QUANTITATIVE COMPUTED TOMOGRAPHY IN SYSTEMIC SCLEROSIS-
ASSOCIATED INTERSTITIAL LUNG DISEASE

by

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Quantitative computed tomography in systemic sclerosis-associated interstitial lung disease

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Abstract

Rationale: Systemic sclerosis (SSc) is frequently complicated by interstitial lung disease (ILD), which is associated with significant morbidity and mortality in this population. Measuring disease extent and progression of SSc-ILD is challenging, with recent studies suggesting potential utility of quantitative measurements from computed tomography (CT) scans. Our objective was to determine the associations of CT density-based measurements with physiological parameters, visual CT scores, and survival in patients with SSc-ILD.

Methods: Patients with SSc-ILD and volumetric high-resolution CT images with ≤1.25mm slice thickness were retrospectively identified. Cardiothoracic radiologists with >5 years’ experience produced visual CT scores of ground-glass, reticulation, and honeycombing, to the nearest 5%. Visual fibrosis scores were calculated as the sum of reticulation and honeycombing. CT density measurements included high attenuation areas (HAA), skewness, kurtosis, and mean lung attenuation (MLA), which were determined after excluding large airways and blood vessels. Associations of qCT measures with pulmonary physiology, visual CT scores, and mortality were analyzed using Spearman rank correlation and Cox regression.

Results: 502 CT scans and 1084 PFTs from 170 patients with SSc-ILD were included. Baseline HAA, skewness, kurtosis, and MLA were associated with FVC (p<0.001), DLCO (p≤0.001), and visual fibrosis scores (p≤0.004). Changes in the qCT variables also correlated with concurrent changes in FVC (p≤0.02), DLCO (p≤0.01), and visual fibrosis scores (p≤0.004). Associations with physiology measures and visual CT scores did not change after adjustment for age, sex, and pack-years. All four baseline qCT variables (p≤0.005), ΔHAA (p<0.001), Δkurtosis (p=0.04), and ΔMLA (p=0.006) predicted mortality on unadjusted analysis. ΔHAA and ΔMLA remained predictors of mortality after adjustment for visual CT scores. Changes in all four qCT variables remained independent predictors of survival after adjustment for baseline FVC, DLCO, and the ILD-GAP and SADL indices, but not when adjusting for changes in lung function.
Conclusion: CT density-based measures correlate with physiologic impairment and visual CT scores in patients with SSc-ILD. Baseline and change in CT density measurements predict mortality, but not with adjustment for pulmonary function measures, indicating that the clinical utility of more sophisticated qCT variables should be explored.
Lay Summary

Systemic sclerosis (SSc) is a rare condition of the immune system in which thickening of the tissues occurs in many parts of the body. These patients often develop interstitial lung disease (ILD), a progressive scarring disease of the lung that is a leading cause of death in SSc patients. The current methods of monitoring ILD are non-specific and difficult to measure. Recent advances in imaging analysis may allow a more precise assessment of disease severity.

We used automated computer algorithms to assess disease severity based on the lung density of computed tomography (CT) scans. We found that this computer-based approach predicts disease severity, progression, and survival in patients with SSc-ILD. The findings of our study support the use of this strategy as a complementary method of monitoring disease severity, which has significant implications for patient care and clinical trial design in SSc-ILD, along with the management of other ILD subtypes.
Preface

This thesis is based on work conducted at the Centre for Heart Lung Innovation at St. Paul’s Hospital, Vancouver, British Columbia. All of the work presented received ethical approval from the University of British Columbia Providence Health Care Research Ethics Board (H17-02556). At the time of thesis submission, Chapter 2 was also being prepared for submission to a peer-reviewed journal, although at the time of writing, the thesis was original and unpublished.

This thesis contains the work of Daniela Castillo Saldana, under the supervision of Dr. Christopher J. Ryerson, who designed the study protocol, provided access to patient records, oversaw all aspects of the project, and was involved in manuscript and thesis improvements. The author was primarily responsible for a comprehensive literature review, study design, ethics approval, data collection, statistical analysis, results interpretation, and manuscript preparation. Drs. Miranda Kirby, Cameron Hague, and Darra Murphy, members of the author’s thesis committee, along with Dr. Harvey Coxson, assisted with study design, data interpretation, and document improvements. VIDA Diagnostics, Inc. was involved in data processing and collection presented in Chapter 2.
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<th>Full Form</th>
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<tbody>
<tr>
<td>ACA</td>
<td>Anti-Centromere Antibodies</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>AMFM</td>
<td>Adaptive Multiple Feature Method</td>
</tr>
<tr>
<td>ANA</td>
<td>Anti-Nuclear Antibodies</td>
</tr>
<tr>
<td>Anti-Scl-70</td>
<td>Anti-topoisomerase I Antibodies</td>
</tr>
<tr>
<td>CALIPER</td>
<td>Computer-Aided Lung Informatics for Pathology Evaluation and Rating</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>CPI</td>
<td>Composite Physiologic Index</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CTD-ILD</td>
<td>Connective Tissue Disease-associated ILD</td>
</tr>
<tr>
<td>CYC</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>dcSSc</td>
<td>diffuse cutaneous Systemic Sclerosis</td>
</tr>
<tr>
<td>DLCO</td>
<td>Diffusing Capacity of the Lungs for Carbon Monoxide</td>
</tr>
<tr>
<td>DTA</td>
<td>Driven Textural Analysis</td>
</tr>
<tr>
<td>FDA</td>
<td>United States Food and Drug Administration</td>
</tr>
<tr>
<td>FEV₁</td>
<td>Forced Expiratory Volume in One Second</td>
</tr>
<tr>
<td>FRI</td>
<td>Functional Respiratory Imaging</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced Vital Capacity</td>
</tr>
<tr>
<td>GGR</td>
<td>Ground-Glass and Reticular densities</td>
</tr>
<tr>
<td>GRCS</td>
<td>Global Rank Composite Score</td>
</tr>
<tr>
<td>HAA</td>
<td>High Attenuation Areas</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>Health Assessment Questionnaire Disability Index</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>HP</td>
<td>Hypersensitivity Pneumonitis</td>
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<tr>
<td>HU</td>
<td>Hounsfield Unit</td>
</tr>
<tr>
<td>ILD</td>
<td>Interstitial Lung Disease</td>
</tr>
<tr>
<td>IPF</td>
<td>Idiopathic Pulmonary Fibrosis</td>
</tr>
<tr>
<td>lcSSc</td>
<td>limited cutaneous Systemic Sclerosis</td>
</tr>
<tr>
<td>MLA</td>
<td>Mean Lung Attenuation</td>
</tr>
<tr>
<td>MMF</td>
<td>Mycophenolate Mofetil</td>
</tr>
<tr>
<td>mRSS</td>
<td>modified Rodnan Skin Score</td>
</tr>
<tr>
<td>NL</td>
<td>Normal Lung</td>
</tr>
<tr>
<td>NSIP</td>
<td>Nonspecific Interstitial Pneumonitis</td>
</tr>
<tr>
<td>PF-ILD</td>
<td>Progressive Fibrosing ILD</td>
</tr>
<tr>
<td>PFT</td>
<td>Pulmonary Function Test</td>
</tr>
<tr>
<td>PVV</td>
<td>Pulmonary Vessel Volume</td>
</tr>
<tr>
<td>qCT</td>
<td>quantitative Computed Tomography</td>
</tr>
<tr>
<td>QIBA</td>
<td>Quantitative Imaging Biomarkers Alliance</td>
</tr>
<tr>
<td>QILD</td>
<td>Quantitative Interstitial Lung Disease</td>
</tr>
<tr>
<td>QLF</td>
<td>Quantitative Lung Fibrosis</td>
</tr>
<tr>
<td>ROI</td>
<td>Region Of Interest</td>
</tr>
<tr>
<td>RV</td>
<td>Residual Volume</td>
</tr>
<tr>
<td>RVSP</td>
<td>Right Ventricular Systolic Pressure</td>
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<tr>
<td>SCOT</td>
<td>Scleroderma: Cyclophosphamide Or Transplantation</td>
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<tr>
<td>SGRQ</td>
<td>St. George’s Respiratory Questionnaire</td>
</tr>
<tr>
<td>SLS-I</td>
<td>Scleroderma Lung Study I</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>SLS-II</td>
<td>Scleroderma Lung Study II</td>
</tr>
<tr>
<td>SSc</td>
<td>Systemic Sclerosis</td>
</tr>
<tr>
<td>SSc-ILD</td>
<td>Systemic Sclerosis-associated Interstitial Lung Disease</td>
</tr>
<tr>
<td>TDI</td>
<td>Transitional Dyspnea Index</td>
</tr>
<tr>
<td>TLC</td>
<td>Total Lung Capacity</td>
</tr>
<tr>
<td>UIP</td>
<td>Usual Interstitial Pneumonitis</td>
</tr>
<tr>
<td>VOI</td>
<td>Volume Of Interest</td>
</tr>
<tr>
<td>VRS</td>
<td>Vessel-Related Structures</td>
</tr>
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</table>
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I offer my enduring gratitude to my supervisor, Dr. Ryerson, for his guidance throughout my graduate studies. I express my sincere appreciation for his invaluable mentorship, kind patience, and expert advice that have not only made this work possible but contributed tremendously to my professional growth.

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Lastly, special thanks are owed to my friends and family, I will forever be in debt to the love and support you have provided me with throughout the years.
Dedication

To my family for their endless support and encouragement.
Chapter 1: Introduction

This introduction provides a comprehensive overview of systemic sclerosis-associated interstitial lung disease (SSc-ILD), measures of disease severity and progression in SSc-ILD, the use of CT density and texture-based measurements to predict health outcomes in ILD, and semi-automatic structural segmentations from computed tomography (CT) scans.

This thesis includes a research chapter based on a large retrospective cohort investigating the use of computer-based methods to measure disease severity on CT scans of patients with SSc-ILD. Chapter 2 explores the baseline associations of quantitative CT (qCT) measures with baseline pulmonary function, visual CT scores, and survival. Chapter 2 also investigates the associations of annual changes in qCT with concurrent changes in pulmonary physiology and visual CT scores, along with the prognostic ability of change in qCT measures. Chapter 3 serves to provide overall conclusions and significance of the work presented, in addition to future directions in the context of current research in the field of qCT.

1.1 Overview of SSc-ILD

1.1.1 Interstitial lung disease (ILD)

ILD includes over 200 diseases characterized by inflammation and fibrosis of the pulmonary interstitium. Idiopathic pulmonary fibrosis (IPF) is the best characterized and most common fibrotic ILD,\(^1\) with a significantly worse survival compared to other subtypes, such as fibrotic hypersensitivity pneumonitis (HP), connective tissue disease-associated ILD (CTD-ILD), and idiopathic nonspecific interstitial pneumonia (NSIP).\(^2\) ILD subtypes are difficult to distinguish due to their overlapping clinical, radiological, and histopathological features,\(^1\) with these heterogenous characteristics reflecting the complex pathogenesis of the disease.

Patients with fibrotic ILD experience unpredictable but typically progressive fibrosis that often results in organ failure and death.\(^3\) Pulmonary function testing in ILD reveals restrictive physiology and impaired gas exchange, with reduced forced expiratory volume in 1 second.
(FEV$_1$), forced vital capacity (FVC), and diffusion capacity of the lung for carbon monoxide (DLCO). Patients generally present with exertional dyspnea, nonproductive cough, impaired functional capacity, and decreased quality of life.

### 1.1.2 Systemic sclerosis (SSc)

SSc is a chronic autoimmune disease characterized by dysregulation of fibroblasts resulting in an overproduction of collagen and deposition of connective tissue in many organs. There are two major subgroups of scleroderma: limited cutaneous and diffuse cutaneous scleroderma. The hands, face, and lower arms and legs can be affected in limited cutaneous scleroderma (lcSSc). In diffuse cutaneous scleroderma (dcSSc), extensive internal organ involvement occurs in addition to skin disfigurement.

### 1.1.3 SSc-ILD

Pulmonary involvement is common in SSc, including ILD, which can occur in both diffuse and limited cutaneous disease. ILD is diagnosed in patients with SSc when there is radiographic evidence of diffuse parenchymal disease. ILD is a significant contributor to morbidity and a leading cause of mortality in SSc. Epidemiological data of SSc has not been reported in Canada. In the United States, SSc incidence is estimated at 50-300 cases per million, predominantly occurring in women between 30-55 years old and with 25-90% of patients developing ILD depending on diagnostic criteria. Prognostication in SSc-ILD is difficult given its highly variable disease course, with previous cohorts reporting a median survival between 5 and 15 years.

SSc-ILD has few effective and well tolerated treatment options. Immunosuppressants are currently being used as the leading pharmacotherapy in SSc-ILD; however, they are costly, have limited benefits, and have potential for significant toxicity. There have been three main clinical trials in SSc-ILD: Scleroderma Lung Study (SLS-I), Scleroderma Lung Study II (SLS-II), and SENSCIS trial. SLS-I is a randomized, double blind, placebo-controlled study that investigated the efficacy and safety of cyclophosphamide (CYC) on the
progression of ILD in patients with SSc. SLS-I found that cyclophosphamide improved both lung function and dyspnea severity compared to placebo. With a similar study design, SLS-II compared the efficacy and safety of CYC to mycophenolate mofetil (MMF) in patients with SSc-ILD. SLS-II found that MMF had less toxicity compared to CYC, while comparably improving lung function from baseline. Both studies included change in FVC as the primary outcome and change in total lung capacity (TLC) and DLCO as secondary outcomes. Additional secondary endpoints were included in SLS-II: computer-based score of lung fibrosis and ILD on CT, Transitional Dyspnea Index (TDI), modified Rodnan Skin Score (mRSS), Health Assessment Questionnaire Disability Index (HAQ-DI), toxicity, and tolerability. The TDI measured change in breathlessness while mRSS assessed skin thickness. The HAQ-DI is a self-reported questionnaire of functionality that includes questions in 8 activity domains (dressing, arising, eating, walking, hygiene, reach, grip, and common daily activities). Toxicity was measured by frequency of adverse events and death, and tolerability by time to withdrawal from the study drug or treatment failure. Lower TDI scores and higher mRSS, HAQ-DI, and quantitative lung fibrosis and ILD scores indicated worse disease severity. SLS-II found improvements in TDI, mRSS, and quantitative ILD scores in both CYC and MMF treatment groups. The SENSCIS trial investigated the efficacy and safety of nintedanib in patients with SSc-ILD. Nintedanib is an antifibrotic medication that slows the rate of lung function decline in IPF. The primary endpoint was change in FVC and key secondary endpoints included changes in mRSS and the St. George’s Respiratory Questionnaire (SGRQ). The SGRQ includes three domains (symptoms, activity, and impact) that evaluate health-related quality of life in patients with respiratory disease. The SENCSIS trial found that nintedanib improved lung function compared to placebo but found no differences in mRSS and SGRQ between trial groups. The SENSCIS study also found greater preservation of lung function in patients who were receiving MMF in the nintedanib group compared to those who were not. These findings have important implications for the use of antifibrotic therapy in other fibrotic ILDs, which is currently being investigated in the ongoing INBUILD trial, where the efficacy and safety of nintedanib is being assessed in patients with Progressive Fibrosing ILD (PF-ILD).
The Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial examined the impact of stem-cell transplantation compared to high-dose CYC for the treatment of severe SSc,\(^2\) with 97% of patients in this study having ILD. The SCOT trial used the Global Rank Composite Score (GRCS) as the primary outcome, a score reflecting a participant’s order relative to other participants based on a hierarchy of outcomes: death, event-free survival, FVC, HAQ-DI, and mRSS. This study found that event-free and overall survival was improved with stem-cell transplantation compared to cyclophosphamide; however, at a cost of increased toxicity.

1.1.4 Radiographic features

The most common radiological patterns of ILD are usual interstitial pneumonia (UIP), NSIP, and HP. Typical features of UIP on CT include honeycombing, traction bronchiectasis, and traction bronchiolectasis, with minimal ground-glass.\(^1\) The typical distribution of UIP is subpleural with basal predominance.\(^1\) Honeycombing is defined as clustered cystic airspaces with thick, well-defined walls.\(^2\) Traction bronchiectasis/bronchiolectasis refers to the non-tapering of the bronchial/bronchiolar wall.\(^2\) Ground-glass opacification is defined as hazy increased opacity of the lung with preservation of bronchial and vascular margins.\(^2\) NSIP carries a better prognosis compared to UIP and its predominant features include ground-glass and reticulation, where subpleural sparing helps in distinguishing it from UIP.\(^3\)\(^,\)\(^2\) HP is frequently difficult to distinguish from UIP radiographically, but the presence of centrilobular nodules, mosaic air-trapping and upper-lobe distribution can aid their differentiation.\(^3\)\(^,\)\(^2\)

Although guidelines exist for the diagnosis of IPF (i.e., idiopathic UIP),\(^1\) there is an absence of diagnostic criteria for idiopathic NSIP and HP. In the majority of patients with SSc-ILD, the radiological phenotype is most commonly characterized by an NSIP pattern, with ground-glass opacities as a dominant feature.\(^3\)\(^,\)\(^2\)\(^,\)\(^2\) It remains poorly understood how these characteristic patterns progress on CT, which is the standard imaging tool used in the diagnosis and management of ILD. In particular, it remains unknown whether pure ground-glass represents reversible inflammation that may improve with time or immunosuppressive
medication. Ground-glass admixed with fibrosis is thought to represent micro-fibrosis, although it is unknown how quickly the transition into fibrosis occurs. Novel CT techniques are needed to address these questions and accurately assess disease progression in ILD.

1.2 Measures of disease severity and progression in SSc-ILD

1.2.1 Physiology measures

Measuring disease severity and progression of SSc-ILD is commonly done using pulmonary function tests (PFTs). FVC is the amount of air that can be forcibly exhaled after a full breath. FVC is the primary endpoint in most SSc-ILD clinical trials, with rates of change in FVC used to measure disease progression. Although FVC is a readily available, non-invasive, non-radiation-based method of measuring disease severity, it is influenced by multiple factors, such as inspiratory effort and respiratory muscle weakness, that reduce its specificity for monitoring disease. Due to its high variability, FVC is insensitive to subtle changes in disease progression and response to therapy within individual patients. DLCO indirectly measures the ability of the lungs to transfer oxygen from inhaled air into the blood. There is recent evidence suggesting DLCO provides a better estimate of outcome and disease extent on CT in patients with SSc-ILD; however, DLCO shares the same limitations as FVC. In addition to these limitations in FVC and DLCO, PFTs are commonly normal in early disease and often contradictory to patient symptoms, where patients often experience worsening symptoms with minimal changes in their functional indices, or vice versa. For these reasons, there is increasing consensus among members of the respiratory community that patient history and lung function testing is not sufficient for the monitoring of ILD.

1.2.2 CT

CT has been proposed as a more sensitive and reliable measure of ILD as it has the potential to capture the spatial processes of the disease rather than just providing a single summary value like FVC or DLCO. In clinical practice, CT is used to evaluate patients with diffuse lung disease and characterize ILD subtypes, playing a key role in treatment decisions and
prognostication. The recommended scanning protocol for fibrotic ILD includes a non-contrast examination acquired at full inspiration and reconstructed using a high-spatial-frequency algorithm with contiguous or overlapping thin-section images (≤1.5mm), which allow minimization of partial volume effects. Reducing motion artifacts and using consistent acquisition parameters is crucial for minimizing image noise and obtaining accurate image analysis. Expiratory scans can also be useful for detecting air trapping, and prone scans for differentiating dependent change from early posterior subpleural fibrosis.

1.2.3 Visual CT scoring

In a clinical care setting, expert radiologists visually analyze CT scans to identify lung abnormalities and qualitatively assess disease burden. Previous studies have also used visual assessments to quantify disease severity on CT. Scores of radiological patterns are produced by radiologists typically to the nearest 5% in 3-5 regions of each lung. Several studies have demonstrated that visual CT scores show a greater sensitivity for the detection of early ILD compared to FVC and predict disease progression and mortality. However, these visual scores are associated with significant intra- and inter-observer variability due to a lack of agreement on the methods to quantify disease. The absence of standardized quantification criteria results in underestimation of radiological findings in mild disease and overestimation in severe disease. In addition to the subjective nature of these semi-quantitative scores, the manual process is too tedious to incorporate into routine clinical practice. The contraction of densely fibrotic regions and compensatory expansion of normal areas of the lung as ILD progresses may also result in visual CT scores remaining the same over time. Visual CT scoring therefore has a limited application in patient care and clinical trials due to the availability of expert radiologists, its time-consuming quality, and low inter- and intra-observer agreement.

1.2.4 Quantitative CT scoring

qCT has been proposed as a method of providing a more precise and sensitive assessment of ILD severity by measuring the density of discrete regions (voxels) of the lung in Hounsfield
units (HU), the standard unit of measure for density attenuation.\textsuperscript{53} qCT increases the ability of measuring early or subtle changes in disease progression by measuring lung density, as a surrogate of disease severity, in hundreds of thousands to millions of voxels per lung.\textsuperscript{54} There is growing evidence that qCT may be a useful tool for characterizing lung abnormalities and monitoring disease.\textsuperscript{53,55} qCT overcomes the limitations of visual CT scores by being an objective and reliable measure of disease severity\textsuperscript{56,57} and correlates more strongly with PFTs.\textsuperscript{32,58,59} For these reasons, qCT has been increasingly used in research as a reproducible and efficient measure of disease burden compared to other outcome measures.

1.2.5 Mortality prediction tools

Other methods of assessing prognosis include composite models that use demographic and clinical variables to predict mortality. The ILD-GAP Index predicts mortality in a variety of ILD subtypes based on gender, age, and lung physiology (FVC and DLCO),\textsuperscript{2} estimating risk of mortality at 1, 2, and 3 years. The ILD-GAP model was created by adding an ILD subtype variable to the GAP model,\textsuperscript{60} a mortality prediction tool that was derived and validated in IPF. The SADL model is used to predict mortality in patients with SSc-ILD, and is based on smoking history, age, and DLCO.\textsuperscript{61} Similar to the GAP indices, the SADL model also provides 1-, 2-, and 3-year mortality risks, and has comparable overall prognostic ability.

1.3 CT density and texture-based measurements

1.3.1 Density-based qCT

Densitometric techniques use the distribution of voxel densities to estimate disease severity. The whole lung CT density histogram allows the measurement of mean lung attenuation (MLA), kurtosis, skewness, variance, entropy, and percent high attenuation areas (HAA). Kurtosis and skewness describe the shape of the density distribution curve, with kurtosis referring to the sharpness or peakedness of the histogram, and skewness reflecting the degree of asymmetry.\textsuperscript{62} In ILD, the density distribution shifts to the right (towards a normal distribution) with increasing disease, resulting in higher attenuation values in more diseased
lungs (Figure 1.1). As a result, the skewness and kurtosis of the histogram decrease, while MLA and HAA increase.

Normal lung on CT is defined by a density between -950 and -701 HU.\textsuperscript{63} Regions of the lung with an x-ray attenuation above -700 HU are consistent with interstitial lung disease\textsuperscript{64,65} with HAA commonly categorized between -600 and -250 HU and thought to represent ground-glass opacities and fibrosis\textsuperscript{66-68} (Figure 1.2). Classifications of ground-glass vary, with studies citing ranges between -750 and -174 HU.\textsuperscript{69,70} Regions below -950 HU are considered emphysematous, which has been validated with histology-based studies.\textsuperscript{71} Density masks can be applied to CT images to extract regions that fall between specific thresholds, with the amount of lung containing the radiological pattern of interest expressed as a percentage of total lung volume.\textsuperscript{72} The 85\textsuperscript{th} percentile from the density histogram has also been investigated as a measure of disease severity in ILD,\textsuperscript{73,74} and is defined as the density value at which 85 percent of voxels have an attenuation below it. Voxel-based histogram analyses have also been used in ILD;\textsuperscript{75} however, these measures have only been used for the classification of image patches. Further studies are needed to determine the physiologic and prognostic significance of local histogram information and to follow these measures over time.

Associations between density histogram features and health outcomes have been described in multiple ILD subtypes, demonstrating their potential utility in monitoring disease severity and progression.\textsuperscript{75-80} These qCT indices correlate more strongly with pulmonary function measures and better predict mortality compared to visual scores.\textsuperscript{47,79,81,82} Changes in these qCT parameters also indicate disease progression and correlate with physiological decline in IPF;\textsuperscript{83,84} however, there are no current studies investigating correlations of changes in these densitometric measures with survival in ILD.

1.3.2 Texture-based qCT

More sophisticated qCT measures use the density of voxels in addition to their spatial distributions to quantify disease severity and identify abnormalities.\textsuperscript{75,85,86} This higher-order
The Adaptive Multiple Feature Method (AMFM) is a texture-based analysis that characterizes and quantifies radiological patterns on CT. AMFM in ILD was trained using volumes of interest (VOIs) labeled by experts as honeycombing, ground-glass, combined ground-glass and reticular densities (GGR), bronchovascular, emphysema, or normal. AMFM software provides proportions of lung parenchyma volume containing each pattern based on the number of VOIs assigned to each feature category. Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER) is a more recent texture analysis tool that combines local histogram analysis of individual voxels with morphological analysis to identify and quantify parenchymal patterns. CALIPER was trained using expert-labeled VOIs in pathologically confirmed ILD: normal, emphysematous, ground-glass, reticulation, or honeycombing. Quantitative lung fibrosis (QLF), together with quantitative honeycombing, ground-glass, and a composite ILD score (QILD), are texture features derived from expert-labeled regions of interest (ROIs). In the training phase of the QLF classifier, ROIs from airways, fissures, and vessels were included as normal lung. Data-Driven Textural Analysis (DTA) was developed using unsupervised feature learning, which uses an initial clustering analysis to learn features from unlabeled images. Unsupervised feature learning differs from the more traditional approach, where features are manually calculated using statistical or image processing computations. ROIs containing characteristic fibrotic patterns of UIP were delineated by expert radiologists. Features within the ROIs were produced using the outputs from the initial clustering analysis, allowing DTA to classify
novel regions as either fibrotic or non-fibrotic. DTA provides a fibrosis score as the proportion of fibrotic ROIs.

1.3.3 Limitations of qCT

Several limitations of computer-based quantification of disease severity exist that have hindered incorporation of qCT into clinical trials and practice. First, a significant amount of human input is required to process each CT scan prior to the generation of qCT scores. Trained analysts are often required to verify the semi-automatic lung, airway, and vessel segmentations. Moreover, both density and texture-based analyses are affected by the technical parameters used to obtain CT images. Further limitations of qCT include cost and radiation exposure in comparison to others measures of disease severity and progression (i.e. PFTs, patient-reported outcomes).

1.3.3.1 Semi-automatic segmentation of non-parenchymal structures

Lung extraction is required to separate the lung parenchyma from surrounding structures. Lung segmentation can be achieved using optimal thresholding, which uses automatic selection of an optimal density range for a given image volume to allow for slight variability in density across scans. The voxels within the lung are separated from voxels of similar density in a CT scan (i.e., air surrounding the body, interior cavities) through the analysis of voxel connectivity. The large pulmonary vessels can be excluded from the lung mask through gray-level processing or they can be segmented using a tubular structure enhancement filter based on the Hessian matrix that determines the likelihood of voxels belonging to a dense tubular structure.

Segmentation of the large airways must also be done in order to perform quantitative analysis of the lung parenchyma. The airways can be automatically segmented using grey-level thresholding and a 3D region growing process. First, automatic identification of a seed point occurs in the luminal area of the trachea. New neighboring voxels are added to the seed point region if they have similar densities. Limits to the differences in density are selected so
that the growing region is able to overcome subtle changes in attenuation while also avoiding inaccurate airway segmentation. Voxel connectivity is also analyzed to prevent non-luminal regions in the reconstruction. The segmented airway may contain false branches as a result of leaking, where similarities in attenuation can cause a luminal voxel to discontinue out of the airway border. The seed growing algorithm leaks into the lungs when discontinuity of an airway wall occurs as a result of a loss in resolution or increased noise on a CT image. Stricter thresholds for the addition of neighboring voxels can be used to minimize leaking. Leak detection algorithms can be used to reduce the risk of artifactual measurement and include deletion of terminal edges that are less than a predefined threshold length.

Following airway segmentation, the centerlines of branches are found by symmetrically deleting border points on each side of an airway until no more points can be removed. The remaining centerline consists of a one voxel thick, n-connected central axis. Skeletonization allows identification of the airway tree branchpoints when a bifurcation occurs (Figure 1.3). The branchpoints can then be used to label the major airways, segment the lung lobes, and separate the left and right lung (Figures 1.4, 1.5).

Commercially available software makes the segmentation process a widely applicable analysis. For example, VIDA vision, the software used to process CT data in this thesis, has been approved by the United States Food and Drug Administration (FDA) for clinical use, which allows utilization of segmentation software for virtual bronchoscopy-guided biopsy or monitoring of airway disease. Although an accessible tool, the segmentation process remains limited by the need of analysts to not only confirm the segmentation outputs but also troubleshoot processing complications that occur with scans that have non-compatible parameters.

1.3.3.2 Technical parameters

HU accuracy is influenced by radiation dose, slice thickness, and reconstruction algorithms, all of which vary with the use of different scanners and clinical protocols. However,
several qCT methods are robust against varying acquisition parameters. Functional Respiratory Imaging (FRI) techniques improve disease quantification through enhanced visualization of anatomical structures using computer-based flow simulations, which includes respiratory gating through the use of a handheld spirometer during scan acquisition. FRI reduces variability in airway volumes, blood vessel volumes, and airway resistances. QLF analyses also include a denoising step prior to the calculation of texture features to improve robustness against varying slice thickness, reconstruction kernels, and radiation dose. However, a challenge remains in training of these texture-based approaches, where standardized image quality is required for accurate feature learning.

1.3.3.3 Addressing the limitations

Likely due to these limitations, regulatory bodies have yet to approve the use of qCT for ILD quantification in clinical trials or patient management. The Radiological Society of North America has created a Quantitative Imaging Biomarkers Alliance (QIBA) in an attempt to address the factors that currently hinder the routine use of qCT. They are in the process of completing a CT protocol for asthma, ILD, and chronic obstructive pulmonary disease (COPD), which includes a recommended lung density profile. This standardization will support further use of qCT in clinical and research settings.

Despite the current limitations, findings suggest the potential use of qCT as a complementary or alternative measure of disease severity and progression in clinical trials and practice. The use of qCT in clinical trials would increase statistical power through the measurement of disease severity in regional voxels, allowing a potential reduction in study size or duration. The increased ability of qCT to detect subtle changes in progression thus provides a sensitive endpoint in evaluating response to novel therapies, along with assisting in the identification of patients at an increased risk of progression or with the early diagnosis of ILD, which is needed to improve the prognosis of the disease. The clinical application of qCT can also be extended to the management and prognostication of other ILD subtypes.
1.4 Summary

The objective of this study was to investigate whether CT density-based measures correlate with different health outcomes in SSc-ILD. We were also interested in exploring whether these density-based scores were more prognostically useful than other measures of outcome in SSc-ILD.

1.5 Specific aims

To achieve our objective, our specific aims included:

1. To determine the relationship between baseline CT density histogram properties and concurrent physiological parameters, visual CT scores, and mortality in patients with SSc-ILD.

2. To determine the relationship between changes in CT density histogram properties and worsening physiological parameters, visual CT scores, and mortality in patients with SSc-ILD.

1.6 Hypotheses

1. Higher MLA and HAA and lower skewness and kurtosis are each independently associated with lower pulmonary function values, and greater visual CT scores and risk of mortality.

2. Worsening HAA, MLA, skewness, and kurtosis are each independently associated with pulmonary function decline, and worse visual CT scores and survival.
Chapter 2: Predicting disease severity, functional decline, and survival using computed tomography densitometry in systemic sclerosis-associated interstitial lung disease

2.1 Introduction

SSc is a chronic autoimmune disease characterized by an overproduction of collagen and deposition of connective tissue.\textsuperscript{113} ILD is a major contributor to morbidity and a leading cause of mortality in patients with SSc.\textsuperscript{6} FVC is the primary method of measuring disease severity and progression in both clinical and research settings; however, FVC and other pulmonary function measurements have significant limitations in precisely monitoring disease.\textsuperscript{32,48}

CT can provide a spatial distribution of disease severity. Previous studies have used visual estimates of ILD severity and found that these qualitative assessments have high intra- and inter-observer variability.\textsuperscript{52,81,114} Additional studies have recently suggested the potential utility of quantitative measurements from CT images.\textsuperscript{32,53} For example, density-based analyses use the density of discrete regions of lung (voxels) to measure disease extent on CT images, which correlates with health outcomes in several fibrotic ILD subtypes.\textsuperscript{81,32,115} The objective of this study was to investigate the associations of CT density-based measurements with physiological parameters, visual CT scores, and survival in patients with SSc-ILD.

2.2 Methods

2.2.1 Study cohort

SSc-ILD patients with at least one evaluable CT were retrospectively identified from a single-center prospective ILD registry. All patients provided written informed consent (UBC H10-03435) and had an American College of Rheumatology (ACR) diagnosis of SSc confirmed by a rheumatologist.\textsuperscript{113} The date of ILD diagnosis was defined as the first CT evidence of ILD related to SSc.
2.2.2 Image acquisition and CT eligibility

All included CTs were volumetric high-resolution scans (slice thickness ≤1.25mm) that were performed without contrast in the supine position at full inspiration and reconstructed with a sharp kernel. Exclusion criteria included visual extent of emphysema >10% of total lung volume, CTs taken after lobectomy or pneumonectomy, and CTs demonstrating an acute non-fibrotic ILD abnormality (e.g., exacerbation, acute or chronic infection, pulmonary edema, pleural effusion). The baseline scan was defined as the first CT that was acceptable for quantitative analysis.

2.2.3 CT quantitative scoring

De-identified CTs were evaluated using the VIDA Vision software package (VIDA Diagnostics Inc.). Image processing included automatic detection of the major airways and blood vessels, airway branchpoints, lungs, and lobes. Major blood vessels and five orders of bronchi (up to the subsegmental bronchi) were excluded from the lung masks.

Within the lung masks, voxels were identified with a precision of at least 0.7mm, allowing each CT to be divided into an average of approximately 1,500,000 voxels per lung. Density was measured within each voxel to produce whole lung density histograms, from which MLA, skewness, kurtosis, and HAA were obtained.

Skewness and kurtosis describe the shape of the density distribution curve, with skewness indicating the degree of asymmetry and kurtosis referring to the peakedness of the histogram. HAA was defined as the number of voxels between -600 and -250 HU, representing both ground glass and fibrosis, divided by the total number of voxels in the lung x100. In ILD, the density distribution shifts to the right with increasing disease severity, resulting in higher attenuation values in more diseased lung. Normal lung has a mean density of approximately -800 HU, while higher kurtosis values generally indicate mild fibrosis and a kurtosis close to or below 0 indicates more severe fibrosis. With advancing ILD, HAA and MLA increase, while kurtosis and skewness decrease and approach 0.
2.2.4 CT visual scoring

CTs were visually scored as part of an unrelated study by one of two cardiothoracic radiologists, each with >5 years of experience. Both lungs were divided into 3 anatomical zones: upper (above right superior pulmonary vein ostia), middle (right superior pulmonary vein ostia to lower margin of right inferior pulmonary vein), and lower (below the lower margin of the inferior pulmonary vein). Percentages of ground glass, honeycombing, and reticulation were recorded in each zone to the nearest 5%. Visual fibrosis scores were calculated as the averaged sum of reticulation and honeycombing across the 6 zones.

2.2.5 Other measurements

PFTs were performed approximately every 6 months or as clinically indicated, including spirometry (FVC, FEV\textsubscript{1}), lung volumes (TLC, residual volume [RV]), and DLCO. Lung function data were considered concurrent with a CT if obtained within 3 months of the scan. For the longitudinal PFT analysis, lung function measures were included if taken between the baseline CT (-3 months) and the last CT (+3 months) for a given patient. Age, sex, smoking status, and smoking pack-years were obtained from patient records. A serology panel included anti-nuclear antibodies (ANA), anti-topoisomerase I antibodies (anti-Scl-70), and anti-centromere antibodies (ACA). The ILD-GAP and SADL models were calculated as previously described.

2.2.6 Statistical analysis

Data are described as mean±standard deviation, median (interquartile range), or number (percent). Spearman rank correlation was used to examine the relationships between the four qCT variables. Annual rate of change was calculated for HAA, skewness, kurtosis, MLA, visual fibrosis scores, FVC, and DLCO by finding the annual slope from the corresponding lines of best fit. Multivariable linear regression was used to determine the association of baseline qCT with concurrent lung function measurements and visual fibrosis scores. FVC, FEV\textsubscript{1}, TLC, RV, DLCO and visual fibrosis scores were each used as an outcome variable in separate models, with the predictor variables in each model including HAA, skewness,
kurtosis, and MLA. Age, sex, smoking pack-years, and disease duration were tested in each model as potential confounders. Associations of each qCT variable with DLCO were also adjusted for ACA and echocardiographic right ventricular systolic pressure (RVSP) in order to account for the possibility of a distinct disease phenotype predisposing to concurrent pulmonary vascular disease. Similar multivariable linear regressions were performed to investigate the correlations between changes in qCT (ΔHAA, Δskewness, Δkurtosis, ΔMLA) and changes in pulmonary physiology (ΔFVC, ΔDLCO) and visual fibrosis scores (Δfibrosis), with adjustments for age, sex, and smoking pack-years (plus ACA and RVSP only for ΔDLCO). Cox proportional hazards analysis was used to determine the prognostic utility of both baseline and change in qCT. HAA, skewness, kurtosis, MLA, ΔHAA, Δskewness, Δkurtosis, and ΔMLA were each evaluated for potential association with time to death, adjusting for age, sex, smoking pack-years, ACA and RVSP, with lung transplantation treated as a competing risk. Additional confounders were tested for in separate models including the ILD-GAP index, the SADL model, baseline PFTs, baseline fibrosis scores, changes in PFTs measurements, and Δfibrosis. Weak, moderate, and strong correlations were defined by absolute values of r coefficients (|r|): 0.2-0.39, 0.40-0.59, and 0.6-0.79, respectively. P-values <0.05 were considered significant. All analyses were performed with R Statistical Software 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

2.3 Results

2.3.1 Patient characteristics at baseline

A total of 1302 CTs from 206 patients with SSc-ILD were screened for potential eligibility from June 1997 to April 2018. The final study population included 170 patients with 503 CTs eligible for quantitative analysis and 1084 PFTs. Patients were followed for up to 19.6 years after diagnosis (median 7.2 years). A total of 52 patients were deceased at the time of data analysis and 3 patients underwent lung transplant. Median survival was 13.5 years from time of diagnosis (Figure 2.1). Baseline characteristics are summarized in Table 2.1.

A total of 370 CTs from the 1302 scans were visually scored, of which 150 were also eligible for quantitative analysis, including 71 baseline CTs. HAA, skewness, kurtosis, and MLA
were very strongly correlated with one another (|r| ≥ 0.84, p < 0.001 for all), with skewness and kurtosis having the strongest association (r = 0.98).

2.3.2 Association of qCT with pulmonary function

Associations of baseline HAA, skewness, kurtosis, and MLA with baseline pulmonary function are shown in Figure 2.2. HAA and MLA correlated negatively with all pulmonary function measurements, while skewness and kurtosis correlated positively. On unadjusted analysis, all four qCT scores were moderately associated with FVC, FEV₁, TLC, and RV, and weakly correlated with DLCO (Table 2.2). HAA, skewness, kurtosis, and MLA remained associated with pulmonary function measurements after adjustment for age, sex, pack-years, and disease duration.

Associations of changes in HAA, skewness, kurtosis, and MLA with changes in pulmonary function are shown in Figure 2.3. On unadjusted analysis, changes in the qCT measures all correlated with ΔFVC and ΔDLCO, except for ΔHAA with ΔFVC. ΔHAA and ΔMLA correlated negatively with change in pulmonary function measurements, while Δskewness and Δkurtosis correlated positively. All correlations of qCT variables with ΔFVC and ΔDLCO were weak, with the exception of a moderate association between ΔMLA and ΔDLCO. ΔHAA, Δskewness, Δkurtosis, and ΔMLA were associated with ΔFVC and ΔDLCO after adjustment for age, sex, and pack-years (Table 2.3).

2.3.3 Association of qCT with visual CT scores

Associations of baseline HAA, skewness, kurtosis, and MLA with baseline visual fibrosis scores are shown in Figure 2.2. Visual fibrosis score was positively correlated with HAA and MLA and negatively correlated with skewness and kurtosis. All associations were moderate (|r| = 0.42-0.55) excluding HAA, which was weakly correlated. Ground glass was not correlated with any of the qCT variables. HAA, skewness, kurtosis, and MLA remained associated with visual fibrosis scores after adjustment for age, sex, pack-years, and disease duration (Table 2.4).
The association of changes in HAA, skewness, kurtosis, and MLA with changes in visual fibrosis scores are shown in Figure 2.3. ΔFibrosis correlated positively with ΔHAA and ΔMLA and negatively with Δskewness and Δkurtosis, with all correlations being moderate in strength. ΔHAA, Δskewness, Δkurtosis, and ΔMLA remained associated with concurrent changes in visual fibrosis scores after adjustment for age, sex, and pack-years (Table 2.3).

2.3.4 Ability of qCT to predict progression and mortality

Baseline HAA, skewness, kurtosis, and MLA were weakly correlated with future change in FVC (|r|=0.23-0.31, p≤0.02), but were not associated with changes in DLCO. qCT variables were no longer predictive of future ΔFVC after adjustment for age, sex, and pack-years.

HAA, skewness, kurtosis, and MLA each predicted mortality in separate unadjusted multivariable models (Figure 2.4). Male sex, worse visual fibrosis scores, lower FVC, lower DLCO, and higher ILD-GAP and SADL indices also predicted mortality on unadjusted analysis. Using only baseline data, HAA, skewness, and kurtosis remained predictors of mortality after adjustment for age, sex, and pack-years, but no longer predicted survival after adjustment for any other measure of ILD severity, including visual fibrosis score, FVC and DLCO, the ILD-GAP Index, or the SADL model (Table 2.5).

Among longitudinal change variables, ΔHAA, Δkurtosis, and ΔMLA predicted mortality on unadjusted analysis (Figure 2.5), as did Δfibrosis, ΔFVC, and ΔDLCO. ΔHAA and ΔMLA remained predictive of mortality after adjustment for age, sex, and pack-years. Changes in all four qCT variables were independent predictors of mortality after adjustment for age, sex, pack-years, and baseline measures of ILD severity, including FVC and DLCO, the ILD-GAP index, or the SADL model (Table 2.6). None of the qCT change measures independently predicted mortality after adjustment for changes in lung function, while ΔHAA and ΔMLA remained predictive of mortality after adjustment for age, sex, pack-years, and change in visual CT scores.
2.4 Discussion

The majority of previous CT densitometry studies have examined associations with physiological variables and survival in IPF.\(^{76,77,84}\) To our knowledge, this is the first study evaluating the physiologic correlation and prognostic utility of longitudinal densitometric qCT measurements in SSc-ILD. We show that although densitometric qCT is associated with other measurements of ILD severity, including both baseline and change variables, density-based qCT measures did not add prognostic information beyond what is obtained using PFTs. These findings suggest that CT densitometry is an additional marker of disease severity, but that its prognostically redundant with more readily available measures of ILD severity.

We showed that all densitometric qCT measurements were associated with pulmonary function and visual CT assessment of ILD severity. This association was present for both baseline data and changes in each qCT variable, independent of age, sex, and pack-years. These findings are similar to the results of previous studies showing moderate correlation between qCT density-based measures and ILD severity in a variety of ILD subtypes.\(^{79,76,78}\) Despite these consistent associations, it is uncertain whether the ability of qCT to measure ILD severity has any clinical utility. For example, it is unknown whether densitometric qCT analysis can be used to confirm or exclude disease progression in patients with inconclusive or marginal changes in clinical and physiological findings.

All four qCT measures were associated with mortality; however, the association of baseline and change qCT variables with mortality was not maintained with adjustment for baseline and change in lung function, respectively. We found that annual changes in HAA, MLA, skewness, and kurtosis were more prognostically informative than baseline pulmonary function and previously validated mortality risk prediction models. However, these changes in densitometric measures were not prognostically useful compared against longitudinal measures of pulmonary physiology. Although some studies have suggested that visual CT scores predict mortality in a variety of ILD subtypes,\(^{50,94,119,120}\) we found that annual changes in HAA and MLA were each independent predictors of mortality after adjustment for change in visual fibrosis scores, suggesting that these qCT measurements may be more
prognostically valuable compared to visual CT assessments. Combined with other challenges in visual CT scoring systems, including poor inter-observer agreement\textsuperscript{121} and significant time requirements, these findings further decrease the support for the incorporation of visual CT measures into routine clinical practice.

Our findings suggest that densitometric qCT is not informative beyond what is provided by currently available physiological variables. Given the current limitations in PFT measures and the disappointing utility of density-based analysis, better tools are needed to monitor ILD that provide a more sensitive indication of disease progression and response to therapy. Global CT summary measures, such as the density measures used in our study, reduce the amount of information available from CT compared to regional density analysis that can be applied to many thousands of finite regions (voxels) per CT and then compared over time. The ability of qCT to follow the density of each voxel over time could reduce the cost of early phase clinical trials by allowing a decrease in study size or duration.\textsuperscript{122} An additional approach is texture-based analysis that can be used to assess disease morphology.\textsuperscript{78,84} Previous studies have found that changes in texture similarly predict survival in patients with ILD after adjustments for baseline disease severity, including baseline pulmonary function, suggesting greater potential utility of these more complex qCT variables.\textsuperscript{93-96} However, it remains unknown if longitudinal changes in texture qCT predict mortality independent of changes in pulmonary function. In all likelihood, a combination of approaches is needed to take full advantage of the opportunities provided by qCT.

Although our study is based on a single center and has a retrospective design, we had a large cohort of 170 patients with long-follow up that permitted adjustment for several important variables. For example, all of our analyses related to DLCO included a sensitivity analysis that adjusted for ACA and RVSP, which was done to investigate the possibility of a distinct phenotype of SSc-ILD with greater likelihood of pulmonary vascular involvement. Another potential limitation of our analysis is the confounding effects of lower attenuation emphysematous regions that impact whole-lung densitometric measures. For this reason we excluded CTs with extent of emphysema exceeding 10% of total lung volume. Finally, we were only able to quantitatively analyze 38% of all performed CTs after excluding CTs that
were not high-resolution, had intravenous contrast, were performed in a prone position, or yielded acute processes. This is a frequent limitation of current approaches to qCT analysis and highlight the need for prospective studies to ensure rigorous quality control.

2.5 Conclusion

In summary, we show that qCT densitometric measures correlate with physiologic impairment and visual CT scores in patients with SSc-ILD at baseline and during long-term follow-up; however, these densitometric measurements are not independent predictors of outcome with adjustment for changes in pulmonary physiology. These findings demonstrate that density-based measures are redundant with pulmonary physiology in estimating prognosis of SSc-ILD, indicating that the prognostic utility of more sophisticated qCT measurements needs to be explored.
Chapter 3: Conclusions

3.1 Conclusions of aims and hypotheses

While we replicated previous findings that show density-based qCT measures correlate with other measures of health outcomes in SSc-ILD, we report that longitudinal densitometric measures are not more prognostically informative than longitudinal pulmonary function indices. Our findings on these density-based measures indicate the need to study more robust qCT tools for the quantification of disease severity, particularly ones showing worth over readily available, more economical, non-radiation-based techniques.

In addition to highlighting the correlations of both baseline and changes in CT density histogram properties with physiological parameters, visual CT scores, and mortality, our work showed that changes in density-based qCT scores are more prognostically useful than visual CT scores provided by experienced radiologists. This finding suggests the ability of unbiased automated qCT tools to identify abnormalities that may be visually subliminal.

3.2 Future directions

3.2.1 Other qCT measures

Additional qCT tools have been investigated to measure outcome in ILD, including pulmonary vessel measurements. It is thought that pulmonary blood flow is reduced in fibrotic areas as a result of hypoxic vasoconstriction, which may cause increased pulmonary arterial pressure and vessel size and numbers in normal regions of the lung. CT derived measures of pulmonary vasculature are strongly linked to pulmonary function and mortality.\textsuperscript{123-126} For these reasons, it is believed that qCT vessel scores can be useful markers of disease extent in fibrotic ILD.

A study by Jacob and colleagues found that pulmonary vessel-related structures (VRS) outperform functional indices in predicting a combined outcome of 10% FVC decline or death within 12 months in IPF.\textsuperscript{123} This study additionally found that VRS reduced trial size by 26%. Pulmonary vessel volume (PVV) also predicts mortality independent of visual CT
variables, baseline pulmonary function, and the composite physiologic index (CPI) in ILD, a tool that uses PFTs to estimate pulmonary fibrosis extent on CT.\textsuperscript{127} PVV has also shown superiority over CALIPER and visual assessments of ILD extent in predicting survival.\textsuperscript{124} It has been hypothesized that this could relate to the volume loss that occurs as the lung contracts secondary to the progression of fibrosis. This would result in decreased qCT fibrotic scores with increasing fibrosis, thus underestimating disease extent. However, PVV increases with increasing disease, potentially making it a more sensitive marker of disease progression. Although the investigation of vasculature measures is in its infancy, algorithm advancements will allow the examination of these vessel related scores in longitudinal analyses.

\subsection*{3.2.2 Longitudinal analysis}

Recent studies have investigated changes in radiological abnormalities by using summary measures over time (i.e., total percentage of lung containing fibrosis). However, modern qCT techniques could allow individual voxels to be followed over time so that voxel A at time point 1 can be compared to voxel B at time point 2. Anatomical matching can be used for voxel identification. Anatomical matching includes the direct comparison of airway trees, where branchpoints are matched between longitudinal scans or scans taken at differing lung volumes.\textsuperscript{128} The carina (where the trachea splits into the two main bronchi) is the first main branchpoint of the airway tree. Superimposing the carinas is as an accurate and reliable method for positioning voxels.\textsuperscript{129}

Specific patterns have also not been followed over time. Particularly, evaluating the same regions of lung on serial CT scans can be used to identify whether isolated ground-glass reverts back to normal lung and if this type of ground-glass differs from ground-glass mixed with fibrosis in regard to rate of progression. Future studies are needed to evaluate whether regional specific changes are associated with physiology or prognosis.
3.2.3 Prognostic models

Several studies have incorporated or replaced variables in staging systems with qCT scores to improve their prognostic capability. Staging of IPF improved when percent normal lung (NL%) was both added and when used to replace FVC and DLCO in the GAP index.\(^{63,130}\)

Prognostication using the ILD-GAP model also improved when combined with CALIPER stratified groups in HP and CTD-ILD.\(^{119,124}\) CALIPER variables are also stronger mortality predictors compared to the GAP Index.\(^{131}\) These studies demonstrate the potential utility of computer derived qCT measures to better predict mortality in ILD, whether used in combination with staging systems or as individual variables.

3.2.4 Management applications

In clinic, disease extent can be visualized as a graphical overlay using qCT. This would help radiologists and respirologists more easily identify and follow changes in disease progression. Moreover, the ability of longitudinal qCT to measure disease progression through modern technological advancements demonstrates its potential to provide a sensitive indication of treatment response. Improvements in texture qCT scores with treatment have been reported in ILD.\(^{91,132-135}\) In addition to the use of qCT to measure therapeutic response in clinical trials, the role of qCT in this setting can also be extended to patient stratification on the basis of disease severity.

Further studies are needed to determine clinically meaningful units of qCT scores. A PVV threshold of 6.5% has previously been used to predict mortality in HP.\(^{125}\) A threshold of 25% has also been used for QLF scores.\(^{53}\) Moreover, disease extent of 10-30% on CT served as an equivalent measure to an FVC threshold of 70% when predicting mortality.\(^{48}\) Additional qCT cut-offs have not been explored to determine disease progression. It could be useful to know how much qCT change is equivalent to a 5% or 10% decline in FVC, which are commonly used thresholds in research and clinical settings to measure ILD progression.\(^{136}\)

qCT could also be used to assist the diagnosis of ILD. Previous diagnostic algorithms have distinguished ILD subtypes through pattern recognition techniques.\(^{87,137,138}\)
texture features have differentiated alveolitis from fibrosis in SSc-ILD.\textsuperscript{139} There are also computer-aided diagnosis systems that discriminate between UIP and NSIP, with accuracies ranging from 70- 91%.\textsuperscript{140,141} The performances of these diagnostic systems show promise for the use of qCT in the characterization of various ILDs.

### 3.3 Overall summary

In summary, this thesis presents one of the largest retrospective cohort studies with long follow-up periods to assess density-based qCT in SSc-ILD. Chapter 2 presents the first study to demonstrate that serial densitometric measures do not provide additional prognostic information compared to longitudinal PFTs. These findings improve our understanding of the role qCT plays in the management and prognostication of patients with ILD. Our work suggests that optimized qCT techniques are needed to take advantage of the analyses made possible by recent advances in image processing, so to more effectively measure disease severity and progression in ILD.
## Tables

**Table 2.1** Baseline patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
<th>Median (IQR) or Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>57 (13)</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>139 (82%)</td>
<td></td>
</tr>
<tr>
<td>Ever-smoker</td>
<td>67 (39%)</td>
<td></td>
</tr>
<tr>
<td>Smoking pack-years</td>
<td>0 (0-10)</td>
<td></td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive anti-nuclear antibodies</td>
<td>142 (97%)</td>
<td></td>
</tr>
<tr>
<td>Positive anti-topoisomerase 1 antibodies</td>
<td>52 (39%)</td>
<td></td>
</tr>
<tr>
<td>Positive anti-centromere antibodies</td>
<td>13 (19%)</td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC, %-predicted</td>
<td>77 (21)</td>
<td></td>
</tr>
<tr>
<td>FEV1, %-predicted</td>
<td>79 (21)</td>
<td></td>
</tr>
<tr>
<td>TLC, %-predicted</td>
<td>84 (19)</td>
<td></td>
</tr>
<tr>
<td>RV, %-predicted</td>
<td>91 (27)</td>
<td></td>
</tr>
<tr>
<td>DLCO, %-predicted</td>
<td>54 (19)</td>
<td></td>
</tr>
<tr>
<td><strong>Quantitative CT scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High attenuation areas, %</td>
<td>7.5 (5.2, 10.6)</td>
<td></td>
</tr>
<tr>
<td>Skewness</td>
<td>2.0 (1.6, 2.5)</td>
<td></td>
</tr>
<tr>
<td>Kurtosis</td>
<td>5.3 (2.8, 7.6)</td>
<td></td>
</tr>
<tr>
<td>Mean lung attenuation, HU</td>
<td>-727 (-775, -683)</td>
<td></td>
</tr>
<tr>
<td><strong>Visual CT scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual fibrosis score</td>
<td>7.5 (3.3, 12.9)</td>
<td></td>
</tr>
<tr>
<td>Visual ground glass score</td>
<td>1.7 (0.0, 5.0)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; DLCO, diffusion capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HU, Hounsfield unit; RV, residual volume; TLC, total lung capacity.
Table 2.2 Associations of baseline qCT and baseline pulmonary function. Spearman’s r values are shown for the unadjusted associations.

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted analysis*</th>
<th>Adjusted for age, sex, pack-years, disease duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FVC</td>
<td>FEV₁</td>
</tr>
<tr>
<td>HAA, %</td>
<td>-0.44</td>
<td>-0.41</td>
</tr>
<tr>
<td>Skewness</td>
<td>0.54</td>
<td>0.50</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>0.54</td>
<td>0.51</td>
</tr>
<tr>
<td>MLA, HU</td>
<td>-0.51</td>
<td>-0.46</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DLCO, diffusion capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; HAA, high attenuation areas; HU, Hounsfield unit; MLA, mean lung attenuation; RV, residual volume; TLC, total lung capacity; qCT, quantitative computed tomography.

*All p-values were ≤0.001
Table 2.3 Adjusted associations of change in qCT with pulmonary function decline and change in visual CT scores.

<table>
<thead>
<tr>
<th>ΔHAA, %</th>
<th>ΔSkewness</th>
<th>ΔKurtosis</th>
<th>ΔMLA, HU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient (95% CI)</td>
<td>p-value</td>
<td>Coefficient (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>-0.40 (-0.77, -0.03)</td>
<td>0.04</td>
<td>-0.75 (-1.24, -0.27)</td>
<td>0.003</td>
</tr>
<tr>
<td>4.50 (0.09, 8.90)</td>
<td>0.046</td>
<td>7.10 (1.87, 12.33)</td>
<td>0.008</td>
</tr>
<tr>
<td>1.13 (0.21, 2.05)</td>
<td>0.02</td>
<td>1.50 (0.42, 2.58)</td>
<td>0.007</td>
</tr>
<tr>
<td>-0.06 (-0.10, -0.03)</td>
<td>&lt; 0.001</td>
<td>-0.11 (-0.15, -0.06)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DLCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; HAA, high attenuation areas; HU, Hounsfield unit; MLA, mean lung attenuation; qCT, quantitative computed tomography.
Table 2.4 Adjusted associations of baseline qCT measures with baseline visual CT scores.

<table>
<thead>
<tr>
<th>Visual fibrosis</th>
<th>Coefficient (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAA, %</td>
<td>0.71 (0.25, 1.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Skewness</td>
<td>-9.59 (-12.6, -6.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>-1.58 (-2.15, -1.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MLA, HU</td>
<td>0.07 (0.05, 0.10)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HAA, high attenuation areas; HU, Hounsfield unit; MLA, mean lung attenuation; qCT, quantitative computed tomography.
Table 2.5 Adjusted associations of baseline qCT measures with survival.

<table>
<thead>
<tr>
<th></th>
<th>Adjusted for age, sex,</th>
<th>Adjusted for age, sex,</th>
<th>Adjusted for the ILD-GAP Index</th>
<th>Adjusted for the SADL model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pack-years, visual</td>
<td>pack-years, FVC,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>fibrosis scores</td>
<td>DLCO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>HAA, %</td>
<td>1.02 (0.95-1.11)</td>
<td>0.54</td>
<td>1.03 (0.96-1.11)</td>
<td>0.41</td>
</tr>
<tr>
<td>Skewness</td>
<td>0.50 (0.23-1.11)</td>
<td>0.09</td>
<td>0.79 (0.36-1.71)</td>
<td>0.55</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>0.88 (0.75-1.05)</td>
<td>0.15</td>
<td>0.97 (0.84-1.13)</td>
<td>0.70</td>
</tr>
<tr>
<td>MLA, HU</td>
<td>1.06 (0.99-1.13)*</td>
<td>0.07</td>
<td>0.98 (0.91-1.05)*</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HAA, high attenuation areas; HU, Hounsfield unit; ILD-GAP, interstitial lung disease-gender, age, and physiology; MLA, mean lung attenuation; SADL, smoking history, age, and DLCO; qCT, quantitative computed tomography.

*per 10-unit increase in MLA
Table 2.6 Adjusted associations of change in qCT with survival.

<table>
<thead>
<tr>
<th></th>
<th>Adjusted for age, sex, pack-years, change in visual fibrosis scores</th>
<th>Adjusted for age, sex, pack-years, baseline FVC and DLCO</th>
<th>Adjusted for the ILD-GAP index</th>
<th>Adjusted for the SADL model</th>
<th>Adjusted for age, sex, pack-years, change in FVC and DLCO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>ΔHAA, %</td>
<td>1.25 (1.05-1.50)</td>
<td>0.01</td>
<td>1.36 (1.17-1.59)</td>
<td>&lt;0.001</td>
<td>1.36 (1.19-1.55)</td>
</tr>
<tr>
<td>ΔSkewness</td>
<td>0.23 (0.02-3.29)</td>
<td>0.28</td>
<td>0.04 (0.01-0.31)</td>
<td>0.002</td>
<td>0.05 (0.01-0.32)</td>
</tr>
<tr>
<td>ΔKurtosis</td>
<td>0.70 (0.43-1.15)</td>
<td>0.16</td>
<td>0.47 (0.30-0.74)</td>
<td>&lt;0.001</td>
<td>0.51 (0.35-0.76)</td>
</tr>
<tr>
<td>ΔMLA, HU</td>
<td>1.02 (1.01-1.04)</td>
<td>0.007</td>
<td>1.05 (1.03-1.06)</td>
<td>&lt;0.001</td>
<td>1.04 (1.02-1.05)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HAA, high attenuation areas; HU, Hounsfield unit; ILD-GAP, interstitial lung disease-gender, age, and physiology; MLA, mean lung attenuation; SADL, smoking history, age, and DLCO; qCT, quantitative computed tomography.
Figure 1.1 Longitudinal comparison of density histograms from a patient with systemic sclerosis-associated interstitial lung disease.
The distribution of x-ray attenuation values from the baseline CT scan (solid blue line) has a mean of -730.6 HU, with a skewness of 2.3 and kurtosis of 5.7. The CT density distributions of the subsequent CT scans 3 years later (dashed red line) and four years later (dotted black line) are shifted towards the right (higher density lung), with a mean of -693.0 and -649.4, skewness of 1.7 and 1.5, and kurtosis of 3.4 and 2.1, respectively. Corresponding pulmonary function values decreased over time, with FVC %-predicted declining from 78 to 54 to 48, FEV1 % -predicted from 78 to 71 to 59, and DLCO % -predicted from 68 to 26 to then being unmeasurable. The sudden drop in density at approximately -400HU represents the outer lung boundary. Image courtesy of VIDA Diagnostics, Coralville, IA.
Figure 1.2 CT density histograms from a patient with interstitial lung disease (solid black line) and a normal subject (grey dashed line). The x-ray attenuation values shown by the histograms are directly related to the density of the tissue in the lung. The lowest density, emphysematous, range is highlighted in yellow (-1000 to -950 HU). Normal lung density is shown in red from -950 to -701 HU. Lung density in the ILD range is shown in green from -700 to 0 HU while the high attenuation areas (HAA) is shown in dashed blue lines from -600 to -250 HU. Density distributions courtesy of Dr. Harvey Coxson.
Figure 1.3 Illustration of the automatic airway branchpoint identification from a CT of a patient with systemic sclerosis-associated interstitial lung disease. Image courtesy of VIDA Diagnostics, Coralville, IA, using VIDA Vision® image analysis workstation.
Figure 1.4 Illustration of the automatic airway segmentation and airway label identification in the axial, coronal, and sagittal views from a CT of a patient with systemic sclerosis-associated interstitial lung disease. Image courtesy of VIDA Diagnostics, Coralville, IA, using VIDA Vision® image analysis workstation.
Figure 1.5 Illustration of the automatic lobar and lung mask segmentation in the axial, coronal, and sagittal views from a CT of a patient with systemic sclerosis-associated interstitial lung disease. Image courtesy of VIDA Diagnostics, Coralville, IA, using VIDA Vision® image analysis workstation.
Figure 2.1 Kaplan-Meier survival curve for the entire cohort (n=170), stratified by sex.
Figure 2.2 Scatterplot matrix of the associations of baseline HAA, skewness, kurtosis, and MLA with FVC, DLCO, visual fibrosis scores, and visual ground-glass scores. HAA, skewness, kurtosis and MLA were calculated for 170 patients. Fibrosis and ground-glass were calculated for 97 patients given the number of CT scans that were visually scored. FVC and DLCO were calculated for 134 and 122 patients, respectively, due to missing data.
Figure 2.3 Scatterplot matrix of the associations of annual change in HAA, skewness, kurtosis, and MLA with annual change in FVC, DLCO, and visual fibrosis scores.

ΔHAA, Δskewness, Δkurtosis, and ΔMLA were calculated for 123 patients as patients who had less than 2 eligible CT scans were excluded. ΔFibrosis was calculated for 38 patients given the number of scans that were visually scored. ΔFVC and ΔDLCO were calculated for 101 and 90 patients, respectively.
Figure 2.4 Kaplan-Meier survival curves of baseline HAA, skewness, kurtosis, and MLA.
*Per 10 unit increase in MLA
Figure 2.5 Kaplan-Meier survival curves of annual change in HAA, skewness, kurtosis, and MLA.

*Per 10 unit increase in MLA
References


47. Khanna D, Nagaraja V, Tseng CH, et al. Predictors of lung function decline in scleroderma-related interstitial lung disease based on high-resolution computed


Appendices

Appendix A  Flow diagram of the CT screening process (A) and a bar graph showing the number of CT scans and PFTs over 3-year intervals from baseline (B). In B, the number of CT scans visually and quantitatively scored are shown in red and grey, respectively. The number of patients contributing PFT and CT data for each interval are shown above each bar.
Appendix B  Distributions of qCT variables at baseline and 3-year follow-up.
Appendix C  Additional variables predictive of survival. Unadjusted Cox proportional hazards analysis of various predictor variables are shown below.

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>1.885 (1.004-3.538)</td>
<td>0.049</td>
</tr>
<tr>
<td>Visual fibrosis scores</td>
<td>1.045 (1.018-1.072)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FVC</td>
<td>0.975 (0.958-0.992)</td>
<td>0.004</td>
</tr>
<tr>
<td>DLCO</td>
<td>0.963 (0.941-0.986)</td>
<td>0.002</td>
</tr>
<tr>
<td>ILD-GAP</td>
<td>1.334 (1.064-1.673)</td>
<td>0.013</td>
</tr>
<tr>
<td>SADL</td>
<td>1.426 (1.156-1.759)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ΔFibrosis</td>
<td>1.437 (1.090-1.895)</td>
<td>0.010</td>
</tr>
<tr>
<td>ΔFVC</td>
<td>0.834 (0.784-0.887)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ΔDLCO</td>
<td>0.870 (0.818-0.926)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviations: FVC; forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide.