Improving lung cancer outcomes: the association of high blood eosinophil counts and poor surgical outcomes in early-stage lung cancer.

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A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science.

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ABSTRACT

Introduction

Lung cancer remains the leading cause of cancer death worldwide and in Canada despite the advances in screening, diagnosis, and therapeutic options including minimally invasive surgery. The advanced median age at diagnosis and the common risk factors of smoking contribute to the high comorbidity burden among lung cancer patients, especially those with Chronic Obstructive Pulmonary Disease. Several risk stratification methods that make use of statistical models and clinical tests and measures have been developed but provide limited usefulness in selecting high-risk patients that would benefit from interventions perioperatively. Blood eosinophil counts have been used as a surrogate marker of airway inflammation, increased risk for exacerbations, and a prognostic measure of inhaled corticosteroid responsiveness. In lung cancer patients who often have some degree of airway inflammation and airway obstruction, blood eosinophil counts have not been explored as a marker of surgical outcomes in early disease.

Objectives

We will determine the association of high blood eosinophil counts (BECs) with surgical outcomes among patients with early-stage lung cancer. We will determine the association between high BECs and 90-day healthcare utilization after lung resection. Additionally, we will examine the association between high BECs and survival at 1 year and 3 years follow-up.

Methods

This is a retrospective cohort study of lung cancer cases treated at the McGill University Health Centre between September 2017 and July 2021. Data was obtained from the MUHC Data

Warehouse, linked to Pulmonary Function data, and then complemented by rigorous chart reviews. Inclusion criteria were all stage I and II non-small cell lung cancers treated by lobectomy, segmentectomy, or wedge resection. Excluded were stage III and IV cases, and any bi-lobectomies or pneumonectomies. The primary outcome was 90-day post-surgical readmission. Secondary outcomes were 1 and 3-year survival, prolonged hospital stay, and 90-day mortality. Descriptive statistics were done and log Poisson regression with standard variance was employed as the primary method of analysis with risk ratios reported. Cox proportional hazard regression was used for survival analysis. Blood eosinophil counts were explored as a continuous variable using natural cubic spines and as a categorical variable of <200 cells/μL and greater than or equal to 200 cells/μL (high blood eosinophil group).

Results

Our cohort (n=715) was primarily female (58%), with a mean age of 67.9 ± 7.9, with COPD comorbidity present in 20%. Unscheduled readmissions within 90 days following surgery occurred in 110(15.3%) cases. Readmission was higher in the group with higher BECs,19.7% (n=28/146) compared to 14.4% (n=82/569). BECs of more than 200 cells/ μL were associated with 1.5 times the risk of readmission (RR 1.54; 95% CI, 1.04-2.28) after adjustment for age, sex, COPD status, smoking, Charlson comorbidity index, surgical approach, TNM stage, white cell counts, hemoglobin level and creatinine concentration. At one year, those with high BECs had higher hazards of mortality (HR 2.42, 95% CI: 1.08-5.37), after adjustment for covariates. This was not observed at 3 years (HR 1.59, 95 CI: 0.90-2.81) but the other well-established factors associated with poor survival such as male sex, greater tumor size, and nodal involvement remained significant.

Conclusions

Our study suggests that there is a role for blood eosinophil counts to be a useful biomarker for defining patients who are likely to be readmitted and those who have poor overall survival regardless of COPD status. This study provides a background for future clinical trials that can investigate perioperative interventions such as inhaled corticosteroid treatment among patients with established airway obstruction who have imminent lung cancer resection surgery.

RÉSUMÉ

Introduction

Le cancer du poumon demeure la principale cause de décès par cancer dans le monde et au Canada malgré les progrès réalisés en matière de dépistage, de diagnostic et d'options thérapeutiques, y compris la chirurgie mini-invasive. L'âge médian avancé au moment du diagnostic et les facteurs de risque communs du tabagisme contribuent au fardeau élevé de comorbidité chez les patients atteints d'un cancer du poumon, en particulier ceux atteints de maladie pulmonaire obstructive chronique (MPOC). Plusieurs méthodes de stratification des risques qui utilisent des modèles statistiques et des tests et mesures cliniques ont été développées, mais offrent une utilité limitée dans la sélection des patients à haut risque qui bénéficieraient d'interventions périopératoires. Des comptes éosinophiles de sang ont été employés comme marqueur de remplacement de l'inflammation de voie aérienne, du plus grand risque pour des exacerbations, et d'une mesure pronostique de la réponse inhalée de corticostéroïde. Dans les patients de cancer de poumon qui ont souvent un certain degré d'inflammation des voies respiratoires et d'obstruction des voies respiratoires, des comptes éosinophiles de sang n'ont pas été explorés comme marqueur des résultats chirurgicaux dans la maladie tôt.

Objectifs

Nous allons demontrer l'association du nombre élevé d'éosinophiles dans le sang avec les résultats chirurgicaux chez les patients atteints d'un cancer du poumon à un stade précoce. Nous déterminerons l'association entre les eosinophils élevés et la réadmission a l'hopital dans les 90 jours suivant une chirurgie pulmonaire. En plus, nous examinerons l'association entre le compte d'eosinophils élevés et la survie à 1 an et 3 ans de suivi.

Méthodes

Il s'agit d'une étude de cohorte rétrospective des cas de cancer du poumon traités au Centre Universitaire de Santé McGill entre septembre 2017 et juillet 2021. Les données ont été obtenues de l'entrepôt de données du CUSM, couplées aux données de la fonction pulmonaire. Les critères d'inclusion étaient des patients avec un cancer de poumon non-petits de cellules de stade I et II traités par la résection (lobectomie, segmentectomie, ou resection sous lobaire) excluant des cas de stade III et IV, et tous les bi-lobectomies ou pneumonectomies. Le resultat primaure primaire est la réadmission post- chirurgicale dans les 90 jours post operatoire. L"objectif secondaire étaient la survie à 1 et 3 ans, un séjour prolongé à l'hôpital et une mortalité à 90 jours. Des statistiques descriptives ont été effectuées et une régression log de Poisson avec variance standard a été utilisée comme principale méthode d'analyse avec des rapports de risque rapportés. La régression proportionnelle de risque de Cox a été employée pour l'analyse de survie. Le nombre d'éosinophiles dans le sang a été exploré en tant que variable continue à l'aide d'épines cubiques naturelles et en tant que variable catégorique de <200 cellules/μL et supérieure ou égale à 200 cellules/μL (groupe éosinophile sanguin élevé).

Résultats

Notre cohorte (n = 715) était principalement féminine (58 %), avec un âge moyen de 67.9 (SD 7.9), avec une comorbidité de MPOC présente dans 20 % des cas. Les réadmissions imprévues dans les 90 jours suivant la chirurgie se sont produites dans 110 (15.3%) cas. La réadmission était plus élevée dans le groupe où les BEC étaient plus élevés, 19.7 % (n = 28/146) comparativement à 14.4 % (n = 82/569). Des BEC de plus de 200 cellules/μL ont été associés à 1.5 fois le risque de réadmission (RR = 1.54, CI à 95%, 1.04-2.28) après ajustement en fonction de l'âge, du sexe, du statut de MPOC, du tabagisme, de l'indice de comorbidité de Charlson, de l'approche chirurgicale, du stade TNM, du nombre de globules blancs, du taux d'hémoglobine et de la concentration en créatinine. À un an, les personnes ayant des BEC élevés présentaient des risques de mortalité plus élevés (HR 2.52, IC à 95% : 1.14-5.60), après ajustement pour tenir compte des covariables. On n'a pas observé ceci à 3 ans (HR 1.59, CI à 95% : 0.90-2.81) mais les autres facteurs bien établis liés à la survie pauvre telle que le sexe masculin, la plus grande taille de tumeur, et la participation nodale sont demeurés significatifs.

Conclusions

Notre étude suggère que le nombre d'éosinophiles sanguins joue un rôle important pour identifier les patients susceptibles d'être réadmis et ceux qui ont une faible survie globale, quel que soit le statut de MPOC. Cette étude fournit un fond pour de futurs tests cliniques qui peuvent étudier des interventions perioperative telles que le traitement inhalé de corticostéroïde parmi des patients présentant l'obstruction des voies respiratoires établie qui ont la chirurgie imminente de résection de cancer de poumon.

ACKNOWLEDGEMENTS

I was honored to receive the 2022-2023 Becklake Fellowship in Respiratory Research. This funding contributed immensely to helping me carry out my research work and explore a barely touched research area.

My supervisor, Nicole Ezer, who saw untapped potential in me, took me under her tutelage and showed me a path that I had not quite comprehended before. She worked tirelessly and patiently with me, helping to shape me as an independent researcher capable of thinking out of the box. There were times when she would be on service and extremely busy, but she made my work a priority.

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I'm grateful to the phenomenal team I worked with, Cedric Roux and Charlotte Besson for helping me navigate the administrative components and data management aspects of my project.

I want to thank my husband whose constant support kept me going even when the road seemed impossible. He walked this road with me hand in hand and side by side, as he was also working on his PhD. From him I derive my inspiration.

I want to give my heartfelt thanks to my family and friends whose encouragement always made the prize seem more attainable.

To my unborn child, who changed my outlook on life and encouraged me to not only do better but to surpass my best even when all I wanted to do was sleep.

Above all, my eternal gratitude goes to my Maker, who sustained me every step of the way.

PREFACE AND CONTRIBUTION OF AUTHORS

The main goal of this Master's thesis was to contribute towards the improvement of lung cancer outcomes. This thesis complies with the Graduate and Postdoctoral Studies' guidelines and general requirements of a manuscript-based (article-based) Master's thesis at McGill University. This thesis consists of one manuscript that addresses an important research topic related to lung cancer.

This thesis contains **six chapters**:

Chapter 1 provides a comprehensive literature review on lung cancer epidemiology, staging, co-existence with COPD and the clinical significance of blood eosinophil counts as a treatable trait. It also provides an in-depth explanation of the statistical methods used in the analysis of this study.

Chapter 2 introduces the thesis rationale, hypothesis, and objectives of the project.

Chapter 3 contains the manuscript, which constitutes my thesis. The manuscript is a project on lung cancer that assesses the association between high blood eosinophil counts and increased healthcare utilization as well as poor overall survival among patients with early-stage lung cancer presenting for surgical resection.

Chapter 4 provides a comprehensive discussion of the overall findings of the project.

Chapter 5 summarises the findings of this study and provides the final conclusions.

Chapter 6 provides all references cited throughout sections of the thesis excluding the manuscript.

Nicole Ezer, my thesis supervisor, played a crucial role in every phase of the research process, starting from the inception and design of the project to the analysis and discussion of results, and engaging in thoughtful revisions of the manuscript. Mariya Yordanova and Sara Elatris assisted with rigorous chart reviews. Ankita Ghatak consolidated some of the data sources used in this project. Cedric Roux of the bioinformatics team at the MUHC assisted in storing our data securely, parsing and cleaning the data from the MUHC Data Warehouse. Benjamin Smith assisted with the methodology and contributed ideas on exploring different thresholds of eosinophil counts.

All chapters were written and completed by Everglad Mugutso. Nicole Ezer reviewed and edited the text in this thesis.

Chapter 3 (Manuscript) is still ongoing. Nicole Ezer contributed to the conception, planning, and design of the study. Everglad Mugutso is the first author. Nicole Ezer is the senior author. Figures and tables are embedded in the manuscript.

All authors approved the version of the submitted manuscript, as it appears in this thesis. Figures and tables are embedded in the manuscript.

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LIST OF ABBREVIATIONS

BEC- blood eosinophil counts

CCI- Charlson comorbidity index

COPD-Chronic Obstructive Pulmonary Disease

CPET-cardiopulmonary exercise test

ICD- International classification of disease

LABA- long-acting beta-agonist

LAMA- long-acting muscarinic antagonist

LDCT- low-dose computed tomography

LOS- length of stay

NSCLC- Non-Small Cell Lung Cancer

PFT- pulmonary function test

SCLC- small cell lung cancer

SEER- Surveillance, Epidemiology, and End Results (SEER)

TNM- tumor, node, metastasis

VATS- Video-assisted thoracoscopic surgery

CHAPTER 1: BACKGROUND

1.1 Lung Cancer Epidemiology

Lung cancer persists as the leading cause of cancer death globally, with a rising incidence and an advanced stage at diagnosis [1-3]. In Canada, its incidence has been declining since 1990 among men and since 2013 among women however, there is still substantial mortality attributable to lung cancer [4]. In 2023 it was projected that 13% of all new cancer diagnoses in Canada would be due to lung cancer, and it would contribute to up to 1 in 4 of all cancer deaths[4].

There are various reasons for this significant mortality observed in lung cancer. Firstly, over 51% of lung cancer cases are diagnosed at stages III and IV which are considered advanced. The occult nature of early-stage lung cancer makes it hard to diagnose and lung nodules are often found incidentally on routine imaging. Symptoms that may be seen in lung cancer such as cough, dyspnea, pain, and weight loss occur in less than 50% of cases but can be non-specific and depend on the location and extent of the tumor[5,6]. This leads to delays in diagnosis and subsequent advanced disease at diagnosis. Secondly, lung cancer has poor overall survival at similar stages as other types of cancers. When comparing 5-year survival, it is around 22% for all stages combined, 60% at localized stages, and drops sharply to 6 % at advanced stages (Figure 1)[7]. Lastly, the

presence of competing comorbidities such as chronic obstructive pulmonary disease (COPD) may have an impact on survival [8].

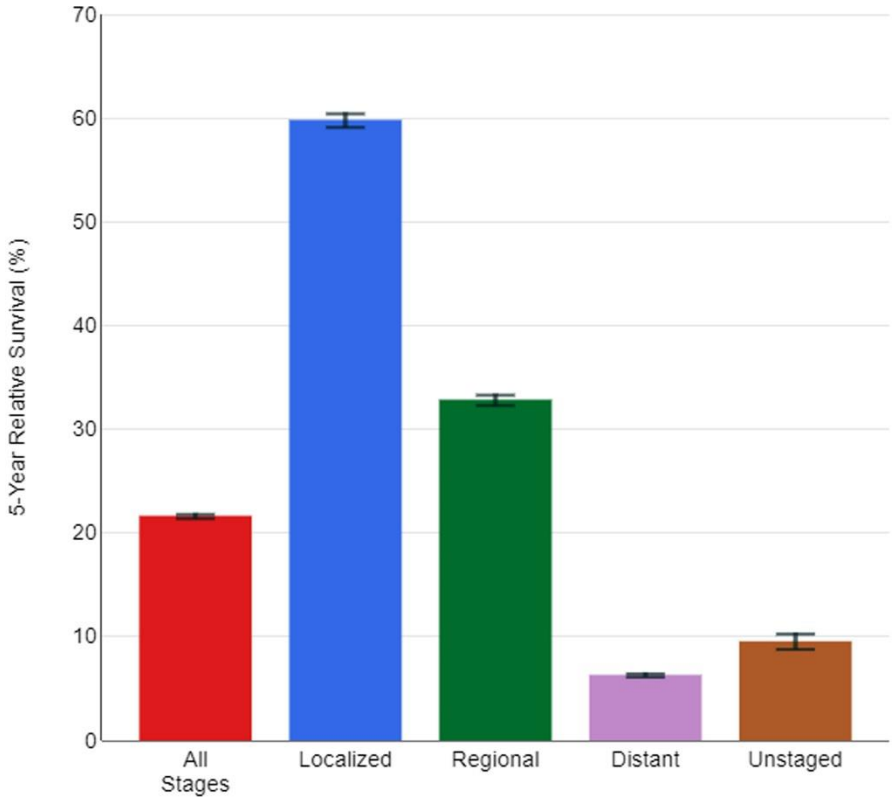

Figure 1: Lung and bronchus SEER 5-year relative survival rates, 2011 to 2017 by stage at diagnosis, both sexes, all races, all ages (https://seer.cancer.gov/explorer). This figure shows the percentage of lung cancer cases diagnosed in the U.S. by stage and their respective 5-year survival using data from SEER. Adapted from Oliver A *et al* [7]

There are 2 main histological types, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), which contribute 85% and 15%, respectively[9]. The predominant type, NSCLC, comprises different subtypes including adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and a few others, and is the focus of this thesis.

NSCLC is often diagnosed among septuagenarians with a mean age at diagnosis of 70 years[10]. In the US, women represented 55% of those living with lung cancer in 2010 possibly due to a slower decline in incidence among women compared to men[7]. In Canada, more men than women are diagnosed with lung cancer. This is likely due to differences in tobacco use between men and women. However, though there are more male smokers, women tend to have a higher susceptibility to developing lung cancer if they smoke. These sex differences may be explained by steroidal hormone influences and how they interact with different carcinogens found in tobacco to cause DNA damage[11]. It is noteworthy that only a small percentage of smokers develop lung cancer. The risk of lung cancer increases with the pack years of cigarettes smoked and declines with the number of years since smoking cessation[12].

Advances in improving lung cancer outcomes including Low Dose Computed Tomography (LDCT) lung cancer screening have increased the number of patients with early-stage lung cancer, eligible for curative surgical resection. The groundbreaking National Lung Cancer Screening Trial (NLST) showed a significant reduction in mortality with lung cancer screening using LDCT[13]. This was also substantiated by the NELSON trial which showed that lung cancer mortality was significantly lower among those who underwent volume CT screening than among those who underwent no screening[14].

1.2 Lung Cancer Staging

Lung cancer staging is a system of describing the anatomical extent of the tumor. It allows for consistency in communication in healthcare and more adept clinical decision-making. Staging is based on the TNM classification, which assesses tumor size, nodal involvement, and the presence of metastasis. Figure 2 shows the clinical staging of stage 0 to stage IIB lung cancer which is the focus of this thesis[15].

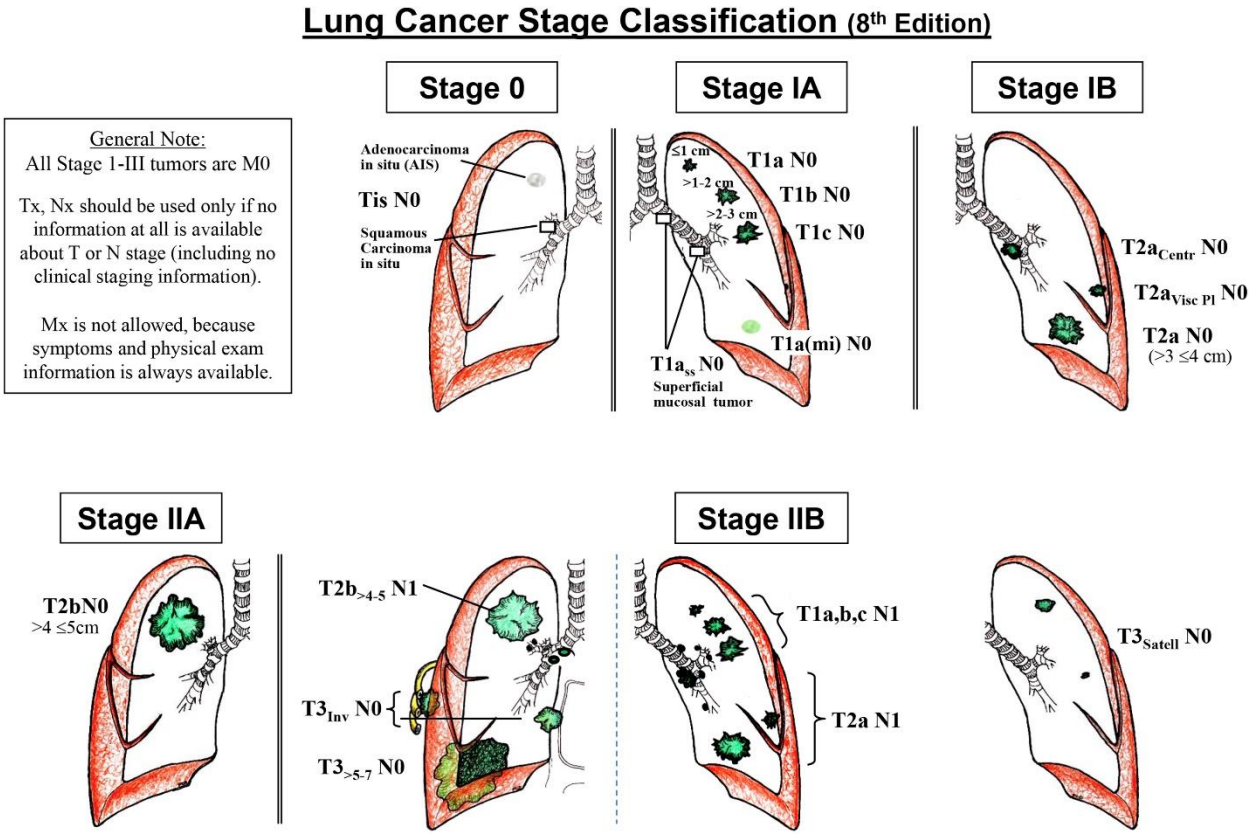

Figure 2: Graphical illustration of lung cancer staging showing stages 0 to stage IIB. Adapted from Detterbeck F.C et al [15]

1.3 Surgical Treatment of lung cancer and risk prediction

Surgical resection with curative intent remains the standard of care for stage I and stage II NSCLC. Tumor-specific factors and the risk of recurrence determine the use of adjuvant chemotherapy or radiotherapy in select patients[16].

Lung resection surgery has evolved in recent years in an effort to minimize its inherent risks. Minimally invasive approaches such as Video Assisted Thoracoscopic Surgery (VATS) are largely being used now compared to the thoracotomy approach. Several retrospective cohort studies have

shown that VATS is associated with shorter length of stay, emergency department use, and 90-day readmission among patients undergoing lobectomy[17]. A parallel-group multicenter randomized controlled trial (VIOLET) showed that VATS is superior to open surgery and is associated with better physical function 5 weeks post-surgery (mean difference, 4.65 [95% CI, 1.69 to 7.61]; P=0.009), shorter postoperative hospital stay (hazard ratio, 1.34 [95% CI, 1.09 to 1.65]), fewer severe adverse effects after discharge (risk ratio, 0.74 [95% CI, 0.66 to 0.84]) and readmissions (risk ratio, 0.80 [95% CI, 0.62 to 1.04]), and less pain (mean difference, risk ratio, 0.82 [95% CI, 0.72 to 0.94]) [18].

The extent of surgical resection is another important factor in lung cancer surgery as an extensive nodal dissection and resection of intrapulmonary lymph nodes is a marker of good oncologic outcomes. Lobectomy remains the gold standard for unilateral tumors affecting a single lung lobe. Pneumonectomy involves the removal of the whole lung on either side and is associated with higher rates of postoperative complications and prolonged hospital stay[19]. Wedge resection and segmentectomy are often offered to patients with a high surgical risk or who have poor pulmonary reserve[20]. However, the smaller the resection, the greater the risk of incomplete removal of the tumor, its draining lymph nodes, and subsequent recurrence[20]. A meta-analysis by Shi *et al* showed that lobectomy leads to a higher overall survival than lung-sparing surgery[21]. However, when stratified by tumor size lobectomy and wedge resection have been shown to have similar cancer-free survival rates[22]. Despite all this, risk stratification remains crucial for consideration for surgery. Guidelines recommend thorough presurgical assessment. Fig 2 shows an algorithm for the physiological evaluation of patients who are being assessed for major anatomic resection defined as lobectomy or greater that was proposed by Brunelli et al[23].

It shows that patients can preoperatively be stratified into low risk, medium risk, and high risk based on several clinical investigations and validated tests. The algorithm is stepwise and can be used to guide clinicians on which patients require more investigations preoperatively and targeted support postoperatively. However, the main limitation is that it was designed for patients whose planned surgery is lobectomy or greater and does not apply to patients undergoing sublobar resection.

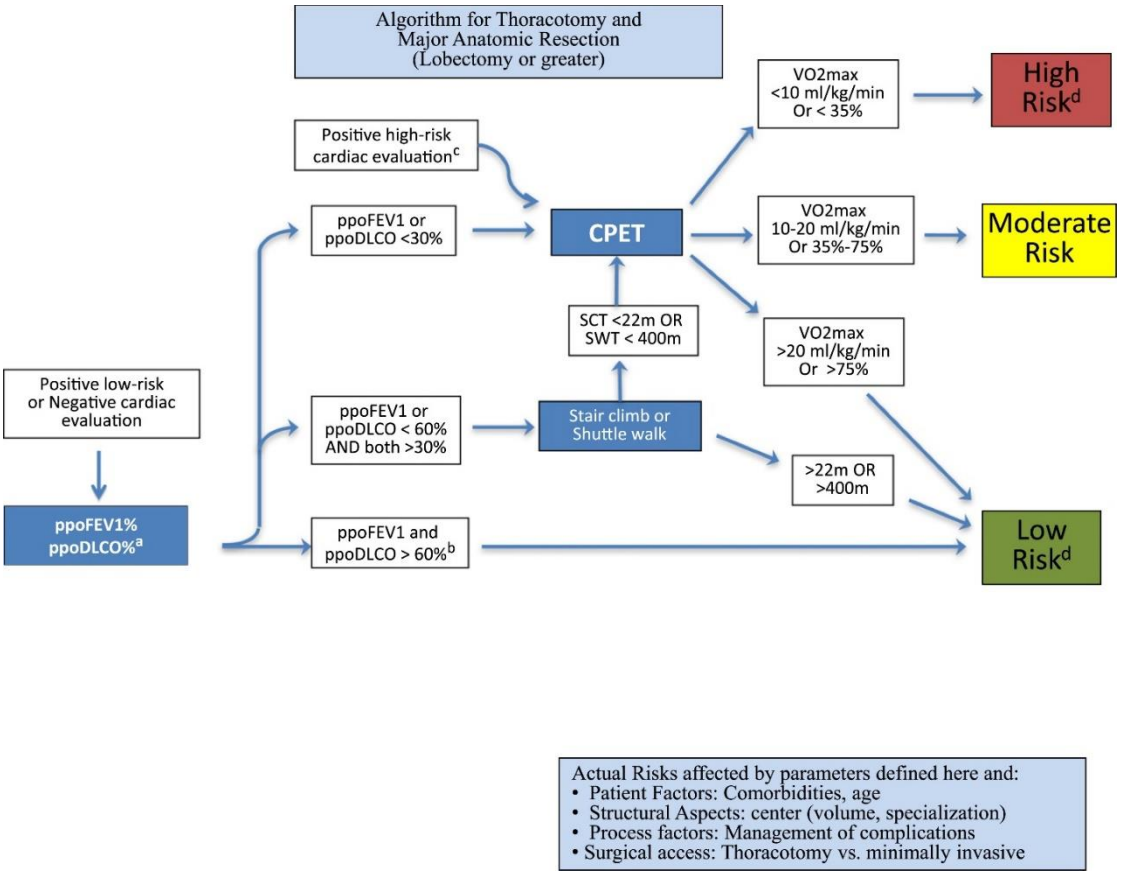

Figure 3*:* Physiologic evaluation for lung resection algorithm stratifying candidates into low risk, moderate risk, and high risk based on different levels of clinical tests namely pulmonary function test (PFT), cardiopulmonary exercise test (CPET), and stair climb or shuttle walk. PpoFEV1% - percentage predicted postoperative forced expiratory volume in 1 second. PpoDLCO% -

percentage predicted postoperative diffusion capacity for carbon monoxide. VO2 max- maximum oxygen consumption. Adapted from Brunelli A *et al*[23]

Risk prediction models for patients undergoing lung resection have been developed but only a few are useful clinically. The Eurolung2, for example, was trained on 47,960 patients undergoing lung resection and predicts 30-day mortality and cardiopulmonary morbidity with an AUC of 0.78 [24]. Another commonly used risk score is the Thoracic Revised Cardiac Risk Index (ThRCRI) which predicts cardiac complications in lung resection patients and was trained on data from 1,696 non-cardiac surgical patients[25]. Lastly, the Thoracoscore was developed to predict in-hospital mortality and has limited ability to predict postoperative complications[26]. Among these risk scores, the Eurolung2 score offered the best performance in predicting 30-day mortality in a large prospective study that compared the risk scores[27]. The variable performance of these risk scores demonstrates that clinicians would benefit from measures that would easily be able to be applied in their practice and have high utility for predicting poor patient outcomes (Refer to **Table 1** for a description of scores).

Predictors used on these models include age, sex, BMI, performance status, comorbidity, procedure class, predicted postoperative FEV1, predicted postoperative DLCO, and procedure class. Among the risk stratification models, only the ThRCRI includes a laboratory variable, creatinine, as a predictor. The availability of a wealth of clinical, laboratory, radiomics, and genomics data provides an opportunity to find other predictors that may offer more granularity of preoperative risk stratification for lung cancer patients.

Table 1: Risk Prediction Scores used in thoracic surgery

	Thoracoscore	**Thoracic Revised Cardiac Risk Index (ThRCRI)**	**Eurolung2**

Training Population	n=10,122	n=1,696 elective major non-cardiac surgery patients	n=47,960 ESTS database
Target population	Lung resection	Lung resection	Lung resection
Outcome	In-hospital mortality	Cardiac complications	30-day mortality, cardiopulmonary morbidity
Components	Age, Sex, ASA, performance status score, priority of surgery, procedure class, comorbidity	History of IHD History of CVD Serum creatinine > 2mg/ml Pneumonectomy	Age, ppoFEV1, BMI, ASA, ppoDLCO, male sex, procedure class
Performance (AUC)	0.85	0.72	0.78

The advances in screening, diagnosis, and pre-operative care of lung cancer have resulted in an increasing number of patients being eligible for lung resection with curative intent. These patients are usually elderly, with multiple co-morbidities and clinical or subclinical frailty.

1.4 Lung cancer and COPD

Chronic obstructive pulmonary disease (COPD) exists as a co-morbid condition in 50-70% of patients diagnosed with lung cancer[28,29]. The mechanisms by which these two co-exist are not well understood. However, it has been proposed that since smoking is a risk factor for both, it causes DNA damage leading to epithelial transformation and subsequent tumorigenesis[30]. There is a genetic predisposition facet to this association however because only a small percentage of smokers develop lung cancer or COPD. Patients with COPD and who undergo lung cancer resection have a worse lung cancer-specific survival [31,32], and have a higher rate of postoperative respiratory complications, such as pneumonia and prolonged air leak [32,33].

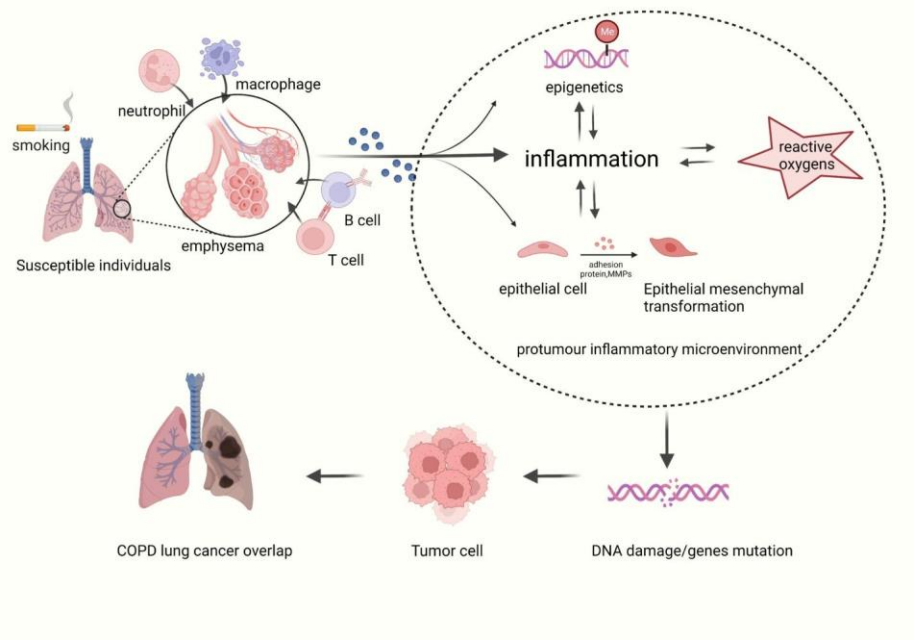

Figure 4: Proposed mechanisms involved in the development of COPD and lung cancer overlap in smokers. Adapted from Qi C *et al*[30] International Journal of COPD 2022 17 2603-2621. Originally published by and used with permission from Dove Medical Press Ltd.

1.5 COPD phenotypes and exacerbations

COPD is a heterogeneous disease, and patients exhibit pathophysiological changes and clinical symptoms to various degrees. This is true in stable disease as well as during exacerbations.

A landmark study by Bafadhel *et al* characterized the endotypes of COPD exacerbations into 4 main categories: bacteria-predominant, virus-predominant, eosinophilic, and pauciinflammatory [34]. They showed that bacterial and eosinophilic clinical exacerbation phenotypes can be identified in the stable state. The ability to identify these phenotypes even in the stable state offers an opportunity for interventions that could prevent clinical deterioration.

COPD is punctuated by acute exacerbations, [35] which are events characterized by worsening in the day-to-day symptoms from baseline requiring a change in treatment or hospitalization. These exacerbations have detrimental consequences increasing the risk of mortality with an incremental response the higher the number of events[36,37]. The retrospective study by Whittaker *et al* included a large sample of patients (n= 340,515) who collectively experienced close to 2 million events over 5 years and they found that the more severe or the higher the number of baseline exacerbations the higher the risk of future exacerbations[36].

Suisa *et al* performed a retrospective database follow-up of over 17 years looking at the event free survival following the first ever COPD exacerbation. **Figure 5** shows the declining survival over time that was described in this study. They also described that the highest risk for mortality was in the first 3 months following an exacerbation and this risk decreased over time if there were no other intermediate events. Up to 30% of COPD exacerbations are associated with eosinophilic inflammation [34,38].

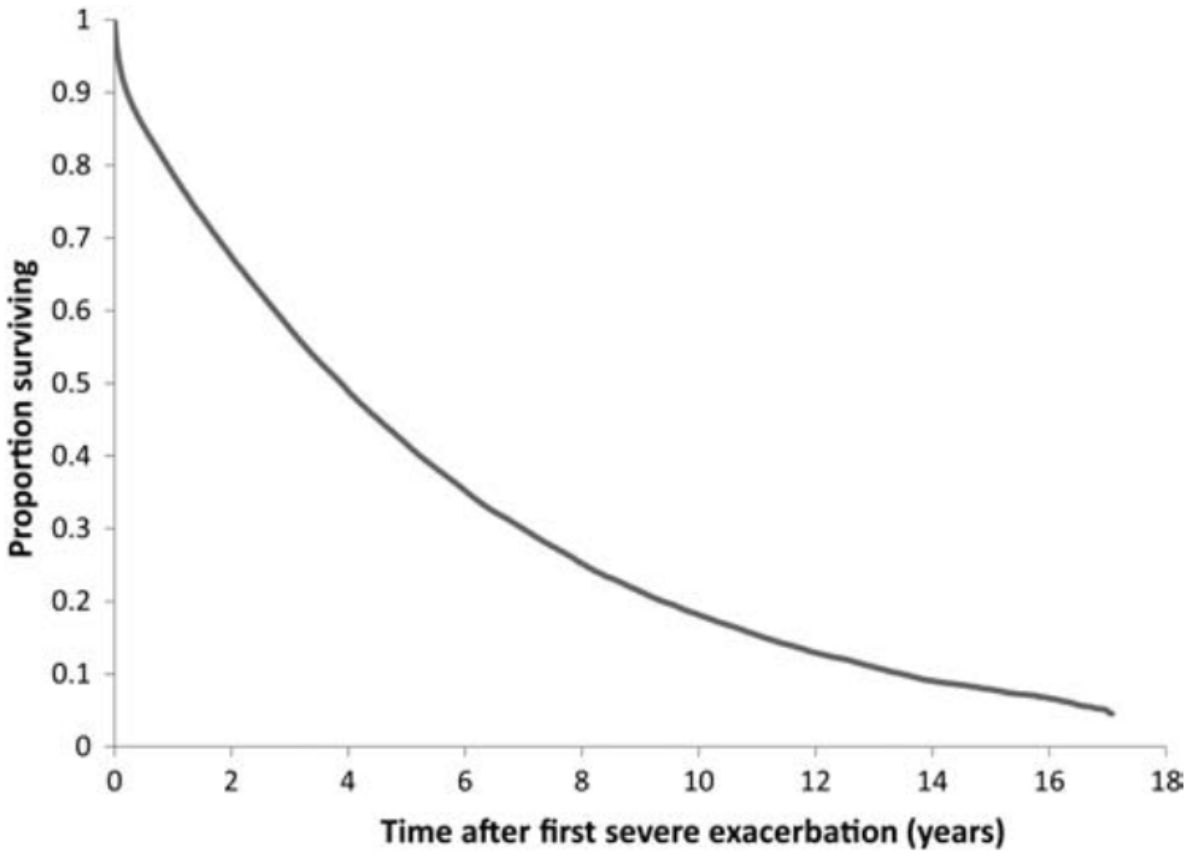

Figure 5: Shows the declining survival from the first ever hospitalisation for COPD exacerbation over a 17-year follow-up period (n=73,106). Adapted from Suissa *et al* [39]

1.6 Clinical significance of eosinophilia: a treatable trait

Elevated blood and sputum eosinophil counts have been associated with a greater propensity to exacerbations of COPD[40]. Acute exacerbations are associated with an increased all-cause and respiratory mortality at 1 year and serve as a predictor of future exacerbations the higher the number of events as shown in **Figure 6**[36,37]. Factors reported in the Lung, Heart, Social, Body (LEAD) study to be associated with higher blood eosinophil counts in the general population include current smoking, elevated total immunoglobin E (IgE), comorbid allergic rhinitis, age ⩽18

years, male sex, spirometry asthma/ COPD diagnosis, metabolic syndrome, and a high body fat composition[41].

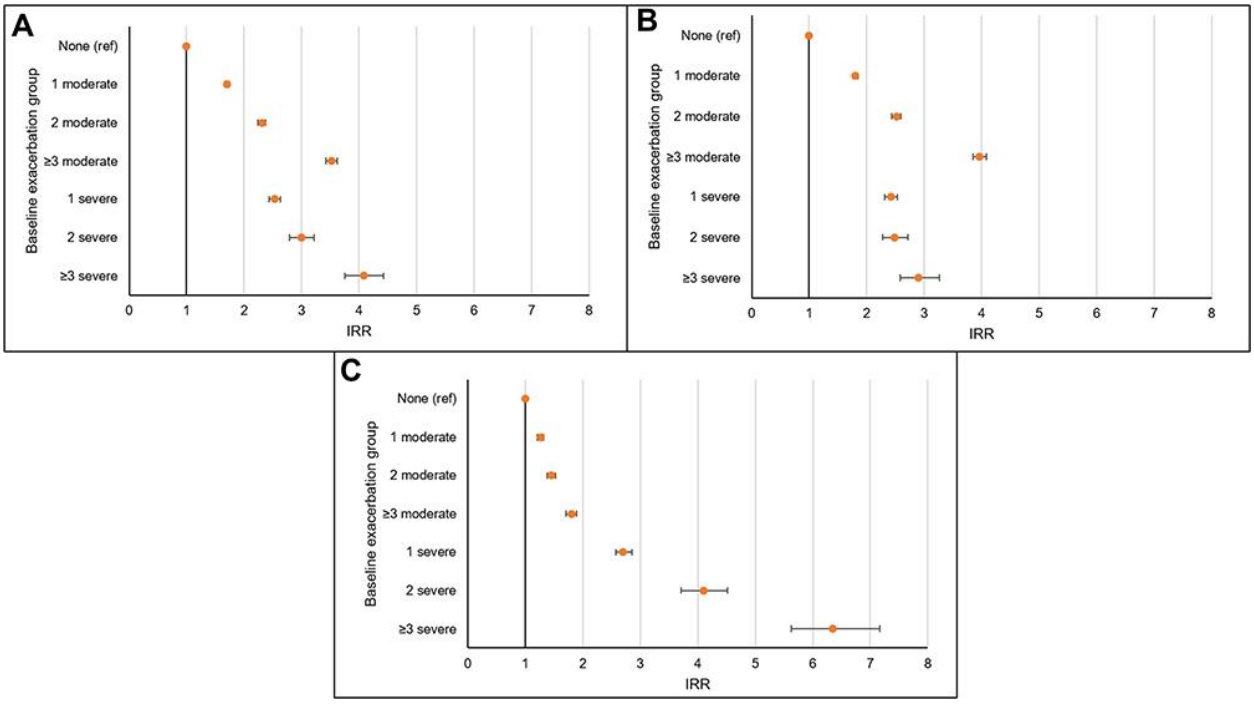

Figure 6: Incidence rate ratios (IRR) for the association between baseline frequency and severity of exacerbations and rate of (**A**) any future exacerbations, (**B**) moderate exacerbations, and (**C**) severe exacerbations. Adapted from Whittaker H et al [36]. International Journal of COPD 2022 17 427-437. Originally published by and used with permission from Dove Medical Press Ltd.

A weak but significant association between sputum eosinophils, which are more reflective of airway inflammation, and blood eosinophil counts has been described [40]. An analysis of the SPIROMICS study found that blood eosinophil counts in isolation were not associated with COPD exacerbations[40] but the association became more apparent if sputum eosinophils were also taken into consideration. The correlation between blood and sputum eosinophil counts is depicted in **Figure 7**.Similar findings were also described in the ECLIPSE study, where they followed up participants with and without COPD for 3 years[42]. They concluded that high blood eosinophil

counts (>2% or > 150 cells/µL) may be a predictor of higher sputum eosinophil counts in COPD patients[42]. This is especially useful because sputum eosinophil counts are not routinely measured, and blood eosinophil counts can be used as a surrogate marker of airway inflammation[43].

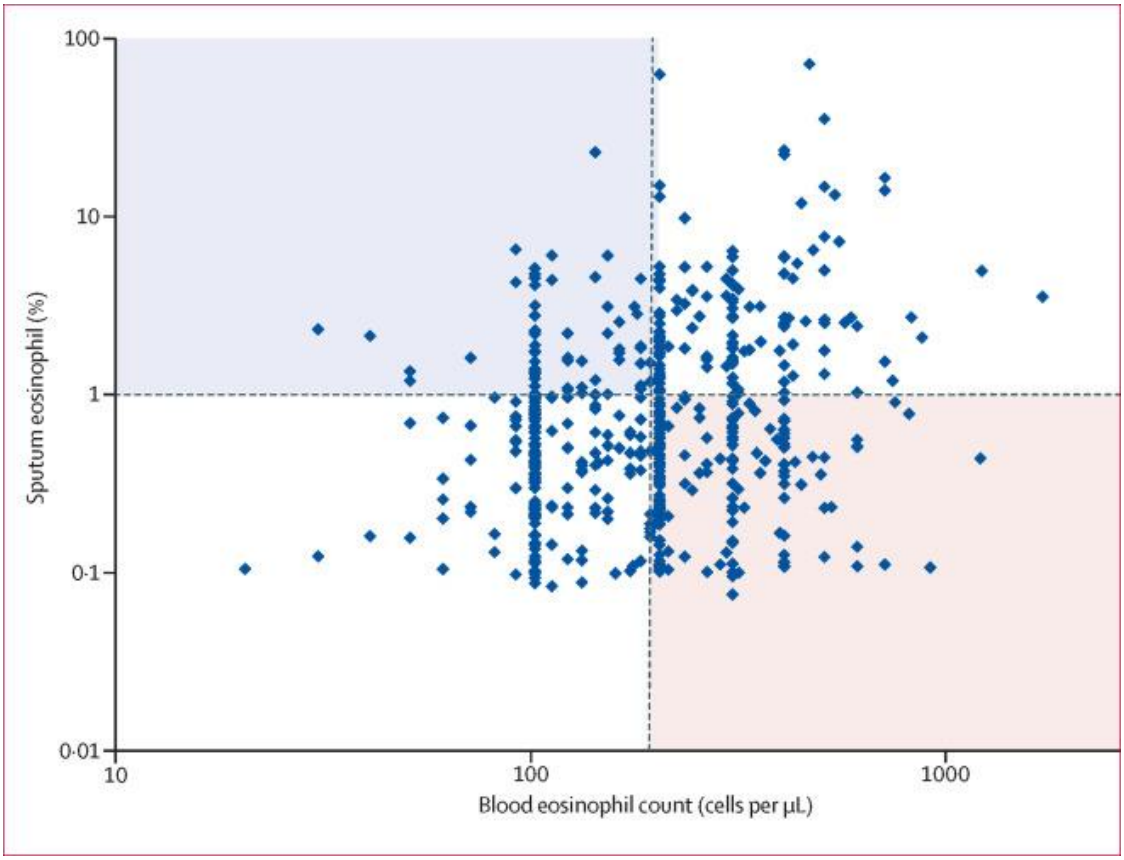

Figure 7: The correlation between sputum eosinophil counts and blood eosinophil counts in the SPIROMICS study (correlation coefficient r=0.178). A cutoff of blood eosinophil counts of 200 cells/µL and sputum eosinophil of 1.25% was used to classify the results into 4 quadrants. Adapted from Hastie A.T et al[40]

There is another concern regarding the variability of blood eosinophils and how this may limit their clinical use as a surrogate marker of airway inflammation. Several studies have looked at the stability of blood eosinophil counts. In a systemic review and meta-analysis, Benson and

colleagues explored values for eosinophil counts in the general population and among patients with either COPD or asthma[41]. The highest median levels were found among patients with asthma, followed by those with COPD and finally those with neither. In two Japanese cohorts, COPD patients with high blood eosinophil counts tended to have more variability over time in their counts compared to those who have low BECs (<150 cells/μL)[44]. The opposite was true for asthma where patients who have counts of more than 300 cells/μL had more stability over time than those with lower eosinophil counts[44]. Inhaled corticosteroid use does not seem to influence peripheral blood eosinophil count stability in COPD[44,45].

The Global Initiative for Chronic Obstructive Disease (GOLD) recommends using blood eosinophil counts to guide therapy as evidence has shown that those with higher blood eosinophil counts have a better response to inhaled corticosteroids[35]. Inhaled corticosteroid use as part of triple therapy was shown to reduce all-cause mortality in the IMPACT and ETHOS trials[46,47]. In the ETHOS trial for example, the higher the eosinophil count the greater the effect of triple therapy containing ICS on reducing the incidence of death (**Figure 8**) [47]. A recent meta-analysis of COPD trials involving the use of inhaled corticosteroids showed that the single best predictor of reduction in all-cause mortality among patients who have been on ICS for 6 or more months is a blood eosinophil count of ≥ 200 cells/μL [48]. In the CanCOLD cohort high blood eosinophils were associated with a more rapid decline in FEV1 in the presence or absence of COPD [49].

Studies investigating the significance of blood eosinophil counts in patients with early-stage lung cancer presenting for surgical resection are lacking.

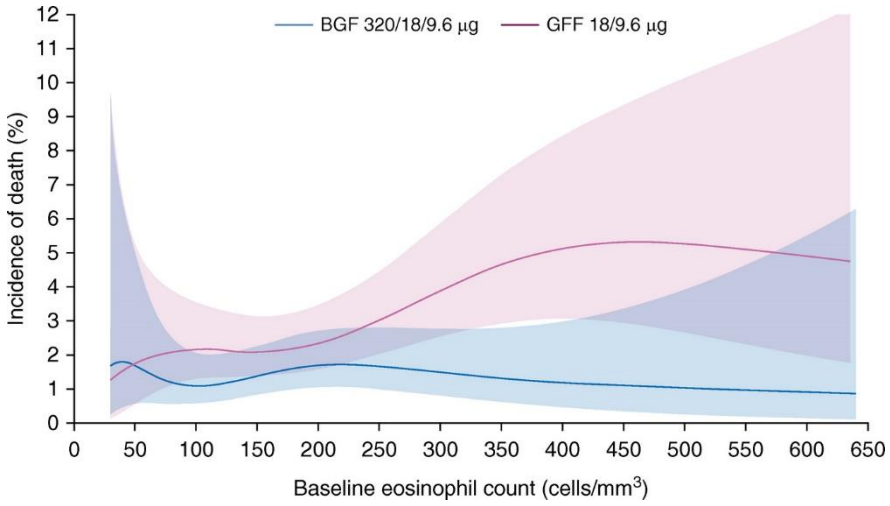

Figure 8: Incidence of death by baseline blood eosinophil counts in 2 groups of the ETHOS trial. BGF- budesonide/glycopyrrolate/formoterol. GFF- glycopyrrolate/ formoterol fumarate. In the BGF group, there was a reduction in the incidence of death at higher blood eosinophil counts. Adapted from Martinez et al [47]

1.7 Natural cubic splines

In clinical research, outcomes are usually binary, for example, having post-surgical pneumonia or not. The independent variables that are associated with or predict the binary outcome can be manipulated in different ways according to Gauthier et al[50].

Firstly, by categorization of continuous variables into 2 or more groups. An example of this would be the categorization of age into <40 or ≥ 40 years and using this to predict an outcome. It is unlikely that a patient who is 38 years old would have such a remarkable difference in the likelihood of outcome compared to a 41-year-old. Therefore, even though categorization is a valuable method of dealing with independent variables, it often leads to a loss of valuable information.

Secondly, using linear modeling techniques may be limited in observing the nuances of the relationship at different segments of the continuous variable.

Cubic splines are piecewise polynomials, with the number of segments determined by the number of knots used, and that use smoothing functions to join these segments. They are an excellent alternative to categorizing independent variables or modeling linear relationships between a continuous variable and a binary outcome. The general structure of a cubic spline is defined by the equation below:

$$g(y) = B_0 + B_1 x + \sum_{i=2}^{k-1} B_i \cdot C_i(x)$$

Where k is the number of knots, $C_i(x)$ is the cubic component that falls in the ith segment, and g is a link function of the probability of an outcome. For logistic regression, for example, g is the logit link function.

A graph can then be plotted to visualize the relationship between the continuous independent variable and the likelihood of the outcome (for example odds ratio in logistic regression). This is particularly useful when modeling the relationship between blood eosinophil counts and outcomes in COPD because this relationship is not dichotomous as shown by Bafadhel M *et al* [51].

1.8 Modified log Poisson regression with standard variance

Logistic regression is a reliable and robust statistical method for modeling the relationship between different covariates and a binary outcome. It allows for the calculation of the odds ratio which is defined as the chance of an outcome occurring in the exposed group over the chance of the outcome in the unexposed group. The odds ratio is recommended as the most appropriate measure for assessing associations in traditional case-control studies, especially cumulative case-control

studies, due to concerns about the sampling method of controls and its impact on estimating the risk of exposure in the broader population[52]. For cohort studies and randomized controlled trials, the risk ratio is the preferred measure of association because the sampling is based on the exposure of interest. It is defined as the risk of outcome in the exposed group over the risk of outcome in the unexposed group.

When the outcome is rare, that is occurring in less than 10%, OR can approximate RR. However, in cases where the outcome is common OR tends to overestimate RR[53]. When unadjusted risk ratios are reported the simple formula of finding the ratio of the proportion who experience the outcome in the exposed group over the proportion who experience the outcome in the unexposed group can be used (Table 2). However, if multiple variables need to be adjusted as is the case in clinical research, other methods of estimating the risk ratios must be employed.

Table 2: Matrix showing the number of exposed (yes/no) and outcome (yes/no)

		Outcome		
		Yes	No	
Exposed	Yes	a	b	a + b
	No	c	d	c + d

$$RR = \frac{\frac{a}{a+b}}{\frac{c}{c+d}} \xrightarrow{if\ a\ and\ c\ are\ small} \approx \frac{\frac{a}{b}}{\frac{c}{d}} = OR$$

a is the number who were exposed who experienced the outcome, b is the number who were exposed but did not experience the outcome, c is the number of unexposed individuals who get the outcome and d is the number of unexposed individuals who do not experience the outcome. This

table allows calculating unadjusted odds ratios and relative risks using the formula shown below the table.

Modified Log Poisson regression with standard variance estimation has been proposed as an alternative to logistic regression for common binary outcomes. Because binary outcome data does not follow a Poisson distribution, the standard errors that are produced are larger and inaccurate compared to what would be obtained from a binomial distribution. Robust variance estimation is therefore used to mitigate the overestimation of parameter estimates standard errors [54]. Robust Poisson models produce nearly unbiased point estimates even when the link function is misspecified or when there are slight changes in the distribution of exposed individuals. They use a quasi-likelihood method which allows for coefficient estimation without necessarily specifying the distribution of the observed data; specifying the mean and variance is necessary, however[55]. A quasi-likelihood function has properties similar to log-likelihood functions and can be depicted as follows:

$$S_j(\beta) = \frac{1}{\phi} \Sigma_{i=1}^{n} (y_i - u_i) x_{ij}$$

Where, $S_j(\beta)$ represents the j-th component of the quasi-score function, β is a parameter vector, ϕ is the dispersion parameter, $\Sigma_{i=1}^{n}$ is the summation over *i* from 1 to *n*, where *n* is the number of observations, *yi* is be an observed response or outcome for the i-th observation, *ui* represents a predicted or estimated value for the i-th observation, *xij* represents the j-th covariate (independent variable) for the i-th observation.

The standard variance estimates can then be calculated using a variance-covariance matrix and the exponents of the coefficient standard errors.

Whereas the general formula of log-binomial regression looks like this:

$$\log(\pi) = \beta_0 + \beta_1 X_{1i} + \beta_2 X_{2i} + \cdots \ldots \ldots \beta_k X_{ki}$$

where πi is the probability of experiencing the outcome of interest for subject i, and $X_1 i$, $X_2 i$, … X_{ki} are predictor variables.

CHAPTER 2: RATIONALE, HYPOTHESIS AND OBJECTIVES

2.1 Rationale

Lung cancer surgery is becoming increasingly common as advances in screening and early detection have taken stride. Among patients having surgery for lung cancer who have a history of smoking, there is an important burden of underdiagnosis of chronic airway disease that may impact surgical outcomes.

Eosinophilia may be a marker of a treatable trait among these patients, both in those diagnosed with COPD, and those patients who are potentially undiagnosed. Blood eosinophil counts are an easy-to-use clinical biomarker for adverse events in patients presenting for surgery and can be used to target healthcare resources and treatments for the patients most likely to benefit.

Considering the substantial body of evidence linking elevated blood eosinophil counts in COPD with poor health outcomes (COPD exacerbations, hospitalizations, and mortality) and the high prevalence of COPD among individuals with lung cancer, this study seeks to investigate whether high blood eosinophil counts are a useful biomarker of surgical outcomes in early-stage lung cancer patients**.**

2.2 Hypothesis

We hypothesize that:

a) Among patients undergoing resection for early-stage lung cancer, high blood eosinophil counts are predictive of poor surgical outcomes at 90 days, 1 year, and 3 years.

b) Among patients with known COPD undergoing early-stage lung cancer, high blood eosinophil counts are predictive of poor surgical outcomes 90 days, 1 year, and 3 years.

2.3 Objectives

1. Using electronic health records linked to laboratory test results we will identify whether there is an association between blood eosinophil counts and 90-day health outcomes (readmission, prolonged length of stay, and mortality) in patients who had lung resection at the McGill University Health Center.

2. Identify whether eosinophilia is a useful biomarker for mortality in early-stage lung cancer patients at 1 and 3 years.

CHAPTER 3: MANUSCRIPT

Improving Lung Cancer Outcomes: The association between high blood eosinophil counts and poor surgical outcomes in early-stage lung cancer.

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Abstract

Introduction: Lung cancer and Chronic Obstructive Pulmonary Disease (COPD) often co-exist, and patients with COPD are reported to have lower surgical resection rates and poorer surgical outcomes, including higher postoperative pulmonary complications. Blood eosinophil counts (BEC) have been used as a criterion for inhaled corticosteroid therapy in COPD and have also been associated with a greater propensity to exacerbations. We aimed to find out if elevated BECs predict poor surgical outcomes in early-stage lung cancer both in patients with comorbid COPD and those without COPD.

Methods: Data for 715, stage I and II lung cancer patients treated by lobectomy **(**or segmentectomy or wedge resection**)** between September 2017 and June 2021 was identified from the McGill University Health Centre (MUHC) Data Warehouse. Data includes the cancer registry, hospitalization data, emergency room (ER) visits, laboratory data, and vital status. Our primary outcome was 90-day readmission defined as any unscheduled readmission to the hospital or the ER within 90 days post-operatively. Secondary outcomes were postoperative complication rates; index hospitalization length of stay, and 1-year and 3-year survival. BEC results within 90 days before surgery were included for analysis. We used 200 cells/ μL as a cutoff to categorize patients

into high BECs and low BECs and used log Poisson regression for the analysis of 90-day readmission. We used a Cox proportional hazard model for our survival analysis.

Results: Of the 715 cases, 42% were males, with a mean (SD) age of 67.9 years (7.9), and 20 % had COPD confirmed by spirometry. One hundred and forty-six patients(20.4%) in the cohort had BECs that were more than or equal to 200 cells/ µL and among those individuals 27% had COPD defined by spirometry vs 18% in the low blood eosinophil count group. Unscheduled readmissions within 90 days following surgery occurred in 110(15.3%) cases. Readmission was higher in the group with higher BECs, 19.7% (n=28/146) compared to 14.4% (n=82/569) in patients with low BECs. BECs of more than 200 cells/ µL were associated with 1.5 times the risk of readmission (RR 1.54; 95% CI, 1.04-2.28) after adjustment for age, sex, COPD status, smoking, Charlson comorbidity index, surgical approach, TNM stage, white cell counts, hemoglobin level and creatinine concentration. The most common indication for readmission was pulmonary complications in 46.3% (51/110). Median survival after lung resection was not reached during the 3-year follow-up period. At 1 year the survival probability was 96% (95% CI: 93%-97%) in the high BEC stratum vs 92% (95% CI: 88%-96%) in patients with BEC below 200 cells/ µL. In adjusted analyses, BECs above 200 cells/µL were associated with a higher probability of death in 1 year (HR 2.22, 95% CI: 1.4-5.60), after adjustment for age, sex, COPD status, smoking, Charlson comorbidity index, surgical approach, TNM stage, white cell counts, hemoglobin level and creatinine concentration. Survival probability at 3 years after surgery was 85% (95% CI: 79%-91%) among the high eosinophil stratum vs 90% (95% CI: 88%-93%) in patients with low eosinophils. Death occurred in 88(12.3%) individuals within 3 years, of whom 20 (13.6%) had eosinophil count above 200 cells/µL, vs 68(11.9%). In adjusted analyses, BECs above 200 cells/µL

were not associated with a difference in probability of death in 3 years (HR 1.59, 95% CI: 0.90-2.81), after adjustment for the same covariates adjusted for in the 1-year analysis.

Conclusions: This study shows that elevated blood eosinophil counts are associated with a higher risk of post-surgical readmissions and a lower 1-year survival probability in early lung cancer among those with or without COPD. Blood eosinophil counts are a modifiable risk factor, and further studies are warranted to demonstrate whether targeting them could improve surgical outcomes among lung cancer patients.

Introduction

Lung cancer remains the leading cause of cancer death worldwide, with a rising incidence and an advanced stage at diagnosis [1-3]. Advances in lung cancer screening, diagnosis, and pre-operative care have resulted in a larger cohort of patients being eligible for lung resection with curative intent[4]. Lung cancer patients presenting for resection are usually elderly, with multiple co-morbidities due to the shared risk factor of smoking and clinical or subclinical frailty[5]. Chronic obstructive pulmonary disease (COPD) exists as a co-morbid condition in 50-70% of patients diagnosed with lung cancer[6,7]. COPD is punctuated by acute exacerbations, [8] which increase the risk of mortality with an incremental response the higher the number of events[9,10]. Up to 30% of COPD exacerbations are associated with eosinophilic inflammation [11,12]. Patients with COPD and lung cancer have a worse lung cancer-specific survival [13,14], and have a higher rate of respiratory complications, such as pneumonia and prolonged air leak [14,15]. Up to 30% of COPD exacerbations are associated with eosinophilic inflammation [11,12].

Elevated blood and sputum eosinophil counts have been associated with a greater propensity to acute exacerbations of COPD[16]. Acute exacerbations are associated with an

increased all-cause and respiratory mortality at 1 year with an incremental response the higher the number of events[9,10]. Factors reportedly associated with higher blood EOS counts include current smoking, elevated total immunoglobin E (IgE), comorbid allergic rhinitis, age ⩽18 years, male sex, spirometry asthma/ COPD diagnosis, metabolic syndrome, and a high body fat composition[17]. The Global Initiative for Chronic Obstructive Disease (GOLD) recommends the use of blood eosinophil counts to guide therapy as evidence has shown that those with higher blood eosinophil counts have a better response to inhaled corticosteroids[8]. Inhaled corticosteroid use as part of triple therapy was shown to reduce all-cause mortality in the IMPACT and ETHOS trials[18,19]. Studies investigating the significance of blood eosinophil counts in patients with early-stage lung cancer presenting for surgical resection are lacking. In the CanCOLD cohort high blood eosinophils were associated with a more rapid decline in FEV1 in the presence or absence of COPD [20].

The aim of this study is to establish if in patients with early-stage lung cancer undergoing resection surgery, high blood eosinophil counts are associated with poor surgical outcomes.

Methods

Study population.

This is a retrospective cohort study of early-stage lung cancer patients undergoing thoracic surgery at the McGill University Health Centre (MUHC) from September 2017 to June 2021.We included individuals with stage I and II non-small cell lung cancer (NSCLC), treated surgically by lobectomy, segmentectomy, or wedge resection, and with available blood eosinophil count results within 90 days before surgery. We excluded individuals with small cell lung cancer and carcinoid which are not frequently treated by surgical resection, as well as patients with bi-lobectomies or

pneumonectomies as their post-operative course is often more complex requiring a prolonged length of stay and with a higher risk of complications.

Data was acquired from the MUHC Data Warehouse which contains the cancer registry, hospitalization data, emergency room visits, International Classification of Disease codes for encounter episodes, laboratory data, and imaging metadata. We also linked pulmonary function tests (PFTs) done at the MUHC, which provided information about smoking status. We treated missing data as not missing at random by adding a missing', for each of the derived variables from that data because patients that are younger and healthy do not routinely get PFTs prior to surgery. Our primary outcome was 90-day healthcare utilization, defined as any unscheduled readmission to the index hospital or the emergency room within 90 days following surgery. We chose 90-day readmission as our primary outcome as this is less likely to be affected by surgical technique, and surgical volume, and more likely to be impacted by patient-specific factors and is representative of the postoperative recovery [21]. Secondary outcomes included postoperative pulmonary complications measured as a composite outcome comprising postoperative pneumonia, and prolonged air leak (defined by ICD10 codes; J14, J15.0, J15.1, J15.2, J15.5, J15.8, J18.9, J85.1, and T81.83). Prolonged air leak was defined as a persistent air leak lasting more than five days. The Charlson Comorbidity Index was calculated as a score by adding the weights of individual comorbidities on mortality using the ICD-10 codes. We defined prolonged hospital stay as ≥ 7 days. A composite of poor outcomes within 90 days of surgery was defined as readmission to the hospital or an emergency room visit, death, or prolonged hospital stay.

The main exposure of Interest was blood eosinophil count (BEC) results within 90 days before the surgery date. The maximum eosinophil count was considered in cases where more than one result was available for that period. Covariates in our model were age, sex, smoking status,

Charlson comorbidity index, COPD, tumor size, nodal status, surgical approach (open vs video-assisted thoracoscopy), WBC count, hemoglobin level, and creatinine concentration. Given the limitations of ICD codes to identify airway disease, we used two methods: first COPD was defined by spirometry where available, the FEV/FVC ratio was less than 0.7, and second by ICD10 codes COPD J44.0, J44.1, J44.8, and J44.9. History of asthma was defined by ICD10 codes beginning with the prefix J45. We used a blood eosinophil count of 200 cells/μL to categorize the patients into 2 strata basing the cutoff on the nature of our cohort and previous randomized clinical trials [22,23].

Natural cubic splines were used to model the nature of the relationship between eosinophil count as a continuous variable and the log odds of 90-day healthcare utilization. The spline for eosinophil count was a regression spline with 3 knots at the 25^{th}, 50^{th}, and 75^{th} percentile. We calculated unadjusted and adjusted relative risks of 90-day healthcare utilization, death, and prolonged length of stay. We used modified log-Poisson regression with robust variance estimation to adjust for age, sex, and comorbidities. A Cox proportional hazard model was used for 1 and 3-year survival analysis. All analysis was done using RStudio. The study was approved by the Research Ethics Board of the MUHC.

Results

Population

Between September 2017 and June 2021, 715 patients underwent lobectomy, segmentectomy, or wedge resection at the MUHC for stage I and II NSCLC. The clinicodemographic features are described in **Table 1** and the distribution of eosinophil counts is shown in **Figure 1**. The median (IQR) age at the time of surgery in years was 69 (62-74), and 42%

were males. Most patients had a Charlson Comorbidity index of 2 (IQR: 1-3) and 75% (535/715) of lobectomies were performed by Video Assisted Thoracoscopic Surgery (VATS). Those with eosinophil counts above 200 cells/µL were more likely to be smokers (21% vs 14%, p-value: <0.01) and have spirometry evidence of COPD (27% vs 18%, p-value: 0.01). Moderate comorbidity burden was higher in the group high BECs (70.5% vs 59.5%, p-value: <0.01, defined as a CCI of 2-3). Among the group with higher blood eosinophil count significantly more patients underwent open thoracotomy (37% vs 25%, p value: 0.01).

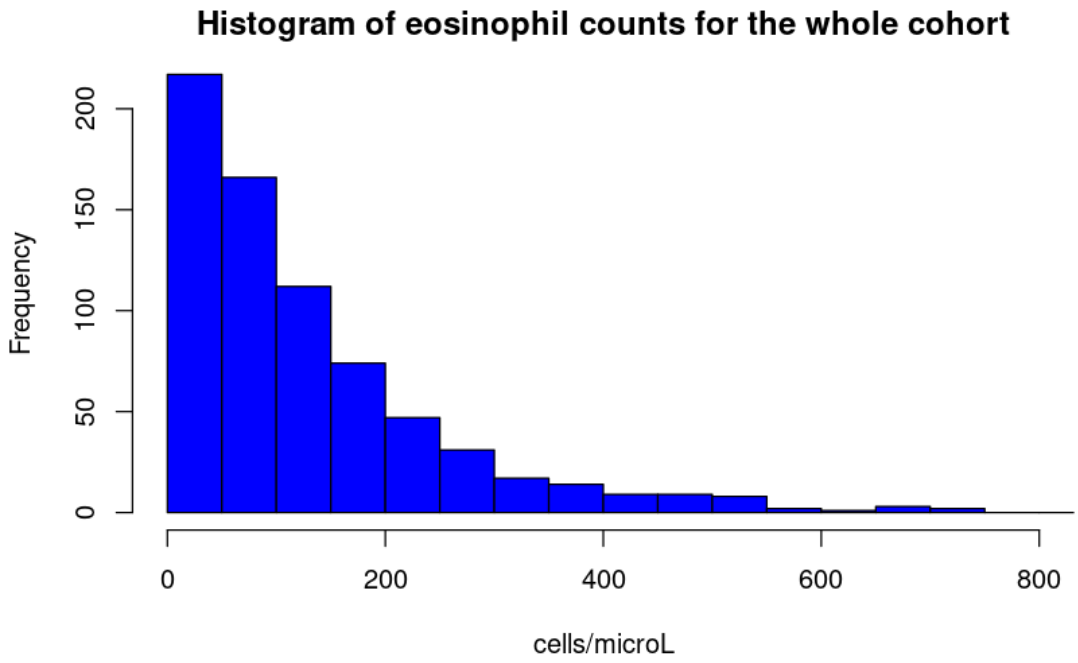


Figure 1: Right skewed distribution for blood eosinophil counts representative of the whole cohort(n=715)

Table 1: Clinical and demographic characteristics of the study population stratified by blood eosinophil count

Variable	Total	Eos <200	Eos ≥ 200
	715	**569**	**146**
Sex, n (%)			
Male	299(42%)	229(40%)	70(48%)
Female	416(58%)	340(60%)	76(52%)
Age group, years, n (%)			
<65	251(35%)	199(35%)	52(36%)
65-79	434(61%)	345(61%)	89(61%)
>=80	30(4%)	25(4%)	5(3%)
Age, median (IQR)	69(63-74)	69(63-73)	69(63-74)
Smoking history, n (%)			
Current	112(16%)	81(14%)	31(21%)
Former	196(27%)	143(25%)	53(36%)
Never	31(4%)	27(5%)	4(3%)
Missing	376(53%)	318(56%)	58(40%)
Charlson Comorbidity Index			
≤1	222(31%)	193(34%)	29(20%)
2-3	442(62%)	339(59.5%)	103(70.5)
≥4	51(7%)	37(6.5%)	14(9.5%)
Median (IQR)	2(1-3)	2(1-2)	2(2-3)
COPD (spirometry defined), n (%)			
Yes	141(20%)	101(18%)	40(27%)
No	134(19%)	105(18%	29(20%)
Missing	440(61%)	363(64%)	77(53%)
COPD (defined by ICD), n (%)			
Yes	208(29%)	154 (27%)	54(37%)
No	507(71%)	415(73%)	92(63%)
Asthma (defined by ICD, n %			
Yes	82(11.5%)	63(11%)	19(13%)
No	633(88.5%)	506(89%)	127(87%)
Tumor size, n (%)			
T1	445(62%)	353(62%)	92(63%)
T2	224(31%)	181(32%)	43(29%)
T3	46(7%)	35(6%)	11(8%)
Nodal status, n (%)			
Nx	37(5%)	32(6%)	5(3%)
N0	617(86%)	491(86%)	126(86%)
N1	60(8%)	45(8%)	15(10%)
Surgical approach, n (%)			
Open	180(25%)	125(22%)	55(38%)
VATS	535(75%)	444(78%)	91(62%)
Blood results, mean (SD)			

Hemoglobin, g/dL	132(14.8)	131.3(14.5)	136.3(15.2
White cell count, cells/μL	9.9(4.6)	10.1(4.8)	9.0(3.0)
Creatinine, μmoles/L	78.6(28.3)	78.7(30.2)	78.2(19.1)

90-day healthcare utilization

One hundred and ten patients (15.3%, n=110/715) had unscheduled readmissions or emergency room visits within 90 days following surgery. Those with high blood eosinophil counts had higher rates of readmission 21.2% (n=31/146) compared with the low BEC group 13.8% (n=79/569, p-value: 0.02). The leading causes of readmission were pulmonary complications occurring in 59% (n=65/110) of patients. Blood eosinophil counts of more than 200 cells/μL were associated with 1.5 times the risk of readmission within 90 days of surgery (RR 1.54; 95% CI, 1.04-2.28, p-value: 0.02) after adjustment for age, sex, presence/absence of COPD, smoking, Charlson comorbidity index, surgical approach, tumor size, nodal status, white blood cell counts, hemoglobin and creatinine (**Table 2**). When blood eosinophil counts were used as a continuous variable, the risk of readmission per increase of 100cell/μL in eosinophil counts doubled (RR 2.18, 95% CI:1.53-3.12, p-value <0.0001) after adjustments for the aforementioned covariates (**appendix 2**).

Postoperative pulmonary complications

130 patients (18%) experienced postoperative pulmonary complications; of which 27/ 146(18.5%) were in those with blood eosinophil counts above 200 cells/μL compared to 103/569 (18.1%) in patients with no eosinophilia (p-value: 0.54). The most common post-operative pulmonary complication was prolonged air leak occurring in 50 (38.4%) cases (**Figure 2**). There was no difference in the risk of postoperative pulmonary complications between those with high blood eosinophil counts compared with those with low eosinophil counts after adjustment for

covariates (RR 0.86; 95% CI, 0.58-1.27, p-value;0.15). Similarly, there was no impact of VATS versus open thoracotomy on postoperative pulmonary complications (RR 1.09; 95% CI, 0.76-1.56, p-value 0.63). The presence of COPD, however, was associated with an increased risk for postoperative pulmonary complications (RR 2.01; 95% CI, 1.14-3.54, p-value 0.01).

Table 2: Factors associated with 90-day healthcare utilization

Variable		**Unadjusted RR 95% CI**	**p-value**	**Adjusted RR 95% CI**	**p-value**
Eosinophil count, cells/µL	**<200**	1(Ref)		1(Ref)	
	≥200	**1.55(1.07-2.25)**	**0.02**	**1.54(1.04-2.28)**	**0.02**
Sex	**Female**	1(Ref)		1(Ref)	
	Male	1.26(0.89-1.77)	0.18	1.26(0.86-1.85)	0.21
Age, years		1.01(0.99-1.03)	0.14	1.01(0.99-1.03)	0.20
CCI	**≤1**	1(Ref)		1(Ref)	
	2-3	1.05(0.71-1.57)	0.78	1.01(0.67-1.52)	0.95
	≥4	**2.02(1.16-3.51)**	**0.01**	**2.06(1.15-3.70)**	**0.01**
Smoking	**Current**	1(Ref)		1(Ref)	
	Former	0.95(0.57-1.60)	0.87	0.91(0.35-2.33)	0.85
	Never	0.93(0.52-1.35)	0.48	0.90(0.38-2.18)	0.81
	Missing	0.84(0.37-2.29)	0.88	0.86(0.33-2.21)	0.76
COPD	**No**	1(Ref)		1(Ref)	
	Yes	1.08(0.63-1.85)	0.76	0.94(0.55-1.61)	0.93
		0.94(0.59-1.47)	0.79	0.96(O.55-1.67)	0.78
Tumor size	**T1**	1(Ref)		1(Ref)	
	T2	1.10(0.76-1.59)	0.58	1.13(0.78-1.65)	0.49
	T3	0.89(0.41-1.94)	0.78	0.73(0.35-1.58)	0.46
Nodal status	**N0**	1(Ref)		1(Ref)	
	N1	**0.31(0.10-0.95)**	**0.04**	**0.28(0.09-0.86)**	**0.02**
Surgical Approach	**VATS**	1(Ref)		1(Ref)	
	Open	1.27(0.87-1.85)	0.88	0.84(0.56-1.26)	0.45

WBC	1.00(0.95-1.04)	0.93	1.00(0.95-1.05)	0.73
HGB	1.00(0.99-1.01)	0.75	0.99(0.98-1.01)	0.94
CR	1.00(0.99-1.00)	0.94	0.99(0.98-1.00)	0.18

Modified log Poisson regression model results. 10 patients who died within 90 days following surgery and who had not been readmitted were excluded from the analysis for 90-day healcare utilization leaving 705 patients. The RRs for significant variables are in bold text. Adjustments were made for the covariates depicted in the table. RR= risk ratio; CCI-Charlson Comorbidity Index; WBC- white blood cells; HGB-hemoglobin; CR- creatinine.

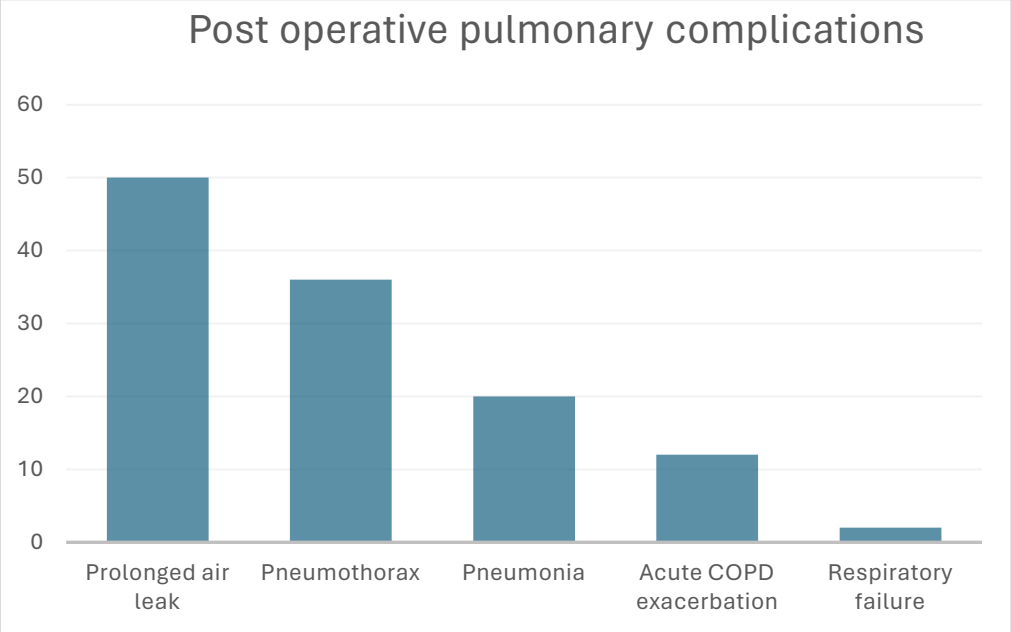


Figure 2: Frequency of postoperative complications. Prolonged air leak was the most common complication. Note that some patients experienced more than one complication

Length of hospital stay.

The median length of the index hospital stay (LOS) was 3 days (IQR 2-5). Prolonged hospital stay was defined as an index hospital stay lasting for 7 days or more. There was a difference in the rates of prolonged hospital stay between those with BECs ≥ 200cells/ μL and

those with low BECs (RR 1.41, 95% CI: 0.97-2.06, p-value: 0.07), even though this was not statistically significant. VATS surgical approach was associated with reduced risk of prolonged hospital stay compared with open surgical approach (RR 0.35, 95% CI: 0.25-0.49, p-value: <0.0001).

Composite Outcome

Given patients may experience the impact of high BEC in different ways, some with a prolonged hospitalization, some with an early death following surgery, and some with increased healthcare utilization after discharge we chose to evaluate a composite outcome to capture all the adverse health outcomes that are meaningful for patients.

To explore the relationship between eosinophil count and the composite of prolonged length of stay, hospital admission or ED visit, and death within 90 days we performed a sensitivity analysis by BEC threshold. Those with higher preoperative blood eosinophil count (BEC) experienced a significantly higher risk of the composite outcome (see **Table 3).** Patients with preoperative BECs 150 cells/μL had a 30% higher relative risk (95%CI: 1.02 to 1.62; p=0.0368) of prolonged surgery LOS, acute care re-admission or death by postoperative day 90 when compared to patients with preoperative BEC 150 cells/μL. The associations were consistent for each of the composite outcomes (**Table 3**) and the magnitude of excess risk tended to increase with BEC threshold: RR 1.44 (95%CI: 1.12 to 1.85; p=0.006) at a preoperative BEC threshold of 200 cells/μL, and RR 1.81 (95%CI: 1.37 to 2.38; p<0.0001) at a preoperative BEC threshold of 300 cells/μL.

Table 3: Adverse event risks and unadjusted risk ratios by preoperative BEC threshold among 715 patients undergoing lung resection at the McGill University Health Centre

BEC cells/ µL	No. of patients	Composite: Surgery LOS ≥7, ED/hospital readmission, or death by postop day 90		Surgery LOS ≥ 7 days		ED/hospital readmission by postop day 90		Death by postop day 90	
<150	495 (69%)	135 (27%)	RR 1.30 P=0.037	71 (14%)	RR 1.32	69 (14%)	RR 1.33	7 (1.4%)	RR 1.57
≥150	220 (31%)	77 (35%)		42 (19%)		41 (19%)		5 (2.2%)	
<200	569 (80%)	152 (27%)	RR 1.44 P=0.006	83 (14%)	RR 1.41	82 (14%)	RR 1.32	8 (1.4%)	RR 1.92
≥200	146 (20%)	56 (38%)		30 (21%)		28 (19%)		4 (2.7%)	
<300	647 (90%)	174 (27%)	RR 1.81 P<0.001	93 (14%)	RR 2.02	97 (15%)	RR 1.21	8 (1.2%)	RR 4.83
≥300	68 (10%)	33 (49%)		20 (29%)		13 (19%)		4 (5.9%)	

Postoperative adverse event risks and risk ratios are summarized at various BEC thresholds. BEC = blood eosinophil count (cells/µL); LOS = length of stay; ED = emergency department; RR=relative risk.

Survival

Ten (1.4%) patients died within 90 days of surgery with the earliest death occurring 8 days postoperatively. The rates of 90-day mortality were similar between those with high BECs compared with those with no eosinophilia (3.5% vs 1.4%, p-value: 0.10).

All 715 patients had adequate survival data for 1-year survival analysis. Median survival was not reached in the 3 years of follow-up for the entire cohort. Among patients with high blood eosinophil counts survival probability 1 year following surgery was lower at 92% (95% CI: 88%-96%) compared with 96% (95% CI: 93%-97%) in the low blood eosinophils group. A total of 36/715(5%), died within this period, 11/146(7.5%) of whom were in the high eosinophil count

group compared to 25/569(4.3%) in the low eosinophil count group. In the adjusted Cox proportional hazard model, high blood eosinophil counts above 200cells/µL were associated with a higher probability of death at 1 year (HR 2.52, 95% CI: 1.14-5.60) after adjustment for age, gender, comorbidity burden, COPD status, smoking status, surgical approach (open vs VATS), tumor size, nodal status, white cell count, hemoglobin, and creatinine.

There were 588 patients who had adequate 3-year follow-up data were included in the 3-year survival analysis. Similar to our analysis at one year, there was a lower three-year survival probability after surgery of 85% (95% CI: 79%-91%) among the high eosinophil stratum vs 90% (95% CI: 88%-93%). Eighty-eight (12.3%) died within 3 years, of whom 20(13.6%) had eosinophil count above 200 cells/µL, vs 68(11.9%). On adjusted analysis of 3-year survival analysis using a Cox proportional hazard model, there was no difference in death at 3 years among those with high blood eosinophil counts compared with those with low BECs (HR 1.44, 95% CI: 0.84-2.47) when eosinophils were modeled as a binary variable (above or below 200cells/µl). However, when blood eosinophil counts were used as a continuous variable, for every 100cells/µl increase in eosinophil count, the hazard of death increased 2.4 times (HR 2.45, 95 CI: 1.12-5.36) suggesting an important association with mortality. This warrants further study with a larger cohort or a prospective study that has adequate power for mortality given our sample size is small to detect differences in mortality at three years.

Table 4: Cox proportional hazard model for 1-year survival in 715 patients

Variable		**Adjusted HR**	**p-value**
		95% CI	
***Eosinophil count, cells/µL**	**<200**	Ref	-
	>200	**2.52(1.14-5.60)**	**0.02**
Age at surgery		1.06(1.01-1.11)	0.01
Charlson Comorbidity index	**≤1**	Ref	
	2-3	1.05(0.46-2.39)	0.83
	≥4	**3.00(1.04-8.69)**	**0.04**
Smoking	**Current**	Ref	-

	Former	1.64(0.49-5.46)	0.41
	Never	1.27(0.43-3.69)	0.65
	Missing	2.71(0.25-28.5)	0.40
Sex	**Female**	Ref	-
	Male	**2.06(1.00-3.12)**	**0.04**
COPD	**No**	Ref	-
	Yes	0.74(0.19-2.78)	0.65
	Missing	2.34(0.61-8.98)	0.21
Surgical approach	**VATS**	Ref	
	Open	0.58(0.24-1.40)	0.22
Tumor size	**T1**	Ref	-
	T2	1.67(0.74-3.78)	0.21
	T3	**3.54(1.35-9.24)**	**<0.01**
Nodal status, N1	**N0**	Ref	-
	N1	**2.72(1.01-7.31)**	**0.04**
WBC		1.01(0.95-1.07)	0.59
Hemoglobin		**0.96(0.94-0.98)**	**<0.01**
Creatinine		0.99(0.99-1.00)	0.63

Significant hazard ratios are in bold text. HR=risk ratio, WBC-white blood cells, VATS-video assisted thoracoscopy.

Table 5: Cox proportional hazard model for 3-year survival in 588 patients

Variable		**Adjusted HR**	**p-value**
		95% CI	
Eosinophil count, cells/µL	**<200**	Ref	-
	>200	1.59(0.90-2.81)	0.11
Age, years		1.02(0.99-1.05)	0.20
Sex	**Female**	Ref	
	Male	**1.98(1.17-3.37)**	**0.01**
CCI	**≤1**	Ref	
	2-3	0.92(0.53-1.61)	0.83
	≥4	1.95(0.87-4.37)	0.10
COPD	**No**	Ref	
	Yes	1.42(0.63-3.21)	0.40
	Missing	1.52(0.65-3.54)	0.30
Smoking	**Current**	Ref	
	Former	1.87(0.88-3.96)	0.10
	Never	1.70(0.83-3.48)	0.15
	Missing	1.02(0.12-8.63)	0.90
Surgical approach	**VATS**	Ref	
	Open	0.73(0.43-1.27)	0.30

Tumor size	**T1**	Ref	
	T2	**2.51(1.49-4.21)**	**<0.01**
	T3	**3.54(1.66-7.54)**	**<0.01**
Nodal status	**N0**	**2.25(1.20-4.22)**	**0.01**
	N1	**2.25(1.20-4.22)**	**0.01**
WBC		1.00(0.96-1.05)	0.90
Hemoglobin		**0.97(0.96-0.98)**	**<0.01**
Creatinine		1.01(1.00-1.02)	0.20

Statistically significant hazard ratios are depicted in bold text. 588 patients who had adequate 3 year follow up data were included in the analysis. CCI- Charlson Comorbidity Index, VATS-video assisted thoracoscopy, WBC- white blood cells.

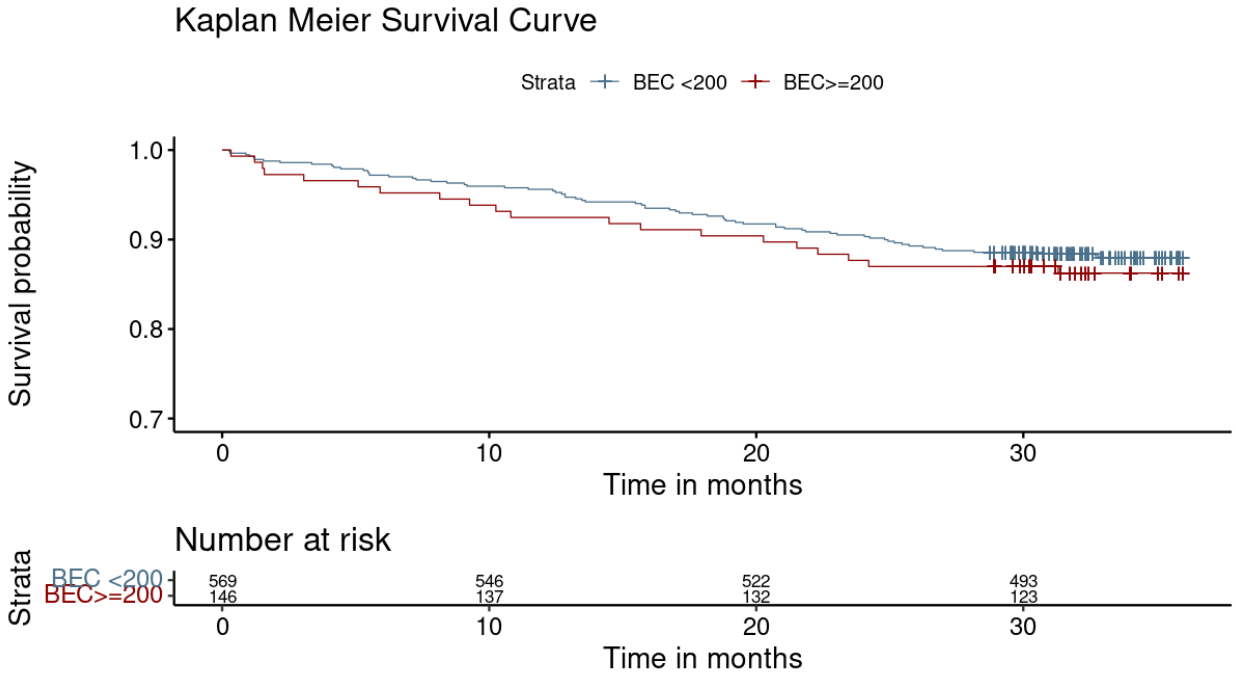


Figure 3: Kaplan-Meier Curve showing the event free survival probability over 3 years stratified by blood eosinophil count category. Note that the median survival was not reached within the study period. There is no significant difference in survival probability at 3 years (p=0.5).

Discussion

This is the first study to report a significant association between high blood eosinophil counts, and post-operative outcomes and survival in early-stage lung cancer patients presenting for pulmonary resection.

The readmission rate of 15.3% in our study was consistent with that reported in other studies which showed between 7% and 23%, with most studies having 90-day readmission rates above 18%[24,25]. Those who were readmitted had a lower overall survival consistent with previous studies[26,27].

To our knowledge, this is the first study that has explored blood eosinophil counts as a predictor of surgical outcomes and mortality among patients with early-stage lung cancer. Since very little is known about the significance of BECs in early lung cancer, this study provides an interesting intersection for 2 diseases that often coexist, lung cancer and airways disease. Lung resection is a high-risk procedure and despite the many advances in surgical technique and post-operative care, mortality and readmission rates remain high[28].

The thoracic surgery literature has focused on immediate post-operative complications within 30 days rather than 90 days [26,29,30], however we hypothesize that as the time since surgery increases, the complication rates and readmissions are more reflective of patient baseline health status and comorbidities than surgical technique. Readmissions after lung cancer resection surgery have been associated with a significant increase in mortality [26], similar to the association with COPD readmissions and mortality [31]. In their study, Suissa et al showed that the risk of death increased 30-40 fold within the first 3 months after a COPD admission, with the adjusted hazard

ratio of death increasing from 1.0 to 5.2 (95% CI: 4.9-5.5) from the first to the tenth readmission [31].

Postoperative pulmonary complications contribute to 25-55% of readmissions following lobectomy[29,32]. Consistent with other studies the commonest causes of unplanned readmissions in the current study were pulmonary, mainly pneumonia, empyema, and pneumothorax. Furthermore, we found out that having open thoracotomy was not significantly associated with a higher risk of readmission compared to having VATS consistent with other studies[29,33]. However, we did not observe a significant association between surgical approach and post operative pulmonary complications, as reported by Bhagat et el[29]. These differences could be explained by the differences in the study population since we only included early-stage lung cancer and excluded bi-lobectomies and pneumonectomies.

Some studies have found benefit in separating the pulmonary complications instead of using them as a composite variable[32]. For example, complications like pulmonary embolus, and empyema had a greater association with readmissions than prolonged air leak for example[32]. Because of our small sample size, we found that using the composite pulmonary complications variable was more feasible. Recently much of the surgical literature has focused on open versus VATS technique to reduce post operative complications but less focus has been made on the management of comorbidities such as airways disease, that may have an even more important contribution to mortality. In COPD, eosinophil counts have been identified as an important actionable biomarker for mortality [34].Eosinophil counts above 200cells/μL were found to be the strongest predictor of reduction in all cause mortality among patients with COPD who are on more than 6 months of inhaled corticosteroid therapy[34].

To find ways to level the increased risk among COPD patients presenting for lung resection surgery, some small studies have explored the use of inhaler therapy that includes inhaled steroid therapy (LAMA/LABA and triple therapy combinations) for COPD prescribed a few weeks before lung cancer surgery continuing for up to 3 months with promising results[35,36]. Given the substantial evidence about the improvement of clinical symptoms in patients with type 2 inflammation COPD who are put on inhaled corticosteroid (ICS) therapy[16,37], there may be a benefit in exploring ICS or biologic anti-IL5 use among patients who have high BECs in the pre-op surgical period.

An important limitation of this study is that it is a retrospective single-institution cohort. Rates of complications while in line with published rates, are consistent with high-volume surgical centers such as ours. Secondly, this study did not exclusively focus on patients with a diagnosis of COPD or asthma given we had a significant amount of missing pulmonary function data as pulmonary function tests performed outside our institution. While it does limit the interpretation of our results, it increases the generalizability of the utility of eosinophils in all patients presenting for resection of early-stage lung cancer. Furthermore, the eosinophil counts used were taken at different time points before surgery for participants. Variability in blood eosinophil counts has been well studied and there is a suggestion that there may be a diurnal as well as seasonal variation[17]. In one study, up to 22% of patients with COPD had significant variability in their BECs at 1 year follow-up[38]. To mitigate this limitation, we used the maximum blood eosinophil count in the 90-day preoperative window for each patient.

Another important limitation of our study is the lack of data on baseline respiratory inhalers in individuals presenting for resection. It has been well established that systemic corticosteroid use influences blood eosinophil counts[39] although the effect of inhaled corticosteroids on blood

eosinophils is more limited. Given this background, it is proper that an interaction term should have been included in our models.

In conclusion, this study confirms that eosinophils should be considered an important biomarker for both readmission and mortality in all individuals presenting for early-stage lung cancer resection. Further study should identify the role of combined inhaled corticosteroid and bronchodilator therapy to improve postoperative outcomes and, potentially, mortality.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.

3. Bryan S, Masoud H, Weir HK, et al. Cancer in Canada: Stage at diagnosis. Health Rep 2018;29:21-5.

4. Li C, Wang H, Jiang Y, et al. Advances in lung cancer screening and early detection. Cancer Biol Med 2022;19:591-608.

5. Gajra A, Akbar SA, Din NU. Management of Lung Cancer in the Elderly. Clinics in Geriatric Medicine 2016;32:81-95.

6. Loganathan RS, Stover DE, Shi W, Venkatraman E. Prevalence of COPD in women compared to men around the time of diagnosis of primary lung cancer. Chest 2006;129:1305-12.

7. Roy E, Rheault J, Pigeon M-A, et al. Lung cancer resection and postoperative outcomes in COPD: A single-center experience. Chronic Respiratory Disease 2020;17:1479973120925430.

8. Disease GIfCOP. Global strategy for the diagnosis, management,

and prevention of chronic obstructive pulmonary

disease2023.

9. Whittaker H, Rubino A, Müllerová H, et al. Frequency and Severity of Exacerbations of COPD Associated with Future Risk of Exacerbations and Mortality: A UK Routine Health Care Data Study. Int J Chron Obstruct Pulmon Dis 2022;17:427-37.

10. Slenter RH, Sprooten RT, Kotz D, Wesseling G, Wouters EF, Rohde GG. Predictors of 1-year mortality at hospital admission for acute exacerbations of chronic obstructive pulmonary disease. Respiration 2013;85:15-26.

11. Bathoorn E, Liesker JJ, Postma DS, et al. Change in inflammation in out-patient COPD patients from stable phase to a subsequent exacerbation. Int J Chron Obstruct Pulmon Dis 2009;4:101-9.

12. Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med 2011;184:662-71.

13. García-Pardo M, Chang A, Schmid S, et al. Respiratory and Cardiometabolic Comorbidities and Stages I to III NSCLC Survival: A Pooled Analysis From the International Lung Cancer Consortium. J Thorac Oncol 2023;18:313-23.

14. Goffin JR, Corriveau S, Tang GH, Pond GR. Management and outcomes of patients with chronic obstructive lung disease and lung cancer in a public healthcare system. PLoS One 2021;16:e0251886.

15. Perrotta F, D'Agnano V, Scialò F, et al. Evolving concepts in COPD and lung cancer: a narrative review. Minerva Med 2022;113:436-48.

16. Hastie AT, Martinez FJ, Curtis JL, et al. Association of sputum and blood eosinophil concentrations with clinical measures of COPD severity: an analysis of the SPIROMICS cohort. Lancet Respir Med 2017;5:956-67.

17. Benson VS, Hartl S, Barnes N, Galwey N, Van Dyke MK, Kwon N. Blood eosinophil counts in the general population and airways disease: a comprehensive review and meta-analysis. Eur Respir J 2022;59.

18. Lipson DA, Barnhart F, Brealey N, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med 2018;378:1671-80.

19. Martinez FJ, Rabe KF, Ferguson GT, et al. Reduced All-Cause Mortality in the ETHOS Trial of Budesonide/Glycopyrrolate/Formoterol for Chronic Obstructive Pulmonary Disease. A Randomized, Double-Blind, Multicenter, Parallel-Group Study. Am J Respir Crit Care Med 2021;203:553-64.

20. Tan WC, Bourbeau J, Nadeau G, et al. High eosinophil counts predict decline in FEV(1): results from the CanCOLD study. Eur Respir J 2021;57.

21. Konstantinidis K, Woodcock-Shaw J, Dinesh P, Brunelli A. Incidence and risk factors for 90-day hospital readmission following video-assisted thoracoscopic anatomical lung resection†. European Journal of Cardio-Thoracic Surgery 2019;55:666-72.

22. Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. Lancet 2018;391:1076-84.

23. Bafadhel M, Greening NJ, Harvey-Dunstan TC, et al. Blood Eosinophils and Outcomes in Severe Hospitalized Exacerbations of COPD. Chest 2016;150:320-8.

24. García-Tirado J, Júdez-Legaristi D, Landa-Oviedo HS, Miguelena-Bobadilla JM. Unplanned readmission after lung resection surgery: A systematic review. Cir Esp (Engl Ed) 2019;97:128-44.

25. Konstantinidis K, Woodcock-Shaw J, Dinesh P, Brunelli A. Incidence and risk factors for 90-day hospital readmission following video-assisted thoracoscopic anatomical lung resection†. Eur J Cardiothorac Surg 2019;55:666-72.

26. Hu Y, McMurry TL, Isbell JM, Stukenborg GJ, Kozower BD. Readmission after lung cancer resection is associated with a 6-fold increase in 90-day postoperative mortality. J Thorac Cardiovasc Surg 2014;148:2261-7.e1.

27. Hu Y, McMurry TL, Stukenborg GJ, Kozower BD. Readmission predicts 90-day mortality after esophagectomy: Analysis of Surveillance, Epidemiology, and End Results Registry linked to Medicare outcomes. J Thorac Cardiovasc Surg 2015;150:1254-60.

28. Granger C, Cavalheri V. Preoperative exercise training for people with non-small cell lung cancer. Cochrane Database of Systematic Reviews 2022.

29. Bhagat R, Bronsert MR, Ward AN, et al. National Analysis of Unplanned Readmissions After Thoracoscopic Versus Open Lung Cancer Resection. The Annals of Thoracic Surgery 2017;104:1782-90.

30. Hendriksen BS, Reed MF, Taylor MD, Hollenbeak CS. Readmissions After Lobectomy in an Era of Increasing Minimally Invasive Surgery: A Statewide Analysis. Innovations (Phila) 2019;14:453-62.

31. Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax 2012;67:957-63.

32. Stiles BM, Poon A, Giambrone GP, et al. Incidence and Factors Associated With Hospital Readmission After Pulmonary Lobectomy. The Annals of Thoracic Surgery 2016;101:434-43.

33. Assi R, Wong DJ, Boffa DJ, et al. Hospital readmission after pulmonary lobectomy is not affected by surgical approach. Ann Thorac Surg 2015;99:393-8.

34. Chen H, Deng ZX, Sun J, et al. Association of Inhaled Corticosteroids With All-Cause Mortality Risk in Patients With COPD: A Meta-analysis of 60 Randomized Controlled Trials. Chest 2023;163:100-14.

35. Homma T. Preoperative umeclidinium/vilanterol or tiotropium improves postoperative FEV 1 in lung cancer patients with comorbid untreated chronic obstructive pulmonary disease. Journal of Thoracic Disease 2023;15:1584-94.

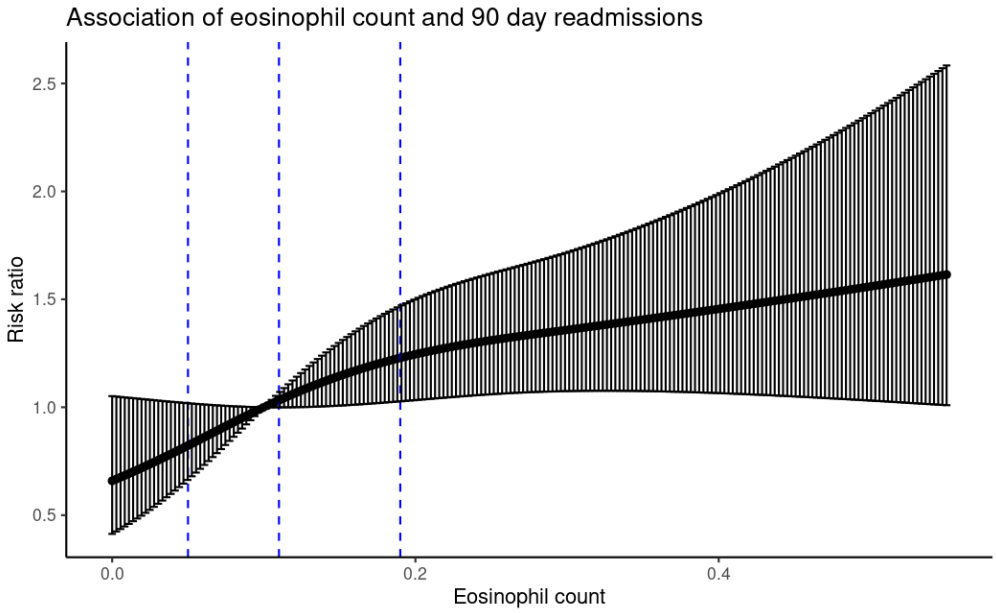
36. Bölükbas S, Eberlein M, Eckhoff J, Schirren J. Short-term effects of inhalative tiotropium/formoterol/budenoside versus tiotropium/formoterol in patients with newly diagnosed chronic obstructive pulmonary disease requiring surgery for lung cancer: a prospective randomized trial☆. European Journal of Cardio-Thoracic Surgery 2011;39:995-1000.

37. Pascoe S, Barnes N, Brusselle G, et al. Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial. Lancet Respir Med 2019;7:745-56.

38. Yoon JK, Lee JK, Lee CH, et al. The Association Between Eosinophil Variability Patterns and the Efficacy of Inhaled Corticosteroids in Stable COPD Patients. Int J Chron Obstruct Pulmon Dis 2020;15:2061-70.

39. Bafadhel M, McKenna S, Terry S, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. Am J Respir Crit Care Med 2012;186:48-55.

Appendices



Appendix 1: The spline function for eosinophil counts (10^9 cells/L) as a continuous variable and the associated risk ratio of 90-day healthcare utilization. The knots are at 0.05, 0.11 and 0.19 cells x 10^9/L (25^{th}, 50^{th} and 75^{th} percentile).

Appendix 2: Factors independently associated with 90-day healthcare utilization.

Variable	Unadjusted RR 95% CI	p-value	Adjusted RR 95% CI	p-value
Eosinophil count, cells/μL	2.04(1.60-2.60)	<0.0001	2.18(1.53-3.12)	<0.0001
Charlson comorbidity index	1.23(1.10-1.39)	<0.01	1.26(1.10-1.45)	<0.001
Nodal status				
N0	1(Ref)	-	1(Ref)	-
N1	0.31(0.10-0.95)	0.04	0.28(0.09-0.86)	0.02

Eosinophil counts were used as a continuous variable. Adjusted for age, sex, COPD status, smoking, tumor size, comorbidity index, nodal status, white cell count, creatinine, and hemoglobin.

CHAPTER 4: DISCUSSION

Despite all the advances in screening, diagnosis, and treatment, lung cancer remains the leading cause of cancer-related mortality in the world and Canada. The improvements in early diagnosis and the development of new surgical techniques have resulted in more patients being eligible for lung cancer resection surgery. Among the group that presents for surgery, there is a profound comorbidity burden with chronic obstructive pulmonary disease. These patients are often undertreated because of their poor pulmonary reserve and risk for postoperative complications. Risk stratification becomes even more important in this group of patients because COPD is not a homogenous disease and its different endotypes may have different effects on treatment outcomes. In this thesis, we set out to explore the relationship between high blood eosinophil counts and poor postoperative outcomes in early-stage lung cancer patients.

The characteristics of the cohort presented here are consistent with cohorts published in other studies. Firstly, a mean age of 69 years was described. Most studies report the mean age at diagnosis rather than the mean age at surgery. However, there was consistency between this study and previous studies despite the differences in the time points. The SEER database describes a mean age at diagnosis of 70 years among both men and women[76]. Male sex represented 42% in this present study.

VATS was the main surgical approach used representing 75% of cases. Despite the gain in the popularity of VATS, this figure is much higher than what has previously been reported. Using the Premier Healthcare database, two studies indicated that VATS lobectomy accounts for between 40% and 44% of all non-emergent lobectomies done for lung cancer at high-volume centers [77,78]. A decade ago, the analysis of the National Cancer Database showed that only 17% of lobectomies were performed by VATS. The discrepancies observed here may be due to the clinical coding of our database, where some cases may have been converted to open thoracotomy, but this was not well recorded. Another reason could be that our center is highly specialized with surgeries being performed by thoracic surgeons who are well-trained in VATS whereas other studies have used databases where some of the surgeries were performed by general surgeons who may not be specialized enough to perform VATS. In keeping with previous studies, however, VATS was associated with a shorter length of index hospital stay compared with open lobectomy [79].

In our study, the prevalence of COPD using ICD codes was 29%, and 20% using spirometry (where available). However, among the group with high blood eosinophil counts these rates were higher at 34.9% and 27% (ICD and spirometry), respectively, as expected. A small retrospective study (n=174) defined COPD in patients if a diagnosis was present in their medical records, or if they had spirometry results, arterial blood-gas results, and visual detection of emphysema in their CT

scan that indicated COPD, and found a prevalence of 39% COPD (59% emphysema) at the time of lung cancer diagnosis[80]. A larger retrospective cohort (n= 105,304) using data from Ontario had a COPD prevalence of 34.9% based on the ICES-derived COPD cohort which uses physician billing and hospital records to define COPD[32]. These differences may be due to our smaller sample size and misclassification of COPD by history and classification by ICD10 codes. Moreover, we had PFTs in only 34.4% of the patients. This would suggest a higher prevalence if more PFTs were available.

Asthma on the other hand was represented in 11.4% of our patients. A Korean population-based cross-sectional study (n=51,586) found an asthma prevalence of 17.3% among lung cancer patients[81]. Poorly controlled asthma was identified as a risk factor for lung cancer development in the prospective HUNT study [82]. A meta-analysis with a pooled total of more than 16 million patients concluded that asthma was an independent risk factor for the development of lung cancer[83]. On the contrary, a recent analysis of more than 20,000 did not find a correlation between asthma and lung cancer[84]. The prevalence of asthma among lung cancer patients are not well reported in the literature.

The distribution of blood eosinophil counts presented in this study was right skewed as has been described before[44]. Higher blood eosinophil counts were observed more among those with COPD than those who did not have COPD. This is expected because of Type 2 inflammation that has been described and substantiated in 10-40% of patients with COPD[34,60]. Furthermore, male sex was associated with higher blood eosinophil count in keeping with previous literature[41,44].

The readmission rate of 15.3% in our study was consistent with that reported in other studies which showed. Readmissions within 30 days of surgery are associated with increased mortality following lung resection surgery. Including readmission events up to 90 days allows for the capturing of the

contribution of patient level factors. 80 % of the factors associated with higher rates of unscheduled postoperative healthcare utilization are at the patient level[85]. However, studies that have used administrative databases and clinical registries may underestimate the patient-level factors associated with readmissions because these sources do not capture detailed perioperative data[86].

Factors associated with increased unplanned postoperative healthcare utilization within 30 days of discharge were determined in a large (n=39,734) retrospective cohort study that used the Society of Thoracic Surgeons (STS) General Thoracic Surgery Database. In that study, they found that interstitial fibrosis, steroid use, history of stroke, and a performance status of 2 or 3 were independent predictors of 30-day readmission. Of these predictors, interstitial lung disease was the most significant[86]. Surgical approach was one of the intraoperative predictors of readmission. However, we and others did not observe this association in our study [63,87]. Some of the differences may be explained by the differences in how readmissions were defined, with ours defining 90-day readmission from the date of index surgery. Of note is that our readmission data was inclusive only of readmissions to the index hospital as we did not have data about readmissions to other centers.

As has been described in other literature, pulmonary complications remained the commonest cause for increased healthcare utilization within the first 90 days post-surgery[63,66,68]. Prolonged air leak (PAL), a well-established morbidity of lung resection surgery, contributed to more than half of the pulmonary causes for healthcare utilization in this study. COPD, low body mass index, and a history of smoking are all associated with a higher risk of PAL. It has been suggested that adequate management of air leaks by reinforced stapling intraoperatively and using digital chest drainage systems could ameliorate the problem and maximize the gains of minimally invasive surgery [88].

Postoperative pulmonary complications do not contribute to increased healthcare utilization equally. Where granularity was available and there were enough events to separate pulmonary

complications individually instead of using a composite complication outcome, pulmonary embolus, empyema, pleural effusion requiring drainage, and pneumothorax were associated with a greater increase in odds of readmission. While these results suggest a trend in respiratory complications the main limitation is misclassification due to the use of ICD codes.

As observed in this study, having a spirometry diagnosis of COPD was associated with a higher risk of experiencing postoperative pulmonary complications. A previous prospective study comparing the odds of postoperative pulmonary complications between 2 groups, one with COPD and the other with normal spirometry, reported similar findings[89]. Another retrospective cohort study of lung cancer resection patients, mainly those with GOLD 1 and GOLD 2 class COPD, found higher odds of pneumonia and prolonged air leak among the COPD group compared with those who had normal spirometry[29].

Previous studies investigating postoperative outcomes after lung resection surgery rarely used laboratory values in their statistical models. Much emphasis has been, justifiably, placed on demographic factors, comorbidities, and pulmonary function results. Airway inflammation, as reflected by blood eosinophil counts, can potentially provide another layer into our understanding of postoperative outcomes.

The results of our study show that blood eosinophil counts, at least those done within 90 days before surgery, are independently associated with increased postoperative healthcare utilization. Taking BECs as a continuous variable, we observed a similar association when natural cubic splines were used for modeling. Starting from 110 cells/μL we observed an incremental relationship between blood eosinophils and the risk of readmission. Our sensitivity analysis in which we compared adverse outcomes and different cutoff points for blood eosinophil counts (150, 200, and 300 cells/μL), showed an incremental effect size the higher the BECs. This is consistent

with what has been described in the literature where higher blood eosinophil counts are associated with more adverse outcomes in COPD and a better response to inhaled corticosteroid therapy.

Less focus has been made on the management of comorbidities such as airway disease, that may have an even more important contribution to mortality in lung cancer. In COPD, eosinophil counts have been identified as an important actionable biomarker for mortality [70]. Eosinophil counts above 200cells/μL were found to be the strongest predictor of reduction in all-cause mortality among patients with COPD who are on more than 6 months of inhaled corticosteroid therapy[70].

Our study found a significant relationship between blood eosinophil counts above 200 cells/μL and poorer 1-year survival. However, after 3 years of follow-up, this association was not observed. This suggests that blood eosinophil counts, reflective of airway inflammation, may have better sensitivity for short-term outcomes (< 1 year) than long-term outcomes. Given the variability of blood eosinophil counts and the ever-evolving phenotypical characteristics of COPD, it is not surprising that the relationship is time-limited. Beyond 1 year, the more established and non-modifiable factors such as male sex, and tumor stage maintained their association with survival.

To find ways to level the increased risk among COPD patients presenting for lung resection surgery, some small studies have explored the use of inhaler therapy that includes inhaled steroid therapy (LAMA/LABA and triple therapy combinations) for COPD prescribed preoperatively continuing into the postoperative period [71,72]. Given the substantial evidence about the improvement of clinical symptoms in patients with type 2 inflammation COPD who are put on inhaled corticosteroid (ICS) therapy[40,73], there may be a benefit in exploring ICS or biologic anti-IL5 use among patients who have high BECs in the pre-operative surgical period.

Several limitations should be made note of. An important limitation of this study is that it is a retrospective cohort study. The data we used in this study was not primarily collected for research purposes. Clinical data is vulnerable to a lack of completeness[90]. A significant amount of data preprocessing is required before clinical data can be useable for analysis and appropriate interpretation. While important variables can be obtained from this data, some meaningful patient-reported outcomes tend to be missing as they are not routinely collected during clinical care. Despite this, retrospective studies have their role in building knowledge from which prospective studies can then be designed.

Secondly, this is a single-institution cohort analysis. The rates of adverse outcomes, while in line with published rates, are slightly lower but consistent with high-volume surgical centers such as ours. High-volume centers tend to have more expertise and therefore achieve superior outcomes, and this may dampen the observed rates of adverse outcomes. In a study that compared the surgical outcomes at a high-volume thoracic surgery clinic, their outcomes were superior to those predicted by the Society of Thoracic Surgeons risk scores[4]. The findings of this study would therefore need to be validated by other centres.

Thirdly, this study did not exclusively focus on patients with a diagnosis of COPD or asthma given we had a significant amount of missing pulmonary function data as pulmonary function tests performed outside our institution. We regarded the missingness in PFTs as missing not at random (MNAR) because patients who are healthy and younger tend not to be sent for PFTs if their cardiopulmonary evaluation is negative[23]. Smokers and patients with a history of respiratory disease almost always get PFTs done before lung resection surgery. The two groups of patients with available PFTs compared with those without PFTs would then have heterogeneous values for lung function. Seeing this, we could not perform multiple imputations for the missing PFTs

because the primary assumption required to perform such a method of dealing with missing values was not met[91]. While it does limit the interpretation of our results, it increases the generalizability of the utility of eosinophils in all patients presenting for resection of early-stage lung cancer.

The use of ICD codes to classify postoperative complications is another limiting factor of this study. There is a risk of misclassification given that this data was not prospectively collected and was primarily for clinical and not for research purposes. A study published a few years ago approached this misclassification problem using Bayesian inference by comparing the odds ratio obtained using an administrative database ICD codes versus those obtained from Bayesian analysis. They found that using the Bayesian approach was useful in reducing outcome misclassification. In that study, ICD codes were shown to have a low sensitivity but high specificity[92]. This could suggest that the rates of pulmonary complications presented here are an underestimate. We did not address this issue in our study because it was beyond our scope and main aim.

Furthermore, the eosinophil counts used were taken at different time points before surgery for participants. Variability in blood eosinophil counts has been well studied and there is a suggestion that there may be a diurnal as well as seasonal variation[41]. In one study, up to 22% of patients with COPD had significant variability in their BECs at 1-year follow-up [74]. To mitigate this limitation, we used the maximum blood eosinophil count in the 90-day preoperative window for each patient.

Lastly, we did not have data about frailty or functional status. Sarcopenia is quite common among lung cancer patients with a prevalence of between 42.8%-45% and has been linked to poor surgical outcomes in patients presenting for lung resection[84]. We could have used BMI as a surrogate, but this was linked to pulmonary function data which was available in only a third of the cohort.

In conclusion, this study confirms that eosinophils should be considered an important biomarker for both increased healthcare utilization and mortality in all individuals presenting for early-stage lung cancer resection. Further studies should identify the role of combined inhaled corticosteroid and bronchodilator therapy to improve post-operative outcomes among lung cancer patients presenting for lung resection surgery. This could potentially combat the undertreatment of patients with chronic airway disease and make them more suitable surgical candidates.

CHAPTER 5: CONCLUSIONS AND SUMMARY

Despite the burden of underlying chronic airway disease among lung cancer patients because of shared risk factors, few studies have examined how to improve outcomes in this group of patients. It is well established that patients with chronic obstructive airway disease (COPD) are undertreated and when they do have surgery, they experience a more complicated post-operative course.

The primary goal of this Master's thesis was to contribute to new knowledge in improving lung cancer outcomes. Our study addressed a key aspect of lung cancer care where there is a notable lack of data, that is, improving risk stratification in early lung cancer patients by identifying a readily available and clinically useful biomarker already used in patients with chronic airways disease.

The manuscript tries to address the paucity of data on the role of eosinophilia as a biomarker in early-stage lung cancer patients who often have undiagnosed chronic airway disease. It showed that high blood eosinophil counts are useful biomarkers that are associated with increased postoperative 90-day healthcare utilization and poor overall survival. Blood eosinophil counts are routinely measured and provide a surrogate marker of airway inflammation. Their utility lies in

their inexpensive nature and the ease with which they can be measured. The thesis also showed that even after adjusting for COPD by available spirometry results, eosinophilia remained an independently associated with poor outcomes. This suggests that eosinophils may have a poorly understood role in lung cancer in the of presence or absence of COPD.

Future directions

The work presented in this thesis provides a background for future exploration on the role of blood eosinophil counts as a biomarker for personalization of therapy pre-operatively with inhaled corticosteroids. Because this is a single-center study, it would be useful to find other cohorts in which to validate the association established in this study, perhaps starting with another retrospective database with a larger sample size. Furthermore, prospective studies can subsequently be done to observe if this relationship is consistent. One of the limiting factors of our study is that we only had pulmonary function test data for 35% of the patients. This limited our ability to diagnose COPD by spirometry. Having all PFTs available would provide far greater granularity that would help determine if the observed association is present in all comers or only in those with some degree of airway obstruction by spirometry. If the association is indeed in all patients with lung cancer regardless of COPD status, it would open a doorway into more studies that can look at the biology of this immune cell in lung cancer.

In patients with a spirometry diagnosis of COPD presenting for lung cancer resection, it would be justifiable to do a randomized controlled trial to explore the use of targeted inhaled corticosteroid therapy and measure healthcare utilization as an outcome. This would then address the undertreatment of patients with co-existing lung cancer and COPD and subsequently reduce the excess poor outcomes observed in this group of patients.

CHAPTER 6: REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.

3. Bryan S, Masoud H, Weir HK, et al. Cancer in Canada: Stage at diagnosis. Health Rep 2018;29:21-5.

4. Lung Cancer Statistics. 2022. (Accessed 2023-05-10, at https://cancer.ca/en/cancer-information/cancer-types/lung/statistics.)

5. Harðardottir H, Jonsson S, Gunnarsson O, et al. [Advances in lung cancer diagnosis and treatment - a review]. Laeknabladid 2022;108:17-29.

6. Ruano-Raviña A, Provencio M, Calvo de Juan V, et al. Lung cancer symptoms at diagnosis: results of a nationwide registry study. ESMO Open 2020;5:e001021.

7. Oliver AL. Lung Cancer: Epidemiology and Screening. Surgical Clinics of North America 2022;102:335-44.

8. Tan LE, A MR, Lim CS. Association of chronic obstructive pulmonary disease and postresection lung cancer survival: a systematic review and meta-analysis. J Investig Med 2017;65:342-52.

9. Lemjabbar-Alaoui H, Hassan OU, Yang YW, Buchanan P. Lung cancer: Biology and treatment options. Biochim Biophys Acta 2015;1856:189-210.

10. Bade BC, Dela Cruz CS. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. Clinics in Chest Medicine 2020;41:1-24.

11. Stapelfeld C, Dammann C, Maser E. Sex-specificity in lung cancer risk. International Journal of Cancer 2020;146:2376-82.

12. Risch HA, Howe GR, Jain M, Burch JD, Holowaty EJ, Miller AB. Are Female Smokers at Higher Risk for Lung Cancer than Male Smokers?: A Case-Control Analysis by Histologic Type. American Journal of Epidemiology 1993;138:281-93.

13. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.

14. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med 2020;382:503-13.

15. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The Eighth Edition Lung Cancer Stage Classification. Chest 2017;151:193-203.

16. Mithoowani H, Febbraro M. Non-Small-Cell Lung Cancer in 2022: A Review for General Practitioners in Oncology. Current Oncology 2022;29:1828-39.

17. Farjah F, Backhus LM, Varghese TK, et al. Ninety-day costs of video-assisted thoracic surgery versus open lobectomy for lung cancer. Ann Thorac Surg 2014;98:191-6.

18. Lim E, Batchelor TJP, Dunning J, et al. Video-Assisted Thoracoscopic or Open Lobectomy in Early-Stage Lung Cancer. NEJM Evid 2022;1:EVIDoa2100016.

19. Hoy H, Lynch T, Beck M. Surgical Treatment of Lung Cancer. Critical Care Nursing Clinics of North America 2019;31:303-13.

20. Saji H, Okada M, Tsuboi M, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. Lancet 2022;399:1607-17.

21. Cao J, Yuan P, Wang Y, et al. Survival Rates After Lobectomy, Segmentectomy, and Wedge Resection for Non-Small Cell Lung Cancer. Ann Thorac Surg 2018;105:1483-91.

22. Song C, Lu Z, Li D, Pan S, Li N, Geng Q. Survival after wedge resection versus lobectomy for stage IA second primary NSCLC with previous lung cancer-directed surgery. Front Oncol 2022;12:890033.

23. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e166S-e90S.

24. Brunelli A, Salati M, Rocco G, et al. European risk models for morbidity (EuroLung1) and mortality (EuroLung2) to predict outcome following anatomic lung resections: an analysis from the European Society of Thoracic Surgeons database†,‡. European Journal of Cardio-Thoracic Surgery 2016;51:490-7.

25. Brunelli A, Varela G, Salati M, et al. Recalibration of the Revised Cardiac Risk Index in Lung Resection Candidates. The Annals of Thoracic Surgery 2010;90:199-203.

26. Taylor M, Hashmi SF, Martin GP, et al. A systematic review of risk prediction models for perioperative mortality after thoracic surgery. Interact Cardiovasc Thorac Surg 2021;32:333-42.

27. Schlachtenberger G, Doerr F, Menghesha H, et al. A comparative study of four thoracic mortality scores. Asian Cardiovasc Thorac Ann 2023;31:244-52.

28. Loganathan RS, Stover DE, Shi W, Venkatraman E. Prevalence of COPD in women compared to men around the time of diagnosis of primary lung cancer. Chest 2006;129:1305-12.

29. Roy E, Rheault J, Pigeon M-A, et al. Lung cancer resection and postoperative outcomes in COPD: A single-center experience. Chronic Respiratory Disease 2020;17:1479973120925430.

30. Qi C, Sun SW, Xiong XZ. From COPD to Lung Cancer: Mechanisms Linking, Diagnosis, Treatment, and Prognosis. Int J Chron Obstruct Pulmon Dis 2022;17:2603-21.

31. García-Pardo M, Chang A, Schmid S, et al. Respiratory and Cardiometabolic Comorbidities and Stages I to III NSCLC Survival: A Pooled Analysis From the International Lung Cancer Consortium. J Thorac Oncol 2023;18:313-23.

32. Goffin JR, Corriveau S, Tang GH, Pond GR. Management and outcomes of patients with chronic obstructive lung disease and lung cancer in a public healthcare system. PLoS One 2021;16:e0251886.

33. Perrotta F, D'Agnano V, Scialò F, et al. Evolving concepts in COPD and lung cancer: a narrative review. Minerva Med 2022;113:436-48.

34. Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med 2011;184:662-71.

35. Disease GIfCOP. Global strategy for the diagnosis, management,

and prevention of chronic obstructive pulmonary

disease2023.

36. Whittaker H, Rubino A, Müllerová H, et al. Frequency and Severity of Exacerbations of COPD Associated with Future Risk of Exacerbations and Mortality: A UK Routine Health Care Data Study. Int J Chron Obstruct Pulmon Dis 2022;17:427-37.

37. Slenter RH, Sprooten RT, Kotz D, Wesseling G, Wouters EF, Rohde GG. Predictors of 1-year mortality at hospital admission for acute exacerbations of chronic obstructive pulmonary disease. Respiration 2013;85:15-26.

38. Bathoorn E, Liesker JJ, Postma DS, et al. Change in inflammation in out-patient COPD patients from stable phase to a subsequent exacerbation. Int J Chron Obstruct Pulmon Dis 2009;4:101-9.

39. Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax 2012;67:957-63.

40. Hastie AT, Martinez FJ, Curtis JL, et al. Association of sputum and blood eosinophil concentrations with clinical measures of COPD severity: an analysis of the SPIROMICS cohort. Lancet Respir Med 2017;5:956-67.

41. Benson VS, Hartl S, Barnes N, Galwey N, Van Dyke MK, Kwon N. Blood eosinophil counts in the general population and airways disease: a comprehensive review and meta-analysis. Eur Respir J 2022;59.

42. Singh D, Kolsum U, Brightling CE, Locantore N, Agusti A, Tal-Singer R. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. Eur Respir J 2014;44:1697-700.

43. Pignatti P, Visca D, Cherubino F, et al. Do blood eosinophils strictly reflect airway inflammation in COPD? Comparison with asthmatic patients. Respiratory Research 2019;20:145.

44. Abe Y, Suzuki M, Kimura H, et al. Blood eosinophil count variability in chronic obstructive pulmonary disease and severe asthma. Allergology International 2022.

45. Kreindler JL, Watkins ML, Lettis S, Tal-Singer R, Locantore N. Effect of inhaled corticosteroids on blood eosinophil count in steroid-naïve patients with COPD. BMJ Open Respir Res 2016;3:e000151.

46. Lipson DA, Barnhart F, Brealey N, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med 2018;378:1671-80.

47. Martinez FJ, Rabe KF, Ferguson GT, et al. Reduced All-Cause Mortality in the ETHOS Trial of Budesonide/Glycopyrrolate/Formoterol for Chronic Obstructive Pulmonary Disease. A Randomized, Double-Blind, Multicenter, Parallel-Group Study. Am J Respir Crit Care Med 2021;203:553-64.

48. Chen H, Deng Z-X, Sun J, et al. Association of Inhaled Corticosteroids With All-Cause Mortality Risk in Patients With COPD: A Meta-analysis of 60 Randomized Controlled Trials. Chest 2023;163:100-14.

49. Tan WC, Bourbeau J, Nadeau G, et al. High eosinophil counts predict decline in FEV(1): results from the CanCOLD study. Eur Respir J 2021;57.

50. Gauthier J, Wu QV, Gooley TA. Cubic splines to model relationships between continuous variables and outcomes: a guide for clinicians. Bone Marrow Transplantation 2020;55:675-80.

51. Bafadhel M, Peterson S, De Blas MA, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. Lancet Respir Med 2018;6:117-26.

52. Gallis JA, Turner EL. Relative Measures of Association for Binary Outcomes: Challenges and Recommendations for the Global Health Researcher. Ann Glob Health 2019;85:137.

53. Schmidt CO, Kohlmann T. When to use the odds ratio or the relative risk? International Journal of Public Health 2008;53:165-7.

54. Yelland LN, Salter AB, Ryan P. Performance of the Modified Poisson Regression Approach for Estimating Relative Risks From Clustered Prospective Data. American Journal of Epidemiology 2011;174:984-92.

55. Chen W, Qian L, Shi J, Franklin M. Comparing performance between log-binomial and robust Poisson regression models for estimating risk ratios under model misspecification. BMC Medical Research Methodology 2018;18:63.

56. Torre LA, Siegel RL, Jemal A. Lung Cancer Statistics. Adv Exp Med Biol 2016;893:1-19.

57. Blasberg JD, Seder CW, Leverson G, Shan Y, Maloney JD, Macke RA. Video-Assisted Thoracoscopic Lobectomy for Lung Cancer: Current Practice Patterns and Predictors of Adoption. Ann Thorac Surg 2016;102:1854-62.

58. Oh DS, Reddy RM, Gorrepati ML, Mehendale S, Reed MF. Robotic-Assisted, Video-Assisted Thoracoscopic and Open Lobectomy: Propensity-Matched Analysis of Recent Premier Data. Ann Thorac Surg 2017;104:1733-40.

59. Berfield KS, Farjah F, Mulligan MS. Video-Assisted Thoracoscopic Lobectomy for Lung Cancer. Ann Thorac Surg 2019;107:603-9.

60. Ytterstad E, Moe PC, Hjalmarsen A. COPD in primary lung cancer patients: prevalence and mortality. Int J Chron Obstruct Pulmon Dis 2016;11:625-36.

61. Chang-Mo O, Sanghee L, Hoejun K, Bin H, Hyunsoon C. Prevalence of pre-existing lung diseases and their association with income level among patients with lung cancer: a nationwide population-based case-control study in South Korea. BMJ Open Respiratory Research 2023;10:e001772.

62. Jiang L, Sun YQ, Langhammer A, et al. Asthma and asthma symptom control in relation to incidence of lung cancer in the HUNT study. Sci Rep 2021;11:4539.

63. Qu YL, Liu J, Zhang LX, et al. Asthma and the risk of lung cancer: a meta-analysis. Oncotarget 2017;8:11614-20.

64. Rahman HH, Niemann D, Munson-McGee SH. Association between asthma, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, and lung cancer in the US population. Environ Sci Pollut Res Int 2023;30:20147-58.

65. Bafadhel M, Greening NJ, Harvey-Dunstan TC, et al. Blood Eosinophils and Outcomes in Severe Hospitalized Exacerbations of COPD. Chest 2016;150:320-8.

66. García-Tirado J, Júdez-Legaristi D, Landa-Oviedo HS, Miguelena-Bobadilla JM. Unplanned readmission after lung resection surgery: A systematic review. Cir Esp (Engl Ed) 2019;97:128-44.

67. Konstantinidis K, Woodcock-Shaw J, Dinesh P, Brunelli A. Incidence and risk factors for 90-day hospital readmission following video-assisted thoracoscopic anatomical lung resection†. Eur J Cardiothorac Surg 2019;55:666-72.

68. Hu Y, McMurry TL, Isbell JM, Stukenborg GJ, Kozower BD. Readmission after lung cancer resection is associated with a 6-fold increase in 90-day postoperative mortality. J Thorac Cardiovasc Surg 2014;148:2261-7.e1.

69. Hu Y, McMurry TL, Stukenborg GJ, Kozower BD. Readmission predicts 90-day mortality after esophagectomy: Analysis of Surveillance, Epidemiology, and End Results Registry linked to Medicare outcomes. J Thorac Cardiovasc Surg 2015;150:1254-60.

70. Gani F, Lucas DJ, Kim Y, Schneider EB, Pawlik TM. Understanding Variation in 30-Day Surgical Readmission in the Era of Accountable Care: Effect of the Patient, Surgeon, and Surgical Subspecialties. JAMA Surg 2015;150:1042-9.

71. Brown LM, Thibault DP, Kosinski AS, et al. Readmission After Lobectomy for Lung Cancer: Not All Complications Contribute Equally. Annals of Surgery 2021;274.

72. Rajaram R, Ju MH, Bilimoria KY, Ko CY, DeCamp MM. National evaluation of hospital readmission after pulmonary resection. J Thorac Cardiovasc Surg 2015;150:1508-14.e2.

73. Stiles BM, Poon A, Giambrone GP, et al. Incidence and Factors Associated With Hospital Readmission After Pulmonary Lobectomy. The Annals of Thoracic Surgery 2016;101:434-43.

74. Bhagat R, Bronsert MR, Ward AN, et al. National Analysis of Unplanned Readmissions After Thoracoscopic Versus Open Lung Cancer Resection. The Annals of Thoracic Surgery 2017;104:1782-90.

75. Rathore K, Newman M. Prolonged air leak following video-assisted thoracoscopic major lung resection: newer avenues to manage an age-old problem. Indian J Thorac Cardiovasc Surg 2022;38:394-7.

76. Kim ES, Kim YT, Kang CH, et al. Prevalence of and risk factors for postoperative pulmonary complications after lung cancer surgery in patients with early-stage COPD. Int J Chron Obstruct Pulmon Dis 2016;11:1317-26.

77. Granger C, Cavalheri V. Preoperative exercise training for people with non-small cell lung cancer. Cochrane Database of Systematic Reviews 2022.

78. Chen H, Deng ZX, Sun J, et al. Association of Inhaled Corticosteroids With All-Cause Mortality Risk in Patients With COPD: A Meta-analysis of 60 Randomized Controlled Trials. Chest 2023;163:100-14.

79. Hendriksen BS, Reed MF, Taylor MD, Hollenbeak CS. Readmissions After Lobectomy in an Era of Increasing Minimally Invasive Surgery: A Statewide Analysis. Innovations (Phila) 2019;14:453-62.

80. Homma T. Preoperative umeclidinium/vilanterol or tiotropium improves postoperative FEV 1 in lung cancer patients with comorbid untreated chronic obstructive pulmonary disease. Journal of Thoracic Disease 2023;15:1584-94.

81. Bölükbas S, Eberlein M, Eckhoff J, Schirren J. Short-term effects of inhalative tiotropium/formoterol/budenoside versus tiotropium/formoterol in patients with newly diagnosed chronic obstructive pulmonary disease requiring surgery for lung cancer: a prospective randomized trial☆. European Journal of Cardio-Thoracic Surgery 2011;39:995-1000.

82. Pascoe S, Barnes N, Brusselle G, et al. Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial. Lancet Respir Med 2019;7:745-56.

83. Talari K, Goyal M. Retrospective studies - utility and caveats. J R Coll Physicians Edinb 2020;50:398-402.

84. Austin PC, White IR, Lee DS, van Buuren S. Missing Data in Clinical Research: A Tutorial on Multiple Imputation. Canadian Journal of Cardiology 2021;37:1322-31.

85. Ni J, Dasgupta K, Kahn SR, et al. Comparing external and internal validation methods in correcting outcome misclassification bias in logistic regression: A simulation study and application to the case of postsurgical venous thromboembolism following total hip and knee arthroplasty. Pharmacoepidemiol Drug Saf 2019;28:217-26.

86. Yoon JK, Lee JK, Lee CH, et al. The Association Between Eosinophil Variability Patterns and the Efficacy of Inhaled Corticosteroids in Stable COPD Patients. Int J Chron Obstruct Pulmon Dis 2020;15:2061-70.