importance of being able to deal with physical stress and the impact of muscle health on clinical outcomes. About 50 participants...
from the lung transplant program at UHN (Toronto General Hospital) will be included this study.

**Study Design**
This is a longitudinal study. This means that assessments will be take place over a period of time. There will be one major testing session at the initial visit and then some brief testing sessions every 3 months until you receive your lung transplant. The following testing sessions will be scheduled around times you are at UHN for rehabilitation or other medical appointments.

**Study Visits and Procedures**
The initial testing session will take place at the University of Toronto, Muscle Function Lab approximately 4 weeks into the start of pulmonary rehabilitation. The following testing sessions will take place at Toronto General Hospital.

**Testing at University of Toronto, Muscle Function & Performance Lab (~1.5 hours):**

*Muscle Mass* – your body composition (amount of muscle and fat) will be calculated using a special commercial machine (bioelectrical impedance device). We will have you lie down comfortably and attach two small leads (one to your hand and foot). By passing an electrical current, the machine will be able to assess the various compartments of your body (muscle, fat, and water). The entire measurement will take less than 5 minutes and has no side effects. You will not feel the electrical current since it is very low intensity.

*Muscle Strength testing* – you will be seated on a machine that is used to test your leg muscle strength. You will be asked to push against a pad as hard as you can to determine your maximal muscle strength. Similarly, the study investigator will use a hand held device to test the strength of your handgrip and thigh muscles.

*Short Performance Physical Battery (SPPB)* – this is a test of walking and balance. You will be asked to stand in one position holding your balance, rise from a chair 5 times and walk for 4 metres while being timed.

*Quality of Life Measures* – we will ask you to complete several questionnaires that have patient, community, general and respiratory disease-specific questions that will be done through an Internet-site, with an average completion time of 25 minutes. This will be done during your first visit on the muscle lab computer with no personal health information recorded and all answers stored safely in a database using a password.

*Physical Activity Questionnaires* - you will also be asked to complete two brief physical activity questionnaires to assess your level of activity in the last week.

**Testing at Toronto General Hospital after initial testing (~ additional 10 minutes)**

*6 Minute Walk Test* – you will be asked to walk in a hallway for 6 minutes and we will measure how far you walk. You will be able to take a rest if needed. This test is part of
the routine care at UHN for people awaiting lung transplant and is usually done every 3
months.

Muscle Strength testing – Similar to your first visit, the study investigator will use a hand
held device to test the strength of your thigh muscles only.

One page questionnaire – this will assess your physical activity level, a question related
to your grip strength, your energy level, and your ability to cope with physical stress. It
will also examine any recent visits to the emergency department, admissions to hospital
or use of any antibiotics and/or steroids for respiratory infections.

Calendar of Visits:
Boxes marked with an X show what will happen at each visit:

<table>
<thead>
<tr>
<th>Visit</th>
<th>Initial Test (4 weeks)</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>Every 3 Months</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>U of T procedures:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle Mass</td>
<td>X</td>
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<td></td>
<td>10 min</td>
</tr>
<tr>
<td>Muscle Strength</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>15 min</td>
</tr>
<tr>
<td>SPPB</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 min</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>X</td>
<td></td>
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<td></td>
<td></td>
<td>25 min</td>
</tr>
<tr>
<td>Physical Activity Questionnaires</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15 min</td>
</tr>
<tr>
<td>TGH procedures:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*6 MWT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>10 min</td>
</tr>
<tr>
<td>One Page Questionnaire</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>5 min</td>
</tr>
<tr>
<td>Thigh Muscle Strength</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>5 min</td>
</tr>
</tbody>
</table>

*6 MWT will be routinely done every 3 months as part of normal care.

Reminders

It is important to remember the following things during this study:

- Wear comfortable clothing for exercise during the study visits.
- Ask your study team about anything that worries you.
- Tell study staff anything about your health that has changed.
- Tell your study team if you change your mind about being in this study.
For the muscle mass measurement performed on your initial visit, we ask you kindly not to do strenuous exercise (i.e. walking fast, lifting objects > 5 kg) for 12 hours prior to testing and avoid having anything to eat or drink 2 hours prior to the test. You may have a light breakfast that morning.

Risks Related to Being in the Study
The possible risks from participating in this study are:

*Muscle fatigue and soreness* - It is common to feel that your muscles are sore or tired after the strength testing and functional testing (occurs in about 20% of people). The tiredness should go away after a few hours and the soreness should go away after 1 to 2 days. If your muscle soreness lasts for more than 48 hours, please call the study team to let them know.

There are no known risks to bioelectrical impedance but please notify our team if you have a heart device (i.e. pacemaker or defibrillator) or you may be pregnant as the device has not been studied in these populations.

Benefits to Being in the Study
You may receive potential benefit from being in the study by finding out more about your muscle health and ability to cope with physical stress while awaiting lung transplantation.

Voluntary Participation
Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now and then change your mind later. You may leave the study at any time without affecting your care. You may refuse to answer any questions you do not want to answer, or not answer an interview question by saying "pass".

Confidentiality
If you agree to join this study, the study doctor and his/her study team will look at your personal health information and collect only the information they need for the study. Personal health information is any information that could be used to identify you and includes your:
- name
- age
- new or existing medical records, that includes types, dates and results of medical tests or procedures.

The information that is collected for the study will be kept in a locked and secure area by the study doctor for 10 years. Only the study team or the people or groups listed above (page 1) will be allowed to look at your records. Your participation in this study also may be recorded in your medical record at this hospital.

Representatives of the University Health Network Research Ethics Board may look at the study records and at your personal health information to check that the information
collected for the study is correct and to make sure the study followed proper laws and guidelines.

All information collected during this study, including your personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law. You will not be named in any reports, publications, or presentations that may come from this study.

If you decide to leave the study, the information about you that was collected before you leave the study will still be used in order to help answer the research question. No new information will be collected without your permission.

**In Case You Are Harmed in the Study**

If you are harmed as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost. By signing this form you do not give up any of your legal rights against the investigators, sponsor or involved institutions for compensation, nor does this form relieve the investigators, sponsor or involved institutions of their legal and professional responsibilities.

**Expenses Associated with Participating in the Study**

You will not have to pay for any of the testing procedures involved with this study. You will be given $10 for your initial visit to the University of Toronto, Muscle function lab to assist with parking costs.

**Conflict of Interest**

The study team has an interest in completing this study. Their interests should not effect your decision to participate in this study. You should not feel pressured to join this study.

**Questions about the Study**

If you have any questions, concerns or would like to speak to the study team for any reason, please call: Dr. Dmitry Rozenberg at 416-946-0418 or page him at 416-790-4732. You can also call: Dr. Lianne Singer at 416-340-4800 x 4996 or Dr. Sunita Mathur at 416-978-7761.

If you have any questions about your rights as a research participant or have concerns about this study, call the Chair of the University Health Network Research Ethics Board (REB) or the Research Ethics office number at 416-581-7849. The REB is a group of people who oversee the ethical conduct of research studies. These people are not part of the study team. Everything that you discuss will be kept confidential.
Consent

This study has been explained to me and any questions I had have been answered. I know that I may leave the study at any time. I agree to take part in this study.

Print Study Participant’s Name  Signature  Date

(You will be given a signed copy of this consent form)

My signature means that I have explained the study to the participant named above. I have answered all questions.

Print Name of Person Obtaining Consent  Signature  Date

☐ The consent form was read to the participant. The person signing below agrees that the study as set out in this form was properly explained to the participant and he/she has had all questions answered.

Print Name of Witness  Signature  Date

Relationship to Participant
**Instructions:**

Thank you for agreeing to participate in this research study titled:

**Evaluation of Frailty and Sarcopenia in Advanced Lung Disease**

Your initial testing session will be at the University of Toronto, Muscle Function and Performance Lab on: ________________________________

**Address:** 500 University Avenue, Toronto, ON, M5G 1V7. You will be greeted on the main level and brought down to the muscle lab.

**Reminders:**

- Please wear comfortable clothing and shoes suitable for exercise

- **Muscle Mass Measurement:** In order to ensure accurate results, **we ask you kindly not to do any strenuous exercise for 12 hours prior to testing and avoid having anything to eat or drink 2 hours prior to your test.**

- You may have a light breakfast that morning.

If you have any questions, concerns or unable to attend for any reason, please do not hesitate to page Dr. Dmitry Rozenberg at (416) 790-4732.