PREDICTORS OF HEALTH-RELATED QUALITY OF LIFE AFTER LUNG CANCER SURGERY

by

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Abstract

Globally, lung cancer is the leading cause of death. Surgical removal of a primary non-small cell lung cancer (NSCLC) tumour offers a significant chance of cure for those suffering. Additionally, it is anticipated that the introduction of screening programs for lung cancer will result in an increase in survival rates. Therefore, health-related quality of life (HRQOL) following surgery has become an important consideration for these patients. However, a considerable number of lung cancer patients who have undergone surgery have not experienced improvement in their breathing afterwards, a condition that can persist for several months following surgery. Computed Tomography (CT) scans of lung cancer patients often demonstrate concurrent emphysema with low attenuation areas (LAAs), the significance of which is unclear. Moreover, sarcopenia is observed in about half of lung cancer patients and is linked to impaired health outcomes and lower survival rates. Identifying the predictors of postoperative HRQOL decline is vital; however, little information is available regarding the relationship between baseline HRQOL, quantitative computed tomography (QCT) of emphysema, or CT-based body composition with postoperative dyspnoea and global health.

This thesis aims to examine the predictors of HRQOL of dyspnoea and global health six months following lung cancer surgery.

This is a prospective observational study. The European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30) questionnaire and lung cancer module LC13 were introduced at baseline pre-surgery, eight weeks, and six months after lung surgery. Using the CT scans, lung density measurements using %LAA at thresholds of -950 Hounsfield Units (HU) and -910 HU for the assessment of emphysema were quantified and the cross-sectional area of thoracic and abdominal muscles, specifically pectoralis (PM), erector spinae (ESM), psoas (PSM), and skeletal muscles (SM), were analysed using an open-access software.

Univariate and multivariate linear, ordinal and multinational regression analyses were performed to find out the predictive value of preoperative HRQOL and CT scan density measurements. Comparative analyses, as well as intra-class correlation coefficients and Bland Altman plots, have also been employed.

A total of 1064 patients were recruited over 10 years, and 906 consented patients were included in the study. A significant increase in dyspnoea scores was observed beyond the minimal clinical difference, with values at baseline, eight weeks, and six months were 20.5 ± 22.6, 39.6 ± 24.5, and 33.2 ± 24.7, respectively. In an eight-week period, global health scores dropped from 73.2 ± 20.5 to 63.3 ± 20.5, with only a minimal improvement observed at six months (66.6 ± 22.2).

In the multivariate regression analyses, we have demonstrated that baseline dyspnoea is a strong predictor for patients' postoperative HRQOL after lung cancer surgery (OR = 3.07 – 12.3, p = 0.00). Additionally, baseline global health significantly predicts postoperative HRQOL (coefficient = 0.45 – 0.5, p = 0.00).

The data demonstrate that %LAA-950 is a significant predictor of postoperative dyspnoea and global health (OR = 1.2-1.3, p = 0.00), while %LAA-910 is not consistently a strong predictor after adjusting for clinical and perioperative factors.

AI-based and semi-automated software showed strong consistency in measuring %LAA-950 and whole lung volume, 15th percentile, and mean lung density. However, there was a lower degree of agreement between the two programs in lobar measurements. Finally, no statistically significant differences were observed in the changes in HRQOL following lung surgery among the small number of patients with sarcopenia.

In conclusion, QCT of emphysema could be a valuable tool in assessing patients undergoing lung cancer surgery in terms of dyspnoea and global health QoL. Leveraging existing patient information in their perioperative care is vital for improving treatment strategies and patients' outcomes.

Dedications

I dedicate this thesis to my mother and father

Your unwavering love, support, and belief in me have been the pillars of my strength.

To my husband, Abdulelah

Your belief in my dreams, your encouragement during the challenging times, and your endless optimism have been the guiding lights on this journey. This accomplishment is as much yours as it is mine.

To my dearest daughters, Leen and Lama

Your laughter and love have filled our home with warmth and light, inspiring me to pursue my goals with a heart full of hope. May this accomplishment encourage you to pursue your dreams with courage and heart.

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Publications and presentations

Publications

- Can Patient Reported Outcome (PRO) predict patients' quality of life after lung cancer surgery?

  Saffana K Algaeed[1,2], Veena Surendrakumar[3,4], Rajnikant L Mehta [5], Salma Bibi Kadiri[6], Helen Shackleford[6], Hazem Fallouh[3], Ehab Bishay[3], Richard Steyn[3], Vanessa Rogers[3], A menon[3], Maninder Kalkat[3], David Thickett[1,3], Babu Naidu[1,3] (yet to be submitted to Journal of Thoracic Oncology).

- %LAA-950 is a non-invasive biomarker for postoperative dyspnoea in lung cancer surgery

  Saffana K Algaeed[1,2], Hazem Fallouh[3], Ehab Bishay[3], Richard Steyn[3], Vanessa Rogers[3], A menon[3], Maninder Kalkat[3], David Thickett[1,3] Babu Naidu[1,3] (yet to be submitted to Thorax Journal).

Oral presentations

- Predictors of Dyspnoea in Cancer Patients after Lung Resection

  SK Algaeed, V Surendrakumar, RL Metha, S Kadiri, H Shackleford, H Fallouh, E Bishay, V Rogers, A menon, M Kalkat, B Naidu

  21st Annual BTOG Conference, Belfast, UK 2023

  (Best poster Award)

- What are the Predictors of the Increase in Dyspnoea after Lung Cancer surgery?

  SK Algaeed , V Surendrakumar, RL Metha, H Fallouh, E Bishay, V Rogers, A menon, M Kalkat, B Naidu

  19th SCTS Annual meeting and NAHP Cardiothoracic forum, Birmingham, UK, 2023.

- %LAA-950 is a Non-invasive Biomarker for Postoperative Dyspnoea in Lung Cancer Surgery

  SK Algaeed, H Fallouh, E Bishay, V Rogers, A menon, M Kalkat, B Naidu

  SCTS Annual meeting and NAHP Cardiothoracic forum, Newport, UK, 2024 (to be presented in March 2024)

Poster presentations

- Can EORTC QLQ-C30 Predict Postoperative Dyspnoea in Lung Cancer Patients?

  SK Algaeed, H Fallouh, E Bishay, V Rogers, A menon, M Kalkat, B Naidu

  Midland Thoracic Society Autumn Meeting, Birmingham, UK, 2022.

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List of Abbreviations

3D	Three dimensional
15-D	Fifteen-dimensional health-related quality of life instrument
ACC	American College of Cardiology
AI	Artificial intelligence
ANOVA	Analysis of variance
ASA score	American Society of Anaesthesiologists physical status classification
BDI	Baseline dyspnoea index
BIA	Body impedance analysis
BMI	Body mass index
BODE index	Body mass index, airflow obstruction, dyspnoea, and exercise capacity
BP	Body pain
BTS	The British Thoracic Society
CDS	Cancer dyspnoea scale
CI	Confidence interval
CIP	Chest Imaging Platform
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
DLCO	Diffusing capacity for carbon monoxide
DXA	Dual-energy X-ray Absorptiometry
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core Module
EORTC QLQ-LC13	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (lung cancer module)
EQ-5D	Euroqol-5 Dimension
ERAS	The Enhanced Recovery After Surgery Society

ESAS	The Edmonton Symptom Assessment System
ESMA	Erector Spinae muscle area
ESMD	Erector Spinae muscle density
ESMI	Erector Spinae muscle index
EST	The European Society of Thoracic Surgeons
EWGSOP	The European Working Group on Sarcopenia in Older People
FACT-G	Functional Assessment of Cancer Therapy-General Version
FACT-L	Functional Assessment of Cancer Therapy-Lung Cancer version
FEV_1	Forced expiratory volume for 1 second
FVC	Forced vital capacity
GEE	Generalised estimating equation models
GH	General health perception
GOLD	The Global Initiative for Obstructive Lung Disease
HAA	High attenuation area
HRCT	High-resolution Computed Tomography
HRQOL	Health-related Quality of Life
HU	Hounsfield unit
ICC	Intraclass correlation coefficient
ICU	Intensive Care Unit
IGC	Individual growth curve
IQR	Inter quartile range
KPS	Karnofsky's performance status
LAA	Low attenuation area
LCSS	Lung Cancer Symptom Scale
LLL	Left lower lobe
LOA	Limits of agreement
LOS	Length of hospital stay
LUL	Left upper lobe
M stage	Metastasis
mBODE	Modified Body mass index, airflow obstruction, dyspnoea, and exercise capacity
MBS	Modified Borg Scale

MDT	Multidisciplinary team
MH	Mental health
MLD	Mean lung density
N stage	Lymph node involvement
NSCLC	Non-small cell lung cancer
OR	Odds ratio
PD15	15^{th} Percentile
PF	Physical functioning
PMA	Pectoralis muscle area
PMD	Pectoralis muscle density
PMI	Pectoralis muscle index
$PPOFEV_1$	predicted postoperative forced expiratory volume in 1 second
PPODLCO	predicted postoperative diffusing capacity for carbon monoxide
QCT	Quantitative Computed Tomography
QoL	Quality of life
QWB	Quality of Well Being scale
RCT	Randomised controlled trial
RE	Emotional health-related role
RLL	Right lower lobe
RML	Right middle lobe
RP	Physical health-related role
RS	Raw scores
RUL	Right upper lobe
RV	Residual volume
SCLC	Small cell lung cancer
SD	Standard deviation
SF	Social functioning
SF36	Short Form 36-item Health Survey
SGRQ	St. George Respiratory Questionnaire
SOB	Shortness of breath
T stage	Size of the tumour
TLC	Total lung capacity

TLV	Total lung volume
TPS	Thin plate splines
UCSD-SOBQ	The University of California and Sand Diego Shortness of Breath Questionnaire
UHB	University Hospitals Birmingham
VAS	Visual analogue scale
VIF	Variance inflation factor
VO_2	Maximum rate of oxygen consumption
VRS-D	Verbal rating scale for dyspnoea
VT	Vitality

Chapter 1. Introduction

1.1 Lung cancer

Lung cancer has been the most prevalent cancer type worldwide for decades [1]. In the United Kingdom, lung cancer has a high prevalence, morbidity, and mortality rate [2]. In 2021, there were 43,478 new lung cancer cases in the UK [3]. Among all cancers, lung cancer has one of the lowest survival rates, with only 16.2% living more than five years and only 9.5% living more than ten [2]. According to epidemiological studies, more cases are anticipated in the upcoming years due to an increase in the global smoking population [4]. Although the direct expenses of lung cancer in the UK are projected to be £163 million per year, the majority of the costs associated with the disease are intangible costs estimated to be £45 billion [5]. According to the National Lung Cancer Audit (2021), 41% of the patients were readmitted to NHS hospitals after lung cancer surgery in 90 days in 2018, mainly for the management of complications, comorbidities and emergencies (Figure 1.1) [6].

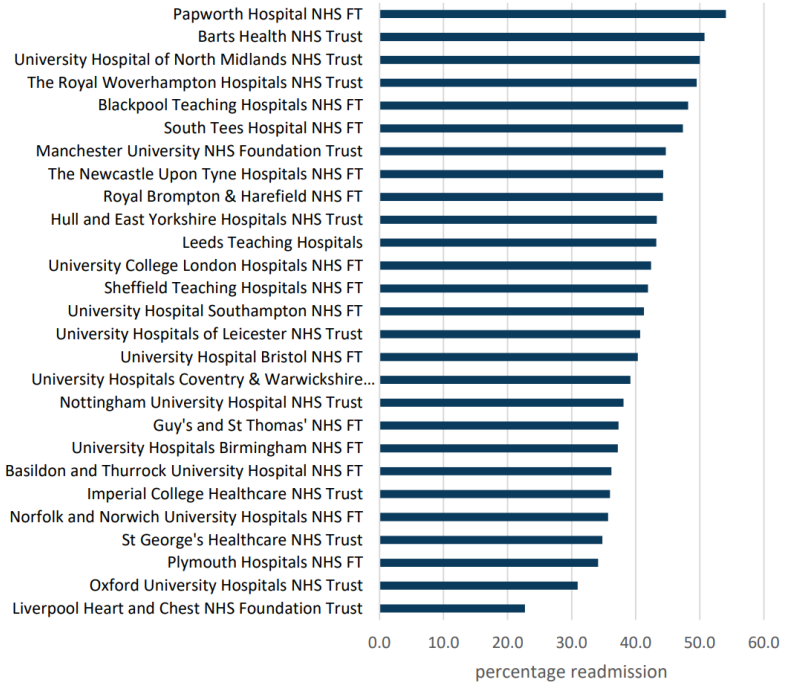

Figure 1.1 Percentages of readmission 90 days after lung cancer surgery in NHS hospital. Taken with permission National Lung Cancer Audit, Lung cancer clinical outcomes publication (2021).

High readmission rates are connected with worse patient outcomes, resulting in a significant financial burden [7], not to mention the costs of suffering, pain and lives lost. Studies found that HRQOL is associated with prolonged hospital stay and readmission [8, 9].

However, with the introduction of lung cancer screening and early detection of lung cancer, lung cancer survival will increase [10]. The risk of poor HRQOL after surgery is an essential concern for many patients, as expressed in pre-surgery counselling [11, 12]. Consequently, assessing patients who reported HRQOL is vital to identifying the patients at high risk of poor HRQOL after lung cancer treatment.

1.2 Lung resection of cancer

Generally, lung cancer is categorised into small cell lung cancer and non-small cell lung cancer (NSCLC), and resection of primary lung cancer marked a major part of the workload of thoracic surgery, which is operated with curative intent and ranged up to 32.3% [6].

The gold standard surgery is anatomical resection of a lung tumour, which comprises segmentectomy, lobectomy, bilobectomy, or pneumonectomy; these treatments entail lymphatic dissection with removal of a lung segment, a single lobe, two lobes, or an entire lung, respectively [13]. As the lungs contain five lobes divided into 19 anatomical segments, each lobe has between two to five segments; hence, anatomical resection involves removing a varying extent of functional lung tissue that does not include a tumour. Consequently, 53% of the people who have undergone lung cancer surgery suffer from dyspnoea [14] (Figures 1.2 and 1.3).

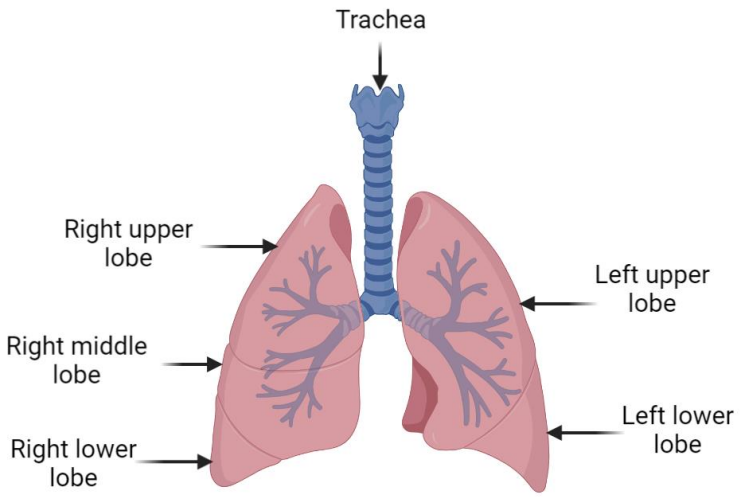

Figure 1.2 Lung lobes

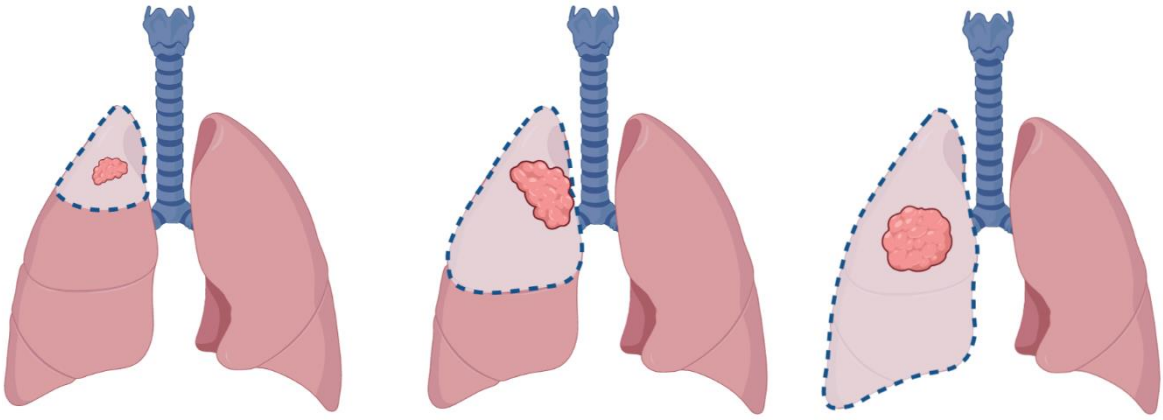

Figure 1.3 Lung resection types

1.2.1 Assessment of the risk of lung surgery: conventional risk assessment

A tripartite approach is adopted by the British Thoracic Society (BTS) and the American College of Cardiology (ACC) for quantifying surgical risk, facilitating the calculation and assessment of individual outcomes for the patient and multidisciplinary team (MDT) to discuss [13]. The estimated risk of post-operative cardiac events, peri-operative death, and post-operative dyspnoea must be considered before a patient is offered surgery; the patient must be involved in the assessment and discussion of these risks so that specific outcomes can be predicted. A patient should be aware of the potential impact of the surgery on the patient's QoL before deciding whether to proceed with surgery (shared decision-making). Preoperative risk stratification for lung resection patients will be discussed in this section.

1.2.1.1 Risk assessment for postoperative dyspnoea

The traditional method for estimating risk in individuals evaluated for lung resection surgery uses dynamic lung volumes and transfer factor (Figure 1.4). Shortness of breath (SOB) is a common complication of lung resection, with more than 50% of patients reporting disabling symptoms [15] (section 1.5). However, in preoperative risk assessment, SOB is always secondary to hard clinical outcomes such as mortality and morbidity [13]. Nevertheless, this symptom should not be overlooked.

The British Thoracic Society Guidelines recommend segment counting for evaluating lung function and predicting postoperative lung function [16]. Additional functional assessment by shuttle walk tests or cardiopulmonary exercise testing is used to classify patients into moderate or high-risk groups of dyspnoea postoperatively (Figure 1.4) [13].

It is considered an average risk when predicted postoperative forced expiratory volume in 1 second (%ppoFEV$_1$) and predicted postoperative diffusing capacity for carbon monoxide (%ppoDLCO) are greater than 40% predicted, and when oxygen saturation on air is greater than 90% [13].

On the contrary, patients are classed as high risk if they have %ppoFEV$_1$ and %ppoDLCO lower than 40% [13]. Exercise testing is taken into consideration for patients with any other combinations. The following formula is used to calculate segment counting for the patients [16]:

$$Postoperative\ FEV_1 = \text{preoperative}\ FEV_1 \times \frac{((19 - obstructed\ segments) - unobstructed\ segments\ to\ be\ resected)}{(19 - obstructed\ segments)}$$

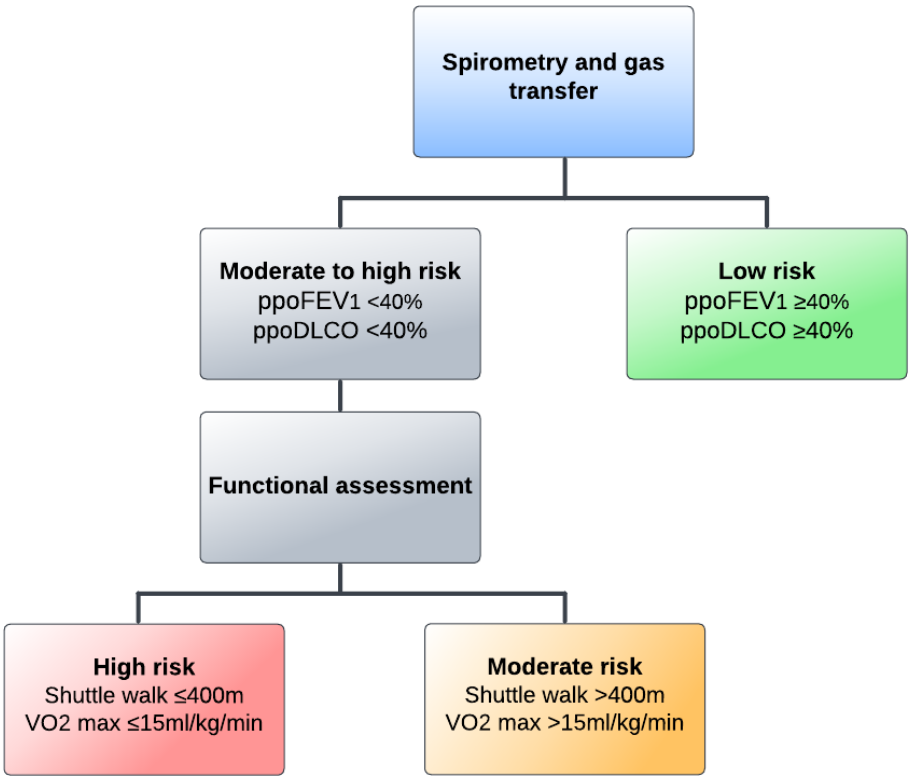

Figure 1.4 Risk assessment prior to lung resection for cancer, ppo; predicted postoperative, FEV1; forced expiratory volume in 1 second, DLCO; diffusing capacity for carbon monoxide, VO2 max; maximum rate of oxygen consumption, adapted from: Lim, E., et al., Guidelines on the radical management of patients with lung cancer. Thorax, 2010. 65(Suppl 3): p. iii1-iii27

A previous study noted a strong correlation between predicted and measured postoperative ppoFEV_1 and ppoDLCO assessed by quantitative ventilation and perfusion scintigraphy for lungs in 55 patients [17]. FEV_1 (r = 0.86, p 0.001) and DLCO (r = 0.8, p 0.001) were associated with predicted post-operative lung function. The relationship between predicted and measured FEV_1 values after pneumonectomy was significant, although weaker when divided by whether lobectomy or pneumonectomy was performed ($r=0.51$, $p<0.05$). There was no association between measured and predicted DLCO values after pneumonectomy ($r=0.17$, $p>0.05$). These patients had received aggressive radiotherapy; without radiotherapy, postoperative DLCO values were more closely related to predicted values ($r=0.84$, $p<0.01$) [17]. As a result, segment counting may not always be accurate.

Patients with obstructive disease may have inaccurate ppoFEV_1 values that cannot be applied alone in patients' risk assessment. In a study by Brunelli and colleagues, patients with COPD had lower losses of FEV_1 and DLCO three months after lung cancer lobectomy than those without COPD. They also revealed that FEV_1 and DLCO were higher than predicted after lung surgery in COPD patients. [18, 19]. However, the authors did not assess the correlations between these measures and HRQOL.

The disease may not affect the lung uniformly. Therefore, lung segments can function differently. Consequently, future research may be necessary to determine the regional contribution from the lung that needs surgery in any patient with borderline ppoFEV_1 or ppoDLCO after simple segment counting or those with a bronchial lesion blocking flow.

Several studies have investigated ppoFEV_1 in risk prediction and surgical patient selection. In an early study, Olsen et al. determined that patients with a ppoFEV_1 as low as 0.8 litres could tolerate

resection. However, this was found in a study involving only 13 participants [20]. As a result of surgery, FEV_1 (L) and $\%FEV_1$ are reduced and can be accurately predicted [21]. Nonetheless, many studies have questioned the ability of $FEV_1\%$ or $ppoFEV_1\%$ to predict dyspnoea [22-24]. Bousamra and colleagues investigated whether baseline %DLCO could predict postoperative morbidity and mortality in 325 patients with lung resection. The authors found that low baseline %DLCO, <60% for pneumonectomy or <50% for lobectomy, was associated with postoperative breathlessness at six months ($p<0.01$). However, it was limited by assessing nine patients with increased dyspnoea after lung surgery, seven of whom had extensive resection and concurrent radiation therapy [25]. Despite showing a correlation between pulmonary function and dyspnoea, the study did not predict dyspnoea after lung resection.

Others found that lung function could predict postoperative dyspnoea in lung resection patients. The dyspnoea on exertion was classified into four stages using a simple unnamed questionnaire: one on intense work and four on minimal effort. Patients with class three and four dyspnoea had decreased $\%FEV_1$ and %FVC than patients with class one and two dyspnoea. Based on multiple regression analyses, $\%FEV_1$ and %FVC were independent predictors of postoperative dyspnoea. [26]. It was concluded that pulmonary function could predict postoperative dyspnoea; however, the study was limited to 35 patients who had undergone pneumonectomy.

Measuring predicted postoperative values of FEV_1, DLCO, and baseline pulmonary function is important to classify the risk of postoperative dyspnoea and mortality [13]. However, the need for a more precise estimate of dyspnoea and QoL in patients having lung resection is paramount. If a prediction results in a high risk, treatment may be altered for a limited resection or alternative therapy such as Stereotactic Ablative Body Radiotherapy (SABR). In addition, it helps counselling the patients on surgery and its long-term impacts. As a result, the best course of action

should be determined by considering various risk factors. Risk factors for dyspnoea following lung resection in previous studies are reviewed (Section 1.8.1).

1.2.1.2 Risk assessment for postoperative quality of life

The British Thoracic Society and the Society for Cardiothoracic Surgery guidelines involved the quality of life as one element for assessing the risks of surgery [13]. Their recommendations included minimally invasive approaches and non-anatomic resection where appropriate. Evaluating the quality of life is not recommended solely based on pulmonary function and exercise tests. Finally, they recommend assessing the quality of life using validated instruments (section 1.7.3) [13]. Several studies found a poor correlation between preoperative FEV_1, DLCO and quality of life in lung cancer surgery [27, 28]. Predictors of postoperative quality of life will be discussed in detail (Section 1.8.2).

1.3 Assessment of lung function in routine clinics

Existing methods for assessing lung function include spirometry, lung volume, and gas transfer factor measurements. As these measurements are widely recorded in normal individuals in various populations, they can be compared to the expected values based on the gender, height, age, and ethnicity of each patient. This makes it possible for clinicians to interpret the absolute value and the percentage predicted value [29]. Understanding the fundamental principles underlying these routine tests is necessary for appreciating the difference between novel methods and, consequently, where valuable clinical data can be added.

1.3.1 Spirometry

In order to perform spirometry, patients must cooperate in fully breathing, forcefully exhaling, and then continuously exhaling to measure gas volume changes and the passage of time. The patient blows into a sealed tube between the mouth and the tube, and a nose clip is placed so all measurements are taken externally. The FVC and FEV_1 are crucial measures this process generated [30].

1.3.2 Gas transfer

DLCO assesses the ability of carbon monoxide (CO) to bind to erythrocyte haemoglobin after administration of inspired CO. Before a vital capacity (VC) manoeuvre, a small amount of CO is administered to the patient. The patients hold their breath and then exhale [31]. To measure the concentration of CO in the air exhaled from the alveolar space, the volume of gas originally exhaled from the respiratory system is discarded and the remaining concentration is measured. As CO passes through the alveolar wall and into the red blood cells, the change in concentration is used to determine how much has passed into the bloodstream instead of being restricted by blood delivery to the alveolar bed. It is necessary to add an inert gas, such as helium, to the inhaled gas mixture to measure the initial dilution of inspired gases into the residual volume (RV) of the lung for the exhaled concentration of CO to be adjusted for this and a total lung capacity (TLC) to be determined [32].

Clearly, these tests determine how well the respiratory system is functioning as a whole, although pathological processes may be distributed heterogeneously in the lungs. Identifying other measures can thus be helpful to aid in diagnosis and gauge how a particular lung disease will respond to treatment.

1.4 Chronic Obstructive Pulmonary Disease (COPD)

COPD, also known as chronic obstructive pulmonary disease, is characterized by symptoms that manifest in the respiratory system and the restriction of airflow [33]. COPD is distinguished by a persistent inflammatory reaction in the lung tissue that develops due to inhaling harmful gases or particles, most often tobacco smoke. The persistent limitation of airflow is caused by parenchymal damage (emphysema) and small airway disease (obstructive bronchitis); their influence varies from patient to patient [33]. COPD affects almost 200 million individuals worldwide [34], and this disease's prevalence is on the rise. COPD is projected to be the third most common cause of death worldwide by 2030 [35]. Additionally, emphysema is an independent risk factor for lung cancer, and the risk increases with smoking. It is undeniable that smoking is one of the primary risk factors for emphysema and lung cancer, indicating shared pathways in these disease development [36].

1.4.1 Emphysema

Emphysema is a chronic condition that causes the adjacent walls of the air spaces distal to the terminal bronchiole to dilate abnormally over time [37]. This causes the capillary and alveolar surface area to diminish, which reduces the gas exchange [38] (Figure 1.5).

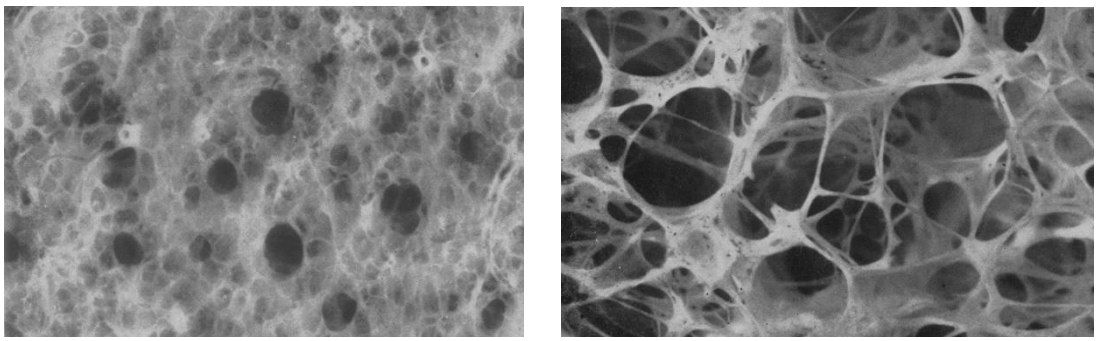

Figure 1.5 Normal lung tissue (left) and severe emphysema (right), taken from: DEFINITION lN, G.P.O., Terminology, definitions, and classification of chronic pulmonary emphysema and related conditions. Thorax, 1959. 14: p. 286

1.4.2 Emphysema types

1.4.2.1 Centrilobular emphysema

Most commonly associated with smoking, it is the most prevalent type of emphysema [38]. It is described as the destruction of the centre tissue of the lung lobule [39].

1.4.2.2 Panlobular emphysema

Typically, panlobular emphysema affects the lower lobes and is associated with airway narrowing and inflammation [40]. One of the leading causes of panlobular emphysema is alpha-1 antitrypsin deficiency [41].

1.4.2.3 Paraseptal emphysema

Paraseptal emphysema is commonly found near the pleural surface in the upper lung regions, destroying lung lobules at their periphery near the lobular septa [42] (Figure 1.6).

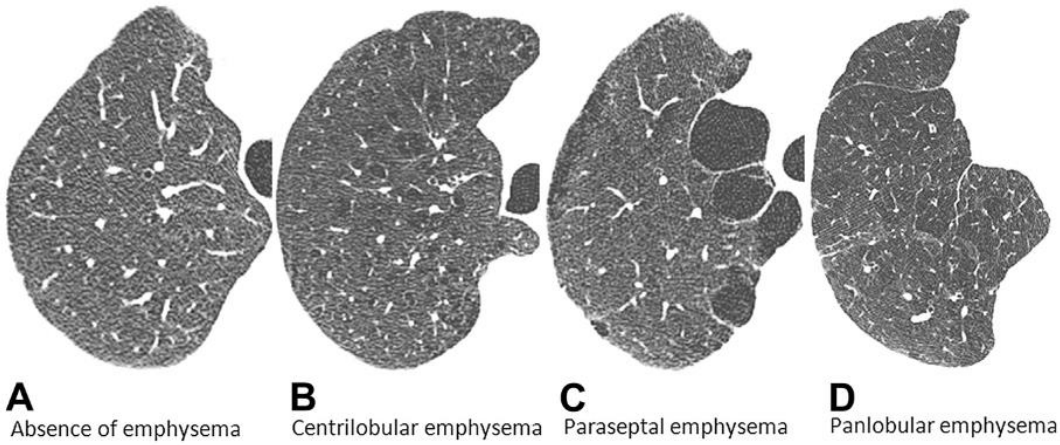

Figure 1.6 Computed tomography images for normal and different emphysema types, taken from: Smith, B.M., et al., Pulmonary emphysema subtypes on computed tomography: the MESA COPD study. The American journal of medicine, 2014. 127(1): p. 94. e7-94. e23.

1.4.3 Diagnosis of COPD

Patients with dyspnoea, chronic coughing, sputum production, and/or a history of exposure to risk factors should be evaluated for COPD [43]. Evaluation of COPD aims to ascertain the severity of airflow limitation, its effect on the patient's health condition, and the risk of future events to guide therapy.

In this clinical setting, diagnosis requires a spirometry test [44]; a post-bronchodilator FEV1/FVC <0.7 proves persistent airflow limitation and, therefore, COPD in patients with specific symptoms and substantial exposures to noxious stimuli [43]. The following assessments of COPD must be considered separately:

1.4.3.1 Classification of severity of airflow obstruction

In order to simplify the process, specific cut-points are used in spirometry. A short-acting inhaled bronchodilator should be administered before spirometry to minimize variability [43]. The severity of airflow limitations is illustrated in Table 1.1.

Table 1.1 Classification of COPD severity according to the Gold stage

Patients with FEV_1/FVC <0.7		
Gold 1	Mild	$FEV_1 \geq 80\%$ predicted
Gold 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
Gold 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
Gold 4	Very severe	$FEV_1 < 30\%$ predicted

It is worth noting that the correlation between FEV_1, symptoms and patient's health status is weak [45, 46]. Consequently, conducting a formal assessment of symptoms is imperative as well.

1.4.3.2 Symptoms assessment

Traditionally, COPD has been viewed as a disease characterized by breathlessness. It was considered adequate to measure breathlessness using the Modified British Medical Research Council (mMRC) Questionnaire because it correlates well with other health status measures and predicts future mortality [47, 48]. mMRC is described later (Section 1.6.3.2).

Despite this, dyspnoea is not the only effect of COPD patients [45]. A comprehensive assessment tool is necessary to assess symptoms in patients with COPD [33]. CAT stands for Chronic Obstructive Pulmonary Disease Test, which is a small test that can be used to evaluate the symptoms of COPD [49]. However, studies conducted among COPD patients found a moderate correlation between mMRC and CAT score [50, 51] and a weak correlation between CAT score and $\%FEV_1$ [50].

1.4.4 COPD in lung cancer

A study stated that 40%-70% of lung cancer patients suffer from COPD and noted that the probability of COPD is six times greater in lung cancer patients than in matched controls with a smoking history [52], implying that COPD and lung cancer might have some risk factors in common that are not related to smoking [4]. According to other research, 50% to 80% of lung cancer patients with a smoking history are affected by COPD [53]. There is evidence that patients with lung cancer who have COPD have a worse prognosis than those without COPD [54, 55]. In addition, Zhai et al., in their extensive study, involved 902 patients with NSCLC who had a

pulmonary resection. The authors found that COPD existed in 54.4% of the patients and reported that patients with COPD had a significantly lower 5-year overall survival (P = 0.000) than those without COPD.

Furthermore, among patients with and without COPD, the 5-year progression-free survival rates were 50.1% and 60.6%, correspondingly (P = 0.007) [56]. Evaluation and diagnosis of COPD at an early stage of lung cancer may improve prognosis and treatment decisions [57]. Due to the impact of COPD on lung cancer patients, it is vital to assess COPD in this cohort.

1.5 Sarcopenia in lung cancer

In 1988, the term sarcopenia was first defined [58] and was used to describe the physical component of a group of disorders characterised by significant loss of skeletal muscle mass and function. It has been identified as a predictive factor for various malignancies, including physical disability, poor quality of life, and mortality [59]. Historically, sarcopenia has been defined as the loss of skeletal muscle mass due to ageing. Nevertheless, it has now been established that loss of skeletal muscle mass can be caused by a variety of factors, including inactivity, a lack of adequate nutrition, disease, or a combination of these [59].

The prevalence of sarcopenia in lung cancer cohorts varies in the literature. According to Baracos et al., sarcopenia is more prevalent in lung cancer than in other types of cancer [60]. In contrast, another meta-analysis of 81,814 cancer patients stated that sarcopenia in lung cancer was less prevalent (36%) than in other cancer types [61]. While the prevalence of sarcopenia varies by the diagnostic criteria used to define the condition, it can reach 43% in patients with non-small cell lung cancer (NSCLC) and 52% in patients with small cell lung cancer (SCLC) [62].

Sarcopenia is correlated with poor overall survival in lung cancer patients. The findings of Kim et al. indicate that patients with sarcopenia and SCLC have a significantly shorter median overall survival (8.6 vs 16.8 months; P = 0.03) [63]. Tsukioka et al. [64] and Rossi et al. [65] discovered comparable findings in patients with stage I NSCLC and stage IV NSCLC ($p < 0.01$ and $p = 0.03$, respectively). Additionally, several studies have demonstrated Sarcopenia as a significant independent predictor of poor postoperative survival [66, 67]. It has been suggested that attention should be given to preventing perioperative sarcopenia after lung cancer resection [68]. It has been demonstrated that sarcopenia is associated with short-term postoperative outcomes, such as complications after surgery, hospital length of stay (LOS), and readmission [69-71].

Therefore, Identifying sarcopenia in patients with lung cancer who are undergoing lobectomy via thoracotomy, as well as those who experience other thoracic operations, may assist in the decision-making process before interventions and will contribute to future studies to improve risk stratification [69].

1.5.1 Diagnosis of Sarcopenia

In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) released the first consensus statement regarding the diagnosis of sarcopenia [72]. The working group identified Three stages of sarcopenia: pre-sarcopenia, sarcopenia, and severe sarcopenia [72]. An individual with pre-sarcopenia is defined as having a low level of skeletal muscle mass. In contrast, someone with sarcopenia has low skeletal muscle mass but does not have sufficient muscle strength or function, and someone with severe sarcopenia has low mass, strength and performance [72].

In 2019, the EWGSOP published an updated consensus statement on the diagnosis of sarcopenia. Instead of referring to pre-sarcopenia, the revised report provided an alternative algorithm that

can be used to facilitate the diagnosis of sarcopenia in clinical practice. It was recommended by the working group that sarcopenia be assessed by assessing muscle strength first. If this measurement is low, a measure of muscle mass or quality would be conducted [73]. Even though EWGSOP criteria are commonly used to define sarcopenia, there are several different definitions of the condition, and there is no consensus within the international community on diagnostic criteria for sarcopenia in older people.

As of today, there is no consensus regarding the optimal method of measuring muscle mass in cancer patients regarding their body composition. Sarcopenia measurements are performed using a variety of instruments, including anthropometric measurements, dual-energy x-ray absorptiometry (DXA), bioimpedance measurements, or computed tomography scans [74]. The anthropometric measurement, however, is limited by the overestimation of muscularity by 15-25% compared to CT measurements [75]. In addition, bioimpedance measurement is only beneficial for patients without "gross altered body composition" [76]. Moreover, DXA is not routinely used on patients with these conditions [77]. Muscle wasting has typically been assessed using body mass index (BMI) and body weight in patients with COPD [78]. The BMI cannot distinguish between the relative proportion of lean muscle and adipose tissue, so it may not be sensitive to early pathologic changes in body composition [79]. Cogswell et al. observed that early loss of skeletal muscle and functional alterations are often preceded by a measurable body weight loss [80]. In their discussion, the authors demonstrated how imaging was the only method of identifying early changes in skeletal muscles, thus the importance of these quantitative measurements of muscle changes [80]. There is a need to pay attention to the chest CT scan as it is routinely utilised to evaluate the disease's severity, eliminate other conditions, and assess extrapulmonary manifestations in patients suffering from COPD [78]. A number of studies have found that measuring the cross-sectional area of skeletal muscle on a single axial chest CT slice

may be a useful method of assessing local skeletal muscle mass [79, 81]. It is also important to note that chest CT scans and abdominal CT scans are applied as part of the routine clinical assessment of patients with COPD and lung cancer.

1.5.2 Sarcopenia and respiratory muscles' function

Sarcopenia has a profound effect on respiratory muscles' function, specifically in patients with COPD [82]. Respiratory sarcopenia characterised by respiratory muscles' weakening and atrophy resulting in respiratory muscles' fatigue and then may lead to a decline in lung function [83]. The main respiratory muscle, the diaphragm, is weakened in sarcopenia, resulting in diminished diaphragmatic mobility and inspiratory strength which increases respiratory deficiency [84]. Respiratory sarcopenia can negatively impact the ability of respiratory muscles to generate force, and lung function, which then negatively impact exercise tolerance and quality of life [84].

1.5.3 Sarcopenia and Health-Related Quality of Life

Few studies have examined the relationship between low muscle mass and quality of life among lung cancer patients. Researchers reported an association between lower skeletal muscle mass and lower global quality of life scores among men with advanced lung cancer who had first-line chemotherapy and reported a significant association between low muscle density and dyspnoea (n=734) [85]. Another study examined the difference in features of muscle cachexia measured on CT and quality of life in 241 cancer patients, of whom 36% were lung cancer patients. The authors reported clinically and statistically significant differences in global health scores between those with low muscle mass and those without (52 vs 64, respectively, $p < 0.001$) [86]. However, the study was limited as the skeletal muscle mass was measured at T4 level, which was not validated.

Furthermore, the authors used two different levels (T4 and L3) for the same muscle which may not offer reliable estimate of sarcopenia.

On the contrary, another study examined the association between HRQOL and low muscle mass in 1027 cancer patients. The research found no significant association between low muscle mass with different domains and overall quality of life scores [87]. However, data collection on QoL was not performed in timely manner, and patients might have been at various stages of their disease trajectory (81% received therapy in the preceding four weeks). It is also possible that patients have previously received treatment, which may have affected the QoL scores. These limitations make an overall conclusion about the relationship between QoL and low muscle mass extremely difficult. Additional discussion regarding CT assessment of sarcopenia in previous studies will be discussed in detail (Section 1.10)

Efforts should be made to conduct studies with a more consistent approach to HRQOL assessment. Data can be compared with pre-existing evidence when the EORTC QLQ-C30 is used for HRQOL assessment [88]. However, limited studies have examined the relationship between sarcopenia measured on CT and quality of life using EORTC QLQ-C30 in lung cancer patients [85-87]. Therefore, there is a need for more exploration in this area.

1.6 Dyspnoea following lung surgery

1.6.1 Dyspnoea overview

Comroe (1966) defined dyspnoea as “a subjective experience of difficult, laboured, and uncomfortable breathing that occurs when the demand for ventilation exceeds the individual’s ventilation capacity” [89]. Breathing difficulties include a variety of sensations that patients describe with an even more comprehensive range of words [90, 91]. Some common complaints

of dyspnoea include breathing too much or not breathing enough, taking deep breaths, gasping for air, or feeling tight in the chest or throat [92].

Objective measurement and subjective feeling may not be correlated, and the degree of physical modification may or may not mirror the subjective perception. On the one hand, some patients may have acute dyspnoea while exhibiting mild pathophysiological changes. On the other hand, other patients may have mild dyspnoea and a significant decrease in pulmonary function. Dyspnoea may have an impact on a patient's life in a variety of ways, decreasing activity and creating pain and suffering.

Apart from its significant burden, clinicians frequently underestimate dyspnoea [93]. More than half of lung cancer patients reported clinically significant dyspnoea symptoms, a common and distressing problem in these patients, ranging between 50% and 71% [15, 94-97].

1.6.2 Dyspnoea following lung surgery

Dyspnoea is a typical complaint in patients who have had pulmonary resection [98], and it is generally related to the loss of alveolar volume and limitation of the pulmonary vascular bed [99]. In a study that included 52 patients following lung resection, the authors found that dyspnoea was the most common and severe single complaint [100]. Additionally, they found that patients with pneumonectomy suffered worse dyspnoea than those with lobectomy [100-102].

It is worth noting that dyspnoea was reported in many longitudinal studies of lung cancer surgery. Although the short-term dyspnoea increase in these studies was consistent, the long-term dyspnoea results differed [11, 28, 101, 103, 104]. Studies noted that SOB recovered to preoperative scales at three months [105] and six months after lung resection [11]. There have

been several studies showing dyspnoea increase following lung resection surgery, with a start of recovery three months [106] and six months [107] after the surgery.

Therefore, the first six months are a critical period for observing the most pronounced and consistent changes in dyspnoea, thus justifying our targeted recruitment period for PROs. Additionally, evaluating perioperative factors and covariates that might affect the recovery of postoperative dyspnoea are paramount. Furthermore, It is imperative to investigate the aetiology of these high and persistent rates of dyspnoea since it negatively affects patients' mood, functional status, and QoL [103].

1.6.3 Dyspnoea measures

There are several grading systems available to quantify dyspnoea. Using instruments to measure dyspnoea contributes to standardising the symptom's description.

1.6.3.1 The Modified Borg Scale (MBS)

It is one of the most common scales used to measure dyspnoea during exercise tests. It has a vertical line to denote severity on the scale, with numbers 0-10 corresponding to severity descriptors [108]. To quantify dyspnoea, the patient can choose a number or a verbal description (Table 1.2).

Table 1.2 Modified Borg scale (mBorg).

Score	Description of difficulty of breathing
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	-------
7	Very severe
8	-------
9	Very, very severe (almost maximal)
10	maximal

On this scale, dyspnoea can be rated based on severity as long as the verbal descriptions describe the same intensity for each individual. While the mBorg scale can provide dimensional measurements of dyspnoea severity, it does not consider the factors contributing to breathlessness. It is also unclear whether the scale can be consistently used by different observers because there are no apparent criteria or standard principles for using it. While serial mBorg measurements of dyspnoea might provide information about changes within an individual patient, they are not suitable for comparing dyspnoea among patients or the conditions of groupings of patients. [109].

1.6.3.2 Medical Research Council Scale (MRC)

For many years, the Medical Research Council (MRC) dyspnoea scale has been used to measure the effect of breathlessness on daily activities. It is simple to administer since patients indicate the extent to which breathlessness affects their mobility [110]. The MRC score does not quantify

dyspnoea; instead, it quantifies breathing difficulty because it identifies dyspnoea that should not exist (grades one and two) or exercise limitations (grades three to five) (Table 1.3). MRC scoring is widely used in COPD-related pulmonary rehabilitation to stratify risk [111] and is commonly used to describe dyspnoea in lung cancer patients at multidisciplinary meetings.

Despite its widespread use in the medical literature, the scoring tool may not be sensitive enough to detect small but important changes in dyspnoea levels due to its broad grading system [112]. Several grades do not have precise definitions, which may contribute to this insensitivity. For example, someone who leaves the house but walks less than 100 yards does not clearly belong in grade 4 or 5 [113].

Table 1.3 Medical Research Council (MRC) dyspnoea scale [114]

Grade	Description
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on level ground or up a slight hill
3	Walks slower than most people on the level stops after a mile or so or stops after 15 minutes walking at own pace.
4	I stop for breath after walking 100 yards or after a few minutes on the level ground
5	I am too breathless to leave the house, or breathless when dressing/undressing

There has been a 'modification' of the scale, based on more simplified statements and referring to 'people' instead of just men, but it remains based on the same five stages of breathlessness [115]. There is confusion between the original grades, which range from 1 to 5 and the modified versions, which range from 0 to 4 (Table 1.4).

Table 1.4 Modified Medical Research Council (mMRC) dyspnoea scale [116]

Grade	Description
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness or have to stop for breath when walking at my own pace on the level.
3	I stop for breath after walking 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house, or I am breathless when dressing

1.6.3.3 The University of California and Sand Diego Shortness of Breath Questionnaire to measure dyspnoea (UCSD-SOBQ)

The UCSD-SOBQ is a standard and validated tool for measuring dyspnoea in the past week [117], and it includes 24 items with a range of 0 to 120 points. The questionnaire is similar to the MRC in that it is self-administered. In the UCSD-SOBQ, dyspnoea is measured by rating 21 everyday activities on a 6-point scale (0 = "not at all" to 5 = "maximal or unable to do because of breathlessness"). Nevertheless, using these daily activities does not account for the differences in effort [118].

1.7 Health-Related Quality of Life after lung surgery

1.7.1 HRQOL Overview

The World Health Organization defined quality of life (QoL) as “individuals’ perceptions of their position in life in the context of their culture and value systems in which they live and concerning their goals, expectations, standards and concerns” [119]. HRQOL indicates “how well a person functions in their life and his or her perceived wellbeing in physical, mental, and social health domains” [120].

The ability to measure patients' HRQOL, including physical, psychological, and social aspects, has been demonstrated using several patient-reported outcome (PRO) measuring tools. The term PRO encompasses any outcome directly informed by a patient (usually via a standardized questionnaire) [121]. When selecting the appropriate treatment for a patient, one should consider the patient's fears, expectations, and judgment. Moreover, HRQOL is a helpful tool for determining the effectiveness of different treatments. A clear and accurate understanding of how HRQOL changes after lung cancer surgery may allow the patient to engage actively in the

decision-making process [121]. Guidelines on radical patient management emphasise the importance of patient acceptance or refusal of surgical risks based on expected postoperative QoL [13]. Notwithstanding the expanding interest in PRO, the collection of HQOL data in clinics is still entirely lacking [122].

Nevertheless, it has been shown that objective parameters commonly used to estimate surgical risks, such as pulmonary function tests, diffusing capacity for carbon monoxide (DLCO), and age, are inaccurate when used to predict postoperative QoL, which is a subjective measure [27, 123]. Therefore, evaluating the predictive role of HRQOL in lung cancer patients is beneficial.

1.7.2 HRQOL after lung surgery

Health deterioration is a risk for lung cancer patients receiving curative treatments [124]. Patients with NSCLC commonly report worsened HRQOL prior to surgery [27, 125]. Several studies highlighted the deterioration in lung cancer patients' HRQOL immediately post-lung resection [11, 126-128], and other studies showed different recovery times in patients' HRQOL. The majority of studies found that lung cancer surgery negatively impacts physical HRQOL [14, 106, 129, 130]. Although symptoms burden reduced in the first few months after surgical treatment, they remained higher than preoperative levels after surgery [103, 106, 126]. Additionally, Pompili et al. (2018) indicated that global health/overall QOL had the most impairment in HRQOL and did not show recovery in 12 months after surgery [106].

There has been controversy about the time it takes for patients' HRQOL to return to normal after lung surgery, leading to questions about the factors that could affect a patient's HRQOL. In addition, it is crucial to identify lung cancer patients at an elevated risk of reduced HRQOL soon after receiving a lung cancer diagnosis [131].

1.7.3 HRQOL scoring instruments

Juniper et al. suggested selecting HRQOL questionnaire based on tools that have already been validated [132]. There are several factors to take into account when choosing a questionnaire, including the study's purpose, population, measurement properties, design issues, scoring, and data analysis [121].

HRQOL questionnaires are divided into generic and cancer-specific questionnaires. The two commonly implemented generic tools are the Short Form 36-item Health Survey (SF-36) and Euroqol-5 Dimension (EQ-5D) questionnaire [121]. The lung cancer-specific tools include the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core Module (EORTC QLQ-C30), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-LC13), Functional Assessment of Cancer Therapy-General Version (FACT-G) and Lung Cancer version (FACT-L), and Lung Cancer Symptom Scale (LCSS) [121].

According to a recent survey among European thoracic surgeons to understand the current practices of gathering and using data about QoL, 50% of thoracic surgeons used generic questionnaires. In comparison, 48.5% used cancer-specific questionnaires [133]. An illustration of the frequency of HRQOL questionnaires used is shown in Figure 1.7.

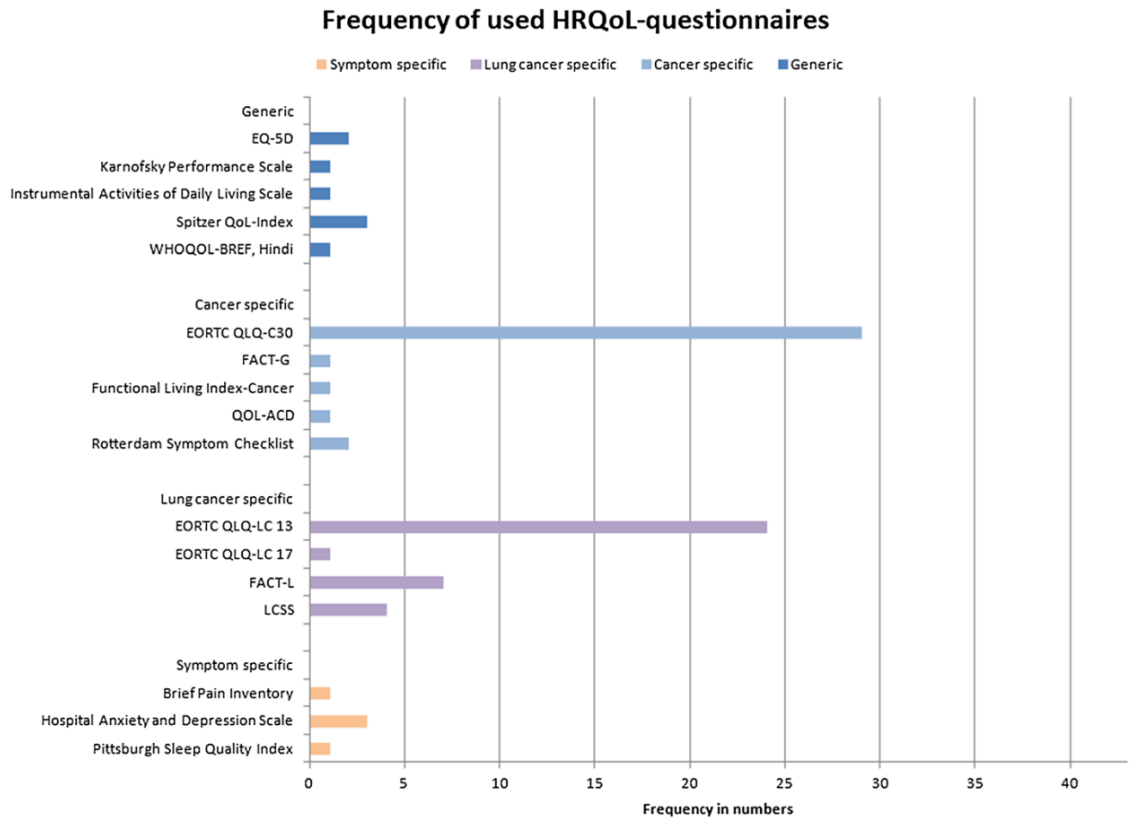

Figure 1.7 the frequency of different HRQOL questionnaires applied, EQ-5D; Euroqol-5 Dimension, QoL; quality of life, WHOQOL-BREF; World Health Organization Quality of Life- BREF, EORTC QLQ-C30; The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module, LC13; lung cancer module 13, LC17; lung cancer module 17, FACT-G; Functional Assessment of Cancer Therapy-General Version, FACT-L; Lung Cancer version, QOL-ACD; Quality of life assessment of chemotherapy for advanced cancer patients, LCSS; Lung Cancer Symptom Scale. taken from: Damm, K., N. Roeske, and C. Jacob, Health-related quality of life questionnaires in lung cancer trials: a systematic literature review. Health economics review, 2013. 3: p. 1-10.

1.7.3.1 SF-36 survey

SF-36 is a patient reported survey designed in the USA to provide valid normative data on the state of health of the general population in different countries using a wide range of medical conditions [134]. A major feature of this method is that it can be used to compare health status between populations and diseases [121]. This 36-item questionnaire assesses eight different areas of health: body pain (BP), general health perception (GH), mental health (MH), physical functioning (PF), emotional health-related role limitations (RE), physical health-related role limitations (RP), social functioning (SF), and vitality (VT) [121]. A linear transformation of data

initially scored on a 0–100 scale standardizes all health dimension scores in the SF-36 (v2). The mean of norm-based scores is 50, and the standard deviation is 10. A score of less than 50 implies a lower quality of life than the general population [121]. One advantage of this feature is that when the baseline assessment is unavailable, it helps the researchers compare measures directly and evaluate the long-term effectiveness of the treatment [121]. Yet, it is uncertain if SF-36 can detect small changes in physical or emotional functioning [135].

Moreover, SF-36 is a generic measure of HRQOL that attempts to cover all critical areas [135]. This was confirmed by a multi-centre study that measured HRQOL in 95 patients with NSCLC. They found that SF-36 failed to capture lung cancer symptoms and adverse effects caused by treatments; consequently, a disease-specific questionnaire would be more beneficial in assessing HRQOL elements [136].

1.7.3.2 EQ-5D questionnaire

EQ-5D is a generic measure used in health economic evaluations [137]. The EuroQol Group created it to define and evaluate health across various conditions [138]. This instrument outlines five single items: mobility, self-care, usual function status, pain and/or discomfort, and anxiety and/or depression. Though developers estimated that it just takes 5 minutes to complete the brief questionnaire, the EQ-5D is a generic measure and may not be sensitive to detect disease-specific conditions [139]. It has been shown to be effective in many areas of health. Nevertheless, there are some apparent gaps since it does not include all aspects of health and may not adequately reflect the advantages of specific interventions [140].

1.7.3.3 FACT-G and FACT-L tools

The FACT-G is a 27-item cancer-specific tool with four sections: physical, social, emotional, and functional wellness and a total score [141]. All items are statements rather than questions and are scored on a 5-point Likert scale. The FACT-G was created to assess the quality of life in cancer patients undergoing treatment [121]. The FACT instrument series has a core plus module. The FACT-L is a 10-item lung cancer-specific module that adds to the FACT-G to create a 37-item questionnaire. It has five sub-scales of self-assessment designed to evaluate lung cancer patients' quality of life during the last seven days, with each sub-scale utilising a 0–4 Likert scale. The FACT-L instrument takes 10 minutes to complete and consists of four general cancer-specific domains and one subscale specific to lung cancer [121]. Compared to the broad usage in oncological settings, it has been utilised less often in lung cancer surgery patients [121]. A study compared FACT-G and EORTC QLQ-C30 to Karnofsky's performance status (KPS) and found that EORTC QLQ-C30 had a superior ratio of true positive to false positive relative to KPS [142]. In another study, EORTC QLQ-C30 was compared to FACT-G regarding patient preference and was more favoured by patients than FACT-G [143]. Patients' preference for the EORTC may be explained by its emphasis on symptoms and traditional functional scales [143]. Failure to complete all questions is one of the potential consequences of PRO; therefore, patients' preference and acceptability for PRO are essential. During the FACT-G survey, there was a relatively low rate of missing items where they were reported; however, the rates tended to be higher [144].

1.7.3.4 LCSS

The LCSS measures QoL in clinical trials, specifically for disease-specific symptoms, and includes observer and patient sections [145]. On the patient form, nine questions evaluate seven symptoms (appetite, tiredness, cough, shortness of breath, pain, and overall symptom load), plus

two summary questions on functional activity and general quality of life in the context of lung cancer [121]. The same six symptoms, minus the overall symptom load, are evaluated in the LCSS observer's section. Each item is graded using a 100-mm Visual analogue scale (VAS), with 0 being the worst and 100 the best [121]. The first time, it takes 4 to 8 minutes to interpret the VAS; subsequent administrations take less time. The observer section takes two minutes to finish. Although LCSS showed high levels of reliability and validity [145], it lacks many of the critical elements of HRQOL, and its introductory statement mentions the word "lung cancer," which might be viewed as a limitation [146].

1.7.3.5 EORTC QLQ-C30

The European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire gauges patients' perceptions of QoL during clinical trials. The core questionnaire QLQ-C30 was published in 1993 and contains 33 questions that use single-item and multi-item scales (Appendix 1) [147]. The questionnaire involves five functional scales (physical, role, emotional, social and cognitive), nine symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties), and a global health scale. The 28 other questions use 4-point Likert scales ranging from "not at all" to "very much", whereas the two measures for global health use 7-point Likert scales [147]. The method for scoring these scales is to estimate the average of the scale's contributing elements (raw score) and then standardise the raw score such that it ranges from 0 to 100 using a linear transformation [147]. Higher scores on the symptom scales correspond to more severe symptoms, whereas higher scores on the functional and global measures suggest improved functioning and global health. This tool has undergone extensive reliability and validity testing [148, 149]. Besides, this survey has been considerably applied in lung cancer surgery [101, 150-153].

1.7.3.6 EORTC QLQ-LC13

The QLQ-LC13 is a lung cancer module produced by the EORTC research group as a supplementary disease-specific modular system to complement the main QLQ-C30 questionnaire and measure disease-specific QoL. A total of 13 questions on lung cancer-related symptoms such as haemoptysis, dyspnoea, discomfort, coughing, sore mouth, peripheral neuropathy, and hair loss are included in the questionnaire (Appendix 2) [147]. Patients with lung cancer were given this questionnaire in addition to the QLQ-C30, which was proven to be a clinically relevant and helpful instrument for assessing disease and treatment-specific symptoms. The time required to complete both questions is predicted to be 11–12 minutes [121]. Disease-related symptoms and treatment toxicity are the key scales.

It was validated in 883 lung cancer patients in 1994 and found effective. The dyspnoea score, for instance, had high psychometric qualities with a Cronbach's alpha value of better than 0.80 in numerous analyses [154]. The survey has also been translated into more than 60 other languages.

A substantial portion of surgeons supported using SF-36 as a generic tool for assessing the quality of life after lung cancer surgery. However, it is likely to miss some specific symptoms associated with lung cancer surgery used to compare general populations [133]. Several studies have shown that cancer-specific questionnaires are helpful for lung cancer clinical trials, incorporating the quality of life as a specific endpoint [155-158]. Furthermore, the patients need to consider how surgery affects their subjective symptoms when accepting the surgery's risks [159]. The British Thoracic Society and the Society for Cardiothoracic Surgery guidelines recommend using a validated HRQOL tool and not solely depending on pulmonary function and exercise testing [13].

The more recent lung cancer module (EORTC QLQ-LC29) is of particular interest because it retains 12 of the original 13 QLQ-LC13 items, and includes new items assessing side effects of targeted therapy, immunotherapy, chemoradiotherapy, and thoracic surgery [160]. In our study, we did not incorporate it since this module was not available at the time the study was conducted. Consequently, EORTC QLQ-C30 and LC-13 have been implemented in this thesis.

1.8 Predictors of Health-Related Quality of Life after lung surgery

This section aims to examine the evidence and literature for predictors of postoperative dyspnoea and global health/overall quality of life.

1.8.1 Predictors of Dyspnoea

Even though breathlessness is a significant symptom of advanced cancer, there is little knowledge regarding its trajectory and predictors [161]. A key aspect of managing breathlessness is identifying and treating any potential underlying cause [162]. A randomised clinical trial (RCT) evaluating interventions for possible underlying causes rarely includes breathlessness as a primary outcome. In contrast, validated patient-reported outcomes are infrequently used to assess breathlessness as a secondary outcome [163].

Several studies assessed the relationship between pulmonary function tests and postoperative HRQOL. A study stated that preoperative pulmonary function testing should be cautiously utilised in predicting postoperative HRQOL [28].

A prospective study involved 1689 cancer patients with palliative care to define predictors of dyspnoea measured by the Edmonton Symptom Assessment System (ESAS). The authors highlighted that lung cancer involvement was the strongest predictor for higher breathlessness scales. COPD was found to be a predictor for breathlessness as well. Interestingly, BMI was not

associated with higher dyspnoea. Lastly, pain and performance status measured by Karnofsky Performance Scale (KPS) were modifiable factors for future breathlessness. Nevertheless, the study was limited in many ways; one of these limitations is that data was collected from palliative care with different types of cancer with varying settings of treatment and was not focused on lung cancer patients only [161]. Because of the various types of cancer involved in the analysis, it is challenging to translate symptom burden to individual patients or cancer types [164].

Another prospective study collected data from 124 subjects who underwent primary pulmonary resection to evaluate the impact of age, comorbidities and postoperative complications on postoperative HRQOL to determine predictors of poor HRQOL more than six months postoperatively [165]. The study employed EORTC QLQ-C30 and LC13 to assess patients' HRQOL. The authors compared postoperative HRQOL between older (≥70-year-old) and younger (<70-year-old) patients. They found no difference between the two groups, although dyspnoea was slightly higher in the older group, not to a statistically significant difference. Additionally, the authors found that postoperative pulmonary complications (PPC) were associated with dyspnoea from QLQ-C30 ($p = 0.002$) and QLQ-LC13 at six months ($p = 0.019$). Not surprisingly, length of hospital stay (LOS) was positively associated with dyspnoea from both QLQ-C30 and QLQ-LC13 ($p = 0.026$ and $p < 0.001$, respectively) [165]. Lastly, the study highlighted that $\%FEV_1$ was a strong predictor of many components in functioning and symptoms scales and dyspnoea.

However, the above studies involved limited baseline and perioperative data, whereas other factors can be included to answer the research question better. For example, the latter study [163] assessed only respiratory rate, comorbidities and performance status along with QoL in the analysis. At the same time, other factors, such as lung function and BMI are essential in the assessment of postoperative HRQOL dyspnoea.

Other research was conducted on 252 palliative care patients to identify dyspnoea predictors using ESAS scores. The study noted that lymph node metastasis ($p < 0.01$), a history of the respiratory condition ($p = 0.04$) and pulse oximetry <90 ($p < 0.001$) were predictors of moderate/ severe dyspnoea over time [166]. Again, the study suffered from the diversity of cancer types and did not concentrate on one type. Similar to the studies above, the study did not assess other vital factors, such as lung function, in determining predictors of dyspnoea. Despite the controversy surrounding lung function tests' role as predictors of dyspnoea [22-24, 26, 125], they should be evaluated to have a comprehensive picture. Table 1.5 summarises various factors assessed in predicting postoperative dyspnoea in the literature.

Table 1.5 Summary of studies identified predictors of dyspnoea.

Author and year	Dyspnoea measure	Time frame for dyspnoea measure	Predictors assessed	Number of patients	Statistical Method	Factors with statistically significant associations
Dudgeon et al. 2001 [94]	1- Visual analogue scale (VAS) with 100 mm 2- Verbal rating scale for dyspnoea (VRS-D) graded as: none, mild, moderate, severe, horrible.	NA	Lung radiation, COPD, Asthma, Smoking.	923 patients with different cancer types	Stepwise logistic regression modelling	Lung radiation, p = 0.002 COPD, p = 0.019 Asthma, p = 0.001 Smoking, p = 0.003
Tanaka et al. 2002 [167]	Cancer Dyspnoea Scale (CDS)	NA	Psychological stress, anxiety, pain, cough, organic causes	171 outpatients with advanced lung cancer	Univariate Pearson correlation. Stepwise backward Multiple regression analysis	Psychological stress, coefficient = 0.29, p <0.01 Organic cause, coefficient = 3.55, p <0.01 Cough, coefficient = 2.09, p <0.01 Pain, coefficient = 1.39, p = 0.04

Sarna et al. 2004 [168]	modified version of the Division of Lung Disease American Thoracic Society (ATS) questionnaire	Within the past year	Sex, current smoking, ventilatory abnormality (obstructive and restrictive spirometry), number of comorbidity and bronchodilator use	142 disease-free patients who had NSCLC	Multivariate logistic regression analysis	Number of comorbidities, OR = 1.38, p = 0.03 Ventilatory abnormality, OR = 3.46, p <0.01
Feinstein et al. 2010 [169]	1- Preoperative dyspnoea (yes/no) 2- Baseline Dyspnoea Index (BDI) measured postoperatively	Postoperative dyspnoea measured 1-6 years post-surgery (current dyspnoea)	Age, sex, employment, education, preoperative dyspnoea, preoperative $\%FEV_1$, preoperative DLCO, presence of lung disease,	342 patients with disease-free, stage I, non-small cell lung cancer	Bivariate Pearson correlation and Multivariate logistic regression analysis	Preoperative dyspnoea, OR = 5.31, p <0.01. Preoperative DLCO, OR = 0.98, p <0.01 Any moderate/ strenuous physical activity (current), OR = 0.41, p <0.01.

			smoking, current physical activity			
Sterzi et al. 2013 [170]	EORTC QLQ-C30 and LC13	5 years following surgery (No baseline dyspnoea)	Age, sex, education, COPD, cardiovascular disease, myocardial infarction, type of surgery, %FEV_1, FEV_1, %FVC, FVC.	67 lung cancer patients with surgery	Student t test And analysis of variance (ANOVA)	dyspnoea was significantly different between age groups (age: >70 and <70), $P < 0.05$ dyspnoea in male vs female (15.2 vs 20.4, respectively), $p < 0.1$. dyspnoea in %FEV_1 1 quartile vs >1 quartile (41 vs 21.6, respectively), $p < 0.1$.
Ekström et al. 2016 [171]	Numerical rating of breathlessness (0-10)	Breathlessness was measured during the seven days before death	Gender, age, KPS, nausea and pain	12,778 Patients with palliative care (different cancer types)	multivariate random-effects linear regression	Male, $p = 0.02$ Age, $p = 0.001$ KPS, nausea, and pain $p < 0.001$

Bubis et al. 2018 [172]	ESAS	During the first year of disease diagnosis	Age, gender, and comorbidity burden	729,861 patients with newly diagnosed cancer (different cancer types)	Multivariable logistic regression	Female, OR = 0.93, p <0.05 Age > 70, OR = 1.14, p <0.05 High comorbidity burden, OR = 1.68, p <0.05
Marzorati et al. 2020 [128]	EORTC QLQ-C30	Baseline, 1, 4, 8, and 12 months after surgery.	age, gender, clinical perioperative complications, and type of surgery	176 lung cancer patients underwent lobectomy	Individual growth curve (IGC) models.	Association with dyspnoea at 1st month post operation: Baseline dyspnoea, coefficient = 0.42, p <0.001 perioperative complications, coefficient = 9.41, p <0.01
Matsunuma et al. 2022 [173]	Dyspnoea was classified into 3 levels: no dyspnoea, dyspnoea only during exertion,	7 days after hospital admission, (No baseline dyspnoea)	Age, gender, smoking, primary lung cancer, COPD, pain, pleural effusion, ascites, KPS score	1159 terminally ill cancer patients (different cancer types)	Univariate and multivariate logistic regression analyses	Primary lung cancer, OR = 2.8, p = 0.002 KPS ≤ 40, OR = 1.84, p = 0.04 Ascites, OR = 2.34, p = 0.002

	and dyspnoea at rest.					
Lin et al. 2022 [107]	EORTC QLQ-C30 And LC13	Baseline, 3, 6, 9, and 12 months after surgery	Age, gender, marital status, employment, smoking, alcohol consumption, history of cancer and lobectomy	53 lung cancer patients with VATS	Generalised estimating equation models (GEE)	Marital status, coefficient = 12.9, $p < 0.05$ Smoking, coefficient = 12.3, $p < 0.01$

There were different factors implicated in predicting dyspnoea in the studies described above. Most of the studies on lung cancer included a relatively smaller number of patients and a somewhat limited number of factors. It has been noted that some previous studies have had inconsistent results; for example, some studies have indicated that age is a good predictor for dyspnoea in cancer patients [170-172], while others have not [107, 128, 169, 173]. Moreover, smoking has been shown to predict postoperative dyspnoea in some previous research [94, 107], whereas others have not [168, 169, 173]. All of the studies summarised above (Table 1.5) have produced inconsistent results, which can be attributed to limited factors in their studies or the focus on different cohorts besides lung cancer patients. Besides, it is necessary to define predictors of dyspnoea using a large sample and investigating various demographic and perioperative factors that have been shown to impact a patient's dyspnoea.

The value of using EORTC QLQ-C30 and LC13 was discussed previously (Section 1.7.3.5. and 1.7.3.6). In addition, Pompili et al. defined EORTC QLQ-C30 and LC13 as “The Instrument of choice” for measuring the quality of life in the context of thoracic surgery due to its detailed analysis of particular symptoms and disease specificity in its validation [156].

The dyspnoea scale from EORTC QLQ-C30 has been selected as the primary outcome measure in the presented thesis.

1.8.2 Predictors of Global Health

The quality of life declines more in lung cancer patients than in other cancers and conditions [174]. Recently, there has been a growing interest in the quality of life following lung resection [101]. The assessment of a patient's QoL should be conducted using a validated instrument to optimise the delivery of care and improve the patient's health outcomes [13]. When attempting to predict surgery risks and suitability, clinicians rarely consider QoL [175] and cancer treatment benefits must be weighed against side effects and potential impairments in quality of life [101].

A recent influx of literature offers contradictory conclusions about predictors of postoperative HRQOL. In the assessment of lung function, Brunelli et al. conducted prospective research on 156 subjects and measured QoL using SF-36 at baseline, one, and three months following the intervention. The study revealed that patients who underwent lung cancer resection had a worse QoL at one month following lung surgery compared to baseline levels ($p<0.001$) [27]. It was found that preoperative FEV_1 or DLCO did not correlate with QoL ($r = 0.2$, $p = 0.9$, and 0.8, respectively). The study also demonstrated that 'high-risk' patients (as defined by ppoFEV_1% and ppoDLCO% <40%) could undertake lung resection safely and have acceptable QoL values after surgery. There was no difference between the QoL scores from the high-risk group (n=12) and their low-risk group counterparts at three months ($p=0.3$). Additionally, Ilonen et al. examined associates with QoL measured by 15-D tool in 53 patients with NSCLC who underwent lobectomy or bilobectomy. The authors found a reduction in QoL breathing ($p = 0.003$) and total score of QoL ($p = 0.028$) between those with %FEV_1 <70 (n=13) and %FEV_1 ≥70% (n=30) at 3, 12, and 24 months after surgery [28]. In contrast, earlier studies assessed predictors of quality of life by SF-36 6 months following lung cancer surgery in 139 patients. They found that baseline DLCO but not FEV_1 predicted poor postoperative QoL. Age, 6-minute walk test, cancer stage, induction chemotherapy, adjuvant therapy, the extent of surgery, and postoperative complications

were not associated with poor QoL [125]. Other studies agreed with the previous results that FEV_1 [11, 176-178] and $ppoFEV_1$ [179] were not associated with postoperative QoL. While some studies demonstrated that DLCO predicted postoperative QoL [11, 125], others found no association between DLCO and postoperative QoL [27]. In terms of smoking, previous studies have shown conflicts in the association between smoking and QoL [104, 107, 177]. In addition, a similar study found no association between smoking habits and postoperative global health measured in 53 patients after treatment [107]. A previous study evaluated modifiable factors associated with the global health of EORTC QLQ-C30 measured 12 months after treatment in 75 lung cancer patients and found that smoking was not associated with post-treatment global health [177]. This can be due to the limited sample size in the previous studies. In contrast, other research revealed an association between smoking and QoL in lung cancer patients [180]. Additionally, age and gender were not associated with QoL in several studies [104, 107, 176, 177]. Researchers consistently report that residual quality of life is adversely affected by the extent of lung surgery [27, 181, 182]. Schulte and colleagues reported that pain, function, role functioning, global health, and general health scales clinically significantly improved three months postoperatively after lobectomy compared to pneumonectomy [181]. Previous studies noted that baseline global health was associated with postoperative QoL [128, 179]. Other studies found no significant association between tumour stage or adjuvant therapy and postoperative global health [170, 182]. Moreover, postoperative complications [182] and comorbidity scores [183] have been shown to affect postoperative quality of life. However, there has been little comprehensive evaluation of the factors associated with postoperative QoL, and most studies have used small samples [28, 183] or assessed relatively limited factors [125, 182]. This thesis will employ a wide range of baseline and perioperative factors to define predictors of postoperative global health in lung cancer patients.

1.9 Quantitative Computed Tomography of emphysema

1.9.1 Computed Tomography

Computed tomography (CT) is a non-invasive radiation imaging tool for assessing structural and pathophysiological abnormalities, leading to a deeper understanding of COPD disease and its classifications [184, 185]. Although CT scan is known for its radiation risks, it is a valuable tool in diagnosis and research.

High-resolution CT (HRCT) is a method for evaluating emphysema in vivo and owing to its high spatial resolution, it is a favourable tool for detecting small patches of emphysema visually [186]. Pulmonary emphysema can be assessed visually or through quantitative techniques such as CT density analyses [187].

Visual grading of emphysema using CT scans was the basis for detecting and classifying structural abnormality of the lungs [5] before introducing sophisticated software for emphysema quantification. Emphysema is recognised as low attenuation areas with hypo-vascularity [188]. Several techniques are applied in visual scoring, and one of the most common techniques is the modified Goddard system [188]. This scoring system involves four grades starting with zero for the lung scans with no visualised abnormality and ending with 4 for complete emphysema involvement and absence of normal structure [188]. However, The principal limitations of this approach are that it is time-consuming and exhibits an inter and intra-observer variability that increases with emphysema severity [187]. Moreover, Miller et al. noted that small emphysema lesions, less than 5 mm, are difficult to detect [189]. Hence, objective approaches for emphysema detection are highly beneficial.

1.9.2 CT densitometry

CT densitometry is a technique for measuring radiation attenuation through the lungs by means of technological and methodological tools [190]. X-ray photons emitted may pass, be scattered by a structure or be absorbed to different extents depending on the beam's energy and the structure's characteristics, and this absorption is termed attenuation [191]. Figure 1.8 represents the process of CT scan acquisition. In CT scan, radiation beam attenuation is measured, and radiodensity is expressed by a unit called Hounsfield unit (HU), where 1000 HU represents bone density, whereas -1000 represents air [192] (Figure 1.9).

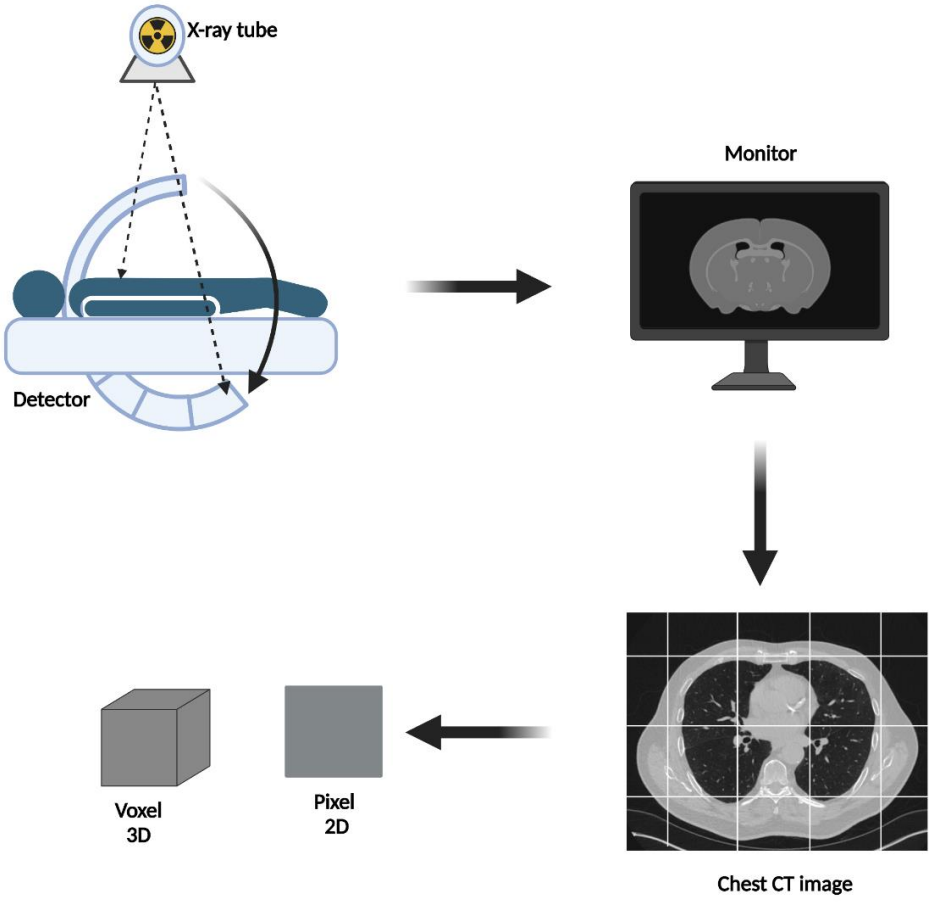

Figure 1.8 Image acquisition process of CT scan.

X-ray photons that pass through the patient reach the detectors. Then a number of processes occur until they are converted into digital format to create an image with different density levels [191]. The data from each CT slice is divided into sections. These sections are 2D squares called pixels that contain Hounsfield unit value, and a 3D volume element is a voxel [191]. A CT image on the monitor is a combination of thousands of pixels [191]. Objects shown on CT scan images are presented by different shades of grey; for example, white areas in the CT images represent those objects that completely absorb X-ray photons and vice versa [191].

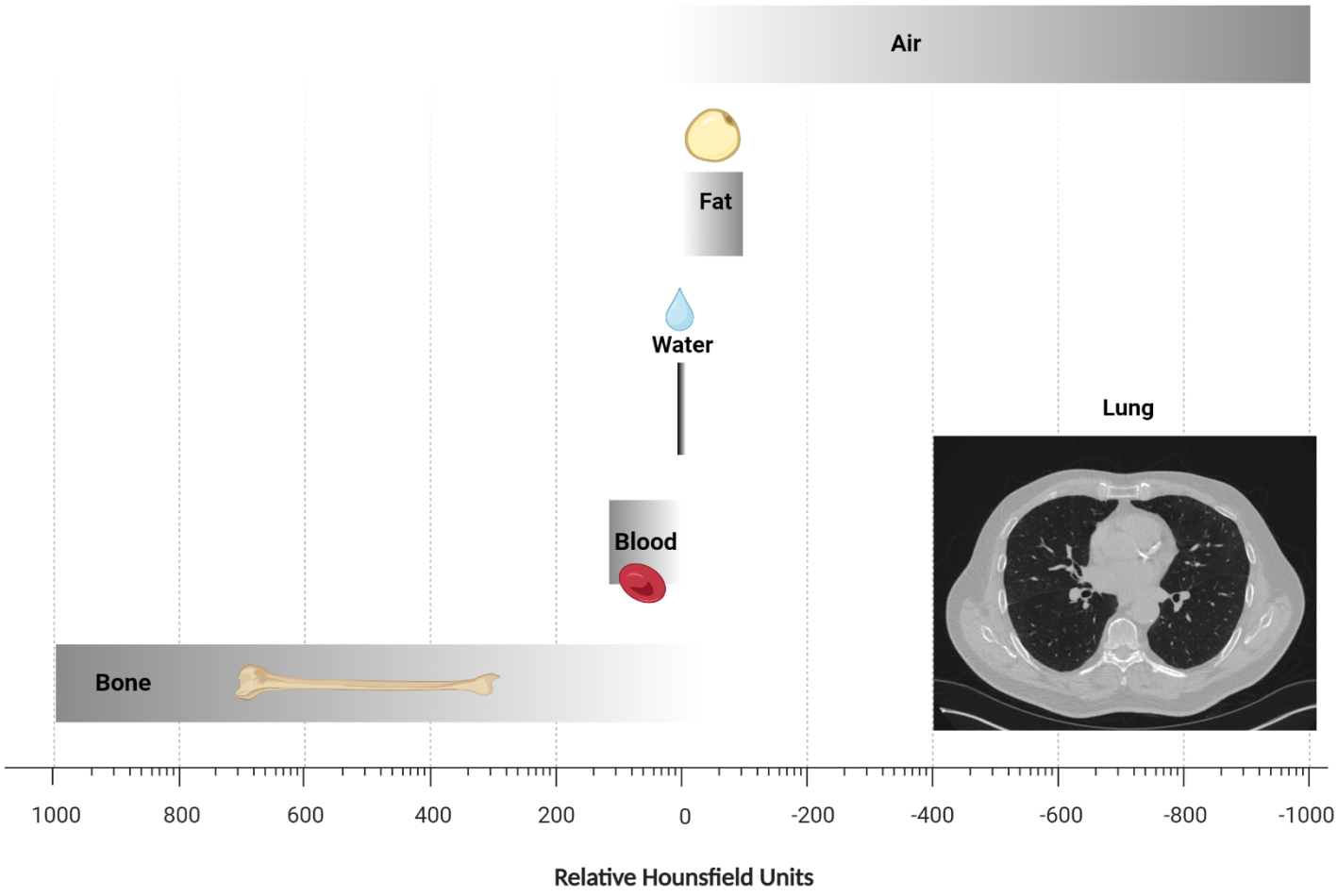

Figure 1.9 Relative density ranges of CT scan in Hounsfield Units (HU) for different structures

1.9.3 CT densitometry for emphysema

At first, basic emphysema quantification was employed using a visual scoring system [188]. Then objective quantification was developed, and two main techniques were used. One method is where the low attenuation percentage (%LAA) is calculated by applying a density mask to lung parenchyma below a threshold, which indicates emphysema. The threshold of -950 and -910 HU are frequently used; while the former has shown a strong association with microscopic and macroscopic emphysema [193, 194], the latter was initially used and showed a high correlation with pathologic measures of emphysema [195]. The emphysema severity can be read by calculating the percentage of low attenuation area (%LAA) for a particular density threshold under the histogram curve [196] or through the percentile density. The 15^{th} percentile (PD15) is commonly utilised, a point under the curve with a set HU threshold below which 15% of the lowest density voxels are distributed [196-198]. Also, the PD15 of the threshold -950 HU was found to have a significant correlation with FEV_1 [199]. An example of a lung density histogram is represented in Figure 1.10.

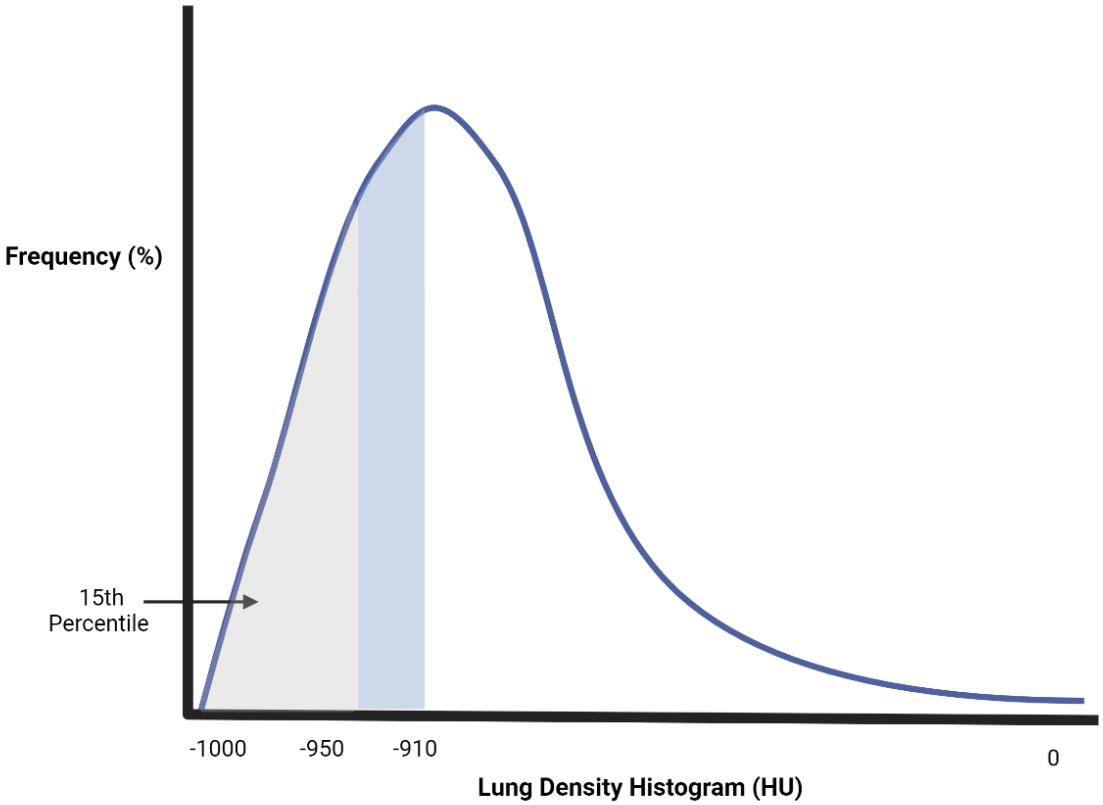

Figure 1.10 An example demonstrating lung density histogram using 15th percentile at the thresholds -950 and -910 HU

1.9.3.1 CT densitometry and dyspnoea

CT densitometry for pulmonary emphysema has been associated with increased dyspnoea [200-202]. The COPDGene trial (2012) included 10192 current and ex-smokers with comprehensive clinical data and baseline CT; almost 50% of their cohort suffered from COPD. In a subset analysis of 1200 individuals, they investigated the relationship between quantitative CT of emphysema and dyspnoea along with other measures, such as body mass index, airflow obstruction, dyspnoea, and exercise capacity (BODE index). They noted that quantitative CT emphysema (%LAA-950) had significantly

influenced the BODE index (regression coefficient 1.23, 95% CI; 1.20-1.26) [202]. In comparison, another study investigated the relationship between dyspnoea measured by MRC and quantitative %LAA emphysema on CT using -950, -910 and -856 HU [203]. In the study, %LAA -950 HU was an independent factor to dyspnoea, whereas other thresholds were not (OR 1.87, 95% CI; 1.52 - 2.31) [203]. National Emphysema Treatment Trial (NETT), a widely-cited randomised controlled trial, investigated gender differences in severe emphysema involving 1053 patients and measured %LAA -910 HU on QCT [204]. The authors measured dyspnoea using the University of California, San Diego Shortness of Breath Questionnaire (UCSD SOBQ) and employed a modified BODE index (mBODE). The study conducted a separate multivariate regression analysis to predict mBODE, dyspnoea and other factors adjusted for age, sex, pack-years and $\%FEV_1$ and reported a significant association between whole lung emphysema and the mBODE index but not the UCSD SOBQ measure [204]. Another study showed a weak correlation between baseline %LAA -960 HU and dyspnoea using modified British Medical Research Council mMRC ($r^2 = 0.06$) [205]. However, this study involved 65 patients with stable COPD; most of the cohort were male. The results are in agreement with previous findings that reported a weak correlation between %LAA-950 and -856 HU with BODE index [206]. A retrospective study incorporated 350 patients who underwent lung resection for primary lung cancer and calculated %LAA -910 HU and total lung volume (TLV) with densities -600 - -910 HU. The study compared patients who suffered from postoperative dyspnoea against controls and found that patients who had dyspnoea following surgery had significantly higher %LAA/TLV [207]. However, the study was limited to the number of patients who experienced dyspnoea which was 14 compared to 276 controls. Another limitation of this study is that the study did not state the tool used to measure dyspnoea [207]. Overall, previous studies have not assessed longitudinal changes in dyspnoea in lung cancer patients. Thoracic symptoms can be evaluated longitudinally to produce comprehensive and robust results. Currently, no information is available

regarding whether CT emphysema is associated with EORTC QLQ-C30 dyspnoea following lung cancer surgery. Table 1.6 summarises the studies that implemented QCT density and different dyspnoea measurements.

Table 1.6 Summary of studies demonstrated the relationship between QCT densitometry of emphysema and dyspnoea.

Author and year	CT densitometry	Dyspnoea measures	Cohort	Statistical method	Other variables studies	Results
Camiciottoli et al. 2006 [208]	%LAA-950	MRC	51 patients with COPD	Univariate logistic regression	NA	%LAA-950 vs MRC, OR = 1.41, P <0.005
Martinez et al. 2007 [204]	Whole lung %LAA-910	UCSD SOBQ	101 patients with COPD	Multivariate linear regression	Adjusted for age, sex, pack years and $\%FEV_1$	%LAA-910 vs UCSD SOBQ, r^2= -5.5, P = 0.2
Grydeland et al. 2010 [203]	%LAA-950 %LAA -910 %LAA -856	MRC	463 participants with COPD 488 participants without COPD	Multiple ordinal logistic regression	Adjusted for sex, age, smoking, and	%LAA-950 vs MRC, OR = 1.87, P <0.05

					level of inflation	
Haruna et al. 2010 [205]	%LAA-960	mMRC	65 participants with COPD	stepwise multiple regression analyses	Adjusted for FEV_1, RV/TLC and other functional measures	%LAA-960 vs mMRC, r^2= 0.06, P <0.05
Martinez et al. 2011 [202]	%LAA-950	BODE	1200 patients with COPD	Univariate zero-inflated Poisson regression	age, gender, smoking status and scanner type	%LAA-950 vs BODE, Coefficient = 1.23, P < 0.001
de Torres et al. 2011 [209]	%LAA-960	BODE mMRC	115 patients with COPD	Pearson correlation	NA	%LAA-960 vs BODE, r = -0.08, P = 0.53 %LAA-960 vs mMRC, r = -0.19, P = 0.14

Camiciottoli et al. 2012 [210]	%LAA -950 %LAA -910	BODE	72 participants with COPD	Person correlation	NA	%LAA -950 vs BODE, r = 0.58, %LAA -910 vs BODE, r = 0.67,
Oelsner et al. 2015 [211]	%LAA -950	mMRC	1969 participants without cardiopulmonary diseasr 1796 participants without dyspnoea, 173 participants with dyspnoea	multivariable logistic regression	Adjusted for age, sex, BMI, physical activity, anxiety, and leg pain	%LAA -950 vs mMRC, Wald X^2= 7.07, P = 0.008
Nambu et al. 2016 [206]	%LAA-950 %LAA -856	BODE	188 current and former smokers	Univariate Multivariate	NA	In the univariate regression: %LAA -950 vs BODE, r^2= 0.29, P < 0.001

				Linear regression		%LAA -856 vs BODE, r^2= 0.35, P 0.35
Cui et al. 2017 [212]	%LAA-950	mMRC	124 patients with COPD	Comparison	NA	%LAA-950 ≥ 9.99, mMRC = 2.3 vs %LAA-950 <9.9, mMRC = 1.6 P < 0.001
Yasui et al. 2019 [213]	%LAA-950	mMRC	42 patients with COPD	Spearman correlation	NA	%LAA-950 vs mMRC, r = 0.29, P = 0.06

The above studies focused on measuring dyspnoea using MRC or other metrics, such as the BODE index that measures dyspnoea combined with other measures to assess COPD exacerbations.

To our knowledge, no studies have investigated the association between QCT emphysema measurements and dyspnoea scores measured by EORTC QLQ-C30. This tool is a validated cancer-specific tool, and its greater sensitivity to detect changes in cancer patients [214] makes it attractive to implement in the thoracic surgery setting. Pompili et al. concluded that EORTC should be considered in thoracic surgery due to its thorough assessment of lung cancer-specific symptoms [156]. To our knowledge, there is a current lack of studies investigating the role of QCT in predicting the long-term effect of surgery on lung cancer patients' dyspnoea. Consequently, examining the relationship between QCT measures and dyspnoea using EORTC QLQ-C30 is vital.

1.9.3.2 CT densitometry and Quality of life (QoL)

Previous studies have shown a significant association between QoL measures and QCT of emphysema. Several studies assessed the connection between QCT emphysema and QoL using St. George Respiratory Questionnaire (SGRQ) in COPD participants with a smoking history and found that SGRQ was associated with %LAA-950 [201, 215]. The COPDGene study analysed 8034 CT scans using %LAA-910 and %LAA-856 to define their association with a variety of factors involving QoL measured by SGRQ. The study found that there is a significant relationship between %LAA-910 and SGRQ (regression coefficient 0.19, 95% CI; 0.16 – 0.22) and %LAA-856 and SGRQ (regression coefficient 0.28, 95% CI; 0.25-0.31) adjusted for $\%FEV_1$, age, sex, race, BMI, smoking information, CT scanner type, and CT airway wall thickness [216]. However, this study focused on baseline QoL only as their cohort were only current or former smokers without therapeutic interventions. Another study investigated the role of regional emphysema measures in predicting overall survival, QoL, and pulmonary function recovery in 1,073 patients with early-stage lung cancer. QoL was measured within two years post-surgery using Lung Cancer Symptom Scales (LCSS) while regional emphysema scores were assessed using %LAA-950 for six lung zones, and regional emphysema scores were divided into mild (≤5%), moderate (6%-24%), and severe (25%-60%). The patients were divided into groups according to the tumour location: lung cancer in the emphysema region with surgery, lung cancer in the non-emphysema region with surgery, and lung cancer without surgery treatment. There was no significant difference in QoL between the three groups [217]. However, the study only collected the survey postoperatively and did not collect baseline surveys to determine the difference in QoL after an intervention. COPDGene study noted an association between %LAA-950 and SGRQ quality of life in a subset study of 1200 COPD patients [202]. Similarly, Gietema et al. [215] found that %LAA-950 was associated with SGRQ quality of life in 1778 COPD cases. To the best of our knowledge, there has been no study investigated the

relationship between QCT emphysema measurements and lung cancer patients' EORTC QLQ-C30 global health scores. Therefore, our research investigated the relationship between QCT emphysema and global health in the lung cancer cohort.

1.10 Quantitative Computed Tomography of Body Composition

1.10.1 Overview

The impact of sarcopenia on lung cancer patients has been reviewed (Section 1.5). In radiographic imaging, muscles can be quantified objectively, known as body composition analysis [218]. CT offers a new lens for evaluating skeletal muscles in vivo, incorporating the quantification area, volume, and attenuation of specific tissue [219]. CT scan images are acquired as part of routine care, and body composition is analysed on these images to leverage existing information without exposing patients to additional tests or radiation [220]. CT-based body composition analysis allows radiologists to derive additional information from images acquired for tumour staging, surgical planning, and treatment monitoring in patients with lung cancer [221]. The significance of body composition as a marker of skeletal muscle dysfunction is increasingly recognised. The use of CT to measure the body composition of different muscle types in interventional cardiology, intensive care, and oncology has been investigated previously [221-224].

Nevertheless, a literature search revealed very few studies evaluating the impact of CT-based body composition on quality of life and dyspnoea in lung cancer patients. Most of these studies assessed multiple cancer cohorts simultaneously rather than focusing exclusively on patients with lung cancer. Furthermore, these studies demonstrated inconsistent findings between muscle measurements and HRQOL (Section 1.5.2) [85-87, 225, 226].

1.10.2 QCT of pectoralis muscles

Pectoralis muscle area, index and density have been investigated in different fields. A well-recognised study (COPDGene) assessed the pectoralis muscle area (PMA) on CT in 484 COPD cases and 484 healthy controls. They indicated significantly reduced pectoralis area in COPD patients compared with the controls. The study found that PMA was associated with the GOLD stage of the disease and the functional disease markers, including the BODE index, MRC dyspnoea score and 6MWD [79]. Similarly, Kinsey and colleagues prospectively assessed PMA on CT scans in 252 NSCLC cases and found that lower PMA was linked with a higher hazard of death by 2%. The authors also highlighted that PMA was independently associated with age and BMI [77].

In contrast, Bak et al. evaluated PMA and pectoralis muscle density (PMD) in 222 participants with COPD. Based on PMA (cm^2) or PMD (HU), participants were categorised into three tertiles: tertiles 1 (lowest), 2, and 3 (highest). They found that PMA was significantly associated with the CAT score ($p = 0.03$) but not the mMRC score, whereas PMD was not associated with either factor. There were no associations between PMA or PMD and changes in FEV_1 for three years [78]. The researchers imply that these measures can help predict disease severity but not longitudinal changes in lung function [78]. Another large study measured PMA in 1696 participants who underwent CT lung cancer screening and found that lower PMA was associated with lung cancer development [227]. These studies, however, used pectoralis muscle area but not index in their analysis, and some of them have not used a cut-off or stratifications in muscle measurements to define low pectoralis muscles.

Inversely, Miller and colleagues employed different approaches and separately measured pectoralis muscle index (PMI) and erector spinae index (ESMI) in 299 patients with lobectomy. The researchers reported that ESMI and PMI were not associated with all complications, ICU stay, or readmission. However, ESMI was significantly associated with 30-day mortality ($p = 0.03$) and length of hospital stay ($p = 0.01$) but not PMI [71]. Nevertheless, this study was limited to the lack of defining

sarcopenic patients as there was no cut-off value or group stratification for determining low muscle measurement. On the contrary, a recent study investigated the pulmonary and extra-pulmonary features of 193 COPD patients. The authors assessed PMI and ESMI and demonstrated that PMI, but not ESMI, was associated with low physical activity scores [228]. However, there was no stratification for low PMI or ESMI. The authors stratified the patients based on CAT scores only.

There has been heterogeneity in the approach used by previous researchers to measure pectoralis muscle. In addition, we noted no assessment of the association between low pectoralis muscle and HRQOL in lung cancer surgery patients. In addition, pectoralis muscle measurement is easy to perform. It can be acquired from a wide range of CT scans where abdominal scans are unavailable, such as lung cancer screening cohort [229]. Therefore, the presented study aims to investigate the association between pectoralis muscle and postoperative dyspnoea and quality of life after lung cancer surgery. A summary of the methodology implemented for measuring pectoralis muscle on CT scan is summarised below (Table 1.7)

1.10.3 QCT of Erector spinae muscles

Previous studies assessed the impact of ESM wasting and postoperative outcomes in different cohorts and revealed conflicting conclusions [71, 228]. A study was conducted on 3705 smokers without airflow obstruction and measured CT-based PMA and erector spinae muscle area (ESMA). They found that PMA but not ESMA was associated with increased mortality [229]. Similarly, another study evaluated 117 COPD candidates for lung volume reduction procedures. They indicated that PMA was positively associated with FEV_1, FVC, DLCO, and FEV_1/FVC ratio and was negatively associated with emphysema scoring. However, ESMA was positively associated with DLCO and

negatively associated with the radiographic severity of emphysema. Moreover, lower PMA but not lower ESMA was associated with mortality [230].

Yet, these results were inconsistent with other studies that highlighted the impact of low ESM on the outcomes of different cohorts, including lung cancer patients. In contrast to the above studies, previous research investigated the effect of low PMA, PMD, ESMA and erector spinae muscle density (ESMD) on 199 patients with idiopathic pulmonary fibrosis. They revealed that only ESMA was significantly associated with all-cause mortality but not PMA, PMD or ESMD [231]. In agreement with that, Takamori et al. stated that lower ESMA was an independent prognostic factor for short disease-free survival ($p = 0.01$) and overall survival ($p = 0.007$) in 101 patients with NSCLC patients with lung resection [232]. Notably, the authors observed that poor performance status and poor FEV_1 (<70%) were independent risk factors for ESM loss [232]. Likewise, Tanimura and colleagues investigated ESMA's impact on 130 male COPD patients. Their Cox proportional hazard model revealed that ESMA was the strongest risk factor for mortality. However, the authors reported that ESMA was significantly but moderately correlated with BMI, dyspnoea (mMRC), QoL (SGRQ), DLCO and CT emphysema (%LAA<-960 HU) [233]. The results were limited, however, by measuring ESM from male patients only. Overall, there was a discrepancy between the approaches, cohorts, and results of the studies described above. Also, there is a lack of information concerning the association between ESM and QoL following lung cancer surgery. The approaches used in measuring ESM are summarised below (Table 1.7).

1.10.4 QCT of Psoas muscles

Previous researchers recommended measuring the psoas muscle index (PSMI) on CT at the third lumbar level, and it was found to strongly predict the total body's skeletal muscle mass [234]. Kawaguchi et al. assessed sarcopenia using PSMI in 173 who had lobectomy for NSCLC. The authors measured PSMI at L3 on CT and used cut-off values of 3.7 (cm^2/m^2) for male and 2.5 (cm^2/m^2) for female participants. The results demonstrated that postoperative complications were more prevalent in patients with sarcopenia than those without (62.5% vs. 22.7%). In addition, the 5-year survival rate was 39.8% lower in patients with sarcopenia than those without sarcopenia [235]. Nakamura et al. confirmed these findings and demonstrated that sarcopenia in psoas muscles was associated with major postoperative complications and prognosis in a cohort of 328 patients with NSCLC who underwent curative resection [236]. Another study assessed sarcopenia by measuring psoas muscle in 391 NSCLC with lung resection and found that sarcopenia was associated with poor overall survival and shortened disease-free survival [237]. However, a comparison of sarcopenic and nonsarcopenic patients did not reveal any differences in the incidence of postoperative complications [237]. Their results, however, were based on the measurement of the psoas muscle index only, without considering other parameters. This result was also supported by Nakada and colleagues, who demonstrated that sarcopenia measured on the psoas muscle was not associated with postoperative complications in 173 NSCLC patients with lobectomy ($p = 0.7$). In addition, they indicated that sarcopenia was not associated with disease-free survival [238]. Despite the results being in agreement with recent results [239, 240], the analysis did not take into account emphysema, an essential measure in the lung cancer population.

Previous studies on sarcopenia in lung cancer patients have only focused on its relationship with overall survival, disease-free survival, and postoperative complications and pay little attention to

patients' dyspnoea or global health measured on PRO. Table 1.7 summarises the methods employed to measure psoas muscles.

1.10.5 QCT of Skeletal muscles

Research has demonstrated that the cross-sectional area of skeletal muscles (SMA) at the level of the third lumbar vertebra (L3) on axial CT scans is an accurate indicator of total body mass [241]. Although other studies have investigated whether the T4 vertebral level could serve as an alternative to the L3 level, the results have demonstrated that the T4 level cannot effectively replace the L3 level [242]. Nonetheless, some patients may not necessarily undergo an abdominal CT scan as part of their routine clinical examinations.

Skeletal muscle index (SMI) has been used as a surrogate for sarcopenia in several studies, and it is calculated by dividing SMA by height^2 [243, 244]. It has been shown that sarcopenia measured by L3SMI is associated with clinical outcomes, including survival and hospital length of stay, in various patient populations, including NSCLC patients [245, 246]. In contrast, Halpern et al. have identified no relationship between sarcopenia of L3SMI and survival after lung transplantation [244]. Furthermore, the authors concluded that sarcopenia was not predictive of patients' postoperative outcomes related to hospital length of stay, readmission, complications, or discharge destination [244]. This study was limited, however, by the inclusion of heterogeneous thoracic diseases that may result in varying degrees of muscle wasting. In addition, Stene et al. reported that skeletal muscle mass change, rather than baseline sarcopenia, was a significant predictor of response to chemotherapy in patients with NSCLC [247]. It should be noted, however, that their conclusions were based on a small sample size, limiting the power of survival analysis.

It was noted that there was a significant variation in the approaches used by these studies, particularly in the choice of the measurement levels for skeletal muscle and the cut-offs for defining sarcopenia. For instance, Stene et al. have chosen the cut-off values established by Prado et al., which is summarised in Table 1.7 [243, 247]. This cutoff value, however, was derived from obese individuals without taking into account data from normal or low-BMI individuals. Therefore, applying these cutoff values to subjects with different BMIs may not be appropriate. Martin et al. proposed alternative sarcopenia thresholds based on a study of 1473 lung and gastrointestinal cancer patients. Compared with previous methods, these thresholds offer a more inclusive approach, encompassing a range of BMI categories [221]. This method may aid in identifying muscle loss in cancer patients more precisely. Muscle depletion can negatively impact health, and individuals with higher BMIs may experience muscle loss that is not immediately evident [221]. Hence, the author has employed these cut-offs in the present study. Table 1.7 illustrates the methods used in the literature for skeletal muscles.

Table 1.7 Summary of methodologies employed in CT body composition analysis in the literature.

Author Year	Cohort	Type of muscle measured	Anatomical level and density threshold	Method of analysis and software used	Cut-off value for sarcopenia	Measurement
Pectoralis and/or erector spinae muscles:						
McDonald et al. (COPDGene) 2013 [79]	482 patients with COPD And 482 controls	PMA (cm^2).	On a single axial slice The first axial slice above the Aortic arch	manually shaded under density threshold: (-50 to 90 HU) Software: in-house software	No cut-off Use sex-stratified analysis	PMA was measured by the sum of major and minor muscles
Kinsey et al. 2017 [77]	252 NSCLC patients	PMA (cm^2).	On a single axial slice The first axial slice above the Aortic arch	Manual tracing under thresholds: (-50 to 90 HU) Software: 3D slicer	PMA 50^{th} Percentile	PMA was measured by the sum of major and minor muscles
Miller et al. 2018 [71]	299 patients with lobectomy	PMI (cm^2/m^2) ESMI (cm^2/m^2)	On a single axial slice PMI: 1 cm within sternoclavicular joint ESMI: T12 level	manually shaded Software: the AW Server 3.2 Workstation 3D volume viewer (General Electric	Used as continuous variable Not cut-off or stratification	The muscles' area was normalised to height (cm^2/m^2)

				Healthcare Inc., Chicago USA).		
Bak et al. 2019 [78]	222 patients with COPD	PMA (cm^2) PMD (HU)	On a single axial slice just above the aortic arch	By manual tracing Density use: mean attenuation in area of interest Software: in-house software	PMA and PMD were categorised into tertiles (high, medium, and low)	PMA was measured by the sum of major and minor muscles
Gazourian et al. 2020 [227]	1696 subjects with lung cancer screening	PMA (mm^2)	On a single axial slice just above the aortic arch	Bilateral manual segmentation Software: 3D slicer (Chest imaging platform)	25^{th} Percentile of PMA	PMA was measured by the sum of major and minor muscles
Sun et al. 2020 [248]	120 NSCLC patients with surgery	PMI (mm^2/m^2)	On a single axial slice at the level of T4	Manual tracing under thresholds: (-50 to 90 HU) Software: SYNAPSE VINCENT (Fujifilm Medical, Tokyo, Japan)	Lowest gender-specific tertile	PMA was measured then PMI was normalised to height (mm^2/m^2)
Zhang et al. 2021 [249]	163 NSCLC patients with lobectomy	PMI (cm^2/m^2)	On a single axial slice	Manual tracing Software:	Cut-off was set to the lowest tertile	The muscles' area was normalised to height

		PMD (HU)	just above the aortic arch	Picture Archiving and Communication System (PACS) software	and separated based on gender	(cm^2/m^2) PMD was calculated as: PMD = the sum of (PMA x PMD for each muscle) /total pectoralis muscle area (HU)
Hamakawa et al. 2022 [228]	193 COPD participants	PMI (cm^2/m^2) ESMI (cm^2/m^2)	On a single axial slice PMI: just above the aortic arch ESMI: lower margin of T12	Manual segmentation Using threshold: (-29 to 150 HU) Software: Image J (Fiji) software	NA	The muscles' area was normalised to height (cm^2/m^2)
Maetani et al. 2023 [250]	310 current smokers with air flow limitation	PMA (cm^2) ESMA (cm^2)	On a single axial slice PMI: first axial slice above the aortic arch ESM: at the level of the lower margin of T12	Manual tracing under thresholds: (-50 to 90 HU) Software: Image J (Fiji) software	NA	NA
Tanimura et al. 2016 [233]	130 COPD male patients	PMA	On a single axial slice	manually shaded	mean -1 SD, and mean - 2 SD	NA

		ESMA	PMA: the first axial slice above the Aortic arch ESMA: at the level of lower margin of T12	Software: SYNAPSE VINCENT volume analyser (FUJIFILM Medical Co., Ltd., Tokyo, Japan).		
Asakura et al. 2018 [251]	260 with mycobacterium Avium lung disease	ESMA	at the level of lower margin of T12	Manual tracing Software: commercially available workstation (AZE Virtual Place, AZE, Tokyo, Japan)	Mean – 1 SD for each gender	The sum of right and left ESM
Takamori et al. 2018 [232]	101 NSCLC patients with lung surgery	ESM post/pre ratio (cm^2/m^2)	At the level of T12	Manual tracing under threshold (-29 to 150 HU) Software: OsiriX software (32-bit, version 5.8; OsiriX, Geneva, Switzerland)	ESM Post/pre ratio <0.9	ESMI was calculated by: ESMA/height squared. (cm^2/m^2) ESM post/pre ratio: postoperative ESMI /baseline ESMI
Yoshikawa et al. 2021 [252]	588 survivors with pneumonia 101 Non-survivors	ESMI	at the level of lower margin of T12	manually shaded Software:	75^{th}, 50^{th}, and 25^{th} percentile of ESMI	ESMA was calculated as the sum of right and left ESM (cm^2)

				SYNAPSE VINCENT volume analyser (FUJIFILM Medical Co., Ltd., Tokyo, Japan).		ESMI was adjusted to body surface area
Psoas muscles:						
Dolan et al. 2019 [253]	163 patients with colorectal cancer surgery	Total psoas index (PSMI) (mm^2/ m^2).	L3 vertebra with transverse processes were maximally viewed	By manual tracing Software: Picture Archiving and Communication System (PACS) software	524 mm^2 / m^2 for males 385 mm^2 / m^2 for females	The PSMI (mm^2): aggregating muscles area PSMA was standardised for patient height for total psoas index (PSMI): PSMA (mm^2)/height (m^2).
Nakada et al. 2019 [238]	173 NSCLC patients with lobectomy	PSMI (cm^2/m^2)	L3 vertebra	By manual shading Software: SYNAPSE VINCENT volume analyser (FUJIFILM Medical Co., Ltd., Tokyo, Japan).	Median-1 SD 4.61 cm^2/m^2 for men 3.26 cm^2/m^2 for women.	aggregating muscles area PSMA was standardised for patient height for total psoas index (PSMI): PSMA (cm^2)/height (m^2).
Ozeki et al. 2020 [254]	165 patients with lung squamous cell carcinoma 556 lung adenocarcinoma	PSMI (cm^2/m^2)	umbilical level	By manual tracing Software: Picture Archive and Communication System	NA	aggregating muscles area PSMA was standardised for patient height for total psoas index (PSMI): PSMA (cm^2)/height (m^2).

	patients with surgery					
Shinohara et al. 2020 [237]	391 NSCLC patients with lung resection	PSMI (cm^2/m^2)	At the level of caudal end of L3 vertebra	By manual tracing Software: volume-analysing software (Advantage Workstation 4.3; GE Healthcare).	6.36 cm^2/m^2 for men 3.92 cm^2/m^2 for women	aggregating muscles area PSMA was standardised for patient height for total psoas index (PSMI): PSMA (cm^2)/height (m^2).
Miura et al. 2021 [240]	259 NSCLC patients with lung resection	PSMI (cm^2/m^2)	L3 vertebra	By manual tracing Software: NA	6.36 cm^2/m^2 for men 3.92 cm^2/m^2 for women	aggregating muscles area PSMA was standardised for patient height for total psoas index (PSMI): PSMA (cm^2)/height (m^2).
Ozeki et al. 2021 [255]	78 patients with surgery for suspected stage I NSCLC	PSMI (cm^2/m^2)	L3 vertebra	NA Software: NA	NA	PMI (%) = PMA (cm^2)／[height (m^2) × 8.85 (in men) or 5.77(in women)]
Skeletal muscles:						
Prado et al. 2008 [243]	2115 patients with respiratory tract or gastrointestinal tumours	SMI (cm^2/m^2)	L3 vertebra	under CT density threshold: (-29 to 150 HU) Software: Slice-O-matic software, version 4.3	52·4 cm^2/m^2 for male 38·5 cm^2/m^2 for female	SMA: cross-sectional area (cm^2) of the sum of all measured muscles (psoas, erector spinae, quadratus lumborum, and abdominal wall muscles)

						SMI: obtained by normalising SMA for height (m^2).
Martin et al. 2013 [221]	1473 patients with lung or gastrointestinal cancer	SMI (cm^2/m^2)	L3 vertebra	under CT density threshold: (-29 to 150 HU) Software: Slice-O-matic Software V 4.3 (Tomovision, Magog, Canada	Using BMI and gender specific cut-off: for underweight and normal weight men: 43 cm^2/m^2 For overweight and obese men: 53 cm^2/m^2 For all women: <41 cm^2/m^2	SMI: obtained by normalising SMA for height (m^2).
Blauwhoff-Buskermolen et al. 2017 [86]	241 patients with advanced cancer	SMI (cm^2/m^2)	L3 vertebra	under CT density threshold: (-29 to 150 HU) Software: Slice-O-matic Software V 5.0 (Tomovision, Magog, Canada	55 cm^2/m^2 for male 39 cm^2/m^2 for female	SMI: obtained by normalising SMA for height (m^2).

Kim et al. 2018 [256]	272 NSCLC patients with surgery	SMI (cm^2/m^2)	Using two adjacent CT scans extending inferiorly from L3 vertebra	Automatic analysis under CT density threshold: (-29 to 150 HU) Software: (Terarecon 3.4.2.11, San Mateo, CA, USA)	55 cm^2/m^2 for male 39 cm^2/m^2 for female	SMA: cross-sectional area (cm^2) of the sum of all measured muscles SMI: obtained by normalising SMA for height (m^2).
Halpern et al. 2020 [244]	132 patients with lung transplants	SMI (cm^2/m^2)	L3 vertebra	Automated Software: Slice-O-matic Software V 4.2 (Tomovision, Magog, Canada	Using BMI and gender specific cut-off: for underweight and normal weight men: 43 cm^2/m^2 For overweight and obese men: 53 cm^2/m^2 For all women: <41 cm^2/m^2	SMA: cross-sectional area (cm^2) of the sum of all measured muscles SMI: obtained by normalising SMA for height (m^2).

Although CT is the gold standard for assessing body composition, consensus sarcopenia cut-offs have only been reported for DXA and body impedance analysis (BIA) measurements [257]. There are substantial differences in approach among CT-based studies, especially regarding different body regions, muscle groups, radiodensity boundaries, contrast agents used, and cut-off points [219].

To the best of our knowledge, no study has investigated the impact of body composition analysis on postoperative dyspnoea scores or global health using EORTC QLQ-C30 in patients after lung cancer surgery. Only one study investigated the relationship between sarcopenia and quality of life in lung cancer patients [85]. This study aimed to examine the effects of sarcopenia on the quality of life in lung cancer patients with chemotherapy but not surgery [85]. Other studies assessed a wide range of cancer populations rather than concentrating on lung cancer [86, 87, 258].

This thesis has examined the relationship between different muscle types and the outcomes of patients. The pectoralis and erector spinae muscles have been assessed in the literature and have shown a significant relationship with different outcomes of different cohorts, as well as being fast and easy to measure. They can be acquired from thoracic CT scans, which are more frequently acquired than abdominal scans in this cohort. The data are readily available on patient CT scans. Psoas muscles have been evaluated as well using abdominal CT scans. There is a lack of clarity regarding the usefulness of these measures in predicting patients' quality of life. In addition, by evaluating different measures of sarcopenia, different results might be obtained [237]. Therefore, our study will evaluate the predictive value or association of these muscles in QoL for patients with lung cancer resection.

1.11 AI-based software in CT-based emphysema quantification

Artificial intelligence (AI) has become considerably an important tool in the diagnosis of COPD, offering a promising venue for precision and efficiency in the medical practice [259]. Conventional approaches, such as qualitative CT assessment of COPD depend heavily on subjective evaluation of the clinicians, this may end with variability or misdiagnosis. AI-based software has provided a fully automated and quantitative methods to the analyses of CT-based pulmonary imaging via advanced machine learning algorithms such as convolutional neural networks (CNN), thus improving diagnostic potential [260]. AI-based systems can identify intricate patterns on CT scans that may not be detected by human observer, allowing for more accurate and reliable detection of emphysema [261]. One of the major benefits of using AI-based approaches in diagnosis of COPD is its capability to process large amount of data reducing time and providing objective evaluation of COPD [262]. One example, AI-based software can automatically quantify %LAA in thoracic CT scans. Nevertheless, the utilisation of AI-based tools in diagnosis of COPD has a number of challenges. One of which, the quality and the size of data employed to train AI software are important [262].

AI tools continue to advance, allowing for personalised interventions resulting on improved outcomes for COPD. Semi-automated quantification of emphysema has been utilised for several years to evaluate emphysema by CT density measurements. It is vital to compare AI-based emphysema quantifications on CT scans against semi-automated emphysema quantifications to better understand the advantages and limitations of each approach. Therefore, this thesis will examine these two methods in lung cancer patients with emphysema.

From the studies reviewed in this chapter, this thesis will evaluate the importance of PRO in predicting QoL after lung cancer surgery, focusing on dyspnoea and global health. Moreover, the thesis will evaluate the role of CT densitometry and CT-based body composition in predicting patients' QoL, highlighting the value of advanced imaging techniques in clinical investigations. In addition, the thesis will compare CT semi-automated density measurements and AI-based fully automated measurements of emphysema, emphasising advancements in imaging technologies. Building on these aspects, this thesis aims to expand the understanding of how these factors can predict patients HRQOL after lung cancer surgery.

Chapter 2. Aims of the Thesis

This thesis comprehensively investigates the factors associated with HRQOL in patients with lung cancer following surgery. In this thesis, the following aims are proposed:

Chapter 4: The primary aim will be to investigate the predictors of HRQOL of dyspnoea and global health using the EORTC QLQ-C30 questionnaire following lung cancer surgery after six months. Moreover, exploratory aims will be to reveal the response rates at six months and illustrate the difference between respondents and non-respondents, to examine the trajectories of HRQOL six months following lung cancer surgery and compare the differences between HRQOL domains.

Chapter 5: The study aim will be to assess the predictive value of QCT of emphysema (%LAA-950 and -910) using contrast-enhanced and unenhanced CT scans in predicting HRQOL of dyspnoea and global health at six months. Further exploration aims will be to determine the differences between contrast-enhanced and unenhanced CT scans and to evaluate the intra-observer reproducibility of CT quantification of emphysema.

Chapter 6: The primary objective of this study will be to explore the differences between patients with sarcopenia of pectoralis, erector spinae, psoas, and skeletal muscles in those with worsened and recovered HRQOL of dyspnoea and global health. In addition, this thesis will examine the differences in body composition between females and males with higher and lower BMI. In addition, this study

will investigate the relationship between sarcopenia and lung function, and sarcopenia and postoperative clinical outcomes.

Chapter 7: The main objective of this study will be to evaluate the variability between fully automated emphysema quantification on CT scan using AI-based software and semi-automated emphysema quantification using 3D slicer, an open-source software. This study will assess QCT measures of %LAA-950, 15th Percentile, mean lung density and lung volume.

Chapter 3. Methods

3.1 Patient reported outcomes in predicting postoperative Quality of Life

3.1.1 Study design and participants

The study is a prospective, longitudinal, single-centre study. The research protocol for this study was approved (Research Ethics Committee reference: 10/H1208/41), where patients who underwent lung resection at University Hospital Birmingham (UHB) NHS Foundation Trust were recruited consecutively. Informed consent was obtained from all participants, who were asked to self-report quality of life (QoL) measures. A variety of other data, which were not systematically collected, were collected from the patients' medical records.

3.1.1.1 Patients' selection

Patients who met all the following criteria were included in the study

The inclusion criteria for patients were:

- Patients aged 18 years or older.
- Patients with primary or metastatic cancer undergoing lung resection
- Patients with pulmonary function testing.

Exclusion criteria:

- Patients who could not provide written informed consent.
- Patients without lung lesions or with benign lung tumours
- Patients who had not undergone lung resection were excluded from the study.

3.1.2 Sample size

Our sample size determination was aimed at ensuring that we would be able to detect meaningful changes in patients' HRQOL, assessed by the EORTC QLQ-C30. Our estimation was based on an earlier study in which 115 patients provided HRQOL data before surgery [263]. To detect an absolute minimum difference of 5.0 points in the EORTC QLQ-C30 scale, assuming a standard deviation of 15.2 as reported in the study which derived it, with 95% power and 5% significance level (2-sided type I error), a total of 482 participants will be needed in total. Assuming and adjusting for approximately 35% attrition, 741 participants will need to be recruited.

3.1.3 Quality of life assessment

In order to obtain a measure of quality of life, The European Organization for Research and Treatment Quality of Life Questionnaire (EORTC QLQ-C30) (version 3) and its Lung Cancer Specific Module (LC13) were administered at baseline, eight weeks, and six months following surgery. Six months represents an optimal period for capturing the most significant and stable alterations in dyspnea, which allows a reasonable selection of a recruitment period. As a self-rating questionnaire consisting of 30 questions, the EORTC QLQ-C30 consists of five functional scales (physical, role, emotional, cognitive, and social) as well as nine symptoms' scales/items (fate, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties), as well as global health status/quality of life. Additionally, EORTC QLQ-LC13 is a module specified for lung cancer patients and consists of 13 questions assessing lung cancer symptoms and associated side effects.

EORTC questionnaire answers were rated on a four-point Likert scale and linearly transformed into scores between 0 and 100. In general, higher functional scores indicate improved functionality. Higher global health/quality of life score represents higher quality of life. Finally, higher symptom scores reflect worse symptoms [147].

3.1.3.1 Quality of life scoring

EORTC QLQ-C30 and LC13 were scored using the EORTC scoring manual [147].

For all EORTC QLQ-C30 scales, raw scores (RS) were calculated for each scale as the mean of the component items:

$$Raw\ score = (I_1 + I_2 + \cdots + I_n)$$

Then, for each functional scales, we used the following equation:

$$Score = 1 - \frac{(RS - 1)}{range} \times 100$$

For each symptoms scales/items or global health/quality of life, we calculated the scores using the formula:

$$Scores = \{(RS - 1)/range\} \times 100$$

It should be noted that an item's range is defined as the difference between the maximum and minimum possible responses; the majority of the items take values from 0 to 4, thus creating range = 3 [147].

In principle, the scoring approach for the QLQ-LC13 is the same as that used in the QLQ-C30 symptom scales / single items.

3.1.4 Statistical analysis

Statistical consultation and mentorship were sought from a senior statistician (RM) at The Institute of Applied Health Research, University of Birmingham, both prior to and during the statistical analysis phase.

3.1.4.1 Descriptive statistics

We described the data as mean ± standard deviation, median ± interquartile range, or numbers (proportions), as appropriate. Our primary outcome in this study is postoperative dyspnoea at six months, while global health is our secondary outcome.

An assessment of the normality of numeric variables (including the Quality of Life scores) was conducted using the Shapiro-Wilk test. A one-way analysis of variance (ANOVA) was used to compare parametric data between unpaired groups. ANOVA was employed to identify statistically significant differences between the means of multiple groups. For the comparison of non-parametric data between unpaired groups, Mann-Whitney U-tests or Kruskal-Wallis tests were employed. Analyses of categorical variables were conducted using the Chi-square test or Fisher's exact test. A p-value of <0.05 is considered statistically significant. All our statistical analyses were performed using Stata 18.0 statistical software (Stata Co., College Station, TX) or SPSS version 29 (IBM Corp.).

3.1.4.2 Quality of life questionnaire completion rate

We calculated the proportion of completed questionnaires from those expected (excluding withdrawals and deaths) at each time point. We used number and percentages to calculate completion rates at each time point.

An analysis of the demographic and clinical characteristics of responders and non-responders was conducted in order to identify potential reasons for missing data at baseline. To calculate the

difference between respondents and non-respondents of completion of PRO, we used the independent t-test for numeric variables with a normal distribution or the Wilcoxon rank-sum test for numeric variables that did not have a normal distribution. To compare categorical variables, the Chi-square test or Fisher's exact test was used.

3.1.4.3 Quality of life change over time

Analysis of variance (ANOVA) with repeated measures was used to assess changes over time with post-hoc pairwise comparisons using the paired t-test. For non-parametric data, Friedman's test with post-hoc pairwise comparisons using the Wilcoxon rank sum test was used to assess changes over time. In addition, Bonferroni correction was applied to the significance level for multiple comparisons to reduce the possibility of a type I error. The adjusted significance level was determined to be 0.017 (i.e., $\alpha = 0.05/3$). We calculated the difference in EORTC scores between baseline and eight weeks, baseline and six months or eight weeks and six months by subtracting the score of the mean (median) domain at a specific time point from the previous time point's mean (median) score.

Changes of ≥ 10 points in any of the EORTC QLQ-C30 scores or ≥ ½ SD at any scores of QLQ-LC13 are considered clinically meaningful (MCID) [148]. A procedure was followed to deal with missing items in accordance with the guidelines established by the EORTC by applying the equations provided in the EORTC guidelines for calculating the scale scores [147].

3.1.4.4 Difference between the first five years and the last five years' cohort

For demonstrating the difference between the two groups, the difference in surgical approach, resection and lobe as well as the outcome measures of postoperative dyspnoea and global health were evaluated. Chi-square or Fisher exact tests were performed in categorical data, and independent t-test

or Mann-Whitney U test were performed for the continuous data based on the normality of the data. $P< 0.05$ indicates statistically significant difference between the two groups.

3.1.4.5 Modelling for the prediction of postoperative dyspnoea

For the PRO outcome (postoperative dyspnoea at six months), univariate and multivariate regression analyses were used in this investigation. As a first step, we planned to examine the individual predictors of dyspnoea outcomes at six months. Dyspnoea is an ordered categorical variable with four levels, with 0 representing the least affected category and 100 representing the most affected category. Considering this order, ordinal logistic regression was our first analysis to assess relationships with the predictors. Ordinal logistic regression assumptions were tested, and if the proportional odds assumption was not met, a multinomial logistic regression analysis was performed.

The factors screened in the univariate analyses were age, gender, body mass index (BMI), smoking, lung function comprising FEV_1, FVC, DLCO, $ppoFEV_1$, ppoDLCO, surgical incision, resection type, comorbidities, American Society of Anaesthesiologists Physical Status Classification (ASA score), Eastern Cooperative Oncology Group (ECOG) performance scale, postoperative pulmonary complications (PPC), hospital length of stay (LOS), hospital readmission, chemotherapy and baseline dyspnoea.

Based on the univariate regression results, I selected subsets of variables to include together in separate multivariate models to predict six-month dyspnoea. Also, in the multiple regression analyses, multicollinearity was avoided by separating highly correlated factors into different models. In addition, the parallel line assumption was tested to assure no violation occurred in ordinal regression analyses. A failure to maintain the assumption would result in incorrect interpretations of the results; therefore, it is recommended to use alternative models instead of ordinal logit regression models in order to find the correct results [264].

All the variables included in these models were individually statistically significant at the 0.10 level in the univariate analyses.

We then performed multivariate ordinal or multinomial logistic regression analysis using a backward selection by p-value for each model. We removed the variable with the highest p-value greater than 0.05, reran the model, and repeated the process until all variables remained statistically significant for the 0.05 level. All the models were tested for ordinal regression assumptions and adhered to.

3.1.4.6 Modelling for the prediction of postoperative global health

For the EORTC QLQ-C30 six-month global health score, we conducted univariate and multivariate linear regression analyses. For the prediction model, linear regression analysis is appropriate since the global health score is a continuous variable from 0 to 100. A score of zero indicates the worst overall quality of life, whereas a score of 100 indicates a better overall quality of life. As a first step, we intended to examine the individual predictors of global health outcomes at six months. The assumptions underlying linear regression were examined as well to ensure they were met for each model. In the univariate analysis, the following factors were examined: gender, age, BMI, smoking quit time, pack years, lung function including FEV_1 (L), $\%FEV_1$, FVC (L), %FVC, %DLCO, $ppoFEV_1$, ppoDLCO, surgical side, lobe, resection type, comorbidities including COPD, IHD, cardiac failure, hypertension, thyroid disease, renal failure, diabetes, stroke, anticoagulant use, ASA score, ECOG performance, perioperative factors such as PPC, LOS, hospital readmission, chemotherapy and EORTC QLQ-C30 baseline global health.

Using the results of univariate regression, the researcher selected subsets of variables to be included in separate multivariate models to make predictions about postoperative global health at six months. By separating highly correlated factors into different models, multicollinearity was also avoided in

the multiple regression analyses. The variables included in these models were all statistically significant at a level of $p < 0.10$ in the univariate analyses.

A multivariate linear regression analysis was conducted using a backward selection process based on the p-value of each model, including removing the variable whose p-value exceeded 0.05, rerunning the model, and repeating the process until all variables remained statistically significant at the 0.05 level. All the models were tested for the linear regression assumptions and adhered to.

3.2 Quantitative CT of emphysema

3.2.1 Study design and participants

This is a retrospective study, and the research protocol was approved (Research Ethics Committee reference: 10/H1208/41). The study included a cohort of patients similar to our previous study, and the protocol has been previously described (Section 3.1). Patients with no baseline thoracic CT scans were excluded from the study. CT scans were retrospectively collected and assessed for inclusion in the analysis.

3.2.2 CT acquisition

This is a retrospective study; thus, the CT scans were acquired using two scanner types: Aquilion ONE scanner (Toshiba Medical Systems Corporation, Tokyo, Japan) and Somatom Definition (Siemens Medical Solutions, Forchheim, Germany). With the patient in a supine position, scans were acquired during breath-hold. An automated voice instruction system was used to assist the patient in performing respiratory manoeuvres. The CT scanner settings were 120 kVp voltage, current of 100 to 200 mA, rotation time of 500 ms, cut thickness of 1 mm, and matrix 512 x

512 pixels. Our study involved both contrast and non-contrast CT scans. The study employed smooth reconstruction filters (FC07, FC08, I26f and I30f), the use of a thin slice thickness of 1 mm [190], and a smooth reconstruction filter [265] is recommended in CT quantification of emphysema. The median days between CT scan acquisition and surgery is 55 days.

3.2.3 CT scan analysis software

This study utilised an open-access software for emphysema analysis:

- 3D slicer v 4.10; Chest Imaging Platform (CIP) module.

We only used the open-source software 3D slicer CIP extension in order to complete the emphysema analysis in this study [266]. The software extension (CIP) was initially developed for researchers for quantitative analysis of lung parenchyma and was designed to focus on its potential application in studying COPD [267]. The 3D slicer can be used as a clinical research tool, is capable of supporting a wide range of visualisations and offers advanced functionality such as automatic segmentation and registration [268]. Several studies have used the software in their emphysema quantification research, among other areas [269-272].

The 3D slicer works in a similar manner to other commonly used software in this field (e.g. Pulmonary Workstation) by applying region growing to label the airways outside the lung area [273]. When two adjacent voxels are compared, the software program applies an algorithm to determine whether they have the same or different densities. The voxels will be connected if they are the same, creating a structure two voxels wide. In addition, spatial consistency over a number of slices confirms that the object is the trachea rather than a false foreground object [273]. This program processes all adjacent voxels until the final image is created.

The software developer created the novel Interactive Lung Lobe Segmentation tool in which the users can produce segmentations of the lung lobes quickly, easily, and accurately [273]. Using thin plate

splines (TPS) as the underlying algorithm to define three fissure height surfaces, lobe segmentation is accomplished [273]. For each of the three fissures, a separate 3D surface is defined. The height surface algorithm provides the type of value "oblique fissure" or "horizontal fissure" to voxels that fall on the surface within the tolerance of a voxel width. Then, by using region growing algorithm, the upper and lower lobes in the left lung are distinguished from those above and below the left oblique fissure and similarly to the right lung [273].

3.2.4 CT density analysis using Chest Imaging Platform

The CT scans must first be converted into DICOM (Digital Imaging and Communications in Medicine) format prior to analysis by CIP. First, CT scans were imported into 3D Slicer. Following this, the ‘interactive lobe segmentation’ module of CIP extension was applied to segment the lobe of the lung parenchyma. Then, the input CT Volume was selected as ‘lung’. Sagittal, coronal and axial planes were viewed. Afterwards, the researcher selected the sagittal plane and placed 15-20 fiducial points for each oblique fissure and 5-15 points for the right horizontal fissure. Then, the researcher reviewed the other planes and added extra fiducial points when necessary. The interactive lung label map was generated after lobe segmentation, and five lobes with different colours were shown in axial, coronal, and sagittal views (Figure 3.1).

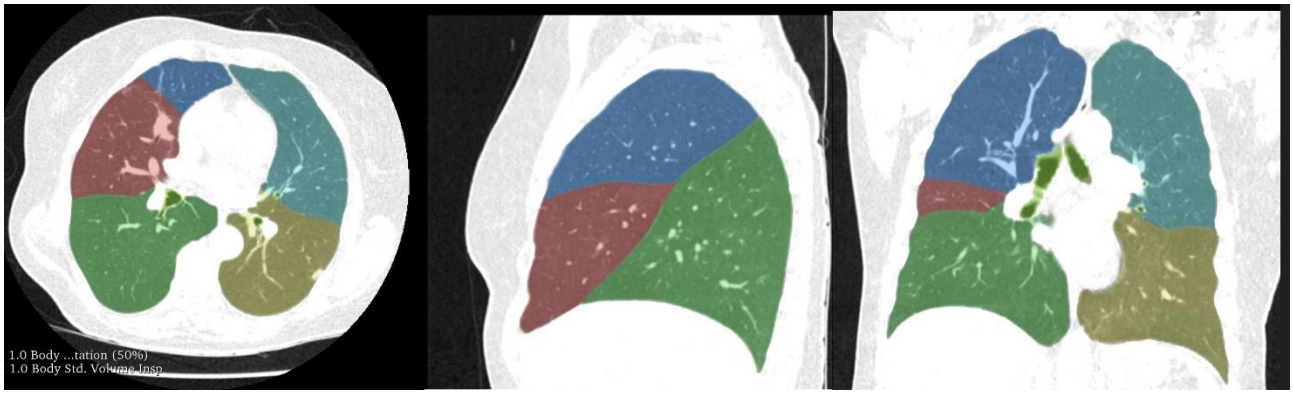

Figure 3.1 Lung lobar segmentation using CIP extension of 3D slicer

The researcher checked the mapping and segmentation accuracy by viewing the three planes, adding extra fiducial points, and repeating the segmentation until accurate lobes segmentation was achieved. After that, the researcher employed ‘parenchyma analyses for emphysema quantification, and then the attenuation of the voxels for the whole lung lobe and each lobe was automatically quantified. The data obtained are %LAA-950, %LAA-925, %LAA-910, PD15, and volume for the whole lung and each lobe.

3.2.5 Statistical Analysis

3.2.5.1 Descriptive statistics

We illustrated the data as mean ± standard deviation, median ± interquartile range, or numbers (proportions), as appropriate. Our primary outcome in this study was postoperative dyspnoea at six months, while global health is our secondary outcome.

An assessment of the normality of numeric variables was conducted using the Shapiro-Wilk test.

3.2.5.2 Modelling for the prediction of postoperative dyspnoea

To investigate QCT density as a predictor of postoperative dyspnoea, univariate ordinal logistic regression analyses were employed in this investigation. The factors screened in the univariate analyses were QCT density for emphysema for the whole lung, including %LAA-950, %LAA-925 (for contrast CT only), %LAA-910, PD15, and lung volume.

The factors assessed in Section 3.1.4.4, were be assessed again for univariate association with postoperative dyspnoea.

If one of these factors was individually statistically significant at the 0.10 level, then it would be added to the multiple regression analyses.

The multivariate ordinal or multinomial logistic regression analyses were performed based on the univariate regression results. The reason for using multinomial regression analysis was explained in Section 3.1.4.4. The author selected subsets of variables to include in separate multivariate models to regress on six-month dyspnoea; all models included %LAA-950 as a predictor adjusted for different factors. The outcome of six-month dyspnoea was collapsed to just three levels, labelled 0 (originally 0), 1 (originally 33.33), or 2 (originally 66.67 or 100). This was due to the small sample size and relatively small number of patients with dyspnoea levels of 66.67 (only 7 patients) or 100 (only 5 patients). This way, the analysis was be processed without violating the parallel line assumption suggested as an appropriate method in the literature [274]. Also, the combination of categories (66.67 and 100) was justified as they represented the most severe dyspnoea levels, and all of these scores increased compared to baseline levels.

The researcher individually selected all of the variables included in these models. Each model underwent a backwards selection process by p-value, where the variable with the highest p-value

greater or equal to 0.05 was removed, the model was rerun, and the process was repeated until all remaining variables were statistically significant at the 0.05 level.

3.2.5.3 Modelling for the prediction of postoperative global health

We conducted univariate and multivariate linear regression analyses for postoperative global health scores. The univariate analysis examined the following factors: QCT density for emphysema for whole lung, including %LAA-950, %LAA-925 (for contrast CT), %LAA-910, and PD15, and lung volume. In addition, we assessed baseline demographic, clinical, perioperative data and baseline global health.

Using the results of univariate regression, the researcher selected subsets of variables to be included in separate multivariate models to make predictions about postoperative global health at six months using a significance level of $p < 0.1$. A multivariate linear regression analysis was conducted as well. A $p < 0.05$ is considered statistically significant. The details regarding the regression analysis and examined factors were explained in detail in Section 3.1.4.5.

3.2.5.4 Intra-observer Reproducibility of QCT emphysema analysis

In order to determine the reproducibility of the CT density analysis, an analysis of CT density was conducted twice, on two separate occasions, with an interval of two months between the CT scans of 30 consecutive patients. To ensure a robust analysis, it is recommended to use a minimum of 30 observations in Intra-class Correlation Coefficient (ICC) studies, allowing for a comprehensive evaluation of variability and ensuring the reliability of the results [275]. The trained observer was blinded to the results of the analysis. However, the inter-observer agreement was not conducted due to unavailability of the second reviewer. Yet, this study evaluated the agreement between the

observer's analyses and AI-based software analyses. The level of intra-observer reliability was evaluated using ICC [275]. Based on the correlation coefficients, the level of intra-software reliability is summarised in Table 3.1

Table 3.1 levels of ICC [275]

Correlation coefficient (r)	Interpretation of reliability
0 - 0.5	Poor
0.5 - 0.75	Moderate
0.75 - 0. 9	Good
>0.9	Excellent

In addition, Bland Altman plots were assessed for the agreement between the measurements of %LAA-950 and %LAA-910. The mean difference between the two groups will be calculated, and the limits of agreement (LOA) was calculated as follows:

$$\text{LOA} = \text{mean difference} \pm 1.96 \times \text{SD}$$ [276].

Differences of %LAA-950 <5%, or ≤ 35% for %LAA-910 between the two measurements were considered reasonable differences [277].

3.2.5.5 Investigating levels of agreement between contrast-enhanced and unenhanced CT scans

In this study, contrast-enhanced and non-enhanced CT scans were compared in 27 lung cancer patients. Comparison between QCT measurements of %LAA-950 and %LAA-910 was performed using Wilcoxon signed rank test [278]. P-value of <0.05 indicates a statistically significant difference between the two groups. In addition, Bland Altman plots were assessed for the agreement between the measurements. The mean difference between the two groups and the reasonable difference cut-off values were described above (Section 3.2.5.4).

All our statistical analyses were performed using Stata 18.0 statistical software (Stata Co., College Station, TX) or SPSS version 29 (IBM Corp.).

3.3 Quantitative CT of body composition

3.3.1 Study design and participants

We conducted this study retrospectively. The study protocol was approved (Research Ethics Committee reference: 10/H1208/41). This study involved the same cohort of patients as our previous study, which was described previously in detail (Section 3.1-3.2). Patients with no baseline thoracic and abdominal CT scans were excluded from the study. CT scans were retrospectively collected and assessed for inclusion in the analysis.

3.3.2 CT acquisition

CT scan acquisition details were previously described (Section 3.2.2). Overall, the CT scan involved was contrast-enhanced, which was part of lung cancer patients' clinical investigation. The scanner settings were 120 kVp voltage, current of 100 to 200 mA, rotation time 500 ms, cut thickness was 1

mm, matrix 512 x 512 pixels. The study utilised smooth reconstruction filters (FC07, FC08, I26f and I30f). The median days between CT scan acquisition and lung cancer surgery was 55 days.

3.3.3 CT scan analysis of body composition

3D slicer v 4.10; Chest Imaging Platform (CIP) module software program was used in the analysis of body composition. Skeletal muscles area (SMA), pectoralis muscles area (PMA), erector spinae muscles area (ESMA), and psoas muscles area (PSMA) were measured on a single axial slice for each measurement. The investigator selected the vertebral levels for each measured muscles, which is L3 transverse process CT scan slice for SMA and PSMA [221, 279], transverse process of T4 for PMA [248], and lower margin of T12 for ESMA [233]. Predefined density thresholds were set using the range of -29 – 150 HU for PM [228], PSM [280], and SM [221], whereas a threshold of -50 – 90 HU was used for ESM [250]. All muscles were analysed using manual shading.

For skeletal muscles area measurements, the measured muscles involved psoas muscles, paraspinal muscles including erector spinae and quadratus lumborum, and abdominal wall muscles including transverse abdominis, internal and external obliques and rectus abdominus [243]. The cross-sectional area of all muscles measurements was calculated by aggregating all muscles' area (cm^2).

Similarly, the cross-sectional area of pectoralis muscles (cm^2) is calculated by aggregating the right and left major and minor pectoralis muscles. Furthermore, the cross-sectional area of erector spinae muscle was measured by the sum of the right and left muscles. Likewise, the cross-sectional area of psoas muscle was measured by the sum of right and left psoas muscles. The index of skeletal muscles (SMI) was calculated by adjusting SMA to the height^2 (cm^2/m^2) [281]. Similar adjustment applies to the rest of the muscles; PMI [248], ESMI [228], and PSMI [238] were calculated by adjusting the cross-sectional muscle area to the height^2 (cm^2/m^2) (Figure 3.2).

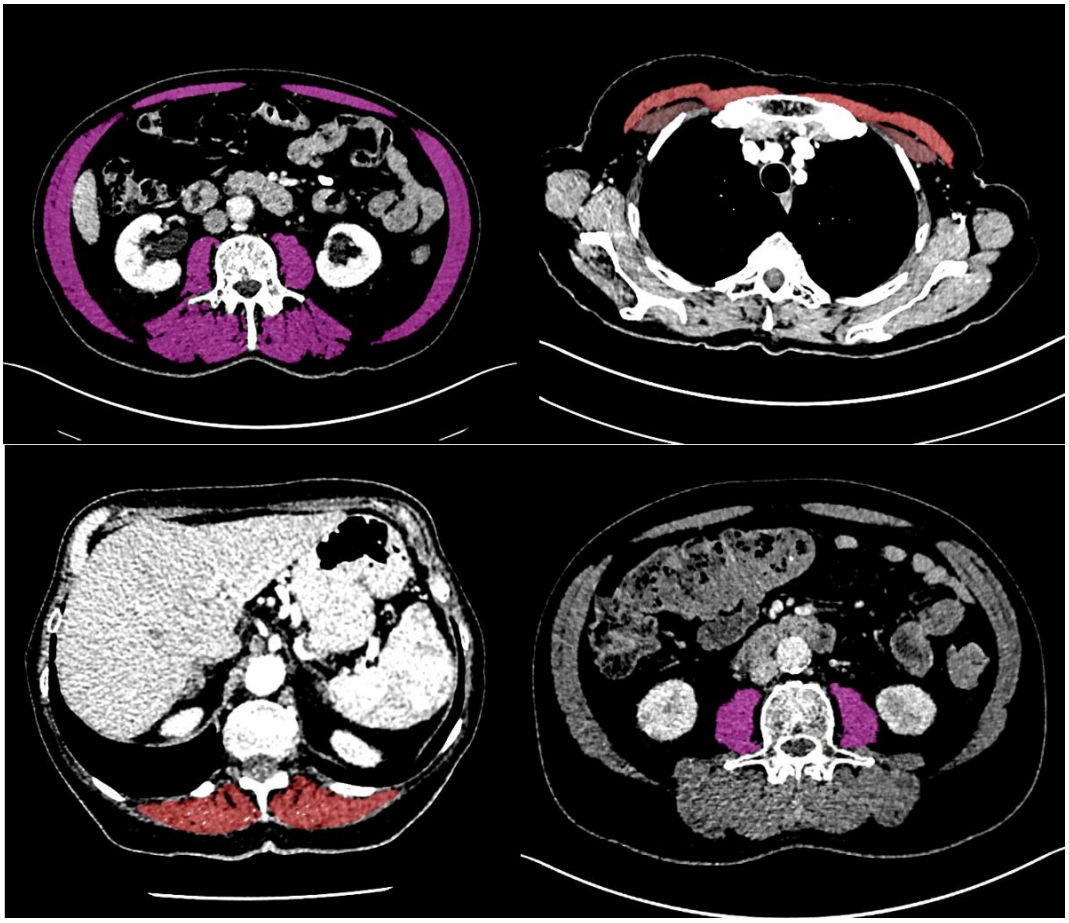

Figure 3.2 Body composition analysis using CIP extension of 3D slicer manually shaded; upper left: skeletal muscle area at L3 level, upper right: pectoralis muscle area at T4 level, lower left: erector spinae muscle area at T12 level, lower right: psoas muscle area at L3 level

3.3.4 Sarcopenia definition

Researchers suggested different cut-offs and definitions for sarcopenia based on skeletal muscle mass and investigated outcomes of their cohorts using single axial slice CT images at the level of mid-L3 [221, 243, 281]. It was noted that the cut-off value established by Martin and colleagues was the most common sex-specific and BMI-defined sarcopenia. Using this approach may identify muscle loss in cancer patients more accurately. The importance of this is that muscle loss can adversely affect individuals' health, and people with a higher BMI may still lose muscle without it being apparent [221]. The cut-off values defined by Martin at al. are as follow: for male participants; SMI <43 cm^2/m^2

for BMI ≤ 24.9 kg/m^2, and SMI<53 cm^2/m^2 for BMI > 24.9 kg/m^2. For female participants; SMI <41 cm^2/m^2 for all BMI categories [221].

For the PMI, ESMI and PSMI, there has been no generally established cut-off value for sarcopenia. Therefore, sex-specific quartile was calculated, and the group with the lowest quartile in this study were considered to have sarcopenia [282].

3.3.5 Statistical Analysis

3.3.5.1 Descriptive statistics

Our primary outcome in this study was the change of postoperative dyspnoea at six months, while global health change was the secondary outcome. The MCID and QoL calculations were explained in Section 3.1.3. The data were presented as mean ± standard deviation, median ± interquartile range, or numbers (proportions), as appropriate. The normality of numeric variables was tested using the Shapiro-Wilk test. Baseline characteristics were presented as the difference between male and female participants in age, BMI, lung function, and COPD using an independent t-test for numeric normally distributed data or Mann-Whitney U test for non-normally distributed data. Analyses of categorical variables were conducted using the Chi-square test or Fisher's exact test. A p-value of <0.05 was considered statistically significant.

3.3.5.2 Muscles differences

Similar to the above methods, we compared the differences between male and female participants and high or low BMI (BMI >24.9 vs BMI ≤ 24.9) in SMI, PMI, ESMI, and PSMI using an independent t-test due to the normality of these data. A comparison between male and female or participants with high and low BMI in the proportion of sarcopenia of skeletal, pectoralis, erector

spinae, and psoas muscles was performed using the Chi-square test or Fisher's exact test. A p-value of <0.05 was considered statistically significant.

3.3.5.3 Correlation between muscles indices

We assessed the correlation between SMI and PMI, ESMI and PSMI. Pearson's or Spearman's correlation coefficients were used as appropriate. Based on the correlation coefficients, the strength of association between variables is illustrated in Table 3.2

Table 3.2 Correlation coefficients classification [283]

Correlation coefficient (r)	Interpretation
0 - 0.19	Very weak
0.2 - 0.39	Weak
0.4 - 0.59	Moderate
0.6 - 0.79	Strong
0.8 - 1.0	Very strong

3.3.5.4 The difference of CT body composition in recovered and worsen HRQOL

This study investigated the differences between SMI, PMI, ESMI, and PSMI and the proportion of sarcopenia of skeletal, pectoralis, erector spinae and psoas muscles in patients who had increased dyspnoea or deteriorated global health six months after surgery and those with lower dyspnoea or recovered global health. Further exploratory analyses were conducted to investigate differences in body composition between individuals with improved and decreased physical functioning, as well as

fatigue levels. Comparison of continuous factors was accomplished using an independent t-test due to the normality of these data. Comparison of the proportion of sarcopenia was completed by Chi-square test or Fisher's exact test. A p-value of <0.05 is considered statistically significant.

3.3.5.5 The difference of CT body composition in postoperative clinical outcomes

This sub-study explored the difference between patients with longer and shorter LOS. The median LOS was set as a threshold for determination patients with longer versus shorter LOS. A hospital stay exceeding five days was considered long, whereas a stay of five days or less was considered short. The statistical method employed in this study is explained in Section 3.3.5.4.

3.3.5.6 Reproducibility of CT based body composition

In order to determine the reproducibility of the CT body composition measurements, the analysis of CT measurement of body composition was performed twice separately, CT scan analysis of 30 consecutive patients was separated by two months. The observer was blinded to the results of the study. The level of intra-observer reliability was evaluated using Intra-class correlation coefficients (ICC) and Bland Altman plots as explained in Section 3.2.5.5.

Previous studies reported an intra-observer mean difference of 0.98 cm^2 using the same slice and LOAs of 2.92 cm^2 [284].

All our statistical analyses were performed using Stata 18.0 statistical software (Stata Co., College Station, TX) or SPSS version 29 (IBM Corp.).

3.3.5.7 Comparison between contrast-enhanced and unenhanced CT body composition

In this study, contrast-enhanced and non-enhanced CT scans measurements of right and left ESM area were compared in 10 lung cancer patients. In addition, the Bland Altman plots were implemented. Details of the method is described in Section 3.2.5.5.

3.4 An investigation of the agreement between AI-based software and semi-automated software quantification of emphysema

3.4.1 Study design and participants

We used the data from the previously approved protocol for this study to conduct a retrospective analysis (Research Ethics Committee reference: 10/H1208/41). Similar to our earlier study that was described in detail previously, we examined the same cohort of patients in this study as well (Section 3.1-3.2). CT scans were retrospectively collected and assessed for inclusion in the analysis.

3.4.2 CT acquisition

The data for this study were obtained using two CT scanner types; an Aquilion ONE scanner (Toshiba Medical Systems Corporation, Tokyo, Japan) and a Somatom Definition scanner (Siemens Medical Solutions, Forchheim, Germany). CT scan acquisition details involving scanner setting, and reconstruction kernel have been described before (Section 3.2.2). This study involved only unenhanced CT scans.

3.4.3 CT scan analysis software

The purpose of this study was to investigate the inter-software agreement in the analysis of lung volume and density on CT scans using two software programs, an open-access program and a commercial program:

- 3D slicer v 4.10; Chest Imaging Platform (CIP) module
- AI-assisted Aview ® system (Coreline Soft Inc., Seoul, South Korea).

3D Slicer CIP module is the primary software utilised in this thesis. A description of the method and algorithm used in CT quantification of emphysema using CIP module is provided in Section 3.2.4. An image analysis using the CIP module required a minimum of 15 minutes per scan.

Aview system is a commercial AI-based platform that involves quantitative image analysis with automated lobar segmentation to assess emphysema, airway, fissure integrity and small airway disease [285] and is approved by the FDA [286]. Several studies have utilised the software to quantify emphysema, among other diseases [287-291]. The Coreline Aview developer has employed a 2.5D convolutional neural network for voxel-by-voxel segmentation and compared it with its gold-standard semi-automated segmentation algorithm [285]. The time elapsed for image analysis was dramatically reduced to 2-3 minutes.

3.4.4 Emphysema quantification using Aview system

As with CIP module, CT scans were converted to DICOM format for analysis by the Aview software. The first step was importing the DICOM into Aview system. After that, the lung segmentation and quantification were automatically performed by the software using the three planes; sagittal, coronal and axial. Each of the five lobes was shown in a different colour and presented in a sagittal, coronal, and axial planes for viewing and assessment (Figure 3.3). While errors in the segmentation could be corrected manually, the researcher intended to assess the performance of the AI-based software without intervention for better assessment of the standard measures of the software. The data were generated and detailed reports were provided containing quantified data (Figure 3.4-3.5). The data assessed were: %LAA-950, PD15, MLD and lung volume.

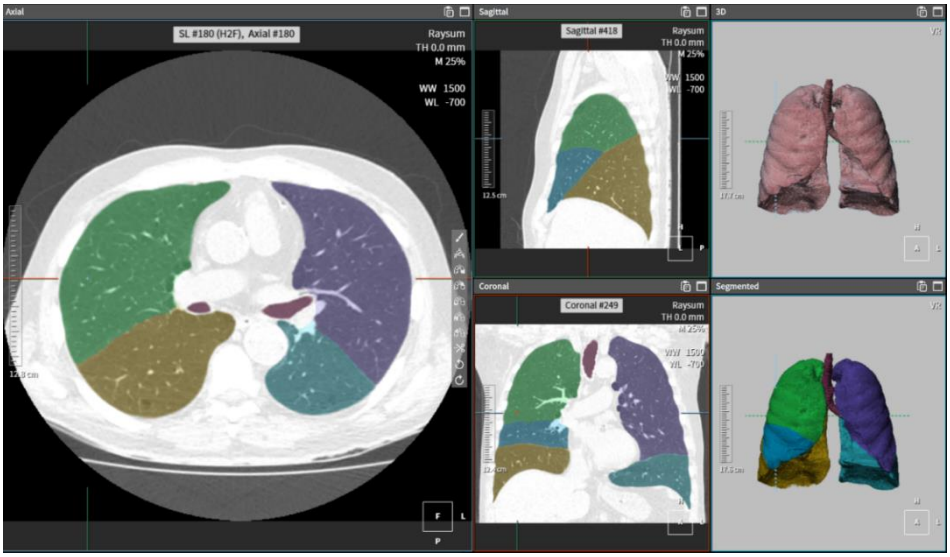

Figure 3.3 An example of automated lobar segmentation in sagittal, coronal, and axial planes performed by Aview system

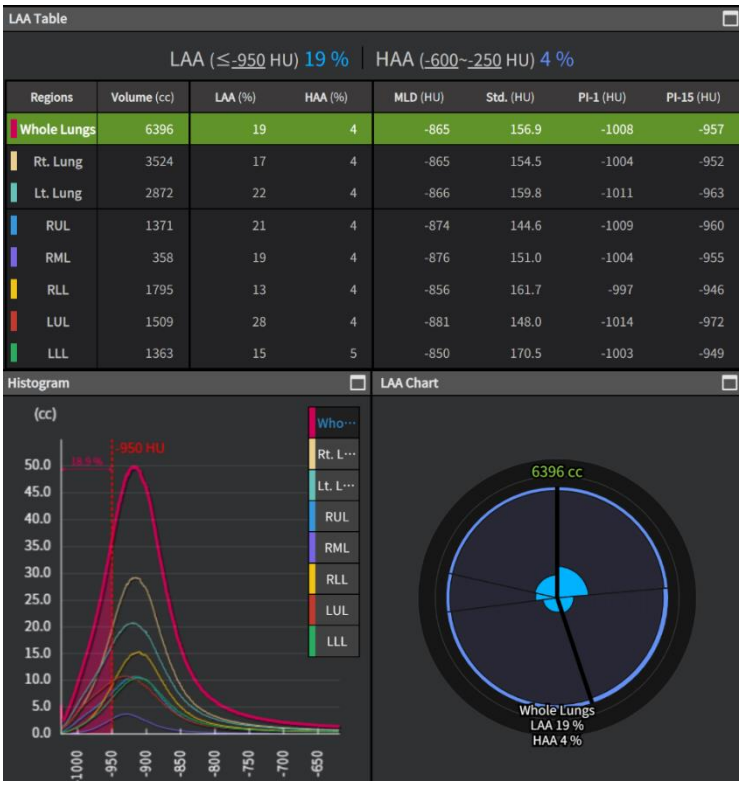

Figure 3.4 LAA analysis data quantified by Aview system

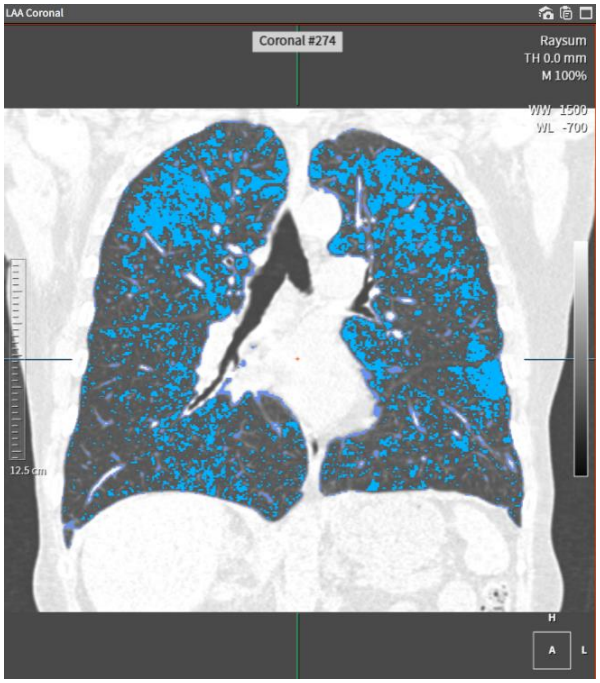

Figure 3.5 An example of a CT scan with LAA coloured in blue in a coronal view, quantified by the Aview system

3.4.5 Statistical Analysis

3.4.5.1 Descriptive statistics

We presented the data as mean ± standard deviation, median ± interquartile range, or numbers (proportions), as appropriate. An assessment of the normality of numeric variables was conducted using the Shapiro-Wilk test.

3.4.5.2 Investigating levels of agreement between two software programs

In this study, intra-software agreement was assessed using unenhanced CT scans. The level of intra-software reliability was evaluated using Intra-class correlation coefficients (ICC) [275] and Bland Altman plots. The mean difference between the two groups and the limits of agreement (LOA) were calculated as described in Section 3.2.5.5.

In line with previous reports, differences of %LAA-950 <5%, 15PD, MLD <10 HU, or lung volume <0.05 L between the two software programs were considered reasonable differences [267, 277, 292]. All our statistical analyses were performed using Stata 18.0 statistical software (Stata Co., College Station, TX) or SPSS version 29 (IBM Corp.).

Chapter 4. Patients Reported Outcomes in Predicting Postoperative Quality of Life

4.1 Introduction

Patients with NSCLC typically report a deterioration in their health-related quality of life pre-operatively [125], despite the fact that opposite findings have also been reported [28]. HRQOL tends to deteriorate immediately after surgery, but it may recover to pre-operative levels within 3-9 months of the operation [100]. Conversely, studies have also demonstrated the impairment of HRQOL lasting for a much more extended time after surgery in some domains [104]. As a result of controversy about when a patient's HRQOL returns to normal following lung surgery and concerns about factors contributing to this, questions have arisen regarding the factors that could affect a patient's HRQOL. A clear and accurate understanding of HRQOL changes after lung cancer surgery may allow the patient to participate actively in decision-making. In addition, identifying lung cancer patients at an elevated risk of reduced quality of life after treatment is fundamental.

A systematic review found that EORTC QLQ-C30 and lung cancer-specific module LC13 are the most widely used tools in lung cancer research [293]. Montazeri et al. acknowledged that EORTC QLQ-C30 and LC13 are the most sophisticated instruments to measure the HRQOL of lung cancer patients, compared to more than fifty other instruments [146]. Several HRQOL questionnaires do not assess all HRQOL domains, while EORTC questionnaires do [293]. Thus, EORTC QLQ-C30 and LC13 have been chosen in this research to evaluate lung cancer patients.

Across the studies, dyspnoea was reported to be a common complaint among lung cancer patients, with moderate intensity of dyspnoea interfering with daily living activities [96]. Dyspnoea following operative procedures is not fully understood, but there is a likelihood that multiple factors are involved. This study aims to better understand these complex mechanisms and predict long-term disabling dyspnoea risk. Developing better methods of predicting dyspnoea following lung surgery would improve the shared surgical decisions and facilitate the interventions and inclusion of patients in clinical trials designed to alleviate postoperative breathlessness.

It has been reported that there is a higher risk of HRQOL disruption associated with lung cancer compared to other chronic diseases and cancers, and there is a possibility that the reduction in quality of life may last for more than five years [294]. It is well known that lung cancer patients' QoL is significantly impacted by surgical management [13]. Furthermore, it has been noted that VATS has lower impact on physical performance and respiratory symptoms compared to thoracotomy [295]. In addition, patients with VATS had significant improvement in physical and emotional functioning compared to those with thoracotomy [10]. However, Avery et al. indicated that the use VATS approach in preference to thoracotomy may not prevent long-term significant deteriorations in HRQOL and that VATS may have more extensive detrimental impact on HRQOL of lung cancer patients than once believed [126]. Similarly, previous studies found no significant difference between VATS and thoracotomy in HRQOL using EORTC QLQ-C30 and LC13 [153, 296]. Moreover, Pompili et al. revealed that VATS patients with good functioning and lower symptoms at baseline experienced significant worsening of HRQOL six months following lung cancer surgery [106]. Despite the improvement in reporting and use of QoL measurements in thoracic surgery, their relevance in clinical practice remains unclear, and their value is underestimated [122].

In addition, surgical approach may have an impact on short-term QoL following lung cancer surgery. Surgical techniques may affect initial postoperative recovery including pain and physical functioning

[98, 296]. However, our major focus of this study is the long-term postoperative HRQOL. By evaluating the outcomes beyond the short-term stage, this thesis aims to capture the more enduring impact of lung cancer surgery on patients' HRQOL, providing a broader insight of how patients' HRQOL changes over time. The decision to focus this study on a six-month period following lung cancer surgery is supported by existing literature indicating meaningful milestones in recovery trajectories. Handy et al. showed that HRQOL deteriorated until six months following lung cancer surgery [125]. Another study of 117 patients with thoracotomy indicated that HRQOL restored to baseline levels at six to nine months following lung cancer surgery [98]. We emphasise on the six-month period to better focus of the crucial early recovery period, which is most representative of the immediate effects of surgical intervention on HRQOL.

This chapter aims to investigate the HRQOL trajectories through six months following lung cancer resection using EORTC QLQ-C30 and lung cancer-specific module LC13. Moreover, our study examined various factors to predict postoperative dyspnoea and global health six months after the intervention. As part of this longitudinal study, we used the EORTC QLQ-C30 and LC13. We did not employ other PRO tools, primarily because they are one of the most commonly used PRO tools among lung cancer cohorts and for comparison in the present longitudinal study.

4.2 Methods

This study is a prospective, longitudinal, single-centre study. The Institutional Review Board approved the study (REC number: 10/H1208/41). The study was commenced by the thoracic surgery research team at UHB NHS Foundation Trust before my PhD study. The primary aim was to evaluate whether a rehabilitation program could recognise potential surgical candidates weeks before surgery, optimise their physical status, prepare them for the inpatient journey, and support post-surgery recovery. HRQOL was one of the primary outcomes in this study. This study involved consecutive recruitment of patients undergoing lung resection at University Hospital Birmingham NHS Foundation Trust. Informed consent was collected from all participants, and quality of life (QoL) measures were self-reported by all participants at baseline, eight weeks and six months following lung surgery. The patients' medical records were used as a source of other data that were not systematically collected.

The thoracic research team have prospectively collected data on paper CRFs some of which had been entered onto a database over the past ten years, and was the first hurdle to overcome. In order to develop a comprehensive and up-to-date database, it was necessary to input remaining CRF data, clean the data and collect additional data prospectively from patients' electronic medical records.

Missing data has also been investigated and analysed for the response rates, and a comparison between respondents and non-respondents to the questionnaire has been explored.

Detailed patient selection criteria and other methods, including statistical methods, can be found in Chapter 3.

4.3 Results

4.3.1 Baseline characteristics

A total of 1064 patients were recruited from 2010 until 2020, and 906 consented patients were eligible for the study (Figure 4.1). Patients excluded were 109 patients with benign lung tumours, 18 patients with lung infections, and six patients without lesions were not eligible for this study. Other 23 patients withdrew from the study, and two who had just had a biopsy have also been excluded. Patients' baseline characteristics and clinical data are shown in Tables 4.1- 4.5.

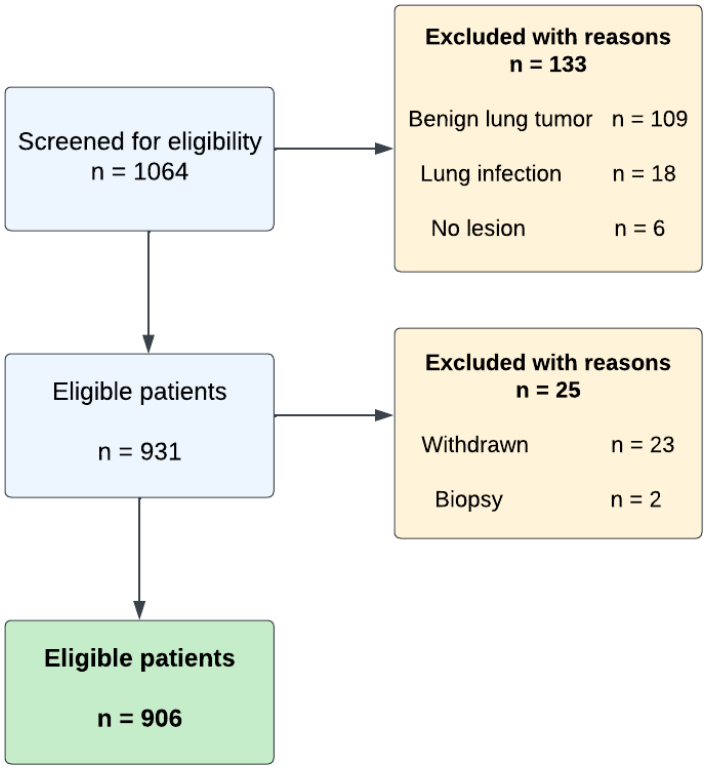

Figure 4.1 Patients' flow diagram through the study

Table 4.1 Baseline characteristics of 906 patients included in the study

Characteristic	Total (n = 906)
Patient demographics	
Age	70 ± 11
Gender (male)	465 (51.32)
BMI	27.29 ± 5.14
Smoking Status	
Current	187 (20.8)
Ex-smoker	544 (60.6)
Never smoker	156 (17.3)
Smoking quit time	
Current	184 (21.05)
Ex-smoker (6 weeks ≥ 1 year)	107 (12.24)
Ex-smoker (> 1 year)	427 (48.85)
Never smoker	156 (17.84)
Pack years	30 ± 39

Data are presented as mean (median), standard deviation (interquartile range), or numbers and percentages for categorical data.

Table 4.1 above represents baseline demographic and smoking data for 906 patients. The median age was 70 years old, and we can notice that around half of the patients were male. We can see that the mean BMI for 906 was 27.2. Almost 50% of the patients have quit smoking for over a year; 21% were current smokers, while only 17.8% were never smokers.

Table 4.2 Baseline lung function for 906 patients included in the study

Characteristic	Total (n = 906)
FEV_1 (L)	2.21 ±0 .73
% FEV_1	87.76 ± 21.49
FVC (L)	3.31 ± 1.007
% FVC	104.96 ± 21.77
%DLCO	77.14 ± 18.76
$ppoFEV_1$	71.48 ± 20.07
ppoDLCO	62.66 ± 16.82

Data are presented as mean (median) and standard deviation (interquartile range), FEV_1; forced expiratory volume for 1 second, FVC; forced vital capacity, DLCO; diffusing capacity for carbon monoxide, $ppoFEV_1$ or ppoDLCO; predicted postoperative FEV_1 or DLCO.

The table above represents baseline lung function information for 906 patients. Lung function involves FEV_1 (L), FEV_1 Percentage predicted, FVC (L), FVC percentage predicted, and DLCO collected before lung surgery. The author collected any missing data on lung function from patients' medical records and doctors' reports. $ppoFEV_1$ and ppoDLCO were calculated using the formula of segment counting that is stated in the literature review (Section 1.2.1.1). We can see that the mean values of FEV_1 (L) and % FEV_1 are 2.21 and 87, respectively. DLCO mean value is 77.14.

Table 4.3 Baseline lung surgery information for 906 patients included in the study

Characteristic	Total (n = 906)
Surgical incision	
Open	407 (45.02)
VATS	497 (54.98)
Surgery side	
Right	531 (58.61)
Lobe	
Upper	493 (55.77)
Middle	52 (5.88)
Lower	281 (31.79)
Upper Bilobe	13 (1.47)
Lower Bilobe	10 (1.13)
Entire lung	29 (3.28)
Lung resection	
Wedge	148 (16.34)
Segmentectomy	33 (3.64)
Lobectomy	672 (74.17)
Bilobectomy	21 (2.32)
Sleeve	3 (0.33)
Pneumonectomy	29 (3.28)

Data are presented as numbers and percentages for categorical data. VATS; video-assisted thoracic surgery.

The above table demonstrates lung surgery information. Almost 55% of the surgical incisions were Video-assisted thoracic surgery (VATS), whereas 45% were thoracotomy (open surgery). In addition, 55% of the surgeries were performed on the upper lobes, while 3% of the surgeries removed the entire lung (pneumonectomy).

Table 4.4 Postoperative lung cancer information of 906 patients included in the study

Characteristic	Total (n = 906)
Postoperative histology	
Adenocarcinoma	480 (52.98)
Squamous cell carcinoma	209 (23.07)
Carcinoid	74 (8.2)
Metastasis	92 (10.15)
Primary Lung Cancer stage (No)	
T1	391 (49.1)
T2	298 (37.48)
T3	83 (10.44)
T4	23 (2.89)
N0	590 (77.12)
N1	113 (14.77)
N2	62 (8.1)
M0	770 (99.4)
M1	4 (0.5)
Clear Margin (R0)	825 (91.56)
Postoperative Chemotherapy	123 (13.5)

Data are presented as numbers and percentages for categorical data. T; tumour size staging, N; lymph node involvement, M; metastasis.

Table 4.4 shows postoperative lung cancer histology and staging. We can see that nearly 53% of the cancer histology was adenocarcinoma. In addition, 49% of the cancers were in stage T1 and over 77% of the cancers did not involve lymph nodes (N0). Additionally, 99% of the patients did not have metastasis. Around 92% of these cancers had clear margins, and 13.5% had chemotherapy.

Table 4.5 Baseline comorbidities and postoperative information for 906 patients included in the study

Characteristic	Total (n = 906)
Comorbidity	
COPD	210 (23.26)
IHD	90 (10.31)
Cardiac failure	32 (3.64)
Hypertension	386 (46.45)
Diabetes	129 (14.68)
Renal failure	8 (0.88)
Stroke	54 (6.26)
Thyroid	62 (7.49)
Anticoagulants use	197 (23.01)
Other measures	
ASA score ≥3	474 (52.85)
ECOG Performance Score < 2	827 (95.38)
MRC dyspnoea score > 2	105 (11.8)
Perioperative Outcomes	
Hospital mortality	6 (0.66%)
Postoperative pulmonary complications	74 (8.1%)
Hospital readmission	95 (11.5%)
Hospital length of stay (days)	4 ± (3)

Data are presented as mean (median), standard deviation (interquartile range), or numbers and percentages for categorical data. COPD; chronic obstructive pulmonary disease, IHD; ischemic heart disease, ASA score; American Society of Anaesthesiologists' classification of physical health, ECOG; Eastern Cooperative Oncology Group performance status

An overview of the preoperative comorbidities, other measures, and postoperative information in 906 patients is presented in the table above (Table 4.5). It is apparent that 46% of the patients suffered from hypertension, and 23% had COPD. We observed that more than half of the participants had an American Society of Anaesthesiologists (ASA) score of 3 or higher. The Eastern Cooperative Oncology Group performance status (ECOG) score was less than 2 in 95% of the patients.

Regarding postoperative outcomes, interestingly, only 8% of patients had postoperative pulmonary complications (PPC), the median length of hospital stay (LOS) was four days, which is considered relatively short, and only 0.6% of patients died from the procedure.

4.3.2 Health Related Quality of Life questionnaire overall completion

Baseline, eight weeks, and six months EORTC QLQ-C30 received rates are 97.6%, 96.5% and 76%, respectively. The expected rates for the QLQ-C30 at baseline, eight weeks and six months following surgery were 100%, 97%, and 95%, respectively. Additionally, baseline, eight weeks, and six months EORTC QLQ-LC13 received rates are 96.3%, 96% and 75.3%, respectively. The expected rates for QLQ-LC13 collection are 100%, 97% and 95%, respectively. The median time between the baseline questionnaires' collection and lung surgery is 6±7 (days). The median time between eight weeks questionnaires' collection and lung surgery is 56 ± 16 (days). For six-month-questionnaires the median time extends to 165 ± 21 (days). Figures 4.2 and 4.3 show the received and expected rates for EORTC QLQ-C30 and LC13.

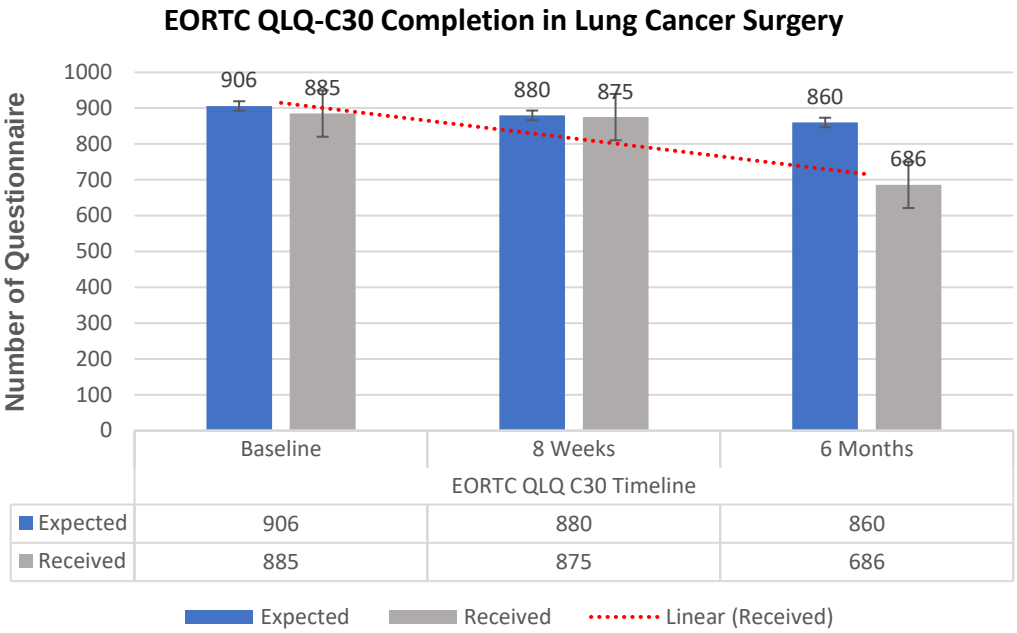

Figure 4.2 EORTC QLQ-C30 completion in lung cancer surgery

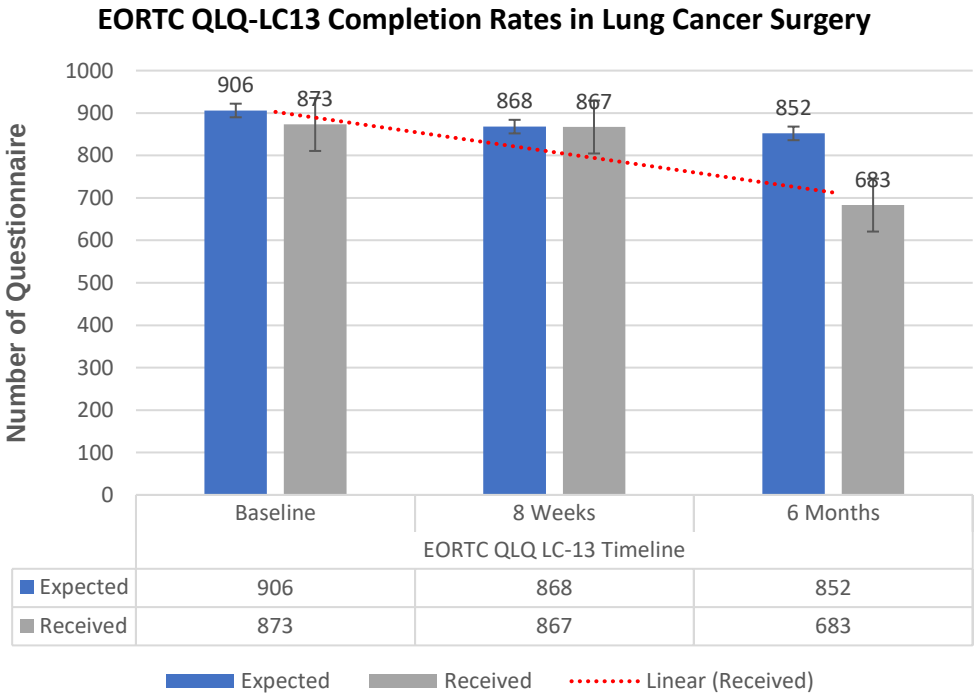

Figure 4.3 EORTC QLQ-LC13 completion in lung cancer surgery

4.3.2.1 Health Related Quality of Life respondents vs non-respondents

In order to have a better understanding of the reasons behind missing data in EORTC QLQ-C30, the author conducted a comparison between QoL respondents (the questionnaire completers) and non-respondents in baseline data. No difference was seen in age (p = 0.05), gender (p = 0.8), BMI (p = 0.4), baseline %FEV_1 (p = 0.2), baseline %DLCO (p = 0.9), pack-years (p = 0.1), postoperative histology (p = 0.3), and TNM staging (p >0.5) (Table 4.6).

Table 4.6 Difference in baseline characteristics between respondents and non-respondents

Factor	Respondents (n = 686)	Non-respondents (n = 220)	P value
Age	70 ± (11)	69 ± (10.5)	0.05
Gender (male)	351 (51.1)	114 (51.8)	0.8
BMI	27.2 ± (5)	27.5 ± (5.3)	0.4
%FEV_1	88.2 ± (21.8)	86.3 ± (20.2)	0.2
%DLCO	77.2 ± (18.5)	76.9 ± (19.4)	0.9
Pack years	30 ± (39)	30 ± (37.5)	0.1
Postoperative histology			
Adenocarcinoma	364 (53)	116 (52.7)	0.3
Squamous cell carcinoma	155 (22.5)	54 (24.5)	0.3
Metastasis	77 (11)	15 (7)	0.3
Lung cancer stage			
T (2)	223 (33.7)	77 (35.4)	0.1
N (1)	78 (11.9)	35 (16)	0.4
M (0)	573 (99.4)	197 (99.4)	0.6

Data are presented as mean (median), standard deviation (interquartile range), or numbers and percentages for categorical data. BMI; body mass index, FEV_1; forced expiratory volume for 1 second, DLCO; diffusing capacity for carbon monoxide, ECOG; Eastern Cooperative Oncology Group .*p<0.05; **p<0.01; ***p<0.001

4.3.3 Health Related Quality of Life change

4.3.3.1 Assessment of the change and trajectories of EORTC QLQ-C30 functioning and global health scores at different time points

To investigate the change in EORTC QLQ-C30 and LC13 domains, we assessed the difference between these domains at baseline, eight weeks and six months. The minimal clinically important difference is 10 points for QLQ-C30 domains and half the standard deviation for LC-13 domains.

In the three time points, there is a statistically significant difference between the domains of functioning and global health ($p = 0.00$) (Table 4.7). It is important to note that the change between two-time points may not be minimally clinically significant in all of these domains. To investigate the change in depth, we performed a pairwise comparison with Bonferroni correction.

Table 4.7 Comparison between EORTC QLQ-C30 functioning and global health domains

QoL domain	baseline	8 weeks	6 months	P value
Global health	73.2 ± (20.5)	63.3 ± (20.5)	66.6 ± (22.2)	***
Physical functioning	85 ± (18.9)	72 ± (21.5)	75.2 ± (21.3)	***
Role functioning	85 ± (24.6)	63 ± (30.1)	70.6 ± (29.9)	***
Emotional functioning	76± (23.2)	76.6 ± (23.8)	79 ± (22.8)	***
Cognitive functioning	86.2 ± (18.6)	81.4 ± (22.5)	82.3 ± (21)	***
Social functioning	86.3 ± (22.6)	70.7 ± (28.4)	77.7 ± (27.5)	***

Statistical tests: Repeated measures ANOVA, Friedman test. Data are presented as mean (median) and standard deviation (interquartile range). *p<0.05; **p<0.01; ***p<0.001

Table 4.8 Post hoc pairwise comparison for EORTC QLQ-C30 functional and global health domains

EORTC QLQ-C30 Functioning and global health domain	Baseline vs 8 weeks Difference	P value	95% CI	Baseline vs 6 months Difference	P value	95% CI	8 weeks vs 6 months Difference	P value	95% CI
Global health	10	**	8.4 -11.3	7	**	5.3 -8.7	-3.3	*	-3.8 - -0.6
Physical functioning	13	**	11.1 -13.6	10	**	9.1 -11.8	-3.2	*	-2.6 - -0.2
Role functioning	22	**	19.3 -23.6	14.4	**	13 -17.3	-7.6	**	-7.7- -3.2
Emotional functioning	-0.6	0.2	-2.4 - 0.5	-3	0.02	-3.6 - -0.2	-2.4	0.2	-2.4 - 0.6
Cognitive functioning	4.8	**	3.2 - 6.2	3.9	**	3.1 - 6.1	-0.9	0.4	-0.8 - 2.0
Social functioning	15.6	**	13.4 -17.2	8.6	**	7.3 -11.4	-7	**	-7.7 - -3.3

Post-hoc pairwise comparison with Bonferroni correction. Statistical tests: paired t-test or Wilcoxon signed-rank test. *p<0.017; **p<0.001

Table 4.8 shows the difference in functional or global health domains at different time points. Statistically and clinically, global health has deteriorated from baseline to eight weeks, generally indicating lower quality of life. In addition, there was a statistically significant but no clinical difference between eight weeks and six months, implying that global health has not recovered at six months following surgery. Similarly, physical functioning has statistically and clinically declined between preoperative and eight-week scores; however, there has been a marginal improvement, but not to the point of clinical difference.

Role and social functioning have demonstrated statistical and clinical differences between baseline and eight weeks; both have decreased. However, both domains have recovered (i.e., nearly 7 points) but not to the minimal clinical difference. In contrast, emotional and cognitive functioning have not presented any clinically meaningful change at any time point. However, cognitive functioning has a statistically significant difference between baseline and eight weeks and baseline and six months (p = 0.00). Figure 4.4 shows EORTC QLQ-C30 functioning and global health trajectories over six months following lung cancer intervention.

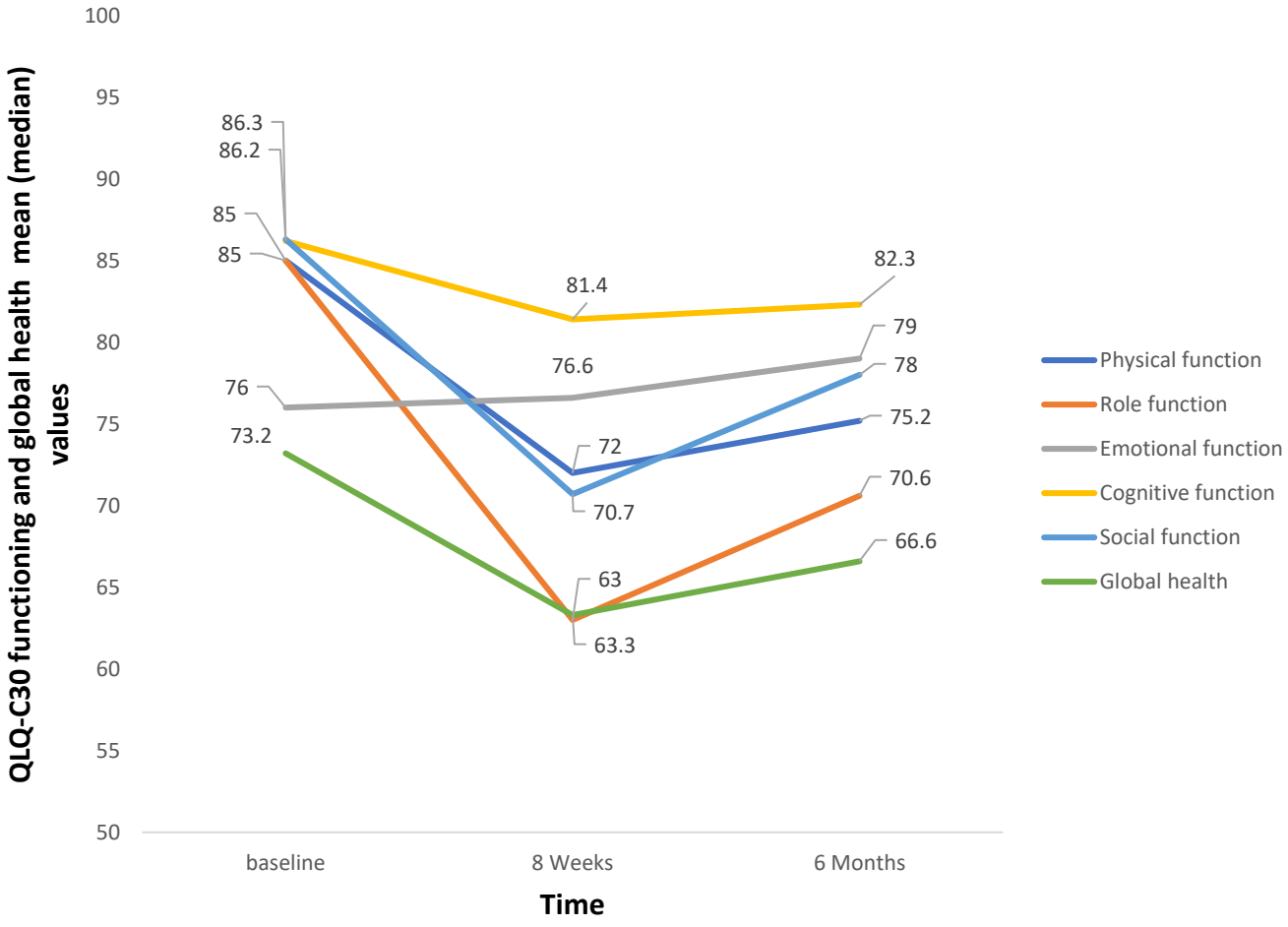

Figure 4.4 The trajectories of EORTC QLQ-C30 functioning and global health domains at baseline, eight weeks, and six months after lung cancer surgery.

4.3.3.2 Assessment of the change and trajectories of EORTC QLQ-C30 symptoms scores at different time points

Table 4.9 Comparison between EORTC QLQ-C30 symptoms domains

QoL domain	baseline	8 weeks	6 months	P value
Fatigue	21.9 ± (22.6)	39.6 ± (24.5)	33.2 ± (24.7)	***
Nausea and vomiting	4.2 ± (11.6)	9.7 ± (18.2)	6.3 ± (14.6)	0.9
Pain	15.7 ± (25.1)	31.4 ± (28.4)	22.4 ± (26.2)	***
Dyspnoea	20.5 ± (25.4)	41.9 ± (29.6)	39.2 ± (29.4)	***
Insomnia	27.5 ± (32.7)	33 ± (32.6)	27 ± (31.1)	***
Appetite loss	11.8 ± (23.3)	25.9 ± (32.4)	16.2 ± (26.6)	***
Constipation	10 ± (21.8)	24.2 ± (31)	16.1 ± (25.8)	***
Diarrhoea	6 ± (15)	8.9 ± (18.7)	8.2 ± (18.4)	1.00
Financial difficulties	8.4 ± (21)	13.7 ± (26.8)	10.5 ± (22.6)	0.6

Statistical tests: Repeated measures ANOVA, Friedman test, independent t-test or Mann-Whitney U test. Data are presented as mean (median) and standard deviation (interquartile range). *p<0.05; **p<0.01; ***p<0.001

Table 4.9 compares the difference between symptom domains at baseline, eight weeks, and six months after treatment. Fatigue, pain, dyspnoea, insomnia, appetite loss, and constipation have demonstrated statistically significant differences at the three-time points (p = 0.00). On the contrary, nausea and vomiting, diarrhoea and financial difficulties have no statistically significant difference. We conducted a post-hoc pairwise comparison for each symptom domain to explore the differences in more detail.

Table 4.10 Post hoc pairwise comparison for EORTC QLQ-C30 symptoms domains

EORTC QLQ-C30 symptoms domain	Baseline vs 8 weeks Difference	P value	95% CI	Baseline vs 6 months Difference	P value	95% CI	8 weeks vs 6 months Difference	P value	95% CI
Fatigue	-17.7	**	-19.5- -16.3	-11.3	**	-14 - -10.6	6.4	*	3 - 6.4
Nausea and vomiting	-5.5	**	-6.6 - -4.2	-2.1	**	-3.6 - -1.3	3.4	**	1.5 - 4.2
Pain	-15.7	**	-17.6 - -13.7	-6.7	**	-10 - -6	9	**	20.5 - 24.5
Dyspnoea	-21.4	**	-23.4 - -19.4	-18.7	**	-21.8 - -17.4	2.7	0.2	-0.7 - 3.1
Insomnia	-5.5	**	-7.6 - -2.8	0.5	0.6	-3.1 - 1.9	6	**	1.8 - 6.6
Appetite loss	-14.1	**	-16.1 - -11.9	-4.4	**	-7.4 - -3.1	10	**	5.8 - 10.6
Constipation	-14.2	**	-16.4 - -12.4	-6.1	**	-8.8 - -4.9	8.1	**	4.8 - 9.1
Diarrhoea	-2.9	**	-4.3 - -1.5	-2.2	*	-3.9 - -0.8	0.7	0.6	-2 - 1.2
Financial difficulties	-5.3	**	-6.7 - -3.5	-2.1	**	-4.6 - -1.5	3.2	*	0.6 - 3.8

Post-hoc pairwise comparison with Bonferroni correction. Statistical tests: paired t-test or Wilcoxon signed-rank test. *p<0.017; **p<0.001

Table 4.10 shows the pairwise comparison within the symptoms' domains of the EORTC QLQ-C30. A significant increase in fatigue and constipation compared to baseline levels has been observed eight weeks postoperatively, demonstrating the worst symptoms. The level of both domains has increased significantly in the last six months but has not reached the minimal clinical threshold. Additionally, nausea and vomiting, insomnia, diarrhoea, and financial difficulties have not demonstrated a minimal clinical difference at all time points; however, they have been statistically significant at most time points. This implies that lung surgery has not affected these domains. It has been shown, however, that the treatment has a short-term effect on pain, with a statistical and clinical increase to more than double eight weeks after the intervention. It has been found that pain levels had almost recovered to baseline levels (9 points change, $p = 0.00$) at six months. The short-term impact of surgery on appetite loss was also found to be statistically and clinically significant at eight weeks after the operation (14.1 points change, $p = 0.00$). There has been a minimal decrease in appetite loss at six months, but it has not returned entirely to the preoperative level (10 points change, $p = 0.00$). The surgery has demonstrated both short-term and long-term detrimental effects on dyspnoea, increasing to more than double baseline levels after eight weeks (21.4 points, $p = 0.00$). Moreover, dyspnoea has not improved, showing a very slight decrease (2.7 points), indicating the treatment is having a long-term impact on dyspnoea. Figure 4.5 illustrates trajectories of EORTC QLQ-C30 symptoms domains.

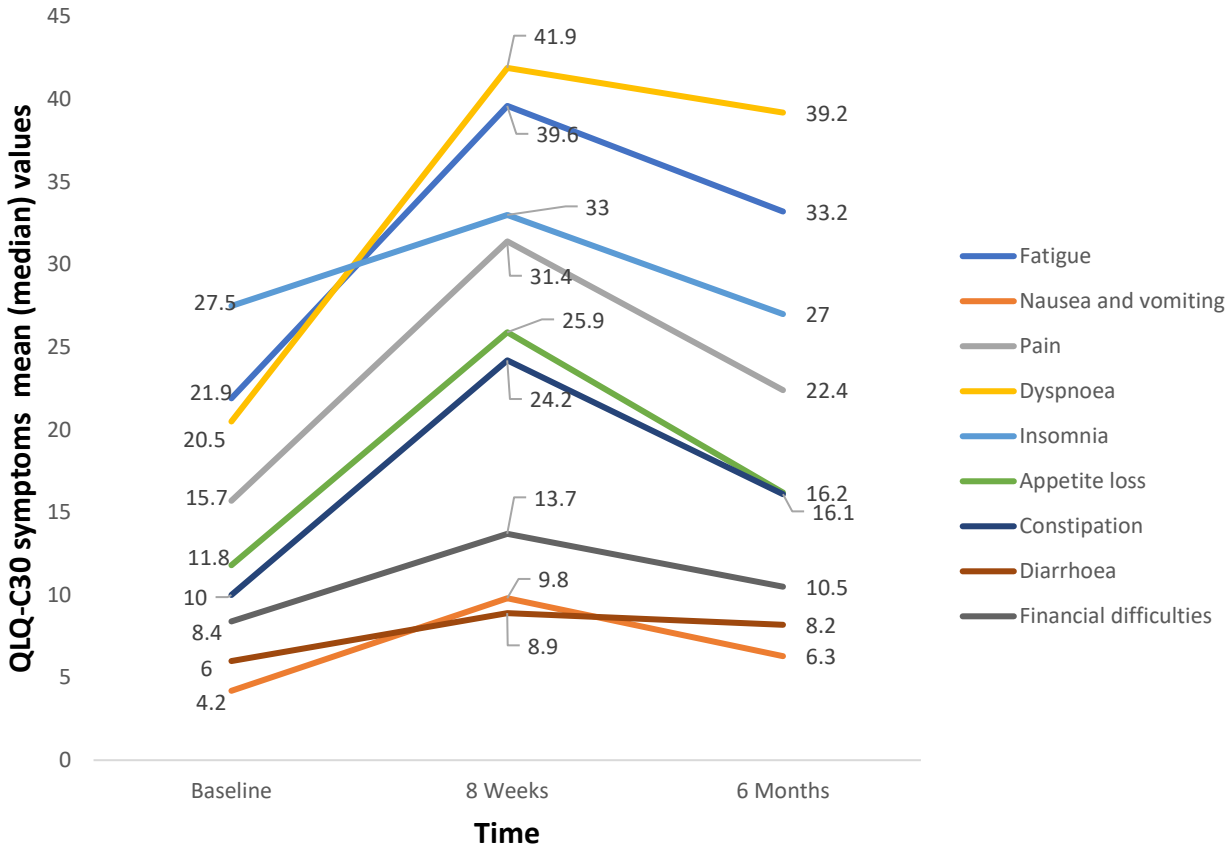

Figure 4.5 The trajectories of EORTC QLQ-C30 symptoms domains at baseline, eight weeks, and six months after lung cancer surgery.

4.3.3.3 Assessment of the change and trajectories of EORTC QLQ-LC13 lung cancer symptoms scores at different time points

Table 4.11 Comparison between EORTC QLQ-LC13 lung cancer symptoms domains

QoL domain	baseline	8 weeks	6 months	P value
Dyspnoea	16.3 ± (20.2)	31.2 ± (23.7)	29.8 ± (23.9)	***
Coughing	31.9 ± (26.4)	35.9 ± (26.6)	33.6 ± (27)	***
Haemoptysis	2.3 ± (9.8)	1.1 ± (7.1)	0.6 ± (5.5)	1.00
Sore mouth	4.5 ± (14.8)	8.1 ± (20.1)	8.2 ± (19.4)	1.00
Dysphagia	3.2 ± (12)	6.7 ± (17)	6.9 ± (18.7)	1.00
Peripheral neuropathy	9.4 ± (21)	10.3 ± (22)	15.4 ± (26)	0.8
Alopecia	3.2 ± (12.7)	4.3 ± (14)	9.6 ± (21.3)	1.00
Pain in chest	7.7 ± (17.3)	21.8 ± (25.4)	16.6 ± (24.5)	***
Pain in arm or shoulder	13.3 ± (24.3)	19.4 ± (26.9)	17.5 ± (26.8)	***
Pain in other parts	21.6 ± (30.3)	24 ± (31.1)	24 ± (30.2)	***

Statistical tests: Repeated measures ANOVA, Friedman test, independent t-test or Mann-Whitney U test. Data are presented as mean (median) and standard deviation (interquartile range). *p<0.05; **p<0.01; ***p<0.001

In Table 4.11, we have highlighted the differences within the EORTC QLQ-LC13 lung cancer symptom domains in baseline, eight weeks, and six months afterwards. Significant differences were not observed across all lung cancer symptom domains in this longitudinal study. It can be seen that dyspnoea, coughing, pain in the chest, pain in the arm or shoulder, and pain in other parts differ significantly across all the time points (p = 0.00). On the contrary, there have been no differences within haemoptysis, sore mouth, dysphagia, peripheral neuropathy, and alopecia in baseline, eight

weeks and six months post-treatment ($p > 0.05$). For more information regarding the differences between the domains in two-time points, we conducted post-hoc pairwise comparisons (Table 4.9).

Table 4.12 Post hoc pairwise comparison for EORTC QLQ-LC13 lung cancer symptoms domains

EORTC QLQ-LC13 symptoms domain	Baseline vs 8 weeks Difference	P value	95% CI	Baseline vs 6 months Difference	P value	95% CI	8 weeks vs 6 months Difference	P value	95% CI
Dyspnoea	-14.9	**	-16.1 - -13.2	-13.5	**	-16 - -12.8	1.4	0.6	-1.7 - 1
Coughing	-4	**	-5.9 - -1.9	-1.7	0.02	-4.6 - -0.3	2.3	0.2	-0.8 - 3.3
Haemoptysis	1.2	*	0.3 - 2	1.7	*	0.5 - 2.1	0.5	0.8	-0.4 - 0.5
Sore mouth	-3.6	**	-5.2 - -2.3	-3.7	**	-4.5 - -1.2	-0.1	0.2	-2.5 - 0.7
Dysphagia	-3.5	**	-4.7 - -2.4	-3.7	**	-4.7 - -2	-0.2	0.1	-2.2 - 0.3
Peripheral neuropathy	-0.9	0.1	-2.5 - 0.4	-6	**	-8.2 - -4.1	-5.1	**	-7.8 - -4
Alopecia	-1.1	0.03	-2.2 - -0.07	-6.4	**	-8.2 - -4.7	-5.3	**	-7.1 - -3.8
Pain in chest	-14.1	**	-15.8 - -12.3	-8.9	*	-11.9 - -8	5.2	**	3 - 6.9
Pain in arm or shoulder	-6.1	**	-8.4 - -4.2	-4.2	**	-7.8 - -3.2	1.9	0.1	-0.5 - 3.6
Pain in other parts	-2.4	0.04	-5 - -0.1	-2.4	*	-5.7 - -0.7	0	0.2	-3.9 - 1.1

Post-hoc pairwise comparison with Bonferroni correction. Statistical tests: paired t-test or Wilcoxon signed-rank test. *p<0.017; **p<0.001

The above result (Table 4.12) represents a post-hoc pairwise comparison within each EORTC QLQ-LC13 lung cancer-specific symptoms' domains. Dyspnoea has a significant statistical and clinical difference between the scores at baseline and those at eight weeks (14.9 points increase, $p = 0.00$). In comparison, the scores between eight weeks and six months reveal no statistical or clinical difference, indicating that dyspnoea has not recovered six months following the surgery. In most of the symptoms' domains, including coughing, haemoptysis, sore mouth, dysphagia, and pain in other parts, there is no clinically meaningful difference between all the time points, although some of these symptoms present statistically significant differences. This demonstrates that lung surgery has no or little effect on these symptoms.

Additionally, peripheral neuropathy and alopecia did not change statistically or clinically from baseline to eight weeks following surgery. Despite this, they have statistically increased from eight weeks to six months, but not to the minimum clinical difference (5 points change, $p = 0.00$). However, pain in the arm or shoulder has statistical but not minimal clinical increases eight weeks after lung surgery (6.1 points increase, $p = 0.00$), whereas no statistical or clinical recovery appears to be evident after six months. Figure 4.6 provides a representation of the trajectories of EORTC QLQ-LC13 symptoms scales.

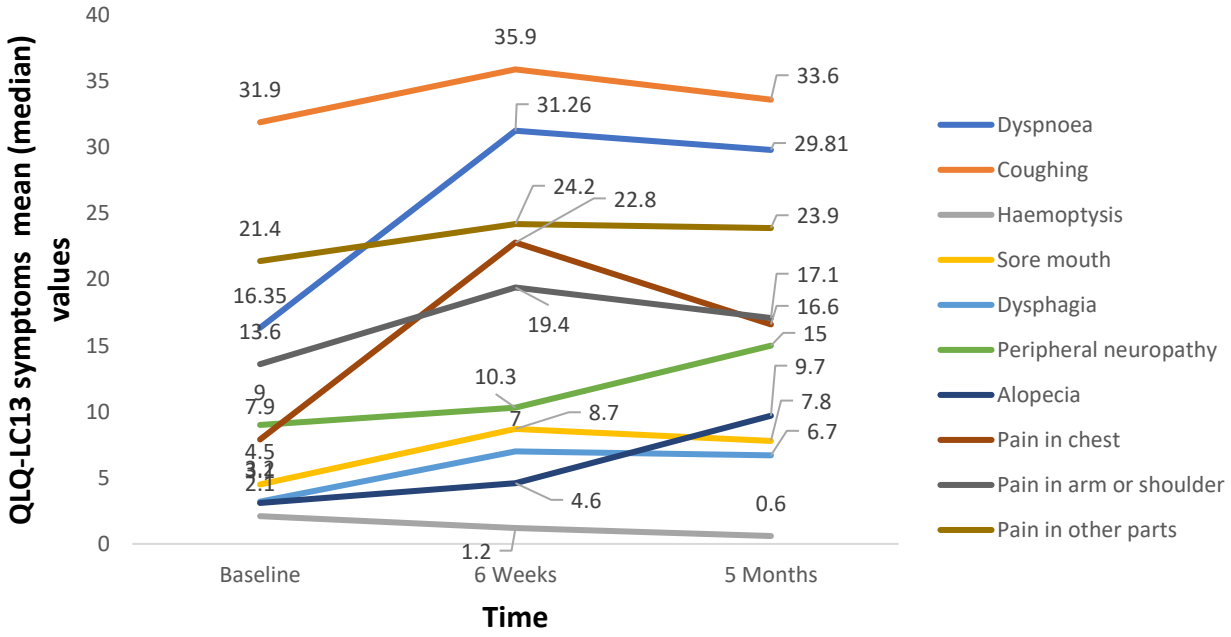

Figure 4.6 The trajectories of EORTC QLQ-LC13 symptoms domains at baseline, eight weeks, and six months after lung cancer surgery.

4.3.4 First five years vs last five years' difference

This section examines the differences in quality of life and surgery data over the first five and last five years. It is vital to confirm that there has been no difference in the entire cohort's surgical approach or quality of life over the past ten years. Incision, resection, lobe, and six months postoperative global health and dyspnoea were assessed (Table 4.13).

The results demonstrated no statistically significant difference in terms of resection type between the two groups, p = 0.2. Similarly, the two groups have no statistically significant difference in the resected lobe, p = 0.1. Only the surgical approach differs between the two groups (VATS versus Thoracotomy). In the earlier group, VATS accounts for 45%, whereas VATS accounts for 59% in the

latter group. Among the first group of patients, thoracotomy accounts for 54%, while in the second group, it accounts for 40%.

The outcome measures of dyspnoea and global health are similar among the two groups, with p = 0.1 and 0.052, respectively (Figure 4.7-4.8).

Table 4.13 Difference in baseline characteristics between patients recruited in first five years vs. last five years

Factor	Group 1 (n = 302)	Group 2 (n = 604)	P value
Incision			
Thoracotomy	163 (54.3)	244 (40.4)	***
VATS	137 (45.6)	360 (59.6)	
Resection			
Lobectomy	214 (71.5)	458 (75.8)	0.2
Segmentectomy	9 (3)	24 (3.9)	
Wedge	55 (18.3)	93 (15.4)	
Pneumonectomy	10 (3.3)	19 (3.1)	
Bilobectomy	11 (3.6)	10 (1.6)	
Lobe			
Upper	150 (52.8)	343 (57.1)	0.1
Lower	90 (31.6)	191 (31.8)	
Entire lung	10 (3.5)	19 (3.1)	
Upper bilobe	6 (2.1)	7 (1.1)	
Lower bilobe	6 (2.1)	4 (0.6)	
Middle	18 (6.3)	34 (5.6)	
6 months dyspnoea	33.3 ± 33.3	33.3 ± 33.3	0.1
6 months global health	64.3 ± 22.7	67.8 ± 21.8	0.052

Data are presented as numbers and percentages for categorical data. Group 1; 2010-2015, Group 2; 2016-2020, VATS; video-assisted thoracic surgery. *p<0.05; **p<0.01; ***p<0.001

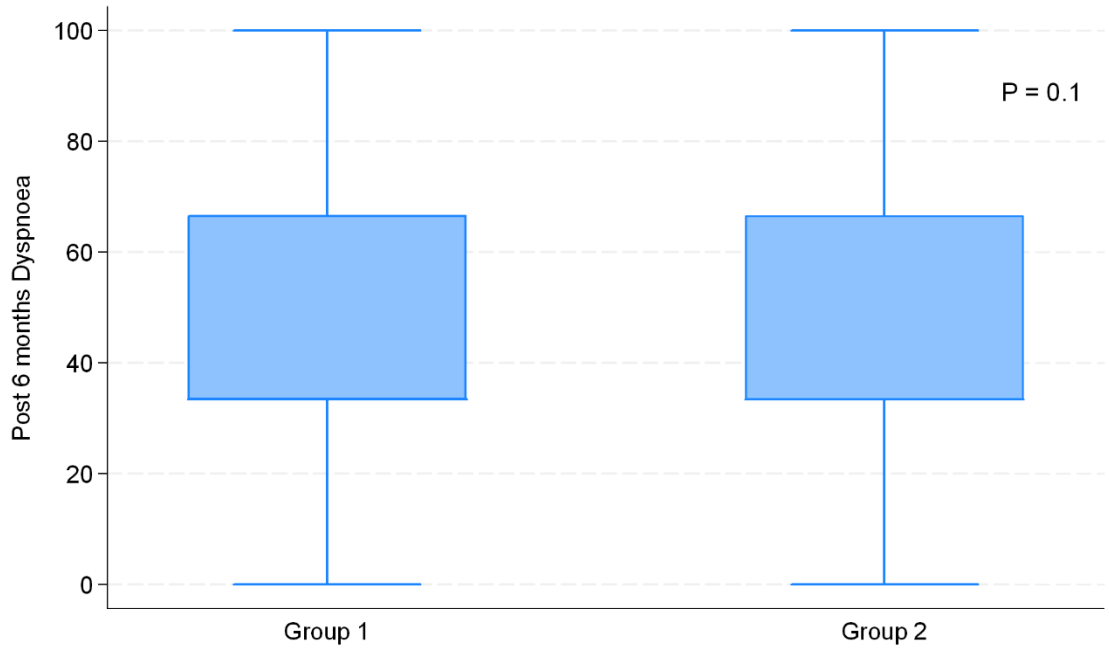

Figure 4.7 The difference in 6 months postoperative dyspnoea between two groups of first five years versus last five years, Group 1; 2010-2015, Group 2; 2016-2020

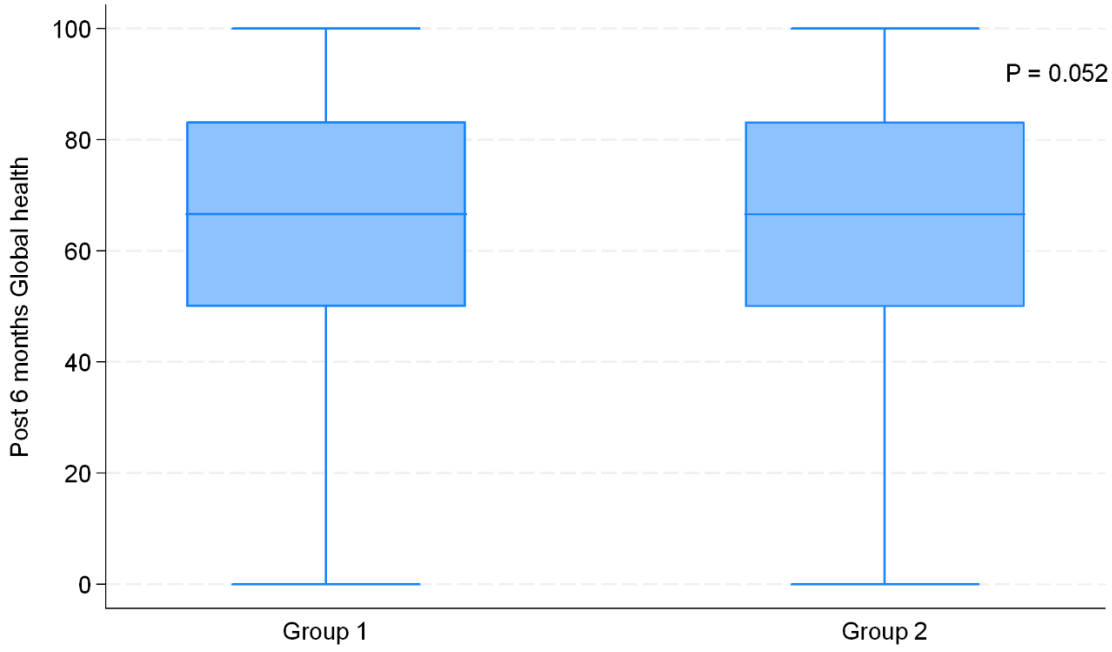

Figure 4.8 The difference in 6 months postoperative global health between two groups of first five years versus last five years, Group 1; 2010-2015, Group 2; 2016-2020

4.3.5 Prediction of dyspnoea following lung resection of cancer

In this section, we examined predictors of dyspnoea six months after surgery (the primary outcome). The median (IQR) time to completion of 6 months of PRO follow-up was 165 (± 21) days. Among the respondents, 343 (50.9%) reported increased dyspnoea six months after resection, while 44 (6.5%) reported decreased dyspnoea and 286 (42.4%) reported no change in dyspnoea. The completion rates for EORTC QLQ-C30 scores have been reported previously (Section 4.3.2).

4.3.5.1 Univariate analysis

Our initial goal is to examine the individual predictors of 6-month dyspnoea outcomes. Dyspnoea is an ordered categorial variable with four levels, where 0 represents the least affected category of dyspnoea, and 100 represents the most affected category of dyspnoea. Because of this order, ordinal logistic regression is the first analysis type employed to analyse relationships between each factor and six months dyspnoea. Consequently, those variables with a significance level of $p < 0.1$ were examined using multivariate ordinal or multinomial logistic regression analysis. Univariate ordinal regression analyses for six months dyspnoea are summarised in Tables 4.14 – 4.19.

Table 4.14 Univariate Ordinal Regression analysis evaluating the associations between demographic factors for six months dyspnoea

Parameter	OR	P value	95 % CI
Gender	0.8	0.3	0.6 - 1.1
Age	1.01	0.3	0.9 - 1.02
BMI	1.06	***	1.02 - 1.08

BMI; body mass index, OR; odd ratio, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

Table 4.14 illustrates univariate regression using demographic factors. There is no statistically significant association between age and gender and postoperative dyspnoea six months after surgery. Conversely, BMI has a statistically significant relationship with postoperative dyspnoea at six months (OR; 1.06, p = 0.00). Therefore, BMI will be assessed in multivariate regression analysis.

Table 4.15 Univariate Ordinal Regression analysis evaluating the associations between smoking factors and six months dyspnoea

Parameter	OR	P value	95 % CI
Smoking quit time			
Ref: Never			
Current	4.1	***	2.5 - 6.6
Ex-smoker <1 year	2.8	***	1.6 - 4.7
Ex-smoker >1 year	2.4	***	1.6 - 3.5
Pack years	1.01	***	1.01 - 1.02

Ref; reference level, OR; odd ratio, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

Table 4.15 represents univariate ordinal logistic regression analysis for six months dyspnoea examining the predictive value of smoking information. We can see that smoking quit time has a positive significant relationship with six months dyspnoea (current smoker; OR; 4.1, p =0.00). Also, we can note that the longer the quit time, the lower the odds of developing higher levels of dyspnoea at six months. We can observe that Ex-smokers <1 year vs Ex-smokers>1 year have OR; 2.8 vs 2.4, respectively. Pack years is also significantly associated with six months dyspnoea (OR; 1.01, p = 0.00).

Table 4.16 Univariate Ordinal Regression analysis evaluating the associations between lung function and six months dyspnoea

Parameter	OR	P value	95 % CI
FEV_1(L)	0.68	***	0.5 - 0.8
%FEV_1	0.98	***	0.97 - 0.98
FVC (L)	0.88	*	0.7 - 1.0
%FVC	0.99	*	0.98 - 0.99
%DLCO	0.97	***	0.96 - 0.98
%ppoFEV_1	0.98	***	0.97 - 0.99
%ppoDLCO	0.96	***	0.96 - 0.97

FEV_1; forced expiratory volume for 1 second, FVC; forced vital capacity, DLCO; diffusing capacity for carbon monoxide, ppoFEV_1 or ppoDLCO; predicted postoperative FEV_1 or DLCO, OR; odd ratio, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

Table 4.16 shows univariate regression analysis to investigate the association between lung function and postoperative dyspnoea at six months. We can see that all lung function measures, including FEV_1, FVC, DLCO, ppoFEV_1, and ppoDLCO are associated with six months dyspnoea. However, we can note that FVC(L) has a marginal association with six months dyspnoea (p = 0.08). Yet, the multivariate regression analysis will include all lung function factors for more evaluation.

Table 4.17 Univariate Ordinal Regression analysis evaluating the associations between lung surgery and six months dyspnoea

Parameter	OR	P value	95 % CI
Incision (Ref: VATS)	1.2	*	0.97 - 1.7
Side (Ref: Right)	1.02	0.8	0.7 - 1.3
Resection (Ref: bilobectomy)			
Lobectomy	0.5	0.16	0.19 - 1.3
Segmentectomy	0.6	0.5	0.2 - 2.2
Wedge	0.2	*	0.1 - 0.7
Pneumonectomy	1.2	0.7	0.3 - 4.0

Ref; reference, VATS; video-assisted thoracic surgery, OR; odd ratio, CI; confidence interval.

*p<0.1; **p<0.01; ***p<0.001

The above results (Table 4.17) represent the associations between lung surgery information and six months of postoperative dyspnoea. We can observe that baseline incision is only marginally significant with our outcome (p = 0.07). On the other hand, the side is not associated with dyspnoea at six months. Among types of surgery, we can note that only wedge resection is statistically significantly associated with six months dyspnoea (OR; 0.2, p = 0.01), yet other surgery types (lobectomy, segmentectomy, and pneumonectomy) are not significantly associated with our outcomes. Hence, the previous factors will be included in the multiple regression modelling, excluding the surgery side.

Table 4.18 Univariate Ordinal Regression analysis evaluating the associations between comorbidities and six months dyspnoea

Parameter	OR	P value	95 % CI
COPD	2.7	***	1.9 - 3.8
IHD	1.4	*0.09	0.9 - 2.3
Cardiac failure	1.01	0.9	0.4 - 2.2
Hypertension	1.07	0.6	0.8 - 1.4
Diabetes	1.1	*	1.1 - 4.5
Renal failure	9.9	0.11	0.6 - 149
Stroke	1.4	0.1	0.8 - 2.4
Thyroid disease	1.1	0.3	0.8 - 1.5
Anticoagulant use	1.03	0.5	0.9 - 1.1
ASA score	1.6	***	1.3 - 2.1

COPD; chronic obstructive pulmonary disease, IHD; ischemic heart disease, ASA; American Society of Anaesthesiologists score, OR; odd ratio, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

The above analysis (Table 4.18) investigates the association between baseline comorbidities and postoperative dyspnoea at six months. Clearly, there are positive associations between baseline COPD and postoperative dyspnoea (OR; 2.7, p = 0.00). Moreover, IHD has a positive association with the primary outcome, but the significance level is minor (OR; 1.4, p = 0.09). By contrast, cardiac failure, hypertension, renal failure, stroke, thyroid disease, and anticoagulant use have not exhibited significant associations with six months dyspnoea (p >0.1). We can note that diabetes is statistically significantly associated with postoperative dyspnoea in the univariate analysis (OR; 1.1, p = 0.02). Lastly, the ASA score significantly correlates with dyspnoea at six months (OR; 1.6, p =0.00). Therefore, we will involve COPD, IHD, diabetes and ASA score in the multivariate regression model.

Table 4.19 Univariate Ordinal Regression analysis evaluating the associations between baseline dyspnoea, and postoperative factors and six months dyspnoea

Parameter	OR	P value	95 % CI
Baseline dyspnoea	1.03	***	1.03 - 1.04
ECOG	2.3	***	1.7 - 2.9
Perioperative factors			
PPC	3.6	***	2.0 - 6.6
LOS	1.1	***	1.07 - 1.15
Hospital readmission	1.6	*	1.0 - 2.5
Chemotherapy	1.6	*	1.05 - 2.5

ECOG; The Eastern Cooperative Oncology Group performance status, PPC; postoperative pulmonary complications, LOS; length of hospital stay, OR; odd ratio, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

Univariate analysis (Table 4.19) evaluates the relationship between baseline performance, perioperative factors, and postoperative dyspnoea at six months. We can find that baseline dyspnoea from EORTC QLQ-C30 has a significant positive relationship with six months dyspnoea (OR; 1.03, p = 0.00). In addition, ECOG performance status is significantly associated with postoperative dyspnoea at six months (p = 0.00). Moreover, all perioperative factors, such as PPC, LOS, and hospital readmission, are positively associated with 6-month dyspnoea. Lastly, chemotherapy is positively associated with dyspnoea (OR = 1.6, p = 0.02). For this reason, all the above factors will be involved in the multivariate analyses and assessed for their predictive values.

4.3.5.2 Multivariate analysis

In the present thesis the regression models were carefully selected based on extensive literature review. Initially, I performed univariate regression analyses to recognise the factors that had p-value less than 0.1, which were selected for inclusion in the multivariate models. To enhance the reliability of the regression models, I evaluated multicollinearity among the factors included in the multiple regression models and separated highly correlated factors [297, 298]. This assessment was one of the key factors in the selection of models and determining which variables to include. Multicollinearity can lead to unreliable estimates [298, 299]. In addition, it is important to limit the number of factors in each model to avoid multicollinearity, which can result in model overfitting and affect the stability of the results [298, 300]. Each model involved a key predictor (i.e., baseline dyspnoea, or baseline global health) that was adjusted for other relevant factors, ensuring that its effects were accurately estimated while accounting for potential confounders.

The independent variables included in the first model following the univariate regression analyses were baseline dyspnoea adjusted for BMI, incision, resection, %ppoFEV_1, %ppoDLCO, and %FVC. There were 555 observations with all these variables that were included in the modelling process. The numeric variables (Baseline dyspnoea, BMI, % ppoFEV_1, %ppoDLCO, and %FVC) were tested for multicollinearity using variance inflation factors (VIF), and the largest VIF was found to be 2.358, which is not generally considered too large to include in the same model with other variables. Table 4.20 demonstrates the final model with three remaining variables.

Table 4.20 Multivariate Ordinal Regression analysis for six months dyspnoea (Model 1)

Parameter	OR	P value	95 % CI
Baseline dyspnoea	3.07	***	2.4 - 3.9
BMI	1.06	***	1.02 - 1.09
ppoDLCO	0.97	***	0.96 - 0.98
ppoFEV$_1$	0.99	0.1	0.97 - 1.0
%FVC	1.0	0.1	0.99 - 1.0
Incision: VATS	1.0	0.8	0.7 - 1.4
(Ref: Thoracotomy)			
Resection: Wedge	0.4	0.2	0.1 - 1.7
Segmentectomy	0.7	0.6	0.1 - 3.1
Pneumonectomy	0.5	0.4	0.1 - 2.4
Lobectomy	0.5	0.2	0.1 - 1.7
(Ref: Bilobectomy)			

Ref; reference, BMI; body mass index, ppoFEV$_1$ or ppoDLCO; predicted postoperative forced expiratory volume for 1 second or diffusing capacity for carbon monoxide, FVC; forced vital capacity, VATS; video-assisted thoracic surgery, OR; odd ratio, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The proportional odds assumption was tested, and the result was $\chi^2(18) = 2.6$, $p = 0.300$; there was no evidence that the proportional odds assumption was unmet. Considering Table 4.20, it can be seen that baseline dyspnoea and BMI both have positive associations with 6-month dyspnoea ($p < 0.001$ for both), and thus, those with higher baseline dyspnoea and higher BMIs will be at greater risk for more severe dyspnoea. As can be seen, ppoDLCO has a negative association with 6-month dyspnoea ($p < 0.001$), and patients with higher ppoDLCO are less likely to experience higher levels of dyspnoea, Wald $\chi^2(11) = 157$, $p < 0.001$. It can be noted that incision, resection, %ppoFEV$_1$, and %FVC are not

statistically significantly associated with postoperative dyspnoea at six months ($p = 0.6$, $p = 0.4$, and $p = 0.2$, respectively).

We intended to use ordinal logistic regression analysis to produce this model; however, the model did not pass the test of the proportional odds assumption ($\chi^2(4) = 11.293$, $p = 0.023$). Therefore, the second model employed multinomial logistic regression to assess the predictive role of baseline dyspnoea, preoperative FEV_1, preoperative % FEV_1, preoperative FVC, %DLCO, smoking quit time, and pack years. It is worth mentioning that due to the high correlation between the factors in the previous model and these factors, we tend to separate them into two different models. There were 528 observations with all of these variables that were included in the modelling process. The numeric variables (Baseline dyspnoea, Preoperative FEV_1, Preoperative %FEV_1, Preoperative forced vital capacity (FVC), DLCO%, and pack-years) were tested for multicollinearity using variance inflation factors (VIF). The largest VIF was 3.886, which is not generally considered too large to include in the same model with other variables. Using the significance level ($p<0.05$), the variables removed accordingly are preoperative FEV_1, % FEV_1, and FVC. Table 4.21 shows multivariate regression analysis for the second model.

Table 4.21 Multivariate multinomial Regression analysis for six months dyspnoea (Model 2)

Parameter	OR	P value	95 % CI
Baseline dyspnoea	3.23	***	2.5 - 4.1
Current smoking	2.53	**	1.33 - 4.82
(Ref: never)			
%DLCO	0.98	**	0.97 - 0.99
Pack years	1.009	**	1.002 - 1.01
FEV_1 (L)	0.9	0.5	0.9 - 1.0
$\%FEV_1$	1.0	0.6	0.9 - 1.0
FVC (L)	1.0	0.3	0.9 - 1.0

Ref; reference, FEV_1; forced expiratory volume for 1 second, FVC; forced vital capacity, DLCO; diffusing capacity for carbon monoxide, OR; odd ratio, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The proportional odds assumption was tested, and the result was $\chi^2(14) = 18.304$, $p = 0.193$; there was no evidence that the assumption was unmet. Table 4.21 shows that current smoking is the only smoking quit time that is statistically significantly different from never smoking (OR; 2.53, $p = 0.005$). Current smoking has an odds ratio greater than one, meaning there is a greater probability that one will experience dyspnoea than someone who has never smoked. Moreover, we can see that baseline dyspnoea and pack years have significant positive associations with six-month dyspnoea ($p = 0.002$ for baseline dyspnoea and $p = 0.009$ for pack years), which means that individuals with higher baseline dyspnoea and higher pack years will be at a greater risk for suffering from severe dyspnoea. Based on our analysis, it can be seen that %DLCO is negatively associated with dyspnoea at six months ($p = 0.01$), indicating that those with higher %DLCO are at lower risk of experiencing dyspnoea, overall model fitness; Wald χ^2 (7) = 155.8, $p < 0.001$. However, the rest of lung function

parameters (Preoperative FEV_1, Preoperative $\%FEV_1$, and Preoperative FVC) are not significantly associated with postoperative dyspnoea at six months ($p = 0.5$, $p = 0.6$, and $p = 0.3$, respectively).

Using multinomial logistic regression analysis, the third model assessed the predictive value of baseline dyspnoea, COPD, IHD, ASA score, and ECOG performance. There were 587 observations with all of these variables that were included in the modelling process. All six variables are numeric or indicator variables and were tested for multicollinearity using variance inflation factors (VIF). The largest VIF was 1.323, which is not generally considered too large to include in the same model with other variables. The variables removed from the model according to the significance level ($p < 0.05$) were COPD, ASA score, and IHD. Table 4.22 provides the final model with three completely separate equations, one comparing the probability of the higher level of six-month dyspnoea (100) to the probability of no dyspnoea.

Table 4.22 Multivariate multinomial Regression analysis for 6 months dyspnoea (Model 3)

Parameter	OR	P value	95 % CI
Baseline dyspnoea	11.5	***	6.4 - 20.5
ECOG	2.6	***	1.4 - 4.6
COPD	1.2	0.5	0.6 - 2.3
IHD	0.5	0.2	0.2 - 1.5
ASA Score	1.4	0.2	0.8 - 2.4

ECOG; The Eastern Cooperative Oncology Group performance status, COPD; chronic obstructive pulmonary disease, IHD; ischemic heart disease, ASA; American Society of Anaesthesiologists score, OR; odd ratio, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

According to the analysis, baseline dyspnoea significantly increases the relative probability (relative to no dyspnoea) of dyspnoea level (100) (odds ratio 11.535). The effect of ECOG is to significantly increase the relative probability of experiencing the highest level of dyspnoea (odds ratio 2.6, p = 0.0001). Overall model fitness; Wald χ^2 (15) = 171.1, p <0.001. On the other hand, COPD, IHD and ASA score are not significantly associated with postoperative dyspnoea (p = 0.5, p = 0.2, and p = 0.2, respectively).

In the last model below (Table 4.23), we primarily intended to use ordinal logistic regression modelling; however, this model failed to pass the proportional odds assumptions (χ^2(6) = 20.420, p = 0.002). Therefore, the multinomial logistic regression analysis is applied to this model.

The independent variables involved in this model were baseline dyspnoea, PPC, LOS, hospital readmission, and chemotherapy. There were 671 observations with all of these variables that were included in the modelling process. All the variables were tested for multicollinearity using VIF, and the largest VIF was found to be 1.173, which is not generally considered too large to include in the same model with other variables. Backward selection removed hospital readmission only.

Table 4.23 Multivariate multinomial Regression analysis for 6 months dyspnoea (Model 4)

Parameter	OR	P value	95 % CI
Baseline dyspnoea	12.3	***	7.1 - 21.5
LOS	1.15	**	1.0 - 1.2
PPC	3.1	*	1.0 - 9.4
Readmission	2.2	0.1	0.8 - 6.1
Chemotherapy	1.5	0.3	0.6 - 3.6

LOS; length of hospital stay, PPC; postoperative pulmonary complications, OR; odd ratio, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The relationship between baseline dyspnoea and postoperative dyspnoea remains significant even after adjustment for LOS, PPC, hospital readmission, and chemotherapy. Clearly, baseline dyspnoea has a positive association with the postoperative dyspnoea at six months ($p<0.001$). Moreover, the effects of LOS are significant in that they increase the relative probability (relative to no dyspnoea) of the highest level of dyspnoea (100) (OR 1.15, p value $p = 0.004$). Lastly, it is evident from the results that PPC has a significant effect on increasing the relative probability (relative to no dyspnoea) of the highest level of dyspnoea (100) (OR = 3.1), $p <0.001$. However, Hospital readmission and chemotherapy are not significantly associated with postoperative dyspnoea ($p = 0.1$, and $p = 0.3$, respectively).

4.3.6 Prediction of global health following lung resection of cancer

In this section, we assessed predictors of postoperative six months global health after lung cancer surgery (secondary outcome) using baseline demographic, clinical and perioperative data along with baseline global health measured from EORTC QLQ-C30. Approximately 234 (53.3%) respondents reported a decline in their global health six months after surgery. On the other hand, respondents who experienced an improvement or no change in their global health six months following surgery were 113 (25.7%) and 92 (20.9%), respectively. The completion rates for EORTC QLQ-C30 scores have been stated earlier (Section 4.3.2).

4.3.6.1 Univariate analysis

Our objective is to explore the individual predictors of 6-month global health. Global health is a continuous variable where the lowest score represents the lowest global health (worst overall quality of life), and the highest score represents the best overall quality of life. Because of this, we used linear regression analysis. Accordingly, multivariate linear regression analysis assessed any variables with a significance level of $p < 0.1$. Table 4.24 – 4.26 demonstrates univariate regression analysis for six-month global health.

Table 4.24 Univariate linear Regression analysis for six months global health

Parameter	Coefficient	P value	95 % CI
Gender (Ref: male)	-0.47	0.7	-3.83 - 2.89
Age	0.03	0.7	-0.14 - 0.21
BMI	-0.37	*	-0.7 - -0.04
Smoking quit time Ref: Never			
Current	-14.3	***	-19.7 - -8.9
Ex-smoker <1 year	-11.6	***	-17.6 - -5.6
Ex-smoker >1 year	-6.3	**	-10.7 - -1.8
Pack years	-0.12	***	-0.17 - -0.06
FEV_1(L)	4.21	**	1.9 - 6.5
%FEV_1	0.14	***	0.06 - 0.2
FVC (L)	1.7	*	0.11 - 3.4
%FVC	0.08	*	-0.001 - 0.16
%DLCO	0.27	***	0.17 - 0.37
%ppoFEV_1	0.14	**	0.05 - 0.22
%ppoDLCO	0.29	***	0.18 - 0.39
Incision (Ref: VATS)	-1.3	0.4	-4.7 - 2.0
Side (Ref: Right)	2.36	0.17	-1.04 - 5.7

Ref; reference, BMI; body mass index, FEV_1; Forced expiratory volume in 1 second, FVC; forced vital capacity, DLCO; diffusing capacity for carbon monoxide, ppo; predicted postoperative, VATS; video-assisted thoracic surgery, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

Table 4.25 Univariate linear Regression analysis for six months global health (continue)

Parameter	Coefficient	P value	95 % CI
Resection			
(Ref: bilobectomy)			
Lobectomy	13.6	*	1.3 - 25.8
Segmentectomy	10.04	0.18	-4.9 - 25.0
Wedge	12.04	0.6	-0.6 - 24.8
Pneumonectomy	9.7	0.2	-5.4 - 25.0
COPD	-8.3	***	-12.4 - -4.2
IHD	-1.8	0.5	-7.6 - 3.9
Cardiac failure	-3.0	0.5	-12.5 - 6.9
Hypertension	0.4	0.8	-3.0 - 3.9
Diabetes	-1.1	0.3	-3.7 - 1.4
Renal failure	-16.7	0.19	-41.9 - 8.5
Stroke	-3.7	0.2	-9.8 - 2.4
Thyroid disease	-2.7	0.11	-6.1 - 0.6
Anticoagulant use	-0.5	0.3	-1.8 - 0.6
ASA score	-5.9	***	-8.7 - -3.11

Ref; reference, COPD; chronic obstructive pulmonary disease, IHD; ischemic heart disease, ASA; American Society of Anaesthesiologists score, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

Table 4.26 Univariate linear Regression analysis for six months global health (continue)

Parameter	coefficient	P value	95 % CI
Baseline global health	0.49	***	0.4 - 0.5
ECOG	-8.6	***	-11.5 - -5.7
PPC	-13.5	***	-20.0 - -7.0
LOS	-0.99	***	-1.4 - -0.5
Hospital readmission	-5.7	*	-11.1 - -0.2
Chemotherapy	-8.08	**	-13.2 - -2.9

ECOG; The Eastern Cooperative Oncology Group performance status, PPC; postoperative pulmonary complications, LOS; length of hospital stay, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

We examined 31 baseline demographic, clinical data, and perioperative factors in the univariate linear regression analysis. Table 4.24 shows that BMI, smoking quit time, pack years, FEV_1, FVC, DLCO, $ppoFEV_1$, and ppoDLCO are significantly associated with postoperative global health at six months using the significance level 0.1. Therefore, these factors will be included in the multiple linear regression analyses. On the contrary, gender, age, incision, and surgery side are not significantly associated with six months global health. Hence, these factors will not be assessed in our multivariate regression.

In Table 4.25-4.26, lobectomy, COPD, ASA score, baseline global health, ECOG, PPC, LOS, hospital readmission and chemotherapy are statistically significantly associated with six months global health ($P<0.1$). In contrast, other types of resection and other comorbidities have no statistically significant association with six-month global health.

4.3.6.2 Multivariate analyses

To assess the role of baseline global health in predicting postoperative global health at six months, we performed multivariate linear regression analysis adjusting baseline global health for different factors in each model.

The independent factors included in the first model following the univariate regression analyses for predicting six months global health were baseline global health adjusted for BMI, preoperative smoking quit time, pack years, resection, %ppoFEV$_1$, %ppoDLCO. There were 557 observations with all these variables that were included in the modelling process. The numeric variables (Baseline global health, BMI, % ppoFEV$_1$, %ppoDLCO, and pack-years) were tested for multicollinearity using variance inflation factors (VIF), and the largest VIF was found to be 1.43, which is not generally considered too large to include in the same model with other variables. In addition, the researcher assessed the linearity between each continuous variable, and the outcome evaluated the residual errors for each regression model and found that the residual errors of the regression line are approximately normally distributed. Lastly, almost all our data is homoscedastic; if otherwise noted, the author followed a method for reducing the effect of heteroskedasticity by utilising a heteroskedasticity-consistent standard error (HCSE) estimator of OLS parameter estimates [301]. Table 4.27 represents the first multivariate regression analysis for six months global health.

Table 4.27 Multivariate linear Regression analysis for 6 months global health (Model 1)

Parameter	coefficient	P value	95 % CI
Baseline global health	0.45	***	0.35 - 0.55
BMI	-0.44	**	-0.75 -0.14
Current smoking	-9.1	**	-14.8 - -3.4
(Ref: Never)			
ppoDLCO	0.17	**	0.06 - 0.27
$ppoFEV_1$	0.01	0.7	-0.7 - 0.1
pack-years	-0.02	0.4	-0.8 - 0.3
Resection: Wedge	-31.3	0.1	-69.2 - 6.4
Segmentectomy	-30.4	0.1	-68.9 - 8.0
Pneumonectomy	-24.0	0.2	-62.6 - 14.6
Lobectomy	-25.8	0.1	-63.4 - 11.7
(Ref: Bilobectomy)			

Ref; reference, BMI; body mass index, $ppoFEV_1$ or ppoDLCO; predicted postoperative forced expiratory volume for 1 second or diffusing capacity for carbon monoxide, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

As shown in Model 1, the variables statistically significantly predicted six months global health F (4, 534) = 44.9, p = 0.00, and $R^2 = 0.25$. Baseline global health is still statistically significant even after adjusting for several factors (coefficient; 0.45, p <0.00). BMI shows a negative association with global health six months following lung surgery, meaning that a 1 unit increase in BMI can lead to a 0.44 decrease in postoperative global health. In addition, current smoking has a negative significant association with six months global health, meaning the patients who are current smokers at the time of surgery would exhibit 9.1 scores lower in global health compared to those who had never smoked. Lastly, ten units increase in ppoDLCO can lead to a nearly two points increase in postoperative global

health (p=0.001). We can also conclude that ppoFEV_1, pack years, and resection type are not significantly associated with postoperative global health at six months (p>0.05).

The second model incorporated baseline global health adjusted for lung function, including preoperative FEV_1, preoperative %FEV_1, %DLCO, and preoperative FVC. Note that VIF is 2.1, which is not considered too large to include these factors in the model. Table 4.28 illustrates the final model for this analysis.

Table 4.28 Multivariate linear Regression analysis for six months global health (Model 2)

Parameter	coefficient	P value	95 % CI
Baseline global health	0.49	***	0.39 - 0.58
%DLCO	0.16	***	0.07 - 0.25
FEV_1 (L)	-0.01	0.5	-0.07 - 0.04
%FEV_1	0.06	0.1	-0.3 - 0.1
FVC (L)	0.01	0.3	-0.02 - 0.05

DLCO; diffusing capacity for carbon monoxide, FEV_1; Forced expiratory volume in 1 second, FVC; forced vital capacity, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The factors in Model 2 predicted the postoperative global health at six months; F (2, 535) = 75.07, p = 0.00 and R^2= 0.19. Even after adjusting for lung function, baseline global health remains an important predictor of postoperative global health. Those with a high level of baseline global health have a relatively higher level of postoperative global health. A patient with a baseline global health score of 10 units greater can be predicted to have at least five scores higher in the six-month global health score when compared to a patient with a baseline health score of 10 units lower. The %DLCO has also been found to be positively related to postoperative global health after six months.

Accordingly, those with DLCOs that are ten units higher will have nearly two points higher in their global health scores six months after surgery. Neither preoperative FEV_1, nor preoperative FVC are significantly associated with postoperative global health (P >0.05).

The third model below involved baseline global health, COPD, ASA score, and ECOG performance status. It should be noted that VIF is 1.1, which is not deemed too large to include these factors in the model. The remaining factors in the model statistically significantly predicted postoperative global health: F (2, 559) = 47.08, p = 0.00 and R^2 = 0.19 (Table 4.29). Baseline global health is still statistically significantly predicting postoperative global health (p = 0.00). COPD and ASA score are not significantly associated with six-months global health. In contrast, ECOG performance score of 1 compared to a better ECOG score of 0 has a significant relationship with six months global health. Consequently, patients with an ECOG score of 1 would experience a nearly 5-point reduction in global health at six months compared to those with a score of 0 (p = 0.01).

Table 4.29 Multivariate linear Regression analysis for six months global health (Model 3)

Parameter	coefficient	P value	95 % CI
Baseline global health	0.44	***	0.33 - 0.55
ECOG (1)	-4.6	*	-8.2 - -1.0
Ref: 0			
COPD	-2.4	0.2	-6.2 - 1.4
ASA score	-2.1	0.1	-6.0 - -0.3

ECOG; The Eastern Cooperative Oncology Group performance status, Ref: reference, COPD; chronic obstructive pulmonary disease, IHD; ischemic heart disease, ASA; American Society of Anaesthesiologists score, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The fourth model (Table 4.30) evaluated the association between baseline global health, perioperative factors involving LOS, PPC and hospital readmission, as well as chemotherapy with postoperative global health at six months. We have investigated multicollinearity and found that VIF = 1.01, which is considered not too large to include these factors in the model.

Table 4.30 Multivariate linear Regression analysis for 6 months global health (Model 4)

Parameter	coefficient	P value	95 % CI
Baseline global health	0.5	***	0.41 - 0.59
Chemotherapy	-7.4	**	-11.9 - -3.02
LOS	-0.6	**	-1.1 - -0.19
PPC	-0.6	0.8	-9.4 - 8.2
Readmission	-1.9	0.5	-7.8 - 3.8

LOS; length of hospital stay, PPC; postoperative pulmonary complications, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

From the above model, we can clearly see that the factors statistically significantly predicted the six months global health; F (6,411) = 26.64, p = 0.00 and R^2 =0.26. We can note that baseline global health has a positive significant relationship with postoperative six-months global health. In contrast, LOS and chemotherapy have a negative association with six months global health; as patients have ten days longer hospital stay, the six-months global health would reduce by almost six scores (p = 0.01). Similarly, a 1 unit increase in chemotherapy would reduce the postoperative global health by 7.5 scores (p = 0.001). On the other hand, PPC and hospital readmission show no association with postoperative global health at six months (p = 0.8, and p = 0.5, respectively).

4.4 Discussion

As demonstrated in this study, collecting PRO from cancer patients who underwent lung resection is feasible. Additionally, we found that the main characteristics of the respondent and non-respondent patients that may impact PRO completion were parallel. The reduction in baseline completion rate is small and could be due to the short time between receiving the questionnaire and the operation date. This data showed that 75% of the patients completed the questionnaire at six months. According to the present results, we achieved a reasonable response rate for a large cohort compared with other studies with smaller sample sizes, as our longitudinal study involved 906 cancer patients. Our study also included older cancer patients undergoing lung resection therapy and other coexisting comorbidities. A similar study involved 95 lung cancer patients with VATS had 72% completion rate at six months [106]. This study has a higher response rate even though nearly half of the patients had a thoracotomy approach and a larger sample size.

This study indicates that cancer patients with lung resection have suffered from deterioration in global health and most functioning domains, including physical, role and social functioning. In addition, the patients have not experienced any recovery in their global health or physical functioning even after six months of intervention, while the rest of the functioning domains have recovered at that time. Previous studies have confirmed that global health and physical functioning have declined immediately after lung surgery and have not been restored to baseline levels six months after surgery [126]. In contrast, other studies noted that both physical domain and global health declined shortly following the lung surgery but returned to the preoperative levels. Yet, these studies explored patients with minimally invasive surgeries and smaller sample sizes [11, 106, 107].

Regarding symptom change, our study demonstrated that dyspnoea increased significantly in scores after surgery without recovery at six months and was the symptom with the greatest increase in score among the other symptoms. Our results align with previous findings that noticed that following lung

surgery, patients continued to experience increased dyspnoea [104]. Our results revealed that fatigue, pain, appetite loss, and constipation worsened eight weeks after the procedure. Still, these symptoms have improved six months later but have not returned to preoperative levels. These findings mirror those of the prior studies that highlighted the improvement of these symptoms but did not return to baseline scores six months after intervention [106].

EORTC QLQ-LC13 trajectories confirmed our QLQ-C30 findings and showed a long-term detrimental effect of surgery on dyspnoea, with no recovery found in this symptom at six months. Moreover, chest pain was impacted shortly by the lung surgery; however, it showed steady improvement but hasn't returned to baseline levels in six months after treatment. This result is in accordance with previous results that acknowledged that pain in the chest had improved but not reached the baseline levels [106, 126].

In this study, we found that there have been no differences between the patients recruited in the first five years and last five years in terms of surgical resection and resected lobe; the only difference found was in the surgical incision, as the tendency of using a minimal invasive approach (VATS) has increased in the last five years. Yet the patients' outcome measures of dyspnoea and global health were not significantly different between the two groups.

The patient-reported outcome (PRO) for patients undergoing various treatment types has attracted increasing interest in recent years. Despite the fact that some studies have shown that many patients undergoing lung cancer surgery suffer from a continuous increase in dyspnoea for a long time [104], few studies have treated patients and reported dyspnoea in detail.

This prospective longitudinal study aimed to examine baseline and perioperative predictors of postoperative quality of life six months after surgery, focusing on global health and dyspnoea. The present study investigated risk factors for dyspnoea deterioration six months following lung surgery

in 673 patients, assessing several baseline demographics, clinical, QoL and perioperative factors. Nearly half of the respondents in our study suffered from dyspnoea increase compared to their baseline scores, surpassing the MCID threshold.

Our study revealed that baseline dyspnoea is significantly associated with postoperative dyspnoea even after adjusting for these factors. Similarly, previous studies that evaluated baseline dyspnoea and its correlation with long-term dyspnoea after lung cancer surgery found that it was associated with long-term dyspnoea after lung cancer surgery (OR = 5.31) [169]. In our results, surgical approach was not significantly associated with postoperative HRQOL at six months. Although studies reported that VATS was superior to open surgery in terms of postoperative outcomes, including HRQOL [153, 302], other studies revealed a significant decline in short-term HRQOL within one to three months in patients with thoracotomy, but returned to preoperative levels by six to nine months [98, 296]. This indicates that thoracotomy has a noticeable effect on patients' HRQOL in the short-term following lung resection, while the long-term impact on HRQOL may be comparable to the other approach. Additionally, our study found that increased BMI is associated with worse postoperative dyspnoea. In other studies, BMI was associated with breathlessness in different cohorts [303, 304]. One reason why only a higher BMI was associated with dyspnoea is that our cohort has a mean BMI of 27.2, which is considered overweight, whereas only 22 participants (2.4%) are deemed underweight (BMI <18.5). As expected, our analysis indicates that ppoDLCO and preoperative DLCO have a negative relationship with dyspnoea. This means that increased baseline DLCO or ppoDLCO would increase the odds of having lower levels of dyspnoea.

Moreover, our results confirmed the positive association between smoking and postoperative dyspnoea. It was not surprising that patients who did not quit smoking before surgery had a significantly higher risk of experiencing dyspnoea compared to those who had never smoked. Additionally, we noted a positive association between increased pack years and an increase in

dyspnoea 6 months after surgery. Our results revealed that patients with high baseline ECOG level (poorer performance) are expected to higher chances for experiencing higher levels of dyspnoea compared to those with low ECOG. A careful evaluation of baseline ECOG performance is essential.

The results of this study are consistent with those reported in previous literature. According to a large study that examined the associated factors of dyspnoea in 923 patients with different types of cancer, smoking history represents a significant risk factor [94]. Other studies have confirmed that people with a smoking history of more than 20 pack-years' experience more frequent breathlessness [303]. Similarly, another study evaluated correlations with dyspnoea after lung resection in a period of one to six years, finding that an increase in DLCO was negatively associated with long-term dyspnoea with an odd ratio of 0.98, which is equal to the odd ratio in our analysis [169]. Furthermore, it has been demonstrated that low performance at baseline is one of the major risk factors for many cancer patients [161, 173, 305].

In addition, our analyses found that perioperative events impact postoperative dyspnoea; both PPC and LOS have been positively associated with the highest levels of dyspnoea. Our finding is in line with previous research that examined HRQOL for cancer survivors over 5 and 10 years; dyspnoea statistically significantly deteriorated in patients who had postoperative complications versus those who did not experience any complications during the follow-up period [306, 307]. Lastly, our results show that dyspnoea is not significantly associated with adjuvant chemotherapy. These findings are consistent with those of previous studies. Park et al. evaluated the change of HRQOL using EORTC QLQ-C30 and LC13 in 139 patients with resected lung cancer and received adjuvant chemotherapy treatment [308]. They noted no significant change in dyspnoea score after four chemotherapy cycles and stated that chemotherapy has no major impact on dyspnoea. These findings were highlighted in previous research [94]. Although it is widely acknowledged that chemotherapy could induce pulmonary pneumonitis or other chronic pulmonary injury [309], the results demonstrate that

chemotherapy did not affect patients' dyspnoea. Possibly, this result can be explained by the fact that this study did not include information regarding the difference in chemotherapy doses and the number of cycles received by the patients. Yamada et al. concluded that pulmonary injury in patients receiving chemotherapy depends on the dose and the volume of received chemotherapy [309]

For cancer patients undergoing lung resection, we demonstrated that subjective viewpoints of baseline global health scores are significantly associated with postoperative global health scores. The findings of our study suggest that preoperative QoL measures should be considered alongside other preoperative factors when assessing cancer patients prior to lung resection. To our knowledge, most studies focused on determining predictors of HRQOL in cancer patients after lung surgery come from smaller samples or concentrate on different outcomes. We noticed that more than half of the patients suffered from lower global health six months following lung surgery, implying a worse overall quality of life. This research indicates that patients with higher baseline global health scores can end up with higher postoperative global health scores. The results of our study are supported by the results of a study conducted by Marzorati et al., which examined one-year quality of life trends among lung cancer patients following lobectomy using the EORTC QLQ-C30, indicated that patients with higher global health scores in the first month following their treatment had better scores after a year and even experienced a better recovery [128]. Based on our regression model, we have found a negative relationship between baseline BMI and global health. The global health of patients with higher BMI is more likely to worsen six months after lung surgery. The findings were noted in the dyspnoea outcome section, as well as a possible explanation was provided. This finding is in agreement with those reported in Gil and colleagues' prospective study of 157 cancer patients using the SF-36 and FACT-G questionnaires to assess HRQOL and BMI. A majority of the subjects in their cohort were obese or overweight, and they reported that higher BMI was negatively correlated with HRQOL when analysed using both univariate and multivariate regression methods. This study's results indicate that

BMI is a significant factor in determining HRQOL in cancer patients [310]. A recent research by Montagnese and colleagues included breast cancer survivors and found that those who lost weight had an improved global health status [311].

Evidence shows that continuing to smoke after lung cancer surgery is associated with a poor quality of life following surgery [180, 312]. Following the recommendations of the European Society of Thoracic Surgeons (EST) and the Enhanced Recovery After Surgery Society (ERAS), smokers should quit for at least four weeks before surgery [313]. Similarly, our findings demonstrate that patients who haven't quit smoking would experience a negative impact on their global health and overall QoL afterwards. Additionally, patients with a lower baseline ppoDLCO were found to have a greater risk of global health decline. In previous studies, similar results have been observed [11, 168].

In line with our findings that DLCO is positively associated with postoperative global health, Pompili et al. noted that patients with poor global health had relatively lower DLCO ($p = 0.02$) [150]. Our analyses also showed that patients with higher ECOG performance status, implying lower performance at baseline, significantly decreased global health six months after surgery. For example, patients with an ECOG performance of 1 are likely to have a nearly 5 scores decline in postoperative global health compared to those with an ECOG performance of 0. A similar finding was reported by other studies, which found a relationship between ECOG performance and QoL, including global health and overall QoL [314-316]. As for perioperative factors, our study indicates that patients who have a longer hospital stay are likely to have the worst quality of life at 6 months due to profound health consequences [317]. This result is consistent with the findings of other studies that found a significant correlation between LOS and quality of life [8, 317]. This finding differs from that of Stricker et al., who found that HRQOL was comparable between patients with short and long LOS (i.e., longer than seven days) a year following intensive care unit (ICU) admission [318]. Their study,

however, has limitations due to its small sample size (75 patients per group) and low response rate (65%). In our study, 906 patients were examined, with a response rate of around 75%. Lastly, adjuvant chemotherapy is associated with reduced postoperative global health. This is in line with previous literature that demonstrated the effect of chemotherapy on postoperative QoL in resected lung cancer patients [183]. However, their study suffered from the small sample size. In addition, they utilised the FACT-G and L instruments, which are less sensitive than the EORTC-QLQ C30 [142].

4.5 Limitation and Future Work

One limitation of this study is that the response rate to PRO from the total cohort of participants had declined to 75% at six months following lung cancer surgery. Nevertheless, there is a significant strength of this study, which is the fact that it represents one of the largest studies available on HRQOL and dyspnoea for cancer patients who have undergone lung surgery, as it examines these factors in a great deal of clinical detail. Also, the size and robust nature of this study make it a valuable contribution to the field. Another limitation is that the investigation has not collected the possible reasons for the baseline dropdown, eight weeks and six months PRO. Yet, this study demonstrated no difference between those who completed the questionnaire and those who haven't completed the questionnaire in a wide range of factors.

Some patients received adjuvant chemotherapy in addition to surgery, which would also negatively impact their QoL, and the dose and number of cycles were not collected and included in the analyses; however, we investigated the impact of chemotherapy on patients' QoL. Lastly, our study involved low incidence of postoperative pulmonary complications, relatively short hospital length of stay and low hospital readmission rates. It would be desirable to perform a predictive analysis for these outcomes. This study identified the critical factors associated with postoperative dyspnoea and global health in lung cancer surgery patients in six months. In addition, extended research is needed to

determine the factors contributing to the reduction in patient compliance concerning completing longitudinal PROs. In conclusion, baseline PRO, including dyspnoea and global health, is significantly associated with postoperative HRQOL and assessment of PRO in parallel with clinical factors is vital. Using data from both the early and late years of recruitment, we concluded that there is no significant difference in the baseline surgical data or the QoL outcomes between these two groups of patients.

Chapter 5. Quantitative Computed Tomography of Emphysema in Predicting Postoperative Quality of Life

5.1 Introduction

5.1.1 CT-based prediction of postoperative quality of life

Increasing evidence suggests that chronic obstructive pulmonary disease (COPD) may impact lung cancer [319]. COPD itself does not affect long-term survival in lung cancer patients undergoing surgical treatment. However, patients with COPD are at higher risk of developing postoperative complications than those with normal pulmonary function [320]. In addition, COPD was found to be associated with dyspnoea and, subsequently, poor HRQOL in a large study involving 923 cancer patients [94].

CT densitometry is a highly accurate approach for quantifying emphysema. Clinical studies have shown a significant correlation between CT densitometry measurements in HU and microscopic and macroscopic measurements of pulmonary emphysema [193, 194].

Dyspnoea is a common symptom of lung cancer that can negatively affect the physical, social, and psychological well-being of lung cancer patients [91]. There is a lack of information regarding the relationship between CT emphysema and patients' reported outcomes using EORTC QLQ-C30.

Contrast administration on CT scans has been reported to influence density measurements of emphysema [321]. Previous reports showed that contrast application may increase the density of emphysema to some extent [322]. Since contrast-enhanced CT scans are part of clinical investigations for lung cancer patients, this study aimed to assess the association between contrast-enhanced QCT of emphysema using %LAA and lung volume and postoperative QoL. Besides, we will employ

several density thresholds due to the impact of contrast administration on shifting these densities. In addition, we aimed to investigate the association between unenhanced CT scans of emphysema and QoL as well. Lastly, we will compare the density measures of contrast-enhanced and unenhanced CT scans.

5.2 Methods

5.2.1 CT scan

This is a retrospective study; as part of lung cancer patients' clinical assessment, clinics employed contrast CT scans in almost all CT scans. As a result, this study involved two sets of CT scans, contrast and non-contrast CT scans, while the latter was limited in number. Due to the impact of contrast application on the CT density measurements, it was reported that contrast CT could increase the density [321]; this study involved %LAA-925 as an extra threshold to %LAA-950 and %LAA-910 in contrast-enhanced CT scan analysis.

5.2.2 CT scan analysis software

In recent years, several commercial software and open platforms have been developed, making it relatively easy for users to access and use lung densitometry [190]. The presented study employed 3D slicer, an open platform involving morphometric and lung parenchyma analysis [190]. Chest Imaging Platform (CIP) is an extension module of 3D slicer that allows segmentation of the lung lobes and quantification of the emphysema; the method of utilising this tool was explained in Section 3.2.4, whereas data output is demonstrated below in Section 5.3.2. This process takes approximately 15 minutes per patient's scan for semi-automated quantification of emphysema. The detailed methodology for this chapter is described in Section 3.2.

5.2.3 Statistical analysis

The predictive value of CT scans was tested using ordinal and linear regression analyses. A comparison between contrast-enhanced and unenhanced CT scans was investigated, and Bland Altman Plots were illustrated. Details of statistical analysis are explained in Section 3.2.5. All statistical analyses implemented Stata 18.0 statistical software (Stata Co., College Station, TX) or SPSS version 29 (IBM Corp.).

5.3 Results

5.3.1 Baseline Characteristics for Patients Included in Contrast-enhanced CT Analysis

A total of 906 patients were screened for inclusion in contrast-enhanced CT scan analysis for emphysema; the CT scans were acquired between 2010-2020. 94 consented patients with contrast CT scans were included in the final analysis. Subjects excluded were 243 with no CT scan records, 183 had unenhanced CT scans, and 271 had no baseline CT scans. Also, 105 CT scans were excluded for other reasons, such as CT scans were only thoracic or abdominal, CT scans were acquired one year before the intervention, sharp kernel use, or more than 1 mm slice thickness. Other 10 CT scans were excluded due to the failure of the software to analyse the scans (Figure 5.1). Table 5.1-5.3 summarises the included patients' baseline characteristics. Details about EORTC QLQ-C30 global health and dyspnoea scores at baseline and six months following lung cancer surgery are presented in Table 5.4.

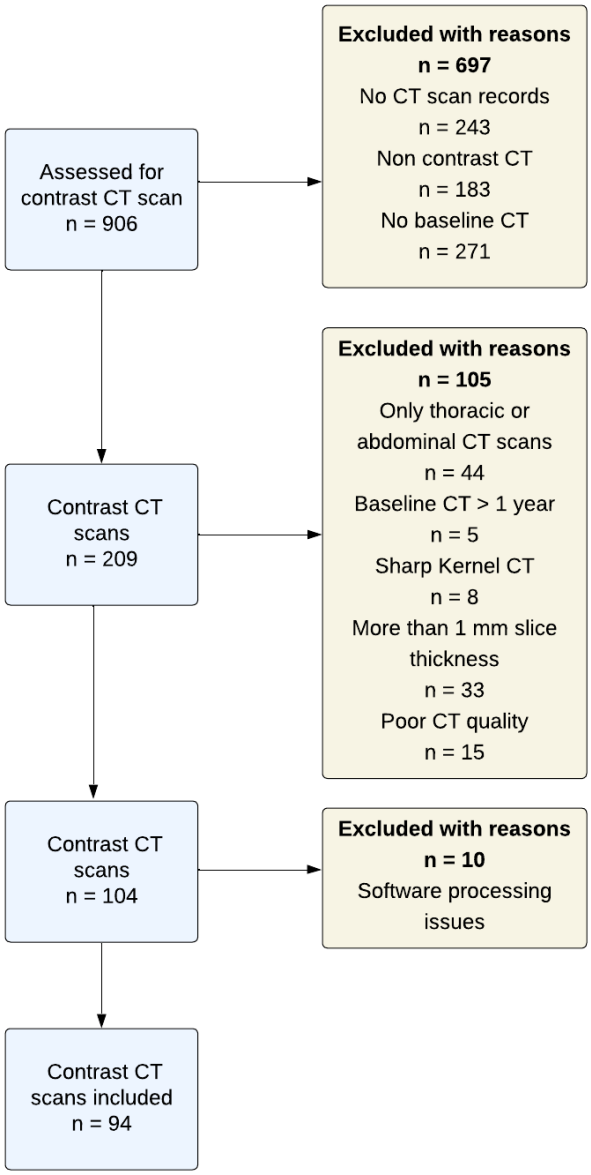

Figure 5.1 Flow chart of Contrast CT inclusion in the study

Table 5.1 Baseline characteristics of 94 patients included in the study

Characteristic	Total (n = 94)
Age	69.4 ± 6.9
Gender (male)	56 (59.57)
BMI	27.04 ± 4.8
Smoking quit time	
Current	22 (23.91)
Ex-smoker (6 weeks ≥ 1 year)	11 (11.96)
Ex-smoker (> 1 year)	51 (55.43)
Never smoker	8 (8.7)
Pack years	42.1 ± 30.3
FEV_1 (L)	2.7 ±0 .7
% FEV_1	77.7 ± 20
FVC (L)	3.4 ± 0.99
% FVC	103.3 ± 20.05
%DLCO	77.09 ± 18.8
$ppoFEV_1$	63.55 ± 18.1
ppoDLCO	62.55 ± 14.6
Surgical Incision (VATS)	45 (57.45)
Surgery Side (Right)	48 (51)
Upper lobe	59 (63.4)
Lower lobe	28 (30.1)
Bilobe	3 (3.2)
Middle lobe	3 (3.2)
Lobectomy	78 (82.9)
Segmentectomy	3 (3.2)
Wedge	11 (11.7)
Bilobectomy	3 (3.2)

Data are presented as mean (median) and standard deviation (interquartile range) or numbers and percentages for categorical data. BMI; body mass index, FEV_1; forced expiratory volume in 1 second, FVC; forced vital capacity, DLCO; diffusing capacity for carbon monoxide, $ppoFEV_1$ or ppoDLCO; predicted postoperative FEV_1 or DLCO. VATS; video-assisted thoracic surgery.

Table 5.1 summarises baseline demographic and smoking data for 94 patients with baseline contrast CT scans. Median age is 69 years, and more than half of the patients are male (59.5%). The mean BMI is 27.04, and 55% of the patients have quit smoking for more than one year, while the minority of the patients are never smokers (8%). Mean FEV_1(L) is 2.7 and mean %FEV_1 is 77.7. The mean DLCO is 77, and the mean ppoDLCO is 62.5. Regarding surgical information, we can note that more than half of the cohorts (57%) had VATS surgical approach, and half had their surgery on the right side. Furthermore, most surgeries were on the upper lobe (63.4%) and lobectomy (82.9%).

Table 5.2 Baseline characteristics of 94 patients included in the study (continue)

Characteristic	Total (n = 94)
Postoperative histology	
Adenocarcinoma	51 (54.84)
Squamous cell carcinoma	26 (27.96)
Carcinoid	7 (7.53)
Cancer stage	
T1	41 (47.67)
T2	32 (37.21)
T3	9 (10.47)
T4	3 (3.49)
N0	65 (78.31)
N1	9 (10.84)
N2	9 (10.84)
M0	80 (85.1)

Data are presented as numbers and percentages for categorical data. T; tumour size staging, N; lymph node involvement, M; metastasis, COPD; chronic obstructive pulmonary disease, IHD; ischemic heart disease.

Table 5.2 represents postoperative histology as well as patients' comorbidities. We can note that 54% of the cancers were adenocarcinoma, while 27% were squamous cell carcinoma. The majority of the patients had stages T1 stage (48%), N0 stage (78%), and M0 (85%).

Table 5.3 Baseline characteristics of 94 patients included in the study (continue)

Characteristic	Total (n = 94)
Other measures	
ASA score ≥3	59 (62.77)
ECOG Performance Score < 2	92 (97.88)
MRC 0	58 (61.7)
MRC 1	36 (38.2)
Perioperative Outcomes	
Hospital mortality	0 (0%)
Postoperative pulmonary complications	10 (10.64%)
Hospital readmission	13 (14.29%)
Hospital length of stay (days)	5 ± (5)

Data are presented as mean (median) and standard deviation (interquartile range) or numbers and percentages for categorical data. ASA score; American Society of Anaesthesiologists' classification of physical health, ECOG; Eastern Cooperative Oncology Group performance status.

As seen in Table 5.3, 63% of participants had an ASA score of 3 or higher, whereas 98% of the patients had an ECOG performance score of less than 2. Moreover, 61.7% of the patients had MRC score of 0. In terms of perioperative outcomes, we can find that most patients did not suffer from these outcomes, with 0% hospital mortality, 14% hospital readmission, 10% postoperative pulmonary complications and a median hospital length of stay of 5 days.

Table 5.4 Summary of EORTC QLQ-C30 dyspnoea and global health scores of 94 patients

EORTC QLQ-C30 domain	Total (n = 94)
Baseline dyspnoea	0 ± 33.33
Baseline global health	83.33 ± 25
six months dyspnoea	33.33 ± 33.33
six months global health	75 ± 33.33

Data are presented as mean (median) and standard deviation (interquartile range).

Table 5.4 illustrates EORTC QLQ-C30 dyspnoea and global health scores at baseline and six months after this cohort's intervention. In this cohort, dyspnoea has increased above the minimal clinically significant difference in six months to 33.33 compared to a baseline value of 0. The global health index has decreased to 75 from 83 at baseline, but the amount of reduction has not reached the minimally clinically significant level.

5.3.2 Quantitative CT of emphysema output

CIP provides data in the form of a spreadsheet, which includes values for the whole lungs, the right lung, the left lung, and each of the five lobes. Measures include:

- %LAA-950, %LAA-925, %LAA-910, %LAA-856
- 10^{th} percentile and 15^{th} Percentile
- Mean lung density (MLD) and standard deviation
- Volume
- Other measures were not employed in this analysis, including the high attenuation area (HAA) percentage.
- Lung density histogram (Figure 5.2)

Most scans passed through the CIP analysis steps without difficulties (Figure 3.2, Section 3.2.4); however, ten scans could not be processed. Despite the placement of additional fiducials, the lobes failed to segment as intended. Figure 5.3 represents the failure of the lobar segmentation.

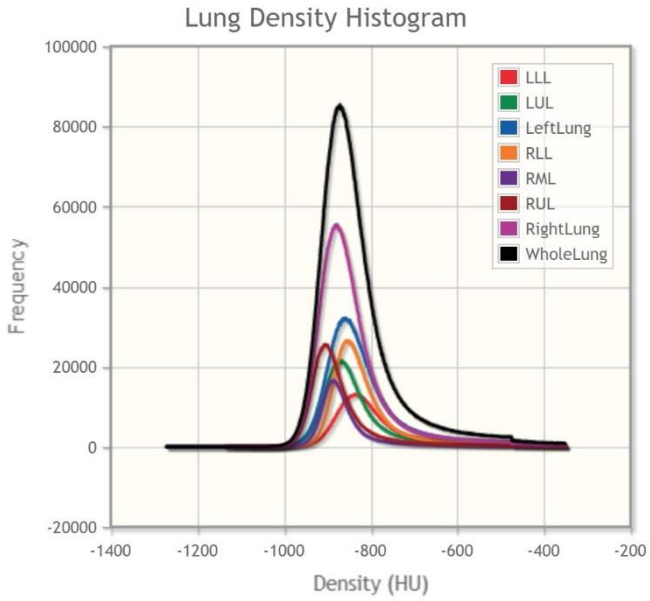

Figure 5.2 An example of CIP lung density histogram output, LLL; left lower lobe, LUL; left upper lobe, RLL; right lower lobe, RML; right middle lobe, RUL; right upper lobe

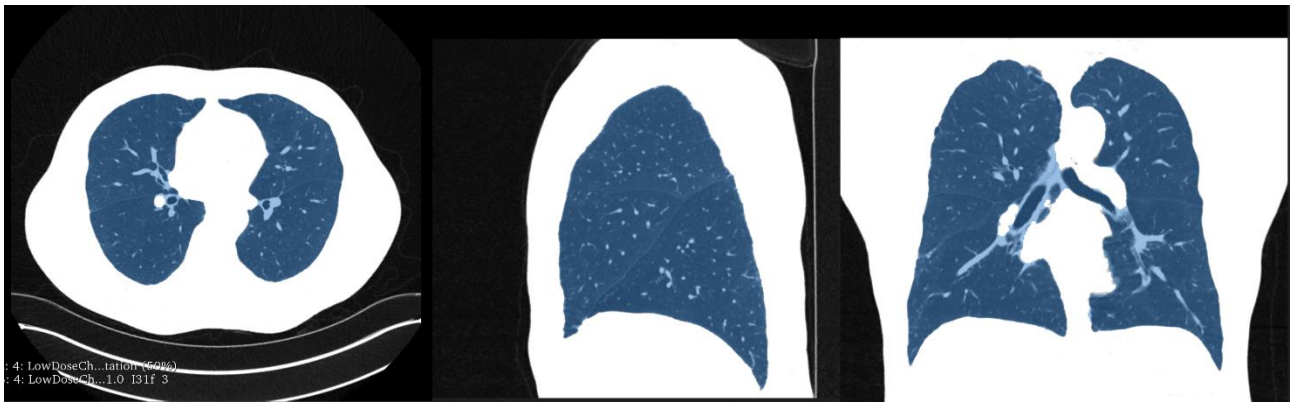

Figure 5.3 An example of failure of lobar segmentation by CIP

Table 5.5 Summary of CIP data output of 94 contrast-enhanced CT scans

Measured Lung	%LAA-950	%LAA-925	%LAA-910	PD15	Volume (L)
Whole lung	1.2 ± 3.7	5.2 ± 10.6	11 ± 15.1	-902.3 ± 25.8	5.3 ± 1.1
Right lung	1.1 ± 3.92	5.6 ± 12.5	10.6 ± 16	-902.5 ± 26.9	2.8 ± 0.6
Left lung	1.09 ± 3.8	4.7 ± 9.3	10.5 ± 14.1	-900.9 ± 25.5	2.4 ± 0.5
RUL	1.17 ± 0.18	5.3 ± 11.9	9.6 ± 18.9	-902.6 ± 29.5	1.07 ± 0.2
RML	1.7 ± 4.28	6.9 ± 13.4	14.8 ± 22.75	-891.9 ± 189.1	0.49 ± 0.1
RLL	0.67 ± 2.5	3.1 ± 7.1	6.9 ± 11.6	-893.3 ± 30.3	1.3 ± 0.3
LUL	1.4 ± 3.4	6.5 ± 11.7	12.9 ± 19.4	-906 ± 25.8	1.3 ± 0.2
LLL	0.63 ± 1.54	2.5 ± 5.4	5.1 ± 10.9	-889.1 ± 29.2	1.1 ± 0.3

Data are presented as mean (median) and standard deviation (interquartile range). Lung volume is measured in Litre. %LAA; percentage low attenuation area, PD15; 15^{th} percentile, RUL; right upper lobe, RML; right middle lobe, RLL; right lower lobe, LUL; left upper lobe, LLL; left lower lobe.

The table above (Table 5.5) summarises the data output by CIP analyses using 94 contrast CT scans. The presented results include %LAA-950, %LAA-925, %LAA-910, PD15, and volume for the whole lung, right, left lungs and each lung lobe.

5.3.3 Prediction of postoperative dyspnoea using contrast-enhanced CT density

5.3.3.1 Univariate analysis

Our primary goal is to assess the individual predictors of 6-month dyspnoea outcome using baseline quantitative CT measurements. The first analysis was employed to determine relationships between each quantitative CT measure and six months of dyspnoea is ordinal logistic regression. If any of these factors statistically significantly predicted the dyspnoea outcome (significance level $p < 0.1$), then this factor will be assessed in multiple regression analyses. Univariate ordinal regression analysis for six months dyspnoea is summarised in Table 5.6.

Table 5.6 Univariate Ordinal Regression analysis evaluating the associations between contrast-enhanced quantitative CT measures and six months dyspnoea.

Parameter	OR	P value	95 % CI
%LAA-950 whole lung	1.05	0.3	0.9 - 1.1
%LAA-925 whole lung	1.02	0.2	0.9 - 1.08
%LAA-910 whole lung	1.02	0.2	0.9 - 1.06
PD15	0.99	0.7	0.98 - 1.01
Whole lung volume	1.12	0.6	0.7 - 1.7

%LAA; percentage of low attenuation area, PD15; 15th percentile, OR; odd ratio, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

The above table (Table 5.6) illustrates univariate regression using CT density measures. There is no statistically significant association between all densitometric measurements and postoperative dyspnoea six months after surgery $P > 0.1$. Therefore, the measures from contrast CT will not be assessed in the multiple regression analyses.

5.3.4 Prediction of postoperative global health using contrast-enhanced CT density

5.3.4.1 Univariate analysis

In order to assess predictors of six months global health after lung surgery, we performed univariate linear regression analyses. This was performed to evaluate relationships between baseline contrast CT density measures, including whole lung %LAA-950, %LAA-925, %LAA-910, PD15, and whole lung volume with the postoperative global health at six months.

Table 5.7 demonstrates the results of the univariate regression, and as can be seen, none of these variables have significantly predicted postoperative global health. Therefore, the quantitative contrast CT measures will not be assessed in multiple regression analyses (P>0.1).

Table 5.7 Univariate linear Regression analysis evaluating the associations between contrast-enhanced quantitative CT measures and 6 months global health.

Parameter	Coefficient	P value	95 % CI
%LAA-950 whole lung	-0.6	0.2	-1.9 - 0.6
%LAA-925 whole lung	-0.2	0.3	-0.9 - 0.3
%LAA-910 whole lung	-0.2	0.3	-0.6 - 0.2
PD15	0.06	0.5	-0.1 - 0.2
Lung volume	-1.9	0.4	-7.1 - 3.2

%LAA; percentage of low attenuation area, PD15; 15th percentile, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

5.3.5 Baseline characteristics for patients included in unenhanced CT analysis

A similar cohort in Section 5.3.1 was screened, and 60 patients with unenhanced CT were included in the analysis. The excluded subjects were 243 with no CT scan records, and 480 had only contrast CT scans. The remaining 123 CT scans were excluded for other reasons, including CT scans acquired one year before the intervention, sharp kernel use, or slice thickness greater than 1 mm. CT scans from the other three patients were excluded due to software failure to analyse them (Figure 5.10). The baseline characteristics of the patients, EORTC QLQ-C30 global health and dyspnoea scores, and CT data output are summarised in Table 5.8-5.12.

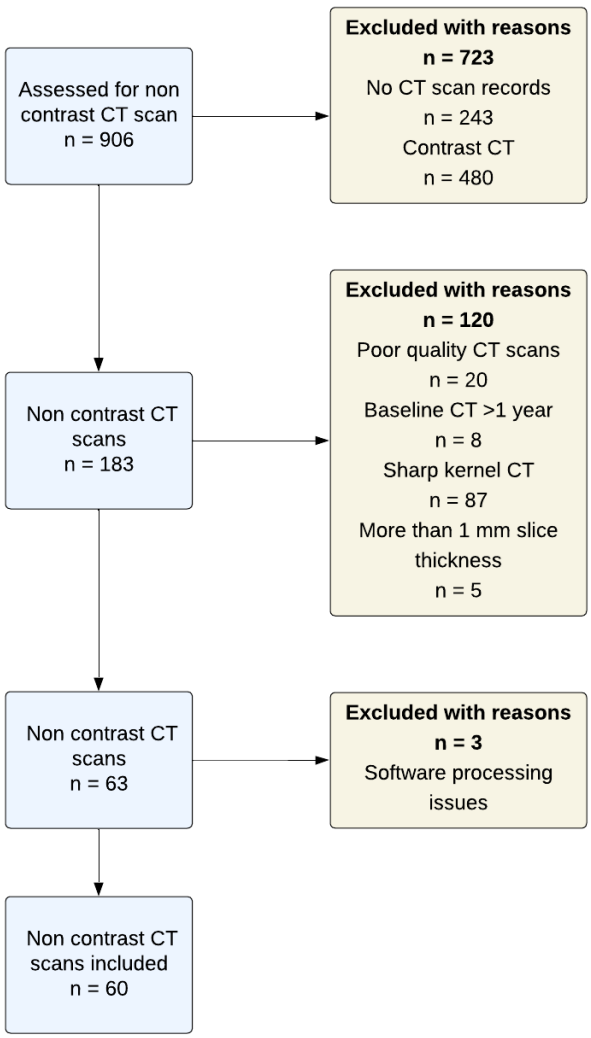

Figure 5.4 Flow chart for inclusion of non-contrast CT

Table 5.8 Baseline characteristics of 60 patients included in the study

Characteristic	Total (n = 60)
Age	70 ± 8.5
Gender (male)	28 (46. 7)
BMI	28 ± 6
Smoking quit time	
Current	8 (14)
Ex-smoker (6 weeks ≥ 1 year)	8 (14)
Ex-smoker (> 1 year)	30 (52.6)
Never smoker	11 (19)
Pack years	30 ± 40
FEV_1 (L)	2 ± 0 .7
% FEV_1	84.6 ± 23.5
FVC (L)	3.1 ± 0.8
% FVC	101.1 ± 0.8
%DLCO	76.3 ± 20.1
ppoFEV_1	70.8 ± 23.6
ppoDLCO	64.7 ± 17.5
Surgical Incision (VATS)	38 (63.3)
Surgery Side (Right)	40 (66.6)
Upper lobe	40 (69)
Lower lobe	14 (24.1)
Lobectomy	41 (68.3)
Segmentectomy	3 (3.2)
Wedge	16 (26.6)

Data are presented as mean (median) and standard deviation (interquartile range) or numbers and percentages for categorical data. BMI; body mass index, FEV_1; forced expiratory volume in 1 second, FVC; forced vital capacity, DLCO; diffusing capacity for carbon monoxide, ppoFEV_1 or ppoDLCO; predicted postoperative FEV_1 or DLCO. VATS; video-assisted thoracic surgery.

Table 5.8 summarises patients' demographics, lung function, smoking and surgery data. As can be seen, the median age is 70 years, and nearly half of the sample are male patients (46.7%). The mean BMI is 28, and more than half of the patients have quit smoking for more than a year (52.6%). The mean FEV_1(L) is 2, and the mean %FEV_1 is 84.6. The mean DLCO is 76.3, and the mean ppoDLCO is 64.7. Additionally, more than half of the cohorts (63.3%) had VATS surgical approach, with 66.6% right side surgery. The majority of the surgeries were on the upper lobe (69%), and the majority of the resections were lobectomy (68%).

Table 5.9 Baseline characteristics of 60 patients included in the study (continue)

Characteristic	Total (n = 60)
Postoperative histology	
Adenocarcinoma	37 (62.7)
Squamous cell carcinoma	11 (18. 6)
Cancer stage	
T1	35 (67.31)
T2	10 (19.23)
N0	41 (83.6)
N1	4 (8.1)
N2	4 (8.1)
M0	52 (100)

Data are presented as numbers and percentages for categorical data. T; tumour size staging, N; lymph node involvement, M; metastasis.

Table 5.9 summarises postoperative histology and patients' cancer stage. Approximately 62% of all cancers are adenocarcinomas, while 18% are squamous cell carcinomas. The majority of the patients had stages T1 stage (76%), N0 stage (83%) and M0 (100%).

Table 5.10 Baseline characteristics of 60 patients included in the study (continue)

Characteristic	Total (n = 60)
Other measures	
ASA score ≥3	40 (66.6)
ECOG Performance Score >2	60 (100)
MRC dyspnoea score ≥ 2	59 (98.2)
Perioperative Outcomes	
Hospital mortality	0 (0%)
Postoperative pulmonary complications	4 (6.6%)
Hospital readmission	7 (12.5%)
Hospital length of stay (days)	3 ± (3.5)

Data are presented as mean (median) and standard deviation (interquartile range) or numbers and percentages for categorical data. ASA score; American Society of Anaesthesiologists' classification of physical health, ECOG; Eastern Cooperative Oncology Group performance status.

Table 5.10 shows that 66.6% of the participants had an ASA score greater than or equal to 3, whereas 100% had an ECOG performance score less than 2. Moreover, 98% of the patients had MRC scores greater than or equal to 2. The perioperative outcomes revealed that most patients did not have these outcomes, with an incidence of 0% mortality, 12% readmissions, 6% postoperative pulmonary complications, and a median hospital stay of 3 days in terms of hospitalisation length of stay.

Table 5.11 Summary of EORTC QLQ-C30 dyspnoea and global health scores of 60 patients

EORTC QLQ-C30 domain	Total (n = 60)
Baseline dyspnoea	0 ± 33.3
Baseline global health	74.8 ± 20.3
six months dyspnoea	33.3 ± 66.6
six months global health	69.1 ± 22.4

Data are presented as mean (median) and standard deviation (interquartile range).

Table 5.11 shows dyspnoea and global health scores at baseline and six months following the lung surgery. Compared to the baseline value of 0, dyspnoea in this cohort has increased above the minimal clinically important difference in six months to 33.3. Global health has decreased from 75 to 69 from baseline, although the reduction has not reached the minimal clinically important level.

5.3.6 Non-contrast CT density of emphysema output

A description of CIP-provided data is described in Section 5.3.2. Table 5.12 demonstrates the data output by CIP analyses using 60 unenhanced CT scans. The presented results include %LAA-950, %LAA-910, PD15, and volume for the whole lung, right, left lungs and each lung lobe.

Table 5.12 Summary of CIP data output of 60 unenhanced CT scans

Measured Lung	%LAA-950	%LAA-910	PD15	Lung volume
Whole lung	1.3 ± 7	14.6 ± 24.1	-907 ± 33	4.6 ± 1.7
Right lung	1.2 ± 7	12.8 ± 23	-907.2 ± 32.6	2.5 ± 0.9
Left lung	1.4 ± 6.7	15.8 ± 25.8	-906.2 ± 34.4	2.2 ± 0.9
RUL	0.96 ± 7.6	11.1 ± 28.3	-907.2 ± 32.9	1 ± 0.4
RML	1.9 ± 7.6	19.4 ± 32	-917 ± 30.2	0.4 ± 0.2
RLL	0.62 ± 5	8.7 ± 22.7	-897 ± 39.7	1.2 ± 0.5
LUL	1.6 ± 6.8	17.9 ± 28.8	-910.7 ± 33.5	1.1 ± 0.4
LLL	1.1 ± 4.6	10 ± 20.6	-895.8 ± 42	1 ± 0.4

Data are presented as mean (median) and standard deviation (interquartile range). Lung volume is measured in Litre. %LAA; percentage low attenuation area, RUL; right upper lobe, RML; right middle lobe, RLL; right lower lobe, LUL; left upper lobe, LLL; left lower lobe.

5.3.7 Prediction of postoperative dyspnoea using unenhanced CT density

5.3.7.1 Univariate analysis

The primary goal is to assess the individual predictors of 6-month dyspnoea outcome using baseline quantitative CT. The first analysis was employed to evaluate relationships between each CT density and volume measure, and six months dyspnoea is ordinal logistic regression. If any of these factors statistically significantly predicts the dyspnoea outcome (significance level $p < 0.1$), then this factor will be assessed in multiple regression analyses. The results in Table 5.13 summarises univariate ordinal regression analyses for predicting six months dyspnoea, and the results clearly demonstrate that %LAA-950 and %LAA-910 are statistically significantly associated with postoperative dyspnoea ($P < 0.05$). In contrast, PD15 and lung volume are not significantly associated with postoperative dyspnoea ($p > 0.1$). Therefore, the PD15 and lung volume will not be included in the multiple regression analyses.

Table 5.13 Univariate Ordinal Regression analysis evaluating the associations between unenhanced quantitative CT measures and six months dyspnoea.

Parameter	OR	P value	95 % CI
%LAA-950 whole lung	1.2	**	1.07 - 1.3
%LAA-910 whole lung	1.03	*	1.008 - 1.06
PD15	0.99	0.2	0.9 - 1.006
Lung volume	1.1	0.5	0.7 - 1.7

%LAA; percentage of low attenuation area, PD15, 15th percentile, OR; odd ratio, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

Table 5.14 summarises univariate regression analyses between baseline demographic, clinical data, and postoperative dyspnoea. Age, wedge resection, ppoFEV_1, ppoDLCO, FEV_1(L), and %DLCO are statistically significantly associated with postoperative dyspnoea, $p<0.1$.

Table 5.14 Univariate Ordinal Regression analysis evaluating the associations between baseline factors and six months dyspnoea.

Parameter	OR	P value	95 % CI
Age	1.07	*	1.003 - 1.1
Gender (male)	1.4	0.4	0.5 - 4.4
BMI	1.07	0.13	0.97 - 1.1
Incision (VATS)	0.6	0.4	0.2 - 2.0
Surgical side (right)	1.3	0.5	0.4 - 4.3
Upper lobe	2.4	0.5	0.17 - 34.4
Lower lobe	4.3	0.3	0.2 - 73.1
Ref: middle			
Wedge resection	0.2	*	0.06 - 0.9
(Ref: Lobectomy)			
ppoFEV_1	0.97	*	0.95 - 0.99
ppoDLCO	0.95	**	0.92 - 0.98
FEV_1(L)	0.37	*	0.1 - 0.9
%FEV_1	0.98	0.11	0.95 - 1.0
FVC (L)	1.1	0.6	0.5 - 0.2
%FVC	1.0	0.5	0.9 - 1.0
%DLCO	0.97	*	0.9 - 1.001

Ref; reference, BMI; body mass index, FEV_1; Forced expiratory volume in 1 second, FVC; forced vital capacity, DLCO; diffusing capacity for carbon monoxide, ppo; predicted postoperative, VATS; video-assisted thoracic surgery, OR; odd ratio, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

Table 5.15 demonstrates univariate regression analyses for the rest of the factors. Smoking quit time, ASA score, ECOG performance, MRC dyspnoea score, LOS, and baseline dyspnoea are statistically significantly associated with postoperative dyspnoea in the univariate regression, $p<0.1$.

Table 5.15 Univariate Ordinal Regression analysis evaluating the associations between baseline factors and six months dyspnoea.

Parameter	OR	P value	95 % CI
Never smoking	0.05	*	0.002 - 1.04
Ref: current smoking			
Pack years	1.007	0.5	0.9 - 1.02
ASA score	3.4	*	1.1 - 9.8
ECOG	3.9	*	1.2 - 12.2
MRC	4.6	**	1.6 - 12.7
PPC	2.9	0.9	0.0 - 3.1
Hospital readmission	2.1	0.3	0.4 - 10.5
LOS	1.1	*	0.9 - 1.4
Baseline dyspnoea	1.07	**	1.02 - 1.1

Ref; reference, ASA score; American Society of Anaesthesiologists' classification of physical health, ECOG; Eastern Cooperative Oncology Group performance status; MRC; Medical Research Council Scale, PPC; postoperative pulmonary complications, LOS; length of hospital stay, OR; odd ratio, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

5.3.7.2 Multivariate analyses

Based on the univariate regression results, the researcher selected subsets of variables to include together in separate multivariate models to regress on six-month dyspnoea; all models include %LAA-950 and %LAA-910 of the whole lung as predictors.

To assess the role of %LAA-950 and %LAA-910 of the whole lung in predicting postoperative dyspnoea at six months, multivariate ordinal or multinomial regression analyses were conducted, with each model adjusted for the different factors. The author conducted separate analyses for %LAA-950 and %LAA-910 due to their high correlation, $r = 0.78$, $p = 0.00$. To this end, regression models for %LAA-950 were conducted first, and regression models for %LAA-910 were conducted in the same manner and adjusted for similar factors.

The first regression model involves %LAA-950 of the whole lung adjusted for age, ppoFEV_1, ppoDLCO, and resection.

There were 45 observations with all these variables that were included in the modelling process. The numeric variables (age, ppoFEV_1, ppoDLCO, and %LAA-950) were tested for multicollinearity using VIF, and the largest VIF was found to be 1.4, which is not too large for inclusion in the model.

Table 5.16 demonstrates the final model. The proportional odds assumption was tested, and the result was $\chi^2(4) = 3.9$, $p = 0.4$; there was no evidence of a violation of proportional odds.

It can be seen that %LAA-950 has positive association with six-month dyspnoea (OR = 1.23, $p = 0.001$); thus, those with higher baseline %LAA-950 have a greater risk of dyspnoea, Wald $\chi^2(4) = 19.86$, $p < 0.001$. Age, ppoFEV_1, ppoDLCO and resection do not have a significant relationship with the highest level of dyspnoea.

Table 5.16 Multivariate Ordinal Regression analysis for six months dyspnoea (Model 1)

Parameter	OR	P value	95 % CI
%LAA-950 whole lung	1.24	**	1.09 - 1.4
Age	1.02	0.05	0.9 - 1.1
ppoFEV_1	0.99	0.9	0.9 - 1.03
ppoDLCO	0.97	0.3	0.9 - 1.02
Segmentectomy	1.4	0.8	0.07 - 27.7
Wedge	0.2	0.09	0.05 - 1.2
Bilobectomy	16.6	0.1	0.4 – 5.4
Ref: Lobectomy			

Ref; reference, LAA; low attenuation area, FEV_1; Forced expiratory volume in 1 second, DLCO; diffusing capacity for carbon monoxide, ppo; predicted postoperative, OR; odd ratio, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The second regression model below includes %LAA-950 whole lung adjusted for smoking quit time, FEV_1 (L), and %DLCO. There were 41 observations with all these variables that were included in the modelling process (Table 5.17).

The continuous independent variables were tested for multicollinearity using VIF, and the largest VIF was found to be 1.4, which is not considered too large to include in a model. The proportional odds assumption was also met $\chi^2(6) = 9.9$, $p = 0.24$.

From Table 5.17, %LAA-950 whole lung has an odds ratio greater than one, which leads to a greater probability of higher dyspnoea as it increases. For each one-unit increase in %LAA-950, the odds of the patient experiencing a higher level of dyspnoea are multiplied by 1.31 (CI; 1.1, 1.5). There is also a statistically significant difference between never smoking and current smoking (the reference level); those who never smoke have a lower probability of higher dyspnoea than those who still smoke, Wald $\chi^2(4) = 26.55$, $p < 0.001$.

Table 5.17 Multivariate Ordinal Regression analysis for six months dyspnoea (Model 2)

Parameter	OR	P value	95 % CI
%LAA-950 whole lung	1.31	**	1.1 - 1.5
Never smoking	0.01	*	0.005 - 0.38
Ref: current			
FEV_1 (L)	1.4	0.5	0.4 - 4.6
DLCO	0.99	0.8	0.9 - 1.03

Ref; reference, LAA; low attenuation area, FEV_1; Forced expiratory volume in 1 second, DLCO; diffusing capacity for carbon monoxide, OR; odd ratio, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The third model includes %LAA-950 adjusted for ASA score, ECOG performance, and MRC dyspnoea score. Modelling included 45 observations with all these variables (Table 5.18).

The variables were tested for multicollinearity using VIF, and the largest VIF was found to be 1.1, which is not considered too large to include in a model. Additionally, the proportional odds assumption was met $\chi^2(6) = 6.8$, $p = 0.3$.

From Table 5.18, %LAA-950 whole lung still significantly predicted higher levels of dyspnoea (OR = 1.2, p = 0.003). There is also a statistically significant positive relationship between ASA score and dyspnoea; for each one-unit increase in ASA score, the odds of the patient experiencing a higher level of dyspnoea are multiplied by 3.01, Wald $\chi^2(2) = 15.75$, $p < 0.001$. ECOG performance and MRC dyspnoea score were not significantly associated with postoperative dyspnoea.

Table 5.18 Multivariate Ordinal Regression analysis for six months dyspnoea (Model 3)

Parameter	OR	P value	95 % CI
%LAA-950 whole lung	1.2	**	1.06 - 1.36
ASA score	3.01	*	1.02 - 8.9
ECOG	2.6	0.1	0.8 - 8.6
MRC	2.0	0.3	0.5 - 8.3

LAA; low attenuation area, ASA score; American Society of Anaesthesiologists' classification of physical health, ECOG; Eastern Cooperative Oncology Group performance status; MRC; Medical Research Council Scale, OR; odd ratio, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The last model includes %LAA-950 adjusted for baseline dyspnoea and LOS. Modelling included 44 observations with all of these variables (Table 5.19).

The variables were tested for multicollinearity using VIF, and the largest VIF was found to be 1.07, which is not considered too large to include in a model. Additionally, the proportional odds assumption was met $\chi^2(3) = 3.4$, $p = 0.3$.

From Table 5.19, all parameters are significantly associated with postoperative dyspnoea, and %LAA-950 whole lung is still significantly predicting higher levels of dyspnoea (OR = 1.27, $p = 0.002$). A statistically significant positive relationship exists between baseline dyspnoea score and postoperative dyspnoea at six months (OR = 1.08, $p = 0.001$). LOS is also positively associated with the highest levels of dyspnoea, so for each unit increase in LOS, the odds of the patient experiencing a higher level of dyspnoea are multiplied by 1.33 ($p = 0.018$), Wald $\chi^2(3) = 33.86$, $p < 0.001$.

Table 5.19 Multivariate Ordinal Regression analysis for six months dyspnoea (Model 4)

Parameter	OR	P value	95 % CI
%LAA-950 whole lung	1.27	**	1.09 - 1.48
Baseline dyspnoea	1.08	**	1.03 - 1.13
LOS	1.33	*	1.05 - 1.68

LAA; low attenuation area, LOS; length of hospital stay, OR; odd ratio, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The next set of regression models assessed the predictive role of %LAA-910 adjusted for several factors.

The first regression model included %LAA-910 whole lung adjusted for age, resection, $ppoFEV_1$, ppoDLCO. Modelling included 45 observations with all these variables (Table 5.20).

The variables were tested for multicollinearity using VIF, and the largest VIF was found to be 1.5, which is considered not too large to run the model with these variables. the proportional odds assumption was met $\chi^2(7) = 2.5$, $p = 0.9$.

The results below show that %LAA-910 whole lung statistically significantly predicts postoperative dyspnoea (OR = 1.04, p = 0.03). Patients with a higher %LAA-910 are more likely to develop higher levels of dyspnoea, Wald $\chi^2(4) = 12.04$, $p = 0.01$. However, age, $ppoFEV_1$, ppoDLCO, and resection were not significantly associated with postoperative dyspnoea.

Table 5.20 Multivariate Ordinal Regression analysis for six months dyspnoea (Model 1)

Parameter	OR	P value	95 % CI
%LAA-910 whole lung	1.04	*	1.003 - 1.07
Age	1.05	0.3	0.9 - 1.1
ppoFEV_1	0.99	0.5	0.9 - 1.02
ppoDLCO	0.97	0.3	0.9 - 1.02
Segmentectomy	0.91	0.9	0.04 - 16.8
Wedge	0.26	0.09	0.05 - 1.2
Bilobectomy	8.8	0.2	0.2 - 28.8
Ref: Lobectomy			

Ref; reference, LAA; low attenuation area, FEV_1; Forced expiratory volume in 1 second, DLCO; diffusing capacity for carbon monoxide, ppo; predicted postoperative, OR; odd ratio, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The second regression model (Table 5.21) assessed %LAA-910 adjusted for preoperative FEV_1 (L), DLCO, and smoking quit time. There are 41 variables were included in the model. The variables were tested for multicollinearity using VIF, and the largest VIF was found to be 2.95, which is considered not too large to run the model with these variables. the proportional odds assumption was met $\chi^2(6) = 11.6$, $p = 0.07$.

The results below (Table 5.21) show that %LAA-910 whole lung is positively associated with postoperative dyspnoea (OR = 1.06, p = 0.003). In addition, never smoking has a negative relationship with the highest levels of dyspnoea (OR = 0.015, p = 0.01), so those who never smoke would have lower odds of developing dyspnoea after surgery compared to current smokers, Wald $\chi^2(4) = 20.61$, $p < 0.001$. In contrast, preoperative FEV_1 and DLCO are not significantly associated with dyspnoea.

Table 5.21 Multivariate Ordinal Regression Analysis for six months dyspnoea (Model 2)

Parameter	OR	P value	95 % CI
%LAA-910 whole lung	1.06	**	1.02 - 1.1
Never smoking	0.015	*	0.005 - 0.39
Ref: current			
FEV_1 (L)	1.08	0.8	0.3 - 3.4
DLCO	1.0	0.9	0.9 - 1.03

Ref; reference, LAA; low attenuation area, FEV_1; Forced expiratory volume in 1 second, DLCO; diffusing capacity for carbon monoxide, OR; odd ratio, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The third model incorporated %LAA-910 adjusted for ASA score, MRC dyspnoea score and ECOG performance. VIF was tested and found to be 1.18, implying no multicollinearity between the factors. The modelling process included 44 variables, and the proportional odds assumption was tested, and there was a good fit to the proportional odds assumption $\chi^2(4) = 2.03$, $p = 0.7$.

Table 5.22 summarises the results of the regression model. The results indicate that %LAA-910 did not significantly predict dyspnoea following surgery. Both ASA score and ECOG performance status have a positive association with the highest levels of dyspnoea. As the ASA score increases by one point, the likelihood of experiencing a greater degree of dyspnoea increases by 3.5. There is a 3.8-fold increase in dyspnoea risk among individuals with ECOG 1 against those with ECOG 0, Wald $\chi^2(2) = 10.36$, $p = 0.004$. However, MRC showed no significant relationship with dyspnoea at six months.

Table 5.22 Multivariate Ordinal Regression Analysis for six months dyspnoea (Model 3)

Parameter	OR	P value	95 % CI
%LAA-910 whole lung	1.02	0.2	0.9 - 1.05
ASA score	3.5	*	1.2 - 10.2
ECOG (1)	3.8	*	1.1 - 12.4
Ref: 0			
MRC	2.3	0.2	0.5 - 9.4

Ref; reference, LAA; low attenuation area, ASA score; American Society of Anaesthesiologists' classification of physical health, ECOG; Eastern Cooperative Oncology Group performance status, MRC; Medical Research Council Scale, OR; odd ratio, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The last model below assessed baseline %LAA-910 adjusted for baseline dyspnoea and LOS. The modelling process included 44 observations, and VIF = 1.04, considered not too large to be included in the model. The proportional odds assumption was tested, and there was a good fit to the proportional odds assumption $\chi^2(3) = 4.6$, p = 0.2.

We can see from Table 5.23 that %LAA-910 is not significantly associated with postoperative dyspnoea. In contrast, baseline dyspnoea remained significant (OR = 1.07, p = **0.001). Those with higher baseline dyspnoea would have higher odds of developing higher levels of dyspnoea compared to patients with lower levels of dyspnoea at baseline. Additionally, LOS has a positive relationship with six months dyspnoea; for each one-unit increase in LOS, the odds of the patient experiencing a higher level of dyspnoea are multiplied by 1.2 (p = 0.04), Wald $\chi^2(2) = 22.08$, p <0.001.

Table 5.23 Multivariate Ordinal Regression Analysis for six months dyspnoea (Model 4)

Parameter	OR	P value	95 % CI
%LAA-910 whole lung	1.02	0.2	0.9 - 1.06
Baseline dyspnoea	1.07	*	1.03 - 1.1
LOS	1.24	*	1.01 - 1.5

LAA; low attenuation area, LOS; length of hospital stay, OR; odd ratio, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

5.3.8 Prediction of postoperative global health using unenhanced CT density

5.3.8.1 Univariate analysis

This study primarily aims to determine the individual predictors of six-month global health outcomes using baseline quantitative CT measurements. Initially, univariate linear regression was used to assess the relationship between CT density and volume measures and six months global health. If any of these factors statistically significantly predict the six-month global health (significance level p <0.1), then this factor will be assessed in multiple regression analyses. The results in Table 5.24 demonstrates that %LAA-950, and %LAA-910 for whole lungs are significantly associated with postoperative global health (p<0.1). In contrast, the PD15 and lung volume are not associated with the outcome.

Table 5.24 Univariate Linear Regression analysis evaluating the associations between unenhanced quantitative CT measures and six months global health.

Parameter	Coefficient	P value	95 % CI
%LAA-950 whole lung	-1.5	*	-2.7 - -0.3
%LAA-910 whole lung	-0.3	*	-0.7 - 0.04
15^{th} Percentile	0.08	0.39	-0.11 - 0.29
Lung volume	-1.4	0.5	-6.6 - 3.7

%LAA; percentage of low attenuation area, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

Table 5.25 below summarises univariate regression analyses between baseline demographic, clinical factors, and postoperative global health. Wedge resection, ppoFEV_1, ppoDLCO, FEV_1(L), %FEV_1, and %DLCO are statistically significantly associated with postoperative global health (p<0.1).

Table 5.25 Univariate Linear Regression analysis evaluating the associations between baseline factors and six months global health.

Parameter	Coefficient	P value	95 % CI
Age	-0.3	0.3	-1.2 - 0.4
Gender (male)	0.06	0.9	-13.8 - 13.9
BMI	-0.5	0.3	-1.6 - 0.5
Incision (VATS)	7.2	0.3	-6.8 - 21.2
Surgical side (right)	3.07	0.6	-17.5 - 11.5
Upper lobe	-9.7	0.4	-33.1 - 13.6
Lower lobe	-11.8	0.3	-37.9 - 14.3
Ref: middle			
Wedge resection	12.09	*	-1.9 - 26.1
(Ref: Lobectomy)			
ppoFEV_1	0.39	**	0.15 - 0.6
ppoDLCO	0.53	**	0.16 - 0.89
FEV_1(L)	14.2	**	3.9 - 24.6
%FEV_1	0.34	*	0.08 - 0.5
FVC (L)	2.6	0.5	-5.8 - 11.2
%FVC	0.1	0.4	-0.1 - 0.3
%DLCO	0.35	*	0.01 - 0.6

Ref; reference, BMI; body mass index, FEV_1; Forced expiratory volume in 1 second, FVC; forced vital capacity, DLCO; diffusing capacity for carbon monoxide, ppo; predicted postoperative, VATS; video-assisted thoracic surgery, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

The univariate regression analyses for the remaining factors are illustrated in Table 5.26. Smoking quit time, ASA score, ECOG performance, and baseline global health are statistically significantly associated with postoperative global health at six months ($p<0.1$).

Table 5.26 Univariate Linear Regression analysis evaluating the associations between baseline factors and six months global health.

Parameter	Coefficient	P value	95 % CI
Ex-smoker >1 year	-16.1	*	-32.9 - 0.75
Ref: current smoking			
Pack years	-0.02	0.8	-0.2 - 0. 2
Hypertension	2.2	0.7	-11.6 - 16.1
ASA score	-10.8	*	-23.06 - 1.3
ECOG	-14.08	*	-27.5 - -0.6
MRC	-0.5	0.9	-16.0 - 15.0
PPC	-14.1	0.2	-37.8 - 9.5
Hospital readmission	5.8	0.5	-14.1 - 25.7
LOS	-0.4	0.6	-2.8 - 1.8
Baseline global health	0.53	**	0. 24 - 0.82

Ref; reference, ASA score; American Society of Anaesthesiologists' classification of physical health, ECOG; Eastern Cooperative Oncology Group performance status, MRC; Medical Research Council Scale, PPC; postoperative pulmonary complications, LOS; length of hospital stay, CI; confidence interval. *p<0.1; **p<0.01; ***p<0.001

5.3.8.2 Multivariate analyses

The role of %LAA-950 and %LAA-910 of the whole lung in predicting postoperative global health at six months was assessed using multivariate linear regression analysis, in which these factors were adjusted for a set of factors at each model. Due to the high correlation between %LAA-950 and %LAA-910 (R = 0.78, p = 0.00), the researcher separated these two factors.

The independent factors included in the first model for predicting six months global health were %LAA-950 adjusted for %ppoFEV_1, %ppoDLCO, and surgical resection. There were 42 observations with all these variables included in the modelling process.

The numeric variables (%LAA-950, % ppoFEV_1, %ppoDLCO) were tested for multicollinearity using VIF, and the largest VIF was found to be 1.34, which represents no multicollinearity between the variables. In addition, the researcher assessed the linearity between each continuous variable and the outcome, assessed the residual errors for each regression model, and found that the residual errors of the regression line are approximately normally distributed. Furthermore, all factors were evaluated and confirmed to be homoscedastic.

As shown in Model 1 (Table 5.27), the model statistically significantly predicted six months global health F (4, 39) = 5.9, p = 0.00, and R^2= 0.37. A statistically significant effect of %LAA-950 is still observed regardless of several factors that have been adjusted (coefficient; -1.54, p = 0.007). Compared with lobectomy, bilobectomy is negatively associated with global health at six months; in other words, those who undergo bilobectomy are likely to have a postoperative global health score 65 units worse than those who undergo lobectomy. However, ppoFEV_1 and ppoDLCO are not significantly associated with postoperative global health at six months.

Table 5.27 Multivariate linear Regression analysis for six months global health (Model 1)

Parameter	coefficient	P value	95 % CI
%LAA-950 whole lung	-1.54	**	-2.6 - -0.45
Bilobectomy	-65.00	**	-103.65 - -26.3
Segmentectomy	13.7	0.3	-15.6 - 43.2
Wedge	8.2	0.2	-5.8 - 22.3
Ref: lobectomy			
ppoFEV_1	0.12	0.4	-0.1 - 0.44
ppoDLCO	0.26	0.1	-0.1 - 0.6

Ref; reference, LAA; low attenuation area, FEV_1; Forced expiratory volume in 1 second, DLCO; diffusing capacity for carbon monoxide, ppo; predicted postoperative, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The second model involved %LAA-950 adjusted for; FEV_1 (L), % FEV_1, and DLCO. A total of 42 observations were analysed using all these variables. The VIF was used to assess all independent variables, and it was found to be equal to 1.43, indicating that there wasn't any multicollinearity. All other regression assumptions were tested and adhered to. The variables that showed no statistical significance (p>0.05) were removed in the following order: FEV_1 (L), %FEV_1, and DLCO. The model statistically significantly predicted six months global health F (1, 42) = 7.72, p = 0.008, and R^2 = 0.15. The only factor that remained in the model was preoperative FEV_1 (L), implying that this factor significantly predicted postoperative global health (Table 5.28). However, %LAA-950 % FEV_1 and DLCO are not significantly associated with postoperative global health.

Table 5.28 Multivariate linear Regression analysis for six months global health (Model 2)

Parameter	coefficient	P value	95 % CI
%LAA-950 whole lung	-0.8	0.2	-2.1 - 0.5
FEV_1 (L)	14.29	**	3.9 - 24.6
$\%FEV_1$	0.14	0.3	-0.17 - 0.4
DLCO	0.13	0.4	-0.23 - 0.5

LAA; low attenuation area, FEV_1; Forced expiratory volume in 1 second, DLCO; diffusing capacity for carbon monoxide, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The third model (Table 5.29) involved %LAA-950 adjusted for smoking quit time, ASA score, ECOG performance and preoperative global health. Based on all these variables, a total of 40 observations were analysed. The independent numerical variables were assessed using VIF, equal to 3.12, indicating no multicollinearity. Assumptions for the regression analysis were tested and adhered to. The model statistically significantly predicted six months global health $F(2, 37) = 10.45$, $p < 0.001$, and $R^2 = 0.36$.

The analysis revealed that ECOG performance, ASA score, and smoking quit time were not statistically significantly associated with postoperative global health. The only two factors that remained statistically significantly associated with postoperative global health were %LAA-950 whole lung and baseline global health. There is a negative association between %LAA-950 and postoperative global health (coefficient; -1.21, $p = 0.03$), whereas there is a positive association between baseline global health and postoperative global health.

Table 5.29 Multivariate linear Regression analysis for six months global health (Model 3)

Parameter	coefficient	P value	95 % CI
%LAA-950 whole lung	-1.21	*	-2.7 - -0.3
Baseline global health	0.39	**	0.11 - 0.68
ASA score	-5.5	0.3	-16.8 - 5.7
ECOG	-8.6	0.1	-21.1 - 3.8

%LAA; percentage of low attenuation area, ASA score; American Society of Anaesthesiologists' classification of physical health, ECOG; Eastern Cooperative Oncology Group performance status, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The next set of regression models assessed the predictive role of %LAA-910 whole lung adjusted for different factors for each model.

The first regression model included %LAA-910 adjusted for %ppoFEV$_1$, %ppoDLCO, and surgical resection (Table 5.30).

A total of 42 observations were included in the modelling process. There was no multicollinearity between the variables (VIF = 1.33). All other assumptions were adhered to. The model statistically significantly predicted six months global health F (4, 36) = 5.5, p = 0.001, and R2= 0.37.

In the model, two factors were removed as they were insignificant: %LAA-910 and %ppoFEV$_1$ (p >0.05). Notably, %LAA-910 is not associated with postoperative global health. Conversely, bilobectomy negatively affects postoperative global health (coefficient; -45.87, p = 0.02). An individual undergoing bilobectomy is likely to have a postoperative global health score lower than an individual undergoing lobectomy by 45.87 units. Moreover, PpoDLCO is positively associated with postoperative global health (p = 0.01)

Table 5.30 Multivariate linear Regression analysis for six months global health (Model 1)

Parameter	coefficient	P value	95 % CI
%LAA-910	-0.17	0.4	-0.5 - 0.2
ppoFEV_1	0.16	0.3	-0.1 - 0.4
PpoDLCO	0.44	*	0.09 - 0.7
Bilobectomy	-45.87	*	-86.5 - -5.1
Ref: lobectomy			

%LAA; percentage of low attenuation area, Forced expiratory volume in 1 second, DLCO; diffusing capacity for carbon monoxide, ppo; predicted postoperative, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The second model incorporated %LAA-910 adjusted for; FEV_1 (L), % FEV_1, and DLCO. A total of 44 observations were analysed using all these variables. The VIF was used to assess all independent variables and was found to be equal to 1.41, revealing no multicollinearity between the variables. All other regression assumptions were tested and adhered to.

The model statistically significantly predicted six months global health F (1, 42) = 7.72, p = 0.008, and R^2= 0.15. The variables that showed no statistical significance (p>0.05) were removed in the following order: %LAA-910, %DLCO, and %FEV_1. The only factor that remained significantly associated with postoperative global health is FEV_1 (L) (coefficient; 14.2, p = 0.008). For each unit increase in baseline FEV_1, postoperative global health is expected to increase by 14.2 scores (Table 5.31).

Table 5.31 Multivariate linear Regression analysis for six months global health (Model 2)

Parameter	coefficient	P value	95 % CI
%LAA-910	-0.11	0.6	-0.5 - 0.3
FEV_1 (L)	14.2	**	3.9 - 24.6
$\%FEV_1$	0.16	0.3	-0.16 - 0.4
DLCO	0.13	0.4	-0.2 - 0.5

LAA; low attenuation area, FEV_1; Forced expiratory volume in 1 second, DLCO; diffusing capacity for carbon monoxide, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

The last model included %LAA-910 adjusted for smoking quit time, ECOG performance, ASA score and baseline global health. There were 40 observations in the modelling process. There was no multicollinearity between the variables (VIF = 3.12), and all other assumptions were tested and adhered to. The statistical regression analysis revealed that %LAA-910 was not a significant predictor of postoperative global health. Moreover, smoking quit time, ECOG performance, and ASA score were not significantly associated with postoperative global health. The only factor that remained significantly positively associated with postoperative global health was baseline global health (coefficient = 0.52, $p < 0.001$), $F(1, 38) = 14.66$, $R^2 = 0.27$, and $p < 0.001$ (Table 5.32).

Table 5.32 Multivariate linear Regression analysis for six months global health (Model 3)

Parameter	coefficient	P value	95 % CI
%LAA-910	-0.3	0.07	-0.7 - 0.03
Never smoking	3.6	0.8	-28.9 - 36.3
Ref: current smoking			
ASA score	-8.5	0.1	-19.7 - 2.5
ECOG	-3.8	0.5	-17.6 - 9.8
Baseline global health	0.52	***	0.24 - 0.79

Ref; reference, %LAA; percentage of low attenuation area, ASA score; American Society of Anaesthesiologists' classification of physical health, ECOG; Eastern Cooperative Oncology Group performance status, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

5.3.9 Intra-observer validation

To investigate the intra-observer reproducibility in emphysema quantification, intra-class correlation coefficient and Bland Altman plots were performed to compare the measurements. A total of 30 observations were tested for reproducibility of %LAA-950 and %LAA-910 of the whole lung and each lobe.

Based on the results below, the two measurements of %LAA-950 of the whole lung and each lobe are in excellent agreement with an ICC of 1 (Table 5.33). The mean difference of %LAA-950 for the whole lung was 0.05, and the upper LOA was 0.4, whereas the lower LOA was -0.3, which are considered relatively narrow and lower than 5, with few points lying outside LOA (Figure 5.5).

Table 5.33 Intra-class correlation coefficient for intra-observer reproducibility when measuring %LAA-950 (95% CI)

	ICC	Lower bond	Upper bond
Whole lung	1.0	1.0	1.0
Right lung	1.0	1.0	1.0
Left lung	1.0	1.0	1.0
Right upper lobe	1.0	1.0	1.0
Right middle lobe	1.0	0.99	1.0
Right lower lobe	1.0	1.0	1.0
Left upper lobe	1.0	1.0	1.0
Left lower lobe	1.0	1.0	1.0

ICC; Intra-class correlation coefficient, P <0.05

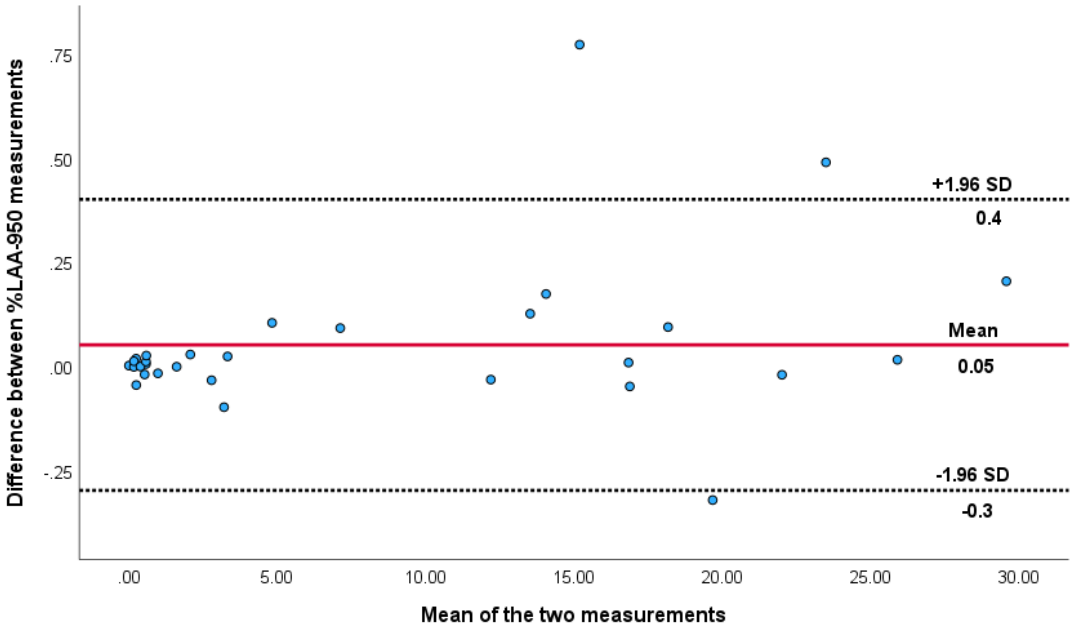

Figure 5.5 Intra-observer agreement when measuring %LAA-950

Similarly, the agreement between the two measurements was excellent when measuring %LAA-910, with the ICC ranging between 1 and 0.99 for the whole lung and each lobe (Table 5.34). In addition, the Bland Altman plots show a small mean difference between the two measurements (0.01) and relatively narrow LOAs (-0.7 and 0.7), with only two points lying outside LOAs (Figure 5.6).

Table 5.34 Intra-class correlation coefficient for intra-observer reproducibility when measuring %LAA-910 (95% CI)

	ICC	Lower bond	Upper bond
Whole lung	1.0	1.0	1.0
Right lung	1.0	1.0	1.0
Left lung	1.0	1.0	1.0
Right upper lobe	1.0	1.0	1.0
Right middle lobe	0.99	0.997	0.999
Right lower lobe	1.0	1.0	1.0
Left upper lobe	1.0	1.0	1.0
Left lower lobe	1.0	1.0	1.0

ICC; Intra-class correlation coefficient, P <0.05

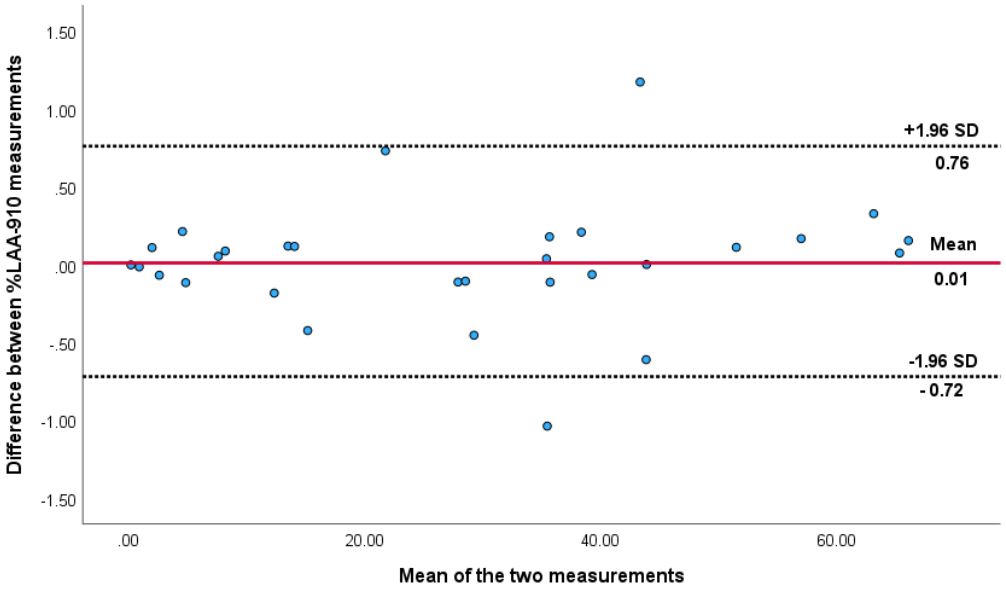

Figure 5.6 Intra-observer agreement when measuring %LAA-910

5.3.10 Comparison between contrast-enhanced CT and unenhanced CT data output

In order to compare contrast-enhanced and unenhanced CT scans in emphysema quantification, Wilcoxon signed-rank test was used to compare the two measures. A total of 27 observations were tested for the difference in %LAA-950 and -910 measures. As can be seen, there is a statistically significant difference between the two measures in %LAA-910 and %LAA-950. The median value of %LAA-950 for unenhanced CT scans was 11.1 while 1.0 for enhanced CT scans. Median values for %LAA-910 for unenhanced and enhanced CT scans were 27.3.8 vs 9.5, respectively (Table 5.35).

Table 5.35 Comparison between contrast-enhanced and unenhanced CT scans emphysema quantification.

	Unenhanced		Enhanced		
QCT measure	Median	IQR	Median	IQR	P-value
%LAA -950	11.1	14.1	1.0	2.12	***
%LAA-910	27.3	30.5	9.5	16	*

Wilcoxon signed-rank test, IQR; Inter Quartile Range, QCT; quantitative computed tomography, LAA; low attenuation area, *p<0.05; **p<0.01; ***p<0.001

Below, Figures 5.7- 5.8 represent Bland Altman plots demonstrating agreement between contrast-enhanced and unenhanced %LAA-950 and %LAA-910. The mean difference between the measures was 11.5% for %LAA-950 and 14.1% for %LAA-910. The LOAs were wider than clinically acceptable limits for both measures, with some points lying outside the LOA. Cut-off values for emphysema severity are ≥ 5% for %LAA-950 and ≥ 35% for %LAA-910, and in this study, the mean and LOA are wider than these thresholds for %LAA-950 (33.6 for upper LOA and -10.5 for lower LOA). The upper LOA is above the acceptable threshold (36.3 for upper LOA) for %LAA-910 [277].

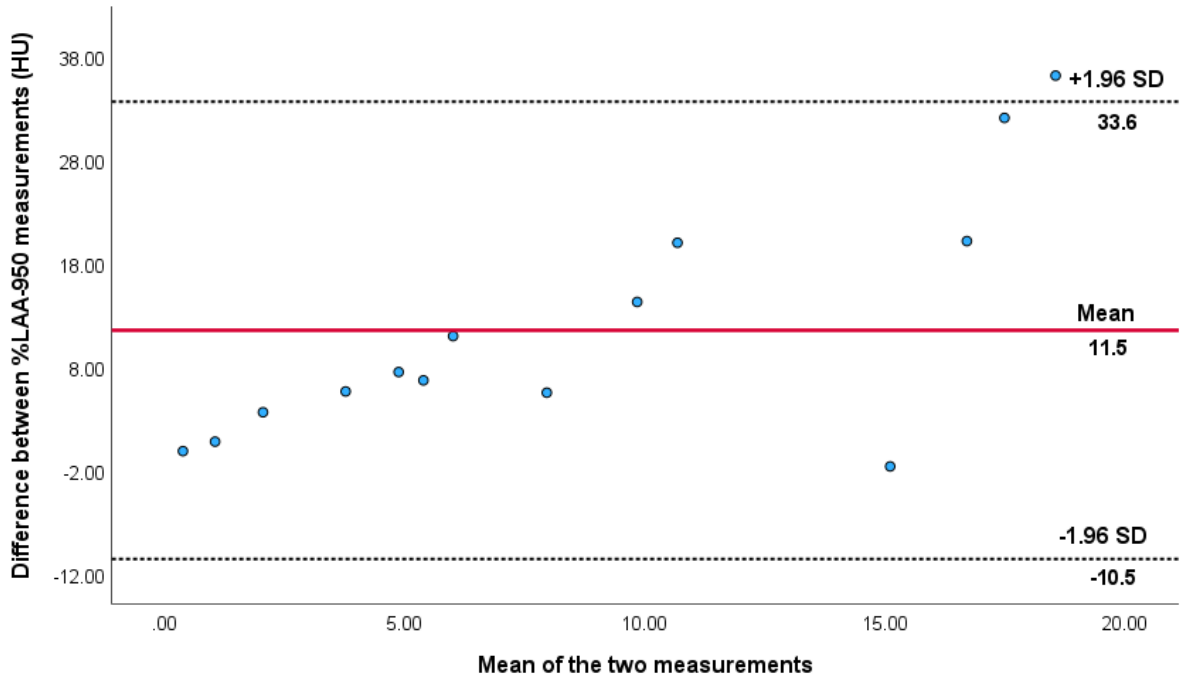

Figure 5.7 Agreement between contrast-enhanced and unenhanced CT scans for %LAA-950

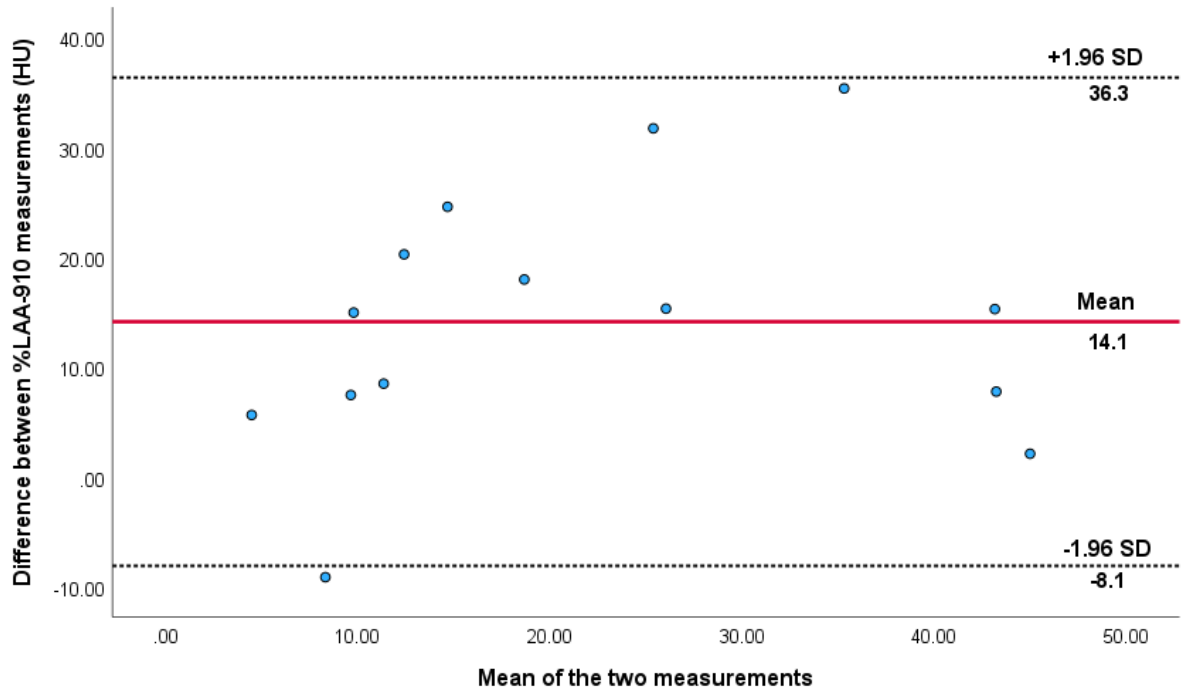

Figure 5.8 Agreement between contrast-enhanced and unenhanced CT scans for %LAA-910

5.4 Discussion

The primary objective of this study was to investigate the predictive value of CT density measurements in predicting postoperative dyspnoea and global health. Due to the retrospective nature of this study and the fact that almost all baseline CT scans were contrast-enhanced as part of routine clinical investigations for lung cancer patients, this study assessed two sets of CT scans, contrast-enhanced and unenhanced CT, knowing that the latter ones were limited. Undoubtedly, CT scan is considered the most sensitive tool for emphysema detection [323].

To our knowledge, this is the first study that assessed the predictive value of QCT measures of emphysema and postoperative dyspnoea and global health using EORTC QLQ-C30. In addition, no study evaluated the role of QCT of emphysema in predicting the changes in postoperative dyspnoea after lung cancer surgery. Available information is limited to the relationship between QCT of emphysema and COPD symptoms using other instruments such as MRC or BODE index [206, 212, 213]. Previous research has also evaluated the relationship between QCT of emphysema and QoL using other QoL instruments on only COPD patients [215, 216] or lung cancer patients without considering the changes in QoL following the intervention [217]. Understanding the relationship between QCT of emphysema and patients' HRQOL and dyspnoea is still underestimated.

This study showed that QCT of emphysema using unenhanced CT scans is a valuable predictor of postoperative quality of life and dyspnoea after lung cancer surgery. The finding is consistent with other research, which found a strong association between QCT of emphysema and dyspnoea [203, 205, 208] and QCT of emphysema and QoL [201, 215]. In contrast, one study employed the LCSS instrument and reported no difference in overall QoL between mild, moderate, and severe QCT of emphysema in lung cancer surgery patients [217]. However, the study has not measured preoperative QoL scores to provide a clear idea regarding the change of that measure.

The present findings indicated that %LAA-950 could predict postoperative dyspnoea and global health even after adjusting for baseline clinical and perioperative factors. Those patients with a higher %LAA-950 are expected to suffer from higher levels of dyspnoea and deterioration in their global health, indicating worsening overall quality of life. This finding is in agreement with previous studies that reported a significant association between %LAA-950 and dyspnoea [211, 213]. However, these studies have been restricted to the use of %LAA-950 and have not measure the other metrics. While studies found a significant association between %LAA-950 and global health [202, 215]. However, all these studies have only assessed patients with COPD and did not assess lung cancer patients after surgery. In addition, previous studies have only investigated %LAA-950 and have not been able to determine the association between QCT emphysema measures and QoL after an intervention. The present study has demonstrated the association between preoperative QCT of emphysema measurements and postoperative QoL after surgery in lung cancer patients. Unlike previous studies, this study employed EORTC QLQ-C30 to assess patients' dyspnoea and global health over six months.

Conversely, the present study showed that %LAA-910 was not consistently a predictor for postoperative dyspnoea after adjusting for clinical and perioperative factors. This is in accordance with the results of the NETT trial, which investigated 1053 COPD patients and found that %LAA-910 was not associated with dyspnoea [204]. Furthermore, this result is supported by Grydeland et al., who confirmed that %LAA-910 has a weaker relationship with dyspnoea compared to %LAA-950 in 463 patients with COPD [203]. In addition, the present study found that %LAA-910 was not a predictor for postoperative global health (overall QoL). This was noted in previous literature; the NETT trial assessed predictors for overall quality of life in COPD subjects and found that %LAA-910 was not significantly associated with quality of life as measured by the Quality of Well Being scale (QWB) [204]. However, they noted a

statistically significant association between the two when they measured QoL using the SGRQ total score [204].

According to Madani et al., %LAA-910 was not correlated with macroscopic measurement of emphysema [193], while other studies noted that %LAA-950 was significantly correlated with microscopic emphysema [194]. Therefore, our results identified that QCT of emphysema can predict postoperative dyspnoea and global health. Additionally, the results highlighted that %LAA-950 is a better predictor of dyspnoea and QoL compared to %LAA-910.

Although our results showed that contrast-enhanced CT of emphysema was not a predictor of postoperative quality of life, this was not entirely surprising. As contrast-enhanced CT is part of lung cancer patients' investigation, gaining a deeper understanding of its potential was desirable. It has been reported that contrast agents may alter the density of emphysema to a certain degree [322]. At present, the relationship between baseline QCT of emphysema and postoperative HRQOL in patients with lung cancer has not been explored. The majority of existing research has examined the association between baseline QCT of emphysema and postoperative dyspnoea in patients with COPD, who undergo unenhanced CT scans as part of their standard clinical evaluations [212, 213]. The present study utilised a variety of emphysema thresholds to account for the increased density associated with contrast administration [321]. However, none of these measures were significantly associated with postoperative dyspnoea or global health.

Moreover, this study showed that unenhanced CT scans are more effective than contrast-enhanced CT scans in quantifying emphysema and predicting postoperative dyspnoea and global health outcomes. This finding supports what was reported in previous studies, that contrast-enhanced CT was not comparable to unenhanced scans in the measurements of emphysema [322]. One study measured %LAA-950 on contrast CT scans and argued that the

results would not differ whether contrast agents were used or not, as emphysematous parenchyma is not prone to accumulating contrast agents [324]. Yet, their argument was contradicted by an earlier explanation by Heussel et al., who provided a comprehensive justification in this respect. The authors explained that quantification of emphysema can recognise small emphysematous regions, and after contrast agents' administration, they might be enhanced and not recognised as emphysema [322]. This could be one of the reasons that QCT of emphysema on contrast-enhanced CT was not predictive of postoperative dyspnoea and global health. Emphysema quantification may be affected by disease progression as well; however, studies have shown differences between contrast-enhanced and unenhanced CT scans acquired simultaneously for the same patients using similar settings [322]. The determination of a correction factor would be highly beneficial, and as far as we are aware, this has not been addressed in the literature. However, when determining the correction factor, it is essential to take into account factors such as contrast agents' administration, disease progression, smoking, patients' inspiration, scanner manufacturer and settings, as well as the software kernel [321]. Due to the retrospective nature of this study, addressing this question would not be achievable. There may be several possible reasons for not addressing this question until now, one of which is that double CT scans are associated with higher radiation doses and unnecessary administration of contrast agents to the patients.

In order to assess the difference between contrast-enhanced and unenhanced CT scans, we compared those scans acquired for the same patients. We found a statistically significant difference between enhanced and unenhanced scans in %LAA-950 and %LAA-910. This was consistent with the previous literature that confirmed the difference exists between the contrast-enhanced and unenhanced CT quantification of emphysema [321, 322]. Also, Bland Altman plots for the differences between contrast-enhanced and unenhanced CT scans for %LAA-950 and %LAA-910 show disagreement and wider LOA between the two sets. As expected, the

values measured on contrast CT scans are not comparable to non-enhanced CT scans, as the present finding revealed that quantification of emphysema on contrast CT scans showed normal density in emphysematous parenchyma due to the fact that contrast agents tend to increase voxels' density [198]. Using unenhanced CT quantification of %LAA-950 is valuable in predicting postoperative quality of life and dyspnoea for lung cancer surgery.

Finally, patients with 1% LAA-950 are 20% more likely to experience highest level of dyspnoea compared to those with 0% LAA-950. This finding shed light on the importance of understanding the extent of emphysema when planning a lung cancer intervention and informing patients about their postoperative recovery trajectory, including the likelihood of dyspnoea.

5.5 Limitations and Future Research

In this study, have demonstrate that %LAA-950 stands out as a non-invasive biomarker, offering valuable insights into postoperative dyspnoea in patients with lung cancer. There are several limitations in the present study due to its retrospective nature, such as the selection bias of contrast-enhanced and unenhanced CT scans for this cohort, which is unavoidable. The second limitation is the small sample size of the study. Additionally, the variety of manufacturer CT scanners, acquisition protocol, and reconstruction kernels, which could affect the density quantification. Yet, all reconstruction kernels were smooth, KVp and slice thickness were similar, and as the study is a single-centre study, only two scanners were utilised for all scans.

Moreover, it was not possible to confirm whether there was CT scanner calibration for air water using phantoms. All these factors may influence the measured lung density [190]. In addition, CIP software showed some failure in analysing some CT scans, leading to the exclusion of some data that could be valuable. Also, we could not perform an inter-observer agreement study

due to unavailability of the second observer. Nonetheless, we conducted an agreement study between these analyses with AI-based software analyses. Another limitation of the current study was related to the analysis of the association between emphysema heterogeneity and dyspnoea recovery. Our ability to elucidate this relationship was constrained by the small sample size of only two participants with heterogeneous emphysema and confirmed COPD.

However, the study contributes to developing an emerging field of clinical research that is becoming increasingly important. Emphysema quantification on contrast CT scans has higher lung density than on unenhanced scans; thus, future study on defining corrective factors for the difference in lung density is warranted. Implementing these measures on contrast CT scans without exposing patients to additional radiation would be beneficial. In addition, since PET CT scans are acquired as part of routine clinical investigations for these patients, investigating the predictive value of QCT scans of emphysema from these CT scans would be desirable. With the introduction of low-dose CT scans for lung cancer screening, it would be worthwhile to study QCT of emphysema on these scans in the future. Lastly, there is a need to perform the same analysis on a larger sample of patients to confirm our results.

Chapter 6. An Exploratory Study: Investigating the Impact of CT-Measured Sarcopenia on the Quality of Life after Lung Cancer Surgery

6.1 Introduction

Current studies indicate that both cancer and its treatment contribute to exacerbating muscle loss, with patients experiencing a continuous reduction in muscle mass during their treatment [87]. Aside from muscle loss occurring as a natural part of ageing, this syndrome can also be associated with other diseases, such as cancer [325]. Research reported that sarcopenia is associated with impaired physical functioning, poor health outcomes [326], and low survival in several populations [253, 327].

Recently, CT-based assessments of sarcopenia and body composition have attracted considerable attention since CT density enables accurate differentiation of fat tissues from muscles and other soft tissues and is routinely performed in cancer patients for diagnostic purposes [282]. Sarcopenia associated with adverse outcomes has traditionally been observed at the level of the third lumbar vertebra (L3) in patients with other solid organ cancers [232, 243, 328]. Additionally, the skeletal landmark of L3 is commonly used to quantify skeletal muscle mass and is considered a surrogate marker for measuring skeletal muscle mass of the whole body [241]. Nevertheless, this vertebral level may not be included in CT scans acquired from patients with thoracic malignancies. Therefore, it is desirable to assess the impact of sarcopenia measured on multiple vertebral levels, i.e., the level of the fourth, and twelfth thoracic vertebra as well as the third lumbar vertebra and assessing different muscles. As far as we are aware, there have been limited studies examining the impact of sarcopenia on

postoperative quality of life, dyspnoea, and global health after lung cancer surgery. Previous investigations have examined the impact of sarcopenia on QoL assessed different cohorts [225, 258, 329-331] or evaluated sarcopenia and quality of life in lung cancer patients treated with chemotherapy [85, 247] or chemoradiotherapy [63]. There is a lack of studies assessing the impact of sarcopenia on patients' QoL after lung cancer surgery using EORTC QLQ-C13 or LC13. This indicates the need for a better understanding of how sarcopenia impacts QoL following lung cancer surgery. This study aimed to assess the impact of CT-based sarcopenia of skeletal, pectoralis, erector spinae, and psoas muscles on QoL following lung cancer resection.

6.2 Methods

6.2.1 CT scan

This is a retrospective study, and all CT scans employed in this study are contrast-enhanced CT scans acquired in patients' routine clinical investigations and similar CT scan settings used in Section 5.2.1. There is no doubt that the administration of contrast agents has considerable effects on the measurements of the density of these muscles [332]. Yet, several studies have demonstrated that contrast agents have a negligible impact on measuring muscles' indices [332, 333]. Therefore, a sub-analysis was conducted to compare contrast-enhanced and unenhanced CT scans of body composition and Bland Altman plots were conducted to demonstrate their agreement. Consequently, this study employed muscle indices only and contrast-enhanced CT scans were analysed. Details of the study's methodology are explained in Section 3.3.

6.2.2 CT scan analysis software

This study implemented semi-automated segmentation of the muscles using open-source 3D slicer software (CIP platform, body composition extension) [334]. With this software, a segmentation process can be carried out easily, and macro-based solutions for post-processing images are provided [335]. Extensive research studies have used 3D slicers to analyse CT-based body compositions [335-338]. An area and indices of the skeletal, pectoralis, erector spinae, and psoas muscles were measured in this study. Section 3.3 provides a detailed description of the methods of the analyses, including the CT slice level used for each muscle and the cut-off for sarcopenia.

6.2.3 Statistical analysis

Comparison between the data was performed using an independent t-test or Mann-Whitney U test, whereas comparison between categorical data was performed using the Chi-square test or Fisher's exact test. Correlation between numeric data was completed using Pearson's or Spearman's correlation coefficients where appropriate. A p-value of <0.05 is considered statistically significant. Details of the statistical methods are provided in Section 3.3.5.

All the statistical analyses were performed using Stata 18.0 statistical software (Stata Co., College Station, TX) or SPSS version 29 (IBM Corp.).

6.3 Results

6.3.1 Baseline characteristics

A total of 94 patients were included in this study. The flow chart of the patients' inclusion in this study is summarised and shown in the previous chapter (Figure 5.1, Section 5.3.1). Table 6.1 illustrates the baseline characteristics of 56 male and 38 female lung cancer patients. The

mean age of male and female patients is 69 and 68 years, respectively (P = 0.5). BMI is statistically significantly different in male and female participants in BMI (27.9 vs 25.7, respectively, P = 0.03). All lung function measures are similar between the two groups except for FEV_1, and FVC (P = 0.00). Lastly, there was no statistically significant difference between the two groups in airway obstruction or COPD (P>0.05).

Table 6.1 Baseline characteristics of 94 patients included in the study

Characteristic	Male (n = 56)	Female (n = 38)	P value
Age	69.78 ± 7.0	68.94 ± 6.9	0.5
BMI	27.93 ± 4.3	25.74 ± 5.3	0.03
Pack years	47.66 ± 31.7	34.36 ± 26.6	0.03
FEV_1 (L)	2.33 ± 1.1	1.64 ± 0.7	0.00
% FEV_1	78.5 ± 21.9	78.2 ± 18.4	0.9
FVC (L)	3.93 ± 0.8	2.7 ± 0.7	0.00
% FVC	104.4 ± 20.0	101.6 ± 20.1	0.5
%DLCO	77.6 ± 19.0	76.3 ± 18.8	0.7
ppoFEV_1	64.1 ± 23	66.6 ± 25	0.9
ppoDLCO	63.4 ± 15.6	61.2 ± 13.2	0.4
Airway obstruction (FEV1/FVC <0.7)	21 (37.5)	14 (36.8)	0.9
COPD	15 (26.7)	11 (28.9)	0.8
Age	69.78 ± 7.0	68.94 ± 6.9	0.5

Data are presented as mean (median) and standard deviation (interquartile range) or numbers and percentages for categorical data. BMI; body mass index, FEV_1; forced expiratory volume in 1 second, FVC; forced vital capacity, DLCO; diffusing capacity for carbon monoxide, ppoFEV_1 or ppoDLCO; predicted postoperative FEV_1 or DLCO, COPD; Chronic obstructive pulmonary disease. *p<0.05; **p<0.01; ***p<0.001

6.3.2 Determination of sarcopenia

Since there has been no established cut-off values for PM, ESM, and PSM, the researcher chose sex-specific quartile using the lowest quartile as the cut-off value for sarcopenia. While for SM, the researcher employed a previously established cut-off value which was described in Section 3.3.4. The cut-off values are summarised in Table 6.2.

Table 6.2 Summary of sex-specific sarcopenia cut-off values

Muscle type	Male cut-off value	Female cut-off value
PM	11.7 cm^2/m^2	8.1 cm^2/m^2
ESM	9.8 cm^2/m^2	8.1 cm^2/m^2
PSM	5 cm^2/m^2	3.6 cm^2/m^2

PM; pectoralis muscles, ESM; erector spinae muscles, PSM; psoas muscles.

6.3.3 Muscles' differences

Table 6.3 below represents gender differences in different muscles including skeletal muscle index (SMI), sarcopenia in SMI, pectoralis muscle index (PMI) (cm^2/m^2), sarcopenia in PMI, erector spinae muscle index (ESMI) (cm^2/m^2), sarcopenia in ESMI, psoas muscle index (PSMI) (cm^2/m^2), sarcopenia in PSMI. From the table below, it can be seen that there is a statistically significant difference between male and female participants in SMI, PMI, ESMI and PSMI, with male patients having larger muscles indices compared to female patients (P = 0.00). On the other hand, sarcopenia is statistically significantly different between the two groups in PMI and PSMI only, with female patients having a greater proportion of sarcopenia compared to male patients (P = 0.04 and 0.009, respectively). There is no statistically significant difference in the proportion of sarcopenia between the two groups in SMI and ESMI (Figure 6.1-6.4).

Table 6.3 Muscles differences between male and female

Muscle	Male (n = 56)	Female (n = 38)	Diff.	P value	95% CI
SMI	48.47 ± 7.6	37.06 ± 7.4	11.4	***	8.2 - 14.5
Sarcopenia (SMI)	35 (62.5%)	29 (78.3%)	-	0.1	-
PMI	13.8 ± 3.8	10 ± 2.5	3.7	***	2.3 - 5.1
Sarcopenia (PMI)	14 (24%)	17 (44.7%)	-	*	-
ESMI	12.1 ± 2.6	10.3 ± 2.5	1.7	**	0.6 - 2.8
Sarcopenia (ESMI)	14 (25%)	16 (42.1%)	-	0.08	-
PSMI	6.1 ± 1.3	4.2 ± 1.2	1.8	***	1.2 - 2.3
Sarcopenia (PSMI)	14 (25%)	19 (50%)	-	**	-

Independent t-test or Mann-Whitney U test for comparing continuous data and Chi-squared test for comparing categorical data in male and female participants. Data are presented as mean (median) and standard deviation (interquartile range) or numbers and percentages for categorical data. SMI; Skeletal muscle index, PMI; Pectoralis muscle index, ESMI; Erector spinae muscle index, PSMI; Psoas muscle index, Diff; difference, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

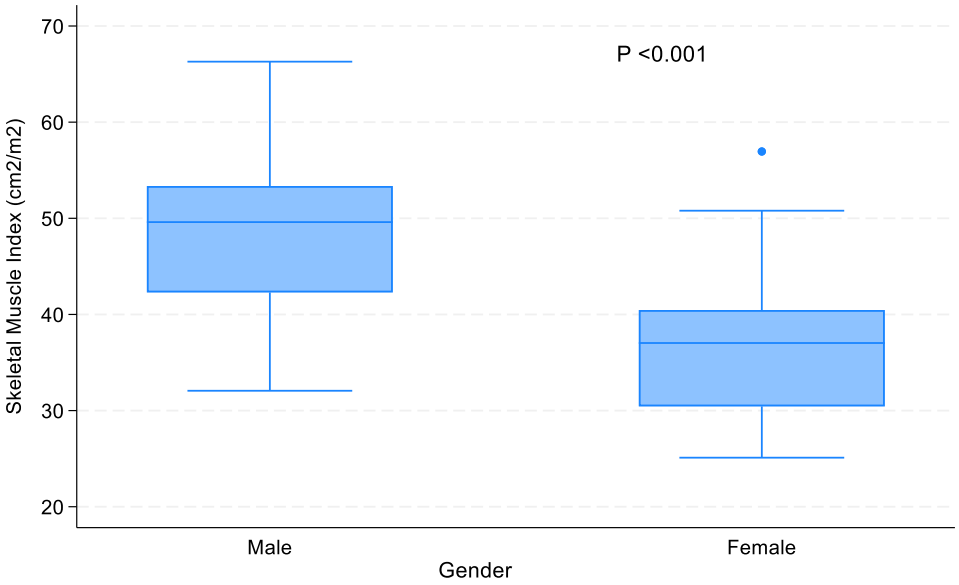

Figure 6.1 Difference between male and female patients in skeletal muscle index

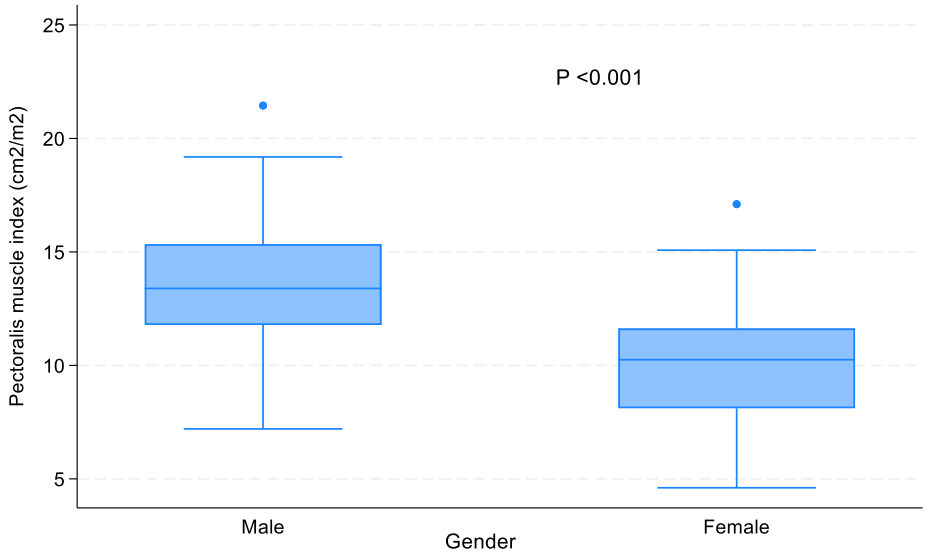

Figure 6.2 Difference between male and female patients in pectoralis muscle index

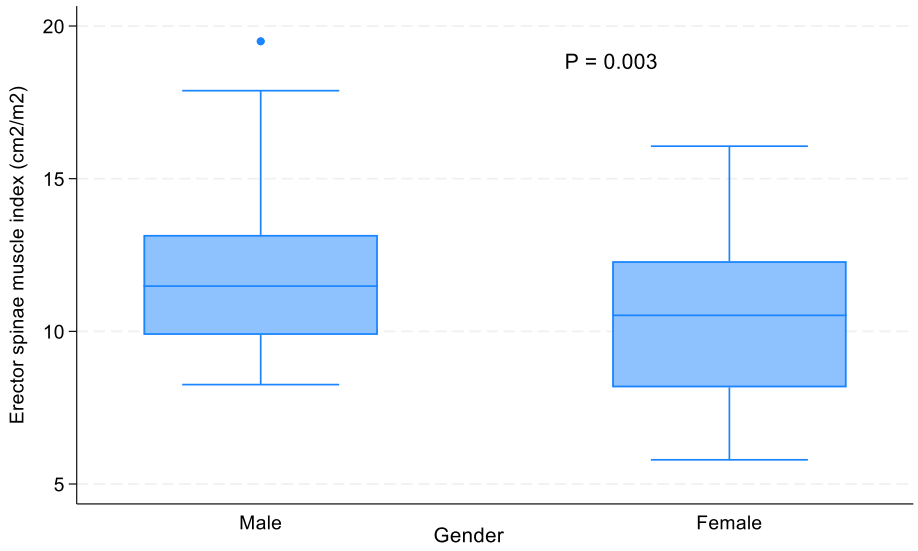

Figure 6.3 Difference between male and female patients in erector spinae muscle index

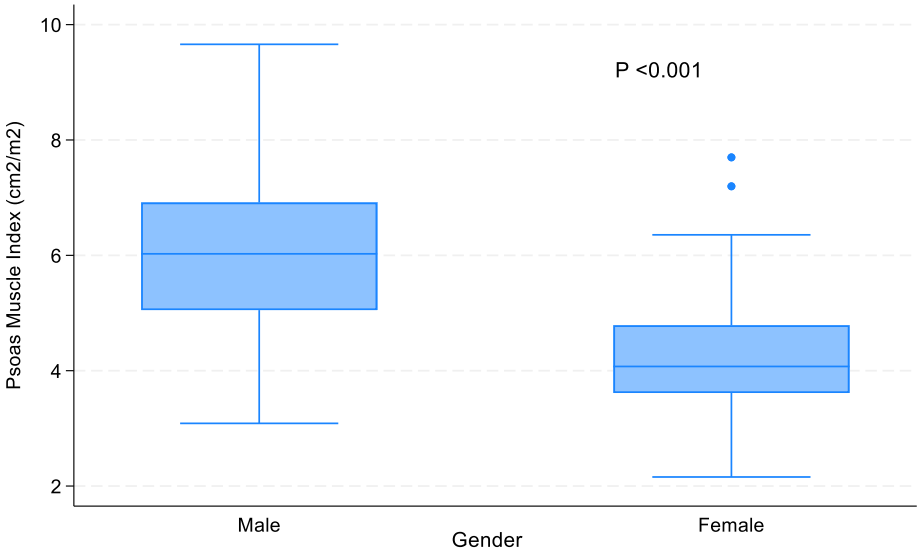

Figure 6.4 Difference between male and female patients in psoas muscle index

Table 6.4 demonstrates differences in muscles indices and sarcopenia proportions between patients with BMI >24.9 and BMI ≤ 24.9. As can be seen, SMI, ESMI, and PSMI are statistically significantly different in the two groups (p = 0.00). In all muscles indices, patients with high BMI have relatively larger muscles indices compared to those with lower BMI.

Moreover, PMI tends to be larger in patients with higher BMI (11.4 vs 12.7), although not statistically significant. Interestingly, the proportion of sarcopenia between the two groups is not different when comparing sarcopenia of SMI or PMI. Yet, the proportion of sarcopenia is higher in patients with lower BMI. While there is a statistically significant difference between the two groups in the frequency of sarcopenia of ESMI and PSMI, with higher percentage of sarcopenia in those with relatively lower BMI (p = 0.00, for both factors) (Figure 6.5-6.8).

Table 6.4 Muscles differences between BMI groups

Muscle	BMI ≤ 24.9 (n = 34)	BMI >24.9 (n = 60)	Diff.	P value	95% CI
SMI	38.23 ± 8.4	47.06 ± 8.4	-8.8	***	-12.4 - -5.1
Sarcopenia (SMI)	24 (70.5%)	40 (66.6%)	-	0.5	-
PMI	11.46 ± 2.9	12.7 ± 4.2	-1.3	0.1	-2.9 - 0.2
Sarcopenia (PMI)	12 (35.2%)	19 (31.6%)	-	0.7	-
ESMI	9.8 ± 1.8	12.2 ± 2.7	-2.4	***	-3.5 - -1.3
Sarcopenia (ESMI)	17 (50%)	13 (21%)	-	**	-
PSMI	4.5 ± 1.2	5.8 ± 1.5	-1.3	***	-1.9 - -0.7
Sarcopenia (PSMI)	18 (52.9%)	15 (25%)	-	**	-

Independent t-test or Mann-Whitney U test for comparing continuous data and Chi-squared test for comparing categorical data in male and female participants. Data are presented as mean (median) and standard deviation (interquartile range) or numbers and percentages for categorical data. BMI; body mass index, SMI; Skeletal muscle index, PMI; Pectoralis muscle index, ESMI; Erector spinae muscle index, PSMI; Psoas muscle index, Diff; difference, CI; confidence interval.*p<0.05; **p<0.01; ***p<0.001

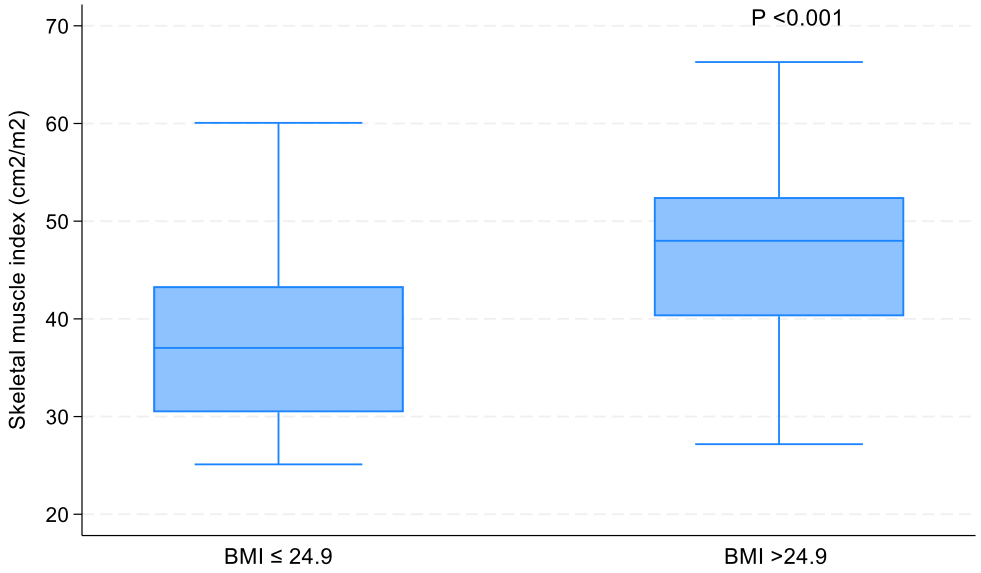

Figure 6.5 Difference between high BMI and normal BMI patients in skeletal muscle index

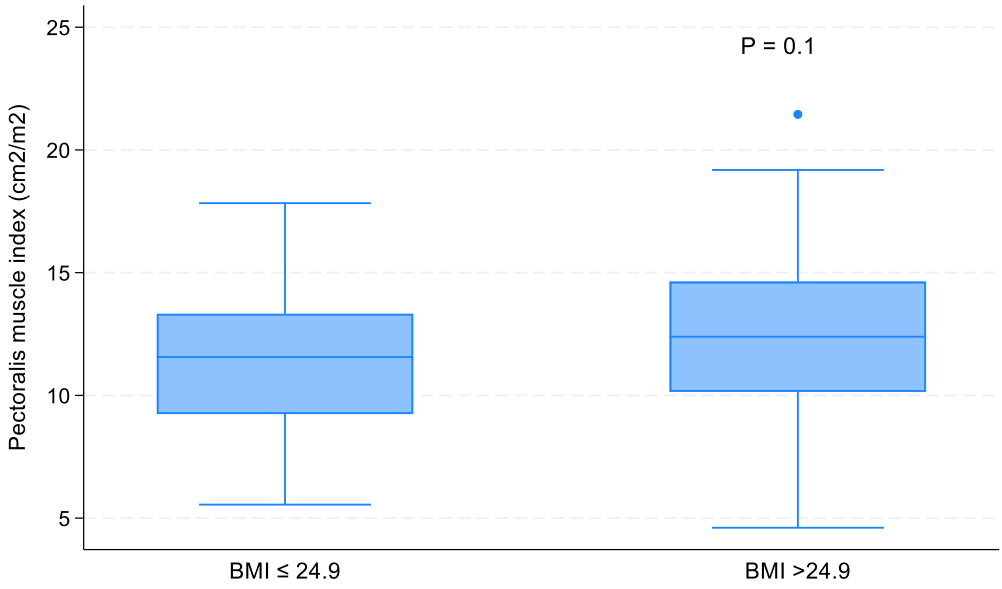

Figure 6.6 Difference between high BMI and normal BMI patients in pectoralis muscle index

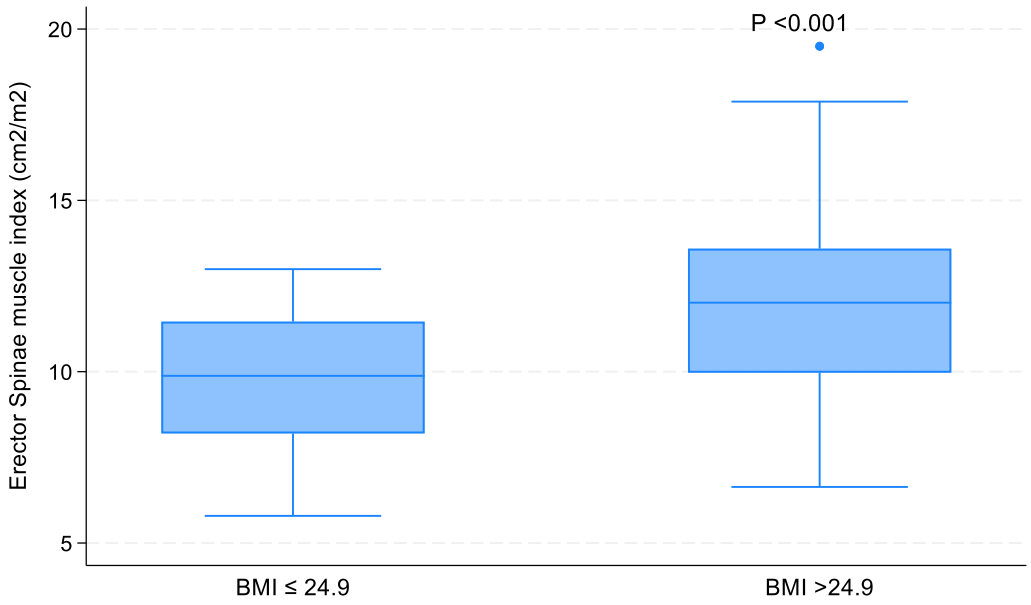

Figure 6.7 Difference between high BMI and normal BMI patients in erector spinae muscle index

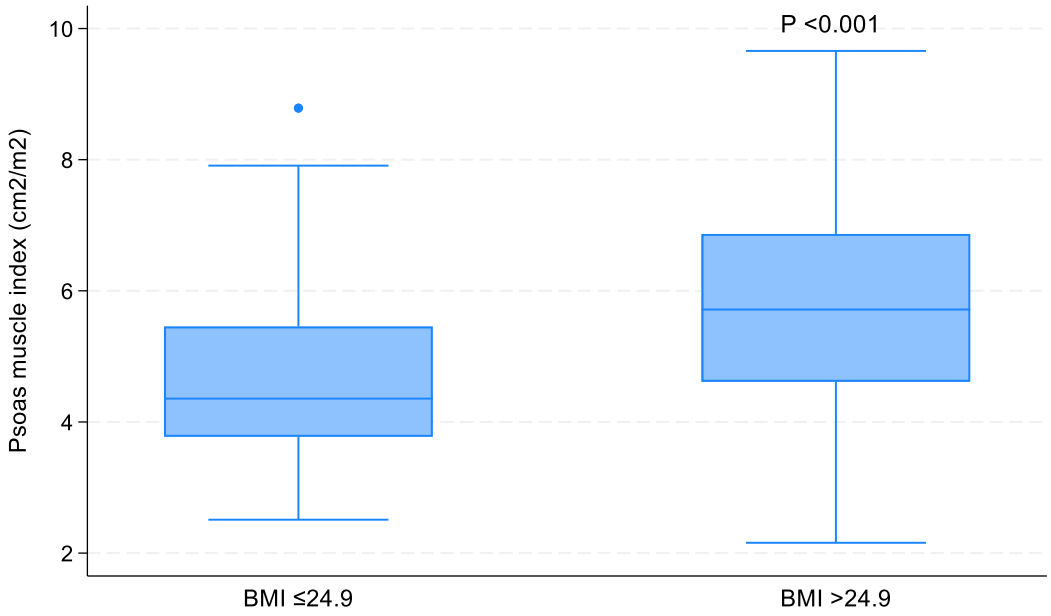

Figure 6.8 Difference between high BMI and normal BMI patients in psoas muscle index

6.3.4 Relationship between skeletal muscle index and pectoralis, erector spinae, and psoas muscles' indices

The below results (Table 6.5) summarise the correlation between SMI and PMI, ESMI, and PSMI. All muscle indices show a statistically significant correlation with SMI. PSMI has a strong positive correlation with SMI (r = 0.77, p = 0.00), while ESMI and PMI have moderate positive correlation (r = 0.65 and 0.62, respectively, p = 0.00) (Figure 6.9- 6.11).

Table 6.5 correlation between SMI with PMI, ESMI or PSMI

Muscle	r	P value
PMI	0.62	***
ESMI	0.65	***
PSMI	0.77	***

Pearson correlation, SMI; Skeletal muscle index, PMI; Pectoralis muscle index, ESMI; Erector spinae muscle index, PSMI; Psoas muscle index. *p<0.05; **p<0.01; ***p<0.001

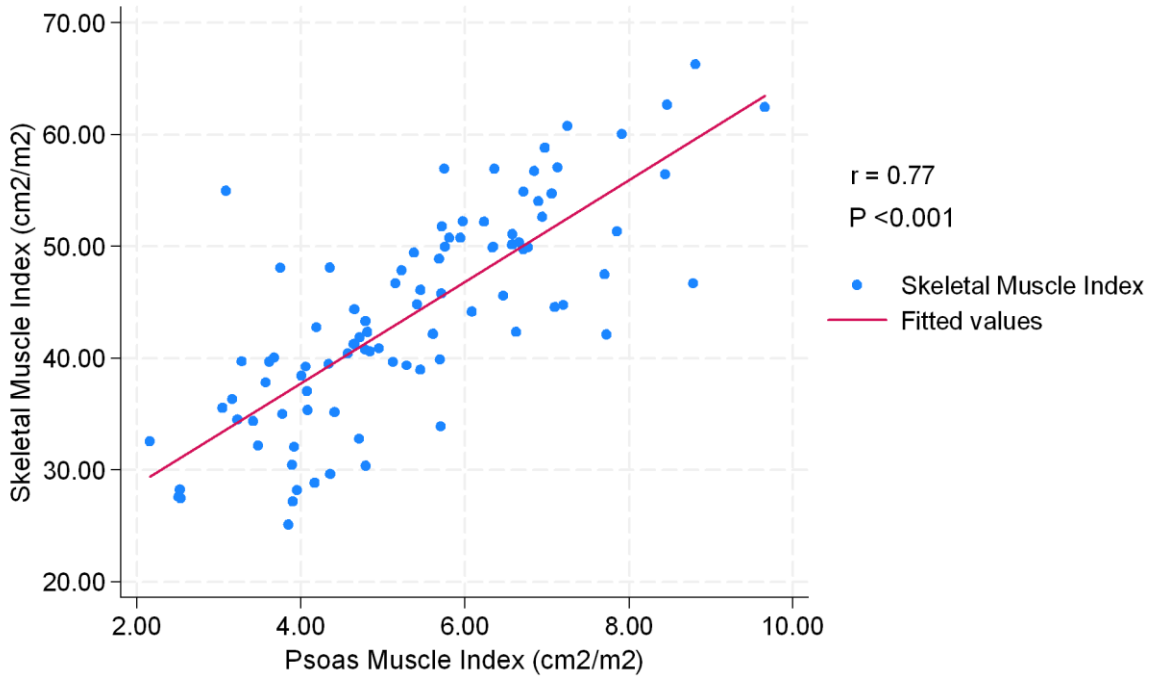

Figure 6.9 Correlation between PSMI and SMI

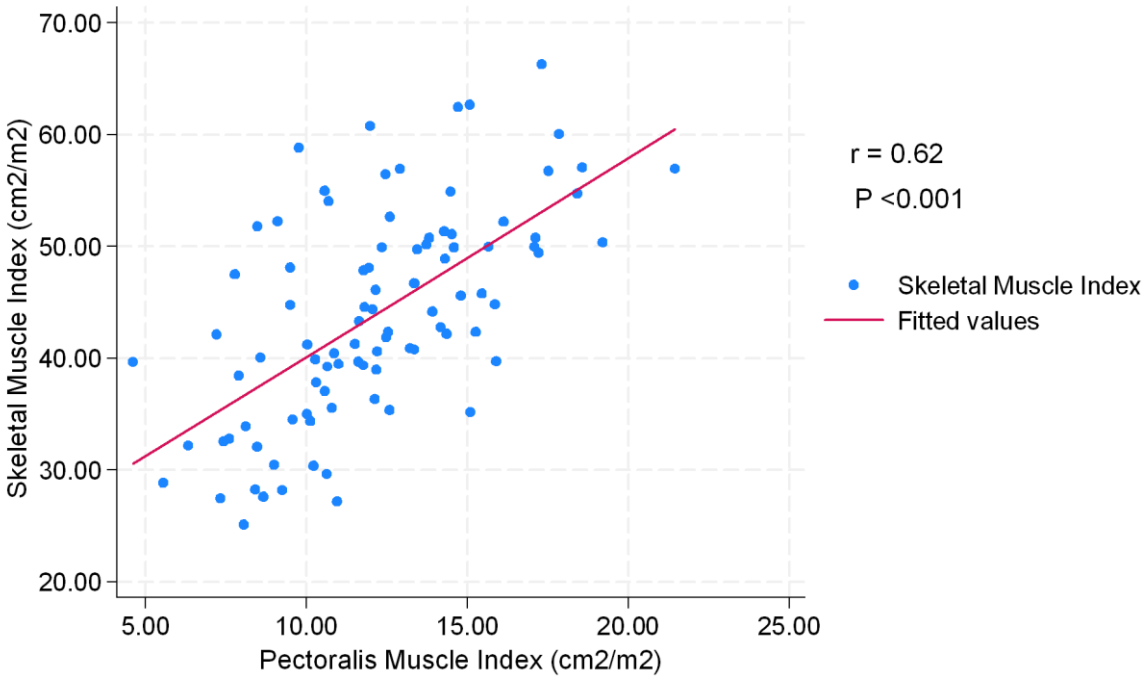

Figure 6.10 Correlation between PMI and SMI

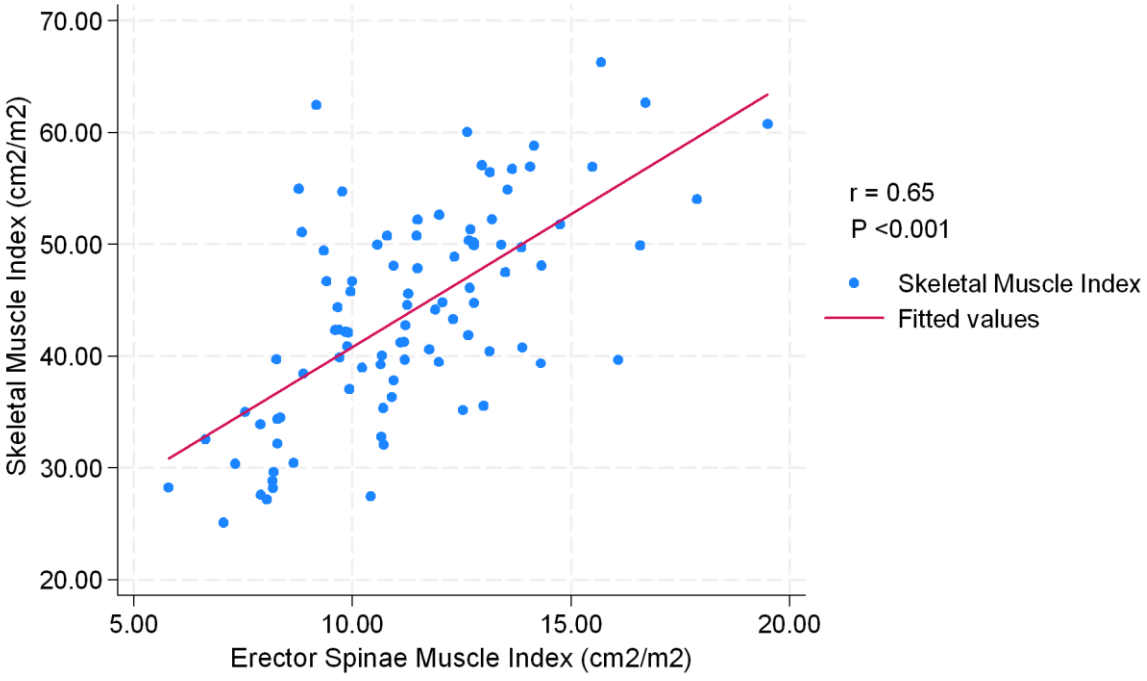

Figure 6.11 Correlation between PMI and SMI

6.3.5 Correlation between CT body composition and lung function

Table 6.6 below demonstrates the correlation between CT body composition involving SMI, PMI, ESMI, and PSMI with lung function. Preoperative FVC (L) has a significant correlation with all muscles' indices ($p<0.001$), knowing that all muscles' indices have a positive moderate correlation with FVC, except ESMI has a weak correlation with preoperative FVC ($r = 0.34$).

Moreover, Preoperative FEV_1 (L) is statistically significantly correlated with all muscles' indices ($p <0.05$). However, all correlations with preoperative FEV_1 are weak for all muscles. In addition, the SMI is the only muscle index that exhibits a significant but weak correlation with %DLCO ($r = 0.22$, $p = 0.03$), while PMI only has a statistically significant but weak correlation with preoperative %FVC ($r = 0.2$, $p = 0.03$) (Figure 6.12-6.13).

Table 6.6 correlation between body composition and lung function

Lung function	SMI		PMI		ESMI		PSMI	
	r	P value	r	P value	r	P value	r	P value
%Preoperative FEV_1	0.04	0.6	0.05	0.6	0.1	0.2	0.03	0.7
Preoperative FEV_1 (L)	0.35	***	0.34	***	0.24	*	0.32	**
%Preoperative FVC	0.1	0.3	0.2	*	0.1	0.1	0.1	0.1
Preoperative FVC (L)	0.47	***	0.5	***	0.34	***	0.41	***
DLCO	0.22	*	0.1	0.1	0.1	0.08	0.1	0.1
ppoFEV_1	0.05	0.5	0.3	0.1	0.08	0.4	0.03	0.7
ppoDLCO	0.2	0.05	0.1	0.1	0.1	0.1	0.1	0.2
FEV_1/FVC	0.1	0.2	0.04	0.6	0.04	0.6	0.07	0.4

Pearson or Spearman correlation, SMI; Skeletal muscle index, PMI; Pectoralis muscle index, ESMI; Erector spinae muscle index, PSMI; Psoas muscle index. FEV_1; forced expiratory volume in 1 second, FVC; forced vital capacity, DLCO; diffusing capacity for carbon monoxide, ppoFEV_1 or ppoDLCO; predicted postoperative FEV_1 or DLCO. *p<0.05; **p<0.01; ***p<0.001

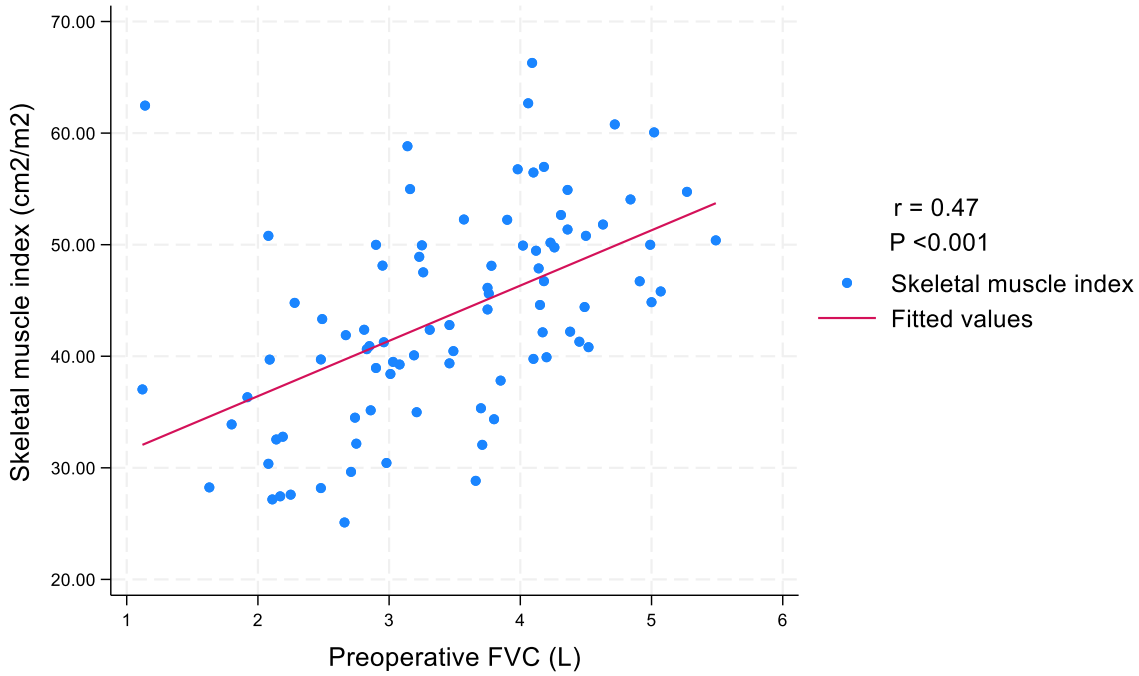

Figure 6.12 Correlation between SMI and FVC

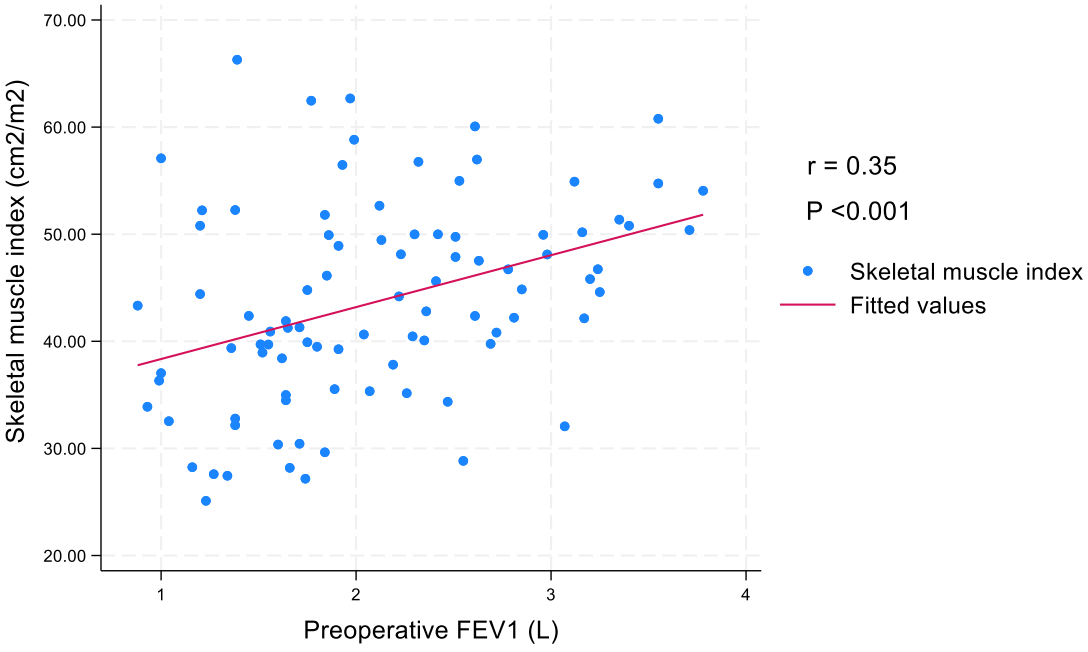

Figure 6.13 Correlation between SMI and FEV_1

6.3.6 Intra-observer variability

To investigate the intra-observer variability in CT-based body composition measurements, intraclass correlation coefficient and the Bland Altman plot were carried out. A total of 30 CT scans were involved in the intra-observer reproducibility of measuring the PM, ESM, PSM, and SM areas.

Based on the results below, the agreement between the two measurements was excellent, with ICC ranging between 0.995 and 1 (Table 6.7). The mean differences for right and left ESM were -0.03 and -0.07, respectively. The widest upper and lower LOAs were 0.7 and 0.8, respectively, considered reasonably narrow.

The largest mean difference of PM major and minor areas was 0.1, which is lower than 0.98 cm^2 [284]. The widest upper LOA was 0.7, whereas the lower LOA was -0.4, which are considered relatively narrow with only two points lying outside LOA.

Similarly, the mean difference of PSM area measurements was 0.01 and upper and lower LOAs were relatively narrow (0.39 and 0.4). Lastly, the mean difference between SM measurements was 0.02 with upper and lower LOAs of 0.5, which is reasonably narrow (Figure 6.14-6.22).

Table 6.7 Intra-class correlation coefficient for intra-observer reproducibility when measuring CT-based body composition (95% CI)

Muscle area (cm^2)	ICC	Lower bond	Upper bond
Rt ESM	0.999	0.997	0.999
Lt ESM	0.998	0.996	0.999
Rt PM major	0.999	0.997	0.999
Rt PM minor	0.995	0.989	0.998
Lt PM major	0.999	0.998	1.0
Lt PM minor	0.997	0.993	0.998
Rt PSM	0.999	0.997	0.999
Lt PSM	0.999	0.997	0.999
SM	1.0	1.0	1.0

ICC; Intra-class correlation coefficient, ESM; Erector spinae muscle, PM; Pectoralis muscle, PSM; Psoas muscle, SM; Skeletal muscle, P <0.05

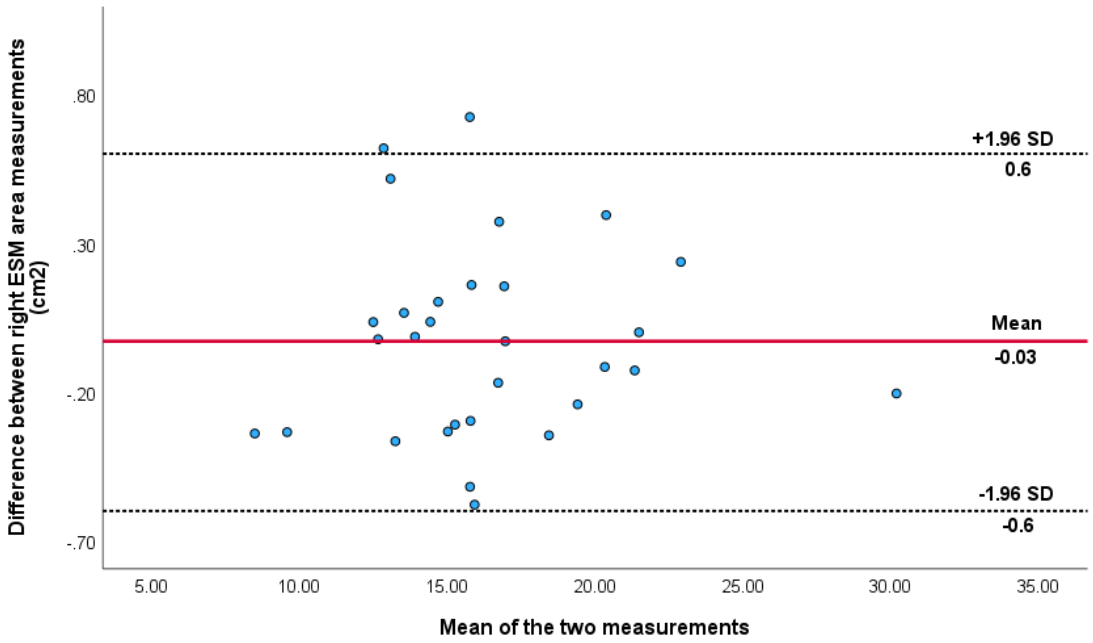

Figure 6.14 Intra-observer agreement of right ESM area measurement (cm^2)

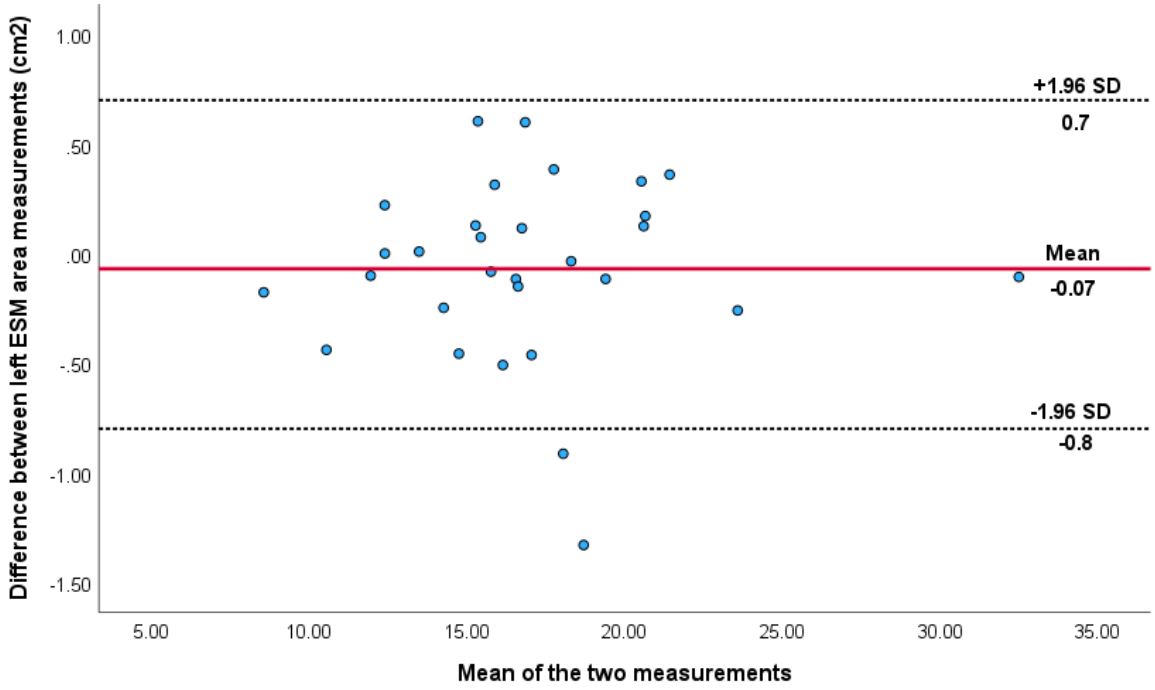

Figure 6.15 Intra-observer agreement of left ESM area measurement (cm^2)

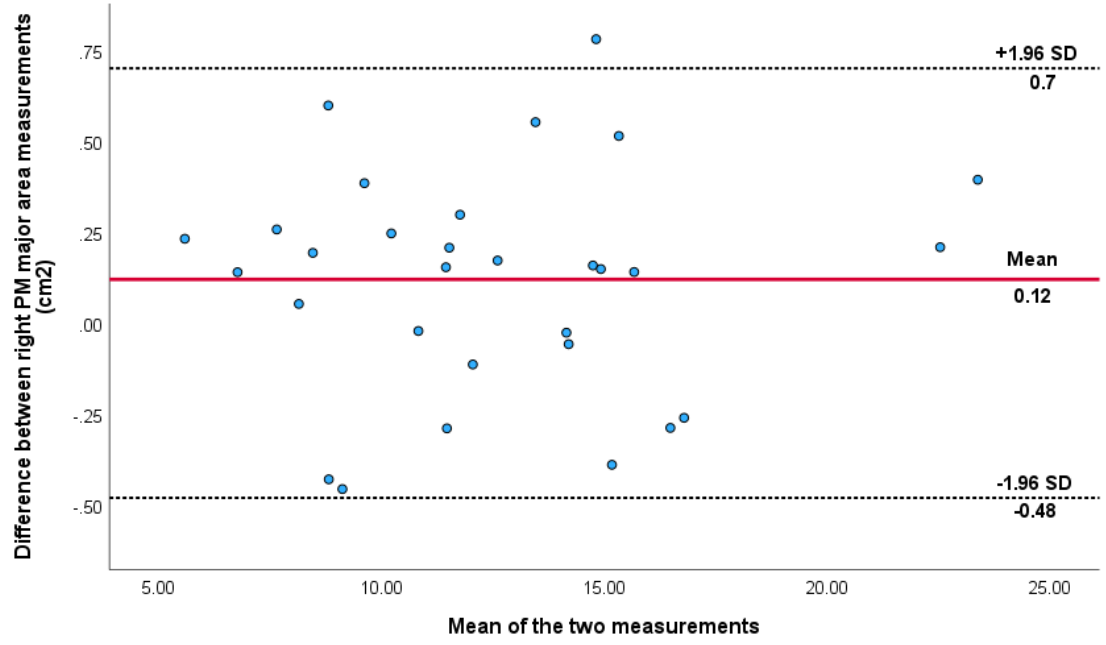

Figure 6.16 Intra-observer agreement of right PM major area measurement (cm^2)

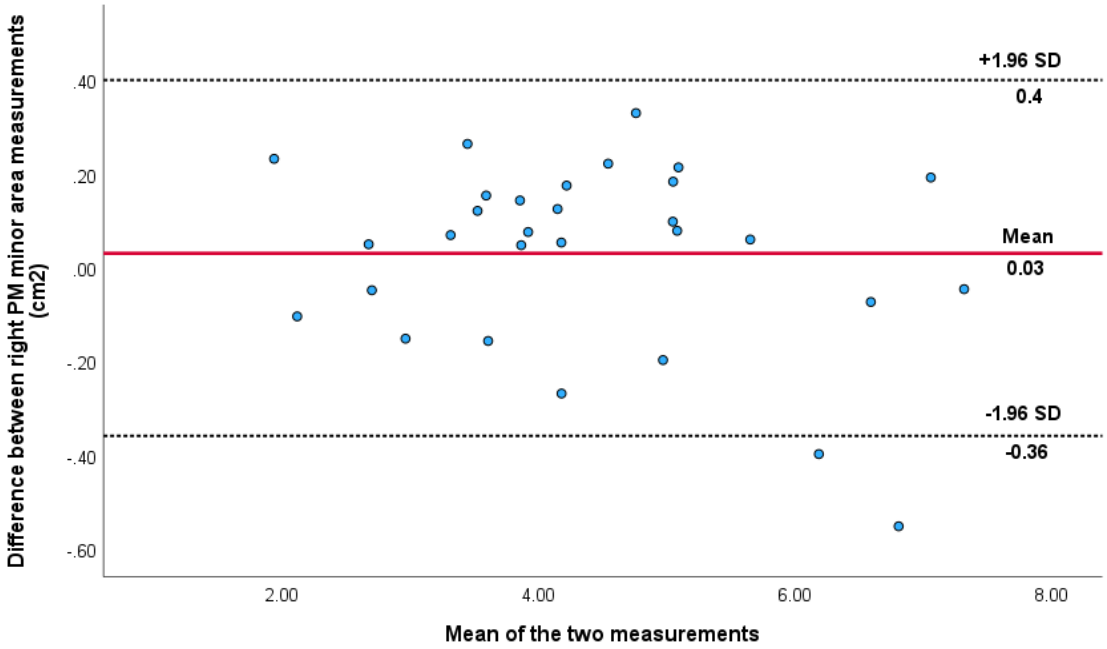

Figure 6.17 Intra-observer agreement of right PM minor area measurement (cm^2)

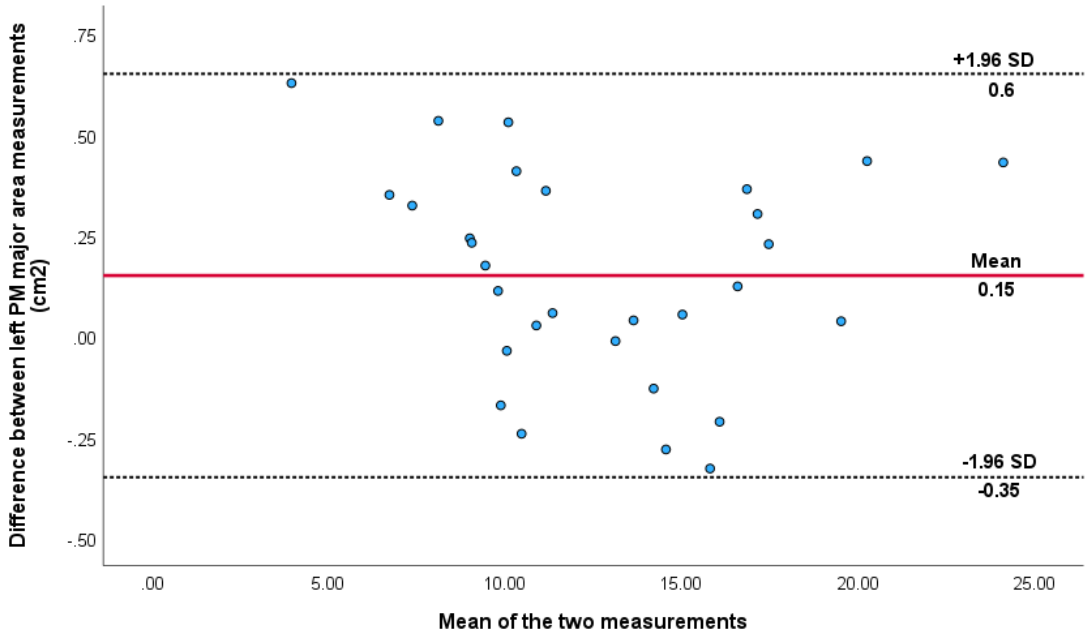

Figure 6.18 Intra-observer agreement of left PM major area measurement (cm^2)

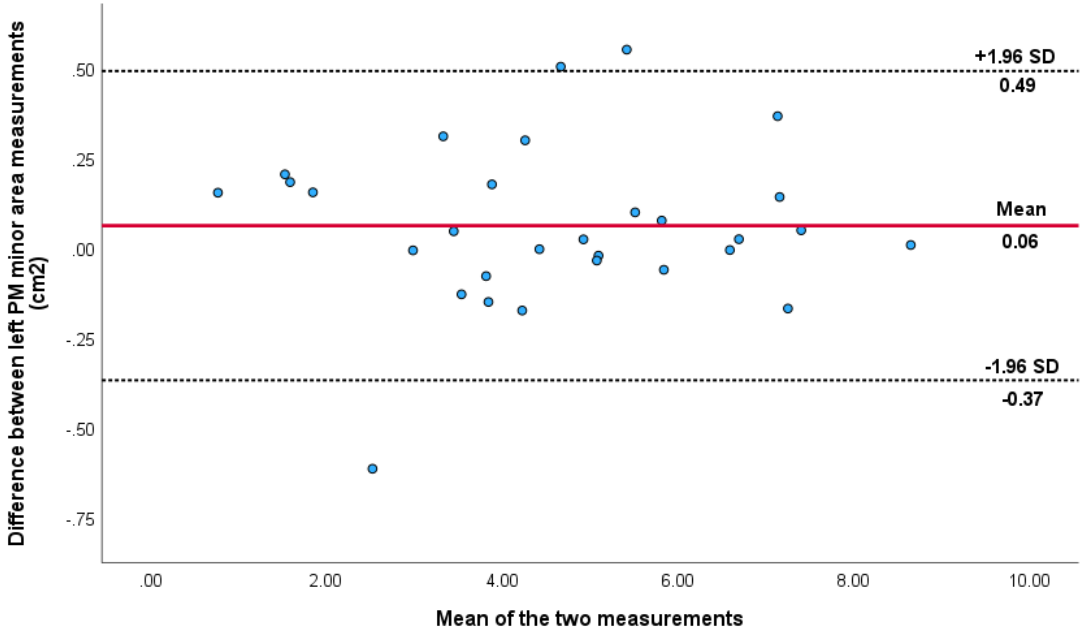

Figure 6.19 Intra-observer agreement of left PM minor area measurement (cm^2)

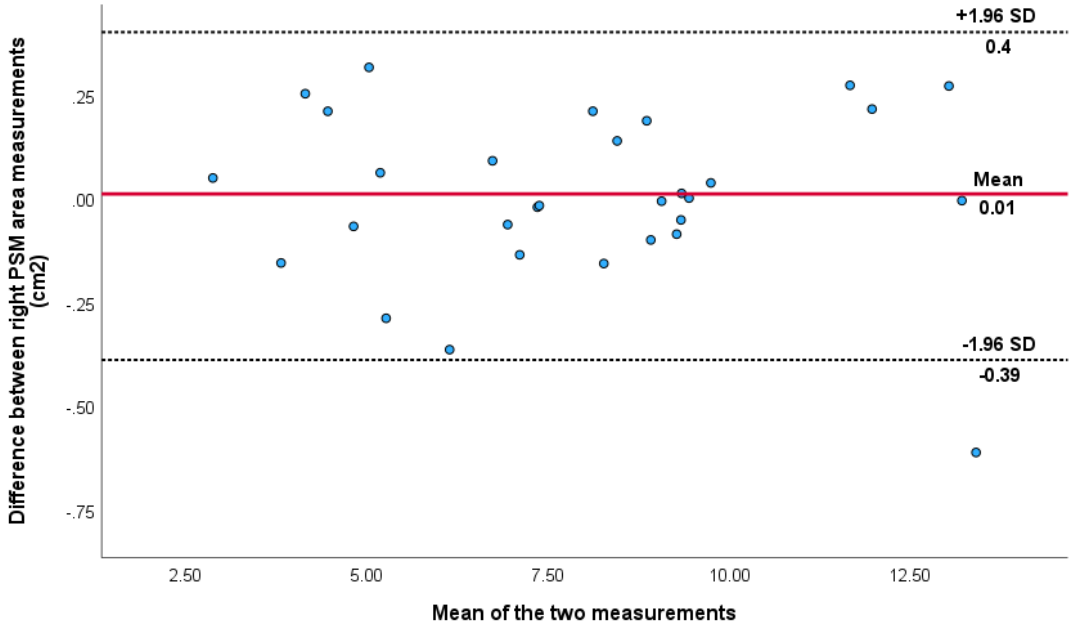

Figure 6.20 Intra-observer agreement of right PSM area measurement (cm^2)

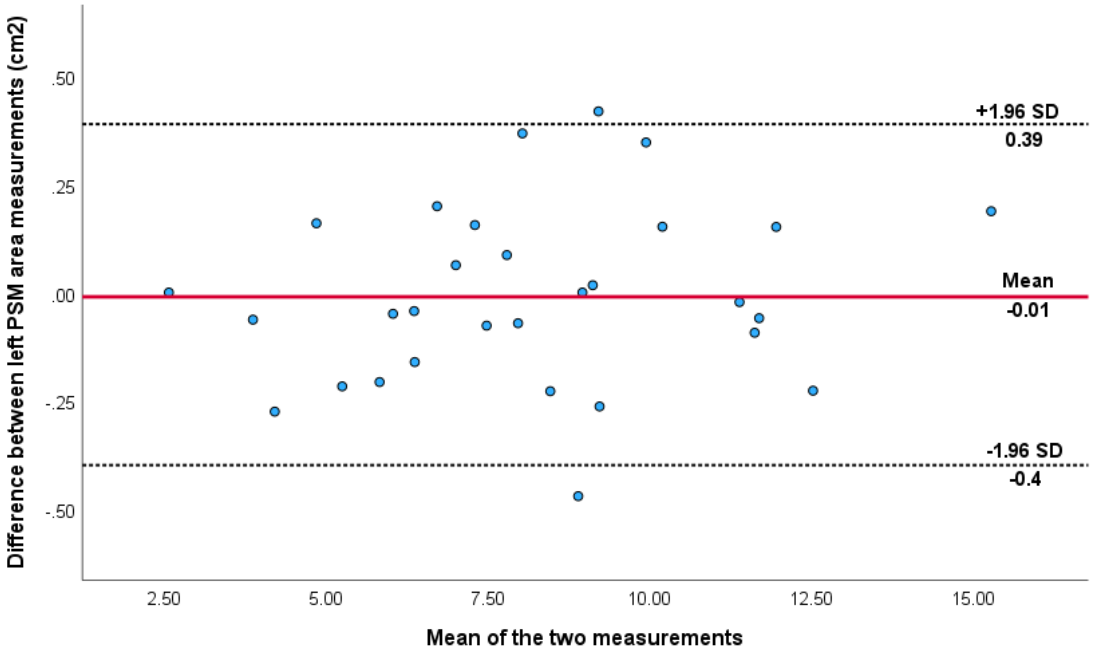

Figure 6.21 Intra-observer agreement of left PSM area measurement (cm^2)

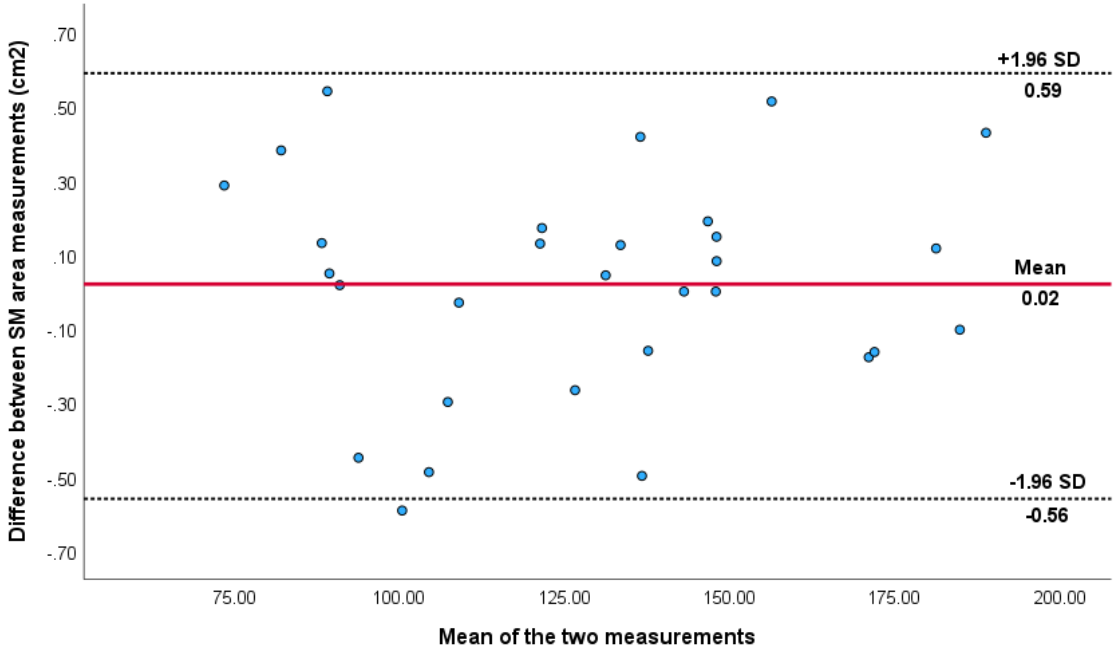

Figure 6.22 Intra-observer agreement of SM area measurement (cm^2)

6.3.7 Relationship between CT body composition and QoL

6.3.7.1 Relationship between CT body composition and dyspnoea at eight weeks

Table 8.6 illustrates the differences between patients with increased dyspnoea and those with reduced dyspnoea eight weeks after lung surgery. The results incorporate 52 patients with increased dyspnoea versus 36 patients with lower dyspnoea using MCID to assess deterioration and improvement. Overall, there is no statistically significant difference between the two groups in muscles' indices, with a negligible mean difference between the two groups and no statistically significant difference in the proportion of sarcopenia between the two groups ($p > 0.05$).

Table 6.8 The difference between patients with increased dyspnoea and reduced dyspnoea at eight weeks in CT body composition measures

Muscle	Increased dyspnoea (n = 52)	Reduced dyspnoea (n = 36)	Mean Diff.	P value	95% CI
SMI	44.9 ± 9.4	42.4 ± 9.6	-2.5	0.2	-6.6 - 1.6
Sarcopenia SMI	30 (57.6%)	27 (75%)	-	0.4	-
PMI	12.4 ± 3.4	12.2 ± 3.5	-0.2	0.7	-1.7 - 1.2
Sarcopenia (PMI)	10 (19.2%)	14 (38.8%)	-	0.1	-
ESMI	12.1 ± 2.5	11.6 ± 2.7	-0.5	0.3	-1.6 - 0.6
Sarcopenia (ESMI)	11 (21.1%)	11 (30.5%)	-	0.5	-
PSMI	5.3 ± 1.6	5.2 ± 1.5	-0.1	0.7	-0.7 - 0.5
Sarcopenia (PSMI)	19 (36.5%)	13 (36.1%)	-	0.6	-

Independent t-test for comparing continuous data and Chi-squared test for comparing categorical data in those with increased and reduced dyspnoea after surgery. Data are presented as mean and standard deviation or numbers and percentages for categorical data. SMI; skeletal muscle index, PMI; Pectoralis muscle index, ESMI; Erector spinae muscle index, PSMI; Psoas muscle index, Diff; difference, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

6.3.7.2 Relationship between CT body composition and dyspnoea at six months

The results below highlight the differences between patients with increased dyspnoea symptoms and those with reduced dyspnoea six months after surgery in body composition (Table 6.9). The results incorporate 52 patients with higher dyspnoea versus 36 patients with lower dyspnoea. In terms of all muscles' indices, there is no statistically significant difference between the two groups ($p > 0.05$). In terms of sarcopenia, the proportion of sarcopenia of SMI, PMI, and PSMI tends to be higher in patients with increased dyspnoea compared to the other group, although the results did not reach statistical significance ($p > 0.05$). The proportion of sarcopenia of SMI is somewhat higher in patients with increased dyspnoea compared to the rest (67.3% vs 63.8%, respectively). Similarly, the proportion of sarcopenia of PMI and PSMI is marginally higher in patients with increased dyspnoea compared to the rest of the patients (38.8% vs 30.7% for PMI, and 38.4% vs 30.5% for PSMI respectively). However, the proportion of sarcopenia of ESMI is nearly equal in the two groups (32.6% vs 33.3%, respectively).

Table 6.9 The difference between patients with increased dyspnoea and recovered dyspnoea at six months in CT body composition measures

Muscle	Increased dyspnoea (n = 52)	Recovered dyspnoea (n = 36)	Mean Diff.	P value	95% CI
SMI	44.6 ± 9.7	43.0 ± 9.3	-1.5	0.4	-5.7 - 2.5
Sarcopenia SMI	35 (67.3%)	23 (63.8%)	-	0.8	-
PMI	12.4 ± 3.2	12.1 ± 3.7	-0.2	0.9	-1.7 - 1.2
Sarcopenia (PMI)	14 (38.8%)	16 (30.7%)	-	0.08	-
ESMI	11.5 ± 2.7	11.3 ± 2.9	-0.1	0.7	-1.3 - 1.0
Sarcopenia (ESMI)	17 (32.6%)	12 (33.3%)	-	0.9	-
PSMI	5.4 ± 1.5	5.35 ± 1.6	-0.05	0.9	-0.7 - 0.6
Sarcopenia (PSMI)	20 (38.4%)	11 (30.5%)	-	0.5	-

Independent t-test for comparing continuous data and Chi-squared test for comparing categorical data in those with increased or decreased and no change dyspnoea after surgery. Data are presented as mean and standard deviation or numbers and percentages for categorical data. SMI; skeletal muscle index, PMI; Pectoralis muscle index, ESMI; Erector spinae muscle index, PSMI; Psoas muscle index, Diff; difference, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

6.3.7.3 Relationship between CT body composition and global health at eight weeks

The results below show the difference in the indices and proportion of sarcopenia in SM, ESM, PM, and PSM between patients with worsened and recovered global health eight weeks following lung cancer surgery (Table 6.10). As can be seen, there is no statistically significant difference between the two groups in muscle mass or sarcopenia proportion between those with improved global health or deteriorated global health eight weeks following lung surgery (p >0.05).

Table 6.10 The difference between patients with reduced global health and recovered global health at eight weeks in CT body composition measures

Muscle	reduced global health (n = 46)	recovered global health (n = 41)	Diff.	P value	95% CI
SMI	44.3 ± 10.1	43.1 ± 8.9	-1.2	0.5	-5.3 - 2.8
Sarcopenia SMI	31 (67.3%)	26 (63.4%)	-	0.8	-
PMI	12.4 ± 3.5	12.2 ± 3.4	-0.2	0.7	-1.7 - 1.2
Sarcopenia (PMI)	11 (23.9%)	13 (31.7%)	-	0.4	-
ESMI	12 ± 2.5	11.8 ± 2.7	-0.2	0.6	-1.3 - 0.8
Sarcopenia (ESMI)	11 (23.9%)	11 (26.8%)	-	0.7	-
PSMI	5.3 ± 1.6	5.2 ± 1.4	-0.1	0.6	-0.8 - 0.5
Sarcopenia (PSMI)	17 (36.9%)	15 (36.5%)	-	0.3	-

Independent t-test for comparing continuous data and Chi-squared test for comparing categorical data in those with decreased and recovered global health after surgery. Data are presented as mean and standard deviation or numbers and percentages for categorical data. SMI; skeletal muscle index, PMI; Pectoralis muscle index, ESMI; Erector spinae muscle index, PSMI; Psoas muscle index, Diff; difference, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

6.3.7.4 Relationship between CT body composition and global health at six months

Table 6.11 compares patients with worsened global health and those with recovered global health six months following lung surgery in in sarcopenia and muscles' indices. Assessing of the improvement or worsening of global health is based on MCID. Overall, there is no statistically significant difference between muscles indices in the two groups (p >0.05). As can be seen, indices of skeletal, pectoralis, erector spinae, and psoas muscles are equal or slightly higher in patients with lower global health. Moreover, there is no statistically significant difference between the proportion of sarcopenia of all muscles in the two groups (p >0.5). Yet, it can be noticed that the percentage of sarcopenic skeletal muscles is marginally higher in the patients with reduced global health compared to those recovered

(68.7% vs 62.5%, respectively). Conversely, sarcopenia in ESM, PM and PSM is slightly higher in the other group.

Table 6.11 The difference between patients with reduced global health and recovered global health in CT body composition measures

Muscle	reduced global health (n = 32)	recovered global health (n = 32)	Diff.	P value	95% CI
SMI	44.3 ± 11.3	41.7 ± 7.7	-2.5	0.2	-7.5 - 2.3
Sarcopenia SMI	22 (68.7%)	20 (62.5%)	-	0.7	-
PMI	12.6 ± 4.3	11.2 ± 2.4	-1.3	0.1	-3.1 - 0.3
Sarcopenia (PMI)	12 (37.5%)	14 (43.7%)	-	0.6	-
ESMI	12 ± 2.6	11.1 ± 2	-0.8	0.1	-1.9 - 0.3
Sarcopenia (ESMI)	10 (31.2%)	14 (34.7%)	-	0.3	-
PSMI	5.6 ± 1.5	5 ± 1.5	-0.5	0.1	-1.4 - 0.2
Sarcopenia (PSMI)	11 (34.3%)	13 (40.6%)	-	0.5	-

Independent t-test for comparing continuous data and Chi-squared test for comparing categorical data in those with increased or decreased and no change dyspnoea after surgery. Data are presented as mean and standard deviation or numbers and percentages for categorical data. SMI; skeletal muscle index, PMI; Pectoralis muscle index, ESMI; Erector spinae muscle index, PSMI; Psoas muscle index, Diff; difference, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

6.3.7.5 Relationship between CT body composition and physical functioning at six months

As the previous results have not shown a significant difference between the compared groups with respect to sarcopenia and muscle mass. It was of interest to the author to perform an additional exploratory analysis to determine whether there are significant differences when assessing other HRQOL domains of physical functioning and fatigue.

The results below (Table 6.12) investigate the difference between patients with deteriorated and improved physical functioning six months after lung cancer surgery. Accordingly, there are no statistically significant differences between the two groups in regard to sarcopenia across all muscle types ($p>0.05$). Additionally, there is no statistically significant difference in muscle mass between individuals who have declined and improved physical functioning six months following lung surgery.

Table 6.12 The difference between patients with decreased physical functioning and recovered physical functioning at six months in CT body composition measures

Muscle	Decreased Physical functioning (n = 40)	Recovered Physical functioning (n = 25)	Mean Diff.	P value	95% CI
SMI	44.5 ± 10	40.5 ± 8.9	-4	0.1	-8.8 - 0.8
Sarcopenia SMI	25 (62.5%)	18 (72%)	-	0.5	-
PMI	12.2 ± 3.8	11.5 ± 3	-0.6	0.4	-2.3 - 1.0
Sarcopenia (PMI)	12 (30%)	10 (40%)	-	0.4	-
ESMI	11.8 ± 2.5	11.2 ± 1.9	-0.6	0.2	-1.7 - 0.5
Sarcopenia (ESMI)	12 (30%)	8 (32%)	-	0.8	-
PSMI	5.6 ± 1.5	4.9 ± 1.7	-0.6	0.1	-1.5 - 0.1
Sarcopenia (PSMI)	11 (27.5%)	13 (52%)	-	0.055	-

Independent t-test for comparing continuous data and Chi-squared test for comparing categorical data in those with decreased and recovered physical functioning after surgery. Data are presented as mean and standard deviation or numbers and percentages for categorical data. SMI; skeletal muscle index, PMI; Pectoralis muscle index, ESMI; Erector spinae muscle index, PSMI; Psoas muscle index, Diff; difference, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

6.3.7.6 Relationship between CT body composition and fatigue at six months

Table 6.13 compares patients with increased and lower fatigue six months after lung cancer surgery in CT body composition of SM, PM, ESM, and PSM. There are no statistically significant differences in sarcopenia or muscle mass between the two groups ($p>0.05$).

Table 6.13 The difference between patients with increased fatigue and reduced fatigue at six months in CT body composition measures

Muscle	Increased fatigue (n =35)	reduced fatigue (n =30)	Mean Diff.	P value	95% CI
SMI	43 ± 9.2	42.3 ± 10.5	0.7	0.7	-5.7 - 4.3
Sarcopenia SMI	24 (68%)	20 (66%)	-	0.9	-
PMI	11.8 ± 3.5	12 ± 3.7	0.1	0.8	-1.6 - 1.9
Sarcopenia (PMI)	12 (34%)	11 (36%)	-	0.8	-
ESMI	11.8 ± 2.5	11.1 ± 2.1	0.6	0.3	-1.7 - 0.5
Sarcopenia (ESMI)	8 (22%)	13 (43%)	-	0.07	-
PSMI	5.1 ± 1.6	5.4 ± 1.8	0.2	0.6	-0.6 - 1.0
Sarcopenia (PSMI)	12 (34%)	13 (43%)	-	0.3	-

Independent t-test for comparing continuous data and Chi-squared test for comparing categorical data in those with increased or decreased fatigue after surgery. Data are presented as mean and standard deviation or numbers and percentages for categorical data. SMI; skeletal muscle index, PMI; Pectoralis muscle index, ESMI; Erector spinae muscle index, PSMI; Psoas muscle index, Diff; difference, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

6.3.8 Relationship between CT body composition and postoperative clinical outcomes

The author undertook additional exploratory analyses to examine the relationship between CT body composition and postoperative clinical outcomes, focusing on understanding sarcopenia. As part of this investigation, we intend to investigate how body composition affects recovery and health following surgery, thereby contributing to a better understanding of the clinical implications of sarcopenia.

In this subset of the study, only 10 patients experienced PPC, as compared with 84 patients who did not experience such complications after surgery. In addition, there was a low readmission rate, with 13 patients who were readmitted as opposed to 78 who were not. Accordingly, given the low incidence of PPC and readmission, the author concentrated primarily on investigating LOS. To this end, the median LOS of 5 days was employed as a threshold to differentiate between patients with longer versus shorter hospital stays.

The results (Table 6.14) show no significant difference in sarcopenia and muscle mass between patients with longer and shorter LOS ($p>0.05$).

Table 6.14 The difference between patients with longer and shorter length of hospital stay in CT body composition measures

Muscle	long LOS >5 days (n =37)	Short LOS ≤5 days (n =57)	Mean Diff.	P value	95% CI
SMI	44.6 ± 8.5	43.4 ± 9.9	1.1	0.5	-5.0 - 2.7
Sarcopenia SMI	24 (64.8%)	40 (70%)	-	0.7	-
PMI	12.5 ± 2.9	12.2 ± 3.7	0.3	0.6	-1.0 - 1.7
Sarcopenia (PMI)	9 (24%)	15 (26%)	-	0.8	-
ESMI	12.2 ± 2.3	11.8 ± 2.7	0.4	0.4	-1.5 - 0.6
Sarcopenia (ESMI)	8 (21.6%)	15 (26.3%)	-	0.6	-
PSMI	5.4 ± 1.4	5.3 ± 1.6	0.06	0.8	-0.7 - 0.5
Sarcopenia (PSMI)	13 (35%)	20 (35%)	-	0.9	-

Independent t-test for comparing continuous data and Chi-squared test for comparing categorical data in those with long or short LOS after surgery. Data are presented as mean and standard deviation or numbers and percentages for categorical data. SMI; skeletal muscle index, PMI; Pectoralis muscle index, ESMI; Erector spinae muscle index, PSMI; Psoas muscle index, Diff; difference, CI; confidence interval. *p<0.05; **p<0.01; ***p<0.001

6.3.9 Comparison between contrast-enhanced and unenhanced CT body composition

In order to compare contrast-enhanced and unenhanced CT body composition, Wilcoxon signed-rank test was used to compare ESM area. A total of 10 observations were tested for the difference in right and left ESM cross-sectional area measures. There is no statistically significant difference between the contrast-enhanced and unenhanced CT scan measurements of the right and left ESM areas. Furthermore, the median value of right ESM area for unenhanced CT scans was 13.9 ± 7 cm^2 and 13.9 ± 7.2 cm^2 for the enhanced CT scans. The median values for left ESM area for unenhanced and enhanced CT scans were 15.1 ± 7 cm^2 and 15.2 ± 7.1 cm^2, respectively (Table 6.15).

Table 6.15 Comparison between contrast-enhanced and unenhanced CT body composition

	Unenhanced		Enhanced		
QCT measure	Median	IQR	Median	IQR	P-value
Rt ESM area	13.9	7	13.9	7.2	0.7
Lt ESM area	15.1	7	15.2	7.1	0.2

Wilcoxon signed-rank test, IQR; Inter Quartile Range, QCT; quantitative computed tomography, ESM; Erector spinae muscle, Rt; right, Lt; left, *p<0.05; **p<0.01; ***p<0.001

Below, Figures 6.23- 6.24 show Bland Altman plots demonstrating agreement between contrast-enhanced and unenhanced CT measurements of right and left ESM areas (cm^2). The mean difference between the measures was 0.02% for right ESM area and -0.08% for left ESM area. The LOAs were narrow and clinically acceptable for both measures, with only 1 point lying outside the LOA for both plots. In this study, the mean difference is small for both right and left ESM areas in contrast-enhanced and unenhanced CT scans.

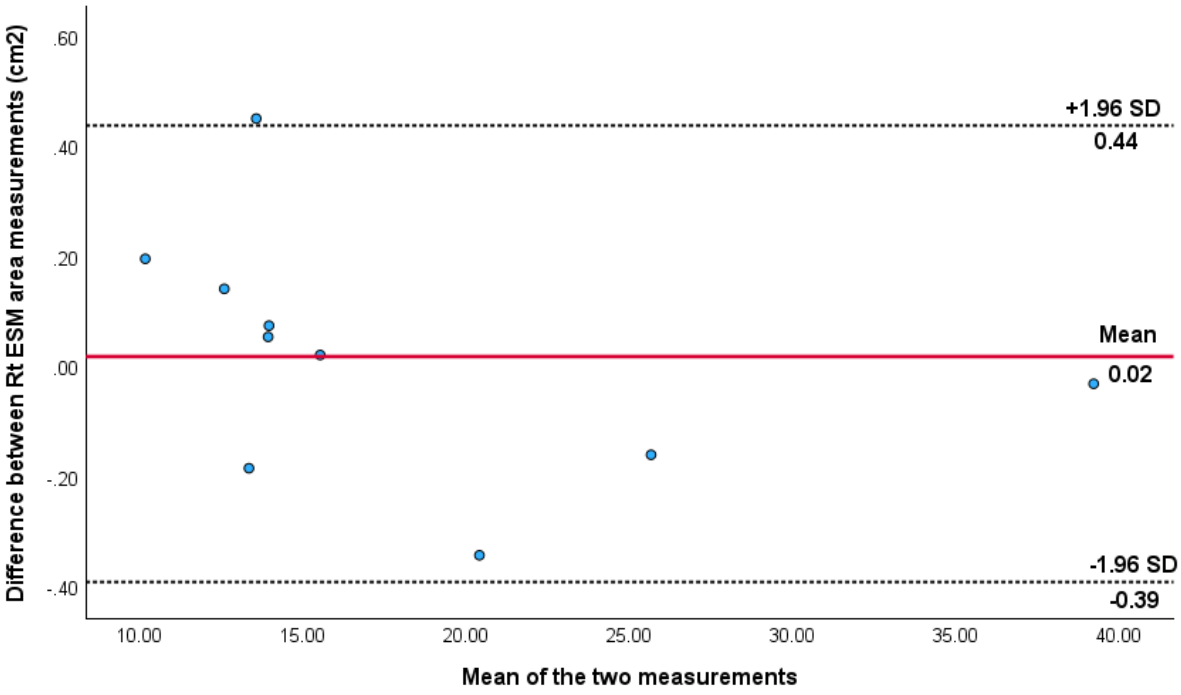

Figure 6.23 Agreement between contrast-enhanced and unenhanced CT scans for right ESM areas

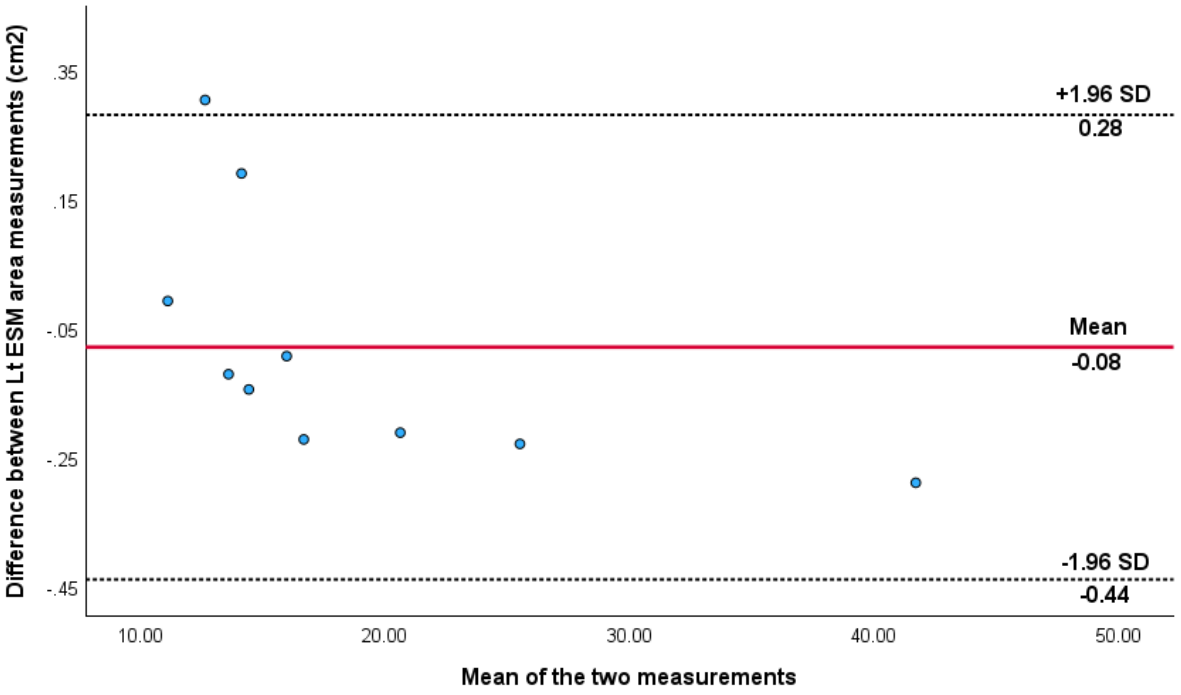

Figure 6.24 Agreement between contrast-enhanced and unenhanced CT scans for left ESM areas

6.4 Discussion

This study investigated the difference in sarcopenia between patients who experienced worse HRQOL and those with recovered HRQOL after lung cancer surgery. To our knowledge, there is insufficient evidence of CT-measured sarcopenia and QoL after lung cancer surgery. Also, we examined multiple muscles at thoracic and abdominal scans to better understand sarcopenia and capture variations between these muscles. This study utilised contrast-enhanced CT scans as they are routinely performed on lung cancer patients. The contrast-enhanced CT scanning protocol included not only thoracic, but also abdominal scans, allowing for a comprehensive evaluation of the patient. We have shown that there is no statistically significant difference in the cross-sectional area of the ESM between contrast-enhanced and unenhanced CT scans and the Bland Altman plots represented good agreement between the two measures. This is in accordance with previous studies which have demonstrated that contrast administration did not affect the quantification of the muscle area, but only muscle quality [339].

Several studies showed that sarcopenia and cancer cachexia were more frequent in men than women [340-342], whereas other studies noticed that sarcopenia in cancer patients was not associated with gender [343, 344]. There is an interesting difference between the current findings and those previously reported, as female subjects were significantly more likely to have sarcopenia of the pectoralis and psoas muscles than male subjects, while female subjects also exhibited more sarcopenia of the erector spinae and skeletal muscles; however, this was not statistically significant. This may be explained by the small number of females compared to males in this study (38 vs. 56, respectively).

Furthermore, indices of all muscles were higher in overweight and obese patients compared to those with normal BMI. This study demonstrated that the frequency of sarcopenia was higher in patients with relatively lower BMI compared to overweight and obese patients. These results support previous reports which emphasised that BMI was inversely related to sarcopenia [345, 346]. One possible

explanation is that overweight and obese individuals may have higher fat mass and higher lean mass that could be inadequate for their size [347]. Interestingly, nearly two-thirds (64%) of the subjects in this study were overweight and obese patients, which might explain the presented results.

One of our exploratory aims was to determine the correlation between SMI and the three muscles' indices (PMI, ESMI, and PSMI). All muscles were positively correlated with SMI. These findings are comparable to those stated by Hamaguchi et al., who investigated the relationship between PSMI and SMI and found a significant strong correlation between the two muscles ($r = 0.73$, $p < 0.001$) [234]. Similar results were also noted for PM and ESM correlations [338, 348]. Additionally, the results found that PSMI was strongly correlated with SMI while PMI and ESMI were moderately correlated. In agreement with this result, previous studies have shown that the correlation between SM and PM is not as strong as between SM and skeletal muscles measured on lumbar scans [349].

As part of the exploratory analysis, we assessed the correlation between SMI, PMI, ESMI, and PSMI with lung function. This analysis was vital as this study involved lung cancer patients, whose lung function plays a significant role in their clinical investigation and decision-making processes. Hence, finding the relationship between CT-based body composition and lung function was necessary. The results identified that preoperative FEV_1 (L) and preoperative FVC (L) were the only factors of lung function that significantly correlated with all muscles' indices. Notably, DLCO was significantly but weakly correlated with SMI. The results are parallel to previous findings that found a correlation between lung function and ESM [233], PM [78, 350], PSM [351], or SM [328]. Conversely, FEV_1/FVC was not significantly correlated with the measured muscles. Despite that forced vital capacity (FVC) and forced expiratory volume (FEV_1) may decline with sarcopenia, FEV_1/FVC ratio represents an upper airway obstruction that may not differ regardless of the presence of sarcopenia [352]. In addition, previous findings paralleled our results and showed that DLCO was not correlated with muscles' indices [256, 353]. Moreover, there was no relationship between muscles' indices and

ppoFEV$_1$ or ppoDLCO which was noted in other literature [353, 354]. Nevertheless, some reports indicated impaired pulmonary function could lead to muscle atrophy [232].

Additionally, we performed a reproducibility study by evaluating intra-observer variability and found good agreement between the measurements. Our results showed an excellent ICC and a small mean difference between the measurements compared to the previous reports [284, 355].

Lastly, the main objective of this research was to explore the relationship between sarcopenia and HRQOL. This study assessed the differences between those with recovered HRQOL at eight weeks and six months (dyspnoea and global health) as measured by EORTC QLQ-C30 and sarcopenia. Generally, we have shown no significant difference between those with recovered and those with worsened dyspnoea or global health in sarcopenia at all time points. Although there were no significant differences between individuals with increased dyspnoea and those with lower dyspnoea six months after lung surgery, we observed that those with higher dyspnoea at six months tend to have more sarcopenic muscles. Our findings were in agreement with those reported by Daly et al., who examined the relationship between QoL using EORTC QLQ-C30 and low skeletal muscle index in 428 patients with advanced cancer and found no correlation between dyspnoea and low SMI ($r = 0.01$, $p = 0.8$) [87]. In the same vein, Bye et al. assessed 734 lung cancer patients treated with chemotherapy and found no significant association between skeletal muscle index and dyspnoea ($p = 0.4$) [85]. Conversely, other reports demonstrated a significant association between PMA and dyspnoea using MRC score [356]. However, the author used the aortic arch as an anatomic landmark for measuring pectoralis muscles, which may limit the reproducibility of their image analysis. Our results demonstrated no statistically significant difference in sarcopenia between patients with deteriorated global health and those with recovered global health at eight weeks and six months after lung cancer surgery. Likewise, other research stated no relationship between global health and sarcopenia [87, 357]. We performed exploratory analyses to determine whether sarcopenia differs between

individuals with deteriorated and improved HRQOL of physical functioning and fatigue six months after lung surgery. The results showed no significant difference between the two groups. These results were in accordance with the findings in previous reports that stated no difference in fatigue and physical functioning between pre-sarcopenic and non-sarcopenic [329]. In the same vein, another study compared fatigue in 104 advanced cancer patients and found no significant difference between those with sarcopenia and those without [331]. Likewise, a study included 138 colorectal cancer patients and found no association between skeletal muscle mass and physical functioning and fatigue at six months [357]. Lastly, we conducted additional investigations in order to gain a deeper understanding of the impact of sarcopenia on clinical outcomes following lung surgery including LOS, PPC and hospital readmission. However, due to the small number of individuals experiencing PPC and hospital readmission, we were unable to assess these two outcomes. Thus, we have examined differences in sarcopenia among patients who had longer LOS (more than five days) compared to those who had shorter hosptal stays (five days or less). Similarly, the result showed no significant difference between the two groups. This finding is in agreement with a previous study stating that there is no significant difference in LOS between 355 patients [358] and 1121 patients [226] with and without sarcopenia.

There is inconsistent evidence in the literature regarding the relationship between HRQOL and sarcopenia [225]. While many studies revealed no relationship between HRQOL and sarcopenia [359], others highlighted a significant relationship between quality of life using the FACT-G tool and sarcopenia [360]. However, dyspnoea score was not considered in their evaluation since this instrument does not incorporate it [144]. There are several explanations for the present results; one reason may be due to a limited sample size, which suggests that a larger sample size might be necessary. There is also the possibility that measuring the longitudinal change in skeletal muscle mass may provide better evidence of the loss of skeletal muscle mass; since skeletal muscle mass is

measured at one-time point, it may not be indicative of patients' level of muscularity [325]. It is also important to note that a reduction in skeletal muscle mass, measured through muscles' indices, may not necessarily represent a loss of muscle function [85]. Evidence suggested that assessing thoracic muscle mass along with functional deficits related to muscle strength may be more effective in assessing lung cancer patients' outcomes [359]. The mechanism of muscle loss is complex and is affected by a variety of factors, including aging, nutritional status and physical fitness [232]. The EWGSOP2 guidelines recommend assessing muscle strength as the first step in the initial assessment of sarcopenia. In the event that muscle strength is determined to be deficient, additional validation must be obtained by analysing muscle quantity and quality on medical imaging modalities [73]. Thus, a study assessing muscle strength along with CT-based body composition would be highly beneficial.

6.5 Limitations and future research

This study was able to assess the relationship between CT-based body composition and postoperative quality of life after lung cancer surgery. Moreover, we were able to evaluate more than one muscle at different levels of thoracic and abdominal scans for more comprehensive assessment. However, there are some limitations encountered in the study. First and foremost, the small sample size of this study may limit the generalisability. Moreover, the retrospective nature of this study. In addition, we have not assessed muscle attenuation, an important indicator of muscle quality due to the use of contrast-enhanced CT scans that can affect the readings of muscle density and provide inaccurate measures. Nevertheless, we focused primarily on contrast-enhanced CT scans which are routinely utilised in clinical investigations involving cancer patients. In this study, we sought to evaluate the feasibility of measuring sarcopenia using these scans without exposing patients to additional radiation using additional CT scans. Furthermore, the study could not examine changes in skeletal muscle over time, which might be more indicative of postoperative outcomes. Extended research on monitoring

malnutrition and reducing weight loss and its impact on patients' outcomes and QoL is warranted. Conducting a longitudinal study is crucial for gaining insights into the progression of sarcopenia and after lung cancer surgery its impact on QoL and clinical outcomes. Additional investigation into the risk factors and mechanisms of muscle loss is warranted to enable referrals to rehabilitation programs such as pulmonary rehabilitation and appropriate therapeutic plans.

Chapter 7. An Investigation of the Agreement between AI-based Software and A Semi-automated Software in Quantification of Emphysema on CT

7.1 Introduction

Significant changes in medicine and radiology have occurred due to the introduction of informatics, machine learning, and personalised medicine [361]. A considerable increase in the use of Artificial Intelligence (AI) in the last decade has altered the way diagnostics are made in the age of the 4th Industrial Revolution [362, 363]. Despite continuous research into the use of AI in clinical settings, these systems have not been widely implemented [364]. Because AI can be used to diagnose lung disease involving COPD with various benefits, significant use of these systems is anticipated in hospitals in the near future [262].

In general, reproducible CT measurements are believed to be difficult to generate due to technical challenges. The reconstruction parameters such as slice thickness and reconstruction kernel [265, 365], breathing techniques, such as submaximal inspiration [366] and dose [193] have all been presented to affect CT quantification. However, several large trials have managed to standardise these parameters by using dedicated phantoms and breath-hold coaching techniques [367]. Another factor that should be considered for the reproducibility of QCT measures is the software utilised for image analysis. However, even when constant image acquisition and reconstruction parameters are used, QCT measures variability can occur due to differences in the lobar segmentation, segmentation of the large airways or pulmonary vessels [368]. Previous studies have reported the high variability of different software programs in emphysema quantification [369-371].

COPD is a challenging disease to diagnose, and the potential complications of mistreatment or non-treatment highlight the importance of using any new means of diagnosis, including AI [262]. Quantifying emphysema in CT is an objective and accurate approach to detecting the disease [261]; however, manual methods are time-consuming and may result in high variability between observers [272]. Therefore, AI-based algorithms can save time and reduce variability compared to manual and semi-automated methods. While AI-based image analysis is promising in medical image analysis, including COPD detection, it is vital to understand the variations between this approach and semi-automated analysis. It is imperative to assess the reliability and reproducibility of the software in order to ensure confidence in the results produced. In addition, it is essential to validate the implementation of AI-based image analysis software and investigate the software programs' reliability. This study aimed to examine the agreement between AI software and semi-automated analysis of CT emphysema.

7.2 Methods

7.2.1 CT scan

This is a retrospective study that used all unenhanced CT scans analysed in Chapter 5 to compare the measurements of two software programs. A subset of 60 patients who underwent unenhanced CT scans at University Hospital Birmingham (UHB) NHS Foundation Trust were screened. Details of the methodology of this chapter including patients' inclusion criteria is detailed in Section 3.4.

7.2.2 CT scan analysis software

In this study, we analysed the same CT scans using two software programs: 3D slicer v 4.10; Chest Imaging Platform (CIP) module, and AI-assisted Aview ® system (Coreline Soft Inc., Seoul, South Korea). Lung segmentation and quantification of emphysema using %LAA-950, PD15, MLD and lung volume were measured for whole lung and lung lobes. Details about the software programs and their methods in the image analysis is explained in the Methods Chapter (Section 3.2 and 3.4).

7.2.3 Statistical analysis

Intra-class correlation coefficients (ICC) and Bland Altman plots were used to assess the agreement between the two software. P-value of <0.05 is considered statistically significant. The statistical analysis method is described in Section 3.4.

All the statistical analyses were performed using Stata 18.0 statistical software (Stata Co., College Station, TX) or SPSS version 29 (IBM Corp.).

7.3 Results

7.3.1 Baseline characteristics and image analysis

A total of 60 patients with unenhanced CT scans which were analysed using 3D Slicer in the previous study were screened for inclusion (Chapter 5, Section 5.3.5). CIP was able to process more than 95% of the CT scans successfully, whereas Aview system analysed nearly 82% of the CT scans successfully. The excluded subjects were 10 CT scans due to the inability of Aview software to analyse the %LAA-950 due to the protocol of CT scans not being optimised for the software. One CT scan was also excluded due to the software's failure to exclude the airway (Figure 7.1). Aview software requires only 2-3 minutes for an image analysis, as opposed to 15 minutes for the CIP module. The baseline characteristics of the patients, and CT data output are summarised in Tables 7.1-7.2.

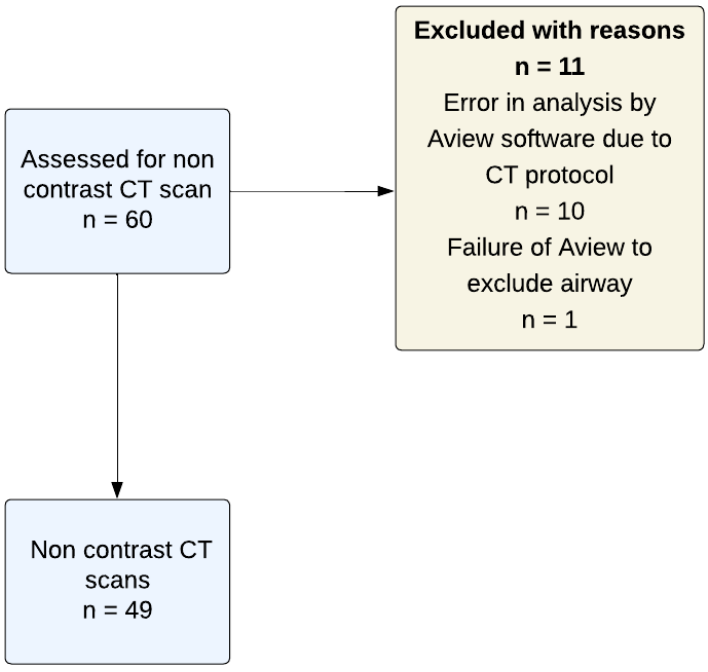

Figure 7.1 Flow chart for inclusion of unenhanced CT scans

Table 7.1 Baseline characteristics of 49 patients included in the study

Characteristic	Total (n = 49)
Age	70 ± 8.5
Gender (male)	28 (46. 7)
BMI	28 ± 6
Smoking quit time	
Current	8 (14)
Ex-smoker (6 weeks ≥ 1 year)	8 (14)
Ex-smoker (> 1 year)	30 (52.6)
Never smoker	11 (19)
FEV_1 (L)	2 ± 0 .7
% FEV_1	84.6 ± 23.5
FVC (L)	3.1 ± 0.8
% FVC	101.1 ± 0.8
%DLCO	76.3 ± 20.1

Data are presented as mean (median) and standard deviation (interquartile range) or numbers and percentages for categorical data. BMI; body mass index, FEV_1; forced expiratory volume in 1 second, FVC; forced vital capacity, DLCO; diffusing capacity for carbon monoxide.

Table 7.1 illustrates patients' demographics, smoking quit time and lung function. The median age is 70, and almost half of the patients are male (46.7%). The mean BMI is 28, and over half of the patients have stopped smoking for over a year (52.6%). The mean FEV_1 (L) is 2, and mean %FEV_1 is 84.6. The median values of FVC (L) and %FVC are 3.1 and 101.1, respectively, and mean DLCO is 76.3.

7.3.2 Aview system CT quantification output

Aview software offers the data in the form of a pdf report, which involves values for the whole lungs, the right and left lungs, and each of the five lobes. Measurements contain:

- %LAA-950
- 15th Percentile
- Mean lung density and standard deviation
- Volume
- Other measures were not employed in this analysis, including the %HAA.
- Lung density histogram (Figure 7.2)
- LAA chart presented as a Bull's eye chart (Figure 7.2)

Most scans have been analysed successfully; however, the software failed to process 11 scans, mostly due to CT scans' protocol that were not optimised for the software's specifications.

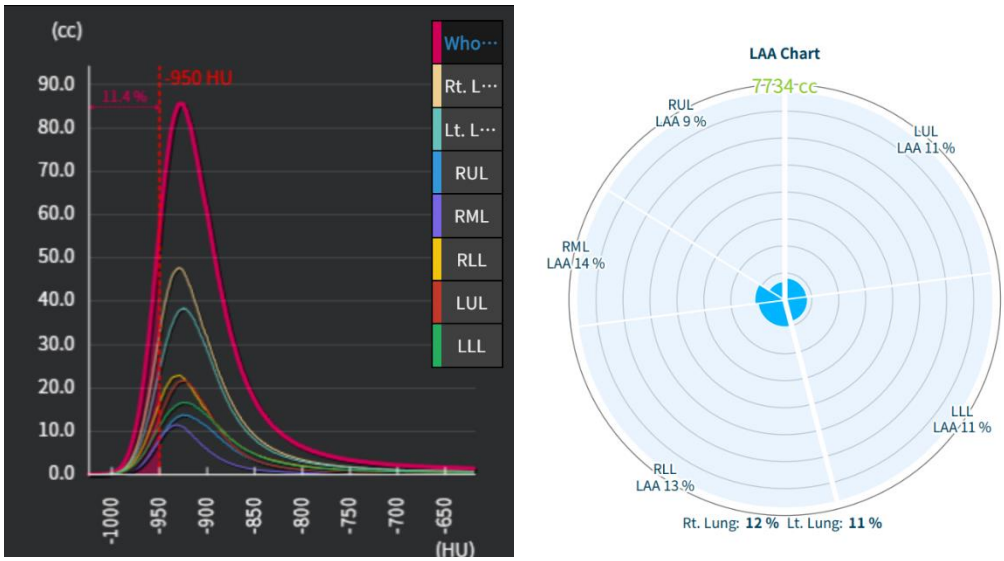

Figure 7.2 An example of lung density histogram and Bull's eye chart by Aview software, RUL; right upper lobe, RML; right middle lobe, RLL; right lower lobe, LUL; left upper lobe, LLL; left lower lobe, HU; Hounsfield Units.

The mean (median) measurements for each software program are provided in Tables 7.2, and 7.3. For %LAA-950, the median value for the whole lung and each lobe for Aview is 1, while the median value for CIP for the whole lung and each lobe ranges between 0.46 and 1.1. For PD15, the mean value for the whole lung for Aview is -900.1 HU whereas the mean value for CIP is -900.3 HU. The right upper, middle and left upper lobes represent the lowest densities. For the right upper lobe, Aview and CIP have PD15 of -900.2 and -900.6, respectively. The mean values of PD15 for the right middle and left lower lobes for Aview are -907.6 and -891.8 HU, respectively, and for CIP, they are -911.4 and -889.1 HU, respectively.

Table 7.2 summary of the densitometry measurements of Aview and CIP of 49 patients

		Aview	CIP
%LAA-950 (HU)	**Whole lung**	1 ± 4	0.86 ± 3
	Right lung	1 ± 3	0.68 ± 2.78
	Left lung	1 ± 4	1.1 ± 3.3
	Right upper lobe	1 ± 4	0.75 ± 3.06
	Right middle lobe	1 ± 3	1.1 ± 3.9
	Right lower lobe	1 ± 4	0.46 ± 2.9
	Left upper lobe	1 ± 3	1 ± 2.6
	Left lower lobe	1 ± 3	0.75 ± 2.2
15 PD (HU)	**Whole lung**	-900.1 ± 30.4	-900.3 ± 30.3
	Right lung	-900.4 ± 29.6	-900.7 ± 29.5
	Left lung	-899 ± 32.5	-899.3 ± 32.3
	Right upper lobe	-900.2 ± 30	-900.6 ± 29.7
	Right middle lobe	-907.6 ± 27.4	-911.4 ± 26.6
	Right lower lobe	-893.8 ± 35.5	-890.2 ± 37.6
	Left upper lobe	-902.6 ± 31	-903.6 ± 30.9
	Left lower lobe	-891.8 ± 38.1	-889.1 ± 41.2

Data are presented as mean (median) and standard deviation (interquartile range). CIP; Chest Imaging Platform, LAA; low attenuation area, 15 PD; 15th Percentile.

Table 7.3 demonstrates MLD and lung volume measurements of the two software programs for the whole lung and individual lobes. As can be seen, the right middle and left upper lobe have the lowest densities with MLD measures using Aview are -828.5 and -824.5 HU, respectively, and MLD using CIP for the same lobes are -836.2 and -827.7 HU, correspondingly. The whole lung mean density measurement using Aview is -812.9, whereas CIP is -816.6 HU. The lower right and left lobes exhibit the highest mean density measurements. For the lung volume measurements (L), both software programs have similar values for whole lung and each lobe except the right lung, right middle lobe and right lower lobe, as summarised in Table 7.3.

Table 7.3 A summary of the densitometry measurements of Aview and CIP of 49 patients

		Aview	CIP
MLD (HU)	**Whole lung**	-812.9 ± 43.8	-816.6 ± 41.7
	Right lung	-813.7 ± 42.7	-817.5 ± 40.4
	Left lung	-811.4 ± 46.4	-826.6 ± 66
	Right upper lobe	-827 ± 68	-827.6 ± 63.5
	Right middle lobe	-828.5 ± 38.2	-836.2 ± 35.9
	Right lower lobe	-805 ± 67	-809.1 ± 75
	Left upper lobe	-824.5 ± 39.3	-827.7 ± 39
	Left lower lobe	-807 ± 74	-816.7 ± 72.4
Lung volume (L)	**Whole lung**	4.6 ± 1.8	4.6 ± 1.9
	Right lung	2.6 ± 1	2.5 ± 1
	Left lung	2.3 ± 0.6	2.3 ± 0.6
	Right upper lobe	0.9 ± 0.5	0.9 ± 0.4
	Right middle lobe	0.46 ± 0.1	0.4 ± 0.1
	Right lower lobe	1.2 ± 0.3	1.1 ± 0.3
	Left upper lobe	1.1 ± 0.5	1.1 ± 0.5
	Left lower lobe	1 ± 0.3	1 ± 0.3

Data are presented as mean (median) and standard deviation (interquartile range). CIP; Chest Imaging Platform, MLD; Mean lung density.

7.3.3 Assessment of the agreement between Aview and CIP data output

To investigate the agreement between Aview and CIP in emphysema quantification, intra-class correlation coefficient and Bland Altman plots were employed to compare the measurements of the two software programs. A total of 49 observations were tested for the difference in %LAA-950, MLD, PD15, and lung volume of the whole lung and each lobe.

The results below show excellent agreement between the two software programs in %LAA-950 with ICC of the whole lung and each lobe between 0.999 and 0.987 (Table 7.4). The mean differences of %LAA-950 for the whole lung and each lobe were between -0.44 and 0.05%, and the largest LOA was 2%, which is considered relatively narrow and less than 5%, with few points lying outside LOA (Figure 7.3-7.10).

Table 7.4 Intra-class correlation coefficient between Aview and CIP in %LAA-950 (95% CI)

	ICC	Lower bond	Upper bond
Whole lung	0.998	0.997	0.999
Right lung	0.998	0.997	0.999
Left lung	0.999	0.998	0.999
Right upper lobe	0.995	0.992	0.997
Right middle lobe	0.987	0.974	0.993
Right lower lobe	0.99	0.98	0.995
Left upper lobe	0.997	0.995	0.998
Left lower lobe	0.992	0.986	0.996

ICC; Intra-class correlation coefficient, P <0.05

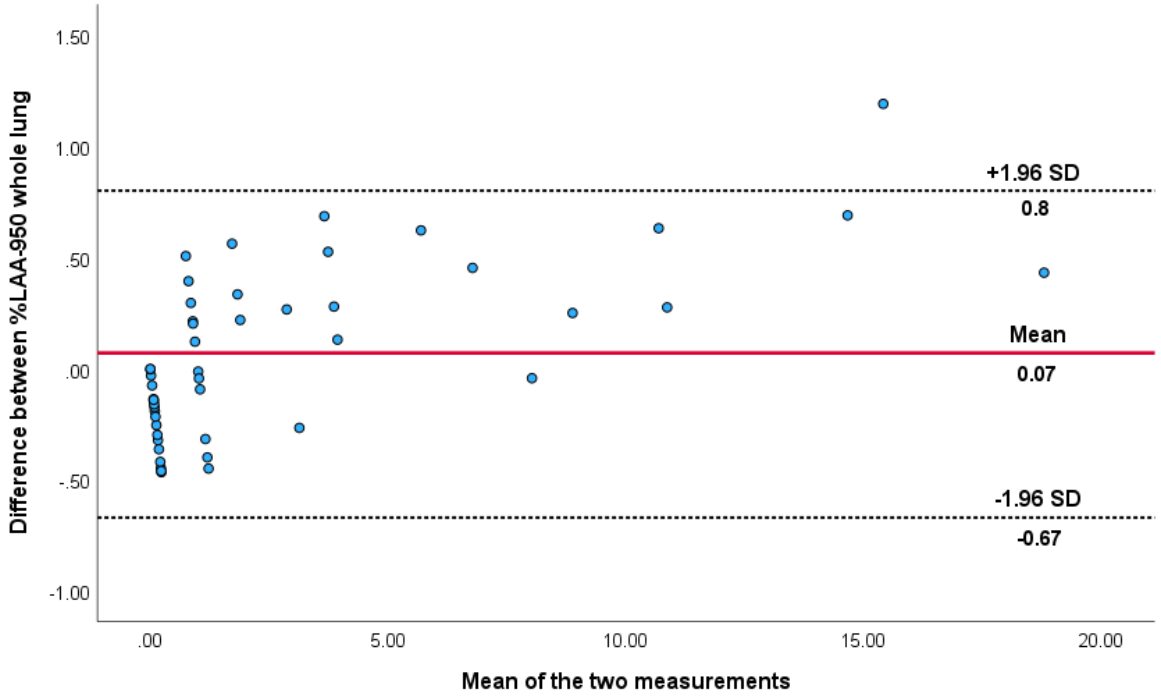

Figure 7.3 Agreement between Aview and CIP software programs for %LAA-950 of whole lung

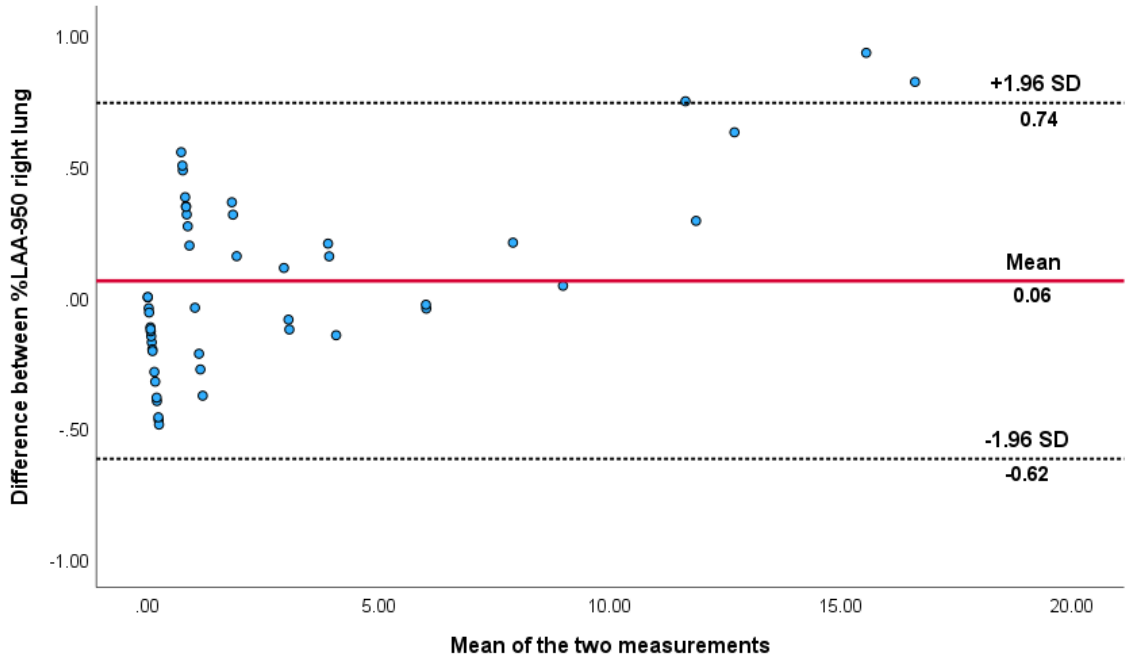

Figure 7.4 Agreement between Aview and CIP software programs for %LAA-950 of right lung

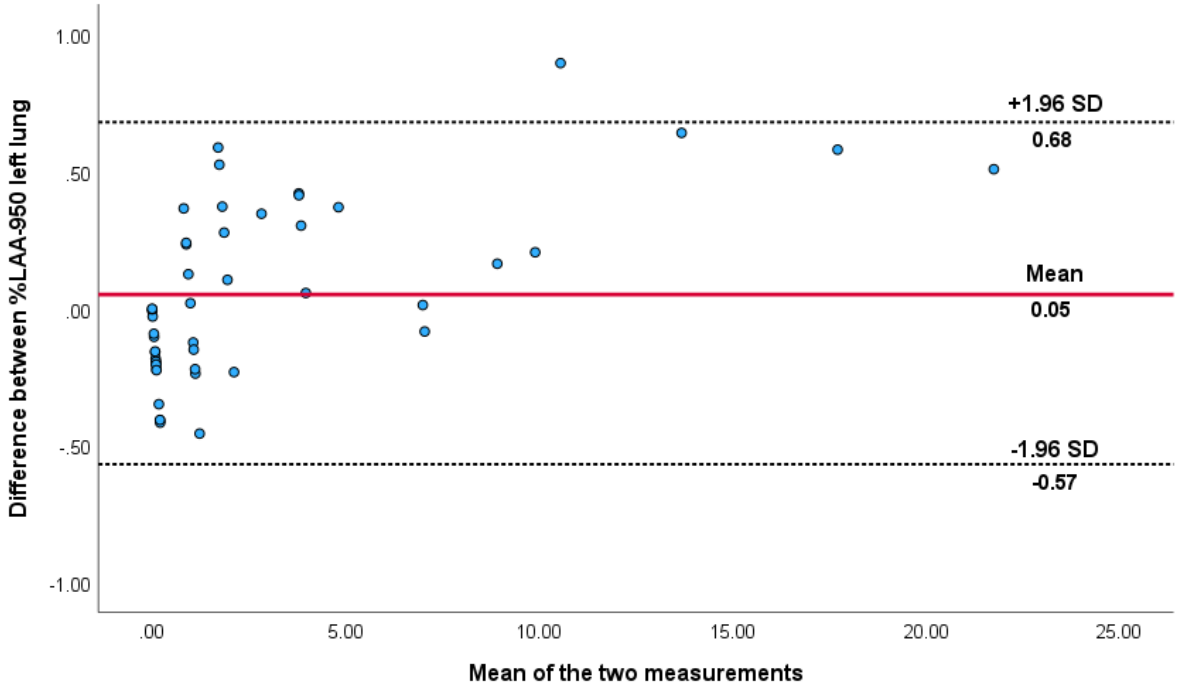

Figure 7.5 Agreement between Aview and CIP software programs for %LAA-950 of left lung

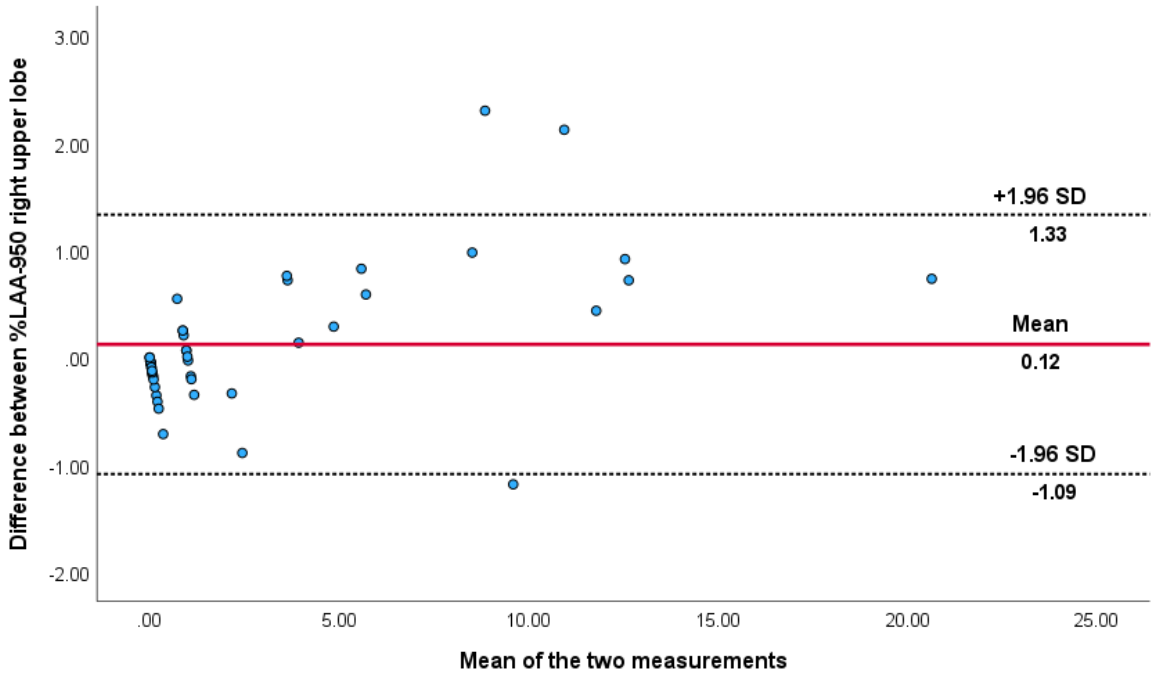

Figure 7.6 Agreement between Aview and CIP software programs for %LAA-950 of right upper lobe

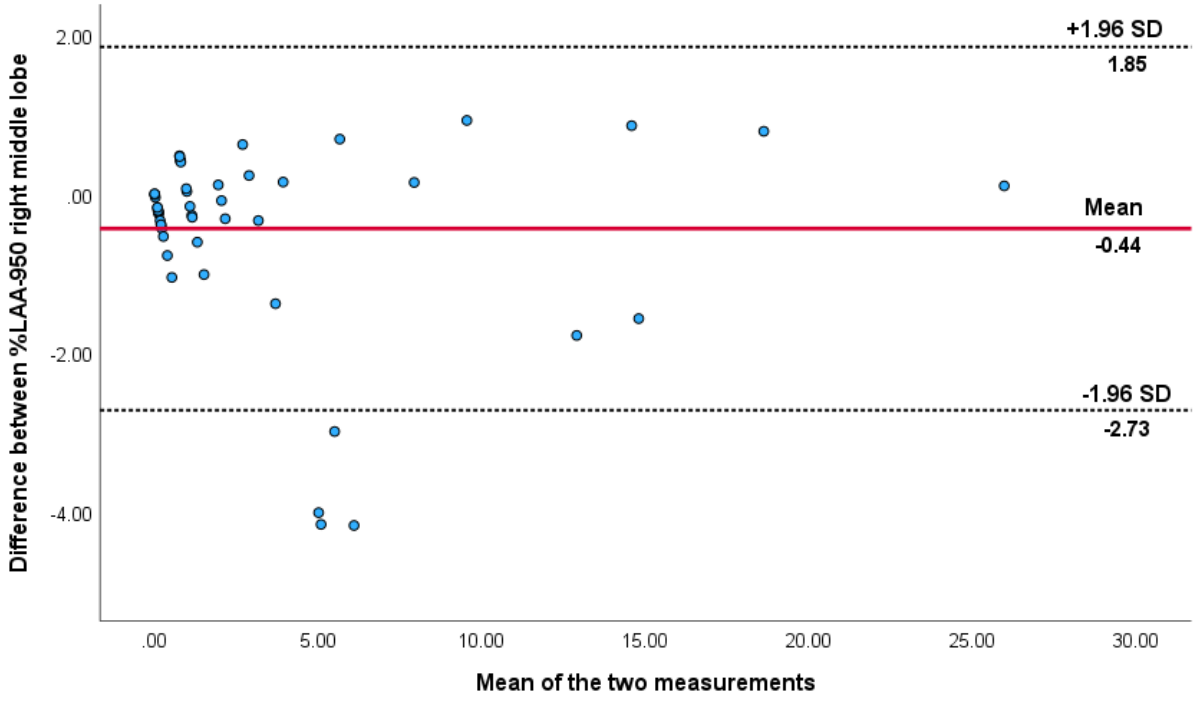

Figure 7.7 Agreement between Aview and CIP software programs for %LAA-950 of right middle lobe

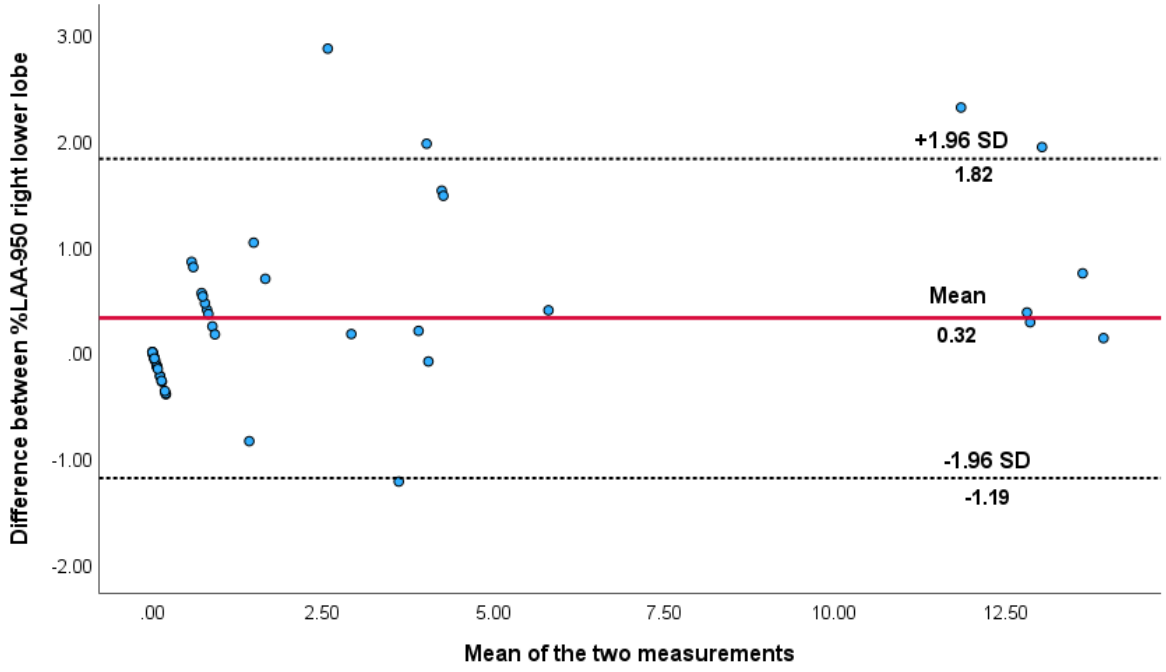

Figure 7.8 Agreement between Aview and CIP software programs for %LAA-950 of right lower lobe

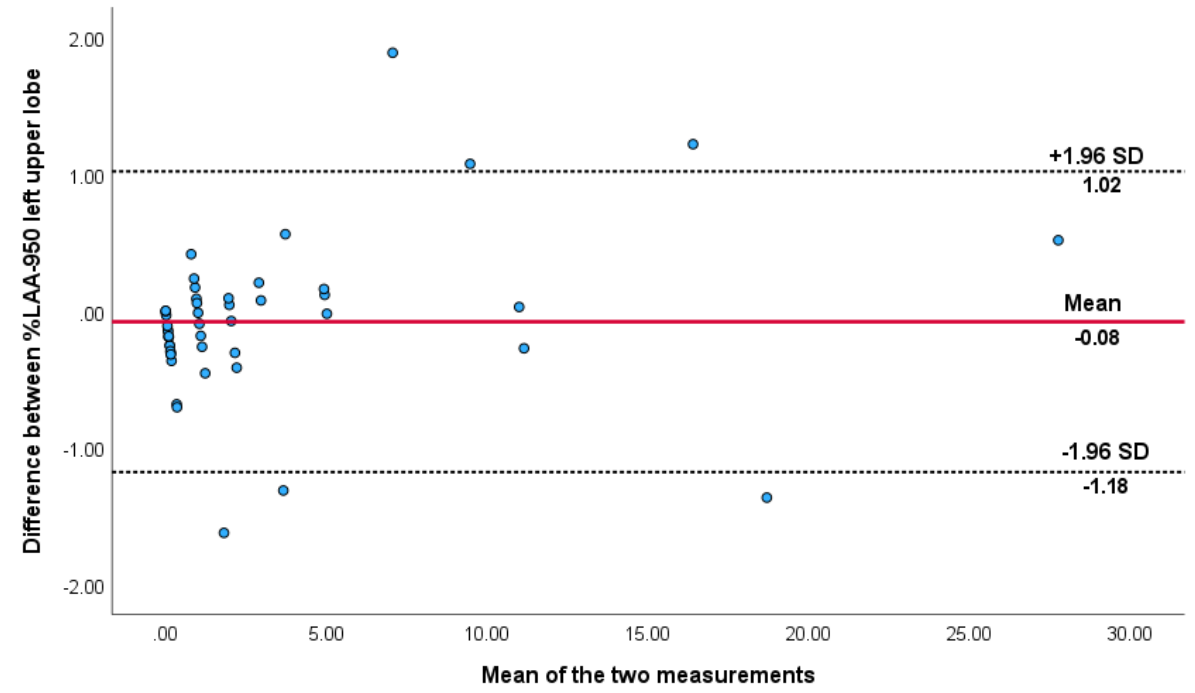

Figure 7.9 Agreement between Aview and CIP software programs for %LAA-950 of left upper lobe

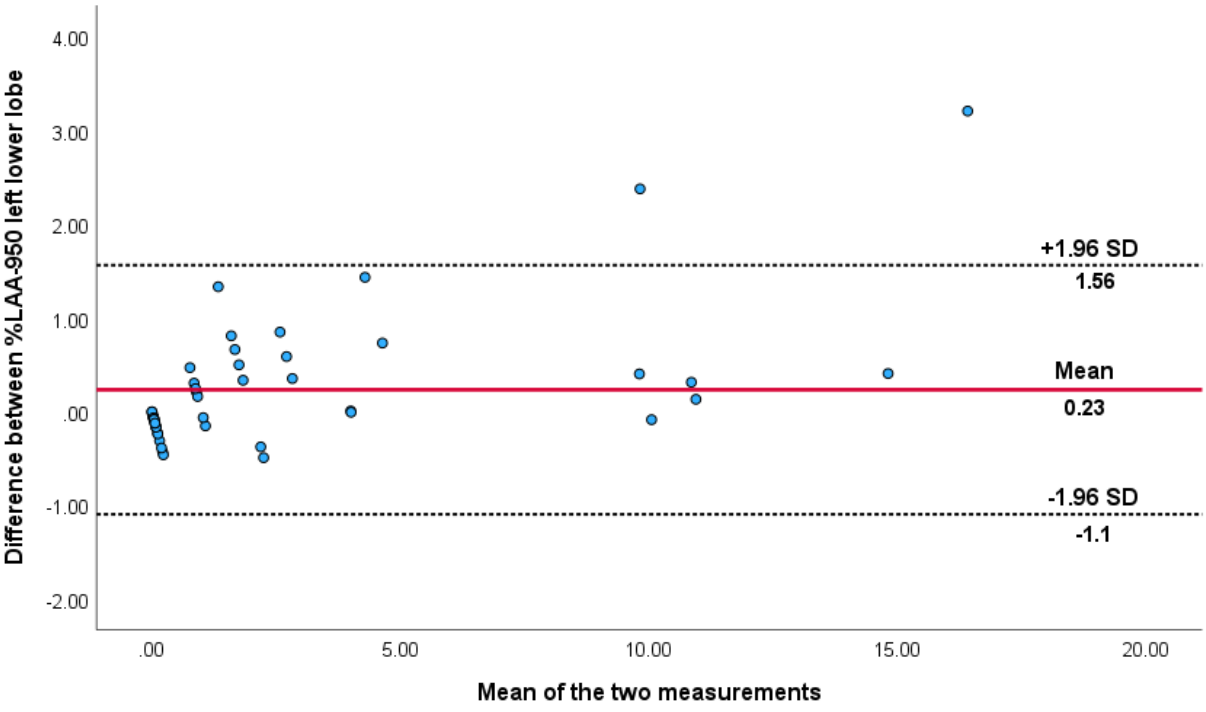

Figure 7.10 Agreement between Aview and CIP software programs for %LAA-950 of left lower lobe

In terms of the PD15, the two software programs had excellent agreement, with best agreement found in the whole lung, right and left lung (ICC = 1.0), and in each lobe with ICC ranges between 0.998 and 0.98 (Table 7.5). The Bland Altman plots show the mean difference in the PD15 between 0.22 and 3.8 HU, which is considered relatively small. The LOA for the whole lung, right lung, left lung, right upper lobe and left upper lobe were reasonably narrow with few points lying outside LOA, given that 10 HU generally represents disease progression in the PD15 in the literature [372, 373]. Although the largest mean difference of PD15 in the right middle, right lower lobe, and left lower lobe is 3.8, the LOA were wider than acceptable limits, with the largest upper LOA is 16.28 HU seen in the right middle lobe. The upper LOA for the right lower lobe and left lower lobe are 15.37 and 15.89 HU, respectively (Figure 7.11-7.18).

Table 7.5 Intra-class correlation coefficient between Aview and CIP in 15th percentile (95% CI)

	ICC	Lower bond	Upper bond
Whole lung	1.0	1.0	1.0
Right lung	1.0	1.0	1.0
Left lung	1.0	1.0	1.0
Right upper lobe	0.997	0.995	0.998
Right middle lobe	0.981	0.948	0.991
Right lower lobe	0.98	0.962	0.989
Left upper lobe	0.998	0.996	0.999
Left lower lobe	0.984	0.971	0.991

ICC; Intra-class correlation coefficient, P <0.05

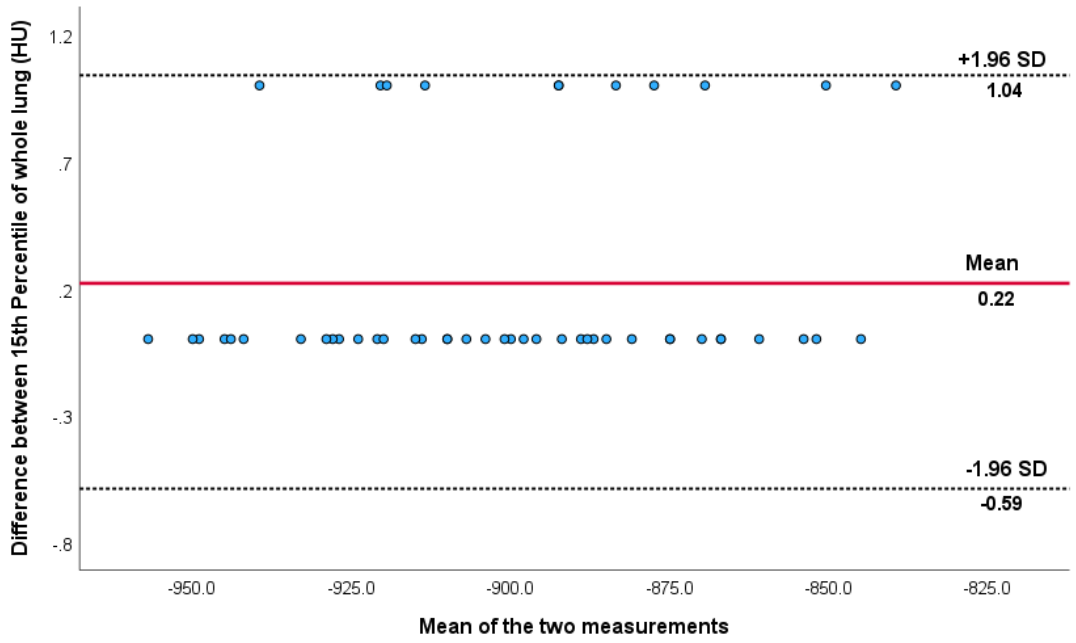

Figure 7.11 Agreement between Aview and CIP software programs for 15th percentile of whole lung

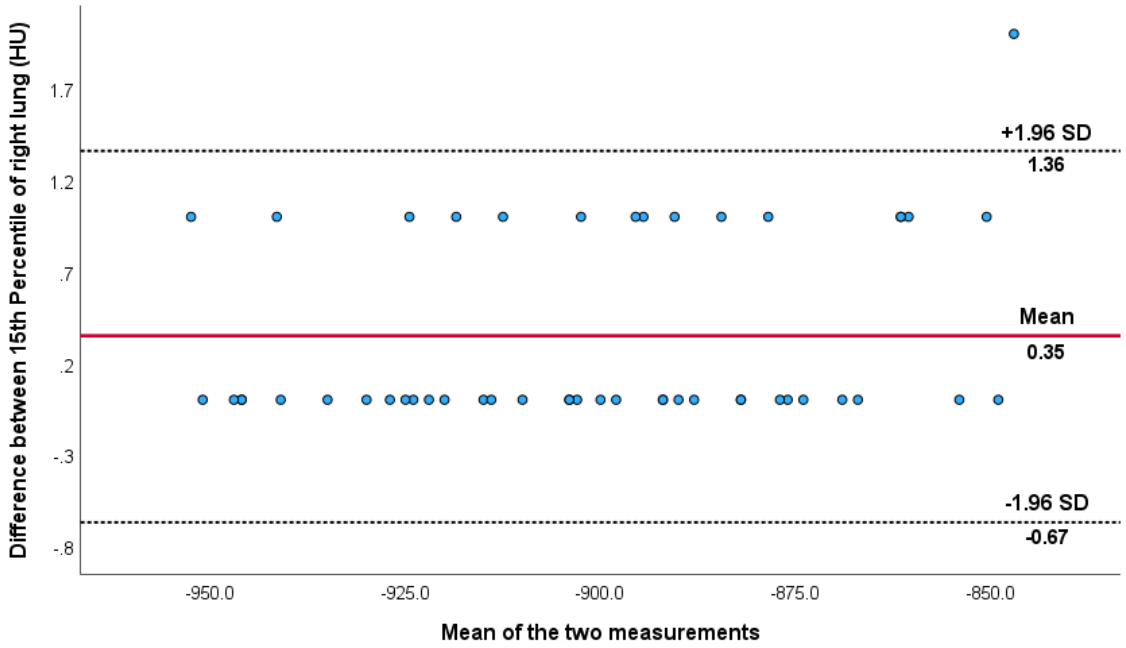

Figure 7.12 Agreement between Aview and CIP software programs for 15th percentile of right lung

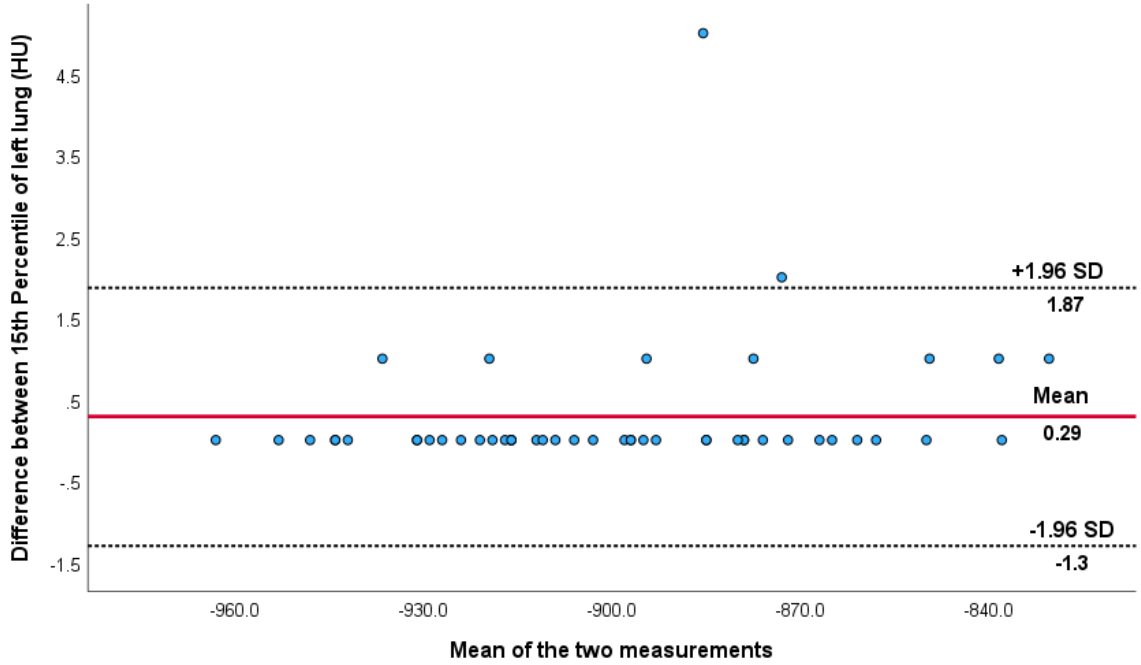

Figure 7.13 Agreement between Aview and CIP software programs for 15th percentile of left lung

Figure 7.14 Agreement between Aview and CIP software programs for 15th percentile of right upper lobe

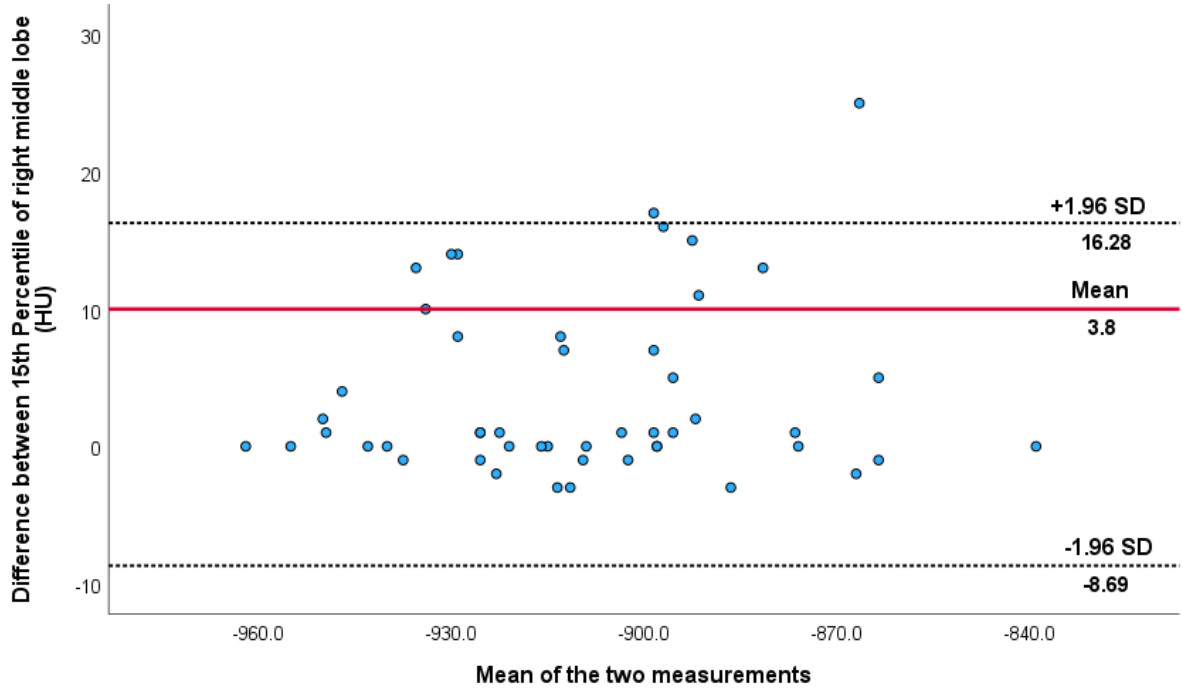

Figure 7.15 Agreement between Aview and CIP software programs for 15th percentile of right middle lobe

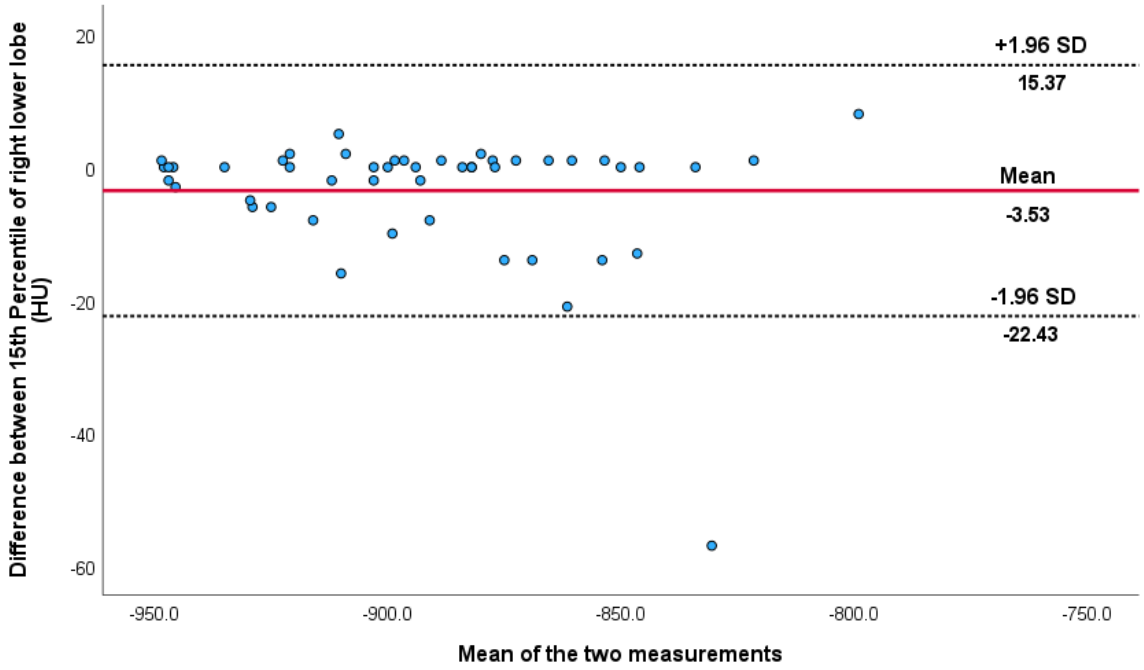

Figure 7.16 Agreement between Aview and CIP software programs for 15th percentile of right lower lobe

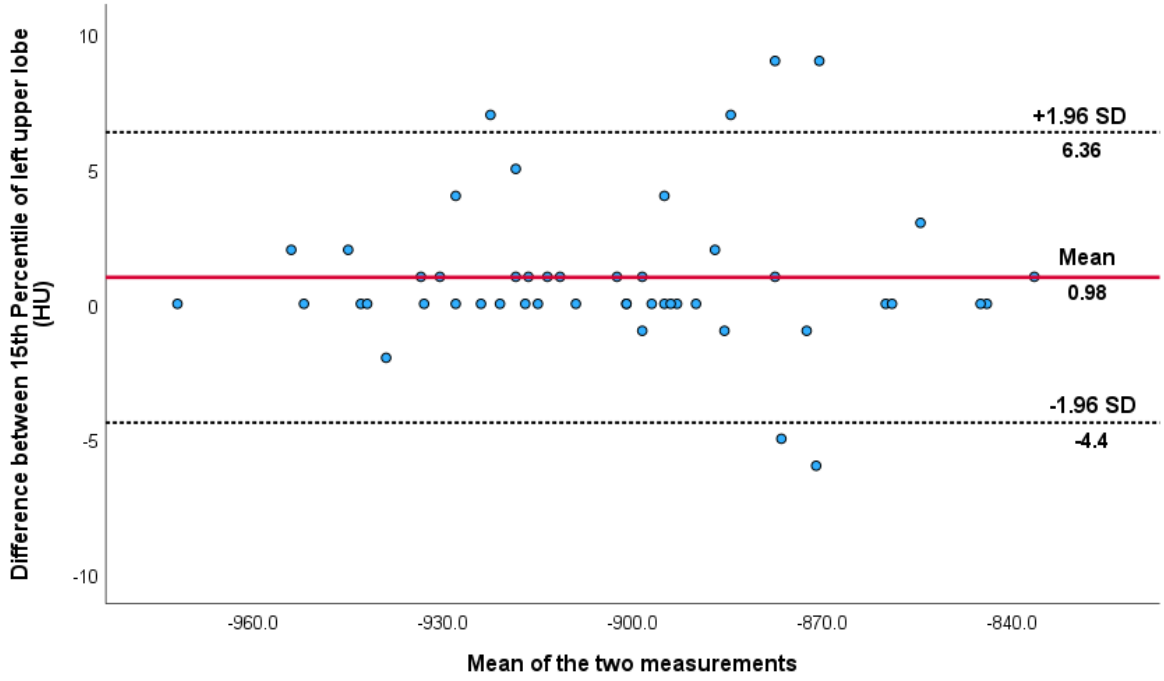

Figure 7.17 Agreement between Aview and CIP software programs for 15th percentile of left upper lobe

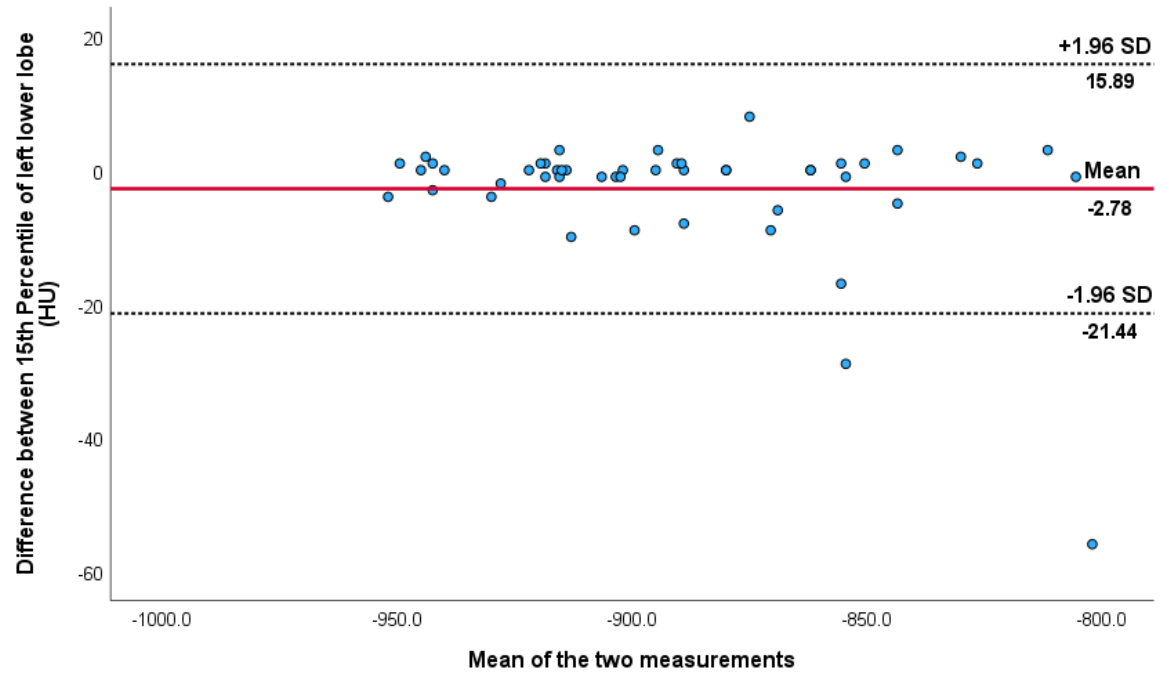

Figure 7.18 Agreement between Aview and CIP software programs for 15th percentile of left lower lobe

Next, we assessed Aview and CIP's agreement in MLD measurements. The ICC values demonstrate excellent agreement between the two software programs for the whole lung, right lung, left lung, right upper, lower lobes and left upper and lower lobes and range between 0.995 and 0.98 (Table 7.6). The mean difference of the MLD was reasonable with a difference between 1.8 and 7.6 HU; MLD difference of ≤ 10 HU is considered acceptable [292]. However, the LOAs were too wide for all measurements, with the widest seen in the right middle lobe and right lower lobe with upper LOA values of 24.8 and 34.5 HU, respectively. While the lower LOAs for the same lobes were -9.4 and -30 HU, respectively (Figure 7.19-7.26).

Table 7.6 Intra-class correlation coefficient between Aview and CIP in mean lung density (95% CI)

	ICC	Lower bond	Upper bond
Whole lung	0.992	0.979	0.996
Right lung	0.991	0.977	0.996
Left lung	0.993	0.982	0.996
Right upper lobe	0.995	0.989	0.997
Right middle lobe	0.975	0.863	0.991
Right lower lobe	0.977	0.959	0.987
Left upper lobe	0.995	0.982	0.998
Left lower lobe	0.98	0.965	0.989

ICC; Intra-class correlation coefficient, P <0.05

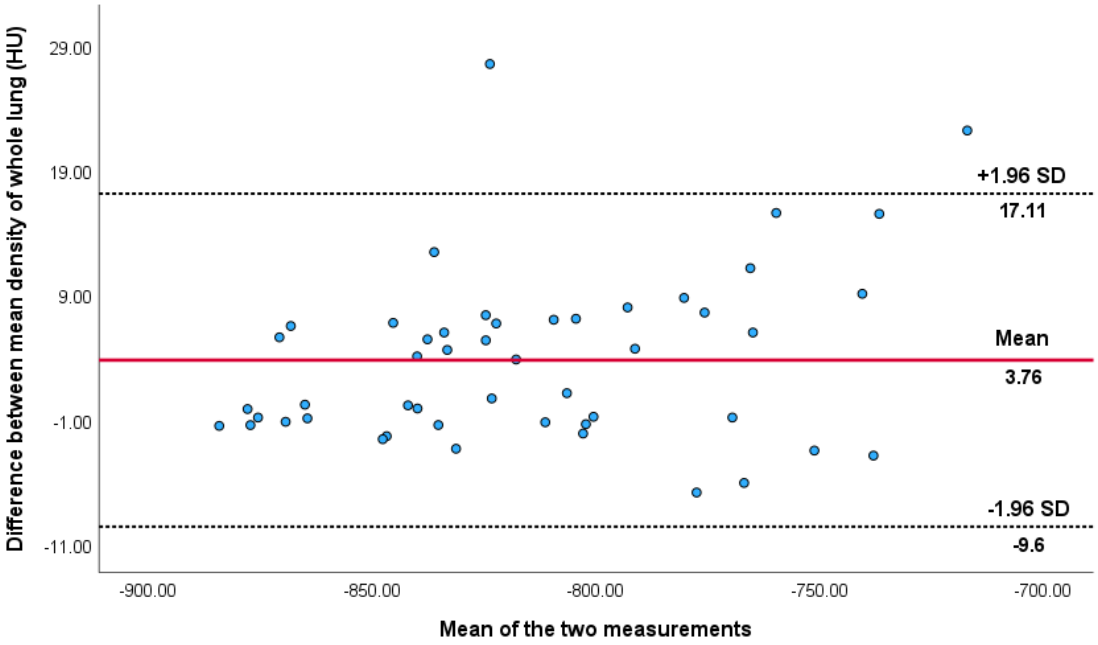

Figure 7.19 Agreement between Aview and CIP software programs for mean lung density of whole lung

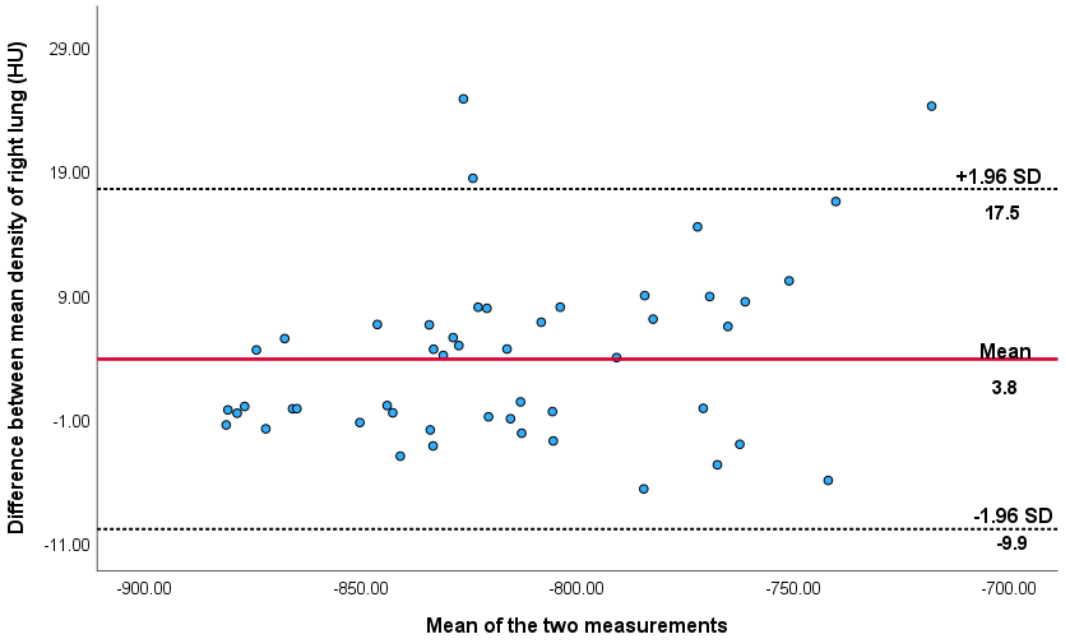

Figure 7.20 Agreement between Aview and CIP software programs for mean lung density of right lung

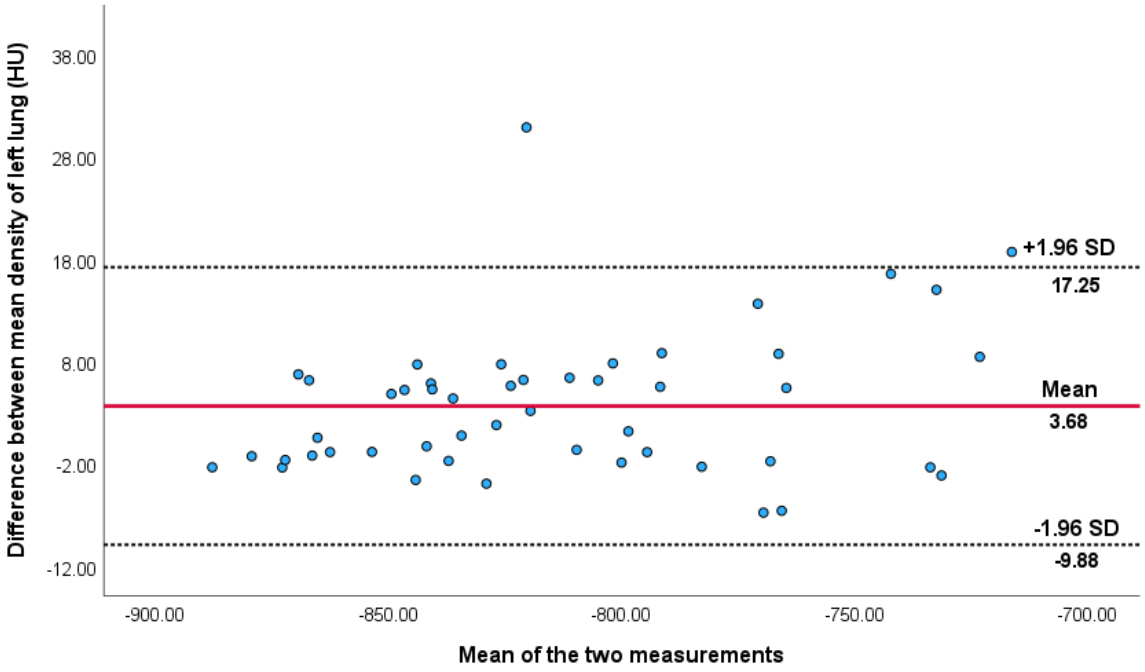

Figure 7.21 Agreement between Aview and CIP software programs for mean lung density of left lung

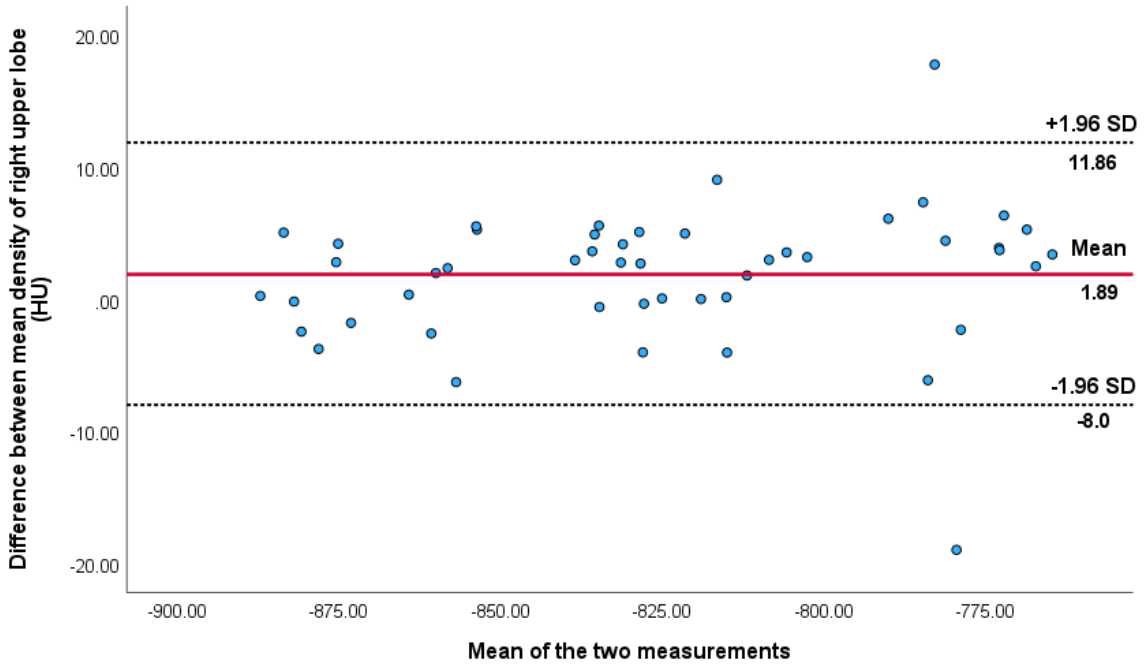

Figure 7.22 Agreement between Aview and CIP software programs for mean lung density of right upper lobe

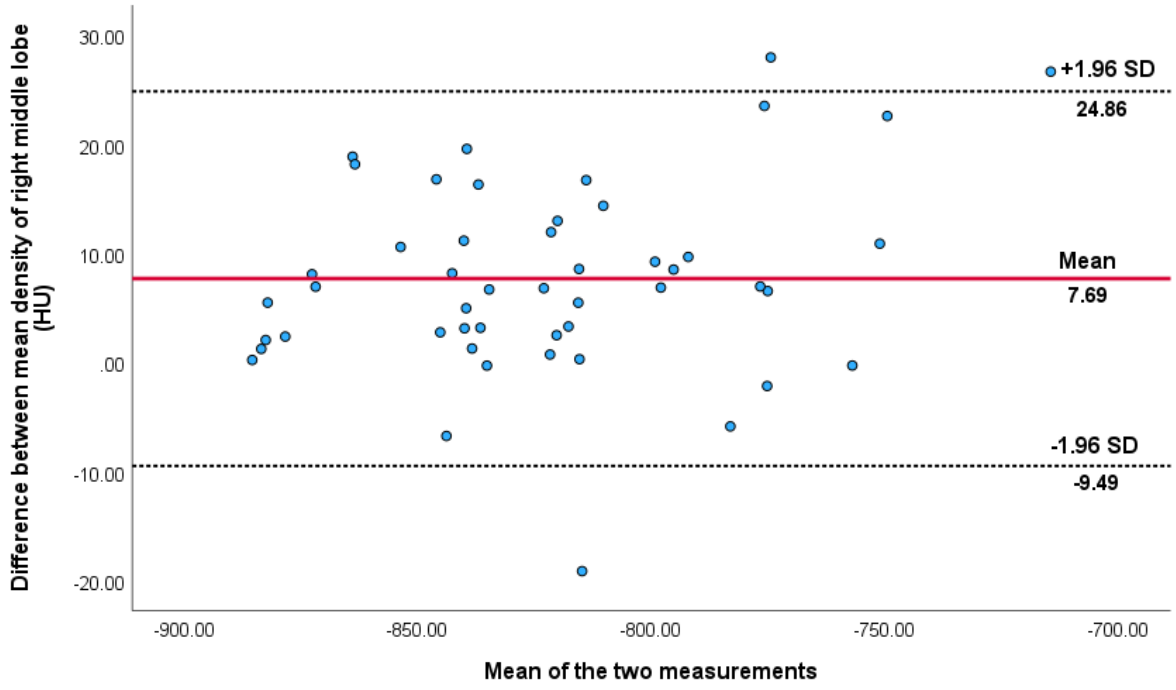

Figure 7.23 Agreement between Aview and CIP software programs for mean lung density of right middle lobe

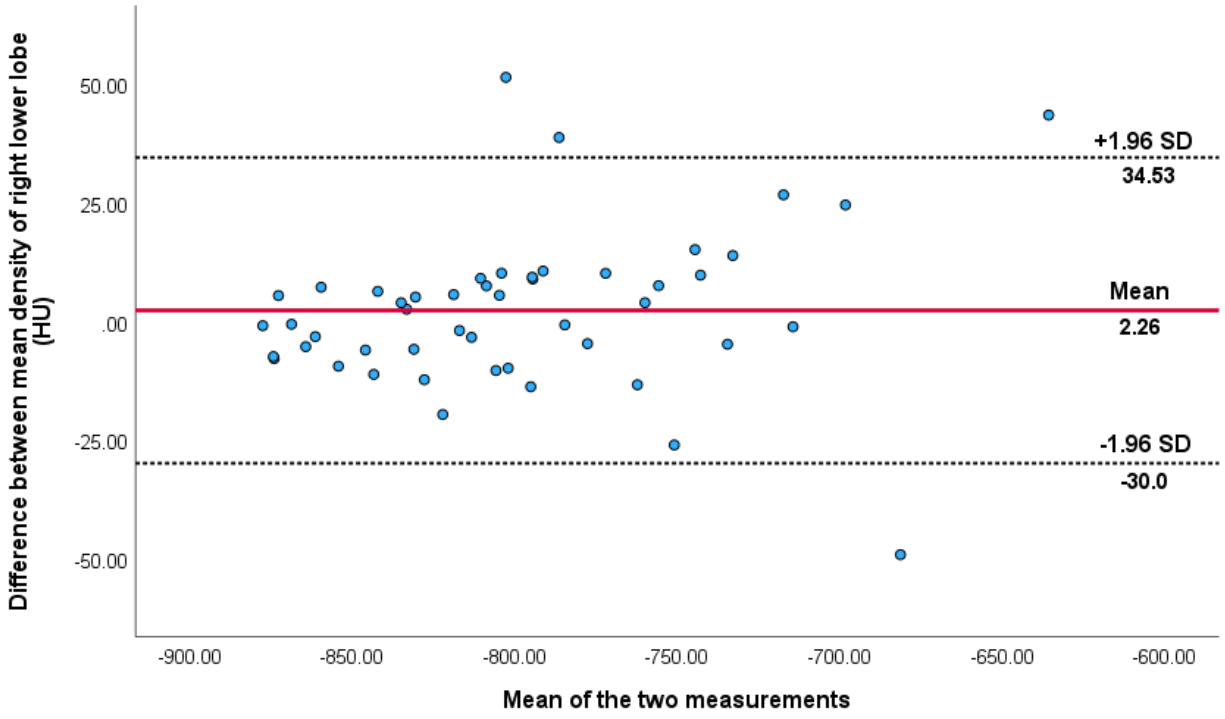

Figure 7.24 Agreement between Aview and CIP software programs for mean lung density of right lower lobe

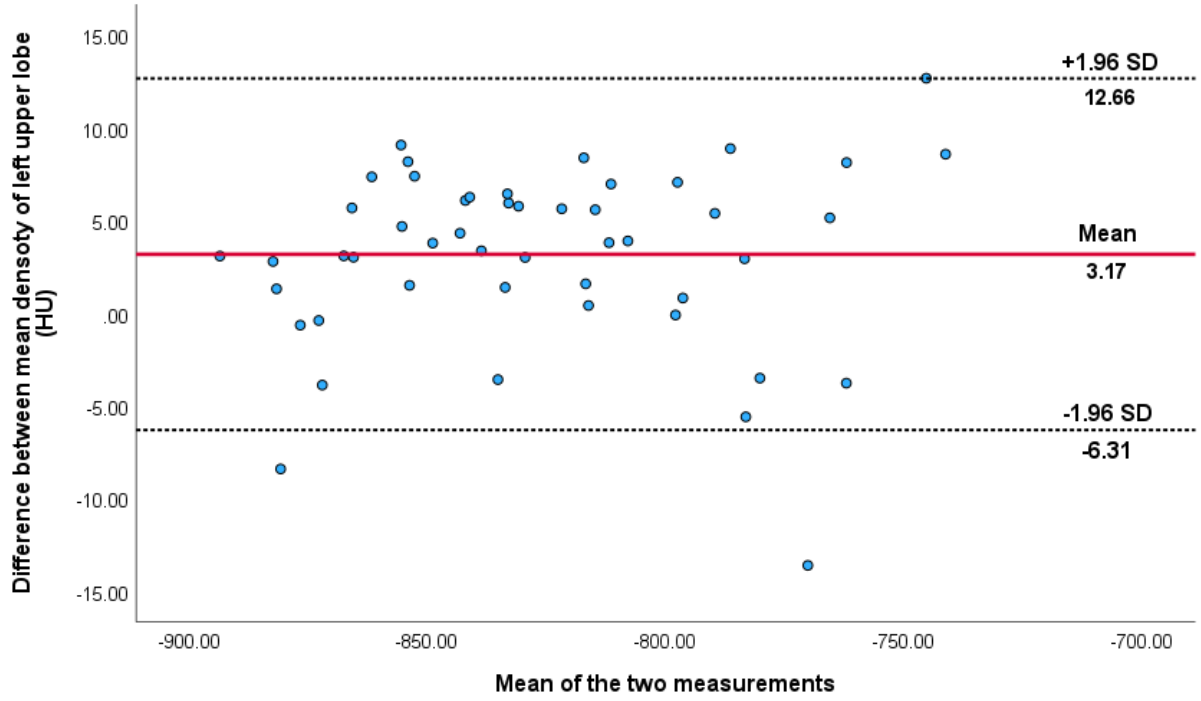

Figure 7.26 Agreement between Aview and CIP software programs for mean lung density of left upper lobe

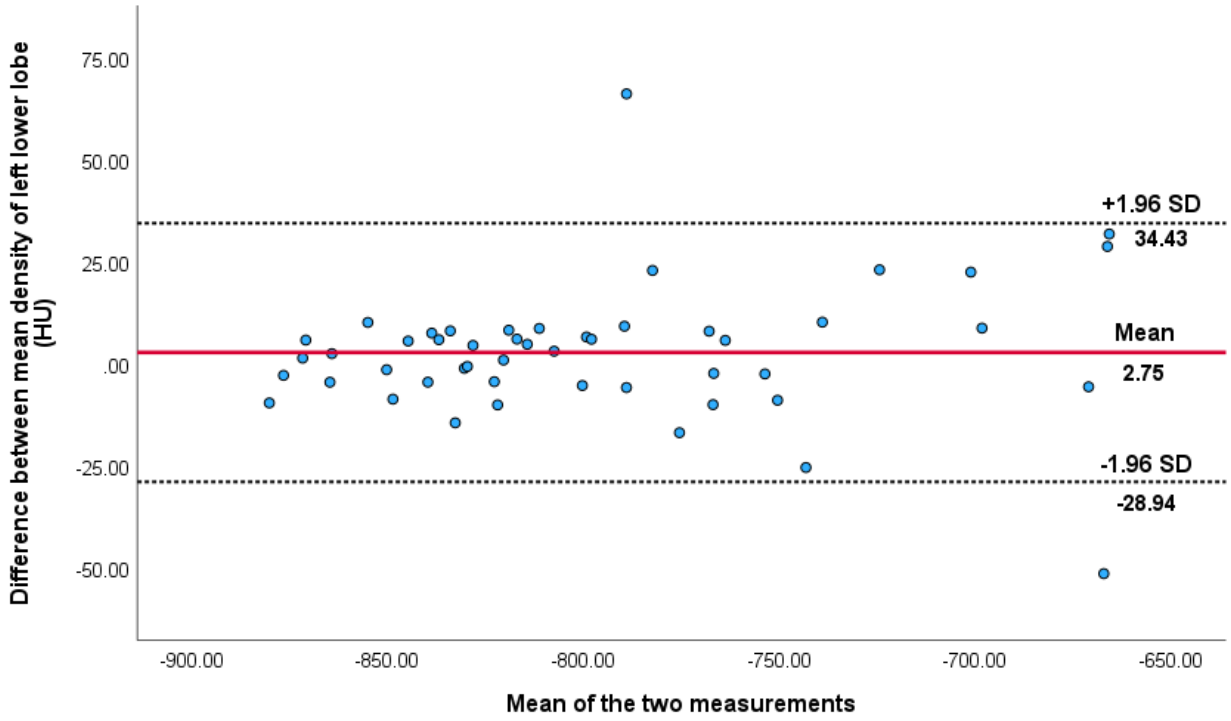

Figure 7.25 Agreement between Aview and CIP software programs for mean lung density of left lower lobe

Lastly, we have investigated the agreement between Aview and CIP in measuring lung and lobar volumes (L). The ICC showed excellent agreement between the two in measuring the volume of the whole, right and left lung (ICC = 1.0). Similarly for the right lower lobe, left upper lobe and left lower lobe, the two software programs exhibited excellent agreement (ICC = 0.97, 0.969, and 0.977, respectively). However, for the right upper and middle lobes, there was good agreement between the two (ICC = 0.886 and 0.846, respectively) (Table 7.7). The Bland Altman plots present reasonable mean difference between the two software programs in the whole lung, right and left lungs, and right middle lobe with a mean difference between 0.00 and 0.01 (L). A difference of ≤0.05 (L) is considered clinically acceptable [267]. However, the mean difference between the two in the right upper lobe was larger than the acceptable difference with a value of 0.06 (L). The LOAs are relatively wide, with multiple points lying outside for all measurements, and ranged from 0.03 to 0.2 (L) (Figure 7.27-7.34).

Table 7.7 Intra-class correlation coefficient between Aview and CIP in lung volume (95% CI)

	ICC	Lower bond	Upper bond
Whole lung	1.0	0.999	1.0
Right lung	1.0	0.999	1.0
Left lung	1.0	0.999	1.0
Right upper lobe	0.886	0.791	0.937
Right middle lobe	0.846	0.726	0.913
Right lower lobe	0.97	0.917	0.986
Left upper lobe	0.969	0.945	0.983
Left lower lobe	0.977	0.959	0.987

ICC; Intra-class correlation coefficient, P <0.05

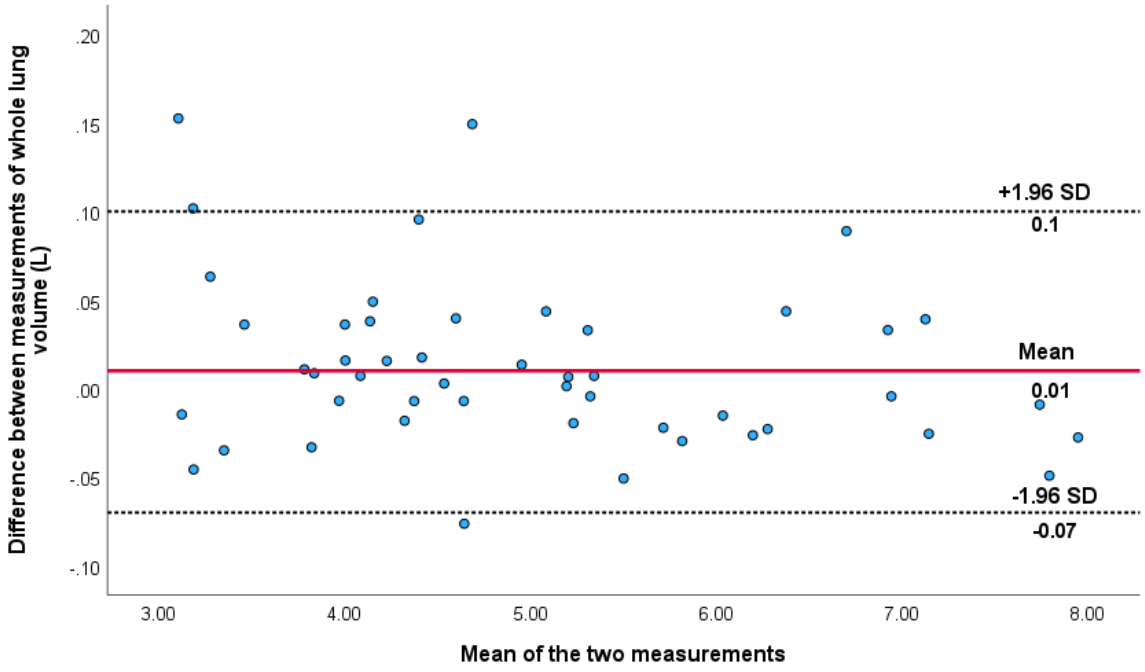

Figure 7.27 Agreement between Aview and CIP software programs for whole lung volume

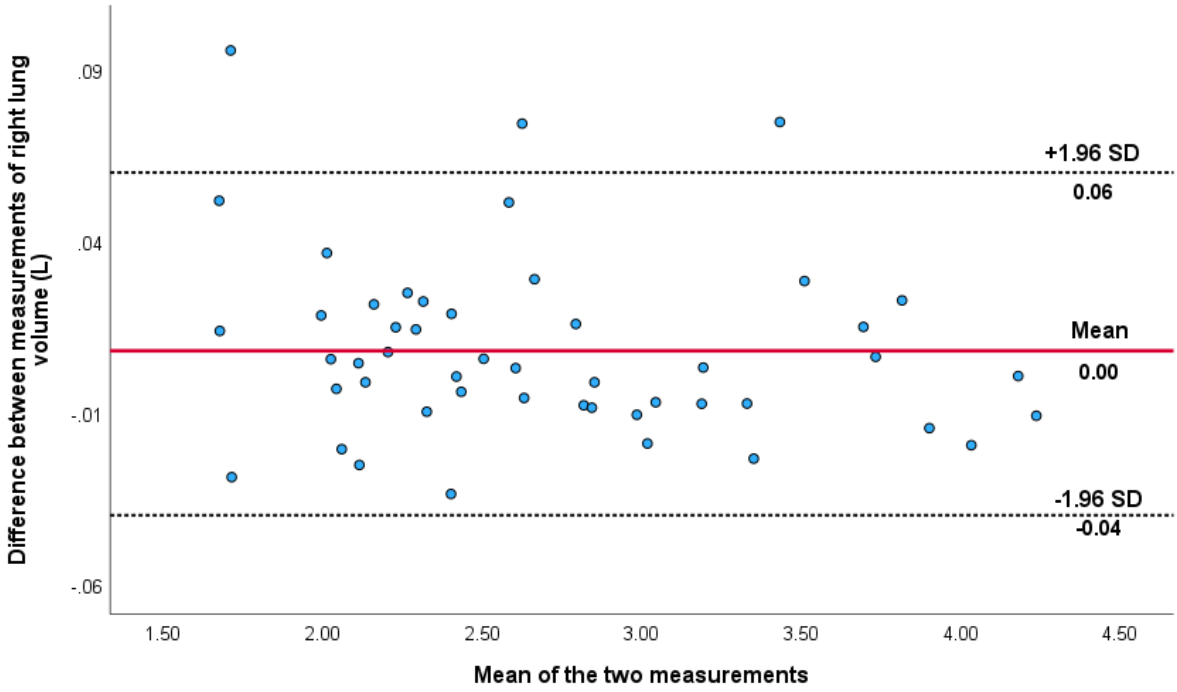

Figure 7.28 Agreement between Aview and CIP software programs for right lung volume

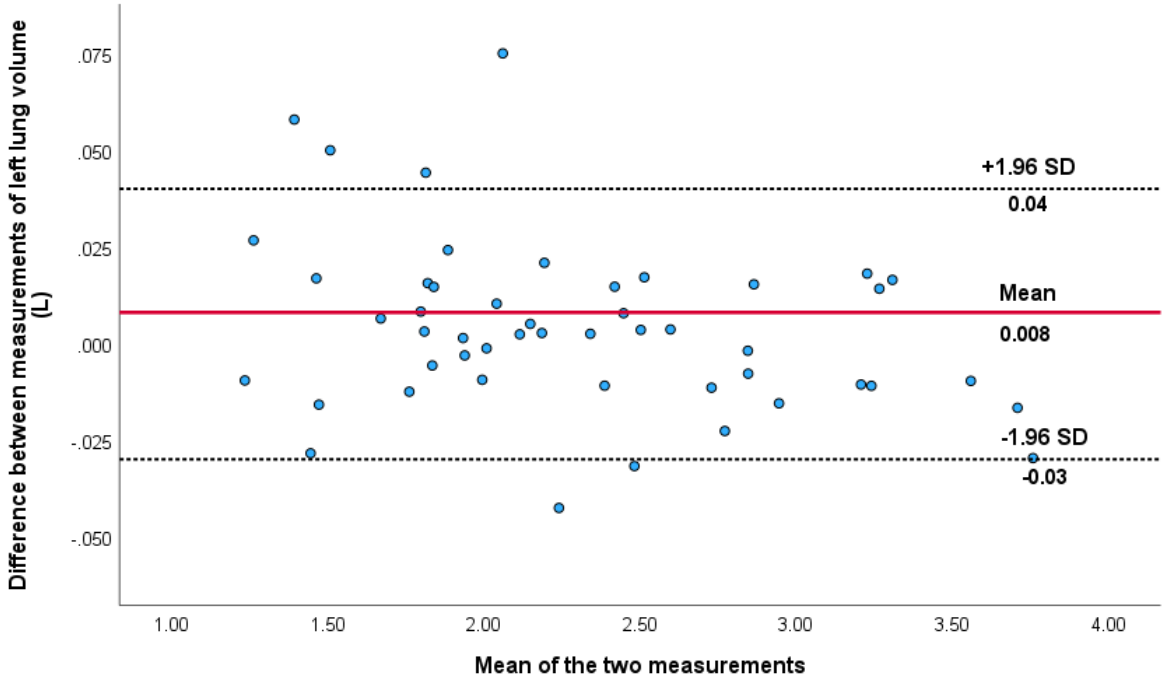

Figure 7.29 Agreement between Aview and CIP software programs for left lung volume

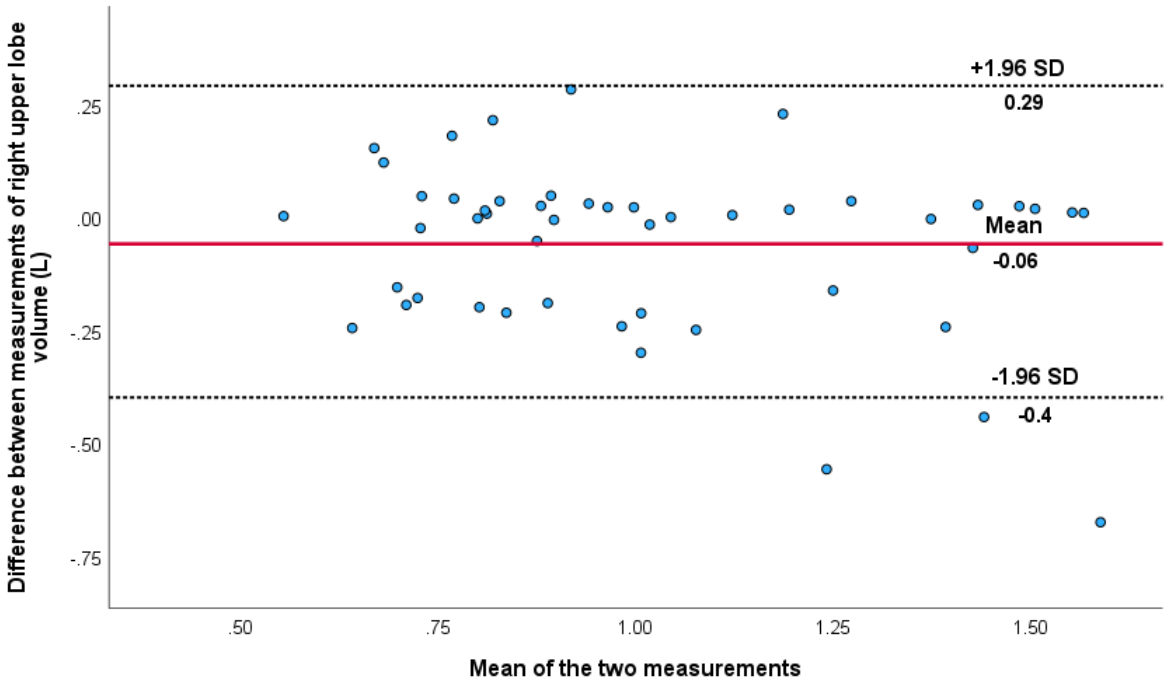

Figure 7.30 Agreement between Aview and CIP software programs for right upper lobe volume

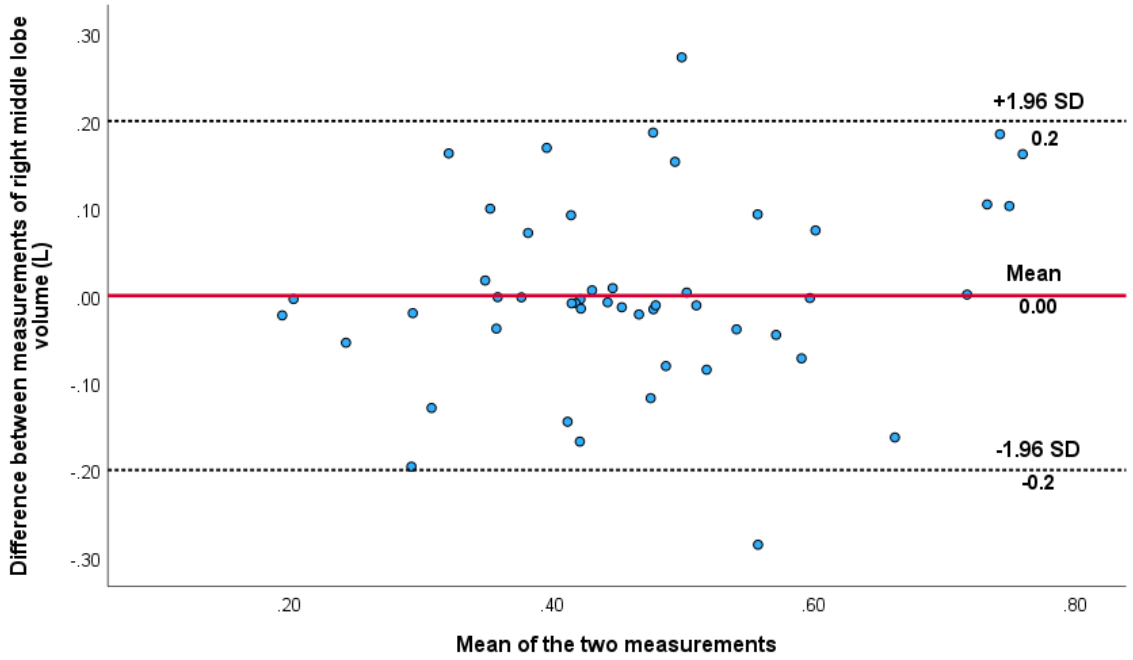

Figure 7.31 Agreement between Aview and CIP software programs for right middle lobe volume

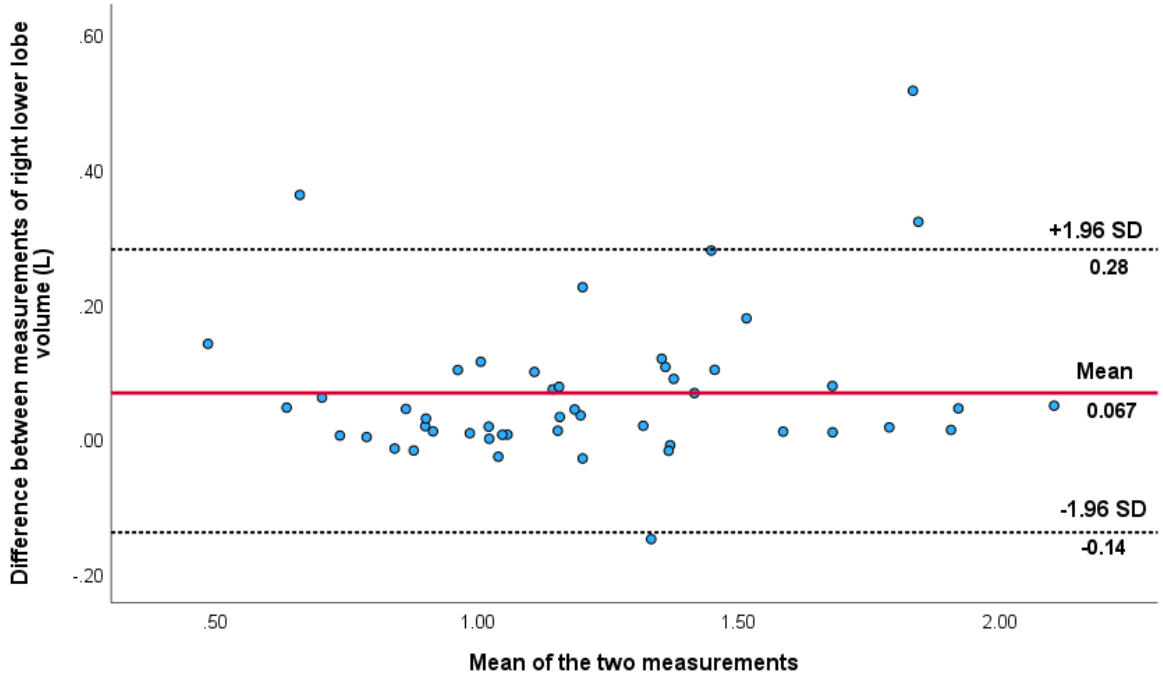

Figure 7.32 Agreement between Aview and CIP software programs for right lower lobe volume

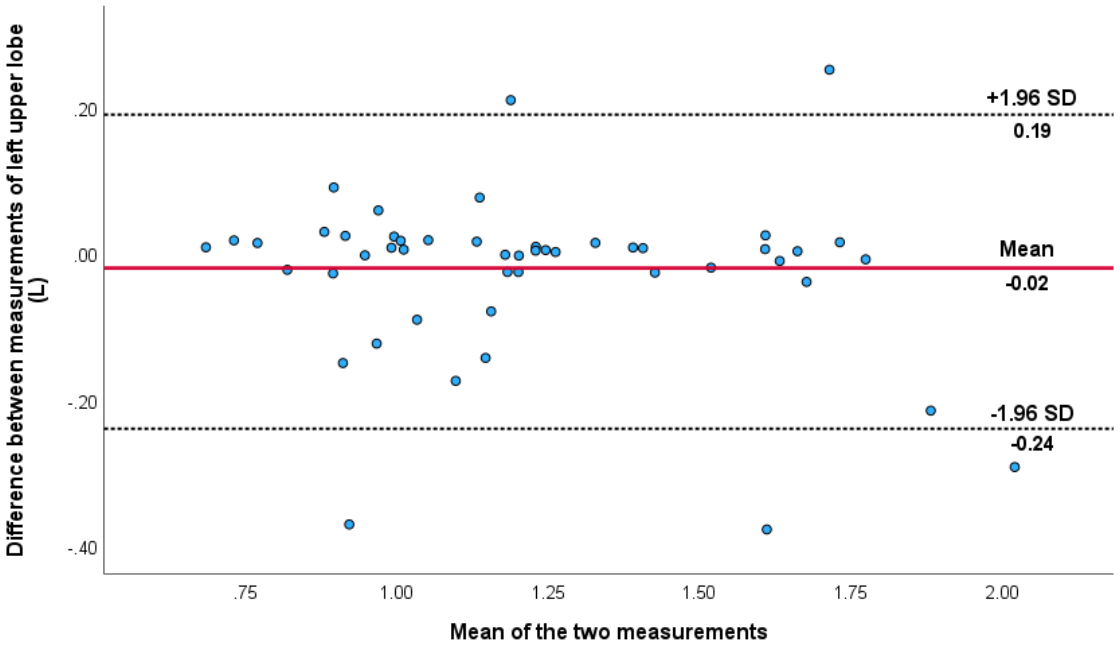

Figure 7.33 Agreement between Aview and CIP software programs for left upper lobe volume

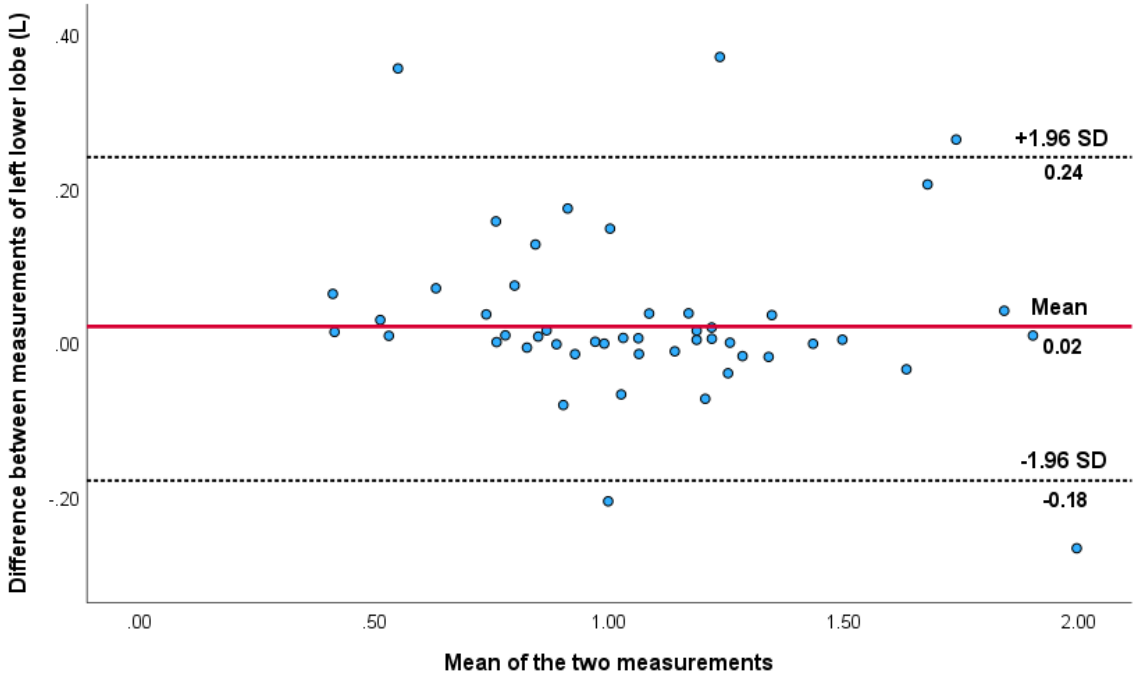

Figure 7.34 Agreement between Aview and CIP software programs for left lower lobe volume

7.4 Discussion

In large-scale studies, considerable efforts have been performed to minimize the variability of QCT so that it can be used as a biomarker for emphysema, one of which is the standardisation of CT scan parameters [367]. Nevertheless, with the rapid development of emerging technologies and the innovations of a variety of software programs, some of which require manual or semi-automated analysis while others are based on AI using different algorithms, the assessment of reproducibility of CT measurements among these programs is fundamental.

In the present study, we successfully analysed 95% and 82% of the CT scans using CIP and Aview, respectively, which is much higher than 43% of analysed CT scans achieved by previous research [278]. This study assessed the agreement between AI-based software that provides fully automated quantification of emphysema and CIP extension that allows for semi-automated quantification of emphysema on the whole lung and each lobe using unenhanced thoracic CT scans. The main finding of this study is that the inter-software agreement is excellent in all measurements. The intra-software reproducibility of %LAA-950 is excellent, and the mean differences (mean bias) and LOAs of whole lung and lobar measurements between the two software programs are minimal. Although we noted differences in some of the lobar volume segmentation, as shown in the Bland Altman plots, the high reproducibility of %LAA-950 among the two software programs is clear. These results are consistent with those observed by Kirby et al., who found that %LAA-950 was highly reproducible among eight different software programs even with the variation noted in lung volume segmentation [368]. In addition, the inter-software mean difference of %LAA-950 of the whole lung is smaller than those reported in previous studies which assessed the mean difference of %LAA-950 of the whole lung between eight different software programs [368], four software programs [369] and between three software programs [278].

In this research, we found good agreement and reasonable mean difference between the two programs in 15PD measurements for the whole lung and each lobe. The mean bias of whole lung PD15 measured in our results is smaller than in previous reports [368, 369]. In addition, the 95% upper and lower LOAs were reasonably narrow and less than 2 HU for the whole lung, right, and left lungs. In contrast, the LOAs of the lobar measurements of PD15 were slightly wider than the reasonable difference.

Similarly, the inter-software agreement in MLD and lung volume measurements is excellent. Despite the relatively small mean differences between these two programs, there are quite broad LOAs in both whole lungs and lung lobes. The variability between different software programs in MLD and lung volume has been reported previously [278].

A recent similar study by Kirby et al. examined eight commercial and academic software programs measuring whole lung volume, %LAA-950 and 15th Percentile of the whole lung in 50 patients with COPD [368]. They found relatively large variability between the eight software programs. In our results, the two software programs have shown reproducible quantifications of whole lung densitometry measurements except for the whole lung volume, which has a minor mean difference but slightly wider upper LOAs. This can be explained by the variation of the lobar volume segmentation by the AI software that requires manual correction, as has been noticed by the observer. The AI-based software produced a notification stating that the segmentation accuracy was suboptimal. Furthermore, studies performed in the past have mainly examined the reproducibility of different software programs in whole lung densitometry measurements, while variations in lobar measurements have not been examined in more detail as in the present study [368, 369].

According to Wielpütz et al., there is a possibility that the errors in CT quantification of emphysema are caused by the different algorithms that were employed in the software programs, airway

segmentation errors, and segmentation leakage; any of these factors could have contributed to inaccurate estimates of lung and lobar volumes [278].

It was not surprising to observe that the major sources of errors were in the right upper and middle lobes due to the horizontal fissure. Although several studies preferred fully automated quantification of emphysema parameters on CT scans due to its time efficiency, which is essential in clinical practice, it may not be completely reliable and improvements are still needed, imposing caution and a recognition of its limitations in clinical applications.

7.5 Limitations and Future research

This study was able to determine the agreement between AI-based software and semi-automated software in lung volume and density measurements. The main finding is that the intra-software variability is negligible in %LAA-950 quantifications. The retrospective nature of this study, however, results in a number of limitations. The sample size in this study is one of its limitations, although similar studies investigating inter-software reproducibility employed a similar number of observations [278, 368-370]. Moreover, we have not interfered with the automatic segmentation by manually adjusting the automatic lobar segmentation. We aimed, however, to assess the reproducibility of both software programs with an emphasis on standardising the measurement of the automatic CT lung volume and density. The AI-based software and other image analysis software should be evaluated to assess reproducibility using different acquisition parameters of CT scans and different manufacturer CT scanners. It is also necessary to assess the repeatability of these software programs over the long term in order to ensure the accuracy of the measurements.

Chapter 8. Overall Conclusions, General Discussions and Future Directions

8.1 Overall conclusions

Overall, the primary objectives of this thesis were:

- To investigate patients' HRQOL trajectories after lung cancer surgery and explore the association between patients' baseline demographic and perioperative factors with postoperative HRQOL.
- To evaluate the relationship between QCT measurements of lung density and postoperative HRQOL.
- To assess the relationship between sarcopenia and postoperative HRQOL.
- To compare fully automated AI-based software and semi-automated software programs in emphysema quantification.

Chapter 4: This study found that neither global health nor dyspnoea assessed by PRO returned to baseline levels six months following lung cancer surgery. Long-term consequences of lung cancer surgery are illustrated by the persistence of dyspnoea and the decline of patients' global health. Furthermore, the study revealed that baseline dyspnoea is strongly predictive of postoperative dyspnoea, even when controlling for baseline and perioperative factors. Similarly, baseline global health was an excellent predictor of postoperative global health. In light of these findings, it may be possible to use dyspnoea and global health scores prior to surgery to predict the future recovery of breathing and global health in lung cancer patients after surgery.

Chapter 5: This study demonstrated that %LAA-950, measured on unenhanced CT scans, is a valuable predictor of postoperative HRQOL, including dyspnoea and global health. Thus, %LAA-950 can serve as a valuable indicator for evaluating the potential impact of lung cancer surgery on QoL for patients with lung cancer. In contrast, %LAA-910 emerged as a weaker predictor for postoperative dyspnoea and was not found to be a reliable predictor for postoperative global health. %LAA-950 from contrast-enhanced CT scans is not comparable with unenhanced CT scans and, therefore, cannot be used to assess emphysema. These results confirm that alterations in CT density caused by contrast agents and differences in CT scanners and settings, among other factors, may impact the accuracy of emphysema quantification.

Chapter 6: The study results showed no statistically significant differences in muscle mass and sarcopenia between patients with increased and decreased dyspnoea based on computed tomography. Based on this finding, it is suggested that sarcopenia and muscle mass are not directly linked to the severity of dyspnoea after lung cancer surgery. Though the observations are not statistically significant, it appears that individuals who suffer from dyspnoea after surgery have more sarcopenic skeletal muscles at baseline. Considering this trend, it is reasonable to conclude that there may be a relationship between sarcopenia and dyspnoea, which warrants more investigation in greater detail. Moreover, we found no significant difference in sarcopenia between patients with recovered and declining global health. Lastly, the study showed significant correlations between lung function parameters (FEV_1 and FVC) and muscle mass. This correlation highlights the interaction between respiratory function and musculature, suggesting taking into account both aspects in assessing and treating patients.

Chapter 7: It was found that %LAA-950 was highly reproducible across AI-based and semi-automated software programs. There is a small mean bias and narrow 95% upper and lower LOAs in both methods, suggesting a strong consistency in measurements of emphysema. It was found that the two types of software had excellent agreement when measuring whole lung volume, PD15 and MLD. For lobar measurements, however, there was less agreement between the two software programs. There is a discrepancy between these two measurements, which may result from the limitations of present algorithms for measuring lung density and volume at the lobar level. Extended research in this area is necessary to guide the future development of software for the quantification of emphysema, aiming to improve accuracy and reliability in the lobar analysis.

8.2 General discussion

8.2.1 Patients reported outcomes in predicting postoperative quality of life

In recent years, there has been a continuing academic interest in applying PRO across various cancer types worldwide. The questionnaire response rate in our study was 75%, which is considered a good response rate considering the large cohort compared to previous research that collected smaller sample sizes. In our study, we assessed 906 patients with lung cancer surgery, and nearly half of these patients underwent thoracotomy. In contrast, similar research investigated only 95 lung cancer patients with minimally invasive surgery and acquired only 72% questionnaire completion rate [106]. Therefore, the contribution of this study may extend the body of knowledge in this field.

This thesis presents evidence illustrating that patients experienced significant declines in several HRQOL domains immediately after lung cancer surgery. Most of these domains had recovered at six months; however, dyspnoea and global health had not recovered. Similarly, the EORTC QLQ-LC13

trajectories confirmed our findings for QLQ-C30 symptoms and indicated that surgery had a detrimental effect on dyspnoea at six months, with no improvement found. Moreover, our results revealed that nearly 50% of the respondents suffered from worsening in their global health and dyspnoea at six months following lung cancer surgery.

In light of the results of these trajectories, this prospective longitudinal study aimed to explore the factors associated with postoperative dyspnoea and global health at six months, with around 673 patients completing the PRO involved in the analyses. In this study, patients' baseline PRO remained a significant predictor of postoperative HRQOL even after adjusting for baseline demographic and clinical factors. In other words, patients with high baseline dyspnoea or poor baseline global health are more likely to experience worsened postoperative dyspnoea or global health. Moreover, we revealed that patients' lung function measures were not significantly associated with postoperative dyspnoea or global health, except for %DLCO and PpoDLCO. Thus, lung function volumes alone should no longer determine a patient's risk for postoperative dyspnoea or global health after lung cancer surgery.

Furthermore, the current result highlighted that overweight and obese patients might experience impaired postoperative HRQOL, including dyspnoea and global health, after lung cancer surgery. However, there were no patients in this study with low BMI, which has been associated with adverse health outcomes in previous reports. Additionally, we have shown preoperative smoking has been shown to impact postoperative dyspnoea and global health. Moreover, as measured by ECOG, poor patient performance was significantly associated with impaired patient HRQOL. As a consequence of these results, it is suggested that patients' BMI be considered when counselling the patients regarding their breathlessness after lung cancer surgery. Surgical patients should be encouraged to participate in lung rehabilitation and smoking cessation programs before undergoing surgery for lung cancer. This study found that patients with prolonged hospitalisation may suffer more deterioration

to their global health and increased dyspnoea. Lastly, this study revealed that chemotherapy was significantly associated with postoperative global health but not dyspnoea. Overall, the current finding highlights the importance of using PRO and other clinical data in assessing patients' suitability for lung cancer surgery.

8.2.2 Quantitative computed tomography of emphysema in predicting postoperative quality of life

While medical research has made significant progress, there is still an insufficient understanding of how lung disease affects patients with lung cancer after lung cancer surgery, particularly dyspnoea and global health. Since CT scans are commonly used to stage lung cancer, utilising the additional information obtained from these readily available scans offers a valuable opportunity for improving clinical knowledge. In addition, lung cancer screening programs designed to enhance early detection are expected to improve survival rates significantly [10]. As a result, patients' HRQOL may become an increasingly important concern in their treatment journey.

Our study demonstrated that preoperative QCT of %LAA-950 could be a non-invasive biomarker for postoperative dyspnoea and global health after lung cancer resection. Despite the initial intention of evaluating contrast-enhanced CT scans using several thresholds of CT emphysema, the effectiveness of these scans in predicting postoperative HRQOL was not comparable to that of non-enhanced CT scans. We noted that the extent of emphysema density on CT scans nonuniformly enhanced among the patients, which multiple factors may explain. Aside from the administration of contrast agents, the type and settings of the CT scanners, the depth at which the patient breathes, as well as smoking history all play vital roles in influencing the density of emphysema. Consequently, determining a

correction factor was difficult without simultaneously performing several paired contrast-enhanced and unenhanced CT scans while maintaining other variables as constant as possible.

This study showed that %LAA-950 effectively predicted postoperative dyspnoea and global health, remaining a strong predictor even after controlling for baseline demographic and clinical factors. As has been revealed previously, patients with a higher %LAA-950 at baseline may have higher probabilities of increased dyspnoea and worsened global health after lung surgery.

Additionally, our results confirmed previous studies that %LAA-910 has a weaker relationship with dyspnoea than %LAA-950 [203]. In the present study, %LAA-910 was not consistently effective for predicting postoperative dyspnoea, especially when adjusted for the PRO dyspnoea domain. Moreover, the current study found that %LAA-910 could not predict postoperative global health.

Lastly, we have compared contrast-enhanced and unenhanced CT and reported the significant differences between the two techniques in %LAA-950 and -910 quantification. Therefore, this thesis confirms previous recommendations of employing unenhanced CT scans for emphysema quantification, emphasising utilising %LAA-950.

8.2.3 Investigating the impact of CT-measured sarcopenia on the quality of life after lung cancer surgery

The primary objective of this study was to explore the relationship between CT-based body composition and HRQOL after lung cancer surgery. This study measured four types of muscles on thoracic and abdominal CT scans, including PM and ESM on thoracic CT scans and PSM and SM on abdominal CT scans. The author considered it essential to involve various muscle types to fully assess these muscles, considering that not all patients undergo abdominal CT scans.

We found that muscle mass or sarcopenia did not significantly affect patients' HRQOL. Nevertheless, we observed that individuals with higher levels of dyspnoea tend to have more sarcopenic muscles. Additionally, there was no difference in sarcopenia for those with recovered vs. deteriorated global health. Though the results of this study did not reach statistical significance.

This can be attributed to several factors, including measuring muscle mass, which does not always reflect its functional state, so the relationship between these two measures might be weak. The EWGSOP2 has updated its algorithm for diagnosing sarcopenia, recommending muscle strength as the first step in the initial assessment of the condition. When muscle strength is determined to be insufficient, additional confirmation must be obtained through analysis of quality and quantity of muscle on medical imaging [73].

In order to illustrate this, two athletes can be compared: a bodybuilder and a marathon runner. The typical bodybuilder has large muscles built through weightlifting for muscle hypertrophy. It can be concluded that this individual has large muscle mass, which indicates strength and power. However, it is vital to note that bodybuilders do not necessarily possess high functional muscle strength for all activity types. The muscle mass of a marathon runner may appear less visible than a bodybuilder's. While marathon runners possess lower muscle mass, they have a high level of muscular strength, which allows them to perform long-distance activities efficiently [374].

Another possible factor is that measuring muscle mass at a single time point may not reflect the level of muscularity of the patients. It might be more helpful to measure longitudinal skeletal muscle loss to understand the severity of sarcopenia in patients better.

It is vital to consider that muscle quality, instead of muscle mass, maybe a more accurate indicator in this study. Due to the use of contrast agents in the scans, it was not feasible to evaluate muscle quality

typically estimated by muscle density. Given this limitation, a comprehensive investigation of the muscle quality may have provided a deeper understanding of the association.

While investigating the relationship between muscle mass and lung function was not one of the primary objectives of this study, the author was interested in a better understanding of these relationships as the cohorts being examined are lung cancer patients who are primarily assessed for their risk based on their lung function; therefore, a better understanding of these relationships is of value. The result of this exploratory analysis highlighted a significant correlation between FEV_1 and FVC with muscle mass. On the other hand, there was no meaningful relationship between FEV_1/FVC and muscle mass. This perhaps can be attributed to the fact that the FEV_1/FVC ratio represents the obstruction of the upper airway that may not be affected by sarcopenia [352].

8.2.4 An investigation of the agreement between AI-based software and semi-automated software in quantification of emphysema on CT

We live in the Fourth Industrial Revolution, and there has been a significant increase in the use of AI in the last decade, which has influenced how diagnoses are made [259]. In this study, AI-based software and semi-automated software were evaluated for CT quantification of emphysema. As a key finding, %LAA-950 was highly reproducible, and there was excellent agreement between the two software programs. While the Bland Altman plots revealed differences in some lobar volume segmentation, %LAA-950 is highly reproducible between the two software programs.

While AI promises automation, time efficiency, and accuracy, our study found inaccuracies when it comes to segmenting the lobar lungs with AI-based software. While image analysis has progressed significantly through AI software, its ability to segment lobar lung regions remains limited, requiring manual intervention by professionals. The author deliberately refrained from intervening in its image

analysis process to gain a more in-depth understanding of the AI's inherent accuracy and capabilities. Notably, these findings are particularly relevant to the expanding use of imaging for diagnosing and treating lung diseases, in which accurate lung segmentation plays a vital role. There are many reasons lobar volume segmentation on CT was inaccurate, including using different algorithms in the analysis software, errors in segmentation of the airways, and segmentation leakage. These elements might have contributed to the erroneous estimation of lung and lobar volumes [278].

Even though accurate and repeatable measurements of lobar volume and density on CT scans are essential, research tends to focus primarily on the reproducibility of whole lung measurements. Consequently, a critical gap exists in understanding lobar CT quantification's reproducibility, which is crucial in investigating lung diseases. In our study, we have excellent agreement, small bias, and narrow 95% upper and lower LOAs for whole lung CT quantification of volume and density metrics.

In addition, we revealed that the mean bias of PD15 and MLD was relatively small in all measurements; however, 95% upper and lower LOAs for the lobar analyses were somewhat wider than reasonable differences. A significant source of errors was observed in the right upper and middle lobes, mainly due to the horizontal fissure. Despite that, many studies have emphasised the advantages of fully automated quantification of emphysema parameters on CT scans in terms of its time efficiency - an important factor in clinical practice - and the accuracy of these tools. While AI-based CT image analysis is advancing rapidly, significant development and training remain required. Currently, the accuracy of the assessed AI software is not optimal, highlighting the need for continued research and development. Future studies are warranted to improve the precision and reliability of these software programs, assuring they meet the standards required for clinical application.

8.3 Clinical implications

8.3.1 Utilising PRO in evaluating patients' risk

This research has demonstrated that baseline HRQOL predicts postoperative dyspnoea and global health in lung cancer surgery patients. We have shown that longitudinal PRO collection in lung cancer patients with surgery is feasible. Moreover, PRO can assist in preoperative counselling, tailoring the patient's plan, and providing the patient with an expectation of what their HRQOL might be post-surgery. The current study found that every 1 unit increase in baseline dyspnoea is associated with 207% greater risk for higher levels of dyspnoea compared to those with score 0. In addition, patients with 10 units higher baseline global health are more likely to experience a 5 units improvement in the postoperative global health compared to those with lower baseline scores. Hence, patients with higher baseline dyspnoea and poorer global health may require more monitoring after surgery; customised pulmonary rehabilitation programs may address the effects of long-term dyspnoea increase and poor HRQOL following surgery.

8.3.2 Using QCT of emphysema in patients' risk assessment

In this study, we have revealed that preoperative QCT of emphysema can predict postoperative dyspnoea and global health. Every 1 unit increase in %LAA-950 is associated with 20% greater risk to experience the highest level of dyspnoea. Considering that CT scans are readily available through routine clinical investigations, researchers and clinicians may find using this non-invasive biomarker appealing. By integrating PRO and QCT measures of emphysema into clinical practice, significant clinical implications could be achieved, involving comprehensive patient assessment, improving treatment planning and monitoring, all of which contribute to enhanced patient outcomes and care.

8.3.3 QCT body composition: Potential clinical implications

In the present study, we have compared sarcopenia in patients with improved or deteriorated HRQOL. There was a noticeable pattern in the results despite the lack of statistical significance; patients who demonstrated lower HRQOL following lung cancer surgery were more likely to have sarcopenia. Thus, patients with sarcopenia may experience poorer recovery outcomes following surgery. Consequently, this underscores the importance of assessing muscle mass before surgery during a comprehensive evaluation of patients with lung cancer. The study emphasised the potential benefits of targeted interventions aimed at improving muscle mass prior to surgery, such as nutritional support or physiotherapy. The potential benefits of this proactive approach include enhanced postoperative recovery and improved HRQOL overall. Future research should involve larger sample sizes and longitudinal studies to explore this relationship in greater detail and validate these preliminary observations.

8.3.4 Utilising AI-based tools for the quantification of CT emphysema in clinical settings

The disagreement detected in this study between AI-based software and semi-automated lobar quantification of emphysema, mainly due to AI software's imprecise segmentation of the lobes, has important clinical implications. First, the results pointed out the need for careful integration of AI tools in this area. This study suggests that some AI tools may lack the accuracy to make complex clinical decisions for patients with emphysema despite their promise of being fully automated and efficacious and reducing workloads for healthcare professionals. This segmentation error may result in inaccurate assessments, which in turn may negatively affect treatment planning and patient outcomes. Consequently, rigorous clinical validation of AI tools is essential before they are widely implemented in healthcare facilities.

8.4 Limitations

In the relevant chapters, we discussed the limitations of the methods employed in the individual studies. As with most previous studies, compared to the baseline number of responses, this study has imposed some limitations, one of which is a decrease in the number of PRO responses. However, the strength of this study is the large sample size employed in the analyses and the investigation of several baseline demographic and perioperative factors that can add information to the knowledge gap. The dose and number of cycles of adjuvant chemotherapy some patients received may also negatively impact their QoL. Yet, we investigated the impact of chemotherapy on patients' QoL in this study. The main limitation in the assessment QCT of emphysema is the selection bias, which was unavoidable due to its retrospective nature. The small sample size of this study is due to the limited number of unenhanced CT scans available for the study. Another limitation is the variety of the CT scanner manufacturers, acquisition protocols, and settings. For CT body composition study, as a first point, the small sample size due to the retrospective nature may limit the generalisability of this study. The attenuation of the muscle, which reflects the muscle quality, was not assessed due to the use of contrast-enhanced CT scans that may affect the measurement of the muscle density and produce inaccurate results. Additionally, the limitation of our study is that it involved only intra-observer agreement and did not extend to assessing inter-observer agreement. Still, the study did evaluate the agreement between our semi-automated analyses and those analysed by fully automated AI-based software. Besides, the study could not examine the change in skeletal muscles over time, which might be a more accurate indicator of the outcome of postoperative surgery. Lastly, the small sample size in the last study was the main limitation. Yet, several studies investigating the reproducibility of different software measurements employed similar sample sizes.

8.5 Future directions

During the first study, we evaluated the HRQOL of patients following lung cancer surgery over six months. In the future, it is imperative that this research be extended to monitor HRQOL for a longer time. The study will allow for a better understanding of the long-term effects of lung cancer surgery on the HRQOL of the patients. Future research on the compliance of patients with PRO measures is clearly required. In longitudinal studies, it is imperative to identify the factors responsible for the observed decline in response rates. By gaining such insights, we will not only enhance the reliability of PRO data but also enhance the engagement of patients and ensure that their responses are consistent during future HRQOL assessments. Additionally, future research will employ propensity score matching analyses to compare QoL between patients undergoing lobectomy and those undergoing wedge resection, to gain a deeper understanding of the surgery's impact on HRQOL.

In routine examinations for lung cancer patients, contrast-enhanced CT scans are mainly used. Among the key areas of focus will be the development of corrective factors to account for variations in lung density induced by contrast administration in order to enhance the accuracy and reliability of these assessments. It is also relevant and valuable to explore the potential benefits of QCT scans from PET in predicting postoperative HRQOL, given that PET CT scans are routinely incorporated into clinical investigations for lung cancer patients. The sample size of this study was limited. Ideally, future research should be conducted with a larger cohort to enhance the findings' robustness and generalisability.

In body composition research, there is a critical need for additional studies focused on examining malnutrition and weight loss to understand better how these factors affect patient outcomes and HRQOL. Longitudinal research is vital to a better understanding of sarcopenia progression after lung cancer surgery and its impact on HRQL and other clinical outcomes.

Lastly, it is essential to evaluate the repeatability of the software programs utilised for emphysema quantification over the long term to ensure the accuracy of the measurements and assess the AI-based software on diverse datasets to ensure its reliability.

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Appendices

Appendix1: EORTC QLQ-C30 Questionnaire

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋
Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋
Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

Appendix2: EORTC

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

QLQ-LC13 Questionnaire

ENGLISH

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4