NT-proBNP as a Predictor of Postoperative Atrial Fibrillation After Thoracic Surgery

by

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Abstract

Background: Postoperative atrial fibrillation following lung resection is associated with increased morbidity and mortality. The extent of pulmonary resection and preoperative N-terminal pro-BNP (NT-proBNP) levels have been suggested as contributing factors in the development of postoperative atrial fibrillation. This study aims to determine if a relationship exists between the extent of lung parenchyma resected and perioperative changes in serum NT-proBNP levels.

Methods: We conducted a prospective cohort study enrolling patients aged ≥55 years undergoing pulmonary resection with no documented history of atrial fibrillation. Baseline NT-proBNP levels were measured preoperatively (PRE), in the post-anesthesia care unit (PACU), and on postoperative day 1 (POD1). The weight and volume of lung resection was determined from pathological review of the surgical specimen. Statistical analysis utilized repeated measure regression models with NT-proBNP as the outcome, incorporating measurement time (PRE/PACU/POD1), the extent of lung resection, and their interaction as predictor variables. Trajectory plots were generated to assess NT-proBNP changes after surgery and Spearman correlations were used to determine the relationship between NT-proBNP and extent of resection at each time point.

Results: 105 patients were enrolled, and 102 patients were analyzed. Postoperative atrial fibrillation occurred in 5 (4.9%) cases. Relative to PRE NT-proBNP measurements, the change in NT-proBNP levels at PACU and POD1 was -0.5 ± 37.9 pg/mL ($p=0.905$) and 320 ± 472.5 pg/mL ($p <0.0001$), respectively. No relationship between NT-proBNP and the extent of lung resection, defined using multiple outcomes, was demonstrated across all measurement times.

Conclusions: Lung resection was followed by a near four-fold elevation in NT-proBNP levels from baseline on the first postoperative day. However, there was no relationship between perioperative elevations in NT-proBNP and the extent of lung resection.

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Introduction

Postoperative atrial fibrillation is a common and potentially serious complication following lung resection. It is associated with an increased risk of perioperative stroke and mortality, prolonged hospital stays, and greater utilization of critical care resources[1]. Numerous patient and operative factors, both modifiable and non-modifiable, have been linked to an elevated risk of postoperative atrial fibrillation following thoracic surgery[1,2].

Brain natriuretic peptide (BNP) is a hormone secreted in response to myocardial wall stretch, promoting systemic and pulmonary vasodilation as well as natriuresis[3]. Elevated serum levels of natriuretic peptides, including BNP and its inactive cleavage product, N-terminal pro-brain natriuretic peptide (NT-proBNP), are associated with an increased incidence of postoperative atrial fibrillation in patients undergoing noncardiac surgery[4].

NT-proBNP is employed to diagnose and assess the severity of heart failure[5]. Lung resection alters normal cardiopulmonary physiology, notably by increasing pulmonary arterial afterload which can provoke right ventricular dysfunction[6]. In patients with pulmonary hypertension, B-type natriuretic peptide levels are inversely correlated with right ventricular systolic function[7,8].

The risk of postoperative atrial fibrillation after thoracic surgery appears to be increased by the extent of lung resection, perioperative right ventricular dysfunction, and elevated NT-proBNP levels[1,4,9]. As more extensive resections are associated with greater increases in pulmonary afterload and acute right ventricular strain, a dose-response relationship between resection extent and NT-proBNP elevation is biologically plausible[6,10]. Previous studies have shown that natriuretic peptide levels increase in most patients following lung resection[10–13]. However, the relationship, if any, between the extent of lung resection and natriuretic peptide levels is unknown.

The primary objective of this study is to examine the association between the extent of lung resection and perioperative changes in NT-proBNP levels. A deeper understanding of this relationship may yield novel insights into the multifactorial pathophysiology of postoperative atrial fibrillation following lung resection.

Background

Postoperative Atrial Fibrillation

The incidence of postoperative atrial fibrillation following lung resection ranges from 3% to 39%, typically occurring at a median of two days postoperatively[1,14,15]. Historically,

postoperative atrial fibrillation was considered a transient, benign, and self-limiting arrhythmia. However, emerging evidence from meta-analyses has challenged this perception, demonstrating its association with adverse clinical outcomes.

Patients who develop postoperative atrial fibrillation experience two-fold worse outcomes compared to those who do not. Among individuals undergoing noncardiac surgery, postoperative atrial fibrillation significantly increases the risk of stroke (OR 2.83, 95% CI 2.15-3.70) and myocardial infarction (OR 3.96, 95% CI 2.80-5.59) within one month of surgery[16]. The long-term consequences are similarly concerning, with elevated risks of stroke (OR 4.12, 95% CI 3.34-5.11) and mortality (OR 3.35, 95% CI 2.13-5.31) associated with postoperative atrial fibrillation at one year follow-up[16]. Beyond its clinical implications, postoperative atrial fibrillation imposes a substantial burden on healthcare systems. Affected patients have longer hospital stays and an increased likelihood of requiring intensive care unit admission[1,17].

Despite its prevalence and impact, high-quality evidence regarding the prevention and management of postoperative atrial fibrillation remains limited. Current recommendations for perioperative management of atrial fibrillation in noncardiac surgical patients are frequently derived from studies in non-operative or cardiac surgery populations[18,19]. While some risk factors are shared across these groups, patients undergoing lung resection have unique perioperative pathophysiological changes that predispose them to developing arrhythmias. Continued research on the etiology of postoperative atrial fibrillation and its management following thoracic surgery is required to decrease its incidence, and subsequent adverse effects on patient outcomes.

Etiology of Postoperative Atrial Fibrillation

The etiology of postoperative atrial fibrillation is multifactorial. In elderly individuals or those with preexisting cardiac disease, fibrosis of the atrial myocardium creates a vulnerable substrate that facilitates the initiation and propagation of abnormal electrical activity, thereby increasing the risk of atrial fibrillation[18,19]. Intrathoracic surgical procedures, performed in close proximity to or on the pericardium induce procedure specific physiological changes that further heighten the risk of arrhythmia development[1].

The pulmonary veins play a particularly important role in the development of atrial fibrillation following lung resection. Myocytes located near the junction of the pulmonary veins and left atrium are characterized by higher resting membrane potentials and shorter action potential durations[1]. These electrophysiologic properties make them susceptible to ectopic firing, especially in the context of heightened adrenergic stimulation and manipulation during intrathoracic surgical procedures[1,19,20]. Additional intraoperative

maneuvers such as hilar or mediastinal lymph node dissection, pulmonary vein ligation, and vagal nerve irritation cause further disruption to the myocardium's normal electrical activity[1,19]. In patients with a structurally or electrically compromised atrial substrate, thoracic surgery creates an environment highly conducive to arrhythmogenesis. Various surgical and physiological stressors further exacerbate this pro-arrhythmogenic state.

The body's response to surgical trauma involves systemic inflammation and increased adrenergic activity, both of which are recognized contributors to arrhythmia development[19]. Elevated levels of circulating inflammatory biomarkers have been associated with an increased incidence of postoperative atrial fibrillation in patients undergoing noncardiac surgery[21]. In addition to this systemic inflammatory response, local inflammation of the pericardium or at the resected pulmonary vein stumps may serve as direct triggers for atrial fibrillation[19]. Furthermore, high postoperative norepinephrine levels and the intraoperative administration of vasoactive medications have been independently linked to an elevated risk of developing postoperative atrial fibrillation[22]. Alongside these inflammatory and adrenergic pathways, perioperative changes in cardiopulmonary hemodynamics significantly contribute to arrhythmia risk[6,19,20].

Lung resection acutely alters normal cardiopulmonary physiology. Studies utilizing intravascular catheters and cardiac magnetic resonance imaging in human and animal models have demonstrated that pulmonary artery pressures and pulmonary vascular resistance can rise significantly after lung resection[6,10]. These elevations are most pronounced following larger lung resections. Compared to lobectomy, patients undergoing pneumonectomy experience greater increases in pulmonary artery pressure and vascular resistance[10]. When the right heart is unable to adequately adapt to these elevated pressures, it may become acutely strained and dilated[6,23]. Echocardiographic studies in patients undergoing lung resection have shown a correlation between intra- and postoperative right ventricular dysfunction and the development of atrial arrhythmias[9,24].

The physiological stress of surgery in susceptible individuals compounded by thoracic surgery specific factors culminates in a markedly pro-arrhythmogenic state. Informed by these pathophysiological mechanisms, research efforts have sought to identify and evaluate interventions aimed at reducing the incidence of postoperative atrial fibrillation.

Prevention of Postoperative Atrial Fibrillation

Due to the adverse clinical outcomes associated with postoperative atrial fibrillation, there has been considerable interest in identifying pharmacologic strategies to reduce its incidence. Given the multifactorial nature of atrial fibrillation pathophysiology, a variety of medications targeting different mechanistic pathways have been evaluated. While some

investigations have demonstrated therapeutic benefit, the existing literature is marked by significant heterogeneity in study design, patient populations, and reported outcomes[18]. Additionally, concerns regarding medication-related adverse effects and challenges in selecting appropriate candidates for pharmacologic prophylaxis further complicate the clinical application of these therapies[18,19,25]. Specifically, the narrow therapeutic window of current strategies calls for the need to identify patients at increased risk of atrial fibrillation to warrant the use of these interventions.

β-adrenergic blockers mitigate sympathetic nervous system activity and reduce sinus node automaticity[18,19]. According to the American Association for Thoracic Surgery clinical practice guidelines, the continuation of β-adrenergic blockers in patients already receiving them chronically is the sole Class I recommendation for atrial fibrillation prevention in the thoracic surgical population[19]. Prophylactic initiation of β-adrenergic blockers in patients undergoing thoracic surgery has been associated with a reduced risk of postoperative atrial fibrillation in some studies[26,27]. However, the use of these agents raises safety concerns, including hypotension and bronchospasm, and supporting data for their prophylactic administration remains limited[19]. Importantly, the PeriOperative ISchemic Evaluation (POISE) trial, which evaluated perioperative β-adrenergic blocker use in noncardiac surgery patients, found an increased incidence of stroke and mortality in individuals who were newly initiated on β-adrenergic blockers medications[28].

Amiodarone, a class III antiarrhythmic agent that prolongs myocardial action potential duration and raises the depolarization threshold, has also been studied for prophylactic use in thoracic surgery patients[18]. Randomized controlled trials have demonstrated that perioperative administration of amiodarone reduces the incidence of postoperative atrial fibrillation following lung resection and esophagectomy[18,19]. Early studies raised concern for an increased risk of acute respiratory distress syndrome associated with amiodarone use. However, more recent investigations have not corroborated these findings[18,19]. As such, the American Association for Thoracic Surgery guidelines support the use of amiodarone in selected intermediate- to high-risk patients undergoing lung resection[19].

In patients undergoing cardiac surgery, anti-inflammatory therapy with colchicine has been shown to decrease the incidence of postoperative atrial fibrillation[29]. The recently published Colchicine for the Prevention of Atrial Fibrillation after Thoracic Surgery (COP-AF) trial evaluated this agent in the thoracic surgery setting. Although colchicine did not reduce the incidence of clinically important atrial fibrillation in the overall cohort (HR 0.89, 95% CI 0.65-1.10), subgroup analyses suggested a potential benefit in specific patient populations[21]. The benefit of prophylactic anti-inflammatory treatment in thoracic surgery patients remains unclear.

A variety of other antiarrhythmic agents have been investigated for their potential to prevent postoperative atrial fibrillation. However, a detailed analysis of each is beyond the scope of the current discussion. While pharmacologic therapies may help stabilize the electrical disturbances induced by inflammatory and adrenergic responses to thoracic surgery, they do not address the broader physiologic and hemodynamic alterations that occur following lung resection. The variable treatment efficacy observed across different pharmacologic interventions highlights the complex and multifactorial pathogenesis of postoperative atrial fibrillation, suggesting that no single agent is likely to be universally effective for all patients[25]. Furthermore, the absence of standardized criteria for patient selection presents a persistent challenge, limiting the clinical applicability of existing prophylactic strategies.

Although several pharmacologic approaches have been shown to reduce the risk of postoperative atrial fibrillation following lung resection, their use must be balanced against the potential for adverse effects[19]. Prophylactic medications should be targeted to patients most likely to benefit, while avoiding overtreatment in those at low risk for arrhythmia development[25]. Accordingly, future research and clinical practice should prioritize the identification of high-risk individuals to facilitate a tailored approach to prophylactic treatments and optimize patient outcomes[25].

Prediction of Postoperative Atrial Fibrillation

Identification of patients at high risk for developing postoperative atrial fibrillation following thoracic surgery remains a clinical challenge. Several preoperative risk factors have been consistently reported, including advanced age, male sex, congestive heart failure, and a history of paroxysmal atrial fibrillation[1,30]. In thoracic surgery populations, additional predictors such as idiopathic pulmonary fibrosis, lung cancer, and receipt of neoadjuvant chemotherapy or radiotherapy further increase the risk of postoperative atrial fibrillation[1,30]. Operative risk factors such as lobar resections, pneumonectomy, postoperative pericarditis, mediastinal lymphadenectomy, and left-sided surgery have also been associated with heightened risk[1,6]. As multiple patient- and procedure-related risk factors frequently coexist and are often non-modifiable, prediction tools have been developed to assist clinicians in determining a patient's risk of postoperative atrial fibrillation.

Passman et al. introduced a clinical prediction rule designed to stratify risk for postoperative atrial fibrillation in patients undergoing noncardiac thoracic surgery. Their analysis identified male sex, advanced age, and preoperative heart rate greater than 72 beats per minute as independent predictors of postoperative atrial fibrillation. A corresponding scoring system was derived by assigning weighted values to each of these variables. The authors validated their risk score and found using easily obtainable clinical information that their prediction rule was a significant predictor of postoperative atrial

fibrillation after thoracic surgery[31]. Building on this work, subsequent studies sought to refine risk prediction by incorporating biomarkers.

In 2019, Amar et al. expanded and validated a more comprehensive predictive model by integrating preoperative BNP levels with additional patient and operative factors. Their multivariable regression analysis identified age, body mass index, preoperative BNP, history of atrial fibrillation, and extent of surgery as independent predictors of postoperative atrial fibrillation. The inclusion of preoperative BNP levels significantly enhanced the model's predictive performance[2].

Despite the development of validated risk prediction tools using accessible clinical and biochemical parameters, these instruments have not been widely adopted in practice. This is an issue from both clinical and research perspectives. Implementation of prophylactic strategies from clinical practice guidelines at the patient level requires risk stratification. Presently, guidelines estimate a patients risk of atrial fibrillation based on the reported incidence of postoperative arrhythmias according to surgical procedure, rather than incorporating individualized risk prediction models that account for both patient and operative variables[19]. From a research perspective, the variable effect of prophylactic strategies in reducing postoperative atrial fibrillation may be in-part caused by heterogeneity in patient selection due to inadequate determination of a patient's preoperative risk of developing a postoperative arrhythmia. Notably, the most recent guidelines from the American Association for Thoracic Surgery on the prevention and management of atrial fibrillation were published in 2014, preceding much of the contemporary research on postoperative atrial fibrillation risk prediction and recent interest in the use of biomarkers for perioperative risk stratification.

Natriuretic Peptides

Ventricular cardiomyocytes secrete pro-brain natriuretic peptide (proBNP) in response to myocardial wall stretch resulting from volume or pressure overload[3]. The active hormone, BNP, promotes systemic and pulmonary vasodilation and stimulates natriuresis to restore cardiovascular homeostasis[32]. B-type natriuretic peptides, including BNP and its inactive cleavage product NT-proBNP can be measured in the serum and are routinely used to diagnose and assess the severity of heart failure[5]. Although these biomarkers are most commonly employed in non-surgical cardiology populations, their utility in perioperative medicine has become increasingly recognized. In particular, b-type natriuretic peptides have been demonstrated as strong predictors of postoperative cardiovascular complications. The Canadian Cardiovascular Society recommends preoperative measurement of BNP or NT-proBNP in patients over 65 years of age or those with a revised

cardiac risk index score greater than one, due to its strong association with adverse postoperative cardiac complications[33].

Elevated b-type natriuretic peptide concentrations are a strong predictor of adverse postoperative outcomes in patients undergoing noncardiac surgery. A meta-analysis by Rodseth et al. demonstrated that preoperative elevations in b-type natriuretic peptide levels are associated with an increased risk of a composite endpoint comprising all-cause mortality and non-fatal myocardial infarction within thirty days of surgery (OR 1.9, 95% CI 1.44-2.40)[34]. In thoracic surgery patients, elevated b-type natriuretic peptide levels are associated with an increased risk of cardiopulmonary complications (OR 2.94, 95% CI 1.32-6.57)[12] and postoperative atrial fibrillation[4,35].

Natriuretic Peptides and Postoperative Atrial Fibrillation

Elevated b-type natriuretic peptide levels are strong predictors of postoperative atrial fibrillation. The study by Cardinale et al. was the first prospective trial to examine the predictive role of NT-proBNP for postoperative atrial fibrillation following lung resection. In a cohort of 400 patients, elevated preoperative and postoperative NT-proBNP levels had a relative risk of 27.9 (95% CI 13.2-58.9) and 20.1 (95% CI 5.8-69.4), respectively. Combined, elevated NT-proBNP levels at any time point was associated with a relative risk of 35.7 (95% CI 16.7-76.7)[35]. Following this study, several investigations have evaluated the prognostic value of b-type natriuretic peptides in predicting atrial fibrillation after noncardiac thoracic surgery.

In 2015, Simmers et al. conducted a meta-analysis of five studies investigating the role of b-type natriuretic peptide levels as predictors of postoperative atrial fibrillation in thoracic surgery patients. They found elevated b-type natriuretic peptide levels were significantly associated with an increased risk of postoperative atrial fibrillation (OR 9.51, 95% CI 4.66-19.40)[4]. Amar et al. similarly demonstrated that patients who develop postoperative atrial fibrillation had significantly higher preoperative BNP levels compared to those who did not[2]. Moreover, the incorporation of preoperative BNP into their risk stratification model significantly enhanced its predictive accuracy[2]. Together with patient age and the extent of lung resection, preoperative b-type natriuretic peptide levels serve as robust predictors for postoperative atrial fibrillation following thoracic surgery procedures.

Extent of Resection and Postoperative Atrial Fibrillation

The risk of postoperative atrial fibrillation is associated with the amount of lung parenchyma that is surgically removed[1,20]. Compared to the reference of segmentectomy, patients undergoing pneumonectomy face a significantly higher risk of postoperative atrial fibrillation (OR 6.70, 95% CI 1.91-24.70)[2]. Although reported incidence rates vary across

studies, the estimated frequency of postoperative atrial fibrillation ranges from 2-4% for wedge resections, 10-15% for lobectomies, and 20-30% for pneumonectomies[14]. Several mechanisms have been proposed to explain the increased incidence following more extensive resections. These include a heightened systemic inflammatory response that promotes sympathetic nervous system activation and greater cardiovascular strain secondary to a considerably larger reduction in the remaining pulmonary vascular bed[20,36,37].

Hemodynamics of Lung Resection

Thoracic surgery alters normal cardiopulmonary hemodynamics, imposing unique stress on the cardiovascular system. During thoracic surgery procedures, the operative lung is frequently isolated and non-ventilated to facilitate surgical exposure within the thoracic cavity. During periods of one-lung ventilation, pulmonary blood flow is redistributed to the ventilated lung, resulting in an acute increase in pulmonary artery pressures and vascular resistance. The right ventricle must adapt to these hemodynamic changes to maintain cardiac output. Initially, this adaptation occurs through dilation, whereby myocardial stretch enhances contractility through the Frank-Starling mechanism. Subsequently, the Anrep effect, an intrinsic autoregulatory response, further augments contractile force in response to the elevated afterload[6]. Although most patients can tolerate these acute hemodynamic changes, impairment of right ventricular function following lung resection has been extensively documented[6,23].

Numerous studies have shown that lung resection induces right ventricular dysfunction both in the immediate perioperative period and during long-term follow-up[6,38]. Using cardiac magnetic resonance imaging, McCall et al. demonstrated a reduction in right ventricular ejection fraction as early as postoperative day two, with sustained impairments observed months after surgery[23]. Notably, this study by McCall et al. did not identify concurrent deterioration in left ventricular function during follow-up[23]. In animal models, Greyson et al. performed temporary occlusion of the pulmonary artery to simulate the hemodynamic consequences of a massive pulmonary embolism. They found the temporary increase in pulmonary artery pressures resulted in both acute and persistent right ventricular afterload, even after normal pulmonary blood flow was restored[39]. Histologic examination of myocardial tissue in this study revealed elevated levels of inflammatory markers, suggesting the hemodynamic effects of increased afterload are exacerbated by inflammatory injury[39]. These findings provide mechanistic support for the hypothesis that right ventricular dysfunction following lung resection results from increased pulmonary vascular afterload.

Studies employing invasive intravascular monitoring have demonstrated significant postoperative elevations in pulmonary artery pressure and vascular resistance following anatomical lung resection[10]. In response to this increased afterload, pulmonary blood flow is redistributed to the contralateral lung[6]. Cardiac magnetic resonance imaging has confirmed that this redistribution is associated with reduced right ventricular ejection fraction and persistent right ventricular free wall strain[23]. Collectively, the findings from multiple studies utilizing invasive hemodynamic monitoring and advanced imaging support the long-standing hypothesis that increased right ventricular afterload contributes to postoperative right ventricular dysfunction following lung resection. Compared to resource-intensive and invasive modalities such as invasive hemodynamic monitoring, b-type natriuretic peptide levels can serve as a non-invasive surrogate marker of right ventricular function.

Although b-type natriuretic peptide concentrations are highest in the left ventricle, these peptides are clinically valuable in the assessment of right heart function as well[5,8]. In patients with pulmonary hypertension, elevated b-type natriuretic peptide levels are associated with right ventricular dysfunction, increased pulmonary artery pressures, and reduced functional status[8,38]. Previous studies have demonstrated that BNP levels increase proportionally to the severity of right ventricular dysfunction, and that NT-proBNP levels reflect the extent of right ventricular dilatation and impaired systolic function[8,40]. Given that right ventricular dysfunction after lung resection typically occurs in the absence of concurrent left-sided impairment[23], perioperative elevations in b-type natriuretic peptides may serve as a surrogate marker of acute right ventricular strain in this context.

Lung Resection and Natriuretic Peptides

Prior studies suggest that b-type natriuretic peptide levels increase following lung resection. Investigations by Hoksch and Cagini et al. demonstrated that postoperative b-type natriuretic peptide concentrations were elevated in patients who developed cardiopulmonary complications after lung resection. Additionally, they reported that natriuretic peptide levels generally rose in all patients following lung resection[11,12]. However, these studies did not stratify patients by the extent of surgical resection, thereby limiting conclusions regarding the relationship between surgical magnitude and biomarker elevation.

Two studies have directly examined the influence of the extent of lung resection on postoperative natriuretic peptide levels. In a cohort of 25 patients, Tayama et al. found that patients undergoing pneumonectomy had significantly higher postoperative BNP levels compared to individuals who received lobar resections. Furthermore, a positive correlation was observed between BNP levels and total pulmonary vascular resistance in the

pneumonectomy group, suggesting the increased hemodynamic burden of a larger lung resection may be responsible for the proportionally larger increase in BNP following pneumonectomy[10]. Muley et al. assessed the impact of lung resection on multiple biomarkers, including pre- and postoperative NT-proBNP levels. In a cohort of 64 patients, they reported that NT-proBNP levels rose from baseline on the first postoperative day across all surgical procedures. Regarding the relationship between the extent of resection and NT-proBNP levels, they found NT-proBNP concentrations were significantly higher following pneumonectomy compared to wedge or lobar resections[13].

Taken together, these findings support a relationship between the extent of lung resection and postoperative increases in b-type natriuretic peptide levels. The observed correlation between surgical magnitude and biomarker elevation may reflect greater cardiopulmonary stress, with resultant right ventricular strain and dysfunction following more extensive lung resections.

Summary and Study Rationale

Lung resection is associated with a high incidence of postoperative atrial fibrillation[1,19]. This arrhythmia is clinically significant, increasing a patient's risk of postoperative morbidity and mortality[16]. Impaired right ventricular function, the extent of lung resection, and elevated b-type natriuretic peptide levels have all been independently associated with a heightened risk of postoperative atrial fibrillation following lung resection in multiple studies[1,4,6,9].

Pulmonary vascular resistance and right ventricular afterload increase in proportion to the volume of lung resected[10]. Right ventricular strain following lung resection has been shown to occur in the absence of concurrent left ventricular dysfunction, suggesting a unique physiological stress on the right heart[23]. As b-type natriuretic peptides are secreted in response to myocardial stretch, particularly from the ventricles, elevations in these biomarkers following lung resection may reflect acute postoperative right ventricular strain[5,40]. Although a biologically plausible relationship between the extent of lung resection and postoperative b-type natriuretic peptide levels has been proposed, this association has only been reported in two small studies to date[10,13]. Demonstrating a consistent, proportional relationship between the extent of lung resection and natriuretic peptide elevation would support the hypothesis that right ventricular dysfunction is one of the underlying mechanisms behind the elevated risk of postoperative atrial fibrillation in patients with postoperative elevations in b-type natriuretic peptides.

The objective of the present study, and thesis for the Master of Surgery program, is to characterize the relationship between perioperative NT-proBNP levels and the extent of lung resection. We hypothesized that postoperative NT-proBNP concentrations would rise

in proportion to the volume of lung parenchyma resected. If a relationship is demonstrated between perioperative NT-proBNP levels and the extent of lung resection, future investigation will be required to further define the relationship between NT-proBNP, extent of resection and postoperative atrial fibrillation.

Study Hypotheses and Objectives

Hypotheses

1. There is a proportional relationship between the amount of lung parenchyma resected and postoperative elevations in NT-proBNP levels. Specifically, more extensive lung resections (e.g. lobectomy or pneumonectomy) are associated with greater postoperative increases in NT-proBNP compared to less extensive resections (e.g. wedge resection or segmentectomy).
2. Elevations in postoperative NT-proBNP levels are associated with an increased risk of developing postoperative atrial fibrillation in patients undergoing lung resection.

Pilot Study Objectives

1. Determine the association between the extent of lung parenchyma resected and postoperative NT-proBNP measurements.
2. Demonstrate the feasibility of recruiting 100 patients and completing postoperative follow-up over 12 months.
3. Demonstrate the feasibility of collecting and analyzing NT-proBNP values using the Health Sciences Centre (HSC - Winnipeg, MB) laboratory Roche Cobas analyzer at three-time points: preoperatively (PREOP), postoperatively (PACU) and on the first postoperative day (POD1).
4. Demonstrate the feasibility of acquiring preoperative clinical predictors necessary to establish a clinical model to predict the development of postoperative atrial fibrillation.
5. Generate cost calculations to inform the design of the larger main cohort study (if required).

Main Study Objectives

1. Determine the role of NT-proBNP as an independent predictor for the development of postoperative atrial fibrillation.
2. Develop a clinical model for the prediction of postoperative atrial fibrillation incorporating preoperative clinical risk factors, and postoperative elevations of NT-proBNP.

Methodology

Study Design

A prospective observational cohort study was conducted at the Health Sciences Centre (HSC) in Winnipeg, Manitoba, between August 2023 and February 2024. The study's design, including its outcomes, arrhythmia monitoring protocol, inclusion criteria, and exclusion criteria, was informed by the protocol established in the COP-AF trial[21]. The successful implementation of the COP-AF trial by our research team at HSC confirmed the feasibility of employing this protocol in the local clinical environment.

Participants

All patients scheduled to undergo an intrathoracic surgical procedure at HSC were screened for eligibility during the study period. To qualify for inclusion, patients were required to be at least 55 years of age on the day of surgery, provide written informed consent, and undergo their scheduled lung resection (for any indication) under general anesthesia.

Exclusion criteria included a documented history of end-stage renal disease requiring renal replacement therapy, a known history of atrial fibrillation or atrial flutter, or the need for preoperative anti-arrhythmic therapy with agents other than β-blockers, calcium channel blockers, or digoxin. Patients scheduled for hiatal surgery, esophageal or mediastinal resections, or for minor thoracic procedures such as pleural or lung biopsies, were excluded.

Following enrollment, patients were excluded from the analysis if a baseline NT-proBNP measurement was not obtained or if the planned lung resection was not performed for any reason during the study period (e.g. cancellation, or lung malignancy determined to be unresectable at the time of surgery). As the primary objective of the study was to assess the relationship between the extent of lung resection and perioperative NT-proBNP levels using multiple objective measurements, a predefined sample size stratified by operation type was not required.

Study Protocol

Following the provision of informed consent, baseline patient characteristics were collected through a combination of telephone interviews and medical chart review. These included clinical variables known to be associated with the development of postoperative atrial fibrillation.

On the day of surgery, patients were met in the preoperative holding area by a member of the research team. After vascular access was established by the clinical team, a 5 mL sample of whole blood, arterial or venous, was collected to measure the baseline preoperative NT-proBNP concentration (PREOP). A second NT-proBNP measurement (PACU) was obtained within 1 to 4 hours following completion of the surgical procedure, prior to leaving the post-anesthesia care unit. A third measurement was collected on the morning of the first postoperative day (POD1). All serum NT-proBNP samples were analyzed at the HSC Central Laboratory using the Roche Cobas analyzer. Concentrations were quantified using an electrochemiluminescence immunoassay (Elecsys proBNP II Test, Roche Diagnostics, Rotkreuz, Switzerland) on a semi-automated analyzer (Roche Diagnostics, Rotkreuz, Switzerland).

At the conclusion of the operation, a member of the research team reviewed the operation with the anesthesia team. Time on one-lung ventilation, and any intraoperative arrhythmias were documented. The type of surgical procedure performed was documented either through direct communication with the attending Thoracic surgeon or by review of the operative report.

Between postoperative days one and three, if the patient remained hospitalized, daily serum high-sensitivity troponin (hsTnT) measurements were obtained to screen for myocardial ischemia. Routine electrocardiograms (ECGs) were also performed daily during this period to detect the development of postoperative arrhythmias. Additional ECGs ordered at the discretion of the clinical team were reviewed and recorded by the research team.

Prior to discharge, each patient's medical chart and laboratory data were reviewed, and final ECG interpretations, reported by a cardiologist, were documented. A virtual follow-up was completed on postoperative day 30. In addition to virtual discussion with the research participant, a chart review was conducted to identify any postoperative complications. Surgical pathology reports were reviewed, and both the weight and volume of the resected lung specimen were recorded as objective indicators of the extent of lung resection.

Statistical Analysis

The association between the volume of lung parenchyma resected and postoperative changes in NT-proBNP levels was examined using several complementary approaches. First, both absolute and log-transformed NT-proBNP values were visually assessed for patterns over time using trajectory plots.

Subsequently, the extent of lung resection, treated as a continuous variable, was plotted against NT-proBNP measurements. Spearman correlation coefficients were calculated to

assess the relationship between the volume and weight of the surgical specimen and NT-proBNP concentrations, both as absolute values and as changes between measurement points.

To formally assess changes in NT-proBNP levels over time, repeated measures (mixed-effects) regression models were constructed using change from baseline as the outcome variable. Two models were developed: one using absolute differences (i.e. raw change in NT-proBNP from preoperative to postoperative values), and another using ratios (i.e. relative change or percent increase in NT-proBNP). The ratio-based model was included to capture biologically meaningful proportional changes, such as a doubling of NT-proBNP, which may be clinically relevant regardless of baseline levels. By using change in NT-proBNP from baseline to PACU and POD1 as the outcome, each patient effectively served as their own control, to mitigate the potential confounding influence of pre-existing cardiac or renal comorbidities that may result in baseline elevations of NT-proBNP.

These models were designed to test whether the extent of lung resected was independently associated with NT-proBNP levels measured in PACU, POD1, or at both time points after adjusting for baseline preoperative values.

In addition to the primary analysis, post hoc exploratory analyses were conducted to investigate whether other recorded perioperative variables were associated with changes in NT-proBNP levels on POD1. Specifically, the duration of time on one-lung ventilation and the neutrophil-lymphocyte ratio (as a proxy for systemic inflammation)[41] were examined using the same modeling framework.

A complete case analysis was used to address missing data. Across the three NT-proBNP measurement times, only 3/306 (<1%) NT-proBNP data points were missing among included patients.

All hypothesis testing was two-sided with a pre-specified significance level of $\alpha < 0.05$. Statistical analyses were conducted using R version 4.3.1. The lme4 package was employed to fit mixed-effects models.

Ethics

The study has been approved by the Health Research Ethics Board at the University of Manitoba (Ethics#: HS22397).

Results

A total of 258 patients were screened for enrollment. Of these, 122 patients were excluded for not meeting the study's inclusion criteria: 84 due to ineligible procedure type, 21 were younger than 55 years of age, 14 had a documented history of previous or current atrial arrhythmias, and 3 had end-stage renal disease requiring renal replacement therapy. Among the 136 patients who met all inclusion criteria, 29 either declined participation or could not be contacted for consent prior to their procedure, and 2 patients had their procedures cancelled prior to the surgery date. The remaining 105 patients were enrolled in the study. Preoperative NT-proBNP samples were not obtained in 3 patients, resulting in a cohort of 102 patients for final analysis (Figure A).

The median age of the 102 enrolled patients was 71 years (range: 57-91), and females comprised 57.3% of the cohort (n = 59). The most frequently performed operation was wedge resection (n = 61), followed by lobectomy (n = 30) and segmentectomy (n = 8). Bilobectomy (n=2) and pneumonectomy (n=1) were rarely performed, as such in the analysis these procedures were grouped together and represent the "other" category. Baseline patient characteristics stratified by procedure type are summarized in Table 1. No significant differences in baseline variables were observed between the operative groups.

Median specimen volume varied significantly by procedure type: 195 cm^3 (range: 17.2-1080) for wedge resections, 513 cm^3 (range: 290-855) for segmental resections, and 1500 cm^3 (range: 23.6-2310) for lobectomies ($p < 0.001$). Median specimen weight differed significantly between groups: 34.0 grams (range: 4.00-636) for wedge resections, 97.0 grams (range: 41.9-189) for segmentectomies, and 195 grams (range: 71.0-408) for lobectomies ($p < 0.001$). The duration of one-lung ventilation differed significantly across procedure types. Median one-lung ventilation time was 48.0 minutes (range: 22.0-132) for wedge resections, 99.5 minutes (range: 55.0-138) for segmentectomies, and 120 minutes (range: 0-237) for lobectomies ($p < 0.001$) (Table 2).

Postoperative atrial fibrillation occurred in 4.9% of patients (n = 5), with a median time to onset of 2 days postoperatively (range: 1-3). Myocardial injury after noncardiac surgery (MINS) was observed in 11.7% of the cohort (n = 12). Lobectomy was the most common procedure among patients who developed postoperative atrial fibrillation (n = 4, p = 0.08) and MINS (n = 7, p = 0.06).

The median NT-proBNP concentrations at the preoperative (PREOP), post-anesthesia care unit (PACU), and first postoperative day (POD1) time points were 98.5 pg/mL (range: 10-3840), 106 pg/mL (range: 10-3710), and 462 pg/mL (range: 35-3760), respectively. There were no statistically significant differences in NT-proBNP measurements at any time point

between operative groups ($p > 0.431$). As illustrated in Figure B, absolute NT-proBNP data revealed a plateau between the PREOP and PACU time points. Apart from few outliers, nearly all patients exhibited an increase in NT-proBNP levels by POD1. Summary statistics for changes in NT-proBNP values support this visual trend. The median change from PREOP to PACU was -0.5 pg/mL (range: [-135]-225), while the median change from PREOP to POD1 was 320.0 pg/mL (range: [-963]-3324).

Analysis of the log-transformed NT-proBNP data, which stabilizes variance in the data by compressing values proportionally to their magnitude, demonstrated a similar pattern. In Figure C, the parallel nature of patient trajectories suggests a proportional increase in NT-proBNP from PACU to POD1 across the cohort. Figures D and E depict density estimates of the POD1/PREOP and POD1/PACU NT-proBNP ratios, respectively. These ratios represent the multiplicative change in NT-proBNP levels and can be interpreted as the slope of each patient's trajectory between measurement times in Figure C. The median POD1/PREOP and POD1/PACU ratios were 3.56 and 3.68, respectively. A strong correlation was observed between PACU and POD1 NT-proBNP levels ($r = 0.641$, $p < 0.001$), indicating that NT-proBNP measurements in PACU were predictive of POD1 levels. Taken together, these findings indicate that, regardless of baseline NT-proBNP values, patients typically experienced an approximate four-fold increase in NT-proBNP concentration on the first postoperative day following lung resection.

Scatterplots and Spearman correlation analyses examining the relationship between lung resection weight and NT-proBNP concentrations are presented in Figures F and G. Figure F displays absolute NT-proBNP values across the three measurement time points, while Figure G illustrates the change in NT-proBNP levels from baseline. At each time point, no statistically significant correlation was observed between specimen weight and absolute NT-proBNP concentration ($p >0.16$) . Likewise, changes in NT-proBNP from PREOP to PACU and from PREOP to POD1 were not correlated with specimen weight ($p>0.23$).

A similar analysis was performed using resection volume rather than weight. Scatterplots and Spearman correlations between lung resection volume and NT-proBNP concentrations are depicted in Figures H and I. Figure H illustrates absolute NT-proBNP levels, and Figure I illustrate changes from baseline. No statistically significant relationships were observed between lung resection volume and NT-proBNP concentrations at any measurement time point ($p>0.20$) , nor between resection volume and change in NT-proBNP values from baseline to PACU or POD1 ($p>0.19$).

These findings were corroborated by results from mixed-effects regression models that included either specimen weight or volume as predictors. There was a statistically

significant increase in NT-proBNP levels on POD1 ($p < 0.01$), however, the marginal effects of specimen weight ($p = 0.51$) and specimen volume ($p = 0.28$) were not significant.

To assess the association between NT-proBNP changes and resection extent categorized by procedure type, further comparisons were made between wedge, segmental, and lobar resections. Patients who underwent bilobectomy or pneumonectomy ($n = 3$) were excluded from this analysis due to small sample size. Figure J presents boxplots of change in NT-proBNP from baseline, stratified by procedure type. No significant association was found between procedure type and change in NT-proBNP from PREOP to PACU ($p = 0.93$) or PREOP to POD1 ($p = 0.11$).

Given the lack of association between NT-proBNP elevation and the extent of lung resection, exploratory analyses were undertaken to evaluate other perioperative variables. Specifically, we examined the association between change in NT-proBNP and time spent on one-lung ventilation as well as NT-proBNP and neutrophil-lymphocyte ratio, a surrogate marker of systemic inflammation.

The relationship between time on one-lung ventilation and change in NT-proBNP from PREOP to PACU and POD1 is illustrated in Figure K. No significant correlations were observed ($p > 0.09$). Neutrophil-lymphocyte ratio was calculated using the patient's complete blood count obtained on POD1. Figure L depicts a scatterplot of neutrophil-lymphocyte ratio against change in NT-proBNP from PREOP to POD1. A weak, inverse association was observed ($r = -0.19$), though this did not reach statistical significance ($p = 0.06$).

Table 3 provides summary statistics for various predictors stratified by postoperative atrial fibrillation status. No significant associations were found between the volume ($p = 0.77$) or weight ($p = 0.16$) of lung resection and the development of postoperative atrial fibrillation. Similarly, NT-proBNP concentrations at baseline ($p = 0.63$), PACU ($p = 0.59$), and POD1 ($p = 0.32$) were not associated with the occurrence of postoperative atrial fibrillation.

Discussion

Principle Study Findings

The objective of this prospective observational study was to determine the relationship between the extent of lung resection and perioperative changes in NT-proBNP concentrations. To our knowledge, this is the largest study to examine this relationship. Employing an approach that incorporated multiple objective measures to quantify the extent of resection, we observed that NT-proBNP levels increased nearly four-fold on the

first postoperative day. However, the postoperative elevation in NT-proBNP occurred independent of the surgical procedure, volume, or weight of lung tissue resected. Our exploratory analyses did not reveal any significant associations between the extent of lung resection and either the duration of one-lung ventilation, or a surrogate marker for systemic inflammation. Lastly, NT-proBNP at all measurement points was not associated with the occurrence of postoperative atrial fibrillation. However, this study is not powered to assess serial NT-proBNP measurements to predict the risk of postoperative atrial fibrillation.

Interpretation and Comparison of Study Findings to Existing Literature

Four studies have previously examined the relationship between b-type natriuretic peptides and lung resection, either as primary or secondary outcomes.

Tayama et al. investigated the relationship between hemodynamic parameters and natriuretic peptide levels following lung resection in a cohort of 25 patients (15 lobectomies, 10 pneumonectomies). They found significant BNP elevations on postoperative days three and seven, with significantly higher levels observed in pneumonectomy patients compared to those undergoing lobectomy. A positive correlation was also noted between BNP levels and total pulmonary vascular resistance in the pneumonectomy group. The authors concluded that BNP elevation reflected right ventricular strain, proportional to the extent of lung resection[10].

Hoksch et al. conducted a pilot study evaluating biomarkers, including BNP, procalcitonin, and C-reactive protein, as predictors of complications following lung resection. BNP was measured preoperatively then daily for five days in 22 patients (14 lobectomies, 2 bilobectomies, and 6 pneumonectomies) undergoing lung resection. BNP increased in all patients, with greater elevations among those who developed cardiac or infectious complications[11].

Muley et al. assessed the impact of lung resection on several cardiac biomarkers, including NT-proBNP, in 64 patients (20 wedge resections, 24 lobectomies or bilobectomies, and 20 pneumonectomies) having elective lung resections. While their primary objective was to examine postoperative troponin elevation, NT-proBNP was also measured preoperatively and on postoperative day one. NT-proBNP increased across all surgical groups, with significantly greater elevations observed in pneumonectomy patients compared to those undergoing lobectomy or wedge resection[13].

Cagini et al. investigated the prognostic value of BNP for cardiopulmonary complications in 294 patients undergoing elective lung resections (68 wedge or segmental resections, 176 lobectomies, 13 bilobectomies, 13 sleeve lobectomies, and 24 pneumonectomies). BNP was measured preoperatively and through postoperative day four. BNP levels peaked on

postoperative day one, and patients with elevated BNP levels postoperatively had a three-fold increase in complication risk. This risk was highest among those undergoing pneumonectomy or lobar resections[12].

In our study, NT-proBNP levels also increased significantly on postoperative day one, consistent with the previously cited reports. Additionally, the plateau in BNP and NTproBNP measurements in Tayama and Muley et al.'s studies were similar, with no significant changes from baseline in the first hours after surgery. However, unlike Tayama and Muley et al., we did not observe a relationship between the extent of lung resection and the magnitude of NT-proBNP elevation. This discrepancy may be partly attributed to key differences in study populations. Pneumonectomy was performed in 31% and 40% of patients in the studies by Muley and Tayama, respectively, while only one patient (0.98%) underwent pneumonectomy in our cohort. Recognizing that these studies were published 14 and 23 years prior, pneumonectomy patients were enrolled at a rate that far exceeds the contemporary practice of thoracic surgery[42]. Moreover, neither study thoroughly detailed their screening protocols for patient recruitment or inclusion and exclusion criteria. The high pneumonectomy rates in these studies limits our ability to directly compare our findings with the results from these studies.

These population differences limit the comparability of findings but also raise the possibility that rather than a continuous dose-response relationship between the extent of lung resection and NT-proBNP elevation, a threshold effect may exist. That is, smaller resections (e.g., lobectomy or segmentectomy) may not result in sufficient hemodynamic stress to elevate NT-proBNP, whereas pneumonectomy may exceed a physiological threshold resulting in significant cardiac strain and subsequent elevation of b-type natriuretic peptides. This hypothesis is supported by the markedly greater disruption to cardiopulmonary hemodynamics caused by pneumonectomy, where the main pulmonary artery and veins are transected. In contrast, lobar and segmental resections involve division of more distal pulmonary vessels, resulting in less pronounced hemodynamic consequences. Based on our review of the literature, there is no available evidence to support this hypothesis. While speculative, this theoretical threshold effect could explain both the lack of a dose-response relationship in our findings and the discordance with prior studies that heavily enrolled pneumonectomy patients.

It is also notable that Tayama et al. did not detect significant difference in BNP until the third and seventh postoperative day, whereas our measurements were limited to the first postoperative day[10]. While Cagini et al.'s results suggest that natriuretic peptide levels peak after lung resection on the first postoperative day, our data cannot determine whether NT-proBNP levels would continue to rise, plateau or decline past this point[12]. Importantly,

McCall et al. demonstrated that right ventricular dysfunction may occur as early as the second postoperative day following lung resection[23]. This raises the possibility that the hemodynamic consequences of lung resection responsible for postoperative elevations in natriuretic peptide levels develop more gradually. In this case, our study only having measured NT-proBNP on POD1 may have missed its true peak. Alternatively, elevations in b-type natriuretic peptides after postoperative day one may be entirely unrelated to the extent of lung resection due to additional confounding factors.

Postoperative complications may confound the association between the extent of lung resection and b-type natriuretic peptide levels. Tayama et al. did not report or control for complications during their seven-day follow-up, and Cagini et al. found that patients experiencing cardiopulmonary or infectious complications had higher BNP levels. Given that most complications arise later in the postoperative course than the first postoperative day, the late BNP elevations observed in prior studies may reflect these events rather than the extent of lung resection. Accordingly, attributing natriuretic peptide changes to the type of surgical procedure, especially beyond the immediate postoperative period, may be misleading without adjusting for postoperative complications. In addition to complications or other confounding variables that may impact natriuretic peptide levels, exposure to anesthesia and surgical trauma is common amongst all patients in our study.

Elevations in natriuretic peptide levels are common amongst patients undergoing major noncardiac surgical procedures. Rodseth et al. conducted a meta-analysis of over 2,000 patients, the majority of whom were not thoracic surgery patients. They reported that 76% of patients experienced postoperative increases in b-type natriuretic peptides, suggesting that these biomarkers reflect a general physiological response to surgical stress rather than being specific to thoracic procedures. Our results support this interpretation as NT-proBNP went up in nearly all patients in our cohort. This may suggest NT-proBNP elevations after lung resection reflect systemic perioperative stress rather than the extent of lung resection.

As no relationship was demonstrated between the extent of lung resection and postoperative elevations in NT-proBNP levels, exploratory analyses were undertaken to investigate alternative etiologies. We first examined the potential association between the duration of one-lung ventilation and NT-proBNP levels. One-lung ventilation is commonly employed to optimize exposure to intrathoracic structures, particularly in thoracoscopic procedures.

One-lung ventilation induces significant intraoperative alterations in cardiopulmonary physiology. Following lung isolation, cardiac output is redirected to the non-operative lung. This redistribution increases both pulmonary artery pressure and vascular resistance. Consequently, the right ventricle must adapt to the increased afterload by dilating and

subsequently augmenting contractility. Although one-lung ventilation is generally well tolerated, some patients may not possess sufficient right ventricular reserve to accommodate these acute changes[6]. Given the abrupt hemodynamic shifts associated with one-lung ventilation, we investigated whether longer durations of one-lung ventilation could contribute to perioperative elevations in NT-proBNP levels.

In our cohort, we found no association between time on one-lung ventilation and NT-proBNP elevation. The duration of time on one-lung ventilation was significantly longer in patients undergoing lobectomy compared to wedge resection. These findings are consistent with prior reports. Cagini et al. did not specifically evaluate one-lung ventilation in their analysis, and the proportion of their sample exposed to one-lung ventilation is unclear, as it was selectively applied in their study. However, they found no correlation between perioperative BNP levels and anesthesia duration[12]. As their study included only lung resection patients, it is reasonable to infer that anesthesia time may roughly approximate time on one-lung ventilation, though this remains an assumption. Given the absence of an association between NT-proBNP levels and duration of one-lung ventilation in our study, we proceeded to investigate the potential role of systemic inflammation.

Tissue injury during surgical procedures induces both local and systemic inflammatory responses. Inflammatory markers, such as leukocyte count, C-reactive protein, and interleukins, have been associated with the development and persistence of atrial fibrillation in both surgical and non-surgical populations[3,43]. Similarly, b-type natriuretic peptide levels are elevated in patients with atrial fibrillation across these populations[3,4]. Until recently, few studies have explored the relationship between systemic inflammation and b-type natriuretic peptide levels.

Emerging experimental evidence from both human and animal models suggests that inflammatory cytokines may stimulate the release of natriuretic peptides from cardiomyocytes. Fish-Trotter et al. conducted a review examining the association between inflammation and b-type natriuretic peptides, which incorporated two observational and one experimental study in non-surgical patients. They reported that elevated interleukin-6 levels were associated with increased NT-proBNP concentrations. Additionally, they found that b-type natriuretic peptide levels were significantly higher in patients hospitalized with acute inflammatory conditions, after controlling for heart failure. The authors concluded that systemic inflammation may independently trigger the release of natriuretic peptides[32].

In light of Fish-Trotter et al.'s findings, postoperative inflammation is a plausible explanation for the NT-proBNP elevations we observed following lung resection. This interpretation is further supported by the meta-analysis conducted by Rodseth et al., which demonstrated in a large cohort of patients, only a minority of which underwent thoracic surgery, that

postoperative b-type natriuretic peptide elevations are common. Based on this interpretation of the available literature, we furthered out exploratory analyses to investigate the relationship between systemic inflammation and NT-proBNP levels following lung resection, using the postoperative day one neutrophil-lymphocyte ratio as a surrogate marker of systemic inflammation.

The neutrophil-lymphocyte ratio is a simple, readily available measure of systemic inflammation that can be derived from a standard complete blood count. While the predictive utility of the neutrophil-lymphocyte ratio in the immediate postoperative period, or as a prognostic marker following thoracic surgery, has not been clearly established, it is considered a valid indicator of inflammatory processes in hospitalized and ambulatory patients[41]. As our study did not collect other, more traditionally used inflammatory biomarkers (such as C-reactive protein or interleukin-6), the neutrophil-lymphocyte ratio provided the only available measure to explore the potential association between systemic inflammation and NT-proBNP elevations. Given prior studies suggesting a positive correlation between inflammatory markers and b-type natriuretic peptides, we hypothesized that these two variables would increase proportionally.

Using the change in NT-proBNP from baseline to postoperative day one and the neutrophil-lymphocyte ratio on postoperative day one, we observed an inverse relationship between NT-proBNP and systemic inflammation. Inflammatory markers appeared to decrease when the change in NT-proBNP levels increased. However, this association did not reach statistical significance. This analysis was intended to generate hypotheses that may help explain the observed four-fold increase in NT-proBNP levels following lung resection, which occurred independent of the extent of resection. The mechanism underlying the inverse relationship between NT-proBNP and the neutrophil-lymphocyte ratio remains unclear. It is important to note that the neutrophil-lymphocyte ratio has not been extensively studied in the postoperative setting, and our study was not designed to formally assess this relationship, thus limiting the interpretability of our findings. Amar et al. previously demonstrated that in patients undergoing lung or esophageal resection, both C-reactive protein and interleukin-6 levels increase significantly in the postoperative period. However, they found no difference in inflammatory markers between patients who developed atrial fibrillation and those who did not[43]. When considering these results alongside the well-established association between b-type natriuretic peptides and postoperative atrial fibrillation, it suggests that although systemic inflammation is likely implicated in the development of postoperative atrial fibrillation, inflammatory markers may not reliably predict arrhythmia development.

This study was conceptualized as a pilot project to determine the feasibility of conducting a prospective investigation into the role of serial NT-proBNP measurements as independent predictors of postoperative atrial fibrillation. The incidence of postoperative atrial fibrillation in our cohort was 4.9%. Although significant heterogeneity exists in the rates of postoperative atrial fibrillation following lung resection, our findings are similar to previous reports. We used the postoperative monitoring protocols recommended in the COP-AF trial, which had a 6.9% incidence of atrial fibrillation in their cohort of thoracic surgery patients[21].

In our study, there was no difference in NT-proBNP levels at any of the three measurement points between patients who developed postoperative atrial fibrillation and those who did not. Although there was a trend suggesting that patients who developed atrial fibrillation had undergone larger lung resections (lobectomy), this association did not reach statistical significance. These findings contrast with those of previously published high-quality studies and meta-analyses, which have identified both larger resections[14] and elevated natriuretic peptide levels[4] as significant predictors of postoperative atrial fibrillation. However, it is essential to recognize that our pilot study was not adequately powered to assess the predictive capacity of NT-proBNP levels or the extent of lung resection for postoperative atrial fibrillation as primary outcomes. This secondary analysis was conducted primarily to establish the local incidence of postoperative atrial fibrillation using our defined postoperative ECG monitoring protocol, and secondarily to apply the statistical methods that would be necessary in a larger, adequately powered study designed to evaluate these predictive relationships.

Although our study did not demonstrate a statistically significant association between NT-proBNP levels and the development of postoperative atrial fibrillation, we confirmed that the study protocol is feasible to implement at our centre. NT-proBNP levels at all measurement time points did not differ between those who developed postoperative atrial fibrillation and those without postoperative arrhythmia. However, it is notable that the median postoperative day one NT-proBNP level was higher in patients who developed atrial fibrillation (882 pg/mL) compared to those who did not (461 pg/mL), though this difference did not reach statistical significance in our underpowered study with a low event rate. Despite this limitation and the absence of statistically significant findings, the observed trends from our study align with prior research suggesting that elevated postoperative NT-proBNP is associated with the development of atrial fibrillation[4,35].

Strengths and Limitations of the Study

A primary strength of this study is its prospective observational design and methodological rigor. The prospective design allowed for the systematic collection of perioperative data

and NT-proBNP measurements in a real-world surgical population. Similarly, this methodology minimizes the potential for recall bias and ensured the consistent application of predefined study protocols, enhancing the internal validity of the study. The aim, protocol and outcomes of the study were clearly defined and followed throughout. As such, the results should be reproducible. Lastly, as all patients undergoing thoracic surgery at our centre were screened for enrollment, and patients were not selected based on procedure type, our results should not be subjected to the same degree of selection bias that may have impacted the findings of previous studies investigating the relationship between the extent of lung resection and perioperative natriuretic peptide levels.

The study was further strengthened by very low rates of missing data across the primary outcome measures. Serial NT-proBNP measurements were successfully obtained at all designated time points for nearly all (99.0%) patients, and relevant perioperative variables were consistently captured. Only three patients had missing postoperative day one NT-proBNP measurements, all of whom were discharged on the first postoperative day before the standard morning blood draw. This high degree of data completeness strengthens the reliability of the reported results and minimizes the potential impact of selection bias. Additionally, the minimization of incomplete data collection negated the need for imputation or other statistical adjustments which could introduce sources of error or bias into the analysis.

Another important strength of this study is the methodological depth of the statistical analysis. Both raw and log-transformed NT-proBNP data were used to explore perioperative trends. The log transformation helped normalize the data, reducing the variability in measurements and allowing for a more accurate description of relative changes in NT-proBNP concentrations. This dual approach provided complementary perspectives. The raw data allowed for intuitive, clinically meaningful interpretation of absolute biomarker changes, while the log-transformed analyses addressed the skewed distribution and outliers in NT-proBNP measurements, offering a more statistically robust assessment of percent changes and multiplicative effects following lung resection.

To our knowledge, this is the first study to use quantitative measurements of resection weight and volume to define the extent of lung resection. Although the validity of this approach has not been previously established, it represents an important strength of our study. Objective measurements were deliberately chosen to improve our understanding of the mechanisms contributing to the increased risk of postoperative atrial fibrillation following larger lung resections. This approach was particularly important because prior studies have typically compared outcomes by procedure type alone. However, we have observed, both anecdotally and in clinical practice, that significant variability can exist in

the amount of lung parenchyma resected within the same procedural category, especially following non-anatomical resections. This is highlighted by the wide range of weight and volume measurements seen in all operative subgroups. By applying this methodological approach, alongside multiple complementary analytical techniques, we believe our findings are both methodologically sound and credible.

Multiple statistical models were used to rigorously examine the relationship between the extent of lung resection and perioperative NT-proBNP levels. Spearman correlations, mixed-effects regression models, and subgroup comparisons across operative types were all employed to provide a multidimensional evaluation of this relationship. The consistent finding across these independent analyses, that the extent of lung resection was not associated with NT-proBNP elevation, strengthens the credibility of our conclusion. The consistency of our findings was demonstrated whether the extent of lung resection was treated as a continuous variable (using weight or volume) or as a categorical variable (by procedure type).

Finally, the inclusion of exploratory analyses to investigate potential alternative mechanisms, specifically, the role of one-lung ventilation duration and systemic inflammation, further enhances the depth of this study. Although these analyses were secondary, they reflect a deliberate effort to comprehensively examine potential contributors to perioperative NT-proBNP elevation beyond the primary study aim.

Taken together, the strengths of this study include its prospective design, methodological rigor, near-complete data acquisition, careful statistical methodology, and thoughtful exploration of alternative explanatory factors. These features contribute to the overall reliability and clinical relevance of the study, which we feel provides a meaningful addition to the literature on perioperative medicine. Despite the study's strengths, several limitations must be acknowledged.

First, this was a single-centre study with a modest sample size. Although the prospective design strengthens the reliability of data collection and both the protocol and outcome measures were clearly defined, the findings of a single-centre study may not fully represent the broader surgical population, thereby limiting generalizability. Our results may not be reproducible or applicable to centres with differing surgical volumes, surgical complexity, patient demographics, or perioperative management strategies. Additionally, while our study demonstrated internal consistency, it included a relatively small number of patients, particularly those undergoing more extensive resections such as bilobectomy or pneumonectomy. Although the low frequency of these larger resections reflects real-world thoracic surgical practice, it limits our ability to draw definitive conclusions regarding the

presence of a dose-response relationship or the potential for a threshold effect across the full spectrum of lung resections as defined by procedure type.

Second, our study was not powered to detect associations between NT-proBNP levels and postoperative atrial fibrillation as a primary outcome. In this pilot study, this was explicitly designated as a secondary outcome. The low event rate of postoperative atrial fibrillation in our cohort, while consistent with expected incidence rates based on prior studies, limited our ability to draw firm conclusions regarding the predictive capacity of NT-proBNP for this complication. As such, our analysis of postoperative atrial fibrillation should be interpreted as exploratory and specific to the local context of our centre. These findings should not be considered contradictory to the conclusions of larger, high-quality studies and subsequent meta-analyses that have established elevated b-type natriuretic peptides as significant predictors of postoperative atrial fibrillation.

Third, the timing of biomarker measurements in our study was limited to the preoperative period, the post-anesthetic care unit, and postoperative day one. Although previous studies suggest that NT-proBNP levels typically peak within the first day following surgery, some evidence indicates that further elevations may occur later in the postoperative course, particularly after postoperative day three. In our study, the decision to limit biomarker collection to the early postoperative period was intentional and guided by our primary objective of defining the relationship between NT-proBNP and lung resection. We aimed to capture NT-proBNP changes attributable to the surgical intervention itself, whereas later elevations may be more reflective of postoperative complications. Additionally, if NT-proBNP levels are going to be used as a predictive tool, measurements should be taken relatively soon after the operation or at least prior to the second or third postoperative day, which is the median time of onset for postoperative atrial fibrillation development. Nevertheless, the absence of later postoperative measurements limits our ability to fully characterize whether NT-proBNP levels would have continued to rise, plateau, or decline beyond postoperative day one. This may influence the interpretation of the timing and trajectory of cardiac stress following lung resection.

Fourth, although our study employed the use of novel, objective measures to quantify the extent of lung resection, this methodology has not been previously validated in the thoracic surgery literature. While our findings were consistent across all definitions of resection extent, it remains possible that specimen weight and volume do not fully capture the complex alterations to cardiopulmonary physiology induced by lung resection. Additionally, these measurements are subject to potential sources of error, including venous congestion depending on the sequence of pulmonary artery and vein ligation, and variability in specimen weight due to parenchymal replacement with malignant tumours of

varying size or the inclusion of non-parenchymal tissue in the pathology specimen (e.g. en-bloc resection of the chest wall).

Fifth, while the exploratory analyses examining systemic inflammation provided valuable additional insights, our reliance on the neutrophil-lymphocyte ratio as the sole marker of inflammation may not have fully captured the complexity of the postoperative inflammatory response. Although the neutrophil-lymphocyte ratio is readily obtainable from routine laboratory tests, it may not be as sensitive or specific as other biomarkers such as interleukin-6 or C-reactive protein in this clinical context. Furthermore, to our knowledge, the neutrophil-lymphocyte ratio has not been specifically validated as a marker of perioperative inflammation in thoracic surgery patients. Finally, our inflammatory analysis was limited to measurements obtained on postoperative day one, which may not correspond to the peak of systemic inflammation following lung resection.

Lastly, although our study achieved excellent data completeness, the potential influence of unmeasured confounders must be considered. Important perioperative variables, including anesthetic and postoperative analgesia strategies, intraoperative hemodynamics, and the use of vasoactive medications, were not captured, but could impact NT-proBNP measurements. Additionally, the presence of pre-existing heart failure was determined based on patient history alone, without routine echocardiographic assessment to objectively evaluate right or left ventricular function. Patients with end-stage renal disease were excluded, consistent with previous study protocols, as the timing of dialysis and resultant fluctuations in volume status would render NT-proBNP levels difficult to interpret. However, other variables such as intraoperative fluid administration, volume status, and postoperative acute kidney injury were not collected. NT-proBNP measurements were serially collected to allow the patients preoperative value to act as an internal control to mitigate the impacts of these potential confounders. Nonetheless, the potential influence of these unmeasured confounders and other factors affecting NT-proBNP release and hormonal regulation may influence biomarker levels in ways that were not fully accounted for in our analyses.

While this study offers valuable insights, several limitations have been highlighted. As a single-centre study with a modest sample size, the generalizability of the findings may be limited. The small number of patients undergoing extensive resections restricts the ability to draw definitive conclusions regarding relationship between NT-proBNP and the extent of lung resection across the full spectrum of lung resection procedures. Additionally, the study was not powered to evaluate postoperative atrial fibrillation as a primary outcome, and the timing of biomarker measurements was limited to the early postoperative period. The novel use of specimen weight and volume to quantify resection extent, though

internally valid based on our findings, requires further investigation and may not account for individual patient characteristics. Despite these limitations, our demonstration of a four-fold increase in NT-proBNP after lung resection independent of the amount of lung removed in a methodologically sound study is clinically relevant.

Clinical Implications

The primary clinical relevance of our study lies in demonstrating that lung resection is associated with significant elevations in postoperative NT-proBNP levels. Prior meta-analyses have established that postoperative elevations in b-type natriuretic peptides are associated with an increased risk of mortality and non-fatal myocardial infarction within one month of noncardiac surgery[34]. Additionally, both preoperative and postoperative elevations in b-type natriuretic peptides have been identified as strong predictors of postoperative atrial fibrillation following noncardiac thoracic surgery[4]. When our findings, a four-fold increase in NT-proBNP on postoperative day one, are considered in the context of these meta-analyses, they reinforce the notion that patients undergoing lung resection, regardless of procedure type, are at elevated risk for adverse cardiovascular events. Consequently, perioperative NT-proBNP monitoring may offer a valuable opportunity to identify high-risk patients who could benefit from intensified surveillance or tailored perioperative management strategies to mitigate the risk of significant postoperative morbidity.

Importantly, although our experimental hypothesis was rejected, our finding of no significant difference in NT-proBNP levels between wedge, segmental, and lobar resections provides additional clinically relevant insights. Recent publications have demonstrated that sublobar resections are non-inferior to lobectomy with respect to oncologic outcomes for early-stage lung cancers[44]. This emerging evidence will presumably continue to shift surgical practice patterns toward maximal preservation of lung parenchyma when clinically, and oncologically appropriate to do so. Traditionally, lobectomy has been associated with a higher incidence of postoperative complications compared to sublobar resections, with prior studies suggesting that these differences may result from the greater hemodynamic alterations induced by the removal of a larger portion of the pulmonary vascular bed[20,45]. However, our results demonstrated that NT-proBNP levels increase from baseline following all lung resections, irrespective of whether the resection is sublobar or lobar in extent. Taken together, it should be considered that even when lung parenchyma is maximally preserved, patients remain at an elevated risk for postoperative cardiovascular complications.

In addition to the present study's clinical relevance, its findings in the context of existing literature highlight multiple opportunities for future research opportunities. If readily

obtainable biomarkers can be used to determine a patient's perioperative risk, future investigations should be focused on how to use this information, such that either this assessment of risk, or biomarker-guided treatments can improve our ability to provide perioperative care with the primary aim of improving clinical outcomes.

Future Directions

As the present study was designed as a pilot, the first potential avenue for future research to discuss is the role and utility of a follow-up, appropriately powered main study. A multi-centre prospective trial was conceptualized simultaneously with design of the pilot study to further explore the relationship between NT-proBNP and the amount of lung parenchyma resected, while also assessing the predictive value of NT-proBNP for postoperative atrial fibrillation after lung resection. An additional aim of the main study was to develop a predictive model for postoperative atrial fibrillation incorporating both preoperative clinical risk factors and perioperative NT-proBNP measurements. The pilot study successfully met its objectives and demonstrated the feasibility of the study design; however, the necessity and potential impact of a larger follow-up study is debateable.

While a larger study could theoretically clarify whether a relationship exists between the extent of lung resection and NT-proBNP elevation, our findings suggest that pursuing this question further may have limited clinical value. The primary goal of our study was to contribute to the understanding of the multifactorial etiology of postoperative atrial fibrillation after lung resection, with the hope of informing future treatment and risk stratification. However, the existing literature has clearly demonstrated that the incidence of postoperative atrial fibrillation increases in patients with elevated NT-proBNP levels and after larger resections. Whether demonstrating a relationship between resection extent and NT-proBNP in a larger cohort with adequate numbers of patients undergoing major resections (eg. Bilobectomy or pneumonectomy), would meaningfully influence patient management is uncertain.

Our findings of NT-proBNP elevation in nearly all patients after lung resection are clinically significant and suggest that this biomarker could have broad applicability for perioperative risk assessment, regardless of the extent of resection. Additionally, prior high-quality studies have already developed and validated risk prediction models using preoperative natriuretic peptide measurements. Our study further supports this by demonstrating a strong correlation between preoperative and postoperative NT-proBNP values, indicating that pre- or postoperative measurements in isolation may be sufficient for risk stratification.

Taken together, while our study adds important data to the existing literature, the development of a follow-up trial with the sole focus of risk prediction is unlikely to significantly advance the field. The next step in perioperative research should focus not on further refining of prediction models, but on developing and testing interventions that can reduce postoperative morbidity in patients identified as high-risk based on their elevated NT-proBNP levels.

While previous studies have established the prognostic value of perioperative biomarkers, including NT-proBNP, in predicting postoperative morbidity and mortality, the next critical step is to develop actionable interventions based on these findings. Further research on risk identification alone is insufficient if it does not translate into improved patient care. Future studies should aim to design and protocolize biomarker driven perioperative strategies. These investigations may include evaluating the role of NT-proBNP in guiding postoperative surveillance intensity, informing postoperative disposition planning (e.g. telemetry, intensive care, etc.), and identifying high-risk patients who may benefit from targeted cardiovascular monitoring or early multidisciplinary follow-up. There is also an opportunity to explore how collaboration between surgeons, perioperative medicine specialists, family medicine practitioners and cardiologists can improve long-term patient outcomes through development of multidisciplinary care teams focused on addressing a patient's perioperative cardiovascular risk. Although these proposed research directions are broad, the utility of NT-proBNP in risk stratifying patients has been robustly demonstrated and there is now a clear need to move beyond risk stratification toward the development of evidence-based, biomarker-guided interventions to reduce postoperative morbidity.

Our study introduced a novel methodology to objectively define the extent of lung resection using quantitative measures of resection weight and volume. The internal consistency of our findings using this approach supports its validity within our study, but whether this methodology is broadly applicable to other clinical questions remains uncertain. Future research is required to validate this protocol and assess its generalizability. Depending on the clinical objectives of such studies, several refinements could be considered. These may include correlating the extent of resection with preoperative and postoperative pulmonary function tests, exploring the impact of measuring fresh specimens prior to formalin fixation, and investigating associations between the size of the resected lung parenchyma, preoperative lung volumes, and body surface area. Importantly, future validation studies should aim to include patients undergoing larger lung resections to ensure this methodology is applicable across the full spectrum of lung resection procedures.

Finally, although our study demonstrated that NT-proBNP levels consistently increase following lung resection, the underlying mechanism driving this elevation remains unclear. This finding is consistent with previous meta-analyses in noncardiac surgery populations, where postoperative NT-proBNP elevations are common but seemingly unexplained. Presumably, the unclear mechanism behind NT-proBNP elevations is like that of postoperative atrial fibrillation, such that it is multifactorial and difficult to isolate a single mechanism or risk factor. However, given the well-established association between elevated NT-proBNP and adverse postoperative outcomes, future research should prioritize efforts to elucidate the physiological mechanisms responsible for these elevations. A more comprehensive understanding of the drivers of perioperative NT-proBNP release could inform both in-hospital and long-term management strategies, ultimately leading to tailored interventions to improve the outcomes of patients undergoing any type of high-risk surgical procedure.

Conclusion

This prospective observational study investigated the relationship between the extent of lung resection and perioperative changes in NT-proBNP levels. Using a novel approach that incorporated multiple definitions of resection extent, we demonstrated that NT-proBNP levels increased nearly four-fold on the first postoperative day. However, contrary to our experimental hypothesis, the magnitude of NT-proBNP elevation did not correlate with the extent of lung resection when quantified by objective measures of specimen weight and volume, or when classified by operative procedure. These findings suggest that postoperative elevations in NT-proBNP may not be driven by the amount of lung resected but rather may reflect a generalized physiological response to surgical stress.

Our exploratory analyses further supported this interpretation, as neither the duration of one-lung ventilation nor surrogate markers of systemic inflammation demonstrated a significant association with NT-proBNP elevations. Although the study was not powered to assess postoperative atrial fibrillation as a primary outcome, no association was found between NT-proBNP levels and the development of this arrhythmia in our cohort.

Our findings contribute to the growing body of evidence that perioperative NT-proBNP elevations are not unique to larger lung resections and that NT-proBNP may serve as a general marker of physiological stress rather than a surrogate for resection magnitude. As elevated NT-proBNP levels are known to increase the risk of perioperative morbidity, our results highlight that patients undergoing lung resection, regardless of procedure type or volume of lung removed, remain at elevated risk of postoperative complications. NT-

proBNP remains a valuable, easily obtainable biomarker for perioperative risk stratification, and predictor of postoperative cardiovascular complications such as atrial fibrillation.

While our study demonstrated a consistent increase in NT-proBNP after lung resection, the precise mechanism underlying this physiological response remains unclear. Future research should further investigate the drivers of NT-proBNP elevations in noncardiac surgery populations and explore how this biomarker can be integrated into postoperative management strategies to improve patient outcomes.

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Figures and Tables

Figure A: CONSORT diagram

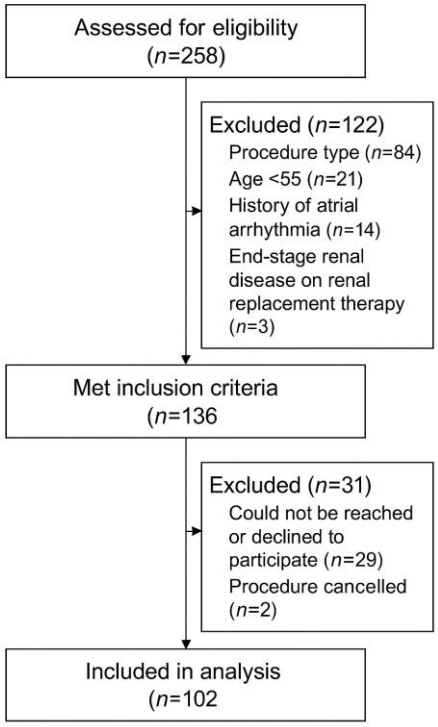

Figure B: Trajectory plot of NT-proBNP measurements at PREOP, PACU and POD1

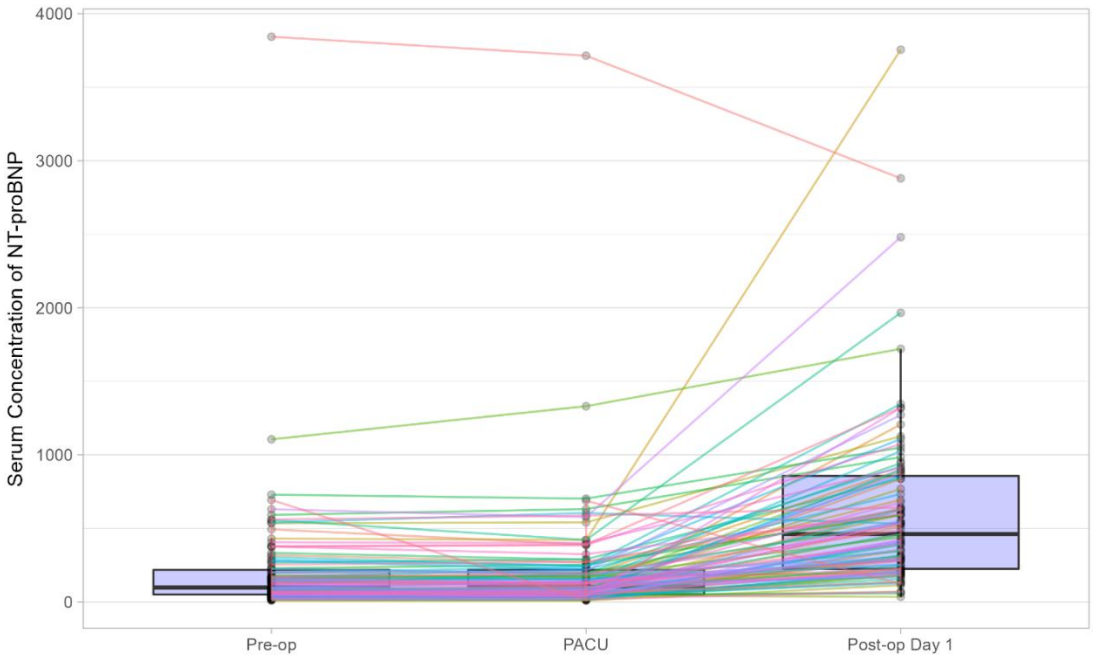

Figure C: Trajectory plot of NT-proBNP measurements (log-transformed) at PREOP, PACU and POD1

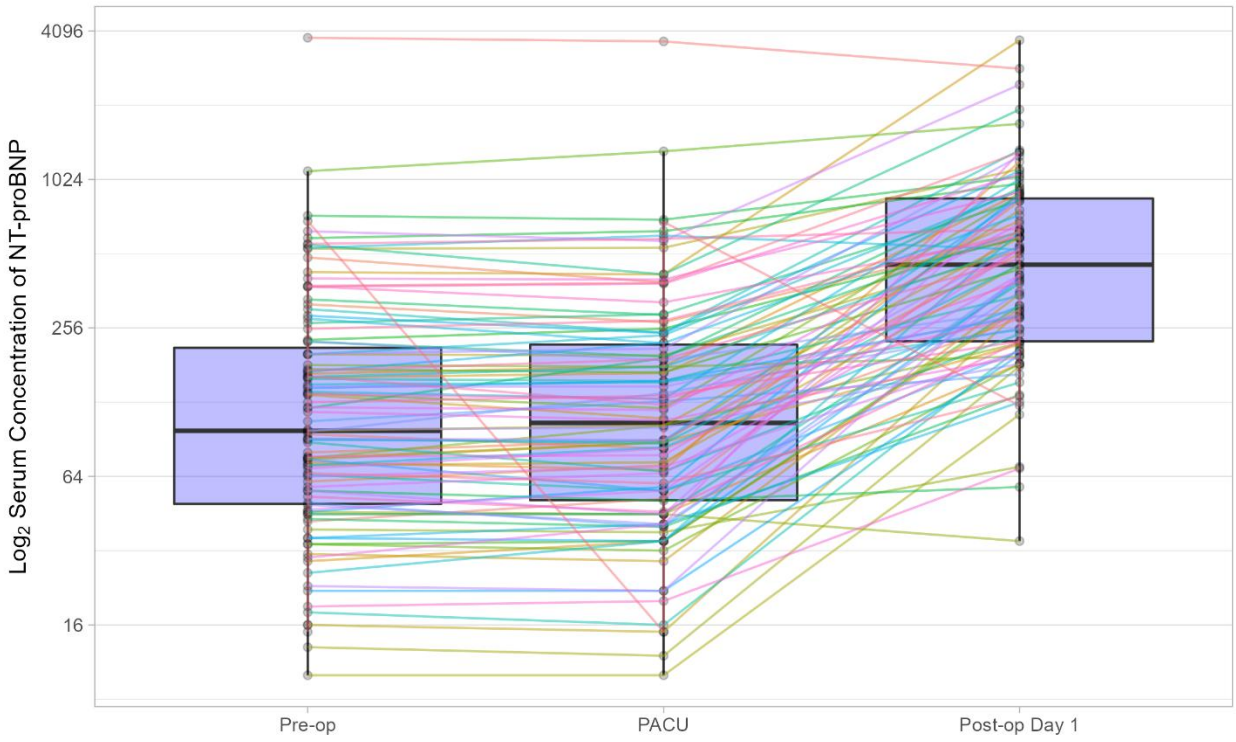

Figure D: Density estimate of NT-proBNP POD1/PRE ratio

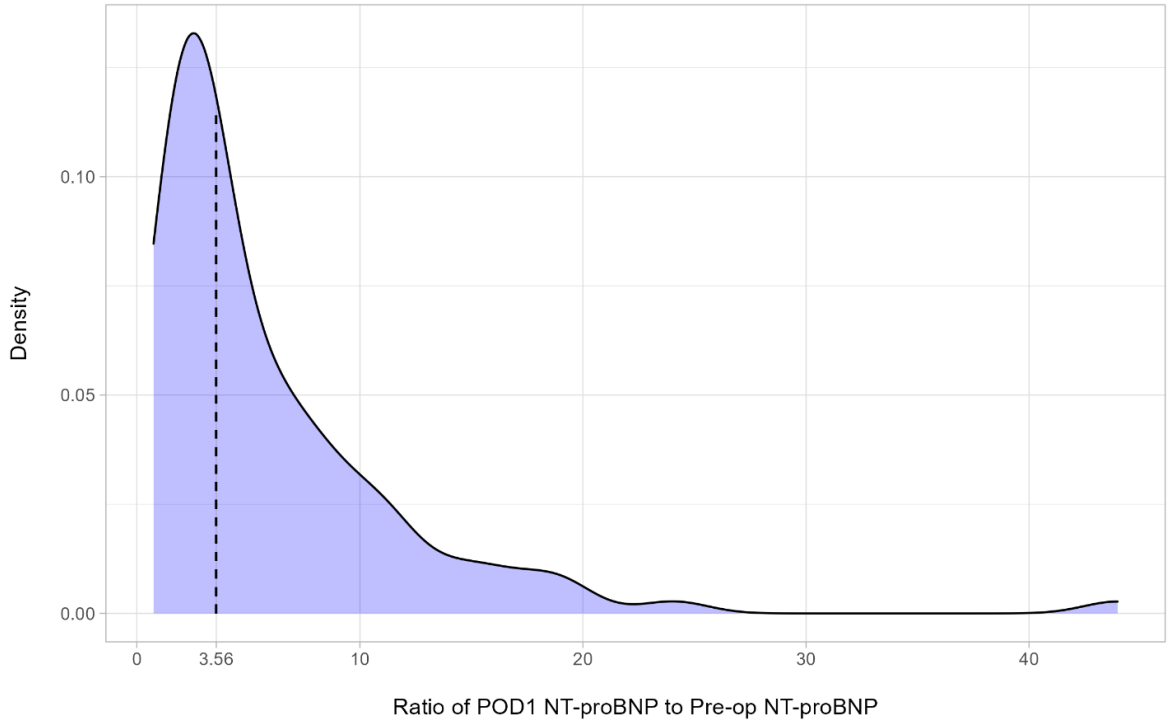

Figure E: Density estimate of NT-proBNP POD1/PACU ratio

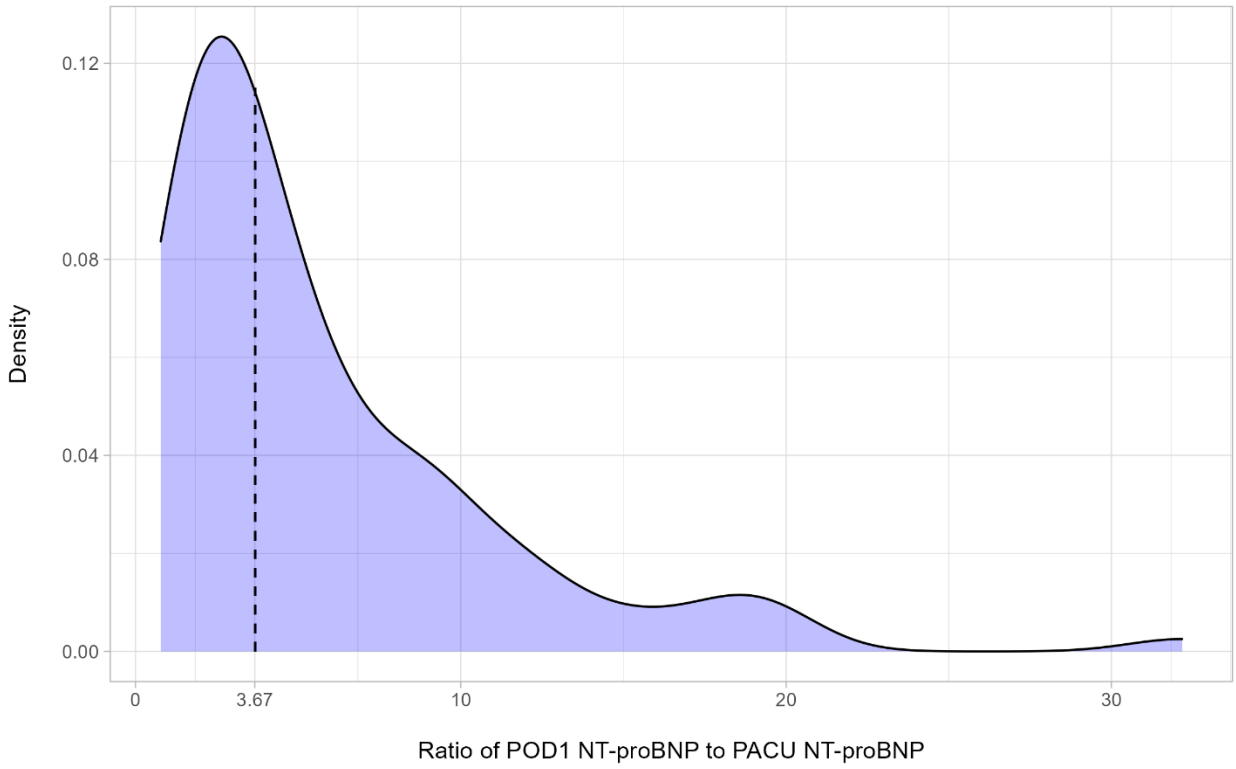

Figure F: Spearman correlation between lung resection weight and NT-proBNP measurements at PREOP, PACU and POD1

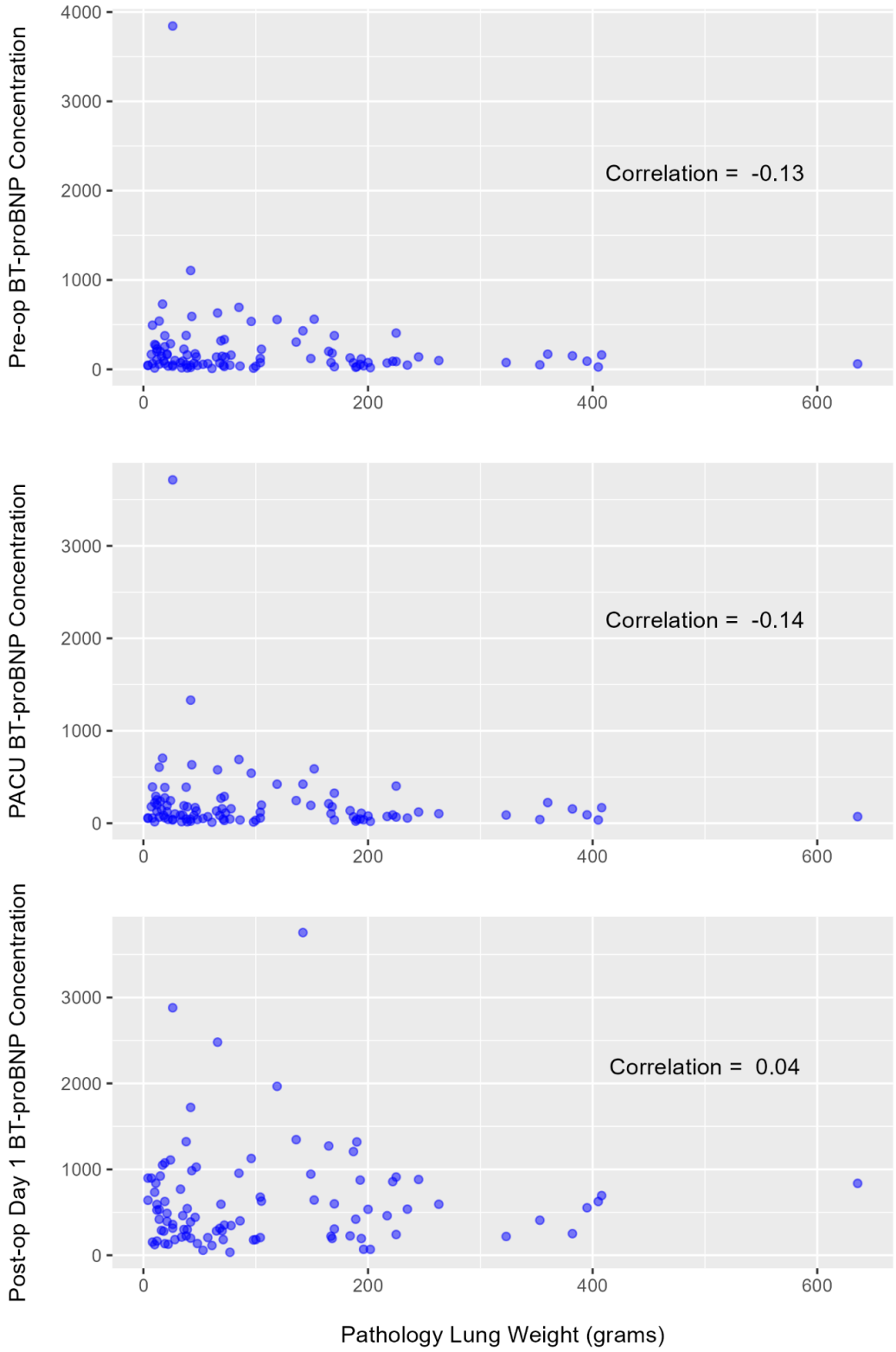

Figure G: Spearman correlation between lung resection weight and change in NT-proBNP measurements from baseline

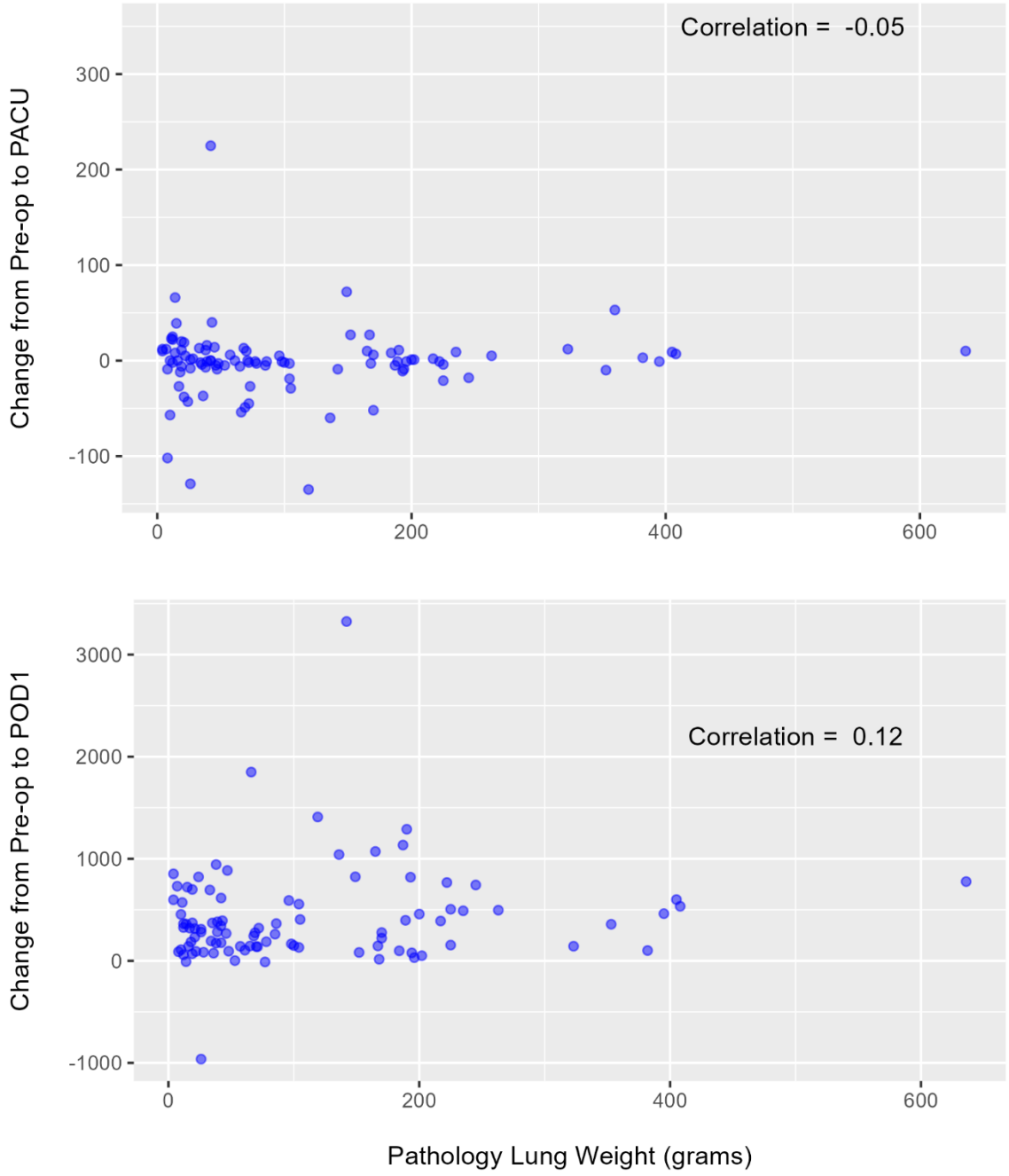

Figure H: Spearman correlation between lung resection volume and NT-proBNP measurements at PREOP, PACU and POD1

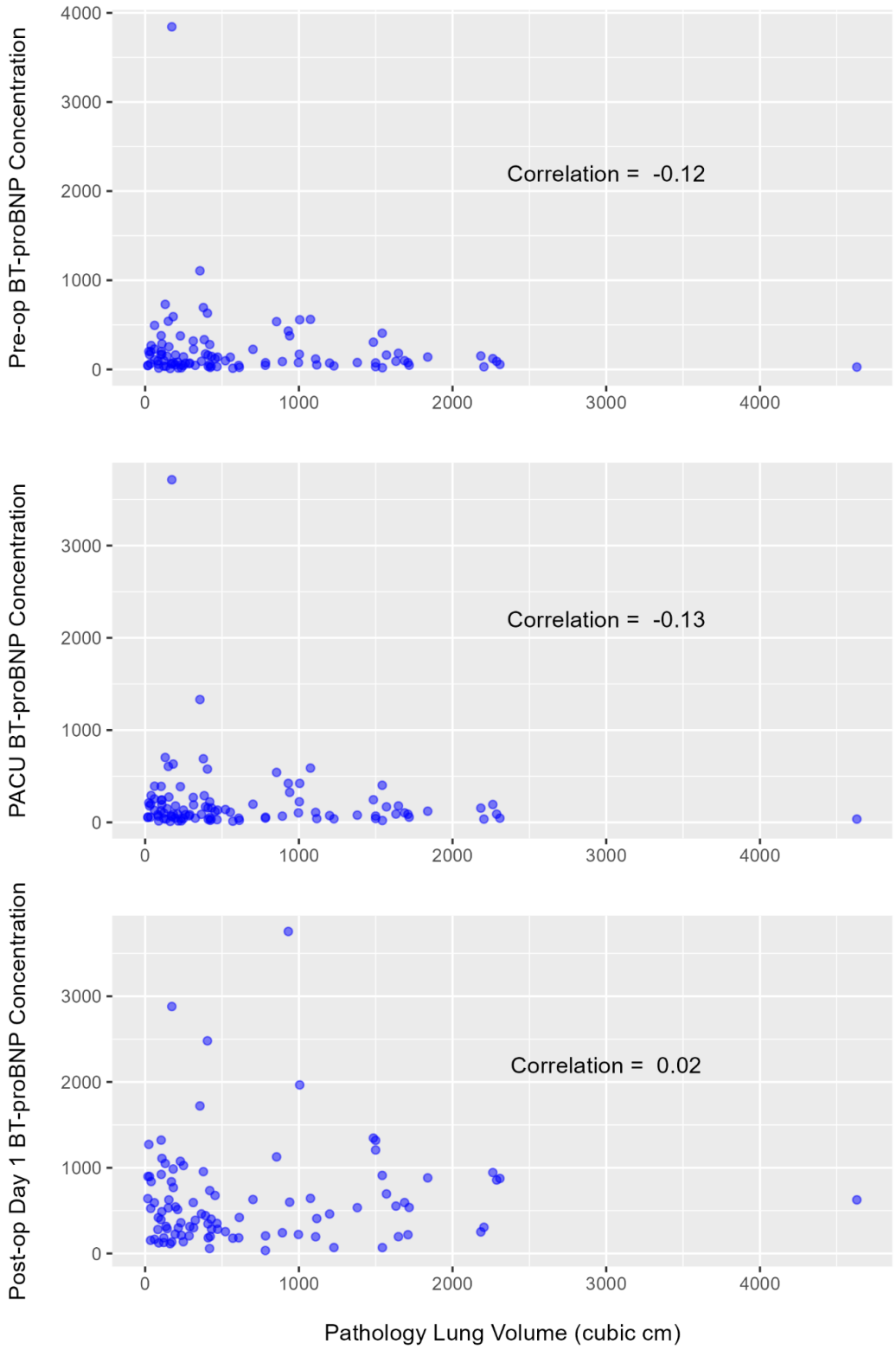

Figure I: Spearman correlation between lung resection volume and change in NT-proBNP measurements from baseline

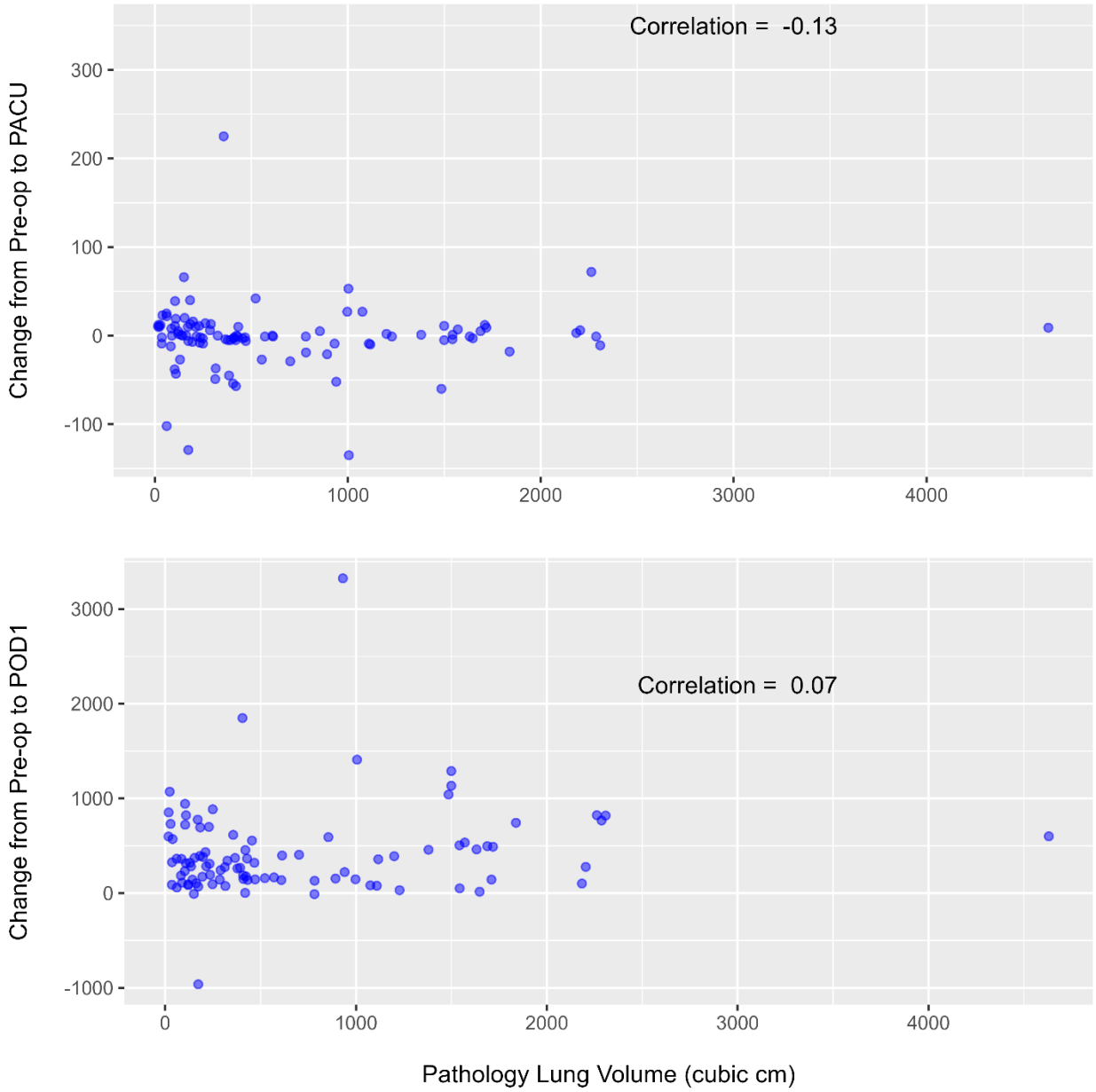

Figure J: Box and whisker-plot demonstrating change in NT-proBNP measurements from baseline by operative procedure

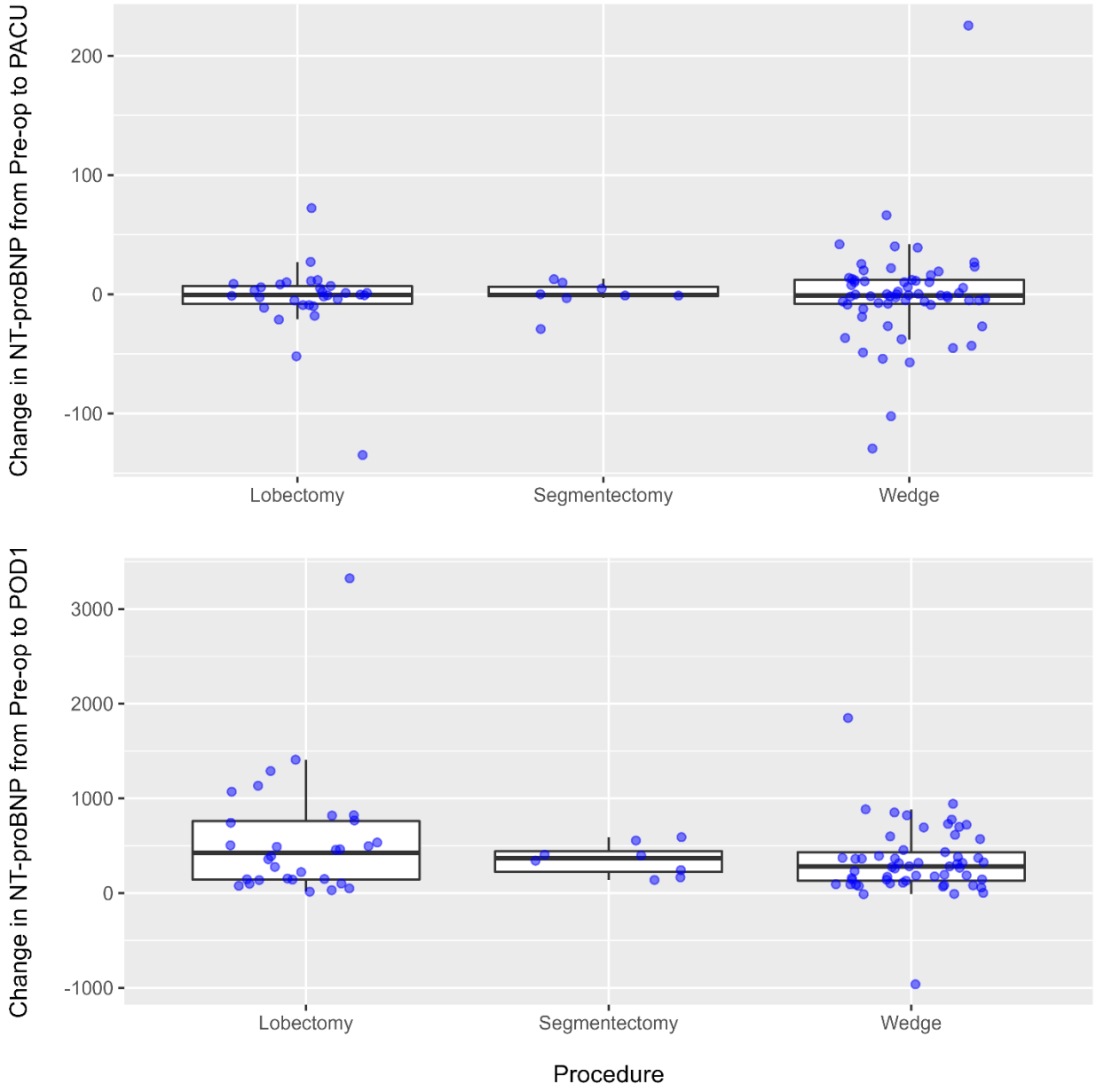

Figure K: Spearman correlation between time on one-lung ventilation and change in NT-proBNP measurements from baseline

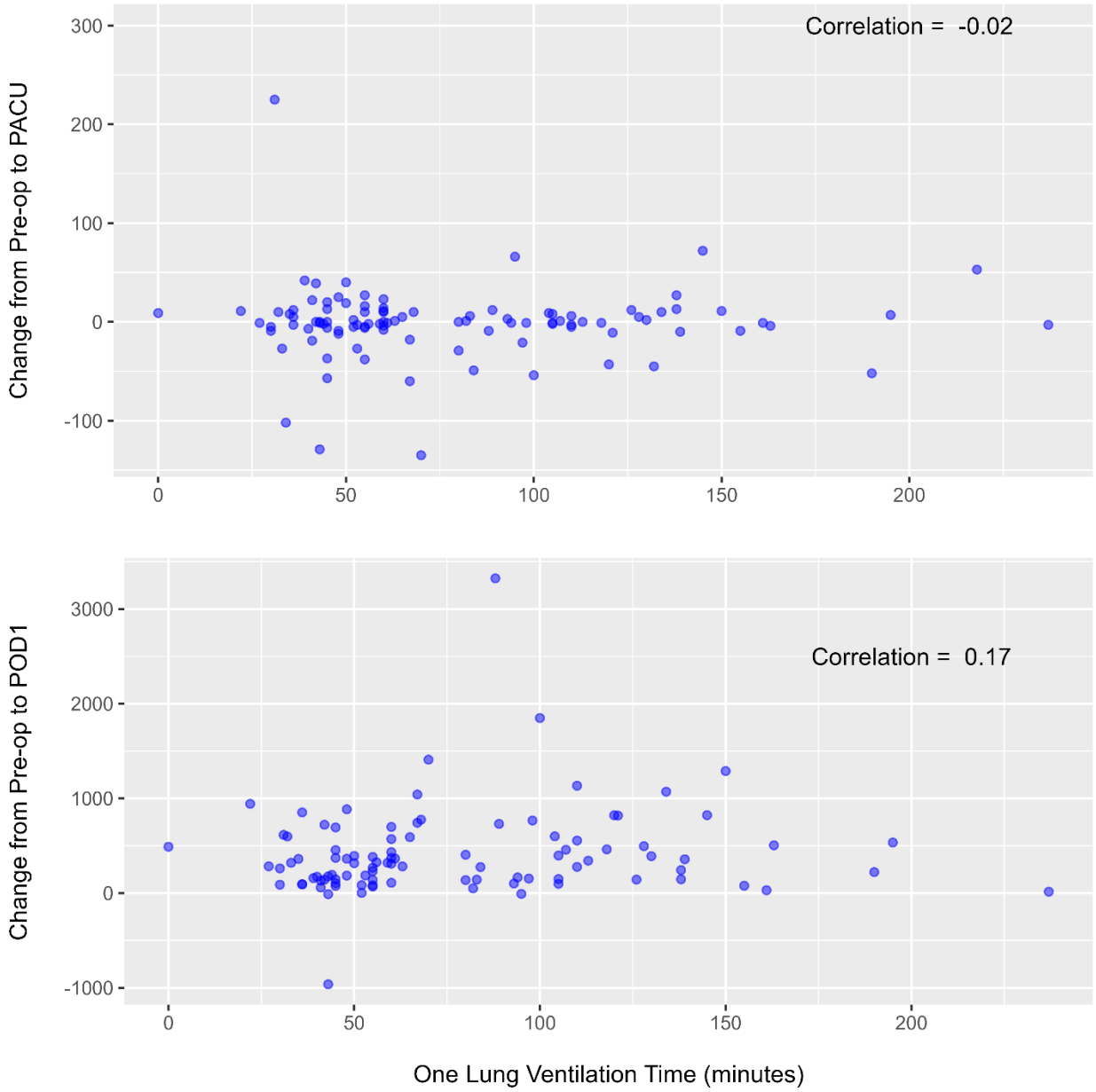

Figure L: Spearman correlation between neutrophil-lymphocyte ratio and change in NT-proBNP from PREOP-POD1

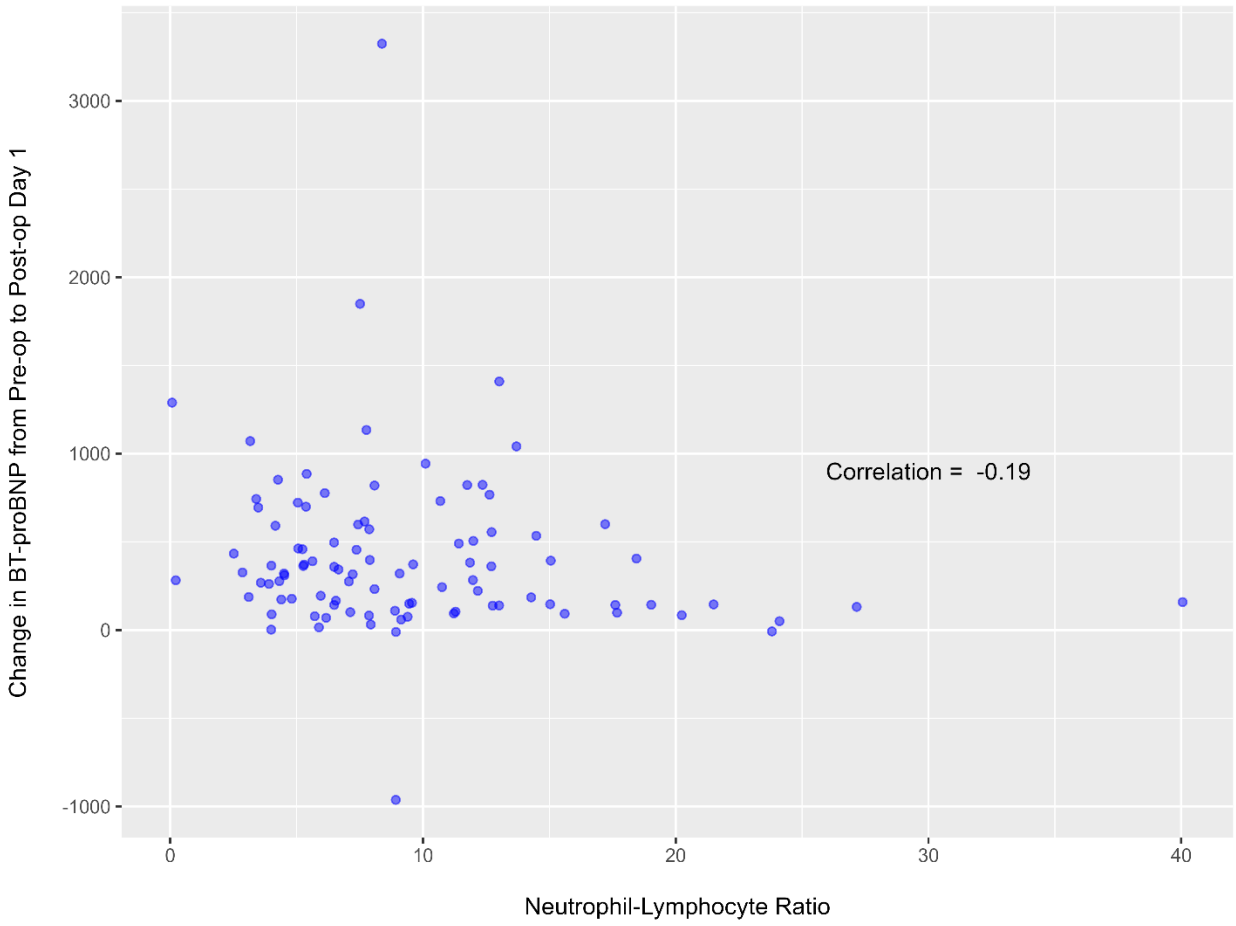

Table 1: Baseline characteristics

	LOBECTOMY	SEGMENTECTOMY	WEDGE	Other	P-value
	(N=30)	(N=8)	(N=61)	(N=3)	
AGE					
Median [Min, Max]	71.5 [58.0, 82.0]	71.5 [62.0, 91.0]	71.0 [57.0, 86.0]	75.0 [68.0, 76.0]	0.96
GENDER					
F	20 (66.7%)	6 (75.0%)	31 (50.8%)	2 (66.7%)	0.25
M	10 (33.3%)	2 (25.0%)	30 (49.2%)	1 (33.3%)	
BMI					
Median [Min, Max]	27.4 [18.6, 37.9]	33.7 [25.0, 38.4]	26.8 [19.1, 44.2]	23.5 [19.9, 24.9]	0.07
STROKE					
NO	30 (100%)	7 (87.5%)	58 (95.1%)	3 (100%)	0.25
YES	0 (0%)	1 (12.5%)	3 (4.92%)	0 (0%)	
TIA					
NO	30 (100%)	7 (87.5%)	57 (93.4%)	3 (100%)	0.17
YES	0 (0%)	1 (12.5%)	4 (6.56%)	0 (0%)	
CHF					
NO	30 (100%)	7 (87.5%)	59 (96.7%)	3 (100%)	0.25
YES	0 (0%)	1 (12.5%)	2 (3.28%)	0 (0%)	
VTE					
NO	28 (93.3%)	8 (100%)	59 (96.7%)	3 (100%)	0.71
YES	2 (6.67%)	0 (0%)	2 (3.28%)	0 (0%)	
MI					
NO	27 (90.0%)	8 (100%)	55 (90.2%)	3 (100%)	1.00
YES	3 (10.0%)	0 (0%)	6 (9.84%)	0 (0%)	
CAD					
NO	27 (90.0%)	7 (87.5%)	51 (83.6%)	3 (100%)	0.81
YES	3 (10.0%)	1 (12.5%)	10 (16.4%)	0 (0%)	
PVD					
NO	30 (100%)	7 (87.5%)	53 (86.9%)	3 (100%)	0.08
YES	0 (0%)	1 (12.5%)	8 (13.1%)	0 (0%)	
DM					
NO	27 (90.0%)	6 (75.0%)	50 (82.0%)	3 (100%)	0.36
YES	3 (10.0%)	2 (25.0%)	11 (18.0%)	0 (0%)	
HTN					
NO	16 (53.3%)	5 (62.5%)	29 (47.5%)	2 (66.7%)	0.67
YES	14 (46.7%)	3 (37.5%)	32 (52.5%)	1 (33.3%)	
COPD					
NO	20 (66.7%)	7 (87.5%)	41 (67.2%)	2 (66.7%)	0.62
YES	10 (33.3%)	1 (12.5%)	20 (32.8%)	1 (33.3%)	
ASTHMA					
NO	30 (100%)	8 (100%)	56 (91.8%)	3 (100%)	0.25
YES	0 (0%)	0 (0%)	5 (8.20%)	0 (0%)	
ILD					
NO	27 (90.0%)	8 (100%)	59 (96.7%)	3 (100%)	0.30
YES	3 (10.0%)	0 (0%)	1 (1.64%)	0 (0%)	
SMOKING HISTORY					
NO	7 (23.3%)	2 (25.0%)	12 (19.7%)	0 (0%)	0.80
YES	23 (76.7%)	6 (75.0%)	49 (80.3%)	3 (100%)	
FEV1 (L)					
Median [Min, Max]	2.05 [1.36, 3.18]	2.00 [1.28, 2.72]	2.28 [0.990, 3.72]	2.15 [1.51, 2.18]	0.46
FVC (L)					
Median [Min, Max]	2.80 [1.95, 4.41]	2.75 [1.74, 4.09]	3.20 [1.50, 5.51]	3.47 [1.90, 3.95]	0.43
FEV1/FVC RATIO					
Median [Min, Max]	0.740 [0.480, 0.870]	0.730 [0.630, 0.800]	0.725 [0.450, 0.880]	0.630 [0.550, 0.790]	0.63

Table 2: Operative characteristics and postoperative events

	LOBECTOMY	SEGMENTECTOMY	WEDGE	Other	P-value
	(N=30)	(N=8)	(N=61)	(N=3)	
OPERATIVE SIDE					
LEFT	10 (33.3%)	4 (50.0%)	24 (39.3%)	1 (33.3%)	0.71
RIGHT	20 (66.7%)	4 (50.0%)	35 (57.4%)	2 (66.7%)	
RIGHT+LEFT	0 (0%)	0 (0%)	2 (3.28%)	0 (0%)	
OLV (minutes)					
Median [Min, Max]	120 [0, 237]	99.5 [55.0, 138]	48.0 [22.0, 132]	104 [67.0, 218]	<0.001
LUNG RESECTION WEIGHT (grams)					
Median [Min, Max]	195 [71.0, 408]	97.0 [41.9, 189]	34.0 [4.00, 636]	360 [136, 405]	<0.001
LUNG RESECTION VOLUME (cubic cm)					
Median [Min, Max]	1500 [23.6, 2310]	513 [290, 855]	195 [17.2, 1080]	1480 [1000, 4630]	<0.001
NTproBNP PREOP (pg/mL)					
Median [Min, Max]	89.0 [19.0, 557]	96.5 [13.0, 536]	137 [10.0, 3840]	170 [26.0, 305]	0.43
NTproBNP PACU (pg/mL)					
Median [Min, Max]	89.5 [20.0, 422]	102 [12.0, 541]	129 [10.0, 3710]	223 [35.0, 245]	0.47
NTproBNP POD1 (pg/mL)					
Median [Min, Max]	536 [69.0, 3760]	404 [179, 1130]	442 [35.0, 2880]	986 [626, 1350]	0.90
Postoperative AF					
NO	26 (86.7%)	8 (100%)	60 (98.4%)	3 (100%)	0.08
YES	4 (13.3%)	0 (0%)	1 (1.64%)	0 (0%)	
Postoperative MINS					
NO	23 (76.7%)	8 (100%)	57 (93.4%)	2 (66.7%)	0.06
YES	7 (23.3%)	0 (0%)	4 (6.56%)	1 (33.3%)	

Table 3: Clinical predictor variables stratified by occurrence of postoperative atrial fibrillation

	Postoperative AF	n	Min	Median	Max	Std Dev	P-value
LUNG RESECTION WEIGHT (g)							
	NO	95	4	66	636	112.066	0.117
	YES	5	4	245	353	140.164	
LUNG RESECTION VOLUME (cubic cm)							
	NO	96	17.16	388.305	4630.5	736.691	0.778
	YES	5	17.95	1116.5	1838.16	883.225	
NT-proBNP PREOP (pg/mL)							
	NO	97	10	99	3843	419.578	0.625
	YES	5	46	76	201	66.493	
NT-proBNP PACU (pg/mL)							
	NO	97	10	108	3714	411.791	0.593
	YES	5	40	88	211	67.463	
NT-proBNP POD1 (pg/mL)							
	NO	92	35	461	3755	596.017	0.316
	YES	5	219	882	1272	421.227	

Appendicies

Appendix A: Patient Consent Form

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Research Participant Information and Consent Form

NT-proBNP AS A PREDICTOR OF POSTOPERATIVE ATRIAL FIBRILLATION AFTER THORACIC SURGERY A PILOT STUDY FOR A MULTINATIONAL PROSCPECTIVE COHORT STUDY

You are being asked to participate in a research study. Please take your time to review this consent form and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this study and you may discuss it with your family, friends or (if applicable) your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

Purpose of Study: The purpose of this study is to see if a change in blood test (elevation in NT-proBNP) is associated with an increased risk of atrial fibrillation (abnormal heart rhythm) after lung resection. To determine this, we will need to take blood samples. This study consists of 3 blood samples which are taken while you are in hospital. We will also speak with you 30-days after your surgery, which can be done over the telephone and takes about 15 minutes.

Study Procedures: If you consent, we will obtain 15ml of blood when the intravenous (IV) line is inserted just before the operation in the pre-operative area. After surgery, the second and third blood samples will be taken 1-4 hours post-surgery and at 12-24 hours post-surgery from your IV. While you are in hospital, you will have routine bloodwork done as part of your standard postoperative care. We will aim to retrieve the study samples at the same time to minimize samples needed. You will also have daily electrocardiograms (ECG ie. heart tracing) on the first three postoperative days.

If your study bloodwork, or ECG come back abnormal, your treating physician will be notified, and course of treatment will be left to their discretion. Your participation in this study will continue for 30 days after your surgery. There is no long-term follow-up.

Risks and Discomfort: With this study, there is no physical risk besides possible pain or bruising around the site of needle puncture that the blood sample will be taken from. To minimize risk and discomfort we will attempt to obtain all our samples at same time as your routine blood work in hospital, although this cannot be guaranteed.

Benefits: There is no direct medical benefit to you participating. However, by participating, you will be helping researchers better understand the predictors and risk after thoracic surgery for the future.

Costs and Payment: You will not incur any costs or be paid for your participation.

Confidentiality: All information collected for this study will be kept strictly confidential in accordance with the Personal Health Information Act of Manitoba (PHIA). The data will be stored in such a way that no one outside of the study team can identify you. Despite efforts to keep your personal information confidential absolute confidentiality cannot be guaranteed. The University of Manitoba Health Research Ethics Board may review records related to this research for quality assurance purposes.

Information gathered in this research study may be published or presented, however, your name or any identifying information will not be used or revealed.

Voluntary Participation/Withdrawal: Your decision to take part in this study is completely voluntary. You may refuse to participate or withdrawal at any time, this will not affect your care. You will be informed of any new information that may affect your health, welfare or willingness to stay in the study.

Questions: You are free to ask any questions that you may have about your treatment and your rights as a research participant. If any questions come up during or after the study, contact the study doctor and/or study staff:

PI - Dr. Sadeesh Srinathan:
Research Coordinator – Dr. Braden Cruise: [redacted]

The University of Manitoba - REB: Office: (204) 789-3255

By signing this consent form, you have not waived any of the legal rights that you have as a participant in a research study. Your decision to take part in this study is voluntary. You may refuse to participate, or you may withdraw from the whole or part of the study at any time. Your decision will not affect your medical care.

Participant		**Person Obtaining Consent**	
Signature:	_____	Signature:	_____
Printed Name:	_____	Printed Name:	_____
Date:	_____	Date (Verbal):	_____
		Date (signed):	_____