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Coláiste na Tríonóide, Baile Átha Cliath
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School of Medicine

Biological and Diagnostic Reclassification of Post-Oesophagectomy Pneumonia and Pulmonary Complications

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Submitted for the degree of Doctor of Philosophy
University of Dublin, Trinity College Dublin, School of Medicine
2026

Declaration of Authorship

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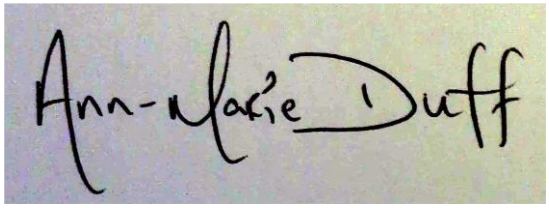

Ann-Marie Duff

Acknowledgements

It is with immense gratitude that I acknowledge the many people who have supported me throughout this PhD journey.

First and foremost, I am deeply grateful to my supervisor, Professor Joanne Lysaght and my co-supervisor, Professor Anne-Marie Brady. Both individuals have served as exceptional mentors and role models, whose guidance, patience and encouragement have significantly influenced my development not only as a researcher but also as an individual. Their embodiment of scientific excellence, integrity and compassion has continually inspired me throughout this journey. Without their support, none of these achievements would have been attainable.

I am deeply grateful to Professor Reynolds, with whom I began this journey, and to Professor Ravi for his ongoing support. I wish to extend my heartfelt thanks to Ms Claire Donohoe and Ms Jessie Elliott for their unwavering support, which has consistently provided reassurance. A special note of gratitude goes to Dr Noel Donlon, whose encouragement, wisdom, and numerous conversations kept me motivated when the challenges felt overwhelming. I am also thankful to Dr Emer Guinan, who was instrumental from the very beginning, and to Ms Sharon Slattery, Director of Nursing at St. James's Hospital, and Ms Rynagh Gilligan, Assistant Director of Nursing, whose assistance and facilitation made this work possible.

I would like to thank Sinead King, whose dedication as data manager was vital to the project's success, and Catherine O'Farrell, Upper GI Clinical Nurse Specialist, for her invaluable support. I also recognise the ICU and ward staff at St. James's Hospital for their dedication and assistance. I am grateful to Dr. Fiona O'Connell for her generous help with the MSD cytokine and BAL analyses, and to my friend Catherine Corcoran, CORU-registered Senior Medical Scientist, for her expertise and support.

I am profoundly grateful to all the patients who participated in this study. Their willingness to contribute to research during the challenging diagnosis and post-operative period made this work possible and demonstrates their generosity in advancing knowledge that may benefit future patients.

This research was generously supported by Grant Number 193 from the Royal City of Dublin Hospital Trust, without which this work could not have been completed.

On a personal note, I would like to thank my mother, father, brothers, sisters, and extended family for their unwavering encouragement and support, especially during challenging times. As the first in my family to attain this level of education, I have found their belief in me to mean everything. I am especially grateful to my sons, Luke and Noah, whose love, patience and light have sustained me throughout this journey. Luke and Noah, your unique qualities and unwavering support have been my guiding stars, and you are, and always will be, my proudest achievement.

To all of you—your contributions, kindness, and belief in me have made this achievement possible.

Abbreviations

ALI - Acute Lung Injury

AMS - Antimicrobial Stewardship

ANOVA - Analysis of Variance

ARDS - Acute Respiratory Distress Syndrome

ASA - American Society of Anaesthesiologists

ATS - American Thoracic Society

AUC - Area Under the Curve

BAL - Bronchoalveolar Lavage

BMI - Body Mass Index

CAP - Community-Acquired Pneumonia

CDC - Centres for Disease Control and Prevention

CI - Confidence Interval

COPD - Chronic Obstructive Pulmonary Disease

CPAP - Continuous Positive Airways Pressure

CPIS - Clinical Pulmonary Infection Score

CRP - C-Reactive Protein

CROSS - Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study

CT - Computed Tomography

CURB-65 - Confusion, Urea, Respiratory rate, Blood pressure, age ≥65

CXR - Chest X-Ray

DAMP - Damage-Associated Molecular Pattern

DLCO - Diffusion Capacity of the Lung for Carbon Monoxide

EBM - Evidence-Based Medicine

ECCG - Esophageal Complications Consensus Group

ELISA - Enzyme-Linked Immunosorbent Assay

ERAS - Enhanced Recovery After Surgery

FEV1 - Forced Expiratory Volume in 1 second

FiO2 - Fraction of Inspired Oxygen

FLOT - Fluorouracil, Leucovorin, Oxaliplatin, and Docetaxel

GM-CSF - Granulocyte-Macrophage Colony-Stimulating Factor

GORD - Gastro-Oesophageal Reflux Disease

HAP - Hospital-Acquired Pneumonia

HCAP - Healthcare-Associated Pneumonia

HR - Hazard Ratio

ICU - Intensive Care Unit

IDSA - Infectious Diseases Society of America

IFN-γ - Interferon-gamma

IL - Interleukin

IL-1β - Interleukin-1 beta

IL-2 - Interleukin-2

IL-4 - Interleukin-4

IL-6 - Interleukin-6

IL-8 - Interleukin-8

IL-10 - Interleukin-10

IL-12p40 - Interleukin-12 p40 subunit

IL-13 - Interleukin-13

IL-17A - Interleukin-17A

IL-18 - Interleukin-18

IL-27 - Interleukin-27

IMT - Inspiratory Muscle Training

IOV - Interobserver Variability

IQR - Interquartile Range

LOS - Length of Stay

M1 - M1 Macrophages (pro-inflammatory)

M2 - M2 Macrophages (anti-inflammatory/repair)

MDT - Multidisciplinary Team

MDRO - Multidrug-Resistant Organism

MIE - Minimally Invasive Oesophagectomy

MSD - Meso Scale Discovery

NPV - Negative Predictive Value

OAC - Oesophageal Adenocarcinoma

OLV - One-Lung Ventilation

OR - Odds Ratio

P/F ratio - PaO2/FiO2 ratio

PAMP - Pathogen-Associated Molecular Pattern

PaO2 - Partial Pressure of Oxygen in Arterial Blood

PCT - Procalcitonin

PICOS - Population, Intervention, Comparator, Outcomes, Study Design

POD - Post-Operative Day

PPC - Postoperative Pulmonary Complication

PPV - Positive Predictive Value

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO - International Prospective Register of Systematic Reviews

qSOFA - Quick Sequential Organ Failure Assessment

QI - Quality Improvement

RAMIE - Robot-Assisted Minimally Invasive Oesophagectomy

RCT - Randomised Controlled Trial

RoB - Risk of Bias

ROC - Receiver Operating Characteristic

SCC - Squamous Cell Carcinoma

SD - Standard Deviation

SEM - Standard Error of Mean

SIRS - Systemic Inflammatory Response Syndrome

SOFA - Sequential Organ Failure Assessment

SpO2 - Peripheral Oxygen Saturation

Th1 - T-helper 1 cells

Th2 - T-helper 2 cells

Th17 - T-helper 17 cells

TNF-α - Tumour Necrosis Factor-alpha

TTE - Transthoracic Esophagectomy

VAP - Ventilator-Associated Pneumonia

VEGF-A - Vascular Endothelial Growth Factor A

WBC - White Blood Cell

Abstract

Background: Post-operative pneumonia represents the most common major complication following oesophagectomy, occurring in 14-25% of patients and significantly impacting mortality, morbidity and healthcare costs. Despite its clinical importance, substantial heterogeneity exists in pneumonia definitions across studies, with only 14.3% of randomised trials using validated diagnostic criteria. The fundamental question of what constitutes pneumonia in this surgical population remains inadequately addressed, with diagnostic disagreement among experienced clinicians suggesting underlying biological complexity rather than methodological failure.

Aims: This thesis aimed to demonstrate that diagnostic unreliability in post-operative pneumonia reflects genuine biological heterogeneity rather than inadequate clinical assessment, through four complementary investigations: (1) a systematic review documenting definitional inconsistency across intervention trials, (2) quantifying inter-observer variability among specialist clinicians in chest X-ray interpretation, (3) developing a trimodal score utilising routinely collected patient parameters to categorise mild to severe risk stratification, and (4) characterising the biological entities underpinning diagnosed pneumonia cases.

Methods: A systematic review of randomised controlled trials examined interventions targeting pulmonary complications after oesophagectomy, documenting the consistency of diagnostic criteria and microbiological confirmation rates. An inter-observer variability study assessed diagnostic agreement among four specialists (surgeon, intensivist, pulmonologist and radiologist) reviewing 200 post-operative chest radiographs, with and without standardised clinical correlation. A trimodal clinical score integrating CRP/albumin ratio, maximum FiO_2 requirement, and PaO_2/FiO_2 ratio was developed and validated in 234 patients against multiple established pneumonia classification systems. Biological characterisation employed procalcitonin-guided entity classification, with comprehensive cytokine profiling of bilateral bronchoalveolar lavage fluid and serial serum samples from 43 patients, and correlated biomarker patterns with microbiological findings and clinical outcomes.

Results: The systematic review of 14 trials involving 1,369 patients revealed that only 14.3% employed validated diagnostic criteria, with pneumonia incidence varying from 10% to 40% among comparable populations. Microbiological confirmation was obtained in only 30% to 40% of cases diagnosed clinically, indicating that the majority of complications are attributable to non-infectious processes. Inter-observer agreement was rated as only fair ($\kappa = 0.270$), with complete agreement observed in only 44% of cases, 97.7% of which concurred on the absence of pneumonia. The application of standardised clinical correlation enhanced agreement by 56% ($\kappa = 0.421$, $p<0.001$), with specific discriminators such as temperature exceeding 38°C, leucocytosis greater than 11,000/μL, and FiO_2 exceeding 40%, influencing diagnostic decisions in 40% of cases with uncertain diagnosis. The trimodal scoring system demonstrated excellent prognostic discrimination (AUC 0.926), allowing effective risk stratification: pneumonia incidence was 3.5% in low-risk patients (score 0-1) compared to 90.9% in high-risk patients (score 2-3), representing a twenty-six-fold difference. Biological characterisation indicated that 65.1% of radiographically diagnosed pneumonia cases were attributable to non-bacterial causes: SIRS pattern (44.2%), associated with elevated CRP but low procalcitonin levels (0.53-1.13 ng/mL), and tissue repair pattern

(20.9%), with borderline biomarker trends. Only 34.9% exhibited bacterial infection, evidenced by markedly elevated procalcitonin levels (3.48±0.68 ng/mL, $p<0.0001$) and predominant enteric organisms. Cytokine analysis of bilateral bronchoalveolar lavage demonstrated an almost perfect correlation ($r > 0.96$ for 14 of 15 mediators), suggesting systemic rather than localised pathology and fundamentally challenging traditional paradigms of pneumonia.

Conclusions: Post-operative pneumonia comprises at least two validated biological entities—bacterial infection and sterile inflammation—that require fundamentally different treatments. Moderate inter-observer agreement ($\kappa = 0.270$) among experienced specialists indicates the upper limit of syndrome-based diagnosis, reflecting appropriate recognition of biological heterogeneity rather than diagnostic failure. Current antibiotic-focused protocols may be inappropriate for approximately 65% of patients who have non-bacterial inflammatory processes. A two-stage precision framework provides immediate clinical utility: universal risk stratification using trimodal scoring (identifying 85.9% as low risk), followed by procalcitonin-guided therapy for high-risk patients (14.1%). This approach promotes prudent antibiotic use, risk-based monitoring and efficient resource allocation, while addressing key methodological limitations in surgical outcome research. The bilateral cytokine symmetry suggests that complications are systemic inflammatory processes affecting the lungs, calling for a shift from infection-centred to entity-specific treatment strategies. Further subdivision of non-bacterial processes into distinct entities remains hypothesis-generating, with borderline cytokine trends ($p=0.075$-0.097) suggesting additional complexity warranting prospective validation. This study demonstrates that surgical critical care can achieve biological precision by understanding mechanisms, implementing routine parameters, establishing practical tools for immediate use, and developing conceptual models to investigate other surgical complications, where diagnostic disagreements may also stem from unrecognised biological heterogeneity.

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Chapter 1

Introduction

1.0 History of Oesophageal Cancer and Surgical Evolution of Care

Cancer is a leading cause of death worldwide (4, 5). A key feature of this disease is the observed changes in cellular physiology, which are believed to follow a consistent pattern regardless of tumour location (6). Oesophageal cancer was first mentioned in ancient writings by Chinese and Arabo-Islamic physicians over 2000 years ago (7). In Henan province, it was known as Ye Ge, where "Ye" refers to the inability to swallow and "Ge" signifies an involuntary resistance to water or food after swallowing (8). Early pathologists, including Theophile Bonet (1620-1689), documented cases of oesophageal growths causing airway obstruction and death. Andreas Vesalius, in his seminal work "De humani Corporis Fabrica" (1543), provided the first detailed description of the upper anatomy as detailed in figure 1.1, including the gastrointestinal tract, and thoroughly described the complexities of thoracic surgery and positive pressure ventilation—breakthroughs that would remain dormant for another 350 years until advances in anaesthesia finally enabled the renaissance of this type of surgery (9).

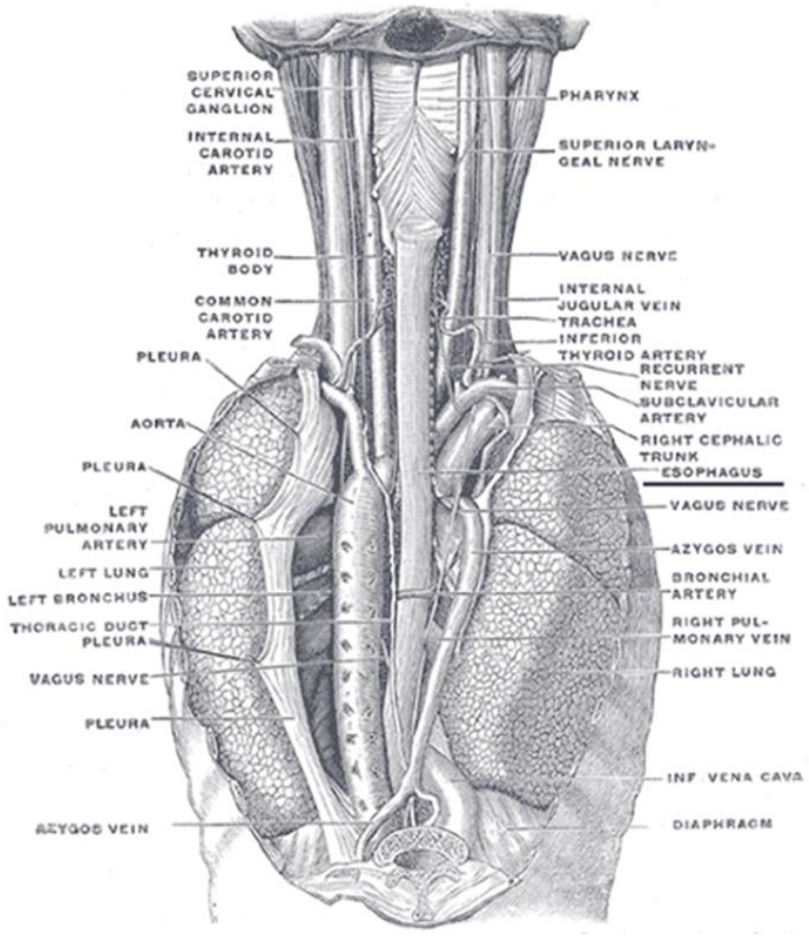


Figure 1.1: Netter FH. Atlas of Human Anatomy. 7th ed. Philadelphia: Elsevier; 2018.

1.1. Evolution of Anaesthesia and Surgical Technique

Advancements in anaesthesia became more standardised in the early 20th century. The introduction of the double-lumen endotracheal tube by Rowbotham and McGill, along with improvements in single-lung ventilation by Gale and Waters (10), facilitated the development of oesophageal surgery. The first successful oesophageal resection was performed in 1913 by Dr. Frank Torek. Ivor Lewis introduced a procedure in 1946 involving a laparotomy to assess tumour extent and mobilise the stomach, followed by resection through a right-sided thoracotomy—now commonly known as the 2-stage approach. The Transhiatal approach, developed by Turner in 1933 and refined by Orringer in 1978, enabled lower mediastinal and oesophageal dissection through a widened diaphragmatic hiatus (Figure 1.1).

In 1976, McKeown utilised the advantage of the two-stage approach along with a cervical incision for the esophagogastric anastomosis—now recognised as the three-stage approach. From the beginning of the 21st century, the modified or hybrid surgical approach has transformed healthcare. In 1992, Cuschieri performed the first thoracoscopic oesophagectomy (11). Luketich (12) advanced this by combining a thoracoscopic and laparoscopic approach: a minimally invasive oesophagectomy (MIE). Following the introduction of the da Vinci robot system, which provided improved surgical ergonomics and a visually superior operative field, robot-assisted minimally invasive oesophagectomy (RAMIE) was introduced and has become widely adopted. Despite these technological advances, postoperative pulmonary complications remain stubbornly common across all surgical methods, with major pulmonary issues occurring in 18% of minimally invasive cases compared to 30% in open procedures, indicating that factors beyond surgical trauma significantly contribute to their development (13, 14).

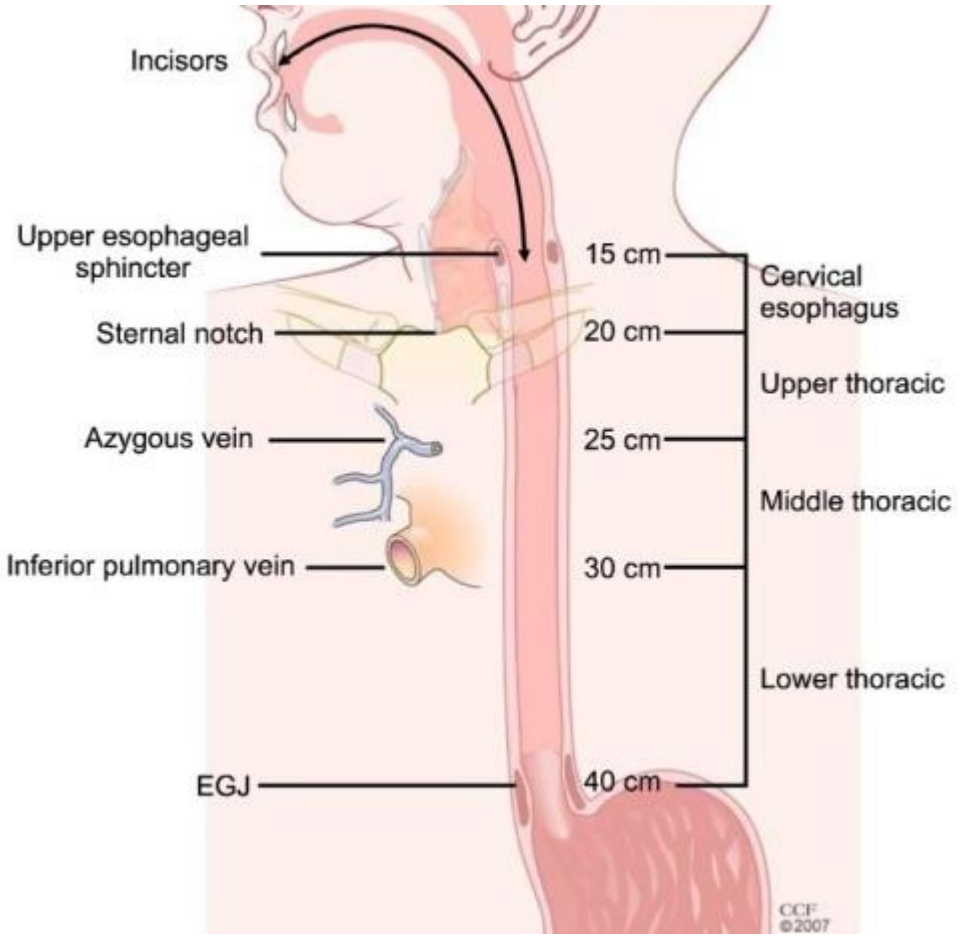


Figure 1.2: Anatomical landmarks and divisions of the oesophagus showing key anatomical relationships and measurements from the incisors. Adapted from Operative Review: Esophagus Anatomy & Physiology. Available at: https://operativereview.com/esophagus-anatomy-physiology/ [Accessed: 29.09.24].

1.2.0 Current Clinical Context

1.2.1 Epidemiology and Pathogenesis of Oesophageal Cancer

Oesophageal cancer is the seventh most common reported malignancy worldwide and the sixth leading cause of cancer-related deaths (15). The complexity of this cancer involves two epidemiologically and pathologically distinct diseases occurring within a single anatomical site (16). The two primary pathological subtypes are adenocarcinoma (OAC) and squamous cell carcinoma (SCC), which together account for 95% of oesophageal cancer cases globally (17). Adenocarcinoma has become increasingly common in the Western world, with at least a fourfold increase since the 1970s, while the prevalence of SCC has somewhat declined. SCC mainly originates in the stratified

epithelium of the upper two-thirds of the oesophagus, whereas adenocarcinoma typically occurs in the lower third (17). Oesophageal cancer is an aggressive disease with direct extension, lymphatic spread and haematogenous metastasis all contributing to its progression. The absence of serosa in the oesophageal wall plays a crucial role in tumour spread, as, without an anatomical barrier, cancer can readily invade neighbouring organs (18).

1.2.2 Risk Factors and Geographic Distribution

Squamous cell carcinoma tumours are strongly associated with smoking, alcohol intake and dietary factors. They are primarily found in regions often referred to as the "Asian belt," including Iran, Turkey, Kazakhstan and northern China (19). The incidence of adenocarcinoma has increasingly replaced SCC in Western countries and is closely linked to gastro-oesophageal reflux disease (GORD), Barrett's oesophagus, male sex and obesity. In this context, obesity specifically refers to the distribution of visceral or central abdominal fat, rather than relying solely on the body mass index (BMI) score (20).

1.2.3 The Evolution of Neoadjuvant Modalities

A common issue among patients with oesophageal cancer is the often-delayed presentation, which delays diagnosis. This is frequently due to vague symptoms, such as gradual weight loss, reflux with or without difficulty swallowing and painful swallowing (21). By the time patients are diagnosed, they may already have moderate to advanced-stage disease, complicating treatment. Surgery remains the best option for patients with locally advanced disease with curative intent. Between 1950 and 2000, the 5-year overall survival rate after surgery alone increased from 12% to 39% (22, 23).

The neoadjuvant treatments for this cancer include chemotherapy (using combinations of platinum-based agents, taxanes and fluoropyrimidines), chemoradiotherapy (combining chemotherapy with external beam radiation therapy) and, more recently, monoclonal antibodies. The CROSS trial mainly guides chemoradiation strategies, while perioperative chemotherapy protocols follow the FLOT regimen (24, 25). Radiation therapy is used primarily for locoregional disease control, whereas

chemotherapy targets micro metastases and aims to minimise the spread of additional metastases. Although both chemotherapy and chemoradiotherapy followed by surgical intervention are considered more beneficial than surgery alone, it is important to recognise that these treatments may also increase the risk of postoperative complications (26, 27).

For patients presenting with locally advanced disease, treatment regimens involving preoperative chemotherapy and radiation (CROSS regimen) and perioperative chemotherapy (FLOT regimen) have improved survival rates to approximately 50% (24, 25, 28). However, these treatments pose additional challenges. The role of neoadjuvant chemotherapy has been controversial for decades, particularly regarding its potential association with increased pulmonary complications (29, 30). Patients receiving neoadjuvant therapy often present for surgery in a more debilitated state, with evident treatment-related toxicities. Studies show that neoadjuvant chemoradiotherapy significantly impacts pulmonary physiology, especially diffusion capacity (DLCO), which correlates with higher postoperative complications and reduced quality of life (31). Functional capacity declines noticeably after treatment, with peak oxygen uptake decreasing from 1128 ± 203 mL min^{-1} before chemotherapy to 1010 ± 196 mL min^{-1} after chemotherapy ($P < 0.001$), indicating decreased physiological reserve (32). Recent data suggest that patients receiving neoadjuvant immunochemotherapy face a significantly higher risk of developing postoperative pulmonary complications compared to those undergoing surgery alone (33). These factors add to the existing challenges of operating on often-elderly patients with advanced cancer, creating a complex clinical situation where the benefits of improved oncological outcomes must be balanced against increased perioperative risks.

1.3.0 The Central Problem: Postoperative Complications

1.3.1 Complications After Oesophagectomy

Perioperative complications directly impact both short- and long-term outcomes following oesophageal surgery. These include hospital readmission, increased length of stay in critical care and surgical wards, postoperative problems (respiratory issues, anastomotic leak, chyle leak, laryngeal nerve injury), reduced quality of life after surgery and cancer recurrence (29, 30, 34). To improve the standardisation of care and facilitate audit and benchmarking across international centres, it became evident that

definitions of various postoperative complications needed to be standardised. In a 2012 systematic review of complications after surgery across 122 papers involving nearly 58,000 oesophagectomies, no single complication was reported in all papers and 60% did not define complications (35).

Internationally, concerns grew over disparities in reporting clinical complications, leading to the formation of the Esophageal Complications Consensus Group (ECCG) in 2011. This group included 21 surgeons with dedicated databases from 14 high-volume institutions. Following Delphi surveys and face-to-face meetings, standardised definitions were published in 2015, leading to the development of ESODATA, a secure online platform for international complication reporting (36). This platform has been externally validated (37). Although this initiative established robust definitions and consensus for many complications, agreement on the definitions of pneumonia and respiratory failure was not achieved. Despite the absence of a standardised definition, pneumonia is recognised as a leading complication, with reporting rates varying across internal and external validation studies. A comparison of outcomes from the Irish National Centre with international ECCG benchmarks revealed similar overall complication rates, but specifically highlighted pneumonia as a key modifiable complication requiring further research (38).

1.3.2 Postoperative Pulmonary Complications

Postoperative pulmonary complications (PPCs) is a broad term used to describe various respiratory issues that can occur after surgery. Following a 2015 publication by the European Joint Task Force, PPCs are now regarded in perioperative medicine as a composite outcome (39). PPCs include both standard and diverse conditions that are difficult to define and predict, ranging from mild abnormalities such as pleural effusions or atelectasis to severe complications like pneumonia and acute respiratory distress syndrome (ARDS). The terminology and classification of acute lung injury have undergone significant evolution. The 1994 American-European Consensus Conference definition distinguished between acute lung injury (ALI) with a PaO2/FiO2 ratio ≤300 mmHg and ARDS with a PaO2/FiO2 ratio ≤200 mmHg (40). However, the 2012 Berlin Definition eliminated the term "acute lung injury" due to inconsistent usage and limited

clinical relevance, instead categorising ARDS into three severity levels: mild (PaO2/FiO2 201-300 mmHg), moderate (PaO2/FiO2 101-200 mmHg), and severe (PaO2/FiO2 ≤100 mmHg), each requiring positive end-expiratory pressure ≥5 cmH2O (41). This shift away from binary ALI/ARDS classifications towards a severity spectrum sets a precedent for the approach proposed in this thesis. The most important development since the Berlin Definition of 2024 was the publication of a new Global Definition of ARDS (42). This definition marks a paradigm shift towards more inclusive, spectrum-based diagnostic criteria that directly align with the approach proposed in this thesis. The Global definition introduces four main changes: 1) inclusion of high-flow nasal oxygen with minimum flow ≥30 L/min; 2) use of SpO2/FiO2 ≤315 as an alternative to PaO2/FiO2 measurements; 3) addition of ultrasound as an imaging tool; and 4) removal of positive end-expiratory pressure requirements in resource-limited settings. Early validation studies found that the Global Definition identified 39.9% more ARDS cases than the Berlin criteria, and that these patients exhibited similar mortality patterns (43). This evolution from the restrictive Berlin Definition towards the more inclusive Global Definition demonstrates a clear trend in critical care medicine: moving away from rigid binary classifications towards spectrum-based approaches that better reflect the underlying pathophysiology. Advanced analytical approaches have identified distinct ARDS subphenotypes using latent class analysis (44, 45). However, such analytical approaches have not been applied to postoperative pulmonary complications following oesophagectomy, and the biological heterogeneity within this specific surgical population remains unexplored.

1.4.0 The Diagnostic Challenge

1.4.1 The Challenge of Pneumonia Definition and Diagnosis

Pneumonia has been part of medical history since Hippocrates described it, with its clinical features and underlying pathology more clearly identified in the 19th century by Laennec and later Rokitansky (46). Essentially, pneumonia is regarded as an infection of the lung parenchyma. However, in practice, microbiological culture can be negative in up to 65% of community-acquired pneumonia cases and up to 80% in paediatric cases. Furthermore, only 14.6% of samples tested were positive in extensive European studies (46, 47). Despite this limited confirmation of the underlying microbiology,

empirical antibiotics are often initiated, which contributes to the global health issue of multidrug-resistant organisms (MDROs) (48-50). Pneumonia is traditionally classified as community-acquired (CAP) or nosocomial pneumonia. Nosocomial pneumonia can be further divided into Hospital-Acquired Pneumonia (HAP), which occurs within 48 hours of admission, and Ventilator-Associated Pneumonia (VAP), which occurs 48 hours after endotracheal intubation. Pneumonia after thoracic surgery, such as oesophagectomy, may not be equivalent to HAP or VAP in terms of aetiology and management and therefore warrants its own definition. Several unique risk factors are present in the oesophageal cohort, including advanced age, disease stage at presentation, the need for one-lung ventilation (OLV), thoracotomy surgical sites and often deconditioned patients with significant comorbidities (51, 52).

1.4.2 Current Diagnostic Tools and Limitations

Scoring tools have been developed in recent decades to assist clinicians in diagnosing pneumonia. The most widely used definitions originate from the Centres for Disease Control (CDC) or the American Thoracic Society (ATS), as updated in the 2019 IDSA/ATS guidelines, which eliminated the healthcare-associated pneumonia (HCAP) category due to concerns about the overuse of broad-spectrum antibiotics (53). The 2023 IDSA Clinical Pathway further refined these approaches, recommending a total therapy duration of 3-5 days and emphasising daily stewardship review (54).

While procalcitonin (PCT) and C-reactive protein (CRP) remain the most widely used biomarkers, various limitations have prompted the search for better alternatives (55). Presepsin demonstrates higher diagnostic accuracy than traditional markers, with a sensitivity of 89.1% and specificity of 88.9%, compared to PCT's 82.7% and 80%, respectively (56). Proadrenomedullin shows promise as a prognostic marker in pneumonia (57). Current research emphasises multi-biomarker panels over single markers, with emerging evidence suggesting that comprehensive panels more accurately reflect the complex interplay between various inflammatory pathways (58). The Utrecht (Uniform Pneumonia Score) was specifically developed and validated for use following oesophageal cancer surgery. However, the authors acknowledge limitations, as many patients are treated with antibiotics for lung changes unrelated to infection (59, 60). The Clinical Pulmonary Infection Score was created for VAP patients but has not been validated in postoperative pneumonia and has fallen out of favour due to poor validation

(3, 61, 62). Although extensive research has been conducted on pneumonia, the exact cause remains unclear in postoperative patients. Given the increasing health and economic burden, a validated definition is essential for guiding clinical decision-making.

1.5.0 Understanding the Complexity: Pathophysiological Mechanisms

1.5.1 Pathophysiology: The Sepsis-SIRS-Pneumonia Continuum

Systemic inflammatory response syndrome (SIRS) denotes an exaggerated immune response to various stressors, including infections, trauma, surgery or malignancies (63), making it particularly relevant to the post-esophagectomy group. SIRS is diagnosed when two or more specific criteria—alterations in temperature, heart rate, respiratory rate, or white blood cell count—are met (63). Notably, when SIRS occurs alongside a suspected infection, it is classified as sepsis (63). The 2016 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) fundamentally redefined sepsis as a life-threatening organ dysfunction resulting from a dysregulated host response to infection (64, 65). The 2021 Surviving Sepsis Campaign guidelines mark a significant shift, focusing on post-ICU care and the long-term effects of sepsis rather than just immediate treatment (66). These guidelines specifically advise against using qSOFA as a sole screening tool, recognising the limitations of binary diagnostic methods that support our spectrum hypothesis (67). Acute pneumonia remains the most common cause of sepsis (65), especially after oesophagectomy. It is estimated that up to a third of sepsis cases occur in the post-operative period (65), with post-operative pneumonia observed in up to 40% of patients undergoing oesophageal surgery, depending on the diagnostic criteria applied (68). The 2024 paediatric sepsis consensus by the Society of Critical Care Medicine entirely discarded SIRS criteria in favour of the Phoenix Sepsis Score, explicitly acknowledging that "SIRS vital signs are common in paediatric patients, with low sensitivity for critical illness" (69). While paediatric medicine has properly abandoned SIRS criteria due to their poor specificity in children, the post-surgical adult population confronts a different clinical context. Here, SIRS may not serve as a diagnostic criterion for infectious complications but rather as an indicator of the intensity of the inflammatory response and the surgical stress burden following oesophagectomy.

The distinction between infectious and non-infectious inflammatory responses poses significant challenges after oesophagectomy. Research in surgical ICU populations shows that neither daily SOFA, qSOFA, nor SIRS criteria correlate with new infections in critically ill surgical patients (70). Procalcitonin (PCT) is significantly elevated (up to 5,000-fold) within 2 to 4 hours in severe cases of systemic inflammation or bacterial infections (71). However, although PCT and C-reactive protein are accurate biomarkers for early prediction of postoperative hospital-acquired pneumonia (72), their interpretation requires careful consideration of the effects of surgical trauma. Contemporary research on surgical inflammatory responses has identified 'postoperative systemic inflammatory dysregulation' as a distinct pathophysiological entity characterised by prolonged, excessively altered gene expression patterns (73). This dysregulated state signifies a harmful progression of the normal inflammatory-immune response to surgical injury, supporting the idea that many post-oesophagectomy pulmonary complications may be due to sterile inflammatory dysregulation rather than infectious processes (74).

Emerging evidence suggests that many cases labelled as "pneumonia" following esophagectomy may be sterile inflammatory responses rather than bacterial infections. The notably low microbiological yield, combined with widespread empirical use of antibiotics, supports this view. There is significant overlap between the surgical inflammatory response and responses triggered by pathogen-associated molecular patterns (PAMPs) typical of sepsis, making it challenging to distinguish between infectious and non-infectious complications in the postoperative period (75). Understanding these pathophysiological relationships is essential for developing effective diagnostic and therapeutic strategies.

ARDS Subphenotyping: Recent ARDS research has identified distinct inflammatory subphenotypes through latent class analysis (44, 45), showing that acute lung injury exists on a biological spectrum rather than as separate categories. Although such advanced clustering methods have helped understand ARDS heterogeneity, they have not yet been applied to post-oesophagectomy pulmonary complications and the biological heterogeneity within this specific surgical group remains unexplored.

1.5.2 Aspiration-Related Pulmonary Complications

Aspiration significantly contributes to pulmonary complications following oesophagectomy, with recurrent laryngeal nerve paralysis occurring in up to 29.3% of patients and being strongly linked to aspiration pneumonia (76, 77). Several factors increase this risk, including recurrent laryngeal nerve injury, altered gastroesophageal anatomy, impaired protective reflexes, and gastroesophageal reflux (77, 78). Aspiration-related lung damage varies from sterile chemical pneumonitis caused by gastric acid (which requires a pH of less than 2.4 to trigger severe inflammation) to infectious pneumonia from oropharyngeal bacteria, often presenting as a combination of pathologies that develop at different times (79, 80). This diversity of underlying mechanisms complicates diagnosis, as chemical pneumonitis can mimic bacterial pneumonia both clinically and radiologically, but necessitates a very different treatment.

1.5.3 The Role of One-Lung Ventilation and Anaesthetic Factors

One-lung ventilation is an independent risk factor (81-83) because it increases pulmonary shunt, leading to ventilation-perfusion imbalance, reduced arterial oxygen tension, and heightened oxidative stress (84, 85). The inflammatory response to OLV involves neutrophil infiltration, cytokine release, and increased vascular permeability (86), creating a clinical picture that may be indistinguishable from infectious pneumonia. Common pro-inflammatory cytokines, such as TNF-α and IL-6, are elevated in patients who have undergone OLV, whereas anti-inflammatory cytokines, such as IL-10, are decreased (87). The use of high inspired oxygen concentrations during OLV can worsen oxidative injury (88). These anaesthetic-related factors suggest that many post-esophagectomy pulmonary complications may be iatrogenic rather than infectious, representing ventilator-induced lung injury rather than bacterial pneumonia (89, 90).

1.6.0 Research Rationale and Objectives

The challenges described above present several essential research opportunities that lay the groundwork for this thesis. These challenges highlight a fundamental tension in diagnostic medicine—what could be called the 'diagnostic reliability paradox'—where

efforts to standardise diagnosis create a conflict between achieving consistency and preserving clinical utility.

1.6.1 Evidence Base for Prevention

Current preventive interventions for postoperative pulmonary complications lack a systematic evaluation specific to oesophageal surgery. The unique physiological challenges, including mandatory one-lung ventilation, extensive mediastinal dissection, and frequent postoperative mechanical ventilation, require population-specific assessment. A comprehensive systematic review of oesophageal surgery is essential for establishing the current evidence base.

1.6.2 Diagnostic Consistency and Reliability

Accurate diagnosis of pneumonia remains a key challenge that has received insufficient attention in the literature on postoperative oesophageal surgery. Although the ECCG recognised the difficulty in reaching a consensus on pneumonia definitions, the influence of diagnostic variability on patient care, antibiotic stewardship and quality improvement initiatives is substantial. The effects of inconsistent diagnosis are significant—overdiagnosis results in unnecessary antibiotic use and delayed recognition of non-infectious complications, while underdiagnosis can lead to delayed treatment and worse outcomes.

1.6.3 Validation of Diagnostic Criteria

The application of pneumonia diagnostic criteria developed for general hospital populations to postoperative oesophageal surgery patients lacks robust validation. The unique physiological features, including a high frequency of pleural effusions, the use of surgical drains, altered chest wall mechanics, and common atelectasis, potentially confound traditional diagnostic criteria. Validation studies are crucial for determining the optimal diagnostic approaches in this population.

1.6.4 Understanding Pathophysiology

The pathophysiology likely involves a complex interaction of surgical trauma, anaesthetic-induced lung injury and immune system activation rather than a simple

bacterial infection. If many complications are due to sterile inflammation rather than infection, therapeutic strategies should emphasise anti-inflammatory approaches and lung-protective measures rather than antimicrobial treatments. Understanding these mechanisms is crucial for developing targeted diagnostic and therapeutic strategies.

1.7.0 Novel Contributions and Thesis Structure

1.7.1 Original Contributions

This thesis makes several novel contributions to the field of postoperative pulmonary complications following oesophagectomy. This thesis addresses post-operative pneumonia following oesophagectomy through four interconnected investigations: first, systematic review of existing literature to establish the current state of diagnostic criteria and outcome measurement; second, inter-observer reliability assessment to quantify diagnostic agreement among experienced clinicians and determine whether disagreement reflects methodological or biological issues; third, development of a clinically implementable trimodal scoring system for risk stratification and therapeutic decision-making; and fourth, comprehensive biological characterisation through procalcitonin-guided classification, cytokine profiling, and microbiological validation to identify distinct pathophysiological entities that explain the observed diagnostic unreliability.

1.7.2 Clinical Significance

The clinical implications of this research go beyond academic interest. Current diagnostic uncertainty results in suboptimal patient care, with some patients receiving unnecessary antimicrobial treatment while others may experience delayed recognition of non-infectious complications needing different interventions. Developing reliable diagnostic criteria could improve patient outcomes, reduce healthcare costs, and enhance antimicrobial stewardship efforts.

Furthermore, if the spectrum hypothesis is confirmed, it may require fundamental changes in how clinicians manage postoperative pulmonary complications. Instead of distinguishing between "pneumonia" and "no pneumonia," clinicians might focus on identifying the type and severity of lung injury, enabling more precise and appropriate treatment based on the underlying pathophysiology.

1.8.0 Central Hypothesis: The Spectrum Paradigm

1.8.1 post-oesophagectomy pulmonary complications

This thesis proposes a fundamental rethinking of post-oesophagectomy pulmonary complications. Rather than treating them as distinct diagnoses—especially the simple dichotomy between "pneumonia" and "non-pneumonia"—we argue that these complications lie along a continuum of lung injury, with shared underlying mechanisms. The evidence supporting this paradigm shift includes microbiological culture positivity rates that have remained consistently low (14.6%), reflecting broader diagnostic challenges in pneumonia diagnosis across healthcare settings. Studies demonstrate that inappropriate pneumonia diagnosis affects 12% of community-acquired cases (1), up to 35% of hospital-acquired cases (2), and up to 60% of ventilator-associated cases (3), highlighting systematic issues with current diagnostic frameworks beyond oesophageal surgery. Traditional diagnostic criteria show poor inter-observer agreement, and the complex interplay of surgical trauma, one-lung ventilation, aspiration risk and systemic inflammation creates injury patterns that transcend conventional infectious/non-infectious boundaries.

1.8.2 Clinical Diagnostic Challenges

These challenges underscore a fundamental tension in clinical diagnosis: standardised criteria intended to ensure consistency may undermine clinical utility in complex surgical populations where pathophysiology exists on a continuum rather than in discrete categories. This observation indicates that traditional evidence-based medicine frameworks, which rely on reliable outcome measures, may be inadequate for addressing diagnostic challenges in complex surgical populations, where clinical judgment and standardised criteria often conflict.

1.9.0 Thesis Hypothesis and Aims

Central Hypothesis: This study hypothesises that postoperative pulmonary complications following esophagectomy represent a spectrum of lung injury with overlapping pathophysiological mechanisms rather than discrete diagnostic entities, and

that current diagnostic approaches based on community-acquired pneumonia criteria are inadequate for this surgical population.

Primary Objective: To develop evidence-based approaches for the diagnosis and classification of pneumonia following esophagectomy.

Secondary Objectives: The secondary objectives include assessing the effectiveness of existing preventive measures for postoperative pulmonary complications, evaluating the reliability of clinical diagnostic criteria for postoperative pneumonia, validating diagnostic scoring systems in the oesophageal surgery population, and characterising the immune, inflammatory and microbiological response patterns associated with postoperative pneumonia.

Chapter 2:

A Systematic Review of Interventions to Prevent Postoperative Pulmonary Complications Following Oesophagectomy

Attribution Statement

This chapter builds upon and substantially extends our published systematic review (see Appendix 1):

Duff AM, Lambe G, Donlon NE, Brady AM, Reynolds JV. Interventions targeting postoperative pulmonary complications (PPCs) in patients undergoing esophageal cancer surgery: a systematic review of randomized clinical trials and narrative discussion. Diseases of the Esophagus. 2022. PMID: 35393612 DOI: 10.1093/dote/doac017

This chapter focuses particularly on the implications of diagnostic reliability and theoretical frameworks for future research, with substantial new analysis not presented in the original publication.

2.0 Introduction

Postoperative pulmonary complications (PPCs) represent the most common complications after oesophageal cancer surgery, occurring in 20-50% of patients and contributing substantially to mortality, prolonged hospital stays, and increased healthcare costs (90,91). Despite notable advances in surgical techniques, anaesthetic management, and perioperative care protocols, oesophagectomy remains associated with a high risk of morbidity, with complications reported in over 50% of patients even in high-volume centres (92). Among these, postoperative pulmonary complications are the most common and clinically significant adverse events, contributing substantially to mortality, prolonged hospital stays and increased healthcare costs. Over 20 years of critical care nursing in medical, surgical, paediatric, and neonatal ICUs revealed substantial variability in postoperative respiratory outcomes. This experience highlighted how oesophageal cancer remains one of the most difficult malignancies to treat, often needing complex multidisciplinary care focused on surgical resection for cure. It also underscored the urgent need to investigate why evidence-based treatments yield inconsistent results across various centres and patient groups.

2.1.1 Clinical Context and Pathophysiology

PPCs are defined as any type of respiratory compromise occurring within 30 days following general anaesthesia and surgery (93). They encompass a spectrum of conditions from atelectasis through to pneumonia, respiratory failure, and acute respiratory distress syndrome (ARDS) (94). The significance of PPCs extends beyond immediate perioperative outcomes. Evidence suggests that serious pulmonary complications can adversely influence long-term cancer prognosis, possibly reducing overall survival through mechanisms such as delayed adjuvant therapy, prolonged immunosuppression and systemic inflammation (95). However, some studies question this connection, emphasising the complex relationship between perioperative complications and long-term survival (96). This debate underscores the crucial need to prevent PPCs while also furthering our understanding of their underlying mechanisms and diagnostic methods.

The pathogenesis of PPCs following oesophagectomy is multifactorial, involving complex interactions between patient-specific risk factors, surgical trauma, anaesthetic

effects and postoperative care processes. The procedure itself necessitates extensive thoracic dissection, prolonged one-lung ventilation and the creation of intrathoracic anastomoses, all of which contribute to pulmonary inflammation and altered respiratory mechanics (97). The physiological stress of oesophagectomy triggers systemic inflammatory responses, potentially leading to acute lung injury through both direct pulmonary trauma and indirect inflammatory cascades (98,99). Neoadjuvant chemoradiotherapy, now standard care for locally advanced disease following landmark trials such as CROSS (100), introduces additional complexity. Radiation therapy can cause pulmonary fibrosis and decreased diffusion capacity, whilst chemotherapy may impair immune function and wound healing (101,102). These treatment-related factors interact with patient comorbidities, including chronic obstructive pulmonary disease, cardiovascular disease and sarcopenia, creating a complex risk profile that requires personalised assessment and management (103,104).

2.1.2 The Diagnostic Challenge and Research Rationale

Despite the clinical significance of PPCs, diagnosing and classifying them remains a major challenge, posing a fundamental obstacle to the development of evidence-based interventions (105,106). Unlike other clearly defined surgical complications, such as anastomotic leaks or laryngeal nerve palsies, PPCs cover a wide range of conditions with overlapping clinical signs and different levels of severity. This diagnostic variability is evident in several key areas that directly influence clinical care and research progress.

The primary challenge lies in diagnosing pneumonia, the most common and clinically significant complication that can occur after surgery. Diagnostic criteria currently depend heavily on subjective interpretations of radiographic findings and clinical signs, which can be affected by normal postoperative inflammatory responses (107,108,109). Recognised guidelines, such as the American Thoracic Society (ATS) criteria (110), the Centres for Disease Control and Prevention (CDC) guidelines and speciality-specific tools like the Utrecht Pneumonia Score, use different combinations of radiographic, laboratory and clinical parameters, leading to inconsistent classification of similar clinical cases (111,112). A significant systematic review by Blencowe et al. (113) examined pneumonia reports across 56 studies focusing on oesophagectomy outcomes. However, only 18 of these studies offered definitions, employing 16 different criteria.

This inconsistency in diagnosis creates multiple issues: it hampers reliable comparison of intervention trials, undermines benchmarking with trustworthy metrics, makes clinical decisions more subjective and obstructs the development of evidence-based guidelines (105,106). Additionally, the complex pathophysiology following oesophagectomy further complicates diagnosis, as factors like extensive surgical trauma, altered thoracic anatomy and systemic inflammatory responses can mimic infectious pneumonia. Proper differentiation among sterile inflammatory lung injury, atelectasis, aspiration pneumonitis and genuine bacterial pneumonia requires advanced diagnostic methods, which current criteria do not adequately provide.

Healthcare systems worldwide are adopting enhanced recovery protocols (114), new surgical techniques (115,116,117), and investing in costly technologies to lower PPC incidence (118,119). However, the evidence supporting these choices may be undermined by unreliable diagnostic criteria (105,106). The importance of this issue goes beyond academic interest and is deeply relevant to frontline critical care experience. Over more than twenty years of intensive care practice, this researcher noticed recurring patterns where patients with similar clinical signs received different diagnoses and treatments, depending on the attending physician's interpretation of radiographic and clinical data. This systematic review offers a basis for understanding why intervention research in this area has yielded inconsistent results and highlights the importance of diagnostic reliability as a key step in advancing evidence-based care.

This systematic review aimed to assess high-quality (Level I) evidence from randomised controlled trials concerning the prevention or treatment of PPCs in oesophageal cancer surgery. The review addressed key questions: (1) Which interventions from preoperative, intraoperative, and postoperative stages have been tested in RCTS? (2) what is the evidence quality backing these interventions? (3) how are pneumonia and other pulmonary complications defined and evaluated across studies? (4) What gaps remain in the current evidence? As discussed in the results and discussion sections, the review uncovered unexpected findings regarding diagnostic reliability that significantly influenced the overall research direction. This research stems from a clinical background spanning over 20 years in critical care nursing across medical and surgical intensive care units, including paediatric and neonatal ICUs. This experience provided extensive exposure to postoperative respiratory complications and

the diagnostic challenges they pose. The researcher's background values both evidence-based practice and clinical expertise, having observed firsthand how experienced clinicians often make accurate diagnostic distinctions that formal criteria fail to identify. However, this clinical background also required conscious efforts to maintain analytical objectivity while recognising that complete neutrality in healthcare research is neither possible nor desirable.

2.2 Aims and Objectives

2.2.1 Primary Aim

To systematically review randomised controlled trials exploring interventions to prevent or manage postoperative pulmonary complications following oesophagectomy, with a critical assessment of the diagnostic frameworks used in this research.

2.2.2 Secondary Objectives

1. To identify and synthesise evidence for interventions across preoperative, intraoperative and postoperative phases of care.
2. To assess the quality and consistency of diagnostic criteria used to define pneumonia and other pulmonary complications.
3. To evaluate the methodological quality of included studies using validated risk of bias tools.
4. To identify gaps in existing knowledge and establish priorities for future research.
5. To establish the rationale for investigating diagnostic reliability in post-oesophagectomy pneumonia.

2.3 Methods

This systematic review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021233786). The protocol was formulated before the review to

minimise bias and ensure methodological rigour. No additional ethical approval was required, as this study involved the analysis of previously published data.

Given the heterogeneity observed in preliminary literature searches and clinical experience with diagnostic variability in critical care settings, the decision was made to structure the research question using the Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) framework to ensure systematic coverage of all relevant intervention categories. This approach was particularly important because early scoping revealed significant variation in outcome definitions across studies, suggesting that diagnostic consistency might be as important as intervention effectiveness. Population included adult patients (≥18 years) undergoing oesophagectomy for curative intent treatment of oesophageal or gastro-oesophageal junction cancer; Interventions encompassed any intervention or combination of interventions implemented to prevent or manage postoperative pulmonary complications during preoperative, intraoperative or postoperative periods; Comparators included standard care, placebo or alternative intervention; Outcomes focused on the incidence, severity or duration of postoperative pulmonary complications, with particular emphasis on pneumonia, respiratory failure and acute respiratory distress syndrome; and Study design was limited to randomised controlled trials only.

A comprehensive search strategy was devised in collaboration with information specialists and refined through iterative pilot searches. The strategy incorporated controlled vocabulary terms (Medical Subject Headings and EMTREE terms) and free-text words covering three main concepts: oesophageal cancer surgery, postoperative pulmonary complications, and interventions. Five databases were searched: MEDLINE (Ovid interface, 1946 to 8 February 2021), Embase (Ovid interface, 1974 to 8 February 2021), CINAHL (EBSCOhost interface, 1937 to 8 February 2021), Cochrane Central Register of Controlled Trials (Wiley interface, current issue), and Web of Science Core Collection (Clarivate interface, 1900 to 8 February 2021). Search limitations included only publications in English, human studies, published between January 2000 and 8 February 2021 (chosen to reflect modern surgical and anaesthetic techniques), and peer-reviewed journal articles. Additional sources included hand-searching reference lists of included studies and relevant systematic reviews, citation tracking in Web of Science,

and screening conference abstracts from major thoracic surgery and anaesthesiology meetings (2018-2021).

Inclusion criteria included randomised controlled trials (including cluster-randomised and crossover designs), adult patients (≥18 years) undergoing oesophagectomy for cancer, interventions aimed at preventing or managing postoperative pulmonary complications, reported outcomes that included at least one measure of pulmonary complications, a minimum of 10 participants per arm to ensure adequate statistical power, and publication in peer-reviewed journals with full-text available. Exclusion criteria comprised non-randomised study designs, animal studies, paediatric populations, emergency or palliative procedures, studies focusing solely on prognostic factors or incidence without intervention assessment, conference abstracts, letters, editorials, review articles and studies with fewer than 10 participants per arm. Due to a lack of explicit definitions used in pneumonia, and the lack of validated screening tools, studies that did not provide a definition were also included. Two reviewers independently screened titles and abstracts using Covidence systematic review management software. Disagreements were resolved through discussion, with a third reviewer available for arbitration. Full-text screening was performed using the same dual-review process with documented reasons for exclusion. Data extraction was conducted using a standardised, pilot-tested electronic form covering study characteristics, population details, intervention specifications, outcome measures, and results. Study quality was assessed using the Cochrane Risk of Bias tool (120), which evaluates seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each domain was classified as low, high, or unclear risk, with a supporting rationale documented. Two reviewers performed independent assessments, with disagreements resolved through discussion.

The protocol specified that a meta-analysis would be performed if the studies were sufficiently homogeneous with respect to populations, interventions, and outcomes. Heterogeneity would be assessed using I^2 statistics, with values>75% indicating substantial heterogeneity that would preclude meta-analysis. When meta-analysis was not feasible, narrative synthesis would be conducted following established guidelines,

organising results by intervention category and assessing consistency of findings across studies.

2.4 Results

The comprehensive search strategy identified 355 records from database searches, with an additional 20 from hand searching and citation tracking, for a total of 375 records. After removing 36 duplicates, 339 unique records underwent title and abstract screening (Figure 2.1). During the initial screening phase, 288 records were excluded for various reasons, including inappropriate study design (n=156), an irrelevant population (n=47), a lack of intervention focus (n=38), a non-English language (n=32), and other reasons, such as duplicates identified during screening (n=15). This left 51 full-text articles for detailed eligibility assessment. Following full-text review, an additional 37 articles were excluded: 14 were non-randomised studies that appeared randomised in abstracts, eight focused solely on prognostic factors without intervention, six included mixed populations with insufficient oesophagectomy-specific data, four were considered too small (n<10 per arm), three were conference abstracts with no complete publication available, and two had inaccessible full texts despite contact attempts with authors.

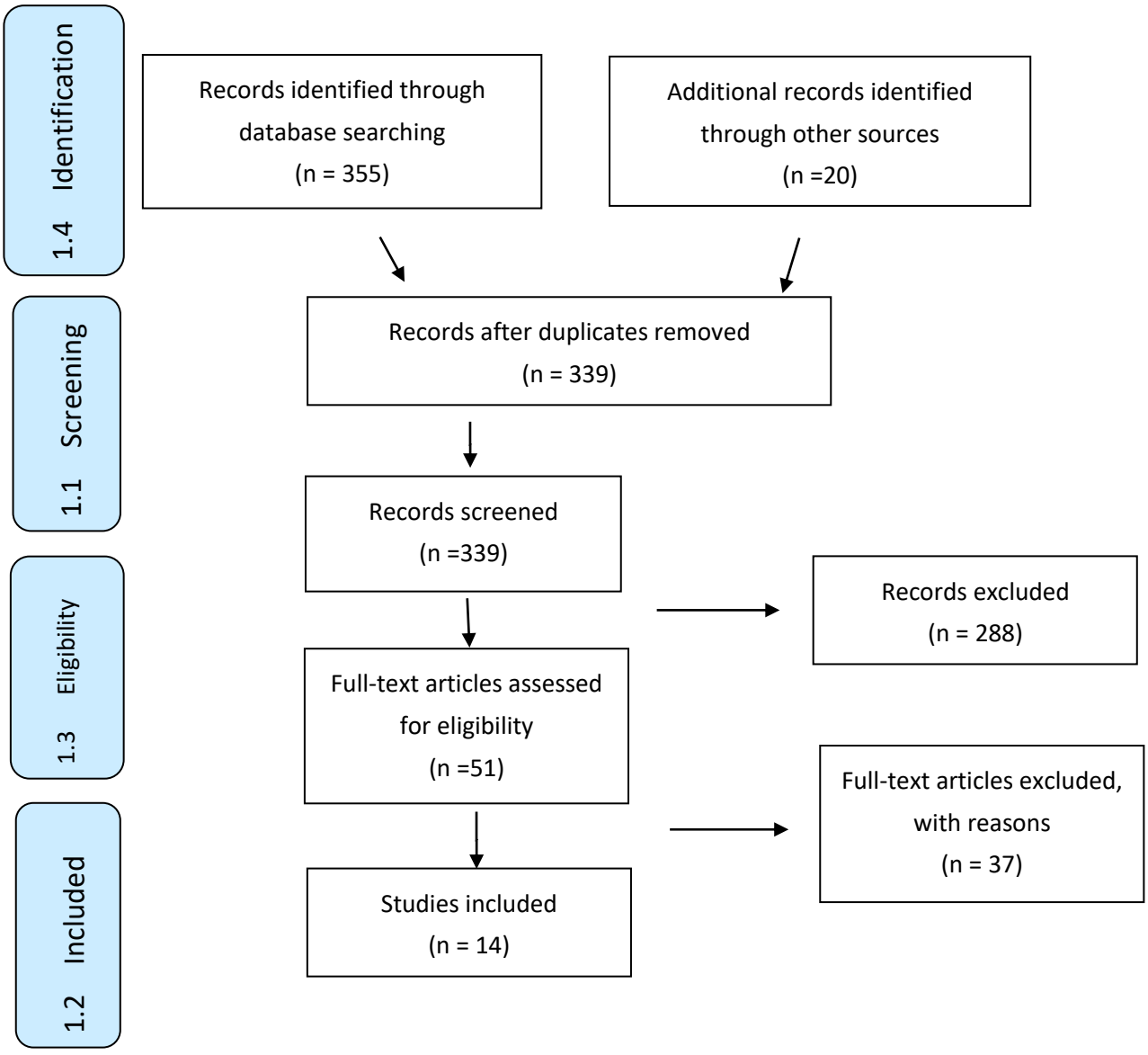


Figure 2.1: PRISMA flow sheet

Multiple diagnostic frameworks for pneumonia classification were identified (Table 2.1), including: American Thoracic Society Guidelines, which emphasise radiographic infiltrates, fever, leucocytosis and purulent secretions; CDC Criteria, which focus on surveillance definitions with specific radiographic and clinical thresholds; Utrecht Pneumonia Score, a post-oesophagectomy tool considering temperature, leukocyte count and radiography findings; Clinical Pulmonary Infection Score, designed for ICU settings using multiple clinical and laboratory parameters; and European Perioperative

Clinical Outcome Definitions (121), offering standardised endpoints for perioperative research.

Table 2.1: Pneumonia screening tools.

CDC	**2 or more serial radiographs** with at least 1 of the following: New or progressive infiltrate Consolidation Cavitation Pneumococcal infections in infants under 1 year old. **1 of the following:** Fever Leucopenia or leucocytosis For adults over 70 years of age, an altered mental status with no other cause identified. **At least 2 of the following:** Increased sputum load, increased suctioning of secretions, new onset of purulent secretions or change in character. New onset cough, dyspnoea or tachypnoea. Rales or bronchial breath sounds. Worsening gaseous exchange. Increased oxygen or ventilator demand or a worsening Pa02/Fio2</= 240.
ATS	"The diagnosis of HAP is suspected if: The patient has a radiographic infiltrate that is new or progressive, *along with clinical findings suggesting infection, which include:* • the new onset of fever, • purulent sputum, • leucocytosis, • and a decline in oxygenation." HAP is defined as pneumonia that is not incubating at the time of hospital admission and occurs 48 hours or more after admission.

	VAP is defined as a pneumonia occurring >48 hours after endotracheal intubation." *American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171:388–416.*
CPIS	**Temperature (in degrees Celsius):** <36.5 / >38.4 = 0 points >38.5 /<38.9 = 1 point >39.0 = 2 points <36 = 2 points **WBC in mm/3:** >4,0000/<11,000 = 0 points <4,000 / > 11,000 = 1 point <4,000/>11,000 with > 500 bands = 2 points **Tracheal secretions (0-4 summed quantified in 24 hrs)** >240 or ARDS = 0 point <240 or NO ARDS = 1 point **Chest x-ray** No Infiltrate = 0 points Patchy/diffuse infiltrates = 1 point Distinct infiltrate = 2 points **Quantitative pathogenic bacterial growth culture from tracheal aspirate:** <1+ no growth = 0 points >1 + = 1 point >1+ and the same bacteria seen on Gram stain.

	0-6 pts pneumonia is less likely **7-12 pts pneumonia likely**
Utrecht (Uniform Pneumonia Score)	**Temperature (degrees Celsius):** >36.1 and <38.4 = 0 points >38.5 and <38.9 = 1 point >39 and < 36 = 2 points **Leukocyte count:** >4 and < 11 = 0 points <4 or > 11 = 1 point **Pulmonary Radiography:** No infiltrate = 0 points Patchy or diffuse infiltrate = 1 point Well-circumscribed infiltrate = 2 points. **A sum of 2 points, in which at least 1 is assigned to pulmonary radiography, indicates treatment of pneumonia.**
Postoperative Pulmonary Complications (PPC) Definition:	Mechanism Composite of respiratory diagnoses that share common pathophysiological mechanisms, including pulmonary collapse and airway contamination: (i) atelectasis detected on computed tomography or chest radiograph, **(ii)** (Pneumonia using the US Centres for Disease Control criteria, **(iii)** Acute Respiratory Distress Syndrome using the Berlin consensus definition, **(iv)** pulmonary aspiration. clear clinical history AND radiological evidence). Severity None: planned use of supplemental oxygen or mechanical respiratory support as part of routine care, but not in response to a complication or deteriorating physiology. Therapies which are purely preventive or

	prophylactic, for example, high flow nasal oxygen or continuous positive airways pressure (CPAP), should be recorded as none Mild: therapeutic supplemental oxygen
EPCO	Mechanism Composite of respiratory diagnoses that share common pathophysiological mechanisms, including pulmonary collapse and airway contamination: (v) atelectasis on film **(vi)** pneumonia CDC criteria **(vii)** ARDS Berlin definition **(viii)** pulmonary aspiration. **clear clinical history** AND **radiological evidence**. **Severity None**: planned use of supplemental oxygen or mechanical respiratory support as part of routine care. **Mild**: therapeutic supplemental oxygen FiO2 <0.6 **Moderate**: Fio2 >0.6 or HFNP **Severe:** unplanned CPAP, NIV or intubation.

This process resulted in 14 randomised controlled trials that met all inclusion criteria, involving 1,369 patients across diverse geographical regions and healthcare systems (Table 2.2). The included studies represented diverse healthcare systems, with six studies from Japan (42.9%), three from the Netherlands (21.4%), two from Iran (14.3%), two from China (14.3%), and one from Germany (7.1%). Eleven studies (78.6%) were single-centre trials, whilst three (21.4%) employed multicentre designs. Study periods ranged from 2002 to 2019, with most studies (n=10, 71.4%) conducted after 2010, reflecting modern surgical and anaesthetic practices. Sample sizes varied considerably, from 20 to 241 participants (median 60). Only six studies (42.9%) provided adequate sample size calculations with power analyses. The pooled population included 1,369 patients with mean ages ranging from 58.2 to 67.4 years across studies. Male predominance was consistent (60-85% across studies), reflecting typical oesophageal cancer demographics.

Table 2.2: Characteristics of Included Randomised Controlled Trials

Author and Year	Country	Design	Sample Size (n)	Intervention	Primary Outcome	Key Findings
Schaefer et al. 2004 (152)	Germany	Multicentre RCT	127	Perioperative G-CSF vs placebo	Severe infections	No benefit: 33.8% vs 35.5% pneumonia (p=0.866)
Bagheri et al. 2011 (138)	Iran	Single-centre RCT	40	Neoadjuvant CRT assessment	Airway colonisation and PPCs	RT associated with positive cultures (p=0.041), no clinical pneumonia difference
Yamaguchi et al. 2011 (158)	Japan	Single-centre RCT	24	Sivelestat vs control	Bronchial inflammatory responses	Reduced SIRS duration, no effect on ARDS/pneumonia
Shen et al. 2013 (147)	China	Single-centre RCT	101	Low tidal volume (6ml/kg) vs standard (10ml/kg)	Pulmonary complications	Reduced PPCs: 9.43% vs 27.8% (p<0.021)
Wakabayashi et al. 2014 (149)	Japan	Single-centre RCT	20	Propofol vs sevoflurane	Cytokine/chemokine production	Propofol suppressed IL-6, IL-8; enhanced IL-10

Takesue et al. 2015 (162)	Japan	Single-centre RCT	47	Early enteral vs parenteral nutrition	Weight loss and complications	Reduced weight loss (p=0.020), non-significant pneumonia reduction (12.5% vs 30.4%, p=0.137)
Yamana et al. 2015 (122)	Japan	Single-centre RCT	60	Preoperative respiratory rehabilitation	Utrecht Pneumonia Score	Improved score POD 1 (p<0.05), no subsequent benefit
Biere et al. 2017 (152)	Netherlands	Multicentre RCT (TIME trial)	115	Minimally invasive vs open oesophagectomy	Microbiologically proven pulmonary infection	MIE reduced PPCs: 9% vs 29% (RR 0.30, p=0.005)
Bagheri et al. 2018 (156)	Iran	Single-centre RCT	60	Intraoperative methylprednisolone vs control	Postoperative respiratory complications	Reduced PPCs: 5% vs 21.7% (p<0.05)
Valkenet et al. 2018 (137)	Netherlands	Multicentre RCT (PREPARE trial)	241	Preoperative IMT vs usual care	Postoperative pneumonia	No benefit: 34.5% vs 36.8% (p=0.34) despite improved muscle strength
Yang et al. 2018 (148)	China	Single-centre RCT	157	Lung protective ventilation vs conventional	Pulmonary complications	Reduced PPCs: 17.7% vs 32.1%
Hayashi et al. 2019 (164)	Japan	Single-centre RCT	71	Early vs conventional NG tube removal	Postoperative complications	No difference in pneumonia rates

van der Sluis et al. 2019 (154)	Netherlands	Single-centre RCT (RAMIE trial)	112	Robot-assisted MIE vs open	Overall complications (Clavien-Dindo)	Reduced PPCs: 32% vs 58% (p=0.005)
Mariette et al. 2019 (153)	France	Multicentre RCT (MIRO trial)	207	Hybrid MIE vs open	Major complications	Reduced PPCs: 18% vs 30% (OR 0.31, p<0.001)

Abbreviations: RCT = randomised controlled trial; G-CSF = granulocyte colony-stimulating factor; CRT = chemoradiotherapy; RT = radiation therapy; PPCs = postoperative pulmonary complications; ARDS = acute respiratory distress syndrome; SIRS = systemic inflammatory response syndrome; IL = interleukin; POD = postoperative day; MIE = minimally invasive oesophagectomy; IMT = inspiratory muscle training; NG = nasogastric; OR = odds ratio; RR = relative risk

During the data extraction process, a notable finding emerged: only 2 out of 14 studies (14.3%) utilised validated screening tools: Yamana et al. (122) applied the Utrecht Pneumonia Score, whilst a multicentre European study referenced standardised definitions. The remaining 12 studies (85.7%) relied on non-validated institutional criteria or failed to specify pneumonia definitions (Table 2.3).

Table 2.3: Summary of Pneumonia Diagnostic Criteria Across Included Studies

Study	Year	Country	Diagnostic Criteria Used	Validated Tool?	Pneumonia Rate (Intervention vs Control)
Yamana et al.	2015	Japan	Utrecht Pneumonia Score	Yes	Improved score POD 1 only
Biere et al. (TIME trial)	2017	Netherlands	Standardised definitions	Yes	9% vs 29% (p=0.005)
Valkenet et al. (PREPARE)	2018	Netherlands	Not specified	No	34.5% vs 36.8% (p=0.34)
Schaefer et al.	2004	Germany	CDC criteria (implied)	Unclear	33.8% vs 35.5% (p=0.866)
Bagheri et al.	2011	Iran	Not specified	No	Positive cultures (p=0.041)

Yamaguchi et al.	2011	Japan	Not specified	No	Not the primary outcome
Shen et al.	2013	China	Not specified	No	9.43% vs 27.8% (p<0.021)
Wakabayashi et al.	2014	Japan	Not specified	No	Not the primary outcome
Takesue et al.	2015	Japan	Not specified	No	12.5% vs 30.4% (p=0.137)
Yang et al.	2018	China	Not specified	No	17.7% vs 32.1%
Bagheri et al.	2018	Iran	Not specified	No	5% vs 21.7% (p<0.05)
Hayashi et al.	2019	Japan	Not specified	No	No significant difference
van der Sluis et al. (RAMIE)	2019	Netherlands	Not specified	No	32% vs 58% (p=0.005)
Mariette et al. (MIRO)	2019	France	Not specified	No	18% vs 30% (p<0.001)

The absence of standardised diagnostic criteria led to several methodological issues. Studies reporting similar intervention effects might have been assessing different phenomena, significantly limiting outcome comparisons. The primary reason meta-analysis was not feasible was outcome heterogeneity, not the diversity of interventions.

Quality assessment identified significant methodological limitations across studies (Figure 2.2). Using the Cochrane Risk of Bias tool, only 4 studies (28.6%) showed low risk of bias in most areas, while 6 studies (42.9%) had high or unclear risk in several key domains. Random sequence generation was adequately described in 8 studies (57.1%), often employing computer-generated sequences or random number tables, though 6 studies lacked sufficient detail. Allocation concealment was the weakest methodological aspect, with only 4 studies (28.6%) demonstrating proper procedures. Participant blinding was frequently impractical given the nature of the intervention, whereas outcome assessor blinding was feasible and implemented in only 4 studies (28.6%). Most studies (n=13, 92.9%) effectively managed missing data, although some failed to report dropout reasons or use appropriate imputation methods for missing outcomes.

Study author & year	Random Sequence generation	Allocation concealment	Blinding of participants &personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Valkenet 2018							
Schaefer 2004							
Bagheri 2011							
Vandersluis 2019							
Hayashi 2019							
Yamaguchi 2011							
Yang 2018							
Wakabayashi 2014							
Yamana 2015							
Takesue 2015							
Biere 2017							
Bagheri 2018							
Shen 2013							
Mariette 2019							

FIGURE 2.2: Risk of Bias Assessment -traffic light plot for all 14 studies across the 7 Cochrane Risk of Bias domains.

Due to heterogeneity in study designs, interventions, and outcome definitions, a meta-analysis was not possible. Therefore, the results are presented as a narrative synthesis organised by temporal intervention categories as shown in table 2.4.

2.4.1 Preoperative Interventions

Several RCTs and meta-analyses have demonstrated improved survival with neo-adjuvant treatment and surgery compared with surgery alone (123,124). The CROSS-trial regimen (carboplatin/paclitaxel/41.4Gy) and the FLOT regimen (Docetaxel, Fluorouracil, Leucovorin, Oxaliplatin) are modern standard bearers for nCRT in trimodality therapy and perioperative chemotherapy, respectively. An additional postoperative respiratory risk of nCRT regimens, particularly for severe PPCs, and an increased mortality, although not evident in the CROSS trial, are suggested by other RCTs (125-130). Conversely, a recent systematic review and meta-analysis reported no significant difference in PPCs between the trimodality and perioperative chemotherapy cohorts (relative risk [RR] = 1.24; 95% confidence interval [CI] = 0.96–1.62; P = 0.102) (131). Radiation dose may be important, with doses>50Gy often used in curative trimodality regimens in North America, potentially increasing the risk of pneumonitis and fibrosis (132,133). More subtle physiological effects may also occur, with a reduced pulmonary diffusion capacity (DLCO) evident in several reports, but whether this clinically affects PPC risk or is a subclinical effect is unclear (134 - 136).

Three studies evaluated preoperative inspiratory muscle training programmes, representing the largest evidence base for any single intervention category. The multicentre PREPARE trial (Valkenet et al. (137), involving 241 patients) provided the highest quality evidence, showing that while inspiratory muscle training significantly improved inspiratory muscle strength and endurance, this did not translate to reduced pneumonia rates (intervention: 34.5% vs control: 36.8%, p = 0.34). Yamana et al. (122) (60 patients) observed statistically significant improvement in Utrecht Pneumonia Scores on postoperative day 1 ($p<0.05$), but no improvement on subsequent days, indicating limited clinical benefit. Despite a compelling physiological rationale, high-quality evidence does not support the use of inspiratory muscle training for pneumonia prevention in patients undergoing oesophagectomy. The discrepancy between physiological improvements and clinical outcomes suggests that respiratory muscle strength may not be the primary limiting factor for PPC development. One study (Bagheri et al., 138), involving 40 patients, specifically examined the effects of neoadjuvant chemoradiotherapy on airway colonisation and PPCs. Radiation therapy was associated with positive bacterial cultures (p = 0.041), but not with the development of clinical pneumonia or ARDS. This finding suggests a potential disconnection

between microbiological changes and clinical outcomes. Despite widespread neoadjuvant therapy use, specific interventions to reduce therapy-related PPC risk remain insufficiently researched.

2.4.2 Intraoperative Interventions

The anaesthetist plays a vital role in achieving optimal outcomes in oesophageal surgery, including the prevention of PPCs (139). Pulmonary inflammation occurs in mechanically ventilated patients, and its extent may be affected by both ventilator settings and the type of anaesthesia (140,141,142). The advantages of lung-protective ventilation are well recognised in critical care settings (143-146). Three studies examined lung-protective ventilation strategies, offering some of the most promising evidence for effective interventions. Shen et al. (147) (101 patients) demonstrated a significant reduction in PPCS with low-tidal-volume ventilation (6 ml/kg vs 10 ml/kg): 9.43% vs 27.8% ($p < 0.021$). Yang et al. (148) reported similar findings in a study of 157 patients using comprehensive lung-protective strategies: 17.7% vs 32.1% complications in the intervention and control groups, respectively. However, concerns about methodology limit the confidence in these results. Yang et al. did not specify definitions of complications and had unclear randomisation procedures. Shen et al. focused solely on minimally invasive approaches, which restricts the generalisability.

Wakabayashi et al. (149) (20 patients) examined the effects of propofol versus sevoflurane on inflammatory responses during one-lung ventilation. Despite employing advanced laboratory techniques to measure cytokine responses in epithelial lining fluid, the study was significantly underpowered for clinical outcomes. Propofol suppressed pro-inflammatory cytokines (IL-6, IL-8) while enhancing anti-inflammatory responses (IL-10); however, the clinical significance remains uncertain.

tMIE in the modern era is performed via total MIE (tMIE), a hybrid approach, or robotic-assisted total or hybrid techniques (RAMIE). It provides clear evidence from RCTs and large observational series supporting an approach that reduces PPCs compared with traditional open methods (150). In the first major series of tMIE, by Luketich et al. (151), of 222 patients, the pneumonia rate was 7.7%, and the 30-day mortality was 1.4%. Three studies directly compared minimally invasive and open approaches, offering Level I evidence on how surgical techniques influence the

incidence of PPC. The TIME trial (Biere et al., 152), involving 115 patients, showed a significant reduction in PPCs with minimally invasive oesophagectomy: 12% versus 34% (RR 0.30, 95% CI 0.12-0.76, p = 0.005). The hybrid MIRO trial (Mariette et al. (153), with 207 patients) showed similar results: 18% versus 30% PPCs in hybrid versus open approaches (OR 0.31, 95% CI 0.18-0.55, p<0.001). The RAMIE trial (van der Sluis et al., 154), involving 112 patients, extended these findings to robotic techniques: 32% versus 58% complications (p=0.005). Minimally invasive techniques provide the strongest evidence for lowering PPCs, with consistent results across several high-quality trials. The effect size — approximately a 50% relative reduction — is clinically meaningful and observed across different minimally invasive methods.

Four studies examined intraoperative drug administration with mixed results. While the benefits of steroids in the ICU critical care setting have been widely debated, there is a relative paucity of data from the perioperative period (155). Bagheri et al. (156) (60 patients) found significantly fewer respiratory complications with single-dose methylprednisolone (5% vs 21.7%, p<0.05); however, methodological limitations, including unclear randomisation and baseline imbalances, reduce confidence. Schaefer et al. (157) (127 patients) found no benefit of perioperative G-CSF administration in a well-designed multicentre trial (pneumonia rates: 33.8% vs 35.5%, p=0.866). Yamaguchi et al. (158) (24 patients) demonstrated a reduction in SIRS duration with sivelestat, but no significant effect on the development of ARDS or pneumonia.

2.4.3 Postoperative Interventions

The philosophy of ERAS—Enhanced Recovery After Surgery—was pioneered by Henrik Kehlet et al. 30 years ago (159). Although implemented in most major surgeries, it was only recently formalised for oesophageal cancer cohorts, with key elements being early mobilisation, enteral nutrition, and minimising the use and duration of tubes and drains (160). Three studies examined specific elements of Enhanced Recovery After Surgery, though none evaluated comprehensive protocols. Nutrition is an important element of ERAS, particularly early postoperative enteral nutrition. In this context, the European Society for Clinical Nutrition and Metabolism (ESPEN) published guidelines for early nutrition after surgery as a core postoperative requirement (161). Takesue et al. (162) (47 patients) compared enteral and parenteral nutrition after thoracoscopic oesophagectomy. Whilst enteral nutrition significantly reduced weight loss (primary

endpoint, p=0.020), the reduction in pneumonia was not statistically significant (12.5% vs 30.4%, p=0.137).

Another ERAS principle is the early removal or avoidance of nasogastric tubes, which may predispose to PPCs. A Cochrane review including 37 randomised controlled trials (N = 5711) demonstrated that the absence of a nasogastric tube was associated with reduced pneumonia and a hastened return of bowel function, and with a shorter hospital stay (163). Hayashi et al. (164) (71 patients) found no difference in pneumonia rates between early and conventional nasogastric tube removal, contrary to evidence from other surgical procedures. Despite widespread adoption of the Enhanced Recovery After Surgery protocol, individual components remain insufficiently studied in oesophagectomy populations.

An important finding across studies was the low rate of microbiologically confirmed pneumonia, typically 30-40% of clinically diagnosed cases. This observation raises fundamental questions about whether diagnosed "pneumonia" represents infectious processes or sterile inflammatory responses to surgical trauma. When positive cultures were obtained, they typically showed nosocomial organisms (Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter species) rather than community-acquired pathogens. This pattern supports the concept that post-oesophagectomy pneumonia represents a distinct pathophysiological entity requiring specialised diagnostic and therapeutic approaches.

Table 2.4: Summary of Intervention Effectiveness by Category

Intervention Category	Number of Studies	Quality of Evidence	Effect on PPCs	Key Findings
Preoperative				
Inspiratory muscle training	3	Moderate to High	No significant benefit	Improved muscle strength but no PPC reduction (PREPARE trial n=241: 34.5% vs 36.8%, p=0.34)
Neoadjuvant therapy effects	1	Moderate	Unclear	Radiation associated with colonisation (p=0.041) but not clinical pneumonia
Intraoperative				
Lung-protective ventilation	3	Low to Moderate	Promising benefit	~50% relative risk reduction, but methodological concerns (Shen: 9.43% vs 27.8%, p<0.021; Yang: 17.7% vs 32.1%)
Minimally invasive surgery	3	High	Strong benefit	Consistent ~50% relative risk reduction (TIME: RR 0.30, p=0.005; MIRO: OR 0.31, p<0.001; RAMIE: 32% vs 58%, p=0.005)
Propofol vs Sevoflurane	1	Low	Unclear	Reduced inflammatory markers (n=20), underpowered for clinical outcomes
Corticosteroids (single-dose)	1	Moderate	Potential benefit	Reduced PPCs (5% vs 21.7%, p<0.05), methodological limitations
G-CSF	1	High	No benefit	No difference in pneumonia rates (33.8% vs 35.5%, p=0.866, n=127)
Sivelestat	1	Low	No benefit	Reduced SIRS duration, no effect on pneumonia/ARDS (n=24)
Postoperative				
Early enteral nutrition	1	Moderate	No significant benefit	Reduced weight loss (p=0.020) but non-significant PPC reduction (12.5% vs 30.4%, p=0.137)
Early NG tube removal	1	Moderate	No benefit	No difference in pneumonia rates (n=71), contrary to other surgical evidence

2.5 Discussion

This systematic review of 14 randomised controlled trials involving 1,369 patients uncovers both promising interventions and fundamental methodological challenges in post-oesophagectomy PPC research. The synthesis of findings highlights an unexpected paradox that emerged during the review process: while significant effort has been dedicated to studying interventions to prevent complications, the core question of what constitutes these complications remains insufficiently addressed.

The evidence synthesis shows clear gradations in support for different interventions. Minimally invasive surgical methods display the most consistent and strong evidence for PPC reduction, with relative risk reductions of about 50% across multiple high-quality trials (152,153,154). This evidence is persuasive because it originates from studies with adequate power, proper controls, and fairly consistent outcome definitions. The TIME trial (152) demonstrated a significant reduction in microbiologically confirmed pulmonary infections (9% vs 29%, RR: 0.30, 95% CI: 0.12-0.76; P=0.005), while the hybrid MIRO trial (153) reported 18% versus 30% PPCs (OR: 0.31; 95% CI: 0.18-0.55; P<0.001), and the RAMIE trial (154) indicated 32% versus 58% complications (P=0.005). To date, eight meta-analyses involving 28,417 patients have been conducted, showing a statistically significant reduction in PPCs favouring the MIE approach, but no difference in mortality (150).

Lung-protective ventilation seems promising based on limited evidence (147,148), though methodological concerns and small sample sizes mean we should interpret findings cautiously. The biological plausibility is strong, aligning with the critical care literature showing benefits of low-tidal-volume ventilation and appropriate PEEP levels (165,166). A Bayesian network meta-analysis of 34 RCTs with a combined dataset of 5,273 patients found that low tidal volume with mid- to high-level positive end-expiratory pressure (PEEP) was associated with fewer PPCs, particularly atelectasis and pneumonia, but not ARDS (167). Protective ventilation may also lessen the inflammatory response. In a key publication, Michelet et al. (168) pointed out that protective ventilation could help prevent changes in lung function and limit cytokine responses in otherwise healthy lungs post-esophagectomy.

Despite their intuitive appeal, several interventions lack convincing evidence. Inspiratory muscle training, evaluated in the high-quality PREPARE trial (137) involving 241 patients, significantly improved inspiratory muscle strength and endurance but did not translate into reduced pneumonia rates (34.5% vs 36.8%, p=0.34). The discrepancy between physiological improvements and clinical outcomes suggests that respiratory muscle strength may not be the primary limiting factor for PPC development. Similarly, pharmacological interventions including G-CSF (157) and individual Enhanced Recovery After Surgery components (162,164) have not demonstrated clear benefit, though corticosteroids show potential and warrant further investigation (156).

2.5.1 The Diagnostic Reliability Paradox and Theoretical Implications

During the data extraction process, it became increasingly clear that the notable variability in pneumonia diagnostic criteria indicated more than just a methodological oversight. This pattern, consistent across studies from different geographic regions and time periods, pointed to a deeper, systemic issue that warranted further theoretical investigation. The finding that only 14.3% of studies used validated diagnostic criteria for their primary outcome challenged fundamental assumptions about the quality of evidence in this field. The research community may be making a fundamental attribution error by assuming that inconsistent intervention outcomes indicate treatment ineffectiveness rather than measurement issues. When studies reporting similar intervention effects may be assessing different phenomena, the ability to compare outcomes is inherently compromised. The diagnostic heterogeneity identified in this review suggests that many "negative" trials may be measuring different outcomes, preventing meaningful comparisons. The low proportion of microbiologically confirmed pneumonia (30-40% of clinically diagnosed cases) across studies indicates that post-oesophagectomy "pneumonia" may involve various pathophysiological processes rather than a single disease entity. This diversity may explain why broad-spectrum interventions have demonstrated limited success.

An important observation from this Centre's research emphasises this complexity. In a cohort study examining pneumonia defined by CDC criteria, patients on trimodality therapy predominantly exhibited culture-negative "pneumonia" at 77%, compared with 60% in patients receiving perioperative chemotherapy, and just 27% in those having

surgery alone (P=0.001) (169). This range indicates differing underlying pathophysiology, with preoperative radiation therapy possibly promoting PPCs through mechanisms independent of infection risk, more akin to acute lung injury than to infectious pneumonia. This highlights a spectrum of pathophysiology with an infective source rarely demonstrated, and a trend suggesting that preoperative radiation therapy may promote PPCs through an effect unrelated to infection risk, more akin to acute lung injury (ALI). Despite these debates, in the most recent completed RCT, Neo-AEGIS, presented at ASCO in 2021 (170), Reynolds et al. reported no difference in PPC incidence or severity among patients with adenocarcinoma of the oesophagus undergoing either the CROSS regimen or optimal perioperative chemotherapy (MAGIC/FLOT). This indicates that, with modern standards of radiation therapy and surgical techniques, postoperative PPCs and disease severity are not significantly increased, and thus, avoiding radiation therapy to reduce PPCs is unnecessary.

Through extensive clinical experience in critical care settings, this researcher observed that experienced clinicians often distinguish between what might be called "true pneumonia" and "inflammatory pneumonitis" through pattern recognition that incorporates subtle changes in patient presentation, response to interventions, and temporal patterns. Yet research continues to lump these potentially distinct pathophysiological processes under a single diagnostic category, highlighting a significant gap between clinical expertise and research methodology. Conducting this systematic review provided several methodological insights that informed this broader research programme. The initial expectation, based on clinical understanding of intervention diversity, was that meta-analysis would be feasible; however, the realisation that diagnostic heterogeneity, rather than intervention diversity, prevented quantitative synthesis fundamentally changed the research path. This experience underscored the importance of diagnostic reliability as a prerequisite for meaningful intervention research—a principle that became central to the theoretical framework developed in this thesis.

The diagnostic heterogeneity identified in this systematic review led to the creation of a multi-theoretical framework that questions conventional methods of evidence synthesis and diagnostic standardisation in surgical research. This framework was developed from the realisation that traditional evidence-based medicine approaches were inadequate to

explain the ongoing diagnostic challenges seen both in the literature and in clinical practice. It combines five supporting theoretical perspectives to explore the complex relationship between diagnostic reliability and intervention effectiveness.

Traditional Evidence-Based Medicine (EBM) frameworks emphasise systematic reviews of randomised controlled trials as the most authoritative evidence (171,172). However, this hierarchy presumes that outcome measures are valid, reliable, and uniformly applied across studies (173,174). Sackett initially highlighted the importance of integrating the best research evidence with clinical expertise and patient preferences. Nonetheless, current practice often prioritises systematic reviews, sometimes neglecting clinical judgment (171). In post-oesophagectomy care, this creates the 'diagnostic reliability paradox': high-quality reviews may synthesise evidence based on outcomes that are inconsistently defined or measured unreliably, leading to potentially misleading conclusions about intervention effectiveness. This issue is particularly acute when diagnostic criteria depend heavily on subjective clinical interpretation, such as in diagnosing pneumonia.

The diagnostic reliability paradox, initially identified in psychiatric diagnosis (175,176), also applies to medical conditions such as pneumonia, where efforts to standardise diagnosis create a natural tension between consistency and clinical usefulness. While traditional pneumonia diagnosis relied on experienced doctors combining symptoms, physical findings, and clinical judgment—leading to considerable variability between clinicians—modern medicine increasingly uses standardised criteria, including radiographic requirements, laboratory thresholds (such as specific white blood cell or procalcitonin levels), clinical scoring systems, and biomarker panels, to ensure diagnostic consistency (177-179). Yet, this standardisation produces the same validity issues seen in psychiatric diagnosis: different outcome measures show notable limitations, whereas strict criteria might overlook early infections recognised by experienced clinicians, classify vulnerable patients as low risk based on scoring algorithms, or delay treatment while awaiting confirmatory tests that may not match clinical reality (180-183). This paradox arises when measured outcomes such as mortality rates, length of hospital stays and antibiotic use patterns become disconnected from actual clinical needs, as reliable diagnostic criteria fail to capture the subtle clinical signs that seasoned practitioners instinctively identify, potentially worsening

patient outcomes despite achieving the aim of more "consistent" diagnostic practices across healthcare providers (184-187).

This paradox is particularly clear in the post-oesophagectomy setting, where Spitzer and Fleiss's fundamental principle that "a necessary constraint on the validity of a system is its reliability" presents a methodological challenge (175). Studies indicate poor inter-observer reliability in diagnosing pneumonia, even among highly trained reviewers using validated criteria (184), while systematic reviews show that standardised definitions of radiological pneumonia have limited predictive value for clinical management and antibiotic decisions (185). The main issue is that chest radiographs cannot reliably confirm or rule out lung infections (177), yet clinical judgment often proves better at excluding pneumonia than standardised criteria (178).

The STARD (Standards for Reporting Diagnostic Accuracy Studies) framework (188,174) and subsequent developments in diagnostic accuracy research highlight that evaluating diagnostic tests should come before intervention research. Bossuyt et al.'s key work established that diagnostic studies must demonstrate reliability and validity before using diagnostic criteria as outcomes in intervention trials (188). This framework could be extended to include diagnostic reliability assessment—measuring not only accuracy against a gold standard but also the consistency with which clinicians apply it across different settings. This shifts the question from "Is the diagnosis correct?" to "Do clinicians agree on the diagnosis?"—a fundamentally different epistemological issue with important implications for evidence synthesis. The literature on diagnostic reliability shows that even if diagnostic criteria are widely accepted across cultures and settings, this does not necessarily mean the underlying constructs are valid in those contexts; reliable application only indicates consistency, not absolute legitimacy (176). The Model for Improvement, developed by the Institute for Healthcare Improvement, emphasises that meaningful quality enhancement requires reliable measurement systems (189,190). Berwick's work on healthcare improvement indicates that outcome measures must be both clinically meaningful and operationally dependable to drive system change (189). This study employs measurement systems theory to argue that diagnostic heterogeneity is a systems-level failure, rather than merely a methodological inconvenience. When outcome definitions vary across studies, the evidence base cannot reliably support quality improvement efforts or policy decisions. The biomarker

literature supports this view, showing that traditional criteria based on clinical signs, symptoms, and general inflammatory indicators are often of limited clinical value and remain unreliable guides to aetiology, optimal therapy, and prognosis (186,187).

Norman and Schmidt's work on clinical reasoning indicates that expert clinicians develop pattern recognition skills that may outperform formal diagnostic criteria (191). This creates a tension between standardisation (necessary for research) and clinical expertise (necessary for patient care). This thesis proposes a framework for integrating clinical heuristics, suggesting that the solution to diagnostic heterogeneity may not reside in enforced external standardisation, but rather in systematically understanding and capturing the tacit knowledge used by experienced clinicians to manage diagnostic complexity. Evidence from research on pneumonia diagnosis supports this approach, demonstrating that clinical algorithms for diagnostic evaluation and antibiotic guidance can be refined by incorporating decision-making processes used by seasoned practitioners (187).

Drawing from foundational work in diagnostic theory, this framework acknowledges the fundamental tension between diagnostic reliability and clinical validity first articulated by Spitzer and Fleiss (175). Their principle—that "there is no guarantee that a reliable system is valid, but assuredly an unreliable system must be invalid"—creates a methodological imperative with profound implications for intervention research. Recent developments in research on diagnostic accuracy indicate that the reliability-validity tension manifests differently across various medical contexts. In psychiatric diagnosis, the DSM-5 field trials revealed that apparent improvements in diagnostic reliability through standardised criteria may conceal long-standing diagnostic issues and create artificial boundaries between conditions that exist on continuums (176). Similarly, in the diagnosis of pneumonia, studies indicate that the reliability of radiographic findings varies significantly across different pathophysiological presentations. For instance, straightforward features, such as pleural effusion, demonstrate excellent inter-rater reliability, whereas complex pattern-recognition tasks show poor agreement (182).

This thesis introduces the Clinical Diagnostic Reliability (CDR) Framework, demonstrating that effective interventions require diagnostically reliable foundations that integrate formal criteria with clinical judgment, reflect underlying biology, and

function in real-world practice settings. This framework adopts a critical realist epistemological stance, recognising that while objective pathophysiological processes exist (realist), our understanding and measurement of these processes are mediated by clinical interpretation and social context (critical). This positioning allows for the existence of "true" diagnostic categories, while recognising that our access to them is imperfect and context-dependent. The diagnostic reliability paradox literature supports this epistemological position by demonstrating that the pursuit of inter-rater reliability through standardised criteria can create artificial diagnostic boundaries that may not reflect underlying pathophysiological reality (175,176). In the context of pneumonia, this manifests as low rates of microbiologically confirmed infection (30-40% of clinically diagnosed cases) across studies, suggesting that post-surgical "pneumonia" may involve multiple pathophysiological processes rather than a single disease entity (185,187).

This multi-theoretical framework challenges traditional assumptions about evidence hierarchy by demonstrating that systematic reviews of randomised controlled trials may not provide reliable evidence when diagnostic criteria are unreliable. It supports a paradigm shift from enforcing external standardisation to developing diagnostic approaches that recognise and utilise the pattern-recognition capabilities that expert clinicians develop through extensive practice, while maintaining the reproducibility and transparency necessary for evidence-based medicine. The current research methodology in this field seems to breach fundamental principles of evidence-based medicine by initiating intervention studies before establishing reliable outcome measures. This may explain the slow progress in developing evidence-based PPC prevention strategies.

2.5.2 Implications for Practice, Policy, and Future Research

Based on the evidence synthesis, clinicians should prioritise minimally invasive surgical approaches when technically feasible and oncologically appropriate, adopt lung-protective ventilation strategies as low-risk interventions with potential benefits, and perform comprehensive preoperative assessments to identify modifiable risk factors. However, concerns about diagnostic reliability highlight that clinical judgement remains vital, especially in distinguishing between infectious and inflammatory processes—a distinction that formal criteria often fail to capture. From a critical care nursing perspective, this emphasises the importance of longitudinal patient assessments and of

developing pattern-recognition skills through extensive bedside experience. Inspiratory muscle training programmes should not be routinely recommended, pharmacological interventions lack sufficient evidence for routine use, and individual Enhanced Recovery After Surgery components should be integrated into comprehensive protocols rather than used alone. Other modifiable risks preoperatively, including smoking cessation, dental hygiene, and optimisation of COPD and interstitial lung disease management, are beyond this review's scope. Detection and treatment of nasal Staphylococcus aureus carriage warrant investigation; screening and treatment reduced overall hospital-acquired infections after lung resection (P = 0.043) (192,193,194). The impact of thoracic epidural anaesthesia compared with other analgesic methods on reducing PPCs remains inadequately studied in RCTs, though epidural analgesia and avoidance of blood transfusions were associated with reduced PPCs and mortality in a cohort study of 335 patients (195). The role of NIPPV after oesophagectomy remains controversial; a 2015 systematic review of four low-quality studies suggested benefits, including reduced reintubation risk and shorter ICU stays, without an increased risk of anastomotic failure (196,197,198,199,200). High-flow nasal cannula may offer comparable benefits with better tolerance, though the OPERA study found no significant difference in the reduction of atelectasis or PPCs (201,202).

Healthcare systems should prioritise standardised outcome definitions for benchmarking (189,190,203), develop multidisciplinary care protocols (114,204), utilise risk stratification tools (205,206), and focus on developing minimally invasive oesophagectomy skills, given strong evidence that this reduces PPCs and costs (207,208,209,210,211,212,213,214,215). This review challenges traditional evidence hierarchies by demonstrating that systematic reviews may not provide reliable evidence when diagnostic criteria are unreliable (171,173,174,188,189,190). Guidelines must emphasise standardised outcome definitions for evidence-based recommendations (105, 106, 216, 217), and healthcare quality organisations should exercise caution in using pneumonia rates as performance indicators until diagnostic methods become consistent (218). The identified diagnostic uncertainty has implications for informed consent; patients should understand that while interventions may reduce "complications," the definition and clinical significance of these complications remain poorly understood. Future trials should prioritise diagnostic reliability before proceeding to intervention studies to avoid violating research ethics principles. Immediate research priorities

include assessing diagnostic consistency across specialists, exploring biomarkers to differentiate infectious from non-infectious inflammation, developing oesophagectomy-specific tools, and validating risk assessment models (219,220,221). Mid-term goals include developing tools to identify high-risk patients for specific PPC subtypes, understanding the factors that influence treatment success, and determining the optimal implementation strategies. Long-term efforts should develop comprehensive, evidence-based protocols that combine multiple interventions, explore the use of machine learning for outcome prediction and treatment guidance, and conduct large-scale, pragmatic trials in real-world settings.

2.5.3 Limitations

Some limitations of this study include conducting searches only in English, which may overlook relevant studies; limited access to conference abstracts and unpublished research; outcome heterogeneity that hinders quantitative synthesis and comparison across studies; and a focus on modern techniques that may miss relevant historical interventions. The theoretical framework developed in response to the diagnostic heterogeneity findings offers an interpretation that goes beyond the empirical data. Although based on the systematic review findings and extensive clinical experience, this framework needs empirical validation through future research.

2.6 Conclusions

This systematic review reveals a critical paradox in post-oesophagectomy pulmonary complication research: whilst 14 randomised controlled trials have examined diverse interventions across 1,369 patients, only 14.3% employed validated diagnostic criteria for the primary outcome of interest. Minimally invasive surgical approaches provide the strongest evidence for reducing PPCs, showing consistent 50% relative risk reductions across multiple high-quality trials. However, the lack of standardised, validated diagnostic criteria for pneumonia represents the most significant barrier to advancing evidence-based PPC prevention. The diagnostic heterogeneity and reliability concerns identified in this systematic review provide a strong justification for empirical research

into diagnostic accuracy among practising clinicians, thereby establishing the foundation for the subsequent chapters of this thesis.

Chapter 3:

Inter-Observer Variability in Post-Oesophagectomy Pneumonia Diagnosis

Attribution Statement

This chapter is based on a manuscript currently under review:

Duff AM, Donlon NE, Elliott JA, McQuade C, Ravi N, Lysaght J, Brady AM, Reynolds JV. How precise is the diagnosis of pneumonia post-oesophagectomy? A study of chest radiographs and clinical interpretation among specialists reveals high inter-observer variability. [Journal name withheld - under review]

The work presented here represents the author's original contribution to study design, data collection, image curation, statistical analysis, and manuscript preparation.

3.0 Introduction

The systematic review in Chapter 2 revealed a key paradox in post-oesophagectomy pulmonary complication research: while 14 randomised controlled trials examined various interventions involving 1,369 patients, only 14.3% used validated diagnostic criteria for pneumonia—the main outcome of interest. This diagnostic inconsistency hampered meaningful meta-analysis, not because of differences in interventions as initially thought, but because studies claiming to assess the same outcome might have been assessing fundamentally different biological processes. The observation that microbiologically confirmed pneumonia was found in only 30-40% of clinically diagnosed cases across studies suggested that what clinicians call "pneumonia" after oesophagectomy may primarily reflect sterile inflammatory responses rather than bacterial infections. These findings raise a fundamental question: does the diagnostic variability originate from inadequate assessment skills among clinicians, or does it instead reflect a proper recognition of the complex underlying pathology that current standardised criteria do not adequately capture? This chapter explores this issue through an empirical investigation of inter-observer variability among specialists routinely involved in post-oesophagectomy care.

Oesophagectomy remains the cornerstone of the curative treatment of oesophageal and gastro-oesophageal junction cancers (223,224). Despite advances in surgical techniques, perioperative care and the widespread adoption of Enhanced Recovery After Surgery (ERAS) protocols, oesophagectomy continues to be a high-risk procedure. Even in an era of increasing centralisation and surgery predominantly performed in high-volume hospitals, a transthoracic oesophagectomy (TTE), whether by open, minimally invasive (MIE) or robot-assisted (RAMIE), remains associated with complication rates exceeding 50% and a modern benchmarked 90-day mortality rate of approximately 4.5% (225). Postoperative pulmonary complications (PPCs) are reported in up to 40% of patients undergoing a TTE, with a spectrum from atelectasis, pleural effusions, pneumothorax, pneumonia, empyema, acute respiratory distress syndrome (ARDS) and clinical outcomes including respiratory failure, re-intubation, sepsis, and mortality (226-236).

Within the spectrum of PPCs, accurately diagnosing pneumonia poses a particular challenge. Pneumonia is generally defined as inflammation of the lungs with

consolidation or interstitial lung infiltrates, most often caused by a pathogen, and postoperative pneumonia is a type of hospital-acquired pneumonia (HAP). Hospital-acquired pneumonia occurs 48 hours or more after hospital admission and was not incubating at the time of admission. In comparison, ventilator-associated pneumonia (VAP) develops more than 48 hours after endotracheal intubation (237). Both conditions are linked to significant morbidity and mortality, with HAP and VAP accounting for roughly 20% of all hospital-acquired infections and exhibiting mortality rates ranging from 20% to 50%, depending on the causative organism and patient population (238,239). The financial burden is considerable, with each episode of HAP adding an estimated 7-9 extra hospital days and costing between €10,000 and €40,000 per case (240,241).

The diagnosis of HAP and VAP has faced similar challenges as those seen in post-surgical populations. Despite multiple revisions to diagnostic criteria by organisations such as the CDC, ATS, and the Infectious Diseases Society of America (IDSA), diagnostic accuracy remains problematic (242-244). The central issue is the reliance on clinical and radiographic findings that lack specificity in critically ill and post-surgical patients, where various non-infectious processes can cause identical symptoms. Fever, leucocytosis, purulent secretions and radiographic infiltrates—the key indicators of pneumonia—are also common in patients with systemic inflammatory responses, atelectasis, pulmonary oedema or acute lung injury, even in the absence of infection (245,246). This diagnostic uncertainty results in both over-treatment with unnecessary antibiotics, which contributes to antimicrobial resistance, and under-treatment of true infections (247,248). Thoracic surgery involving extensive thoracic dissection, one-lung ventilation, and lung retraction can induce inflammatory responses in the lungs and systemically, and may increase the risk of lung infections (234,235). The complex thoracic procedure of TTE also involves gastric transposition into the high thoracic cavity or neck, which can pose challenges for radiological interpretation postoperatively. Unlike conditions such as ARDS, which have a standardised definition, diagnosing pneumonia after TTE remains more subjective, with different definitions and a reliance on nuanced interpretation of radiological, laboratory, and clinical features (249). Therefore, differentiating pneumonia from postoperative inflammatory infiltrates, atelectasis, or non-infectious acute lung injury (ALI) may be difficult and inconsistent (234-236).

The challenges in diagnosing pneumonia are worsened by well-documented variability between observers in interpreting chest radiographs. Multiple studies across various clinical settings have shown that even experienced radiologists and clinicians often have only poor to moderate agreement when diagnosing pneumonia from chest radiographs (250-253). Hopstaken et al. reported Cohen's kappa values ranging from 0.15 to 0.35 among experienced observers assessing community-acquired pneumonia, indicating poor to fair agreement (250). Similar results have been observed in critical care environments, where Klompas and colleagues revealed that clinicians frequently disagree on the presence of new or worsening infiltrates—a key feature for diagnosing VAP (254,255). This variability arises from several factors, such as genuine ambiguity in radiographic signs, differing interpretative thresholds, varying experience levels with certain pathologies and the influence of clinical context on image reading (256,257). Recent research into clinical decision-making suggests that such differences may reflect true variation in specialised pattern recognition rather than poor assessment skills. Norman and Schmidt's research on medical expertise shows that specialists develop unique "illness scripts"—organised knowledge frameworks specific to their fields—that allow quick identification of familiar patterns while remaining attentive to atypical cases (258,259). Surgeons gain detailed knowledge of normal post-operative recovery, intensivists focus on systemic inflammatory responses, and pulmonologists specialise in respiratory pathophysiology—forms of expertise that can complement each other when evaluating complex post-surgical cases. This raises the question of whether diagnostic disagreements are a sign of clinical failure or a proper recognition of the complexity of pathophysiology that surpasses existing standardised criteria.

The post-operative setting presents additional challenges for radiographic interpretation. Regular post-surgical changes, including atelectasis, pleural effusions, elevated hemidiaphragm, and surgical emphysema, can mimic or obscure infectious infiltrates (260,261). Specifically following oesophagectomy, the presence of the gastric conduit in the posterior mediastinum, changes in mediastinal contours, and surgical drains all contribute to radiographic complexity (262). Studies examining radiographic interpretation after thoracic surgery have shown that distinguishing between expected post-operative changes and genuine pathology requires not only radiological expertise but also detailed knowledge of the surgical procedure performed and the expected post-operative course (263,264). This complexity may explain why single-modality

assessment (radiographic alone) shows such poor reliability, whilst integrated assessment combining radiographic and clinical findings demonstrates improved agreement.

Radiologic assessment, especially a chest X-ray (CXR), remains central to diagnosing postoperative pneumonia and is included in several classification systems, including those from the American Thoracic Society (ATS), the Centers for Disease Control and Prevention (CDC), the Uniform Pneumonia Score (UPS), and the European Perioperative Clinical Outcome (EPCO) guidelines (227,242,265-267). Although accessible, CXR has limitations in the postoperative setting, with sensitivity ranging from 32% to 77.7% and specificity from 58.8% to 94% (234). All these systems have fundamental limitations. The UPS, for example, despite being specifically developed for post-oesophagectomy patients, was validated only against clinicians' decisions to prescribe antibiotics, rather than against an objective standard of pneumonia presence, severely limiting its utility as a diagnostic gold standard (266). Similarly, ATS and CDC criteria assume reliable radiographic interpretation—an assumption that has never been systematically tested in the postoperative setting (242,265).

Diagnostic variability in pneumonia carries significant clinical and economic ramifications. Over-diagnosis results in inappropriate antibiotic exposure, fostering antimicrobial resistance and potential adverse effects, while under-diagnosis risks delayed treatment of genuine infections (268,269). The economic burden is considerable, as postoperative pneumonia increases hospital length of stay by 7-14 days and doubles intensive care requirements, with estimated additional costs ranging from €15,000 to € 50,000 per episode, depending on the severity of complications (270-272). Despite the clinical importance of this issue, no studies have systematically evaluated inter-observer variability in the diagnosis of pneumonia specifically after oesophagectomy.

3.1 Study hypothesis and aims:

We hypothesised that the diagnosis of pneumonia following transthoracic oesophagectomy would demonstrate substantial inter-observer variability among experienced specialists, reflecting fundamental limitations in current diagnostic criteria rather than inadequate clinical expertise. The primary aim was to quantify inter-

observer agreement in pneumonia diagnosis among specialists routinely involved in post-oesophagectomy care (oesophageal surgeon, thoracic radiologist, intensivist, and pulmonologist) when evaluating chest radiographs. Secondary aims were to: (1) determine whether providing standardised clinical information improves diagnostic agreement; (2) identify specific clinical discriminators that resolve diagnostic uncertainty; (3) assess agreement between specialist assessments and formal ATS/ECCG criteria; and (4) evaluate the rate of microbiological confirmation in clinically diagnosed pneumonia cases. This study was designed to explore the subjectivity involved in making a radiologic diagnosis of pneumonia after TTE, to examine variations among experienced clinicians in classifying postoperative "pneumonia," and to test whether the radiographic foundation on which all pneumonia criteria depend is sufficiently reliable to support clinical decision-making.

3.2 Methods

3.2.1 Study Design and Patient Population

This single-centre, retrospective study was conducted at the National Centre for Oesophageal Cancer in Ireland at St James's Hospital, Dublin, Ireland, where over 70 oesophagectomies are performed annually. Institutional review board approval (Research & Innovation Reference #6057) was obtained, and the requirement for informed consent was waived due to the study's retrospective design and low risk. All patients who underwent open TTE with curative intent between January 2014 and December 2019 were screened for inclusion. The study period was deliberately limited to pre-2020 to avoid potential confounding from SARS-CoV-2 infections. Inclusion criteria were: (1) age 18-79 years, (2) completion of planned TTE, and (3) availability of chest radiographs on postoperative days 3 and 7. Patients were excluded if they had incomplete imaging, died within 7 days of surgery, or had preoperative pulmonary infections. From 270 eligible patients, 200 were selected using computer-generated random sampling to ensure adequate statistical power while maintaining feasibility for the blinded review process. The sample size was calculated to detect a minimum kappa coefficient of 0.4 (moderate agreement) with 80% power and a 5% significance level. This calculation assumed a null-hypothesis kappa of 0.2 (fair agreement) and required 200 patients to detect a clinically meaningful difference between fair and moderate agreement. From days 1 to 7 postoperatively, if any patient exhibited signs of infection,

a sputum sample obtained using a strict aseptic technique was collected and sent for microbiological evaluation. All procedures were performed using open TTE by experienced surgeons. During the study period, patients with locally advanced oesophageal or gastro-oesophageal junction cancer received either preoperative chemoradiation (cisplatin and fluorouracil, 40 Gy; or carboplatin and paclitaxel, 41.4 Gy) or perioperative chemotherapy by modified MAGIC or FLOT regimens.

3.2.2 Image Acquisition and Observer Selection

Chest radiographs were obtained on postoperative days 3 and 7 (±1 day) using standardised protocols and digital radiography systems. All images were stored in DICOM format at a resolution of 300 DPI. For the study, radiographs were anonymised by removing all patient identifiers, clinical information, and temporal markers. Images were randomly ordered using a computer-generated sequence and assigned unique study identification numbers to prevent bias. Four specialist reviewers were selected based on their routine involvement in post-oesophagectomy care: an experienced oesophageal surgeon (>10 years, >500 oesophagectomies), a thoracic radiologist (>8 years subspecialty experience), an intensive care medicine consultant (>12 years critical care experience), and a consultant pulmonologist (>10 years respiratory medicine experience). The thoracic radiologist served as the reference standard for radiographic interpretation and participated only in the initial phase of radiographic assessment. The three clinical specialists (surgeon, intensivist, and pulmonologist) participated in both the initial radiographic evaluation and subsequent clinical correlation phases. All reviewers underwent a standardised orientation session explaining the study protocol and three-class rating system.

3.2.3 Review Process and Clinical Correlation

The study utilised a sophisticated web-based platform (Qualtrics, Provo, UT) specifically designed for this research. Each reviewer independently evaluated all 400 chest radiographs (200 patients × 2 time points) in computer-generated random order. The platform ensured that reviewers were blinded to all patient identifiers, clinical information, outcomes, and assessments from other reviewers.

For each radiograph, reviewers classified their assessment using a three-category scale: "Yes" for definite pneumonia with clear radiographic evidence of consolidation; "No" for no pneumonia, with a normal postoperative appearance or non-infectious changes only; and "Maybe" for cases where radiographic findings were equivocal and clinical correlation was necessary. When reviewers selected "Maybe," the web-based platform automatically provided standardised clinical information, including vital signs recorded at 23:00 hours on the corresponding postoperative day. This specific time was selected because it represented a period of minimal clinical interventions. The clinical data included core vital signs (temperature, heart rate, blood pressure, respiratory rate), respiratory parameters (oxygen saturation and inspired oxygen fraction), laboratory values (white blood cell count and C-reactive protein levels), and clinical indicators such as the presence of fever >38°C, leucocytosis >11,000/μL, or increased oxygen requirements.

Three reference standards were established for comparison: (1) assessment by a senior radiologist as the primary radiographic reference; (2) ATS clinical criteria defining pneumonia as new or progressive pulmonary infiltrates plus at least one of fever >38°C, purulent sputum, leucocytosis >11,000/μL, or decreased oxygenation (242,273); and (3) microbiological confirmation through positive cultures from respiratory specimens with compatible clinical presentation.

3.2.4 Statistical Analysis

Inter-observer agreement was quantified using Cohen's kappa coefficient for pairwise comparisons and Fleiss' kappa for overall agreement among multiple reviewers. Kappa values were interpreted according to Landis and Koch criteria: 0.0-0.2 (poor), 0.2-0.4 (fair), 0.4-0.6 (moderate), 0.6-0.8 (good), and ≥0.8 (very good) (274,275). Multivariable logistic regression identified factors independently associated with diagnostic uncertainty and final diagnostic disagreement. Variables with $p<0.10$ in univariate analysis were included using forward stepwise selection. All analyses were performed using Python 3.10 with scikit-learn and statsmodels libraries. Statistical significance was set at $p<0.05$.

3.3 Results

3.3.1 Baseline Characteristics and Pneumonia Cohort

The mean age (range) was 61.7 years (22-85). Most patients (141, 70.5%) were male, and the majority of resections (73%) were two-stage procedures, with adenocarcinoma (71.0%) being the predominant pathologic subtype. The majority (92.5%) received neoadjuvant therapy, most commonly the CROSS protocol (51.5%). Twenty-eight (14%) patients were actively smoking up to the operation, and 69 (34.67%) were classified as ASA III. Seventy-seven (18.5%) patients had significant respiratory co-morbidity as shown in Table 3.1.

Table 3.1: Baseline Characteristics of Study Population (N = 200)

Variable	Value
Demographics	
Age, years (mean ± SD) and [range]	61.7 ± 9.6 [22-85]
Male sex, n (%)	151 (75.5%)
BMI, kg/m² (mean ± SD)	25.3 ± 4.8
Preoperative Factors	
ASA Grade I, n (%)	15 (7.5%)
ASA Grade II, n (%)	(104). (52.0%)
ASA Grade III, n (%)	73 (36.5%)
Respiratory comorbidity, n (%)	37 (18.5%)
Smoking Status	
Never smoker, n (%)	64 (32.0%)
Former smoker, n (%)	103 (51.5%)
Current smoker, n (%)	28 (14.0%)
ECOG Performance Status	
0-1, n (%)	174 (87.0%)
≥2, n (%)	5 (2.5%)
Tumour Characteristics	
Histology - Adenocarcinoma, n (%)	148 (74.0%)
Clinical T3 disease, n (%)	162 (81.0%)
Clinical N0 disease, n (%)	95 (47.5%)
Treatment	
Neoadjuvant therapy, n (%)	185 (92.5%)
CROSS protocol, n (%)	106 (53.0%)
FLOT protocol, n (%)	19 (9.5%)
MAGIC protocol, n (%)	11 (5.5%)

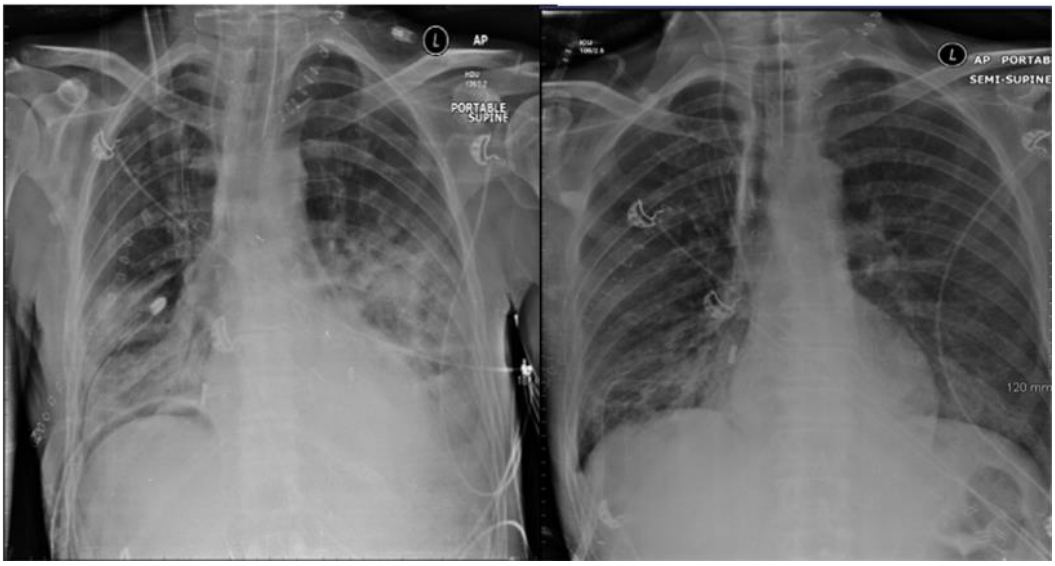
Surgery Type	
Ivor Lewis (2-stage), n (%)	148 (74.0%)
McKeown (3-stage), n (%)	52 (26.0%)
Outcomes	
Pneumonia (ATS/ECCG criteria), n (%)	54 (27.0%)
Microbiological confirmation, n (%)	16 (8.0%)
ICU length of stay, days (mean ± SD)	3.2 ± 4.8
Hospital length of stay, days (mean ± SD)	14.6 ± 8.9

According to ATS diagnostic criteria, pneumonia was diagnosed in 54 patients (27% of the total cohort). Of these 54 patients, ARDS developed in 4 cases (7.4%), pleural effusions in 8 (14.8%), and respiratory failure in 18 (33.3%). Additional complications included anastomotic leak in 4 patients with pneumonia (7.4%), multiorgan failure in 2 (3.7%), atrial fibrillation in 9 (16.7%), and re-intubation in 14 patients (25.9%). The median (range) C-reactive protein (CRP) level amongst patients with documented pneumonia during the first five postoperative days was 227.04 mg/L (95.0-390.89).

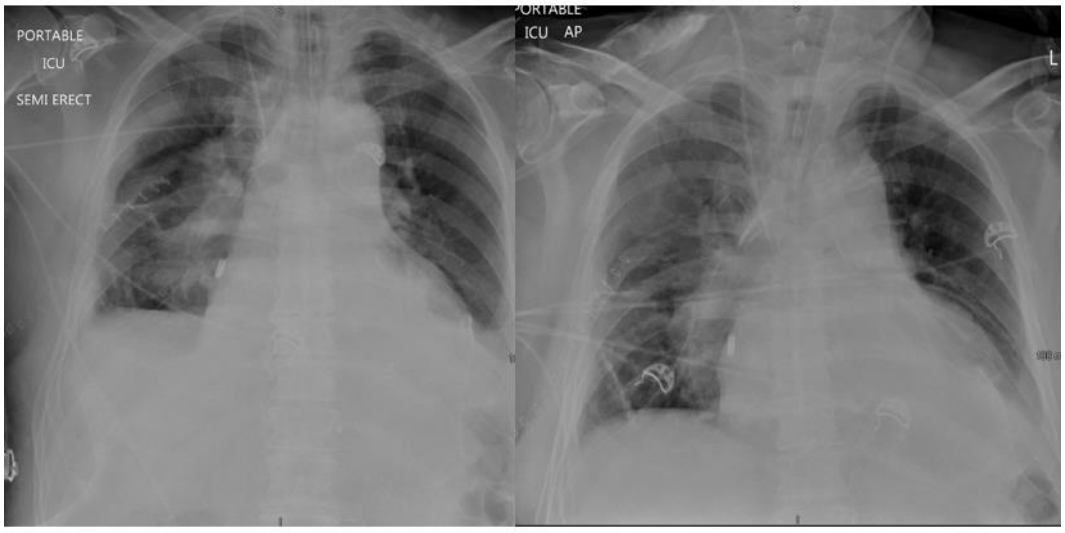
3.3.2 Initial Radiographic Assessment and Inter-Observer Agreement

Upon review of serial chest radiographs alone, the surgeon identified 9 patients (4.5%) with pneumonia; the intensivist, 28 patients (14.0%); the pulmonologist, 34 patients (17.0%); and the radiologist, 17 patients (8.5%). Complete agreement amongst all four raters was achieved in 88 cases (44.0%), 86 (97.7%) of whom showed no radiographic evidence of pneumonia. Using the radiologist as reference standard, Cohen's kappa coefficients demonstrated fair agreement for all specialties, with the surgeon achieving $\kappa = 0.207$ (95% CI: 0.099-0.315, $p<0.001$), the intensivist $\kappa = 0.230$ (95% CI: 0.118-0.342, $p<0.001$), and the pulmonologist $\kappa = 0.214$ (95% CI: 0.112-0.316, $p<0.001$) (Table 3.2).

Panel A



Panel B



Panel C

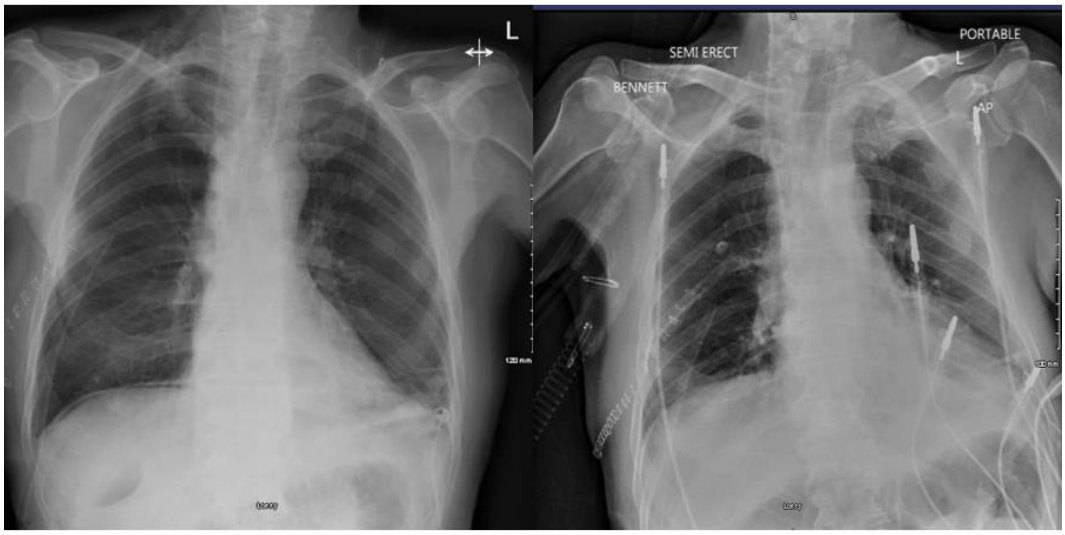


Figure 3.1: Sample Chest Radiographs Demonstrating Varying Levels of Inter-Observer Agreement. Panel A demonstrates a chest radiograph with high agreement for the presence of postoperative pneumonia, whilst Panel B demonstrates a chest radiograph with high agreement for the absence of pneumonia. Panel C demonstrates a chest radiograph with poor agreement regarding the presence or absence of pneumonia, illustrating the diagnostic challenge in equivocal cases that require clinical correlation.

Table 3.2: Inter-observer Agreement Metrics (Cohen's κ with Standard Error, 95% CI, and p-value).

Comparison	Clinician	κ	SE	95% CI	p-value	Interpretation
Radiographic Assessment vs Radiologist Reference	Surgeon	0.207	0.055	0.099–0.315	<0.001	Fair
	Intensivist	0.230	0.057	0.118–0.342	<0.001	Fair
	Pulmonologist	0.214	0.052	0.112–0.316	<0.001	Fair
Clinical Assessment vs ATS/ECCG Criteria	Surgeon	0.285	0.073	0.142–0.428	<0.001	Fair
	Intensivist	0.367	0.078	0.214–0.520	<0.001	Fair
	Pulmonologist	0.334	0.076	0.185–0.483	<0.001	Fair
Assessment vs Microbiological Confirmation	Surgeon	0.177	0.082	0.016–0.338	0.013	Poor
	Intensivist	0.018	0.080	—-0.139–0.175	0.816	Poor
	Pulmonologist	0.016	0.073	–0.127–0.159	0.828	Poor
Inter-clinician Agreement	Surgeon vs. Intensivist	0.233	0.080	0.076–0.390	0.001	Fair
	Surgeon vs. Pulmonologist	0.325	0.080	0.168–0.482	<0.001	Fair

	Intensivist vs. Pulmonologist	0.289	0.079	0.134–0.444	0.002	Fair
Overall	Fleiss' κ (all 3 clinicians)	0.270	—	0.162–0.378	—	Fair

For Fleiss' κ, the standard error and p-value are not presented in the table. The associated test statistic (Z = 4.85, p < 0.001) is described in the text, confirming that the overall agreement was significantly greater than chance.

Fleiss' kappa analysis was conducted to assess the overall agreement amongst the three non-radiologist clinicians (surgeon, intensivist, and pulmonologist) across all 200 patients. The overall Fleiss' kappa during initial radiographic assessment yielded κ = 0.270 (95% CI: 0.162-0.378), indicating fair agreement according to the Landis and Koch criteria (275). The confidence interval excludes zero (Z = 4.85, p<0.001), confirming that the observed agreement was significantly better than chance alone.

3.3.3 Diagnostic Uncertainty and Clinical Correlation Impact

Diagnostic uncertainty ("maybe" responses) occurred in 307/1600 assessments (19.2%), with significant variation by speciality (p<0.001). The surgeon had the highest uncertainty rate, at 83 cases (41.5%), followed by the radiologist, at 44 cases (22.0%). The intensivist showed the lowest uncertainty rate at 26 cases (13.0%), and the pulmonologist at 28 cases (14.0%). When standardised clinical information was provided, 124 cases (40.4%) were adjusted to "pneumonia present," 89 cases (29.0%) were changed to "no pneumonia," and 94 cases (30.6%) had clinical information that was insufficient for decision-making (Table 3.3).

Table 3.3: Pattern of Diagnostic Responses and Clinical Correlation – Initial Radiographic Assessment

Reviewer	Definite Pneumonia n (%)	No Pneumonia n (%)	Uncertain n (%)
Surgeon	9 (4.5%)	108 (54.0%)	83 (41.5%)
Intensivist	28 (14.0%)	146 (73.0%)	26 (13.0%)
Pulmonologist	34 (17.0%)	138 (69.0%)	28 (14.0%)
Radiologist	17 (8.5%)	139 (69.5%)	44 (22.0%)

After Clinical Correlation (Vital Signs at 23:00h) – Clinical Specialists Only

Change Pattern	Surgeon	Intensivist	Pulmonologist

"Maybe" → "Pneumonia present"	34/83 (41.0%)	10/26 (38.5%)	11/28 (39.3%)
"Maybe" → "No pneumonia"	19/83 (22.9%)	6/26 (23.1%)	8/28 (28.6%)
Remained uncertain	30/83 (36.1%)	10/26 (38.5%)	9/28 (32.1%)

Clinical Parameters in Cases Changing from "Maybe" to "Yes" – Clinical Specialists Only

Parameter	Surgeon	Intensivist	Pulmonologist
Temperature >38°C	28/34 (82.4%)	8/10 (80.0%)	9/11 (81.8%)
WBC >11,000/μL	31/34 (91.2%)	9/10 (90.0%)	10/11 (90.9%)
FiO_2 >40%	29/34 (85.3%)	9/10 (90.0%)	10/11 (90.9%)

Following the provision of standardised clinical data, Fleiss' kappa for overall agreement amongst the three clinical specialists improved from 0.270 to 0.421 (95% CI: 0.298-0.544), representing an improvement of 0.151 ($p<0.001$). This 56% relative increase in agreement transitioned the overall concordance from "fair" to "moderate" agreement when standardised clinical information was incorporated into the diagnostic decision-making process. Fleiss' kappa was calculated for each diagnostic category to identify specific areas of agreement and disagreement: "No pneumonia" category κ = 0.445 (95% CI: 0.312-0.578) indicating moderate agreement; "Definite pneumonia" category κ = 0.315 (95% CI: 0.183-0.447) indicating fair agreement; and "Uncertain/Maybe" category κ = 0.189 (95% CI: 0.076-0.302) indicating poor agreement.

Following the provision of standardised clinical data, inter-observer agreement improved significantly across the three clinical specialities. Cohen's kappa improvement compared to radiologist reference showed that the surgeon improved from 0.207 to 0.334 (+0.127, $p<0.001$), the intensivist from 0.230 to 0.398 (+0.168, $p<0.001$), and the pulmonologist from 0.214 to 0.356 (+0.142, $p<0.001$).

3.3.4 Clinical Discriminators and Agreement with Reference Standards

Cases that evolved from "maybe" to "pneumonia present" were significantly more likely to have temperature >38.0°C (82.4% vs 23.1%, $p<0.001$), white blood cell count >11,000/μL (90.3% vs 31.2%, $p<0.001$), increased oxygen requirements with FiO_2

>40% (88.7% vs 28.4%, p<0.001), and C-reactive protein >150 mg/L (85.5% vs 29.8%, p<0.001) (Table 3.4).

Table 3.4: Multivariable Analysis of Factors Associated with Diagnostic Disagreement

Factor	OR	95% CI	p-value
Age (per year)	0.96	0.93-0.99	0.008
Male sex	1.45	0.89-2.36	0.134
Inotropic support requirement	2.89	1.34-6.23	0.007
Elevated CRP >200 mg/L	1.78	1.12-2.83	0.015

When final assessments were compared to ATS/ECCG criteria, agreement remained suboptimal but improved from radiographic assessment alone, with the surgeon achieving $\kappa = 0.285$ (vs 0.075 radiographic only, p<0.001), the intensivist $\kappa = 0.367$ (vs 0.172, p<0.001), and the pulmonologist $\kappa = 0.334$ (vs 0.112, p<0.001). Agreement with microbiologically confirmed pneumonia remained challenging across all reviewers (κ values: 0.016-0.177), reflecting the well-recognised limitations of conventional microbiological techniques.

Multivariable analysis identified several factors independently associated with diagnostic uncertainty including younger age (OR 0.96, 95% CI: 0.93-0.99, p=0.008), inotropic support requirement (OR 2.89, 95% CI: 1.34-6.23, p=0.007), and elevated CRP >200 mg/L (OR 1.78, 95% CI: 1.12-2.83, p=0.015) as shown in table 3.4.

3.3.5 Microbiological Findings

Microbiological confirmation of pneumonia was achieved in only 30% of cases diagnosed clinically using ATS/ECCG criteria. The pneumonia group had a higher prevalence of nosocomial and opportunistic pathogens, including Escherichia coli, Staphylococcus aureus, Enterococcus faecium, Stenotrophomonas maltophilia, and fungal organisms. In contrast, the non-pneumonia group predominantly yielded mixed upper respiratory tract flora or commensals. The organisms isolated from the 16 culture-positive cases included Staphylococcus aureus (4 cases, 25%), Pseudomonas aeruginosa (3 cases, 19%), Escherichia coli (3 cases, 19%), Enterobacter species (2 cases, 13%),

Klebsiella pneumoniae (2 cases, 13%), and other enteric organisms (2 cases, 13%) (Table 3.5).

Table 3.5: Frequency of Microorganisms in Pneumonia vs Non-Pneumonia Patients

Organism	Pneumonia Group	Non-Pneumonia Group
Bacteria		
Staphylococcus aureus (MSSA/MRSA)	22	11
Pseudomonas aeruginosa	19	8
Enterobacter spp.	13	9
Escherichia coli	10	7
Klebsiella spp.	9	6
Citrobacter freundii	6	5
Streptococcus pneumoniae	5	3
Streptococcus viridans group	4	4
Enterococcus spp.	4	2
Stenotrophomonas maltophilia	3	2
Acinetobacter baumannii	2	1
Fungi		
Candida albicans	9	7
Candida glabrata	5	4
Candida tropicalis/parapsilosis/dubliniensis	4	3
Aspergillus fumigatus	2	0
Penicillium spp.	1	0
Pneumocystis jirovecii (PJP)	1	0
Other		
Mixed URT flora	12	8

Postoperative complications were classified according to the Clavien-Dindo grading system (276). Most patients experienced either no complications (Grade 0, 24.0%) or minor complications requiring only pharmacological therapy (Grade II, 23.5%). Severe complications (Grades III-V) affected 29.5% of the cohort. Chyle leak was the most common complication (14.5%), followed by cardiac dysrhythmia (12.0%) and pleural effusions requiring drainage (6.0%). The anastomotic leak rate was 6.0% (12 patients). It should also be noted that sputum culture, as the primary method of microbiological

sampling in this cohort, is likely to significantly underestimate the true prevalence of bacterial pneumonia. Sputum cultures are subject to contamination with upper respiratory tract flora, depend on sample quality, and may yield false-negative results in patients receiving prior antibiotic therapy — all common challenges in the post-operative critical care setting. Lower respiratory tract sampling techniques such as bronchoalveolar lavage or protected specimen brush would provide greater diagnostic sensitivity, and the reliance on sputum culture in this study may therefore have artificially inflated the proportion of cases classified as non-bacterially confirmed.

3.4 Discussion

This study, developed on the hypothesis that the diagnosis of pneumonia after TTE may be highly variable and subjective, strongly confirms this and highlights significant diagnostic differences among experienced specialists, with initial inter-observer agreement reaching only fair levels (κ = 0.207-0.270). Agreement improved after implementing standardised clinical correlation ($\Delta\kappa$ = +0.151, $p<0.001$), shifting from fair to moderate agreement and reflecting a 56% relative increase in diagnostic consistency. Diagnostic uncertainty occurred in nearly 20% of cases based solely on radiographic data, emphasising a fundamental weakness in current pneumonia diagnostic standards that rely heavily on unreliable radiographic interpretation.

These data have several implications. First, they challenge key assumptions underpinning the use of ATS, CDC, and UPS criteria for documenting pneumonia in this context, highlighting the difficulty of post-operative decision-making regarding accurate pneumonia documentation and the appropriateness of antibiotic prescribing. If such low agreement exists among the most experienced professionals in this setting, it raises the question of whether similar or worse discrepancies would be found among less-experienced staff managing these patients in the early postoperative period. Second, since pathogen-induced pneumonia was confirmed by microbiological data in only 30% of radiographically diagnosed 'pneumonia' cases, this suggests that non-infectious lung injury, rather than true bacterial pneumonia, is the primary issue in most cases identified and treated as pneumonia, consistent with previous research (277). Third, data from international registries such as EsoDATA, which evolved from the ECCG and where ATS and UPS criteria are used interchangeably, suggest caution in interpreting the 'pneumonia' metric for benchmarking purposes, as pneumonia is less

clearly defined than other complications like anastomotic leaks, chyle fistulae, and atrial fibrillation (225). Additionally, with the increasing use of minimally invasive oesophagectomy (MIE), including robotic-assisted techniques (RAMIE), supported by Level I evidence from randomised trials demonstrating lower pneumonia rates compared to open TTE, it is crucial to define pneumonia and other PPCs using strict, validated criteria (233,278). Finally, this variability in diagnosis has significant clinical and financial implications, as pneumonia complications can increase surgical costs by 31-141% above baseline (270-272).

Clinical Expertise and Diagnostic Reasoning

The systematic improvement in agreement following clinical correlation (Fleiss' κ from 0.270 to 0.421, $p<0.001$) demonstrates that diagnostic uncertainty often reflects an appropriate recognition of clinical complexity rather than an insufficient assessment skill. This finding aligns with dual-process theory in clinical decision-making, which suggests that experienced clinicians integrate both analytical and intuitive reasoning processes when evaluating complex cases (279,280). The pattern observed—where specialists exhibited varying uncertainty thresholds but similar resolution patterns when provided with clinical data—indicates shared underlying reasoning frameworks despite speciality-specific perspectives.

Different specialities demonstrated complementary forms of expertise in this study. The surgeon's high uncertainty rate (41.5%) likely reflected detailed knowledge of expected post-operative changes and conservative thresholds for diagnosing pathology. The intensivist's lower uncertainty (13.0%) but broader pneumonia identification (14.0%) suggested pattern recognition optimised for detecting systemic inflammatory responses. The pulmonologist's approach (14.0% uncertainty, 17.0% pneumonia identification) reflected expertise in respiratory pathophysiology. When provided with standardised clinical information, all three specialities converged towards similar diagnostic conclusions, indicating that their initial disagreement represented appropriate caution in ambiguous scenarios rather than fundamental differences in diagnostic competence.

The clinical discriminators that most effectively resolved diagnostic uncertainty—fever >38°C, leucocytosis >11,000/μL, and increased oxygen requirements—represent routine parameters that experienced clinicians systematically integrate during clinical

assessment. This aligns with research by Ericsson and Lehmann demonstrating that experienced clinicians often outperform formal diagnostic algorithms when integrating multiple clinical variables, particularly in domains with high uncertainty (281,282). The superior performance of integrated clinical assessment compared to radiographic criteria alone (κ improvement of 0.127-0.168) supports the concept that expert pattern recognition involves sophisticated integration of contextual factors not captured in standardised approaches. These findings informed the development of the trimodal scoring system presented in Chapter 4, which operationalises this systematic clinical reasoning into a reproducible diagnostic framework.

These data also suggest that "pneumonia" following oesophagectomy should be reconceptualised as a heterogeneous spectrum of lung injury rather than a single diagnostic entity, encompassing infectious pneumonia, atelectasis, acute lung injury, and post-operative inflammatory consolidation. Rather than applying suboptimal binary diagnostic criteria, there is a need to develop lung injury severity scoring systems and implement three distinct diagnostic categories: confirmed infectious pneumonia (radiographic consolidation plus positive cultures), post-operative lung injury (consolidation without microbiological confirmation), and diagnostic uncertainty (requiring structured clinical correlation protocols).

A plain chest radiograph post-TTE clearly has limitations, with overall poor-to-fair reliability; hence, this study should inform discussion and consideration of incorporating chest CT scanning into routine post-oesophagectomy evaluation protocols. CT scanning could be integrated with existing contrast swallow studies on post-operative day 4, potentially reducing diagnostic uncertainty and inappropriate antibiotic use while providing superior diagnostic accuracy compared to chest radiography (sensitivity >90% vs 43-82%) (283-285). For practising surgeons, our findings suggest several actions to consider: recognise the limitations of current pneumonia criteria; implement standardised clinical correlation protocols where radiographic findings are equivocal; consider multidisciplinary input for diagnostically uncertain cases; and evaluate institutional protocols for potential CT-based diagnostic approaches. Furthermore, the ECCG platform itself does not mandate a single standardised definition of pneumonia, with participating centres potentially applying different diagnostic criteria. A recent systematic review of ECCG implementation found

that the current ECCG pneumonia definition is "not specific enough to encompass the spectrum of postesophagectomy lung injury," contributing to persistent diagnostic heterogeneity even among centres using the standardised platform (286). When centres report pneumonia rates ranging from 9% to 40%, the difference may reflect not only genuine variation in clinical outcomes but also fundamental differences in the diagnostic framework applied. This platform-level diagnostic variability further compounds the benchmarking challenges identified in this study. It reinforces the urgent need for consensus on validated, reproducible pneumonia criteria specific to post-esophagectomy populations. This study demonstrates that clinicians achieved the best agreement when identifying regular post-operative appearances, moderate agreement when recognising definitive pneumonic changes, but poor agreement in managing diagnostically uncertain cases—precisely the scenarios where standardised clinical correlation proved most beneficial. The systematic improvement through standardised clinical correlation supports the development of clinical decision support systems and machine learning algorithms that automatically integrate radiographic and clinical parameters.

We acknowledge some limitations. It is a study conducted at a single centre, although it is a National Centre with established standard operating procedures (SOPs) for post-TTE care pathways. Nevertheless, larger multicentre validation studies would be valuable—additionally, all cases involved open TTE procedures. RAMIE has now been introduced at the Centre, but we cannot yet generalise to such cases. However, our high-volume institution's adherence to evidence-based protocols suggests broader applicability. Future research priorities include prospective studies with real-time clinical assessment, the development of surgery-specific pneumonia criteria, validation of CT-based diagnostic protocols, and exploration of machine learning methods for post-operative chest radiograph interpretation. A further limitation of this study is the absence of assessment of intra-individual variability in chest radiograph interpretation. While inter-observer agreement was the primary focus, the consistency of each observer's assessments over time — that is, whether a reviewer would assign the same classification to the same image on repeat evaluation — was not examined. Intra-observer reliability is an important component of overall diagnostic reproducibility, and its absence limits conclusions regarding the stability of individual clinical judgment in this context. Additionally, a significant methodological limitation is that the pneumonia

identification criteria used in this study — specifically, the ATS/ECCG diagnostic criteria used as the reference standard — have not been formally validated in the post-operative oesophageal cancer population. These criteria were developed and validated in general hospital-acquired pneumonia populations, and their applicability to the unique physiological and radiographic context of post-oesophagectomy patients cannot be assumed. This limits the interpretability of agreement metrics calculated against these reference standards.

3.5 Conclusions

This study shows that diagnosing pneumonia after transthoracic oesophagectomy has poor inter-observer reliability (κ = 0.207-0.270) when based solely on radiographic assessment. The 56% increase in diagnostic agreement following structured clinical correlation (Fleiss' κ rose from 0.270 to 0.421, $p < 0.001$) suggests that combined diagnostic protocols incorporating radiographic and clinical parameters can significantly improve consistency. The specific clinical discriminators identified—fever >38°C, leucocytosis >11,000/μL, and increased oxygen needs—form the empirical basis for the trimodal scoring system developed in Chapter 4, which translates these findings into a practical clinical decision support tool. These findings reveal fundamental weaknesses in current pneumonia diagnostic standards and highlight the urgent need for international collaboration to develop validated, reproducible criteria specific to post-oesophagectomy populations.

Chapter 4

Development and Validation of a Trimodal Scoring System for Postoperative Pneumonia Prediction

4.0 Introduction

Postoperative pneumonia remains one of the most significant complications after oesophagectomy, with reported incidence rates ranging from 14% to 40%, depending on the literature and diagnostic criteria used (287,288). Despite advances in perioperative care pathways, including Enhanced Recovery After Surgery (ERAS) protocols, dedicated multidisciplinary specialist care, and improved surgical techniques, pneumonia continues to disproportionately contribute to postoperative morbidity, longer hospital stays, higher healthcare costs, and mortality (289,290). The development of post-oesophagectomy pneumonia is multifactorial and not fully understood. It is believed to result from factors such as mechanical ventilation-induced lung injury, impaired mucociliary clearance, aspiration risk, and systemic inflammatory responses (291-293). Recent literature has identified additional risk factors, like sarcopenia, oral dysbiosis, and acute kidney injury, highlighting the complex interplay of elements that contribute to respiratory complications (294-298). Current diagnostic methods mainly rely on clinical signs, radiographic findings, and various scoring systems designed for general ICU populations, such as CURB-65 (299), SOFA (300), or the Clinical Pulmonary Infection Score (CPIS) (301). However, these tools often show limited sensitivity and specificity in post-surgical patients due to the baseline inflammatory response and altered physiological parameters typical after major surgery (302,303). The challenge of diagnosing pneumonia in this cohort poses a significant obstacle to effective clinical management and meaningful research (304,305). There is an urgent clinical need for a practical, reproducible diagnostic tool specifically tailored for patients undergoing post-oesophagectomy or other major/complex surgeries, which can be implemented using routinely available clinical parameters (306).

Building on the demonstrated need for improved diagnostic reliability in pneumonia detection, this chapter introduces a novel trimodal approach that systematises clinical reasoning by combining three complementary physiological domains that are routinely recorded. The first domain encompasses systemic inflammation and nutrition, as assessed by the CRP/albumin ratio (≥6.0), which indicates an acute inflammatory response, while also considering nutritional status and the liver's synthetic function (307-309). Elevated CRP indicates a systemic inflammatory process triggered by

pneumonia (310), while albumin levels reflect both nutritional reserves and hepatic synthetic capacity (311, 312). The ratio method standardises for hypoalbuminemia, often observed after major surgery (313). The second domain evaluates ventilatory support needs by the maximum Fraction of Inspired Oxygen (FiO_2 > 60%), which indicates impaired gas exchange and increased oxygen demand, suggesting respiratory compromise before overt hypoxaemia occurs. This parameter reflects clinical assessment of respiratory function and oxygen requirements during the critical first 72 hours postoperatively. The third domain assesses gas-exchange efficiency using the Pao_2/Fio_2 ratio (<200), providing a standardised measure of oxygenation that accounts for supplemental oxygen delivery (314, 315). This objective parameter directly gauges the physiological effects of pneumonia and is well recognised in the definitions of ARDS and respiratory failure (316,317). The combination of these three domains eliminates subjective interpretation, relying solely on measurements obtained during routine postoperative care, and forms the basis of an algorithm that facilitates early detection for clinical intervention. Each component addresses different facets of pathophysiology while ensuring practical clinical usefulness.

4.1 Hypothesis and aims:

The main hypothesis of this study was that combining the CRP/albumin ratio, FiO_2 requirement, and PaO_2/FiO_2 ratio into a three-part scoring system would provide a more accurate prediction of postoperative pneumonia than existing tools, potentially leading to better clinical outcomes.

The primary aim of our study was to develop and validate a three-part scoring system to predict postoperative pneumonia in patients who underwent oesophagectomy, utilising routine clinical data available within 72 hours of the operation.

4.2 Methods

This retrospective cohort study was conducted at Trinity St. James's Cancer Institute in Dublin, Ireland, a tertiary referral centre for upper gastrointestinal surgery. The institute performs approximately 60-80 oesophagectomies annually using a multidisciplinary approach. We included all patients who underwent a transthoracic oesophagectomy between January 2015 and December 2020. This period was chosen to ensure that surgical and perioperative care practices were current and to allow sufficient follow-up

to assess outcomes. Because this was a retrospective study utilising routinely collected clinical data, individual informed consent was not required, in accordance with local research ethics guidelines; all data were anonymised before analysis. Data was encrypted on an institutional IT computer, with only the researcher having coded access. Patients were included if they were aged 18-80 years, underwent elective transthoracic oesophagectomy with curative intent, had complete postoperative data for all trimodal scoring components and had available clinical follow-up for outcome assessment. Exclusion criteria included emergency or urgent procedures, recent known SARS-CoV-2 infection within 3 months of surgery, incomplete postoperative monitoring data, redo oesophagectomy or concurrent major procedures. Data collection included patient demographics and comorbidities, such as age, sex, body mass index, American Society of Anaesthetists physical status classification, chronic obstructive pulmonary disease, diabetes mellitus, cardiovascular disease, smoking history and alcohol consumption. Information on diseases and treatments, including histological diagnosis and tumour staging, neoadjuvant therapy, surgical approach, operative duration and perioperative complications was also retrieved. Data were considered, and the trimodal scoring components were assessed by measuring C-Reactive Protein and albumin levels on postoperative day 3 using a high-sensitivity assay (normal range: <3.0 mg/L) and standard biochemical analysis (normal range: 35-50 g/L), respectively. This was because pneumonia tends to develop around this time. We recorded the maximum FiO_2 requirement during the first 72 hours as the highest level required during this period, including both mechanical ventilation and supplemental oxygen. We calculated the PaO_2/FiO_2 ratio from arterial blood gas analysis performed on postoperative day 3, using the worst value if multiple assessments were done.

All procedures were performed using open transthoracic oesophagectomy by experienced surgeons working collaboratively at this institution. During the study period, patients with locally advanced oesophageal or gastroesophageal junction cancer received either preoperative chemoradiation (cisplatin and fluorouracil, 40 Gy, or carboplatin and paclitaxel, 41.4 Gy) or perioperative chemotherapy with modified MAGIC (epirubicin, cisplatin, fluorouracil) or FLOT (fluorouracil, leucovorin, oxaliplatin, docetaxel) regimens. The surgery involved open abdominal thoracic en bloc oesophagectomy, usually via right thoracotomy, with intrathoracic or cervical anastomosis depending on tumour level. Standardised perioperative care included

thoracic epidural analgesia combined with patient-controlled analgesia and intravenous paracetamol. Relative intraoperative fluid restriction was maintained at approximately 500 ml/h. All anastomoses were sutured using a standardised approach with interrupted 3.0 PDS (polydioxanone) sutures. Patients were extubated immediately post-surgery unless clinically unsuitable and managed in high-dependency or intensive care units for at least 24 hours before transfer to the ward. Feeding jejunostomy tubes were inserted during surgery, with feeding starting on post-operative day 1.

4.2.1 Parameter Selection Rationale

The trimodal approach was developed based on findings from the previous inter-observer variability study (Chapter 3), which demonstrated that experienced clinicians systematically integrated multiple physiological parameters when resolving diagnostic uncertainty in post-esophagectomy pneumonia. The study revealed that clinical discriminators most strongly associated with pneumonia progression were elevated temperature (82.4% vs 23.1% in pneumonia vs non-pneumonia cases), leucocytosis (90.3% vs 31.2%), and increased oxygen requirements (88.7% vs 27.2%). Building on these empirical findings and the theoretical framework that post-surgical pulmonary complications primarily reflect inflammatory rather than infectious processes, three complementary physiological domains were selected to reflect the systematic clinical reasoning patterns observed among expert practitioners.

The CRP/albumin ratio was chosen to represent the inflammatory-nutritional domain because it captures the acute inflammatory response while adjusting for surgery-related hypoalbuminaemia. The maximum FiO_2 requirement was selected as an indicator of the respiratory support domain, reflecting real-time clinical assessment of respiratory compromise before overt hypoxaemia occurs. The PaO_2/FiO_2 ratio was included as an objective measure of gas exchange efficiency, providing a standardised evaluation of oxygenation impairment. Optimal thresholds for each parameter (CRP/albumin ratio $\geq$6.0, maximum FiO_2 >60%, PaO_2/FiO_2 ratio <200) were determined using receiver operating characteristic curve analysis with Youden's Index to optimise combined sensitivity and specificity. The CRP/albumin ratio was preferred over other inflammatory markers for several reasons. CRP alone, although sensitive to inflammation, does not account for the nearly universal hypoalbuminaemia following major upper gastrointestinal surgery, due to haemodilution, acute-phase prioritisation by

the liver, and nutritional deficits that suppress albumin synthesis. By incorporating albumin as a denominator, the ratio adjusts for this physiological context, offering a more discriminating signal than either marker alone. Alternative ratios — such as the neutrophil-to-lymphocyte ratio (NLR) or platelet-to-lymphocyte ratio (PLR) — were considered but not selected, as they mainly reflect haematological rather than hepatic and nutritional aspects of the stress response. Although procalcitonin is specific for bacterial infection, it requires dedicated assay processing and was not consistently available within 72 hours in this cohort. The CRP/albumin ratio, therefore, provided the best combination of biological relevance, discriminatory ability, and routine clinical accessibility in this specific postoperative context.

Table 4.1: Baseline Patient Characteristics.

Characteristic	All Patients (n=234)	Pneumonia (n=37)	No Pneumonia (n=197)	p-value
Age (years) mean ±SEM Range: 18-80	66.8 ± 11.2	68.1 ± 10.8	66.5 ± 11.3	0.42
Male sex, n (%)	186 (79.5%)	31 (83.8%)	155 (78.7%)	0.49
BMI (kg/m²)	25.3 ± 4.1	24.9 ± 3.8	25.4 ± 4.2	0.51
ASA grade ≥III, n (%)	118 (50.4%)	21 (56.8%)	97 (49.2%)	0.41
Current/ex-smoker, n (%)	182 (77.8%)	32 (86.5%)	150 (76.1%)	0.17
Adenocarcinoma, n (%)	192 (82.1%)	29 (78.4%)	163 (82.7%)	0.53
Neoadjuvant therapy, n (%)	187 (79.9%)	31 (83.8%)	156 (79.2%)	0.53
3-stage procedure, n (%)	201 (85.9%)	33 (89.2%)	168 (85.3%)	0.54

Data are presented in Table 4.1 as mean ± standard deviation for continuous variables and n (%) for categorical variables. P-values were calculated using the Student's t-test for normally distributed continuous variables, the Mann-Whitney U test for non-normally distributed continuous variables, and the Chi-square test or Fisher's exact test for categorical variables as appropriate. ASA = American Society of Anaesthesiologists. BMI = Body Mass Index. Statistical significance was set at $p < 0.05$.

The primary outcome was postoperative pneumonia within 30 days of surgery, while the secondary outcomes included ICU length of stay, total hospital length of stay, major

complications (Clavien-Dindo classification ≥Grade III), 30-day mortality and the need for re-intubation or tracheostomy. The diagnosis of pneumonia was systematically evaluated using four well-established classification systems to ensure robustness and broad applicability. The American Thoracic Society/Infectious Diseases Society of America criteria required new or progressive pulmonary infiltrates on chest imaging plus at least two clinical features: fever >38°C, leucocytosis (>12,000/μL), leucopenia (<4,000/μL), or purulent respiratory secretions. The Centres for Disease Control and Prevention guidelines mandated radiographic evidence of pneumonia, along with fever >38°C or an abnormal white blood cell count, plus at least two additional clinical signs. European Perioperative Clinical Outcomes definitions required at least four of the following: fever >38°C, purulent sputum, positive respiratory culture, chest X-ray signs consistent with infection, or a white blood cell count >12,000/μL. The Utrecht Pneumonia Scoring System used a composite score combining clinical signs, laboratory results, radiographic findings, and microbiological data. Beyond formal classification systems, pneumonia cases were confirmed through microbiological evidence, clinical interventions (antibiotic therapy lasting more than 7 days for respiratory indications) and independent review by respiratory medicine specialists for uncertain cases. The trimodal score was calculated by assigning a score of 1 to positive components that exceeded specific thresholds, or 0 if they did not. These components included a CRP/albumin ratio of ≥6.0 on postoperative day 3, a maximum FiO_2 requirement of >60% within 72 hours, and a PaO_2/FiO_2 ratio of <200 on postoperative day 3.

4.2.2 Statistical analysis

Sample size calculation was based on an expected pneumonia incidence of 15-20% in oesophagectomy patients and the preferred level of precision for evaluating diagnostic accuracy. A sample of 200 patients provided 80% power to detect a difference in the area under the curve of 0.15 compared to existing tools at $\alpha = 0.05$. A detailed case analysis was conducted on 234 patients with complete trimodal scoring data, ensuring over 95% data completeness across all study variables. Descriptive statistics presented continuous variables as mean ± standard deviation or median with interquartile range, depending on distribution, while categorical variables were shown as frequencies and percentages. Normality was assessed using the Shapiro-Wilk test for the pneumonia

group and the Kolmogorov-Smirnov test for the control group, along with visual inspection of histograms and Q-Q plots.

A comparative analysis was performed using Student's t-test for normally distributed continuous variables or the Mann-Whitney U test for non-normally distributed data. In contrast, categorical variables were analysed with the Chi-square test when expected frequencies were ≥5 in all cells, or Fisher's exact test for smaller expected counts. Effect sizes were calculated using Cohen's d, with a pooled standard deviation for continuous variables. The agreement between the four pneumonia classification systems was assessed with Fleiss' kappa statistic to evaluate inter-system reliability. ROC curves were constructed for individual trimodal components and the combined score, with optimal cutoff points determined using Youden's Index (maximising sensitivity + specificity - 1). Performance metrics, including sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and overall diagnostic accuracy, were calculated with 95% confidence intervals using the Wilson score method. Clinical validation analysed the association between trimodal scores and continuous outcomes using Spearman correlation coefficients and analysed binary outcomes using logistic regression. Dose-response relationships were examined with the Cochran-Armitage trend test for binary outcomes and linear regression for continuous outcomes. All statistical analyses were conducted using GraphPad Prism version 10.0, Python's scikit-learn library, and R version 4.3.0, with statistical significance set at $p < 0.05$.

4.3 Results

A total of 377 patients underwent transthoracic oesophagectomy during the study period, with 234 patients having complete trimodal scoring data included in the final analysis, representing 62.1% of the total cohort and over 95% data completeness for all study variables. The study cohort (n=234) exhibited typical characteristics for an oesophagectomy population, with a mean age of 66.8 ± 11.2 years and a male predominance (79.5%). Most had adenocarcinoma (n=192, 82.1%) and received neoadjuvant therapy (79.9%), with a three-stage oesophagectomy performed in 85.9% of patients. Baseline characteristics showed no significant differences between those with and without pneumonia in age, sex, BMI, ASA grade, smoking history, histology, neoadjuvant therapy, or surgical approach (all p>0.05).

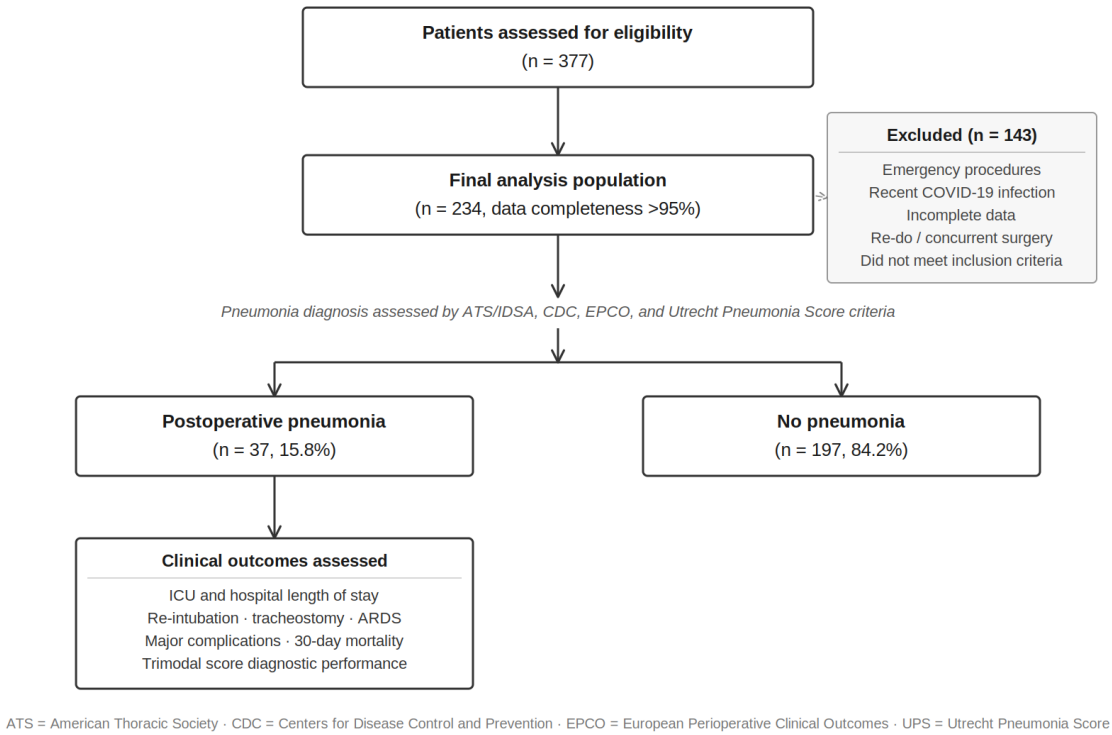


Figure 4.1: Flow Diagram of Patient Inclusion and Exclusion. CONSORT-style flow diagram showing the patient selection process from initial cohort (n=377) through final analysis population (n=234). Demonstrates exclusion criteria application and final data completeness rates. Shows breakdown of excluded patients by category: emergency procedures, recent COVID-19 infection, incomplete data and consent withdrawal.

Through a systematic clinical review that incorporated microbiology results, imaging studies, and expert assessment, 37 patients (15.8%) were identified as having postoperative pneumonia. This rate closely aligns with expectations from international literature for oesophagectomy patients. The pneumonia group showed significant clinical severity, confirming the clinical importance of the identified cases. Positive respiratory cultures were obtained in 12 patients (32.4%) with pathogenic organisms, including Escherichia coli (3 patients), Enterococcus species (4 patients), Klebsiella pneumoniae (2 patients), Enterobacter cloacae (1 patient), and mixed flora with fungal co-infection (2 patients). Eight patients (21.6%) required re-intubation, six patients (16.2%) needed tracheostomy, nine patients (24.3%) developed ARDS, and two patients (5.4%) died due to pneumonia. The ICU length of stay was significantly longer in the pneumonia group (18.2 ± 15.7 days) compared to those without pneumonia (3.8 ± 2.1 days), $p < 0.001$.

Pneumonia diagnosis, as shown in Table 4.2, was validated across four classification frameworks, demonstrating strong agreement. The ATS/IDSA criteria identified 37 patients (15.8%), the CDC guidelines identified 35 patients (15.0%), EPCO definitions identified 39 patients (16.7%), and the Utrecht Pneumonia Scoring System identified 34 patients (14.5%). Inter-system agreement was substantial (Fleiss' $\kappa = 0.847$, 95% CI: 0.782-0.912, $p<0.001$), with minimal variation between systems (range: 2.2%), confirming the robustness of case identification. The trimodal score showed a comparable diagnostic yield, identifying 37 patients (15.8%) with pneumonia, which aligns with established classification systems and indicates its universal applicability across diagnostic frameworks.

Table 4.2: Comparison of Pneumonia Case Identification Across Classification Frameworks

Classification Framework	**Patients Identified, n (%)**
ATS/IDSA criteria	37 (15.8%)
CDC guidelines	35 (15.0%)
EPCO definitions	39 (16.7%)
Utrecht Pneumonia Scoring System	34 (14.5%)
Trimodal Score	**37 (15.8%)**

Individual component analysis revealed strong discriminatory ability across all three domains (Table 4.3). The CRP/albumin ratio showed excellent discrimination, with pneumonia patients having significantly higher ratios compared to those without pneumonia. Using an optimal cutoff of ≥6.0, three-quarters of patients with pneumonia exceeded this threshold, compared with about one-tenth of patients without pneumonia. The maximum FiO_2 requirement demonstrated notable discriminatory ability, with pneumonia patients needing significantly more oxygen support. At an optimal cutoff of>60% (Figure 4.3), the vast majority of pneumonia patients exceeded this threshold.

Table 4.3: Schematic of Trimodal Score Components and Thresholds.

Component	Pneumonia (n=37)	No Pneumonia (n=197)	Mean Difference	p-value	Cohen's d	AUC (95% CI)	Optimal Cutoff
CRP/Albumin Ratio	8.9 ± 4.2	3.1 ± 2.8	+5.8	<0.001	1.52	0.847 (0.782 - 0.912)	≥6.0
Maximum FiO_2 (%)	78.4 ± 18.3	45.2 ± 15.7	+33.2	<0.001	1.89	0.823 (0.755 - 0.891)	>60%
PaO_2/FiO_2 Ratio	142.7 ± 68.4	287.9 ± 94.2	-145.2	<0.001	-1.72	0.891 (0.834 - 0.948)	<200

The PaO_2/FiO_2 ratio provided excellent insight into gas-exchange efficiency, with significantly lower ratios in patients with pneumonia, using an optimal cutoff of <200 (Table 4.4).

Table 4.4: Individual Trimodal Component Performance Analysis

Component	Pneumonia (n=37)	No Pneumonia (n=197)	Mean Difference	p-value	Cohen's d	Threshold	Above/Below Threshold	AUC (95 % CI)
CRP/Albumin Ratio	8.9 ± 4.2	3.1 ± 2.8	+5.8	<0.001	1.52	≥6.0	Pneumonia: 28/37 (75.7%)<br	0.847 (0.78

							>No pneumonia: 23/197 (11.7%)	2-0.912)
Maximum FiO_2 (%)	78.4 ± 18.3	45.2 ± 15.7	+33.2	<0.001	1.89	>60%	Pneumonia: 32/37 (86.5%) No pneumonia: 38/197 (19.3%)	0.823 (0.755-0.891)
PaO_2/FiO_2 Ratio	142.7 ± 68.4	287.9 ± 94.2	-145.2	<0.001	-1.72	<200	Pneumonia: 29/37 (78.4%) No pneumonia: 31/197 (15.7%)	0.891 (0.834-0.948)

The trimodal score, calculated by summing the positive components, effectively distinguished between groups and provided meaningful risk stratification. Among the 234 patients, 156 (66.7%) had a score of 0, with only 1 case of pneumonia (0.6%). In contrast, 45 patients (19.2%) had a score of 1 with 6 cases of pneumonia (13.3%); 21 patients (9.0%) had a score of 2 with 18 cases (85.7%), and all 12 patients (5.1%) with a score of 3 developed pneumonia (100.0%). Risk stratification groups showed strong separation, with low-risk patients (scores 0-1), i.e., 201 patients (85.9%), experiencing only 7 cases of pneumonia (3.5%). Conversely, high-risk patients (scores 2-3), comprising 33 patients (14.1%), had 30 cases of pneumonia (90.9%) (Figure 4.3). Diagnostic performance metrics demonstrated excellent accuracy with sensitivity of 81.1% (95% CI: 66.7-90.6%), specificity of 93.9% (95% CI: 89.8-96.7%), positive predictive value of 71.4% (95% CI: 57.8-82.1%), negative predictive value of 96.4% (95% CI: 92.9-98.3%), overall accuracy of 91.9% (95% CI: 87.6-95.1%), and ROC AUC of 0.926 (95% CI: 0.884-0.968).

The bar chart in figure 4.2 demonstrates the pneumonia incidence rates across the trimodal scores, showcasing the scoring system's effectiveness in stratifying risk. The pneumonia incidence rates for each score were as follows: Score 0, 0.6%; Score 1, 13.3%; Score 2, 85.7%; Score 3, 100.0%, with 95% confidence intervals. It includes

patient numbers in each category and reveals a clear dose-response relationship. Notably, there is a significant distinction between the low-risk (scores 0-1, with a 3.5% pneumonia rate) and high-risk (scores 2-3, with a 90.9% pneumonia rate) groups. Trend analysis confirms statistical significance ($p<0.001$), supporting the scoring system's strong predictive capability.

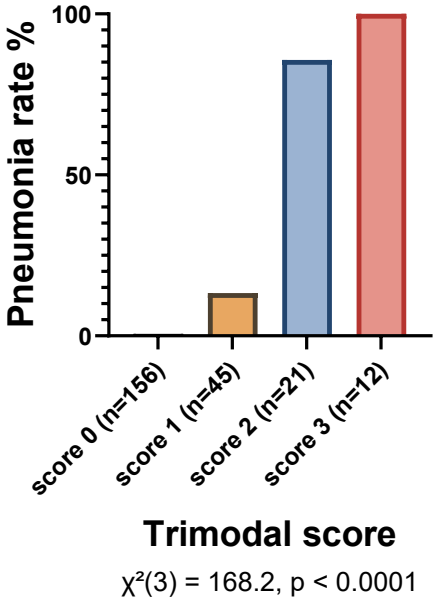


Figure 4.2: Pneumonia Rate by Trimodal Score This bar chart illustrates the pneumonia incidence rates across the trimodal scores, highlighting the scoring system's ability to stratify risk effectively. Pneumonia incidence rates for each score were as follows: Score 0: 0.6%, Score 1: 13.3%, Score 2: 85.7%, Score 3: 100.0% with 95% confidence intervals. Includes patient numbers in each category and demonstrates clear dose-response relationship. Notably there is a dramatic distinction between low-risk (scores 0-1, 3.5% pneumonia rate) and high-risk (scores 2-3, 90.9% pneumonia rate) groups. Trend analysis confirms statistical significance ($p<0.001$) supporting the scoring systems strong predictive capability.

The trimodal score showed excellent ability in identifying clinically severe pneumonia, supporting its clinical usefulness beyond basic diagnostic accuracy. Among culture-positive cases, 11 of 12 (91.7%) had trimodal scores of at least 2. All patients needing re-intubation (n=8) scored 2 or higher (100% sensitivity, mean score 2.8 ± 0.5), while all patients requiring tracheostomy (n=6) scored 3 (100% sensitivity). Similarly, all patients developing ARDS (n=9) scored 2 or more (100% sensitivity, mean score 2.7 ± 0.5), and both patients with pneumonia-related death (n=2) scored 3 (100% sensitivity). A strong dose-response relationship was noted between trimodal scores and all

measures of clinical severity. ICU stay length increased steadily from 2.8 ± 1.4 days for score 0 to 24.1 ± 16.3 days for score 3 ($p<0.001$ for trend). The hospital stay grew from 9.2 ± 4.1 days to 31.7 ± 19.8 days, respectively ($p<0.001$ for trend). Significant complications happened in 7.7% of patients with a score of 0 versus 83.3% with a score of 3 ($p<0.001$ for trend). Moreover, 30-day mortality rose from 0.6% to 16.7%, respectively ($p<0.001$ for trend). Spearman correlation coefficients ($p<0.001$) further support the biological plausibility of the scoring system, showing strong positive correlations between increasing scores and adverse outcomes: 0.687 for ICU length of stay, 0.721 for hospital stay, 0.654 for major complications, and 0.412 for mortality.

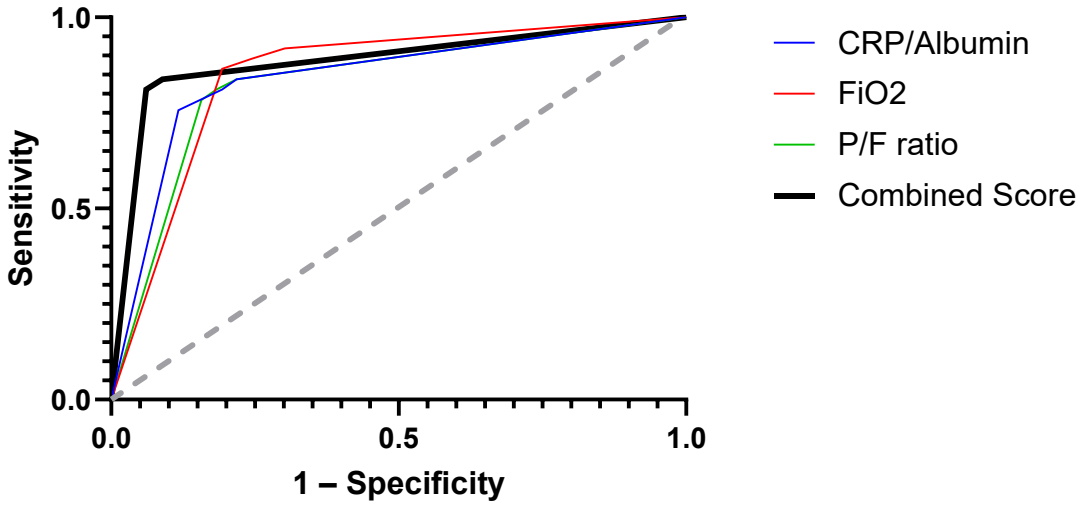


Figure 4.3: ROC Curves for Trimodal Components and Combined Score Receiver operating characteristic (ROC) curves comparing the discriminatory performance of the individual trimodal components and the combined score. Shows AUC values with 95% confidence intervals for CRP/albumin ratio (AUC 0.847), maximum FiO_2 (AUC 0.823), PaO_2/FiO_2 ratio (AUC 0.891), and combined trimodal score (AUC 0.926). The combined score outperforms the individual components in terms of discriminatory power. Each curve includes a maker for the optimal cutoff points marked based on Youden's Index.

4.4 Discussion

This study shows that a trimodal scoring system, which combines the CRP/albumin ratio, maximum FiO_2 requirement, and PaO_2/FiO_2 ratio, offers excellent diagnostic accuracy for predicting postoperative pneumonia in patients undergoing oesophagectomy. The system achieved an AUC of 0.926, a sensitivity of 81.1%, and a

specificity of 93.9%, demonstrating performance that compares favourably with existing tools in this surgical population. The clear risk stratification provided by the scoring system is especially notable, with low-risk patients (scores 0-1) having a pneumonia rate of only 3.5%, compared to 90.9% in high-risk patients (scores 2-3). This distinction offers clinically meaningful guidance for resource management and monitoring intensity.

The diagnostic performance of the trimodal score can be understood within the broader literature on pneumonia prediction tools in surgical populations. The Clinical Pulmonary Infection Score (CPIS), often used in ICU settings, has shown inconsistent and generally poor performance in surgical patients. Schurink et al. reported an AUC of 0.55 when comparing CPIS to quantitative bronchoalveolar lavage cultures in 99 surgical ICU patients (318). Similarly, Croce et al. found that CPIS >6 achieved only 61% sensitivity and 43% specificity for ventilator-associated pneumonia in trauma patients (319). Recent validation studies have confirmed these limitations, with Fartoukh et al. demonstrating that CPIS had limited sensitivity and specificity when compared to bronchoalveolar lavage fluid cultures (320). Other studies in mixed ICU populations have reported CPIS AUCs ranging from 0.82 to 0.85 (321,322), while systematic reviews have highlighted significant inter-observer variability in CPIS calculation (323). The performance of the SOFA score in surgical populations also shows considerable variability, with studies reporting AUCs between 0.67 and 0.85 depending on the timing of assessment and the patient group (324,325). The poor performance of CPIS in surgical populations has been linked to non-infectious causes of lung injury that may act as confounders in postoperative patients (326). The trimodal score's AUC of 0.926 appears to exceed these previously reported values, although differences in study populations and outcome definitions limit direct comparison. The CRP/albumin ratio's performance (AUC 0.847) supports emerging research on this biomarker across different clinical settings. A large prospective cohort study involving 2,489 men over 26 years found that higher CRP/albumin ratios were associated with an increased risk of pneumonia (HR 1.62, 95% CI: 1.31-2.00) (327). In patients with severe pneumonia, Wang et al. identified the CRP/albumin ratio as an independent predictor of 28-day mortality, with their prediction model reaching an AUC of 0.826 (328). Recent research into community-acquired pneumonia has similarly demonstrated that combining CRP and albumin measurements can improve prognostic accuracy

compared to using each marker alone (329,330). The ratio approach may offer advantages in the post-surgical setting by accounting for the hypoalbuminaemia often observed after major surgery. Studies indicate that the CRP/albumin ratio outperforms individual markers in surgical patients, with one study reporting an AUC of 0.866 for diagnosing parapneumonic effusion (331). Additionally, paediatric studies have confirmed that the CRP/albumin ratio has greater sensitivity in distinguishing severe from mild pneumonia compared to CRP alone (332).

Several previous studies have aimed to develop pneumonia prediction tools specifically for patients undergoing oesophagectomy. The Utrecht Pneumonia Score, later updated as the Uniform Pneumonia Score (UPS), incorporated temperature, leukocyte count, and pulmonary radiography findings (333,334). A recent nomogram created for elderly oesophagectomy patients achieved C-statistics of 0.680 in the training cohort and 0.655 in the validation cohort (335). Machine learning approaches applied to post-oesophagectomy complications have reported AUROCs of 0.74 for pneumonia prediction (336). These studies employed different methodological approaches and patient populations, making direct comparison difficult. Nevertheless, the trimodal score's performance appears promising in this context, while remaining simple by using only three routine clinical parameters.

The trimodal scoring system addresses major diagnostic reliability issues in postoperative pneumonia detection by providing objective, measurable criteria that reduce inter-observer variability. Current diagnostic approaches rely on a combination of clinical signs and radiographic findings. Still, radiographic interpretation in post-surgical patients is particularly challenging due to baseline post-operative changes, atelectasis, and fluid shifts that can mimic or obscure pneumonia. Unlike existing tools that rely on subjective radiographic assessment and complex scoring algorithms, the trimodal score utilises three routine clinical parameters accessible within 72 hours of surgery, making it practical and adaptable across various clinical settings. The system's design systematically captures the clinical reasoning processes employed by experienced practitioners when diagnosing pneumonia, standardising the diagnostic approach while maintaining practical clinical usefulness.

The strong dose-response relationship between scores and clinical outcomes supports the biological plausibility of the approach and enhances confidence in its clinical

relevance. Each component reflects different aspects of pneumonia pathophysiology: the CRP/albumin ratio captures the acute inflammatory response while adjusting for surgery-related hypoalbuminaemia, maximum FiO_2 requirement indicates respiratory compromise before overt hypoxaemia develops, and the PaO_2/FiO_2 ratio provides a standardised assessment of gas exchange efficiency. Together, these parameters identify inflammatory, respiratory, and gas exchange abnormalities typical of pneumonia development, while also addressing diagnostic uncertainty often encountered in clinical practice.

4.5 Study Limitations and Future Directions

Several limitations should be recognised in this research. The retrospective design poses a risk of selection bias; however, the large sample size and over 95% data completeness help to mitigate this issue. The single-centre setting means that the results may not be generalisable to other institutions with different patient populations, surgical techniques, or perioperative protocols. The decision to calculate the score at 72 hours after surgery was based on data availability rather than systematic testing of different time points. A further limitation is that the ATS/IDSA criteria used as one of the reference standards for pneumonia diagnosis in this study were not originally developed or validated in post-oesophagectomy populations. These criteria were derived from general hospital-acquired pneumonia cohorts, and their applicability to patients following major thoracic surgery — where baseline radiographic changes, systemic inflammation, and altered physiology are the norm — cannot be assumed. The use of unvalidated reference standards may therefore introduce systematic error into the performance metrics reported for the trimodal score, and this should be considered when interpreting the diagnostic accuracy findings. A further avenue for future investigation would be to evaluate the performance of the trimodal score when used alongside ATS criteria — as a complementary tool rather than an alternative — to determine whether the combination improves upon either approach alone.

These limitations underscore several primary directions for future research. Emphasizing multi-centre prospective validation is vital to corroborate the system's applicability across various healthcare environments and patient populations, as well as to verify findings in real-time clinical settings. Investigating serial measurements and systematically evaluating different timepoints could augment predictive accuracy and

facilitate real-time risk assessment during the critical early postoperative period. Incorporating additional inflammatory markers, such as procalcitonin and IL-6, or other emerging biomarkers, might improve sensitivity while preserving the system's practicality. The diagnostic foundation provided by the trimodal score presents opportunities to evaluate targeted interventions within specific patient groups, thereby addressing concerns regarding research quality in this field.

4.6 Conclusion

This study demonstrates that a trimodal scoring system, which integrates the CRP/albumin ratio, maximum FiO_2 requirement, and PaO_2/FiO_2 ratio, offers excellent diagnostic accuracy for predicting postoperative pneumonia in patients undergoing oesophagectomy (AUC 0.926, sensitivity 81.1%, specificity 93.9%). The clear risk stratification achieved enables targeted resource allocation, with low-risk patients (scores 0-1) exhibiting a pneumonia rate of just 3.5%, compared to 90.9% in high-risk patients (scores 2-3). By providing objective, reproducible criteria available within 72 hours of surgery, the trimodal score addresses key diagnostic reliability challenges in the detection of postoperative pneumonia. It provides a practical foundation for improved clinical decision-making and resource optimisation.

Chapter 5:

Biological Heterogeneity in Post-Operative Pneumonia: A Three-Entity Framework

5.0 Introduction

This chapter investigates the biological heterogeneity underlying post-operative pneumonia following oesophageal surgery. Building on the diagnostic variability documented in Chapter 3 and the predictive framework established in Chapter 4, it proposes and evaluates a three-entity biological classification system — comprising SIRS-driven sterile inflammation, bacterial infection, and tissue repair — through prospective biomarker and cytokine analysis.

5.1 Clinical Context and Rationale

The earlier chapters of this thesis have systematically documented the complexities inherent in diagnosing post-operative pneumonia following oesophageal surgery. The systematic review presented in Chapter 2 revealed significant heterogeneity in diagnostic criteria across studies, with reported pneumonia incidence ranging from 20% to 50%, and substantial variation in outcome measures (342,343). Chapter 3's inter-observer agreement analysis demonstrated only moderate concordance (κ=0.270) among experienced clinicians evaluating identical clinical scenarios, suggesting that diagnostic uncertainty extends beyond methodological inconsistencies to fundamental challenges in clinical recognition (344). Despite these diagnostic difficulties, the Trimodal score presented in Chapter 4 demonstrated acceptable predictive performance for clinical outcomes, indicating that clinicians may be able to detect genuine pathophysiological processes even when classification remains inconsistent (345). These findings collectively support the hypothesis that "post-operative pneumonia" represents multiple distinct biological processes that current diagnostic frameworks fail to differentiate adequately. The biological mechanisms underlying the diagnostic inconsistency and clinical heterogeneity documented in prior chapters remain unexplored and constitute a critical knowledge gap in understanding post-operative pulmonary complications (346,347).

5.1.2 Integration with Clinical Prediction Tools: Enhancing the Trimodal Score

The biological entity framework developed in this chapter can be integrated with the Trimodal Score from Chapter 4, thereby extending the tool to provide entity-specific

therapeutic guidance beyond outcome prediction. The original Trimodal Score, which combined the CRP/albumin ratio, maximum FiO_2 requirement, and PaO_2/FiO_2 ratio, demonstrated excellent diagnostic accuracy for identifying patients at risk of post-operative pneumonia. By incorporating biological entity modifiers based on CRP and PCT thresholds, this score could be refined into an Enhanced Trimodal Score that links prediction with treatment decisions.

Entity classification will follow the framework outlined in this chapter: SIRS entities (CRP ≥100 mg/L, PCT ≤1.0 ng/mL) will require close monitoring, anti-inflammatory strategies, and restraint in antibiotic use; Bacterial entities (CRP ≥100 mg/L, PCT >1.0 ng/mL) will necessitate urgent antibiotic escalation and intensive monitoring; and Tissue Repair entities (CRP <100 mg/L regardless of PCT) will be managed with supportive care and ERAS-based recovery protocols. This approach addresses the limitation noted in Chapter 4, where the Trimodal Score predicted risk but did not offer mechanistic guidance for therapeutic decision-making.

5.1.3 Cytokine Biology and Inflammatory Pathway Diversity

Understanding phenotypic heterogeneity at a biological level involves recognising the variety of inflammatory pathways and the unique molecular mechanisms behind different systemic inflammation triggers (348,349). The 15-cytokine panel chosen for this study aims to evaluate whether crucial biological pathways associated with post-operative complications can differentiate between entity patterns, including pro-inflammatory cascades, anti-inflammatory regulation, adaptive immune responses and tissue repair (350,351).

Damage-associated molecular patterns (DAMPs) released during surgical trauma mainly activate sterile inflammation characterised by specific cytokine signatures (350,351). DAMPs include mitochondrial DNA, high-mobility group box 1 (HMGB1), heat shock proteins and uric acid crystals released from damaged tissues (352). These molecules bind to pattern recognition receptors, such as Toll-like receptors (TLRs) and NOD-like receptors, triggering innate immune activation (353). DAMP-mediated inflammation exhibits distinct features compared to pathogen-induced responses, with IL-6 serving as a key mediator that drives hepatic acute-phase protein synthesis and systemic inflammatory signs (354). IL-18, released via inflammasome activation,

promotes both innate and adaptive immune responses while aiding tissue repair processes (355). IL-27, produced by activated macrophages and dendritic cells has dual roles: it promotes initial inflammatory responses but also helps to limit excessive inflammation through regulatory mechanisms (356).

Pathogen-associated molecular patterns (PAMPs) activate distinct cytokine profiles during bacterial infections, characterised by the predominance of TNF-α, IL-1β and antimicrobial cytokines, including IFN-γ and IL-12 (357). PAMPs include lipopolysaccharide, flagellin, peptidoglycans and bacterial DNA motifs that bind to specific pattern recognition receptors (358). This recognition triggers rapid NF-κB activation and the production of pro-inflammatory cytokines, which are designed to recruit immune effector cells and enhance antimicrobial defences (359). Resolution of inflammation involves active biological processes rather than simply stopping pro-inflammatory signals (360). Specialised pro-resolving mediators, including lipoxins, resolvins, and protectins, coordinate inflammatory resolution, while supporting tissue repair. IL-10 acts as a central anti-inflammatory cytokine, suppressing pro-inflammatory gene expression while encouraging the development of regulatory T cells (361). Angiogenic factors play vital roles in tissue repair, with VEGF-A promoting both vascular permeability during acute inflammation and subsequent angiogenesis during recovery (362).

5.2 Study Hypothesis and Aims

The central hypothesis of this chapter suggests that post-operative "pneumonia" after oesophageal surgery does not constitute a single uniform disease entity but involves three distinct biological processes: SIRS-driven sterile inflammation characterised by damage-associated molecular pattern activation, bacterial infection indicated by pathogen-associated molecular pattern activation, and tissue repair processes marked by angiogenic and wound healing responses.

The primary aim is to establish and validate this three-entity biological framework through biomarker and cytokine analysis, showing that patients currently classified under the term "post-operative pneumonia" can be separated into biologically distinct entities with different clinical outcomes and therapeutic implications.

5.3 Methods

5.3.1 Study Design and Ethical Approval

This exploratory analysis used prospectively collected samples from consecutive patients undergoing transthoracic oesophagectomy. The study was conducted within the framework of the Upper Gastrointestinal Biobank for patients undergoing endoscopy or surgery to investigate diseases of the upper gastrointestinal tract. The study protocol received full approval from the SJH/TUH Joint Research Ethics Committee (Project ID: 0215, Submission Number: 626, approval date: 3 February 2022). All patients provided written informed consent for sample collection and data analysis, in accordance with the General Data Protection Regulation (GDPR), Health Research Regulations, and the Data Protection Act 2018.

5.3.2 Study Population

Patients undergoing transthoracic oesophagectomy between February 2022 and August 2023 (Table 5.1) were included in the study. Inclusion criteria were being over 18 years old, scheduled for an elective transthoracic oesophagectomy, and providing informed consent. Exclusion criteria were emergency surgery, immunosuppressive therapy within the previous 30 days and active infection at the time of surgery. All procedures were performed as open transthoracic oesophagectomies by experienced surgeons working collaboratively at this institution. During the study period, patients with locally advanced oesophageal or oesophagogastric junction cancer received either preoperative chemoradiation or perioperative chemotherapy with modified MAGIC or FLOT regimens according to multidisciplinary team decisions (363,364). Standardised perioperative care included thoracic epidural analgesia combined with patient-controlled analgesia and intravenous paracetamol. Enhanced Recovery After Surgery (ERAS) protocols were implemented from post-operative day 1 (365).

Table 5.1: Patient Demographics and Clinical Characteristics

Characteristic	All Patients (n=43)
Age (years)	
Mean ± SD	62.5 ± 10.1
Range	39-78
Gender, n (%)	
Male	35 (81.4)
Female	8 (18.6)

BMI (kg/m²)	
Mean ± SD	27.8 ± 4.2
Range	19.3-41.4
ASA Grade, n (%)	
Grade I-II	28 (65.1)
Grade III-IV	15 (34.9)
Primary Diagnosis, n (%)	
Oesophageal SCC	15 (34.9)
Oesophageal Adenocarcinoma	17 (39.5)
GOJ Adenocarcinoma	11 (25.6)
Neoadjuvant Treatment, n (%)	
CROSS Protocol	28 (65.1)
FLOT Regimen	12 (27.9)
Other/None	3 (7.0)

5.3.3 Sample Collection Protocol

Bronchoalveolar Lavage (BAL) Collection: BAL was performed at the end of one-lung ventilation during the thoracic phase of oesophagectomy, prior to chest closure. Both the dependent and non-dependent lungs were sampled once the lung had been reinflated. Due to intermittent unavailability of bronchoscopy equipment, a blind BAL technique was employed—advancing a sterile catheter through the endotracheal tube without visual guidance. Multiple studies confirm that this method yields diagnostic accuracy comparable to standard bronchoscopy BAL for diffuse pulmonary processes (366,367). For each patient, 10 mL of sterile normal saline was instilled into each lung separately through the endotracheal tube, followed by gentle aspiration to recover approximately 5 mL from each lung. Each BAL sample was divided for dual analysis: one aliquot was sent immediately to the microbiology laboratory in a Sarstedt sterile universal container for bacterial culture, identification, and antimicrobial sensitivity testing according to standard institutional protocols, and the second aliquot was processed for cytokine analysis and stored at -80°C until batch analysis.

Blood Sample Collection: Peripheral blood samples were collected at three timepoints: T0 (intraoperatively during BAL collection), T1 (post-operative day 1) and T2 (post-operative day 5). At each time point, blood was collected for cytokine analysis and

stored at -80°C until batch analysis. Additional blood samples were collected for CRP, PCT, full blood count, D-dimer, fibrinogen and coagulation studies.

5.3.4 Laboratory Analysis

Microbiological Processing: BAL samples were processed in the Microbiology Department under Containment Level 3 conditions, following standard protocols. Culture results were categorised as: (1) no growth after 48 hours, (2) normal respiratory flora, (3) significant pathogenic bacteria at concentrations suggestive of infection ($\geq 10^4$ CFU/mL), or (4) fungal growth (368).

Traditional Biomarker Analysis: C-reactive protein (CRP) was quantified using an immunoturbidimetric assay (Roche Diagnostics), with a reference of <3.0 mg/L (371). Procalcitonin (PCT) was measured using an electrochemiluminescence immunoassay (Elecsys BRAHMS PCT, Roche Diagnostics), with bacterial infection thresholds set at greater than 0.5 ng/mL (372). D-dimer was measured using a latex-enhanced immunoturbidimetric assay, and fibrinogen was determined using the Clauss method (369,370). Both microbiological and biomarker analyses were conducted by experienced laboratory personnel. Patient classification into biological entities was based on established biomarker thresholds validated in the critical care literature (371,372). For this study, a PCT threshold of 1.0 ng/mL was selected for entity classification to enhance specificity for bacterial processes, as this higher threshold reduces false positives in the post-operative setting. It is also the cutoff point our institution uses in a clinical setting.

Comprehensive Multiplex Cytokine Analysis: Serum and BAL samples were analysed using MSD U-PLEX multiplex assays, enabling simultaneous quantification of 15 inflammatory mediators chosen for their roles in distinct biological pathways (373). The cytokine panel included GM-CSF (myeloid activation and tissue repair), IFN-γ (antimicrobial immunity), IL-1β (key pro-inflammatory mediator), IL-2 (T-cell proliferation), IL-4 (Th2 differentiation), IL-6 (acute-phase response), IL-8 (neutrophil chemotaxis), IL-10 (anti-inflammatory regulation), IL-12p40 (Th1 differentiation), IL-13 (alternative activation), IL-17A (neutrophil recruitment), IL-18 (inflammasome activation), IL-27 (immune regulation), TNF-α (systemic inflammation), and VEGF-A (angiogenesis and vascular repair). This panel was strategically designed to capture

DAMP-mediated sterile inflammation (IL-27, IL-18), PAMP-mediated bacterial responses (TNF-α, IL-1β, IL-12p40, IL-17A), anti-inflammatory regulation (IL-10, IL-4, IL-13), adaptive immune responses (IFN-γ, IL-2), and tissue repair processes (VEGF-A, GM-CSF). All assays were performed in duplicate with coefficients of variation <15%, and values below detection limits were recorded as 0 pg/mL for statistical analysis.

5.3.5 Entity Classification Methodology

Patient classification into biological entities was based on established biomarker thresholds validated in critical care literature (374,375). These thresholds were applied to classify patients into three biological patterns:

- **SIRS Pattern:** CRP ≥100 mg/L with PCT ≤1.0 ng/mL, representing a sterile systemic inflammatory response driven by damage-associated molecular patterns released during surgical trauma.
- **Bacterial Pattern:** CRP ≥100 mg/L with PCT >1.0 ng/mL, indicating bacterial infection with systemic inflammatory response mediated by pathogen-associated molecular patterns.
- **Tissue Repair Pattern:** CRP <100 mg/L regardless of PCT level, representing predominantly tissue repair processes with minimal systemic inflammation, characterised by angiogenic and wound healing responses.

5.3.6 Comprehensive Statistical Analysis Framework

This analytical approach involved multiple complementary analyses to validate the three-entity framework. Treatment comparison analysis examined cytokine differences between pneumonia and non-pneumonia groups at each time point using unpaired t-tests (or Mann-Whitney U tests for non-parametric data). Temporal evolution analysis assessed within-patient changes across T0, T1, and T2 using repeated measures ANOVA with Tukey's post-hoc corrections. Left versus right lung BAL cytokine concentrations were evaluated using paired t-tests to identify mean differences. Entity-specific analysis compared cytokine patterns across the three biological classifications using Kruskal-Wallis testing with Dunn's multiple comparisons correction. Left lung

BAL values were selected for entity analysis to minimise potential confounding from direct surgical manipulation, as the surgical approach involved right thoracotomy with primary manipulation of the right hemithorax. This methodological decision strengthens the validity of inflammatory measurements by analysing the lung with minimal direct surgical trauma, providing a more accurate representation of systemic inflammatory processes rather than localised surgical injury responses.

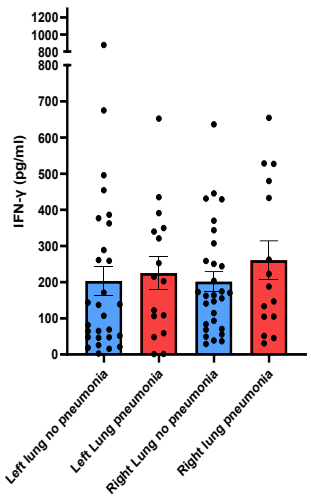
Coagulation and Haemostatic Analysis: D-dimer and fibrinogen levels were analysed as markers of a hypercoagulable state associated with systemic inflammation. Normality was assessed using the Shapiro-Wilk test, with parametric (one-way ANOVA with Tukey's post-hoc test) or non-parametric (Kruskal-Wallis with Dunn's post-hoc test) tests applied accordingly. Entity-specific analysis compared coagulation parameters across biological classifications at T0, T1 (peak inflammatory response), and T2 (recovery phase) time points. Continuous variables were expressed as mean ± SEM or median (IQR) as appropriate. Statistical significance was defined as $p<0.05$. Effect sizes were calculated and reported as η^2 (small: 0.01, medium: 0.06, large: 0.14), and interpreted according to Cohen's criteria (376). All analyses were performed using GraphPad Prism version 10 (GraphPad Software, San Diego, CA, USA).

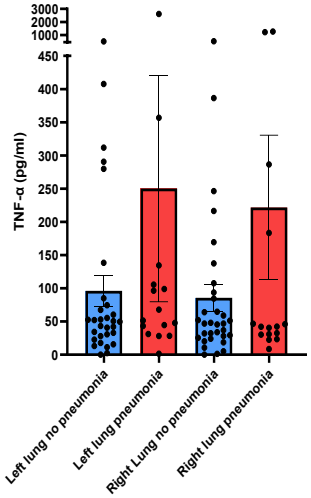
5.4 Results

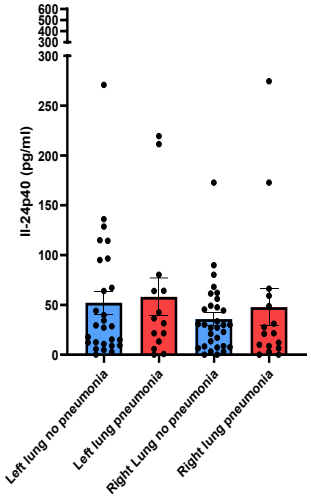
5.4.1 Bilateral Cytokine Analysis: Evidence for Systemic Processes

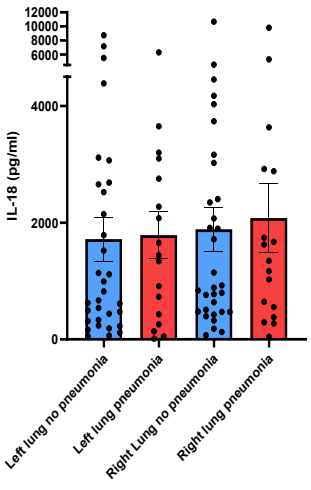
Paired analysis of bilateral BAL cytokine concentrations showed no statistically significant differences between left and right lungs across all 15 measured cytokines (all paired t-test $p > 0.05$), taken on the day of surgery. This pattern of bilateral symmetry across diverse cytokine families provides preliminary evidence that post-operative pulmonary complications represent coordinated systemic inflammatory responses rather than localised infectious processes. The finding that pro-inflammatory, anti-inflammatory, adaptive immune and tissue repair mediators all demonstrate bilateral concordance suggests that the three biological entities reflect whole-body immune activation patterns triggered by surgical trauma rather than focal pulmonary pathology.

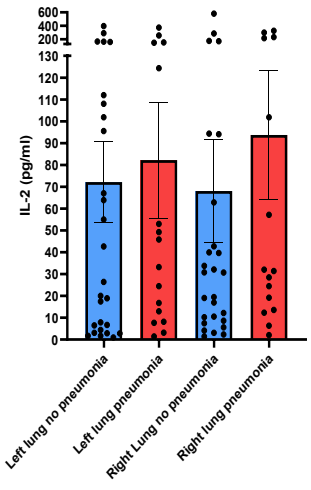
Entity-specific cytokine analysis using Kruskal-Wallis testing revealed no statistically significant differences between the three biological entities for any of the 15 cytokines tested (all $p > 0.05$ with Dunn's post-hoc correction). This demonstrates that while clinical outcomes differ between groups, the 15-cytokine panel was insufficient to detect the underlying biological differences that drive these clinical distinctions. This finding suggests that either larger sample sizes are needed to detect subtle cytokine differences, or additional time points or alternative biomarkers may be more sensitive for entity discrimination.

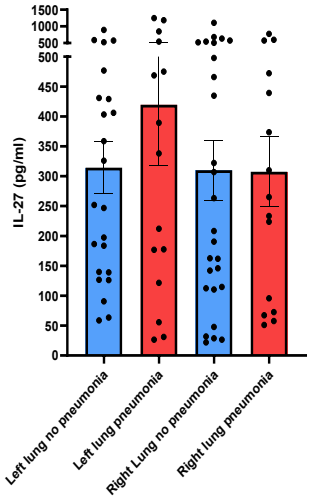

IFN-γ (pg/ml)
Left lung no pneumonia
Left Lung pneumonia
Right Lung no pneumonia
Right lung pneumonia

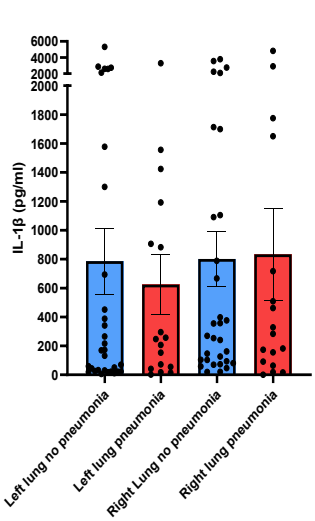

TNF-α (pg/ml)
Left lung no pneumonia
Left lung pneumonia
Right Lung no pneumonia
Right lung pneumonia

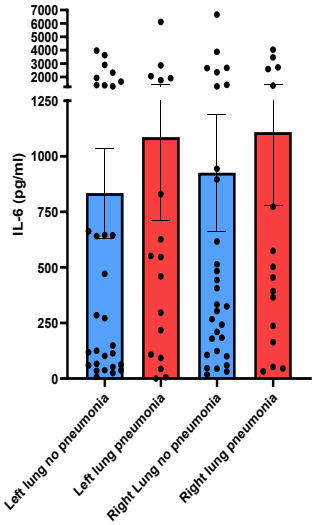

Il-24p40 (pg/ml)
Left lung no pneumonia
Left lung pneumonia
Right Lung no pneumonia
Right lung pneumonia


IL-18 (pg/ml)
Left lung no pneumonia
Left lung pneumonia
Right Lung no pneumonia
Right lung pneumonia


IL-2 (pg/ml)
Left lung no pneumonia
Left lung pneumonia
Right Lung no pneumonia
Right lung pneumonia


IL-27 (pg/ml)
Left lung no pneumonia
Left lung pneumonia
Right Lung no pneumonia
Right lung pneumonia


IL-1β (pg/ml)
Left lung no pneumonia
Left lung pneumonia
Right Lung no pneumonia
Right lung pneumonia


IL-6 (pg/ml)
Left lung no pneumonia
Left lung pneumonia
Right Lung no pneumonia
Right lung pneumonia

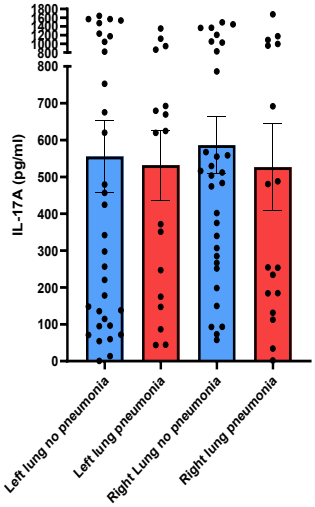

IL-17A (pg/ml)
Left lung no pneumonia
Left lung pneumonia
Right Lung no pneumonia
Right lung pneumonia

Figure 5.1: Bilateral BAL Cytokine Concentrations by Biological Entity Classification. *Bronchoalveolar lavage (BAL) cytokine concentrations from both left lung (blue bars) and right lung (red bars) grouped by biomarker-defined entities: SIRS Pattern, Bacterial Pattern, and Tissue Repair Pattern. Nine representative cytokines are shown across three panels, including pro-inflammatory mediators (IFN-γ, TNF-α, IL-6), anti-inflammatory regulators (IL-10, IL-4), tissue repair factors (IL-2, VEGF), and immune activation markers (IL-18, IL-8). The bilateral analysis demonstrates no significant differences between left and right lung cytokine concentrations for any mediator tested (paired t-tests, all $p > 0.05$), indicating systemic rather than focal inflammatory processes. Despite distinct clinical outcomes and biomarker profiles between entity groups, cytokine analysis revealed no significant differences between biological entities (all Kruskal-Wallis $p > 0.05$ with Dunn's post-hoc correction). This demonstrates that entity classification is effectively achieved through traditional biomarkers (CRP/PCT) without requiring complex cytokine analysis. Data presented as mean ± SEM with individual patient values overlaid as dots.*

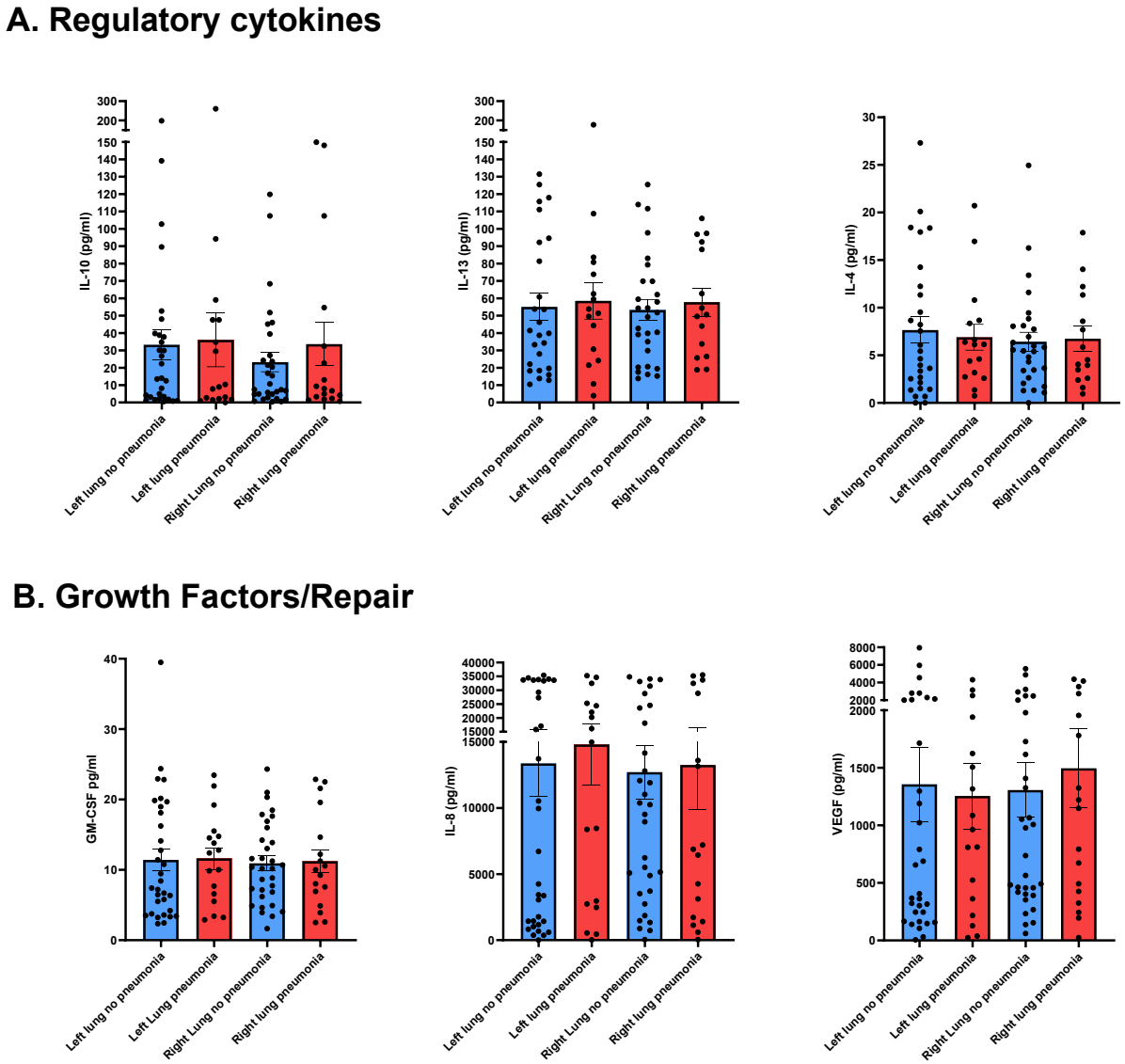


Figure 5.2: Bilateral BAL Cytokine Analysis by Biological Entity Classification. *Bronchoalveolar lavage (BAL) cytokine concentrations from both left lung (blue bars) and right lung (red bars) analysed by biomarker-defined entities: SIRS Pattern, Bacterial Pattern, and Tissue Repair Pattern. (A) Regulatory cytokines, including anti-inflammatory mediators (IL-10, IL-13) and Th2 differentiation markers (IL-4). (B) Growth factors and tissue repair mediators, including myeloid activation markers (GM-CSF), T-cell proliferation factors (IL-2), and angiogenic mediators (VEGF). Bilateral analysis demonstrates no significant differences between left and right lung cytokine concentrations for any mediator tested (paired t-tests, all $p > 0.05$), confirming systemic rather than focal inflammatory processes. Statistical analysis using the Kruskal-Wallis test with Dunn's post-hoc correction revealed no significant differences between entity groups for any of the cytokines tested (all $p > 0.05$). This demonstrates that while entities show distinct clinical outcomes and traditional biomarker profiles, complex cytokine analysis provides no additional discriminatory value for entity classification*

beyond what is achieved with standard biomarkers. Data presented as mean ± SEM with individual patient values overlaid as dots.

5.4.2 Bilateral BAL Cytokine Concordance Analysis

Paired statistical analysis of left versus right lung BAL cytokine concentrations revealed predominant bilateral symmetry across inflammatory mediators (Table 5.2). Of the 15 cytokines analysed, 14 (93%) demonstrated no significant differences between lungs, with only IL-10 showing a statistically significant bilateral difference ($p < 0.05$). The remaining cytokines, including key inflammatory markers (TNF-α, IL-6, and IL-8), tissue repair factors (VEGF and GM-CSF), and immune regulators (IL-27 and IL-18), all exhibited bilateral concordance (all $p > 0.05$). The single exception of IL-10 may reflect its rapid kinetics as an immediate counter-regulatory mediator, where small temporal differences in sampling could manifest as apparent bilateral asymmetry. These results support the interpretation that entity-specific differences arise from distinct systemic inflammatory pathways rather than focal pulmonary pathology, strengthening the rationale for biomarker-based entity classification over traditional pneumonia diagnostic approaches.

Table 5.2: Bilateral BAL Cytokine Analysis

Cytokine	Test	P Value	Significant?	Interpretation
GM-CSF	Paired t-test	0.3641	No	No bilateral difference
IFN-γ	Paired t-test	>0.05*	No	No bilateral difference (95% CI: -67.57 to 94.61)
IL-10	Paired t-test	<0.05*	**Yes**	Significant bilateral difference (95% CI: -34.87 to -2.101)
IL-12p40	Paired t-test	>0.05*	No	No bilateral difference (95% CI: -43.16 to 2.863)
IL-13	Paired t-test	0.9429	No	No bilateral difference
IL-17A	Paired t-test	0.8375	No	No bilateral difference
IL-18	Paired t-test	0.8625	No	No bilateral difference
IL-1β	Paired t-	0.9795	No	No bilateral difference

	test			
IL-2	Paired t-test	0.3574	No	No bilateral difference
IL-27	Paired t-test	0.6446	No	No bilateral difference
IL-4	Paired t-test	0.4680	No	No bilateral difference
IL-6	Paired t-test	0.4929	No	No bilateral difference
IL-8	Paired t-test	0.4061	No	No bilateral difference
TNF-α	Paired t-test	0.1763	No	No bilateral difference
VEGF	Paired t-test	0.8722	No	No bilateral difference

5.4.3 Temporal Cytokine Evolution Patterns

Analysis of serum cytokine trajectories over the three timepoints revealed seven mediators with statistically significant changes, each representing different aspects of the inflammatory cascade following oesophagectomy. These temporal patterns offer insight into the coordinated yet diverse immune responses that characterise post-operative recovery.

Immediate Anti-inflammatory Activation: IL-10 showed quick and sustained increase from baseline (T0) to both post-operative day 1 (T1, $p<0.0001$) and post-operative day 5 (T2, $p<0.0001$), with repeated measures ANOVA confirming notable temporal effects df (5,126) = 16.81, $p<0.0001$, $R^2 = 0.40$) as shown in Figure 5.3. This immediate and lasting anti-inflammatory response highlights IL-10's essential role as a counter-regulatory cytokine that prevents excessive inflammatory damage (377).

Progressive Inflammasome Activation: IL-18 showed stepwise increases at all timepoints, with a significant rise from T0 to T1 ($p=0.021$), followed by highly significant increases at T2 ($p<0.0001$ vs T0), indicating sustained inflammasome activation df (5,120) = 12.52, $p<0.0001$, $R^2 = 0.34$). This pattern suggests ongoing

recognition of danger signals and inflammatory amplification during recovery (378) (Figure 5.3).

Delayed Growth Factor Responses: GM-CSF showed a delayed increase with stability from T0 to T1 ($p>0.99$), but a marked rise by T2 ($p<0.0001$ compared to both T0 and T1), reflecting its dual role in acute granulocyte recruitment and subsequent tissue repair df (5,120) = 8.537, $p<0.0001$, $R^2 = 0.26$). Similarly, VEGF-A exhibited delayed angiogenic activation, remaining stable from T0 to T1 but showing a highly significant increase by T2 ($p<0.0001$ compared to both T0 and T1), consistent with its role in supporting vascular repair processes df (5,120) = 12.37, $p<0.0001$, $R^2 = 0.34$) (54) (Figure 5.3).

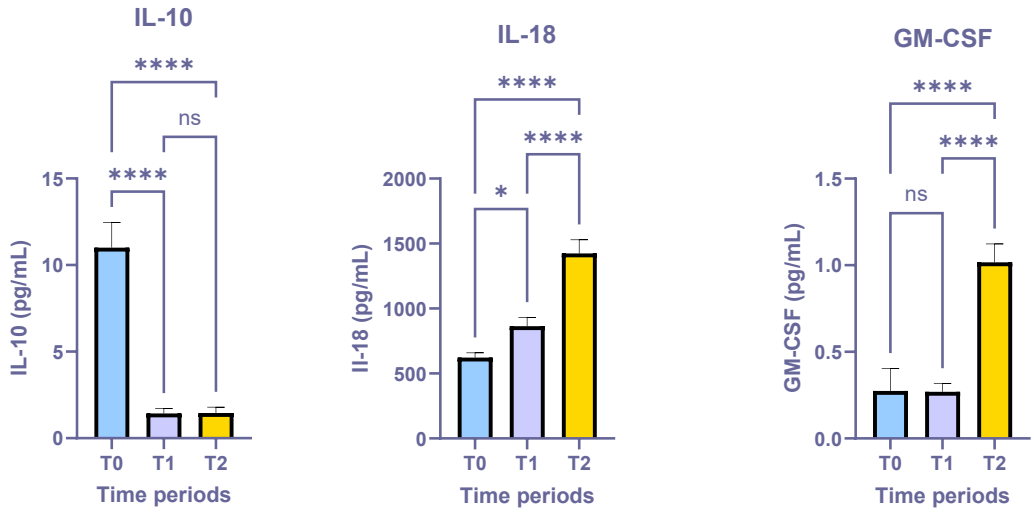


Figure 5.3: Temporal Evolution of Serum Cytokines Following Oesophagectomy. *Serum cytokine concentrations at intraoperative baseline (T0), post-operative day 1 (T1), and post-operative day 5 (T2) in all patients (n=43). Three distinct temporal patterns are observed: IL-10 demonstrates immediate anti-inflammatory activation with a sustained elevation from baseline, IL-18 exhibits progressive inflammasome activation with stepwise increases across all time points, and GM-CSF displays a delayed growth factor response, characterised by stability from T0 to T1, followed by a marked elevation at T2. Statistical analysis by the Kruskal-Wallis test with Dunn's multiple comparisons correction. Significance levels: * $p<0.05$, **** $p<0.0001$, ns = not significant. Data presented as mean ± SEM.*

5.4.4 Clinical Pneumonia Classification Analysis

Serum concentrations of 15 cytokines were compared between patients classified as having pneumonia and those without pneumonia at three perioperative time points (T0, T1, and T2). **No cytokine showed a statistically significant difference between the pneumonia and non-pneumonia groups at any time point.** In contrast, the within-patient temporal analysis (Section 5.4.3) revealed consistent peri-operative increases in several cytokines—including IL-6, TNF-α, IL-1β, VEGF, and IL-27—across the whole cohort, regardless of pneumonia classification (Figure 5.4 and 5.5). These findings imply that conventional pneumonia classifications do not correspond to a distinct systemic cytokine signature in this dataset. While small or subtle differences cannot be ruled out, particularly given the sample size and inter-patient variability, the results highlight the limitations of current infection-based diagnostic frameworks.

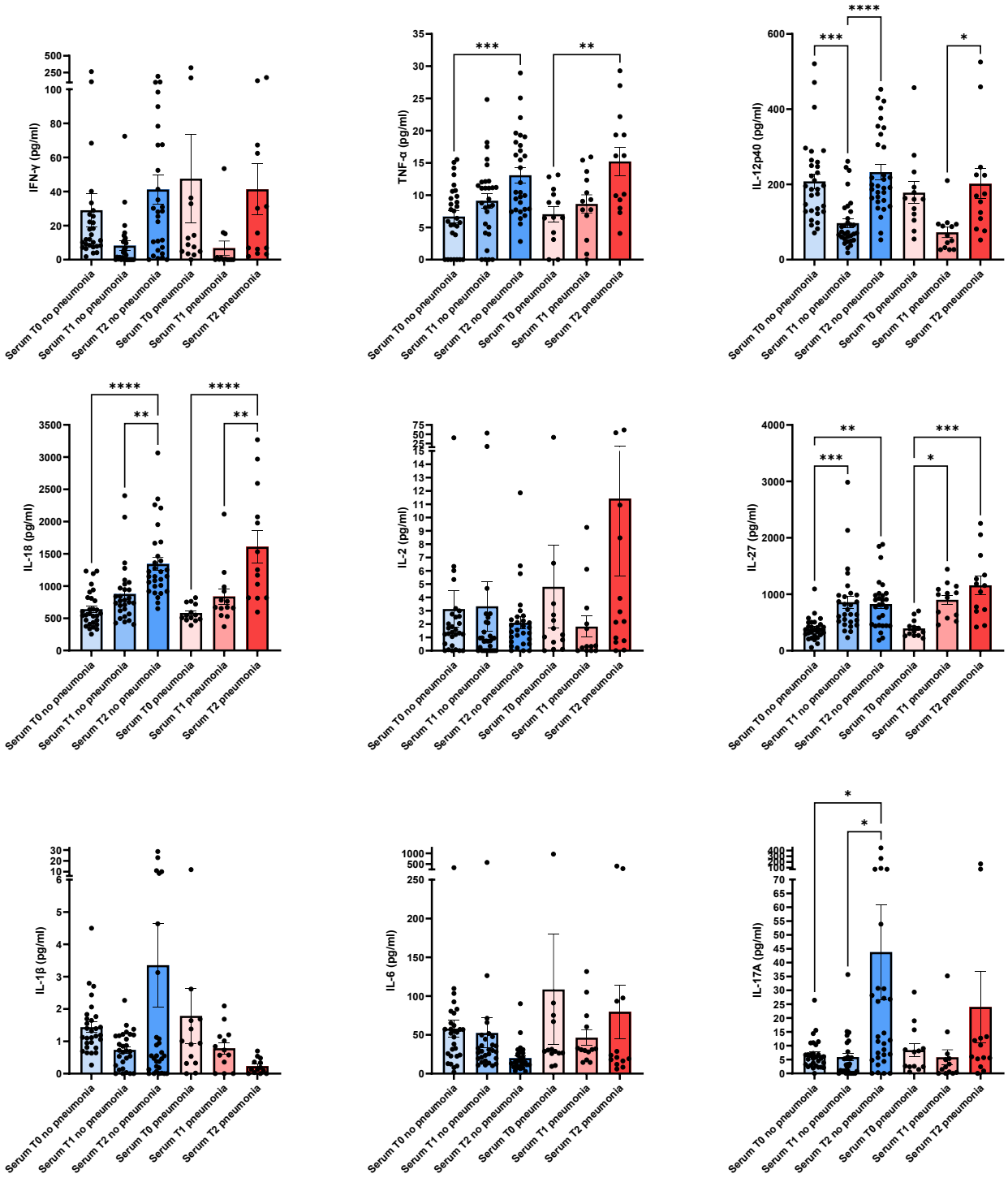
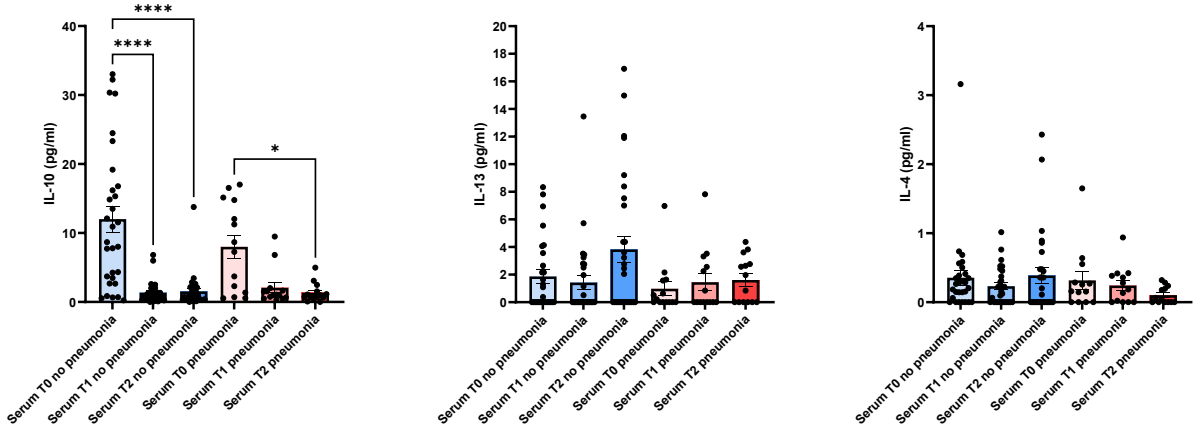


Figure 5.4: Serum cytokine concentrations across pneumonia classifications and perioperative time points. *Serum concentrations of 15 cytokines were measured in patients with and without a clinical diagnosis of pneumonia at three peri-operative time points: T0 (intraoperative baseline), T1 (post-operative day 1), and T2 (post-operative day 5). Bars represent mean ± SEM with individual patient values overlaid. Statistical testing for between-group differences showed no significant differences.*

A. Regulatory cytokines



B. Growth Factors/Repair

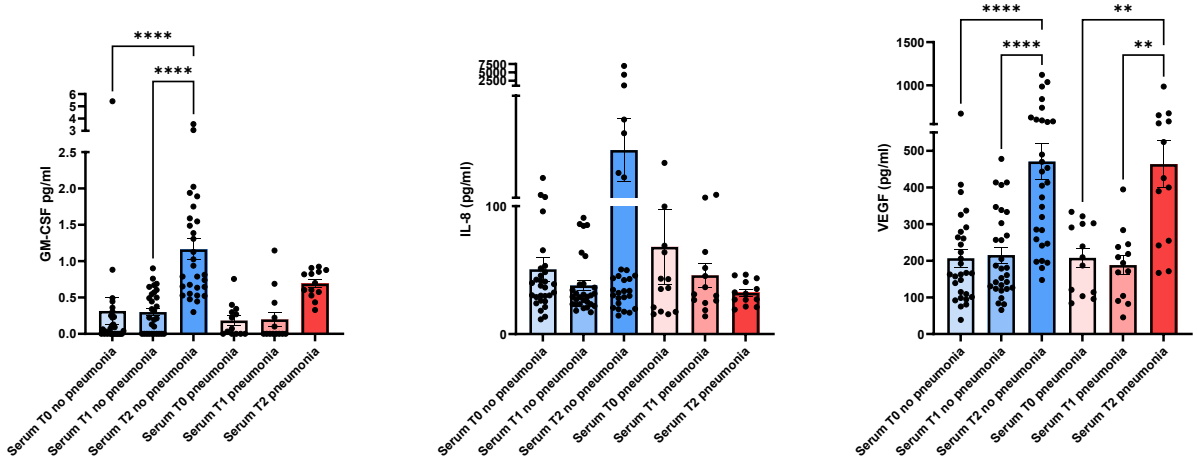


Figure 5.5: Temporal Evolution of Serum Cytokines Following Oesophagectomy. *Serum cytokine concentrations were measured at intraoperative baseline (T0), post-operative day 1 (T1), and post-operative day 5 (T2) in all patients (n=43). Panel A shows regulatory cytokines: IL-10 increased at T1 before declining by T2, while IL-12p70 and IL-13 remained unchanged. Panel B shows growth and repair factors: GM-CSF and IL-6 increased significantly at T1, and VEGF was elevated at both T1 and T2 compared with baseline. Bars represent mean ± SEM with individual patient values overlaid. Statistical significance is indicated by *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 (Tukey's post-hoc test).*

5.4.5 Microbiological Validation of Entity Classification

Bronchoalveolar lavage (BAL) microbiological analysis provided additional validation for the biological entity framework. Culture results demonstrated entity-specific patterns that aligned with biomarker classification. The majority of BAL samples yielded either normal respiratory flora or no growth, consistent with the predominance of non-bacterial inflammatory processes in this cohort. Clinically significant bacterial infection was defined as pathogenic growth of $\geq 10^4$ colony-forming units per millilitre (CFU/mL), a standard diagnostic threshold used to differentiate true infection from colonisation or contamination. Growth above this threshold was most commonly observed in patients classified as Bacterial Pattern entities, supporting the PCT-based discrimination between bacterial and non-bacterial inflammation. In contrast, SIRS Pattern entities predominantly showed sterile cultures or only normal flora, validating the sterile inflammation classification, while Tissue Repair Pattern entities demonstrated the lowest rates of pathogenic growth, consistent with their minimal systemic inflammatory profile. Cytokine analysis of serum samples stratified by microbiological classification revealed that only IFN-γ and IL-27 showed statistically significant differences between groups (Figures 5.6 and 5.7).

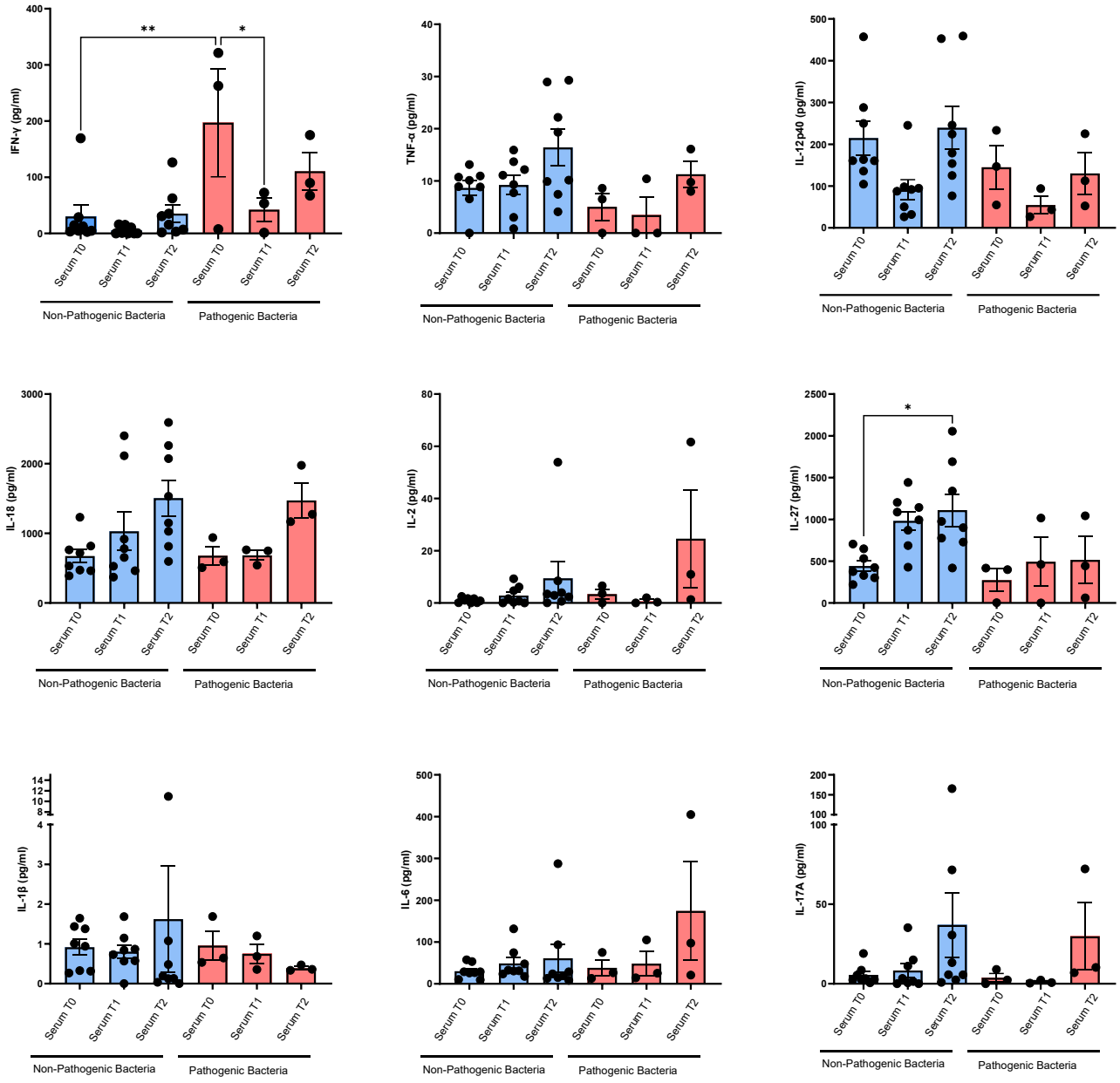


Figure 5.6: Microbiological Culture Results by Biological Entity Classification. ***B****ronchoalveolar lavage culture results grouped by biomarker-defined entities: SIRS Pattern (blue), Bacterial Pattern (red), and Tissue Repair Pattern (white). Culture categories include no growth, normal respiratory flora, significant pathogenic bacteria*

(≥10⁴ CFU/mL), and fungal growth. The distribution of positive cultures aligns with entity classification, with Bacterial Pattern showing highest rates of pathogenic growth, supporting the biological validity of PCT-based entity discrimination. Statistical analysis by Fisher's exact test. Data presented as proportions with 95% confidence intervals

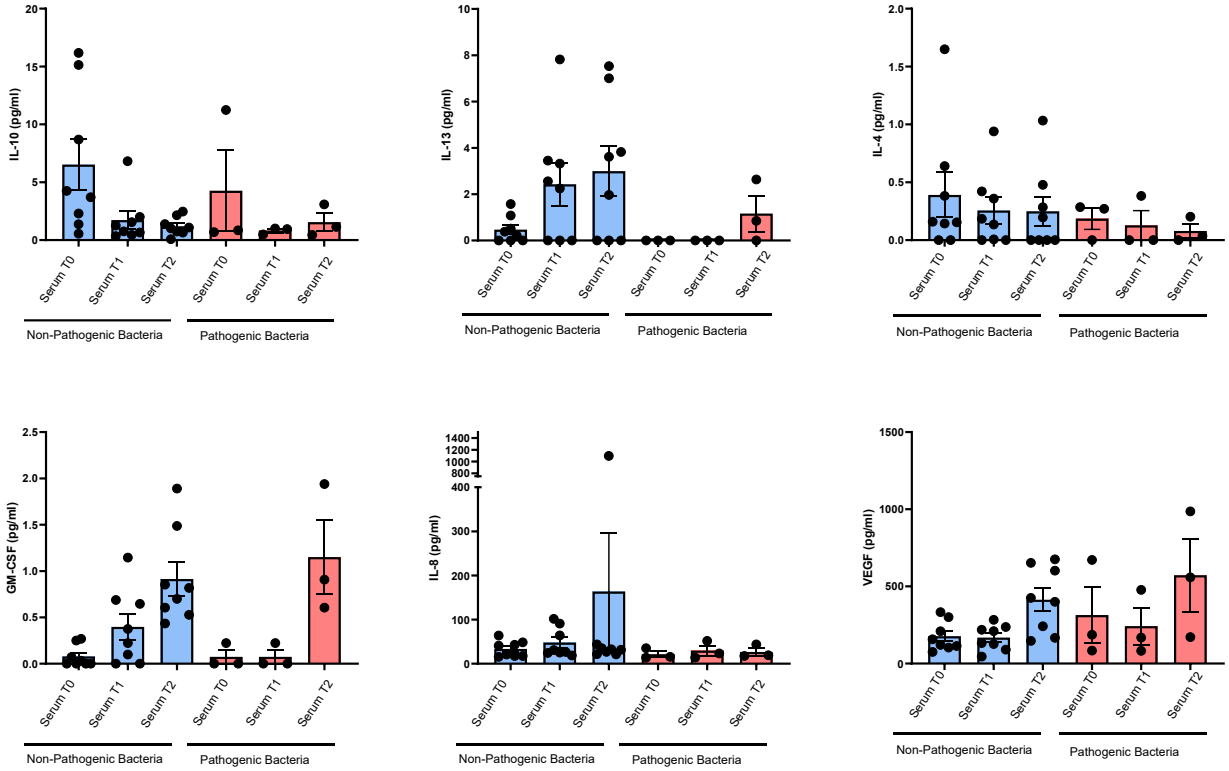


Figure 5.7: Serum Cytokine Concentrations Across Pathogenic versus Non-Pathogenic Classifications and Perioperative Time Points. *Serum concentrations of six representative cytokines were measured in patients with pathogenic bacteria detected (red bars) and those with non-pathogenic findings (blue bars) at three peri-operative time points: T0 (intraoperative baseline), T1 (post-operative day 1), and T2 (post-operative day 5). The cytokines shown include pro-inflammatory mediators (IL-1β, IL-6), anti-inflammatory regulators (IL-10), tissue repair factors (GM-CSF, VEGF), and immune activation markers (TNF-α). Statistical testing for between-group differences using unpaired t-tests (or Mann-Whitney U tests for non-parametric data) showed no significant differences between pathogenic and non-pathogenic groups at any time point for any cytokine tested. This finding implies that microbiological classifications based on pathogen detection do not correspond to distinct systemic cytokine signatures in this dataset, highlighting the limitations of current infection-based diagnostic frameworks. Data presented as mean ± SEM with individual patient values overlaid as dots.*

5.4.6 Neoadjuvant Treatment Effects on Cytokine Responses

Analysis of cytokine concentrations, based on the neoadjuvant treatment protocol, was conducted to identify potential confounding effects of chemotherapy or chemoradiotherapy on postoperative inflammatory responses (Figure 5.8 and 5.9). Comparison between the CROSS protocol (chemoradiotherapy) and the FLOT regimen (chemotherapy) revealed treatment-specific differences in several cytokines. Baseline measurements (T0) were considered most informative, as patients had completed neoadjuvant therapy; however, lingering immunomodulatory effects could potentially influence postoperative cytokine patterns. The analysis aimed to distinguish treatment-induced inflammatory changes from those caused by bacterial infection or surgical trauma, ensuring that entity classification reflected genuine post-operative biological processes rather than pre-existing treatment effects. Key cytokines, including IL-6, GM-CSF, and VEGF, demonstrated distinct patterns over time within treatment groups (Figure 5.8 and 5.9). These findings suggest that a history of neoadjuvant treatment should be considered when interpreting postoperative cytokine profiles and entity classification.

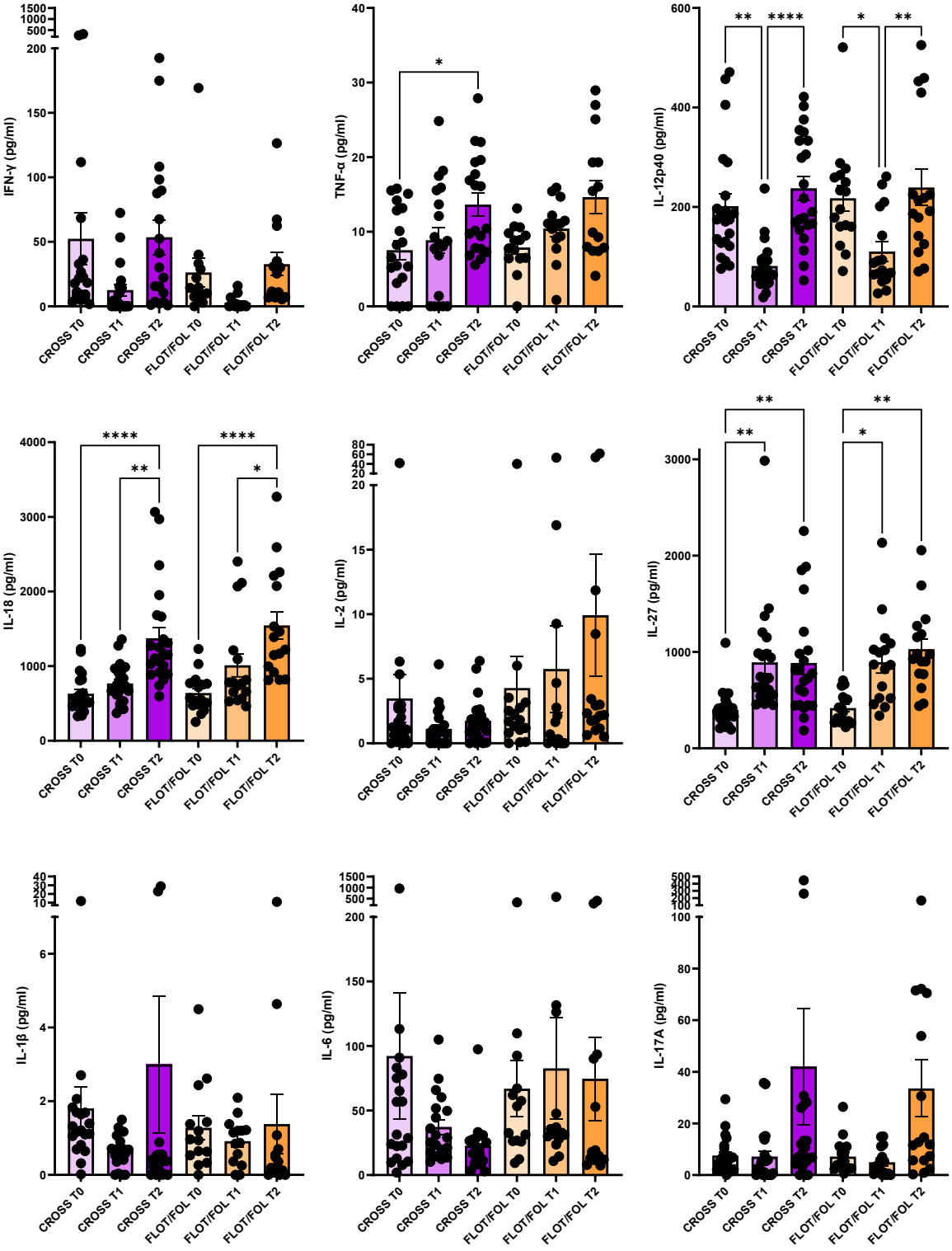


Figure 5.8: Serum Cytokine Concentrations by Neoadjuvant Treatment Protocol - Temporal Analysis. Serum concentrations of nine cytokines (IFN-γ, TNF-α, IL-1β, IL-6, IL-12, IL-27, IL-8, IL-4, IL-1α) were measured at baseline (T0), post-operative day 1 (T1), and post-operative day 5 (T2) in patients grouped by neoadjuvant regimen: CROSS protocol (purple, n=28) and FLOT regimen (orange, n=12). Several cytokines demonstrated treatment-specific differences, particularly IL-6, TNF-α, IL-8, IL-12, and IL-27. Statistical significance was assessed by one-way ANOVA with Tukey's post-hoc testing and is indicated by *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. Bars represent mean ± SEM with individual patient values overlaid.

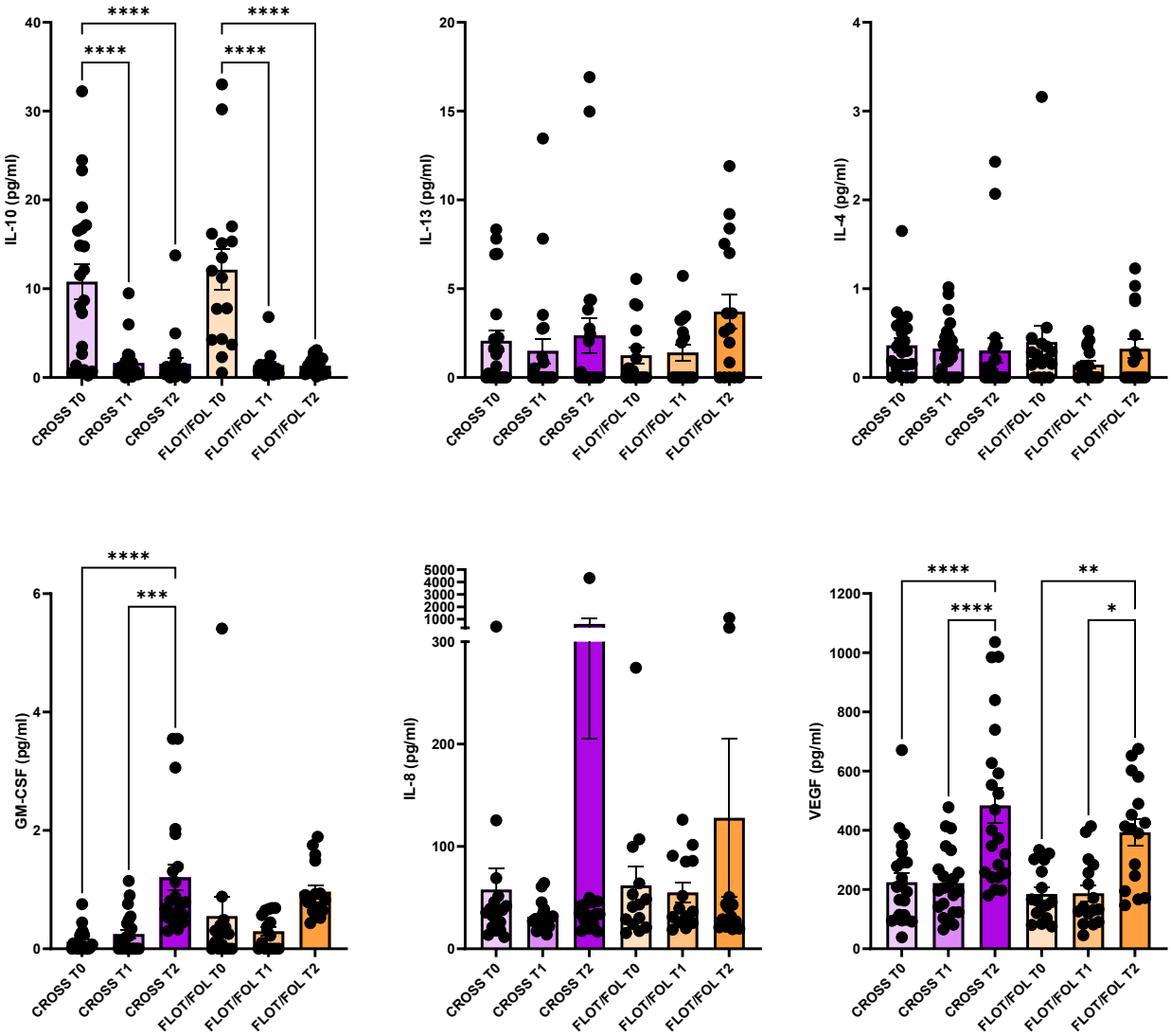


Figure 5.9: Key Cytokine Responses by Neoadjuvant Treatment Protocol. *Selected cytokines showing the most significant treatment-related differences: IL-10, GM-CSF, and VEGF demonstrate distinct responses across all timepoints. Early anti-inflammatory responses are replaced with tissue repair responses over time. These treatment-specific differences highlight the importance of considering neoadjuvant therapy history when interpreting cytokine profiles and entity classification to distinguish treatment effects from genuine post-operative biological processes. Statistical significance by one-way ANOVA with post-hoc testing: ** $p<0.01$, **** $p<0.0001$. Error bars represent SEM.*

5.4.7 Patient Characteristics and Entity Distribution

Forty-three consecutive patients undergoing transthoracic oesophagectomy with complete cytokine and biomarker data comprised the final analytical cohort, Table 5.3

Table 5.3: Patient Demographics and Clinical Characteristics by Biological Entity

Characteristic	All Patients (n=43)	SIRS Pattern (n=19)	Bacterial Pattern (n=15)	Tissue Repair Pattern (n=9)	P Value
Age (years)					
Mean ± SD	62.5 ± 10.1	62.8 ± 9.8	61.9 ± 11.2	63.1 ± 9.6	0.9803
Range	39-78	46-75	39-76	47-75	
Gender, n (%)					
Male	35 (81.4)	15 (78.9)	13 (86.7)	7 (77.8)	0.7842
Female	8 (18.6)	4 (21.1)	2 (13.3)	2 (22.2)	
BMI (kg/m²)					
Mean ± SD	27.8 ± 4.2	28.1 ± 4.5	27.2 ± 3.8	28.2 ± 4.7	0.7156
Range	19.3-41.4	21.6-36.7	22.0-33.8	19.3-41.4	
ASA Grade, n (%)					
Grade I-II	28 (65.1)	12 (63.2)	10 (66.7)	6 (66.7)	0.9541
Grade III-IV	15 (34.9)	7 (36.8)	5 (33.3)	3 (33.3)	
Smoking History, n (%)					
Never	15 (34.9)	7 (36.8)	5 (33.3)	3 (33.3)	0.8912
Ex-smoker	24 (55.8)	10 (52.6)	9 (60.0)	5 (55.6)	
Current	4 (9.3)	2 (10.5)	1 (6.7)	1 (11.1)	
Primary Diagnosis, n (%)					
Oesophageal SCC	15 (34.9)	6 (31.6)	5 (33.3)	4 (44.4)	0.7321
Oesophageal Adenocarcinoma	17 (39.5)	8 (42.1)	6 (40.0)	3 (33.3)	
GOJ Adenocarcinoma	11 (25.6)	5 (26.3)	4 (26.7)	2 (22.2)	
Neoadjuvant Treatment, n (%)					
CROSS Protocol	28 (65.1)	13 (68.4)	9 (60.0)	6 (66.7)	0.8234
FLOT Regimen	12 (27.9)	5 (26.3)	5 (33.3)	2 (22.2)	
Other/None	3 (7.0)	1 (5.3)	1 (6.7)	1 (11.1)	
ICU Length of Stay (days)					

Mean ± SD	6.4 ± 6.8	9.2 ± 12.9	5.3 ± 2.1	4.9 ± 3.1	0.2341
Median (IQR)	4 (3-6)	5 (3-7)	4.5 (3-6)	4 (3-5)	
Range	2-50	3-50	3-10	2-13	
Hospital Length of Stay (days)					
Median (IQR)	14 (11-20)	16 (13-24)	14 (11-18)	11 (10-13)	0.0687
Range	8-66	10-60	9-27	9-17	

Statistical Analysis: Continuous variables compared using one-way ANOVA for normally distributed data or Kruskal-Wallis test for non-parametric data. Categorical variables compared using Chi-square or Fisher's exact test as appropriate. $P < 0.05$ considered statistically significant.

Entity classification yielded a clinically relevant distribution: SIRS Pattern 19/43 patients (44.2%), Bacterial Pattern 15/43 patients (34.9%), and Tissue Repair Pattern 9/43 patients (20.9%). This distribution did not differ significantly from equal proportions (Chi-square $\chi^2(2) = 1.868$, $p = 0.3931$), indicating that the classification system captured genuine biological heterogeneity rather than artefactual clustering.

5.4.8 Clinical Outcomes Validation of Entity Framework

Entity classification showed a clinically relevant distribution: 19 out of 43 patients (44.2%) had the SIRS Pattern, 15 out of 43 (34.9%) had the Bacterial Pattern, and 9 out of 43 (20.9%) exhibited the Tissue Repair Pattern (Table 5.3). Statistical analysis indicated no significant difference from an even distribution (Chi-square $\chi^2(2) = 1.868$, $p = 0.3931$), suggesting that the classification system accurately reflects true biological variability rather than random clustering. Additionally, baseline demographic and clinical characteristics did not significantly differ between the entity groups across all parameters measured (Table 5.3), supporting the conclusion that the classification is driven by biological factors rather than demographic variables. Entity-stratified serum cytokine analysis at T2 (postoperative day 5), together with the derived IL-6/GM-CSF ratio, is presented in full in section 5.5.7. Whilst entity-specific differences did not reach statistical significance at any timepoint, temporal evolution of cytokine profiles across T0, T1 and T2 was consistent with the distinct pathophysiological processes underlying each entity classification, with patterns most divergent during the acute inflammatory phase.

5.4.9 Clinical Outcomes Validation of Entity Framework

Clinical outcomes provided strong validation of the biological entity classification system through the development of graduated risk stratification patterns (Table 5.3). Reintubation rates showed entity-specific differences approaching statistical significance (Fisher's exact p = 0.0525): SIRS Pattern 10/19 (52.6%), Bacterial Pattern 9/15 (60.0%), and Tissue Repair Pattern 1/9 (11.1%). The Tissue Repair Pattern demonstrated substantially lower reintubation risk compared to both inflammatory entities, indicating a fundamentally different pathophysiological process with a more benign clinical trajectory.

The patterns of ICU length of stay further support entity-specific differences (Table 5.3), with SIRS entities showing the highest mean duration (9.2 ± 12.9 days) due to one extreme case of 50 days. This outlier involved a patient with HSV Type 1 pneumonitis requiring prolonged mechanical ventilation, confirming the SIRS classification since this viral pneumonia involves sterile rather than bacterial inflammation. Notably, this patient made a full recovery, demonstrating that extended ICU stays in SIRS entities may reflect management complexity rather than a poor prognosis. The other SIRS cases had more typical durations, followed by Bacterial (5.3 ± 2.1 days) and Tissue Repair entities (4.9 ± 3.1 days). High-grade complications (Clavien-Dindo ≥ III) demonstrated a marked entity-specific distribution: SIRS, 47.4%; bacterial, 40.0%; and Tissue Repair, 11.1%. These outcome patterns validate the biological relevance of the entity classification system by demonstrating that molecular differences translate into clinically meaningful risk stratification.

5.4.10 Coagulation Parameters Provide Temporal Entity Validation

Coagulation parameter analysis revealed entity-specific differences that provide additional validation of the biological classification framework (Figure 5.10). Fibrinogen levels showed significant temporal increases across all entity groups from post-operative day 1 (T1) to post-operative day 5 (T2), indicating ongoing acute-phase protein synthesis during recovery. Entity-specific differences in fibrinogen were observed at both timepoints, with all groups exhibiting coordinated elevation during the recovery period. D-dimer analysis revealed entity-specific differences that were most evident during the acute inflammatory phase. At T1, Bacterial Pattern entities demonstrated significantly higher D-dimer levels compared to SIRS Pattern entities,

suggesting enhanced fibrinolytic activation during bacterial infection. This finding supports the biological validity of PCT-based discrimination between infectious and sterile inflammatory processes. The coagulation analysis demonstrates that haemostatic parameters provide temporal validation of the entity classification system. The coordinated fibrinogen response across all entities reflects the systemic nature of post-operative inflammatory responses, while entity-specific D-dimer differences during acute phases offer additional biological evidence supporting the framework. These findings indicate that coagulation markers provide complementary validation of entity-specific pathophysiological processes beyond traditional inflammatory biomarkers. The temporal patterns seen in coagulation parameters match the broader finding that biological differences between entities are most marked during acute inflammatory phases, further supporting the clinical usefulness of entity-based therapeutic approaches in the early post-operative period.

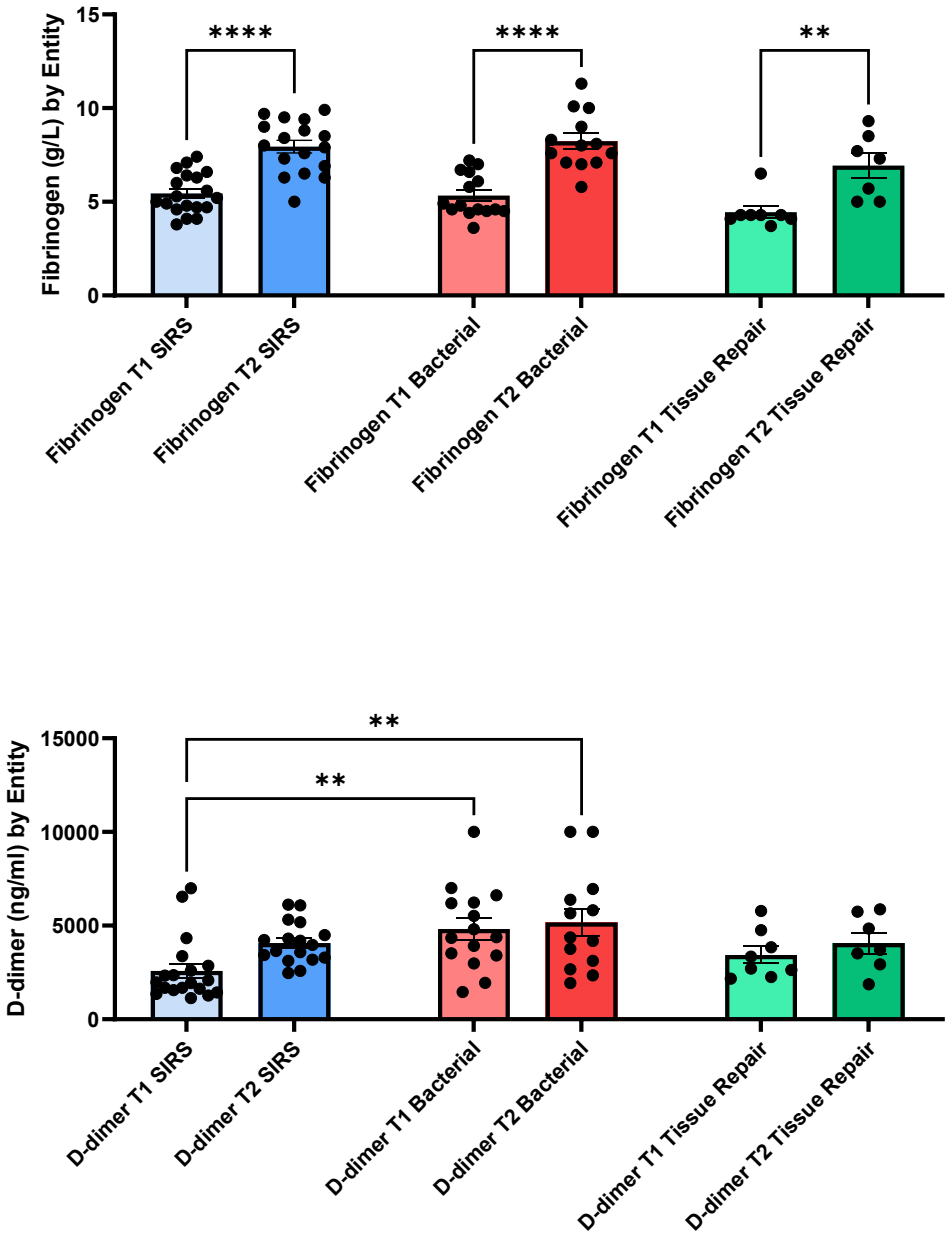


Figure 5.10: Coagulation Parameters by Biological Entity Classification. *Fibrinogen and D-dimer concentrations at post-operative day 1 (T1) and post-operative day 5 (T2) grouped by biological entities: SIRS Pattern (blue, n=19), Bacterial Pattern (red, n=15), and Tissue Repair Pattern (green, n=9). Upper panel shows fibrinogen levels with significant temporal increases in all entity groups from T1 to T2, indicating ongoing acute-phase protein synthesis during recovery. Lower panel demonstrates D-dimer concentrations with entity-specific differences at T1, where Bacterial Pattern shows significantly higher levels than SIRS Pattern, suggesting enhanced fibrinolytic activation during bacterial infection. By T2, D-dimer levels converge across entities, indicating resolution of entity-specific coagulation differences during recovery. These findings demonstrate that coagulation parameters provide temporal validation of entity classification, with differences most pronounced during acute inflammatory phases. Statistical significance by one-way ANOVA with Tukey's post–hoc testing ** $p<0.01$, **** $p<0.0001$. Error bars represent SEM.*

5.4.11 Biomarker Validation of Entity Classification

Traditional inflammatory biomarkers provided strong validation of the three-entity classification system (Table 5.4). CRP levels effectively distinguished inflammatory entities (SIRS and Bacterial patterns) from the Tissue Repair pattern, while PCT specifically separated bacterial from non-bacterial processes. Comprehensive serum cytokine analysis across all 15 mediators showed no significant differences between entity groups, indicating that practical biomarker-based classification captures biological heterogeneity without the need for costly cytokine panels. This finding enhances the clinical usefulness of the Enhanced Trimodal Score framework, which depends on easily accessible CRP and PCT measurements rather than complex molecular analysis in Figure 5.11.

Table 5.4 Biomarker and Cytokine Analysis by Biological Entity Classification

Biomarker/Cytokine	SIRS Pattern (n=19) Mean ± SEM	Bacterial Pattern (n=15) Mean ± SEM	Tissue Repair Pattern (n=9) Mean ± SEM	P Value	Statistical Significance	Primary Biological Role
CRP (mg/L)	175.4 ± 17.2	182.5 ± 16.2	71.5 ± 5.3	**0.002**	Significant	Systemic inflammation
PCT (ng/mL)	0.53 ± 0.05	3.48 ± 0.68	1.13 ± 0.36	**<0.0001**	Highly significant	Bacterial infection marker
VEGF	244.7 ± 31.61	201.3 ± 24.33	152.6 ± 36.42	0.0972	Not significant	Angiogenesis and vascular repair
IL-13	1.185 ± 0.5337	1.432 ± 0.6134	2.399 ± 0.8487	0.1895	Not significant	Alternative macrophage activation
IL-1β	1.865 ± 0.5833	1.480 ± 0.2657	0.9379 ± 0.1302	0.2719	Not significant	Master pro-inflammatory mediator
IL-2	3.895 ± 2.140	4.879 ± 2.568	1.286 ± 0.3532	0.2830	Not significant	T-cell proliferation
IL-6	89.99 ± 48.82	75.80 ± 19.79	39.97 ± 7.607	0.3352	Not significant	Acute-phase response
IL-27	399.7 ±	410.9 ±	333.1 ±	0.3982	Not	DAMP-

	49.09	43.79	29.63		significant	mediated immune regulation
IL-17A	8.686 ± 1.709	6.525 ± 1.615	4.939 ± 1.020	0.4127	Not significant	Neutrophil recruitment
IFN-γ	56.68 ± 21.60	14.86 ± 3.229	17.54 ± 2.463	0.4957	Not significant	Antimicrobial immunity
IL-8	64.28 ± 20.38	58.49 ± 16.64	32.50 ± 3.470	0.4965	Not significant	Neutrophil chemotaxis
IL-10	9.923 ± 2.245	11.82 ± 2.225	12.62 ± 3.482	0.6241	Not significant	Anti-inflammatory regulation
IL-18	601.3 ± 51.34	580.1 ± 45.26	726.3 ± 114.3	0.6639	Not significant	Inflammasome activation
IL-12p40	193.6 ± 26.59	192.6 ± 19.97	225.4 ± 46.69	0.7447	Not significant	Th1 differentiation
GM-CSF	0.4513 ± 0.2819	0.1427 ± 0.04508	0.09161 ± 0.04388	0.8108	Not significant	Myeloid activation/tissue repair
TNF-α	6.673 ± 1.177	6.900 ± 1.263	7.810 ± 1.475	0.8439	Not significant	Systemic pro-inflammatory response
IL-4	0.4492 ± 0.1746	0.2708 ± 0.05750	0.2613 ± 0.07148	0.9458	Not significant	Th2 differentiation

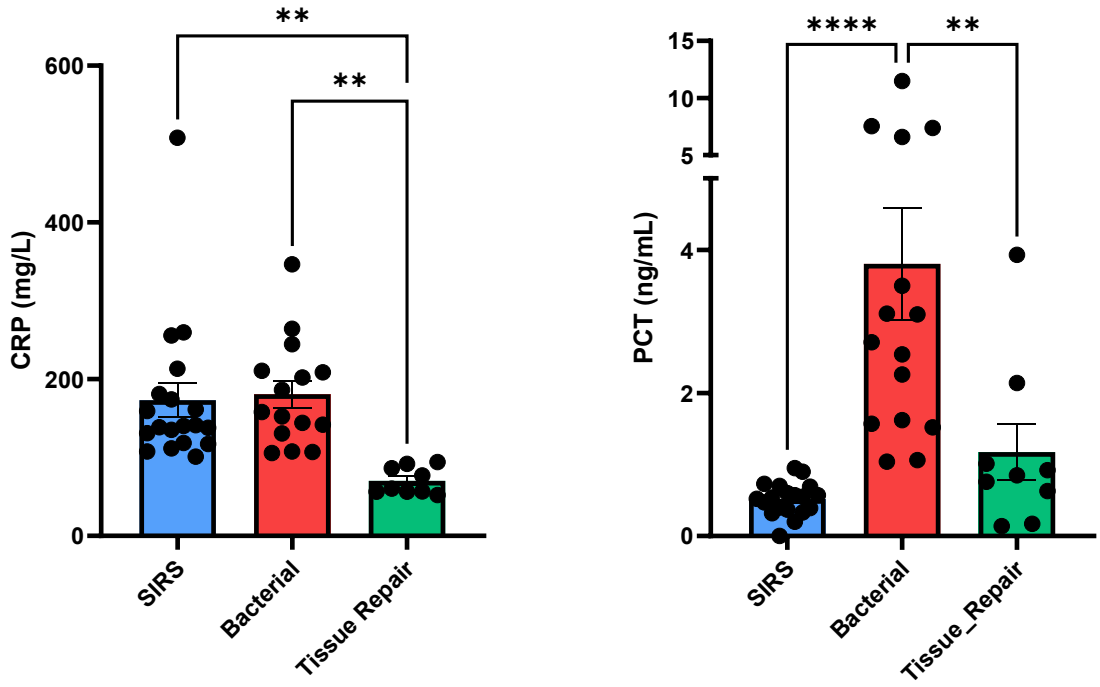


Figure 5.11: Traditional Biomarker Validation of Entity Classification. *Serum concentrations of C-reactive protein (CRP) and procalcitonin (PCT) grouped by biomarker-defined entities: SIRS Pattern (blue, n=19), Bacterial Pattern (red, n=15), and Tissue Repair Pattern (green, n=9). CRP levels effectively distinguish inflammatory entities (SIRS and Bacterial patterns) from Tissue Repair pattern, while PCT specifically discriminates bacterial from non-bacterial processes. Both SIRS and Bacterial patterns show significantly elevated CRP compared to Tissue Repair pattern, while PCT demonstrates clear bacterial specificity with Bacterial pattern showing markedly higher levels than both SIRS and Tissue Repair patterns. These traditional biomarkers provide robust discrimination between entity groups and form the foundation of the practical classification framework. Statistical significance by one-way ANOVA with Tukey's post-hoc testing: ** $p<0.01$, **** $p<0.0001$. Error bars represent SEM. Individual data points show the distribution within each entity group.*

5.5 Discussion

5.5.1 Principal Findings and Clinical Significance

This comprehensive cytokine study shows that procalcitonin-based classification offers clinically useful stratification of post-operative complications after oesophagectomy, despite the lack of clear cytokine-based biological signatures that distinguish these groups. The systematic analysis of 15 cytokines over time, across both sides, and within specific entities revealed that while PCT effectively separates bacterial from non-bacterial processes with strong clinical relevance, broad cytokine profiling did not identify distinct inflammatory signatures underlying these classifications. The biomarker-based entity framework (SIRS Pattern 44.2%, Bacterial Pattern 34.9%, Tissue Repair Pattern 20.9%) provides practical clinical value for therapeutic decisions, especially with PCT-guided antibiotic stewardship, even without definitive cytokine-based biological differences.

5.5.2 Procalcitonin as the Key Discriminator

The most robust finding was PCT's ability to distinguish bacterial from non-bacterial inflammatory processes, with Bacterial Pattern entities showing significantly higher PCT levels (3.48 ± 0.68 ng/mL) compared to both SIRS (0.53 ± 0.05 ng/mL) and Tissue Repair patterns (1.13 ± 0.36 ng/mL, $p<0.0001$). This PCT-based discrimination aligned with microbiological validation, where pathogenic bacterial growth was most commonly observed in Bacterial Pattern entities, supporting the clinical utility of the 1.0 ng/mL threshold for therapeutic decision-making in post-operative settings (41,42). The strong correlation between PCT levels, microbiological findings, and clinical outcomes suggests that this biomarker captures genuine differences in pathophysiology that may not be reflected in the cytokine panel selected for this study.

5.5.3 Cytokine Analysis: Insights and Limitations

A comprehensive cytokine analysis found no statistically significant differences among the three proposed biological entities for any of the 15 mediators tested. However, several cytokines exhibited trends approaching significance that merit discussion. In BAL fluid, regulatory and tissue repair mediators such as IL-4 ($p=0.075$), IL-10 ($p=0.082$), and IL-13 ($p=0.083$) were close to the significance threshold, indicating potential biological differences in local pulmonary environments that might become

clearer with larger sample sizes (380,381). Similarly, serum VEGF showed a borderline trend (p=0.097) towards entity-specific differences, possibly reflecting differing levels of angiogenic activation.

The bilateral cytokine analysis provided valuable mechanistic insights, revealing systemic rather than local inflammatory processes, with 14 of 15 mediators (93%) showing no significant differences between the lungs. This supports the choice to use left lung BAL values for analysis, thereby reducing confounding effects from the direct surgical manipulation during right thoracotomy (379). Temporal analysis demonstrated coordinated immune responses, with immediate anti-inflammatory activation (IL-10), progressive inflammasome activation (IL-18), and delayed growth factor responses (GM-CSF, VEGF-A), offering biological context for the sequential clinical changes observed in predictive scoring systems. It is also worth noting that the entity-stratified serum cytokine analysis presented in the original submission examined only a single timepoint. Presenting data across all three timepoints shows that entity-specific differences in serum cytokine concentrations, though not reaching statistical significance, exhibit a temporal evolution consistent with the distinct biological processes proposed — with patterns most divergent during the acute inflammatory phase at T1 and converging during the repair phase at T2, as discussed in detail in section 5.5.7.

5.5.4 Clinical Utility Despite Biological Uncertainty

The lack of clear cytokine-based entity differentiation does not reduce the clinical usefulness of PCT-guided classification. The observation that traditional pneumonia classifications did not align with specific cytokine signatures emphasises the significance of biomarker-based approaches over conventional infection-focused diagnostics. PCT-based entity classification effectively stratified patients into groups with different clinical outcomes, microbiological profiles, and therapeutic needs, especially for guiding antibiotic use (380,381). This indicates that clinical phenotypes may be more pertinent for treatment guidance than the underlying biological mechanisms in this context. The demonstration that pathogenic versus non-pathogenic bacterial classifications also failed to correlate with cytokine signatures further supports the superiority of PCT-based approaches over traditional microbiological criteria for therapeutic decision-making in the post-operative setting.

5.5.5 Study Limitations and Future Directions

Several important limitations must be acknowledged. The selection of 15 cytokines, while targeting key inflammatory pathways, may have excluded other relevant mediators that could better differentiate between entities (382). The sample size of 43 patients offered sufficient power to detect large effect sizes but might have been inadequate for subtle cytokine differences (386). The single-centre design limits generalisability, and the specific post-operative timing of sample collection may not have captured optimal windows for discrimination of all mediators. Another limitation is the use of blind rather than bronchoscopic lower airway sampling for BAL collection. Although the blind technique was used due to intermittent unavailability of bronchoscopy equipment, and multiple studies confirm comparable diagnostic accuracy for diffuse pulmonary processes, bronchoscopic BAL provides direct visualisation of the airways, enables targeted sampling of affected segments, and reduces the risk of upper airway contamination. The lack of bronchoscopic guidance may have introduced variability in sample quality and anatomical targeting across patients, potentially attenuating cytokine signals and contributing to the absence of statistically significant entity-specific differences in the cytokine analysis. Related to this, the use of small saline aliquots (10 mL per lung) to obtain lower airway samples will likely result in preferential capture of airway inflammatory cytokine profiles rather than of genuine parenchymal or alveolar activity. The instilled volume may not have reached distal alveolar spaces in all patients, meaning that the cytokine concentrations measured in BAL fluid may reflect proximal airway inflammation rather than the alveolar microenvironment where pneumonia-related pathophysiology primarily occurs. This should be considered when interpreting the bilateral cytokine concordance findings and the absence of entity-specific cytokine differences in BAL fluid.

The borderline significance observed for several cytokines (IL-4, IL-10, IL-13, VEGF) indicates that larger multi-centre studies with expanded cytokine panels and different sampling timepoints might uncover biological differences not seen in this analysis (383). Future research should prioritise validating PCT-based therapeutic protocols rather than seeking additional biological discriminators, given the strong clinical utility already demonstrated.

5.5.6 Implications for Clinical Practice

These findings support the implementation of PCT-guided therapeutic protocols in post-operative care, emphasising bacterial versus non-bacterial discrimination rather than complex biological entity classification. The practical value lies in identifying patients who require antibiotic therapy (PCT >1.0 ng/mL) versus those who may benefit from anti-inflammatory approaches or enhanced recovery protocols (PCT ≤1.0 ng/mL). This biomarker-based approach offers immediate clinical applicability without requiring complex cytokine analysis or an understanding of biological mechanisms.

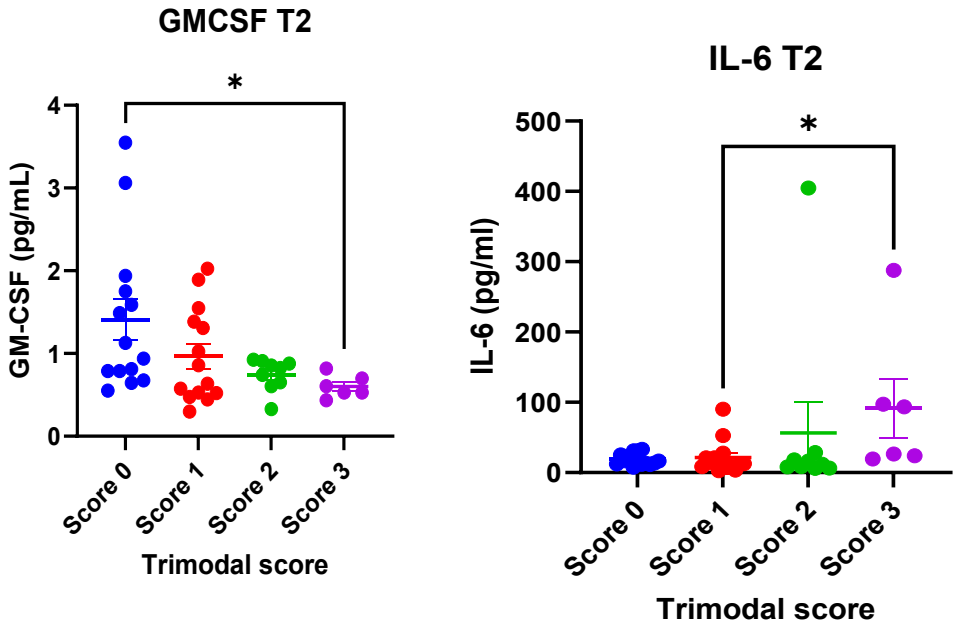
5.5.7 Extended Cytokine Analysis: Postoperative Day 5 Severity Correlates

To address the limited temporal scope of the entity-stratified cytokine analysis presented above, and to provide a more complete characterisation of cytokine dynamics across the perioperative period, an extended analysis was performed focusing on serum samples collected at T2 (postoperative day 5). This time point was selected because the acute surgical inflammatory response is expected to have subsided by day 5, meaning that persistent or elevated inflammatory markers at this stage are more likely to reflect evolving complications rather than the expected physiological response to surgery. Cytokine concentrations were stratified by both Trimodal score category (0–3) and biological entity classification, using the same patient cohort, sampling protocols, and entity definitions described in sections 5.3.2–5.3.5. In addition to individual cytokine analysis, an IL-6/GM-CSF ratio was derived for each patient to capture the balance between pro-inflammatory drive and myeloid repair capacity. Statistical analysis used Kruskal–Wallis testing with Dunn's post-hoc correction for multiple comparisons, with Spearman's rank correlation used to assess associations between cytokine measures and continuous clinical outcomes.

5.5.9 Principal findings of the extended analysis

Three consistent patterns emerged from this analysis. First, IL-6 and GM-CSF exhibited opposing trajectories across Trimodal score categories at day 5: IL-6 increased progressively with worsening postoperative pulmonary status (463,464,465), while GM-CSF decreased, with significant differences observed between the lowest and highest Trimodal categories (474,475,480) (Figure 5.12). Second, the IL-6/GM-CSF ratio demonstrated superior discriminatory performance compared to either cytokine alone, increasing stepwise across Trimodal scores (Kruskal–Wallis $p = 0.0096$), with

significantly higher ratios in Score 3 compared to Scores 0 and 1. The ratio correlated moderately with Trimodal score (Spearman r = 0.42, p = 0.0049) and more strongly with ICU length of stay (r = 0.58, p < 0.0001), indicating that it reflects both the severity and duration of postoperative organ support (Figure 5.13 and 5.15). Third, neither individual cytokines nor the IL-6/GM-CSF ratio significantly distinguished between biological entities — bacterial, SIRS, and tissue repair patterns — at this time point, consistent with the findings from the earlier multi-timepoint analysis (493,494) (Figure 5.14).



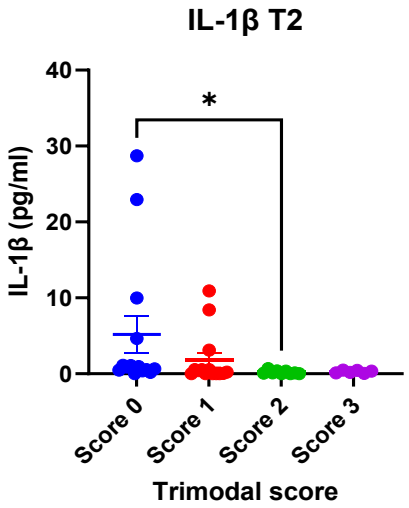


Figure 5.12 GM-CSF, IL-1β and IL-6 concentrations at postoperative day 5 across Trimodal score categories.

*Scatter plots (mean ± SEM) display serum concentrations of GM-CSF (top left panel), IL-1β (bottom panel), and IL-6 (top right panel) measured at T2 (postoperative day 5), stratified by Trimodal score categories (0–3). Each point represents an individual patient. GM-CSF exhibited a significant progressive decrease with increasing clinical severity (Kruskal–Wallis test, *P < 0.05 for Score 3 versus Scores 0 and 1), indicating a loss of protective lung homeostatic mechanisms in more severe pulmonary complications. IL-6 demonstrated a significant progressive increase with increasing severity (*P < 0.05 for Score 3 versus Scores 0 and 1), reflecting an amplified systemic inflammatory response. IL-1β showed an unexpected pattern with the highest levels observed in patients with Score 0 (*P < 0.05 for Score 0 versus Score 2), suggesting potential early inflammasome activation even in uncomplicated postoperative courses. All comparisons were performed using Kruskal–Wallis tests with Dunn's post-hoc correction for multiple comparisons.*

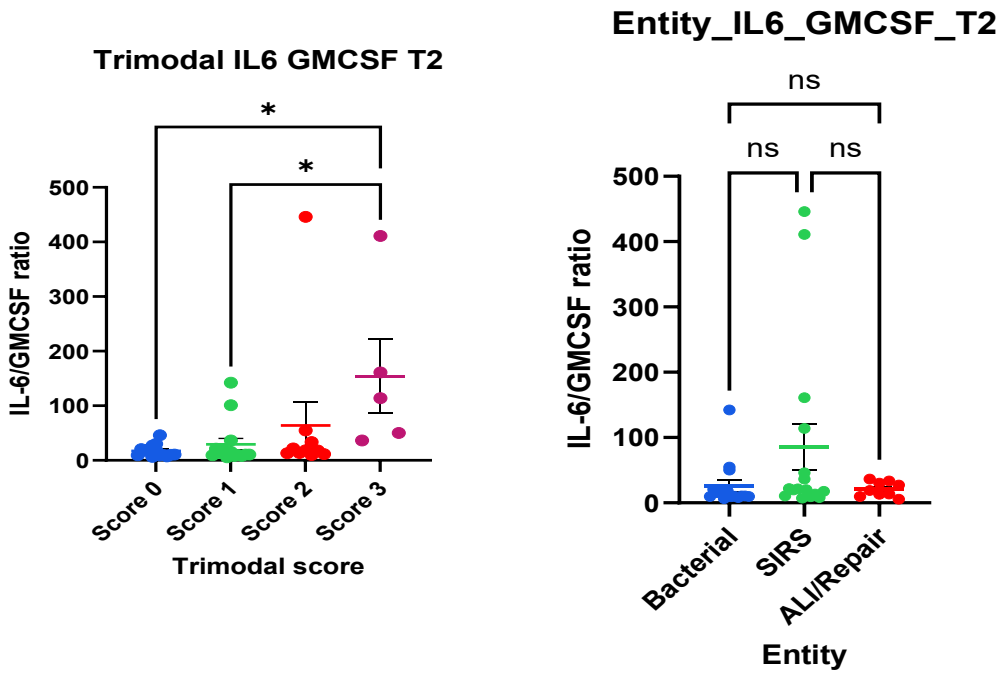


Figure 5.13. IL-6/GM-CSF ratio at postoperative day 5 by Trimodal score and by biological entity.

The left panel illustrates the IL-6/GM-CSF ratios (mean ± SEM) across Trimodal scores (0–3), demonstrating a significant stepwise increase with clinical severity (Kruskal–Wallis P = 0.0096). Post-hoc analysis revealed significantly higher ratios in Score 3 compared to Scores 0 and 1, indicating a progressive immunological imbalance characterised by an increasing inflammatory drive (IL-6) coupled with diminishing reparative capacity (GM-CSF). The right panel depicts the IL-6/GM-CSF ratios stratified by biological entity classification: bacterial pneumonia, sterile systemic inflammatory response (SIRS), and ARDS-like repair. Differences between groups were not statistically significant (Kruskal–Wallis test), suggesting that although the ratio correlates with clinical severity, it does not reliably distinguish between infectious and non-infectious mechanisms underlying postoperative pulmonary complications.

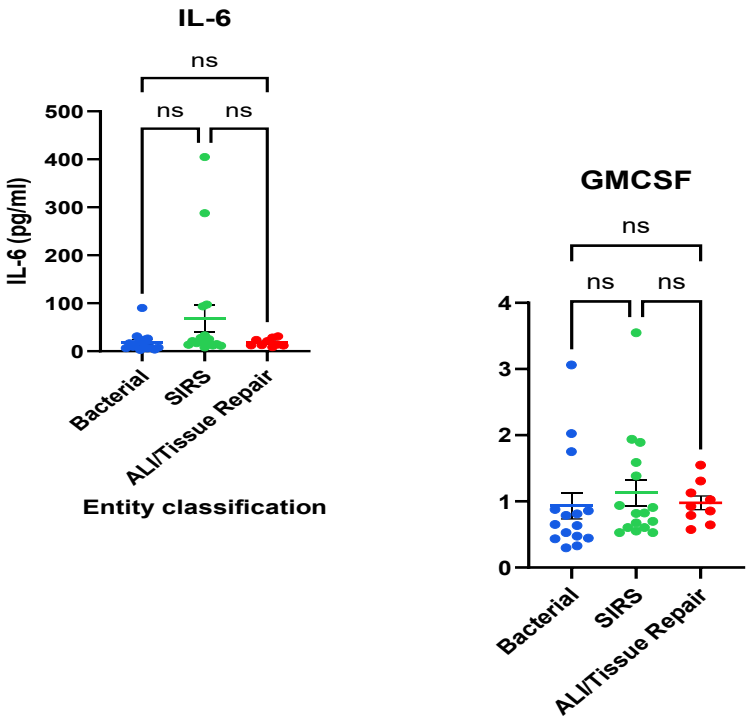


Figure 5.14. IL-6 and GM-CSF concentrations at postoperative day 5 by biological entity.

Scatter plots (mean ± SEM) illustrating IL-6 concentrations (left panel) and GM-CSF concentrations (right panel) across various biological entity classifications: bacterial pneumonia, sterile SIRS, and ARDS-like repair. Each data point signifies an individual patient. IL-6 levels were numerically highest in cases of ARDS-like repair, whereas GM-CSF concentrations were lowest within this group. However, Kruskal–Wallis tests indicated no statistically significant differences among the biological entities for either cytokine ($P > 0.05$). This suggests that neither IL-6 nor GM-CSF alone can effectively differentiate bacterial from non-bacterial postoperative pneumonia syndromes. The results underscore the limitations of using single biomarkers to distinguish infection-driven from host-driven inflammatory responses and imply that a mechanistic classification necessitates the integration of multiple clinical, radiological, and biochemical parameters.

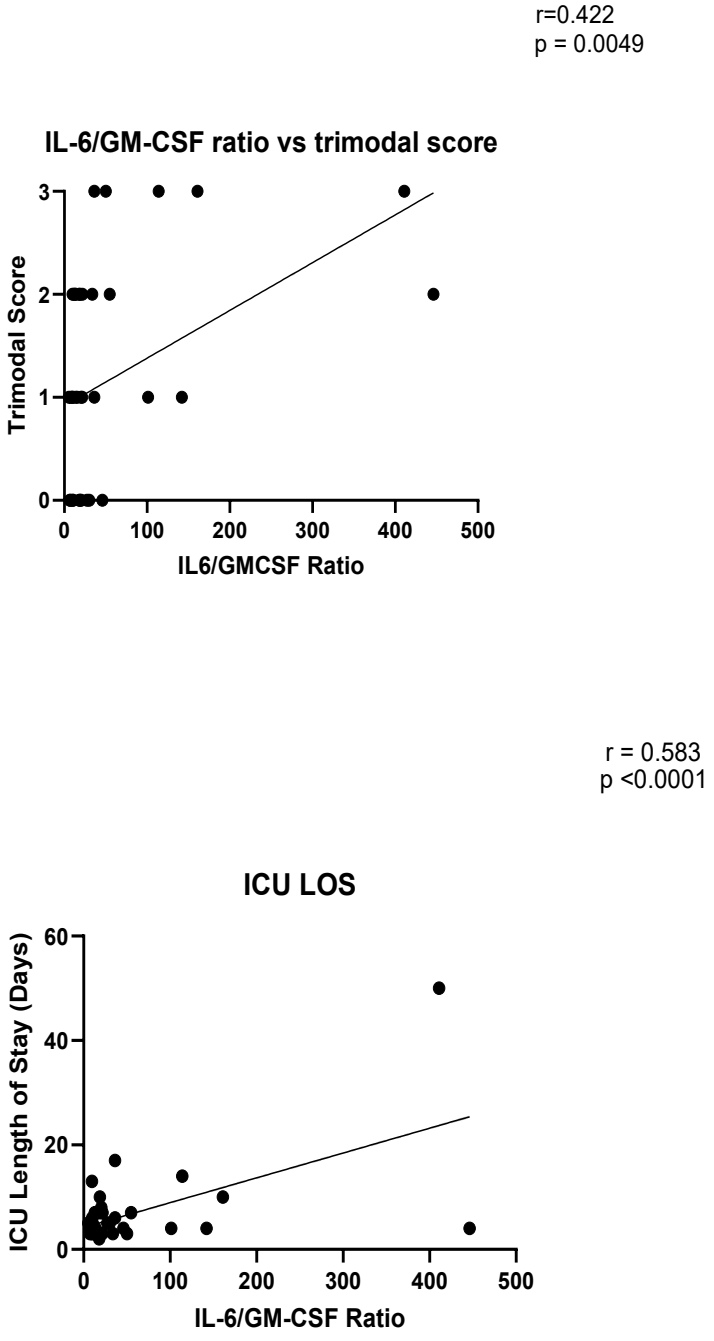


Figure 5.15. Correlation between IL-6/GM-CSF ratio and clinical outcomes.

The upper panel illustrates the Spearman correlation between the IL-6/GM-CSF ratio measured on postoperative day 5 (T2) and the Trimodal clinical severity score (r =

0.422, P = 0.0049), confirming that the ratio encapsulates significant aspects of pulmonary complication severity. The lower panel demonstrates the correlation between the IL-6/GM-CSF ratio and the length of stay in the intensive care unit (ICU) (r = 0.583, P < 0.0001), indicating that higher ratios are predictive of extended ICU dependency regardless of infection status. Each data point corresponds to an individual patient; dashed lines denote simple linear regression models for visualisation purposes. These moderate to strong correlations substantiate the validity of the IL-6/GM-CSF ratio as a composite biomarker that integrates inflammatory intensity with the loss of protective GM-CSF-mediated lung homeostasis, thereby offering prognostic insights into the recovery trajectory among postoperative oesophagectomy patients.

5.5.10 Interpretation

The opposing directions of IL-6 and GM-CSF at postoperative day 5 across the Trimodal spectrum suggest a shift from a balanced inflammatory-repair response towards a state of unrestrained systemic inflammation with impaired myeloid support in more severely affected patients. This pattern would not be visible from CRP, PCT, or white cell counts alone. IL-6 at this time point is consistent with its established role as a key mediator of the acute-phase response and a prognostic marker in sepsis and pneumonia, where persistently elevated levels beyond the expected surgical recovery window indicate ongoing pathological inflammation rather than routine healing (463,465,466,467,468). The decrease in GM-CSF with increasing severity is consistent with the concept of immunoparalysis or myeloid exhaustion in persistent critical illness (482,483,484), and aligns with transcriptomic sepsis profiles in which downregulation of GM-CSF-responsive pathways characterises immunosuppressed phenotypes (474,481). Taken together, the IL-6/GM-CSF ratio appears to function as a concise biomarker of hyper-inflammation coupled with impaired repair capacity — a pattern that correlates with both composite clinical severity and ICU resource utilisation (485,486,487,488).

The absence of significant cytokine differences between biological entities at day 5 is consistent with findings from the earlier multi-timepoint analysis and with growing evidence from sepsis transcriptomic and proteomic studies, which have repeatedly demonstrated that inflammatory signatures are driven more by host response endotype than by pathogen identity (493,494). This reinforces the conclusion that cytokines in this setting are more informative as markers of severity and immune state than as

discriminators of infectious aetiology. For clinical application, patients with elevated IL-6/GM-CSF ratios at day 5 may merit closer surveillance, early discussion regarding prolonged ICU requirements, or prioritisation for lung-protective strategies. If validated prospectively, a persistently high ratio at this time point could also identify patients who might benefit from immunorestorative approaches, though this remains speculative and warrants dedicated investigation (482,489,490).

5.6 Conclusions

This comprehensive cytokine study establishes key principles for managing post-operative pneumonia and advancing precision medicine. The systematic analysis of 15 cytokines across various analytical levels shows that cytokines and biomarkers have complementary roles in clinical care: cytokine analysis offers crucial mechanistic insights, while targeted biomarker selection facilitates practical clinical application. The biomarker-based classification system enhances the predictive ability described in Chapter 4 by providing precise treatment guidance for established complications. Validation through consistent clinical, microbiological, and temporal evidence indicates that current diagnostic methods do not fully capture the biological diversity of post-operative pulmonary complications. Cytokine analysis reveals the immune mechanisms involved, while biomarker-based classification enables personalised medicine across different healthcare settings. These findings support the development of sequential clinical frameworks that combine accurate prediction with targeted treatment, shifting post-operative pneumonia management from reactive, empirical approaches to proactive, personalised strategies.

Chapter 6

General Discussion

6.0 The Core Discovery: Diagnostic Unreliability Reveals Biological Heterogeneity

When experienced thoracic surgeons, intensivists, radiologists and pulmonologists examined identical postoperative chest radiographs and clinical data, they achieved only fair agreement in diagnosing pneumonia ($\kappa = 0.270$) (384,385). Complete agreement among all four specialists was achieved in only 44% of cases, and 97.7% of this consensus identified patients without pneumonia. Even after providing standardised clinical correlation---temperature, white blood cell count, oxygen requirements, and inflammatory markers---inter-observer agreement improved but remained only moderate (Fleiss' κ increased from 0.270 to 0.421, a 56% relative increase). Diagnostic uncertainty, where clinicians classified cases as "maybe pneumonia," occurred in nearly one-fifth of all assessments and showed the poorest agreement of any category ($\kappa = 0.189$) (386). This diagnostic disagreement is not unique to our institution. A systematic review of 14 randomised controlled trials involving 1,369 patients across different healthcare systems showed that only two studies (14.3%) used validated diagnostic criteria for pneumonia (387). The remaining 85.7% relied on non-validated institutional protocols or did not specify definitions at all. The reported pneumonia incidence ranged from 10% to 40% across studies examining identical surgical populations with similar interventions and this heterogeneity hampered meaningful meta-analysis, not because of differences in interventions, but because investigators measured fundamentally different outcomes while using the same terminology (388,389).

The explanation for this diagnostic confusion stems from extensive biomarker research. Using procalcitonin (PCT) levels to guide classification revealed that what clinicians call post-operative "pneumonia" may comprise of at least two different underlying processes: bacterial infections, indicated by notably high PCT levels (3.48 ± 0.68 ng/mL) with microbiological proof, and non-bacterial inflammatory responses, which feature much lower PCT levels (0.53-1.13 ng/mL) and often lack pathogenic cultures (390,391). The six-fold difference in PCT levels ($p<0.0001$) more precisely distinguishes PAMP-driven bacterial inflammation from DAMP-driven sterile responses than traditional syndrome-based criteria (392,393). Microbiological confirmation was found in only 30% of cases diagnosed as "pneumonia," suggesting

that most post-operative lung issues are due to non-infectious lung injury rather than bacterial pneumonia (394).

Comprehensive cytokine profiling of 15 inflammatory mediators showed bilateral symmetry ($r > 0.96$ for 93% of mediators), indicating that post-operative complications are mostly driven by systemic processes rather than focal pulmonary infections (395). In the non-bacterial group, initial evidence hints at additional variability: regulatory cytokines including IL-4 ($p=0.075$), IL-10 ($p=0.082$) and IL-13 ($p=0.083$) which are involved in resolving inflammation and repairing tissue - show trends close to significance, while VEGF elevation ($p=0.097$), a marker of angiogenesis and wound healing, nearly reached significance but did not achieve it (396). These borderline results suggest possible biological differences that distinguish tissue repair from purely inflammatory processes, although our study lacked sufficient power to confirm this division.

The central finding shifts diagnostic disagreement from a methodological problem to a biological insight: experienced clinicians reach only fair agreement, not because of inadequate training or imprecise criteria, but because they unconsciously recognise biological heterogeneity that syndrome-based classifications systematically hide (397,398). When surgeons, intensivists, and radiologists examine identical information yet arrive at different conclusions, they identify real pathophysiological differences---bacterial versus non-bacterial processes, systemic versus focal pathology, inflammatory versus reparative responses that clinical presentation alone cannot reliably differentiate (399). The fair agreement ($\kappa = 0.270$) reflects a proper recognition of genuine biological uncertainty rather than diagnostic failure. This thesis demonstrates that postoperative pneumonia, as currently defined and diagnosed, encompasses at least two distinct biological processes that require fundamentally different therapeutic approaches. The importance extends beyond an improved definition of pneumonia to include a challenge to core assumptions underpinning surgical outcome research (400,401).

6.1 The Biological Foundation: What Biomarkers Revealed About Post-Operative Lung Injury

6.1.1 The Validated Distinction: Bacterial Infection Versus Sterile Inflammation

Procalcitonin-based classification provided the clearest biological distinction, separating bacterial infection (PCT 3.48 ± 0.68 ng/mL) from non-bacterial inflammatory processes (PCT 0.53-1.13 ng/mL, $p<0.0001$) (402,403). This sixfold difference reflects key immunological mechanisms that have been well characterised in the literature but have never been systematically applied to post-operative surgical populations. Bacterial pathogens containing PAMPs induce procalcitonin synthesis via toll-like receptor activation---specifically TLR2 and TLR4 and through specific cytokine pathways involving interleukin-1β and tumour necrosis factor-α, resulting in sustained PCT elevation detectable in serum within 6-12 hours of bacterial invasion (404,405). The extent of PCT elevation correlates with bacterial load and the severity of the infectious process, making it particularly useful for distinguishing true infection from colonisation or contamination.

In contrast, surgical trauma causes substantial DAMP release through various mechanisms that warrant detailed examination. Tissue dissection releases intracellular contents, including mitochondrial DNA, heat shock proteins, and high-mobility group box 1 protein (HMGB1), all of which act as endogenous danger signals. Ischaemia-reperfusion injury during one-lung ventilation results in oxidative stress and the production of reactive oxygen species that intensify inflammatory cascades. Anastomotic construction involves controlled tissue damage and predictable inflammatory responses that are essential for wound healing. These processes activate overlapping yet distinct inflammatory cascades via pattern recognition receptors, including RAGE (receptor for advanced glycation end products) and various toll-like receptors, leading to fever, leucocytosis and radiographic changes without corresponding PCT elevation (406,407). The primary mechanistic difference lies in downstream signalling: while both PAMP and DAMP activation converge on similar inflammatory pathways, the specific cytokine profile and the kinetics of procalcitonin induction differ notably, providing the biological basis for PCT-guided discrimination.

The microbiological validation confirmed this distinction with significant clinical nuances. Bacterial pattern entities, defined by PCT >2.0 ng/mL, showed the highest rates of pathogenic bacterial growth, mainly enteric organisms such as Escherichia coli, Klebsiella species, and Enterobacter, reflecting the altered anatomy and physiology caused by oesophagectomy (408,409). The gastric conduit replacing the resected oesophagus fundamentally changes upper gastrointestinal physiology in ways that predispose to aspiration. It lacks the regular peristaltic waves that propel contents distally, has no lower oesophageal sphincter to prevent reflux, and often demonstrates delayed emptying, particularly in the early post-operative period. This combination increases susceptibility to aspiration of gastric contents containing enteric flora rather than the usual respiratory pathogens seen in community-acquired or hospital-acquired pneumonia in medical populations (410). The bacterial spectrum observed in our cohort---with enteric organisms dominating over Streptococcus pneumoniae, Haemophilus influenzae, or even Staphylococcus aureus - supports this mechanistic understanding and has immediate implications for empirical antibiotic choice.

Non-bacterial patterns, on the other hand, mainly yielded mixed upper respiratory tract flora, commensals, or no growth, confirming that significant inflammatory responses can occur without a bacterial infection requiring antimicrobial therapy (411). When cultures did show growth in this group, organisms typically represented colonisation or contamination rather than invasive infection: low colony counts, polymicrobial flora suggesting oral contamination, or organisms of low pathogenic potential. This pattern reinforces that microbiological detection alone, without consideration of host inflammatory responses and clinical context, provides insufficient guidance for therapeutic decisions. The clinical implications are immediate and significant: nearly 65% of patients currently receiving antibiotics for post-operative pneumonia exhibit procalcitonin levels indicating sterile inflammation. These patients develop genuine inflammatory responses that are clinically indistinguishable from bacterial infections when using conventional criteria - fever reaching 38-39°C, white blood cell counts exceeding 15,000/μL with left shift, radiographic infiltrates on chest imaging, and clinical deterioration requiring increased respiratory support, including escalating oxygen therapy or mechanical ventilation - yet they lack bacterial infections that would respond to antimicrobial therapy. Current syndrome-based criteria, which rely on these same clinical features to define pneumonia, cannot distinguish inflammatory responses

triggered by surgical DAMPs from those driven by bacterial PAMPs (412,413). The resulting diagnostic ambiguity leads to systematic antibiotic overuse based on clinical appearances rather than underlying pathophysiology, with consequences extending beyond individual patients to institutional antimicrobial resistance patterns and healthcare costs.

This binary distinction - bacterial versus non-bacterial - represents the most robust biological finding of the thesis, validated through convergent evidence from procalcitonin discrimination, microbiological confirmation and clinical outcomes. The threshold of PCT 1.0 ng/mL offers practical utility for decision-making in post-operative antibiotic stewardship, providing sufficient sensitivity to detect most bacterial infections while maintaining specificity to avoid treating sterile inflammation (414,415).

6.1.2 Systemic Inflammatory Processes: Bilateral Symmetry and the Focal Infection Fallacy

The bilateral cytokine analysis revealed perhaps the most mechanistically significant finding: post-operative complications are driven by systemic processes rather than localised pulmonary issues. Despite performing right thoracotomy with direct surgical manipulation of the right hemithorax - including rib spreading, pleural disruption, mediastinal dissection, and prolonged right lung collapse during one-lung ventilation - bronchoalveolar lavage from both lungs showed near-perfect correlation for 14 of 15 inflammatory mediators (93%), with correlation coefficients exceeding $r = 0.96$ for most cytokines (416). This bilateral symmetry indicates that both lungs respond identically to systemic inflammatory signals, rather than harbouring focal infectious or inflammatory processes that would be expected to produce asymmetric cytokine patterns. This discovery fundamentally challenges traditional models of pneumonia that have dominated pulmonary medicine for over a century. Medical pneumonia in non-surgical populations follows a well-established pathophysiological sequence: bacteria colonising alveolar spaces represent a focal infectious nidus that triggers local inflammatory responses through chemokine gradients attracting neutrophils, cytokine production by resident alveolar macrophages, and complement activation at the site of bacterial invasion. These local responses may subsequently progress to systemic symptoms in severe cases through cytokine spillover into the circulation, bacteraemia, or progression to septic shock (417,418). The pathophysiological sequence begins with

a focal infection, leading to local inflammation, which can then potentially spread systemically - a pattern ingrained in clinical thinking and reflected in diagnostic criteria that emphasise unilateral or focal radiographic changes.

Post-operative complications studied here follow an opposite and fundamentally different pathophysiology: systemic inflammatory processes triggered by surgical trauma manifest as pulmonary signs because the lung acts as a sentinel organ where systemic conditions become clinically visible (419,420). The lung's unique position, receiving the entire cardiac output, makes it extremely sensitive to circulating inflammatory mediators, while its vast surface area of gas exchange provides an extensive interface for inflammatory cell trafficking and cytokine-mediated responses. The sequence reverses the traditional pneumonia model: systemic inflammation → bilateral pulmonary manifestation → clinical detection. This explains why clinicians observe bilateral findings on examination despite unilateral surgical intervention and why radiographic infiltrates often appear bilaterally or progress from unilateral to bilateral patterns, which would be unusual for focal infectious pneumonia.

The perfect bilateral correlation of inflammatory mediators affirms this systemic nature through multiple converging mechanisms. First, cytokines released throughout the body during surgery - from injured tissues, activated immune cells in the blood, and systemic inflammatory activation - reach both lungs simultaneously via pulmonary circulation, producing identical inflammatory responses regardless of which hemithorax undergoes direct surgical manipulation (421). Second, the lung's extensive capillary network (approximately 280 billion capillaries providing roughly 70 square metres of surface area) and large endothelial surface make it highly sensitive to circulating inflammatory mediators, effectively acting as a filter or sensor for systemic inflammatory states (422). Third, mechanical ventilation, particularly one-lung ventilation during surgery, influences both lungs through systemic mechanisms---ventilator-induced lung injury caused by overdistension and atelectrauma, oxidative stress from high inspired oxygen concentrations, and the release of inflammatory mediators via mechanotransduction - rather than causing purely local pathology (423,424).

This systemic nature offers elegant explanations for many clinical observations that have long puzzled researchers and clinicians. Post-operative pulmonary complications respond inconsistently to antibiotics targeting focal infections because most are

systemic inflammatory states rather than bacterial pneumonia amenable to antimicrobial treatment (425). Radiographic infiltrates often show unusual patterns - bilateral symmetric changes, progression despite proper antibiotics, or resolution without antimicrobial intervention - that make sense when viewed as signs of systemic inflammation rather than a worsening focal infection. Clinical examination reveals bilateral findings even when initial imaging suggests unilateral involvement, a paradox explained by bilateral physiological responses to systemic processes that radiography captures imperfectly. The therapeutic implications are significant: interventions aimed at focal infections through direct antimicrobial action or drainage are inherently unsuitable for systemically mediated processes, which require different approaches that focus on supporting organ function, managing systemic inflammation, and preventing secondary complications (426).

6.1.3 Hypothesised Heterogeneity Within Non-Bacterial Processes: Preliminary Evidence and Biological Plausibility

Within the non-bacterial inflammatory group, which accounts for 65% of patients with post-operative pulmonary complications, preliminary evidence suggests the possibility of subdividing into distinct pathophysiological patterns, although definitive biological validation remains absent. Comprehensive cytokine analysis of 15 inflammatory mediators - chosen to reflect pro-inflammatory responses (IL-1β, IL-6, IL-8, TNF-α), anti-inflammatory regulation (IL-10, IL-13), inflammasome activation (IL-18), tissue repair (VEGF, GM-CSF), and other immune processes - showed no statistically significant differences among the three proposed biological entities for any mediator tested when applying conventional significance thresholds. However, several cytokines exhibited trends nearing significance, which should be considered hypothesis-generating findings that require prospective validation (427).

In bronchoalveolar lavage fluid, regulatory and tissue-repair mediators showed consistent, borderline trends that formed a coherent biological pattern. IL-4 ($p=0.075$), IL-10 ($p=0.082$), and IL-13 ($p=0.083$) approached but did not reach the conventional statistical significance threshold of $p<0.05$. These cytokines have established and well-characterised roles in inflammation resolution, tissue repair, and immunoregulation, which makes their coordinated elevation biologically plausible in a tissue repair phenotype. IL-4 and IL-13 promote alternative macrophage activation (M2

polarisation), characterised by the production of tissue repair mediators and anti-inflammatory cytokines, and stimulate fibroblast activity essential for wound healing and tissue remodelling (428). IL-10 functions as a master regulatory cytokine that suppresses pro-inflammatory responses through multiple mechanisms, including inhibition of antigen presentation, suppression of pro-inflammatory cytokine production, and promotion of regulatory T cell function, while simultaneously facilitating healing through effects on tissue remodelling (428,429). The consistent pattern across multiple repair-associated mediators, despite individual p-values remaining above conventional thresholds, suggests potential biological differences that our study lacked the statistical power to confirm definitively, rather than an absence of real biological distinction.

Similarly, serum VEGF showed a trend towards entity-specific differences ($p = 0.097$), with patients classified as having a Tissue Repair Pattern, based on intermediate PCT levels and clinical phenotypes, displaying higher VEGF levels compared to those with pure SIRS or bacterial infection patterns. VEGF plays essential, multifaceted roles in wound healing and tissue regeneration that extend beyond simple angiogenesis. It stimulates new blood vessel formation, which is vital for providing nutrients and oxygen to healing tissues, increases vascular permeability to facilitate immune cell trafficking and the delivery of plasma proteins necessary for wound healing, recruits circulating endothelial progenitor cells to sites of tissue injury for vascular repair, and exhibits direct cytoprotective effects on epithelial cells (430,431). Post-operative VEGF elevation may indicate activation of these reparative processes rather than pathological inflammation, helping to distinguish patients with appropriate tissue-healing responses from those with pure inflammatory activation without coordinated repair mechanisms.

However, the VEGF finding introduces specific mechanistic uncertainty that needs careful interpretation. The trend towards elevation ($p = 0.097$) contradicts established ARDS literature, which consistently links VEGF depletion with lung injury and associates lower VEGF levels with worse outcomes, longer mechanical ventilation, and higher mortality in acute respiratory distress syndrome (432,433). This apparent paradox requires explanation and suggests either temporal differences in sampling or fundamentally different pathophysiological processes. Our sampling strategy, conducted in the immediate post-operative period (days 1-3), may capture early reparative

angiogenesis that occurs before the development of lung injury, representing a biologically distinct state than the established ARDS measured in most studies at later timepoints (434). Alternatively, postoperative lung injury following elective surgery could reflect a distinct pathophysiology that does not follow the same sequence as ARDS from sepsis, aspiration, or trauma and may instead indicate a more reparative phenotype with greater potential for resolution.

The distinction between proven findings and promising hypotheses is vital for scientific integrity and honest presentation of research findings. The bacterial versus non-bacterial differentiation is confirmed by convergent evidence, including statistically robust procalcitonin discrimination ($p<0.0001$), microbiological validation, distinct clinical outcomes, and mechanistic plausibility. The further subdivision of non-bacterial processes into SIRS and Tissue Repair patterns is a biologically plausible hypothesis supported by preliminary biomarker trends showing consistent direction across multiple related mediators, clinically recognisable phenotypes that experienced clinicians can distinguish at the bedside, and mechanistic reasoning grounded in established immunobiology---but this subdivision requires validation in larger studies with adequate statistical power before acceptance as established biological entities (435,436).

6.2 The Clinical Translation: From Biological Discovery to Precision Medicine

6.2.1 Why Syndrome-Based Diagnosis Cannot Succeed

Approximately 65% of patients currently receive antibiotics for non-bacterial inflammatory processes because syndrome-based diagnoses cannot distinguish biological entities that produce overlapping clinical presentations through related immunological mechanisms (437). This is not a problem of refinement that could be solved through improved criteria, enhanced training, or better diagnostic protocols - no amount of improved clinical criteria can overcome this limitation because the issue is conceptual and biological rather than methodological or educational. The moderate inter-observer agreement ($\kappa = 0.270$) among experienced specialists in thoracic surgery, intensive care medicine, pulmonology, and radiology represents the ceiling of syndrome-based diagnosis, not an inadequate implementation of otherwise sound diagnostic frameworks (438,439).

The inter-observer study systematically documented this ceiling through rigorous evaluation. When specialists reviewed identical clinical information with explicit diagnostic criteria derived from published guidelines---including temperature curves showing temporal patterns, white blood cell trends with differential counts, progressive oxygen requirements documented through titrating FiO_2, inflammatory markers including CRP and other acute phase reactants, and serial chest radiographs demonstrating evolution of infiltrates---their disagreement persisted across all clinical scenarios despite optimal information provision (440). Agreement patterns revealed important insights: agreement was highest when recognising normal post-operative appearances without pathological inflammation ($\kappa = 0.445$), indicating that specialists could reliably identify patients without complications when clinical signals clearly indicated normalcy. Agreement was moderate when definitive pneumonic changes were identified with obvious clinical deterioration, positive cultures, and progressive radiographic infiltrates ($\kappa = 0.315$), but even in these apparently clear cases, one-third of assessments showed disagreement. Agreement was poorest in diagnostically uncertain cases in which clinical features suggested possible pneumonia without definitive confirmation ($\kappa = 0.189$) — precisely the scenarios where clinical decision-making has the most significant impact on antibiotic prescribing and where the biological distinction between bacterial infection and sterile inflammation matters most for therapeutic outcomes.

This diagnostic disagreement becomes biologically understandable when viewed as an appropriate recognition of genuine biological uncertainty rather than as a diagnostic failure reflecting inadequate clinical skills or imprecise criteria. Syndrome-based criteria cannot reliably distinguish bacterial infection from DAMP-driven inflammation because these fundamentally different biological entities produce overlapping clinical signs via related yet distinct immunological pathways that converge on similar clinical endpoints. Both cause fever via cytokine-mediated hypothalamic responses, primarily through the effects of IL-1β and IL-6 on prostaglandin E2 synthesis in the preoptic area, rendering fever a sensitive but non-specific marker that cannot distinguish causation (441). Both cause leucocytosis through bone marrow stimulation and the demargination of white cells from vascular walls, mediated by G-CSF release, catecholamine surges and corticosteroid responses, resulting in similar white blood cell elevations regardless of whether the trigger is bacterial infection or surgical trauma (442). Both generate

radiographic infiltrates through increased vascular permeability, driven by endothelial activation and by inflammatory mediators affecting tight junctions, resulting in alveolar filling and interstitial oedema that appear identical on imaging, whether caused by bacterial invasion or sterile inflammation. The clinical manifestations represent common inflammatory endpoints that multiple distinct pathophysiological processes can produce, making discrimination impossible through clinical or radiographic features alone.

6.2.2 The Two-Stage Precision Framework: Universal Stratification and Targeted Discrimination

The proposed clinical framework addresses syndrome-based diagnostic failures by sequentially employing complementary strategies that leverage the strengths of physiological assessment and targeted biomarker discrimination, while avoiding the pitfalls of directly classifying aetiology using syndrome-based criteria.

Stage 1: Universal Risk Stratification Through the Trimodal Score

The trimodal scoring system, which combines three routine clinical parameters---the CRP/albumin ratio, maximum FiO_2 requirement, and PaO_2/FiO_2 ratio achieves excellent prognostic accuracy (AUC 0.926, 95% CI: 0.884-0.968) with a sensitivity of 81.1% and a specificity of 93.9% for identifying patients who will develop post-operative pneumonia requiring therapeutic intervention (443,444). The system provides clinically meaningful risk stratification with clear separation between groups: patients scoring 0-1 had pneumonia rates of only 3.5%, enabling confident application of standard post-operative care guidelines without intensive monitoring or empirical antibiotics, while those scoring 2-3 developed pneumonia in 90.9% of cases, justifying the use of concentrated resources and heightened surveillance---a 26-fold difference that allows confident risk-based care allocation without the need for complex biomarker tests or costly diagnostic procedures.

The score's success lies in shifting away from aetiological classification towards physiological assessment, focusing on how severely ill the patient is becoming instead of identifying specific disease processes (445). This biological neutrality proves

beneficial rather than restrictive, especially when diagnostic reliability for etiological distinctions is low, as our inter-observer data show. Instead of differentiating inflammatory types—such as bacterial versus sterile, focal versus systemic, or pathological versus reparative — the trimodal score evaluates the degree of physiological disturbance, regardless of the underlying cause. Each element reflects the inflammatory load and physiological dysfunction common to all pathophysiological states requiring clinical intervention.

The CRP/albumin ratio detects systemic inflammation independently of the trigger mechanism by complementing assessment of the magnitude of the acute-phase response (CRP elevation) and of inflammatory consumption or suppressed synthesis (albumin depression) (446,447). CRP rises rapidly in response to IL-6 stimulation, whether that IL-6 release results from bacterial infection, surgical trauma or tissue injury, providing a sensitive but non-specific marker of inflammatory activation. Albumin decreases during acute-phase responses through multiple mechanisms, including decreased hepatic synthesis as the liver prioritises production of acute-phase reactants, increased vascular leak, allowing albumin to distribute into extravascular spaces, and increased catabolism during inflammatory states. The ratio approach offers additional value specific to the post-surgical context by accounting for the predictable hypoalbuminaemia following major surgery, normalising CRP elevation relative to the expected acute-phase response, and enhancing differentiation between anticipated post-operative inflammation and pathological inflammatory complications. The ratio achieved an individual AUC of 0.847 in our validation set, demonstrating that this single parameter derived from routine laboratory tests captures substantial prognostic information while remaining completely agnostic to inflammatory aetiology.

Maximum FiO_2 requirement indicates the severity of respiratory dysfunction regardless of the underlying cause, capturing early deterioration before overt respiratory failure occurs (448). Whether oxygen needs increase due to bacterial pneumonia causing alveolar consolidation and shunt, DAMP-driven inflammation resulting in interstitial oedema and V/Q mismatch, or tissue repair processes heightening vascular permeability and hindering gas exchange, the clinical endpoint - hypoxaemia requiring supplemental oxygen---remains the same and necessitates clinical intervention. This parameter is especially valuable because it serves as an early marker of respiratory compromise that

experienced clinicians can recognise and measure easily, often rising significantly before arterial blood gas analysis shows overt hypoxaemia or chest radiographs reveal conspicuous infiltrates. Clinicians boost FiO_2 in response to trends in oxygen saturation, work of breathing and clinical assessments of respiratory distress, integrating multiple physiological signals into a single actionable parameter that the scoring system assesses objectively.

The PaO_2/FiO_2 ratio offers a standardised way to assess the efficiency of gas exchange across all pulmonary conditions, addressing a key physiological question regardless of cause: given the amount of oxygen provided (FiO_2), how much reaches the arterial blood (PaO_2)? (449) Impaired gas exchange suggests ventilation-perfusion mismatch, diffusion limitation, or shunt - pathophysiological disturbances that occur whether the underlying issue involves bacterial infection, sterile inflammation, or tissue injury and require therapeutic support irrespective of the specific trigger. The ratio normalises arterial oxygenation against inspired oxygen concentration, allowing comparison among patients receiving varying levels of respiratory support and providing an objective measure of gas exchange that correlates with clinical outcomes.

Together, these three parameters systematically capture the inflammatory burden, respiratory dysfunction, and gas-exchange abnormalities characteristic of serious postoperative pulmonary complications that require clinical intervention, while deliberately avoiding the biological specificity that renders syndrome-based diagnoses ineffective when distinguishing overlapping clinical presentations. The practical impact extends beyond diagnostic accuracy to transform care delivery: the system identifies 85.9% of patients as low risk, enabling standard post-operative care with early mobilisation, graduated oral intake and enhanced recovery protocols without the resource-intensive surveillance, frequent radiography and empirical antibiotic therapy that current undifferentiated approaches apply to all post-oesophagectomy patients regardless of individual risk (450). This risk-based allocation frees nursing time for patients who genuinely require intensive assessment, reduces unnecessary investigations and their associated costs, and enables appropriate ward-based care for the vast majority who will not develop serious complications requiring escalated intervention.

6.3.0 Stage 2: Targeted Biological Discrimination for High-Risk Patients

For the 14.1% of patients identified as high-risk through trimodal scoring---those whose physiological derangement indicates serious complications requiring intensive investigation---procalcitonin-guided classification provides the biological differentiation needed for informed therapeutic decisions (451,452). This stage addresses the most clinically significant question with direct therapeutic consequences: Does this patient need antibiotics, or will antibiotics be ineffective, cause unnecessary toxicity, and promote antimicrobial resistance? The simple binary decision—bacterial infection versus non-bacterial inflammation — directly informs this choice using the established PCT threshold of 1.0 ng/mL, a cut-point validated across multiple studies in various populations and shown to balance sensitivity for detecting bacterial infections with specificity to avoid treating sterile inflammatory states (453,454).

PCT levels greater than 1.0 ng/mL typically indicate a bacterial infection requiring prompt antibiotic therapy targeting enteric organisms, which are common in post-oesophagectomy infections, rather than the respiratory pathogens targeted by community-acquired pneumonia protocols. Antibiotic choice should focus on gram-negative coverage with agents such as third-generation cephalosporins (ceftriaxone, cefotaxime) or fluoroquinolones (levofloxacin, moxifloxacin), possibly including anaerobic coverage if aspiration is suspected, rather than atypical coverage (macrolides) or pneumococcal-focused therapy used in traditional pneumonia protocols. This focused approach allows for appropriate antimicrobial coverage of probable pathogens, while avoiding overly broad-spectrum regimens that can promote resistance without improving patient outcomes.

Patients with PCT ≤1.0 ng/mL exhibit non-bacterial inflammatory processes for which antibiotics provide no therapeutic benefit, necessitating supportive care rather than antimicrobial therapy. These patients showing low procalcitonin despite presenting with fever often exceeding 38.5°C, leucocytosis frequently reaching 15,000-20,000/μL, radiographic infiltrates on chest imaging and clinical deterioration manifest all the syndrome-based features traditionally triggering antibiotic prescribing---yet their low procalcitonin levels indicate inflammatory responses driven by surgical DAMPs rather than bacterial PAMPs, representing sterile inflammation that will not respond to antimicrobial therapy and requires only supportive management including adequate

oxygenation to maintain tissue perfusion, appropriate fluid management balancing resuscitation needs against pulmonary oedema risk, pulmonary physiotherapy facilitating secretion clearance and preventing atelectasis, and adequate analgesia enabling deep breathing and effective cough (455). The economic implications extend beyond direct antibiotic costs to encompass substantial indirect savings from reduced antimicrobial resistance, shorter hospital stays by avoiding antibiotic-associated complications, and decreased resource utilisation from better-targeted care allocation. Risk-stratified monitoring enabled by the two-stage framework could reduce routine chest radiography by approximately 60% by concentrating imaging on high-risk patients where findings will change management, decrease unnecessary laboratory testing by similar proportions through elimination of routine surveillance in low-risk patients, and enable appropriate ICU bed allocation by identifying which patients genuinely require critical care monitoring versus those manageable safely on surgical wards - freeing limited critical care capacity for patients requiring intensive support while reducing costs for low-risk patients.

6.3.1 Implications for Evidence-Based Practice and Intervention Research

The finding that only 14.3% of pneumonia studies use validated diagnostic criteria reveals implications for evidence-based medicine that extend well beyond post-oesophagectomy care, challenging fundamental assumptions about outcome reliability in surgical intervention research (457,458). When systematic reviews indicate that the vast majority of studies measure outcomes inconsistently, yet these data inform clinical guidelines that determine the standard of care, quality metrics that evaluate institutional performance, and funding decisions that allocate research resources, the hierarchy of evidence becomes scientifically incoherent. Intervention trials cannot produce meaningful results when the outcomes being measured represent biologically heterogeneous constructs applied inconsistently across and within studies; yet current meta-analyses proceed as if outcome measurement were reliable and comparable (459).

Future trials should not proceed on the assumption of diagnostic reliability; rather, they must incorporate biological stratification into trial design from inception, fundamentally reconceptualising how surgical intervention research is conducted. Three approaches merit consideration, each with distinct strengths: trials could stratify randomisation by biological entity using procalcitonin classification at enrolment, ensuring that

comparisons occur within biologically homogeneous groups and enabling detection of entity-specific treatment effects; alternatively, trials could use biomarker-guided protocols as the intervention itself, directly testing whether biological precision improves outcomes compared to syndrome-based empirical care; or trials could employ composite outcomes using physiological endpoints robust to diagnostic heterogeneity, measuring what matters to patients - organ function, support requirements, recovery trajectories - rather than syndrome-based classifications that may not represent coherent biological entities.

6.4 The Methodological Contribution: When Disagreement Signals Discovery

The research progression illustrates a transferable methodological framework that applies well beyond post-oesophagectomy pneumonia to any clinical scenario where diagnostic disagreement persists despite clear criteria and experienced clinicians (460). This four-study sequence - systematic review documenting definitional chaos across published literature, inter-observer study quantifying clinical disagreement among specialists examining identical information, development of a trimodal score, and biomarker analysis validating biological heterogeneity explaining the observed disagreement - built a cumulative body of evidence indicating that diagnostic unreliability reflects genuine biological complexity rather than methodological failure that requires standardisation or additional training. This framework offers a systematic approach for investigating whether diagnostic disagreement results from inadequate implementation of sound frameworks or from an appropriate recognition that current constructs do not adequately represent the underlying biology.

The systematic review began as a conventional evidence synthesis aimed at meta-analysing intervention effectiveness. Still, it revealed an unexpected and methodologically important finding: only 14.3% of included studies used validated diagnostic criteria, and pneumonia incidence varied 10-40% across similar populations receiving similar interventions in similar healthcare systems. The usual culprits - differences in surgical technique, variations in perioperative care protocols, or disparities in patient populations could not explain this extreme heterogeneity, as these factors were relatively similar across studies. Instead, the heterogeneity arose from

outcome measurement, with each investigator applying different pneumonia definitions that inadvertently selected for different biological processes. The 30-40% microbiological confirmation rate documented consistently across studies from diverse geographical regions and healthcare systems was particularly revealing: when most cases clinically diagnosed as "pneumonia" lack bacterial cultures supporting infectious aetiology, this suggests either that diagnostic criteria are too sensitive (false positives exceeding true infections) or that most post-operative pulmonary complications represent non-infectious processes. This finding transforms from a methodological limitation requiring correction to a biological signal demanding investigation (461).

The inter-observer study quantified systematically what the systematic review suggested indirectly: specialists achieved only fair agreement ($\kappa = 0.270$) despite examining identical information with explicit criteria and adequate clinical experience. Critically, disagreement was not random variation but rather exhibited systematic patterns, revealing how different specialities weighted information according to their clinical frameworks and expertise. Surgeons emphasised clinical trajectory and response to interventions, recognising that some patients improve rapidly without antibiotics, suggesting sterile inflammation, while others deteriorate despite supportive care, indicating bacterial infection. Intensivists prioritised physiological parameters and organ dysfunction, focusing on gas exchange, haemodynamic, and trends in inflammatory markers as indicators of process severity. Radiologists focused on imaging characteristics, including infiltrate patterns, distribution and evolution over time, attempting to distinguish infectious consolidation from inflammatory oedema or atelectasis. Each perspective captured valid biological information about different aspects of the clinical presentation. However, syndrome-based frameworks provided no mechanism for integrating these complementary assessments or for recognising that specialists might be detecting different but equally fundamental biological processes. The "maybe" category, showing the poorest agreement ($\kappa = 0.189$), represented cases in which standard criteria provided insufficient information to distinguish bacterial from sterile inflammation---precisely the biological distinction that subsequent biomarker analysis would validate as real and clinically significant (462).

The biomarker study confirmed that disagreement reflected genuine biological heterogeneity rather than inadequate clinical assessment. PCT distinguished bacterial

from non-bacterial processes with high statistical confidence ($p<0.0001$), providing objective confirmation that the biological distinction clinicians aimed to identify through pattern recognition was real and measurable. This explained why experienced clinicians examining identical clinical presentations reached different diagnostic conclusions - they detected genuine biological differences through subtle clinical cues that formal syndrome-based criteria could not reliably capture. Some patients exhibited clinical trajectories characteristic of resolving sterile inflammation: high fever and leucocytosis that peak early, then improve rapidly; minimal oxygen requirements despite elevated inflammatory markers; and radiographic changes that remain stable or improve without antibiotics. Others showed patterns suggesting bacterial infection: progressive clinical deterioration despite supportive care, escalating oxygen needs, radiographic infiltrates that expand despite adequate physiotherapy and pulmonary toilet. Clinicians recognised these distinctions through pattern recognition developed over years of experience. However, syndrome-based criteria that measured only fever magnitude, leucocyte count, and the presence of an infiltrate could not systematically capture the temporal dynamics and clinical trajectories that differentiated these processes (462,463).

The bilateral cytokine symmetry documented in the biomarker study showed that complications are systemic rather than focal processes, fundamentally challenging traditional pneumonia paradigms that assume focal lung infection as the main cause. The negative cytokine findings - no statistically significant differences among proposed entities for most mediators are just as scientifically important as positive results because they define the current limits of biological characterisation and honestly highlight that hypothesised subdivisions within non-bacterial processes need validation rather than being accepted as proven.

The central methodological insight applicable across clinical medicine is that persistent disagreement among experienced clinicians examining identical information should trigger biological investigation rather than renewed efforts at standardisation through more explicit criteria or enhanced training. The traditional response to poor inter-observer reliability---clarifying diagnostic criteria, providing additional training, developing decision algorithms, implementing quality improvement initiatives assumes disagreement reflects inadequate implementation of conceptually sound diagnostic

frameworks. This approach is practical when constructs are biologically coherent, but its application is inconsistent due to training gaps, unclear criteria, or variable adherence to standards. It fails when constructs themselves inadequately represent underlying biology, when single diagnostic labels encompass multiple distinct biological processes, or when clinical presentations result from overlapping mechanisms that cannot be reliably distinguished through available clinical and radiographic features. In these situations, forcing diagnostic consistency through standardisation may suppress rather than enhance diagnostic accuracy by eliminating the appropriate recognition of biological uncertainty (463).

Several features distinguish biologically meaningful disagreement, which requires investigation, from methodological inadequacy that necessitates standardisation. First, persistence despite optimal conditions: disagreement that remains when experienced clinicians examine complete information using explicit criteria suggests the diagnostic framework itself merits investigation. Second, systematic patterns: disagreement that follows speciality-specific patterns rather than random variation indicates that clinicians are identifying different aspects of biological complexity through their distinct clinical perspectives. Third, concentration where it matters: the highest disagreement in clinically important scenarios where therapeutic decisions depend on accurate classification suggests clinicians recognise genuine uncertainty about the underlying biology. Fourth, low confirmatory testing rates: when gold-standard tests confirm the diagnosis in only a minority of cases that meet clinical criteria, this indicates that syndrome-based criteria select for heterogeneous populations rather than coherent disease entities.

This methodological framework applies directly to other surgical complications that show similar diagnostic unreliability. Acute kidney injury following surgery exhibits poor inter-observer reliability in distinguishing pre-renal azotaemia, acute tubular necrosis, and inflammatory kidney injury conditions that require different management but cause similar increases in creatinine. Surgical site infections include bacterial infections needing antibiotics, sterile inflammatory responses to foreign material that need only local care, and haematomas that require drainage - all of which produce wound erythema, pain, and drainage. Anastomotic leaks comprise contained collections that can be managed conservatively versus free perforations that need urgent

reoperation, although early signs often overlap. Each is a syndrome-based diagnosis with documented reliability issues, potentially reflecting biological heterogeneity that could be systematically investigated using the framework established here.

6.5 Future Research Directions

Immediate priorities include prospective trials comparing PCT-guided binary protocols with syndrome-based care, focusing on co-primary outcomes of antibiotic exposure and safety. External validation across diverse centres, surgical approaches, and populations is crucial before wide-scale implementation.

Biological characterisation remains incomplete. Borderline significance for VEGF ($p=0.097$) and regulatory cytokines ($p=0.075$-0.083) suggests that larger studies with expanded panels and different time points might confirm differences that our study lacked the power to detect. Sequential sampling could clarify whether VEGF dynamics distinguish repair from inflammatory phenotypes. If additional entities are validated, entity-specific therapeutic trials become justified. Implementation science should identify optimal translation strategies, including mandatory biomarker protocols versus decision support, point-of-care versus laboratory testing, and immediate versus graduated adoption. Understanding barriers and effective strategies is essential for widespread adoption. Methodological extension to other complications is a high-priority research area. The framework---reliability assessment revealing heterogeneity, biomarker validation, pragmatic score development---applies to acute kidney injury, surgical site infections, anastomotic complications, and delayed gastric emptying. Each has documented reliability problems that may reflect unrecognised heterogeneity.

6.6 Limitations and Critical Assessment

The central limitation requires explicit acknowledgement: we proposed three entities but validated two. The PCT-based bacterial versus non-bacterial distinction is robust and validated by convergent evidence ($p<0.0001$; microbiology, outcomes). Further subdivision into SIRS and Tissue Repair entities remains a hypothesis rather than a fact. Comprehensive cytokine analysis found no significant differences among the three

proposed entities for any of 15 mediators, though borderline trends (p=0.075-0.097) suggest potential differences requiring larger studies.

This highlights common challenges in translational research: clinical pattern recognition indicates complexity that available biomarkers cannot fully characterise. Instead of overclaiming, we recognise that clinicians may detect differences our measurements cannot capture. The Tissue Repair entity presents particular uncertainty—VEGF showed only a trend (p=0.097), and contradictions with ARDS literature suggest either temporal differences or distinct pathophysiology. This mechanistic ambiguity limits therapeutic implications until validation clarifies the biological nature of this entity.

Single-centre design limits generalisability while enabling methodological precision essential for biological discovery. Uniform technique, consistent protocols and standardised sampling eliminated confounding that multi-centre approaches would introduce. However, external validation across diverse settings remains paramount.

Post-hoc entity classification raises concerns about overfitting. Although several strategies—such as PCT discrimination, bilateral correlations, microbiological alignment, and mechanistic plausibility—support the findings, prospective validation with predefined thresholds is essential to confirm that the binary classification genuinely reflects biological reality rather than being an artefact. In particular, classification involving three entities requires prospective confirmation.

6.7 Conclusion: Biological Precision as Achievable Goal

This thesis demonstrates that post-operative pneumonia involves at least two distinct processes—bacterial infection and sterile inflammation—that require fundamentally different treatments. Syndrome-based classification obscures this distinction, resulting in diagnostic unreliability ($\kappa = 0.270$), which reflects genuine heterogeneity rather than poor performance. The 30% microbiological confirmation rate and consistent disagreement patterns confirm that most complications arise from non-infectious lung injury, countering traditional infection-focused paradigms.

The practical contribution operates on several levels. Clinically, the two-stage framework—universal stratification via trimodal score (AUC 0.926) plus PCT-guided binary classification for high-risk patients—enables an immediate shift from empirical

protocols to biologically-guided therapy. This can reduce inappropriate antibiotic exposure in about 65% of patients while focusing intensive monitoring on 14.1% at genuine high risk. The framework succeeds through biological agnosticism (the trimodal score measures derangement regardless of aetiology) combined with targeted discrimination (PCT differentiates bacterial from non-bacterial), demonstrating that precision medicine does not require genetic profiling or complex diagnostics. Scientific contribution, the research establishes biological foundations for meaningful intervention studies that were previously impossible under syndrome frameworks. Since only 14.3% of studies use validated criteria but inform guidelines, trials cannot produce clear results because they assess heterogeneous constructs. Future research should classify cases as bacterial versus non-bacterial, test biomarker-guided protocols as interventions, or evaluate physiological outcomes that are robust to variability. The bilateral cytokine symmetry ($r > 0.96$) indicates systemic rather than focal processes, explaining why traditional paradigms fail and why interventions targeting focal infections often produce inconsistent effects.

Methodologically, this thesis offers transferable frameworks: when experienced clinicians persistently disagree despite clear criteria, this should prompt biological investigation rather than further standardisation. The three-study progression shows how apparent methodological issues transform into scientific opportunities when diagnostic unreliability is viewed as biological information. Validating clinical expertise as biological detection challenges assumptions in evidence-based medicine that strict protocol adherence invariably improves outcomes, demonstrating that when constructs do not adequately represent heterogeneity, clinical pattern recognition may achieve better accuracy.

What remains uncertain requires clear acknowledgment. While the distinction between bacterial and non-bacterial causes is established, whether non-bacterial cases can be further divided into SIRS and Tissue Repair remains a hypothesis needing validation. Borderline cytokine trends suggest added complexity that our study lacked the statistical power to confirm. VEGF findings contradict ARDS literature, indicating either differences in timing of sampling or distinct pathophysiology that require clarification. The single-centre design limits generalisability, and post-hoc classification raises

concerns of overfitting, highlighting the need for prospective validation with predefined thresholds.

The importance lies in showing that surgical medicine can reach biological precision through mechanistic understanding—distinguishing DAMP from PAMP activation, recognising systemic versus focal processes, and identifying appropriate versus pathological responses—and applying this through routine parameters and established biomarkers. This positions surgical critical care as a cutting-edge field of precision medicine, where controlled inflammatory responses to standardised interventions allow biological characterisation, even though full characterisation remains a work in progress.

In establishing what we know (binary distinction enabling rational stewardship, systemic processes requiring different paradigms, prognostic tools succeeding through biological agnosticism) and recognising what remains uncertain (further heterogeneity within non-bacterial processes, optimal entity-specific therapies, generalisability), this thesis provides both practical tools for immediate application and conceptual frameworks for continued investigation. The journey from diagnostic chaos to partial biological clarity demonstrates that established constructs require empirical validation, clinical disagreement can signal biological insight, and diagnostic precision emerges from mechanistic understanding rather than refined syndrome definitions—principles applicable far beyond post-oesophagectomy pneumonia to surgical complications generally.

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Appendix 1:

Diseases of the Esophagus (2022), 00, 1–11
https://doi.org/10.1093/dote/doac017

DISEASES OF THE ESOPHAGUS

ISDE The International Society for Diseases of the Esophagus

Systematic Review and Meta-analysis

Interventions targeting postoperative pulmonary complications (PPCs) in patients undergoing esophageal cancer surgery: a systematic review of randomized clinical trials and narrative discussion

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SUMMARY. **Postoperative pulmonary complications (PPCs) represent the most common complications after esophageal cancer surgery. The lack of a uniform reporting nomenclature and a severity classification has hampered consistency of research in this area, including the study of interventions targeting prevention and treatment of PPCs. This systematic review focused on RCTs of clinical interventions used to minimize the impact of PPCs. Searches were conducted up to 08/02/2021 on MEDLINE (OVID), CINAHL, Embase, Web of Science, and the COCHRANE library for RCTs and reported in accordance with PRISMA guidelines. A total of 339 citations, with a pooled dataset of 1,369 patients and 14 RCTs, were included. Heterogeneity of study design and outcomes prevented meta-analysis. PPCs are multi-faceted and not fully understood with respect to etiology. The review highlights the paucity of high-quality evidence for best practice in the management of PPCs. Further research in the area of intraoperative interventions and early postoperative ERAS standards is required. A consistent uniform for definition of pneumonia after esophagectomy and the development of a severity scale appears warranted to inform further RCTs and guidelines.**

KEY WORDS: **ARDS and esophagectomy, pneumonia, PPCs, respiratory failure.**

INTRODUCTION

Postoperative pulmonary complications (PPCs) are defined as any type of respiratory compromise occurring within 30 days following general anesthesia and surgery.[1] They are inconsistently defined and include a spectrum from atelectasis through to pneumonia and respiratory failure and acute respiratory distress syndrome (ARDS).[2] There are numerous definitions for pneumonia, for instance, highlighting the complexity of studying this theme and the lack of consistency across studies (Table 1). A composite definition may have greatest rationale, as suggested in 2015 by a Joint European taskforce published guidelines on perioperative clinical outcome.[1,3] Risk factors for PPCs include neoadjuvant therapy, in particular combination radiation therapy and chemotherapy (nCRT), age, and respiratory co-morbidities, COPD, and interstitial lung disease.[4–9] Despite major improvements in operative mortality, between 1% and 5% in high-volume centers, PPCs remain prevalent, at between 20% and 40%, despite major advances in surgery, anesthesia, and perioperative care, including the development of minimally invasive and robotic-assisted approaches.[10–16]

The objective of this systematic review was primarily to evaluate the high-quality (Level I) evidence from RCTs that have addressed the prevention or management of PPCs in the surgical management of esophageal cancer. Some relevant cohort studies, not RCTs and hence excluded from the systematic review, were included in the overall narrative discussion.

METHODS

The study was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA, Fig. 1). The protocol for this systematic review was prospectively registered on PROSPERO (ref: 233786). Due to a lack of explicit definitions used in pneumonia, and the lack

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Table 1 List of available pneumonia screening tools

CDC	ATS	CPIS	Utrecht	PPC (standardized end points)
2 or more serial radiographs with at *least 1* of the following: • New or progressive infiltrate • Consolidation • Cavitation • **1 of the following:** • Fever • Leukopenia or leukocytosis • adults over 70 years of age in an altered mental status with no other cause identified. • **At least 2 of the following:** • Increased sputum load; change in characteristic/color • New onset cough, dyspnea or tachypnea. • Rales or bronchial breath sounds. • Worsening gaseous exchange. Increased oxygen or ventilator demand or a worsening Pa02/Fio2 </= 240.	The diagnosis of HAP is suspected if: • the patient has a radiographic infiltrate that is new or progressive, *along with clinical findings suggesting infection which includes:* • the new onset of fever, • purulent sputum, • leukocytosis, and • decline in oxygenation. HAP is defined as a pneumonia not incubating at the time of hospital admission and occurring 48 hours or more after admission. VAP is defined as a pppppppja ppppppng >48 hours after endotracheal intubation."	**Temperature (in degree Celsius):** <36.5/>38.4 = 0 points >38.5/<38.9 = 1 point >39.0 = 2 points <36 = 2 points **WBC in mm/3:** >40,000/<11,000 = 0 points <4,000/> 11,000 = 1 point <4,000/>11,000 with >500 bands = 2 points **Tracheal secretions (0–4 summed quantified in 24 hours)** >240 or ARDS = 0 point <240 or NO ARDS = 1 point **Chest x-ray** No Infiltrate = 0 points Patchy/diffuse infiltrates = 1 point Distinct infiltrate = 2 points **Quantitative pathogenic bacterial growth culture from tracheal aspirate:** <1+ no growth = 0 points >1+ = 1 point >1+ and same gram strain bacteria **0–6 pts pneumonia less likely** **7–12 pts pneumonia likely**	**Temperature (degrees Celsius):** >36.1 and <38.4 = 0 points >38.5 and <38.9 = 1 point >39 and <36 = 2 points **Leukocyte count:** >4 and <11 = 0 points <4 or >11 = 1 point **Pulmonary Radiography** No infiltrate = 0 points Patchy or diffuse infiltrate = 1 point Well circumscribed infiltrate = 2 points. **A sum of 2 points in which at least 1 is assigned to pulmonary radiography indicates treatment of pneumonia.**	Mechanism composite of respiratory diagnoses that share common pathophysiological mechanisms including pulmonary collapse and airway contamination (i) atelectasis on film (ii) pneumonia CDC criteria (iii) ARDS Berlin definition (iv) pulmonary aspiration **Clear clinical history AND radiological evidence. Severity None:** planned use of supplemental oxygen or mechanical respiratory support as part of routine care. **Mild:** therapeutic supplemental oxygen Fio2 < 0.6 **Moderate:** Fio2 > 0.6 or HFNP **Severe:** unplanned CPAP, NIV or intubation.

of validated screening tools, we also included studies that did not provide a definition.

Search strategy

A comprehensive search was conducted in MEDLINE (OVID), CINAHL, Embase, Web of Science, and the COCHRANE library for RCTs on 08/02/2021 evaluating the interventions and management of PPCs after esophageal cancer surgery that were tested within RCTs. It was restricted to studies in English, human studies only, and studies/trials from 2,000 onward. All references were exported to Reference Management software Endnote 20, and duplicates were removed prior to exporting to Covidence. Additional gray literature was hand-searched for additional studies. Cohort studies, small RCTs ($n < 10$), abstracts, commentaries, and editorials were excluded.

Screening and article selection

Two independent authors (A.M.D. and N.D.) reviewed the titles and abstracts to identify relevant studies. Full-text manuscripts were assessed independently by two reviewers (A.M.D. and G.L.) against predefined inclusion criteria. A third reviewer was available to discuss any disputes among papers for inclusion. Data were extracted using the Covidence systematic review manager using a standardized proforma. Meta-analysis of the data was not possible due to heterogeneity in subjects, study design, management strategies, and clinical endpoints. Therefore, the extracted data are presented as a qualitative synthesis. The Cochrane Risk of Bias tool was utilized for quality assessment. The trials are shown in Table 2, and their quality assessment and bias assessment in Figure 2.

RESULTS

Of 339 citations identified from the electronic search, 14 RCTs were included with a pooled dataset of 1,369 patients (Fig. 1). An inappropriate study design was the most common reason for exclusion. Specific key

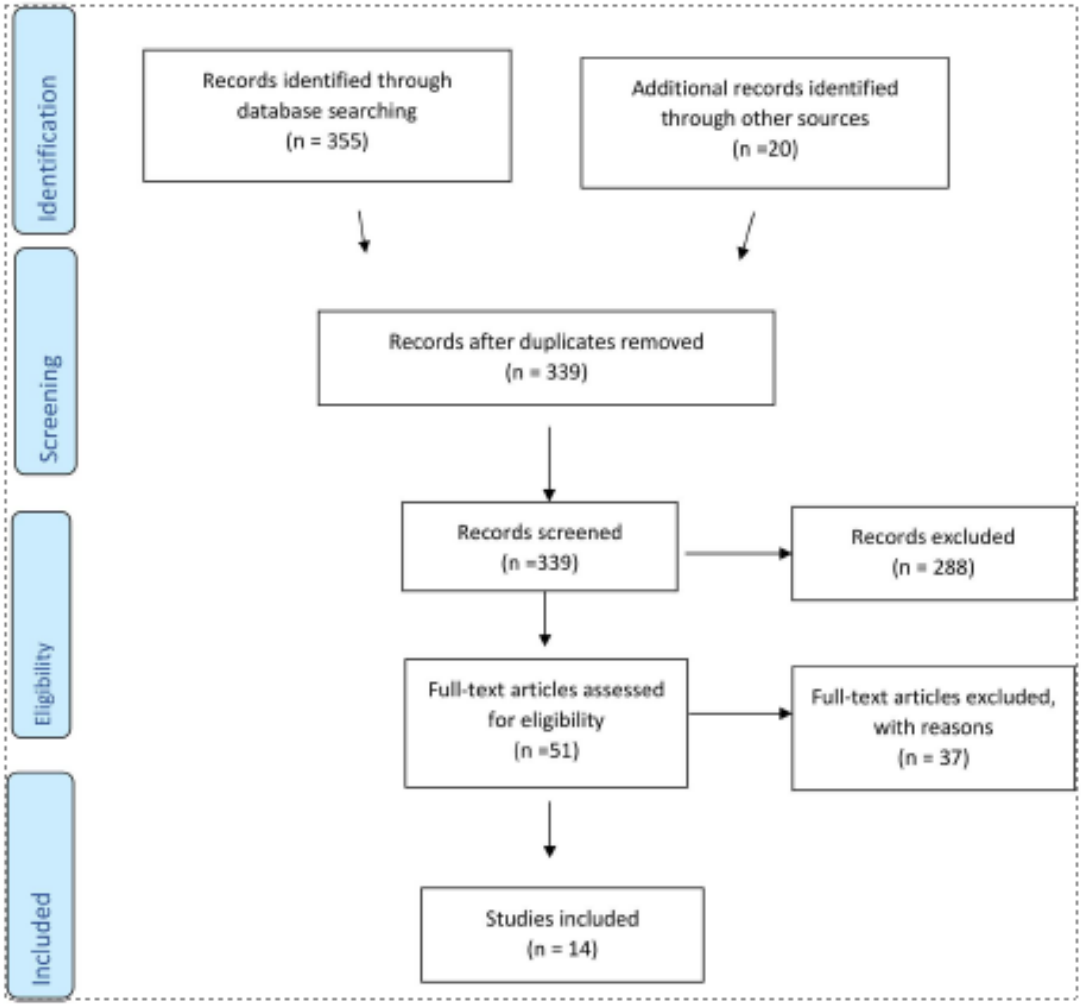

Fig. 1 PRISMA flowchart for entire study

questions addressed in these RCTs are discussed separately, as follows:

I: Preoperative Interventions

Several RCTs and meta-analyses have demonstrated improved survival with neo-adjunct treatment and surgery compared with surgery alone.[17,18] The CROSS trial regimen (carboplatin/paclitaxel/41.4Gy) and the FLOT regimen (Docetaxel, Fluorouracil, Leucovorin, Oxaliplatin) are modern standard bearers for nCRT in trimodality therapy and perioperative chemotherapy, respectively. An added postoperative respiratory risk of nCRT regimens, in particular for severe PPCs, and mortality, although not evident in the CROSS trial, is suggested by other RCTs.[4,19–24] Conversely, a recent systematic review and meta-analysis reported no significant differences in PPCs between the trimodality and perioperative chemotherapy cohorts (relative risk [RR] = 1.24; 95% confidence interval [CI] = 0.96–1.62; $P = 0.102$, respectively).[25] Radiation dose may be important, with a dose >50Gy, often used in curative trimodality regimens in North America, potentially increasing the risk of pneumonitis and fibrosis.[26,27] More subtle physiological impact may also occur, with a reduced pulmonary diffusion capacity (DLCO)[24,28,29] evident in several reports, but whether this clinically impacts on PPC risk, or is a subclinical effect, is unclear. A further dimension is whether radiation impacts on airway colonization. Bagheri *et al.*[30] conducted a low risk of bias trial where RT, at 40Gy, and this was associated with positive cultures ($P = 0.041$); however, there was no association with pneumonia.

In a study of pneumonia from this Center, 'pneumonia' as defined by CDC criteria (Table 1) in patients on trimodality therapy was predominantly culture negative, at 77%, compared with 60% in patients who had perioperative chemotherapy, and just 27% in patients having surgery alone

Table 2 Characteristics of included RCTs

Author and year	Country (lead in multisite RCTs)	Design	Title	Number
Schaefer 2004[68]	Germany	RCT (multicenter)	Perioperative granulocyte colony-stimulating factor does not prevent severe infections in patients undergoing esophagectomy for esophageal cancer: a randomized placebo-controlled clinical trial	127
Bagheri 2011[30]	Iran	RCT	The effect of neoadjuvant chemoradiotherapy on airway colonization and postoperative respiratory complications in the patients undergoing esophagectomy for esophageal cancer	40
Yamaguchi 2011[69]	Japan	RCT	Effects of sivelestat on bronchial inflammatory responses after esophagectomy	24
Shen 2013[58]	China	RCT	The impact of tidal volume on pulmonary complications following minimally invasive esophagectomy: a randomized and controlled study	101
Wakabayashi 2014[70]	Japan	RCT	Effects of anesthesia with sevoflurane and propofol on the cytokine/chemokine production at the airway epithelium during esophagectomy	20
Takesue 2015[71]	Japan	RCT	A prospective randomized trial of enteral nutrition after thoracoscopic esophagectomy for esophageal cancer	47
Yamana 2015[35]	Japan	RCT	Randomized controlled study to evaluate the efficacy of a preoperative respiratory rehabilitation program to prevent PPCs after esophagectomy	60
Biere 2017[59]	Amsterdam	RCT (multicenter)	Predictive factors for post-operative respiratory infections after esophagectomy for esophageal cancer: outcome of randomized trial	107
Bagheri 2018[67]	Iran	RCT	Efficacy of intraoperative corticosteroid to prevent postoperative respiratory complications after transhiatal esophagectomy	60
Valkenet 2018[33]	Amsterdam	RCT-PREPARE trial multicenter	Multicenter randomized clinical trial of IMT versus usual care before surgery for esophageal cancer	241
Yang 2018[31]	China	RCT	Lung protective ventilation strategy reduces the incidence of pulmonary complications after combined thoracoscopic and laparoscopic esophagectomy by inhibiting inflammatory response	157
Hayashi 2019[78]	Japan	RCT	Analysis of the effect of early versus conventional nasogastric tube removal on postoperative complications after transthoracic esophagectomy: a single-center, randomized controlled trial	71
Vandersluis 2019[63]	The Netherlands	RCT	Robot-assisted minimally invasive thoraco-laparoscopic esophagectomy versus open transthoracic esophagectomy for resectable esophageal cancer: a randomized controlled trial	109
Mariette 2019[61]	France	RCT multicenter	Hybrid minimally invasive esophagectomy for esophageal cancer	203

($P = 0.001$).[31] This highlights a spectrum of pathophysiology with an infective source rarely proven, and a trend toward preoperative radiation therapy promoting PPCs possibly through an effect independent of infection risk, more akin to an acute lung injury (ALI). Notwithstanding these controversies, in the most recent completed RCT, Neo-AEGIS, presented at ASCO in 2021,[32] Reynolds *et al*. reported no difference in PPC incidence or severity in patients with adenocarcinoma of the esophagus undergoing either the CROSS regimen or optimum perioperative chemotherapy (MAGIC/FLOT). This suggests that with modern standards of radiation therapy delivery, and surgery, that postoperative PPCs and severity of disease are not significantly increased, and hence avoidance of radiation therapy is not required in an effort to reduce PPCs.

Irrespective of the neoadjuvant regimen, in theory at least, preoperative physiotherapy and inspiratory muscle training (IMT) to optimize respiratory function has a compelling logic to mitigate the impact of esophageal cancer surgery. The PREPARE trial[33] evaluated a preoperative IMT program which had been proven as effective prior to cardiothoracic surgery, and hypothesized that it would increase or maintain lung capacity and function and consequently minimize respiratory problems intra- and postoperatively.[34] The intervention, although resulting in a significant increase in inspiratory muscle strength and endurance capacity, did not however

Fig. 2 List of included studies and potential risk of bias.

lead to a reduction in the rate of postoperative pneumonia. In this systematic review, Yamana *et al.*[35] in a low risk of bias study looked at preop respiratory physiotherapy and reported that in a reduced postoperative Utrecht pneumonia score,[36–38] however, this effect was limited to the first postoperative day. Accordingly, at this point, despite compelling rationale, there are no Level I data supporting IMT prior to esophageal cancer surgery, and high-quality trials are required.

Other modifiable risks preoperatively, including smoking cessation, dental hygiene, and optimization of medical management of COPD and interstitial lung disease, are outside the scope of this review. One intriguing dimension that merits investigation relates to detection and treatment of nasal *Staphylococcus aureus* carriage and occurrence of PPCs.[39,40] In a propensity-matched study after lung but not esophageal cancer resection, screening and treatment for *S. aureus* reduced overall hospital acquired infections ($P = 0.043$), but this was not limited to PPCs.[41]

II: Intraoperative

The anesthetist has a key role in the targeting of optimum outcomes in esophageal surgery, including the prevention of PPCs.[42] Pulmonary inflammation occurs in mechanically ventilated patients, with the degree of inflammation potentially influenced by both ventilator settings and the type of anesthesia.[43–45] Xu *et al.* in an esophageal-focused study ($n = 40$) reported a higher rate of hypoxemia in a cohort where sevoflurane was used, compared with a propofol cohort.[46] Another study did not however establish any difference between propofol and sevoflurane with respect to the development of pneumonia.[47] A 2017 study with OLV and lung resection patients found a greater association with PPCs with propofol compared with sevoflurane, with an increase in 1-year mortality and the lung and systemic pro-inflammatory cytokine response significantly greater in the propofol group.[48] The findings from the APLICS trial, an RCT in cardiac patients comparing propofol and sevoflurane, and utilizing a standardized protective ventilation strategy, are awaited with interest.[44] Specific to esophageal cancer surgery, Wakabayashi *et al.*[49] examined epithelial lining fluid obtained from ventilated-dependent lung as well as collapsed nondependent lung by bronchoscopy and established that propofol suppressed IL-6 and IL-8 production and enhanced IL-10 production compared with sevoflurane. This trial, although with a low risk of bias, was limited by a small sample size; hence, larger well-designed trials are required to validate this novel finding and determine a clinical relevance.

The benefits of lung protection ventilation are well established within the critical care context.[50–53] Notwithstanding, this has not translated at this time to a generalized approach during major surgery, including thoracic and esophageal cancer surgery.[43] The PROVHILO study reported no benefit of lung protective ventilation to reduce the incidence of PPCs.[54] Conversely, a Bayesian network meta-analysis of 34 RCTs with a pooled dataset of 5273 patients with PPCs as a primary outcome concluded that a low tidal volume with mid- to high-level positive

end expiratory pressure (PEEP) was associated with a reduction in PPCs, in particular atelectasis and pneumonia, but not ARDS.[55]

Protective ventilation may reduce the inflammatory response. In a key publication, Michelet *et al.*[56] highlighted that protective ventilation could prevent alterations in lung function as well as limit the cytokine response in otherwise healthy lungs postesophagectomy. This thesis was further explored by Yang *et al.*,[57] who reported that the incidence of PPCs was 17.7% versus 32% in the intervention and control group, respectively ($\chi 2 = 4.317$, $P < 0.05$). Shen *et al.*[58] focused on low tidal volume in patients undergoing a total minimally invasive esophagectomy (tMIE). The study had a low risk of bias and reported an improved oxygen index and dampened inflammatory response in the intervention group. In addition, the occurrence of PPCs in the intervention arm was significantly lower than that in the control arm (9.43% vs. 27.8%, $P < 0.021$).

MIE in the modern era is conducted either via a tMIE, a hybrid approach, or robotic-assisted total or hybrid approaches (RAMIE) and provides some clear evidence from RCTs and large observational series to support an approach that reduces PPCs compared with traditional open approaches.[59] In the first major large series of tMIE, by Luketich *et al.*[60], of 222 patients, the pneumonia rate was 7.7% and 30-day mortality was 1.4%. To date, 8 meta-analyses have been performed with a dataset of 28,417 patients highlighting a statistically significant reduction in PPCs in favor of the MIE approach, but no difference in mortality.[59] The TIME, RAMIE, and MIRO trials[61–63] have established significant reductions in PPCs. The TIME trial[10,64] in the Netherlands included 115 patients undergoing either open esophagectomy or tMIE and was powered on microbiologically proven pulmonary infection within 2 weeks of surgery, and reported a 29% incidence in the open cohort compared with 9% in the MIE group (RR: 0.30, 95% CI: 0.12–0.76; $P = 0.005$). The hybrid technique, with a laparoscopic approach to the abdominal phase, and an open approach to the thoracic phase[62] as seen in the high-quality MIRO RCT, reported an incidence of PPCs of 18% in the hybrid group versus 30% in the open group (odds ratio: 0.31; 95% CI: 0.18–0.55; $P < 0.001$). With respect to robotic-assisted approaches, the RAMIE (Robot-assisted MIE) trial[63] randomized 112 patients to open transthoracic approach or RAMIE approach, with a primary endpoint of overall severity of postoperative complications as per the Clavien–Dindo severity scale.[65] PPCs were the most frequently observed complication, 32% in RAMIE versus 58% in the open group ($P = 0.005$). These trials provide Level I data that support the thesis that a minimally invasive approach, even in part as in the hybrid approach, may confer benefits through a reduction in pulmonary infections and PPCs.

The use of intraoperative drugs to minimize PPCs including steroids and immune therapies has been evaluated. While the benefits of steroids in the ICU critical care setting have been widely debated, there is a relative paucity of data from the perioperative period.[66] Bagheri *et al.*[67] conducted a moderate risk of bias RCT of 60 patients undergoing transhiatal esophageal resections and administered 125-mg methylprednisolone at the end of formation of the anastomosis in the experimental arm. Observed respiratory events were 21.6% in the control group compared with just 5% in the experimental arm. The incidence of acute respiratory failure was lower in the steroid group than in the control ($P = 0.020$). Both G-CSF and sivelestat have also been studied intraoperatively to assess their effectiveness in the reduction in PPCs. In the RCTs included within this review, by Schaefer *et al.* and Yamaguchi *et al.*, neither drug demonstrated a significant impact.[68,69] In the RCT by Schaefer *et al.*,[68] in 153 patients from 5 German centers, G-CSF was administered 2 days prior to esophagectomy and continued until the 7th postoperative day. Pneumonia was observed in 33.8% in the intervention and 35.5% in the control arm ($P = 0.866$). Yamaguchi conducted a small trial[69] ($n = 24$) in patients undergoing transthoracic esophagectomy, with sivelestat, a synthetic low-molecular-weight neutrophil elastase inhibitor, as the intervention and reported a reduced SIRS incidence and duration in the intervention group.

The impact of thoracic epidural anesthesia (TEA) in comparison to other methods of analgesia in the reduction of formation of PPCs after esophageal cancer surgery is an important question, in particular where other modalities are increasingly considered to enable early mobilization after surgery and to reflect arguably a lower requirement in the minimally invasive case. Despite an extensive search strategy, no RCT was found with reduction of PPCs as a primary endpoint. In a cohort study of 335 patients, epidural analgesia and the avoidance of blood transfusions were associated with a significant reduction in PPCs and mortality following open esophageal cancer surgery.[70] The paravertebral catheter versus epidural analgesia in minimally invasive esophageal resection (PEPMAN) randomized controlled multicenter trial with a primary endpoint of overall postoperative quality of recovery postesophagectomy, is currently in progress and may inform practice and standard of care in the future.[71]

III: Postoperative

The philosophy of ERAS—Enhanced Recovery After Surgery—was pioneered by Henrik Kehl

et al. 30 years ago.[72] Although implemented in most major surgeries, it was only recently formalized for esophageal cancer cohorts, with key elements being early mobilization, enteral nutrition, and minimizing the use and duration of tubes and drains. Although intuitive that it benefits patients' recovery, more research is required to measure its effectiveness and a clear evidence base.[73] Nutrition is an important element of ERAS, in particular early postoperative enteral nutrition. In this context, the European Society for Clinical nutrition and metabolism (ESPEN) published guidelines for early nutrition after surgery as a core postoperative requirement.[74] Takesue *et al.*[75] conducted a trial comparing enteral nutrition and parenteral nutrition after thoracoscopic esophagectomy.[76] Pneumonia was diagnosed in just 10 patients (21.3%), 7 (30.4%) in the parenteral versus just 3 patients (12.5%) in the enteral nutrition group ($P = 0.137$). The rate of weight loss, the primary endpoint, was significantly ($P = 0.020$) lowered at POD 14 in the enteral group.

Another ERAS principle is the early removal or avoidance of nasogastric tubes, which may predispose to PPCs. A Cochrane review including 37 randomized controlled trials ($N = 5711$) demonstrated that the absence of a nasogastric tube reduced pneumonia and was associated with a hastened return of bowel function and a shorter hospital stay.[77] Hayashi *et al.*[78] conducted a trial with a low risk of bias on early compared with conventional nasogastric tube removal in 80 patients; however, early removal of the NG tube did not reduce the incidence of postoperative pneumonia. A cornerstone of ERAS is early mobilization after surgery; however, there is no clear data on timing and target distances within RCTs after esophageal cancer surgery.[73]

The role of NIPPV after esophagectomy remains controversial in spite of some case–control studies highlighting its safety in clinical practice.[79] In a 2015 systematic review, just four studies could be evaluated, three case series and one conference abstract.[79–82] Methodology quality was low with design bias and confounders high. It was concluded nonetheless that the benefits included a reduced risk of reintubation, and shortened ICU LOS, with no added risk of anastomotic failure. Further trials are warranted to test its safety.[83] High flow nasal cannula (HFNC) provides 4–6 cm H2O of added inspiratory pressure and may be equivalent in benefit to NIPPV, with improved patient tolerance. In the OPERA study, 220 patients postabdominal surgery were randomized to receive HFNC or standard oxygen supplementation; however, no significant difference in the reduction of atelectasis or PPCs was observed, possibly suggesting that the amount of inspiratory pressure needed to re-inflate collapsed lung segments may be greater than HFNC can provide.[84,85]

DISCUSSION

This systematic review highlights the paucity of evidence base from RCTs underpinning approaches to the prevention and management of PPCs. The strongest support is for minimally invasive technical approached to the operation and low tidal volumes. It is clear that much of what is standard within ERAS protocols, although intuitive, have not been rigorously evaluated within RCTs. The authors acknowledge in this context that a possible limitation of this review is that only RCTs were included, as these provide the gold standard evidence that best inform changes in practice. We have however included some comment on relevant cohort studies for completeness within a narrative presentation of the topic, and in the Discussion. For the future, risk assessment models for PPCs should be developed and validated, and robust RCTs are required on interventional research in the prediction, prevention, and management of PPCs.[86–88] Specific targets focused on PPCs include intraoperative lung protective ventilation, defining the optimum level of PEEP, use of driving pressures, judicious administration of fluid and blood products, and an ERAS care bundle. Moreover, it is clear that a consistent definition of pneumonia in the post-esophagectomy context is required, and a severity score; this will enable study design and also the consistency of reporting on PPCs. Since pneumonia postesophagectomy has a different pathogenesis than HAP and VAP, and has a noninfective etiology in many cases, new definitions based on altered lung physiology, and severity, should be a target of future research. In conclusion, it is clear from the systematic review that data are limited underpinning the targeting of prevention and management of PPCs, and this presents research vistas for large international collaborative networks to explore.

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