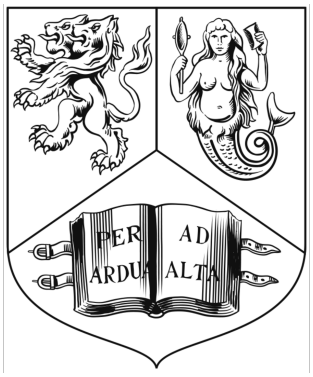
Assessment of the risk of post-operative pulmonary complications and mortality using analytic morphometry in patients undergoing major non-cardiac surgery



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Abstract

Some 20% of patients undergoing major abdominal surgery develop post-operative pulmonary complications (PPC). This is a nebulous group of respiratory pathologies that occur frequently after major abdominal surgery, significantly impacting functional recovery and survival.

Effective preoperative risk stratification and prevention are crucial for optimal clinical outcomes. Thorough pre-operative assessments usually include full-body imaging. However, the valuable information obtained is not fully utilised. This untapped quantitative data provides an opportunity to identify new biomarkers (radiomarkers, morphomarkers) associated with PPC and survival, enhancing preoperative risk assessment understanding and improving patient care.

Two cohorts of patients were retrospectively analysed in this thesis: a cohort of patients with aortic pathology and a cohort of patients with colorectal cancer. The morphometric body composition parameters were analysed prospectively using Terarecon software.

I established the incidence of PPC which were higher than reported in the literature for the vascular cohort (24.2%) and within expected range for the colorectal patients (9.2%). I also established factors associated with PPC and their relation to mid-term survival. The presence of peripheral arterial occlusive disease (PAOD) and aneurysm diameter in vascular patients, as well as pre-existing chronic lung conditions (CLD), lymph node involvement at level N1 and N2, dementia, atrial fibrillation (AF), white cell count (WCC), male gender in colorectal cancer patients, are the most important independent risk factors for the development of PPC. It was established that PPC development was independently associated with survival in colorectal cancer patients.

I investigated the associations between quantitative computed tomography (CT)-derived structural lung morphology with PPC and survival. This resulted in the identification of potential new morphomarkers that could be useful in preoperative stratification of the patient's risk. Lung tissue volumes measured at certain Hounsfield Units (HU) thresholds (high, normal, and low attenuation areas measured at $HAA_{(VOL)}$ -850 to -500 HU, $NAA_{(VOL)}$ -850 to -750 HU, and $LAA_{(VOL)}$ -950 HU) and airway volume were associated with PPC development and survival following vascular and colorectal cancer surgery, respectively.

Evaluation of indices of body composition including psoas, diaphragm muscles, and abdominal adipose tissue identified diaphragm thickness as an important morphomarker that may be useful in identifying patients at risk of developing PPC. I also analysed these in the context of survival, demonstrating a significant association between diaphragm thickness and total psoas muscle area (TPA) and survival in colorectal cancer patients.

The inclusion of lung morphology and body composition morphomarkers to clinical regression models alongside clinical patient-related factors improved their overall performance and predictive ability for PPC and survival.

Lung morphology and body composition morphomarkers can form a useful, otherwise not used, set of factors that should be used in preoperative assessment. Further work is warranted to build predictive, rather than exploratory models using morphomarkers described in this thesis. Machine learning models could be useful in not only facilitating this, but also helping in developing new lung analysis techniques.

Defined PPC by the European Joint Task-Force for Perioperative Clinical Outcomes (EPCO), are a heterogenous group of complications with different aetiology. It is therefore unsurprising that despite their important association with mortality, the relation with lung structure and composition is not uniform. Further research is required to determine usefulness of assessment of lung morphometry and body composition in stratification of perioperative risk in patients after non-thoracic, non-cardiac procedures.

Declaration

DECLARATION CONCERNING THESIS PRESENTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

I, Abdulrhman Gazwani of Institute of Inflammation and Ageing, University of Birmingham, solemnly and sincerely declare, in relation to the thesis entitled: “Assessment of the risk of post-operative pulmonary complications and mortality using analytic morphometry in patients undergoing major non-cardiac surgery” that presented material has not previously been accepted in whole, or in part, for any other degree or diploma.

Signature:  Date:

Dedication

To my beloved wife, for her unwavering
support and endless love that has been the bedrock of my journey.

To my parents, whose sacrifices have shaped my path and whose belief in me has been my guiding light.

And to those colleagues and friends at King Faisal Hospital and Research Centre who ignited my passion for research and paved the way for this academic pursuit.

This work stands as a testament to your collective influence on my life.

Acknowledgements

I praise Almighty Allah for offering me a healthy environment to accomplish this project.

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I would like to acknowledge those who contributed to my research journey: special thanks to Sarah Harley, Clive Allen, Samantha Cheng, and Kathryn Brown for their invaluable support in conducting body composition analysis and collecting data for the vascular cohort. Additionally, I extend my gratitude to Wei Chuen Mak for providing support in conducting lung and diaphragm morphometric analyses for the vascular cohort. Nicola Philips for administrative support and securing flawless access to hospital facilities, and Martin Claridge for enabling the project to be undertaken at UHB.

I am deeply grateful to my wife; I could not have finished this PhD without her. Additionally, I would like to thank my parents, sisters, and brothers for their encouragement to finish this project. Thank you all for your love and prayers. Lastly, to my beloved ones who believed in me.

I would like to express my sincere gratitude to my supervisors. Dr. Maciej Juszczak for his unwavering support. His valuable guidance was always inspiring, and his exceptional patience allowed me to complete my PhD. Professor Fang Gao Smith's wisdom and encouragement have been essential in navigating the challenges of my PhD.

I would like to offer my special thanks to the Ministry of Defence (the Armed Forces Medical Services) and Prince Sultan Military College of Health Sciences in the Kingdom of Saudi Arabia for funding me; without their generous funding, this project would not have been feasible.

I want to highlight that each PhD journey comes with its own set of challenges, and my first and second years, particularly during the COVID-19 pandemic, were demanding. Despite these challenges, I persevered and progressed, with support from the university, supervisors, and clinicians involved.

I would also like to thank Free Software Foundation, R community, Draw.io, LaTeX and LyX teams for providing unmatched quality software for free.

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Description of thesis

Chapter 1 (Introduction) explains the concept of post-operative pulmonary complications (PPC), definitions, classifications, and review of current literature. It also describes the status of pre-operative assessment, national and international guidelines, models used for prediction of PPC and the prevention strategies. This chapter included the overarching hypothesis, general aims, and objectives for the presented study.

Chapter 2 (General Methods) describes generic methods used in this thesis, data curation, analytical techniques, and statistical methods.

Chapter 3 (The incidence of postoperative pulmonary complications and their association with survival) describes the incidence of PPC, clinical risk factors, and the association between PPC and survival of patients with aortic aneurysms and colorectal cancer. This will form the rationale for the study and the basis for further chapters examining the relationship between PPC and clinical and morphometric parameters.

Chapter 4 (Association of lung morphology with postoperative pulmonary complications, and survival) examines the association of CT-derived quantitative lung morphometry parameters with PPC and evaluates their association with survival of patients with aortic aneurysms and colorectal cancer. This chapter also assessed the value of identified parameters in explanatory models, developed in Chapter 3, assessing association of clinical and demographic factors with PPC.

Chapter 5 (Quantitative CT-derived indices of body composition and their association with postoperative pulmonary complications, and survival) examines the association of CT-derived body composition including psoas, diaphragm muscles, and abdominal adipose tissue with PPC and evaluates their association with survival of patients with aortic aneurysms and colorectal cancer.

Chapter 6 (Summary and general discussion) provides the summary of findings, provides general discussion in context of published evidence, limitations and proposes future direction of research.

Chapter 7 (Concluding remarks) includes concluding remarks on the subject matter.

Publications derived from this thesis

Papers & published abstracts:

1. **Abdulrhman Gazwani** MSc, Yui Sze Cheng MBChB, Kathryn Brown MBBS, Chean Wei Mak MBBS, Sarah Harley, Clive Allen Jonathan Wright MD, FRCA, Martin Claridge MD, FRCS, Fang Gao-Smith PhD, FRCA, Donald Adam MD, FRCS, Maciej T Juszczak PhD, FRCS. Utility of the Rockwood Clinical Frailty Scale (CFS) in Preoperative Decision-Making for Aortic Aneurysms: A Prospective, Single-Centre Observational Study - manuscript in submission.

2. D. Stamatiou, **A. Gazwani**, C. Godbole, R. Laloo, M. Juszczak, S. Karandikar; The impact of post-operative pulmonary complications after left-sided resections for colorectal cancer on medium- and long-term survival. (Top 12 ‘Quickfire’ Best Poster Presentations) Colorectal Dis, 23: 21-134. https://doi.org/10.1111/codi.15825

3. **A Gazwani**, S Cheng, K Brown, S Harley, C Allen, M Claridge, D Adam, MT Juszczak; Association of objective risk stratification with frailty, sarcopenia and myopenia in patients with aortic aneurysms. (Conference Abstract); European Society of Vascular Surgery - Scientific Meeting, September 2022, Rome

4. S Cheng, **A Gazwani**, WC Mak, S Harley, C Allen, M Claridge, D Adam, MT Juszczak; Association of frailty and sarcopenia with one-year mortality of patients with aortic aneurysms. (Conference Abstract) European Society of Vascular Surgery - Scientific Meeting, September 2022, Rome

Acronyms and abbreviations

6MWT	6-minute walking test
ABG	Arterial blood gas
ADP	Air displacement plethysmography
AF	Atrial fibrillation
AIC	Akaike’s Information Criterion
AL	Anastomotic Leak
ALB	Albumin
AMT	Abbreviated mental test
APS	Advanced pre-processing
ARDS	Acute Respiratory Distress Syndrome
ARISCAT	The Assess Respiratory Risk in Surgical Patients in Catalonia
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CCC	Concordance Correlation Coefficient
CCS	Clavien Classification System
CDC	Clavien-Dindo Classification
CDS	Clavien-Dindo Score

CE	Conformité Européenne (European conformity)
CI	Confidence Interval
CLD	Chronic lung conditions
COMPAC	Core Outcome Measures in Perioperative and Anaesthetic Care
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardio-pulmonary exercise testing
CRAG	Clinical Research Ambassador Group (PPIE)
CRC	Colorectal cancer cohort
CRP	C-reactive protein
CSA	Cross-sectional area
CT	Computed tomography
DICOM	Digital Imaging and Communications in Medicine
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
EHR	Electronic Health Record
EPCO	European Joint Task-Force for Perioperative Clinical Outcomes
ESA	European Society of Anaesthesiology
ESICM	European Society of Intensive Care Medicine

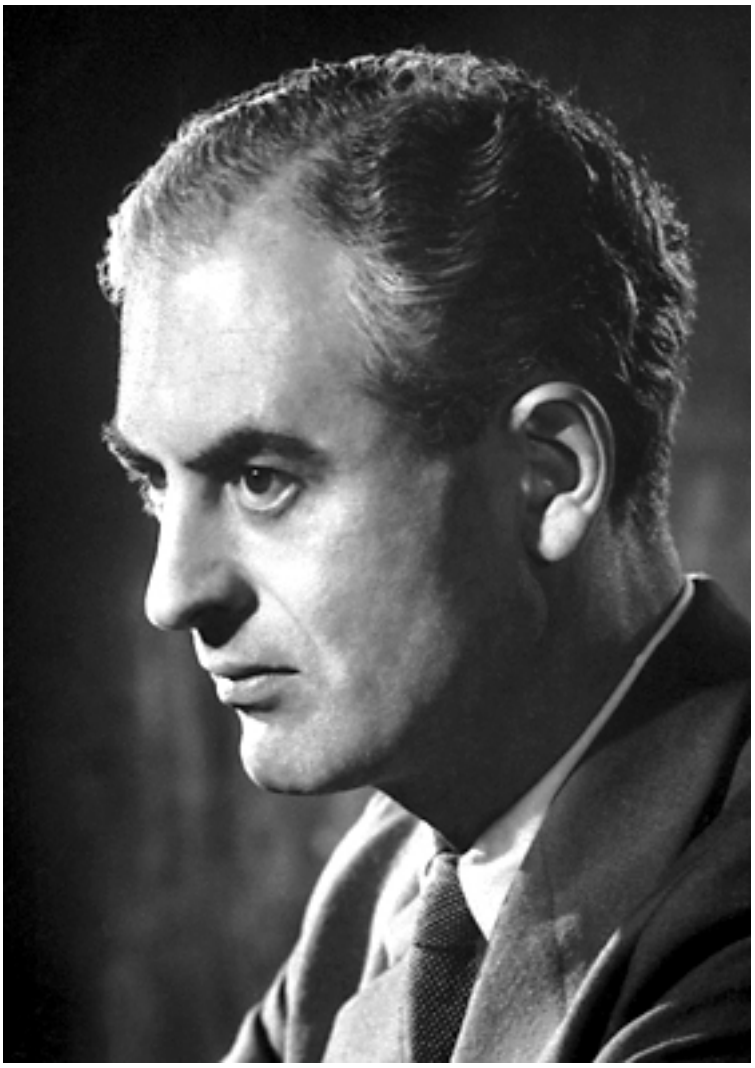
EVAR	Endovascular repair of abdominal aneurysm
FDA	Federal Drug Administration (US)
FEF	Forced expiratory flow
FEV_1	Forced expiratory volume in one second
FEV_1/FVC	Ratio of the forced expiratory volume in the first one second to the forced vital capacity of the lungs
FIF	Forced inspiratory flow
FRC	Functional residual capacity
FVC	Forced vital capacity
GOLD	Global Initiative for Obstructive Lung Disease
HAA	High attenuation area
HR	Hazard Ratio
HU	Hounsfield Units
ICC	Intraclass Correlation Coefficient
ICU	Intensive care unit
ILA	Interstitial Lung Abnormalities
ILD	Interstitial Lung Disease
IMD	Index of Multiple Deprivation
ISWD	Incremental shuttle walk distance
ISWT	Incremental shuttle walk test
KPI	Key Performance Indicator
L_3	Third lumbar vertebra

L_4	Fourth lumbar vertebra
LAA	Low attenuation area
LOS	Length of hospital stay
m	metre (SI unit)
MEF	Maximal expiratory flow
MRI	Magnetic resonance imaging
MRN	Medical record numbers
NAA	Normal attenuation area
NHS	National Health Service
NVR	National Vascular Registry
OR	Odds Ratio
OSR	Open surgical repair
$PaCO_2$	Partial pressure of carbon dioxide
PACS	Picture Archiving and Communication System
PaO_2	Partial pressure of oxygen
PAOD	Peripheral arterial occlusive disease
PEF	Peak expiratory flow
PFT	Pulmonary function test
PLT	Platelet count
PMA	Psoas muscle area
PMI	Psoas muscle index
PPC	Postoperative pulmonary complications

PPIE	Patient and Public Involvement and Engagement
PROP	Proportional relative lung density
PSM	Propensity score matching
QCT	Quantitative computed tomography
QIBA	Quantitative Imaging Biomarkers Alliance
ROI	Regions of Interest
RR	Relative Risk
RV	Residual volume
SAT	Subcutaneous adipose tissue
SCF	Subcutaneous fat
SD	Standard deviation
SFA	Subcutaneous fat area
SpO_2	Arterial oxygen saturation
SSI	Surgical Site Infections
StEP	Standardized Endpoints for Perioperative Medicine
SWD	Shuttle walk distance
TEVAR	Thoracic endovascular aortic repair
TLC	Total lung capacity
TPA	Total psoas muscle area
TPI	Total psoas index
U.S	The United States of America

UHB	University Hospitals Birmingham NHS Foundation Trust
UK	United Kingdom
US	Ultrasound
VAT	Visceral adipose tissue
VC	Vascular cohort
VF	Visceral fat
VFA	Visceral fat area
VIF	Variance inflation factor
VOL	Volumetric
VSQIP	Vascular Surgery Quality Improvement Programme
WC	Waist circumference
WCC	White cell count
WCC	White cell count
YACTA	Yet Another CT Analyser (Software)

Prologue



“I cannot give any scientist of any age better advice than this: the intensity of the conviction that a hypothesis is true has no bearing on whether it is true or not.”

— Peter B. Medawar, Advice To A Young Scientist

The matter

Chapter 1

Introduction

There are around 300 million major surgical procedures performed around the world every year (Karalapillai et al., 2020). An estimated 1.8 million elective surgical procedures are performed annually in the United Kingdom (UK) (Fowler et al., 2022). The risks of surgery vary depending on the condition treated and the type of surgery performed. Improvements in perioperative care and surgical techniques reduced the number of adverse postoperative outcomes, however, complex major surgical procedures still carry a significant risk (Pourlotfi et al., 2022). Out of all postoperative complications *pulmonary complications* are one of the most common and most serious across all surgical specialities (Tegegne et al., 2021; Jensen et al., 2023).

The annual National Vascular Registry (NVR) report for 2018 published recently by the Vascular Surgery Quality Improvement Programme (VSQIP) estimated that in 2016-2017 there were 4208 elective aneurysm repairs and 17475 lower limb bypasses carried out in 83 vascular centres around the UK. Similarly, during the same period the National Bowel Cancer Audit identified 18,849 major colorectal resections performed across the country. Based on these numbers, and given even a conservative estimate of the incidence of *post-operative pulmonary complication* (PPC) between 5% and 20%, it would be expected that up to eight thousand patients would be affected by PPC annually across these two surgical subspecialties alone. This could translate to a potential cost to the NHS between £2,000,000 and £10,000,000 due to increased use of hospital resources (additional tests and investigations, prolonged admissions, admissions to the intensive care unit (ICU), use of antibiotics, readmissions, etc.).

The aetiology of diseases in vascular or colorectal surgeries varies significantly, which could result in substantial consequences for PPC and medical care. Vas-

cular procedures are mostly proposed for treating the patients atherosclerotic diseases, which are characterised by a long-term, persistent, systematic chronic inflammatory response that impacts the arterial walls. On the other hand, colorectal surgical procedures mostly apply for a range of conditions, including diverticular diseases, inflammatory bowel diseases, and colorectal cancer. Chronic inflammation of the intestinal tract and genetic factors are associated with these conditions, and they are relatively less systematic inflammatory disorder in comparison with atherosclerosis.

Atherosclerosis triggers a systematic inflammatory state that increases the risk of PPC in patients undergoing vascular surgery. Prolonged chronic inflammation may reduce the immune system, hinder the healing process, and adversely impact lung function, thereby rendering patients more vulnerable to respiratory infections. Atherosclerosis-induced decreased blood circulation also impedes tissue oxygenation, impairs wound healing and increases infection vulnerability. As a result, the potential for extended immobility following vascular procedures may contribute to PPC. Moreover, patients with vascular diseases frequently exhibit frailty as a result of their persistent conditions, making them more susceptible to surgical complications and a prolong recovery time.

Conversely, chronic inflammations in colorectal surgery are relatively confined in the lower abdomen. May be presumed to be associated with a lower risk of developing PPC. However, colorectal cancer presents a significant indication for surgical intervention. Cancer and its therapies, such as chemotherapy, frequently compromise patients' immune systems, increasing their risk of postoperative complications and infections. Furthermore, the stage of cancer, patient's health, surgical site and techniques, and presence of postoperative ileus could impair diaphragm movement and lung function, making patients more susceptible to PPC. Similar to vascular patients, colorectal cancer patients can also exhibit frailty, particularly when they are malnourished, older, and have cancer-related cachexia. This increases their susceptibility to complications and delays the recovery process.

Despite the prevalence, complexity, and potential impact of vascular and colorectal cancer surgeries on patients' well-being and health, these specialties

receive little recognition in the literature. The exact incidence of PPC in these patient groups in recent years is unknown, and further research is required.

Precision medicine is an emerging model of management of medical conditions tailored to individual patient's needs (Jameson and Longo, 2015). It embraces genomics and phenomics to deliver a set of specific, bespoke therapeutic targets (Goetz and Schork, 2018). It can also be used to predict success of surgery and improve stratification of preoperative risk (Teh and Casali, 2019).

Morphomics, a part of phenomics (Chen et al., 2014), is a study of form, encompassing measurement of novel morphometric features (e.g. core muscle mass (or its surrogate marker - psoas muscle area), pectoralis muscle size, fat volume and distribution, calcification of cardiovascular system, diaphragm thickness, lung density, etc.) using routine, pre-operative modern imaging techniques: computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound (US) (Englesbe et al., 2012; McDonald et al., 2014; Stidham et al., 2015; Kaplan et al., 2015; Ahmed et al., 2015; Singal et al., 2016; Lee et al., 2016; Borga, 2018; Okura et al., 2020). These are promising, potential morphomarkers that could be useful in predicting PPC, mortality and guide preoperative optimisation and prehabilitation of patients at risk (Englesbe et al., 2010; Lee et al., 2011; Shimizu et al., 2011; Sabel et al., 2013; Cakir et al., 2015a; Pienta et al., 2018).

Indeed, the measurement of lung density and functional capacity/volume using various forms of imaging has been the focus of research in respiratory medicine and thoracic/lung transplant surgery in recent years (Ueda et al., 2005; Yoshimoto et al., 2009; Kaplan et al., 2015; Ohno et al., 2015; Yabuuchi et al., 2016). There is an abundance of information present in diagnostic imaging that comes with every CT or MRI that is not used for analytical purposes. Therefore, the thesis described below presents a unique opportunity to explore a vast amount of easily extractable morphometric data, and develop morphometry-based analytics utilising pre-existing diagnostic, planning and staging scans.

Identification of certain morphologic and anthropometric features using morphometric techniques may help building predictive models aiming to identify the bespoke diagnostic, predictive and therapeutic approaches. This may provide

clinicians with a model integrating analytics and clinical medicine to guide decision making.

1.1 Epidemiology and clinical significance of the post-operative pulmonary complications

1.1.1 Postoperative pulmonary complications: definitions and diagnostic criteria

The term PPC refers to a variety of respiratory-related problems that may develop following surgery (Odor et al., 2020). They are typically considered as a composite outcome measure in research studies (Miskovic and Lumb, 2017). In standard clinical practice this term is even more nebulous and encompasses a wide range of pathologies.

The definition and the components have been published in 2015 by the European joint task-force for Perioperative Clinical Outcomes (EPCO) on behalf of the European Society of Anaesthesiology (ESA) and the European Society of Intensive Care Medicine (ESICM) to provide consistent reporting standards in clinical studies (Jammer et al., 2015). The definition is summarised in Table 1.1. This is supposed to replace the previously established Melbourne Group Criteria for PPC, including consolidation, hypoxaemia, respiratory infection, and abnormal breathing sounds, that were lacking both accuracy and validation (Scholes et al., 2009).

Abbott et al. (2018) published a systematic review and a Delphi consensus carried out by and members of the Standardised Endpoints for Perioperative Medicine: Core Outcome Measures in Perioperative and Anaesthetic Care (StEP-COMPAC) in an attempt to establish a standard definition of PPC (Abbott et al., 2018). Despite identifying 27 possible meanings, they were *unable* to agree on the most accurate or appropriate definition. Most proposed definitions scored low due to the specific requirements of resource-intense diagnostic tests. Additionally, many definitions appeared to be inaccurate

and/or difficult to apply consistently in large patient populations. The StEP steering committee put forward a new definition involving diagnoses associated with pneumonia, aspiration pneumonitis, atelectasis, and acute respiratory distress syndrome (ARDS).

Even though this definition contains a measure of severity that can substantially reduce subjectivity when assessing pulmonary complications and facilitate more accurate comparisons between clinical trials, it may not be applicable to every trial and requires additional validation in a larger population of patients involving surgeries in various settings.

Different studies have adopted different approaches to assessing PPC and have used different component definitions for their individual composite outcome measures. Smetana, Lawrence and Cornell (2006) showed that of 16 studies, more than half combined pneumonia and respiratory failure. An additional difficulty is that recording of less serious PPC in patients' notes is very inconsistent (Brinson and Thornton, 2018).

It has to be said that the clinical entities included in definition of PPC have very different pathomechanisms. Therefore, PPC defined in this way cannot and should not be used in clinical intervention studies that aim at prevention of PPC as an outcome of interest.

Table 1.1 – Definitions of the components of postoperative pulmonary complications recommended by the European Perioperative Clinical Outcome (EPCO). FiO_2 - fraction of inspired oxygen; PaO_2 - partial pressure of oxygen (arterial oxygen tension).

Complication	Definition
Respiratory infection	Patient had antibiotics for a suspected respiratory infection and met one or more of the following criteria: new or changed sputum, new or changed lung opacities, fever, white blood cell count > $12 \times 10^9 \times L^{-1}$
Respiratory failure	Postoperative PaO_2 < 8 kPa (60 mmHg) on room air, PaO_2:FiO_2ratio < 40 kPa (300 mmHg) or arterial oxyhaemoglobin saturation measured with pulse oximetry < 90% and requiring oxygen therapy
Pleural effusion	Chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows
Atelectasis	Lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory overinflation in the adjacent non-atelectatic lung
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators
Aspiration pneumonitis	Acute lung injury after the inhalation of regurgitated gastric contents

1.1.2 Epidemiology of postoperative pulmonary complications

The estimated incidence rates of PPC vary significantly between 2.0% to 5.6% in general, and between 2% and 80% in the thoracic and upper abdominal surgery (McAlister et al., 2005; Fernandez-Bustamante et al., 2017; Chandler et al., 2020). This depends on the PPC definition, surgical type and approach, and patient related risk factors (Miskovic and Lumb, 2017). Notably, the heterogeneous nature of PPC makes them more challenging to study than cardiac complications, partially because of conflicting definitions (Lawrence et al., 2002; Khan et al., 2006; Lumb, 2019; Fransen et al., 2021).

Over the last twenty years, many studies have highlighted the scale of this problem. In a large prospective cohort study, Fernandez-Bustamante et al. (2017) demonstrated that more than 33.4% of patients developed PPC after non-cardiac/non-thoracic surgery. A recent retrospective observational study on undergoing abdominal surgery reported PPC rates of 28.8% (Park et al., 2020b), and single centre randomised clinical trial reported higher rates of 38% of adult patients undergoing major surgery (Karalapillai et al., 2020). These studies demonstrated PPC rates higher than indicated by previous reports despite intensive intraoperative optimisation to prevent their occurrence. The incidence of PPC varied significantly in previous studies ranging between 1% and 23%, but many of them failed to accurately capture the outcomes with a sufficient accuracy and this is most probably due to a general lack of adoption of strict criteria of PPC (Smith et al., 2010; Fleisher and Linde-Zwirble, 2014; Yang et al., 2015; Patel et al., 2016).

Table (1.2) summarised evidence of PPC incidence. It is remarkable that in spite of various improvements in perioperative care of patients undergoing major surgery, the incidence and consequences of PPC have not improved in the last 20 years. The heterogeneity of studied populations may be a major confounding factor. More high-quality research using consistent definitions of PPC is needed to confirm the incidence in various surgical cohorts and ascertain efficacy and safety of interventions aimed at prevention.

Table 1.2 – The summary of available evidence of the incidence rates of postoperative pulmonary complications following major surgery. IQA - Interquartile range; BMI - Body mass index; PPC - postoperative pulmonary complications; EPCO - European Perioperative Clinical Outcome.

Author/Year	**Country**	**Study design**	**Surgical procedure**	**Characteristics of patients** (Sample size (n=); gender (n=,%); age (years, ±SD , median, or IQR);BMI (kg/m^2)	**PPC definitions / endpoint**	**PPC incidence** (%)
Wang et al. (2023)	China	Retrospective, single-centre	Hepatectomy	Total = 503; Male 342, Female 161	In hospital follow-up Based on EPCO	55.7
Semmelmann et al. (2023)	Germany	Retrospective, single-centre	Thoracic surgery	Total = 250; Male 184, Female 66	In hospital follow-up Respiratory failure, pneumonia, reintubation, and postoperative ventilation for $\geq$ 2 days	42

Author/Year	Country	Study design	Surgical procedure	Characteristics of patients	PPC definitions / endpoint	PPC incidence
Okada et al. (2022)	Japan	Retrospective, single-centre	Lung cancer	Total = 188; Male 118(62.8), Female 70(37.2); median age 78(75–92); median BMI: 22.9 (20.5-24.7) kg/m^2	30-day follow-up pneumonia, air leak, sputum/atelectasis, bronchopleural fistula, and empyema	36.2
(Jensen et al., 2023)	Denmark	Prospective, single-centre	Cardiothoracic and Abdominal Surgery	Total = 339; Male 107 (31.6), Female 232(68.4)	30-day follow-up Oxygen saturation $\leq$ 92%, and atelectasis	33.3
Xu et al. (2022b)	China	Retrospective, single-centre	Ovarian cancer	Total = 268; mean age 55.1±10.2	30-day follow-up Based on EPCO	26.9

Author/Year	Country	Study design	Surgical procedure	Characteristics of patients	PPC definitions / endpoint	PPC incidence
Shaw et al. (2021)	Australia	Prospective, single-centre	Head and neck cancer	Total = 60; Male 39(65), Female 21(35); mean age 59.0 16.5; median BMI: 27.0 (23.8–30.8) kg/m^2	One week follow-up Based on Melbourne Group Scale	15
Malcolm et al. (2020)	US	Retrospective, single-centre	Total joint arthroplasty (Hip and knee arthroplasty)	Hip arthroplasty = 2,679,351; knee arthroplasty = 5,527,205	In hospital follow-up Respiratory failure, pneumonia, and aspiration	Hip arthroplasty 38.0 knee arthroplasty 94.8
Abd El Aziz et al. (2020)	US	Retrospective, single-centre	Colorectal cancer	Total = 50,150; Male 26120(52.1), Female 24,030 (47.9)	30-day follow-up Unplanned reintubation, pneumonia, and failure to wean from the ventilator	1.3

Author/Year	Country	Study design	Surgical procedure	Characteristics of patients	PPC definitions / endpoint	PPC incidence
Jurt et al. (2018)	Switzerland	Retrospective, single-centre	Colorectal cancer	Total = 1298; Male 318(60.2), Female 210(39.8); mean age 63±15; mean BMI: 25.7 ± 5.1 kg/m^2	30-day follow-up Pneumonia, atelectasis, pleural effusion, hypoxaemic	9.2
Smith et al. (2010)	US	Retrospective, single-centre	Laparotomy	Total = 2,519; mean age 58.3	In hospital follow-up Atelectasis, respiratory failure, preexisting lung disease, respiratory infection, and pulmonary embolism	7.0

Author/Year	Country	Study design	Surgical procedure	Characteristics of patients	PPC definitions / endpoint	PPC incidence
Fleisher and Linde-Zwirble (2014)	US	Retrospective, single-centre	Major small and large bowel procedures	Total = 45,969; Male (45.1), Female 54.9; mean age 62.9 years	In hospital follow-up Pneumonia, pleural effusion, pulmonary collapse, pneumothorax, respiratory failure, tracheobronchitis, and mechanical ventilation > 48 hours	19.0

1.1.3 Clinical significance of postoperative pulmonary complications

Many studies have revealed that PPC can progress to more severe respiratory insufficiency, which can have significant impacts on both the patient and the healthcare system, including higher in-hospital mortality, expensive intensive care treatment, prolonged hospitalisation, 30-day readmissions, and increased healthcare costs (Kassin et al., 2012; investigators, 2017; Matthew Reinersman et al., 2016; Pasin et al., 2017; Neto et al., 2018; Russotto, Sabaté and Canet, 2019; Foster et al., 2019; Jensen et al., 2023).

Xiang et al. (2021) indicated that PPC are caused by pathophysiological decline in respiratory performance, decreased lung volume, airway clearance, and pain-inhibited respiratory muscle contractions. In response to decreasing respiratory efficiency, postoperative medications, inhaled therapies and ventilatory support are usually implemented (Singh, Agumbe Pai and Hosmath, 2023).

It is well-documented that unplanned, supplemental use of oxygen is the most frequent PPC (Griffiths et al., 2018). A patient-level meta-analysis of three trials, including patients from 128 hospitals across 24 countries showed that the event rate of severe pulmonary complications was associated with the need for extra oxygen following surgery (oxygen saturation (SpO_2) less than 92% in room air). Nonetheless, the evidence synthesis revealed that routine non-invasive respiratory support in postoperative period was not linked to a decrease in the incidence of PPC or pneumonia (Hui et al., 2022).

The PPC are common in the patients admitted to ICU. A number of different, large cohort studies (single and multi-centre) have been carried out with trauma patients (Bradburn et al., 2020; Rosen, Bulger and Cuschieri, 2022), in which patients underwent different types of surgeries including non-thoracic (Simonis et al., 2022), non-cardiac (Belcher et al., 2017; Katori et al., 2022; Magor et al., 2022), lung resection (Shelley et al., 2022; Brunelli et al., 2022), neurovascular (Wang et al., 2022) surgeries. Results of these studies indicate that PPC are a leading cause of unplanned admissions to ICU. Researchers have found that the incidence varies between 4% and 82%, based on different definitions of

unplanned ICU admission (Shelley et al., 2022; Brunelli et al., 2022; Katori et al., 2022; Magor et al., 2022; Simonis et al., 2022; Wang et al., 2022; Rosen, Bulger and Cuschieri, 2022). Respiratory failure and pneumonia (Bradburn et al., 2020), hypoxia (Katori et al., 2022), other respiratory infections (Magor et al., 2022), and pulmonary aspiration (Belcher et al., 2017) were found to be the most significant reasons for ICU admission.

In the critical care studies described above, some inter-study variations are evident due to the research designs, differences in patient populations and the availability of critical care resources. Given the heterogeneity of the studies one should be cautious regarding generalisability of findings as these studies may not accurately reflect care patterns in other healthcare settings. Nonetheless, the most striking findings revealed in the studies pertained to the pulmonary events leading to unplanned ICU admission and their relationship with the use of critical care health resources. This includes the administration of antibiotics for a chest-related infection (Shelley et al., 2022), intubation and used mechanical ventilation (Shelley et al., 2022; Katori et al., 2022; Magor et al., 2022; Simonis et al., 2022; Rosen, Bulger and Cuschieri, 2022), re-intubation (Magor et al., 2022), unplanned intubation (Bradburn et al., 2020; Rosen, Bulger and Cuschieri, 2022), and respiratory assessment (Wang et al., 2022). It is quite remarkable that the extent of the relationship between these factors and clinical outcomes is still largely unknown. The effectiveness of decision tools used in preventing unplanned critical care admissions and reducing patient morbidity, including PPC and mortality, is also uncertain and should be the focus of future research.

It has been previously noted that in patients who develop a PPC mortality increases (Miskovic and Lumb, 2017). Before the Coronavirus disease (COVID-19) pandemic outbreak in 2019, data pertaining to major surgeries showed a connection between PPC and a modest risk of death and usage of critical care (Khuri et al., 2005; Patel et al., 2016). This was even more pronounced in patients with COVID (McLean et al., 2021). PCC-related mortality varies between 0 and 48% based on the surgical approach and composite type of PPC (Sabaté, Mazo and Canet, 2014). One in seven patients developing PPC dies

before being discharged from hospital, and even those who survive frequently suffer a reduction in functional status (Canet et al., 2010; Pearse et al., 2012; Mazo et al., 2014; Neto et al., 2018).

Almost a quarter of postoperative deaths occurring in the first week after surgery are linked to the development of PPC (Lakshminarasimhachar and Smetana, 2016). In a previous multi-centre observational study involving patients who underwent non-cardiac, non-thoracic surgery found that early postoperative mortality (within first seven days following surgery) increased in patients experiencing one or multiple PPC (even if the severity was classed as mild). This increase was found to be 2.3% in patients with $\geq$1 PPC vs 0% in patients with no PPC ($p<0.001$) (Fernandez-Bustamante et al., 2017). Moreover, 14-30% of patients experiencing PPC die in the 30 days following major surgery, which is reduced to 0.2–3% in those who do not experience a PPC (Kor et al., 2011; Miskovic and Lumb, 2017). A recent study carried out by Kakavas and colleagues (2020) showed that the 90-day mortality was significantly higher in patients experiencing PPC (50% vs 11.7% in cancer patients after abdominal surgery).

Data taken from two large United States (the U.S.) databases was used in a multi-centre observational study conducted by Khuri et al.(2005). This study revealed that complications play a significant role in determining short- and long-term survival following major surgery. The mortality after major surgery in those sustaining complications was significantly higher than in those without complications: 45.9 vs. 8.7% at 1 year or 71.4 vs. 41.1% at 5 years. In particular, the presence of pulmonary problems in this study population had a detrimental effect on survival. Although the study was considered pioneering when it was published, it only examined eight categories of surgical procedures. Moreover, it was carried out over two decades ago and only be considered representative of clinical experience in one country (Khuri et al., 2005; Fowler et al., 2022).

Malcolm et al. (2020) carried out a large observational study in patients after total joint arthroplasty undertaken between 2004 and 2014. The PPC were identified as pneumonia, aspiration, respiratory failure and pulmonary embolism.

They found that the risk associated with PPC (in comparison to no PPC) on perioperative mortality varied considerably between procedure types and different PPC types: it was found to be 5% (vs 0.02%) for hip arthroplasty and 3% (vs 0.01%) for knee arthroplasty. They observed that respiratory failure significantly increased the risk of mortality in both types of surgery. Similarly, a more recent secondary analysis of data from two prospective observational cohort studies involving patients who had undergone elective surgery in five high-income countries revealed that respiratory failure generated the highest crude rate of death in the year after surgery of all related complications, causing six deaths per 28 patients (21.4%; 95% Confidence Interval (CI) 8.3-41.0%) (Fowler et al., 2022).

On the other hand, in an international multi-centre cohort analysis of patients who underwent oesophageal cancer surgery, Fransen and colleagues (2021) found no correlation between PPC and long-term survival (5-year overall survival). However, this study only examined minimally invasive trans-thoracic oesophagectomies as this approach has been found to reduce pulmonary complications (Mariette et al., 2019). It is essential to emphasise the importance of not only the surgical technique, but also case selection with variable extent of pre-operative assessment and peri-operative care. These factors would have a major impact on patient survival; unfortunately, these are rarely studied.

As well as being a significant clinical concern, PPC also generates a hefty economic burden (Shander et al., 2011). A number of studies (most of which have been carried out in high-income countries) have confirmed that patients experiencing one or multiple PPC after surgery have longer hospital stay, and higher re-admission rates, both of which generate higher hospitalisation costs (Dimick et al., 2004; Manecke, Asemota and Michard, 2014; Vonlanthen et al., 2011; Wang et al., 2018; Malcolm et al., 2020).

As pointed out by Sabaté et al. (2014), the postoperative length of hospital stay (LOS) is a standard variable that is employed to evaluate rates of morbidity and overall healthcare costs. Previous reviews have shown that the average PPC-related increase in hospital LOS is around eight days (Lawrence, Cornell and Smetana, 2006). Other studies have indicated that this can be as long as

13-17 days (Smith et al., 2010; Miskovic and Lumb, 2017). The range varies based on definitions and research populations, with more severe types of PPC likely being associated with a longer hospital stay (Schwartz et al., 2020). For instance, patients with PPC who need unplanned re-intubation following surgery (Rosen, Bulger and Cuschieri, 2022), have significantly increased morbidity and LOS (Burton et al., 2018). Most importantly, prolonged hospital stay can increase the risk of subsequent pneumonia (Jasmijn Smits et al., 2022), and other complications not related to the respiratory system.

Hospital readmission is regarded to be one of the key measures (Key Performance Indicator, KPI) for assessing the quality of surgical care (Chen et al., 2019). Numerous investigations involving various surgical procedures have shown that PPC increased the likelihood of early and 30-day readmission. In a retrospective analysis, Kassin and colleagues (2012) found that PPC as risk factors increases the probability of readmission by 28.2% after general surgery procedures compared to no admission by 71.8% (odds ratio (OR) 3.45, 95%CI 2.08-5.71, p<.0001). Moreover, substantial data was provided by Lawson (2013) to support efforts to reduce hospital readmissions for surgical patients. Although complications from surgical procedures accounted for the majority of readmissions in that research (33.3%), pneumonia and respiratory failure ranked fifth and fifteenth, respectively and contributed to 2.8 and 1.4% of readmissions.

In a recent study of 5419 patients (26.5%) from nine surgical specialities and covering all pneumonia complications were identified post-discharge varying from 18.9% to 36.3% depending on the type of surgery. It is interesting to note that the risk of readmission was 11 times higher for patients experiencing pneumonia post-discharge compared to those experiencing its pre-discharge. Altogether, 3767 (69.5%) patients with post-discharge pneumonia were readmitted to the hospital in comparison to 1087 (6.5%) patients suffering from pre-discharge pneumonia (Relative risk (RR) 10.79, CI 10.15-11.45) (Aasen et al., 2021).

Previous estimates indicate that the annual cost of PPC-related readmission is approximately $835 million (Sabaté, Mazo and Canet, 2014). Research efforts

should include analysing the relationship between PPC and readmissions in more detail, and examining the costs of readmission after different surgical procedures and in different healthcare settings. Prevention of PPC, both peri-operatively and after discharge could bring substantial savings for healthcare providers.

The additional cost associated with PPC vary significantly, depending on the healthcare system, type of hospital, and type of the complications (Hanh et al., 2021). For patients undergoing major bowel surgery it was shown that the financial burden associated with PPC is high at $25,498 (Fleisher and Linde-Zwirble, 2014). In a later observational analysis, Healy et al. (2016) in 2016 assessed the relative financial burden on payers and hospitals, in addition to the expenses associated with surgical intervention. According to this data, hospital expenses for resources used were $49,060 with complications from pneumonia versus $18,939 without complications.

A report by Hanh et al. (2021) used a national database containing details of 1,241,893 surgical patients undergoing surgery in Vietnam. Similarly to the study discussed above, its findings revealed that patients with PPC incurred significantly greater costs across the board. The cost of re-hospitalisation contributed the most to the financial burden associated with PPC occurring within 30 days of surgery, which was $1053.3 (95%CI: 940.7-1,165.8, p<.0001). Surprisingly, pneumonia was the leading cause of the annual cost burdens associated with most postoperative respiratory problems. Thus, understanding the risks associated with PPC and financial implications in various healthcare systems and geographical locations is necessary.

Table (1.3) summarised an evidences of PPC epidemiology and clinical significance. The conclusion that can be drawn from the presented evidence is that the PPC remain a significant challenge. The significant risk and wide variation in PPC, mortality, LOS, ICU, and re-admission rates, are primarily brought on by a combination of various definitions, various patient populations, and particular surgical procedures.

Table 1.3 – The summary of available evidence of the epidemiology and clinical significance of postoperative pulmonary complications following major surgery. IQA - Interquartile range; BMI - Body mass index; LOS - length of hospital stay; ICU - Intensive care unit; OR - Odds ratio; CI - Confidence interval; PPC - postoperative pulmonary complications; EPCO - European Perioperative Clinical Outcomee.

Author/Year	Procedure	Length of stay	30-day hospital readmission	30-day ICU admission associated with PPC	30-day mortality associated with PPC	Survival associated with PPC
		days, mean, median (IQR) range, p-value, (OR, 95% CI)	n(%), p-value,(OR, 95% CI, p-value)	n(%), p-value,(OR, 95% CI, p-value)	n(%), p-value,(OR, 95% CI, p-value)	
Wang et al. (2023)	Liver surgery	18 (15-25) vs. 15 (12-19), p<0.001		2.4 vs. 2.2, p<0.001	2.9 vs. 0.00, p<0.011	

Author/Year	Procedure	Length of stay	30-day hospital readmission	30-day ICU admission associated with PPC	30-day mortality associated with PPC	Survival associated with PPC
Semmelmann et al. (2023)	Thoracic surgery			23 vs. 2, p<0.001	17 vs. 1, p<0.001	90-day mortality 21 vs. 4, p<0.001; 180-day mortality 21 vs. 5, p< 0.001; 360-day mortality 21 vs. 8, p< 0.001
Okada et al. (2022)	Lung cancer	17 (13-28) vs. 10 (8-12), p<0.001				The median survival time 112 months 2.16 (1.12-3.95) p=0.024

Author/Year	Procedure	Length of stay	30-day hospital readmission	30-day ICU admission associated with PPC	30-day mortality associated with PPC	Survival associated with PPC
Jensen et al. (2023)	Cardiothoracic and abdominal surgery	12 (8), 3 to 52 vs. 7 (5), 3 to 48, p<0.001	33 (31.7) vs. 36 (16.8), p=0.007		1 (0.9) vs.2 (0.9), p=0.78	
Xu et al. (2022b)	Ovarian cancer	26.0 (19.0–34.5) vs.17.5 (14.0–23.0),p<0.001	8 (11.1) vs. 5 (2.6), p=0.008	19 (26.4) vs.21 (10.7), p<0.001	2 (2.8) vs.0 (0.0), p=0.071	
Shaw et al. (2021)	Head and neck cancer	15.0 (13.0–18.5) vs. 14.0 (11.0–23.0), p=0.461		11 vs.10		

Author/Year	Procedure	Length of stay	30-day hospital readmission	30-day ICU admission associated with PPC	30-day mortality associated with PPC	Survival associated with PPC
Malcolm et al. (2020)	Total joint arthroplasty	Linear regression; Hip arthroplasty 3.03 days (2.76–3.31), knee arthroplasty 2.72 days (2.58–2.86)			Hip arthroplasty 5.00 vs. 0.02; knee arthroplasty 3.00 vs. 0.01	
Abd El Aziz et al. (2020)	Colorectal cancer				7.5 vs. 0.2, p<0.0001	
Jurt et al. (2018)	Colorectal cancer	21(4-183) vs. 6(1-95),p< 0.001				

Author/Year	Procedure	Length of stay	30-day hospital readmission	30-day ICU admission associated with PPC	30-day mortality associated with PPC	Survival associated with PPC
Smith et al. (2010)	Laparotomy	17.7, p=0.001		68.0 vs. 14.11, 3.0 (5.30-31.76), p<0.001	16 vs. 36.17 (1.79-21.34), p<0.01	
Fleisher and Linde-Zwirble (2014)	Major small and large bowel procedures				11.9 vs. 0.7	

1.1.4 Classification of postoperative complications

The measure of surgical success changed significantly over time. A few decades ago the assessment of this aspect of surgical practice was typically based on mortality (Pearse et al., 2012; Vonlanthen and Clavien, 2012). However, with postoperative mortality significantly reduced, a new measure, morbidity, defined as an adverse outcome of surgery due to perioperative complications, has emerged as the primary indicator of the safety and quality of surgical practice (Balvardi et al., 2021; Smeyers et al., 2022).

Postoperative complications are common and occur in nearly 20% of patients undergoing major surgery across all surgical specialties (Ludbrook, 2022; Stundner and Myles, 2022). They can affect every system and body part. The impact of postoperative complications is significant, both in terms of reduced quality of life and functional performance of patients affected (Tevis and Kennedy, 2013). There are also implications in terms of the economic consequences and clinical workload arising from their management (Smeyers et al., 2022).

To standardise the quality of care, a classification system is required which is capable of grading, risk-adjusting and comparing adverse outcomes utilising a standardised and reproducible method (Balvardi et al., 2021). Reporting systems utilising objective, robust and justified evaluation approaches should be implemented in order to optimise consistency in defining adverse and unexpected events and thus facilitate the accurate analysis of surgical outcomes (Madadi-Sanjani et al., 2021; Smeyers et al., 2022).

Prior to 1990 a number of efforts were made to establish classification methods for surgical complications but these were unsuccessful because they failed to achieve any degree of recognition and acceptance (Clavien et al., 2009). A significant progress was achieved in early 90s with the introduction of an innovative method entitled the T92 Grading System. Also known as the Clavien Classification System (CCS), the technique was developed by Clavien and colleagues, who validated their approach on 650 cholecystectomies (Clavien, Sanabria and Strasberg, 1992; Clavien et al., 1992). The basis of the method

was classification of complications and consequences of surgery according to their severity, deploying a somewhat arbitrary 4-level categorisation. The process defined a postoperative complication as a deviation from the normal postoperative course. The severity of such a complication was defined as ranging from a non-life-threatening complication with no lasting disability to a fatal outcome (Clavien, Sanabria and Strasberg, 1992; Straatman et al., 2015; Dencker et al., 2021). These adverse events were categorised into three distinct groupings — failure to cure, complications, and sequelae (Clavien, Sanabria and Strasberg, 1992; Clavien et al., 1992). The strength of the approach, according to Madadi-Sanjani et al. (2021), lay in the grading of these events based on the therapy deployed to address them. Howevre, the CSS/T92 grading system did not gain wide acceptance within the surgical literature at the time (Dindo, Demartines and Clavien, 2004).

A substantial reworking of the CSS/T92 system was undertaken in 2004 by Clavien and Dindo, who produced a method known as Clavien-Dindo Classification (CDC) (Dindo, Demartines and Clavien, 2004). The principal improvements were the provision of a more detailed approach to grading life-threatening events, and the inclusion of long-term disability arising from complications (Madadi-Sanjani et al., 2021). The revision included a more elaborate scoring method, which introduced subdivisions to the existing groups Grade III and Grade IV — creating new grades of Grade III-a,Grade III-b, Grade IV-a and Grade IV-b, and thus increasing from 5 to 7 the overall count of grades (Dindo, Demartines and Clavien, 2004; Clavien et al., 2009). The reason for subdividing groups 3 and 4 was the low number of cases featuring such complications (Smeyers et al., 2022). The notable difference in the revised approach was the absence of the categories of ‘sequelae’ and ‘failure to cure’ and particularly for the omission of longer LOS as a measure of the severity of the complication (Dindo, Demartines and Clavien, 2004; Dindo and Clavien, 2008).

1.1.5 Classification of pulmonary complications

There is no pragmatic classification of PPC. The definition of PPC only lists various pathologies that should be included within this generic term. However, these clinical entities have often very different pathomechanisms making classification and clinical risk scoring almost impossible. A clinical assessment tool that provides some form of classification of adverse outcomes from surgery is that proposed by Clavien and Dindo (Dindo, Demartines and Clavien, 2004). In previous studies, PPC was proposed to be classified into four grades using the Clavien-Dindo Score (CDS). Degani-Costa at al. (2014) established that the impact of PPC can be graded in terms of the instance of mortality. Major causes of death would include respiratory failure, pneumonia or intubation for more than 48 hours with or without mechanical ventilation, whereas minor causes include purulent trachea-bronchitis, atelectasis and bronchospasm.

Table 1.4 shows classification of PPC according to their immediate requirements, their clinical diagnosis and composite outcome criteria. The PPC can be assessed and evaluated by the direct care clinical team, including specialists from different areas, such as surgeons, intensive care medicine, anaesthesia and respiratory medicine. However, severity of PPC can be underestimated as clinical assessment can be somewhat subjective. Thus, an accurate classification and grading of the PPC is essential to ascertain the best treatment decisions and patient outcomes.

Table 1.4 – Example of clinical case of grading for postoperative pulmonary complications using the Clavien-Dindo Score.

Grades	Examples
Grade I	Atelectasis requiring physiotherapy
Grade II	Pneumonia treated with antibiotics on the ward
Grade IIIa	Bronchopleural fistulas after thoracic surgery requiring surgical closure
Grade IVa	Lung failure requiring intubation
Grade IVb	Same as for IVa but in combination with renal failure
Suffix “d”	Dyspnea after pneumonectomy for severe bleeding after chest tube placement

1.2 Prediction of post-operative pulmonary complications: preoperative clinical assessment and predictive models

Pre-operative risk evaluation is probably the most important element in predicting PPC, and implementing mitigating strategies and interventions to prevent their development (Chandler et al., 2020; Sameed et al., 2021). A multi-modal pre-operative assessment of respiratory system combines clinical and physiological evaluation, and identification of any pre-existing pulmonary disease. Assessment of fitness for surgery should also establish all potential risk factors related to planned surgery, and consider anaesthesia/anaesthetic technique. Careful analysis and consideration of these risk factors can optimise patient outcome and assure good quality care (Adeleke et al., 2021).

Several models for prediction of PPC have been developed (Nijbroek, Schultz and Hemmes, 2019). These are usually based on standard parameters obtained during preoperative assessment of fitness, comorbid status, pathology and the planned procedure. It is fair to say that the multitude of developed models implies that no single model performs well enough at the individual patient level.

1.2.1 Principles of preoperative clinical assessment

In order to adequately assess the risk for PPC, a thorough understanding of the patient's medical history and a physical examination are imperative (Sameed et al., 2021). For all patients who are being planned for elective surgery it is vital to evaluate preoperative pulmonary reserve and the degree of pulmonary impairment (Diaz-Fuentes, Hashmi and Venkatram, 2016). Thus, the overall health of the patient must be considered; in particular evaluating the patient for pulmonary symptoms, such as a rales, cough, and rhonchi, and discovering if the patient has a history of lung or airway disease, or extra-pulmonary factors (Lakshminarasimhachar and Smetana, 2016; Chandler et al., 2020).

A thorough clinical history should be taken with respect to these symptoms. During preoperative assessment, clinicians should inquire about symptoms such as snoring, daytime sleepiness, observed apnea episodes, and respiratory effort during conversations and movement (Bevacqua, 2015; Taylor, DeBoard and Gauvin, 2015). Some patients without a known respiratory disease history might downplay their symptoms to avoid delays to surgery (Lumb, 2019), making an accurate diagnosis of pulmonary conditions challenging and potentially underestimating the risk of PPC. Particular attention should be paid to pre-existing lung conditions: asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), interstitial lung abnormalities (ILA), asbestosis, tuberculosis, and respiratory malignancies.

A thorough clinical examination should be undertaken. Examination of respiratory system should focus on patient's general appearance, neck circumference, thoracic shape, signs of cyanosis, muscle atrophy, finger clubbing, and respiratory rate and pattern (Bevacqua, 2015; Taylor, DeBoard and Gauvin, 2015). Auscultation and percussion still play an important role, however, since additional tests are performed quite liberally, it is less frequently used as critical part of clinical evaluation.

1.2.2 Preoperative tests: basic assessment

In order to assess the risk factors associated with PPC it is appropriate to perform, in addition to taking history and performing clinical examination, some basic preoperative tests (Lakshminarasimhachar and Smetana, 2016; Diaz-Fuentes, Hashmi and Venkatram, 2016). However, these tests may only be advantageous if the results gained cannot be determined from a the basic clinical assessment. These results are likely to help establish the probability of the patient, who is known to have risk factors, suffering complications during surgery (Sameed et al., 2021). However, if not relevant, can lead to additional, unnecessary investigations and potentially risky invasive procedures, both diagnostic and therapeutic (O'Neill et al., 2016).

The following sub-themes identify the tests that can be performed on the routine preoperative evaluation, including: pulse oximetry, arterial blood gas (ABG), laboratory diagnostic testing, and chest X-Ray. These tests may support the detection of unrecognised risk factors that could predict PPC.

1.2.2.1 Pulse oximetry

The oxygen saturation-air pulse oximetry (SpO_2) test was rarely included in older studies (Brinson and Thornton, 2018), but it has become an invaluable tool since Canet Canet et al. (2010) developed and validated a simple method of stratification. Patients were grouped together on the basis of room air SpO_2 $\geq$ 96%, $\leq$ 95%, and $\leq$ 90%, and they observed that the single most important risk factor for PPC was low SpO_2 (Canet et al., 2010; Canet et al., 2015).

Patients with preoperative SpO_2 91–95% were twice as likely to get a PPC compared with those with a $SpO_2 \geq 96\%$. Patients with $SpO_2 \leq 90\%$ were 10 times more likely. This non-invasive, simple test is low in cost to administer and has been validated externally as one of two PPC prediction models (Mazo et al., 2014; Canet et al., 2015). The accuracy of these tests can be impacted for physiological, pathological and technical reasons. These might be the sampling technique used, the quantity and quality of the person's circulating

haemoglobin, their peripheral perfusion, even their skin colour. Also, by the quality of software and hardware used in pulse oximeters (Cabanas et al., 2022; Stell et al., 2022; Silverston, Ferrari and Quaresima, 2022). As a result, more large prospective studies are needed if SpO_2 measurement is going to be considered an accurate screening and diagnostic tool for identifying risk factors and predicting PPC.

1.2.2.2 Arterial blood gas

One of the much-used and invasive procedures used in assessment of respiratory function is an ABG (Rowling et al., 2022). This test is used to determine partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$) levels, and so identifies preoperative hypoxaemia and hypercapnia (Chandler et al., 2020). Serial blood gas results can be monitored using preoperative gases as a baseline reference. This can help determine how severe the respiratory disease is, the type of respiratory failure, the adequacy of compensatory mechanisms and if the surgical and anaesthetic modality being proposed is appropriate. However, these groups of tests are not, in themselves, independent predictors of PPC (Pinto and Pinto, 2022). Oxygen delivery can be calculated by measuring baseline oxygen saturation and PaO_2 along with haemoglobin levels. This can assist with planning perioperative (supplemental) O_2 and blood replacement (Bevacqua, 2015).

1.2.2.3 Laboratory testing

Renal function tests are undertaken for patients undergoing major surgery. Those patients who risk malnutrition, low albumin levels or renal dysfunction are closely monitored since these are known risk factors and predictors for PPC (Johnson et al., 2007; Jeong et al., 2014; Miskovic and Lumb, 2017; Brinson and Thornton, 2018). However, some caution is required, since with an increasing number of laboratory test parameters, there is a stronger likelihood of detecting a value which is randomly outside the normal range, which might indicate a false-positive result (Zwissler, 2019). It is not recommended to

take a complete blood count as routine in asymptomatic individuals (O'Neill et al., 2016). However, a complete blood count should be taken in patients who present with liver diseases, other haematological diseases, or a history of anaemia. It should also be taken if anaemia is suspected when chronic diseases associated with anaemia are present or during a physical examination. This is particularly important if the patient is to undergo moderate or high-risk procedures where a blood transfusion may be needed (Admass et al., 2022) based on physical and history examination (Smetana and Macpherson, 2003).

1.2.2.4 Chest X-Ray

Generally, when a patient is suspected of having a pulmonary disease, a baseline chest X-Ray is not a helpful tool in assessing the risk of preoperative pulmonary evaluation (Chandler et al., 2020). In a trial of 135 patients, McAlister and colleagues (2005) found that patients having a chest X-Ray that was performed at the discretion of a clinician, did not exhibit more frequent PPC after surgery (OR 1.14, 95%CI 0.39-3.34). A chest x-ray for diagnosis of cardiopulmonary diseases in patients with an unremarkable medical history and a physical examination has a low sensitivity (Fritsch et al., 2012; O'Neill et al., 2016). Consequently, preoperative chest X-Ray is only indicated if the clinician suspects issues with perioperative procedures or the results have potential to change the management of the condition (Feely et al., 2013; O'Neill et al., 2016).

In general, it may be true that the values of expanded assessment of basic preoperative diagnostic tests including pulse oximetry, ABG, laboratory diagnostic testing, and chest X-Ray could add important information to preoperative pulmonary assessment. However, there is a lack of strong evidence to accurately diagnose and predict PPC.

1.2.3 Assessment of functional status and overall physical condition

1.2.3.1 American Society of Anaesthesiologists classification system

The American Society of Anaesthesiologist's (ASA) functional status classification can be used to assess the overall physical condition (Table 1.5). This classification system provides an understanding of the burden of comorbidities and is particularly useful in understanding the frequency of post-operative complications (Lakshminarasimhachar and Smetana, 2016; Sameed et al., 2021). The ASA classification is also an important predictor of PPC (Gupta et al., 2011; Gupta et al., 2013; Genovese et al., 2017), despite having a high lack of inter-rater reliability (Aronson, McAuliffe and Miller, 2003). With each classification greater than 1, risk starts to increase (Smetana, Lawrence and Cornell, 2006), and substantial increases with ASA ≥ 3 can be seen in most studies (Yang et al., 2015; Agostini et al., 2010). This is useful because the ASA class mirrors the severity of the underlying illness suffered by the patient (Brinson and Thornton, 2018). However the ASA does not provide specific information about the conditions that should be focussed on in order to minimise risk to the patient (Gallart and Canet, 2015).

Table 1.5 – The American Society of Anaesthesiologists (ASA) physical status classification system. American Society of Anesthesiologists (ASA). ASA Physical Status Classification System. Available from: `https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system`.

ASA Classification	Definition
ASA I	A normal healthy patient
ASA II	A patient with mild systemic disease
ASA III	A patient with severe systemic disease
ASA IV	A patient with severe systemic disease that is a constant threat to life
ASA V	A moribund patient who is not expected to survive without the operation
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes

1.2.3.2 Walk tests

Fitness tests that are cheap to run, scalable and be more acceptable to the patient include the field walking test (6-minute walking test; 6MWT) and the incremental shuttle walking test (ISWT). These tests provide an objective measure of patient physical capability and have a high acceptability in particular amongst elderly patients (Lee et al., 2018a). Patients simply walk to a predefined protocol (Holland et al., 2014). 6MWT is the older test and ISWT the newer, slightly modified version (Hanley and Wijeysundera, 2021). The 6MWT is a straightforward test, where the patient has to walk 30 metres long (m) corridor for 6 minutes; the outcome is the distance the patient was able to walk during this time (Figure 1.1-A) (Holland et al., 2014; Agarwala and Salzman, 2020). During the ISWT the patient walks between 2 cones that are placed 10 m apart, and has to walk at an increasing rate (Figure 1.1-B) (Win et al., 2004; Fennelly et al., 2017).

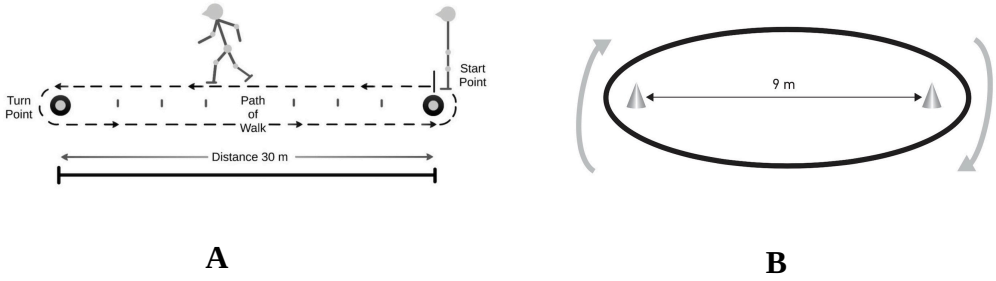


Figure 1.1 – Diagrams demonstrating the 6-minute walk test (6MWT) and incremental shuttle walk test (ISWT) used to assess patients' physical endurance. A) A schematic representation of 6-minute walk test (6MWT) on a 30-metre track. Two plastic cones marked the passageway, and tape marked 2-m intervals. A 2-metre space behind the cones allowed participants to securely turn around. 6MWT has been used . B) A diagram demonstrating incremental shuttle walk test (ISWT). The cones indicating turning points are spaced 9m apart. Reproduced with permission from Calatayud and Párraga (2016) and Holland et al. (2014).

The efficacy of these tests in predicting PPC remains uncertain. Two small, prospective studies looking at patients undergoing elective abdominal, and lung cancer surgery, failed to establish a reliable association between the results of preoperative 6MWT and ISWT tests and any postoperative complications,

including PPC (Win et al., 2004; Paisani et al., 2012). In another study, Nutt and Russell (2012) analysed 120 patients over the age of 60 who were scheduled for major colorectal surgery. They demonstrated that incremental shuttle walk distance (ISWD) of less than 250m predicted major postoperative complications including pneumonia in 7 patients (6%), with good specificity (0.88) but poor sensitivity (0.58) (Nutt and Russell, 2012). Fennelly and colleagues studied patients undergoing lung resection for cancer and identified ISWD of less than 400m as the sole significant factor linked to cardiopulmonary complications (OR: 4.3, 95% CI: 1.4–12.7; p=0.009). The best predictive model included desaturation and (SWD) shorter than 400m. However, the c-statistic of 0.67 suggests relatively low discriminatory accuracy of the predictive model (Fennelly et al., 2017).

In another research analysing data of 112 patients undergoing resection for benign or malignant colorectal disease, Lee et al. (2013) established c-statistic of 0.60 (95%CI 0.44-0.76; p=0.388) for the predictive accuracy of the 6MWD for 30-day morbidity including cardiopulmonary complications. Another study looked at 545 patients scheduled for elective non-cardiac surgery. The 6MWT distance was found to have a modest association with moderate or severe complications including pneumonia and respiratory failure (adjusted OR 1.32 per 100m decrease in 6MWT distance; 95%CI 1.01–1.73; p=0.045). Adding the 6MWD to regression model including sex, age and the type of surgery, did not improve model's performance in predicting postoperative complications (increase in c-statistic from 0.67 to 0.68; p=0.42; Ramos et al. 2021).

In a systematic review Moran and his colleagues investigated whether the walking tests may accurately predict overall patient complications, including PPC, following major intra-abdominal surgery (Moran et al., 2016). ISWT was performed on 171 patients in two of the studies, while 6MWT was performed on 390 patients. The patients were subject to various surgical procedures, including upper and lower abdominal, and thoracic surgery. Results indicated that the patients' performances during the tests might identify those at risk of complications, although the association was weak. Lumb (2019) offered

commentary on walking tests, emphasised that the 6-minute and shuttle walk tests are easy to complete but still contain some element of subjectivity.

1.2.4 Pulmonary function tests

Pulmonary function tests (PFT) have been used extensively to assess the risk of PPC following surgery in patients with underlying pulmonary disease (Chandler et al., 2020). These are well established and validated methods to help diagnose pulmonary disease, monitor symptoms and treatment response as outlined by Stanojevic et al. (2022). In general, there are three major components of PFT: lung volumes measurements, the diffusion capacity for carbon monoxide (DLCO), and spirometry (Tseng et al., 2017). Typically, the assessing clinician decides which tests are required for their patient in line with clinical guidelines (Dempsey and Scanlon, 2018; O'Neill et al., 2016).

The PFT comprises of lung volume testing and includes measurements of total lung capacity (TLC) and its components: residual volume (RV), and functional residual capacity (FRC) (Ruppel and Enright, 2012). Occasionally, the measurement of the total lung capacity is required to establish a complete and accurate physiological diagnosis. However, the measurements of the lung volume parameters are technically challenging , due to their reliance on estimation, which can introduce errors and require specialised procedures and equipment such as helium dilution, body plethysmography, and nitrogen washout, which limits their use in clinical practice (Wanger et al., 2005).

The DLCO provides a surrogate marker that indicates the ability of oxygen to be delivered from inspired air to the haemoglobin within the blood (Saydain et al., 2004; Tseng et al., 2017). Alahmari (2021) described the factors that influence DLCO measurements that must be taken into the account when testing and interpreting results, such as haemoglobin levels, smoking, oxygen therapy and body position.

Unlike the other components of PFT, spirometry is reproducible, non-invasive, and simple test (Oh et al., 2018). It measures multiple parameters, as shown in the flow-volume manoeuvre (Figure 1.2).

Spirometry is a key diagnostic tool because it allows a standard measurement of air flow, thereby providing an objective measure of the progress of a disease on lung function. It assesses preoperative risks, monitors the course of a disease, assesses airway responsiveness, and supports a prognosis for many respiratory conditions (Miller et al., 2005). However, caution should be exercised for patients who have pre-existing medical conditions such as unstable pulmonary embolism, uncontrolled pulmonary hypertension, that could be negatively affected by these physiological consequences (Graham et al., 2019).

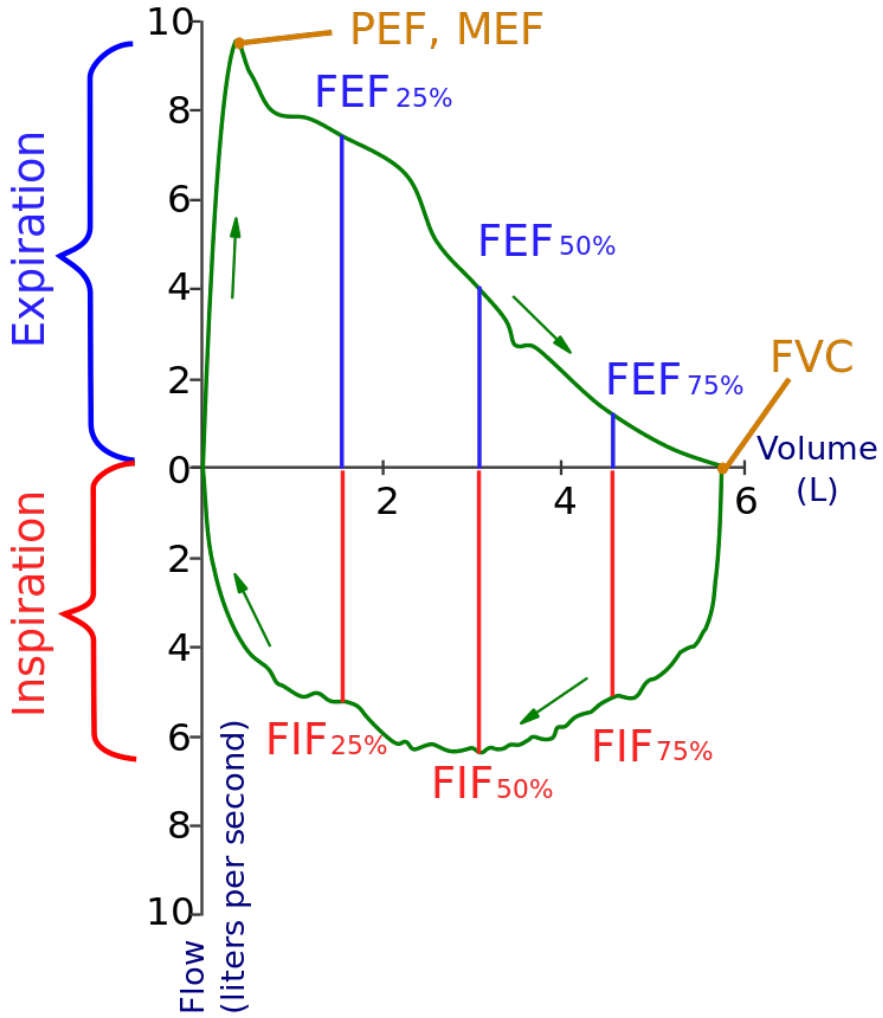


Figure 1.2 – Flow-Volume Loop from Spirometry. The graph illustrates the relationship between the volume of air exhaled and the corresponding flow rates during a forced expiration manoeuvre. PEF - Peak expiratory flow; MEF - Maximal expiratory flow; FEF - Forced expiratory flow; FIF - Forced inspiratory flow. The distinctive loop shape captures key spirometric parameters, including forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and the ratio FEV_1/FVC. Interpretation of the flow-volume loop aids in diagnosing and characterising respiratory conditions, providing insights into pulmonary function. Normal values: FEV_1 predicted > 80% and FEV_1/FVC ratio > 70. Obstructive values: FEV_1% predicted to classify severity according to the Global Initiative for Obstructive Lung Disease (GOLD) (Mild: $FEV_1 \geq 80\%$; Moderate: $50\% \leq FEV_1 < 80\%$; Severe: $30\% \leq FEV_1 < 50\%$; Very Severe: $FEV_1 < 30\%$) and $FEV_1/FVC < 0.70$.

The role of whole PFT components and values remains controversial in clinical practice. PFT may offer benefits in predicting outcomes, which include PPC in patients undergoing lung surgery (Cao et al., 2020; Ko et al., 2021; Sheshadri et al., 2021). However, for those patients undergoing non-cardiothoracic surgery, more recently, in a systematic review, Dankert et al. (2022) showed that due to a lack of flaws with the methods used and robust evidence, it is not clear if preoperative PFT sufficiently predicts PPC.

1.2.5 Cardio-pulmonary exercise testing

Cardio-pulmonary exercise testing (CPET) is a valuable technique that provides information on many aspects of a patients' condition including, cardiovascular, pulmonary, musculoskeletal, neuropsychological systems and metabolic function under the stress of an exercise routine (Albouaini et al., 2007; Boutou et al., 2016; Boutou et al., 2020).

The CPET has been employed to identify the pathophysiological mechanism(s) that are responsible for exercise intolerance and shortness of breath (O'Donnell et al., 2017; Radtke et al., 2019; Stickland et al., 2022), and to provide prediction of perioperative risk (Pritchard et al., 2021). It also helps clinicians understand more about prognosis, a context for analysis of treatment results (Pritchard et al., 2021; Radtke et al., 2019), which plays an important part in process of shared decision-making (Older and Levett, 2017). Diagnosing and objectively assessing the impact of comorbidities on functional status is exponentially guiding preoperative exercise training programmes as part of prehabilitation (Otto, Levett and Grocott, 2020).

CPET measures the body's cardiovascular response to physical stress in a form of exercise. Prior to starting the test, CPET requires a robust medical history, clinical examination, basic laboratory tests, and cardiopulmonary diagnostics. This helps interpret the results (Glaab and Taube, 2022). The CPET equipment include a metabolic cart and pressure display, a blood pressure monitor, a face mask, electrocardiogram (ECG) leads, and a pulse oximeter (Maron et al., 2013; Pritchard et al., 2021). CPET is performed by an adequately trained

healthcare professional, using either bicycle or treadmill modalities. The CPET protocol begins with mask/mouthpiece adaption, including measurements of blood pressure and ECG, then starts the warm-up phase for 3 minutes, incremental exercise for 10 minutes, and the recovery phase ending the exercise (Glaab and Taube, 2022). There are several physiological parameters that are measured and calculated during CPET which then can be interpreted in a context of physiological performance, medical background and planned surgical procedure in order to provide assessment and stratification of risks associated with surgery (Figure 1.3).

Results of this comprehensive test provides clinicians with information about the physiological reserve of the patient (Figure 1.3) (Albouaini et al., 2007; Boutou et al., 2016; Stavrou et al., 2018; Boutou et al., 2020), and enables them to identify and quantify the problems that may not be immediately identified during a snapshot method of testing, many of which are not performed under stress, such as 12-lead ECG or spirometry (American Thoracic and American College of Chest, 2003; Palange et al., 2007; Guazzi et al., 2016; O'Donnell et al., 2016; Radtke et al., 2019).

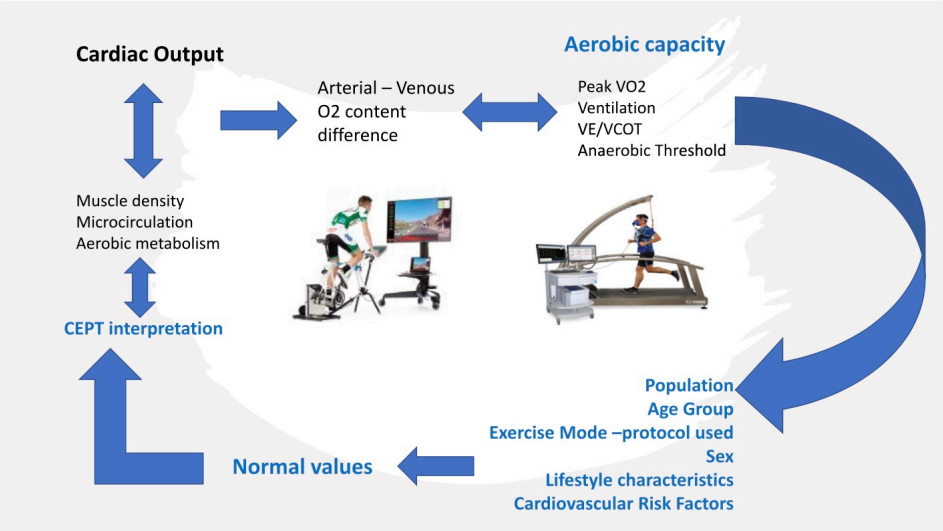


Figure 1.3 – The protocol elements, physiological and ergometric parameters of cardiopulmonary exercise testing (CPET). Physiological parameters:AT - Anaerobic threshold; $\dot{V}O_{2\ (peak)}$ - Oxygen uptake or consumption; $\dot{V}E/\dot{V}CO_2$ - Ventilatory equivalents for carbon dioxide. (Glaab and Taube, 2022; Laveneziana, Di Paolo and Palange, 2021).

The use of CPET as a method of evaluating surgical patients was first written about in 1993, by Older and colleagues in a paper that has pioneered the use of CPET in perioperative care (Older et al., 1993). In a study that they conducted of 184 elderly patients, they found an association between preoperative AT of $<11.0\,mL\,kg^{-1}\,min^{-1}$ and postoperative outcome. All these patients were scheduled for major intra-abdominal surgery. However, it is worth noting that this survey only studied a single metric to assess non-pulmonary complications.

As a result of this study, over the past decade, the use of preoperative CPET as a tool to evaluate the risk of negative perioperative incidents has increased (Levett et al., 2018). Individual studies have shown that CPET can play a role in predicting PPC, but its value is still controversial (Forshaw et al., 2008; Barakat et al., 2015; Patel et al., 2019; Brat et al., 2023). In a recent systematic review of 33 studies of patients who underwent non-cardiothoracic surgery, Stubbs, Grimes and Ercole (2020) analysed diagnostic accuracy of CPET parameters in predicting post-operative complications. Confusion matrices summarise in Table 1.6 were constructed using data from 27 of these studies allowing

to create performance measures. Most of the information generated related to the prediction of PPC and this was combined with data regarding cardiovascular complications from different studies, with data available for AT in 12 studies, $\dot{V}O_{2\ (peak)}$ in 2 studies, and $\dot{V}E/\dot{V}CO_2$ in 2 studies. The cut-offs for these variables were documented: AT from 9.0 to 11.1 mL kg^{-1} min^{-1}, $\dot{V}O_{2\ (peak)}$ from 15.8 to 20.2 mL kg^{-1} min^{-1}, and $\dot{V}E/\dot{V}CO_2$ from 34.5 to 36.5. Importantly, these values had highly variable sensitivity and specificity. Overall, conclusions from this study suggest that CPET may not reliably predict PPC in those patients who suffer from poor functional capacity (Stubbs, Grimes and Ercole, 2020).

Table 1.6 – The results of cardiopulmonary exercise testing (CPET) confusion matrix derived from data collated in the systematic review by Stubbs, Grimes and Ercole (2020). AT – Anaerobic threshold; $\dot{V}O_{2\ (peak)}$ – Oxygen uptake or consumption; $\dot{V}E/\dot{V}CO_2$ – Ventilatory equivalents for carbon dioxide.

CPET Variable	Cut-off values	Sensitivity	Specificity
AT	9.0-11.1	23.3-100	50-88.9
$\dot{V}O_{2\ (peak)}$	15.8-20.2	50-57.1	43.4-66.7
$\dot{V}E/\dot{V}CO_2$	34.5-36.5	39.5-50	81.5-90.7

1.2.6 Preoperative pain management

Pain can result in diaphragmatic immobilisation, leading to the accumulation of sputum and the development of a chest infection (Tegegne et al., 2021). Pain can also prevent patients from attaining sufficient lung expansion, in leading to hypoventilation and atelectasis, and an elevated risk of PPC Chandler et al. (2020). The transmission of pain signals contributes to the suppression of the phrenic nerve's function through spinal reflexes, which in turn affects the diaphragm's function, explaining the impairment of respiratory muscles (Sameed et al., 2021).

Good perioperative pain management could play an important role in reducing surgical stress and PPC risk. However, the published data on preoperative pain management is limited and primarily focuses on postoperative techniques, a

topic beyond the scope of this thesis. Therefore, additional studies are necessary to fully understand the role of preoperative pain management in managing the risk of PPC.

1.2.7 Predictive models of postoperative pulmonary complications

Sabaté, Mazo and Canet (2014) have asserted that one of the key steps towards the achievement of improved PPC management of potential life-threatening complications is to improve risk stratification and prediction methods so that appropriate preemptive means can be planned, and suitable follow-up care can be enabled. In order to identify high-risk patients, facilitate informed consent, and optimise perioperative treatment, predictive models for risk appraisal are essential (Miskovic and Lumb, 2017).

Precise risk classification systems that incorporate risk adjustment enable valid comparisons of surgical outcomes to be made between providers, which is an important benefit for both clinical audits and service evaluation (Moonesinghe et al., 2013). In order to improve patient outcomes and cost-effectiveness, healthcare professionals and policymakers are increasingly promoting the use of risk prediction models to guide treatment choices and resource allocation (Steyerberg et al., 2013; Collins et al., 2015).

Nonetheless, a recent analysis of 21 studies that have examined risk prediction models for PPC exposed serious flaws. The included models failed to completely follow the guidelines for creating a prediction model, which includes sample size, design, and internal and external validation (Nijbroek, Schultz and Hemmes, 2019). Additionally, the research populations employed in developing the current models showed significant variation, ranging from single surgery cohorts (Matthew Reinersman et al., 2016; Yepes-Temiño, Monedero and Pérez-Valdivieso, 2016; Genovese et al., 2017) to larger general surgery cohorts, frequently comprising patients receiving peripheral surgery (Canet et al., 2010; Gupta et al., 2013; Jeong et al., 2014; Mazo et al., 2014; Johnson et al., 2017; Neto et al., 2018; Russotto, Sabaté and Canet, 2019).

Moreover, the study cohorts included a wide range of patients with various demographics and surgery types. Some studies focused specifically on higher-risk patient groups (Parry et al., 2014; Li et al., 2023a), such as the elderly (Wei et al., 2023), whereas others incorporated a wider population. Studies were further limited by inconsistencies in PPC definitions, with some studies employing a combined PPC endpoint (Scholes et al., 2009; Jin et al., 2015; Mazo et al., 2014; Parry et al., 2014; Neto et al., 2018) and EPCO definitions (Jammer et al., 2015), and others focusing on specific complications such as postoperative respiratory failure (Arozullah et al., 2000; Johnson et al., 2007; Gupta et al., 2011; Fischer et al., 2013), or one single PPC (Arozullah et al., 2001; Hua, Brady and Li, 2012; Kor et al., 2014). The time windows employed to evaluate PPC development varied between 48 hours and multiple postoperative days, which added further heterogeneity (Gupta et al., 2011; Kor et al., 2011; Brueckmann et al., 2013; Johnson et al., 2017).

It is important to note that external validation becomes a must before using any type of prediction score in clinical practice. This procedure is critical in ensuring that predictions apply to other patient samples than those used to construct the model, ideally selected from various clinical contexts (Steyerberg et al., 2013). Only the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) risk score has been found in relevant research to have sufficient predictive ability in external validation, despite having a small sample size (Kokotovic et al., 2022). Notably, none of the studies adequately followed all necessary procedures for creating prediction models (Nijbroek, Schultz and Hemmes, 2019; Kouli et al., 2022).

A multitude of various predictive scores implies that none of them is perfect and these predictive models often do not perform well on external validation. There is still no agreement on the most important PPC risk factors, which is probably due to the variety of problems, their definitions, population differences, changes in the risk variables that have been studied, and study design choices. It is still difficult to reach a consensus about these factors in this field. Indeed, it would be rather naive to believe that one predictive model can capture all range of clinical settings and populations/cohorts. In addition,

these scoring systems and predictive models rely heavily on peri-operative parameters, which renders them less useful for pre-operative identification of patients at risk who would benefit from pre-habilitation.

1.2.8 Risks factors of postoperative pulmonary complications

Patients suffering from PPC may be affected by a complex series of conditions; from pre-existing diseases to trauma they have suffered during surgical procedures and the effects of anaesthesia (Schwartz et al., 2020; Sameed et al., 2021). There are also chronic risk factors, which come into effect pre-operation that can include age and lifestyle factors and poor cardiorespiratory health (Shander et al., 2011).

Important to decreasing the risk of PPC following surgery is an understanding of the benefits of non-surgical measures, alternative surgeries, medical interventions, or pre-habilitation, particularly for patients with an increased risk of PPC (Adeleke et al., 2021). Table 1.7 shows more recent evidence of modified and non-modified risk factors using predictive models and their clinical impact on PPC.

Table 1.7 – Overview of the non-modifiable, modifiable, and patient, procedure, and lab-based-related risk factors associated with postoperative pulmonary complications. ARISCAT - The Assess Respiratory Risk in Surgical Patients in Catalonia; COPD - Chronic obstructive pulmonary disease; ASA - American Society of Anaesthesiologists; HTN; Hypertension; CHF - Congestive Heart Failure; SpO_2 - Oxygen saturation.

Study	Surgical procedure/ Predictive model	Risk factors	Odds Ratio
Non-modifiable patient-related risk factors			
Admass et al. (2023)	Thoracic,	Age	1.53
Baar et al. (2022)	abdominal,		1.80
Xu et al. (2022a)	lung cancer,		1.92
Neto et al. (2018)	liver, general		1.01
Canet et al. (2010)	surgeries		5.10
Abd El Aziz et al. (2020)	Colorectal,	Partially dependent	2.35
Foster et al. (2019)	general,		2.55
Arozullah et al. (2001)	non-cardiac		1.83
Arozullah et al. (2000)	surgeries		1.92
		Totally dependent	3.41
			2.55
			2.83
			1.92

Study	Surgical procedure/ Predictive model	Risk factors	Odds Ratio
Xu et al. (2022a)	Liver, ovarian,	Blood transfusion	1.83
Xu et al. (2022b)	non-cardiac		1.89
Arozullah et al. (2001)	surgeries		1.35
Abd El Aziz et al. (2020)	Colorectal	ASA $\geq$ III	2.10
Jurt et al. (2018)	surgery		2.00
Neto et al. (2018)	General surgery	Cancer	1.72
	LAS VEGAS risk		
Baar et al. (2022)	Lung cancer surgery	Male	1.40
Arozullah et al. (2001)	Non-cardiac surgery	Impaired sensorium	1.51
	Pneumonia risk index		
Arozullah et al. (2001)	Non-cardiac surgery	Weight loss > 10%	1.92
	Pneumonia risk index		
Canet et al. (2010)	General surgery	Respiratory infection	5.50
	ARISCAT		

Study	Surgical procedure/ Predictive model	Risk factors	Odds Ratio
Modifiable patient-related risk factors associated			
Abd El Aziz et al. (2020)	Colorectal,	COPD	3.17
Foster et al. (2019)	general,		1.97
Arozullah et al. (2001)	non-cardiac		1.72
Arozullah et al. (2000)	surgeries		1.81
Baar et al. (2022)	Lung cancer,	Smoking	1.60
Abd El Aziz et al. (2020)	colorectal,		1.78
Arozullah et al. (2001)	non-cardiac surgeries		1.28
Morris et al. (2022)	General	HTN	1.30
Foster et al. (2019)	surgery		1.33
Xu et al. (2022b)	Ovarian cancer,	Blood loss	1.47
Jurt et al. (2018)	colorectal surgery		2.06
Xu et al. (2022a)	Liver surgery	Medical diseases	3.52
Smith et al. (2010)	Abdominal surgery	History of lung disease	2.45
Morris et al. (2022)	General surgery	CHF	2.4

Study	Surgical procedure/ Predictive model	Risk factors	Odds Ratio
Non-modifiable procedure-related risk factors			
Admass et al. 2023	Thoracic,	Operation duration	2.45
Xu et al. 2022a	abdominal,		1.89
Xu et al. 2022b	liver, ovarian,		1.81
Neto et al. 2018	general, rectal		1.00
Milone et al. 2017	surgeries		1.00
Jurt et al. 2018	Colorectal,	Emergency surgery	2.70
Neto et al. 2018	general,		2.56
Smith et al. 2010	abdominal,		6.35
Canet et al. 2010	non-cardiac		2.20
Arozullah et al. 2001	surgeries		1.33
Arozullah et al. 2000			3.12
Arozullah et al. 2001	Non-cardiac surgery	Open surgery	1.56
	Pneumonia risk index		

Study	Surgical procedure/ Predictive model	Risk factors	Odds Ratio
Biochemical and haematological risk factors			
Xu et al. (2022b)	Ovarian cancer,	Low albumin	0.92
Foster et al. (2019)	general, non-cardiac		1.77
Arozullah et al. (2000)	surgeries		2.53
Neto et al. (2018)	General	Preoperative $SpO_2 \leq 90$	3.01
Canet et al. (2010)	surgeries		10.7
Neto et al. (2018)	Non-cardiac surgery	Preoperative anaemia	1.77
Canet et al. (2010)	Pneumonia risk index		3.00

1.3 Image-based approaches to risk stratification: morphometric body composition analysis

The pre-operative assessment of risks associated with surgery and appropriateness of intervention is evaluated by analysing patient-related factors in context of the complexity and severity of the surgical procedure (Englesbe et al., 2012). Various methods of risk stratification have been developed, most based on comorbid status and biochemical/haematological parameters, but increasingly now predicated on an assessment of the patient's capacity to engage in activities of daily living and their physiological resilience (Friedman et al., 2015). These methods typically address singular facets of an individual's surgical risk, lack objectivity, and often prove insufficient for application in increasingly aged, multi-morbid individuals who are in need of surgical interventions.

Over the past two decades, there has been significant advancement in the technology that underlies medical imaging. This progress has resulted in advancements that are sophisticated enough to enable the measurement of various parameters related to the anatomy, function, metabolism, and physiology of patients (Huang et al., 2015; Sullivan et al., 2015). These measurements, have the potential to indicate whether an individual's tissue or organs are within normal ranges or are being affected by pathological processes (Sullivan et al., 2015).

During the last half-century, the field of imaging-derived body composition (morphometric features) has essentially been directed towards assessment and the measurement of a range of factors and parameters within the human body. These have encompassed measurements relating to lung density, airways, chest and abdominal musculature, thickness of the diaphragm, mineral content of the bone, dimensions of the pectorals, core and psoas muscles, fat content within the viscera and subcutaneous tissue, and blood vessel evaluation, e.g. to identify site, length and the presence of calcified lesions (Figure 1.4 on the next page).

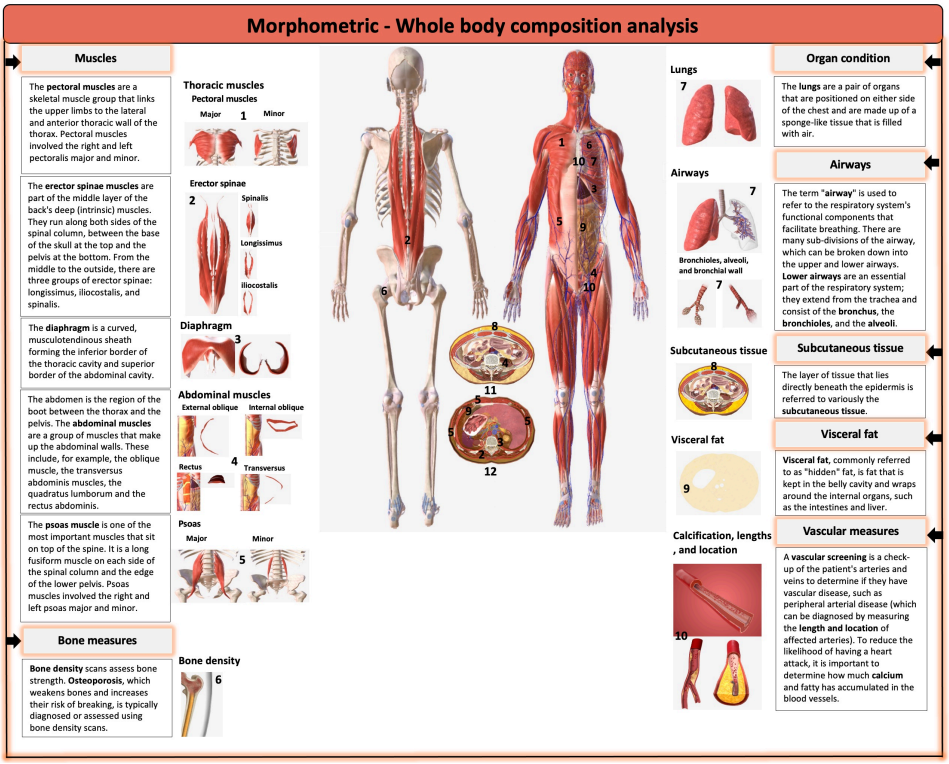


Figure 1.4 – Biomarkers/radiomarkers assessed using opportunistic data form routine medical imaging. A diagram of body elements used as biomarkers: 1) pectoralis muscle, 2) erector spinae muscle, 3) diaphragm, 4) abdominal wall muscles, 5) psoas muscle, 6) bone density, 7) lungs and airways, 8) subcutaneous tissue, 9) visceral fat, 10) calcification, lengths, and location; cross-sections: complete anatomy on an axial slice at the fifth lumbar (L_5) vertebra 11) and 12) twelfth thoracic vertebra (T_{12}), illustrating the distribution of thoracic and abdominal muscles, pelvic, subcutaneous, and visceral fat.

Detailed imaging prior to major surgery is essential for estimation of disease burden, disease severity, and for procedure planning (Englesbe et al., 2012). Generally, the preoperative imaging focuses on two key aspects: presence of gross abnormalities (pathologies unrelated to the primary problem), and specific information relevant for the planned intervention (staging of the disease, anatomical assessment of aneurysm). Only a limited image review and interpretation is usually performed and image-derived biomarkers are likely not to be considered (Emaminejad et al., 2016; Popovici et al., 2017; Scalco and Rizzo, 2017). However, these morphomarkers may have implications for the screening, staging or classification of the disease, for designing operative

procedures or treatments, such as radiotherapy, and for determining prognosis (Aerts et al., 2014; Scalco and Rizzo, 2017; Traverso et al., 2018).

When assessing a patient with chronic respiratory pathology, quantitative imaging methods have been shown to be superior to PFT (Ueda et al., 2005; Na et al., 2014). Although the latter can demonstrate physiological abnormalities relating to lung disease, the former can offer detailed information on alterations in the structure of the lung substance, and its precise extent (Chen et al., 2020). This is particularly the case early in a pathological process, when physiological testing may lack the sensitivity to recognise early changes relating to disease due to sufficient compensation (Chen et al., 2020). Quantitative imaging tools may therefore be a useful adjunct to PFT during the assessment of individuals with chronic pulmonary pathologies (Barros et al., 2022b).

Attention is being increasingly drawn to the application of body composition analysis to identify patients at risk who would gain advantage from targeted assessments and interventions (Mullie and Afilalo, 2019; Campa et al., 2021). A novel strategy, analytical morphomics, which is also referred to as morphomics/morphometry, comprises an all-inclusive analysis of a patient following whole-body imaging of predetermined biomarkers of body composition. The acquired data may be then used to generate models which offer information on clinical outcomes (Stidham et al., 2015; Singal et al., 2016; Benjamin et al., 2017).

Wang et al. (1992) proposed that body composition is a biological category which encompasses the quantification of the constituents of the human body in vivo. Contemporary functional body composition analysis evaluates the cumulative reactions of the body to both intrinsic and extrinsic elements from cellular to molecular levels, and includes intermediary metabolic processes (Andreoli et al., 2016). This setting has demonstrated the essential nature of this science and the fact that a precise assessment can be achieved if performed in an apposite manner (Campa et al., 2021).

Analysis of body composition is often performed using images obtained routinely, eliminating the requirement for patients to undergo additional investigations, and in particular radiation exposure (Troschel et al., 2020). This type of data

source is sometimes termed ’opportunistic’. Earlier research has shown that the utilisation of morphometric parameters gives rise to quantitative information regarding body composition that can enhance the assessment of risk prior to operative interventions (Englesbe et al., 2010; Lee et al., 2011), and also gauge metabolic risks (Cornacchia et al., 2020). These morphomarkers are encouraging indicators which enable the likelihood of potentially preventable complications, such as PPC. Consequently, they may therefore indicate the need for clinical optimisation and prehabilitation in patients undergoing major surgery (Englesbe et al., 2012; Sabel et al., 2013; Cakir et al., 2015b; Pienta et al., 2018; Bak et al., 2019; Choe et al., 2019).

1.3.1 Overview of modalities for morphometric body composition analysis

There are a number of techniques which can be used to determine body composition, of which imaging modalities are the most frequently applied (Troschel et al., 2020). These can also be used to survey the various compartments of the body as well as their distribution (Chaves et al., 2022). Such imaging techniques include anthropometry, air displacement plethysmography (ADP), bioelectrical impedance analysis (BIA), ultrasound, dual-energy X-ray absorptiometry (DXA), CT and MRI.

The main benefits and drawbacks of these methods, as reported by earlier research, are shown in Table 1.8 (Di Sebastiano and Mourtzakis, 2012; MacHann et al., 2013; Andreoli et al., 2016; Lee et al., 2019; Troschel et al., 2020; Holmes and Racette, 2021). Each method has limitations which relate to either technical aspects of image acquisition or the parameters measured (MacHann et al., 2013; Wang, Chen and Eitzman, 2014; Andreoli et al., 2016; Rashmi and Snekhalatha, 2019). The choice of technique utilised should encompass the equipment cost and required staffing, any exposure to ionising radiation, scan duration and data precision (Andreoli et al., 2016).

Of the imaging techniques used, the most precise for the determination of body composition at the level of the tissues in vivo are thought to be either

CT or MRI (Fosbøl and Zerahn, 2015; Tolonen et al., 2021). Both these are included as components of routine care of patients with malignancies (staging, evaluation of response to treatment and follow-up) and aortic disease (surgical procedure planning), and therefore offer an ideal chance to include the assessment of body composition into standard patient care (Yip et al., 2015).

In contrast to CT, MRI can provide anatomical detail on fat deposition without exposure to ionising radiation (Wang, Chen and Eitzman, 2014). Quantification of fatty tissue and details of processes underlying pathologies can enable the recognition of links between fat distribution patterns (Andreoli et al., 2016).

Few studies have addressed whether automated MRI-based body composition analysis techniques are reproducible (Borga, 2018). MRI is not frequently used in a quantitative manner in contrast to the CT where radiodensity can be quantified using Hounsfield Units (HU). In MRI only arbitrary units are used to indicate the degree of intensity on MRI scans; these bear no relation to underlying tissue constituents (Hilmi et al., 2019). Manual segmentation of abdominal images is also uneconomical in terms of time and personnel, and may also be restricted by regional access to experienced staff (Yip et al., 2015; Rashmi and Snekhalatha, 2019). Thus, MRI is not a practical proposition for upscaled research (Fosbøl and Zerahn, 2015). However, an entire image volume can be acquired as there is no requirement for ionising radiation; this diminishes any ambiguity regarding image positioning (Borga et al., 2018).

CT offers the ability to perform an in-depth and full assessment of body tissues, i.e. the skin, musculature, internal viscera and soft tissue, and can provide a measure of adipose deposition within lean tissues (Prado, Birdsell and Baracos, 2009; Di Sebastiano and Mourtzakis, 2012; Yip et al., 2015; Fosbøl and Zerahn, 2015). CT is also an established technique for the verification of alternative methods of body composition assessment owing to its accuracy (Mattsson and Thomas, 2006). There is less than 2% error in reproducibility using CT, which means that this modality is a good choice for the recognition of minute alterations in muscle and adipose tissue (Mourtzakis et al., 2008; Di Sebastiano and Mourtzakis, 2012; Andreoli et al., 2016). The need for ionising radiation is a disadvantage in terms of using CT simply to evaluate body

composition, and so it is deemed a convenience technique (Aubrey et al., 2014; Ceniccola et al., 2019). However, when the CT is indicated for other reasons (procedure planning, disease staging) this can be treated as opportunistic data and used whenever possible.

Table 1.8 – Summary of body composition analysis modalities. BIA - Bioelectrical impedance analysis; ADP - Air displacement plethysmography; DXA - Dual-energy X-ray absorptiometry; CT - Computed tomography; MRI - Magnetic resonance imaging.

Modality	Type of Measurement	Advantages	Disadvantages
Anthropometry	BMI, height, weight	Portable	Insensitive, it is unable to detect changes in body composition over the short period
	Limb, hip, waist circumference	Easy	Not validated in cancer populations
	Waist-to-hip ratio	Non-invasive	Gains in fat may mask muscle loss
			High inter-observer variability
			Overestimate adiposity
			Time consuming
BIA	Uses resistance and reactance dictate fat mass, body water, fat-free mass	Training unnecessary	Underestimates fat-free mass in patients with advanced cancer
		Non-invasive	Only differentiates between fat and fat-free mass
		Inexpensive	Reliant on hydration stability
		Portable	
		Easy	
Ultrasound	Examines tissue with sound waves	Capable of capturing muscles in motion, such as the diaphragm	Just small section of body visualised

Modality	Type of Measurement	Advantages	Disadvantages
		Inexpensive	Operator training needed
		Portable	Artefacts
		Easy	
ADP	Air displacement measures fat percentage, density, and body volume	Suitable for a wide range of populations	Very little research has been done on cancer populations
		Reliable and valid	Inaccessible
		Non-invasive	
DXA	Identifies bone mineral, fat-free mass, and fat mass using high and low energies	Body composition measurements at the regional and whole-body levels	Direct exposure to ionising radiation
		Distinguishes precisely bone, fat-free mass, and fat	Accuracy requires patient positioning
		Very high levels of precision and accuracy	Operator training needed
		Reproducible	Inaccessibility
		Safe	Not portable
CT	Estimates fat mass and whole-body muscle using tissue density and cross-sectional area from routine single-slice CT scans	Separate the sections of muscle, fat, and bone precisely	Technological parameters affect measurements.
		Whole-body composition can be seen in a single image	Not possible to carry out at the bedside

Modality	Type of Measurement	Advantages	Disadvantages
		Images obtained as part of routine care can be used	Direct exposure to ionising radiation
		Attenuation-based tissue quality assessment	Expensive
		Evaluation of visceral and subcutaneous fat	
		High precision	
		Reproducible	
MRI	Magnetic fields produce body images. Images to assess fat mass and muscle based on cross-sectional area and tissue density	Able to discriminate between components of fat mass and components of fat-free mass	May not accommodate obese individuals
		Whole-body composition can be seen in a single image	More time required to acquire images
		No exposure to ionising radiation	Not as widely available as CT
		High precision	Specific software is required
		Reproducible	Very expensive

CT scans have superseded chest X-rays as the premier imaging modality for clinical diagnostic work (Whiting, Singatullina and Rosser, 2015). First utilised in 1971, CT offers a number of benefits over the conventional radiograph. The images acquired are cross-sectional, and so the 2D overlapping of anatomy that is seen on a typical radiographic image is circumvented; attenuation sensitivity is over a factor of ten higher, and 3D images are generated (Brenner and Hall, 2007; Lee et al., 2019). CT scans are therefore in widespread use, and easily

accessible worldwide (Tsujinaka et al., 2008; Pelc, 2014). The images provide extremely useful anatomical and pathological data relating to the viscera and other areas requiring examination. This type of scan is labelled computed tomography; the initial name indicates the calculations performed to create the images, and the latter splits into ‘tomo’ and ‘graphy’ combing the Greek’ words for ‘cut’ or ‘section’ and ‘to describe’, respectively (Jung, 2021). This imaging modality has been a pivotal method of evaluation in individuals with chest pathologies. As the range of recognised thoracic conditions has increased, the number of thoracic CT examinations requested has therefore risen (Bhalla et al., 2019).

A number of benefits are offered by CT compared to other techniques of body composition analysis, e.g. access to currently available imaging sets, the capacity to perform retrospective quantitative image analysis, and the ability to evaluate the amount, quality and distribution of tissue with a high degree of reproducibility and using few assumptions (Mullie and Afilalo, 2019). The assessment of CT images is a well-established and extremely accurate technique with which to gauge the composition of the human body; Andreoli et al. (2016) have suggested that for regions of tissue, the error is only 1.4%. This accuracy means that CT is the favoured technique in a number of clinical settings and especially in patients with malignancy, where the diagnosis, staging and decisions relating to treatment of the tumour are heavily influenced by body composition data.

High resolution cross-sectional representations of the tissues and viscera within the human body are created following image acquisition by CT imagers. X-ray technology and high performance computational algorithms are exploited in order to achieve this. The centre of a traditional CT imaging system comprises a slim X-ray beam which is situated across from a line of detectors. These are positioned in a circular construction that revolves around the subject’s axis over 180˚ in order to generate an image in the transverse plane (Milne and King, 2014).

The X-ray beam decay is quantified as it traverses the differing tissue densities. This, in turn, facilitates the generation of a 2D image (Milne and King, 2014;

Campos and Diaz, 2018). Such axial images are made up pixels, or picture elements, which reflect the densities of the tissues in the area under investigation. Pixels are the empirical unit of a digital picture, and generally form a grid-like pattern. The higher the number of pixels present, the greater the image resolution and the more optimal the representation of the imaged tissue (Campos and Diaz, 2018). A schematic of the basic components of a CT image is shown in Figure 1.5.

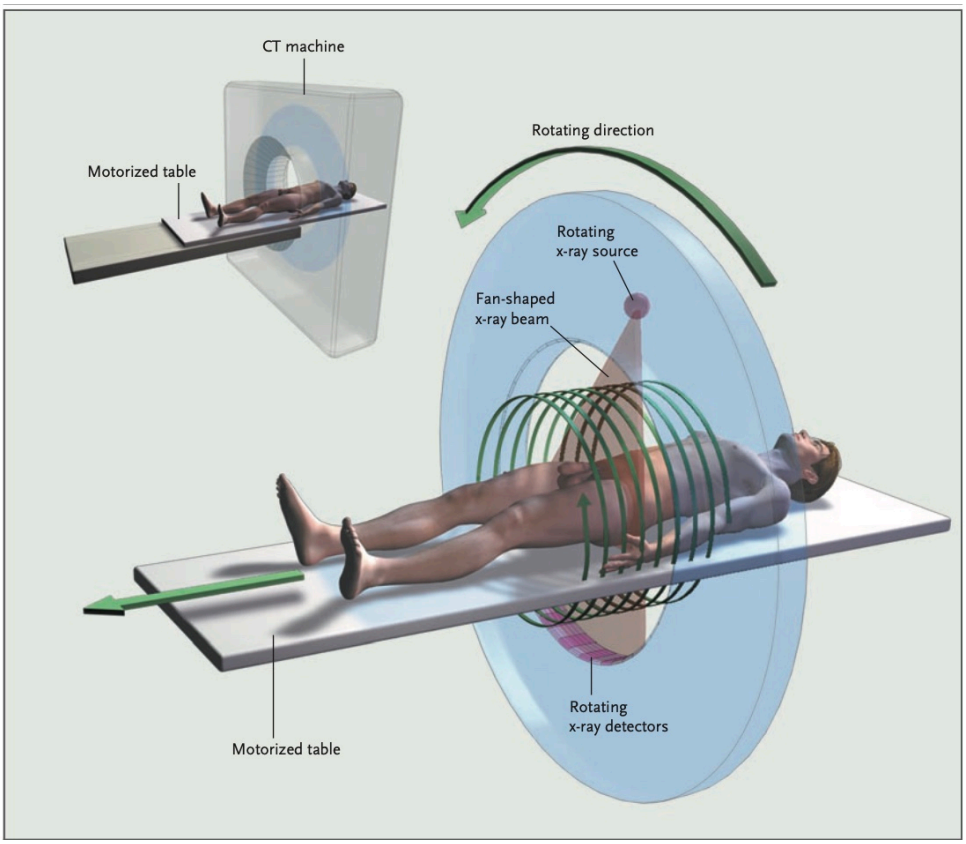


Figure 1.5 – The basic fundamentals steps and technique of computed tomography (CT) scanning, reproduced with permission from Brenner and Hall (2007), Copyright Massachusetts Medical Society. A source of x-rays spins within the torus-shaped scanner with the scanned object position inside; at the same time a set of x-ray detectors rotates in synchrony on the opposite side of the scanned object. The x-ray source generates a narrow beam in the shape of a fan, with widths that can range anywhere from 1 to 20 millimetres. This illustration shows only one row of detectors, but modern machines often operate with many rows of detectors functioning side by side. This allows for the simultaneous imaging of numerous slices (now up to 64), which cuts down on scanning time. A sequence of picture slices reflecting a three-dimensional representation of the target organ or body region are created by the computer's processing of all the data. Reconstructed CT images can be displayed on a computer monitor, allowing radiologists to manipulate and analyse the images.

The sequence of axial images acquired subsequently undergo processing with the use of computer software; the various axial, sagittal and coronal image acquisitions are assembled to create a 3D volume of the imaged area. This volume is comprised of units referred to as voxels (Figure 1.6 on page 65)**.** The value of a voxel in CT images indicates the degree of X-ray decay within the

tissue and consequently, the tissue density. This is quantified using HU and is calculated using a formula in Equation 1.1.

$$HU = (\frac{\mu_{\text{material}} - \mu_{\text{water}}}{\mu_{\text{water}}}) * 1000 \tag{1.1}$$

$$\text{where: } \mu - \text{CT linear attenuation coefficient}$$

The scale applied to tissue density is random, and lies within the spectrum -1000 - +1000 HU where 0 and -1000 HU reflect the attenuation of water and air, respectively (Table 1.9 and Figure (1.6)).

Table 1.9 – Hounsfield Units (HU) of common elements captured on computed tomography (CT) scans.

Tissue/Element	Associated Hounfield Unit
Bone	+1000
Liver	40 to 60
White matter (brain)	-20 to -30
Grey matter (brain)	-37 to -45
Blood	40
Muscle	10 to 40
Kidney	30
Cerebro-Spinal Fluid	15
Water	0
Fat	-50 to -100
Air	-1000

Divergent degrees of decay can be identified within differing tissue types owing to their individual densities and constituents. Those with a higher degree of attenuation than water, such as muscle, hepatic and skeletal tissues, have a positive HU value. Conversely, those with a lower level of decay, e.g. pulmonary and fatty tissues, exhibit a negative HU value.

The 2D cross-sectional images created by CT imagers allow clinicians to assess and to interpret the findings within a range of body tissues in detail (Ceniccola et al., 2019). Such images are essential for the diagnosis and management

of numerous pathologies, and enable a detailed assessment of the patient's anatomy and the design of apposite approaches to treatment.

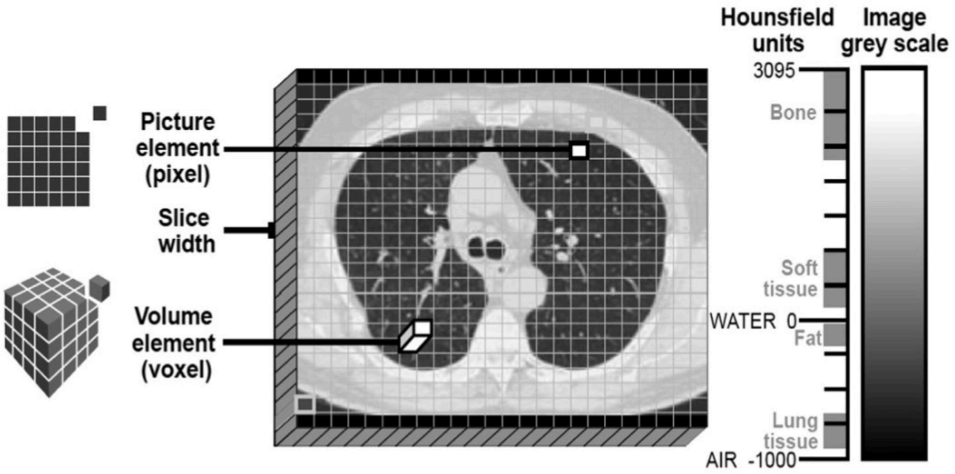


Figure 1.6 – A diagram representing radiodensities of different tissues and materials. Creative Commons Attribution License (CC BY) `https://creativecommons.org/licenses/by/4.0/`. Permission not required.

1.3.2 Morphometric body composition analysis: methodology

A succession of stages is necessary in order to perform morphometric body composition analysis (illustrated in Fig 1.7). The initial phase requires the selection of the ideal type of imaging for the clinical context and objectives. The authors currently find CT imagers are the most popular form of imaging utilised owing to the precision of the related analytical techniques for body analysis computation. CT images are acquired of the required anatomical area, e.g. the abdomen or thorax. These are previewed, and the scan is appraised. A computer monitor is used for viewing the image reconstructions; software enables image readers to manoeuvre and to interpret the data. Typically, 2D stacks of images are presented for review, a method which enables the volumetric images to be viewed in a straightforward manner on the 2D monitor (Tolonen et al., 2021).

A single slice is sufficient to enable 2D body composition analysis to be carried out with ease; volumes can be generated by stacking the images (Sottier et al., 2013). The majority of contemporary imagers use multi-slice methodology, often in association with helical acquisition (Goldman, 2008; Tolonen et al., 2021). In comparison to single-slice image acquisition, multi-slice CT has a number of benefits, such as less heating of the tubes, more rapid image collection, multi-planar reconstructions that are isotropic and have a resolution of less than a millimetre, as well as higher volumes of imaging (Prokop, 2003; Tolonen et al., 2021).

The image processing stage is followed by interpretation using specific image analysis software, which initiates identification of morphemic indicators using dedicated algorithms. These recognise and divide certain body constituents according to a workflow paradigm. Segmenting the images facilitates measurement of the target constituent distribution and quantity. The drawing tools offered by the package allow the user to hand draw regions of interest (ROI); alternatively, semi-automated or fully automated segmentation may be utilised in order to differentiate between pixels within ROI, e.g. adipose, muscle, skeletal or pulmonary tissues. This is achieved by predetermining the threshold HU parameters. Tissue quantification is then performed by the software, during which the volumes or areas of the various types of tissue within the ROIs are computed. This requires the voxel number within the predetermined spectrum of HU to be recorded, or the total area of tissue within the 2D images to be evaluated. The last stage of the process is to observe the quality of the segmentation performed. The calculated data are then evaluated in order to determine body composition, and the information is entered into a detailed report, which encompasses the chosen ROI, the applied threshold values and any pertinent noted similarities or differences. The exact processes and instruments applied may differ according to the software available, and so following the manufacturer's recommendations for software use is paramount in order to ensure that the analytical process is performed precisely.

In summary, morphometric body composition analysis requires images to be obtained, e.g. using a CT imager, image segmentation using dedicated software,

quantification of tissue types, interpretation of the quantitative information, and detailed documentation of the results. Every stage is important in order to produce precise and relevant information with respect to body composition information.

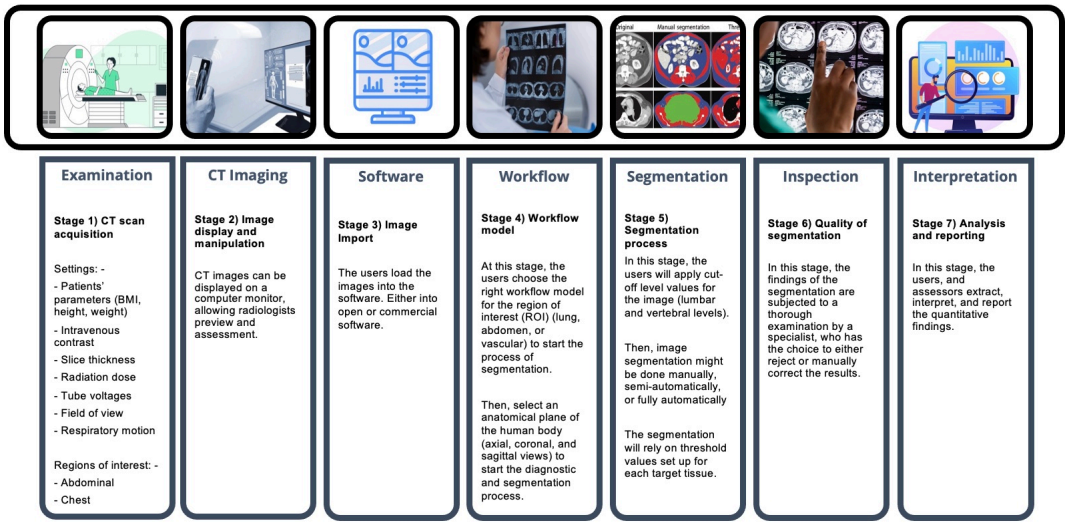


Figure 1.7 – The morphometrics workflow: schematic illustration of the patient's morphometric-body composition analysis.

1.3.3 Software-aided analysis of morphometric body composition: opportunities, challenges and limitations

The majority of clinical imaging techniques were initially evolved for the identification and diagnosis of pathology, with only few endeavours undertaken to assess the findings in a quantitative manner (Raunig et al., 2015). The software used is a major consideration when performing quantitative image analysis in order to generate accurate information (Potretzke, Schmitz and Jensen, 2004). The use of computer software for body composition analysis so as to evaluate the state of a patient's health has become increasingly widespread, especially in nutritional and clinical domains. Advances in technology underpinning various tools and software have led to the ability to measure pathological characteristics, such as alterations in physical or functional reactions (Raunig et al., 2015).

The current literature in the domain of morphometry describes a number of software packages which are either marketed or available on open-source, and which have been employed in order to perform body composition analysis on CT images. A number of these are referenced in Table 1.10. It should, nevertheless, be noted that the software package utilised can impact the interpretation and analysis of the CT data (Irving et al., 2007; Barbalho et al., 2020; Kirby et al., 2020).

Table 1.10 – An overview of software tools used for morphometric-body composition analysis, its features, and limitations (Part 1: General description and compatibility). OA - Open access; C - Commercial; YACTA - Yet Another CT Analyzer; DICOM - Digital Imaging and Communications in Medicine; PACS - Picture Archiving and Communication System; CT - Computed tomography; W - Windows; M - MacOS; L - Linux; C - Chrome OS.
*Open source implies the ability to modify and customise the code without restrictions.

Software	General description	*Open source	Licence	Platform
Lung				
YACTA	In-house medical image analysis software	Yes	OA	W
Pulmo3D	Post-processing software for routine diagnostic	No	C	W, M, L
MeVisPULMO	Medical image processing research and development	No	C	W, L
Muscles and adipose tissue				
ImageJ	A common image processing programme for viewing, editing, analysing, processing, saving, and printing images	Yes	OA	W, M, L
SliceOmatic	Medical image analysis software for muscle and adipose tissue. Enables researchers to measure, segment, and analyse multi-slice scanner data	No	C	W
CoreSlicer	Online interface and toolkit for CT scan analysis morphomics	Yes	OA	W, M, L, C
Whole Body Composition				
OsiriX	Stand-alone software with a simple, interactive user interface, a popular medical picture viewer	No	C	M
3D Slicer	An extensible software for processing and displaying medical images	Yes	OA	W, M, L
TeraRecon (Aquarius iNtuition)	Post-processing software programme. Comprising stand-alone software (Intuition Server) to perform complex image post-processing	No	C	W

Table 1.11 – An overview of software tools used for morphometric-body composition analysis, its features, and limitations (Part 2: Lung analysis). OA - Open access; C - Commercial; YACTA - Yet Another CT Analyzer; DICOM - Digital Imaging and Communications in Medicine; PACS - Picture Archiving and Communication System; CT - Computed tomography. *Open source implies the ability to modify and customise the code without restrictions.

Software	Pros	Cons
YACTA	Freely available - no licence required; compatibility with DICOM and PACS; fully automated segmentation process.	Error in lung segmentation (segmentation algorithms) (Lim et al., 2016; Ley-Zaporozhan et al., 2021); Not used in routine clinical care (Wielpütz et al., 2014); only supports Windows environments.
Pulmo3D	Simple and flexible; customisable; provides an automatic and manual 3D segmentation; compatibility with DICOM and PACS.	Error in lung segmentation, unexpected halt (Lim et al., 2016); requires licence; limited accessibility in clinical practice.
MeVisPULMO	Fast and customizable.; combined 2D/3D rendering; automated assessment; compatibility with DICOM.	Image processing is time-consuming. Requires license, limited accessibility in clinical practice.

Table 1.12 – An overview of software tools used for morphometric-body composition analysis, its features, and limitations (Part 3: Muscles and adipose tissue analysis). OA - Open access; C - Commercial; YACTA - Yet Another CT Analyzer; DICOM - Digital Imaging and Communications in Medicine; PACS - Picture Archiving and Communication System; CT - Computed tomography. *Open source implies the ability to modify and customise the code without restrictions.

Software	Pros	Cons
ImageJ	Freely available - no licence required; flexible; compatibility with DICOM..	Not intuitive (Troschel et al., 2020). Steep learning curve for novice image analysts (Mullie and Afilalo, 2019)
SliceOmatic	Gold standard for body composition analysis (Gomez-Perez et al., 2016); easy to use; batch processing.	Expensive. Requires annual licence fees, which limits its use in daily routine and clinical practice. Only supports Windows environments.
CoreSlicer	Freely available, web-based interface; compatibility with DICOM; useful for non-technical clinicians (Mullie and Afilalo, 2019)	Exclusive to Google Chrome; web-based programme; raises privacy concerns.

Table 1.13 – An overview of software tools used for morphometric-body composition analysis, its features, and limitations (Part 4: Whole body composition analysis). OA - Open access; C - Commercial, YACTA - Yet Another CT Analyzer; DICOM - Digital Imaging and Communications in Medicine; PACS - Picture Archiving and Communication System; CT - Computed tomography. *Open source implies the ability to modify and customise the code without restrictions.

Software	Pros	Cons
OsiriX	Advanced PACS viewer; simple database structure for radiologists; compatibility with DICOM and PACS. Free, open source exists (Horos)	Requires license; only supports MacOS; requires manual segmentation of all tissues of interest, this may impact body composition analysis (Barbalho et al., 2020).
3D Slicer	Freely available; simple; widely used in clinical research so free tutorials and support available.	Not intuitive (Troschel et al., 2020); steep learning curve for novice image analysts (Mullie and Afilalo, 2019).
TeraRecon (Aquarius iNtuition)	Simple and flexible - non-experts can work independently. Encompasses a customisable workflow template; approximately 3% of uncertainties; manages the data (anonymous study or series); used for routine clinical diagnostics.	Only supports Windows environments; requires licence, limit accessibility in clinical practice

Two key tissue types required for body composition analysis are fatty tissue and skeletal muscle. This is especially the case when considering obesity and its associated diseases, ageing and physical performance. A consideration relating to the various software packages is how well segmentation of the images is performed. For instance, a comparison of a locally created clinical imaging software with a marketed equivalent (SliceOMatic) revealed benefits associated with the latter, such as circumventing pixel overestimation of visceral fat deposits (Potretzke, Schmitz and Jensen, 2004), a challenging task for alternative packages. The latter included the National Institute of Health ImageJ free medical imaging software (Irving et al., 2007), or the Osirix

software system when applied to individuals with a body mass index within the obese range (Barbalho et al., 2020).

Van Vugt et al. (2017) noted that in 50 individuals with a diagnosis of rectal carcinoma, there were high levels of concordance and comparability (intraclass correlation coefficient (ICC), 0.979–1.000; $p<0.001$) between parameters of muscle and fatty tissue amongst four different software packages (FatSeg, OsiriX, ImageJ and SliceOmatic). However intraobserver variations and discrepancies between measured parameters were seen within the different packages. Findings were comparable when OsiriX and SliceOmatic were evaluated alongside each other for the analysis of body composition (Rollins et al., 2019). Thus, when making comparisons between body composition data sets, it is essential to note the software used.

Evaluation of the composition of pulmonary tissue is another application for software-assisted analysis but again, various packages can cause heterogeneity within measurements and data reading. Wielpütz et al. (2014) and Lim et al. (2016) demonstrated a lack of reproducibility and data discrepancies within the software packages YACTA, TeraRecon, Pulmo3D and CT COPD with respect to the measurement of lung density within one individual. Thus, the utilisation of the identical software package for longitudinal research is advised in order to diminish result inconsistencies; reproducibility within a single package was a determinate in each instance (Kirby et al., 2020). The algorithm within the software is key in order to obtain precise data; this was shown by Ley-Zaporozhan during the measurement of lung fibrosis (Ley-Zaporozhan et al., 2021). Employing various software packages which contain diverse algorithms for image segmentation was observed to give rise to discrepancies in the degree of pulmonary fibrosis present and its degree of advancement.

The use of different software packages for morphometric whole body composition analysis would reduce the reliability of the results by adding further variables as a result of the divergent algorithms used for segmentation, and heterogeneities in the way in which the volumetric data is processed, analysed and formatted (Wu and Bogie, 2009; Ashraf et al., 2010; Wielpütz et al., 2014; Nemec et al., 2015; Lim et al., 2016; Vugt et al., 2017; Ley-Zaporozhan et al.,

2021). In order to guarantee that precise and reproducible data are produced, there should be standardisation of the methods applied for segmentation, as well as the imaging used and the algorithms employed for the analysis of body composition (Kirby et al., 2020). The guidelines published by the Quantitative Imaging Biomarkers Alliance (QIBA) are one example of this principle (Quantitative Imaging Biomarkers Alliance, 2016). Despite these, the comparison and reading of body composition data obtained from differing software systems remain difficult. The assessment of the choices of available software for this process is key; a software package that fulfils the user's criteria and which can facilitate all the stages of the analysis without a requisite for further software should be selected (Wielpütz et al., 2014; Nemec et al., 2015; Barbalho et al., 2020). This would contribute to mitigating against heterogeneities within the data which could arise when several software systems are applied, and thus promote data uniformity and output reliability as the entire process would be carried out with just one standardised software package (Wu and Bogie, 2009; Ashraf et al., 2010; Lim et al., 2016; Mascalchi, Camiciottoli and Diciotti, 2017; Rollins et al., 2019; Kirby et al., 2020). This is particularly imperative in academic or clinical contexts where data precision may markedly influence the management of patients or research results. Informed judgements can therefore be made by users.

To summarise, morphometric-body composition analysis is an important approach for the evaluation of a patient's state of health. Nevertheless, discrepancies may arise from the utilisation of several different software systems which would cause the data to be less reliable. Where non-identical software packages are utilised, it is difficult to perform inter-study comparisons and to determine the normal ranges for specific patient cohorts. Additionally, when several software systems are used for the analysis of clinical images, data may require transfer and processing by hand, tasks which may prove to be a further source of error or data discrepancies. It is therefore important to be diligent in the choice of software applied and its standardisation in order to create consistency and to guarantee the accuracy of results.

1.3.4 Morphometric body composition analysis in clinical practice: evaluation, prediction of postoperative pulmonary complications, and overall mortality

Under this heading, the key facets and measurements pertaining to the morphometric body composition analysis will be described. In particular, these will include the structure of the pulmonary tissue, muscle mass and its quality, and the distribution of fatty tissue. Schematics will be included in order to illustrate the points made and to promote comprehension of the principles discussed. The objective of this detailed exploration of this topic is to promote knowledge and awareness of the complexities present in relation to morphometric body composition analysis, as well as its ramifications with respect to an evaluation of a patient's general state of health.

1.3.4.1 Lung morphology

The primary viscera comprising the respiratory system, the lungs, are fundamental to life. They are complicated internal organs which developed in order to facilitate the exchange of gases necessary for survival (Suki, Stamenović and Hubmayr, 2011). A description of the anatomical characteristics of these organs will be presented, together with their architecture, alterations in the presence of disease, diagnostic protocols and their performance, and clinical relevance.

Basic anatomy and structure of the lungs A number of components which work in concert to enable respiration make up the respiratory system. The larger anatomical parts comprise the major airways, i.e. the trachea, bronchi and bronchioles, and the alveoli. The trachea forms a passage between the oral and nasal cavities and the lungs; this then subdivides into the bronchi which, in turn, subdivide into the bronchioles, tubes which pass deeper into the lung substance. These terminate in air sacs, or alveoli, which form the site of gaseous exchange. The ribs surround the lungs, and the diaphragm supports

them inferiorly as well as separating them from the abdominal contents (Van Rikxoort and Van Ginneken, 2013).

The lungs are separated by the mediastinum, which is made up of the cardiac structures, the great blood vessels, the oesophagus, the trachea and the left and right bronchi, as well as a number of other components. The pleura forms a lining which provides the lungs with a degree of protection and support.

On inspiration, air enters the trachea and the bronchi, and finally reaches the alveoli, which are often described as appearing like grape bunches. The general appearance and form of the lung is called its gross morphology. The lung is sponge-like and has a grey-pink colouration. Each lung has an apex, three surfaces and three edges. The larger right lung is subdivided into three lobes whereas the left lung only has two lobes.

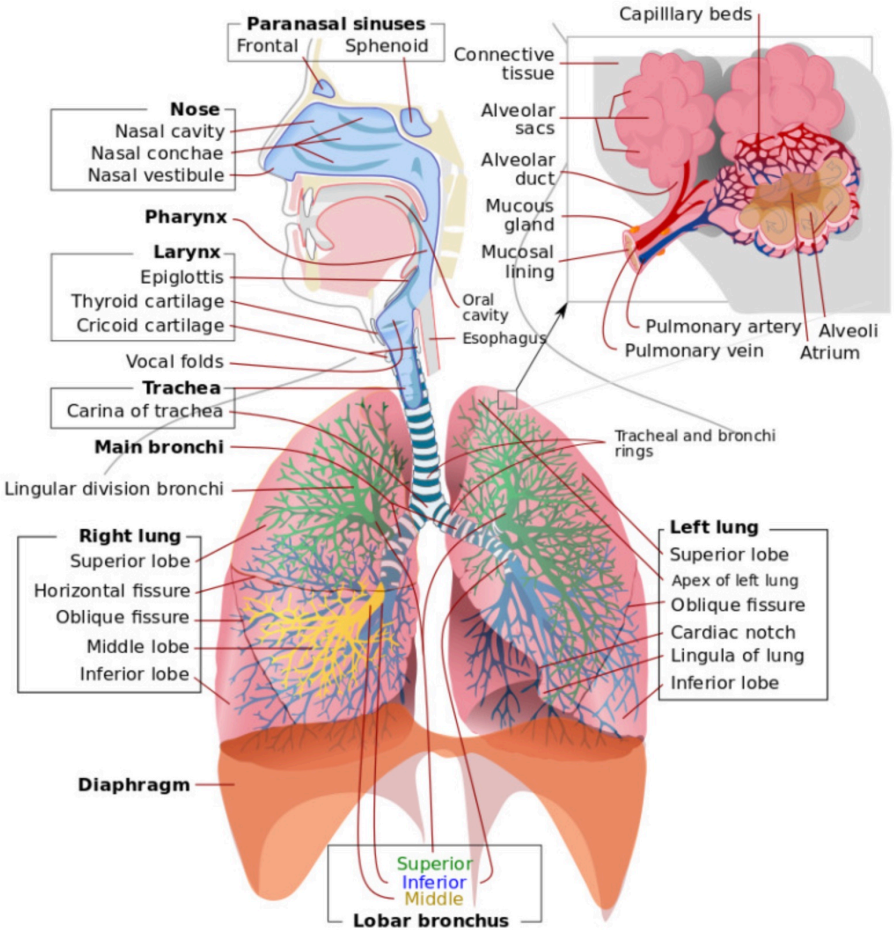


Figure 1.8 – A schematic illustration of the respiratory system and lung anatomy.The graph was adopted from Carvajal and Lopez (2023). Electronic book ebook which is available under the terms of the Creative Commons Attribution License (CC BY) `https://creativecommons.org/licenses/by-nc-nd/4.0/`.Permission is not required for this type of reuse.

Pathological changes in the lungs A number of pathological changes may arise in the appearance of the lungs. They are obstructive lung disorders (e.g., asthma, COPD, and emphysema), inflammation and infections (e.g., pneumonia and tuberculosis), diseases of the pulmonary vasculature (e.g., pulmonary emboli or pulmonary hypertension), and diseases of the interstitium (e.g., honeycomb lung, fibrosis, or traction bronchiectasis). These pathological and lung diseases conditions affect pulmonary tissue density and are characterised by either high or low signal attenuation. (Chen et al., 2020; Gruden et al.,

2020). These diseases can be attributed to socio-economic trends, changes in demographics and the exposures that patients, themselves, create, including smoking, pollution and metabolic risks (Li et al., 2020).

Diagnosis and clinical evaluation of the lung density changes The ideal method for the assessment of and screening for alterations in pulmonary tissue density remains to be determined, although at present, CT is the preferred technique employed to recognise the severity of any such changes (Hatabu et al., 2020; Liu et al., 2021; Bakker et al., 2021). CT images provide a huge amount of data, and so it is important to ensure that developed software packages for image analysis are able to simplify the available quantitative computed tomography (QCT) data such that it is relevant for clinical applications (Herth et al., 2018). Quantitative techniques employed to diagnose pathological changes are both visual and automated.

Images of the lungs can be interpreted following a visual evaluation, which offers a qualitative assessment of the interstitial lung tissue and airway pathologies. This method of scan interpretation provides additional data to those obtained following spirometry and quantitative image assessments, which rely on density measurements (Bhatt et al., 2019). However, visual analysis fails to offer data regarding the severity of obstructive disease (Park et al., 2020a), and image interpretation performed in this way is labour-intensive and subject to variation between readers (Bankier et al., 1999; Cavigli et al., 2009; Barr et al., 2012; Kang et al., 2021a).

Prognostic data can also be obtained from semi-quantitative assessments of CT images performed by experienced readers (Ley et al., 2014). However, the methodologies used lack standardisation for both disease extent and gravity (Weatherley et al., 2019). Further, it failed to offer uniform outcomes and may not be able to take into consideration ambiguous or non-specific changes that may be relevant clinically (Podolanczuk et al., 2016).

The design of computerised techniques to provide non-subjective quantitative methods of pulmonary image analysis has therefore attracted considerable interest (Walsh, 2018). The last ten years have seen a marked rise in the number of studies that have evaluated QCT with respect to abnormalities that may

represent lung diseases. Thus, QCT provides a way of interpreting the rich data set provided by CT, potentially overcomes any lack of subjectivity, and can recognise characteristics that cannot be identified using observational methods alone (Hansell et al., 2015; Jacob et al., 2016).

Analytical software has been demonstrated to offer objective, quantitative, and reproducible evaluations of changes within the lung interstitium that are associated with diffuse pulmonary pathologies and emphysema (Mascalchi, Camiciottoli and Diciotti, 2017; Chen et al., 2020). A number of strategies, such as densitometry and threshold analysis, have been undertaken with respect to CT images, which have endeavoured to assess and to measure characteristics typical of obstructive and interstitial lung pathologies (Mascalchi, Camiciottoli and Diciotti, 2017; Chen et al., 2020). Techniques which use threshold analysis rely on the detection of pixels which fall within a particular attenuation spectrum, defined in HU (Barros et al., 2022b). Densitometry methods are essential for QCT and comprise the recognition of the degree of X-ray attenuation that occurs within the lung parenchyma (Muller et al., 1988). These have encompassed the use of threshold predetermination, densitometric parameters, e.g., recognition and percentage computation of either normal, low, or high attenuation areas.

The lung volume within a particular density spectrum—typically, -950 to -700 HU—represents normal lung attenuation area (NAA). Staging protocols for changes related to pulmonary diseases are enhanced by the quantitation of normal lung tissue density (Ohkubo et al., 2016; Ohkubo et al., 2018),although the diagnostic potential of NAA in relation to specific disease states in individual patients and for the prediction of clinical endpoints has not been studied.

The clinical contribution of lung densitometry in QCT in individuals with emphysematous lung disease has been well-documented, particularly in the context of late-stage pathology (Washko et al., 2017; Labaki et al., 2017). The majority of imager vendors routinely include software for automated densitometry, which increases the access to quantitative assessments of emphysema (Labaki et al., 2017). These systems enable the proportion of pulmonary voxels at a particular density or in relation to a pre-set density threshold to be calcu-

lated (Chen et al., 2020),which gives a measure referred to as the percentage emphysema or percentage low attenuation area (LAA) (Labaki et al., 2017). Researchers have applied several thresholds for CT density, e.g. -970 HU and -960 HU (Madani et al., 2006), -950 HU (Gevenois et al., 1995; Bankier et al., 1999) and -910 HU (Muller et al., 1988), and it has been determined, using microscopic and macroscopic changes seen in histopathology samples as a reference, that the ideal cut-off level lies within the range -950 to -970 HU (Gevenois et al., 1995; Madani et al., 2006). This is taken to indicate the degree of emphysematous change, a parameter which is frequently referred to as the emphysema index or relative area under -950 HU(Mascalchi, Camiciottoli and Diciotti, 2017).

Comparably, a number of cut-off parameters have been suggested with respect to the recognition of high attenuation area (HAA) associated with ILA, e.g. -600 HU (Podolanczuk et al., 2016), -700 HU (Shin et al., 2011) -740 HU (Kim et al., 2005), and -750 HU (Kauczor et al., 2000). A range of between -600 and -250 HU has frequently been applied to automated QCT systems in order to recognise the number of pulmonary voxels displaying high attenuation and which are deemed to indicate interstitial disease (Herth et al., 2018). Additional high density pathologies, e.g. atelectasis, consolidation, medium to large vasculature structures, lung nodules and other space-occupying lesions are thought to fall outside this density spectrum (Podolanczuk et al., 2016; Sack et al., 2017). The existence of HAA has been linked with cigarette use (Lederer et al., 2009), a greater likelihood of ILA (Kliment et al., 2015) and with a greater prevalence of this type of pathology on future CT scans (Choi et al., 2020).

The role of lung morphology in predicting postoperative pulmonary complications The evidence supporting the use of morphometry in predicting PPC comes from thoracic and transplant surgery, where imaging techniques have been studied as a potential tool in risk stratification prior to major lung resections (Ueda et al., 2005; Na et al., 2014; Kaplan et al., 2015; Solyanik et al., 2015; Dettmer et al., 2018). In South Korea, Na et al. (2014) performed a retrospective analysis of 280 patients who had resection of a lung lobe and

found that there was a stronger link between PPC and QCT assessment of emphysematous change than between PPC and PFT. They identified that the predictive ability of the emphysema index defined by the relative sub-threshold area (< -950 HU) compared to FEV_1 was more precise (p=0.0087). The highest predictive power for PPC was given by a cut-off value of 11.46 for the emphysema index; this gave rise to a sensitivity and specificity (83.8% and 74.1%, respectively).

In Turkey, Kaplan et al. (2015) performed another retrospective study evaluating 50 patients who had undergone surgery for pulmonary tumours. Following applied lung density less tan -900 HU, the cut-off value of 5.41% showed sensitivity and specificity of 84.0% and 80.0%, respectively, for predicting PPC.

In another study, researchers in Japan looked retrospectively at whether using both LAA on CT scans and spirometric data would improve the accuracy of PPC predictions in a group of 342 Japanese people who had a lung lobectomy for neoplasia (Kitazawa et al., 2021). In multivariable analysis, they demonstrated that the prevalence of PPC was higher in patients with a cut-off LAA > 10% (OR 1.040, 95%CI 1.001-1.080; p=0.046).

Collectively, the studies listed above show that lung morphometry, especially quantitative estimates of changes in emphysematous changes, can help predict PPC. However, the majority of the studies have been done in Asian settings, focusing on surgical interventions for lung cancer. More research needs to be done to make sure the QCT emphysema index is useful, set the right thresholds, and look into how the emphysema index and parameters from PFT work together to predict PPC after minor and major surgeries.

Additionally, there is no data on the ability of applying QCT methodology to the evaluation of normal lung and existing ILA to predict PPC. This is an important issue for future research.

The role of lung morphology in predicting overall mortality The ability to perform QCT of the lung enables disease of the lung interstitium to be graded. These data have also been shown by a number of studies to be of value in forecasting the likelihood of mortality.

A NAA, obtained from QCT with respect to normal pulmonary tissue, was demonstrated by Barros et al. (2022a) to predict mortality. Sex- and age-adjusted multivariate analysis confirmed that the NAA index was also able to predict mortality in patients with either COPD (HR 3.14, 95%CI 1.09-9.05, p=0.034) or ILA (HR 2.72, 95%CI 1.35–5.48, p=0.005). In contrast, in these two cohorts, TLV had no predictive value for mortality (COPD:HR 1.57, 95%CI 0.84–2.91, p=0.151; ILA: HR 0.99, 95%CI 0.99-1.00, p=0.148).

Few studies have published data regarding the predictive merit of the severity of emphysema as defined by LAA on CT with respect to mortality. Those researchers who have explored this topic have reported conflicting outcomes (Martinez et al., 2006; Haruna et al., 2010; Johannessen et al., 2013). For instance, in a sizeable cohort of individuals with COPD, the total emphysema percentage, which was defined as defined by -950 HU (severe) and -910 to -850 HU (moderate), failed to show correlate with higher mortality, even though most of the patients were diagnosed with severe emphysematous change (Martinez et al., 2006).

In contrast, emphysema extent, as observed on QCT, was shown to be a significant factor for predicting mortality in the context of COPD by (Haruna et al., 2010) and (Johannessen et al., 2013). In the study performed by Haruna et al. (2010), a threshold of -960 HU was applied to distinguish between normal pulmonary tissue density and LAA. The percentage of lung affected by emphysematous changes predicted mortality related to respiratory causes in patients with GOLD stages I-IV (HR 1.74, 95%CI 1.18-2.54, p<0.01).

Johannessen et al. (2013) investigated populations of individuals in whom COPD was either present or absent. The degree of emphysema was assessed by applying a cut-off point of -950 HU, and evidence of the disease was classified as either low (<3% LAA), medium (3–10% LAA), or high (>10% LAA). Patients who were assigned to either of the latter two categories were noted to have a survival rate of 19 months less than those in the first group. Those with a high rating for emphysema had a curtailed survival of 33 months compared to those with a low rating when respiratory causes of mortality were evaluated (p<0.01).

LAA in pulmonary voxels less than -950 HU was used to describe the extent of emphysema in a multi-ethnic population studied by (Oelsner et al., 2016). A robust correlation with respiratory causes of mortality was identified (HR 2.94, 95%CI 1.68–5.15, p<0.001).

Additional QCT parameters, e.g., HAA, have also been recognised as markers of poorer all-cause survival in the general population. HAA is therefore another promising prognostic indicator, being linked with increased mortality from all causes over 12.2 years (HR 1.58, 95%CI 1.39–1.79, p<0.001) (Podolanczuk et al., 2016).

A rise in mortality from respiratory causes has also been correlated with the presence of HAA (HR 1.5, 95%CI 1.2-1.9, p<0.001)(Podolanczuk et al., 2017).

Overall, the data published relating to the QCT lung indices and death rates remain limited, however, especially within the general population and within cohorts of patients anticipating operative interventions. Further studies within larger and more varied populations are required in order to establish the potential of the QCT lung indices as a predictive marker for in-hospital, medium, and long-term mortality.

1.3.4.2 Muscles

Between 30% and 40% of the body mass of humans is made up of skeletal muscle, which comprises the most frequently occurring tissue (Setiawan et al., 2023). Consequently, skeletal muscle is responsible for the governance of many physiological activities, such as body motion and positioning, breathing, and maintenance of metabolic and energy homeostasis (Cheung et al., 2021). Since skeletal muscle plays such a major role, any alterations in the amount and quality of muscular tissue have been well documented and determined to be specific within this context, as they exert a notable influence on the functional disabilities and challenges associated with advancing age (Figueiredo et al., 2021).

Sarcopenia Diminished skeletal mass is referred to as sarcopenia, a word that originates from the Greek for flesh (sarx) and loss (penia) (Lee et al.,

2019). It is linked with poor muscle strength as a consequence of reduced muscle mass and quality, as well as impaired physical function (Cruz-Jentoft et al., 2019). Sarcopenia may be viewed as a condition associated with the failure of skeletal muscle or its inadequacy (Cruz-Jentoft and Sayer, 2019). The decrease in mass and strength of muscle are both separate entities despite being interdependent elements; however, the latter becomes diminished more rapidly than the former, and appears to be a more relevant prognostic factor for poorer clinical endpoints (Wall, Dirks and Van Loon, 2013).

Boutin et al. (2022) observed that it is mainly adults within the older age spectrum that present with sarcopenia, and that the condition is slowly progressive. However, Atlan et al. (2021) and Woolfson et al. (2021) noted that younger patients may also contract this condition, and De Spiegeleer et al. (2021) and Welch et al. (2021) described its rapid advancement (De Spiegeleer et al., 2021; Welch et al., 2021). As sarcopenia has been described prior to the onset of adulthood, the elucidation of the numerous factors that underlie this condition in order to establish preventative and therapeutic approaches is paramount (Atlan et al., 2021; Woolfson et al., 2021).

Muscle analysis: psoas muscle The quantity of muscle can be assessed with the use of a spectrum of techniques, of which CT is generally the most accessible imaging modalities used for the analysis of skeletal muscle throughout the body (Lenchik and Boutin, 2018). A region of interest can be outlined on an axial image obtained by CT; this area can then be quantified in order to obtain the total lumbar cross-sectional area (CSA) of the muscle area (Chianca et al., 2022; Boutin et al., 2022). The adoption of quantification CSA is an objective diagnostic technique for multiple conditions, and this region of the body includes a varied appearance of the abdomen and thoracic muscles (Tolonen et al., 2021). Indeed, this method has been validated and shown to provide an accurate representation of the composition of not only the muscle, but also the entire body (Chianca et al., 2022).

An option for quantifying the CSA of all the muscles within a specific slice for the purposes of body composition evaluation is to use one muscle group, e.g., the psoas muscle. Although a number of researchers have failed to give reasons

to support their choice of this muscle, it may be because it is straightforward to recognise or as a result of its contribution to flexion of the hip (Rutten et al., 2017)(Figure 1.9). This could provide a valuable justification and great importance to the study of the influence of psoas muscle on the general mechanical functions and condition of the body system.

In comparison to the quantification of all the skeletal muscles, assessment of the psoas is more rapid and relatively simple, as it is instantly recognisable adjacent to the level of the third lumbar (L_3) or (L_4) vertebrae. A number of authors have used the umbilicus as a landmark, although this is less reliable (Baracos, 2017; Amini et al., 2019; Abbass et al., 2020).

The CT-psoas muscle analysis used either manual or software-assisted techniques to distinguish tissue-based X-ray attenuation to evaluate the quantity of the area. The HU values facilitate the segmentation of the area of interest and, in the literature, range from -29 to -150 (Martini et al., 2020; Jacobs et al., 2022). However, currently, there is no general agreement regarding the exact thresholds to apply to psoas muscle segmentation.

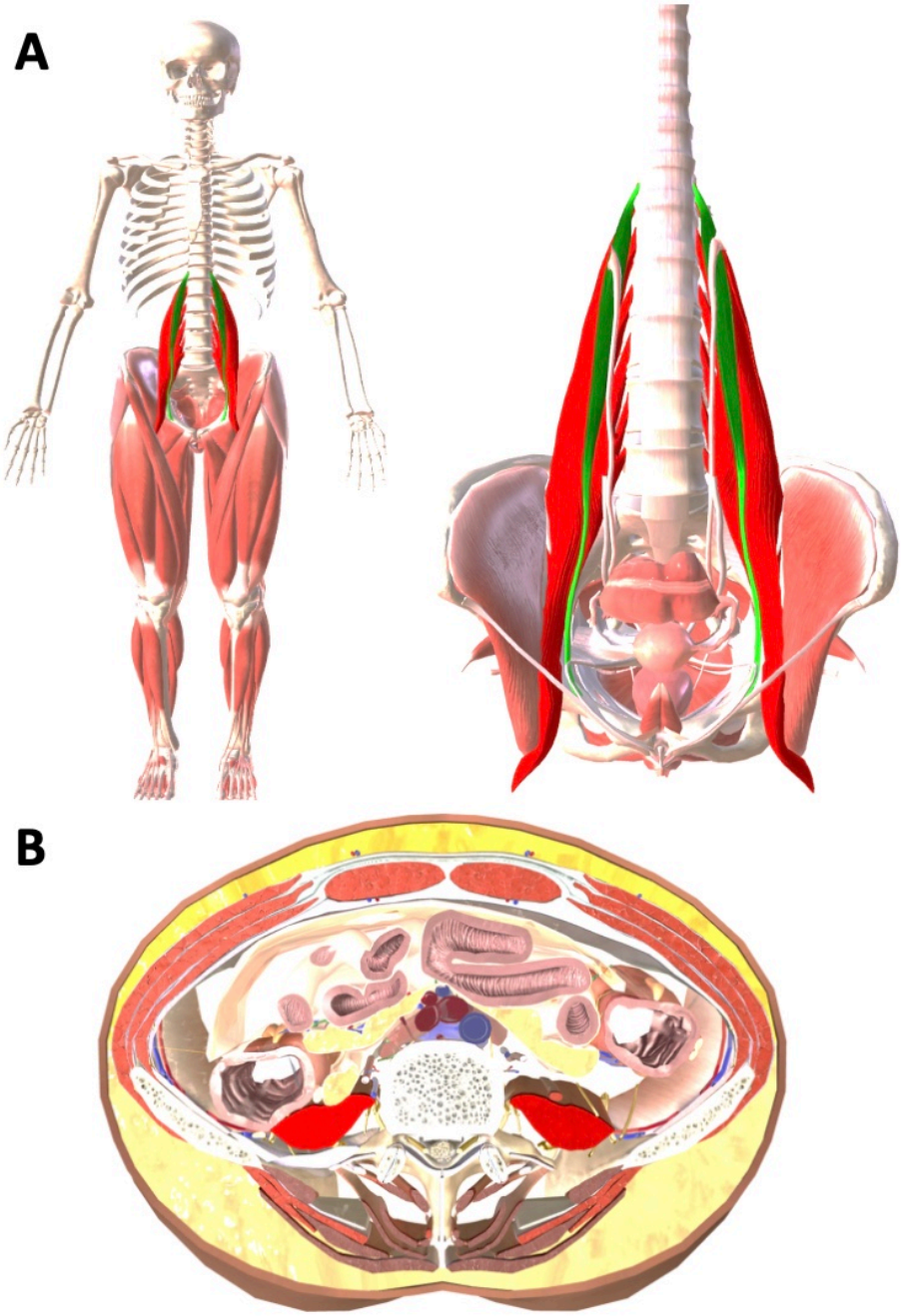


Figure 1.9 – The anatomical position of the psoas muscles. A) The psoas muscle originates in the lower lumbar region of the spine and travels all the way up to the femur. It can be found extending through the pelvis. The psoas muscle, which actually has two parts called major (in red colour) and minor (in green colour). B) The axial plane of the transverse cross section between vertebral levels L_5–S_1 and the psoas major (in red.The graph was constructed using data obtained from the individual's personal account on the IMIOS `https://www.imaios.com/` and human body digital `https://www.biodigital.com` platforms.

The role of psoas muscle in predicting postoperative pulmonary complications To date, the way in which the appearance of the psoas muscle impacts the prediction of PPC is poorly appreciated, and the data published by relevant studies lacks consensus.

A number of techniques have been used to study the relationship between the psoas muscle and PPC. In a Japanese study, among patients who underwent oesophagectomy for oesophageal cancer, Ishida et al. (2019) identified a low psoas muscle index (PMI) post-neoadjuvant chemotherapy as an independent predictive risk factor for postoperative pneumonia with the greatest OR in univariate and multivariate analyses (OR 4.28, 95%CI 1.81-10.1, p=0.0005; OR 7.02, 95%CI 2.60-19.0, p=0.0001, respectively).

In a study in France, Martini et al. (2020) reported that sarcopenia measured as total psoas area (TPA) with a cutoff value less than the sex-related 33rd percentile was associated with a high incidence of ARDS (58.3% vs. 31.9%, p=0.010) and respiratory failure (52.5% vs. 30.9%, p=0.009) in patients with lung cancer undergoing pneumonectomy.

A further recent study, published in 2022 in the U.S., in their descriptive analysis noted an increased respiratory failure rate, necessitating sustained intubation and tracheostomy, in patients in whom endovascular repair of abdominal aneurysm (EVAR) conversion was performed and who had a low as opposed to a normal Psoas muscle area (PMA) ,i.e., (29% vs. 16% (p=0.02)(Jacobs et al., 2022).

In the U.S., Chang et al. (2022) did the largest study of high-risk patients for colorectal resections that looked at total psoas index (TPI) based on CT imaging. They found that sarcopenic patients had a higher rate of unplanned reintubation and mechanical ventilation than non-sarcopenic patients (12.8% vs. 6.6%, p=0.001).

Comparatively, several reports have shown that loss of the psoas muscle is not associated with an increased risk of PPC. Following thoracic endovascular aortic repair (TEVAR) or open surgical repair (OSR) in 282 individuals, a trend was seen for subjects from both intervention arms, in whom sarcopenia was

diagnosed, to exhibit a higher incidence of PPC compared to their sarcopenia-free counterparts, although this only reached significance in those undergoing OSR, i.e., sarcopenia-TEVAR, 9% vs. non-sarcopenia-TEVAR, 5% (p=0.574); sarcopenia-OSR, 40% vs. non-sarcopenia-OSR, 24% (p=0.016; Tanaka et al. (2018)).

On the other hand, in a study that included only those patients undergoing laparoscopic right-sided or transverse colorectal surgery, Tankel et al. (2020) found that TPI did not correlate with the incidence of PPC (p=0.768).

In a more recent study among patients who underwent non-malignant colorectal surgery, Traeger et al. (2023b) reported a decrease in PPC in the matched sarcopenic group using TPA as a surrogate marker when compared to the matched non-sarcopenic group. The propensity score-matched cohort showed no significant difference in PPC (3 (7.7%) vs. 5 (12.8%), p=0.71).

To sum up, despite the lack of statistical significance for some of these data, the results of other studies suggest that psoas muscle evaluation may be of value for the prediction of PPC. Outcome variations may reflect the limited incidence of PPC and operative intervention methodology. There is, therefore, still insufficient evidence to advise the use of the psoas mass index as a predictive marker for PPC.

The role of psoas muscle in predicting overall mortality A number of researchers have paid particular attention to the question of whether a reduced psoas muscle mass has predictive value for post-operative mortality.

Hung et al. (2021) noted that patients presenting with a splenic abscess who also had sarcopenia, as evidenced by diminished psoas muscle mass, were subject to higher in-hospital mortality (multivariate-adjusted HR 7.56, 95%CI 1.55-36.93). These results were substantiated by Rangel et al. (2017) who observed that a low total psoas index, indicative of sarcopenia, was independently related to increased in-patient death rates (RR 2.6, 95%CI 1.6–3.7) and 30-day mortality (HR 3.7; 95%CI 1.9–7.4) in a group of elderly patients who had undergone emergency abdominal operations.

Further evidence of a potential relationship between a reduced psoas index and increased 30-day mortality figures (sarcopenia, 8.0%; no sarcopenia, 2.7%; p<0.001) was provided by Chang et al. (2022) in patients scheduled for colorectal operations. Once age was taken into account, regression analysis revealed that the likelihood of death in the sarcopenic patient group was two-fold greater (OR 2.2, 95%CI 1.2-4.0, p=0.014).

Similar findings were published by Li et al. (2023b) in a cohort of patients in whom surgery for malignancy in the left-sided colon and rectum had been performed; a reduced PMI was linked with higher 30-day mortality (1.7 vs. 0.3, p=0.042). Comparable findings were found in patients undergoing endovascular aneurysm repair; 30-day mortality was 4% in those determined to be sarcopenic, based on reduced total psoas muscle mass, vs. 0% in patients without sarcopenia (p=0.03; Cheng et al. 2019a).

There are numerous studies which have clearly shown that a reduced psoas muscle mass is an independent prognostic indicator for survival with respect to a range of malignancies and disease stages, as well as operative interventions for vascular pathology. A reduced PMI measured prior to surgery was shown by Li et al. (2023b) to be an independent factor for the prediction of poorer overall survival in patients with left-sided colonic or rectal malignancy (HR 1.36, 95%CI 1.049–1.782, p=0.021).

Increased mortality at one year in patients who had undergone resection of colorectal tumours was noted to be associated with sarcopenia (13.9% vs. 0.9%; OR 16.2, 95%CI 4.34–83.4, p<0.01) by Richards and his colleagues (Richards, Senadeera and Frizelle, 2020).

Similarly, PMI-derived sarcopenia, which was classified as severe, was found to be a predictive marker for adverse overall survival statistics at 3 years (54.1% vs. 66.6%; p=0.027) in patients with carcinoma of the oesophagus receiving neoadjuvant chemotherapy. Severe sarcopenia was determined to be an independent factor for predicting a worse prognosis (HR 1.68, p=0.025; Ishida et al. 2021).

Lower 1-year and 5-year survival statistics were observed following endovascular aneurysm repairs in patients identified as having a reduced psoas muscle

area compared to those in whom psoas muscle area was normal (77 ± 5%, 65 ± 6% vs. 86 ± 3%, 82% ± 5%; log-rank p=0.03) (Jacobs et al., 2022). Compared to patients with sarcopenia, 5-year survival rates in individuals without sarcopenia in whom endovascular aortic repair had been carried out were noted to be more optimal, i.e. 52% vs. 74%. Multivariate Cox proportional hazard regression analysis demonstrated that sarcopenia and all-cause mortality were independently related (HR 2.63, 95%CI 1.43–3.36, p=0.009) (D'Oria et al., 2022).

There have been a number of studies that have failed to establish any relationship between diminished psoas muscle and survival; these have included patient populations in whom operative interventions for tumours of the colorectal (Abbass et al., 2020), gastric (Mirkin et al., 2017), kidney (Peyton et al., 2016) and lung (Katsui et al., 2021) have been performed, as well as patients undergoing spinal surgery (Pernik et al., 2023) and AAA (Indrakusuma et al., 2018). The data in these studies may have been influenced by the effect of neoadjuvant treatment on the mass of the psoas muscle, the predictive value of the mass of the psoas muscle being attenuated in the later stages of malignancy, study limitations caused by low sample sizes, and heterogeneity in demographic factors, e.g., age or comorbidity.

1.3.4.3 Diaphragm thickness

A septum that divides the torso into two cavities and forms the abdominal ceiling and floor of the thorax, the diaphragm is comprised of tendinous and muscular tissue. It is the principal muscle used for respiration, being responsible for 80% of breathing associated with normal tidal volumes, but also having additional functionality (Karami et al., 2016; Daly, Prado and Ryan, 2018) (Figure 1.10).

Diaphragm impairment Abnormal diaphragmatic function may range from paresis, i.e., being unable to create adequate pressure, to complete paralysis and total functional loss (Mier-Jedrzejowicz et al., 1988; Wilcox and Pardy, 1989). Symptomatology arising from diaphragmatic impairment includes breathlessness, reduced exercise tolerance, poor sleep quality, and hypersomnia;

fatality may occur where functional loss is severe (Ricoy et al., 2019). Timely recognition of any issue is vital, as efficacious treatments are available (Laghi, Saad and Shaikh, 2021).

Diaphragm function evaluation Diaphragmatic function can be evaluated by measuring the muscle's thickening fraction at the apposition zone, i.e., the point at which, during the breathing process, it lifts away from the inferior ribs (McCool and Tzelepis, 2012). The thickening fraction can be assessed at the bedside using ultrasound, a method that, although lacking in accuracy (Ni et al., 2020), is to some extent comparable to the benchmark parameters obtained more invasively (Matamis et al., 2013; Goligher et al., 2015; Lalwani et al., 2022). A static diaphragmatic assessment is often acquired using CT, which is generally accessible and not reliant on the operator (Ni et al., 2020).

Although respiration is highly dependent on diaphragmatic performance (Kocjan et al., 2017), this muscle is frequently overlooked by physicians and, consequently, not subjected to a full assessment (Nason et al., 2012). This issue may be compounded by its domed morphology, which alters as the patient breathes in and out and which creates difficulties in quantifying the muscle in its entirety (Wada, Matsuoka and Mimura, 2022).

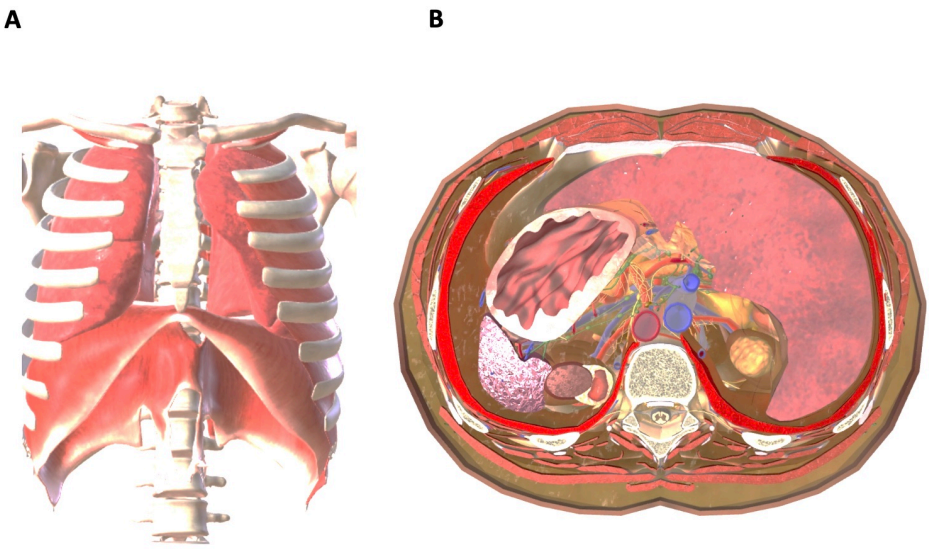


Figure 1.10 – The anatomical space and location of the diaphragm muscle . A) The diaphragm is shaped like a parachute. It presents as two domes rising on either side of a relatively flat central portion inferior to the pericardium, with the apex of the right dome slightly superior to the left due to the location of the heart. Its three parts—sternal, costal, and lumbar—arise from the attachments at the circumference of the inferior thoracic aperture and superior lumbar vertebra. B) The cross-section of the abdomen at the level of the 12^{th} thoracic vertebra; at this level, the diaphragm is identified and delineated by a red colour.The graph was constructed using data obtained from the individual's personal account on the IMIOS `https://www.imaios.com/` and human body digital `https://www.biodigital.com` platforms.

The role of diaphragm thickness in predicting postoperative pulmonary complications It has been suggested that in patients who are in intensive care and require mechanical ventilatory support, CT is the ideal imaging modality for diaphragm thickness measurement (Lee et al., 2016), and to confirm the presence of diaphragmatic functional impairment or paralysis (Sukkasem et al., 2017). Paresis of the diaphragm increases the likelihood of infections of the respiratory tract, such as pneumonia (Elliott et al., 2016), and leads to reduced ventilation of the alveoli, which, in turn, may result in respiratory embarrassment and a requirement for mechanical support (Dal et al., 2022). In this context, if respiratory needs were to rise or if diaphragmatic function were to deteriorate, inapposite accessory respiratory muscles could be recruited, e.g., the intercostal and abdominal expiratory muscles, and respiratory distress

would occur (McCool, Manzoor and Minami, 2018; Dal et al., 2022). Ongoing diaphragmatic thickness evaluation may therefore be of clinical value in the appraisal of PPC and also for the generation of prognostic information prior to surgery.

Few studies have been published using CT in this context.In recent study, Ni et al. (2020) demonstrated the quantification of right diaphragmatic dome thickness in the coronary position. This was determined, using a reconstructed image, to be 1 mm when measured within the ninth and tenth intercostal spaces. A reduction of diaphragmatic thickness of $\geq$1.55mm whilst the patient was supported with mechanical ventilation was linked with a greater requisite for reintubation (33% vs. 12%; OR (adjusted for pH and $PaCO_2$) 0.001; 95%CI 0.001–0.271, p=0.018). This observation indicate that the thickness of the diaphragm prior to surgery is a potential prognostic indicator for PPC. Additional studies are required in order to identify the optimal reference points for CT quantification and, specifically, with regard to the prediction of PPC, as relevant data are currently scarce.

The role of diaphragm thickness in predicting overall mortality Although the thickness of the diaphragm may be a valuable prognostic marker for mortality outcomes following surgery, there has been little interest in previous studies which have evaluated and supported this association. Additional studies are therefore merited in order to delineate this correlation in more detail.

Ni et al. (2020) studied the implications of reduced diaphragmatic thickness, i.e. < 1.55 mm, in 145 patients who were receiving mechanical ventilatory support on an ICU. A preserved thickness was associated with a lower hospital mortality rate (18% vs. 4%; OR 0.001, 95%CI 0.001-0.035, p=0.007), but not with the length of stay required on ICU following extubation, i.e. 9.52 vs. 9.47 days (p=0.98).

Sanli et al. (2016) studied 34 individuals who suffered from amyotrophic lateral sclerosis for whom the diaphragm is a muscle of major import. These researchers observed that post-operative mortality during the follow-up period, which extended between 2 and 24 months, was associated with a diaphragmatic thickness of under 3.50 mm($p<0.001$).

When taken together, these observations highlight the need for additional research so as to explore this interesting area with reference to a broad spectrum of operative interventions. The possibilities offered by the use of diaphragmatic thickness as a prognostic indicator may provide insight into the clinical endpoints seen following surgery, contribute to clinical decision-making, and ultimately enhance patient care quality.

1.3.4.4 Abdominal adipose tissue

Body mass index Previous research has demonstrated the adverse effects fatty tissue within the abdomen exerts on well-being associated with the states of overweight and obesity (Tchernof and Després, 2013). The degree of obesity is frequently described by the body mass index (BMI) (Borga et al., 2018; Yang et al., 2020), although this may be limited in its application to body fat proportions related to age, gender, ethnic origin, and the diversity of specific individuals (Gallagher et al., 2000). Furthermore, BMI is a general descriptor, and fails to describe the way in which obesity is distributed or its extent, especially in relation to the abdomen (Lee et al., 2008; Thomas et al., 2012; Yang et al., 2020; Joo et al., 2021). This parameter is therefore a suboptimal way of describing body composition and the distribution of adipose tissue (Buckley et al., 2022).

Waist circumference These issues have been handled by the well-received proposal to use other measures, e.g., waist circumference (WC), as a way to describe central adiposity (Ma et al., 2013). This parameter has become well-established worldwide as a straightforward method of evaluation (Ross et al., 2020; Joo et al., 2021) which reflects the degree of abdominal adipose tissue (Leitzmann et al., 2011). It also has a good correlation with BMI and can therefore be used as a prognostic marker in terms of health risks associated with obesity (Sonmez et al., 2013).

Waist circumference evaluation Individual images depicting a cross-sectional image of the abdomen taken from archived clinical CT scans have been evaluated for measurement of the circumference of the abdomen. This value, obtained when the patient is supine, has been validated as a representation of the

WC when the patient is erect (Gomez-Perez et al., 2016). Body composition can be assessed from CT cross-sectional images taken at the level of L_3, which offer data on local fatty tissue and WC (Baumgartner et al., 1988; Gomez-Perez et al., 2016). To date, the ideal CT protocol for the evaluation of WC has not been agreed (Brown et al., 2018). The World Health Organisation and the National Institute of Health differ in their guidance, with the former advising that WC is measured at the central point between the superior edge of the iliac crest and the twelfth rib and the latter at the iliac crest's superior border (Sommer et al., 2020). Further proposals of loci for quantification are the minimal waist, umbilicus, and twelfth rib (Wang et al., 2000).

Visceral and subcutaneous adipose tissue Traditionally employed imaging modalities, e.g., CT, are able to provide a precise value of body fat and its distribution with the use of contemporary post-processing software (Pacquelet et al., 2022; Saad et al., 2022). Typically, fatty tissue, which comprises adipocytes, (Troschel et al., 2020), is classified as either visceral adipose tissue (VAT) or subcutaneous adipose tissue (SAT) (Figure 1.11) (Shuster et al., 2012; Pacquelet et al., 2022). The latter is more active from a metabolism perspective, linked with metabolic disorders, and can be used as a robust indicator of risks to health (Ibrahim, 2010; Tappouni et al., 2015; Lee et al., 2018b). The former type of adiposity has been determined to reflect a low-grade inflammatory process that is likely to have a more optimal effect on metabolism (Kim et al., 2021).

Visceral subcutaneous adipose tissue evaluation It has been feasible to measure the amount of VAT and SAT for a number of decades, using methods that are either manual or semi-automated (Jensen et al., 1995; Yoshizumi et al., 1999; Lee, Janssen and Ross, 2004), and which are generally carried out at vertebral levels L_3 to L_5, but also between TL_{12} and L_5 or using the umbilicus as a landmark (Weber-Hamann et al., 2002; Lee, Janssen and Ross, 2004; Pickhardt et al., 2012; Ryckman et al., 2015; Murphy et al., 2019; Pickhardt et al., 2020). Such techniques require a region to be defined on one transverse slice; preset HU spectra are used in order to distinguish between the two types of adipose tissue, e.g. SAT, -190 to -30 HU, and VAT, -150 to -50 HU

(Ceniccola et al., 2019). Within individuals of differing ethnicity, the relative distributions of SAT and VAT have been shown to vary (Nazare et al., 2012; Hakim et al., 2019), a reminder that such heterogeneity should be taken into account during evaluations.

It is of value to quantify fatty tissue within the abdomen precisely and to comprehend the variables relating to the significance of the results in order to interpret the associated health risks. Although the BMI is of limited use as a parameter, additional variables like WC, and the use of imaging modalities, such as CT, can provide essential data pertaining to the distribution of adiposity.

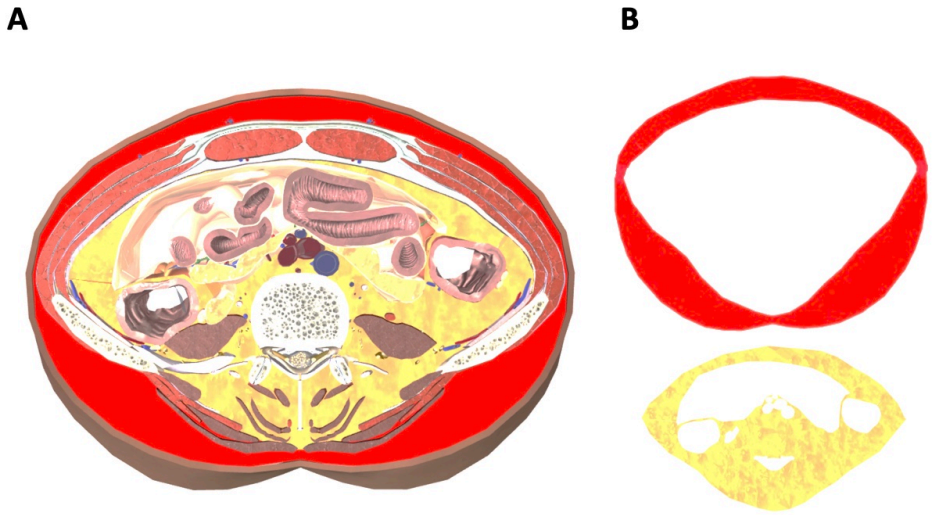


Figure 1.11 – The anatomical space and location of the abdominal adipose tissue . A) Anatomical location and different distributions of the fat tissue; the red area shows the subcutaneous fat tissue, and the yellow area shows the visceral fat tissue. B) Segmentation of the subcutaneous and visceral fat areas.The graph was constructed using data obtained from the individual's personal account on the IMIOS `https://www.imaios.com/` and human body digital `https://www.biodigital.com` platforms.

The role of abdominal adipose tissue in predicting postoperative pulmonary complications The impact of abdominal fatty tissue as a marker for PPC continues to be the subject of discourse, with studies presenting various perspectives on the potential associations between visceral fat (VFA) and subcutaneous fat (SFA) areas and the likelihood of PPC.

A Japanese study by Shimizu et al. (2011), in patients in whom pancreaticoduodenectomy was performed, noted that a raised VFA $\geq$ 130 cm_2, was an independent risk factor for PPC (OR 4.24, 95%CI 1.076–16.759, p=0.039).

Comparable results were obtained in a Dutch population; pneumonia following elective colon carcinoma resection was reported to be more likely in individuals with a VFA > 100 cm_2 (OR 2.4, 95%CI 1.2-4.8, p=0.02)(Cakir et al., 2015a).

In an elderly Chinese population with colorectal carcinoma, it was established that patients with VAT, as defined by VFA cut-off values in males and females of > 130 cm_2 and > 90 cm_2, respectively, were linked with an increased PPC incidence (5.0% vs. 1.5%, p=0.023) (Dong et al., 2022).

Kuritzkes et al. (2018) performed a single-centre retrospective analysis of patients who had undertaken elective colectomy for malignancy. A VFA $\geq$ 191 cm_2 was associated with a greater likelihood of respiratory failure necessitating intubation, i.e. 4.2% vs. 1.5%.

Conversely, a German study, which studied individuals with rectal carcinoma, failed to find any link between PPC and the mass of fatty tissue present, despite PCC being the most frequently arising clinical complication (22, 7.4%). This implies that the influence of VFA on the prediction of PPC may not be uniform within differing patient cohorts and in relation to the various operative interventions performed (Nattenmüller et al., 2019).

Only a small number of studies have investigated the exact role played by SAT in the prediction of PPC, with some refuting any link between these factors and others failing to draw any conclusions. Additional work is required in order to further delineate any potential association between subcutaneous fat content and PPC.

In Germany, Nattenmüller et al. (2019) used univariate logistic regression and demonstrate the lack of correlation between SAT and PPC in patients with rectal carcinoma.

One study demonstrated a higher complication risk in patients with elevated SAT levels (OR 1.00, p=0.027) using binary univariate logistic regression in

a patient population with regionally extensive oesophageal tumours. Interestingly, this relationship failed to hold true in relation to the onset of pneumonia (p=0.065; Fehrenbach et al. 2021).

In a Chinese group of people with colorectal cancer and a low PPC frequency, Feng et al. (2023) found that there was no link between SFA and PPC (p=0.325). However, these results should be viewed cautiously since no cut-off value was given to define SAT.

The potential use of WC for the prediction of PPC has drawn little interest. Despite the fact that this variable has been linked with the generalised incidence of post-surgical complications, any effect WC may have on PPC has not been evaluated in depth. Further research is therefore required(Balentine et al., 2010; Kartheuser et al., 2013; Gurunathan et al., 2019).

It can be concluded that studies that have investigated the effect of abdominal adiposity, e.g., VAT and SAT, on the prediction of PPC have failed to come to a consensus regarding its import, with several authors proposing a correlation between elevated VAT and increased PPC risk and others refuting any relationship between these variables. There is a comparable lack of clarity in relation to the SAT.

Only limited assessments of the predictive value of abdominal adiposity for PPC in pre-operative patients, including those undergoing vascular surgery, have been carried out. In order to attain a greater comprehension of the prognostic significance of SAT, VAT and WC in relation to PPC, additional studies are therefore merited that encompass larger populations, standardised definitions of parameter cut-off values and complications, and detailed analyses of diverse surgical patient cohorts.

The role of abdominal adipose tissue in predicting overall mortality The links between both subcutaneous and visceral adipose tissue and their implications for short-term well-being have been investigated previously, but few studies have evaluated this within the context of hospital environments and the 30-day mortality window following surgery (Shimizu et al., 2011; Kang et al., 2012; Malietzis et al., 2016; Kuritzkes et al., 2018; Saravana-Bawan et al., 2021). The relationship between visceral adiposity and a heightened risk

of overall mortality has been examined by many researchers. However, only a small number of studies have examined the way in which subcutaneous fat impacts mortality statistics (Table 1) (Xiao et al., 2018; Cheng et al., 2022).

The predictive value of visceral adipose content for 30-day mortality was assessed in a systematic review and meta-analysis which encompassed 19 articles relating to both emergency or elective operative interventions (Saravana-Bawan et al., 2021). A correlation between increased visceral adiposity and 30-day mortality was noted in 5 studies, but overall, 30-day mortality was equivalent in patients in whom excess visceral fat was either present (n=562) or absent (n=603) (fixed effect OR 1.34, 95%CI 0.61–2.94, p=0.47). Limitations of this meta-analysis were firstly, that the included studies lacked uniformity in the way that visceral adiposity was evaluated using CT, and secondly, that the majority were carried out in either Japan or South Korea, thus restricting generalisation of the outcomes owing to discrepancies in the frequency of obesity.

Xiao et al. (2018) conducted a systematic review targeted exclusively at the prognostic value of adiposity within the viscera. Despite the inclusion of 22 studies, data remained limited regarding the use of this measure as an indicator of survival following a diagnosis of malignancy. Additionally, varying outcomes were noted between diverse forms of neoplasia: e.g. visceral obesity tended to exhibit a negative effect on survival in individuals with tumours of the large bowel or pancreas, whereas a more positive influence on survival was noted in those with renal cell carcinoma.

A broad spectrum of diverse malignancies was included in a further detailed systematic review in which an analysis was carried out in order to establish any relationships between central obesity and clinical endpoints (Cheng et al., 2022). Unexpectedly, visceral fat tissue failed to confer any additional risk in relation to survival in patients with neoplasms of either the large bowel or pancreas; there was also no reduction of risk identified in patients with renal carcinoma. This systematic review encompassed numerous studies, and so their data can be presumed to provide a more realistic reflection of the link between

visceral adiposity, alternative parameters of fatty tissue, and survival in a range of malignancies compared to Xiao et al. (2018) study.

Researchers that have looked at operations for indications other than malignancy have also failed to link parameters of central obesity, e.g. WC or subcutaneous fat area, with long-term survival outcomes. Abdominal circumference (OR 1.0, 95%CI 0.92–1.2, p=0.52) and subcutaneous fat area (OR 0.99, 95%CI 0.97-1.0, p=0.27) measured at L_3 were not found to be related to mortality at one year in individuals scheduled for revascularisation procedures of the lower limb (Sivaharan et al., 2021). WC failed to be associated with mortality at 4 years in a population of individuals undergoing elective repair of an abdominal aortic aneurysm (OR 0.170, 95%CI 0.001-22.979, p=0.479) (Wall et al., 2022).

It can be concluded that there is a lack of consensus in the current literature regarding the complex association between the fatty tissue content of the abdomen and overall survival. The majority of studies have tended to explore the predictive value of visceral rather than subcutaneous adiposity and WC. A number of researchers have suggested that visceral obesity may have a protective role, being associated with a lower risk of mortality, and inferring that a mechanism of reserve in periods of extreme stress may be involved. The precise processes underlying these diverse results are at present unclear, reflecting an evident gap in the literature.Additional studies are therefore required in order to elucidate the numerous factors underlying the different processes via which both visceral, subcutaneous fat tissue, and WC within the abdomen impact short-term mortality as well as overall survival outcome.

1.4 Summary

Pulmonary complications are the major cause of post-operative morbidity and mortality and are associated with increased utilisation of healthcare resources. PPCs are more difficult to study than, for instance, cardiac complications due in part to difficulties keeping standard definitions, and in part because the less serious PPC are not always recorded in medical records.

Further, surgical outcome analysis has traditionally focused on short- and medium- term survival, with only partial attention to procedure-related and severe perioperative complications such as bleeding, anastomotic leak, myocardial infarction, pulmonary embolism, pneumonia requiring admission to the intensive care unit, stroke and death.

Some specialist tests, such as PFT and CPET are widely accepted tools used for risk stratification in patients awaiting non-cardiac surgery. They are also, to some extent, helpful in the finding patients with underlying lung conditions not causing any problems before surgery. However, their use in risk stratification to predict PPC is somewhat limited.

Existing models predicting PPC rely heavily on intra-operative factors, making identification of patients at risk in the pre-operative period difficult, precluding targeted respiratory prehabilitation.

In context of presented evidence, this project represents a unique opportunity to explore a possibility of developing radiological analytics by utilising pre-existing, routinely performed diagnostic, staging and planning scans and applying novel morphometrics to guide clinical decision making

Medical imaging, such as x-ray and CT, is done to answer specific questions. For instance, to find out if the patient has a lung nodule, bowel cancer or aneurysm. The CT scan can contain around 500-1000 separate images. The new generation of CT scanners can thus generate over 10 million pixels on the computer screen. Most of this information is not used. The radiologists usually look for gross abnormalities and gross anatomical structures. This means that

the project offers an great opportunity to utilise more of the information that is otherwise ignored and not used for clinical purposes.

Identification of specific features using advanced computer-aided image analysis techniques can help getting maximum information out of a single scan. This information could potentially eliminate the need for additional tests such as PFT and CPET.

1.5 Hypothesis, general aims and objectives

1.5.1 Hypothesis

The main hypothesis tested in this project was that opportunistic morphometric-body composition data derived from pre-operative imaging (CT) is associated with clinical outcomes (PPC and survival) and can be used for risk stratification of patients undergoing major, non-cardiac surgery.

1.5.2 General aims

The overarching aim is to develop a pheno/morphotype-body composition-based predictive model utilising pre-operative whole body cross-sectional imagining (CT) in predicting PPC and PPC-associated early and medium-term mortality. It was anticipated that this aim cannot be fully achieved based on presented work, but that this thesis will contribute to this in a significant way laying ground to future work.

Specific aims related to each work package are described in detail in each results chapter.

1.5.3 Objectives

1.5.3.1 Primary objective

The *primary objective* was to establish the incidence of PPC in patients undergoing non-cardiac surgery in high-volume colorectal and vascular centres in a large NHS Trust, and evaluate their association with morphometric parameters (including, but not limited to: lung density, diaphragm thickness, psoas muscle area, subcutaneous and visceral fat) assessed on pre-operative staging/planning imaging (CT).

1.5.4 Secondary objectives

The *secondary objectives* included (but were not limited to):

- Assessed the association of PPC with early, medium and long-term survival.
- Identify clinical risk factors associated with incidence of PPC.
- Identify the risk factors associated with survival.
- To evaluate the association of morphometric parameters with survival.
- To identify the clinical patients factors and morphometric-body composition parameters that can serve as a basis for building and validating predictive models that will help identifying patients at risk of PPC and survival that would benefit from preventative measures such as prehabilitation.

Chapter 2

General methods

2.1 Study design

The studies included in the current thesis were designed as a retrospective observational cohort study using prospectively collated audit databases of patients who presented with aortic aneurysms (vascular cohort; VC) or had surgery for colorectal cancer (colorectal cohort; CRC).

The current project was conducted within the clinical audit framework; no intervention was performed, and patients was not contacted outside their routine clinical care. In the project, the collected data and imaging acquired were used as part of routine patient care.

2.2 Study setting

A large tertiary vascular and colorectal referral centres - University Hospitals Birmingham NHS Foundation Trust (UHB).

2.3 Patient and Public Involvement and Engagement

As part of its development, this projects was presented to Patient and Public Involvement and Engagement (PPIE) group (Clinical Research Ambassador Group, CRAG) in 2018 and received support from patient representatives. Patients commented that the objectives of this study justify analysis of the data (including imaging) without seeking additional consent from patients provided that the data remains de-identified throughout the project.

2.4 Ethical considerations

The retrospective analysis of routinely collected clinical data (retrospective clinical audit), and the prospective analysis of the data related to the incidence of pulmonary complications (prospective clinical audit) are considered as audit. The project required access to patient-identifiable clinical information and, therefore, a formal approval of the project by the Audit Office at the University Hospitals Birmingham NHS Foundation Trust (UHB) was obtained to ensure compliance with Clinical Governance regulations.

An opinion was sought from the University of Birmingham and the University Hospitals Birmingham on whether this project would require registration as research. However, since most of this project took place during COVID-19 pandemic, the project was not considered as a priority for the assessment by neither the University of Birmingham or University Hospitals Birmingham. Considering the retrospective nature of the studies, where no interventions were performed, and patients were not contacted outside their routine clinical, the project was conducted as a clinical audit.

2.5 Population

University Hospitals Birmingham NHS Foundation Trust is one of the largest Trusts in the UK covering over 2.2 million ethnically and socio-economically diverse population. The Department of Vascular Surgery and the Department of Colorectal Surgery at UHB (Heartlands, Good Hope and Solihull Hospitals) are both amongst the busiest in the country in their respective fields. Both departments have excellent surgical outcomes, which reflects the expertise associated with high volume centres.

2.5.1 Aortic aneurysm cohort

The Department of Vascular Surgery at UHB HGS is one of the busiest Aortic Units in the UK and in Europe. A combined number of complex aortic repairs amounts to more than 120 per year. All patients undergoing elective aortic surgery go through an established clinical pathway within a multidisciplinary setting and have an extensive pre-operative assessment which includes staging CT.

The incidence of post-operative complications is similar to reported in the literature, and includes peri-operative mortality of around 1.5%, spinal cord ischaemia with paraplegia under 1% and a cumulative incidence of other complications of around 5%. The incidence of PPC was unknown.

All consecutive patients with juxtarenal, pararenal, thoracic and thoraco-abdominal aneurysms undergoing complex endovascular repair between 01/07/2019 and 29/02/2020 were included. During this time the Department of Vascular Surgery conducted service improvement project assessing frailty in patients with aortic aneurysms. These patients underwent comprehensive workup as part of assessment of fitness for surgery.

2.5.2 Colorectal cancer cohort

A combined number of colorectal resections across the Trust reaches more than 300 per year. The incidence of post-operative complications is similar to reported in the literature (includes mortality of around 2.5% and anastomotic leaks of under 10%) and was considered representative for this group of patients.

This study encompasses patients of all sexes and ages undergoing surgery for left-sided colorectal cancer. The selection criteria did not impose any restrictions based on ethnicity or geographic location, ensuring a diverse patient population from a referral centre with a broad catchment area.

Patients went through an established pathway within a multidisciplinary environment and had a standard pre-operative assessment which includes staging CT. All consecutive patients undergoing large bowel resection for CRC between December 2007 and January 2019 were included. To maintain case homogeneity, only patients who had elective or emergency resection for left-sided colorectal cancer and had a restorative operation were included.

2.6 Data curation

The clinical data model included relevant clinical parameters and risk factors. Text, numerical and binary data were collected.

Data were extracted from the already existing databases and stored in a password-protected spreadsheet available on Trust computer. For the purpose of data curation, patients were identified using medical record numbers (MRN)/ NHS number, name, date of birth, and post code.

2.6.1 Demographic data

The demographic data from the Electronic Health Record (EHR) included date of birth, date of death, age, gender, and post code. Date of death was verified by cross-referencing the EHR with the NHS Spine (NHS Digital) and the cause of death was retrieved from the Primary Care Mortality Database (NHS Digital) where necessary.

2.6.2 Clinical data

The clinical parameters relevant to this project were obtained from EHR and paper-based clinical records as appropriate.

2.6.2.1 Comorbidities, previous interventions and procedures

Diagnoses of medical conditions, intervention, procedures, and common risk factors for post-operative complications identified in published literature (Tevis and Kennedy, 2013; Kehlet, Jensen and Schroeder, 2016; Miskovic and Lumb, 2017; Novello et al., 2019) were retrieved from pre-operative assessment documentation and anaesthetic charts, theatre records, discharge summaries and clinic letters. This information was verified by cross-referencing with the General Practice databases.

For the vascular cohort additional data pertaining to the aortic pathology: aneurysm aetiology, size, anatomical extent, and full preoperative workup were extracted.

For the colorectal cohort, detailed information on the distribution, staging and grading of the malignant disease was retrieved.

2.6.2.2 Diagnosis of lung disease

I collected the identification and diagnosis of chronic lung diseases (e.g., lung abnormality, COPD, and asthma) retrospectively, based on existing diagnoses documented in the electronic health record. Instead of conducting the formal diagnosis independently, I obtained it from an electronic health record code that other healthcare providers had already recorded. Therefore, due to the nature of the retrospective study, the approach was to use an existing diagnosis in the health record rather than establish a new one.

The primary lung diagnosis was based on co-morbid status and coexisting medical conditions reported in electronic health records. In order to find the primary lung diagnosis, a lot of medical records had to be looked at, including the patient's anaesthetic assessment, operation notes, respiratory and physiotherapy reports, admission history, and discharge summary.

Based on radiological evidence of lung abnormality, I recorded the secondary diagnosis of lung disease: I screened CT and plain chest radiography reports for keywords indicating lung disease or structural lung abnormality.

2.6.2.3 Smoking status

The smoking status was recorded from pre-operative assessment documentation and anaesthetic charts and classified into three categories as follows:

- Current smokers: patients who indicated that they currently smoke.
- Ex-smokers: patients who had stopped smoking at least 90 days (three months) prior to the surgery.
- Non-smokers: patients had never smoked cigarettes.

This definition was likely used to interpret the health record data, but the retrospective study made verification impossible.

2.6.2.4 Essential medications

The medications were recorded from the pre-operative assessment documentation and anaesthetic charts. These medications were considered essential for the management of cardiovascular and respiratory risk factors.

2.6.2.5 Biochemical and haematological parameters

Biochemical and haematological parameters were retrieved from the hospital pathology database.

Biochemical parameters included most recent, pre-operative sodium, potassium, urea, creatinine, albumin and C-reactive protein (CRP).

Haematological parameters included pre-operative haemoglobin, white cell count (WCC) and platelet count (PLT).

2.6.3 Surgical intervention

Detailed information on surgical interventions was extracted from EHR and paper-based clinical records as appropriate. This included date of the procedure, procedure name,

2.6.4 Post-operative complications

The post-operative complications were captured from all available electronic clinical information sources (discharge summaries, ICU clinical entries and discharge summaries, infectious disease clinical entry, operating theatre notes/records, picture archiving and communication system (PACS) reports, blood results, electronic prescribing) and were graded using the established and widely used Clavien-Dindo classification of post-operative complications. Three distinct groups of post-operative complications were recorded separately: surgical site infections (SSI), anastomotic leak (AL), cardiovascular, and pulmonary complications.

2.6.5 Post-operative Pulmonary Complications

The PPC were defined according to a modified EPCO criteria. The modification of this definition was a pragmatic decision due to the retrospective nature of the dataset and non-adherence to the established criteria of PPC (EPCO) in the source medical documentation.

Data was captured from all available electronic clinical information sources (discharge summaries, ICU clinical entries and discharge summaries, Infectious disease clinical, entry, operating theatre notes/records, PACS reports, blood results, electronic prescribing).

2.7 Anthropometric and morphometric parameters

The anthropometric and morphometric parameters was included basic parameters measured and calculated in the pre-operative assessment clinic including height, weight and BMI. Also, the following parameters were measured and captured for the purpose of this project: (total) cross-sectional psoas muscle area [mm^2], (total) diaphragm muscle thickness [mm], area of visceral and subcutaneous adipose tissue [cm^2], waist circumference [cm], total lung volume [cm^3], proportion of lung with sub-threshold density [%].

2.8 Morphometric analysis

The basic morphometric and body composition parameters were measured and calculated using the pre-operative CT scans used for diagnostic, staging, and planning purposes.

2.8.1 Computed Tomography

A vast majority of preoperative CT scan examinations were performed using Aquillion One 320 Scanner (Toshiba Medical Systems Corporation, Tokyo, Japan), in the cranio-caudal direction. There was no information available on the equipment used for a small subset of remaining scans performed outside UHB but still available for analyses. However, the equipment used for CT angiograms for aortic disease and staging CT scans for colorectal disease is consistent across the UK. Since there is little variation in how these are performed, the decision was taken to use all available imaging.

Images were acquired using the standard helical acquisition protocol to decrease misregistration from patient breathing and movement. Subjects were requested to inhale fully and to hold this position for the scan duration. They were also instructed to avoid coughing where possible.

The helical mode scans of the entire lung were obtained with intravenous contrast injection; venous phase acquisition in the cranio-caudal direction from the supra-aortic trunks to the femoral vessels.

2.8.2 CT acquisition protocol and data management

Image acquisition parameters were performed as described in Table 2.1. Once the CT images were acquired, the system sent the image data to the central PACS to be processed, manipulated, and reconstructed.

The images were uploaded and stored as data using the international standard format for medical imaging named Digital Imaging and Communications in Medicine (DICOM).

A small proportion of scans were performed in referring hospitals using similar protocols to ensure uniform imaging quality for diagnostic and planning purposes.

Table 2.1 – Summary of image acquisition parameters

Parameter	Setting
Scan type	Helical
Pitch	111 mm
Beam collimation	0.5x80 mm
Field of view “matrix”	512 x 512
Tube voltage (Kv)	100-120
Tube current	80-400
Radiation dose per examination	10 mSv
Reconstructed slice thickness	1-2 mm
Reconstructed interval	0.80-1 mm
Reconstruction kernel algorithm	Soft body reconstruction kernel-FC13
Inspiratory phase	Holding breath in inspiration

2.8.3 Image analysis software

Several software tools are available for clinical image viewing and analysis, such as Siemens, Mim Vista, OsiriX, and ClearCanvas. However, a significant shortcoming of these software tools in this context was a lack of flexibility and the need for specialised proprietary and operating systems, which limited their usability and applicability (Fedorov et al., 2012).

A 3D Slicer is used extensively in clinical research, and it does not need specific tools and operating systems (Fedorov et al., 2012; Yip et al., 2017). However, the disadvantage of this software is that its interface has not been changed to aid measurements by users with only limited knowledge of image analysis (Mullie and Afilalo, 2019).

A comparison of different software programs such as YACTA, LowATT, Pulmo3D, CT, and COPD to process lung density quantification for the same patient, showed poor inter-software reproducibility and variation in the results (Wielpütz et al., 2014; Lim et al., 2016). Consequently, the decision was made to employ software used routinely for clinical work (Lim et al., 2016; Mascalchi, Camiciottoli and Diciotti, 2017).

Aquarius Intuition Workstation from TeraRecon (TeraRecon GmbH, Frankfurt am Main, Germany) is a commercial post-processing software tool for routine clinical diagnostics. It also offers complex workflows for quantitative analysis. The software is connected directly to PACS allowing for direct access to DICOM folders, and was used for all morphometric-body composition analyses.

2.8.4 Software validation

Aquarius Intuition Workstation is a software package widely used as advanced PACS viewer and utilised for complex anatomical measurements in cardiology, neuro-radiology, interventional radiology, vascular surgery and any other branch of surgery where planning of the procedure depends on precise measurement of 3D reconstructed images. Since it has approval of Federal Drug Administration (FDA) in the U.S. and Conformité Européenne (CE) mark marking in the European Union, and is used routinely for clinical work, we decided that further validation for the purpose of this study is not required. The software was used ‘as is’, without modification.

2.8.5 Evaluation of the inter-observer variability

Assessing inter-operator agreement is a crucial aspect of ensuring the reliability of measurements in research studies involving manual segmentation of anatomical structures. In this thesis, the consistency of measurement of the psoas muscle was assessed on 25 randomly selected clinical CT scans using two assessors. Agreement statistics was employed, as detailed in paragraph 2.11.3 on page 133 of the statistical methods.

In addition to the manual segmentation of psoas muscles, the project involved semi-automated lung analysis, which included segmentation and measurement of lung volumes. Two different assessors performed this analysis on 50 images. Similar to the psoas muscle measurements, appropriate statistical methods were applied and outlined in paragraph 2.11.3 to assess inter-operator agreement in lung analysis.

By systematically evaluating the agreement between the assessors, I aimed to ensure the consistency and reproducibility of our results, crucial for the reliability and validity of the study’s findings.

2.8.6 Assessment of psoas muscle area

Two single cross-sectional imaging slice corresponding to the middle of the third lumbar vertebra (L_3) and the upper level of the fourth lumbar vertebra (L_4) were identified, and the borders of the left and right psoas muscles segmented using a polygon ROI tool (Figure 2.1 & 2.2). The area of individual psoas muscles was expressed in millimetres squared [mm^2]. The sum of both areas was constitute the total cross-sectional area of the total psoas muscle area (TPA).

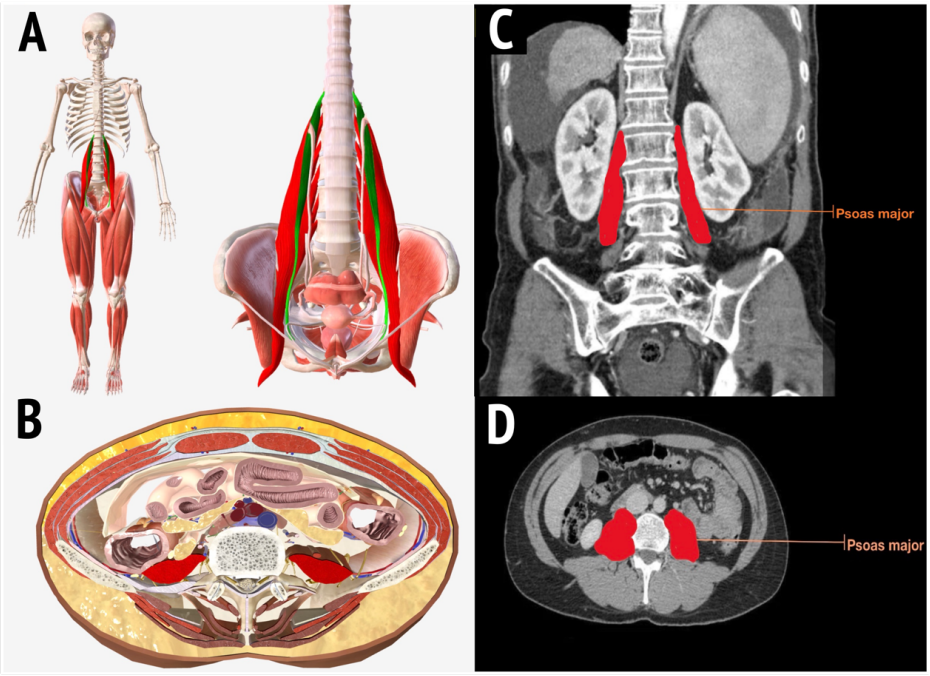


Figure 2.1 – Diagram demonstrating anatomical location of psoas muscle (A & B) and their location on cross-sectional imaging (C & D).

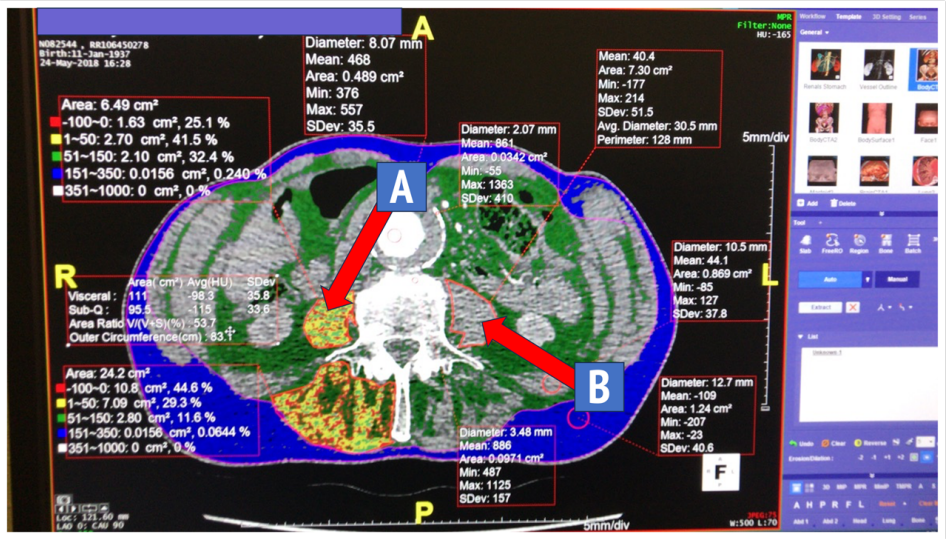


Figure 2.2 – Psoas muscle analysis in TeraRecon Aquarius Intuition software using the polygon region of interest tool: (A) segment the right psoas muscle; (B) segment the left psoas muscle.

2.8.7 Assessment of subcutaneous and visceral fat

Subcutaneous fat (SCF), visceral fat (VF) and waist circumference were measured on the same cross-section as used for measurements of psoas muscle area (L_3 and L_4; Figure 2.3). Automated Fat Analysis workflow based on image density (HU) was used for segmentation (Figure 2.4). Results was expressed in centimetres squared [cm^2] and as a subcutaneous fat to visceral fat ratio.

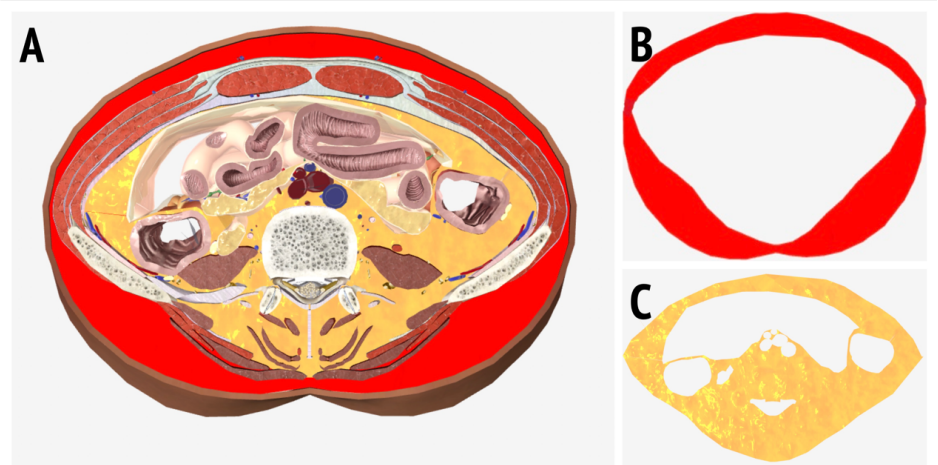


Figure 2.3 – Diagram representing structures seen on cross-sectional imaging (A) and segmented subcutaneous (B) and visceral (C) adipose tissue (fat).

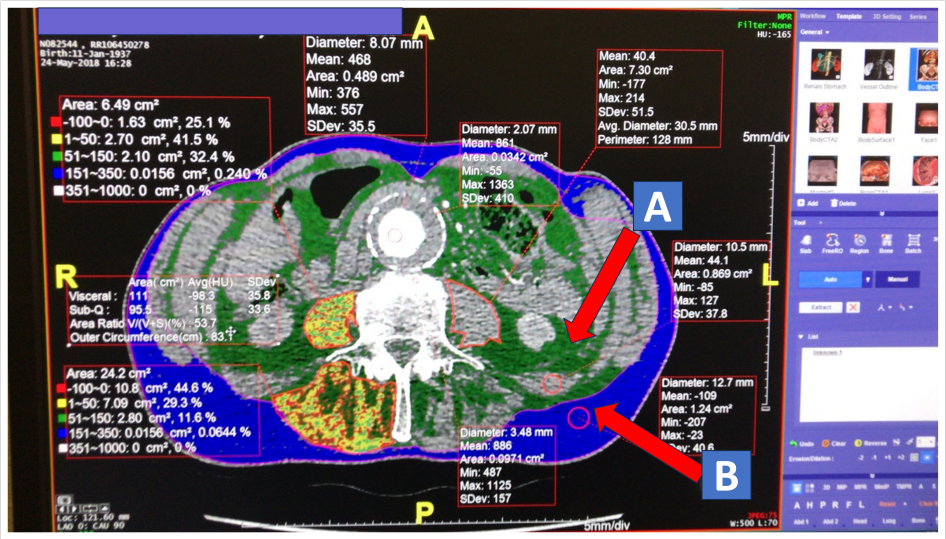


Figure 2.4 – Fat analysis in TeraRecon Aquarius Intuition software using automated fat analysis workflow: A) automatically segmented visceral fat; B) automatically segmented subcutaneous adipose tissue.

2.8.8 Assessment of diaphragm thickness

Six measurements were performed on both axial and coronal images for each left and right diaphragm side, at the level reference of the upper part of the L_1 lumbar vertebra body. The vertebral level was selected on which have a feature of distinguishing the diaphragm muscles from neighbouring solid and soft organs (Lee et al., 2016; Sanli et al., 2016; Kang et al., 2021b).

The thickness of the diaphragm on both axial and coronal reconstructed images at the anterior, middle, and posterior aspect of the L_1 vertebra was measured in transverse plane and recorded in [mm] (Figures 2.5 and 2.6).

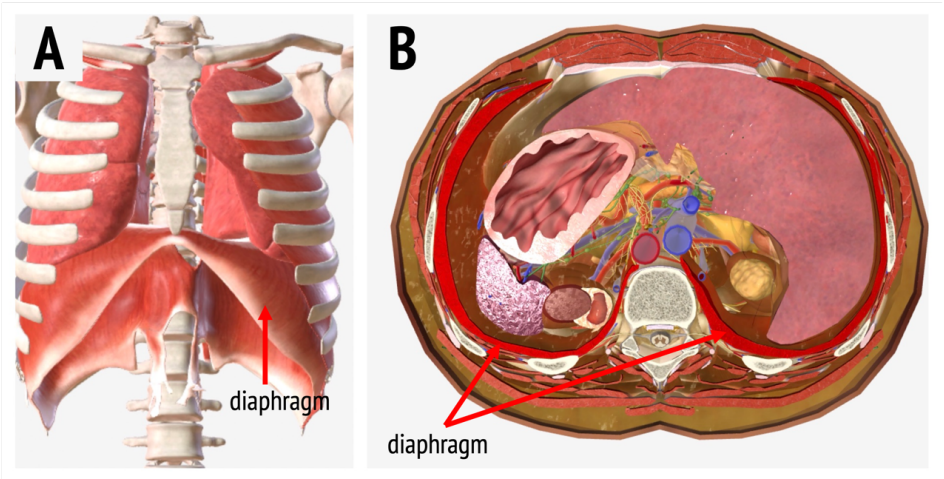


Figure 2.5 – Diagram demonstrating anatomical location of diaphragm muscle in 3D (A) and cross-section (B).

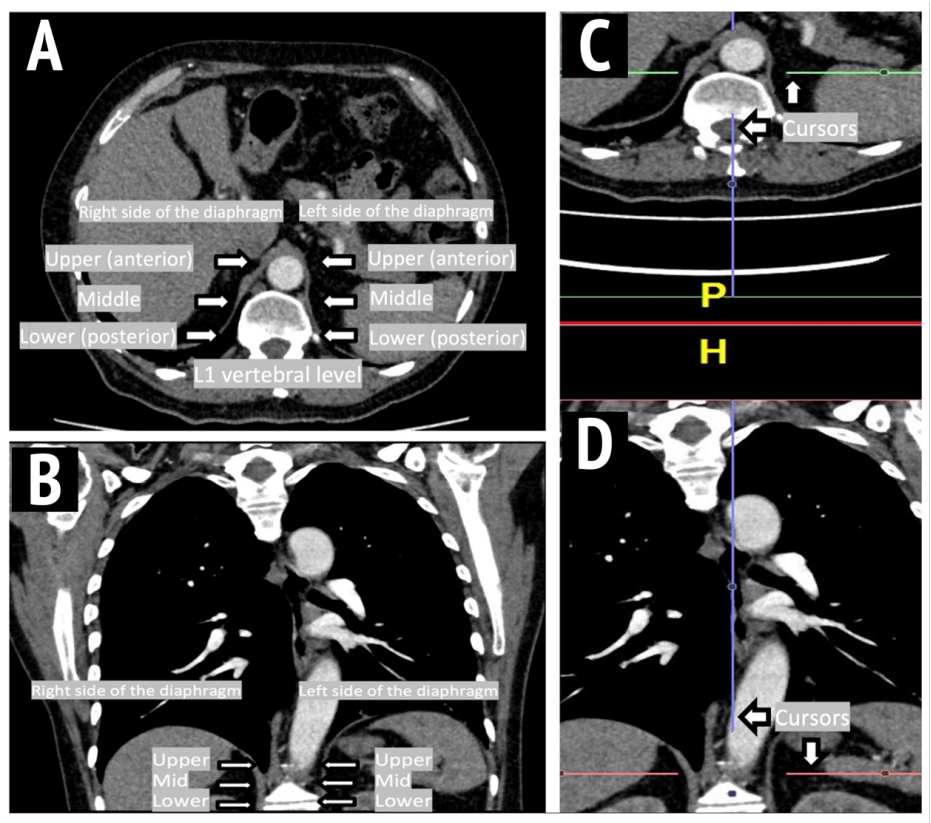


Figure 2.6 – Location of the diaphragm muscle on cross-sectional imaging and the measurement of diaphragm thickness on chest CT scan. Panels A and B demonstrate location of the diaphragm measurements on axial (A) and coronal (B) planes, at the L_1 vertebral body level. The images show upper (anterior), middle, and lower (posterior) aspects of the diaphragm. Panel C and D shows multiplanar reconstruciton demonstrating intersection points of the line and diaphragm on the coronal image when cursors were placed on the points of measurements in the axial image.

2.8.9 Assessment of lung morphometry

All lung CT images were reconstructed and analysed using Aquarius Intuition available on an NHS computer. Figure 2.7 shows the workflow process of the lung analysis.

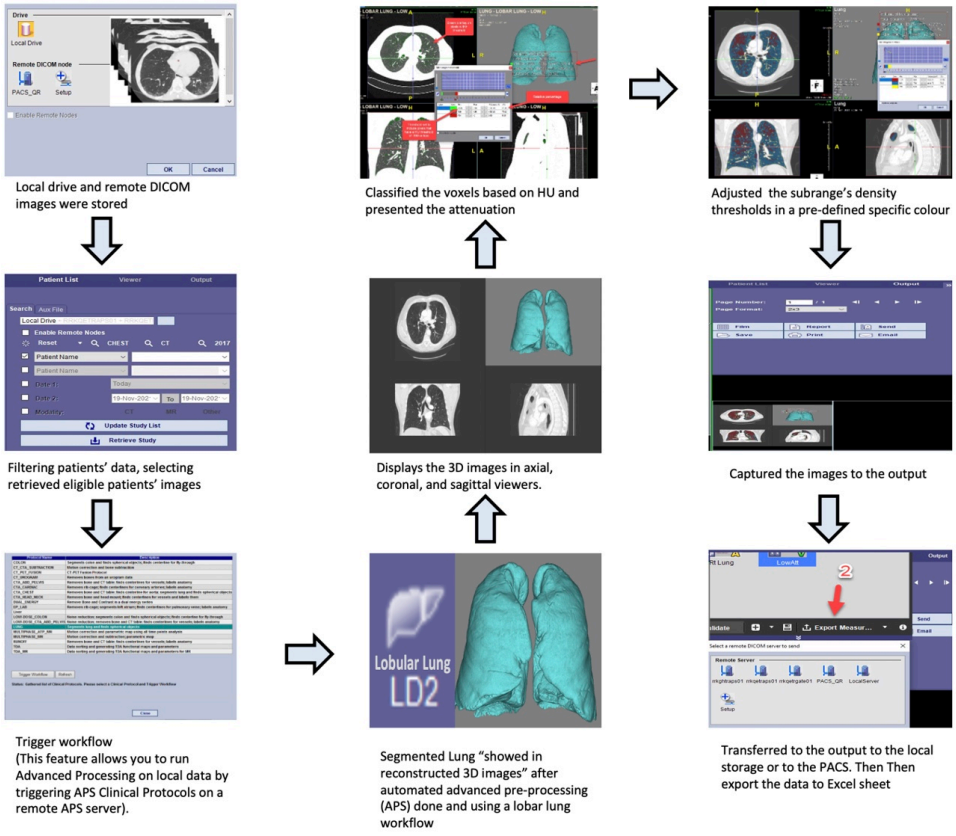


Figure 2.7 – Quantitative lung density analysis process with Aquarius intuition (TeraRecon) software.

The Aquarius Intuition has automatically enabled the extraction of CT images from the PACS and downloaded the CT scans series to the workstation.

The analysis process commenced by filtering patients' data, selecting retrieved eligible patients' images data using a search panel, and querying each patient by ID and CT image modality criteria.

Selection of the workflow feature allowed to process the data (DICOM images), by triggering an automated advanced pre-processing (APS) clinical

protocol, on a remote APS server. The system automatically recognised the lung borders and segmented the lung parenchyma, airways, and vessels.

Once the images had been through the APS, and the lungs were isolated from the surrounded tissues and other structures, the system automatically generated (loaded) reconstructed 3D images of the selected lungs by using a lobular lung workflow.

The software classified the voxels based on the range of pre-set HU threshold values, and presented images with pre-selected colour mask based on threshold ranges (Figure 2.8).

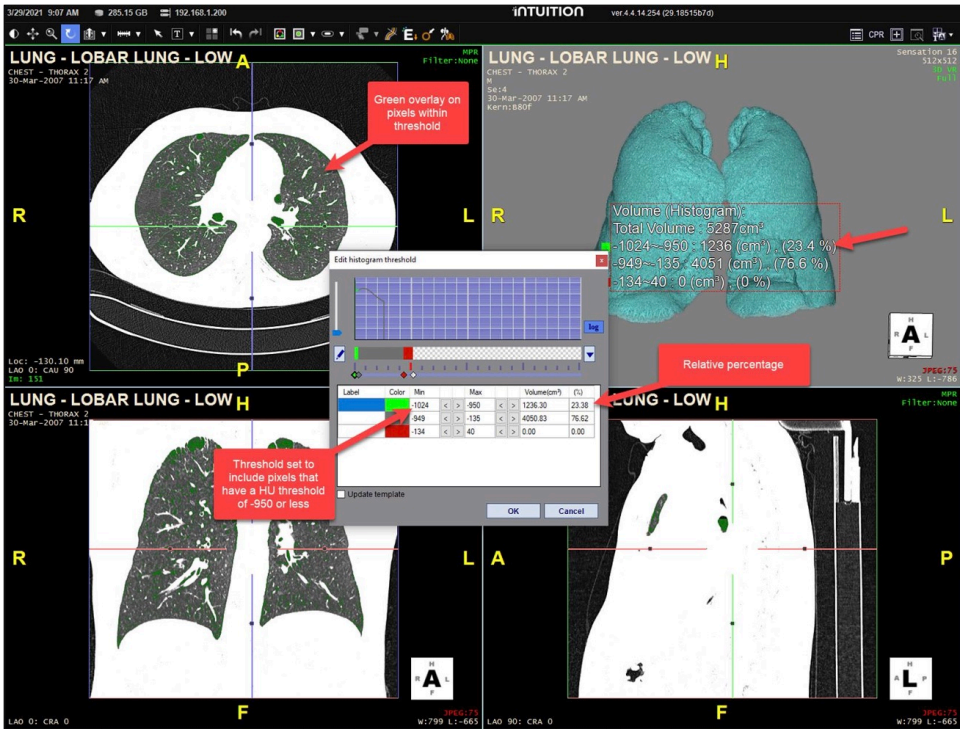


Figure 2.8 – The process of adjusting the subrange's density thresholds to display pixels (voxels) with a Hounsfield units (HU), as well as applying the mask overlay with a pre-defined specific colour to these pixels on the multiplanar reformation (MPR) images.

The red, blue, and yellow colours were selected for voxels with a different density to identify the extent of the emphysema, normal attenuation area, and certain lung pathologies respectively (Figure 2.9).

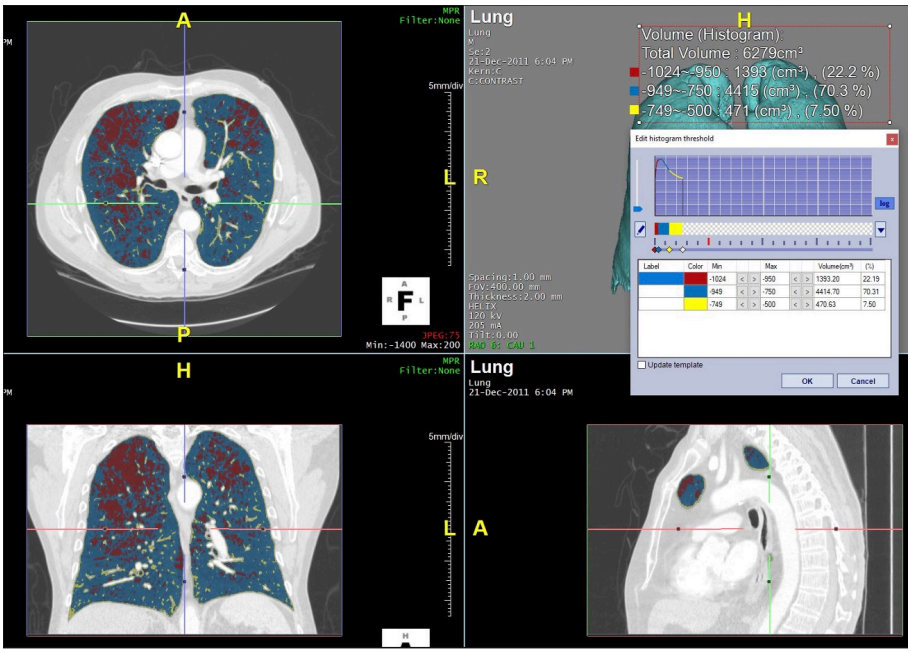


Figure 2.9 – The process of adjusting the range of threshold density values and specific colour mask overlay. The Hounsfield units (HU) values are partitioned into three ranges. For each range, the volume of all data having HU values within that range is displayed, followed by that volume's percentage of the total volume.

The coloured mask overlay of 20 samples was evaluated by external assessors, a radiologist, and a physician, to assess the diagnostic accuracy and optimal threshold for each of the study parameters.

2.8.10 Parameters and threshold settings

The following parameters were acquired and measured for each lung and compared between the study groups:

- Mean lung attenuation (HU),
- Volume (cm^3) and percentage of normal attenuation area (NAA)
- Volume (cm^3) and percentage of low attenuation area (LAA)
- Volume (cm^3) and percentage of high attenuation area (HAA).

The range threshold technique was employed in the current thesis to segment all the pixels as the lung. These ranges include the normal lung structure and thresholds for abnormal lung.

Previous studies reported the estimated NAA, depending on the anatomical location (dorsal or ventral), inspiration or expiration scans, and level of the inspiration.(Wegener, Koeppe and Oeser, 1978; Robinson and Kreel, 1979; Rosenblum et al., 1980). To obtain a quantitative attenuation, a range of volumetric and percentage values from -800 HU (NAA-800) to -900 HU (NAA-900) was selected.

The CT threshold values of lower thresholds greater than -900 HU (NAA-900), -950 HU (NAA-950), and higher thresholds lower than -750 HU (NAA-750), -700 HU (NAA-700) were also considered in the current thesis; these values are the most acceptable thresholds cited in the literature to distinguish NAA (Shin et al., 2011; Karimi et al., 2014; Ohkubo et al., 2016; Temiz Karadag et al., 2021).

The quantification of emphysema was performed by measuring the LAA. In the current project, emphysema was defined as the volumetric and percentage of voxels less dense than -900 HU, -910 HU, and -950 HU (LAA-900, LAA-910, and LAA-950, respectively).

It has been established in previous evaluations that at early stages of lung disease, the cut-off value of (910 HU; LAA-910) helps to detect emphysema Hoffman et al. (2009), (950 HU; LAA-950) correlates better with finding pathological emphysema Gevenois et al. (1995) and Coxson et al. (1995), while (-900 HU; LAA-900) correlates with macroscopic emphysema in a visual assessment of CT-scans and pathological specimens (Muller et al., 1988; Gould et al., 1988; Karimi et al., 2014).

To determine the extent of the lung disease, the volumetric and percentage of lung voxels greater than -700 HU, -750 HU and -850 HU (HAA-700, HAA-750, and HAA-850 respectively) were segmented and defined as the HAA.

In fact, the optimal threshold values to detect lung attenuation area could be influenced by several factors (e.g., subject, scanner, volume and rate of

contrast administration, and protocol-specific factors such as radiation dose and slice thickness)(Muller et al., 1988; Adams, Bernard and McConnochie, 1991; Boedeker et al., 2004; Parr et al., 2004; Yuan et al., 2007; Madani, Van Muylem and Gevenois, 2010; Choromańska and Macura, 2012). Thus, additional higher and lower thresholds than those cited in the literature were adjusted to avoid the influence of external factors on the project outcomes.

To start the analysis, a threshold for voxels with a density range from < -850 HU to < -970 HU to show the extent of the emphysema, voxels with a density range between the lower threshold (> -850 HU to > -970 HU) and the higher threshold (< -600 HU to < -850 HU) to determine the normal lung, and voxels with a density range between the lower threshold (> -600 HU to > -850 HU) and the higher threshold (0 HU to < -500 HU) to identify certain lung pathologies were adjusted.

In TeraRecon, the threshold values could be changed manually. The chest CT scans were analysed using a defined set of normal, low, and high attenuation tissue. Table 2.2 shows a set of lung density thresholds used in this study.

Table 2.2 – The pre-defined set of lung density thresholds in the current study. LAA - Low attenuation area; NAA - Normal attenuation area; HAA - High attenuation area; HU - Hounsfield Units.

Attenuation area	Lower threshold	Higher threshold
LAA	-1024 HU	< -850 HU, < -860 HU, < -870 HU, < -880 HU, < -890 HU, < -900 HU, < -910 HU, < -920 HU,< -930 HU, < -940 HU,< -950 HU,< -960 HU, < -970 HU
NAA	> -850 HU,> -860 HU,> -870 HU,> -880 HU,> -890 HU, > -900 HU, > -910 HU,> -920 HU, > - 930 HU,> -940 HU, > -950 HU, > -960 HU, > -970 HU	< -600 HU, < -610 HU,< -620 HU, < - 630 HU,< -640 HU, < -650 HU, < -660 HU,< - 670 HU, < -700 HU, < - 730 HU, < -750 HU, < -760 HU, < -770 HU, < -780 HU, < -790 HU, < - 800 HU,< -810 HU, < -830 HU, < -850 HU
HAA	> -600 HU,> -610 HU,> -620 HU,> -630 HU,> -640 HU, > -650 HU,> -660 HU,> -670 HU,> -700 HU,> -710 HU, > -720 HU,> -730 HU,> -740 HU,> -750 HU,> -760 HU, > -770 HU,> -780 HU,> -790 HU,> -800 HU,> -810 HU, > -820 HU,> -830 HU,> -840 HU, > -850 HU	0 HU, < -500 HU

2.8.11 Assessment of airway volume

In the current thesis, airway volume biomarker was measured and defined as the air passes through the anatomical structure and passages, including the trachea, bronchi, and bronchioles, which progressively subdivide into smaller airways. In the context of CT imaging, I primarily focused on airway volume analysis due to Terarecon software's insufficient and comprehensive approach to airway analysis. I defined airway volume as the total airway volume in the air routes, which we can measure along the bronchial tree.

TeraRecon software automatically measured airway volume and extracted quantitative information pertaining to airway volume from thoracic CT images using anatomical algorithms. The algorithms segmented irrelevant data from the mediastinum, massive vessels, lungs, and the thorax wall. The recorded data encompassed the total volume of both large and small airways. Airway volume measurement was recorded the in milliliters (ml). Figure 2.10 shows the workflow process of the total airway volume analysis.

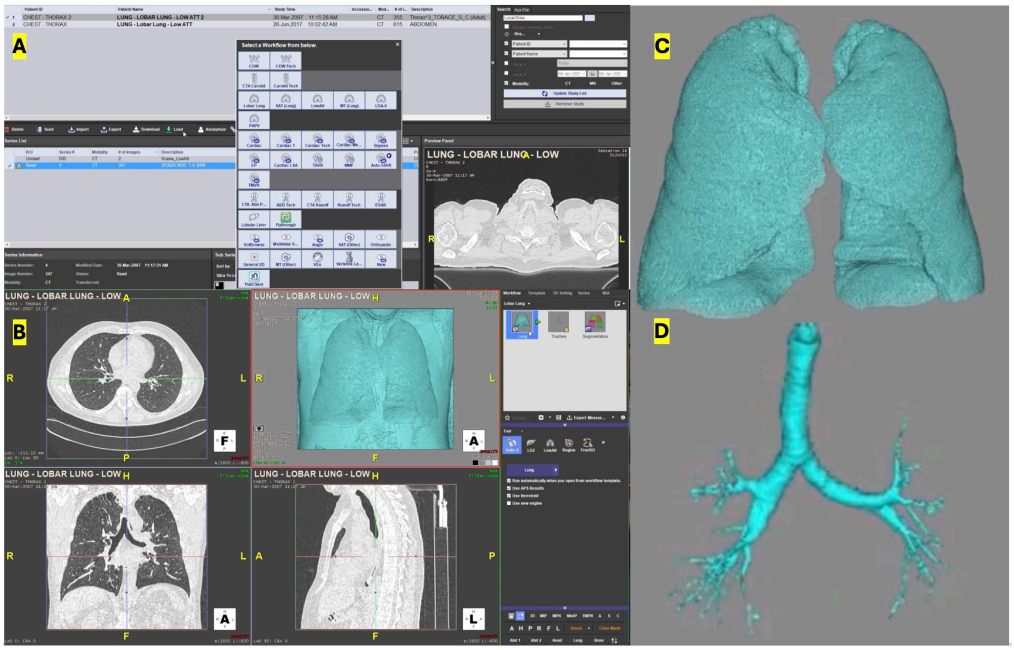


Figure 2.10 – Quantitative total airway volume analysis process with Aquarius intuition (TeraRecon) software. The analysis began with loading the image into the lobar lung workflow, as shown in Panel A. Panels B and C show anatomical algorithms that segmented the massive vessels, lungs, and thorax wall. Panel D is shown. The recorded data encompassed the total volume of both large and small airways.

2.9 Outcomes measures

Primary and secondary outcomes were set for each results chapter separately. The principal outcome was the incidence of *PPC* defined according to the modified EPCO criteria.

The other outcomes included:

- Mortality and estimated survival„
- Morphometric parameters (lung density, muscle area/thickness, waist circumference, subcutaneous and visceral fat)
- Coefficients of association of PCC with morphometric parameters including lung density, diaphragm thickness, total psoas muscle area, waist circumference, subcutaneous and visceral fat,
- Coefficients of association between PPC, morphometric parameters and survival.

2.10 Data management and quality assurance

Data quality and integrity is a critical aspect of any research study. It ascertains the reliability and trustworthiness of obtained results.

2.10.1 Data management and confidentiality

Access to data for monitoring and/or audit of the study to ensure compliance with the NHS Research Governance Framework was facilitated for responsible members of the University Hospitals Birmingham NHS Foundation Trust and external monitors as appropriate.

The data generated from the study was analysed by adequately trained member of the research team. The audit dataset was pseudonymised and coarsened. Patient identifiable data were stored securely on password protected computers managed by UHB. Only anonymised and coarsened data were transferred and used for analyses. Analysis was taken place on the trust computers and on conclusion of the study all electronic copies of data was compressed, encrypted and archived on the Trust OneDrive server.

Stringent measures were taken to ensure security and data confidentiality at all times. Patient information was protected according to the principles outlined in General Data Protection Regulations and Data Protection Act.

This project was taken place at the University Hospitals Birmingham NHS Foundation Trust. Participant identification, data collection, analysis and storage was taken place on adequately configured, password-protected UHB computers. Data was stored exclusively in the electronic format. No paper copies was required. On completion of data collection phase, the dataset was pseudonymised and coarsened. No patient identifiable information was transferred out or shared with third parties.

The dataset was stored in a password protected Microsoft Excel Spreadsheet (Microsoft Office (2010), Excel (Version 2010); Microsoft Corporation. https://www.microsoft.com/excel).

The data is owned by the NHS.

2.10.2 Data quality assurance and validation

The project implemented a structured method to maintain the data quality and compliance. A data collector was designed using Excel spreadsheet for the purpose of this study, and included logic checks and data input restrictions (such as selection from a list) to avoid errors on data entry.

Additional data checks were done at completion of each work package to ensure data quality and integrity.

2.10.3 Long term storage of data

All electronic copies of data were compressed, encrypted and filed on the Trust file server. Personal data were kept in a form which permits identification of individuals for no longer than is necessary for the purposes for which the personal data are processed.

When no longer needed for the purpose for which it was collected, and if there is no lawful basis for continuing to keep it, the personal data will be anonymised or deleted in accordance with the NHS Data Retention Principles.

2.11 Statistical methods and data analysis

2.11.1 Statical environment

Results were analysed in pseudonymous format using R statistical environment (R version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). Data analysis was closely supervised by Mr Maciej Juszczak.

2.11.2 Dataset management

Collection of this comprehensive dataset was facilitated by using a purpose-built spreadsheet incorporating specific data checks and format restrictions to mitigate input errors. Following final checks for quality, consistency, completeness and integrity the dataset was exported to comma-separated values (CSV) format. The CSV data were subsequently imported into an R dataframe, and now in R's native format, was saved as an R data file (.rda).

Further data manipulation was taking in R and was taking advantage of the capabilities provided by packages such as `tidyr` (v. 1.3.0) and `dplyr` (v. 1.1.3), `cli` (v. 3.4.1), `glue` (v. 1.6.2), `lifecycle` (v. 1.0.3), `lubridate` (v. 1.9.3), `magrittr` (v. 2.0.3), `purrr` (v. 1.0.2), `rlang` (v. 1.1.1), `stringr` (v. 1.5.0), `tibble` (v. 3.2.1), `tidyselect` (v. 1.2.0), `utils` (v. 4.2.2), `vctrs` (v. 0.6.4), for efficient data manipulation and conversion to facilitate further analysis.

This process, from data collection with error prevention measures to manipulation using R packages, ensured the integrity and quality of the dataset for robust statistical analysis.

2.11.3 Conventions, statistical methods and data presentation

Descriptive statistics was used to characterise study groups. Continuous variables was presented as mean (standard deviation, (SD)) or median [interquartile range; IQR] as appropriate and compared using t-test for normally distributed data and Wilcoxon rank-sum test for not normally distributed data. Effect size was estimated using Cohen's d and described as "trivial" ($d<0.2$), "small" ($0.2\leq d<0.5$), "medium" ($0.5\leq d<0.8$) and "large" ($d\geq 0.8$).

Categorical variables were presented as counts and proportions. Percentages were used only if the denominator was greater than 50; otherwise only counts and proportions were used. Categorical variable was analysed using contingency tables with Pearson's or Fisher's χ^2 (Chi squared) test and presented as numbers/proportions and percentages. Haldane-Anscombe zero-cell correction was applied as appropriate. Effect size was presented as odds ratio (OR) with

95% confidence intervals (CI) and classed as “small” (OR$<$1.5), “medium” (1.5$\leq$OR$<$5.0) and “large” (OR$\geq$5.0).

Associations between variables was assessed by calculation of Spearman’s rank correlation coefficient (ρ) and Pearson’s product-moment correlation coefficient (r). Correlations were described according to their strength as: “very weak” (0.00$\leq\rho<$0.20), “weak” (0.20$\leq\rho<$0.40), “moderate” (0.40$\leq\rho<$0.60), “strong” (0.60$\leq\rho<$0.80) and “very strong” (0.80$\leq\rho\leq$1.00).

Lin’s statistics was calculated to assess inter-observer agreement (`Agreement` R package v. 0.8-1) for continuous data. Concordance Correlation Coefficient (CCC) of less than 0.8 was considered to indicate “poor agreement” (tolerance of 20% discrepancy between observers), 0.80 to 0.95 - a “moderate agreement”, 0.95 to 0.99 - a “substantial agreement”, and a CCC greater than 0.99 will indicate an “excellent agreement”.

Fleiss’ Kappa (κ) statistics was calculated to assess inter-rater agreement (`irr` R package) for categorical data with multiple raters. Kappa of less than 0 was considered to indicate no agreement, 0.01 – 0.20 a “slight agreement”, 0.21 – 0.40 a “fair agreement”, 0.41 – 0.60 a “moderate agreement”, 0.61 – 0.80 a “substantial agreement” and 0.81 – 1.00 “almost a perfect agreement”.

Multivariate logistic regression with purposeful selection of variables based on threshold p<0.1, clinical importance and data quality was performed to assess the association between postoperative pulmonary complications and clinical and morphometric indices. Multicollinearity was assessed by calculating variance inflation factor (VIF) using `VIF()` and `vif()` functions from `DescTools` and `rms` packages depending on input data. Covariates which demonstrated significant correlation with each other (VIF $>$ 10) were removed from multivariable models. The final model was further developed by performing stepwise minimisation of Akaike’s Information Criterion (AIC). The effect size was reported as odds ratio (OR) with 95% confidence intervals (CI).

Survival analysis was performed utilising `survival`, `survminer`, `survival ROC` and `rms` R packages. Patient survival following surgery was assessed using Kaplan-Meyer estimator with right-censoring of survival data, and the effect of covariates estimated using univariable (log rank test) and multivariable analysis

(Cox proportional hazards model with purposeful selection of variables). Results was reported as the median observed follow-up, median survival (if appropriate) and estimated survival at 1, 3 and 5 years if deemed appropriate. The effect size was reported as hazard ratio (HR) with 95% confidence intervals (CI).

All tests was performed at a 5% 2-sided significance level. P-value correction was not applied to avoid type-2 error.

2.11.4 Sample size calculation

Power calculation is not routinely performed for retrospective analyses since the sample size is limited by the size of the studied cohort. However, the preliminary data allows for estimation of sample size for cox regression model in a context of postoperative pulmonary complication. Based on the assumption of $\alpha = 0.05$, $\beta = 0.80$, the proportion of exposed subjects in the sample (4.5%) and the expected hazard ratio (HR) of 3.14, the number of events (death) in the sample would need to be at least 151, which is close to the number of events observed (130) in the sample of 667 patients.

2.11.5 Propensity Score Matching

The cohort of patients with colorectal cancer was deemed large enough to provide a tightly matched, balanced subset for further analyses. The bivariate analysis compared the prematch baseline characteristics to assess the imbalances of the confounding variables. The propensity score matching (PSM) was performed to reduce the selection and confounding bias, prior to commencing with the morphomic quantitative analysis. This method made it possible to balance the distribution of the observed covariates between patients in chosen study groups.

The exact match accounted for the covariates with the weighting of their impacts. Propensity scores were estimated by constructing a multivariable logistic regression model. Age, gender, TNM stage, type of surgery, surgical

approaches, PPC, and chronic lung disease were included as covariates in the propensity model. These covariates were selected as they were demonstrated to be associated with the study outcomes. Although of possible importance, height, weight, BMI, and smoking were not included in the regression model due to the high rate of missing values.

Patients who developed PPC were matched to patients who did not develop PPC in a $1 : 2$ ratio using a greedy, nearest-neighbour matching with no replacement. A PPC patient was matched with three patients without PPC who had the closest estimated propensity scores.

The standardised differences were used to evaluate the baseline characteristics and balance the covariates between the propensity score-matched groups. A standardised difference of < 0.1 was used to indicate that there was a minor imbalance between the groups.

2.11.6 Data missingness

One of the most important properties of any dataset is data veracity (truthfulness, accuracy) and it is the Achilles' heel of any retrospective analysis. Collection of retrospective clinical data is invariably labour-intense and has its inherent limitations. It often precludes inclusion of some variables of interest since they may have never been recorded or a large proportion of data may be missing. Since the thesis relies largely on the retrospectively collected data, strict measures will be put in place to ensure data veracity, with frequent cross-checks between the electronic patient record (hospital and GP) and paper-based documentation.

Missing data is more frequent in retrospective studies and can seriously impair their veracity. Handling of missing data in the this thesis depends on the nature of missingness and the research objectives. Data missing at random was treated on an individual basis by case-wise deletion. In instances where more than 30% of data missing, that variable will be removed from the analysis.

2.11.7 Data analysis

Exact data analysis plan was tailored to each work package and presented in each results chapter separately.

Chapter 3

The incidence of postoperative pulmonary complications and their association with survival

3.1 Introduction

Although surgical technique and perioperative care have significantly improved in recent years, the risk of postoperative complications persists (Fowler et al., 2022). The PPC are of particular significance, as they have a marked impact on clinical endpoints both immediately after surgery and in the long-term (Miskovic and Lumb, 2017; Pasin et al., 2017; Fernandez-Bustamante et al., 2017; Jurt et al., 2018; Semmelmann et al., 2023).

A standard definition for PPC does not currently exist, but PPC can be thought of as a heterogenous group of disorders affecting the respiratory system that may have a negative influence on the clinical outcome after an operation (Miskovic and Lumb, 2017; Tegegne et al., 2021). The PCC range from mild to severe; some present as self-resolving disorders that respond rapidly to supportive and medical therapy or physiotherapy that can be delivered on the ward, whereas others may cause the patient to become critically ill and need admission to the intensive care unit, where they may require mechanical ventilatory support. The latter carries a high risk of mortality (Patel et al., 2016). The cost of PPC is significant, resulting in excess treatment cost for non-cardiac patients to rise by 55% (Shander et al., 2011; Patel et al., 2016).

The reported incidence of PPC is highly variable mainly as a result of inconsistent reporting. This can vary between 1% and 80% depending on study setup

and healthcare system (Miskovic and Lumb, 2017; Fernandez-Bustamante et al., 2017). The discrepancies may also relate to multiple other factors, encompassing variations in the definitions used, the risk assessment performed prior to surgery, diagnostic parameters, the heterogeneous populations of patients and the range of comorbidities and operative interventions undertaken (Miskovic and Lumb, 2017; Odor et al., 2020).

Colorectal cancer and aortic disease are two areas of surgery in which techniques evolved rapidly moving away from 'maximally invasive' open surgery to minimally invasive laparoscopic and endovascular surgery. The incidence of PPC within these subspecialties has only been sparsely documented in a small number of previous studies; figures between 0% and 21% have been noted following colorectal cancer surgery(Haines, Skinner and Berney, 2013; Fleisher and Linde-Zwirble, 2014; Schiphorst et al., 2015; Jurt et al., 2018), and between 5.4% and 19.1% after vascular procedures (Pasin et al., 2017; Genovese et al., 2017). Studies have consistently shown that the longer hospital stay, and a higher chance of morbidity and mortality are linked with PPC (Fleisher and Linde-Zwirble, 2014; Genovese et al., 2017; Pasin et al., 2017; Jurt et al., 2018; Abd El Aziz et al., 2020). Some evidence suggests that long-term survival may also be negatively affected (Khuri et al., 2005; Pasin et al., 2017; Niemeläinen et al., 2020).

Although PPC occur relatively frequently and have negative consequences, there is little solid evidence relating to the risk factors linked to the onset of PPC following colorectal cancer or vascular surgery in the United Kingdom (UK). The studies that have been published suggest that risk factors pertaining to the patient, e.g. age, ASA score $\geq$3, BMI, smoking status, degree of COPD, kidney failure or congestive cardiac failure, and functional health status, as well as those factors relevant to the operation, e.g. urgency and procedure (Genovese et al., 2017; Jurt et al., 2018; Abd El Aziz et al., 2020).

The incidence of PPC in patients in the UK who are undergoing the colorectal or aortic surgery has been reported sparsely; studies have predominantly related to surgery of the thorax. The exact incidence of PPC in these patient groups, and the factors that may be associated with development of PPC are unknown.

Also, the association of PPC with survival is yet to be reported. In this chapter I attempted to answer these questions and provided the data demonstrating both incidence and the association of PPC with survival.

3.2 Hypothesis and aims

In this chapter, it is proposed that PPC in patients undergoing surgery for aortic pathology and colorectal cancer are common.

The *primary aim* of this chapter was to determine the incidence of PPC in patients who underwent either colorectal resection for malignant disease, and aortic surgery.

The *secondary aims* were to:

- Identify clinical factors associated with PPC incidence and,
- A relationship between the development of PPC and survival.

3.3 Materials & methods

The data was analysed form a large retrospective cohort of patients undergoing colorectal surgery for malignant disease and a prospective cohort of patients with aortic disease undergoing assessment for aortic repair. A deep chart and clinical notes review was performed to identify cases of confirmed and suspected PPC to determine their incidence. Descriptive and inferential statistics was used to determine relationship between PPC and demographic, clinical factors and survival.

3.3.1 Study cohorts

3.3.1.1 Vascular cohort

This study encompasses a comprehensive cohort, drawing patients of all ages and sexes, presenting a wide spectrum of aortic diseases, including juxtarenal, pararenal, thoracic, and thoracoabdominal aneurysms and aortic dissections. Selection criteria did not impose any restrictions based on ethnicity or geographic location, ensuring a diverse patient population from a referral centre with a broad catchment area.

All patients presenting to the specialist Aortic Clinic over the period from July 1, 2019, to February 29, 2020 were included. These patients underwent a thorough pre-operative assessment including staging CT scans within a multidisciplinary clinical pathway, part of a service improvement project aimed at assessing and managing frailty in patients considered for surgery (Specialised Clinical Frailty Network, http://www.scfn.org.uk).

3.3.1.2 Colorectal cohort

This cohort included all patients with colorectal cancer limited to left-sided colon (descending colon, sigmoid colon, and rectum) of any clinical stage, who underwent open or laparoscopic resection between 2010 and 2017. Inclusion criteria ensured a broad representation across various demographics, thus patients of every sex and age were considered, with no exclusions based on ethnicity or geographical provenance, drawn from a referral centre with an extensive catchment area. This approach increased the chances of this cohort being considered representative of this group of patients. The clinical pathway for these patients was structured within a multidisciplinary framework, incorporating a standardised pre-operative assessment that included staging CT scans. To ensure the homogeneity of cases under examination, the study was confined to those patients who underwent either elective or emergency resections for left-sided colorectal cancer.

3.3.2 Ethical considerations

Institutional approval was granted before data collection.

3.3.3 Definitions

Postoperative Pulmonary Complications - for the purpose of this study PPC were defined using a modified EPCO criteria. This was described in detail in Chapter 2/Section 2.6.5 on page 111.

Early/in-hospital mortality was defined as postoperative death occurring during index admission or within 30 days of the index procedure if the patient was discharged from the hospital.

Outcome ascertainment was achieved by cross-referencing of the EHR with the NHS Spine (NHS Digital). The cause of death was retrieved from the Primary Care Mortality Database (NHS Digital).

Tumour staging was based on the Union for International Cancer Control (UICC) classification (8th edition) Available at `https://www.uicc.org/what-we-do/sharing-knowledge/tnm`.

3.3.4 Outcomes

The *primary outcome* was the prevalence rate of PPC. Outcome ascertainment was based on data deriving from medical records, radiology reports, infectious disease clinical entries and discharge summaries.

The *secondary outcomes* were:

- The association between demographic and clinical factors and development of PPC, and
- The association between the development of PPC and survival.

3.3.5 Data collection

Data curation and management was described in Chapter 2, 3.14 Section 2.6 and 2.10.

The UHB Trust sites have combined electronic and paper healthcare records system and share a primary and secondary care record (Your Care Connected, NHS Birmingham and Solihull Clinical Commissioning Group, Birmingham, UK). The electronic medical record contains laboratory, radiology, and pathology reports, operation notes, concise inpatient records (admission history and discharge summary), as well as outpatient attendance records.

For every patient, preoperative, intraoperative and postoperative data were recorded. Preoperative assessment data included comorbidities, ASA score, laboratory biomarkers, smoking status (current smokers, ex-smokers, and non-smokers) and the mode of admission (elective/emergency). Intra-operative data included type of surgery and surgical approach. Postoperative data included the recording of all complications including pulmonary complications, LOS, admission to the ICU, and mortality.

3.3.6 Statistical methods and data analysis plan

Generic statistical methods used in this Chapter were described in Methods Section (Chapter 2 on page 132).

3.3.6.1 Data analysis plan

The data quality was first determined by assessing data missingness using `naniar` and `DescTools` packages. Variables with 20% or more data missingness were removed from the analysis.

The *primary outcome* for the analysis was the post-operative pulmonary complication. The frequency of PPC was established using descriptive statistics.

The predictor variables considered in this analysis were demographic and anatomical and clinical factors listed in Table 3.1. The predictor variables were tested for normality (`shapiro_test()` from `rstatix` library) and performed univariable analysis, using primary outcome as a grouping variable (`univeriateTable()` from `Publish` library).

Multivariable analysis (MVA) was conducted using variable selection criteria were based on p-value < 0.1. Logistic regression models were built based on selected predictors. Multicollinearity was assessed by calculating VIF; `vif()`form `fmsb`/`rms` packages and `VIF()` from `DescTools`). Variables demonstrating high VIF (>10.0) were removed from the models one by one in descending order of VIF. Further to that we used an automated selection of variables based on AIC using stepwise logistic regression (`step()` function from `stats` library).

Table 3.1 – Demographic, anatomical and clinical factors included in analyses. ACE - angiotensin converting enzyme; ARB - angiotensin receptor blocker; ASA - American Society of Anesthesiologists fitness scale; COPD - chronic obstructive pulmonary disease; eGFR - estimated glomerular filtration rate.

Data group	**Variable**
Demographic	
	age, sex, index of multiple deprivations
Anatomical	
	extent of aortic disease, tumour location
Clinical	
Comorbid status	hypertension, ischaemic heart disease, atrial fibrillation, heart failure, peripheral arterial occlusive disease, hypercholesterolemia, diabetes, dementia, chronic lung disease, COPD, chronic kidney disease, abbreviated mental test
Medications	antiplatelet agents, anticoagulation, statin, beta-blockers, ACE inhibitors / ARB
Biochemical/Haematological	creatinine, eGFR, albumin, haemoglobin, white cell count, lymphocyte count, neutrophils
Disease grading	ASA, emergency status, tumour staging
Operative details	surgical modality

3.4 Results

3.4.1 Dataset information: data quality

The dataset used in this project was derived from a prospective audit of patients who underwent colorectal cancer and aortic aneurysms vascular surgery. No information regarding ethnicity was available, since it was not collected for audit purposes. The data was reviewed on an individual case basis. Typing and formatting errors were manually corrected before the data was imported into R software for formal data analysis.

3.4.1.1 Data quality in vascular cohort

The vascular cohort was described in detail in Methods (Section 2.5.1 on page 106). The dataset consisted of 110 observations and 45 variables. There were 81 complete cases (73.6%).

Missing data were found in variables related to Index of Multiple Deprivations (IMD), abbreviated mental test (AMT), ASA classification, and albumin (ALB). Information regarding IMD was missing in 3.6% of cases. The data points in AMT and ASA variables were missing in 5.5% and 7.3% of cases respectively. Twelve data points related to ALB were missing (10.9%). The distribution of data missingness is shown in Figure 3.1.

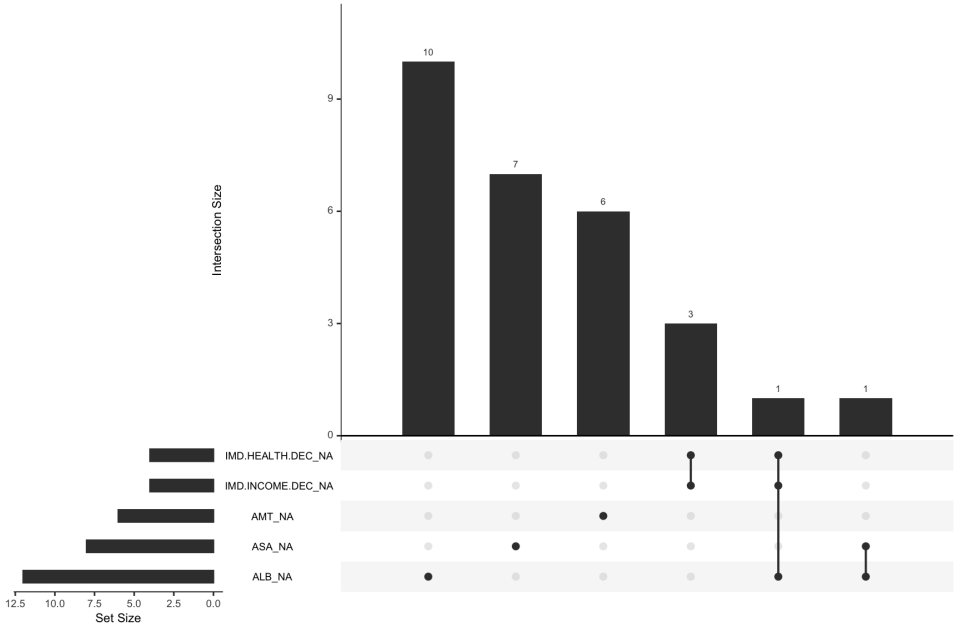


Figure 3.1 – The upset shows the intersections of missing values across different clinical and biological variables in the vascular cohort. The vertical bars represent the number of instances where there are missing data across various combinations of these variables.The categories that are included are related to the missing information for IMD.IMD.HEALTH - Index of multiple health deprivation; IMD.INCOME - Index of multiple income deprivation; AMT - abbreviated mental test; ASA - The American Society of Anesthesiologists (ASA) physical status classification system; ALB - albumin.

Based on the analysis, the proportions of data missing in all domains were judged to be acceptable for pair-wise deletion in further analyses. Imputation was not attempted. Smoking status was excluded as a risk factor in the analysis of the vascular cohort to maintain consistency in data analysis across both study cohorts.

3.4.1.2 Data quality in colorectal cancer cohort

The cohort of patients with colorectal cancer was described in detail in Methods (Section 2.5.2 on page 107). The dataset consisted of 715 observations and 52 variables.

Missing data were found in variables related to patients demographic data, BMI, height, and weigh, ASA classification factors, and smoking. The distribution of data missingness is shown in Figure 3.2.

The data points in BMI, height, and weight were missing in 65.4%, 70.2 %, and 69.9% of cases respectively. Two hundred and forty-nine data points related to ASA classification were missing (34.8%). The data points in smoking status was missing in 71.5% of cases. Variables with data missing in more 20% cases were not included in the analysis.

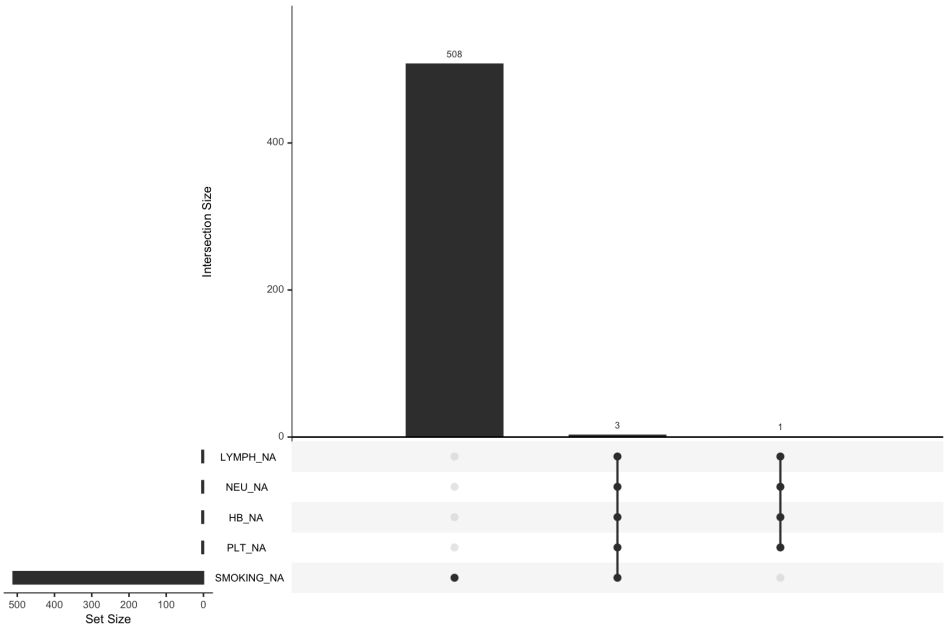


Figure 3.2 – The upset shows the intersections of missing values across different clinical and biological variables in the colorectal cancer cohort. The vertical bars represent the number of instances where there are missing data across various combinations of these variables.The categories that are included are related to the missing information for Lymph, smoking status, NEU - neutrophil; HB - haemoglobin; PLT - Platelets.

The level of data missingness related to smoking, height and weight prompted a decision to drop these variables from the analysis. Attempts were made to mitigate missingness in other domains but checking the data from multiple sources did not result in an increase in the number of complete records. Based on the analysis, the pattern of data missingness in all other domains was analysed and judged to be acceptable for pair-wise deletion in further analyses.

3.4.2 Cohort description

3.4.2.1 Patients with aortic aneurysms

A total of 110 patients with aortic aneurysms were analysed. The median age was 75 [71-80], and 90 patients (81.8%) were male. Demographic characteristics are summarised in Table 3.2.

Table 3.2 – Demographic characteristics of patients with aortic aneurysms. IQA - Interquartile range; IMD - Index of multiple deprivation.

Variable	Level	Total
Age at diagnosis	median [iqr]	75 [71, 80]
Sex	F	20 (18.2)
	M	90 (81.8)
IMD Quintile		
	1st	27 (25.5)
	2nd	19 (17.9)
	3rd	23 (21.7)
	4th	27 (25.5)
	5th	10 (9.4)

Detailed prevalence of comorbidities are presented in Table 3.3. Hypertension (HTN; 72.7%), chronic kidney disease (CKD; 37.3%), ischaemic heart disease (IHD; 35.5%), and chronic lung disease (CLD; 28.2%) were the most common comorbidities. Over a half of patients were multi-morbid (68.2%). Patients declared as current smokers in 25.9% of cases, ex-smokers in 58.3% and in

15.7% as non-smokers. Biochemical and haematological parameters are shown in Table 3.4.

Table 3.3 – The prevalence of comorbidities in patients with aortic aneurysms. PAOD - Peripheral arterial occlusive disease; COPD - Chronic obstructive pulmonary disease.

Variable	Level	Total
Ischaemic Heart Disease		39 (35.5)
Atrial Fibrillation		23 (20.9)
Heart Failure		4 (3.6)
Cerebrovascular event		9 (8.2)
Hypertension		80 (72.7)
PAOD		27 (24.5)
Diabetes		13 (11.8)
Dementia		10 (9.6)
Chronic Lung Disease		31 (28.2)
COPD		26 (23.6)
Chronic Kidney Disease		41 (37.3)
Multi-morbidity		75 (68.2)
Smoking Status	current smokers	28 (25.9)
	ex-smokers	63 (58.3)
	non-smokers	17 (15.7)

Table 3.4 – Biochemical and haematological profile of patients with aortic aneurysms.

Variable	Level	Total
Estimated glomerular filtration rate	median [iqr]	67 [52, 79]
Creatinine	median [iqr]	91 [79, 111]
Albumin	median [iqr]	38 [36, 40]
	missing	12
Haemoglobin	median [iqr]	138 [128, 148]

The median diameter of aortic aneurysms was 6.1cm [5.8-7.0] and was described as infrarenal in 25 patients (22.7%), juxtarenal in 52 (47.3%), and thoracoabdominal in 33 (30.0%) patients (Table 3.5).

Table 3.5 – Type of aneurysm in patients in vascular cohort. IQA - Interquartile range; AAA - Abdominal aortic aneurysm.

Variable	Level	Total
Abdominal aortic aneurysm (AAA)		
Infrarenal		25 (22.7)
Juxtarenal		52 (47.3)
Thoracoabdominal		33 (30.0)
AAA diameter	median [iqr]	6.1 [5.8, 7.0]

Following multi-modal, objective assessment eighty-four patients were deemed fit for surgery (76.4%). Sixty-two patients underwent surgery (56.4%), 17 (15.5%) did not, and 3 (2.7%) declined despite being deemed fit. Procedural characteristics and management are summarised in Table 3.6.

Table 3.6 – Procedural characteristics and management of patients with aortic aneurysms.

Variable	Level	Total
Fitness for surgery		
	Declined	3 (2.7)
	Unsuitable	2 (1.8)
	Not fit	26 (23.6)
	Fit	84 (76.4)
Procedural status		
	Surgery - No	17 (15.5)
	Surgery - Yes	62 (56.4)

3.4.2.2 Patients with colorectal cancer

A total of 715 patients with left-sided colorectal cancer were analysed. The median age was 69 years [61.5, 76.0] and 466 patients (65.2%) were male. Over 99% of patients were deemed fit for surgery (ASA I-III). Demographic characteristics are summarised in Table 3.7.

Table 3.7 – Demographic characteristics of patients with colorectal cancer. IQA - Interquartile range; IMD - Index of multiple deprivation; ASA - American Society of Anesthesiologists (ASA) physical status.

Variable	Level	Total
Age at diagnosis	median [iqr]	69 [61.5, 76.0]
Sex	F	249 (34.8)
	M	466 (65.2)
ASA		
	Grade I - Fit	112 (15.7)
	Grade II - Relevant disease	508 (71.0)
	Grade III - Restrictive disease	90 (12.6)
	Grade IV - Life threatening disease	5 (0.7)
IMD Quintile		
	1^{st}	173 (24.2)
	2^{nd}	124 (17.3)
	3^{rd}	123 (17.2)
	4^{th}	94 (13.1)
	5^{th}	201 (28.1)

The most prevalent co-morbidities were hypertension (HTN; 41.4%), chronic lung disease (CLD; 17.3%) and diabetes mellitus (DM; 15.0%). Patients smoking status was described as current smokers in 58.3% of cases, ex-smokers in 38.2%, and in 3.4% were described as non-smokers. Due to large missingness, this variable was removed from analysis. Biochemical and haematological profile are shown in Table 3.9.

Table 3.8 – The prevalence of comorbidities in patients with colorectal cancer. COPD - Chronic obstructive pulmonary disease

Variable	Level	Total
Ischaemic Heart Disease		17 (2.4)
Heart failure		10 (1.4)
Atrial fibrillation		69 (9.7)
Hypertension		296 (41.4)
Cerebrovascular event		34 (4.8)
Diabetes		107 (15.0)
Chronic Kidney Disease		64 (9.0)
COPD		50 (7.0)
Venous thromboembolism		53 (7.4)
Dementia		9 (1.3)
Asthma		65 (9.1)
Chronic lung disease		124 (17.3)
Smoking status		
	current smokers	119 (58.3)
	ex-smokers	78 (38.2)
	non-smokers	7 (3.4)
	missing	511

Table 3.9 – Biochemical and haematological profile of patients with colorectal cancer. sd - Standard deviation.

Variable	Level	Total
Creatinine	mean (sd)	78.5 (20.2)
	missing	4
Albumin	mean (sd)	38.2 (5.5)
	missing	4
White cell count	mean (sd)	8.2 (3.4)
	missing	4
Lymphocyte count	mean (sd)	1.7 (0.8)
	missing	4
Neutrophil count	mean (sd)	5.4 (2.6)
	missing	4
Haemoglobin	mean (sd)	132.1 (18.9)
	missing	4

The disease severity is demonstrated in Table 3.10. Tumours were located in the descending colon in 325 (45.5%) patients and in the rectum in 390 (54.5%) patients. One hundred and ninety patients (26.6%) undergoing surgery had the malignant disease classified as stage I, 184 (25.7%) as stage II, 295 (41.3%) as stage III, and 46 (6.4%) of patients as stage IV. The majority of patients had T3 tumours (397 patients, 55.5%), no lymph node involvement - N-0 (387 patients, 54.1%) and no detectable metastatic disease - M-0 (669 patients, 93.6%).

Table 3.10 – Disease profile in patients with colorectal cancer. TNM - (Tumor/Nodes/Metastasis) classification of malignant tumors including tumor site, lymph node involvement and distant metastatic spread (`https://www.uicc.org/resources/tnm`)

Variable	Level	Total
Site	Descending colon	325 (45.5)
	Rectum	390 (54.5)
Symptoms at presentation	0	115 (16.1)
	1	600 (83.9)
TNM (Tumour)	T1	40 (5.6)
	T2	199 (27.8)
	T3	397 (55.5)
	T4	62 (8.7)
	T4a	4 (0.6)
	T4b	1 (0.1)
	Tx	12 (1.7)
TNM (Nodes)	N0	387 (54.1)
	N1	259 (36.2)
	N2	69 (9.7)
TNM (Metastases)	M0	669 (93.6)
	M1	46 (6.4)
TNM Stage	1	190 (26.6)
	2	184 (25.7)
	3	295 (41.3)
	4	46 (6.4)

Surgery was performed as an elective procedure in 661 (92.4%) patients, while 54 (7.6%) required emergency surgery. All patients had a restorative procedure. Sigmoid Colectomy was performed in 33 patients (4.6%) and low anterior resection in 682 (95.4%). An intended open operation was performed

in 400 patients (55.9%) via a midline incision, a laparoscopic in 315 patients (44.1%); 51 patients (7.1%) had the laparoscopic procedure converted to open. A temporary defunctioning loop ileostomy was required in 229 patients (32%). Rectal cancer in male patients who had neoadjuvant radiotherapy and patients who had emergency resection were the main reasons for performance of defunctioning ileostomy. Procedural characteristics and management are summarised in Table 3.11.

Table 3.11 – Procedural characteristics and management of patients with colorectal cancer.

Variable	Level	Total
Emergency status	Emergency	54 (7.6)
	Elective	661 (92.4)
Procedure	Anterior Resection	682 (95.4)
	Sigmoid Colectomy	33 (4.6)
Surgical Approach	Open	400 (55.9)
	Laparoscopic	315 (43.9)
Conversion to open	No	400 (55.9)
	Primary Laparoscopic	264 (36.9)
	Laparoscopic converted to open	51 (7.1)
Procedural stoma	Colostomy temporary	11 (1.5)
	Ileostomy permanent	35 (4.9)
	Ileostomy temporary	229 (32.0)
	No stoma	440 (61.5)

3.4.3 Incidence of PPC

3.4.3.1 PPC in patients with aortic aneurysms

PPC within 30 days of surgery occurred in 15 patients (24.2%) (Table 3.12). Atelectasis was the most common complication, developing in 6 patients, followed by pneumonia in 4 patients.

Table 3.12 – Incidence of PPC in patients with aortic aneurysms. ARDS - Adult Respiratory Distress Syndrome; PPC - Postoperative pulmonary complications.

Variable	Total n (%)
PPC	15 (24.2)
Type of the PPC	
Pneumonia	4 (26.7)
Atelectasis	6 (40.0)
Aspiration pneumonia	1 (6.7)
Respiratory tract infection (not pneumonia)	1 (6.7)
Pneumonia	2 (13.3)
Pneumonia and atelectasis	1 (6.7)

3.4.3.2 PPC in patients with colorectal cancer

Postoperative pulmonary complications within 30 days of surgery occurred in 66 patients (9.2%) (Table 3.13). Pneumonia was the most common complication, developing in 50 patients (6.9%), followed by atelectasis in 6 patients (0.8%).

Table 3.13 – Incidence of postoperative pulmonary complications in patients with colorectal cancer. PPC - Postoperative pulmonary complications

Variable	Total
PPC	66 (9.2)
Type of the PPC	
Pneumonia	50 (75.8)
Atelectasis	6 (9.1)
Respiratory failure	2 (3.0)
Pleural effusion	3 (4.5)
Pneumothorax	1 (1.5)
Respiratory tract infection (not pneumonia)	2 (3.0)
Acute respiratory distress syndrome	2 (3.0)

3.4.4 Demographic and clinical factors associated with PPC

3.4.4.1 Factors associated with PPC in patients with aortic aneurysms

Univariable analysis showed that only presence of peripheral arterial disease had a statistically significant association with the development of PPC (Table 3.14). Age was also associated with the development of PPC, but it not reached statistical difference (77 [72.5, 82.0] v. 74 [68, 77], p=0.752).

Multivariable analysis with automated selection of variables using stepwise regression identified presence of PAOD and haemoglobin levels as predictors of PPC. However, only PAOD was independently associated with the development of PPC (Table 3.14). The final model had c-statistic of 0.775 (Figure 3.3).

Table 3.14 – Univariable and multivariable analysis of risk factors influencing the development of PPC in patients with aortic aneurysms. PPC - Postoperative pulmonary complications; PAOD - Peripheral arterial occlusive disease; Hb - Haemoglobin; CI - Confidence interval; Ref - Reference.

Variable	Units	Univariate p-value	Odds Ratio	95% CI	p-value
PAOD	No	Ref	-		
	Yes	0.046806	4.53	1.08–18.94	0.038
Hb	g/L	0.191176	0.95	0.90–1.01	0.103

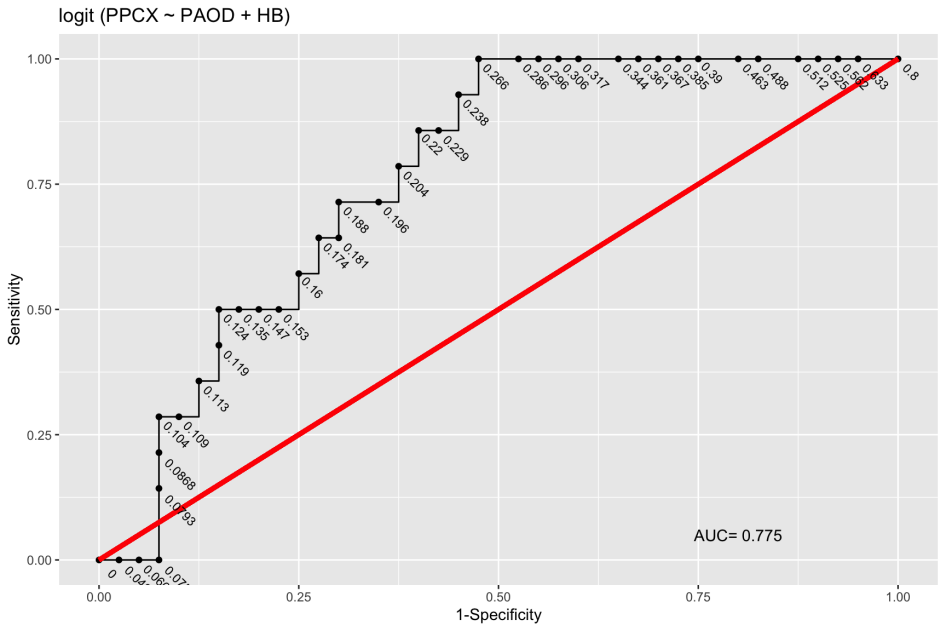


Figure 3.3 – A receiver operating characteristic (ROC) and area under the curve (AUC) analysis demonstrating the diagnostic performance of the final multivariable risk factor logistic regression model to predict the PPC in patients with aortic aneurysms. PPC - Postoperative pulmonary complications; PAOD - Peripheral arterial occlusive disease; Hb - Haemoglobin.

3.4.4.2 Factors associated with PPC in patients with colorectal cancer

Age at diagnosis, sex, ASA grade, NTNM tumour classification and stage (TNM.STAGE), surgical approach, conversion of laparoscopic procedure to open, stoma formation, complications categorised using CD (CD.ALL, CD.MAJOR.MINOR.NONE), CCF, AF, CKD, COPD, Dementia, Asthma,

CLD, preoperative albumin levels, WCC, Hb, and anastomotic leak were significantly associated with development of PPC on univariable analysis.

Based on clinical experience and close relationship between variables we removed some variables so the multivariable model included COPD, CLD, Dementia, surgical approach, asthma, WCC, HB, AF, stoma formation, conversion to open, NTNM grade, age, albumin levels, sex and CCF (Table 3.5).

Table 3.15 – Univariable and multivariable analysis of risk factors associated with development of PPC in patients with colorectal cancer. PPC - Postoperative pulmonary complications; ASA - American Society of Anesthesiologists (ASA) physical status; AF - Atrial fibrillation; CCF - Congestive heart failure; CLD - Chronic lung diseases; COPD - Chronic obstructive pulmonary disease; WCC - White cell count; NTNM - Number of nearby lymph nodes that contain cancer according TNM system; CI - Confidence interval; Ref - Reference.

Variable	Units	Univariate p-value	Odds Ratio	95% CI	p-value
Age at diagnosis		0.044	1.01	0.98–1.04	0.524
Sex	Female		Ref		
	Male	0.077	1.78	0.91–3.48	0.090
ASA	I		Ref		
	II		2.01	0.67–6.05	0.212
	III		2.00	0.55–7.25	0.289
	IV	0.001	2.12	0.14–33.26	0.591
AF		0.022	2.13	0.97–4.66	0.059
CCF		0.083	2.24	0.43–11.73	0.341
CLD			9.52	5.17-17.54	<0.001
COPD		<0.001	1.27	0.63–2.58	0.500
Asthma		0.016	4.77	2.31–9.84	< 0.001
Dementia		<0.001	14.31	3.29–70.13	<0.001
NTNM	N0		Ref		
	N1		1.97	1.03-3.78	0.041
	N2	0.016	4.83	2.00-11.68	<0.001
Open surgery		0.003	1.49	0.83–2.67	0.184
Stoma	Ref		Ref		
	2		1.13	0.60–2.11	0.714
	3		2.45	0.90–6.65	0.078
	4	0.003	0.67	0.08–5.29	0.704
WCC		0.003	1.06	1.00–1.13	0.053
Haemoglobin		<0.01	0.99	0.98–1.01	0.304
Albumin		0.039	0.97	0.92–1.03	0.352

The multivariable logistic regression demonstrated that CLD (OR 9.52, 95%CI 5.17-17.54, p<0.001), NTNM ($OR_{(N1)}$ 1.97, 95%CI 1.03-3.78, p=0.041; $OR_{(N2)}$ 4.83, 95%CI 2.00-11.68, p<0.001), Dementia (OR 22.74, 95%CI 4.60-112.47, p<0.001), AF (OR 2.24, 95%CI 1.05-4.78, p=0.037), WCC (OR 1.07, 95%CI 1.01-1.14, p=0.021), sex (OR 2.11, 95%CI 1.10-4.06, p=0.025), but not Hb (OR 0.99, 95%CI 0.97-1.00, p=0.095) and surgical approach (OR 1.58, 95%CI 0.88-2.84, p=0.123) were independently associated with development of PPC (Table 3.15 and Figure 3.4). The c-statistic of 0.824 for this model indicated good discriminatory performance (Figure 3.5).

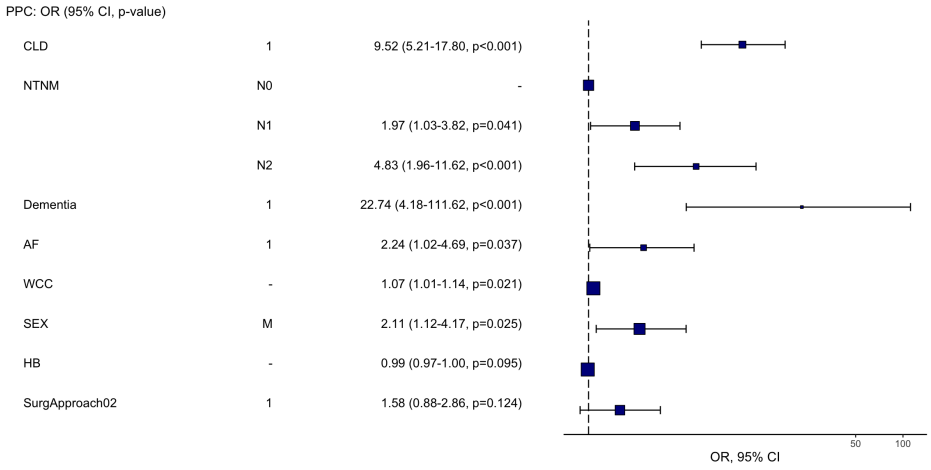


Figure 3.4 – A forest plot demonstrating the multivariable analysis of risk factors associated with PPC in patients with colorectal cancer. PPC – Postoperative pulmonary complication; CLD – Chronic lung diseases; NTNM - Number of nearby lymph nodes that contain cancer according TNM; AF - Atrial fibrillation; WCC - White cell count; Hb - Haemoglobin; OR - Odds Ratio; CI - Confidence interval.

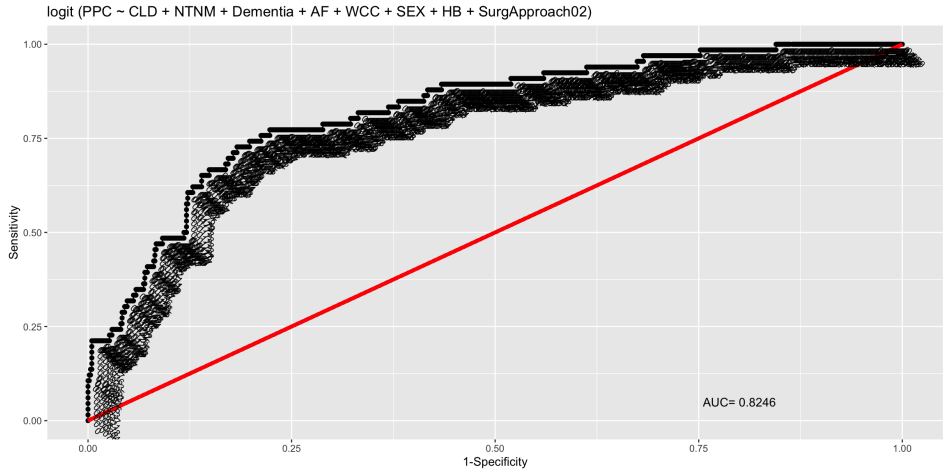


Figure 3.5 – The analysis of the receiver operating characteristic (ROC) and area under the curve (AUC) demonstrates the diagnostic performance of the final multivariable risk factors logistic regression model to predict the PPC in patients with colorectal cancer. PPC - Postoperative pulmonary complications; CLD – Chronic lung diseases; NTNM - Number of nearby lymph nodes that contain cancer according TNM; AF - Atrial fibrillation; WCC - White cell count; Hb - Haemoglobin.

3.4.5 Association of PPC with 30-days mortality

3.4.5.1 Vascular cohort

The overall 30-day mortality was 3.2% (2/62 patients; Table 3.16). PPC (pneumonia) was the sole cause of death for both patients.

Table 3.16 – Association of PPC with 30-day postoperative mortality in patients following aortic aneurysms surgery. PPC - Postoperative pulmonary complications.

Variable	Total (n= 62), n (%)	PPC (n= 15), n
Perioperative 30-day Mortality	2 (3.2)	2
Causes of 30-day Mortality		
Pneumonia leading to respiratory failure	2	2

3.4.5.2 Colorectal cancer cohort

The overall 30-day mortality was 0.6% (4/715 patients; Table 3.17). PC was associated with higher rates of 30-day mortality (4.5% with PPC vs. 0.2% no PPC; OR=30.86; 95% CI 3.16–301.05, p<.001; Table 3). The cause of death was: pneumonia leading to respiratory failure in 2 patients, acute respiratory distress syndrome with hospital-acquired pneumonia in 1 patient and cardiac arrest. (Table 3.17).

Table 3.17 – Association of PPC with 30-day postoperative mortality in patients following colorectal cancer surgery. PPC - Postoperative pulmonary complications.

Variable	Total (n= 715), n (%)	PPC (n= 66), n (%)
Perioperative 30-day Mortality	4 (0.6)	3 (4.5)
Causes of 30-day Mortality		
Pneumonia leading to respiratory failure	2 (0.3)	2 (3.0)
Acute respiratory distress syndrome (ARDS) with pneumonia	1 (0.1)	1 (1.5)
Cardiac arrest (with respiratory failure)	1 (0.1)	

3.4.6 Overall Survival

3.4.6.1 Survival of patients in patients with aortic aneurysms

The median observed follow-up was 13.5 months [IQR 9.3–15.5]. During the follow-up 6 patients died (9.7%).

The overall estimated survival at 1 year was 90.1% (95%CI 82.8–98.0); Figure 3.6).

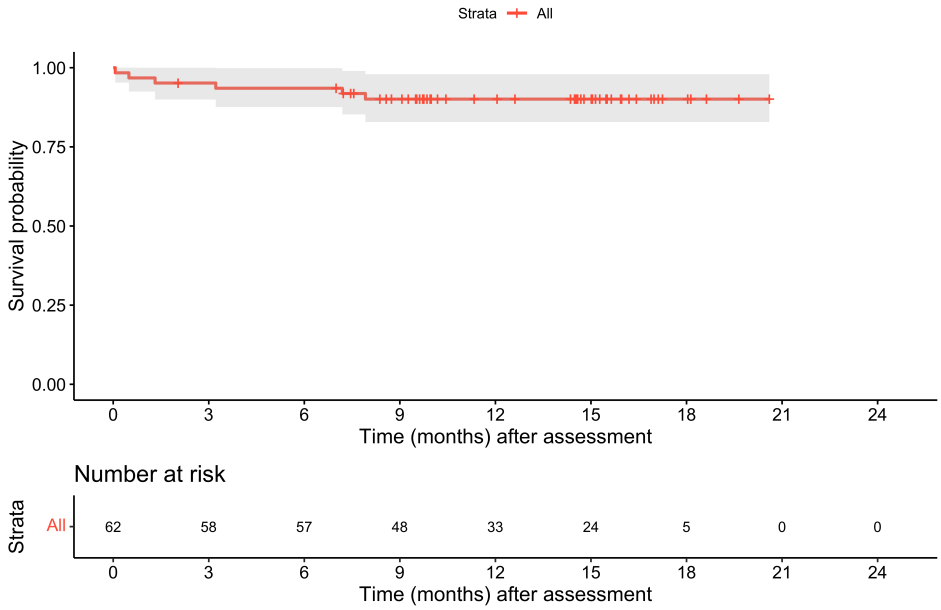


Figure 3.6 – Kaplan-Maier curve representing survival rate of patients after aortic aneurysms surgery.

The multivariable Cox proportional hazard model using step regression identified aneurysm diameter as independent risk factors associated with survival (HR_{AAADIA}=2.05, 95%CI 1.20–3.53, p=0.009; Figure 3.7).

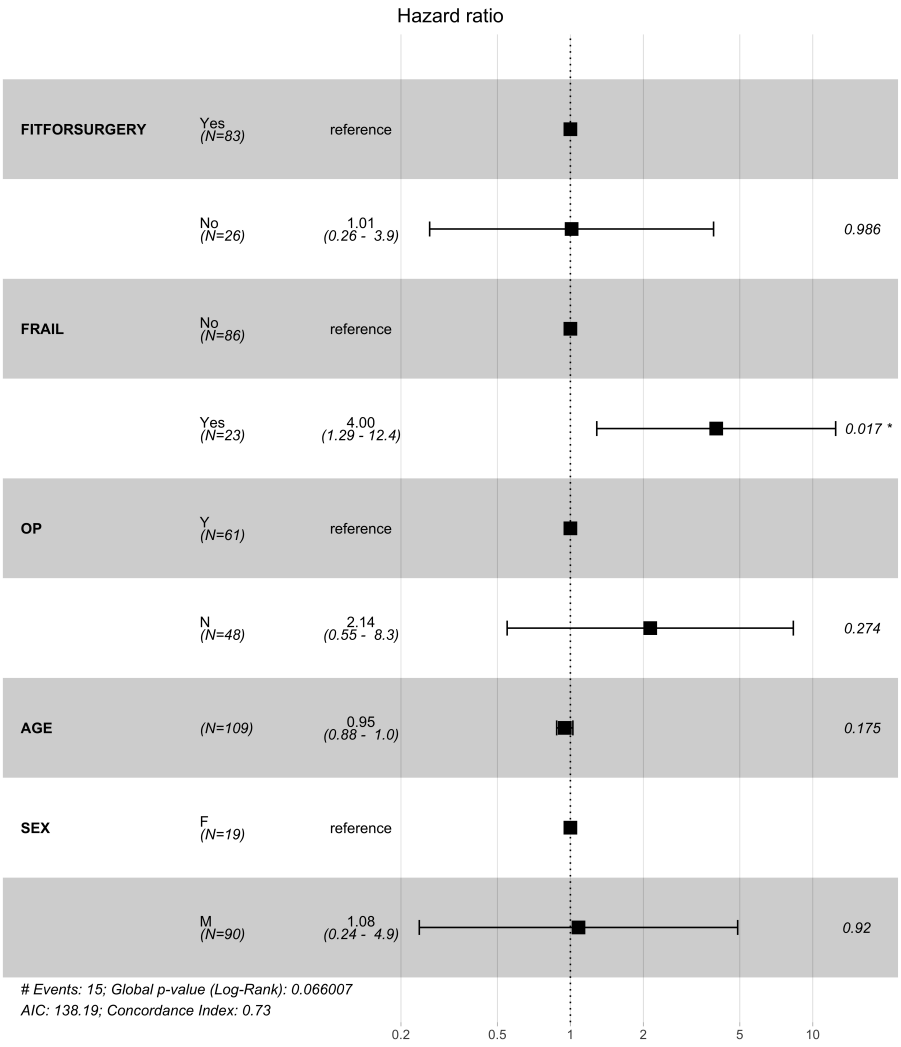


Figure 3.7 – A forest plot demonstrating the results of a stepwise logistic regression analysis for a Cox proportional hazard model of the association between clinical patient-related factors and survival of patients after aortic aneurysms surgery. OP - Operation; AIC - Akaike information criterion.

3.4.6.2 Survival of patients in colorectal cancer cohort

The median observed follow-up was 47.9 months [IQR 26.6–69.4]. During the follow-up 146 patients died (20.4%). The overall survival at 1, 3 and 5 years were 98.0% (95%CI 96.7–98.8), 87.0% (95%CI 84.1–89.4) and 76.8% (95%CI 72.8–80.2; Figure 3.8).

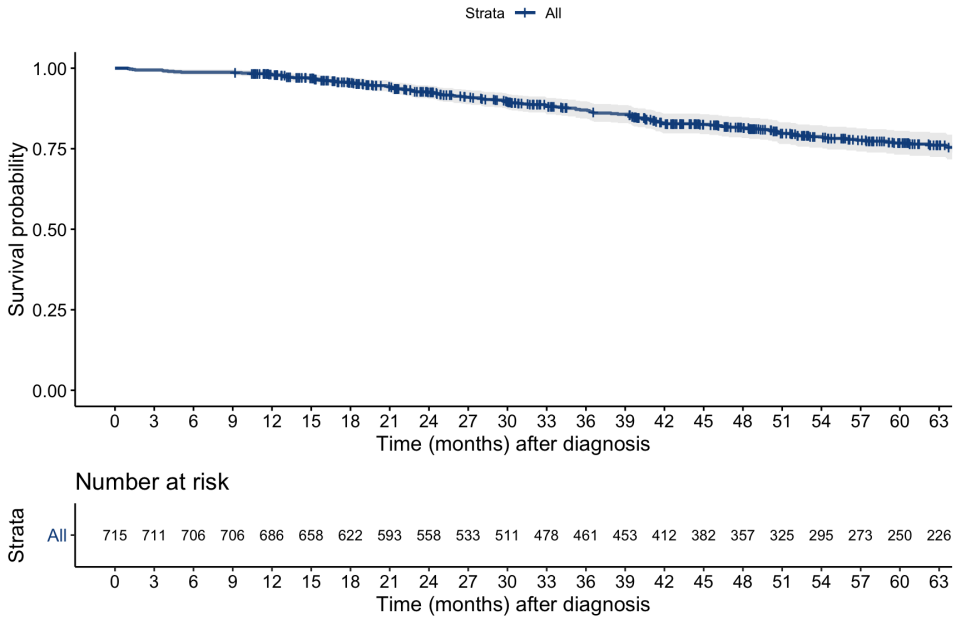


Figure 3.8 – Kaplan-Maier curve representing survival of patients after colorectal cancer surgery

The Cox proportional hazard model identified age at diagnosis (OR_{Year} 1.04, 95%CI 1.02–1.06, p<0.001), development of PPC (OR 1.80, 95%CI 1.11–2.92, p=0.017), presence of major complications ($OR_{CD\ major}$ 1.83, 95%CI 1.15;2.91, p<0.010) and metastatic disease ($HR_{(M+)}$ 4.97, 95%CI 3.23–7.65, p<0.001) as independent risk factors associated with survival (Figure 3.9).

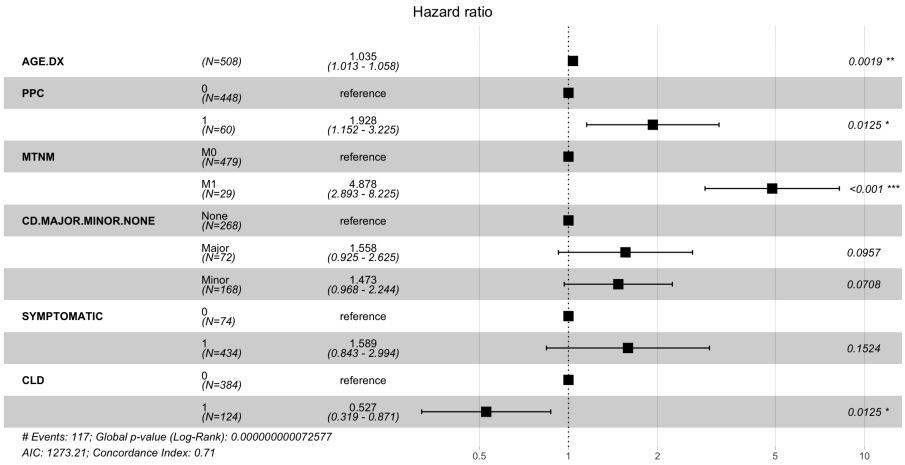


Figure 3.9 – A forest plot demonstrating the results of a stepwise logistic regression analysis for a Cox proportional hazard model of the association between clinical patient-related factors and survival of patients with colorectal cancer. PPC - postoperative pulmonary complications; MTNM – presence of metastatic disease that contain cancer according TNM; AIC - Akaike information criterion; CD.Major.Minor.None - Classify the complication using the Clavien Dindo complication classification system; CLD - Chronic lung diseases..

3.4.7 Association of PPC with survival

3.4.7.1 Vascular cohort

The median follow-up of patients who did not develop PPC was 12.6 months [IQR 9.5–16.1], and for those who developed PPC it was 14.4 months [IQR 8.0–15.1].

Kaplan-Meier estimates for 1 year survival were 93.4% (95%CI 86.4–100) in patients who did not develop PPC, compared with 79.4% (95%CI 61.2–100) for those who experienced PPC ($HR_{(PPC+)}$=3.49, 95%CI 0.70–17.29, p=0.126; Figure 3.10). PPC was not independently associated with survival.

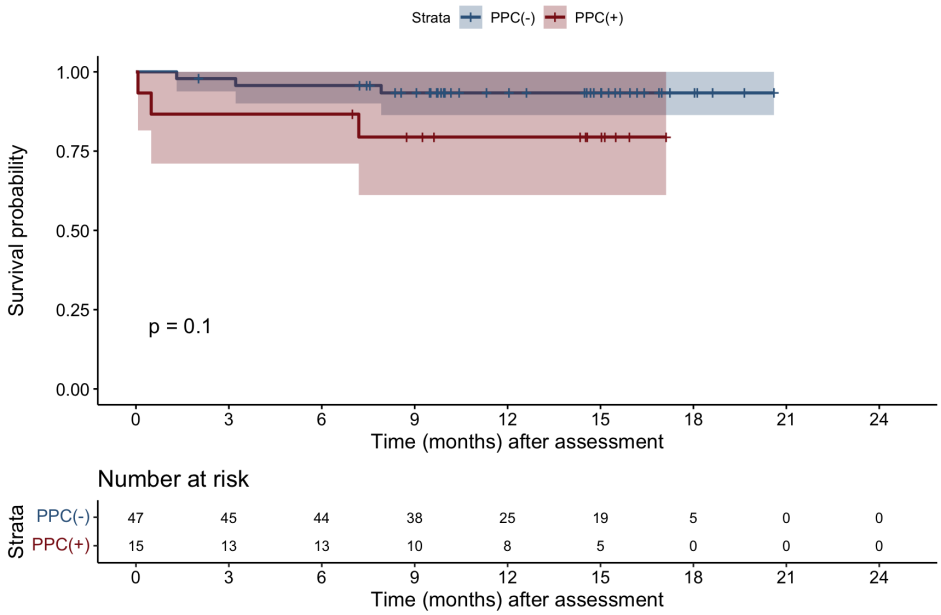


Figure 3.10 – Kaplan-Maier curves representing survival of patients after aneurysm repair who developed (PPC(+)) and did not develop (PPC(-)) post-operative pulmonary complications. PPC - Post-operative pulmonary complications.

3.4.7.2 Colorectal cancer cohort

The median follow-up of patients who did not experience PPC was 48.7 months [IQR 28.0–69.6]. For those who did experience PPC the median follow-up was 40.1 months [IQR 21.4–62.7].

Kaplan-Meier estimates for 1, 3 and 5-year survival were 98.3% (95%CI 96.9–99.1), 88.0% (95%CI 85.1–90.5) and 79.0% (95%CI 75.0–82.4) in patients who did not develop PPC, compared with 95.5% (95%CI 86.6–98.5), 76.0% (95%CI 62.0–85.4) and 54.3% (95%CI 38.5–67.6) for those who experienced PPC ($HR_{(PPC+)}$=2.18, 95%CI 1.40–3.40, p<0.001; Figure 3.11).

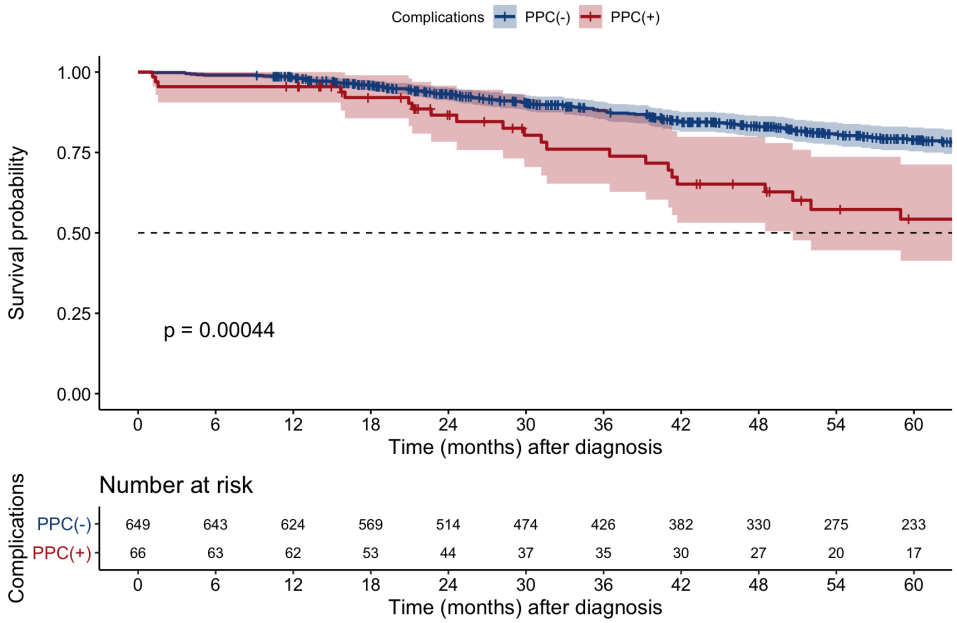


Figure 3.11 – Kaplan-Maier curves representing survival of patients after colorectal cancer who developed (PPC(+)) and did not develop (PPC(-)) post-operative pulmonary complications. PPC - Postoperative pulmonary complications.

3.4.8 Cohort comparison

Association of demographic and clinical factors with PPC rates was considered in context of differences in these factors between the two analysed cohorts. Patients in the vascular cohort were significantly older, predominantly male, with statistically greater burden of cardiovascular, respiratory and renal disease. (Table 3.18).

Table 3.18 – Comparison of demographics and comorbidities between vascular and colorectal cohorts. PAOD-Peripheral arterial occlusive disease; COPD-Chronic obstructive pulmonary disease

Condition	CRC (715)	AAA (110)	p-value
Age	69 [61.5, 76.0]	75 [71, 80]	<0.001
Sex (Male)	466 (65.2)	90 (81.8)	<0.001
Ischaemic Heart Disease	17 (2.4%)	39 (35.5%)	<0.001
Heart Failure	10 (1.4%)	4 (3.6%)	0.195
Atrial Fibrillation	69 (9.7%)	23 (20.9%)	<0.001
Hypertension	296 (41.4%)	80 (72.7%)	<0.001
Cerebrovascular Event	34 (4.8%)	9 (8.2%)	0.132
Diabetes	107 (15.0%)	13 (11.8%)	0.383
Dementia	9 (1.3%)	10 (9.6%)	<0.001
Chronic Kidney Disease	64 (9.0%)	41 (37.3%)	<0.001
COPD	50 (7.0%)	26 (23.6%)	<0.001
Chronic Lung Disease	124 (17.3%)	31 (28.2%)	0.007
Asthma	65 (9.1%)	-	-
Venous Thromboembolism	53 (7.4%)	-	-
PAOD	-	27 (24.5%)	-

The PPC rate in the colorectal cohort was significantly lower than in the vascular cohort (9.2% v. 24.2%; OR 0.32, 95%CI 0.17–0.60, p<0.001).

Due to major differences in baseline demographic and clinical parameters, as well as in the duration of follow-up, it is difficult to perform in-depth comparison of these two cohorts. We therefore did not attempt to proceed with this in this present study. This analysis will form a basis for future studies described in final chapter of this thesis.

3.5 Discussion

The main aims of the analysis presented in current study were: 1) to determine the incidence of PPC after vascular and colorectal procedures, 2) to identify the risk factors that influence the development of PPC, and 3) to establish any association between PPC and survival. The results obtained have highlighted the important implications of PPC which arise within the setting of these surgical specialties.

A significant incidence of PPC was documented in the population included in the study (24.2% for the vascular cohort and 9.2% for colorectal cohort). It confirmed that PPC occur commonly and are of clinical importance in terms of prognosis. Implications of PPC encompass worse mortality, particularly following colorectal cancer procedure for malignancy. In these patients, PPC have a marked negative impact on short, mid-and long-term survival. An interesting observation from the results was the relationship between the onset of PPC, and PAOD, presence of dementia or pre-existing chronic pulmonary pathology.

The majority of previous studies evaluated the incidence and effects of PPC in individuals undergoing general surgical (abdominal) operations (Khuri et al., 2005; Fernandez-Bustamante et al., 2017). Only few studies have looked at those undergoing colorectal procedures for malignancy or vascular surgery (Genovese et al., 2017; Jurt et al., 2018; Abd El Aziz et al., 2020). Patients who are scheduled for these procedures tend to have specific characteristics, frequently being in the older section of the population and being multi-morbid. Additionally, the operations that are being undertaken are frequently more complex.

The overall frequency of PPC within the group of patients who had a repair of an aortic aneurysm performed was 24.2% in the present study; this was greater than that documented by Genovese (2017) in individuals requiring major vascular interventions. It has been observed that open abdominal surgery is associated with the highest complication rate. However, in present study a vast majority of procedures were minimally invasive (EVAR/FBEVAR/TEVAR).

Both, Genovese et al. (2017) and Pasin et al. (2017) reported PPC incidences of 18% and 10.3%, respectively, following open abdominal procedures. Genovese et al. (2017) noted that the respective equivalent figures were 10% and 3% for patients undergoing endovascular procedures in thoracic or abdominal aorta.

Unexpectedly, the data from this current study have demonstrated an increased frequency of PPC in individuals in whom complex endovascular procedures have been carried out. This is in contrast to figures published in a 2017 systematic review and meta-analysis which evaluated patients undergoing an open abdominal approach to aortic surgery (Pasin et al., 2017). This finding may reflect the different types of operations performed, variety in patient-related factors and the complicated nature of the procedures. It is argued that development of PPC is related to inflammatory reaction after surgery. Two-thirds of patients in present study presented with juxtarenal or thoracoabdominal aneurysms. These carry an extremely high burden of atherosclerotic disease. Disruption of this atherosclerotic load during surgery can lead to increased inflammatory response, which in turn can lead to development of cardiovascular as well as respiratory complications.

The overall frequency of PPC for colorectal patients (9.2%) was in keeping with an earlier large observational study (Jurt et al., 2018). However, it was significantly lower than that seen in a large population of patients in the US undergoing operative interventions on the small and large bowel (Fleisher and Linde-Zwirble, 2014), and in older Italian patients in whom surgery was performed for rectal cancer (19.0% and 13.1%) (Milone et al., 2017). When compared with minimally invasive procedures on the colorectal surgery, in which an incidence of 1.3% PPC was noted, the PCC rate in this study is notably higher (Abd El Aziz et al., 2020). These variations in PPC occurrence are likely to reflect discrepancies in the way in which PPC are defined, together with additional, most likely patient-related factors and the type of surgery performed. It is worth mentioning that compared with the vascular cohort, colorectal patients were generally fitter - prevalence of cardiovascular, respiratory and renal disease was significantly lower (Table 3.18). This was

also reflected by a greater proportion of patients who were categorised as either ASA class I or II.

In the current study, a range of preoperative patient-related risk factors associated with the risk of PPC in patients undergoing vascular and colorectal cancer were identified. PAOD proved to be related to PCC, which is contrary to the outcomes of previous studies (Arozullah et al., 2001; Johnson et al., 2007; Genovese et al., 2017). This factor was expected and emphasises the close relationship between inflammatory reactions and atherosclerosis, increasing the risk of vascular patients developing the PPC following the surgery. Therefore, patients with PAOD disorder are likely to have atherosclerotic disease, which results in an increased inflammatory response and lead to development of PPC.

On the other hand, dementia, pre-existing chronic lung disease, and malignant spread to the lymph nodes were the most important risk factors associated with the risk of PPC in patients undergoing colorectal cancer. These factors were associated with a large effect size (OR between 4 and 22) increasing the likelihood of PPC. These variables have not been documented in earlier research, but are in keeping with the complicated way in which clinical patient characteristics can influence the endpoints of surgery. Although these observations are of importance, they are not completely unexpected given the nature of the patients in this group, which encompassed the elderly, and those with late-stage bowel tumours, factors which are intuitively considered to heighten the risk of PPC.

A number of studies have observed that more elderly patients with large colorectal disease frequently have concomitant lung conditions, e.g. COPD or pre-existing lung condition and go on to have complications following surgery (Alves et al., 2005; Al-Refaie et al., 2011; Dekker et al., 2012; Abd El Aziz et al., 2020). In such cases, the pre-existing lung disease means that pulmonary function is impaired, and expansion and clearance of the lung compromised, factors that encourage the development of PPC.

Dementia is associated with cognitive and functional decline (Owens et al., 2020), and so it is likely to lead to difficulties in patients recovering their mobility, reduced compliance with respiratory physiotherapy, and challenges in post-

operative airway maintenance. All these issues may promote the likelihood of PPC in such individuals.

Patients with established malignancy, especially where there is tumour spread to the lymph nodes, may have undergone a deterioration in their general health and demonstrate an impaired ability to function normally. Positive lymph node findings in malignancy are of especial import as they may indicate a cancer that is more aggressive and which therefore requires more radical and complex operative interventions, which are likely to heighten the risk of PPC. This aspect has not been researched in detail and so additional studies are merited in order to determine the way in which lymph node spread impacts the risk of PPC.

Although in the present study, the sample size was relatively low, no relationship between the onset of PPC and mortality during the hospital stay was recognised in patients receiving vascular interventions. However, this has been noted to be linked in larger patient cohorts (Genovese et al., 2017). In addition to sample size, differences in the findings may relate to variations in the characteristics of the included patients and operative methods used, and highlight the requisite for additional studies to delineate the complicated associations between PPC and clinical endpoints following vascular procedures.

In the patients who acquired PPC following colorectal surgery, the consequences were serious. These individuals demonstrated a rise in in-patient mortality. Abd El Aziz et al. (2020) studied a cohort of patients with colorectal tumours following minimally invasive procedures. Of the 94 patients who had PPC, 14.8% died in hospital; there were no deaths in the cohort, which numbered 118, without PCC. Fleisher and Linde-Zwirble (2014) carried an large observational study on 45,969 patients who had been subject to major surgery on the small and large bowel. A PPC rate of 19.0% (8,744) was associated with an in-hospital mortality rate of 11.9%. These patients represented 63.6% of all in-patient mortality.

As can be seen from the literature review, this research is the initial large multicentre investigation which has evaluated potential relationships between PPC and survival, both in the mid- and long-term. The analysis of the survival

data, however, is not in keeping with earlier reports, in that the onset of PPC in patients undergoing vascular procedures was not associated with survival (Khuri et al., 2005).

When patients with and without PPC were compared within the group which underwent colorectal procedures, overall survival rates at 1, 3 and 5 years were 95.5% vs. 98.3%, 76.0% vs. 88.0%, and 54.3% vs. 79.0%, respectively. The multi-variable analysis demonstrated that individuals presenting with PPC had a lower life expectancy than those who had not developed PPC. The effect that PPC has on survival was demonstrated by the Kaplan-Meier survival curves. In the five years of follow-up after surgery, the patients who had suffered PPC were seen to have a higher mortality rate. These statistics are similar to those published for additional studies on colorectal cancer surgery for malignancy, which have demonstrated that various forms of postoperative complications including different type of PPC were linked with a higher death rate. The latter were therefore deemed an independent risk factor for decreased overall survival (Khuri et al., 2005; Beck et al., 2020).

Interestingly, inspection of survival curves for both cohorts shows similar patterns in the first 24 months following surgery (Figure 3.12). This would indicate that the follow-up period in the vascular cohort was too short to see late differences as seen in the colorectal cohort.

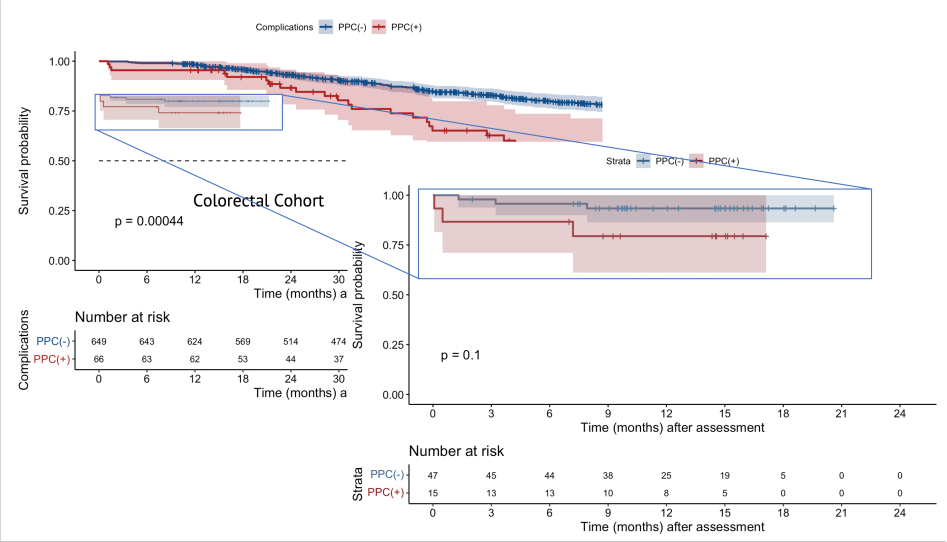


Figure 3.12 – Survival curves for colorectal and vascular cohorts. The scaled down survival curve for vascular cohort superimposed on the graph with colorectal cohort demonstrates difference in follow-up and a similar pattern for survival during the same period. PPC - Postoperative pulmonary complications

Limitations of the current study include its retrospective nature, which may have led to potential misclassification, the failure to incorporate pertinent variables arising from their lack of documentation, and the likelihood that a significant percentage of the data were not available. In an endeavour to counter these issues, multivariate analyses incorporating all characteristics of the patients were conducted in order to account for potential confounding effects of the remaining variables. Furthermore, a precise and strict PPC definition was employed, and two investigators scrutinised all the data, which were acquired from a number of sources independently. The external validity may have been impacted by the fact that patients undergoing left-sided colonic procedures for malignancy were incorporated in the studied population. Earlier studies have indicated that complications are more often seen in this cohort than in patients undergoing right-sided colonic surgery (Hinojosa et al., 2007; Mik et al., 2017). Consequently, a standardised definition to guide the evaluation of PPC in the former group is required. It is also essential to determine the sequelae of PPC by ensuring that these patients are monitored long-term. Furthermore, the vascular patients studied, which were undergoing aortic aneurysm repair, may not reflect all patients with this diagnosis, as they were in relatively good

health (fit for surgery) despite high burden of comorbidities. Smoking status was excluded from the analysis. A degree of selection and information bias may have been present, and so it may be difficult to generalise the findings described and the conclusions drawn to alternative populations, both within the UK and further afield.

3.6 Conclusions

Although this research may be subject to the above limitations, it still offers critical insights into the incidence and implications of PPC in patients undergoing either colorectal resection or aortic procedures. The findings illustrate the ongoing challenge created by PPC, as they formed the principal aetiology underpinning mortality following surgery, and notably impacted survival in both the mid- and long-term following left-sided colorectal procedures. There was no link between PPC and mortality in people who had endovascular surgery. However, the sample size was very modest, the follow-up short and any conclusions would have to be interpreted with caution.

It was evident that the likelihood of PPC is markedly influenced by the presence of pre-existing lung pathologies, which should be noted to be a triggering factor. It is essential to assess pulmonary function prior to surgery in order to recognise those patients who are likely to be at risk of PPC. These patients can then undergo initiatives designed to optimise their respiratory function and consequently, to enhance their physical capabilities and functional status. In order to study these links and to design efficacious prophylactic interventions, larger prospective studies should be undertaken.

Chapter 4

Association of lung morphology with postoperative pulmonary complications, and survival

4.1 Introduction

Although a considerable progress has been made in surgical techniques and perioperative care, the incidence of PPC is still disappointingly high (Pasin et al., 2017; Jurt et al., 2018; Semmelmann et al., 2023). Several previous studies tried to identify factors associated with PPC, and to generate models which can predict the likelihood of PPC in different patient cohorts undergoing surgery (Abd El Aziz et al., 2020; Jensen et al., 2023; Kokotovic et al., 2022). Despite these efforts, the incidence of PPC remains between 33% and 80%, especially after surgery involving the thorax and abdomen (Fernandez-Bustamante et al., 2017; Jensen et al., 2023). The clinical importance of PPC is reflected by their association with mortality following surgery (Pasin et al., 2017; Semmelmann et al., 2023).

Conventionally, the risk of PPC has been evaluated using measurements obtained by spirometry. However, several researchers have demonstrated that such parameters fail to predict the risk of PPC in the context of thoracic or abdominal procedures, and do not add any further information to pre-operative clinical risk profile (Huh et al., 2013; Oh et al., 2018; Choi et al., 2022; Mitsuda et al., 2022). Thus, in this setting, employing spirometry as a screening tool in preoperative assessment has not been recommended by NICE in guidelines on preoperative assessment from 2016 (O'Neill et al., 2016).

Limitations of spirometry include poor inspiratory and expiratory effort by the patient, especially where pulmonary pathologies, such as COPD, severe emphysema or other pulmonary issues, are present(Cheng et al., 2019c; Cheng et al., 2019b).

Previous studies have shown that CPET can play a role in predicting PPC, however, its predictive value has not been proven in high-quality studies (Forshaw et al., 2008; Prentis et al., 2012; Nikolopoulos et al., 2015; Stubbs, Grimes and Ercole, 2020; Brat et al., 2023). Furthermore, the application of CPET in evaluating lung abnormalities in a clinical context remains under-explored, contributing to uncertainty about its potential significant role until further extensive research are conducted.

Considering abdominal surgery, history of lung disease has been documented to be a significant risk factor for PPC (Smith et al., 2010; Abd El Aziz et al., 2020). It is therefore essential that a comprehensive assessment of the patient's lung condition and function is undertaken prior to any planned surgery, and that the results are made available to both the anaesthetist and surgeon to facilitate decision making process and informed consent.

In recent years, CT has emerged as a contemporary technique for assessment of lung morphology. This non-invasive imaging modality offers a method with which to obtain detailed data in relation to pulmonary structure and disease, and can be used for both diagnosis and patient surveillance (Barros et al., 2022b; Barros et al., 2022a). Quantitative CT (QCT) provides additional objective information which can be used to facilitate preoperative assessment, enabling normal and diseased parenchymal pulmonary tissue to be segmented measured and assessed in detail (Podolanczuk et al., 2016; Kitazawa et al., 2021; Barros et al., 2022b; Barros et al., 2022a). Specifically, the loss of the lung parenchyma can be estimated, as this is a pathognomonic sign of emphysematous disease (Kitazawa et al., 2021), as well as other pulmonary conditions (Podolanczuk et al., 2016).

A dedicated, specialist software is required for pulmonary QCT analysis. This facilitates the processing of CT images, and requires the use of lung densitometry threshold analysis, defined by HU, to measure the pulmonary

parenchymal volume and percentage which exhibits a normal lung attenuation area (NAA) index (Barros et al., 2022b; Barros et al., 2022a). The NAA is expressed as the ratio of lung volume exhibiting a density between -950 HU and -700 HU to the total lung volume (Shin et al., 2011; Barros et al., 2022b; Barros et al., 2022a). Areas of low attenuation (LAA), i.e. < -950 HU can additionally be identified using QCT; these also signify the presence of emphysematous change (Gevenois et al., 1995). Further QCT parameters that can be acquired include those indicative of distribution of lung attenuation, e.g. the proportion of high attenuation areas (HAA). A range of cut-off values have been applied for the recognition of interstitial pulmonary disease; attenuation levels > -750 HU or > -600 HU are characteristic of this process (Kauczor et al., 2000; Shin et al., 2011; Podolanczuk et al., 2016). However, the multitude of proposed cut-off values means that the significance of the QCT results remains uncertain.

The LAA index has been the subject of numerous studies which have used QCT to evaluate lung morphology; there has been considerable debate as to its significance in determining the likelihood of PPC. Some studies have suggested that it has a superior accuracy to spirometry testing (Na et al., 2014; Kaplan et al., 2015; Kitazawa et al., 2021). A caveat in this observation is that most of the current studies investigating LAA have been performed in various Asian populations, specifically in relation to patients undergoing surgery for lung cancer.

Evidence demonstrating the clinical utility of QCT lung morphology parameters, e.g. NAA and HAA, is still lacking, and as QCT is not commonly utilised in the clinical arena, correlations between the imaging findings and overall mortality in patients undergoing operative interventions have yet to be established. The majority of data pertaining to QCT have been obtained from studies which have investigated the NAA in patients with both obstructive and restrictive pathologies (Barros et al., 2022a), LAA in individuals undergoing procedures for lung carcinoma, and HAA in the general population (Podolanczuk et al., 2016; Podolanczuk et al., 2017). Such investigations have demonstrated the possible utility of QCT indices as a novel predictive statistical factors for

mortality following surgery. No data exists for patients undergoing aortic or colorectal surgery.

As outlined above, the majority of studies which have investigated the links between indices of lung morphology derived from QCT, and PPC or overall mortality, have been performed in patients undergoing operations on lungs or in general population. This project is an attempt on acquiring such data for patients with aortic disease and those undergoing surgery for colorectal cancer, and to assess feasibility of routine pre-operative planning CT in assessment of lung pathology and prediction of PPC.

4.2 Hypothesis and aims

In this chapter it is proposed that retrospectively acquired opportunistic lung morphology data, derived from routine planning CT, are associated with PPC and survival.

The overarching aim of this chapter, was to establish the clinical value of QCT lung morphology indices in patients undergoing non-cardiac, non-thoracic surgical procedures.

Specific objectives were:

- To define the spectrum of QCT lung morphology values,
- To identify and calculate the strength of any associations between QCT lung indices and PPC,
- To determine whether these indices had impact on survival.

4.3 Materials & methods

4.3.1 Study setting

This study was performed as part of implementation of frailty assessment and management within Specialist Clinical Frailty Network (www.scfn.org.uk). Approval for the project was given by the Department of Vascular Surgery and the Department of Colorectal Surgery prior to study commencement and registered as a clinical audit.

4.3.2 Population

The description of cohorts analysed in this study was given in General Methods, Section 2.5 on page 106.

Vascular cohort: This study encompasses a comprehensive cohort, drawing patients of all ages and sexes, presenting a wide spectrum of aortic diseases, including juxtarenal, pararenal, thoracic, and thoracoabdominal aneurysms and aortic dissections. Selection criteria did not impose any restrictions based on ethnicity or geographic location, ensuring a diverse patient population from a referral centre with a broad catchment area.

All patients presenting to the specialist Aortic Clinic over the period from July 1, 2019, to February 29, 2020 were included. These patients underwent a thorough pre-operative assessment that included staging CT scans within a multidisciplinary clinical pathway, part of a service improvement project aimed at assessing and managing frailty in patients considered for surgery (Specialised Clinical Frailty Network, http://www.scfn.org.uk).

Colorectal cohort: The cohort under investigation constituted of patients undergoing left-sided colorectal cancer surgery. The database included all patients who had surgery between December 2007 and January 2019. Inclusion

criteria ensured a broad representation across various demographics, thus patients of every sex and age were considered, with no exclusions based on ethnicity or geographical provenance, drawn from a referral centre with an extensive catchment area. This approach increased the chances of this cohort being considered representative of this group of patients. The clinical pathway for these patients was structured within a multidisciplinary framework, incorporating a standardised pre-operative assessment that included staging CT scans. To ensure the homogeneity of cases under examination, the study was confined to those patients who underwent either elective or emergency resections for left-sided colorectal cancer.

For this work package, propensity score matching was used to select a subset of patients, stratify patients based on the presence of PPC, and match patients with and without PPC, correcting for factors deemed risk factors for post-operative complications based on an extensive literature review (Section 2.11.5 on page 135). The quantitative lung analysis was performed only on this subset of patients.

4.3.3 Ethical considerations

Institutional approval was granted before data collection.

4.3.4 Definitions

Postoperative Pulmonary Complications – for the purpose of this study PPC were defined using a modified EPCO criteria. This was described in detail in Chapter/Section 2.6.5 on page 111.

Morphometric parameters of lung tissue – definitions of morphometric categories of lung tissue and associated HU thresholds are presented in Table 2.2 on page 127. A significant lung parenchymal disease including emphysematous change and ILA was defined as non-dependent changes that influence more than 5% of any lung region, including traction bronchiectasis,

reticular and linear opacities, patchy ground-glass opacities, honeycombing, non- emphysematous cysts (Washko et al., 2011; Hunninghake et al., 2013; Putman et al., 2016; Podolanczuk et al., 2016).

Early/in-hospital mortality was defined as postoperative death occurring during index admission or within 30 days of the index procedure if the patient was discharged from the hospital.

Tumour staging was based on the Union for International Cancer Control (UICC) classification (8th edition) `https://www.uicc.org/what-we-do/sharing-knowledge/tnm`

4.3.5 Outcomes

The primary outcome for each cohort was to establish the clinical value of QCT lung morphology indices.

The secondary outcomes were:

- Define the spectrum of CT-derived quantitative lung morphology indices,
- Associations of the quantitative CT-derived lung morphology indices with PPC rates defined according to a modified EPCO criteria, and
- Peri-operative mortality and survival.

Mortality Outcome ascertainment was achieved by cross-referencing of the EHR with the NHS Spine (NHS Digital). The cause of death was retrieved from the Primary Care Mortality Database (NHS Digital).

The incidence of PPC was established in Chapter 3 on page 138.

4.3.6 Data collection

Prior to beginning the quantitative lung analysis, 66 patients with PPC were identified in the colorectal cohort and matched with patients who did not develop PPC in 1:2 ratio. This technique allowed to balance the distribution of the covariates between both groups and analyse differences in lung morphometry.

For this study purpose, lung morphology on one thoracic CT scan per patient was analysed in this study. All patients had their comorbid status retrieved from individual electronic health records. This included the primary lung diagnosis.

Ascertainment of primary lung diagnosis involved an extensive evaluation of the history of lung disease through review of the available medical records: anaesthetic assessment, operation notes, respiratory and physiotherapy reports, admission history, and discharge summary. This was complemented by radiological evidence of lung abnormality: CT and plain chest radiography reports were screened for keywords indicating lung disease, or structural lung abnormality. and observations made based on the findings of lung analysis.

Exclusion criteria for the study included patients in whom inferior quality images were acquired, e.g. where respiratory motion artefact degraded the data.

4.3.7 CT acquisition protocols

Thin-section preoperative thoracic CT scans were carried out on all participants for screening purposes. Image acquisition was carried out using an Aquillion One 320 Scanner (Toshiba Medical Systems Corporation, Tokyo, Japan), which is marketed for clinical use. In order to reduce the likelihood of misregistering the images as a result of patient movement or respiration, a whole lung standard helical acquisition protocol was performed. Contrast agent was given intravenously during the scan, and subjects were requested to inhale fully and to hold this position for the scan duration. They were also instructed to avoid coughing where possible.

A CT scan had been carried out in all 255 study subjects (vascular cohort: 62 and colorectal cohort: 193) within 4 weeks prior to their operative intervention. Images were acquired using a low dose radiation with the subjects in a supine position, and at maximal inhalation and maximal expiration. The following image acquisition parameters were set for each scan: tube voltage, 120 kVp; current, 80 mAs; gantry rotation time, 0.5 seconds; beam pitch, 1.5; collimation intervals, 0.5x80 mm; section thickness reconstruction, 1 - 1.2 mm. Reconstruction of the axial images was facilitated using a Soft body reconstruction kernel-FC13 with 512 x 512 matrix, and 0.78 – 0.98 pixel spacing.

4.3.8 Quantitative CT evaluation using an imaging analysis software

The acquired pulmonary imaging data in a DICOM format, were loaded to a workstation with a dedicated commercial software package, Aquarius Intuition Workstation from TeraRecon (TeraRecon GmbH, TeraRecon GmbH, Frankfurt am Main, Germany). This enabled the lung parenchyma to be studied and analysed in detail. Noise was eradicated with the use of a 1.0 Gaussian filter, which also rendered the image data more uniform. Threshold limits of -1024 HU and -500 HU were applied prior to image reconstruction.

Image information pertaining to the lung parenchyma could be extracted semi-automatically by the software from the CT images; irrelevant data from the mediastinum, great vessels, major airways and the wall of the thorax could therefore be excluded. This was achieved by entering in the above threshold limits, and by applying the specialised anatomical algorithms. It was also possible for the operator to adjust the threshold limits manually. The recorded data encompassed: total lung volume (TLV); normal lung density, i.e., lung areas displaying attenuation of voxels with a density range between the lower threshold (> -850 HU to > -950 HU) and the higher threshold (< -600 HU to < -850 HU).

Additional measurements derived from the CT data included low (LAA) and high (HAA) attenuation areas defined as pulmonary tissue with a dens-

ity in a threshold for voxels with a density range from < -850 HU to < -970 HU to show the extent of the emphysema, and voxels with a high density range between the lower threshold (> -600 HU to > -850 HU) and the higher threshold (0 HU to < -500 HU) to identify certain lung pathologies were adjusted, respectively.

Percentages of lung volume displaying these characteristics, i.e., NAA, LAA and HAA were computed by the software.

Two study investigators, AG and CW, who had undergone appropriate training, carried out the analysis of the pulmonary morphology image data. Both parties were blinded to any clinical information or earlier CT analysis results. In order to confirm that the lung morphology analysis method demonstrated both reliability and consistency, 50 image data sets were chosen at random and analysed by blinded qualified readers. Inter-class concordance correlation coefficient were determined.

The final specific density thresholds selected to measure the lung attenuation area is shown in Table 4.1. The selected threshold indicators represented the data of volumetric (VOL) and proportional relative lung density (PROP) , and their stratification based on tertiles.

Table 4.1 – The defined set of lung density thresholds used in analysis of lung morphology. NAA - Normal attenuation area; LAA - Low attenuation area; HAA - High attenuation area; HU - Hounsfield unit..

Surgical cohort	**Lung morphology indices**		
	LAA	NAA	HAA
Vascular			
	< -850 HU, < -860 HU, < -870 HU,	-850 to -750 HU,-860 to -760 HU,-870 to -770 HU,	-600 to 0 HU, -610 to 0 HU, -620 to 0 HU,
	< -880 HU, < -890 HU, < -900 HU,	-880 to -780 HU, -890 to -790 HU, -900 to -600 HU,	-650 to 0 HU,-660 to 0 HU, -710 to -500 HU,
	< -910 HU, < -920 HU,< -930 HU,	-900 to -650 HU,-900 to -700 HU,	-720 to -500 HU, -730 to -500 HU, -790 to -500 HU,
	< -940 HU,< -950 HU,< -960 HU, < -970 HU,	-900 to -730 HU,-910 to -650 HU, -930 to -730 HU, -910 to -650	-810 to -500 HU, -830 to -500 HU, -840 to -500 HU, -850 to -500 HU
Colorectal			
	< -870 HU	-900 to -700 HU	-700 to -500 HU
	< -880 HU	-900 to -750 HU	-750 to -500 HU
	< -890 HU	-900 to -800 HU	-800 to -500 HU
	< -900 HU	-950 to -700 HU	
	< -910 HU	-950 to -750 HU	
	< -950 HU	-950 to -850 HU	

4.3.9 Statistical methods and data analysis plan

Generic statistical methods used in this Chapter were described in Methods Section (Chapter 2 on page 132).

Propensity score matching was used for the colorectal cohort as described in Chapter 2 Section 2.11.5 on page 135.

4.3.9.1 Data analysis plan

The quality of the data was evaluated, assessing missingness using the `naniar` and `DescTools` R packages. Data missingness for both cohorts were calculated and proportion of data missing established and visualised. Variables exhibiting 20% or greater missingness were excluded from further analysis. Since a very small proportion of variables displayed high missingness, these were removed from the analysis. Further assessment of relationship between missing variables to establish the type of missingness (Missing Completely At Random, Missing At Random, Missing Not At Random) was not attempted and imputation was not performed.

The primary outcome of the study was to establish the clinical value of QCT lung morphology indices. The following predictor variables in the analysis were included: CT-derived lung density volumes (a continuous variable), the percentage of lung density volume relative to total lung volume (expressed as a percentage, %), and lung volume categorised into tertiles (a categorical variable).

Normality of the predictor variables was tested using the `shapiro_test()` function from the `rstatix` package. Then univariate analyses was conducted using the `univariateTable()` function from the `Publish` package, with the primary outcome serving as the grouping variable.

Thirty-eight different attenuation thresholds were applied for lung analysis in the vascular cohort (Table 4.1 on the previous page). The number of variables were therefore reduced by constructing logistic regression models using the selected predictors in each lung density category (up to 3 variables in each) and assessing multicollinearity. The VIF using the `vif()` function from the `fmsb` and `rms` packages, and `VIF()` from `DescTools` was calculated. Variables with a VIF exceeding 10.0 were sequentially removed, starting with the highest VIF. Additionally, an automated variable selection process based on the AIC using the `step()` function from the `stats` package was employed.

In the colorectal cancer cohort, fifteen different attenuation thresholds were applied for lung analysis (Table 4.1 on the preceding page). Therefore the

data analysis did not comprise variable reduction as in the vascular cohort. An automated variable selection process based on the AIC was employed using the `step()` function from the `stats` package, and corrected the final explanatory model based on VIF.

The variables identified through this procedure were then incorporated into sensitivity analyses. This step was undertaken to determine if the predictive capacity of regression models, developed in the preceding chapter (Chapter 3 on page 138 ‘The incidence of postoperative pulmonary complications and their association with survival’), could be enhanced by including CT-derived lung morphological parameters alongside clinical and demographic factors. Since the effect sizes for lung morphomics were small, the variables were rescaled. This was dictated by the fact that the unit of measurement was not clinically significant. By rescaling the unit of analysis to 100 mL we increased the threshold for detecting a clinically significant change.

4.4 Results

4.4.1 Data processing

Before commencing the process of quantitative CT-derived lung morphology indices analysis, the datasets were reviewed on a case-by-case basis. Twenty-seven patients were excluded from the vascular dataset subsequent to the data cleaning process due to waiting for surgery (n = 18), declining surgery (n = 4), having no data on the operation (n = 3), and being technically unsuitable (n = 2; Figure 4.1).

As outlined in the methods section (2.11.5 on page 135), for the colorectal cohort, 66 patients who had PPC were matched in a 1 : 2 ratio with patients who did not develop PPC. This technique allowed to balance the distribution of the covariates between both groups and analyse differences in lung morphometry. The outcome of this process is the selection of 198 patients for quantitative lung analysis. Five patients were excluded on account of substandard CT image quality.

Following this process, 62 patients were included in the quantitative lung morphology analysis from the vascular cohort and 193 patients from the colorectal cohort. The details of case inclusion in quantitative lung analysis are shown in a CONSORT-style diagram (Figure 4.1).

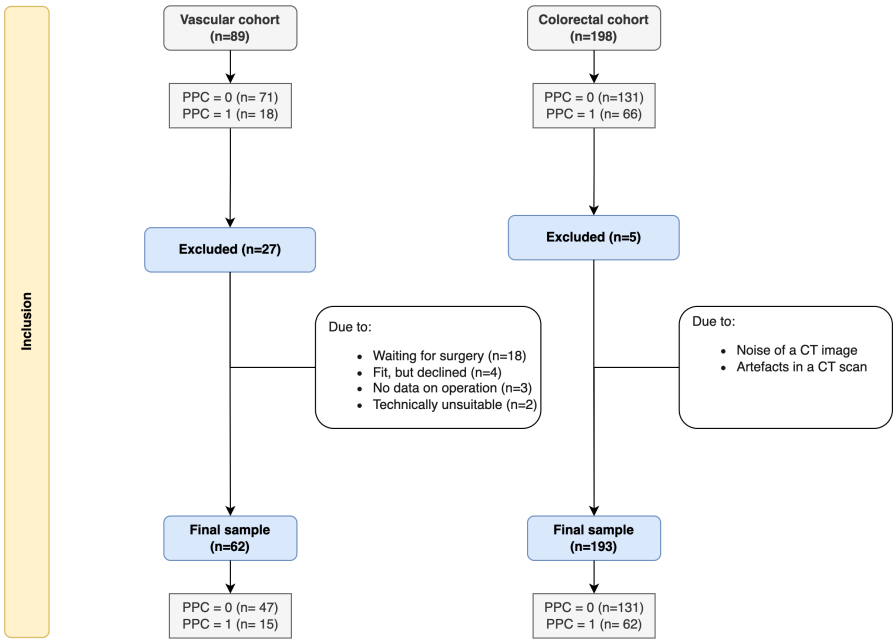


Figure 4.1 – CONSORT flow diagram demonstrating patient inclusion for quantitative lung morphology analysis. PPC - Postoperative pulmonary complications.

4.4.2 Quantitative-CT derived morphometric lung indices

4.4.2.1 Patients with aortic aneurysms

A full analysis of chosen lung density thresholds was carried out. A total of 62 participants were included in the analysis, of whom 50 were male and 12 were female.

There were significant differences between the groups consistently demonstrating that males had significantly higher morphometric lung indices than females across all thresholds.

This demonstrates that there is an inherent, biological difference between sexes in lung volumes and that a proportional volume or tertiles should be used in analyses.

4.4.2.2 Patients with colorectal cancer

A total of 193 participants were included in the analysis, of whom 142 were male and 51 were female.

A full analysis of several lung density thresholds was carried out. Male patients demonstrated a substantial systematic, statistically significant higher mean and median values in lung morphometric parameters across the threshold categories compared with female patients. Therefore, the categorical stratification of these indices using tertiles was done within each sex stratum separately.

4.4.3 Association of quantitative, CT-derived morphometric lung indices with the incidence of PPC

4.4.3.1 PPC in patients with aortic aneurysms

The univariate analysis evaluated the differences in volumetric, proportional and tertile-based categories of lung attenuation areas between PPC groups. The dataset comprised a total of 62 patients, with 15 patients in who developed PPC and 47 patients who did not.

LAA Analysis: The volumetric analysis of lung tissue (VOL) within LAA using predefined threshold settings, ranging from -850 HU to -970 HU, indicated no significant differences between those who developed PCC and those who did not. (Table 4.2).

Table 4.2 – Univariate analysis comparing the differences in volumetric measure of LAA thresholds in patients with aortic aneurysms stratified by PPC. Results presented as median interquartile range [IQR]; LAA - Low attenuation area; PPC - Post-operative pulmonary complications; HU - Hounsfield unit.

Variable	PPC(-) (n=47)	PPC(+) (n=15)	Total (n=62)	p-value
-850 HU	2,027.5 [1,361.2-3,011.8]	2,064 [1,492-2,755]	2,041 [1,418-2,864]	0.918
-860 HU	1,671 [1,102.2-2,880.8]	1,693 [1,157-2,430]	1,674 [1,157-2,511]	0.820
-870 HU	1,280 [794.5-2,153.0]	1,321 [856-2,220]	1,285 [835-2,220]	0.885
-880 HU	936 [493.5-1,879.2]	968 [577-1,991]	948 [494-1,991]	0.804
-890 HU	647 [353-1,618]	655 [345-1,735]	655 [345-1,705]	0.710
-900 HU	412 [213.5-1,372.5]	405 [190-1,385]	409 [200-1,385]	0.687
-910 HU	264.5 [123.0-949.2]	210 [95.9-955.0]	241 [102-955]	0.717
-920 HU	156 [63.6-510.5]	120 [55.2-591.0]	152 [55.2-590.0]	0.820
-930 HU	75.7 [26.4-319.0]	61.6 [30.9-325.0]	67.6 [27.3-319.0]	0.836
-940 HU	38.7 [11.4-156.8]	32.8 [11.1-158.0]	33.3 [11.1-158.0]	0.694
-950 HU	19.7 [7.0-76.9]	18.5 [5.1-68.0]	18.5 [5.6-71.8]	0.967
-960 HU	9.2 [2.3-33.9]	10.6 [2.9-27.2]	9.8 [2.8-28.9]	0.584
-970 HU	4.7 [1.2-15.3]	5.8 [1.7-13.3]	4.8 [1.4-13.3]	0.450

The relative, proportional (PROP) measure of LAA was investigated and indicated that there were no significant differences between those who developed PPC and those who did not either (Table 4.3).

Table 4.3 – Univariate analyses comparing the differences in lung density proportions measure of LAA thresholds between PPC groups of patients with aortic aneurysms. Data presented as mean (standard deviation, (SD)), median, and interquartile range [IQR]. LAA - low attenuation area; PPC - Postoperative pulmonary complications; HU - Hounsfield unit..

Variable	PPC(-) (n=47)	PPC(+) (n=15)	Total (n=62)	p-value
-850 HU	43.3 (17.9)	45.8 (21)	44 (18.6)	0.675
-860 HU	36.8 (17.3)	39.3 (20.8)	37.4 (18)	0.663
-870 HU	28.7 [19.9-39.7]	26.5 [21.0-44.9]	28.5 [19.9-43.4]	0.869
-880 HU	21 [14.7-33.6]	19.4 [13.5-39.7]	20.8 [14.3-38.2]	1.000
-890 HU	13.9 [9.8-27.8]	13.1 [8.6-34.4]	13.9 [9.1-29.7]	0.950
-900 HU	8.7 [6.2-21.1]	8.1 [4.7-29.1]	8.5 [5.4-21.1]	0.918
-910 HU	5.4 [3.6-13.7]	4 [2.8-20.3]	5.2 [3.3-13.7]	0.869
-920 HU	3.2 [1.5-8.5]	2.9 [1.6-12.6]	3.1 [1.6-10.0]	0.598
-930 HU	1.6 [0.6-5.5]	1.8 [0.6-6.9]	1.8 [0.6-5.9]	0.508
-940 HU	0.8 [0.3, 2.8]	0.9 [0.3, 3.4]	0.9 [0.3, 3.3]	0.469
-950 HU	0.4 [0.2-1.4]	0.4 [0.1-1.5]	0.4 [0.1-1.5]	0.687
-960 HU	0.2 [0.1-0.7]	0.2 [0.1-1.1]	0.2 [0.1-1.1]	0.414
-970 HU	0.1 [0.0-0.3]	0.1 [0.0-0.7]	0.1 [0.0-0.7]	0.374

The analysis of VOL and PROP tertiles did not reveal any statistically significant differences between those who developed PPC and those who did not.

NAA Analysis: The volumetric analysis of lung tissue with normal lung attenuation with the thresholds from -850 to -750 HU and -860 to -760 HU, showed significant differences between PPC groups (Table 4.4). The NAA established using other thresholds, including -870 to -770 HU, -900 to -600 HU, -900 to -650 HU, and -900 to -700 HU, showed some *trends*, but the differences were not statistically significant (Table 4.4).

Table 4.4 – Univariate analyses comparing the differences in volumetric measure of NAA between PPC groups of patients with aortic aneurysms. Data presented as mean (sd). NAA – normal attenuation area; VOL – volumetric; sd – standard deviation; PPC – post-operative pulmonary complications; AUC: area under a curve; d: Cohen's d.

Variable	PPC(-) (n=47)	PPC(+) (n=15)	Total (n=62)	p-value	AUC	d
-850 to -750 HU	1,828 (509.6)	1,473.5 (609.4)	1,741 (551.5)	0.0378	0.6481	0.663
-860 to -760 HU	2,058.7 (575.6)	1,690.1 (707.3)	1,968.3 (624.2)	0.0580	0.6462	0.605
-870 to 770 HU	2,283.5 (658.3)	1,907 (801.2)	2,191.1 (707)	0.0895	0.6365	0.542
-900 to -600 HU	3,928.2 (946.2)	3,366.5 (960.5)	3,790.4 (971.5)	0.0639	0.6712	0.592
-900 to -650 HU	3,795.6 (967.3)	3,258.2 (980.7)	3,663.8 (989)	0.0828	0.6538	0.554
-900 to -700 HU	3,654.3 (968.5)	3,129.5 (981.8)	3,525.6 (988.9)	0.0907	0.6558	0.540

The analysis of relative volume for NAA was performed with predefined thresholds ranging from a lower bound of -850 HU to -970 HU and an upper bound of -750 HU to 870 HU. There were *no significant differences* in the PPC stratum (Table 4.5).

The analysis of the tertiles of lung tissue volumes (VOL) with predefined NAA thresholds demonstrated *no significant differences* between PPC groups. The tertiles of proportional (PROP) lung volumes with thresholds including -870 to -770 HU, -880 to -780 HU, -890 to -790 HU, -900 to -760 HU, -900 to -770 HU, -900 to -780 HU, -910 to -650 HU, -910 to -730 HU, -920 to -620 HU, showed some *trend* towards weak associations (Table 4.5). Only the threshold variable -900 to -730 HU showed significant differences between those who developed PPC and those who did not (p=0.017).

Table 4.5 – Univariate analyses of the differences in lung density proportions measured for the tertile categories of NAA between PPC groups of patients with aortic aneurysms. NAA – Normal attenuation area; PROP – proportional relative lung density; PPC – post-operative pulmonary complications; AUC – Area Under the Curve; d – Cohen's d.

Variable	PPC(-) (n=47)	PPC(+) (n=15)	Total (n=62)	p-value	AUC	d
-900 to -730 HU	11 (27.5)	6 (46.2)	17 (32.1)	0.0170	0.451	0.088
-870 to -770 HU	12 (30.0)	5 (38.5)	17 (32.1)	0.0834	0.451	0.098
-880 to -780 HU	12 (30.0)	5 (38.5)	17 (32.1)	0.0834	0.451	0.169
-890 to -790 HU	12 (30.0)	5 (38.5)	17 (32.1)	0.0834	0.451	0.067
-900 to -760 HU	12 (30.0)	5 (38.5)	17 (32.1)	0.0834	0.451	0.102
-900 to -770 HU	12 (30.0)	5 (38.5)	17 (32.1)	0.0834	0.451	0.154
-900 to -780 HU	12 (30.0)	5 (38.5)	17 (32.1)	0.0834	0.451	0.040
-910 to -650 HU	12 (30.0)	5 (38.5)	17 (32.1)	0.0834	0.451	0.158
-910 to -730 HU	12 (30.0)	5 (38.5)	17 (32.1)	0.0834	0.451	0.054
-920 to -620 HU	12 (30.0)	5 (38.5)	17 (32.1)	0.0834	0.451	0.090

Variable selection - the univariate analysis identified the trend and significant NAA threshold variables, which were then used in two distinct models of multivariable logistic regression based on clinical and demographic predictors. Variable selection was based on the p-value less than 0.1. The VIF was used to eliminate variables with significant multi-collinearity (variables with VIF>10). Automated selection of variables was then attempted utilising stepwise logistic regression using reduction of AIC.

This included the volumetric variables measured at predefined thresholds ($NAA_{(VOL)}$ -850 to 750, -900 to -650, and -900 to -700). Following correction for VIF and stepwise regression, it resulted in the inclusion of $NAA_{(VOL)}$ -850 to -750 HU variable in clinical model. The stepwise logistic regression revealed that the $NAA_{(VOL)}$ -850 to -750 HU variable had a ability to discriminate between those patients who developed PPC and those who did not. The effect was trending towards a significant (OR 1.00; 95% CI 1.00-1.00, p=0.054; Table 4.6), and analysis of the ROC curve demonstrated a very modest c-statistic of 0.64 (Figure 4.2).

Table 4.6 – The results of a stepwise logistic regression analysis of the association between volumetric measure NAA thresholds and the development of PPC after aortic aneurysms surgery. NAA – Normal attenuation area; PPC – post-operative pulmonary complications; VOL – Volumetric measure; HU - Hounsfield unit; CI - Confidence interval

Variable	Unit	Odds Ratio	95% CI	p-value
$NAA_{(VOL)}$ -850 to -750 HU		1.00	1.00–1.00	0.054

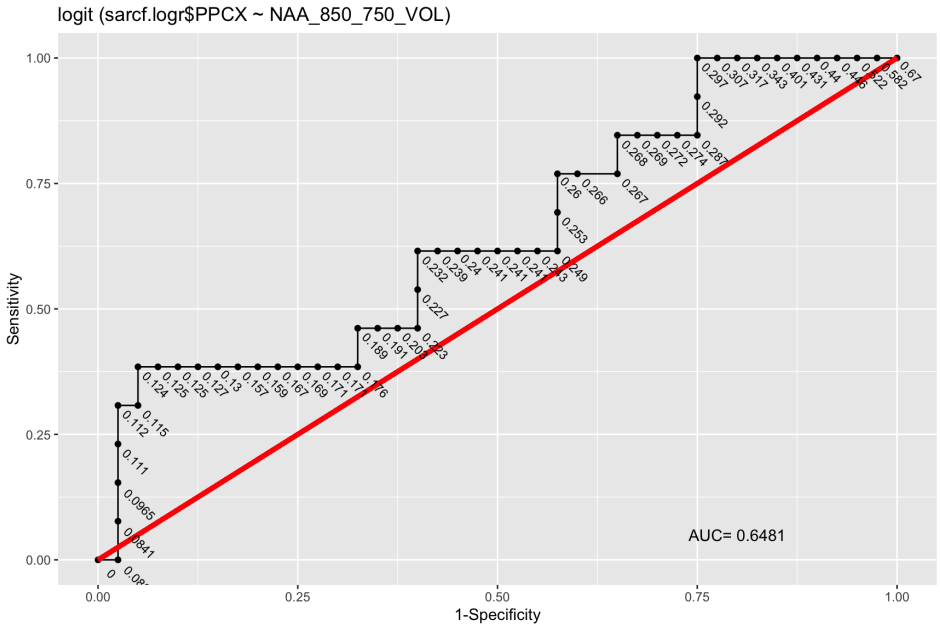


Figure 4.2 – The analysis of the receiver operating characteristic (ROC) and area under the curve (AUC) demonstrates the diagnostic performance ability of the volume of the normal lung attenuation area threshold ($NAA_{(VOL)}$ -850 to -750 Hounsfield unit (HU)) to predict the PPC in patients with aortic aneurysms. PPC - postoperative pulmonary complications; NAA - Normal attenuation area.

Tertiles of PROP for NAA included $NAA_{(PROP\ Tertile)}$ for -900 to -730 HU and -900 to -770 HU thresholds. The logistic regression showed that the $NAA_{(PROP\ Tertile)}$ -900 to -730 HU had no ability to discriminate between those patients who experienced PPC and those who do not. The effect was not significant (OR 0.69; 95% CI 0.30-12.54,p=0.481; Table 4.7). The c-statistic for this model was 0.69 (Figure 4.3).

Table 4.7 – The results of a stepwise logistic regression analysis of the association between tertiles proportional relative lung density measure of NAA thresholds and the development of PPC after aortic aneurysms surgery. NAA – Normal attenuation area; PPC – post-operative pulmonary complications; PROP – proportional relative lung density measure; HU - Hounsfield unit; CI - Confidence interval.

Variable	Unit	Odds Ratio	95%CI	p-value
$NAA_{(PROP\ Tertile)}$ -900 to -730 HU	1	Ref		
	2	0.00	0.00–Inf.	0.992
	3	1.95	0.30–12.54	0.481

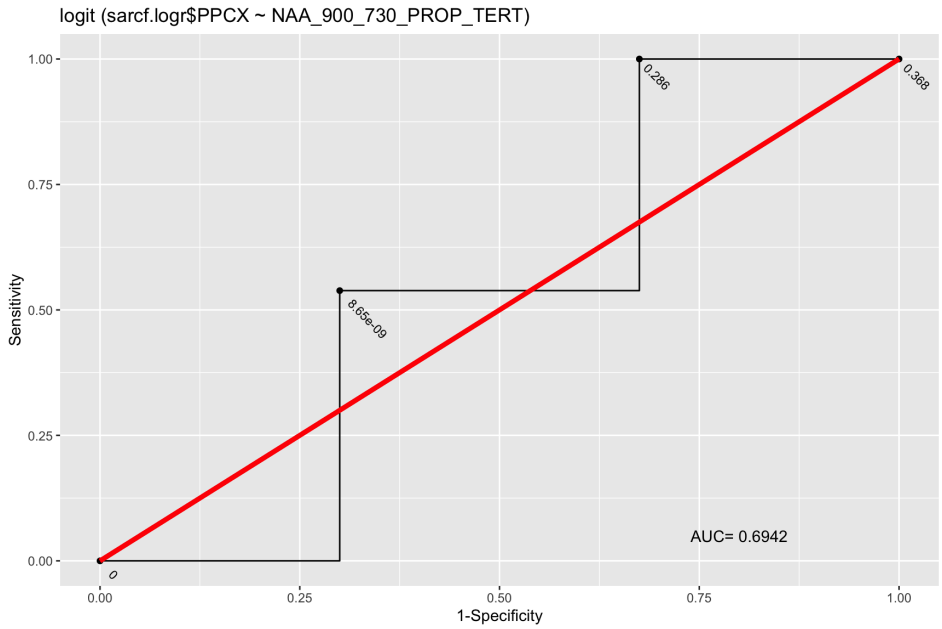


Figure 4.3 – The analysis of the receiver operating characteristic (ROC) and area under the curve (AUC) demonstrates the diagnostic performance ability of the tertiles proportional relative lung density measure of the normal lung attenuation area threshold ($NAA_{(PROP\ Tertile)}$ -900 to -730 Hounsfield unit to predict the PPC in patients with aortic aneurysms. PPC - postoperative pulmonary complications; PPC - postoperative pulmonary complications; NAA - Normal attenuation area.

Combining all above NAA variables, $NAA_{(VOL)}$ -850 to -750 HU and Tertiles of NAA ($NAA_{(PROP\ Tertile)}$) -900 to -730 HU were included. In logistic regression these had no ability to discriminate between those patients who experienced PPC and those who do not. The c-statistic was 0.78 indicating good

overall performance of the model, but the effect of morphometric parameters was not significant (Table 4.8 and Figure 4.4).

Table 4.8 – The results of a stepwise multiple logistic regression analysis of the association between combining volumetric and proportional relative lung density measures of NAA thresholds and the development of PPC after aortic aneurysms surgery. NAA – Normal attenuation area; PPC – post-operative pulmonary complications; VOL – Volumetric measure; PROP – proportional relative lung density measure; HU - Hounsfield unit; CI - Confidence interval.

Variable	Unit	Odds Ratio	95% CI	p-value
$NAA_{(VOL)}$ -850 to -750 HU		1.00	1.00–1.00	0.109
$NAA_{(PROP\ Tertile)}$ -900 to -730 HU	1	Ref		
	2	0.00	0.00–Inf.	0.992
	3	1.95	0.30–12.54	0.481

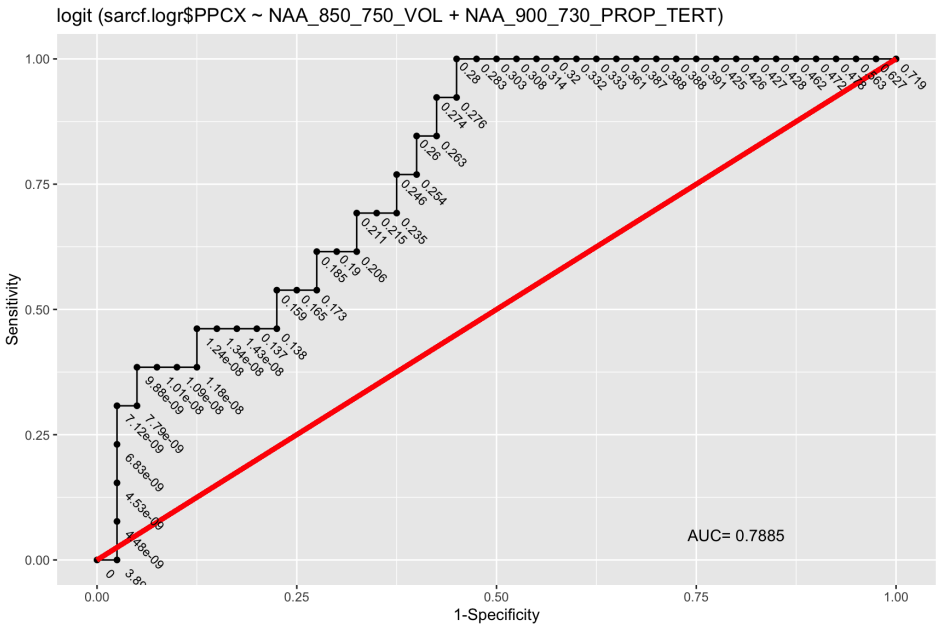


Figure 4.4 – The analysis of the receiver operating characteristic (ROC) and area under the curve (AUC) demonstrates the diagnostic performance ability of the combining volumetric and proportional relative lung density measures of normal lung attenuation area thresholds ($NAA_{(VOL)}$ -850 to -750 Hounsfield unit (HU)) and $NAA_{(PROP\ Tertile)}$ -900 to -730 HU) to predict the PPC in patients with aortic aneurysms. PPC - postoperative pulmonary complications; NAA - Normal attenuation area.

HAA Analysis: The analysis of the volumetric measure of HAA revealed that the majority of the thresholds, ranging from a lower bound of -600 HU to -850 HU to an upper bound of 0 and -500 HU were significantly different between those patients who developed PPC and those who did not. (Table 4.9).

Table 4.9 – Univariate analyses comparing the differences in volumetric measure of measure of HAA thresholds between PPC groups of patients with aortic aneurysms. Data presented as mean (standard deviation, (SD)), median, and interquartile range [IQR]. HAA - High attenuation area; PPC - Postoperative pulmonary complications; HU - Hounsfield unit.

Variable	PPC(-) (n=47)	PPC(+) (n=15)	Total (n=62)	p-value
-600 to 0 HU	150 [132.2-172.5]	118 [107-137]	144 [120-172]	0.024
-610 to 0 HU	171 [149.5-194.8]	133 [121-154]	163 [137-194]	0.023
-620 to 0 HU	192.5 [168.8-218.2]	149 [136-171]	184 [155-217]	0.021
-630 to 0 HU	214.5 [188.2-243.5]	167 [152-188]	206 [173-242]	0.020
-640 to 0 HU	239 [209.8-270.0]	187 [169-207]	230 [191-268]	0.019
-650 to 0 HU	265.5 [232.8-298.5]	208 [187-231]	256 [214-296]	0.019
-660 to 0 HU	293.5 [256.2-331.2]	232 [207-256]	285 [239-329]	0.022
-670 to 0 HU	323.5 [281.8-373.0]	258 [228-284]	315 [267-373]	0.017
-700 to -500 HU	434 [366.0-513.5]	343 [315-389]	407 [343-507]	0.024
-710 to -500 HU	480.5 [416.5-548.2]	370 [328-433]	449 [395-542]	0.012
-720 to -500 HU	531.5 [470.5-610.0]	401 [359-484]	500 [437-601]	0.013
-730 to -500 HU	583.5 [502.5-669.2]	434 [392-543]	550 [473-654]	0.014
-740 to -500 HU	631 [550.8-757.8]	469 [430-612]	604 [504-739]	0.028
-750 to -500 HU	714 [614.8-838.2]	516 [472-694]	694 [570-817]	0.017
-760 to -500 HU	803.5 [685.5-944.8]	576 [519-792]	779 [629-920]	0.021
-770 to -500 HU	900 [769-1,070]	657 [571-911]	856 [697-1,041]	0.023
-780 to -500 HU	1,012.5 [860.2-1,221.5]	760 [632-1,055]	948 [784-1,187]	0.025
-790 to -500 HU	1,142.5 [975.8-1,379.2]	890 [702-1,230]	1,088 [890-1,360]	0.024
-800 to -500 HU	1,254 [1,053.2-1,604.5]	1,068 [789-1,354]	1,214 [1,017-1,575]	0.041
-810 to -500 HU	1,567.5 (444.1)	1,256.9 (500.7)	1,491.4 (473.2)	0.034
-820 to -500 HU	1,783.3 (477.8)	1,429.2 (542.1)	1,696.5 (512.6)	0.025
-830 to -500 HU	2,024.8 (508.9)	1,628.2 (586.1)	1,927.5 (550.7)	0.019
-840 to -500 HU	2,301.1 (539.9)	1,861.7 (642.2)	2,193.3 (591.8)	0.015
-850 to -500 HU	2,598.7 (571.1)	2,121.2 (703.1)	2,481.5 (633.8)	0.013

The proportional measures of HAA lung tissue with the same thresholds demonstrated no significant differences between those who developed PPC and those who did not.

Clinical models combined clinical and demographic variables that were associated with PPC as per analysis reported in Chapter 3, and volumetric parameters with NAA threshold selected in the process described above.

The first model (Model 1) included the following variables: PAOD[1], HB[2], and $NAA_{(VOL)}$ -850 to -750 HU. The stepwise logistic regression analysis indicated that the $NAA_{(VOL)}$ -850 to -750 HU was independently associated with PPC, and the effect was statistically significant[3]. The PAOD appears to substantially increase the risk of developing PPC, but the result did not reach statistical significance (Table 4.10). The c-statistic was 0.74 indicating good predictive value of the model (Figure 4.5). Addition of the CT-derived morphometric lung indices to the clinical model improved its predictive value.

Table 4.10 – The results of a stepwise multiple logistic regression analysis of the association between the combination of clinical patient-related factors and the lung morphomarker of volumetric measure of the NAA threshold (Clinical model 1) and the development of PPC after aortic aneurysm surgery. NAA – normal lung attenuation area; PPC - Postoperative pulmonary complications; VOL – Volumetric; PAOD - Peripheral arterial occlusive disease; HU - Hounsfield unit; CI - Confidence interval

Variable	Unit	Odds Ratio	95% CI	p-value
$NAA_{(VOL)}$ -850 to -750 HU		1.00	1.00–1.00	0.030
PAOD	0	Ref		
	1	4.48	0.96–20.86	0.056

[1]Variable: presence of peripheral arterial occlusive disease;
[2]Variable: haemoglobin concentration;
[3]Changing the unit of measurement from mL to dL would change the precision of the effect size.

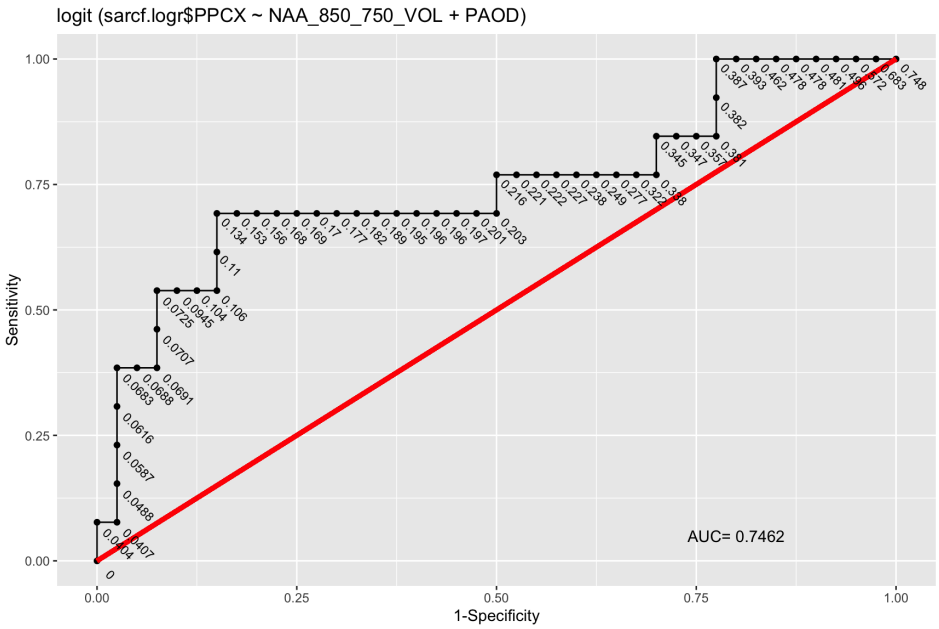


Figure 4.5 – The analysis of the receiver operating characteristic (ROC) and area under the curve (AUC) demonstrates the diagnostic performance ability of the clinical patient-related factor (PAOD) and the lung morphomarker of volumetric measure of the normal lung attenuation area threshold ($NAA_{(VOL)}$ -850 to -750 Hounsfield unit (Clinical model 1) to predict the postoperative pulmonary complications in patients with aortic aneurysms. PPC - postoperative pulmonary complications; NAA - Normal attenuation area; PAOD - peripheral arterial occlusive disease.

Another model (Model 2) combined clinical variables that were associated with PPC in multiple logistic regression analysis (reported in Chapter 3) and all NAA threshold variables. The stepwise logistic regression indicated that the threshold $NAA_{(VOL)}$ -850 to -750 HU shows a tendency towards being discriminative in detecting PPC (OR 1.00; 95%CI 1.00–1.00, p=0.078). The PAOD demonstrated a trend towards the association with the risk of developing PPC, but the results did not reach statistical significance (OR 4.48, 95%CI 0.96–20.86, p=0.056; Table 4.11). The c-statistic of 0.81 was indicative of a good predictive value (Figure 4.6).

Table 4.11 – The results of a stepwise multiple logistic regression analysis of the association between the combination of clinical patient-related factors and the lung morphomarker of volumetric and proportional relative lung density measures of the NAA thresholds (Clinical model 2) and the development of PPC after aortic aneurysm surgery. NAA – normal lung attenuation area. PPC – Postoperative pulmonary complications; VOL – Volumetric; PROP - proportional relative lung density; PAOD - Peripheral arterial occlusive disease; HU - Hounsfield unit; CI - Confidence interval.

Variable	Units	Odds Ratio	95% CI	p-value
NAA(VOL) -850 to -750 HU		1.00	1.00–1.00	0.030
PAOD	0	Ref		
	1	4.48	0.96–20.86	0.056
$NAA_{(PROP\ Tertile)}$ -900 to -730 HU	1	Ref		
	2	0.00	0.00–Inf.	
	3	1.85	0.29–12.00	0.518

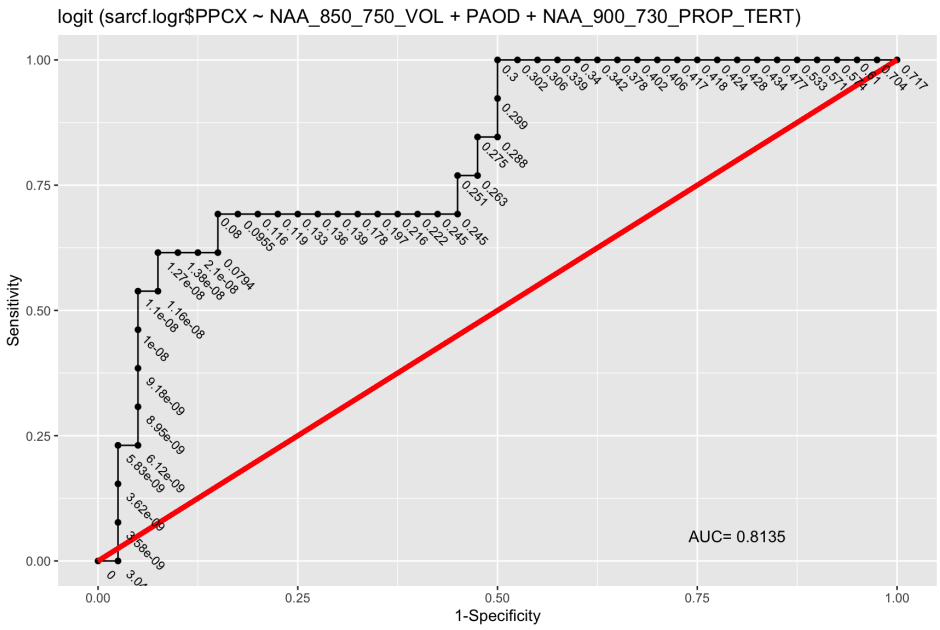


Figure 4.6 – The analysis of the receiver operating characteristic (ROC) and area under the curve (AUC) demonstrates the diagnostic performance ability of the clinical patient-related factor (PAOD) and the lung morphomarker of volumetric and proportional relative lung density measures of the normal lung attenuation area threshold ($NAA_{(VOL)}$ -850 to -750 Hounsfield unit (HU) and $NAA_{(PROP\ Tertile)}$ -900 to -730 HU) (Clinical model 2) to predict the PPC in patients with aortic aneurysms. PPC - postoperative pulmonary complications; NAA - Normal attenuation area; PAOD - peripheral arterial occlusive disease.

The significant HAA variables found on univariate analysis were used in another model (Model 3) including clinical parameters found to be associated with PPC on multivariable logistic regression. The selection of HAA variables based on the same process as described above, combined variable inclusion on the basis of collinearity (VIF) and AIC in stepwise regression. Addition of CT-derived morphometric lung indices to the clinical model improved its predictive value.

Table 4.12 – The results of a stepwise multiple logistic regression analysis of the association between the combination of clinical patient-related factors and the lung morphomarker of volumetric measure of the HAA threshold (Clinical model 3) and the development of PPC after aortic aneurysm surgery. HAA – High attenuation area; PPC – postoperative pulmonary complications. VOL – Volumetric; PAOD - Peripheral arterial occlusive disease; HU - Hounsfield unit; CI - Confidence interval..

Factors	Units	Odds Ratio	95% CI	p-value
HAA(VOL) -850 to -500 HU		1.00	1.00–1.00	0.022
PAOD	0	Ref		
	1	3.65	0.81-16.51	0.093

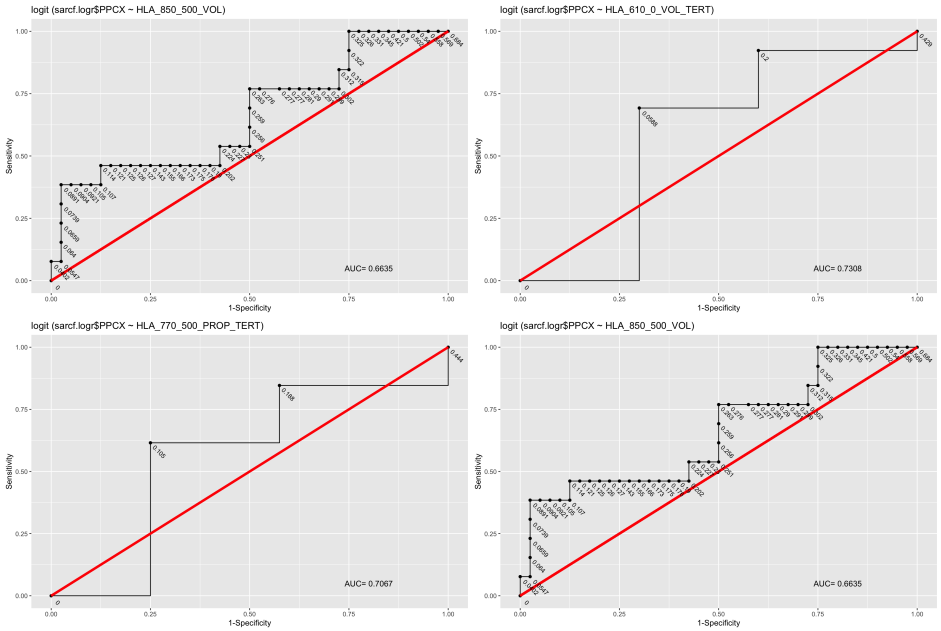


Figure 4.7 – The analysis of the receiver operating characteristic (ROC) and area under the curve (AUC) demonstrates the diagnostic performance ability of the lung morphomarkers of volumetric and proportional relative lung density measures of the high attenuation area thresholds ($HAA_{(VOL)}$ -850 to -500 Hounsfield unit (HU) , $HAA_{(VOL-tertile)}$ -610 to -0 , $NAA_{(PROP-tertile)}$ -770 to -500 HU), and $HAA_{(VOL)}$ -850 to -500 to predict the PPC in patients with aortic aneurysms. PPC – postoperative pulmonary complications; HAA – High attenuation area.

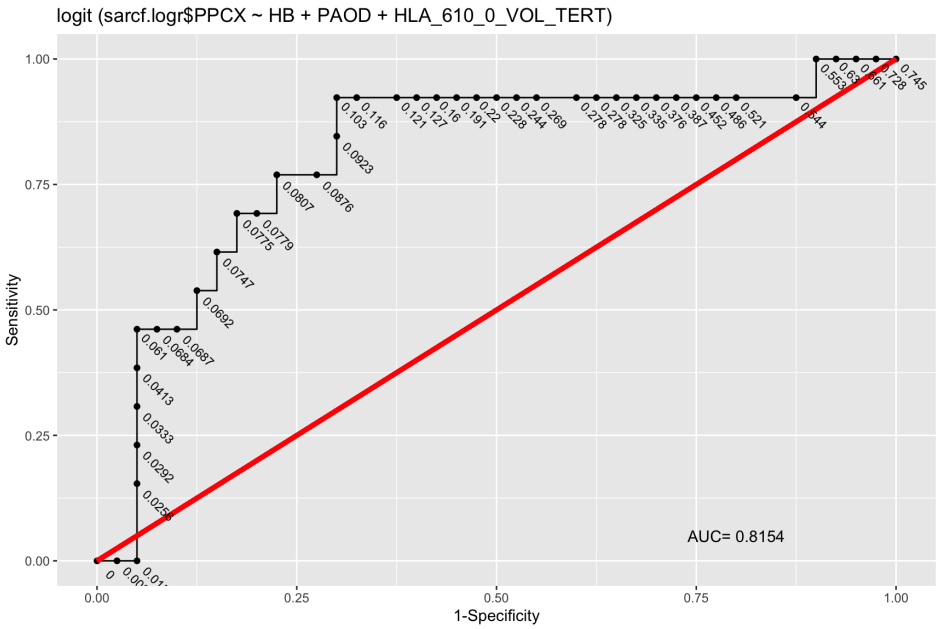


Figure 4.8 – The analysis of the receiver operating characteristic (ROC) and area under the curve (AUC) demonstrates the diagnostic performance ability of the clinical patient-related factor and the lung morphomarker of volumetric measure of the high attenuation area thresholds ($HAA_{(VOL)}$ -610 to -0 Hounsfield unit (HU)) (Clinical model 3) to predict the PPC in patients with aortic aneurysms. PPC - postoperative pulmonary complications; NAA - High attenuation area.

4.4.3.2 PPC in patients with colorectal cancer

The univariate analysis evaluated the differences in volumetric, proportional and tertile-based lung attenuation between PPC groups. The dataset comprised a total of 193 patients, with 62 patients who developed PPC and 131 patients who did not.

Since the lung analysis in this cohort included only 15 attenuation thresholds, the same variable reduction method as in the vascular cohort was not performed, and analysed the data grouped by the type of morphometric indices (volumetric, proportional, and categorised by tertiles).

Volumetric indices: Univariate analysis did not identify any significant associations between CT-derived volumetric lung mophometric indices and PPC (Table 4.13).

Table 4.13 – Univariable analysis of the differences in volumetric density indices between PPC groups of patients with colorectal cancer. Data presented as mean (SD) and median [IQR]. LAA - Low attenuation area; NL - Normal lung, HAA - High attenuation area; TV - Total lung volume; Iqr - Interquartile range; sd - standard deviation; PPC - Postoperative pulmonary complication.

Variable	PPC(-) (n=131)	PPC(+) (n=62)	Total (n=193)	p-value
LAA 870	1,806.4 (1,382.7)	1,841.3 (1,365.8)	1,817.6 (1,373.9)	0.870
LAA 880	1,506.9 (1,270.5)	1,545.9 (1,324.9)	1,519.5 (1,284.9)	0.844
LAA 890	1,209.7 (1,142.5)	1,248.6 (1,189.2)	1,222.2 (1,154.7)	0.828
LAA 900	940.8 (985.6)	974.6 (1,041.7)	951.6 (1,001.4)	0.827
LAA 910	703.3 (816.9)	830.2 (1,171.8)	744.1 (944.3)	0.384
LAA 950	160.8 (291.2)	207.4 (441.1)	175.8 (346)	0.383
NL 950-700	4,081.9 (1,318.6)	4,166.2 (1,267.2)	4,109 (1,299.6)	0.674
NL 950-750	3,812.2 (1,368.4)	3,875 (1,337)	3,832.4 (1,355.2)	0.764
NL 950-850	2,233.3 (1,373.3)	2,283.1 (1,499.5)	2,249.3 (1,411.3)	0.820
NL 900-700	3,319 (989.9)	3,418.7 (918.7)	3,351 (966.3)	0.504
NL 900-750	3,054.1 (1,003.6)	3,130.5 (951.3)	3,078.7 (985.2)	0.615
NL 900-800	2,524.6 (982.9)	2,560.2 (995.4)	2,536.1 (984.5)	0.815
HAA 700-500	408 (149)	431 (157.8)	415.4 (151.8)	0.325
HAA 750-500	680.9 (257.3)	726 (287)	695.4 (267.3)	0.273
HAA 800-500	1,211.2 (430.2)	1,302.4 (514.9)	1,240.5 (459.8)	0.197
TV	4,593.7 (1,351.2)	4,756 (1,336.2)	4,645.8 (1,345)	0.434
AIRWAY	42.1 (13.5)	39.7 (14)	41.4 (13.7)	0.255

Relative indices: Univariate analysis did not identify any significant associations between CT-derived relative lung mophometric indices and PPC (Table 4.14).

Table 4.14 – Univariable analysis of the differences in relative lung density indices between PPC groups of patients with colorectal cancer. Data presented as mean (standard deviation, (SD)), median, and interquartile range [IQR]. LAA - Low attenuation area; NL - Normal lung; HAA - High attenuation area; PPC - Postoperative pulmonary complication.

Variable	PPC(-) (n=131)	PPC(+) (n=62)	Total (n=193)	p-value
LAA 870	35 (20.9)	35 (21.7)	35 (21.1)	0.988
LAA 880	28.9 (19.9)	28.4 (20.4)	28.7 (20)	0.873
LAA 890	23.1 (18.3)	22.7 (18.7)	23 (18.4)	0.903
LAA 900	17.8 (16.2)	17.6 (16.7)	17.7 (16.3)	0.930
LAA 910	14.1 (16.6)	13.3 (14.7)	13.8 (16)	0.726
LAA 950	3.2 (5.5)	3.8 (7.8)	3.3 (6.3)	0.538
NL 950-700	87 (7.6)	98.9 (98.6)	90.8 (56.2)	0.168
NL 950-750	80.2 (11.4)	79.4 (11.2)	80 (11.3)	0.656
NL 950-850	44.2 (19.2)	43 (21)	43.8 (19.8)	0.697
NL 900-700	72.7 (13.8)	72.9 (14.1)	72.8 (13.8)	0.916
NL 900-750	66 (13.7)	66 (13.2)	66 (13.5)	0.972
NL 900-800	53.3 (14)	52.8 (14)	53.1 (14)	0.825
HAA 700-500	10.1 (7)	10.1 (5.8)	10.1 (6.6)	0.974
HAA 750-500	16.9 (11.8)	17.1 (10.3)	17 (11.3)	0.924
HAA 800-500	29.6 (17.4)	30.6 (17.6)	29.9 (17.4)	0.713

Categorical indices stratified by tertiles: Univariate analysis did not identify any significant associations between CT-derived relative lung mophometric indices and PPC (Table 4.15 and 4.16). However, it identified airway volume (AIRWAY, Table 4.17) as demonstrating a trend towards association ($OR_{Airway:LowestTertile}$ 1.93, 95%CI 0.93–4.03, p=0.078). This variable was assessed with the regression model developed in Chapter 3 Subsection 3.4.4.2 on page 159.

Table 4.15 – Univariable analysis of the differences in relative lung density indices categorised by tertiles (low, medium, and high) between PPC groups of patients with colorectal cancer. Data presented as mean (standard deviation, (SD)), median, and interquartile range [IQR]. LAA - Low attenuation area; PPC - Postoperative pulmonary complication.

Variable	Level	PPC(-) (n=131)	PPC(+) (n=62)	Total	p-value
	Low	43 (32.8)	22 (35.5)	65 (33.7)	
LAA 870	Medium	47 (35.9)	17 (27.4)	64 (33.2)	
	High	41 (31.3)	23 (37.1)	64 (33.2)	0.491
	Low	42 (32.1)	23 (37.1)	65 (33.7)	
LAA 880	Medium	45 (34.4)	19 (30.6)	64 (33.2)	
	High	44 (33.6)	20 (32.3)	64 (33.2)	0.774
	Low	43 (32.8)	22 (35.5)	65 (33.7)	
LAA 890	Medium	45 (34.4)	19 (30.6)	64 (33.2)	
	High	43 (32.8)	21 (33.9)	64 (33.2)	0.871
	Low	43 (32.8)	22 (35.5)	65 (33.7)	
LAA 900	Medium	43 (32.8)	21 (33.9)	64 (33.2)	
	High	45 (34.4)	19 (30.6)	64 (33.2)	0.871
	Low	44 (33.6)	21 (33.9)	65 (33.7)	
LAA 910	Medium	41 (31.3)	23 (37.1)	64 (33.2)	
	High	46 (35.1)	18 (29.0)	64 (33.2)	0.639
	Low	45 (34.4)	20 (32.3)	65 (33.7)	
LAA 950	Medium	40 (30.5)	24 (38.7)	64 (33.2)	
	High	46 (35.1)	18 (29.0)	64 (33.2)	0.503

Table 4.16 – Univariable analysis of the differences in relative lung density indices categorised by tertiles (low, medium, and high) between PPC groups of patients with colorectal cancer. Data presented as mean (standard deviation, (SD)), median, and interquartile range [IQR]. NL - normal lung; PPC - postoperative pulmonary complications

Variable	Level	PPC(-) (n=131)	PPC(+) (n=62)	Total	p-value
	Low	44 (33.6)	21 (33.9)	65 (33.7)	
NL 950-700	Medium	46 (35.1)	18 (29.0)	64 (33.2)	
	High	41 (31.3)	23 (37.1)	64 (33.2)	0.639
	Low	42 (32.1)	23 (37.1)	65 (33.7)	
NL 950-750	Medium	48 (36.6)	16 (25.8)	64 (33.2)	
	High	41 (31.3)	23 (37.1)	64 (33.2)	0.327
	Low	45 (34.4)	19 (30.6)	64 (33.2)	
NL 950-850	Medium	43 (32.8)	21 (33.9)	64 (33.2)	
	High	43 (32.8)	22 (35.5)	65 (33.7)	0.871
	Low	47 (35.9)	18 (29.0)	65 (33.7)	
NL 900-700	Medium	42 (32.1)	22 (35.5)	64 (33.2)	
	High	42 (32.1)	22 (35.5)	64 (33.2)	0.491
	Low	46 (35.1)	19 (30.6)	65 (33.7)	
NL 900-750	Medium	43 (32.8)	21 (33.9)	64 (33.2)	
	High	42 (32.1)	22 (35.5)	64 (33.2)	0.814
	Low	45 (34.4)	20 (32.3)	65 (33.7)	
NL 900-800	Medium	41 (31.3)	23 (37.1)	64 (33.2)	
	High	45 (34.4)	19 (30.6)	64 (33.2)	0.720

Table 4.17 – Univariable analysis of the differences in relative lung density indices categorised by tertiles (low, medium, and high) between PPC groups of patients with colorectal cancer. Data presented as mean (standard deviation, (SD)), median, and interquartile range [IQR]. HAA - High attenuation area; TV - Total lung volume; PPC - Postoperative pulmonary complications.

Variable	Level	PPC(-) (n=131)	PPC(+) (n=62)	Total	p-value
	Low	41 (31.3)	24 (38.7)	65 (33.7)	
HAA 700-500	Medium	49 (37.4)	15 (24.2)	64 (33.2)	
	High	41 (31.3)	23 (37.1)	64 (33.2)	0.189
	Low	44 (33.6)	21 (33.9)	65 (33.7)	
HAA 750-500	Medium	45 (34.4)	19 (30.6)	64 (33.2)	
	High	42 (32.1)	22 (35.5)	64 (33.2)	0.850
	Low	45 (34.4)	20 (32.3)	65 (33.7)	
HAA 800-500	Medium	44 (33.6)	20 (32.3)	64 (33.2)	
	High	42 (32.1)	22 (35.5)	64 (33.2)	0.893
	Low	46 (35.1)	19 (30.6)	65 (33.7)	
TV	Medium	44 (33.6)	20 (32.3)	64 (33.2)	
	High	41 (31.3)	23 (37.1)	64 (33.2)	0.893
	Low	37 (28.2)	28 (45.2)	65 (33.7)	
AIRWAY	Medium	48 (36.6)	16 (25.8)	64 (33.2)	
	High	46 (35.1)	18 (29.0)	64 (33.2)	0.063

Clinical model - a model combining demographic and clinical variables that were associated with PPC, as per multivariable analysis in Chapter 3 Subsection 3.4.4.2 on page 159, did not yield similar associations when applied to PSM matched cohort. An alternative model was developed and combined with the morphometric indices selected in the process described above (airway volume tertiles and total lung volume tertiles).

Table 4.18 – The results of stepwise multiple logistic regression of the association between combining clinical patient-related factors and airway volume lung morphomarkers categorised by tertiles and the development of pulmonary complications in patients with colorectal cancer. CLD - Chronic lung diseases; NTNM - Number of nearby lymph nodes that contain cancer according TNM; AF - Atrial fibrillation; WCC - White cell count; Hb - Haemoglobin; CI - Confidence interval.

Variable	Units	Odds Ratio	95% CI	p-value
CLD	0	Ref		
	1	9.90	4.53–21.60	<0.001
NTNM	N0	Ref		
	N1	1.39	0.61–3.19	0.435
	N2	2.30	0.73–7.20	0.153
Dementia		11.99	1.39–103.31	0.024
AF		0.47	0.04–5.67	0.551
WCC		1.12	1.00–1.25	0.061
Sex	M	2.15	0.–5.24	0.092
Hb		1.00	0.98–1.02	0.784
Surgical approach	0	Ref		
	1	0.52	0.23–1.17	0.116
	2	2387415.11	0.00–Inf	0.987
Tertile of airway volume	High	Ref		
	Medium	1.10	043–2.77	0.848
	Low	2.58	1.04–6.39	0.040

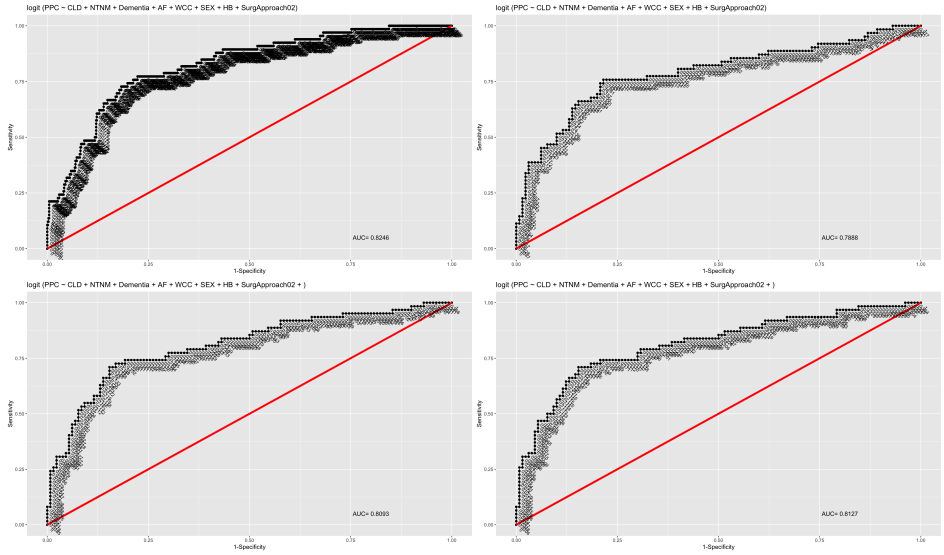


Figure 4.9 – The analysis of the receiver operating characteristic (ROC) and area under the curve (AUC) demonstrates the diagnostic performance ability of the four models combining clinical patient-related factors and the lung morphomarkers of airway volume and total lung volume to predict postoperative pulmonary complications in patients with colorectal cancer.

Table 4.19 – The results of stepwise multiple logistic regression of the association between combining clinical patient-related factors and airway volume and total lung volume lung morphomarkers categorised by tertiles and the development of pulmonary complications in patients with colorectal cancer. CLD - Chronic lung diseases; NTNM - Number of nearby lymph nodes that contain cancer according TNM; AF - Atrial fibrillation; WCC - White cell count; Hb - Haemoglobin; CI - Confidence interval.

Variable	Units	Odds Ratio	95% CI	p-value
CLD	0	Ref		
	1	9.67	4.41–21.20	<0.001
NTNM	N0	Ref		
	N1	1.31	0.57–3.03	0.525
	N2	2.33	0.74–7.35	0.153
Dementia		11.79	1.36–102.44	0.025
AF		0.44	0.04–5.23	0.512
WCC		1.11	0.95–1.25	0.067
Sex	M	1.62	0.59–4.47	0.347
Hb		1.00	0.98–1.01	0.645
Surgical approach	0	Ref		
	1	0.50	0.22–1.15	0.103
	2	2514491.03	0.00–Inf	0.987
Tertile of airway volume	High	Ref		
	Medium	1.16	0.45–2.94	0.760
	Low	3.12	1.18–8.28	0.022
Total lung volume		1.00	1.00–1.00	0.253

The model based on demographic and clinical parameters alone had c-statistic of 0.83 and pseudo-R^2 of 0.28 when developed on the whole colorectal cohort (Figure 4.9-A).Performing regression using the same set of variables on the cohort used for morphometric analysis in this chapter (n=193) reduced c-statistic to 0.77 but the pseudo-R^2 of 0.34 suggested better goodness of fit (Figure 4.9-B). Addition of tertiles of airway volume to this model increased c-statistic to 0.81 and the pseudo-R^2 to 0.37 (Figure 4.9-C), but the ANOVA test did not indicate significant change in model performance (p=0.071). Inclusion of total lung volume increased c-statistic to 0.813 and further increased goodness of fit (pseudo-R^2=0.377) but this improvement compared with the clinical model was still not clinically significant (p=0.086). The total lung volume was not

independently associated with PPC in this model (OR 1.00, 95%CI 1.00–1.00, p=0.253).

4.4.4 Association of quantitative, CT-derived mophometric lung indices with survival

4.4.4.1 Vascular cohort

The univariable analysis evaluated the differences in volumetric, proportional and tertile-based categories of lung attenuation areas between PPC groups. The dataset comprised a total of 62 patients, with 15 patients who developed PPC and 47 patients who did not.

Routine screening for variables with pdid not identify any quantitative, CT-derived morphometric lung indices. The selection process was also conducted automatically using step() function and corrected for collinearity by calculating VIF as described before. This yielded three morphometric lung indices, but they were not independently associated with survival (Table 4.20).

Table 4.20 – The results of a stepwise logistic regression analysis for a Cox proportional hazard model of the association between lung morphomarkers and survival after aortic aneurysms surgery. VOL – Volumetric; LAA - Low attenuation area; NAA – normal attenuation area; HAA - High attenuation area; VIF - variance inflation; HU - Hounsfield unit; CI - Confidence interval.

Variable	VIF	Hazard Ratio	95% CI	p-value
LAA_{VOL} -920 HU	1.622	1.01	0.78;1.30	0.952
NAA_{VOL} -910 to -650 HU	3.064	1.08	0.90;1.31	0.400
NAA_{VOL} -910 to -850 HU	4.074	0.93	0.74;1.16	0.511

4.4.4.2 Colorectal cancer cohort

The univariable analysis evaluated the association of volumetric, proportional and tertile-based categories of lung attenuation areas with survival. The dataset comprised a total of 193 patients, with 62 patients who developed PPC and 131 patients who did not.

Out of 49 variables included only two (airway volume and volumetric measure of LAA categorised by tertiles) were significantly associated with survival and were included in the final model (Table 4.21 and Figure 4.10).

Table 4.21 – The results of a stepwise logistic regression analysis for a Cox proportional hazard model of the association between lung morphomarkers and survival after colorectal cancer surgery. VOL – Volumetric; LAA - Low attenuation area; HU - Hounsfield unit; CI - Confidence interval.

Variable	Units	Hazard Ratio	95% CI	p-value
Airway volume		1.12	1.06–1.25	0.038
Tertile of LAA_{VOL} -950 HU	Highest	Ref		
	Medium	1.52	1.07–2.16	0.021
	Lowest	1.11	0.78–1.58	0.549

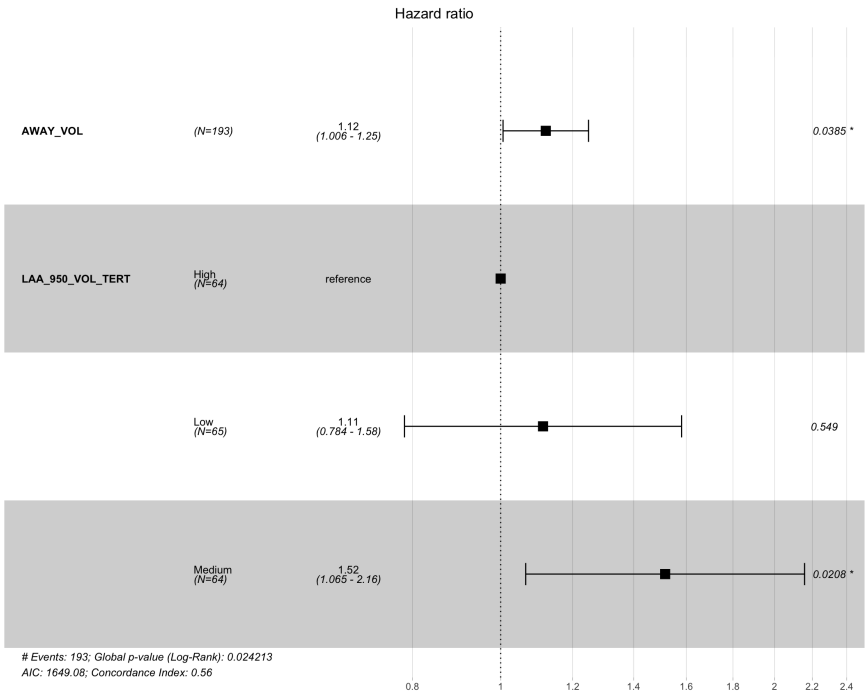


Figure 4.10 – A forest plot demonstrating the results of a stepwise logistic regression analysis for a Cox proportional hazard model of the association between lung morphomarkers (Airway volume and volumetric measure of $LAA_{VOL\text{-}Tertile}$ -950 Hounsfield unit (HU)) and survival after colorectal cancer surgery. LAA - Low attenuation area.

The Receiver Operating Characteristic curves assessing predictive value of the model showed c-statistic of 0.36 at one year, 0.59 at 3 years, and 0.62 at six years indicating poor performance of the model (Figure 4.11).

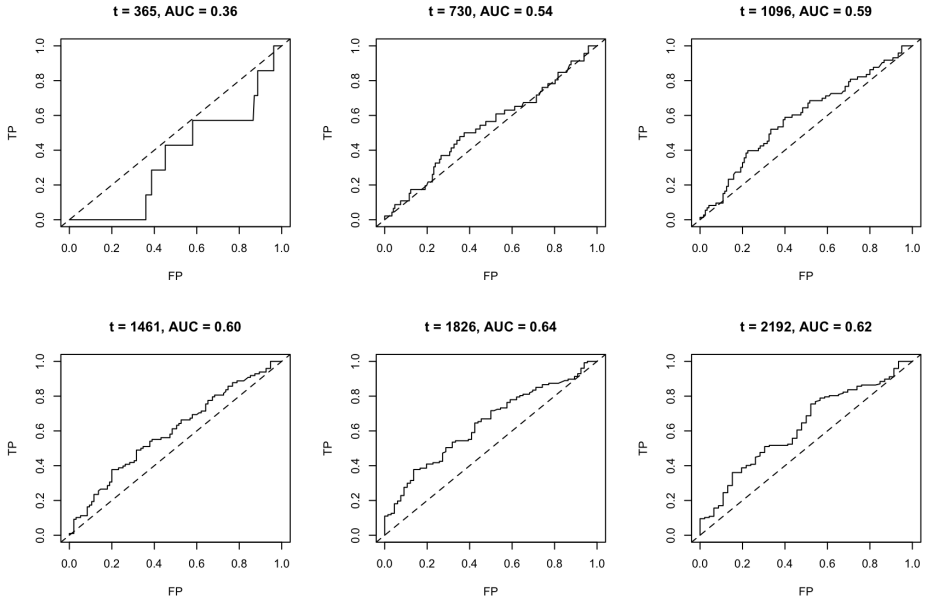


Figure 4.11 – The analysis of the receiver operating characteristic (ROC) and area under the curve (AUC) assesses the predictive value of the model, including lung morphometry for survival. Predictive value (AUC) demonstrated at six different time points: 1 year (t=365), 2 years (t=730), 3 years (t=1096), 4 years (t=1461), 5 years (t=1826) and 6 years (t=2192).

Clinical model described in Chapter 3 in Subsection 3.4.6.2 on page 165 did not demonstrate significant associations for included variables in the propensity score-matched colorectal cohort. We developed another model using stepwise regression and included all clinical and demographic variables used in Chapter 3. This model included ASA grade, procedure (sigmoid colectomy), type of surgery, COPD, preoperative creatinine, albumin and lymphocyte levels, PPC and presence of metastatic disease (MTNM). This model showed that ASA Grade III, open surgery, and pre-operative biochemical and haematological parameters (creatinine, albumin, lymphocytes) were independently associated with survival of patients with colorectal cancer (Table 4.15).

The model had modest performance with c-statistic 0.76 at year 6 (Figure 4.13 on page 222).

Table 4.22 – The results of a stepwise multiple logistic regression analysis for a Cox proportional hazard model of the association between clinical patient-related factors and survival after colorectal cancer surgery. ASA – American Society of Anesthesiologists score systems; COPD – Chronic Obstructive Pulmonary Disease; PPC – Postoperative pulmonary complications; MTNM – presence of metastatic disease that contain cancer according TNM; CI - Confidence interval.

Variable	Units	Hazard Ratio	95% CI	p-value
ASA	Grade I	Ref		
	Grade II	1.49	0.94;2.37	0.092
	Grade III	2.61	1.45;4.71	0.001
	Grade IV	4.22	0.94;19.08	0.061
Procedure	Anterior Resection	Ref		
	Sigmoid Colectomy	0.50	0.25;1.00	0.050
Modality	Laparoscopic	Ref		
	Open	0.55	0.39;0.77	<0.001
	Laparoscopic conversion	0.80	0.46;1.39	0.431
COPD		0.72	0.49;1.05	0.087
Creatinine		1.01	1.00;1.02	0.013
Albumin		0.93	0.91;0.96	<0.001
Lymphocyte count		1.31	1.11;1.54	0.001
PPC		1.30	0.94;1.79	0.116
MTNM	M0	Ref		
	M1	1.76	0.92;3.36	0.087

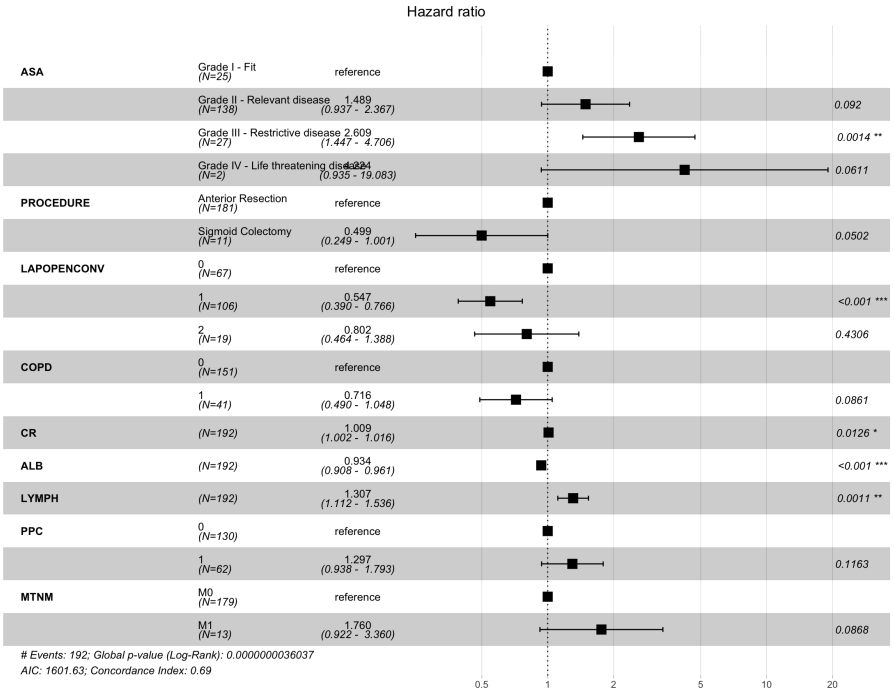


Figure 4.12 – A forest plot demonstrating the results of a stepwise logistic regression analysis for a Cox proportional hazard model of the association between clinical patient-related factors and survival after colorectal cancer surgery. ASA – American Society of Anesthesiologists score systems; COPD – Chronic Obstructive Pulmonary Disease; PPC – Postoperative pulmonary complications; MTNM – presence of metastatic disease that contain cancer according TNM; CR – Creatinine, ALB – Albumin, Lymph – lymphocyte count; AIC - Akaike information criterion.

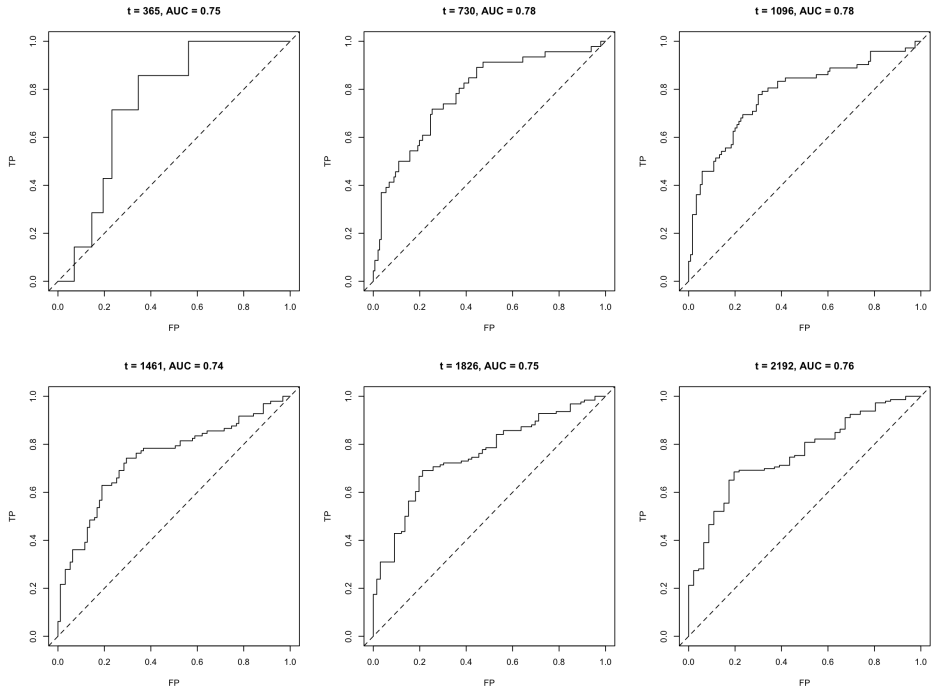


Figure 4.13 – Receiver Operating Characteristic curves assessing predictive value of the model including clinical parameters. Predictive value (c-statistic) demonstrated at six different time points: 1 year (t=365), 2 years (t=730), 3 years (t=1096), 4 years (t=1461), 5 years (t=1826) and 6 years (t=2192).

The Cox proportional hazards model that included quantitative, CT-derived mophometric lung indices demonstrated that ASA Grade III, surgical procedure (sigmoid colectomy), open surgery|, COPD, creatinine, albumin, lymphocyte count, airway volume and mid tertile of lung tissue volume at LLA 950 HU, but not PPC to be independent predictors of survival (Table 4.23).

Addition of quantitative, CT-derived mophometric lung indices to the clinical model resulted in improved its overall performance with increase in c-statistic to 0.80 at year 6 (Figure 4.15).

Table 4.23 – The results of stepwise multiple logistic regression of the association between combining clinical patient-related factors and airway volume and total low attenuation area lung morphomarkers categorised by tertiles and the development of PPC in patients with colorectal cancer. ASA – American Society of Anesthesiologists score systems; COPD – Chronic Obstructive Pulmonary Disease; PPC – Postoperative pulmonary complications; MTNM – presence of metastatic disease that contain cancer according TNM; LAA - Low attenuation area; HU - Hounsfield unit; CI - Confidence interval.

Variable	Units	Odds Ratio	95% CI	p-value
ASA	Grade I	Ref		
	Grade II	1.51	0.95–2.40	0.081
	Grade III	2.75	1.50–5.04	0.001
	Grade IV	4.32	0.93–20.13	0.062
Procedure	Anterior Resection	Ref		
	Sigmoid Colectomy	0.44	0.21–0.90	0.025
Modality	Laparoscopic	Ref		
	Open	0.51	0.36–0.72	<0.001
	Laparoscopic conversion	0.75	0.43–1.33	0.323
COPD		0.62	0.42–0.92	0.017
Creatinine		1.01	1.00–1.02	0.022
Albumin		0.93	0.91–0.96	<0.001
Lymphocyte count		1.29	1.10–1.51	0.001
PPC		1.28	0.91–1.78	0.152
MTNM	M0	Ref		
	M1	1.83	0.93–3.59	0.078
Airway volume		1.02	1.01–1.03	0.003
Tertile of LAA_{VOL} -950 HU	Highest	Ref		
	Middle	1.00	0.68–1.47	0.985
	Lowest	1.52	1.04–2.23	0.033

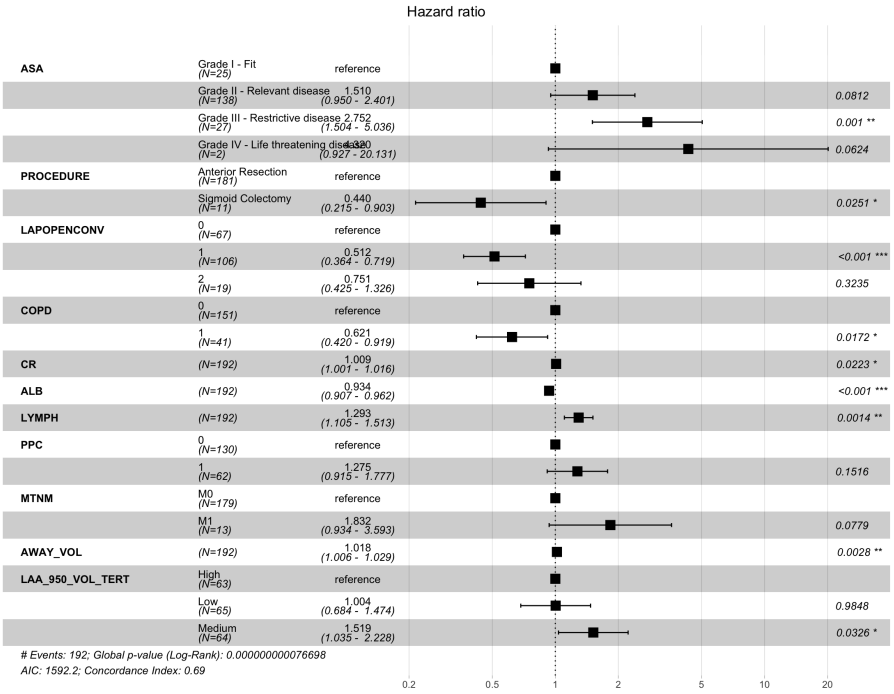


Figure 4.14 – A forest plot demonstrating the results of a stepwise logistic regression analysis for a Cox proportional hazard model of the association between clinical patient-related factors, and lung morphomarkers with survival after colorectal cancer surgery. SA – American Society of Anesthesiologists score systems; COPD – Chronic Obstructive Pulmonary Disease; PPC – Postoperative pulmonary complications; MTNM – presence of metastatic disease that contain cancer according TNM; CR – Creatinine, ALB – Albumin, Lymph – lymphocyte count; AIC - Akaike information criterion; AWAY_VOL – Airway volume; $LAA_{VOL\text{-}Tertiles}$ -950 Hounsfield unit (HU) – Tertile of low attenuation area; VOL – Volumetric.

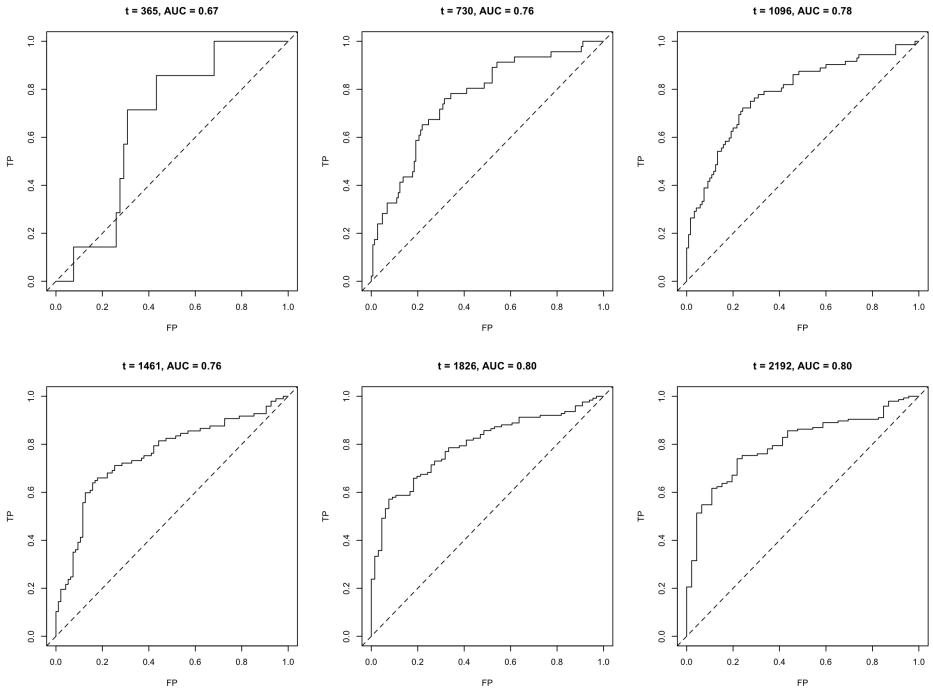


Figure 4.15 – The analysis of the receiver operating characteristic (ROC) and area under the curve (AUC) assesses the predictive value of the model, including clinical factors and lung morphomarkers for survival after colorectal cancer surgery. Predictive value (AUC) demonstrated at six different time points: 1 year (t=365), 2 years (t=730), 3 years (t=1096), 4 years (t=1461), 5 years (t=1826) and 6 years (t=2192).

4.5 Discussion

The aim of this chapter was to establish the clinical value of QCT indices by defining the range of QCT lung morphology values, identify any association between QCT parameters like NAA, LAA, HAA and PPC, and determine whether these indices have an impact on both survival in patients who had surgery for aortic aneurysms and colorectal cancer.

Several major findings were demonstrated: that the LAA values (VOL and PROP) had no significant impact on predicting the PPC using logistic regression analysis in both cohorts. Using multivariable logistic regression, it was evident that the NAA and HAA indices ($NAA_{(VOL)}$ -850 to -750 HU and $HAA_{(VOL)}$ -850 to -500 HU) had the ability to discriminate between patients who encountered PPC and those who did not in patients who underwent aortic aneurysm surgery.

Univariate analysis did not identify any significant associations between QCT lung morphology indices including NAA, LAA, and HAA and PPC in patients who underwent colorectal cancer surgery. However, it identified high tertiles of airway volume demonstrating a trend towards association with PPC.

On the other hand, the indices of lung morphology (airway volume and medium $LAA_{(VOL\ Tertile)}$ <- 950) had a statistically significant influence on the survival outcome only in patients who underwent colorectal cancer surgery. Non of the morphometric lung indices showed associated with survival outcome on vascular cohort.

An accurate evaluation of patients with an increased risk of PPC following major surgery is crucial. It enables the clinicians to determine if the patient is fit for the surgery at present, reveal potential for risk optimisation options and appropriate surgical modality. There has been a recent increase in interest in visualising lung morphology due to the development of CT-derived quantification methods and advances in computer vision (branch of artificial intelligence). The advancement of CT has allowed the acquisition of high-resolution images in a proportional and volumetric manner, capturing the entire lung. Computing

techniques allow for more accurate identification of subtle changes captured on imaging and more comprehensive evaluation of available data (Chen et al., 2020).

Some recent reports discussed the advantages of using preoperative QCT imaging of lung morphology in the field of thoracic surgery and the general population (Washko et al., 2011; Podolanczuk et al., 2016; Kitazawa et al., 2021; Barros et al., 2022a). In the context of the surgical operation, however, the majority of studies have focused on assessing the association of the LAA with PPC.

The LAA index has been accepted as an exceptionally reliable quantitative measure of the pulmonary emphysema (Muller et al., 1988; Madani et al., 2006). Emphysema is pathologically defined as the destruction of the airway beyond the terminal bronchioles. Radiologically, it is identified by abnormally LAA that extend from the surrounding lung tissue (Madani et al., 2006; Litmanovich, Boiselle and Bankier, 2009). These abnormal alterations characterised by lung areas filled by attenuation values below - 900 to - 970 HU (Muller et al., 1988; Madani et al., 2007; Karimi et al., 2014).

Previous studies have demonstrated the clinical value of quantifying pulmonary emphysema by CT imaging evaluation. These studies established significant associations between the quantification of LAA (reflecting the extent of the emphysema) on CT scans and its relation to PPC. These studies were focused on attenuation lower than -950 HU and -900 HU and suggested that the quantification of LAA could potentially be used to predict the PPC in thoracic and lung cancer patients (Kaplan et al., 2015; Makino et al., 2018; Kitazawa et al., 2021).

In this chapter, emphysema was defined as areas with a density range of less than -850 to -970 HU. This was done to facilitate comparing the results to those from other studies and to avoid any possible influence of reconstruction imaging parameters and the scanner model on the outcomes, as suggested in the previous report (Madani, Van Muylem and Gevenois, 2010; Yuan et al., 2007). Despite these efforts, the univariate analysis showed that there was no association between the emphysematous proportional relative lung density,

the measurements of volume from the preoperative CT scan, and PPC in both study cohorts. This might be because of the heterogeneous lung parenchyma, inflammation, and lung disorders of lung cancer patients, which included a high proportion of smokers and emphysematous patients in previous studies. It seems reasonable that these factors could generally increase the risk of PPC and possibly raise the likelihood of an association between lung morphology biomarkers and PPC.

Another simple method of QCT lung morphomarker analysis using NAA, represented by the lung volume within a specific density spectrum of -950 to -700 HU, is to diagnose and stage interstitial lung disease in groups of patients limited to Asian populations (Ohkubo et al., 2016; Ohkubo et al., 2018; Barros et al., 2022a). It is still not known whether NAA plays a role in predicting PPC in a clinical setting. So, one of the main goals of this retrospective study is to find out what role NAA plays. It was found that a normal lung index could help predict the PPC in people who have aortic aneurysms. Various lower thresholds ranging from -805 HU to -930 HU and higher thresholds ranging from -600 HU to -850 HU were evaluated. In the multivariable logistic regression analysis, only $NAA_{(VOL)}$ -850 to -750 HU stood out as a way to tell the difference between patients who developed PPC compared to those who did not (OR 1.00; 95%CI 1.00–1.00, p=0.0541).

The precision of lung tissue measurement and its clinical relevance is important factor here. In clinical research, measurements should not only be statistically significant but also clinically meaningful. If changes of less than 100mL in lung tissue volume are within the range of physiological compensation and therefore not clinically significant, it would be sensible to adjust the unit of analysis to reflect clinically relevant changes. Thus, although with this unit of measurement (mL) there is no distinguishable association of lung parameters with PPC. By rescaling the unit of analysis to 100mL, this effectively increase the threshold for detecting a clinically significant change. This would ensure that the odds ratios reflect differences that are meaningful in a clinical context.

On the other hand, there was no significant association found in logistic regression between CT-derived normal volumetric and relative proportion lung

morphomarkers and PPC in people who had colorectal cancer. This contradictory finding might be explained by the fact that the implemented thresholds were not more sensitive to detecting normal lung attenuation.

The lack of studies related to investigating the association between the PPC and normal lung morphomarkers adds a challenge to direct comparison and validation of the results of this chapter. This means that more research is needed to see if NAA could be used to predict clinical endpoints, such as PPC, after minor and major surgical interventions.

Similarly, no studies have been published assessing the association between QCT of parenchymal lung disease and PPC. These studies focused on the general population (Lederer et al., 2009; Podolanczuk et al., 2016; Podolanczuk et al., 2017; Choi et al., 2020), and came up with a novel method to measure HAA with an attenuation higher than -600 HU. They concluded that HAA accurately helps to predict the existence of lung abnormalities.

To evaluate this gap, this retrospective analysis in the current chapter sought to investigate whether the HAA could help predict the PCC. The result found that a volumetric threshold value of $HAA_{(VOL)}$ -850 to -500 HU had the ability to differentiate between the PPC group in multivariate analysis (OR 0.15; 95%CI 1.00-1.00, p = 0.025). However, the impact of the small sample size and proportion of PPC in the aortic aneurysm cohort hindered a fully conclusive association between the HAA index and PPC. Further large studies are warranted.

Contrary to expectations, none of the adjusted HAA thresholds were able to show a significant difference between the PPC groups in the colorectal cancer cohort, despite the relatively large sample size presented with pre-existing lung diseases. It is difficult to explain this result, but it might be related to the fact that the implemented thresholds in this study, which were cited in the related literature (Shin et al., 2011; Barros et al., 2022a), were not able to detect the distribution of lung disease abnormalities. In fact, this could back up what was seen in the group of people with aortic aneurysms, since the $HAA_{(VOL)}$ -850 to -500 HU threshold helped to predict PPC. This is different from what has been shown in the literature, which indicated using a threshold density

higher than -600 HU. According to these data, it may be inferred that patients may present to different complex surgeries with different severity of lung disease distribution, which would influence the lung density attenuations. This raises the possibility that not all the cited thresholds could be applicable to different cohorts of populations to detect lung abnormalities. Further studies that take these factors into account will need to be undertaken, and more density thresholds should be implemented to confirm if the association is true or not.

There are some interesting, and particularly promising findings in this chapter. Combining patient-related preoperative risk factors and QCT indices produced a number of predictive models. This has led to the important inclusion of lung morphology in the preoperative risk stratification tool, which appears to be clinically useful but requires more research. Another finding that stands out from the results of the clinical models is that the proportion of patient-related factors increased the risk of developing the PPC, which is attributable to its importance. Further large studies, which take these preoperative clinical biomarkers into account, will need to be undertaken to develop reliable preoperative stratification tools.

The impact of the QCT indices of lung morphology on survival outcomes has not been fully investigated in clinical practice. However, few published studies have attempted to investigate the ability of QCT lung morphology analysis to predict survival. In patients experienced COPD and ILD, Barros et al. (2022a) demonstrated a proportional relative lung density of NAA measured between -950 and -700 HU was a significant independent predictor of mortality. Johannessen et al. (2013) observed that the extent of emphysema with LAA $<$ -950 HU $\geq$ 10% was a strong predictor of 8-year long-term survival in smoker patients with COPD. Podolanczuk et al. (2016) identified a significant association between all-cause long-term mortality and the proportional relative lung density of HAA measured between -600 and -250 HU in community-dwelling adults.

However, there is a lack of information in the literature regarding the benefits of assessing the QCT indices of lung morphology before surgery in

terms of the survival of surgical patients. In this context, perhaps the most interesting finding is that the patients with colorectal cancer who were in the medium tertile of proportional relative lung density of $LAA_{(VOL\ Tertile)}$ <- 950 and low airway volume were more likely to have worse survival (OR 1.52; 95%CI 1.07–2.16, p = 0.021;OR 3.13; 95%CI 1.06–9.24, p = 0.038, respectively). These results suggest that QCT indices of lung morphology could be an important part of patient-related factors used before surgery to predict mortality.

The study in current chapter has some limitation. Firstly, the results for colorectal cohort were acquired retrospectively. However, data missingness for most variables was impressively small. The vascular cohort, although prospective with a very small data missingness, featured a small sample size with a short follow-up. Secondly, the rate of recorded chronic lung disease was low (likely misdiagnosed as well), and the smoking status which is expected to play critical role in predicting PPC and survival was recorded poorly and was omitted from the analyses. Thirdly, the threshold values that determine QCT indices of lung morphology may differ with CT scan model, acquisition protocol, and cohort characteristic.

4.6 Conclusions

The quantitative evaluation of lung morphology did not show evidence of strong association with PPC. Hence, the clinical implications of these findings are unclear. However, the findings of the current chapter showed that LAA and airway volume morphomarker are novel risk factors for long-term survival in patients with colorectal cancer. This new understanding should help improve the preoperative risk stratification tools. To prove that QCT indices of lung morphology are useful in clinical settings a larger cohort of patients should be analysed. The data analysis using machine learning techniques should also be considered as the number of variables that we were able to analyse certainly exceeds the numbers used in conventional statistics.

Chapter 5

Quantitative CT-derived indices of body composition and their association with PPC and survival

5.1 Introduction

The previous chapter demonstrated the clinical usefulness of assessment of lung morphology. However, it should be noted that the morphomarkers relating to whole-body composition may have equivalent or a greater weight to lung morphology in this regard.

Existing validated risk stratification tools may be useful the identification of suitable operative candidates (Barnett and Moonesinghe, 2011), but they frequently only target specific aspects of a patient's risk profile. Such tools are often subjective, and do not fully engage with the requirements of a more elderly patient cohort which presents with a number of comorbidities requiring elective operative procedures (Englesbe et al., 2012). Conventional parameters, e.g. chronological age, may be insufficient to describe the frailty of a patient or their general state of well-being. Additionally, morphomarkers of body composition, such as BMI, lack specificity and only offer an indirect assessment of body fat (Sabel et al., 2013). These individual measures, therefore, fail to define the patient's physiological status in its entirety.

Awareness of these issues has stimulated efforts to undertake a more holistic view and which encompass morphometry - body composition analysis. This is a reasonably new method of evaluating the morphological components of body composition (Sabel et al., 2013), and typically, exploits information obtained

from cross-sectional imaging modalities prior to an intervention, e.g. CT scans of the abdomen and pelvis, which are often performed prior to operative procedures for malignancy (Richards, Senadeera and Frizelle, 2020). Body composition derived from CT imaging is of particular pertinence to patients undergoing treatment for colorectal tumours, as imaging data are generally used in order to stage the malignancy, and therefore can be reviewed for body composition information without additional expenditure (Malietzis et al., 2015). Sarcopenia, abdominal adiposity, waist circumference, and the thickness of the diaphragmatic muscle are amongst key pathological body composition changes which may be evident on staging CT images. These parameters are gradually becoming established as prognostic markers for both therapeutic decisions and clinical endpoints.

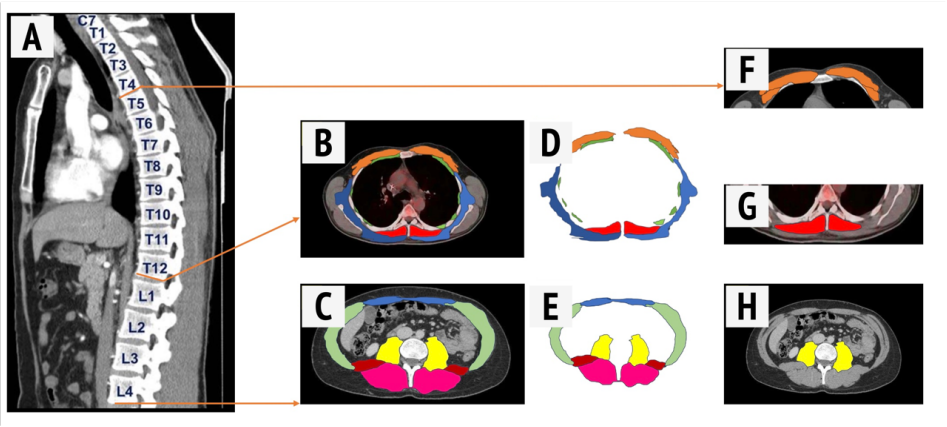


Figure 5.1 – Assessment of muscle mass using morphometric techniques.

Jacobs et al. (2022) noted that quantification of the psoas muscle dimensions is a technique which is rapidly gaining popularity within a number of surgical disciplines for the measurement of the degree of sarcopenia, and the extent of a patient's frailty. These parameters are straightforward to acquire, and require no additional financial outlay, as they can be extracted from CT scans which have already been carried out for clinical indications. Psoas measurements are highly reproducible and have been extensively validated in patients undergoing operative interventions for colorectal lesions. The total psoas index is typically obtained without difficulty from the simple measurement of the cross-sectional

area of the two psoas muscles at the level of the body of the patient's third of fourth lumbar vertebra; the parameter is then normalised for the height of the patient. This index offers a guide to the physiological status of the patient, and adds information to the patient's pre-surgical risk evaluation and therapeutic decision-making processes .

To date, waist circumference has been the conventional parameter utilised (Ma et al., 2013) in order to gain an indication of intra-abdominal and central adiposity (Ross et al., 2020; Joo et al., 2021). Robustly correlated with BMI measurements, waist circumference has prognostic significance in terms of the risk of obesity-related pathologies (Sonmez et al., 2013). When assessed by hand, there is a potential risk of the spread of infectious disease between patient and clinical staff (Joo et al., 2021). In principle, CT images, which have been acquired for routine clinical indications, could be utilised in order to acquire this measurement, especially in patients who are scheduled for colorectal procedures. However, the applicability of this option has not yet been investigated in detail.

Measurement of the amount of intra-abdominal fatty tissue at the level of the third lumbar vertebra has been performed in studies of patients undergoing colorectal procedures (Malietzis et al., 2016; Basile et al., 2021). A number of novel anthropometric parameters have been described, e.g. visceral (VFA), subcutaneous (SFA) and total (TFA) fat areas, as well as the VFA:TFA ratio (Kuritzkes et al., 2018; Pacquelet et al., 2022). These measures describe the different adipose tissue distributions within the human body (Feng et al., 2023). Visceral adiposity is typically found within the abdomen (Basile et al., 2021). In contrast to subcutaneous fat, it has higher metabolic activity and is associated with an abundance of cells from both inflammatory and immune systems (Ibrahim, 2010; Pacquelet et al., 2022). As observed by Pacquelet et al. (2022), these CT-derived parameters of body composition are particularly relevant in view of the well-documented associations between raised BMI and colorectal tumours, and also between obesity and the clinical endpoints of operative interventions.

The relationships between sarcopenia, based on psoas muscle parameters, and the abdominal adipose tissue content, with PPC, have been examined in patients undergoing surgical procedures for colorectal surgery. A limitation of these studies, however, is that frequently, authors have used various classifications of PPC (Cakir et al., 2015a; Heus et al., 2019; Chang et al., 2022), e.g. the Calvien-Dindo classification (Kuritzkes et al., 2018; Tankel et al., 2020; Uehara et al., 2022; Dong et al., 2022; Feng et al., 2023). Additionally, studies have included patients receiving only one type of colorectal procedure, e.g. right-, or left-sided (Li et al., 2023b) elective laparoscopic surgery , and some clinical issues, such as pneumonia, were infrequent in some of the small populations studied (Cakir et al., 2015a; Heus et al., 2019; Tankel et al., 2020; Uehara et al., 2022; Li et al., 2023b). Consequently, the study outcomes were inconsistent. Some authors reported higher frequencies of PPC being linked with low psoas muscle parameters (Chang et al., 2022) and increased levels of visceral adiposity (Cakir et al., 2015a; Kuritzkes et al., 2018), whereas others failed to find evidence of correlations between PPC and either psoas muscle measurements (Traeger et al., 2023a), or degree of subcutaneous adipose tissue (Feng et al., 2023).

There are few studies based on patients undergoing colorectal procedures which have looked at the import of body composition, e.g. parameters of psoas muscle or abdominal adiposity, on mortality long-term. One such study noted that elevated 1-year mortality statistics were linked with a reduced psoas muscle index (13.9% vs 0.9%; OR 16.2; 95%CI 4.34 - 83.4; $p<0.01$)(Richards, Senadeera and Frizelle, 2020). Li et al. (2023b) included patients who had carcinoma of the ascending colon or rectum, and showed that a diminished psoas muscle index measured prior to surgery was an independent predictive factor for poorer 5-year survival (HR 1.367, 95%CI 1.049–1.782; $p=0.021$). This substantiated the observations of Lee et al. (2015) who also noted that patients with visceral obesity was independently linked with impaired 5-year overall survival (HR 7.0; 95%CI 2.0–24.6; $p=0.002$). In patients with colorectal carcinoma and established metastases, a median overall survival of 30.97 months (HR 2.6; $p=0.020$) was correlated with increased levels of visceral adipose tissue (Basile et al., 2021). Although a number of studies have ob-

served that overall survival has been positively impacted by diminished psoas muscle measurements and elevated levels of visceral fat, there continues to be a lack of consensus on this topic, with numerous studies being unable to support these findings (Malietzis et al., 2016; Abbass et al., 2020; Shirdel et al., 2020; Perrin et al., 2021; Blackwell et al., 2023). There is little research that has investigated the prognostic value of subcutaneous adipose tissue, waist circumference or the thickness of the diaphragm in terms of PPC and long-term mortality.

It is difficult to compare the outcomes of these studies directly and to make robust assumption as they include various population cohorts and sizes, and use a range of definitions, methodologies, and cut-off limits. The descriptions of PPC are at times inadequate and lack standardisation, which adds further complexity to the way in which the results can be viewed and applied in the clinical domain. The import of measurements of whole-body composition in patients with colorectal disease is at present unclear, as there are few studies which have evaluated this topic, especially in relation to the site of the tumour, i.e. as to whether it is on the right or left side of the bowel. The latter, especially, is associated with a poorer clinical outcome; few clinical studies have been conducted in order to evaluate the utility of whole-body composition analysis in patients with either left-sided colonic or rectal tumours.

5.2 Hypothesis and aims

In this chapter it is proposed that body composition indices, including psoas, diaphragm and sartorius muscles, visceral and subcutaneous adipose tissue, and waist circumference are associated with the development of PPC and overall survival.

The aim of the this chapter, was to establish the clinical value of QCT body composition indices in patients undergoing non-cardiac, non-thoracic surgical procedures.

Specific objectives were:

- To define the spectrum of QCT body composition values,
- To identify and calculate the strength of any associations between QCT body composition indices and PPC,
- To determine whether these indices had impact on survival.

5.3 Materials & methods

5.3.1 Study setting

This study was performed as part of implementation of frailty assessment and management within Specialist Clinical Frailty Network (www.scfn.org.uk). Approval for the project was given by the Department of Vascular Surgery and the Department of Colorectal Surgery prior to study commencement and registered as a clinical audit.

5.3.2 Population

The description of cohorts analysed in this study was given in General Methods, Section 2.5 on page 106.

Vascular cohort: This was a comprehensive prospective cohort, drawing patients of all ages and sexes, presenting a wide spectrum of aortic diseases, including juxtarenal, pararenal, thoracic, and thoracoabdominal aneurysms and aortic dissections. Selection criteria did not impose any restrictions based on ethnicity or geographic location, ensuring a diverse patient population from a referral centre with a broad catchment area.

All patients presenting to the specialist Aortic Clinic over the period from July 1, 2019, to February 29, 2020 were included. These patients underwent a thorough pre-operative assessment within a multidisciplinary clinical pathway, part of a service improvement project aimed at assessing and managing frailty in patients considered for surgery (Specialised Clinical Frailty Network, http://www.scfn.org.uk).

Colorectal cohort: This cohort comprised of patients undergoing left-sided colorectal cancer cancer who had surgery between December 2007 and January 2019. Inclusion criteria ensured representation across various demographics,

with no exclusions based on ethnicity or geographical provenance, drawn from a referral centre with an extensive catchment area. This approach increased the chances of this cohort being considered representative of this group of patients. The clinical pathway for these patients was structured within a multidisciplinary framework, incorporating a standardised pre-operative assessment that included staging CT scans. To ensure the homogeneity of cases under examination, the study was confined to those patients who underwent either elective or emergency resections for left-sided colorectal cancer.

For this work package we decided to select a subset of patients using propensity score matching as described in the previous Chapter (Section 2.11.5 on page 135).

5.3.3 Ethical considerations

Institutional approval was granted before data collection.

5.3.4 Definitions

Postoperative Pulmonary Complications – for the purpose of this study PPCs were defined using a modified EPCO criteria. This was described in detail in Chapter/Section 2.6.5 on page 111.

Morphometric indices of body composition – definitions of morphometric categories of body composition are presented in 5.3.8.

Early/in-hospital mortality was defined as postoperative death occurring during index admission or within 30 days of the index procedure if the patient was discharged from the hospital.

Outcome ascertainment was achieved by cross-referencing of the EHR with the NHS Spine (NHS Digital). The cause of death was retrieved from the Primary Care Mortality Database (NHS Digital).

5.3.5 Outcomes

The overarching aim of the this chapter, was to establish the clinical value of QCT body composition in patients undergoing non-cardiac, non-thoracic surgical procedures.

Specific objectives were::

- CT-derived quantitative body composition indices (cross-sectional psoas muscle area, diaphragm thickness, area of visceral and subcutaneous fat waist circumference)
- Associations between quantitative body composition parameters with PPC, and
- Perioperative mortality and survival.

5.3.6 Data collection

5.3.7 CT acquisition protocols

These were described in detail in Chapter 4 Subsection 4.3.7 on page 186.

5.3.8 Quantitative evaluation of CT images using an advanced PACS viewer

CT scans of the abdomen and pelvis were analysed to obtain body composition indices including 1) psoas muscle area (PMA), 2) visceral (VFT) and subcutaneous (SFT) adipose tissue area, and 4) waist circumference (WC). Using TeraRecon software, regions of interest were drawn by hand at the levels of the centre and upper border of the third (L_3) and fourth (L_4) lumbar vertebrae in order to obtain the cross-sectional areas of the two psoas muscles (Figure 4.3.7 on page 186, and 2.6 on page 121) at the level where transverse processes of each L_3 and L_4 were optimally visualised. In order to compute

the PMA the cross-sectional area of the left and the right psoas muscle were added and normalised by height squared where height variable was available (Dolan et al., 2019; Uehara et al., 2022; Chang et al., 2022). The final value obtained was the TPA, [cm^2/m^2]. The PMA varies according to gender, and so sex-specific quartiles for the cut-off values were applied for measurements at L_4 (7.4 cm^2/m^2 for male and 5.2 cm^2/m^2 for females; Derstine et al. 2018).

Semi-automated analysis of abdominal adipose tissue indices (VFT, SFT and WC) was carried out on the same cross-sectional image used for the PMA (L_3 and L_4) using 'Fat Analysis Workflow' with automated segmentation of visceral and abdominal fat separately (Subsection 2.11.5, Figure 2.4 on page 119). Where the automated border detection between these two areas lacked precision, this was adjusted by hand. The region of interest (ROI) indicated VFT, the fatty region beyond this area was denoted as SFT. The definition of VFT encompassed the area of fatty tissue in the abdomen within the parietal peritoneum. The paraspinal muscle, intervertebral bodies and adipose tissue within the muscles were excluded. The adipose tissue outside the peritoneum and dorsal musculature was considered to be SFT (Feng et al., 2023).

The WHO and IDF recommend measuring WC mid-way between the lower-most ribs and the iliac crest, which in most cases falls conveniently at the level of the upper part of L_4 on CT. The waist circumference was measured using Fat Analysis workflow as the perimeter of the body at the skin level on axial images at the L_4 level used for TPA measurements (Subsection 2.11.5, Figure 2.4 on page 119). The WC was expressed in centimetres [cm] (Kartheuser et al., 2013; Joo et al., 2021).

The thickness of the diaphragm was obtained from thoracic CT images. Clinical software was used to measure this parameter, i.e. the Aquarius Intuition Workstation from TeraRecon (TeraRecon GmbH, TeraRecon GmbH, Frankfurt am Main, Germany). Axial and coronal scan reconstructions, at the level of the upper border of the first lumbar vertebral body, were used to obtain six parameters from each side of the diaphragm in relation to its anterior, mid and posterior portions (Subsection 2.8.8, Figure 2.6 on page 121). Firstly, the axial

image was utilised in order to establish the reference points. On the sagittal image, the cursors were then positioned with respect to the spinal canal's anterior edge, which facilitated intersection of the diaphragm by the cross-sectional lines, which were then shown by the software on the coronal axis. Parameters obtained in the coronal plane relied on modifying the positions of the lines in relation to the reference points in the axial imaging plane. This was a key process in this study so that the thickness of the diaphragm could be measured in the coronal axis, as in many subjects, abdominal aortic widening could hinder visualisation of the diaphragm. The thickness of the diaphragm was measured in mm.

The analysis of the CT images of the thorax, abdomen and pelvis was carried out by five investigators, AG, MTJ, DS, CW and RL (See *Acknowledgements*), who had undergone relevant training, and who were blinded to any clinical information or quantitative image data obtained previously.

5.3.9 Statistical analysis

Generic statistical methods used in this Chapter were described in Methods Section (Chapter 2 on page 132).

Propensity score matching was used for the colorectal cohort as described in Chapter 2 Section 2.11.5 on page 135.

5.4 Results

5.4.1 Dataset

The dataset used for analyses in this chapter was matching the one from Chapter 4 to ensure consistency of results (Figure 5.2).

All patients who underwent aortic surgery were included in the analysis (n=62). The propensity-matched subset of the colorectal cohort (2.11.5 on page 135) analysed in this chapter included 62 patients who had PPC and 131 who did not. The outcome of this process is the selection of 198 patients for morphometric analysis. Five patients were excluded on account of substandard CT image quality.

Following this process, 62 patients were included for the morphometric analysis from the vascular cohort and 193 patients from the colorectal cohort (Figure 5.2).

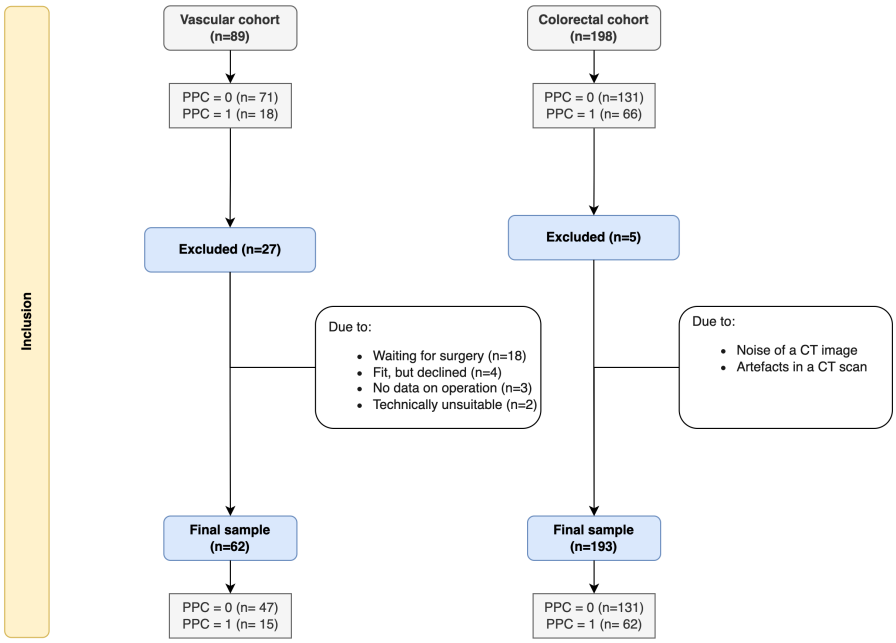


Figure 5.2 – CONSORT flow diagram demonstrating patient inclusion for quantitative body composition analysis. PPC – post-operative pulmonary complications.

5.4.2 Quantitative CT-derived body composition indices

5.4.2.1 Patients with aortic disease

Out of 110 patients included in the vascular cohort 62 patients (50 male and 12 female) who underwent aortic surgery were included in the analysis. The baseline demographic and clinical profile of these patients was described in detail in Chapter 3.

There were significant differences in morphometric body composition indices between males and females (Table 5.1). Therefore we categorised these indices into sex-adjusted tertiles for further analyses).

Table 5.1 – Sex differences between morphometric body composition parameters of patients with aortic disease. BMI – body mass index, Diaphragm – diaphragm thickness, HT – height, iqr – interquartile range, L3 – third lumbar vertebra, L4 – fourth lumbar vertebra, TPA – total psoas area, cTPA – TPA corrected for height, TSMA – total sartorius muscle area, VISCA – area of visceral adipose tissue (fat), VISC_SC_RATIO – ratio of visceral to subcutaneous adipose tissue, WC – waist circumference, sd – standard deviation, SUB.QA – area of subcutaneous adipose tissue (fat).

Variable	Level	Female (n=12)	Male (n=50)	Total (n=62)	p-value
TPA L_4	mean (sd)	14.4 (4)	22.8 (4.5)	21.2 (5.6)	<0.001
	missing	1	5	6	
cTPA L_4	mean (sd)	5.9 (1.5)	7.7 (1.5)	7.3 (1.6)	<0.001
	missing	1	5	6	
TPA L_3	mean (sd)	10.6 (3)	17.1 (4.2)	15.8 (4.7)	<0.001
	missing	1	5	6	
cTPA L_3	mean (sd)	4.4 (1.2)	5.8 (1.3)	5.5 (1.4)	0.0019262
	missing	1	5	6	
TSMA	median (iqr)	3.8 [3.4, 4.3]	5.5 [4.7, 7.0]	5.1 [4.2, 6.4]	<0.001
	missing	1	5	6	
WC4 L_4	mean (sd)	92.4 (14.4)	102.8 (11.1)	100.8 (12.4)	0.008
	missing	1	5	6	
VISCA L_4	mean (sd)	130.5 (68)	235.3 (103)	214.7 (105.3)	0.001
	missing	1	5	6	
SUB.QA L_4	mean (sd)	227.4 (120.8)	216.3 (80.1)	218.5 (88.5)	0.713
	missing	1	6	7	
VISC_SC_RATIO	mean (sd)	0.4 (0.1)	0.5 (0.1)	0.5 (0.1)	<0.001
	missing	1	6	7	
HT	mean (sd)	156.3 (7.6)	172.1 (5.9)	169 (8.8)	<0.001
WT	maen (sd)	67.3 (16.4)	84.8 (16)	81.4 (17.4)	<0.001
BMI	mean (sd)	27.5 (6)	28.4 (4.9)	28.2 (5.1)	
Diaphragm (Axial)	median (iqr)	15.4 [13.6, 17.4]	16 [13.5, 22.3]	15.6 [13.4, 22.2]	0.847
Diaphragm (Coronal)	mean (sd)	15.7 [14.1, 17.4]	15.2 [13.1, 19.9]	15.2 [13.9, 19.6]	0.882

Psoas muscle – a manual segmentation of psoas muscle at the level of L_3 and L_4 was possible in all but 6 cases. The mean, uncorrected TPA area at L_4 was $21.2 \pm 5.6\,cm^2$. The TPA measured at L_3 was considerably smaller as compared to L_4 and yielded $15.8 \pm 4.7\,cm^2$.

Diaphragm muscle – the imaging allowing for assessment of the diaphragm muscle was available in all patients. The diaphragm thickness measured on axial views as per method described in Chapter 2 Section 2.8.8 on page 120 yielded the median of 15.4 [13 6;17 4]mm. The median diaphragm thickness measured on coronal views was 15.2 [13 9;19 6]mm.

Sartorius muscle – the imaging allowing to assess the sartorius muscle was available in 56 patients. The median cross-sectional sartorius muscle area measured 5.1 [4 2;6 4]cm^2.

Subcutaneous, visceral fat and waist circumference – the imaging allowing for assessment of adipose tissue was available in 55 patients. The area of subcutaneous tissue at L_4 measured 218.5 ± 88.5 cm^2 and the visceral fa area measured 214.7 ± 105.3 cm^2.

The waist circumference at L_4 measured 100.8 ± 12.4 cm.

5.4.2.2 Patients with colorectal cancer

Out of 715 patients included in the colorectal cohort a total of 193 patients (mean age 70.2 (10.2); 142 male and 51 female) selected by propensity score matching were included in the analysis. The baseline demographic and clinical profile of these patients was described in detail in Chapter 3.

A full analysis of several morphometric parameters was carried out. We demonstrated substantial, systematic, statistically significant higher mean and median values in lung morphometric parameters in male compared with female patients across the morphometric indices (Table 5.2). Therefore, the categorical stratification of these indices by tertiles was done within each sex stratum separately (Table 5.3).

Table 5.2 – Sex differences between morphometric body composition parameters of patients with colorectal cancer. DIA – diaphragm thickness, L3 – third lumbar vertebra, L4 – fourth lumbar vertebra, TPA – total psoas area, SCF – subcutaneous adipose tissue (fat), WC – waist circumference, sd – standard deviation.

Variable	Level	Female (n=51)	Male (n=142)	Total (n=193)	p-value
Age	mean (sd)	66.6 (10.6)	71.5 (9.8)	70.2 (10.2)	0.002
SCF L_3	mean (sd)	34.9 (10.1)	58.8 (10.9)	52.4 (15)	<0.001
	missing	11	33	44	
WC L_3	mean (sd)	91 (13.7)	99 (10.1)	96.8 (11.7)	<0.001
	missing	11	33	44	
SCF L_4	mean (sd)	35.5 (9.4)	53.3 (11.3)	48.5 (13.4)	<0.001
	missing	11	34	45	
WC L_4	mean (sd)	92.4 (13.5)	98 (10.2)	96.5 (11.4)	0.006
	missing	11	34	45	
TPA L_3	mean (sd)	12.6 (2.9)	17.8 (4.6)	16.4 (4.8)	<0.001
	missing	11	33	44	
TPA L_4	mean (sd)	16.4 (3)	23.5 (5.2)	21.6 (5.6)	<0.001
	missing	11	33	44	
TPA L_4-L_3 difference	mean (sd)	3.8 (1.8)	5.6 (2.4)	5.2 (2.4)	<0.001
	missing	11	33	44	
DIA (axial)	mean (sd)	15.4 (4.9)	18.4 (6.2)	17.6.(6)	<0.002
DIA (coronal)	mean (sd)	22.5 (23.8)	20.4 (7.7)	21 (23.9)	0.344

Table 5.3 – Morphometric indices stratified by sex-adjusted tertiles and quartiles. DIA – diaphragm thickness, SCF – subcutaneous fat, TPA – total psoas area, WC – waist circumference, L3 – third lumbar vertebra, L4 – fourth lumbar vertebra.

Variable	Level	Female (n=51)	Male (n=142)	Total (n=193)	p-value
Tertiles of SCF at L_3	Low	14 (35.0)	37 (33.9)	51 (34.2)	
	Medium	13 (32.5)	36 (33.0)	49 (32.9)	
	High	13 (32.5)	36 (33.0)	49 (32.9)	0.992792
	missing	11	33	44	
Tertiles of TPA at L_3	Low	14 (35.0)	37 (33.9)	51 (34.2)	
	Medium	13 (32.5)	36 (33.0)	49 (32.9)	
	High	13 (32.5)	36 (33.0)	49 (32.9)	0.992792
	Missing	11	33	44	
Tertiles of SCF at L_4	Low	14 (35.0)	36 (33.3)	50 (33.8)	
	Medium	13 (32.5)	36 (33.3)	49 (33.1)	0.982041
	High	13 (32.5)	36 (33.3)	49 (33.1)	
	missing	11	34	45	
Tertiles of WC at L_4	Low	14 (35.0)	36 (33.3)	50 (33.8)	
	Medium	13 (32.5)	36 (33.3)	49 (33.1)	
	High	13 (32.5)	36 (33.3)	49 (33.1)	0.982041
	missing	11	34	45	
Tertiles of TPA at L_3	Low	14 (35.0)	37 (33.9)	51 (34.2)	
	Medium	13 (32.5)	36 (33.0)	49 (32.9)	
	High	13 (32.5)	36 (33.0)	49 (32.9)	0.992792
	missing	11	33	44	
Tertiles of TPA at L_4	Low	14 (35.0)	37 (33.9)	51 (34.2)	
	Medium	13 (32.5)	36 (33.0)	49 (32.9)	
	High	13 (32.5)	36 (33.0)	49 (32.9)	0.992792
	missing	11	33	44	
Tertiles of DIA (axial)	Low	17 (33.3)	48 (33.8)	65 (33.7)	
	Medium	17 (33.3)	47 (33.1)	64 (33.2)	0.998150
	High	17 (33.3)	47 (33.1)	64 (33.2)	
Tertiles of DIA (coronal)	Low	17 (33.3)	48 (33.8)	65 (33.7)	
	Medium	17 (33.3)	47 (33.1)	64 (33.2)	
	High	17 (33.3)	47 (33.1)	64 (33.2)	0.998150

Psoas muscle – a manual segmentation of psoas muscle at the level of L_3 and L_4 was possible in 149 cases. The mean, uncorrected TPA area was $16.4 \pm 4.8\,\mathrm{cm}^2$.

The TPA measured at L_4 was on average greater by a mean $5.2 \pm 2.4\,cm^2$ as compared to L_3 and yielded $21.6 \pm 5.6\,cm^2$.

Diaphragm muscle – the imaging allowing for assessment of the diaphragm muscle was available in all 193 patients. The mean diaphragm thickness measured on axial views as per method described in Chapter 2 Section 2.8.8 on page 120 yielded the mean of 17.6 ± 0.6 mm. The mean diaphragm thickness measured on coronal views was 21.0 ± 13.9 mm.

Subcutaneous, visceral fat and waist circumference – the imaging allowing for assessment of adipose tissue was available in 148 patients. The area of subcutaneous tissue at L_3 measured $52.4 \pm 1.5\,cm^2$ and was smaller at L_4 measuring $48.5 \pm 13.4\,cm^2$.

The waist circumference was no different at L_3 and at L_4 and measured 96.8 ± 11.7 cm and 96.5 ± 11.4 cm.

5.4.3 Association of quantitative-CT body composition indices with the incidence of PPC

5.4.3.1 Patients with aortic disease

Univariate analysis identified visceral adipose tissue area, visceral-to-subcutaneous adipose tissue ratio, height and weight as potential predictors of PPC. However, the automated selection of variables using stepwise logistic regression selected height, diaphragm muscle thickness (coronal) and TPA at L_3 as the best candidate variables for the multivariable model (Table 5.4).

Table 5.4 – The results of a stepwise multiple logistic regression analysis of the association between the body composition morphomarker and the development of pulmonary complications after aortic aneurysm surgery. CI - Confidence interval; TPA - Total psoas area.

Variable	Odds Ratio	95% CI	p-value
Height	0.82	0.72–0.94	0.005
Diaphragm thickness (coronal)	1.17	1.01–1.36	0.042
TPA L_3	1.20	0.97–1.49	0.091

The clinical model developed in Chapter 4 included presence of PAOD and preoperative haemoglobin levels. Neither variable was independently associated with PPC (Table 5.5).

Table 5.5 – The results of a stepwise multiple logistic regression analysis of the association between clinical and demographic and the development of pulmonary complications after aortic aneurysm surgery. CI - Confidence interval; factors. PAOD - Peripheral arterial occlusive disease; Hb - Haemoglobin.

Variable	Units	Odds Ratio	95% CI	p-value
PAOD	0	Ref		
	1	3.83	0.97-15.11	0.055
Hb		0.96	0.90–1.01	0.126

The effect of morphometric body composition indices on performance of this model was tested by adding all morphometric indices automatically selected in

stepwise regression. In this new combined model, hight, diaphragm thickness, and TPA were independently associated with PPC (Table 5.6).

Table 5.6 – The results of a stepwise multiple logistic regression analysis of the association between the combination of clinical patient-related factors and the body composition morphomarker and the development of pulmonary complications after aortic aneurysm surgery. CI - Confidence interval; TPA - Total psoas area; PAOD - Peripheral arterial occlusive disease; Hb - Haemoglobin.

Variable	Units	Odds Ratio	95% CI	p-value
PAOD	0	Ref		
	1	3.83	0.97-15.11	0.055
Hb		0.96	0.90–1.01	0.126
Hight		0.83	0.72;0.96	0.014
Diaphragm (coronal)		1.25	1.01–1.55	0.044
TPA L_3		1.28	1.00–1.64	0.047

Comparison of regression models using ANOVA showed improvement in model performance. The clinical model had the c-statistic of 0.761 which significantly improved when we added morphometric body composition parameters (c-statistic 0.850; ANOVA: Df=1, Deviance=11.732, p<0.001). The model including only morphometric indices had c-statistic of c-statistic of 0.834 and did not improve significantly when combined with the clinical model (ANOVA: Df=2, Deviance=1.708, p=0.426; Figure 5.3).

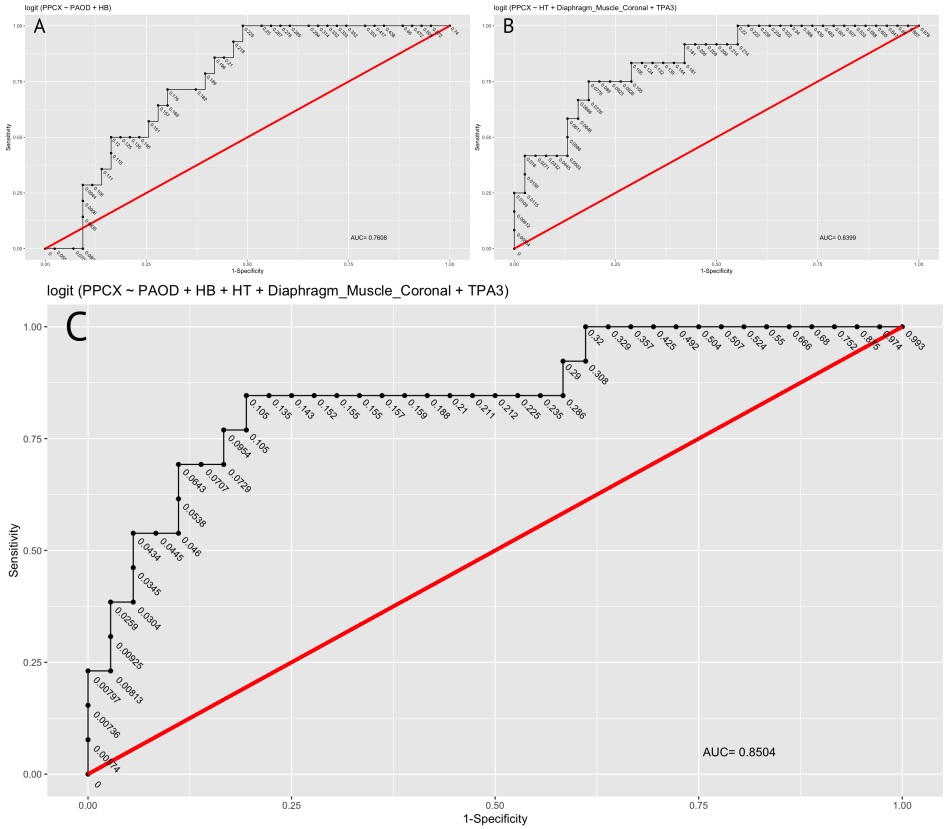


Figure 5.3 – The analysis of the receiver operating characteristic (ROC) and area under the curve (AUC) demonstrates the diagnostic performance ability of the morphometric body composition of three models to predict the pulmonary complications of patients with aortic disease.

5.4.3.2 Patients with colorectal cancer

The univariate analysis did not identify any differences in TPA (L_3 – 16.0 ± 4.9 mm v. 16.6 ± 4.8 mm, p=0.472; L_4 – 21.3 ± 0.6 mm v. 21.7 ± 5.5 mm, p=0.697771), adipose tissue area (L_3 – 53 ± 16 mm v. 52.1 ± 14.7 mm, p=0.753050; L_4 – 49.0 ± 14.2 mm v. 48.3 ± 13.2 mm, p=0.768922), waist circumference (L_3 – 98.9 ± 13.2 mm v. 96.0 ± 10.9 mm, p=0.155356; L_4 – 98.5 ± 12.9 mm v. 95.7 ± 10.7 mm, p=0.162528) and diaphragm thickness measured in coronal views (16.0 ± 4.9 mm v. 20.0 ± 7.5 mm) between those who developed PPC and those who did not. Diaphragm measured on axial views was significantly thicker in those who developed PPC compared with those who did not (19.1 ± 7.2 mm v. 16.9 ± 5.3 mm, p=0.018).

The exploratory model evaluating association of morphometric body composition factors with PPC used stepwise logistic regression. Since there was no difference between L_3 and L_4 measurements for all but diaphragm thickness in axial plane, we decided to simplify the model by using only L_3 measurements. This demonstrated that only medium tertiles of diaphragm thickness in axial plane was independently associated with PPC (Table 5.7).

Table 5.7 – The results of a stepwise multiple logistic regression analysis of the association between the body composition morphomarker and the development of pulmonary complications after colorectal cancer surgery. WC - Waist circumference; CI - Confidence interval; TPA - Total psoas area.

Variable	Unit	Odds Ratio	95% CI	p-value
Tertiles of diaphragm thickness (axial)	High	Ref		
	Medium	0.17	0.06–0.49	0.001
	Low	0.59	0.22–1.57	0.292
Tertiles of WC	High	Ref		
	Medium	0.38	0.14–1.04	0.061
	Low	0.87	0.33–2.28	0.770
Diaphragm thickness (coronal)		1.02	0.99–1.05	0.124
Quartiles of TPA	Q1	Ref		
	Q2	0.33	0.10–1.04	0.059
	Q3	0.34	0.12–1.01	0.052
	Q4	0.73	0.23–2.38	0.604

The final exploratory regression model evaluating association of clinical and demographic factors with PPC, developed in Chapter 3, did not demonstrate associations in the PSM matched cohort. Another model, was developed in Chapter 4 Paragraph 4.4.3.2 on page 213, and used in this analysis (Table 5.8 on the next page).

Table 5.8 – The results of a stepwise multiple logistic regression analysis of the association between clinical and demographic and the development of pulmonary complications after colorectal cancer. CLD - Chronic lung disease, WCC - White cell count.

Variable	Odds Ratio	95% CI	p-value
CLD	8.12	3.84–17.16	<0.001
Anastomotic leak	5.11	1.69–15.49	0.004
Dementia	10.12	1.57–65.40	0.015
WCC	1.10	1.00–1.22	0.049
Albumin	0.94	0.88–1.01	0.096

The effect of morphometric body composition indices on performance of this model was tested by first, adding a single variable that was independently associated with PPC (Table 5.9), and then by adding all morphometric indices automatically selected in stepwise regression (Table 5.10). In both models CLD, anastomotic leak, dementia and tertiles of diaphragm thickness were independently associated with PPC.

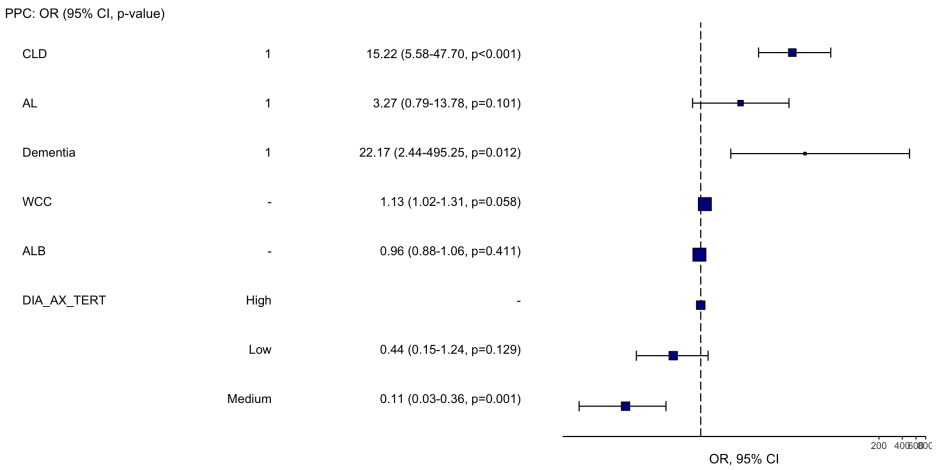


Figure 5.4 – A forest plot demonstrating results of multivariable model combining clinical and demographic variables, and tertiles of diaphragm thickness in patients with colorectal cancer. CLD – Chronic lung diseases; WCC - White cell count; AL – Anastomotic leak; ALB – Albumin; OR - Odds Ratio; CI - Confidence interval.

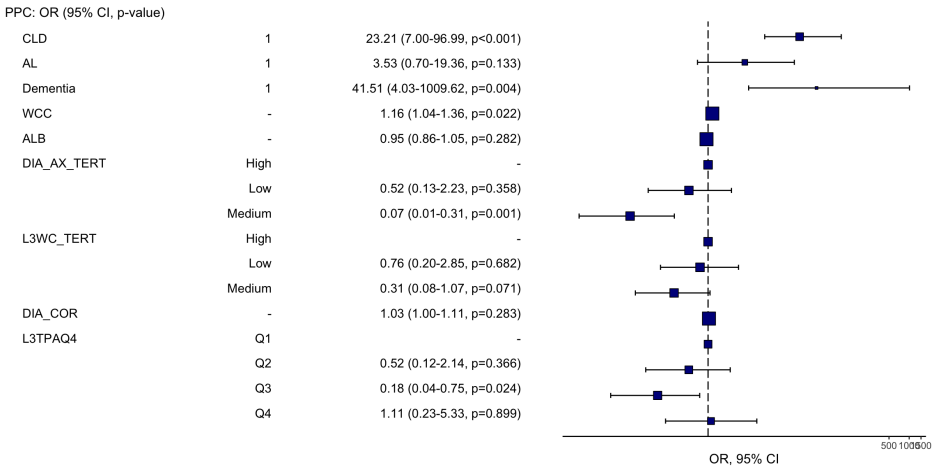


Figure 5.5 – A forest plot demonstrating results of multivariable model combining clinical and demographic variables, and morphometric body composition parameters selected in stepwise regression model in patients with colorectal cancer. CLD – Chronic lung diseases; WCC - White cell count; AL – Anastomotic leak; ALB – Albumin; WC - Waist circumference; TPA - Total psoas area; Q4 - Quartiles 4; OR - Odds Ratio; CI - Confidence interval.

Table 5.9 – The results of a stepwise multiple logistic regression analysis of the association between the combination of clinical patient-related factors and the body composition morphomarker and the development of pulmonary complications after colorectal cancer. CLD - Chronic lung disease, WCC - White cell count.

Variable	Units	Odds Ratio	95% CI	p-value
CLD		8.12	3.84–17.16	<0.001
Anastomotic leak		5.11	1.69–15.49	0.004
Dementia		10.12	1.57–65.40	0.015
WCC		1.10	1.00–1.22	0.049
Albumin		0.94	0.88–1.01	0.096
Tertiles of diaphragm thickness (axial)	High	Ref		
	Medium	0.11	0.03–0.38	<0.001
	Low	0.44	0.15–1.27	0.129

Table 5.10 – The results of a stepwise multiple logistic regression analysis of the association between the combination of clinical patient-related factors and all the body composition morphomarker and the development of pulmonary complications after colorectal cancer.. CLD - Chronic lung disease, WCC - White cell count, WC - Waist circumference, TPA - Total psoas area; Q1-Q4 - quartiles 1 to 4.

Variable	Units	Odds Ratio	95% CI	p-value
CLD		23.21	6.35–84.90	<0.001
Anastomotic leak		3.53	0.68–18.33	0.133
Dementia		41.51	3.26–529.19	0.004
WCC		1.16	1.02–1.31	0.022
Albumin		0.95	0.86–1.05	0.282
Tertiles of diaphragm thickness (axial)	High	Ref		
	Medium	0.07	0.01–0.34	0.001
	Low	0.52	0.13–2.11	0.358
Tertiles of WC	High	Ref		
	Medium	0.31	0.09–1.11	0.071
	Low	0.76	0.20–2.85	0.682
Diaphragm thickness (coronal)		1.03	0.98–1.09	0.283
Quartiles of TPA	Q1	Ref		
	Q2	0.52	0.12–2.17	0.366
	Q3	0.18	0.04–0.80	0.024
	Q4	1.11	0.23–5.22	0.899

Comparison of regression models using ANOVA demonstrated that addition of morphometric body composition factors to the clinical model improved their performance. The clinical model had the c-statistic of 0.784 which significantly improved when we added tertiles of diaphragm thickness (c-statistic 0.845; ANOVA: Df=2, Deviance=14.547, p<0.001). The best model combined clinical factors and all morphometric factors selected on stepwise regression (tertiles of diaphragm thickness, tertiles of WC, diaphragm thickness on coronal views and quartiles of TPA). It was associated with c-statistic of 0.884 and was significantly better than the clinical model (ANOVA: Df=8, Deviance=30.362, p<0.001) and the model combining clinical factors with tertiles of diaphragm thickness (ANOVA: Df=6, Deviance=15.814, p=0.015; Figure 5.6).

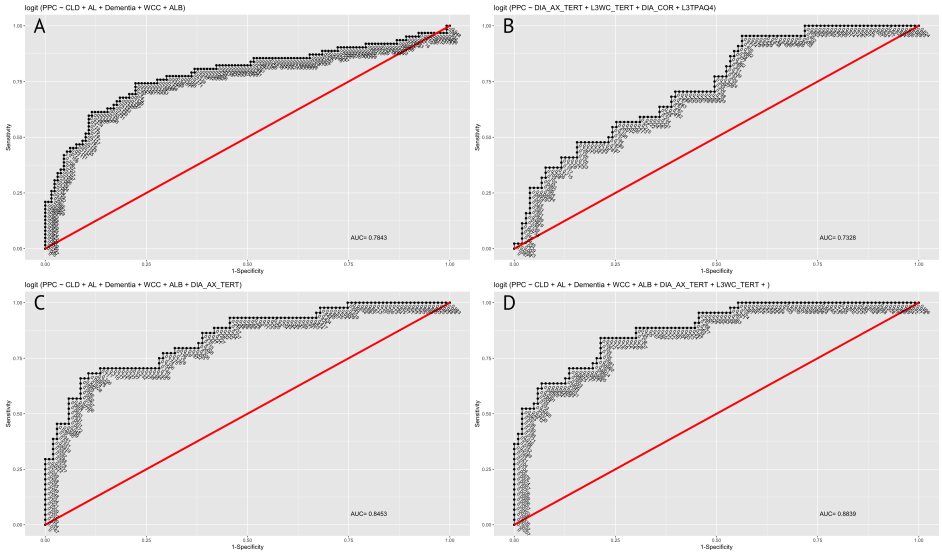


Figure 5.6 – The analysis of the receiver operating characteristic (ROC) and area under the curve (AUC) demonstrates the diagnostic performance ability of the morphometric body composition of three models to predict the pulmonary complications of patients with colorectal cancer.

5.4.4 Association of quantitative-CT body composition indices with survival

5.4.4.1 Patients with aortic disease

The dataset comprised a total of 62 patients who underwent aortic surgery, with 15 patients who developed PPC and 47 patients who did not. Nineteen morphometric variables were included. It was not possible to evaluate the morphometric variables using Cox regression analysis due to a small number of events. Further analysis was not attempted.

A survival model was developed for patients who underwent aortic surgery, evaluating clinical and demographic variables. The automated selection of variables using stepwise regression identified three variables: presence of frailty and dementia, and aneurysm diameter as associated with survival (Table 5.11 & Figure 5.7). Only aneurysm diameter was independently associated with this outcome (HR 2.5, 95%CI 1.28–4.9, p=0.007).

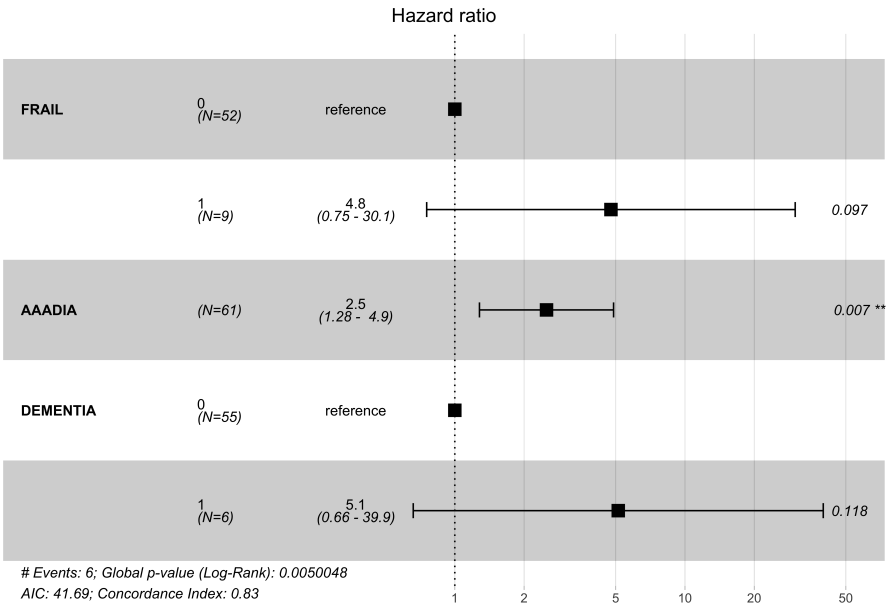


Figure 5.7 – A forest plot demonstrating the results of a stepwise logistic regression analysis for a Cox proportional hazard model of the association between clinical and demographic factors and survival after aortic aneurysms surgery.

Table 5.11 – The results of a stepwise logistic regression analysis for a Cox proportional hazard model of the association between clinical and demographic factors and survival after aortic aneurysms surgery. AAA - Abdominal aortic aneurysm; CI - Confidence interval.

Variable	Units	Hazard Ratio	95%CI	p-value
Frailty		4.8	0.75–30.1	0.097
Dementia		5.1	0.66–39.9	0.118
AAA diameter		2.5	1.28–4.9	0.007

5.4.4.2 Patients with colorectal cancer

The dataset comprised a total of 193 patients, with 62 patients who developed PPC and 131 patients who did not. Nineteen morphometric body composition variables were included. The stepwise Cox regression analysis evaluating the association of morphometric body composition parameters with survival selected seven that were associated with survival. One variable was removed

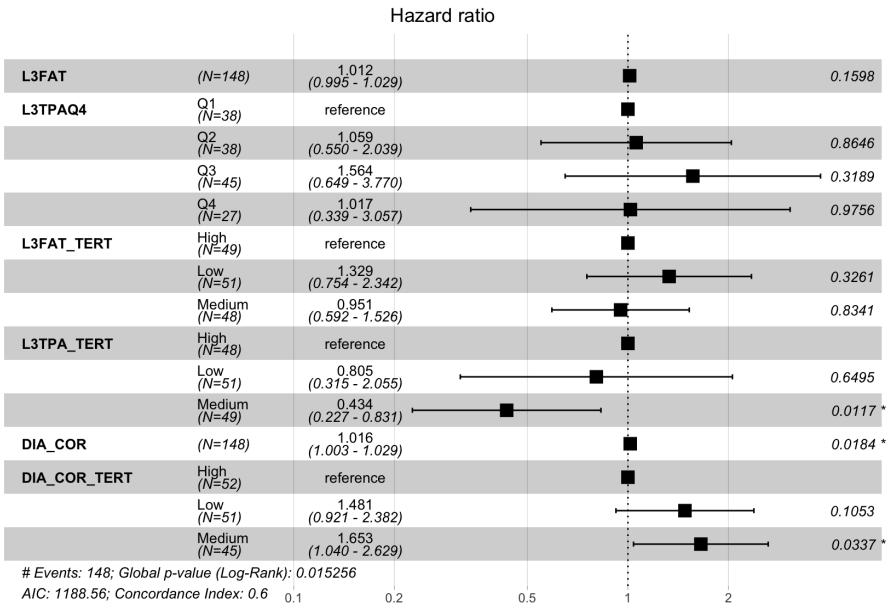


Figure 5.8 – A forest plot demonstrating the results of a stepwise logistic regression analysis for a Cox proportional hazard model of the association between clinical patient-related factors, and body composition with survival after colorectal cancer surgery. L3FAT – area of subcutaneous adipose tissue at L_3, L3FAT_TERT – tertiles of area of subcutaneous adipose tissue at L_3, L3TPAQ4 – quartiles of TPA at L_3, L3TPA_TERT – tertiles of TPA at L_3, DIA_COR – diaphragm thickness (coronal), DIA_COR _TERT– tertiles of diaphragm thickness (coronal).

due to collinearity (VIF > 10) resulting in six variables included in the final model (Figure 5.8).

Table 5.12 – The results of a stepwise multiple logistic regression analysis for a Cox proportional hazard model of the association between morphometric body composition variables and survival after colorectal cancer surgery. TPA – Total psoas area, L_3 – third lumbar vertebra, CI – Confidence interval.

Variable	Units	Hazard Ratio	95%CI	p-value
Diaphragm thickness		1.02	1.00–1.03	0.018
Tertiles of TPA L_3	High	Ref		
	Medium	0.43	0.23–0.83	0.012
	Low	0.80	0.32–2.05	0.649
Tertiles of diaphragm thickness (coronal)	High	Ref		
	Medium	1.65	1.04–2.63	0.034
	Low	1.48	0.92–2.38	0.105

Three out of these were independently associated with survival (diaphragm thickness (coronal), tertiles of diaphragm thickness (coronal), and tertiles of TPA; Table 5.12) and were combined with the clinical model developed in Chapter 4 to evaluate their impact on predictive value of the model (5.13).

Table 5.13 – The results of a stepwise multiple logistic regression analysis for a Cox proportional hazard model of the association between demographic and clinical variables with survival after colorectal cancer surgery. ASA – American Society of Anesthesiologists, COPD – Chronic Obstructive Pulmonary Disease; PPC – Postoperative pulmonary complication, MTNM – Presence of metastatic disease that contain cancer according TNM, CI – Confidence interval.

Variable	Units	Hazard Ratio	95%CI	p-value
ASA	Grade I	Ref		
	Grade II	1.49	0.94–2.37	0.092
	Grade III	2.61	1.45–4.71	0.001
	Grade IV	4.22	0.94–19.08	0.061
Procedure	Anterior Resection	Ref		
	Sigmoid Colectomy	0.50	0.25–1.00	0.050
Modality	Laparoscopic	Ref		
	Open	0.55	0.39–0.77	<0.001
	Laparoscopic conversion	0.80	0.46–1.39	0.431
COPD		0.72	0.49–1.05	0.087
Creatinine		1.01	1.00–1.02	0.013
Albumin		0.93	0.91–0.96	<0.001
Lymphocyte count		1.31	1.11–1.54	0.001
PPC		1.30	0.94–1.79	0.116
MTNM	M0	Ref		
	M1	1.76	0.92–3.36	0.087

The Cox proportional hazard model of combined clinical and morphometric variables showed that TPA at L_3 and diaphragm thickness were independent predictors of survival. Amongst clinical variables, ASA, diagnosis of COPD, preoperative albumin level, lymphocyte count but not PPC, were independently associated with survival (Figure 5.9).

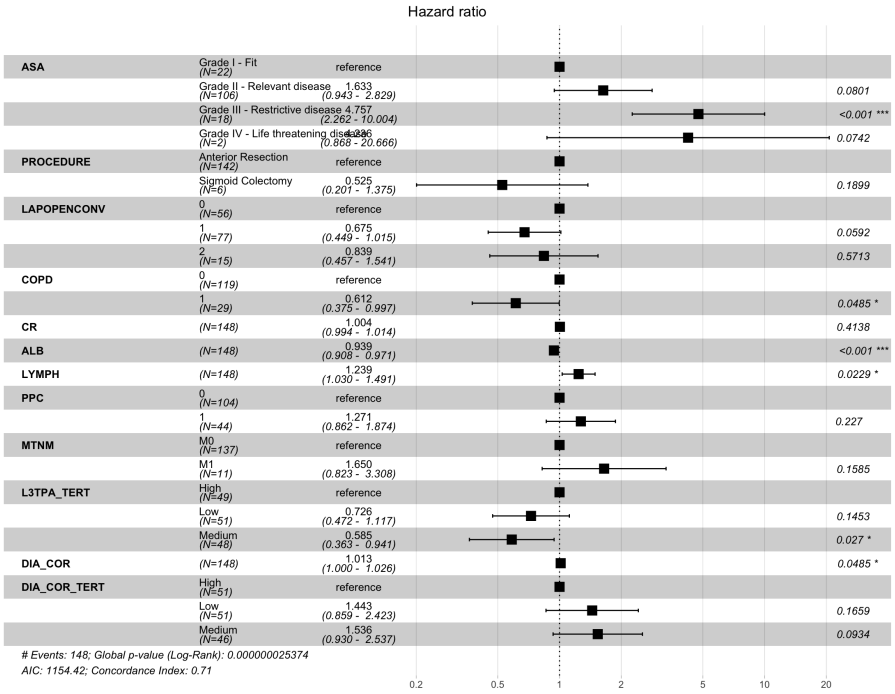


Figure 5.9 – A forest plot demonstrating the results of a stepwise logistic regression analysis for a Cox proportional hazard model of the association between clinical patient-related factors, and body composition with survival after colorectal cancer surgery.ASA – American Society of Anaesthesiologists, PROCEDURE – type of the surgical procedure, LAPOPENCONV – mode of surgery (laparoscopic, open, laparoscopic converted to open), COPD – chronic obstructive pulmonary disease, CR – creatinine, ALB – albumin, LYMPH – lymphocyte count, PPC – postoperative pulmonary complication, MTNM – presence of metastatic disease, L3TPA_TERT – tertiles of TPA at L_3, DIA_COR – diaphragm thickness (coronal), DIA_COR _TERT– tertiles of diaphragm thickness (coronal).

Table 5.14 – The results of a stepwise multiple logistic regression analysis for a Cox proportional hazard model of the association between the combination of clinical patient-related factors and the body composition morphomarker and survival after colorectal cancer surgery. ASA – American Society of Anesthesiologists, COPD – Chronic Obstructive Pulmonary Disease, PPC – Postoperative pulmonary complication, MTNM – Presence of metastatic disease, TPA – Total Psoas Area, L_3 – Third lumbar vertebra; CI – Confidence interval.

Variable	Units	Hazard Ratio	95%CI	p-value
ASA	Grade I	Ref		
	Grade II	1.63	0.94–2.83	0.080
	Grade III	4.76	2.26–10.0	0.001
	Grade IV	4.24	0.87–20.67	0.074
Procedure	Anterior Resection	Ref		
	Sigmoid Colectomy	0.53	0.20–1.38	0.190
Modality	Laparoscopic	Ref		
	Open	0.68	0.45–1.02	0.059
	Laparoscopic conversion	0.84	0.46–1.54	0.571
COPD		0.61	0.38–1.00	0.048
Creatinine		1.00	0.99–1.01	0.4138
Albumin		0.94	0.91–0.97	<0.001
Lymphocyte count		1.24	1.03–1.49	0.023
PPC		1.37	0.86–1.87	0.227
MTNM	M0	Ref		
	M1	1.65	0.82–3.31	0.158
Tertiles of TPA L_3	High			
	Medium	0.58	0.36–0.94	0.027
	Low	0.73	0.47–1.12	0.145
Diaphragm thickness (coronal)		1.01	1.00–1.03	0.048
Tertiles of diaphragm thickness (coronal)	High			
	Medium	1.54	0.93–2.54	0.093
	Low	1.44	0.86–2.42	0.166

Addition of morphometric body composition variables improved performance of the model (c-statistic from 0.78 to 081, and from 0.76 to 0.82 and for 3 and 6 years), but the difference was not statistically significant (ANOVA: Df=5, χ^2=8.960, p=0.111; Figure 5.11 & 5.10).

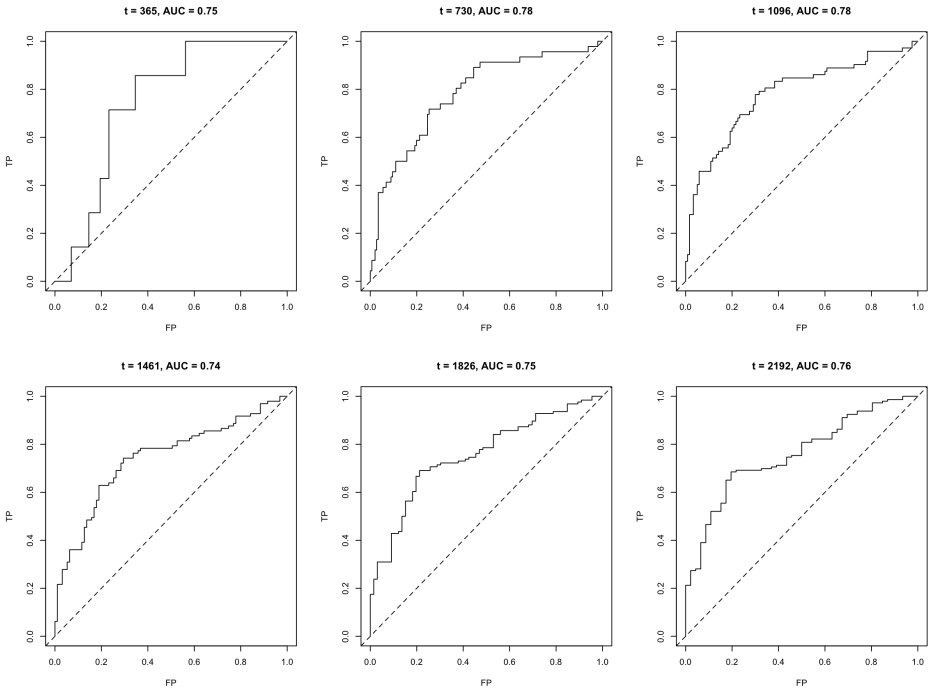


Figure 5.10 – he analysis of the receiver operating characteristic (ROC) and area under the curve (AUC) assesses the predictive value of the model, including clinical factors and morphometric body composition for survival after colorectal cancer surgery. Predictive value (AUC) demonstrated at six different time points: 1 year (t=365), 2 years (t=730), 3 years (t=1096), 4 years (t=1461), 5 years (t=1826) and 6 years (t=2192).

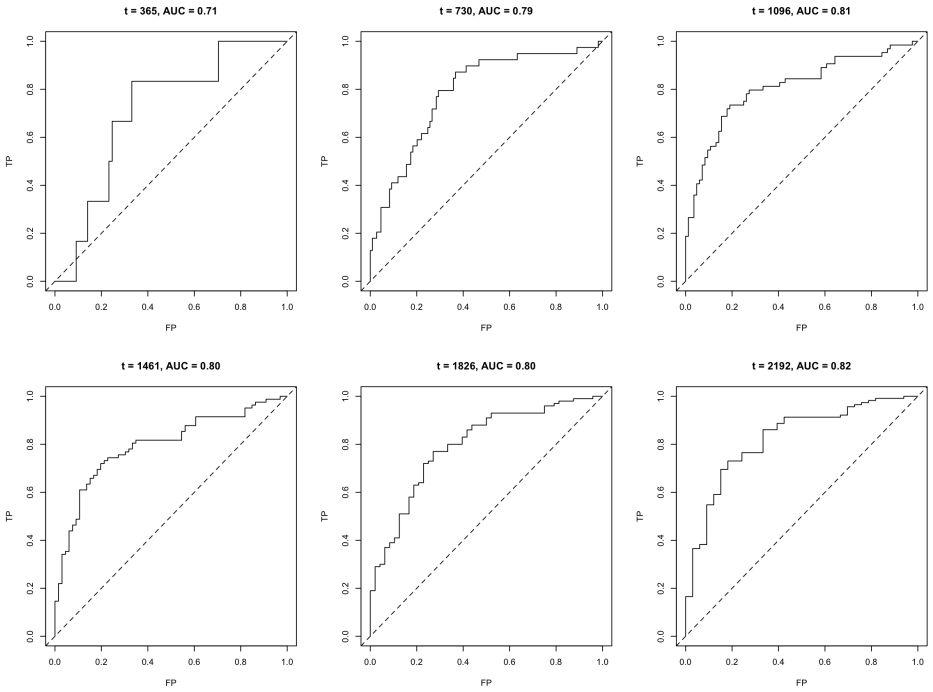


Figure 5.11 – The analysis of the receiver operating characteristic (ROC) and area under the curve (AUC) assesses the predictive value of the model, including clinical factors and morphometric body composition for survival after colorectal cancer surgery. Predictive value (AUC) demonstrated at six different time points: 1 year (t=365), 2 years (t=730), 3 years (t=1096), 4 years (t=1461), 5 years (t=1826) and 6 years (t=2192).

5.5 Discussion

This chapter explored the potential of QCT for body composition indices as predictors for PPC and survival in patients undergoing vascular and colorectal surgical procedures.

In patients with aortic disease, morphometric body composition parameters that were associated with PPC included height, diaphragm thickness and TPA at L_3, with only the first two being independently associated with the outcome of interest. In the colorectal cohort the diaphragm thickness (measure in axial plane), waist circumference, TPA measured at L_3 were demonstrated associated with PPC. This is particularly interesting since diaphragm thickness was independently associated with PPC in both, aortic and colorectal cohorts when combined with clinical parameters.

These findings underscore the significance of diaphragm thickness as a novel morphometric body composition parameter independently associated with PPC irrespective of type of major surgery. This discovery aligns with the emerging body of research emphasising the important role of body composition in patient outcomes post-surgery. The association between body composition indices and PPC is well-documented (Jacobs et al., 2022; Martini et al., 2020; Shimizu et al., 2011), yet this study introduces diaphragm thickness as a unique predictor, diverging from the commonly studied psoas muscle area. Previous studies have not consistently identified diaphragm thickness as a significant factor. This morphomarker, however, has been explored in intensive care medicine and critical COVID-19 patients as an indicator of the integrity of respiratory mechanics and the patient's ability to withstand and recover from surgical stress (Lee et al., 2016; Dal et al., 2022; Ni et al., 2020). The independent association of diaphragm thickness with PPC and survival, particularly in the colorectal cohort, suggests its potential as a marker of surgical risk and recovery capacity. Diaphragm thickness may reflect not only local muscle health but also the overall physiological reserve and resilience of patients undergoing major surgery.

The current study findings demonstrating absence of significant association, a trend at best, of the psoas muscle area with survival in the aortic disease cohort challenging existing literature. The sample size and disease specificity may be potential factors influencing these relationships. The sample size which was used for analysis in the aortic cohort was vary small with only 62 patients and 4 events. In the colorectal cohort, an association of morphomarkers (diaphragm thickness and TPA at L_3) with survival was observed. Amongst all body composition morphomarkers, only diaphragm thickness was independently associated with survival (HR 0.17, 95%CI 0.06–0.49, $p<0.001$) for mid tertile. It is not clear why, compared with related literature (Li et al., 2023b; Jacobs et al., 2022), core muscle area did not show significant relationship with survival. It is possible that the cohort of patients analysed in this study is not representative enough to detect these relationships.Another possible explanation for this is the heterogeneity in patient-related factors and methodologies, including body composition software and the segmentation algorithm process applied in the studies.

The analytical approach, particularly the use of tertiles in body composition morphomarkers and reference points in regression analysis, may have impacted the findings. The significant association observed in the medium tertiles, rather than the lowest, raises questions about the categorisation and interpretation of morphomarker levels. This is most likely due to incorrect designation of tertiles in regression. The use of highest tertile as the reference point, whereas the most appropriate option would perhaps be to use the medium tertile as it should represent the ‘reasonably healthy’ middle. Future studies should consider alternative statistical models and categorisations to validate these findings and explore the most clinically relevant reference groups.

Incorporating pre-operative measurements of diaphragm thickness into clinical assessments could enhance the stratification of PPC risk among surgical patients. This approach could hold promise for personalised medicine, allowing for targeted interventions and monitoring for those identified at higher risk. However, practical implementation would require consideration of cost, ac-

cessibility of QCT imaging, and the development of standardised protocols for measurement and interpretation.

The limitations of this study include its relatively small sample size for the aortic disease cohort and underline the necessity for larger, more diverse studies. Future research should aim at external validation of our findings, exploration of underlying mechanisms linking diaphragm thickness to surgical outcomes, and integration of these morphomarkers into predictive models. Such studies could provide a more comprehensive understanding of the role of body composition in surgical risk and recovery.

5.6 Conclusions

The investigation into QCT body composition indices reveals diaphragm thickness as a potentially useful predictor of PPC and survival post-surgery, marking a significant contribution to the field of surgical risk assessment. These findings hold the potential to enhance pre-operative assessment, offering a novel strategy to assess and mitigate surgical risks. It is imperative that the clinical and research communities collaborate to further elucidate the implications of body composition on surgical outcomes, ultimately aiming to improve patient care through precision medicine.

Chapter 6

Summary and general discussion

6.1 Summary

The main hypothesis tested in this thesis was that the opportunistic morphometric body composition data derived from pre-operative imaging is associated with clinical outcomes and can be used for risk stratification of patients undergoing major, non-cardiac surgery. I demonstrated that some of the CT-derived morphomarkers are associated with the PPC and may have a potential application as factors aiding predictive models. Although, I demonstrated these associations, the task of developing predictive models was not achievable during my PhD fellowship. Due to the COVID-19 pandemic and challenges in obtaining access to patient, and patient data, the current thesis was limited to a retrospective cohort of patients who underwent colorectal and vascular surgery.

The incidence of PPC in colorectal and vascular cohorts has received little attention, thereby being the core concept of the current thesis objectives, which are to answer the main hypothesis by establishing the incidence of PPC. Investigating the perioperative mortality, and medium and long-term survival is essential to developing surgical care, improving patient outcomes, and providing efficient use of medical facilities. Compared to its importance, it was relatively rarely discussed in the literature. An additional challenge is the inconsistency in reporting the overall mortality outcomes across various studies and surgical practices due to variability in patient demographics and comorbidities. This provided a crucial opportunity to investigate its association with PPC.

These implications led to the decision to design Chapter 3 on page 138, which aimed to determine the incidence of PPC and to examine potential associations between PPC and survival. The significant results of this chapter demonstrated a high incidence of PPC in patients who had colorectal and vascular surgery. The impact of PPC on colorectal cancer patients was clear, as it affected postoperative morbidity and increased the risk of mortality rates, both in the short and long term. Also, patient-related factors, including dementia and

pre-existing chronic pulmonary pathology played a critical role in increasing the risk of developing PPC in the same cohort.

Reviewing the definition of PPC (related to pulmonary problems) could develop clinician awareness that it has a relationship with pre-existing chronic pulmonary pathology. However, the literature has not explored this hypothesis, and it has not received much attention despite its clinical importance. The lung diseases are classified according to the appearance of the pathologies changes encompass pulmonary tissue density characterised by low or high attenuations, which could indicate a degree, for example, of emphysema extent, pneumonia, and ILA. In fact, the ideal approach for evaluating and screening changes in lung tissue density has not yet been established. The conventional method using spirometry was considered an unreliable measure because it failed to predict the PPC and diagnose chronic pulmonary pathology due to the poor efficacy demonstrated by patients during the breathing phases, which makes it difficult to detect the early stage of the disease. In recent years, a non-invasive CT approach has emerged. This modality offers quantitative techniques that facilitate the detailed acquisition of objective data related to the anatomy, physiology, and function of the patients.

Over the last half-century, the focus of the imaging-based body composition (morphometric features) analysis has centred on assessing and quantifying various component and parameters in human body. Taking into account the interesting remark formed in Chapter 3 results showed those patients experienced chronic pulmonary pathology had increased risk of developed PPC. This results added the rationale for Chapter 4 which aimed to examine the association of CT-derived quantitative lung morphometry with PPC and evaluates their association with survival. There were several major findings derived from this chapter; the most significant outcomes were that the weak evidence available showed that indices of lung tissue demonstrating NAA and HAA were able to predict the PPC in patients with aortic aneurysms after surgery. Furthermore, the whole quantitative lung morphology indices, including NAA, LAA, and HAA, had significant impact on survival in patients with surgically treated colorectal cancer.

6.2 Discussion

6.2.1 Postoperative pulmonary complications incidence rate, definition, and reporting standards

The PPC encompass a nebulous group of complications affecting respiratory system. Current definitions lack consistency and are still debated. This heterogeneous nature of PPC makes it more challenging to study than cardiac complications (Brinson and Thornton, 2018). In its most extensive scope, PPC is a term for any complication that affects the respiratory system in the postoperative period (Miskovic and Lumb, 2017). Identifying that the clinical measurements of outcome for clinical research studies must be robust and clearly defined, EPCO published a standardised component of a well-defined composite clinical outcome measure (Jammer et al., 2015). The most challenging aspect of PPC is that tis heterogeneity of pathology extends to aetiology and makes it difficult not only to identify the risk factors, but more importantly, makes it almost impossible to design preventative strategies. I propose a more pragmatic approach where PPC should not be treated as one entity, but each component should be addressed separately. It appears that PPC were lumped together from purely statistical/methodological point of view: some of these occur quite rarely and investigating them poses a challenge. This, however, does not justify creation of this composite outcome.

The first result chapter in the presented thesis (Chapter 3) established the incidence of PPC. The analysis found that the incidence of PPC was high in patients who underwent open aneurysm repair (24.2%) and colorectal (9.2%) surgeries. The results of the analysis concur with related literature; the results demonstrated that major and complex surgeries inherently possess a higher rate of PPC (Genovese et al., 2017; Jurt et al., 2018). It is worthy of note that the incidence rates reported in the retrospective analysis were higher than those highlighted in different major vascular interventions by Genovese et al. (2017) with open abdominal aortic repairs (18%), thoracic endovascular aortic repairs

(10%), with only open abdominal aortic intervention (19%) Pasin et al. (2017), and with colorectal procedures (1.3%) (Abd El Aziz et al., 2020).

The definition of PPC indeed varies between studies, which significantly influenced the reported incidence rates of pulmonary complications. None of the previous related studies implemented the standardised EPCO definition; they relied on the general (authors) definition. Using a non-standard definition could lead to studies including broad or specific types of PPC pathology, which results in focusing on severe pulmonary complications. These differences in criteria could significantly overreport or underreport complications. Indeed, due to the absence of a robust system and criteria for recording PPC, the accurate capture of the PPC outcomes between previous studies is questionable. The EPCO definition of PPC used in this thesis may easily explain why the incidence of PPC in vascular and colorectal cohorts is higher than reported before. It is also likely the dataset used in our analysis is of higher quality and accuracy compared to previous studies (Section 3.4.1 on page 147).

Another possible, most likely explanation for the discrepancy in PPC incidence is related to other factors, including study populations, and heterogeneity in cohort characteristics, and the complexity of surgical approaches and procedures. These factors, such as elderly and male patients following small and large bowel Fleisher and Linde-Zwirble (2014), following open vascular Pasin et al. (2017) and rectal Milone et al. (2017) procedures, have been observed to increase the probability of developing PPC compared to more straightforward minimally invasive endovascular aortic repairs Genovese et al. (2017) and colorectal Abd El Aziz et al. (2020) approaches. It has been demonstrated In Chapter 3, Section 3.4.8 on page 170 that the colorectal and vascular cohorts differed significantly in term of basic demographics and disease burden, with vascular patients having significantly worse risk profile. Consequently, the incidence rate of PPC in the vascular cohort is expected to be higher.

The substantial variation of results in the literature is also caused by the challenge of distinguishing between each PPC complications due to their interrelated pathways. This presents more challenges to tailoring an optimal preoperative pulmonary evaluation and preventative strategies. It should also be

acknowledged that the preoperative functional and comorbid status has a major impact on the rate of pulmonary complications. In general, the incidence rates of PPC after colorectal cancer and vascular surgeries are still not described satisfactorily and warrant further studies.

6.2.2 The role of ischaemic-reperfusion injury in vascular patients, on the development of postoperative pulmonary complications

Ischaemic-reperfusion damage poses a significant risk in surgical vascular procedures, as the restoration of blood flow to ischemic tissues can lead to serious molecular and cellular injury. Vascular patients are more vulnerable to ischemic reperfusion damage because of pre-existing conditions, including diabetes and atherosclerosis, which adversely influence vascular function and resilience and result in developing pulmonary complications. Mechanisms that involve increased blood flow in the lungs contribute to the occurrence of pulmonary oedema. In addition, inflammatory responses triggered by ischemia-reperfusion damage may restrict gas exchange and respiratory function.

Despite a considerable understanding of the basic concepts, there is a need for more comprehensive research on the role of ischaemic-reperfusion damage, atherosclerosis, and inflammatory responses in developing the PPC.

6.2.3 The significance of pre-existing lung diseases for postoperative pulmonary complications

The mechanisms causing PPC are complicated and not entirely understood. Although factors related to anaesthesia and surgical trauma are exposing patients to the development of PPC Davies, Husain and Stephens (2017), patients with preoperative comorbidities are more likely to experience PPC (Miskovic and Lumb, 2017). In line with the previous report, the current investigation in Chapter 3 on page 138 found that three important risk factors

were identified on multivariable analysis. PAOD was shown to increase the likelihood of PPC by 4.53 times in individuals scheduled for aortic aneurysms surgery. Whereas CLD and dementia increased the likelihood of developing PPC (6- and 4.5-times) in patients undergoing colorectal cancer surgery. These findings are somewhat surprising given the fact that previous research did not report these co-morbid risk factors. A possible explanation for this might be that PAOD, dementia and frailty are closely interrelated and associate with much lower resilience (Arozullah et al., 2001; Milone et al., 2017). The lack of studies focusing on preoperative risk factors in similar specialties makes comparison challenging. There is a need to conduct more work to determine the factors that increase the risk of pulmonary complications.

In accordance with the current results, previous studies have highlighted that a number of patients presenting for surgical treatment have a history of lung disease, smoking, COPD, or asthma, each of which contributed to the development of PCC. Alves et al. (2005) performed a prospective multi-centre study that focusing solely on postoperative complications. They found that having a cardiorespiratory comorbidity, like smoking or COPD, raised the risk of cardiorespiratory tract complications by 1.50 times (10.7%) in patients who underwent colorectal resections. In a data from a single U.S. centre, Smith et al. (2010) retrospectively reviewed the risk of PPC during the first postoperative week after laparotomy and found that 16% of the PPC were exacerbations of underlying lung disease. A history of chronic lung disease (including asthma, ILD, and COPD) was identified as a 2.45-times greater risk for PPC after operation. In another large study in the U.S. among patients who underwent different types of surgery, Brueckmann et al. (2013) demonstrated that chronic pulmonary disease increased the risk of re-intubation by 1.74 times.

These findings suggest the importance of identifying patients whose symptoms underlie chronic lung disease and reducing the risk before surgery is undertaken. Lung diseases could affect the lung at the time of anaesthesia and surgery, result in reduced lung function efficacy, and increase the risk of intra- and postoperative complications. This is an important issue for future research, and clinicians should take into account that such diseases, to a certain extent,

are modifiable if an optimal preoperative risk stratification and optimisation is identified, which is why the questions remain.

6.2.4 Postoperative pulmonary complications have no significant bearing on survival

Survival is critical for surgical care and patient well-being. However, the association between survival and PPC has received relatively little attention in the literature. This gap offers a critical opportunity for the current thesis to explore such an association and its implications for patient outcomes. Contrary to expectations, the current study did not observe that PPC predicts survival in patients following aortic aneurysm surgery. It seems possible that these results are due to a small sample size and a short of follow-up. Further large prospective longitudinal studies are needed to better understand the influence of PPC on survival outcome following vascular surgeries.

6.2.5 Ability of the CT-derived quantitative lung morphometry to predict postoperative pulmonary complications

The importance of pre-existing lung disease was demonstrated in Chapter 3. Existing methods of preoperative assessment, such as PFT, CPET, and preoperative predictive models lack diagnostic accuracy in identifying the preexisting lung disease. Indeed, this helped to form the rationale for investigating another non-invasive and accurate technique using QCT to diagnose lung pathologies and study its role in optimising perioperative outcomes.

Recently, clinicians and researchers started using analytical morphometry (or simply "morphomics/morphometry") to assess lung abnormalities. These are promising potential morphomarkers that may help predict PPC and mortality and guide pre-operative optimisation and pre-habilitation of patients at risk. However, evidence that supports the use of lung morphomarkers in predicting

PPC and mortality comes from thoracic and transplant surgery, where QCT imaging techniques have been studied as a possible tool in risk stratification before major lung resections.

In fact, most of their attention was on the CT lung densitometry, which explains the approach that uses quantitative lung morphomarker information to precisely diagnose and quantify the extent and severity of emphysema (Crossley et al., 2018). Software applications have since been established that can objectively measure the proportion of pulmonary voxels at a particular density, referred to as the volumetric and relative proportional of LAA (Mascalchi, Camiciottoli and Diciotti, 2017). Studies have applied several pre-defined density thresholds, and it has been determined that the emphysema index, or relative area under -950 HU, is the most frequently used and has been validated in both pathological and therapeutic settings (Gevenois et al., 1995; Gevenois et al., 1996).

On the contrary, coexisting lung diseases, such as emphysematous changes identified using quantitative LAA, had significant impacts on the prediction of PPC in lung cancer patients. Na et al. (2014) and Kitazawa et al. (2021) applied threshold technique that defines emphysema by area less than -950 HU and image reconstructed with a slice thickness range between 1 to 1.25 mm. Kaplan et al. (2015) defined extent of emphysema by lung density area less than -900 HU and slice thickness range between 1.25 to 5 mm. Despite the inconsistencies in the quantitative CT emphysema assessment and density definition, the researchers still supported using quantitative measurements of LAA biomarkers to predict PCC because it was an easy and reproducible preoperative evaluation approach.

In the present study, several predefined LAA threshold values, including an area below -950 HU, were implemented. The volumetric and relative proportional analysis morphomarkers of LAA demonstrated no association with PPC in both study cohorts. It is somewhat surprising since the patients in the vascular and colorectal cohorts in the retrospective analysis (Chapter 4) had significant prevalence of chronic lung disease and COPD (28.2%, 23.6%, 17.3%, and 7%, respectively). It could be speculated that such lung diseases

can result in a decrease or increase in lung density and attenuation areas. This could contribute to impaired pulmonary function in the postoperative phase, increasing the risk of developing PPC.

A possible explanation for the discrepancy between the current study and other previous studies may be the misdiagnosis of lung disease among the included patients. This could have led to an underestimation of the <-950 HU threshold density's ability to detect higher tissue destruction. Furthermore, the distribution and severity of the emphysema extent may have been lower in the included patients, implying that threshold-based parameters were unable to detect pulmonary emphysema.

An implication of a lack of standardisation of the imaging acquisition protocol and CT scanner models could lead to increased variability in emphysematous extent and distribution in individuals, resulting in either overestimating or underestimating the LAA. These factors were not taken into account in many studies, as some researchers did not reveal the full methodology used in analysing the LAA, and this presented a major obstacle in comparing studies. An example of QCT analysis protocol: different reconstruction algorithms, radiation dose, contrast media, and software analysis. These acquisition parameters have been acknowledged as having an effect on lung densitometry results (Na et al., 2014; Mascalchi, Camiciottoli and Diciotti, 2017).

The previously stated factors may explain why the current retrospective analysis is not supporting the related studies on the usability of LAA in predicting PPC. Further, patient-related factors and complex surgical procedures could contribute to the discrepancy in the results of the studies. This is an important issue for future research.

Another important finding from QCT analysis is that $NAA_{(VOL)}$ -850 to -750 HU was able to differentiate between those patients who developed PPC and those who did not. This normal lung density technique is convenient and simple; however, the prediction of clinical endpoints following minor and major operative interventions has yet to be studied. Future studies on integrating NAA morphomarkers as prediction tool in clinical practice are therefore recommended.

Recent recognition of the quantitative nature of pulmonary voxels displaying high attenuation and which are deemed to define interstitial lung abnormalities has advanced current studies to an understanding of this lung morphomarker associated with PPC (Podolanczuk et al., 2016; Lederer et al., 2009). The analysis indicated that a novel measure of increased lung volumetric volume defined as $HAA_{(VOL)}$ -850 to -500 HU provides a valuable prediction of PCC. This finding broadly supports the work of other studies in this area linking HAA with presence of lung disease abnormalities (Choi et al., 2020; Podolanczuk et al., 2017). These findings support HAA, which is still a straightforward parameter to quantify and may prove to be of value for risk prediction in future research.

Even though the volumetric measures of NAA and HAA were significant at predicting the PPC in patients with vascular cohorts, they weren't clinically meaningful; the odds ratio remained at one, indicating caution in interpretation. One possible explanation is that the sample size and proportion of the PPC were too small, making it harder to find a fully conclusive and clinically significant association between the lung morphometrics and the PPC. Changing the analysis's absolute lung volume unit to 100 ml raises the threshold for detecting a clinically significant change and ensures that the odds ratio reflects clinical significance, but it does not necessarily increase the likelihood of reaching clinical significance. The robustness of the study design and the quality of the evidence could determine clinical significance and relevance rather than solely depend on the scale or units of measurement.

A note of caution is due in the current retrospective study since previous related studies identified HAA higher than -600 HU as a measure of lung disease abnormalities. This study, on the other hand, suggests that levels range from $HAA_{(VOL)}$ -850 to -500 HU. This supports the idea that the appearances of lung abnormalities may not be obvious and may also be heterogeneous, which adds to the challenge of distinguishing areas of pathology from normal pulmonary tissue (Hata et al., 2021). Thus, methods that rely on pre-set thresholds do not generally consider the spatial features of the objects in question, i.e., lungs (Mansoor et al., 2015). They are not selective and fail to recognise complicated

pathological appearances or to indicate particular sites containing anomalies (Barnes et al., 2023). Parameters based on threshold therefore lack the ability to distinguish between pathologies that have equivalent levels of attenuation despite being different in both appearance and underlying disease process. It is possible, therefore, that standardising the HAA threshold may not be able to diagnose lung abnormalities in different populations and not predict PCC as observed in the current analysis of patients with colorectal cancer.

Another finding that stands out from the earlier results is that lung volumetric measures (in mL) demonstrated a significant association with PPC compared to proportional lung density (%) measures. The change in the respiratory cycle during CT imaging acquisition could potentially explain this intriguing result. CT scans acquired throughout different phases, such as complete inhalation versus exhalation, could possibly result in varying lung densities and volumes that may influence the measurements.

Evaluating lung volumes, which provides absolute measurements, could potentially have greater precision to reflect changes in lung structure and function, suggesting important clinical abnormalities. Following full inspiration, the lungs expand and are completely filled with air, allowing for an in-depth examination of the lung parenchyma and a precise estimation of the lung volume of a lung disease like emphysema, where hyperventilation occurs and alveolar wall loss results in increasing the lung volume.

However, proportional lung density, which is a relative measure, might not be considered susceptible to these changes and abnormalities, particularly when there is significant variation in the pattern of lung damage among patients. Additionally, variations in the respiratory cycle could contribute to changes in the proper distribution of blood circulation and air inside the lungs, which could influence the identification and measurement of pathological abnormalities.

Interestingly, in the multivariable logistic regression analysis, patients with colorectal cancer who exhibit reduced airway volume demonstrate an increased risk of developing PPC. To the best of my knowledge, this is the first study of an association between quantitative CT airway volume findings and PPC. This finding is somewhat not surprising given the fact that, based on the ae-

tiology of pre-existing lung diseases, patients in the current study present with COP, asthma, and CLD in a total of 239 out of 715. These factors could reduce airway volume, leading to reduced gas exchange efficiency, poorly ventilated lungs, oxygenation, and impaired pulmonary mechanics, all of which increase the risk of developing PPC. More studies using prospective longitudinal designs are needed to investigate the possible link between airway volume limitation and PPC development.

6.2.6 Ability of the CT-derived quantitative lung morphometry to predict mortality

One unanticipated result of a Cox regression model indicated that patients with moderate emphysema in the medium tertile had a 52% higher risk of death compared to those in the lower and higher (reference group) tertiles. Explaining this result is challenging, but it may be associated with patients in the middle stage of the disease, characterised by a significantly large lung volume affected. In this stage, the human body can continue to attempt to adapt to the damaged regions and show noticeable changes, which might result in an increased estimated volume compared to the early (lowest tertile) and advanced (higher tertile) phases. Another possible explanation for this is that when categorising patients into tertiles based on the distribution of volume of LAA, the patients with a moderate amount of LAA may numerically higher than other tertiles. Further, it could be due to overlap of the lung abnormalities; for example, patients in the medium tertile had the greatest proportion of HAA.

The most important result was that for each unit increase in airway volume, the instantaneous risk of death slightly increased by 2%. While the effect appears small, it can have significant clinical implications, particularly when considering the cumulative impact on increased volume or on patients with pre-existing lung diseases. The analysis of the Cox proportional hazards model accounts for multiple confounding factors. This was likely increasing the risk of the interaction of airway volume with other patient-related factors,

resulting in a modest odds ratio and clinical importance. It could argue that airway volume alone has a significant impact on survival.

The volume of the airway may be used as a marker of the overall well-being and performance of the lung. Conditions such as obstructive lung diseases (emphysema and COPD) can cause an increase in airway volume due to damaged alveolar tissue and diminished lung elasticity. This leads to pulmonary hyperinflation and impairs lung function and gas exchange. Patients often become more susceptible to hypercapnia, hypoxia, infection, and other complications, which in turn heightens their risk of mortality.

To sum up, Airway volume is a good indicator of survival and can help clinicians stratify patients into groups based on their preoperative risk. This lets them plan more precise surgeries and make sure that the right pulmonary interventions are done before surgery to lower risks and improve survival rates. Further research is required to understand the fundamental processes and determine whether this association remains consistent across different groups or measurement approaches.

6.2.7 Ability of the CT-derived quantitative diaphragm thickness to predict postoperative pulmonary complications and mortality

An assessment of the diaphragmatic musculature is another essential component of body composition assessment. For clinical purposes, routine CT scans of the thorax often yield a detailed quantitative evaluation of diaphragmatic morphology in three dimensions Donovan et al. (2021). The diaphragm is the major muscle involved in breathing and performs 80% of the work required for physiological tidal respiration Kang et al. (2021b). However, prior to major surgeries, measuring diaphragmatic thickness is often not a priority, unless there are additional comorbidities that warrant this assessment. Consequently, studies evaluating whether diaphragmatic thickness measurements, derived from CT prior to surgery, can predict clinical endpoints, such as PPC and survival, following operative interventions are scarce. As a result, the current

study provides one of the first investigations into the ability of diaphragm thickness to predict PPC and survival outcome following vascular and colorectal surgeries.

The most obvious finding emerges from the analysis: patients with thicker diaphragms were more likely to develop PPC. Pre-existing chronic and obstructive lung disease often induces hyperinflation of the lung, resulting in the thickening (hypertrophy) of the diaphragm due to increased resistance, workload, and effort over time. Increased diaphragm thickness may result in decreased compliance and increased rigidity, compromising their ability to relax a contract efficiently. As result, insufficient ventilation and perfusion in the lung may result in impaired diaphragmatic mobility, which increases the risk of oxygen deprivation and eventual PPC.

Conversely, patients with a thinner diaphragm thickness had a lower survival rate in the colorectal cohort, which contrasted with the PPC outcome. Colorectal cancer may cause cachexia, a medical condition characterised by significant loss of muscle or weakness, including the diaphragm, and a reduction in body weight, which could account for this discrepancy. Another possible explanation for this could be that chemotherapy frequently triggers an inflammatory response, damages muscle cells, and leads to a loss of appetite, ultimately leading to malnutrition. All of these factors could impair respiratory function and the patient's capacity to get involved in physical activity, contributing to respiratory muscle wasting, including the diaphragm, and increasing the risk of complications and death.

6.2.8 Limitations

The limitations of each study conducted in the current thesis have been fully indicated in the related chapters. However, the general limitations of the main methodology and thesis outcome measures are summarised in this section.

- The retrospective observational nature of the studies may introduce bias in collecting data, which may produce misclassification and influence the

accuracy of reporting incidence and rates. Furthermore, failure to report variables of interest may occur since they may have never been recorded or a large proportion of data may be missing (smoking status in the colorectal cohort). Indeed, steps were taken to mitigate these limitations and enhance the reliability and validity of the findings by applying an accurate and rigorous definition of PPC. Multiple independent researchers reviewed all the data twice from multiple sources. Careful data cleaning and validation were implemented to identify data inconsistencies and correct errors. The inclusion and exclusion criteria were clearly specified, and the outcomes were defined to minimise the information bias.

- The results of the QCT lung morphomarkers analysis in the current thesis are limited to using TeraRecon software, which could reduce the external validity and reproducibility. However, several pre-defined lung density thresholds were implemented, which made the extracted quantitative information comparable to different software applications. However, with development of new, AI-based technologies morphometric analysis my take a different direction and allow for automated detection and classification of lung tissue densities.
- Retrospective image analysis was performed as part of research studies, and therefore it was not always possible to pre-set and adjust the image acquisition protocol.

6.2.9 Plans for future work

The results demonstrated that PPC remain a significant challenge, and the incidence following major surgery is considerably high, providing the rationale for future studies. This thesis provided the basic insights into the nature of the problem, setting out the basis for future studies.

- The most imminent work that should arise from this thesis should concentrate on expanding the cohort. This task is underway, but requires additional resources as the morphometric analysis is labour-intense. This

will provide a better, more granular dataset that will be used for building predictive models using advanced statistical methods and machine learning. Designing a multi-centre, prospective observational study for patients undergoing major surgery, allowing control over collecting the data and mitigating the inherent biases in retrospective studies is necessary to obtain representative sample to ascertain generalisation of findings.

- Pre-existing chronic lung disease has not been routinely evaluated in previous studies. The current result analysis stresses the importance of such disease and demonstrates that it plays a critical role in increasing the risk of the development of PPC. To get a full picture of patients who already have chronic lung disease, more research needs to be done on automated identification and classification of lung pathology. This will help develop and implement optimal preventative strategies to improve clinical outcomes after surgery. Future studies on the current topic, related to QCT lung morphomarkers analysis, should standardise the CT imaging admission protocol and use identical, consistent software application to produce more accurate analyses.

- Some of the issues emerging from our findings relate specifically to HAA morphomarkers, since they may not be able to detect lung disease abnormalities. The appearance of lung abnormalities is heterogeneous, which may add challenges and limitations to software applications that use predefined thresholds to distinguish areas of pathology. A further study with more focus on fully automated techniques of analysis, which include artificial intelligence and machine learning, is therefore suggested. The majority of software requires image segmentation and the extraction of specific characteristics; these are extremely sensitive and rely on specific CT scan acquisition pre-sets. Thus, parameters relating to threshold can be highly variable as a consequence of discrepancies between CT manufacturers and acquisition protocol parameters, which may influence study outcomes. Thus, future studies are therefore recommended to take into account the following factors: image noise, image artefacts,

variations in radiation dose, image slice or section depth, contrast media, and the reconstruction kernel and image processing algorithms.

Chapter 7

Concluding remarks

This thesis only provides a superficial understanding of the factors linked to pulmonary complications and mortality, leading to more questions than answers.

The most important message is to recognise that, according to EPCO's definition, PPC are a group of complications that often do not share a common aetiology and clinical features. Therefore, it is advisable to consider each PPC separately, and future research should concentrate on a specific pathology. This focus could potentially lead to the identification of causes, risk factors, and potential interventions that could reduce the risk of PPC.

The quantitative evaluation of morphometric body composition could add value to preoperative risk stratification in PPC and mortality. The current thesis investigation reveals the need for more research with a larger patient group to fully understand the impact of morphology and body composition biomarkers on surgical outcomes.

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Epilogue

"What may be asserted without evidence may be dismissed without evidence."

Hitchens' Razor, Christopher Hitchens (1949-2011)

Colophon

This thesis was typeset using Memoir Document Class in LyX 2.3.7 Document Processor with TeXLive 2023 on Mac OS (Mac OS 12.7.2, Darwin Kernel Version 21.6.0).

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Figures were prepared in RStudio for Mac (RStudio version 2023.06.1+524) using `survplot`, `rocplot` and `ggplot2` libraries for graphic manipulation. Figures illustrating morphometric analysis we exported from TeraRecon Aquarius Intuition and saved in PNG/TIFF format (300dpi). Graphic files were edited using GIMP 2.10 and Inkscape 1.3.2 for Mac. Diagrams were prepared using Dia 0.97.1 and Draw.io (v. 22.1.16) and PowerPoint for Mac, exported and saved in PNG format (300dpi).

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