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# EVALUATING THE ASSOCIATION AMONG DEMOGRAPHIC, DISEASE, AND SYMPTOM PROFILES AND QUALITY OF LIFE IN CONNECTIVE TISSUE DISEASE-RELATED INTERSTITIAL LUNG DISEASE

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A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham,
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

BIRMINGHAM, ALABAMA

2022

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# EVALUATING THE ASSOCIATION AMONG DEMOGRAPHIC, DISEASE, AND SYMPTOM PROFILES AND QUALITY OF LIFE IN CONNECTIVE TISSUE DISEASE-RELATED INTERSTITIAL LUNG DISEASE

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## ABSTRACT

Connective tissue disease-related interstitial lung disease (CTD-ILD) results in an unrelenting symptom burden and may progress to death. The morbidity and mortality associated with CTD-ILD likely has a profound impact on individuals' quality of life (QOL). Quality of life is a phenomenon that has yet to be sufficiently described in the literature on CTD-ILD. The factors associated with QOL in other chronic lung diseases have been described, but because of the different clinical and demographic characteristics of CTD-ILD, it is unknown if these same factors are associated with QOL in CTD-ILD. The purpose of this study was to examine the QOL and associated factors and potential mediating and moderating effect of symptoms for individuals with CTD-ILD. This was a secondary analysis of data from the Pulmonary Fibrosis Foundation Patient Registry. The aims of this study were to describe the association among CTD-ILD patient demographic variables, disease characteristics, and QOL and to examine the relationship between symptoms and QOL in CTD-ILD. Additionally, we examined potential mediation and moderation relationships between symptoms and QOL in CTD-ILD. The study aims and hypotheses were informed by the Factors Affecting Quality of Life Model. This model was used to determine if causal relationships among symptoms and QOL exist using path analysis. The results of the study revealed the majority of paticipants to be female (66%), white (78%), have a disease duration of 1-3 years (30%), the have scleroderma (25%).

The average age was 61 years with a forced vital capacity of 67% predicted. The majority of participants were not on supplemental oxygen (62%), taking immunosuppressive medications (66%), or active in pulmonary rehabilitation (89%). Female gender, lower forced vital capacity, supplemental oxygen use, pulmonary rehabilitation participation, shortness of breath, cough, and fatigue to all be correlated with poorer quality of life. Shortness of breath mediated the relationships between quality of life and the factors of gendeer, forced vital capacity, supplemental oxygen use, and pulmonary rehabilitation. Fatigue mediated the relationship between quality of life and pulmonary rehabilitation. An understanding of QOL and its associated factors may allow for better tailoring of therapies that can result in improved QOL for individuals with CTD-ILD.

Keywords: interstitial lung disease, connective tissue disease, quality of life

DEDICATION
To
My family

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| COPD | chronic obstructive pulmonary disease |
| CTD | connective tissue disease |
| CTD-ILD | connective tissue disease-related ILD |
| FSS | Fatigue Severity Scale |
| FVC | forced vital capacity |
| ILD | interstitial lung disease |
| IPF | idiopathic pulmonary fibrosis |
| LCQ | Leicester Cough Questionnaire |
| MCTD | mixed connective tissue disease |
| PFFPR | Pulmonary Fibrosis Foundation Patient Registry |
| PF-ILD | progressive fibrosing interstitial lung disease |
| PROM | patient reported outcome measure |
| QOL | quality of life |
| SF-6D | Medical Outcome Study Short Form Six-Dimension Health Survey |
| SOBQ | University of California San Diego Shortness of Breath Questionnaire |
| UCTD | undifferentiated connective tissue disease |

# CHAPTER 1

## INTRODUCTION

Interstitial lung disease (ILD) is characterized by lung inflammation and fibrosis that results in significant symptomatic and psychosocial burden for patients with the disease (Kreuter et al., 2017). The mortality rate for ILD has increased over 50% in the past 10 years and is the 40th most common cause of death (Global Burden of Disease Collaborative Network, 2016). Individuals with ILD may suffer varying degrees of cough, shortness of breath, fatigue, depression, and anxiety, all of which may have a profound and debilitating effect on quality of life (QOL) (Saketkoo et al., 2014). While there are many causes of ILD, connective tissue disease (CTD) is responsible for approximately one third of all cases (Barnes et al., 2018). Interstitial lung disease is considered one of the most serious manifestations of CTD in terms of morbidity and mortality (Mathai & Danoff, 2016). Connective tissue disease includes conditions such as scleroderma, inflammatory myopathies (polymyositis, dermatomyositis, antisynthetase syndrome), lupus, rheumatoid arthritis, Sjogren's syndrome, vasculitis, mixed connective tissue disease (MCTD), and undifferentiated connective disease (UCTD) (National Institutes of Health, 2021b). Connective tissue disease is also accompanied by rheumatological-related symptoms such as joint pain and swelling; hence, individuals with connective tissue disease-related interstitial lung disease (CTD-ILD) may also

experience more severe respiratory symptoms such as unrelenting cough and shortness of breath at rest that may affect QOL more than those with ILD alone (Fischer et al., 2019).

Quality of life has been shown to be negatively impacted in other lung diseases, such as chronic obstructive pulmonary disease (COPD) and lung cancer; however, these diseases do not have the extra burden of rheumatoid-related symptoms (Miravitlles & Ribera, 2017; Polanski et al., 2016). Therefore, the impact of CTD-ILD on QOL may be more profound, but this has yet to be sufficiently explained. The paucity of information about QOL in CTD-ILD may be attributed to the heterogeneity of phenotypes associated with the disease (Aronson et al., 2021). Because of the phenotypic heterogeneity associated with CTD-ILD, there may be additional factors affecting QOL in this population. Despite the high symptom burden associated with CTD-ILD, QOL is rarely considered in clinical trials for these patients (Molyneaux & Maher, 2018).

## Problem Statement

Although QOL has been investigated in persons with rheumatological diseases and non-rheumatological forms of ILD, it has yet to be characterized sufficiently in CTD-ILD.

## Background and Significance

### *Epidemiology*

The Global Burden of Disease Study (2016) ranks ILD in the 40th position of all diseases regarding years of life lost. Interstitial lung disease represents an 86% increase in years of life lost since 1990. It ranks higher than cancers such as lymphoma, pancreatic

cancer, and brain cancer. There are approximately 150 different causes of ILD, with CTD accounting for over 30% of the cases (Barnes et al., 2018).

### *Morbidity and Mortality*

Connective tissue disease-related ILD is associated with a high degree of morbidity from impaired lung function, respiratory failure, and pulmonary hypertension characterized by a symptom burden of low blood oxygen levels, constant cough, shortness of breath with minimal exertion, and wheeze. Additional impact on QOL results from rheumatological symptoms including joint pain, muscle pain or weakness, skin thickening or tightening, skin lesions, blood clots, difficulty swallowing, and profound fatigue. Physiologic measures, such as pulmonary function testing, 6-minute walk test, and chest imaging, are used to evaluate the patients' clinical condition and help guide treatment decisions, but QOL is not routinely assessed (Molyneaux & Maher, 2018). Patient perceptions of QOL have been evaluated in other types of ILD such as idiopathic pulmonary fibrosis (IPF). Idiopathic pulmonary fibrosis is a fatal lung disease with a median survival of 2 to 3 years following diagnosis, in which individuals report a poor QOL (Lindell et al., 2017; Lindell et al., 2015; Raghu et al., 2015; Swigris et al., 2005). Patients with CTD-ILD may have progressive ILD, often resulting in a similar disease trajectory and symptom burden as those with IPF, ultimately dying due to complications related to lung manifestation of their disease as opposed to the rheumatological manifestations of their disease (Cottin et al., 2019).

### *Challenges with QOL Assessment in CTD-ILD*

Quality of life has been evaluated as a secondary endpoint in a few investigational drug trials involving CTD-ILD, often with no improvement from the intervention (Distler et al., 2019; Morrisroe et al., 2020; Tashkin et al., 2016). Complicating matters further is the nature of CTD-ILD since it has both pulmonary and extrapulmonary manifestations that may result in a multitude of symptoms affecting QOL. Quality of life measures for CTD such as rheumatoid arthritis include the Rheumatoid Arthritis Quality of Life Questionnaire (RA-QoL). It is a tool validated for the measurement of QOL in rheumatoid arthritis (Pencheva et al., 2020). The RA-QoL evaluates the effect of joint pain and debility on patients' QOL but does not include the effect of respiratory manifestation. Because CTD-ILD often results in a symptom burden similar to, and often worse than, that experienced by patients with lung cancer, rheumatological assessment of QOL may not be sufficient to address QOL in this unique population (Matsunuma et al., 2016).

### *Unique Aspects of CTD-ILD*

It is important to investigate QOL in CTD-ILD not only because of the paucity of data surrounding this phenomenon, but also because it involves unique disease aspects that differentiate it from other chronic lung diseases. These aspects include demographic, disease, and physiologic characteristics.

*Gender*

Connective tissue disease-related ILD is more prominent in women, making it unique from other common chronic lung conditions. The ratio of women to men in CTD-ILD is 75:25, while in IPF, the ratio is 25:75 (Cottin, 2013). The female preponderance in CTD-ILD differs from other chronic lung conditions such as chronic obstructive lung disease (COPD) and lung cancer, in which more men have the disease (Assayag et al., 2020; National Institutes of Health, 2021c; Ntritsos et al., 2018). Gender is a factor associated with QOL. In a study of COPD by de Torres et al. (2006), there were differences in QOL related to gender, with women reporting worse QOL than men. Although men suffer from more life-threatening chronic conditions than women do, women have higher rates of chronic disabling conditions, such as autoimmune and rheumatic diseases, that may affect QOL (Bird & Rieker, 2008). Quality of life gender differences may be related to sociodemographic and socioeconomic differences between men and women (Cherepanov et al., 2010). These differences may have an impact on the labor force. For example, in 2020, women represented 47% of the labor force (Women's Bureau, n.d.), which has an impact on households, since women perform most household tasks among married couples (Brenan, 2020). It is possible that women with CTD-ILD and poor QOL may have the additional burden of work responsibilities or financial stressor due to inability to work.

*Age*

Younger age is another unique aspect of CTD-ILD that differentiates it from other lung diseases. Individuals with CTD-ILD are generally less than 50 years old, while those

with chronic lung conditions such as IPF are usually over 60 years old (Cheng et al., 2018). Age has also been associated with QOL with rheumatological disease, with those under the age of 50 reporting better QOL than those over 50 years old (Bai et al., 2020). In contrast, a study by Adams (2017) found that adults 18-64 years of age with chronic medical conditions reported worse QOL than those 65 years and older with chronic medical conditions. The reasons for this are unclear but may be due to prolonged course of chronic illness and poor access to healthcare associated with younger adults (Adams, 2017). Other factors influencing poor QOL in younger adults with a chronic disease include more negative social impacts, longer disease exposure, and impact on work status (Ge et al., 2019).

*Race*

Black race is associated with an increased risk of developing ILD from certain forms of CTD such as lupus, scleroderma, polymyositis, dermatomyositis, and antisynthetase syndrome (Stojan & Petri, 2018). Additionally, Black individuals with CTD-ILD have increased mortality rates (Solomon et al., 2020).

*Multi-Organ Involvement*

Another aspect of CTD-ILD that makes it unique from other chronic pulmonary conditions is that it is characterized by multi-organ involvement. Individuals with CTD-ILD suffer from cough and shortness of breath, similar to ILD and other chronic lung diseases, but they may also suffer from the effects of their CTD, resulting in profound fatigue, joint pain, muscle pain, muscle weakness, skin thickening, skin tightening, skin

lesions, blood clots, difficulty swallowing, and fever (National Institutes of Health, 2021d; Rajala et al., 2018). The impact of both pulmonary and extrapulmonary symptoms associated with CTD-ILD on QOL has yet to be described.

### *Type of CTD-ILD*

Quality of life may also be affected differently based on the specific type of CTD. For example, rheumatoid arthritis patients report worse shortness of breath than those with Sjogren's disease (Topcu et al., 2021). Additionally, individuals with rheumatoid arthritis show improved QOL over time compared to those with lupus, but this fails to take into account those with ILD (Chaigne et al., 2017).

### *Disease Duration*

Disease duration may affect QOL in ILD. For those with IPF, longer disease duration is associated with worse QOL (Kreuter et al., 2019). It has been suggested that disease duration may be associated with QOL in CTD-ILD, but further investigation is warranted (Yuan et al., 2020).

### *Forced Vital Capacity*

Forced vital capacity (FVC) is a variable associated with QOL in ILD. It is a physiologic variable routinely used as a surrogate for disease severity, as it is a reliable and sensitive measure reflective of the extent of lung disease, with declines correlated with increased morbidity and risk of mortality (du Bois et al., 2011). It is also a predictor

of mortality in MCTD (Reiseter et al., 2018). Male sex and ethnicity have been associated with a rapid decline in FVC for individuals with CTD-ILD (Chan et al., 2019).

### *Supplemental Oxygen*

Supplemental oxygen is fundamental for the treatment of hypoxemia resulting from conditions such as COPD, congestive heart failure, pulmonary infections, and interstitial lung disease (Rengasamy et al., 2021). There are varied results regarding supplemental oxygen use and QOL. In a study by Albert et al. (2016), supplemental oxygen used by individuals with COPD during ambulation did not have an impact on mortality or QOL. However, supplemental oxygen use for those with ILD is associated with improved QOL (Visca et al., 2018). While the latter study included patients with CTD-ILD, those with musculoskeletal or joint involvement or other symptoms were excluded, so the effect of supplemental oxygen on QOL in this population is unknown.

### *Pulmonary Rehabilitation*

Participation in pulmonary rehabilitation is another factor related to QOL. Pulmonary rehabilitation has been shown to improve QOL in both individuals with COPD and IPF (Matsuo et al., 2021; McCarthy et al., 2015; Swigris et al., 2011). In a systematic review, pulmonary rehabilitation was found to improve QOL for individuals with ILD in general, but its impact on CTD-ILD specifically is unknown (Dowman et al., 2021).

*Immunosuppressant Medications*

Medications used to treat CTD-ILD also make it unique from other types of chronic lung diseases. Inhalation therapy is the mainstay of treatment for chronic lung diseases such as asthma and COPD. Side effects from these types of medications include shakiness, sore throat, and rapid heart rate, all of which are usually transient (Mayo Clinic, 2022). Because CTD-ILD is driven by an aberrant immune system resulting in inflammation, immunosuppressive medications are used to treat CTD-ILD. These medications may cause side effects including nausea, vomiting, loss of appetite, hair loss or growth, and oral ulcers (Riminton et al., 2011). In addition to side effects, immunosuppressant medications place individuals at risk for serious complications such as life-threatening infection, malignancy, and fetal toxicity. Because younger individuals are most often afflicted with CTD-ILD, such risks may be present for many years, as lifelong therapy is often required. Additionally, the fetal toxicity associated with immunosuppressive medications impacts individuals' reproductive ability. The side effect profiles and risks associated with immunosuppressive medication may have a profound impact on QOL, more so than the inhalers used to treat other chronic lung conditions. Impaired QOL has been associated with immunosuppressive side effects in patients following renal transplantation (Hilbrands et al., 1995). In a study by Zhu et al. (2017), noncompliance with immunosuppressive medications after kidney transplant was associated with medication side effects. It is unknown if these unique demographic and physiologic factors are associated with QOL in CTD-ILD.

## Study Purpose

The purpose of this study was to investigate the QOL and associated factors as well as the mediating effect of symptoms for individuals with CTD-ILD by performing a secondary data analysis from the Pulmonary Fibrosis Foundation Patient Registry (PFFPR).

## Research Aims and Hypotheses

Investigation of QOL in CTD-ILD was guided by the research aims and hypotheses shown in Table 1. Based on the review of literature, several variables have been identified as potentially affecting QOL in CTD-ILD. Such variables include the demographic factors of age, race, gender, and marital status. The physiologic variables, such as type of ILD, duration of disease, forced vital capacity (FVC) as measured by spirometry, immunosuppressant medication use, and participation in pulmonary rehabilitation, have been identified as potentially impacting QOL in CTD-ILD.

Table 1

*Aims and Corresponding Hypotheses*

| | |
|---|---|
| Aim 1 | Describe the association between patient demographic (age, gender, and race) and disease characteristics (type of CTD-ILD, duration of disease, FVC, supplemental oxygen, immunosuppressant medication use, and pulmonary rehabilitation) and QOL in CTD-ILD |
| | H 1.1 Demographic characteristics (younger age, female gender, and African American race) are associated with worse QOL.<br>H 1.2 Disease characteristics (CTD-ILD type, longer duration of disease, lower FVC, immunosuppressant medication use, supplemental oxygen use, and not participating in pulmonary rehabilitation) are associated with worse QOL. |
| Aim 2 | Describe the relationship between symptoms (shortness of breath, cough, and fatigue) and QOL in CTD-ILD |
| | H 2.1 Increased shortness of breath is associated with worse QOL.<br>H 2.2 Increased cough is associated with worse QOL.<br>H 2.3 Increased fatigue is associated with worse QOL. |
| Aim 3 | Examine potential mediation relationships between symptoms and QOL in CTD-ILD |

## Conceptual Framework

The conceptual model chosen for this study is based on the Symptoms Experience Model, developed in the field of oncology (see Figure 1 in Chapter 2) (Armstrong, 2003).

For this study, the Factors Affecting Quality of Life Model (see Figure 2 in Chapter 2) was used. In it, the effects of relationships among demographic characteristics (age, gender, and race), disease characteristics (FVC, type of ILD, disease duration, supplemental oxygen use, immunosuppressant medication use, and pulmonary rehabilitation), and symptoms (shortness of breath, cough, and fatigue) on QOL are described. The Factors Affecting Quality of Life Model informs the research aims and hypotheses described in Table 1.

## Study Significance

Information from this study will ultimately serve to guide appropriate pharmacologic and non-pharmacologic therapies that may improve QOL for individuals with CTD-ILD. Unfortunately, not enough is known about QOL in this population. This cross-sectional study utilizing data from the PFFPR sought to understand the factors affecting QOL in CTD-ILD and the relationships among them.

## Definition of Terms

The term ILD is inclusive of approximately 200 different disorders causing scarring in the lungs around the air sacs and airways, resulting in cough, shortness of breath, fatigue, and difficulty diffusing oxygen into the bloodstream and carbon dioxide out of the bloodstream (National Heart, Lung, and Blood Institute, 2021). Because CTD-ILD encompasses a heterogeneous group of rheumatological conditions, a more robust explanation of each disease manifestation and its impact from an epidemiological perspective is warranted. Additionally, given the high degree of morbidity associated

with CTD-ILD, a detailed description of the epidemiology of common severe symptoms is also necessary. Variables of interest are also defined.

### *Type of CTD-ILD*

Connective tissue disease-related ILD includes seven conditions: scleroderma, inflammatory myopathy, lupus, rheumatoid arthritis, Sjogren's syndrome, vasculitis, and mixed/undifferentiated CTD. The risk for CTD-ILD is higher in women and for individuals over the age of 50 (Cottin, 2016).

#### *Scleroderma*

An autoimmune CTD, scleroderma causes inflammation in the body resulting in hardening of the skin and fibrosis in the lungs, heart, blood vessels, and kidneys (National Institutes of Health, 2020). Up to 90% of individuals with scleroderma develop ILD during the course of their disease (Volkmann & Fischer, 2021). Of scleroderma-related deaths, 35% are attributed to ILD (Tyndall et al., 2010). The peak onset of scleroderma is 30-70 years of age (Cottin et al., 2018). Females are disproportionately affected, with female to male ratio of 4:1 (Peoples et al., 2016). Gender and race may influence the severity of disease (Hill, 2014).

#### *Inflammatory Myopathy*

There are several conditions that define inflammatory myopathy: polymyositis, dermatomyositis, and antisynthetase syndrome. Polymyositis is characterized by muscle inflammation and results in high degrees of morbidity and mortality (National Institutes

of Health, 2019). Interstitial lung disease occurs in approximately 35% of all polymyositis cases and was found to be the cause of death in 8% of patients with polymyositis (Nuño-Nuño et al., 2017; Sun et al., 2021). Individuals of older age and male gender have a worse prognosis (Nuño-Nuño et al., 2017). Additionally, diagnosis after age 40 is associated with higher mortality rate (Nuño-Nuño et al., 2017).

Dermatomyositis is an inflammatory myopathy involving degenerative changes in the skin and muscles and may also involve the lung tissue, causing diffuse rash, muscle weakness, calcium deposits in the muscles, and skin, gastrointestinal tract, and respiratory symptoms (National Organization for Rare Lung Diseases, 2021). The prevalence of ILD in individuals with dermatomyositis is 42% (Sun et al., 2021). There is higher mortality with older age at diagnosis, although longer disease duration seems to be a better prognostic indicator (Nuño-Nuño et al., 2017). ILD is cited as a frequent cause of death for individuals with dermatomyositis, with one study noting 8% of the mortality in individuals with dermatomyositis was due to ILD (Nuño-Nuño et al., 2017).

Antisynthetase syndrome is a chronic autoimmune disease that causes muscle, joint, and lung inflammation that may result in pain, cough, shortness of breath, difficulty swallowing, thickening of the skin, fever, and weight loss (National Institutes of Health, 2021a). Approximately 86% of individuals with antisynthetase syndrome will develop ILD, often resulting in respiratory failure for those with disease progression (Witt et al., 2016). Longer disease duration, male gender, and older age are associated with disease progression (Cavagna et al., 2015).

*Lupus*

Lupus is an autoimmune disease that causes pain and inflammation in many parts of the body, such as skin, joints, lungs, brain, kidneys, and blood vessels (Centers for Disease Control and Prevention, 2018b). The prevalence of ILD with lupus is approximately 11% (Fidler et al., 2016). Poor prognostic indicators include male gender and older age (Cheema & Quismorio, 2000). The 5-year survival rate for lupus-related ILD is up to 85% (Enomoto et al., 2019). There is a female predominance with lupus, as the female to male ratio is 7:1 (van Vollenhoven, 2009).

*Rheumatoid Arthritis*

Rheumatoid arthritis is an autoimmune disease that involves inflammation resulting in pain, stiffness, and swelling primarily in the joints, though it may also affect the heart and lungs (Centers for Disease Control and Prevention, 2020). Interstitial lung disease occurs in up to 60% of individuals with rheumatoid arthritis (Kim et al., 2009). While women are affected by rheumatoid arthritis more than men, at a ratio of 3:1, men are 3 times more likely to develop ILD (Cottin et al., 2018). The mortality rate of this iteration of ILD is approximately 30% (Nieto et al., 2021).

*Sjogren's Disease*

This inflammatory, autoimmune connective tissue disease most often affects the salivary glands, causing dry eye and dry mouth, but may also result in organ involvement, such as lung inflammation and fibrosis (Duarte, 2019). Up to 40% of those with Sjogren's Disease have ILD (Fischer et al., 2019). Sjogren's-related ILD is

associated with a high degree of morbidity and mortality (Luppi et al., 2020). As with rheumatoid arthritis, there is a female predominance in Sjogren's disease, with a ratio of 9:1 (van Vollenhoven, 2009).

### *Vasculitis*

Vasculitis includes a group of rare diseases that cause inflammation of the blood vessels, resulting in poor blood flow to various body tissues including the lungs and heart, with complications such as organ damage, blood clots, aneurysms, and blindness (Hasan, 2017). Symptoms of vasculitis include fever, headache, generalized pain, fatigue, and weight loss. Approximately 30%-40% of patients with vasculitis will develop ILD (Katsumata et al., 2015). Of those with ILD, there is a high degree of morbidity and mortality, with a 5-year survival rate of 50% (Katsumata et al., 2015).

### *Mixed and Undifferentiated Connective Tissue Disease*

Mixed connective tissue disease involves a constellation of overlapping connective tissue diseases, such as lupus, scleroderma, and polymyositis (National Institutes of Health, 2016). Symptoms may vary and are specific to the types of CTD comprising MCTD. Approximately 40% of those with MCTD will develop ILD, with males being more severely affected, despite the disease having a female predominance (Hajas et al., 2013; Reiseter et al., 2018). The morbidity and mortality of MCTD is primarily associated with progressive ILD (Reiseter et al., 2018). Whites are affected more than Blacks at a ratio of 10:4 (Narula et al., 2018).

Undifferentiated connective tissue disease is considered a diagnosis of exclusion. Individuals with UCTD have both serological findings and clinical manifestations of a particular type of CTD but fail to meet all of the criteria for that diagnosis (Marwa & Anjum, 2021). The majority of individuals with UCTD are women between 32 and 44 years old, and approximately half of individuals with CTD also have UCTD (Marwa & Anjum, 2021).

## *Symptoms*

### *Cough*

Cough occurs frequently in ILD, with up to 83% of individuals reporting this symptom (Sato et al., 2019). Not only does it occur frequently, it also has a negative impact on QOL in patients with ILD in general (Yuan et al., 2020).

### *Fatigue*

Fatigue is characterized by a feeling of tiredness, weariness, lack of energy, or unrelenting exhaustion and is one of the more bothersome symptoms of ILD (Kahlmann et al., 2020). It is a multifactorial problem in ILD, possibly related to the impacts of the disease on the mind and body as well as medication side effects, which can have a dramatic impact on QOL (Kahlmann et al., 2020).

### *Shortness of Breath*

Shortness of breath is characterized by the sensation of air hunger, breathlessness, or difficulty breathing (Mayo Clinic, 2020). It is one of the most common and debilitating

symptoms associated with ILD (Bonini & Fiorenzano, 2017). In general, poor QOL has been associated with shortness of breath for those with ILD (Yuan et al., 2020).

## *Disease Severity*

### *Forced Vital Capacity*

Forced vital capacity is a parameter evaluated by pulmonary function testing. It is the total amount of air exhaled during the test and is considered to be the most important measure of lung function in ILD (du Bois et al., 2011). As such, it is used as a surrogate for ILD disease severity (Heckman & O'Connor, 2015).

### *Supplemental Oxygen*

Supplemental oxygen is required for individuals with a medical condition that limits their ability to maintain adequate oxygenation breathing room air. Interstitial lung disease causes damage to lungs due to inflammation or scarring that may result in an inability to maintain acceptable oxygen levels in the body. The need for supplemental oxygen is cited as a parameter for disease severity in ILD (Robbie et al., 2017).

## *Treatments*

### *Immunosuppressant Medication*

Medications that lower the activity of the immune system are used to prevent rejection of transplanted organs and for the treatment of autoimmune and immune-mediated diseases, such as certain rheumatological conditions (Fireman et al., 2004).

### *Pulmonary Rehabilitation*

Pulmonary rehabilitation is a  monitored, structured medical program that helps people with lung disease gain strength, improve anxiety or depression, and maintain functional status through exercise, education, and counseling (American Lung Association, 2020).

## *Outcome Measure*

### *Quality of Life*

Quality of life is a broad multidimensional concept that usually includes subjective evaluations of both positive and negative aspects of life, while health-related QOL includes physical and mental health perceptions (e.g., energy level, mood) and their correlates, including health risks and conditions, functional status, social support, and socioeconomic status (Centers for Disease Control and Prevention, 2018a).

## Summary

Connective tissue disease-related ILD is a common form of ILD and is inclusive of several rheumatological conditions, often resulting in a high degree of morbidity and mortality due to pulmonary and extrapulmonary disease manifestations. The high symptom burden associated with CTD-ILD may result in impaired QOL. Because QOL in CTD-ILD has yet to be sufficiently described, this study aimed to assess the associations among demographic and disease characteristics and symptom profiles with QOL in this population, as guided by the Factors Affecting Quality of Life Model. The

rationale for investigating these factors was based on the unique aspects of CTD, such as younger age, female predominance, multi-organ involvement, and sequelae of immunosuppressive medications, that differentiate it from other chronic lung diseases. Additionally, these factors have been found to be impactful on QOL in similar disease states. It is by investigation of QOL and its associated factors that individuals with CTD-ILD may have improved QOL, as therapies may be better guided to meet this important endpoint. To address the topic of QOL in CTD-ILD, a comprehensive review of the literature was performed and is described in Chapter 2. Emerging themes from the literature review and the conceptual framework guiding the study aims are also described in Chapter 2.

# CHAPTER 2

# REVIEW OF LITERATURE

This chapter describes the study's conceptual framework and how it addresses issues surrounding QOL in CTD-ILD through both what is known in the literature about potential associated factors and gaps in the literature. It is through an integrative review of the literature that the concept of QOL in CTD-ILD may be better understood by investigation of associated factors such as the type of CTD-ILD, FVC, age, gender, marital status, race, duration of disease, immunosuppressant use, and participation in pulmonary rehabilitation as mediated by symptom experience. Analysis of the literature was guided by the theoretical framework of the Factors Affecting Quality of Life Model, as informed by the Symptoms Experience Model.

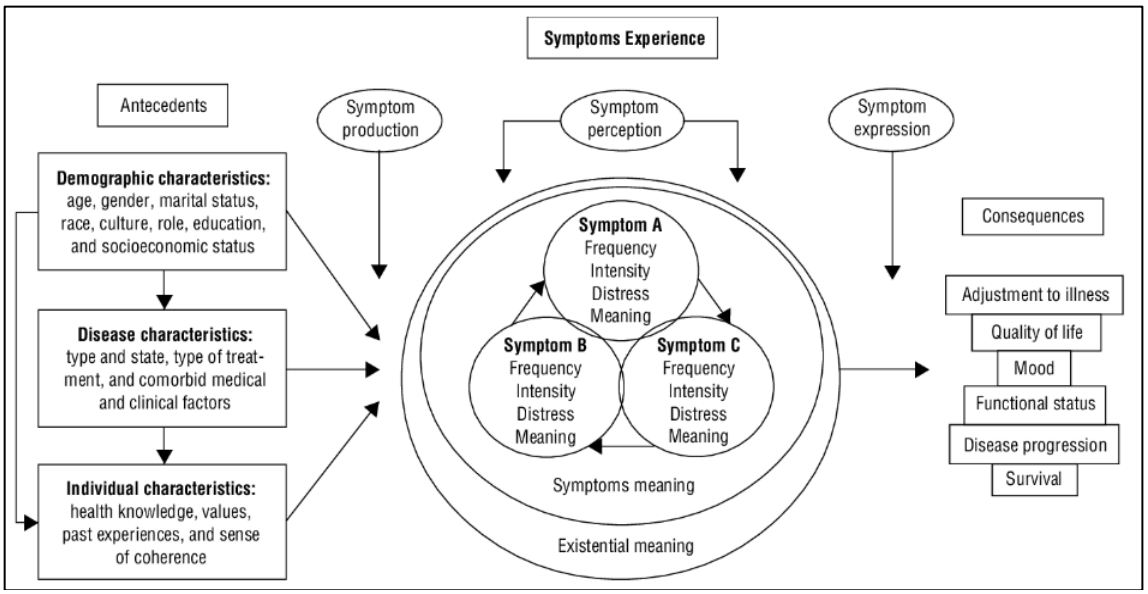
## Conceptual Framework

The conceptual framework chosen for this study is based on the Symptoms Experience Model (see Figure 1) developed in oncology. Armstrong (2003) defines the symptom experience as "the perception of the frequency, intensity, distress, and meaning occurring as symptoms are produced and expressed" (p. 602). The purpose of the conceptual model is to define the concept of the symptom experience by describing its antecedents and their consequences. To clarify the context of the concept, it is necessary

to identify both antecedents and consequences associated with the concept (Armstrong, 2003).

Figure 1

*Symptoms Experience Model*



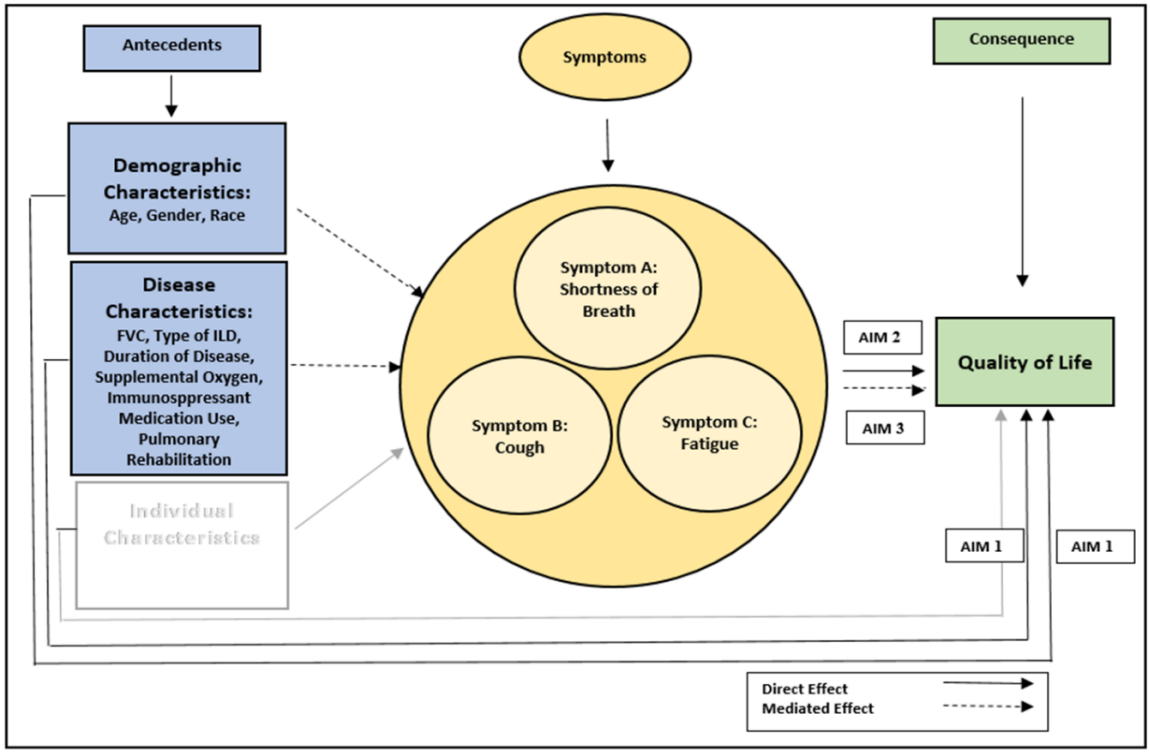

The antecedents to symptoms in the Symptoms Experience Model are demographic characteristics, disease characteristics, and individual characteristics. Demographic characteristics include age, gender, marital status, race, culture, role, education, and socioeconomic status. Disease characteristics are the type of disease, state of treatment, comorbid conditions, and clinical factors. Individual characteristics are those specific to the individual and include their values, health knowledge, and past experiences. The model then describes how the antecedents may influence symptoms, ultimately having an impact on the outcomes of interest. Specific outcomes include

disease progression, survival, psychological status, mood state, functional status, and QOL.

The utility of the Symptom Experience Model in the CTD-ILD population is that it allows for the exploration of the concept of QOL by examination of the direct and indirect relationships of contributing factors and how symptoms may mediate those relationships. For this study, the antecedents included demographic and disease characteristics. This study did not evaluate individual characteristics, as this data was not captured in the parent study. The demographic components are age, gender, and race. Disease characteristics include the specific type of CTD-ILD, disease duration, FVC, supplemental oxygen, immunosuppressant medication use, and pulmonary rehabilitation participation. Based on the literature review, these antecedents may contribute directly to QOL and to the symptom experience of the individual, ultimately influencing their QOL. Additionally, it is postulated that symptoms may affect QOL directly and mediate the relationships between the antecedent factors of demographic and disease characteristics and QOL. These relationships are characterized in the Factors Affecting Quality of Life Model (see Figure 2), which is adapted from the Symptoms Experience Model.

Figure 2

*Factors Affecting Quality of Life Model*




The Factors Affecting Quality of Life Model informs the research aims and hypotheses described in Table 1. The aims and hypotheses in turn informed the study's methodology. Because the conceptual model involves both direct and indirect relationships, path analysis was used to describe the strength of the relationships in the proposed causal model. Based on the conceptual model, there are 31 paths or relationships to consider between the antecedents (demographic and disease characteristics), mediators (symptoms), and outcome (QOL). The available data from the Pulmonary Fibrosis Foundation Patient Registry (PFFPR) included the demographic and disease characteristics listed in Figure 2. Additionally, patient reported measures evaluating QOL, shortness of breath, cough, and fatigue were captured as well.

## Search Strategy

The search strategy used to review literature surrounding QOL in CTD-ILD involved several queries. The search was performed with CTD-ILD as a general term, but due to the paucity of data obtained, the search was then confined to each specific type of CTD-ILD. PubMed and CINAHL databases were queried for literature pertaining to QOL in CTD-ILD. Connective tissue diseases are found in the literature under a variety of other terms, such as collagen vascular disease and autoimmune disease. These terms encompass diseases such as scleroderma, polymyositis, dermatomyositis, antisynthetase syndrome, lupus, rheumatoid arthritis, Sjogren's syndrome, and vasculitis. Interstitial lung disease is also known in the literature as pulmonary fibrosis and progressive fibrosing interstitial lung disease (PF-ILD). The initial search of ("connective tissue disease" AND "interstitial lung disease" AND "quality of life") yielded no results. Another search utilizing surrogate terms for collagen vascular disease and interstitial lung disease ("collagen vascular disease" AND "pulmonary fibrosis" AND "quality of life") returned no results. A search for ["autoimmune disease" AND ("interstitial lung disease" OR "pulmonary fibrosis") AND "quality of life"] returned six results. Then, "PF-ILD" AND "quality of life" was searched and yielded three results. Another search performed using ["connective tissue disease" AND ("interstitial lung disease" OR "pulmonary fibrosis") AND "quality of life"] resulted in 12 articles.

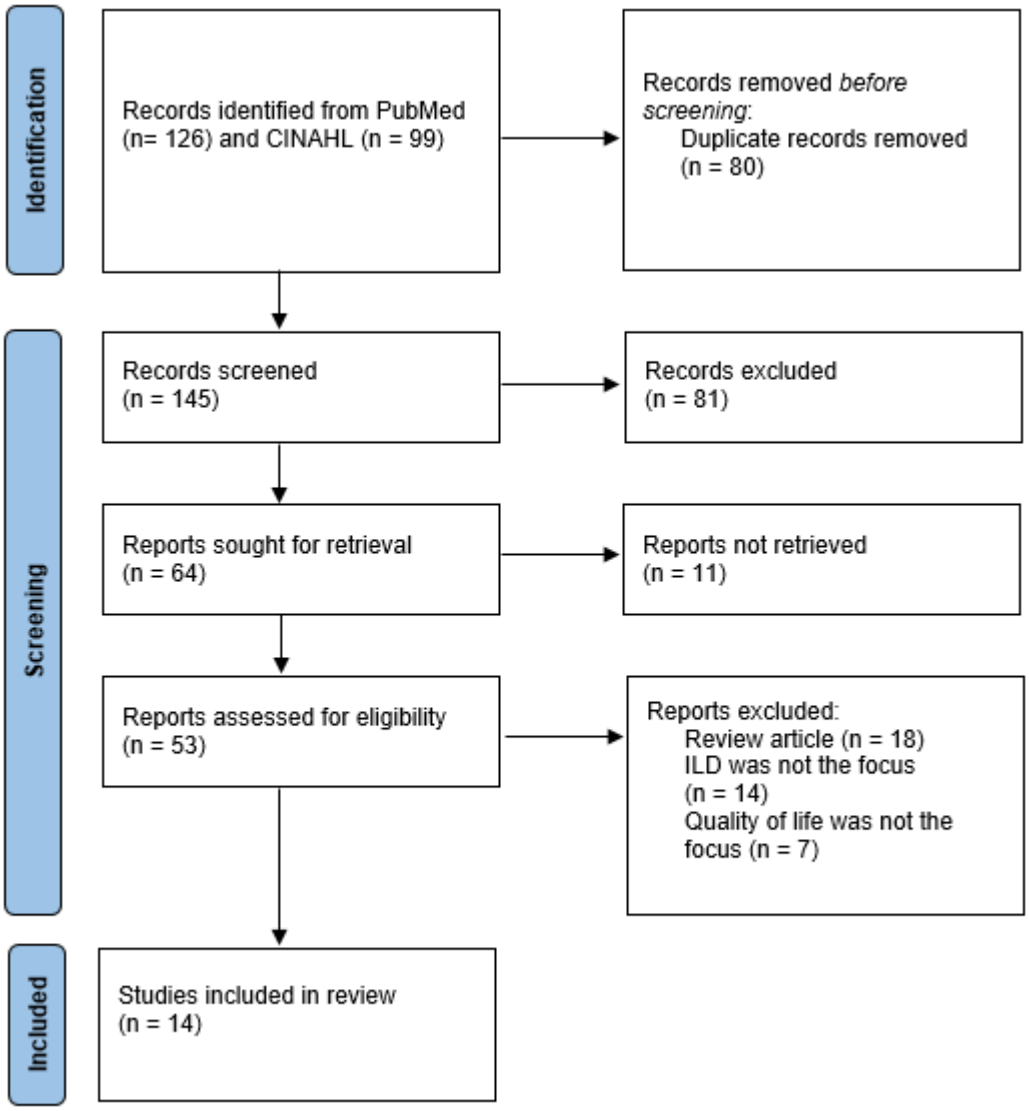
Because of the paucity of data from the prior searches, the decision was made to look at each manifestation of connective tissue disease. The next search involved [("systemic sclerosis" OR "scleroderma") AND ("interstitial lung disease" OR "pulmonary fibrosis") AND "quality of life"], yielding 123 results. Next,

[(“polymyositis” OR “dermatomyositis”) AND (“interstitial lung disease” OR “pulmonary fibrosis”) AND “quality of life”] was searched and five articles were found. Antisynthetase syndrome was searched next as [(“antisynthetase” OR “antisynthetase syndrome”) AND (“interstitial lung disease” OR “pulmonary fibrosis”) AND “quality of life”] and 11 articles were found. The next search, for [(“systemic lupus erythematous” OR “lupus”) AND (“interstitial lung disease” OR “pulmonary fibrosis”) AND “quality of life”], returned 38 results. There were 21 results from a search that involved [“rheumatoid arthritis” AND (“interstitial lung disease” OR “pulmonary fibrosis”) AND “quality of life”]. There were three articles from a search of [(“Sjogren’s” OR “Sjogren’s Syndrome”) AND (“interstitial lung disease” OR “pulmonary fibrosis”) AND “quality of life”]. A search of [“vasculitis” AND (“interstitial lung disease” OR “pulmonary fibrosis”) AND “quality of life”] returned three articles.

Duplicate records were removed, resulting in 145 records for screening. Next, clinical trials and systematic reviews were retained, resulting in 64 articles. After narrowing further for those articles in English and less than 10 years old, 53 remained. Of the remaining articles, 18 were excluded because they were meta-analyses, 14 because ILD was not the focus, and seven because QOL was not the focus. There were 14 remaining articles for review. Search findings are summarized in Figure 3.

Figure 3

*PRISMA Flow Diagram Representing the Literature Review Results*




## Analysis of the Literature

The literature review revealed several themes related to QOL in CTD-ILD. The first involves varying QOL results found for differing types of CTD. The next theme encompasses symptom burden. The third theme involves factors that may be associated with QOL.

### *Varying Results*

Quality of life has been assessed separately in CTD and ILD, but not sufficiently in CTD-ILD. Quality of life was found to be poor in several different types of CTD but did not include patients with ILD. In a multicenter case-controlled study involving 410 participants with vasculitis, QOL was poor, as measured by the RAND 36-Item Health Survey (SF-36) (Basu et al., 2014). However, this study did not involve individuals with ILD. Similarly, QOL as measured by SF-36 was impaired for individuals with rheumatoid arthritis and lupus, but those studied did not include patients with ILD (Luppi et al., 2020).

Quality of life has been measured in some forms of CTD-ILD and other types of ILD and found to be diminished. In a retrospective study using the SF-36 to assess 216 Norwegian patients with Sjogren's disease, those with ILD were found to have worse QOL than those without a pulmonary manifestation of the disease (Palm et al., 2013). Additionally, QOL was measured using the SF-36 in a multicenter study evaluating risk and prognostic factors for important outcomes in scleroderma and was found to be poorer for those with scleroderma-related ILD than the general population (Morrisroe et al., 2020). Quality of life was evaluated using the SF-36 in a study investigating determinants of QOL in IPF and rheumatoid arthritis-related ILD and found to be more severe in rheumatoid arthritis-related ILD (Natalini et al., 2017). In a Cochrane review of randomized controlled trials evaluating the use of cyclophosphamide versus standard of care in CTD-ILD, the health assessment questionnaire disability index (HAQ-DI) in one study and the SF-36 in another measured QOL with varying results; the disparity in results was attributed primarily to the use of different tools (Barnes et al., 2018). In a

study of 193 Japanese patients with CTD-ILD, QOL was found to be diminished as measured by the St. George Respiratory Questionnaire (SGRQ), but it is unclear if these results can be generalized cross culturally to a CTD-ILD population in the United States (Suzuki et al., 2018).

Quality of life was a secondary endpoint in evaluating the use of a medication called nintedanib in progressive fibrotic ILD (PF-ILD) using the King's Brief Interstitial Lung Disease Questionnaire (KBILD). While QOL was impaired at baseline with both treatment arms, there was no significant difference in QOL between treatment groups after receiving study medication (Flaherty et al., 2019). Varying results with QOL could be due to the use of differing patient reported outcome measures and because it was evaluated in different populations: those with CTD, those with ILD, and insufficiently in those with CTD-ILD.

### *Symptom Burden*

Connective tissue disease-related ILD is associated with high morbidity and mortality, with symptom manifestation, such as cough and shortness of breath, often resulting from organ impairment (Fischer et al., 2019; Morrisroe et al., 2020). Cough and shortness of breath are recognized as common and significant findings in CTD-ILD (Saketkoo et al., 2014). Luppi and colleagues (2020) noted that individuals with Sjogren's-related ILD are often affected negatively by symptoms associated with their lung disease. Cough and shortness of breath are reported frequently as untoward symptoms in CTD-ILD (Barnes et al., 2018). For individuals with CTD-ILD with a fibrotic phenotype, symptoms of fatigue, cough, and shortness of breath are found to have

a profound impact on patients' lives, resulting in decreased social interaction, deconditioning, and mood changes (Gulati & Antin-Ozerkis, 2014). England and Hershberger (2020) recognized cough and shortness of breath to be of high importance in the assessment of treatment response given their severity in patients with rheumatoid arthritis-related ILD. Individuals with scleroderma-related ILD are often afflicted with cough, shortness of breath, and fatigue, but these symptoms are rarely addressed in randomized clinical trials investigating the efficacy of pharmacological agents (Hoffmann-Vold et al., 2020). The effect of symptoms on QOL in CTD-ILD has yet to be characterized.

### *Associated Factors*

Several factors may be associated with QOL in CTD. In a study of individuals with vasculitis, an inverse relationship was found between fatigue and QOL. However, this assessment failed to consider patients with vasculitis-related ILD (Basu et al., 2014). While there is likely an association between lung function and QOL in Sjogren's disease-related ILD, there is limited data supporting this and a need for future research has been cited (Palm et al., 2013). Morrisroe and colleagues (2020) suggested that QOL might worsen with increasing severity of ILD, thus alluding to an association between QOL and forced vital capacity (FVC) as measured by pulmonary function testing. The utility of FVC is that it measures the severity of ILD and can be used as a surrogate to assess for disease progression (du Bois et al., 2011). Both shortness of breath and fatigue were found to be associated with QOL in a study evaluating determinants of QOL for individuals with rheumatoid arthritis-related ILD (Natalini et al., 2017). In a small study

involving 30 Chinese individuals with CTD-ILD, QOL was thought to possibly be associated with the duration of their disease, type of ILD, cough, and shortness of breath, warranting further investigation (Yuan et al., 2020).

## Summary

Connective tissue disease is inclusive of several autoimmune, rheumatological diseases such as scleroderma, polymyositis, dermatomyositis, lupus, rheumatoid arthritis, Sjogren's disease, vasculitis, and mixed connective tissue disease. All of these may affect the lungs in the form of ILD, resulting in high levels of morbidity and mortality, potentially influencing QOL.

The Factors Affecting Quality of Life Model, as informed by the Symptoms Experience Model, was chosen to explore QOL in CTD-ILD. This model depicts the associations between antecedents, such as age, gender, race, marital status, type of ILD, disease duration, FVC, immunosuppressant use, and pulmonary rehabilitation as they relate to symptoms of cough, shortness of breath, and fatigue ultimately affecting the outcome of interest: QOL. Direct relationships between the antecedents and the outcome were also assessed, given their associations in similar disease states.

A search of the literature yielded 14 articles for review to explore the phenomenon of QOL in CTD-ILD. Three primary themes emerged: there are varying results for QOL in CTD-ILD, there is a high burden of symptoms, and there may be associated factors. Quality of life has been assessed in individuals with several different types of CTD, such as vasculitis, rheumatoid arthritis, and lupus, and found to be poor, but these studies did not include individuals with ILD. Quality of life has been

investigated in a few types of CTD-ILD, such as Sjogren's disease, scleroderma, and rheumatoid arthritis, as well as a different type of ILD (IPF), and found to be diminished as well, but the tools used for these studies differed and were not validated for use in their respective populations. In both studies involving QOL in CTD-ILD specifically, QOL was found to be impacted negatively, but each study used different tools to measure QOL, and it is unclear if results can be generalized cross-culturally. Connective tissue disease-related ILD is associated with a high burden of symptoms, primarily from lung manifestation of the disease. The most severe, bothersome symptoms appear to be cough, fatigue, and shortness of breath. The relationship of these symptoms to QOL in CTD-ILD as a disease process has not been evaluated sufficiently. There have been factors associated with CTD and QOL, such as fatigue, but ILD patients were not included in the analysis. Additionally, lung function, dyspnea, fatigue, duration of disease, and type of ILD have been identified as potential associated factors with QOL in CTD-ILD, but more research has been recommended by those studies investigating CTD-ILD.

This study sought to gain a better understanding of the varying results of QOL in CTD and ILD by addressing QOL in CTD-ILD specifically. This, coupled with an understanding of both the symptom burden and how it may relate to associated factors and QOL addressed the study problem that QOL has been investigated in rheumatological diseases and other forms of ILD, but not sufficiently in CTD-ILD.

# CHAPTER 3

# METHODOLOGY

The purpose of this study was to investigate QOL and associated factors and the mediating effect of symptoms for individuals with CTD-ILD by performing a secondary data analysis from the Pulmonary Fibrosis Foundation Patient Registry (PFFPR). Investigation of QOL in CTD-ILD was guided by the research aims and hypotheses proposed in Table 1. Based on the review of literature, several variables have been identified as potentially affecting QOL in CTD-ILD. Variables include demographic characteristics such as age, race, gender, and marital status. The disease characteristics of type of ILD, duration of disease, immunosuppressant use, and pulmonary rehabilitation participation have been identified as potentially influencing QOL in CTD-ILD, as has the physiologic variable of FVC.

This chapter discusses the study methodology and design. To this end, the parent study and current study population and sample are described. Additionally, the study instruments are identified and described, as well as data collection and management strategies. Reliability and validity of the proposed study are addressed, as are mechanisms to mitigate potential threats. Ethical considerations for the proposed study are delineated. This chapter also describes the data analysis plan.

## Study Design

Using a secondary data analysis at a single time point from the PFFPR, this study used a cross-sectional design to describe QOL in CTD-ILD. A cross-sectional design is an appropriate mechanism to explore a phenomenon at a single time point by describing both the status of the phenomenon and relationships that may be associated with the phenomenon (Polit & Beck, 2017). The phenomenon of QOL in CTD-ILD has yet to be sufficiently characterized; therefore, a cross-sectional approach was an appropriate mechanism to describe this phenomenon.

## Parent Study Methodology

The parent study, entitled "Pulmonary Fibrosis Foundation Patient Registry," utilizes convenience sampling of individuals with ILD recruited during a clinic visit at one of the 42 participating Pulmonary Fibrosis Foundation Care Centers from March 29, 2016, through April 5, 2022, with an anticipated study completion date of October 2023 (Pulmonary Fibrosis Foundation, 2016). Convenience sampling involves the utilization of the most readily available sample (Polit & Beck, 2017). While difficult to generalize to a larger population, this sampling strategy may be appropriate for rare diseases (Tyrer & Heyman, 2016). The PFFPR is funded by the Pulmonary Fibrosis Foundation. For inclusion in the study, participants must fulfill the following requirements:

1. Be 18 years old or older
2. Understand and sign the informed consent document
3. Have a confirmed ILD diagnosis

4. Be available for additional follow up at the Registry center for at least one year

Criteria used to exclude participation involve inability to complete the study instruments and diagnosis with sarcoidosis, lymphangioleiomyomatosis, pulmonary alveolar proteinosis, cystic fibrosis, or amyloidosis.

The parent study captures data elements at baseline and then every 6 months for the duration of the study, except for demographics, which are only collected at baseline (Pulmonary Fibrosis Foundation, 2016). The data elements include demographics, medical and family history information, diagnostic information, pulmonary function test results, hospitalizations, pulmonary rehabilitation utilization, lung transplant status, medication usage, medical event and mortality data, and patient reported outcome measures (PROMs). Patient reported outcome measure data are used to assess QOL, shortness of breath, cough, and fatigue. Two thousand subjects are anticipated to enroll. Data analysis is not performed by the parent study, as the registry data exist for future analysis by investigators for whom permission has been granted by both the PFFPR Scientific Review Committee and the investigator's institutional review board.

A mechanism used to maintain reliability of the parent study involves query generation. The electronic data capture system has established range checks and generates queries accordingly. Additionally, data managers and statisticians also generate queries based on their continuous review of study data, which are subsequently resolved by study sites (Wang et al., 2020).

## Sampling Strategy

The investigation of QOL in CTD-ILD involves a subset of ILD cases from the PFFPR database inclusive of those diagnosed with CTD-ILD. Connective tissue disease-related ILD cases are identified as subcategories by name of disease. Alternate forms of ILD were excluded for this study, as CTD-ILD is the type of ILD of interest due to the paucity of data known about it. Excluded cases were those in which questionnaires, demographic information, and FVC data were not completed at baseline. After checking to see if missing data were absent completely at random, a listwise deletion was performed.

As of April 5, 2022, the PFFPR had 333 CTD-ILD cases. This sample size of 333 meets the requisite 100 cases for four predictor variables with a mediu significance level of .05 (O'Rourke & Hatcher, 2013). Therefore, an adequate number of cases were extracted for this study.

## Data Collection and Management

With approval by both the PFFPR Scientific Review Committee and the Institutional Review Board, the de-identified data were transferred electronically via encryption and received the same day as the transfer. Cases were reviewed for complete data obtained at baseline. The process of data extraction occurred over the course of one day, while data analysis took several months.

Baseline data for the proposed study included age, race, gender, type of CTD-ILD, duration of disease in days, supplemental oxygen use, immunosuppressant medication use, and pulmonary rehabilitation participation. Baseline PROMs evaluating

QOL and symptoms were collected and are summarized in Table 2. This study involved the use of four PROMs. One tool measured the outcome of QOL, and the remaining three measured independent variables (symptoms).

De-identified, encrypted data were sent via password-protected computer. The data were maintained on a password-protected computer to which only the investigator has access.

## Instruments

### *Quality of Life*

The tool measuring QOL was the Medical Outcome Study Short Form Six-Dimension Health Survey (SF-6D) (Appendix A). It is an instrument derived from the Medical Outcome Study Short Form 36-Item Health Survey (SF-36). The SF-36 is a PROM that addresses QOL and involves eight health domains: physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional, and mental health (Ware & Sherbourne, 1992). Each scale in the SF-36 is transformed into a 0-100 scale, with a higher number indicating better QOL (Ware & Sherbourne, 1992). The SF-36 has demonstrated validity for use in idiopathic pulmonary fibrosis (IPF), a particular type of interstitial lung disease (ILD) (Swigris, Brown et al., 2010). The SF-6D is a PROM that is derived from the SF-36 and includes six of the original eight domains of the SF-36: physical functioning, role limitation, bodily pain, vitality, social functioning, and mental health (Brazier et al., 2002). The SF-6D scoring ranges from 0.3-1.00, with a higher score reflective of better QOL (Brazier et al., 2002). While the SF-6D tool has yet to be validated specifically in CTD-ILD, it has been validated in both

rheumatoid arthritis and scleroderma, two conditions that result in ILD as well as in IPF, with intraclass correlation coefficient (ICC) 0.82, Cronbach's α = 0.83 (Dritsaki et al., 2017; Khanna et al., 2007; Swigris, Brown et al., 2010).

### *Shortness of Breath*

The symptom of shortness of breath was assessed using the University of California San Diego Shortness of Breath Questionnaire (SOBQ) (Appendix B). The SOBQ contains 24 items inclusive of two domains: shortness of breath with activities of daily living and limitations due to shortness of breath. Each of the 24 items is answered on a 6-point scale, resulting in scores ranging from 0-120, with a higher score indicating greater severity of shortness of breath (Eakin et al., 1998). Reliability for SOBQ use in CTD-ILD has been established with Cronbach's α = 0.96 and concurrent validity with $r$ = .58 (Swigris, Yorke et al., 2010).

### *Cough*

Cough was measured by the Leicester Cough Questionnaire (LCQ) (Appendix C). This PROM has 19 items containing three domains in which cough has an effect: social, psychological, and physical. The score range is 3-21, with a higher score indicating less negative effect of cough (Birring et al., 2003). The LCQ has been validated for use for individuals with chronic cough with concurrent validity $r$ = .60 and has also been used in IPF with Cronbach's α = .74 to .86 and ICC 0.79-0.93 (Berkhof et al., 2012; Key et al., 2010). The LCQ has not been validated specifically in CTD-ILD, but reliability will be assessed in this study.

### *Fatigue*

Fatigue was measured using the Fatigue Severity Scale (FSS) (Appendix D). The FSS is a 9-item measurement using a 7-point Likert scale for each of the 9 items. Scores are averaged for a composite score, then divided by 9, with a minimum score of 1 and maximum score of 7; higher scores reflect more severe fatigue (Krupp et al., 1989). Validity has been established with $r = .46$ and reliability with Cronbach's $\alpha = .88$ (Krupp et al., 1989). While not validated specifically in CTD-ILD, the FSS has been used in studies involving advanced lung disease and IPF (Swigris et al., 2011; Talwar et al., 2014).

### *Forced Vital Capacity*

Pulmonary function testing, specifically forced vital capacity, is a mechanism by which the severity of ILD can be measured and is used as a surrogate to assess for disease progression (du Bois et al., 2011). Forced vital capacity is not a patient-reported outcome, as it is a measurement of the volume of air forcibly exhaled. The result is reported as an absolute value in liters and as a predicted percent compared with an expected value based on age, gender, height, weight, and ethnicity (Graham et al., 2019). A value of less than 80% predicted is indicative of lung function impairment (Graham et al., 2019).

Table 2

*Proposed Variable Measures*

| Variable | Instrument | Items; Domains; Score | Reliability | Time Point Collected |
|---|---|---|---|---|
| Quality of life | Medical Outcomes Study Short-Form Six-Dimension (SF-6D) | 11 items; 6 domains: physical functioning, role participation (physical and emotional), social functioning, bodily pain, mental health, and vitality; summary score: 0.3 to 1.0 with 0.3 indicating worst possible quality of life (Brazier et al., 2002) | Intraclass correlation coefficient (ICC) 0.82, Cronbach's $\alpha = 0.83$, construct validity r = -.63 (Dritsaki et al., 2017; Khanna et al., 2007) | Baseline; every 6 months |
| Shortness of breath | University of California San Diego Shortness of Breath Questionnaire (SOBQ) | 24 items; 2 domains: shortness of breath with activities of daily living and limitations due to shortness of breath; 6-point scale, scores ranging from 0-120, with a higher score indicating greater severity of shortness of breath (Eakin et al., 1998) | Chronbach's $\alpha = 0.96$, $r = 0.89$ $p < 0.001$ (Eakin et al., 1998) | Baseline; every 6 months |
| Cough | Leicester Cough Questionnaire (LCQ) | 19 items; 3 domains: social, psychological, and physical; 3-21 score range with a higher score indicating a better QOL (Birring et al., 2003) | Subscales Cronbach's $\alpha = .74$ to .86, ICC 0.79-0.93, concurrent validity r = -.60 (Berkhof et al., 2012) | Baseline; every 6 months |
| Fatigue | Fatigue Severity Scale (FSS) | 9 items; 7-point Likert scale, scores are averaged for a composite score, then divided by 9: minimum score is 1.0, maximum score is 7.0 with higher score | Cronbach's $\alpha = .88$, r = .46 (Krupp et al., 1989) | Baseline; every 6 months |

| | | | | |
|---|---|---|---|---|
| | | indicative of higher severity of fatigue (Krupp et al., 1989) | | |
| Forced Vital Capacity (FVC) | Pulmonary Function Test | The amount of air forcibly exhaled after taking the deepest breath possible, measured in liters and compared with a predicted value based on age, gender, height, weight, and ethnicity, with reading less than 80% predicted indicative of restriction (Graham et al., 2019) | | Baseline; every 6 months |

## Reliability and Validity

Reliability and validity in this study were primarily affected by the tools used and the study population.

### *Study Tools*

Reliability and validity were augmented by the use of PROMs that have been reliable and valid for use in the population of interest (Polit & Beck, 2017). As described in Table 2, each of the four PROMs have been deemed reliable, valid instruments. However, only the SOBQ has been validated for CTD-ILD. While the SF-6D, LCQ, and FSS have not been validated for use in CTD-ILD, they have been used in IPF, which is a similar disease state to CTD-ILD (Berkhof et al., 2012; Swigris, Yorke et al., 2010).

### *Study Population*

Using an existing dataset imposes a threat to external validity in terms of selection bias. The sampling scheme of a parent study is a crucial factor to consider with secondary data (Cheng & Phillips, 2014). The convenience sampling used by the PFFPR may affect generalizability, as all respondents are recruited from Pulmonary Fibrosis Foundation

Care Centers. These Care Centers are academic medical centers and larger pulmonary practices specializing in ILD and are not inclusive of small community-based medical practices. Differences between these populations are not discussed in detail in the literature, but it is recognized that sicker patients are generally associated with larger, academic medical centers (Shahian et al., 2012). Patients with CTD-ILD followed at academic medical centers may be more severely affected by their disease and consequently may have worse QOL. It is unclear if the findings of the study can be extrapolated to individuals with CTD-ILD receiving care in community-based practices who may not be as severely affected by the disease.

### *Mitigating Threats to Reliability and Validity*

The limitation of generalizability associated with utilization of secondary data obtained from patients followed at academic medical centers and larger pulmonary practices specializing in ILD is challenging to overcome, as it is impossible to change the study population. The primary mechanism for mitigating the problem of external validity is by describing it as a limitation in the study's discussion so that study findings can be interpreted appropriately. This limitation may also be somewhat mitigated by understanding the implications of a recent study evaluating the diagnosis, management strategies, and outcomes of interstitial lung disease. A study investigating associations between resources and practices of ILD centers and outcomes found that among the 27 ILD centers, there were no site-specific characteristics (resources and procedures) or organizational practices that were associated with clinically relevant outcomes of death, transplant, or hospitalization (de Andrade et al., 2022). Of the 27 centers, six were non-

academic. This study suggests there are few site-specific differences, given that 21 of the academic centers included in the study are also part of the PFFPR. This study may also support generalizability, as it included several non-academic medical centers. Additionally, descriptive statistics were analyzed to evaluate the case characteristics for comparison with those of individuals with CTD-ILD, thus adding to the external validity of the proposed study.

There are several mechanisms to address the threat to validity involving the use of the SF-6D, LCQ, and FSS in CTD-ILD. Concurrent validity was assessed by evaluating the symptoms of fatigue and cough against shortness of breath. A study by Kahlman et al. (2020) found a positive correlation between fatigue, cough, and shortness of breath in ILD. Additionally, testing can be performed for internal consistency with each patient reported measure.

## Ethical Issues

While secondary data analysis can serve to save money, time, and resources and can provide high-quality data from large samples, there are concerns that must be addressed regarding potential ethical issues (Tripathy, 2013). There are two ethical issues warranting consideration in this study: respect for persons and also beneficence.

### *Respect for Persons*

The Belmont Report states that respect for persons involves the ethical conviction that people should be treated as autonomous individuals and demands that they enter voluntarily into research with adequate information to make this decision (National

Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). The principle of respect for persons mandates consideration of informed consent for voluntary participation in a clinical trial with an understanding of the purpose, procedures, potential benefits, and risks. With secondary analysis of data, there is a risk of violating this principle, as participants do not have the opportunity to give consent for this type of study. However, as a requirement for participation in the PFFPR, enrolled subjects provided consent specifically for their data to be used in future studies involving ILD without the need for additional consent (Pulmonary Fibrosis Foundation Patient Registry, 2016). The purpose and methods of this study fall within the scope of the PFFPR parent trial, thus maintaining the principle of respect for persons.

### *Beneficence*

The ethical principle of beneficence is described as respecting a person's decisions, protecting them from harm, and making efforts to secure their well-being (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Protecting research subjects from harm involves mitigating potential risk to them. One potential risk to study participants is a breach of confidentiality (Brakewood & Poldrack, 2013). There are two ways that this risk may be minimized. The first involves the de-identification of data, which should be completed prior to data sharing (Brakewood & Poldrack, 2013). The PFFPR data have already been de-identified at the time of data entry, so no personal identifiers are associated with the data (Pulmonary Fibrosis Foundation Patient Registry, 2016). The second consideration for risk minimization involves data security measures, which are necessary to prevent

breaches of confidentiality (Tripathy, 2013). The Registry Data Coordinating Center has established certain measures to maintain privacy and confidentiality of the PFFPR data. Their electronic data collection system is in compliance with Good Clinical Practice and FDA 21 CFR Part 11 requirements for electronic data (United States Food and Drug Administration, 2003). Data are stored on password-protected computers and are only accessible to study staff. To access the PFFPR data, this investigator was required to agree to the data security measures established by the Registry Data Coordinating Center and to the transfer of electronic data utilizing encryption (Pulmonary Fibrosis Foundation Patient Registry, 2016).

## Data Analysis Plan

In order to answer different types of research questions based on inference, different statistical approaches were used.

### *Descriptive Statistics*

Means were obtained for the variables of age (years), FVC (in liters), duration of disease (months). Additionally, means scores for the SF-6D, SOBQ, LCS, and FSS were obtained. For those variables, standard deviation was used to assess the index of variability. Frequencies of the categorical variables (race, gender, marital status, and type of ILD) were obtained as well.

### *Bivariate Analysis*

Bivariate analysis of the independent variables (demographic characteristics, clinical characteristics, and symptoms) with the dependent variable of QOL was performed using several techniques. The strength of the linear relationships between the numerical independent and dependent variables involved the Pearson correlation coefficient. Assumptions necessary for this include normality, homoscedasticity, and linearity (Weisberg, 2014). Chi-square test was performed on the categorical variables of gender, race, marital status, and type of CTD-ILD. The assumptions for this test are that the variables are categorical and mutually exclusive (Weisberg, 2014).

### *Path Analysis*

Path analysis uses correlational analysis to provide support for the hypothesized causal models, as depicted in Figure 2. A path coefficient describes the interrelationships and causal flow between each variable, ultimately evaluating the causal path among the dependent variable with independent and mediating variables (Polit & Beck, 2017). For this study, path analysis was used to test the hypothesized causal pathways between demographic characteristics and QOL, disease characteristics and QOL, and symptoms with QOL. The mediating effect of symptoms on the relationship between demographic and disease characteristics on QOL was also investigated. Path analysis was chosen over standard regression analysis because regression analysis only allows for a variable to be either independent or dependent, while the variables in path analysis can be independent and dependent (Jeon, 2015). Additionally, path analysis allows for simultaneous analysis of a complex model, such as that depicted in Figure 2 (Streiner, 2005). If the path

analysis demonstrates a relationship between the three variables in this study, the results of this analysis may inform the design of a subsequent study, perhaps by evaluating the effect of symptom management on QOL for individuals with a particular type of ILD.

## Summary

Using a descriptive, cross-sectional design, the study evaluated QOL in CTD-ILD and the demographic factors, disease factors, and symptoms that affect it both directly and indirectly. The study involved a secondary analysis of data from the PFFPR. Those enrolled in the parent study have confirmed ILD and consented to have their data used in subsequent research. While the parent study collects data at baseline and at 6-month intervals, this study examined baseline data only. Data collected included age, race, gender, marital status, FVC, type of ILD, duration of disease, immunosuppressant use, participation in pulmonary rehabilitation, and PROMs for QOL, shortness of breath, cough, and fatigue.

The SF-6D measures QOL, the SOBQ evaluates severity of shortness of breath, cough is measured with the LCQ, and fatigue is assessed by the FSS. While all of these measures have been deemed reliable and valid instruments, only the SOBQ has been validated specifically for use in CTD-ILD.

Threats to reliability and validity include both the study tools and the patient population. Because neither reliability nor validity has been established for the SF-6D, LCQ, or FSS in CTD-ILD, concurrent validity and internal consistency were assessed in this study. The threat to generalizability imposed by the study population drawn from academic medical centers and large pulmonary practices specializing in ILD is moderated by acknowledging this as a limitation to ensure the study findings are interpreted in this

context. The data analysis plan also addressed validity, as descriptive statistics were performed. Additional data analysis involved bivariate correlational statistics to evaluate the relationships between the variables. Path analysis was also performed to assess the indirect relationships among study variables.

Understanding the association among demographic, disease, and symptom profiles on QOL in CTD-ILD ultimately may improve the patient experience by guiding pharmacologic and non-pharmacologic therapies. Adherence to the study's methodology upholds the quality of the study, its findings, and implications.

# CHAPTER 4

# RESULTS

The goal of this study was to describe QOL and its associated factors in CTD-ILD. To this end, there were three aims: (1) describe the association between patient demographic (age, gender, and race) and disease characteristics (type of CTD-ILD, duration of disease, FVC, supplemental oxygen, immunosuppressant medication use, and pulmonary rehabilitation) and QOL in CTD-ILD; (2) describe the relationship between symptoms (shortness of breath, cough, and fatigue) and QOL in CTD-ILD; and (3) examine potential mediation relationships between symptoms and QOL in CTD-ILD. In this chapter, the results of these aims are described in terms of univariate statistics, bivariate analysis, and path analysis.

## Univariate Statistics

At the time of study entry, the average age of the sample was 61.2 (12.5) years old. Most participants were female (220 [66%]) and White (251 [77.5%]), followed by Black (58 [17.9%]). The mean FVC was 67.1 liters (18.6). Most participants had scleroderma (84 [25.2%]), followed by rheumatoid arthritis (77 [23.1%]), inflammatory myopathy (65 [19.5%]), mixed and undifferentiated CTD (59 [17.7%]), Sjogren's syndrome (24 [7.2%]), lupus (16 [4.8%]), and vasculitis (8 [2.4%]). At enrollment, the majority of participants had their CTD-ILD for 1-3 years (99 [30%]), followed by 3-7

years (90 [27.3%]), less than 1 year (85 [25.8%]), and >7 years (57 [17%]). Most participants did not require supplemental oxygen (206 [61.9%]), were not taking immunosuppressant medications (220 [66.1%]), and were not enrolled in pulmonary rehabilitation (295 [88.6%]). In terms of symptom burden, the mean scores on the PROMs were: Shortness of Breath Questionnaire 44.6 (26.63), Leicester Cough Questionnaire 15.92 (4.43), Fatigue Severity Scale 4.46 (1.79), and the Short Form Six Dimension 0.66 (0.11). The descriptive statistics are summarized in Tables 3 and 4.

Table 3

*Descriptive Statistics of Continuous Variables and Correlation Coefficients in the Analytical Sample (n = 333)*

| Variable | N (% missing) | Mean (SD) | Correlation coefficient of QOL with the continuous variables |
|---|---|---|---|
| 1. QOL: SF-6D score | 305 (8.1) | 0.66 (0.11) | — |
| 2. Age (years) | 333 (0.0) | 61.24 (12.46) | 0.09 |
| 3. FVC (liters) | 319 (4.3) | 67.14 (18.60) | 0.13* |
| 4. Shortness of breath: UCSD_Score | 302 (9.3) | 44.60 (26.63) | -0.67** |
| 5. Cough: LCQ_Total | 311 (6.6) | 15.92 (4.43) | 0.45** |
| 6. Fatigue: FSS_Total | 308 (7.5) | 4.46 (1.79) | -0.68** |

*$p < .05$. **$p < .01$.

**Table 4**

*Descriptive Statistics of the Categorical Variables and Comparisons of QOL by the Categorical Variables in the Analytical Sample (n = 333)*

| Variable | *N* (%) | SF-6D QOL Score | | |
|---|---|---|---|---|
| | | Mean (SD) | Effect Size (Cohen's *d*, H, or η2) | *p*-value |
| Gender | | | | |
| male | 113 (34) | 0.68 (0.11) | *d* = -0.35 | .0042 |
| Female | 220 (66) | 0.64 (0.11) | | |
| Race (*N* = 324) | | | $\eta^2$ = .0046 | .3090 |
| White | 251 (77.5) | 0.66 (0.11) | | |
| Black | 58 (17.9) | 0.64 (0.11) | | |
| Asian | 11 (3.4) | 0.61 (0.16) | | |
| Other | 4 (1.2) | 0.60 (0.04) | | |
| Type of ILD | | | $\eta^2$ = .0022 | .3492 |
| Scleroderma | 84 (25.2) | 0.64 (0.10) | | |
| Rheumatoid arthritis | 77 (23.1) | 0.66 (0.11) | | |
| Inflammatory myopathy | 65 (19.5) | 0.67 (0.12) | | |
| Mixed and undifferentiated CTD | 59 (17.7) | 0.68 (0.12) | | |
| | | | | |
| Sjogren's syndrome | 24 (7.2) | 0.63 (0.15) | | |
| Lupus | 16 (4.8) | 0.63 (0.12) | | |
| | | | | |
| Vasculitis | 8 (2.4) | 0.68 (0.06) | | |
| Duration of Disease (*N* = 331) | | | $\eta^2$ = 0.01 | .1380 |

| | | | | |
|---|---|---|---|---|
| <1 year | 85 (25.8) | 0.65 (0.11) | | |
| 1-3 years | 99 (30) | 0.65 (0.11) | | |
| >3-7 years | 90 (27.3) | 0.68 (0.12) | | |
| >7 years | 57 (17) | 0.64 (0.10) | | |
| Supplemental Oxygen | | | $d = 0.43$ | .0002 |
| Yes | 127 (38.1) | 0.63 (0.10) | | |
| No | 206 (61.9) | 0.67 (0.12) | | |
| Immunosuppressant Medication Use | | | $d = 0.14$ | .2553 |
| Yes | 113 (33.9) | 0.67 (0.11) | | |
| No | 220 (66.1) | 0.65 (0.11) | | |
| Pulmonary Rehabilitation | | | $d = 0.48$ | < .0001 |
| Yes | 38 (11.4) | 0.61 (0.11) | | |
| No | 295 (88.6) | 0.66 (0.11) | | |

## Association Between Demographics and Quality of Life

The first aim was to describe the association between patient demographic and disease characteristics (type of CTD-ILD, duration of disease, FVC, supplemental oxygen, immunosuppressant medication use, and pulmonary rehabilitation) and QOL in CTD-ILD. For these analyses, a significance level of 0.05 was established. Pearson correlation analysis was conducted to assess correlation of age and lung function as measured by FVC with QOL. The normality assumption for both was justified by the Central Limit Theorem. Linearity and homoscedasticity assumptions were evaluated with scatterplots. The assumptions were justified for a Pearson correlation analysis. The results suggested that while QOL is not linearly correlated with age ($r = .09$, $p = .1174$), it does have a positive linear correlation with FVC ($r = 0.13$, $p = .0223$). Specifically, a higher FVC was correlated with better QOL. The effect size of this linear correlation was small (0.13). Welch's *t*-test was conducted to compare means of gender, supplemental oxygen, and immunosuppressive medication use with QOL. The normality assumption was valid under the Central Limit Theorem. Because of uncertain population variance, Welch's *t*-test was used. The effect size was calculated as Cohen's *d*. The results suggested that QOL was statistically different based on gender ($t_{304} = -2.899$, $p = .0042$), and supplemental oxygen use ($t_{261} = 3.779$, $p = .0002$). Women reported lower QOL than men, ~~indicating~~ as indicated by a large effect size ($d = -0.35$). Supplemental oxygen use was associated with poorer QOL, as indicated by a large effect size ($d = 0.43$). Kruskal-Wallis testing was performed to evaluate for differences in QOL based on race and type of CTD-ILD. The results suggest that there was no statistically significant difference in

QOL due to race or type of CTD-ILD ($\eta^2$ = .0046, $p$ = .309; $\eta^2$ = .0022, $p$ = .3492, respectively).

Analysis of variance was conducted to assess duration of disease and QOL. The normality assumption was justified by the Central Limits Theorem. Homogeneity of variance was established using Levene's test ($F_{3,298}$ = 1.2594, $p$ = 02885). The results suggest that there was no statistically significant difference in QOL among duration of disease categories ($F_{3,298}$ = 1.85, $p$ = .138). The Wilcoxon rank-sum test was performed to evaluate for differences in QOL based on pulmonary rehabilitation participation. This test was chosen because the data were not normally distributed based on Shapiro-Wilk testing ($p$ < .0001). Eta squared was used to assess effect size. The results suggest that there was a statistically significant difference in QOL between those in pulmonary rehabilitation and those not in pulmonary rehabilitation, with those participating in pulmonary rehabilitation reporting poorer QOL, indicating a large effect size ($p$ < .0001, $d$ = 0.48).

## Relationships of Symptoms to Quality of Life

The second aim was to describe the relationship between symptoms (shortness of breath, cough, and fatigue) and QOL in CTD-ILD. Pearson correlation analysis was conducted to assess the relationships of shortness of breath, cough, and fatigue to QOL. The normality assumption was justified using the Central Limit Theorem. Linearity and homoscedasticity assumptions were evaluated using scatterplots. The assumptions were justified for a Pearson correlation analysis. The analysis suggests QOL had a positive linear correlation with cough, with higher scores on cough scale indicative of less negative effect of cough being correlated with higher degree of QOL ($r$ = 0.45, $p$ <

.0001). The effect of this linear correlation was medium to large. The Pearson correlation analysis also suggests QOL had a linear correlation with fatigue and shortness of breath, but the correlation in these cases was negative. Fatigue and QOL were linearly correlated, with a lower score on the fatigue scale (indicative of less fatigue) correlated with higher degree of QOL with a large effect size ($r$ = -0.68, $p$ < .0001). Additionally, QOL and shortness of breath had a linear correlation, with lower scores (indicative of less shortness of breath) correlated with a higher degree of QOL ($r$ = -0.67, $p$ < .0001). The effect size of the linear relationship between QOL and shortness of breath was also large.

## Mediating Factors Affecting Quality of Life

Path analysis was used to evaluate aim three, which examined potential mediation effect of symptoms on the pathway from the antecedents to QOL in CTD-ILD as depicted in the Factors Affecting Quality of Life Model (see Figure 2). No goodness of fit was evaluated in this study, as the path model is saturated and there is zero degrees of freedom. The results of the mediation analysis are summarized in Table 5.

### *Mediation Effects*

Mediation analysis for symptoms was performed examining the indirect effects of shortness of breath, cough, and fatigue on each antecedent with QOL. Gender and FVC had small indirect paths to QOL through shortness of breath (standardized coefficient of indirect effect = 0.057, 0.08; $p$-values 0.011, 0.003, respectively). Supplemental oxygen use and pulmonary rehabilitation had small negative indirect paths to QOL through shortness of breath (standardized coefficient of indirect effect = -0.143, -0.049; $p$-values

0.000, 0.026, respectively). Age had a small indirect path to QOL through fatigue (standardized coefficient of indirect effect = 0.053, *p*-value 0.027), while supplemental oxygen use had a small negative indirect path to QOL through fatigue (standardized coefficient of indirect effect = -0.091, *p*-value 0.000). The symptom of cough did not mediate any of the relationships between the antecedents and QOL.

**Table 5**

*Mediation Effect of Symptoms on Quality of Life*

| **Antecedents** | **Direct Effect** | | **Indirect Effect** | | | | | **Overall Effect** | |
|---|---|---|---|---|---|---|---|---|---|
| | Standardized Coefficient | P-value | **Symptoms** | Standardized Coefficient | P-value | Overall Indirect Effect | P-value | Standardized Coefficient | P-value |
| Age | 0.071 | 0.143 | Shortness of breath | -0.028 | 0.23 | | | 0.084 | 0.167 |
| | | | Cough | -0.001 | 0.763 | | | | |
| | | | Fatigue | 0.053 | 0.028 | | | | |
| Gender | 0.054 | 0.086 | Shortness of breath | 0.013 | 0.012 | | | 0.18 | 0.001 |
| | | | Cough | 0.004 | 0.37 | | | | |
| | | | Fatigue | 0.039 | 0.072 | | | | |
| Race2 | 0.026 | 0.567 | Shortness of breath | -0.044 | 0.054 | | | 0.617 | -0.029 |
| | | | Cough | -0.006 | 0.315 | | | | |
| | | | Fatigue | 0 | 0.987 | | | | |
| Race3 | -0.1 | 0.024 | Shortness of breath | 0.008 | 0.698 | | | -0.068 | 0.231 |
| | | | Cough | 0.004 | 0.441 | | | | |
| | | | Fatigue | 0.014 | 0.528 | | | | |
| FVC | -0.112 | 0.027 | Shortness of breath | 0.08 | 0.003 | | | 0.044 | 0.483 |
| | | | Cough | 0.017 | 0.146 | | | | |
| | | | Fatigue | 0.04 | 0.098 | | | | |
| Supplemental Oxygen | 0.045 | 0.38 | Shortness of breath | -0.143 | 0 | | | -0.195 | 0.001 |
| | | | Cough | -0.007 | 0.247 | | | | |
| | | | Fatigue | -0.091 | 0.001 | | | | |
| Immunosuppressant Medication Use | 0.053 | 0.201 | Shortness of breath | 0.032 | 0.117 | | | 0.091 | 0.088 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Cough | -0.003 | 0.498 | | | | |
| | | | Fatigue | 0.018 | 0.378 | | | | |
| Pulmonary Rehabilitation | -0.061 | 0.16 | Shortness of breath | -0.049 | 0.027 | | | -0.127 | 0.022 |
| | | | Cough | 0.003 | 0.49 | | | | |
| | | | Fatigue | -0.027 | 0.206 | | | | |
| Disease Duration 1-3 Years | 0.03 | 0.568 | Shortness of breath | 0.007 | 0.792 | | | 0.115 | 0.084 |
| | | | Cough | 0.003 | 0.587 | | | | |
| | | | Fatigue | 0.017 | 0.495 | | | | |
| Disease Duration 3-7 Years | 0.096 | 0.065 | Shortness of breath | 0.037 | 0.15 | | | 0.184 | 0.006 |
| | | | Cough | 0.008 | 0.257 | | | | |
| | | | Fatigue | 0.051 | 0.048 | | | | |
| Disease Duration >7 Years | 0.008 | 0.87 | Shortness of breath | 0.005 | 0.823 | | | 0.139 | 0.038 |
| | | | Cough | 0.008 | 0.244 | | | | |
| | | | Fatigue | 0.038 | 0.123 | | | | |
| Type of CTD-ILD: Mixed and Undifferentiated CTD | 0.109 | 0.042 | Shortness of breath | -0.037 | 0.158 | | | 0.049 | 0.56 |
| | | | Cough | -0.004 | 0.48 | | | | |
| | | | Fatigue | 0.002 | 0.929 | | | | |
| Type of CTD-ILD: Rheumatoid Arthritis | -0.067 | 0.24 | Shortness of breath | -0.011 | 0.691 | | | 0.049 | 0.56 |
| | | | Cough | 0 | 0.985 | | | | |
| | | | Fatigue | 0.017 | 0.538 | | | | |
| Type of CTD-ILD: Sjogren's Disease | -0.026 | 0.588 | Shortness of breath | -0.028 | 0.227 | | | 0.057 | 0.693 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Cough | -0.002 | 0.706 | | | | |
| | | | Fatigue | -0.001 | 0.971 | | | | |
| Type of CTD-ILD: Lupus | 0.034 | 0.448 | Shortness of breath | -0.034 | 0.131 | | | 0.023 | 0.639 |
| | | | Cough | -0.005 | 0.323 | | | | |
| | | | Fatigue | -0.025 | 0.253 | | | | |
| Type of CTD-ILD: Systemic Sclerosis/Scleroderma | -0.05 | 0.362 | Shortness of breath | -0.043 | 0.109 | | | 0.066 | 0.346 |
| | | | Cough | -0.003 | 0.529 | | | | |
| | | | Fatigue | 0.024 | 0.353 | | | | |
| Type of CTD-ILD: Vasculitis | -0.009 | 0.828 | Shortness of breath | 0.005 | 0.818 | | | 0.089 | 0.468 |
| | | | Cough | 0 | 0.95 | | | | |
| | | | Fatigue | -0.004 | 0.854 | | | | |

| **Antecedents** | **Direct Effect** | | **Indirect Effect** | | | | **Overall Effect** | |
|---|---|---|---|---|---|---|---|---|
| | Standardized Coefficient (SE) | *P*-value | **Symptoms** | Standardized Individual Coefficient (SE) | *P*-value | Standardized Overall Indirect Effect (SE) | Standardized Coefficient (SE) | *P*-value |
| Age | 0.060 (0.043) | 0.164 | Shortness of breath | -0.028 (0.023) | 0.231 | 0.027 (0.041) | 0.087 (0.057) | 0.131 |
| | | | Cough | 0.001 (0.005) | 0.763 | | | |
| | | | Fatigue | 0.053 (0.024) | 0.027 | | | |
| Gender | 0.08 (0.039) | 0.042 | Shortness of breath | 0.057 (0.022) | 0.011 | 0.091 (0.037) | 0.171 (0.053) | 0.001 |
| | | | Cough | -0.004 (0.005) | 0.369 | | | |
| | | | Fatigue | 0.039 (0.022) | 0.07 | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Race2 | 0.02 (0.041) | 0.62 | Shortness of breath | -0.044 (0.023) | 0.053 | -0.038 (0.039) | -0.018 (0.056) | 0.746 |
| | | | Cough | 0.006 (0.006) | 0.315 | | | |
| | | | Fatigue | 0 (0.022) | 0.987 | | | |
| Race3 | -0.094 (0.039) | 0.017 | Shortness of breath | 0.008 (0.022) | 0.698 | 0.019 (0.038) | -0.075 (0.054) | 0.161 |
| | | | Cough | -0.004 (0.005) | 0.441 | | | |
| | | | Fatigue | 0.014 (0.022) | 0.528 | | | |
| FVC | -0.093 (0.045) | 0.038 | Shortness of breath | 0.08 (0.027) | 0.003 | 0.104 (0.045) | 0.011 (0.063) | 0.864 |
| | | | Cough | -0.017 (0.011) | 0.146 | | | |
| | | | Fatigue | 0.04 (0.024) | 0.098 | | | |
| Supplemental Oxygen | 0.047 (0.045) | 0.303 | Shortness of breath | -0.143 (0.031) | 0 | -0.226 (0.043) | -0.18 (0.058) | 0.002 |
| | | | Cough | 0.007 (0.006) | 0.246 | | | |
| | | | Fatigue | -0.091 (0.026) | 0 | | | |
| Immunosuppressant Medication Use | 0.043 (0.037) | 0.241 | Shortness of breath | 0.032 (0.021) | 0.116 | 0.053 (0.035) | 0.096 (0.05) | 0.055 |
| | | | Cough | 0.003 (0.004) | 0.499 | | | |
| | | | Fatigue | 0.018 (0.02) | 0.377 | | | |
| Pulmonary Rehabilitation | -0.055 (0.039) | 0.16 | Shortness of breath | -0.049 (0.022) | 0.026 | -0.079 (0.036) | -0.134 (0.052) | 0.011 |
| | | | Cough | -0.003 (0.005) | 0.49 | | | |
| | | | Fatigue | -0.027 (0.021) | 0.204 | | | |
| Disease Duration 1-3 Years | 0.026 (0.047) | 0.577 | Shortness of breath | 0.007 (0.025) | 0.792 | 0.021 (0.044) | 0.109 (0.063) | 0.086 |
| | | | Cough | -0.003 (0.005) | 0.587 | | | |
| | | | Fatigue | 0.017 (0.025) | 0.495 | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Disease Duration 3-7 Years | 0.088 (0.046) | 0.058 | Shortness of breath | 0.037 (0.025) | 0.147 | 0.037 (0.025) | 0.168 (0.063) | 0.008 |
| | | | Cough | -0.008 (0.007) | 0.256 | | | |
| | | | Fatigue | 0.051 (0.026) | 0.046 | | | |
| Disease Duration >7 Years | 0.008 (0.044) | 0.852 | Shortness of breath | 0.005 (0.024) | 0.823 | 0.035 (0.042) | 0.123 (0.062) | 0.047 |
| | | | Cough | -0.008 (0.007) | 0.244 | | | |
| | | | Fatigue | 0.038 (0.024) | 0.122 | | | |
| Type of CTD-ILD: Mixed and Undifferentiated CTD | 0.096 (0.048) | 0.045 | Shortness of breath | -0.037 (0.026) | 0.159 | -0.031 (0.045) | 0.057 (0.064) | 0.371 |
| | | | Cough | 0.004 (0.006) | 0.48 | | | |
| | | | Fatigue | 0.002 (0.026) | 0.929 | | | |
| Type of CTD-ILD: Rheumatoid Arthritis | -0.06 (0.05) | 0.236 | Shortness of breath | -0.011 (0.027) | 0.691 | 0.006 (0.047) | 0.057 (0.064) | 0.371 |
| | | | Cough | 0 (0.005) | 0.985 | | | |
| | | | Fatigue | 0.017 (0.027) | 0.539 | | | |
| Type of CTD-ILD: Sjogren's Disease | -0.02 (0.042) | 0.629 | Shortness of breath | -0.028 (0.023) | 0.226 | -0.027 (0.04) | 0.061 (0.061) | 0.32 |
| | | | Cough | 0.002 (0.005) | 0.706 | | | |
| | | | Fatigue | -0.001 (0.023) | 0.971 | | | |
| Type of CTD-ILD: Lupus | 0.031 (0.04) | 0.432 | Shortness of breath | -0.034 (0.022) | 0.13 | -0.054 (0.038) | 0.034 (0.06) | 0.575 |
| | | | Cough | 0.005 (0.005) | 0.323 | | | |
| | | | Fatigue | -0.025 (0.022) | 0.253 | | | |
| Type of CTD-ILD: Systemic Sclerosis/Scleroderma | -0.048 (0.049) | 0.324 | Shortness of breath | -0.043 (0.027) | 0.109 | -0.015 (0.046) | 0.073 (0.065) | 0.262 |
| | | | Cough | 0.003 (0.006) | 0.529 | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Fatigue | 0.024 (0.026) | 0.354 | | | |
| Type of CTD-ILD: Vasculitis | -0.009 (0.038) | 0.811 | Shortness of breath | 0.005 (0.021) | 0.818 | 0.001 (0.036) | 0.088 (0.059) | 0.132 |
| | | | Cough | 0 (0.004) | 0.95 | | | |
| | | | Fatigue | -0.004 (0.021) | 0.854 | | | |

## Summary

Our study predominantly involved females (66%), Whites (78%), with a mean age of 61 years and mean FVC of 67 liters. The majority of the sample was diagnosed with scleroderma (25%). Most individuals had been diagnosed with CTD-ILD for 1 to 3 years and were not on oxygen (62%), taking immunosuppressive medications (66%), or active in pulmonary rehabilitation (89%). Bivariate analysis revealed gender, FVC, supplemental oxygen use, pulmonary rehabilitation participation, shortness of breath, cough, and fatigue to all be correlated with QOL. Path analysis demonstrated shortness of breath to mediate the relationships between QOL and gender, FVC, supplemental oxygen use, and pulmonary rehabilitation. Path analysis also demonstrated fatigue to mediate the relationships of QOL and both age and supplemental oxygen use.

# CHAPTER 5

# CONCLUSIONS

This cross-sectional study evaluated QOL and associated factors as well as the mediating effect of symptoms for individuals with CTD-ILD by using a secondary analysis of data from the PFFPR (Pulmonary Fibrosis Foundation, 2016). We found that among the demographic characteristics, there was only an association between gender and QOL, with women reporting poorer QOL than men. We also found that among the disease characteristics, lower FVC, supplemental oxygen use, and pulmonary rehabilitation were associated with poorer QOL. Study results further revealed QOL to be inversely associated with shortness of breath, cough, and fatigue.

## Demographic and Disease Characteristic Impact on QOL

Investigation of the relationships between demographic characteristics and QOL revealed varying results. We found that while neither age nor race was associated with QOL, there was an association between gender and QOL.

As hypothesized, women reported poorer QOL than men. This is a finding also in research on IPF, in which women reported worse emotional QOL than men (Han et al., 2010). Gender differences in QOL were not limited to IPF. In a study by Aurrecoechea and colleagues (2015), women with rheumatoid arthritis reported poorer QOL than men with rheumatoid arthritis.

It was hypothesized that younger age was associated with worse QOL, but the data did not support a relationship between these two factors. This may be a consequence of disease trajectory or coping mechanisms. Investigation of age and QOL with CTD-ILD may better be addressed through a longitudinal study during which the effects of disease trajectory can be better assessed. Another potential reason for the study finding could have to do with coping. Watkins et al. (1999) suggested that younger individuals with rheumatoid arthritis have better coping skills than older adults with rheumatoid arthritis. Coping in chronic illness has been associated with QOL (Megari, 2013).

Based on existing data, it was hypothesized that Black individuals with CTD-ILD would have poorer QOL, but this was not the case in our study. This may be a consequence of the study population. Our data showed that 78% of the individuals were White and 18% were Black. This is not what is generally seen in the CTD-ILD population. There is up to a threefold higher frequency of both lupus and scleroderma in Blacks than in Whites (Chifflot et al., 2008; Pons-Estel et al., 2010). There is also a higher prevalence of rheumatoid arthritis in Blacks compared to Whites (Xu & Wu, 2021). The reasons for racial disparity in the study population is unclear but may be a consequence of location of care. A recent study found that Whites were more than twice as likely than Blacks to receive care at an academic medical center (Tikkanen et al., 2017).

Due to a paucity of data regarding QOL and specific type of CTD-ILD, the relationship between type of CTD-ILD and QOL was examined. Our study found that, while QOL was impaired for patients with CTD-ILD, it did not differ among types of CTD-ILD. This is a similar finding for individuals with CTD. A study by Salaffi et al.

(2019) reported that QOL did not differ between types of CTD. Our data suggests that this finding likely extrapolates to those with CTD-ILD.

In terms of disease duration and QOL in patients with CTD-ILD, our study revealed no relationship between these two factors. This is inconsistent with findings in other types of chronic diseases. Longer duration of disease was associated with worse QOL in individuals with rheumatoid arthritis, asthma, and COPD (Busija et al., 2017; Rosińczuk et al., 2018). The reasons for this are not entirely clear. This may be due in part to a lack of disease progression or perhaps a successful treatment regimen. Neither of these factors were assessed in our study. The impact of adaptation may also explain the study's findings, as those with a longer duration of disease may have developed the ability to adapt to their condition. In a study involving young adults with chronic illness since childhood, the ability to adapt to their illness had an impact on their QOL (Veerhoof et al., 2014).

Supplemental oxygen use was associated with poorer QOL as hypothesized. The reason for this may be twofold, severity of disease and difficulties with oxygen equipment. The need for supplemental oxygen arises as ILD progresses and causes irreversible scarring of lung tissue. With greater severity of disease, QOL is impacted as shown in our study, in which lower FVC was associated with poorer QOL. Additionally, individuals with ILD report portable oxygen tanks to be constraining and cumbersome; using portable oxygen tanks results in not only more shortness of breath from having to pull the tanks along as they walk, but they also walk shorter distances (Ramadurai et al., 2018).

Unlike the association between supplemental oxygen use and QOL, immunosuppressant medication use was not associated with QOL. It was hypothesized that the use of immunosuppressant medication was associated with poorer QOL, based on similar findings in the renal transplant community citing side effects of immunosuppressant drugs (Hilbrands et al., 1995; Zhu et al., 2017). An explanation for differences found in our study could be the number of immunosuppressant medications that a transplant patient must take. Following transplant, it is common for an individual to take three different immunosuppressant drugs for the rest of their life. Each medication has its own side effect profile, potentially resulting in a greater side effect burden for a transplant patient, while those with CTD-ILD often take only one immunosuppressant medication. It was also posited that individuals with CTD-ILD taking immunosuppressant medications have poorer QOL possibly due to the sequelae of having to take them at a younger age, resulting in longer lifetime exposure to side effects and potential reproductive implications related to the fetal toxicity of many immunosuppressive medications. As our study was cross-sectional, duration of immunosuppressant use was not assessed. Additionally, evaluating of the effect of immunosuppressant medication use on QOL was not assessed by age groups.

Contrary to our hypothesis that pulmonary rehabilitation participation is associated with improved QOL, our study showed a negative relationship between QOL and pulmonary rehabilitation participation. While pulmonary rehabilitation is recommended for individuals with ILD (Mikolasch et al., 2017), patients with more severe disease are referred for pulmonary rehabilitation more frequently than those with less severe disease (Hoffman et al., 2017). Our data demonstrate that individuals with a

lower FVC, hence more severe disease, have a lower QOL. Therefore, our finding of poorer QOL associated with pulmonary rehabilitation participation may be explained by the observation that only sicker individuals with ILD are being referred to pulmonary rehabilitation, and they already have a poorer QOL. Additionally, as this was a cross-sectional study, it is unclear how long participants had been participating in pulmonary rehabilitation. Perhaps there may have been improvement in their QOL after completion of a pulmonary rehabilitation program.

## Symptoms and QOL

As hypothesized, symptoms of shortness of breath, cough, and fatigue were associated with QOL. Considering all the study variables, symptoms had the strongest association with QOL. These are similar findings to research in other chronic diseases such as COPD, IPF, and rheumatoid arthritis that are characterized by a high symptom burden (Bove et al., 2020; Katchamart et al., 2019; Miravitlles & Ribera, 2017; Rajala et al., 2018). In addition to cough, shortness of breath, and fatigue, symptoms also impacting QOL in these other chronic diseases include depression and anxiety (Bove et al., 2020; Katchamart et al., 2019; Miravitlles & Ribera, 2017; Rajala et al., 2018).

## Mediation Effects

Shortness of breath mediated the relationships between QOL and the characteristics of gender, FVC, supplemental oxygen use, and pulmonary rehabilitation causing poorer QOL. The effect of shortness of breath as a mediator between the demographic and disease characteristic on QOL may potentially be mitigated by

minimizing the effect of shortness of breath. There are several mechanisms that may improve shortness of breath in ILD. For instance, pulmonary rehabilitation has demonstrated improvement with shortness of breath in individuals with ILD (Dowman et al., 2021). Palliative care may also improve shortness of breath. A study investigating palliative care impact on patients with refractory breathlessness due to several different chronic diseases, including ILD and COPD, found that palliative care improved the degree of shortness of breath (Higginson et al., 2014).

Fatigue was a mediator between QOL and supplemental oxygen such that the presence of fatigue was associated with worse QOL. Mitigating the effect of fatigue may in turn affect the relationship between supplemental oxygen use and QOL. Pulmonary rehabilitation is recommended for individuals with ILD and has been shown to improve fatigue in both COPD and lung cancer (Meek et al., 2013; Shannon, 2010). Fatigue in ILD can be caused by poor sleep hygiene, which can occur in the context of obstructive sleep apnea (Dobson et al., 2019). The incidence of obstructive sleep apnea is up to 88% for individuals with ILD compared to 2%-4% for healthy adults (Lee et al., 2020). Screening for obstructive sleep apnea in CTD-ILD patients and treating this condition as appropriate may improve fatigue.

## Suggestions for Research

The results from our study offer several opportunities for future research to better understand how CTD-ILD impacts QOL. The first involves a different study design to better understand demographic and disease characteristic impact on QOL. Another study involves an investigation of potential treatment to improve QOL in CTD-ILD.

*Study Design*

A longitudinal study design would allow for the exploration of the impact of disease trajectory with duration of disease, age, immunosuppressant medication use, and pulmonary rehabilitation on QOL. Our results demonstrated no association between disease duration and QOL. This could be a consequence of disease stability over time. Also limited by a cross-sectional study was age. It was hypothesized that younger age would be associated with poorer QOL, but this does not take into account the potential impact of the disease trajectory. For example, younger patients living with CTD-ILD over time may have impaired QOL given longer lifetime exposure to disease and treatment effects. Immunosuppressant medication use was not associated with QOL, but the duration of medication use was not assessed. In our study, pulmonary rehabilitation was associated with poorer QOL, which was contrary to its impact in other chronic lung diseases such as COPD and IPF (Matsuo et al., 2021; McCarthy et al., 2015; Swigris et al., 2011). . Our data were collected at a single time point and only assessed if the subject was active in pulmonary rehabilitation at the time of study entry. Therefore, the effect of completing a pulmonary rehabilitation program was not assessed. Because race in our study was not representative of the CTD-ILD population, a study inclusive of more non-academic medical centers would help to make study results more generalizable to this population.

### *Research Involving Palliative Care*

Given the study findings of both a strong correlation between QOL and symptoms and the mediating effect of symptoms, more attention needs to be paid to symptom management in CTD-ILD. The primary goal of pharmacotherapy for CTD-ILD is to prevent ILD progression as measured by FVC (Jee & Corte, 2019). For example, a medication commonly used to treat progressive CTD-ILD, nintedanib, was shown to slow the rate of decline in lung function, but its impact on QOL (as measured by the King's Brief Interstitial Lung Disease questionnaire) was minimal (Flaherty et al., 2019). The impact of additional symptoms, such as depression and anxiety, may also be investigated in a subsequent study, as these conditions are noted to affect QOL in IPF and COPD (Bove et al., 2020; Katchamart et al., 2019; Rajala et al., 2018).

The symptom burden of individuals with chronic lung disease is equivalent to that of lung cancer patients, but palliative care is sought less proactively (Wysham et al., 2015). It is recognized that symptom relief is an essential aspect of caring for ILD patients and that palliative care is a mechanism to achieve this (Lindell & Raghu, 2018). A study investigating palliative care impact on QOL and ILD may be warranted. Prior to an intervention study involving palliative care and QOL in CTD-ILD, a qualitative study evaluating the palliative care needs specific to the CTD-ILD population would be indicated. Such a needs assessment has been performed with both COPD and IPF. In these studies, in addition to symptom management, providing patients and caregivers with information about the disease and treatment, timing of palliative care referral, and advance directives were identified as palliative care needs (Bajwah et al., 2013; Iyer et al., 2019; Lindell et al., 2017). Such a needs assessment would likely illuminate the

palliative care needs specific to the CTD-ILD community. With this assessment, a palliative care intervention may be developed to ultimately help improve QOL for individuals with CTD-ILD.

## Summary

Quality of life is not just an important concept, but also an endpoint in research allowing for treatment modifications and symptom relief (Fayers & Machin, 2016). Healthcare intervention effectiveness has historically been based on biomedical outcomes rather than QOL (Fayers & Machin, 2016). Most research involving CTD-ILD is currently focused on interventions affecting FVC, as opposed to QOL. It is important to consider an intervention's impact not just on a patient's physical perspective but also their emotional and social well-being as they live with their disease. Our data have shown that QOL in individuals with CTD-ILD is associated with both disease severity and disease treatments, specifically lower FVC, supplemental oxygen use, pulmonary rehabilitation participation, and symptoms of shortness of breath, cough, and fatigue. Recognition of these factors and perhaps the treatment of symptoms may improve QOL for individuals with CTD-ILD. The impact on QOL of additional associated factors such as depression and anxiety may also be investigated in order to better assess the needs of CTD-ILD patients. Because symptom burden is strongly associated with QOL, palliative care may be indicated to improve QOL in CTD-ILD. The next steps would be developing a study assessing palliative care impact on QOL in patients with CTD-ILD.

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# APPENDIX A

## Medical Outcome Study Short Form Six-Dimension Health Survey (SF-6D)

**Rand Short Form-6D**

# Your Health and Well-Being

**This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.** ***Thank you for completing this survey!***

**For each of the following questions, please mark an ☒ in the one box that best describes your answer.**

**1. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

| | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|---|---|---|---|
| a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports | ☐1 | ☐2 | ☐3 |
| b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | ☐1 | ☐2 | ☐3 |
| c. Bathing or dressing yourself | ☐1 | ☐2 | ☐3 |

2. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| Were limited in the kind of work or other activities | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

3. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| Accomplished less than you would like | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

4. **How much bodily pain have you had during the past 4 weeks?**

| None | Very mild | Mild | Moderate | Severe | Very Severe |
|---|---|---|---|---|---|
| ☐1 | ☐2 | ☐3 | ☐4 | ☐5 | ☐6 |

5. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

| Not at all | A little bit | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|
| ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

6. **These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>...**

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a. Have you been very nervous? | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| b. Did you have a lot of energy? | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| c. Have you felt downhearted and depressed? | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

7. **During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?**

| All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|
| ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

***THANK YOU FOR COMPLETING THESE QUESTIONS!***

# APPENDIX B

## University of California San Diego Shortness of Breath Questionnaire

**UCSD MEDICAL CENTER**
**PULMONARY REHABILITATION PROGRAM**
**SHORTNESS-OF-BREATH QUESTIONNAIRE**

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Please rate the breathlessness you experience when you do, or if you were to do, each of the following tasks. **Do not skip any items**. If you've never performed a task or no longer perform it, give your best estimate of the breathlessness you would experience while doing that activity. Please review the two sample questions below before turning the page to begin the questionnaire.

**When I do, or if I were to do, the following tasks, I would rate my breathlessness as:**

| | |
|---|---|
| 0 | None at all |
| 1 | |
| 2 | |
| 3 | |
| 4 | Severe |
| 5 | Maximal or unable to do because of breathlessness |

1. Brushing teeth ..... 0 1 2 ③ 4 5

Harry has felt moderately short of breath during the past week while brushing his teeth and so circles a three for this activity.

2. Mowing the lawn ..... 0 1 2 3 4 ⑤

Anne has never mowed the lawn before but estimates that she would have been too breathless to do this activity during the past week. She circles a five for this activity.

**When I do, or if I were to do, the following tasks, I would rate my breathlessness as:**

| | |
|---|---|
| 0 | None at all |
| 1 | |
| 2 | |
| 3 | |
| 4 | Severe |
| 5 | Maximal or unable to do because of breathlessness |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1. | At rest | 0 | 1 | 2 | 3 | 4 | 5 |
| 2. | Walking on a level at your own pace | 0 | 1 | 2 | 3 | 4 | 5 |
| 3. | Walking on a level with others your age | 0 | 1 | 2 | 3 | 4 | 5 |
| 4. | Walking up a hill | 0 | 1 | 2 | 3 | 4 | 5 |
| 5 | Walking up stairs | 0 | 1 | 2 | 3 | 4 | 5 |
| 6. | While eating | 0 | 1 | 2 | 3 | 4 | 5 |
| 7. | Standing up from a chair | 0 | 1 | 2 | 3 | 4 | 5 |
| 8. | Brushing teeth | 0 | 1 | 2 | 3 | 4 | 5 |
| 9. | Shaving and/or brushing hair | 0 | 1 | 2 | 3 | 4 | 5 |
| 10. | Showering/bathing | 0 | 1 | 2 | 3 | 4 | 5 |
| 11. | Dressing | 0 | 1 | 2 | 3 | 4 | 5 |
| 12. | Picking up and straightening | 0 | 1 | 2 | 3 | 4 | 5 |

**When I do, or if I were to do, the following tasks, I would rate my breathlessness as:**

| | |
|---|---|
| 0 | None at all |
| 1 | |
| 2 | |
| 3 | |
| 4 | Severe |
| 5 | Maximal or unable to do because of breathlessness |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 13. | Doing dishes | 0 | 1 | 2 | 3 | 4 | 5 |
| 14. | Sweeping /vacuuming | 0 | 1 | 2 | 3 | 4 | 5 |
| 15. | Making bed | 0 | 1 | 2 | 3 | 4 | 5 |
| 16. | Shopping | 0 | 1 | 2 | 3 | 4 | 5 |
| 17. | Doing laundry | 0 | 1 | 2 | 3 | 4 | 5 |
| 18. | Washing car | 0 | 1 | 2 | 3 | 4 | 5 |
| 19. | Mowing lawn | 0 | 1 | 2 | 3 | 4 | 5 |
| 20. | Watering lawn | 0 | 1 | 2 | 3 | 4 | 5 |
| 21. | Sexual activities | 0 | 1 | 2 | 3 | 4 | 5 |

**How much do these limit you in your daily life?**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 22. | Shortness of breath | 0 | 1 | 2 | 3 | 4 | 5 |
| 23. | Fear of "hurting myself" by overexerting | 0 | 1 | 2 | 3 | 4 | 5 |
| 24. | Fear of shortness of breath | 0 | 1 | 2 | 3 | 4 | 5 |

# APPENDIX C

## Leicester Cough Questionnaire

This questionnaire is designed to assess the impact of cough on various aspects of your life. Read each question carefully and answer by CIRCLING the response that best applies to you. Please answer ALL questions, as honestly as you can.

1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | Hardly any of the time | None of the time |

2. In the last 2 weeks, have you been bothered by sputum (phlegm) production when you cough?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Every time | Most times | Several times | Some times | Occasionally | Rarely | Never |

3. In the last 2 weeks, have you been tired because of your cough?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | Hardly any of the time | None of the time |

4. In the last 2 weeks, have you felt in control of your cough?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| None of the time | Hardly any of the time | A little of the time | Some of the time | A good bit of the time | Most of the time | All of the time |

5. How often during the last 2 weeks have you felt embarrassed by your coughing?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | Hardly any of the time | None of the time |

6. In the last 2 weeks, my cough has made me feel anxious

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | Hardly any of the time | None of the time |

7. In the last 2 weeks, my cough has interfered with my job, or other daily tasks

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | Hardly any of the time | None of the time |

8. In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | Hardly any of the time | None of the time |

9. In the last 2 weeks, exposure to paints or fumes has made me cough

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | Hardly any of the time | None of the time |

10. In the last 2 weeks, has your cough disturbed your sleep?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | Hardly any of the time | None of the time |

11. In the last 2 weeks, how many times a day have you had coughing bouts?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| All of the time (continuously) | Most times during the day | Several times during the day | Some times during the day | Occasionally through the day | Rarely | None |

12. In the last 2 weeks, my cough has made me feel frustrated

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | Hardly any of the time | None of the time |

13. In the last 2 weeks, my cough has made me feel fed up

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | Hardly any of the time | None of the time |

14. In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | Hardly any of the time | None of the time |

15. In the last 2 weeks, have you had a lot of energy?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| None of the time | Hardly any of the time | A little of the time | Some of the time | A good bit of the time | Most of the time | All of the time |

16. In the last 2 weeks, have you worried that your cough may indicate serious illness?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | Hardly any of the time | None of the time |

17. In the last 2 weeks, have you been concerned that other people think something is wrong with you, because of your cough?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | Hardly any of the time | None of the time |

18. In the last 2 weeks, my cough has interrupted conversation or telephone calls

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Every time | Most times | A good bit of the time | Some of the time | A little of the time | Hardly any of the time | None of the time |

19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Every time I cough | Most times when I cough | Several times when I cough | Some times when I cough | Occasionally when I cough | Rarely | Never |

Thank you for completing this questionnaire.

# APPENDIX D

## Fatigue Severity Scale

The FSS questionnaire contains nine statements that attempt to explore severity of fatigue symptoms. Read each statement and circle a number from 1 to 7, depending on how appropriate they felt the statement applied to them over the preceding week. A low value indicates that the statement is not very appropriate whereas a high value indicates agreement (1 disagree, 7 agree).

| FSS Questionnaire | | | | | | | |
|---|---|---|---|---|---|---|---|
| **During the past week, I have found that:** | **Score** | | | | | | |
| 1. My motivation is lower when I am fatigued. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 2. Exercise brings on my fatigue. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 3. I am easily fatigued. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 4. Fatigue interferes with my physical functioning. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 5. Fatigue causes frequent problems for me. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 6. My fatigue prevents sustained physical functioning. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 7. Fatigue interferes with carrying out certain duties and responsibilities. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 8. Fatigue is among my three most disabling symptoms. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 9. Fatigue interferes with my work, family, or social life. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

The scoring is done by calculating the average response to the questions (adding up all the answers and dividing by nine).