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A Clinical Prediction Model for Prolonged Air Leak after Pulmonary Resection

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Abstract

Objective—Prolonged air leak increases cost and worsens outcomes after pulmonary resection. We aimed to develop a clinical prediction tool for prolonged air leak using pretreatment and intraoperative variables.

Methods—Patients who underwent pulmonary resection for lung cancer/nodules (1/2009-6/2014) were stratified by prolonged parenchymal air leak (>5 days). Using backward stepwise logistic regression with bootstrap resampling for internal validation, candidate variables were identified and a nomogram risk calculator developed.

Results—A total of 2317 patients underwent pulmonary resection for lung cancer/nodules. Prolonged air leak (8.6%, n=200) was associated with significantly longer hospital stay (median 10 versus 4 days; p<0.001). Final model variables associated with increased risk included low percent forced expiratory volume in 1 second, smoking history, bilobectomy, higher annual surgeon caseload, prior chest surgery, Zubrod score>2, and interaction terms for right-sided thoracotomy and wedge-resection by thoracotomy. Wedge resection, higher body mass index, and unmeasured percent forced expiratory volume in 1 second were protective. Derived nomogram discriminatory accuracy was 76% (95% CI 0.72–0.79) and facilitated patient stratification into low, intermediate and high risk groups with monotonic increase in observed prolonged air leaks (2.0%; 8.9 %; and 19.2%, respectively; p-value<0.001). Intermediate and high risk patients were 4.80 (95% CI 2.86–8.07) and 11.86 times (95% CI 7.21–19.52) more likely to have prolonged air leak compared to low risk patients.

Conclusions—Using readily available candidate variables, our nomogram predicts increasing risk of prolonged air leak with good discriminatory ability. Risk stratification can support surgical decision-making, and help initiate proactive, patient-specific surgical management.

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Keywords

Prolonged Air Leak; Persistent Air Leak; Air Leak; Pulmonary Resection; Lung Cancer; Multivariable; Risk Factors; Risk Stratification; Funnel Plot

Introduction

When risk factors for undesirable outcomes are identified and used to formulate validated, highly accurate risk stratification algorithms, allocation of effort and resources to individuals most likely to benefit can be optimized. For thoracic surgeons, prolonged air leak (PAL) following pulmonary resection is one such undesirable outcome. Defined in the Society of Thoracic Surgeons General Thoracic Surgery Database (STSGTSD) as a parenchymal air leak lasting >5 days, PAL complicates 6–18% of lung resections.[1–5] PAL is associated with increased cost,[6] hospital length of stay, [4,5,7] and incidence of empyema,[6,8,9] among other complications.[10] Often, persistent parenchymal air leak is the only reason for ongoing hospitalization, resulting in eventual discharge with indwelling chest tubes. If patients are unprepared for this eventuality or their care facilities are unable to accommodate patients with chest tubes, additional delays in discharge may be introduced. Therefore, identification of patients at-risk for PAL could facilitate proactive, patient-specific management.

Three centers, all outside the United States, have published PAL risk stratification models in an effort to improve targeted use of surgical adjuncts.[1–3] Each propose different criteria for stratifying risk based on independent risk factors for PAL, including percent forced expiratory volume in 1 second (%FEV1), body mass index (BMI), and pleural adhesions, among other variables. Study design limitations, differences in how PAL was defined, how patients were selected, and lack of external prospective validation have inhibited wide clinical application. It is also unclear whether risk factors identified in these studies are generalizable and useful for predicting risk for PAL in patients in the United States.

Our study sought to develop a clinical prediction tool for prolonged air leak after pulmonary resection using pretreatment and intraoperative variables in a large patient dataset from a single center in the United States. We hypothesized that standard, readily available predictors could be used to stratify patients into risk classes associated with increasing prolonged air leak risk.

Methods

Patient Population and Data Definitions

Data for all patients were collected at our institution using variables defined by the Society of Thoracic Surgeons General Thoracic Surgery Database (STSGTSD; http://www.sts.org/national-database). Data variables were defined using versions 2.081 and 2.2; data were abstracted by trained data collectors within 4 to 6 weeks after operation for real-time quality monitoring and national benchmarking via bi-annual data submission to the STSGTSD National Data Center. Our Institutional Review Board gave approval for use of this data for the current study.

Pulmonary resection was performed (n=2522; 1/1/2009 – 6/30/2014) at eight hospital sites for malignant and benign lung tumors or nodules using International Classification of Diseases, Ninth Revision[11] diagnosis codes (197.0, 212.3, 162.2, 162.3, 162.4, 162.5, 162.9, 518.89), excluding pneumonectomy, and extended chest wall/diaphragm resections. We did not include volume reduction, bullectomy, or lung biopsy for interstitial lung disease because of the significantly higher rate of PAL and differences in underlying risk factors in these populations, which would have heavily influenced the model and reduced discriminatory accuracy for PAL in lung nodule/cancer patients. Database variables included patient demographics, preoperative evaluation, surgical procedures, cancer staging, and post-operative events. Approach to operation was captured, but granular operative details were not available (e.g. intraoperative adhesiolysis, intraoperative sealant use, pleural tents, etc.).

We excluded 59 sleeve lobectomy patients, to minimize confounding parenchymal and anastomotic air leaks; 32 patients from two hospital sites who did not submit patients to the database over the entire study time frame; and 5 patients who died day 5 or before (prolonged air leak definition). Status of air leak for patients dying day 5 or before is not available in the dataset. Multiple lung resections were noted in 111 patients; data for the most recent surgery date was utilized and prior encounter(s) excluded. (Supplemental Figure 1)

Outcomes

Prolonged air leak (PAL), the dependent variable in our model, was defined as an air leak that persisted >5 days postoperatively. We compared in-hospital mortality, length of hospital stay, and cumulative incidence of hospital discharge by post-operative day (mortality treated as a competing risk),[12] between groups.

Development of the Logistic Regression Model

We compared preoperative and intraoperative variables with chi-squared test or Fisher's exact test for categorical variables expressed as frequencies, and Student's t-test or Wilcoxon rank sum test for continuous variables expressed as mean ± 1 standard deviation or median/interquartile range using Stata/SE 14.1. (StataCorp, 2015; College Station, TX: StataCorp LP) Unless otherwise indicated, p-values were two-tailed; statistical significance defined by $p<0.05$.

Bivariable testing (p-value<0.15), clinical judgment and literature review guided variable selection for the initial multivariable model. We categorized percent forced expiratory volume in 1 second (%FEV1) based on clinical relevance: <60% considered moderate to severe obstruction, >=60 and <80% mild obstruction, >=80% borderline to normal range. We placed the 12.8% of patients who did not undergo preoperative pulmonary function testing, and were therefore missing on %FEV1, in a separate category as the majority had benign or secondary metastatic lung tumors (86.5%) removed with wedge resection (88.9%) suggesting that the data were systematically missing (i.e. pulmonary function testing was not performed intentionally). We excluded diffusing capacity of carbon monoxide (DLCO) due to high level of non-random missingness. We included sex and steroids variables despite p-values>0.15, given their significance in previous work. To assess collinearity, we assessed variance inflation factors (VIF) and ensured that all were <2 (indicating little (>1<2) to no (=1) correlation between variables).

To form a parsimonious model, we employed backward stepwise variable selection with likelihood ratio test p-value stopping rules of 0.15 (to enter model) and 0.10 (to remain in model); PAL was the dependent variable. Bootstrap resampling was used to assess how well variables predict occurrence of PAL outside the original sample.[8,13] We repeated the stepwise algorithm on 1000 resamples drawn randomly with replacement and equal to 100% size of the original. We considered variables selected in >50% of 1000 repetitions for the reduced model and tested plausible two-way interactions.

Development of the PAL Nomogram

Using the Stata program *nomolog*,[14] we assigned points to predictors using proportional rescaling of the logistic equation regression coefficients. We first forced positive coefficients with negative regression coefficients by subtracting all categories of the variable by the category with the most negative coefficient. We then multiplied all coefficients by the scaling factor, F (F=10/ α_i, where α_i is the largest model coefficient) to convert coefficients into point values. We calculated PAL probability based on total points (1/ $(1+e^{-(F*\alpha_0+TP)/F})$, where α_o is the regression equation constant (adjusted accordingly from variables forced positive), and TP is the sum of points across all predictors. We derived a three-level risk table based on the nomogram point scoring system (cutoffs chosen to maximize C-statistics), and classified each patient into a risk class using their total point score (rounded to nearest 0.5). We calculated observed and predicted frequencies, odds ratios, and 95% confidence intervals for each risk class.

Model Performance

We used calibration and discrimination to assess model predictive accuracy.[15] For calibration, we plotted observed and predicted rates of PAL by deciles of risk, and assessed goodness-of-fit (Hosmer-Lemeshow test). We calculated discriminatory accuracy (C-statistic) for the regression equation, nomogram, and risk table. Using a classification probability cutoff of 0.11 (the average PAL rate in five large PAL studies[1–5] combined with ours), we calculated correct classification rates, and positive and negative predictive values. We used bootstrap resampling to adjust the logistic C-statistic for over-optimism or overfitting.[15,16] We repeated the original stepwise multivariable selection with the addition of identified interaction effects in 500 resamples. In each repetition, we calculated the difference between the C-statistic in the resample and the original sample for the selected model. To adjust for optimism, we subtracted the average difference from the C-statistic of the final model in the original sample.

Surgical Caseload Effect

We used a funnel plot to explore the relationship between total surgeon case load and PAL rate,[17] including control limits (95% and 99% confidence intervals) around the average PAL rate in our study. Because unadjusted case volume does not account for variations in patient populations between surgeons, we developed risk-adjusted models for surgeon annual case load effect, adjusting for case mix and clustering. (See Appendix)

Results

A total of 2317 patients met inclusion criteria for bivariable analysis, and 2273 patients for multivariable analysis. Incidence of prolonged air leak was 8.6% (200/2317). The majority of operations were video-assisted thoracoscopic (VATS) lobectomy/segmentectomy for primary lung cancer. (Table 1) PAL significantly prolonged median length of hospital stay (10 versus 4 days, p<0.001); by day 5 and 10, respectively, only 1% and 47% of patients with PAL had been discharged compared to 54% and 90% of patients without PAL. (Figure 1) Patients with PAL had a higher rate of in-hospital death (3.0% vs 1.1%, p=0.034; Table 1).

Development of the Prediction Model

Patients with PAL were more likely to be older, male, have a lower BMI, prior smoking history, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), prior steroid use, higher Zubrod Score, and lower %FEV1. They were less likely to have diabetes or to be hospitalized prior to surgery. Patients with PAL were more likely to have primary lung cancer (versus benign or metastatic tumors), undergo lobectomy/segmentectomy or bilobectomy (versus wedge resection), have right-sided resection, undergo thoracotomy, and be operated on by a surgeon with higher annual caseloads. (Table 1) After backward stepwise logistic regression with bootstrap resampling for reliability, 10 variables comprising 13 separate coefficients were chosen in >50% of resamples and included in the final model. (Figure 2) Among all variables excluded in stepwise variable selection, or on bivariable testing (p-values between 0.15 and 0.30), none except hypertension were found to have adjusted p-values<0.10 or change regression coefficients by >10% with (re)inclusion in the final model. We incorporated the significant interaction effect ‘right-sided thoracotomy’ (between surgical approach and laterality) and ‘wedge resection by thoracotomy’ (between surgical approach and wedge resection) for their regression coefficient adjustment of the individual variables. The final regression model included BMI, %FEV1, annual surgeon caseload, smoking, Zubrod score, preoperative hospitalization, reoperation, procedure type, laterality, surgical approach, right-sided thoracotomy, and wedge resection by thoracotomy. (Table 2)

Categorizing Risk using the Nomogram

Using the regression coefficients and intercept from the final model, (Table 2) we created a nomogram to calculate the probability of PAL. (Figure 3a) For the interaction effects ‘right-sided thoracotomy’ and ‘wedge resection by thoracotomy,’ the main effect variables laterality (right-sided=0.2pts) and surgical approach (VATS=1.6pts) had small point values and are not depicted in the nomogram. We calculated a nomogram point score for each patient, and categorized patients into low, intermediate and high risk groups. (Table 3) Compared to the lowest risk group, patients in the intermediate risk group were >5 times more likely to have a PAL while the high risk group was >12 times more likely. (Table 3) The observed rates of PAL were 2.0%, 8.8% and 19.3% (non-parametric test of trend p-value <0.001), which matched closely with the predicted rates according to the model. A more generalizable nomogram identically derived except for removal of our institution specific annual surgeon caseload variable was also created. (Figure 3b)

Predictive Performance of the Model and Nomogram

Discriminatory accuracy of the final regression model was 75.9% (C-statistic=0.759; 95% CI, 0.725 to 0.792). The Hosmer-Lemeshow goodness-of-fit test was nonsignificant (p=0.735), indicating good model fit for the data, and the calibration slope was 1.000 with an intercept of 0.000 (showing perfect model calibration). After adjusting for optimism using bootstrap resampling, discriminatory accuracy was 73.8%. The model correctly classifies 74.9% of patients with a positive predictive value of 19.4% and a negative predictive value of 95.2% when calculated using a classification probability cutoff of 0.11. The discriminatory accuracy was 75.7% for the nomogram (C-statistic=0.762; 95% CI, 0.724 to 0.790), and 72.9% for the risk table after rounding to the nearest 0.5 for point calculation (C-statistic=0.729; 95% CI, 0.698 to 0.760), respectively.

Surgical Volume Effect on PAL Incidence

To determine the relationship between surgeon volume and PAL incidence, we assessed funnel plots with calculated control limits. (Figure 4) Surgeons with higher annual caseload, on average, have higher PAL incidence (linear correlation 0.38). Data points falling inside control limits are consistent with common cause variation or expected variability in patient population or surgical management. All surgeons lie within the 99% control limit, essentially excluding special cause or unexpected variation, such as inferior (or superior) surgical technique or management practices. After risk-adjustment for case-mix (using available STS data) and clustering of PAL among surgeon, annual surgeon caseload remained a significant predictor. (Appendix Table A1/Figure A1)

Discussion

Using data from a large, United States-based patient dataset, our study tested the hypothesis that standard, readily available predictors could be used to stratify patients into risk classes associated with increasing risk of prolonged air leak. Our analysis identified 10 risk factors for PAL comprising a total of 13 categories with two interaction effects and resulted in a parsimonious, reliable, and accurate clinical prediction model for prolonged air leak (PAL) after pulmonary resection. The model coefficients were used to produce a nomogram which generated probability estimates for PAL and risk classification of patients into low, intermediate, and high risk groups. Importantly, these risk groups showed monotonic increase in the rate of observed PAL, indicating clear differences in risk between categories. As expected, we found that prolonged air leak was associated with delayed hospital discharge, an effect that persists nearly three weeks after surgery.

An accurate and generalizable PAL risk stratification tool could facilitate surgical decision-making and patient-specific care. Some authors have advocated a fast-track discharge pathway for pulmonary resection patients to increase patient satisfaction and reduce hospital costs.[8,18–21] Given the need for carefully developed standardized protocols to effectively manage and monitor patients, the ability to predict PAL preoperatively would be valuable. In addition, both intraoperative (e.g. pleural tenting, sealants, buttressed staple lines) and post-operative (e.g. pneumoperitoneum, water seal, flutter valve) methods for PAL management exist, but their efficacy remains unclear.[10,22–27] For example, Cerfolio showed that digital chest drainage tubes compared to analog systems reduce hospital stay and lead to quicker chest tube removal; they can also be used for remote electronic monitoring.[18] A generalizable risk prediction tool could be used to facilitate randomized controlled trials of air leak reduction methods and help guide cost-effective use of these adjuncts.

We developed the model from patients at our institution who underwent resection for benign and malignant lung tumors operated through lobectomy/segmentectomy, wedge resection, and bilobectomy by either a thoracotomy or VATS surgical approach. Previous risk models from Brunelli[3] and Lee[1] excluded wedge resection and Rivera[2] included volume reduction and bullectomy. Though PAL incidence is lower after VATS wedge, inclusion of resection type and surgical approach as variables in our model allows PAL prediction for these previously excluded, but large patient populations. Similar to Brunelli and Lee, we excluded lung volume reduction patients because their high rate of air leak (approaching 50% in most studies), coupled with significant differences in baseline patient characteristics (e.g. higher rates of bullous emphysema) and surgical management (greater routine use of surgical adjuncts),[25,28] would dominate the model and obscure the relationship between PAL and various predictors for patients with lung cancer and nodules.

The nomogram approach permitted inclusion of more risk factors plus interactions effects compared to previous work, with almost full preservation of predictive capability compared to the regression equation. A larger number of risk factors provides much greater discrimination between patients than would a simpler model that includes only a few binary variables, particularly when the groupings are common (e.g. male patients with low %FEV1). Consistent with prior risk factor studies, our model includes three commonly identified risk factors for PAL: low BMI,[2,3] low %FEV1,[1,3–5,9,29,30], and lobectomy.[2,4,5,29] In addition, our population size allowed for sufficient number of PAL cases to includes prior smoking[4,9] and right-sided resection[2,31] variables that have previously been significant on bivariable but not multivariable analysis. Annual surgeon caseload, preoperative hospitalization, reoperation, Zubrod score and the interaction effects, right-sided thoracotomy and wedge resection by thoracotomy, have not been previously analyzed. Interaction variables allow proper interpretation of risk factors; inclusion of these interactions improved our model discriminatory accuracy. Others have reported age,[3,31] and sex[2,31] as independent predictors of PAL, but we found them to be non-significant after adjusting for the included variables. Emphysema,[4] bronchitis,[4] pleural adhesions,[1–3,30] DLCO[1], and upper lobe resection[2,5,30] are other previously identified PAL risk factors, but were not available for analysis in our dataset.

Prolonged parenchymal air leaks result from impaired healing of disrupted alveoli, often associated with poor apposition of lung with parietal pleura. It is likely that surgeon- and institution-specific technical factors like method of fissure dissection, buttressing staple lines, sealants and glues, and pleural tenting are important.[32] In addition, however, reduced wound healing, increased pulmonary compliance, and inflammation could all be influential factors.[33] Indeed, our finding that increasing BMI was protective against PAL has been observed by others, with underweight patients (BMI<18.5 kg/m^2) experiencing significantly higher PAL incidence ($p<0.001$) in one study.[34] One hypothesis is that lower BMI is a marker of lower nutritional status and poor wound healing.[3,5,32] However, this does not explain the continued decrease of PAL into the overweight and obese weight classes in our study. An alternative explanation may derive from consistent findings of higher respiratory rates, lower tidal volume, reduced total respiratory system compliance, and decreased expiratory reserve volume with preserved spirometry, gas exchange and airway resistance in obese patients,[35] which may produce an intrathoracic milieu that favors sealing of parenchymal defects.

It is not surprising that PAL rates differed across surgeons, as prior studies have shown this to be an important risk factor.[5] We observed higher PAL incidence with increasing case load and surgeon caseload remains a significant predictor after risk-adjustment for case mix and patient clustering among surgeon. This finding cannot be explained by unexpected variation from differences in baseline risk, treatment, or surgical management within the measured variables, as all surgeons fell with the 99% control limits. More likely, higher volume surgeons have different case-mix in which higher volume surgeons operate on subsets of patients with unmeasured variables contributing to higher baseline PAL risk. These unmeasured variables, not currently abstracted for the STSGTSD, could reveal modifiable technical factors to reduce PAL incidence and require further study. Given this, we include a more generalizable nomogram model excluding annual surgeon caseload.

Strengths and Limitations

Model development followed a step-by-step statistical analysis based on published guidelines.[15] Further development requires external validation in a multicenter setting, prospective validation, and inclusion of important independent risk factors for PAL not captured in the STSGTSD (e.g. pleural adhesions and segmental lung resection). We chose to keep patients with unmeasured %FEV1, because the majority of these patients underwent wedge resection for a benign or secondary metastatic tumors. The unmeasured %FEV1 category could apply to patients at other centers who similarly did not undergo preoperative lung function testing, but the finding requires external validation.

Conclusion

We have developed a clinical prediction model for PAL with good discriminatory accuracy. It has the potential to improve patient care through fast track discharge pathways, better informed preoperative patient counseling, and selective use of surgical adjuncts. Discharge planning could be proactive, with patients prepared to be sent home on the second or third day with an indwelling chest tube, rather than waiting 5 or more days for the air leak to resolve. The model supports previous work analyzing risk factors for PAL while presenting a novel perspective on previously and newly identified risk factors. Prospective and external validation of our model is required to realize future clinical application.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

PAL	prolonged air leak
%FEV1	percentage of predicted value of forced expiratory volume in 1 second
STSGTSD	Society of Thoracic Surgeons General Thoracic Surgery Database
DLCO	diffusing capacity of carbon monoxide
OR	odds ratio

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Central Message

Prolonged air leak increases mortality and length of stay after pulmonary resection. Preoperative variables can be combined to predict risk, which may be useful to guide patient-specific management.

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Perspective Statement

We have identified known and new risk factors for prolonged air leak in a large dataset from the United States and developed a prediction nomogram with good discriminatory accuracy. Because prolonged air leak worsens perioperative outcomes, this type of highly accurate risk prediction tool, which uses pre- and intra-operative variables, has the potential to improve patient management and outcomes.

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Central Picture

Points for all risk factors are summed to a total score and probability estimate.

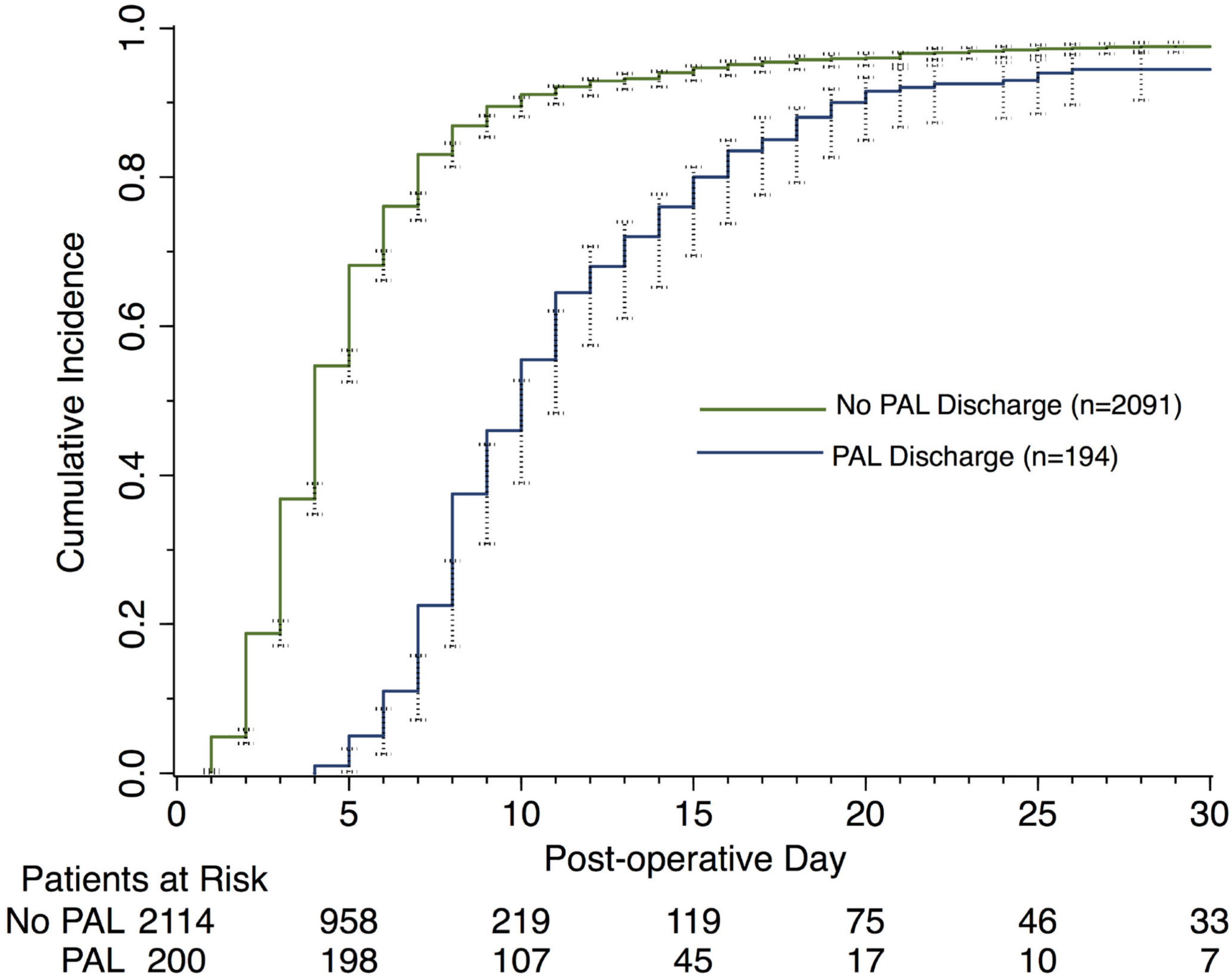


Figure 1. Stratified Cumulative Incidence of Hospital Discharge by Post-Operative Day

(95% confidence intervals indicated by black-capped spikes)

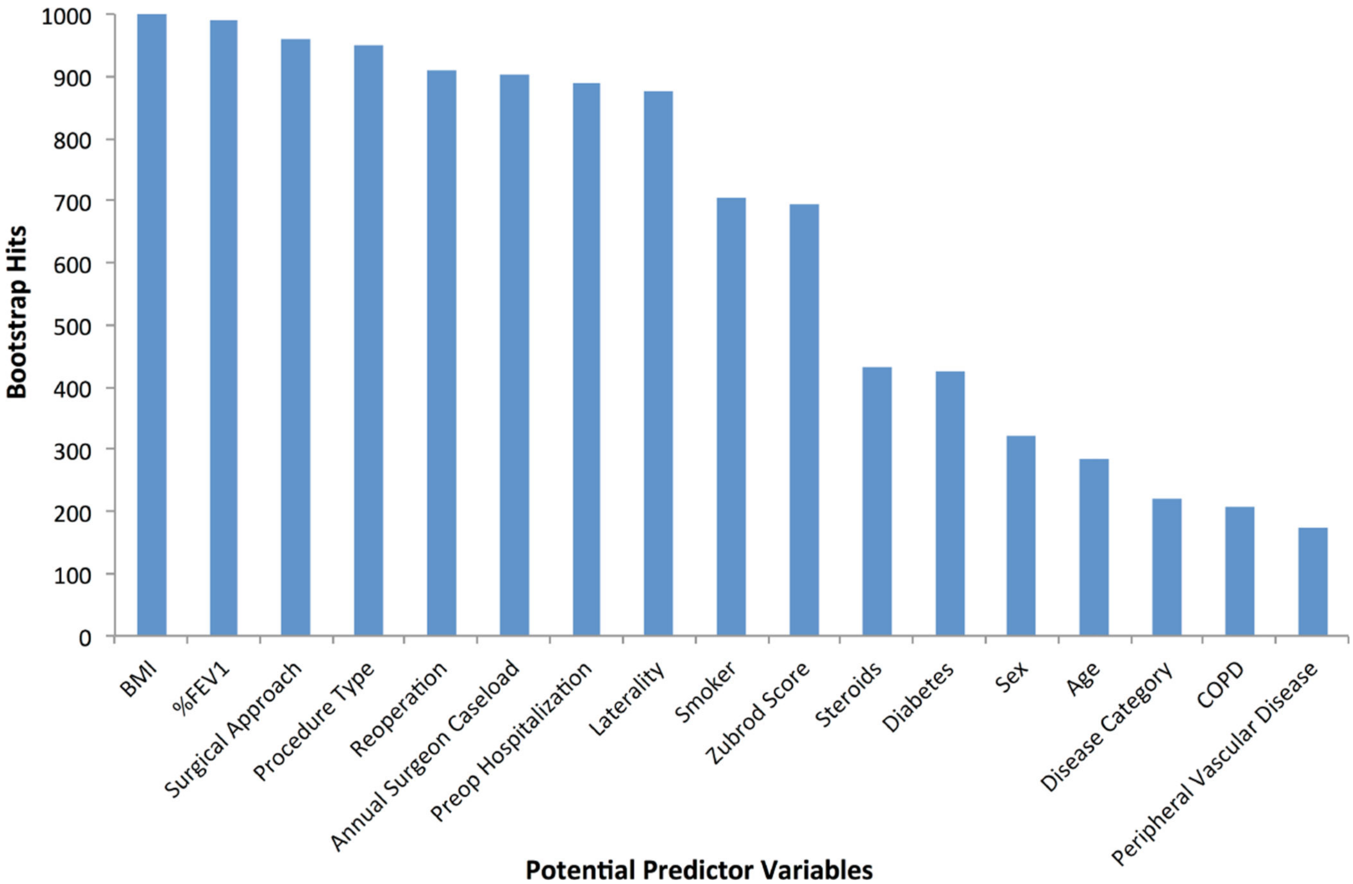


Figure 2. Bootstrap Reliability of Variables Associated with Prolonged Air Leak
Variables selected >50% of the time were considered for forming the final model.

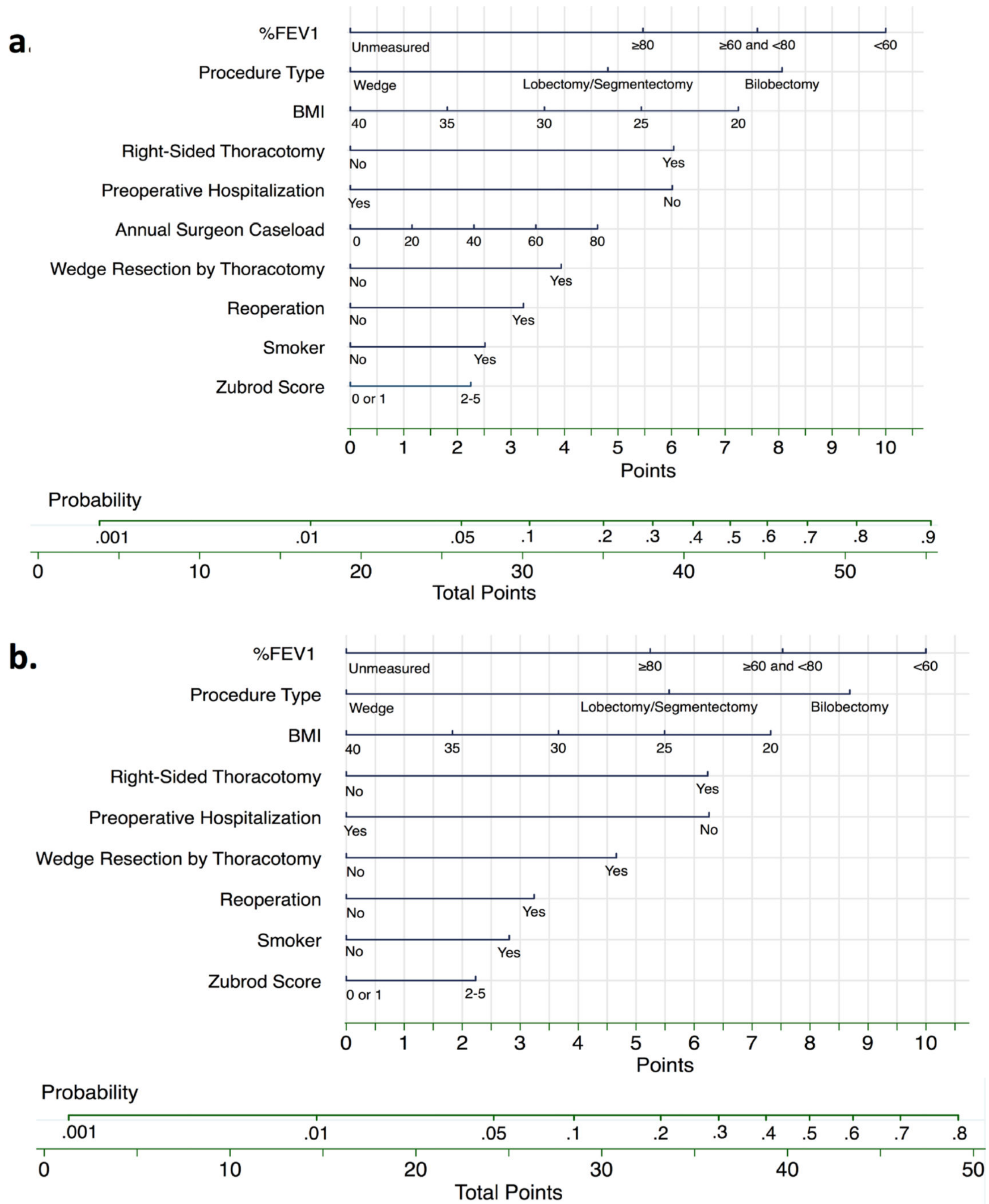
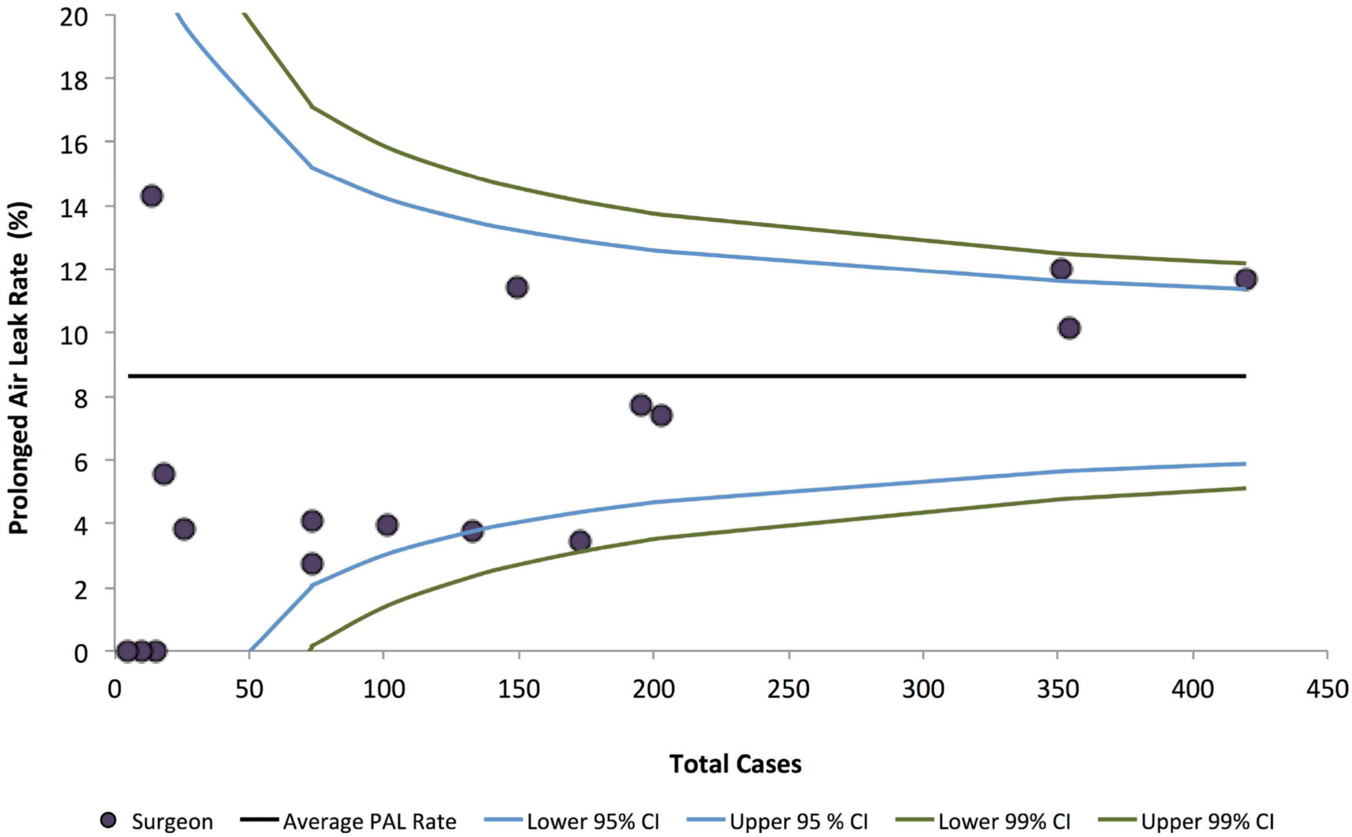


Figure 3. Nomogram for Probability of Prolonged Air Leak

a.) To calculate the probability of prolonged air leak, sum points over all variables to a total point score with its corresponding probability. Example: A smoker (2.5 pts) with a BMI=32 (3 pts), %FEV1=65 (7.5 pts), and Zubrod Score=1 (0 pts) without prior chest operation (0 pts) or preoperative hospitalization ≥1 (6 pts) is having a right-sided open (6 pts) lobectomy (5 pts) by a surgeon who has an annual caseload of 50 (3 pts). Total points=33. Probability of PAL is around 15%. b.) We removed our institution specific variable annual surgeon caseload to create a more generalizable model that had a C-statistic=0.755 (95% CI, 0.722 to 0.788).



Prolonged Air Leak Rate (%)
20
18
16
14
12
10
8
6
4
2
0
0
50
100
150
200
250
300
350
400
450
Total Cases
Surgeon
Average PAL Rate
Lower 95% CI
Upper 95 % CI
Lower 99% CI
Upper 99% CI

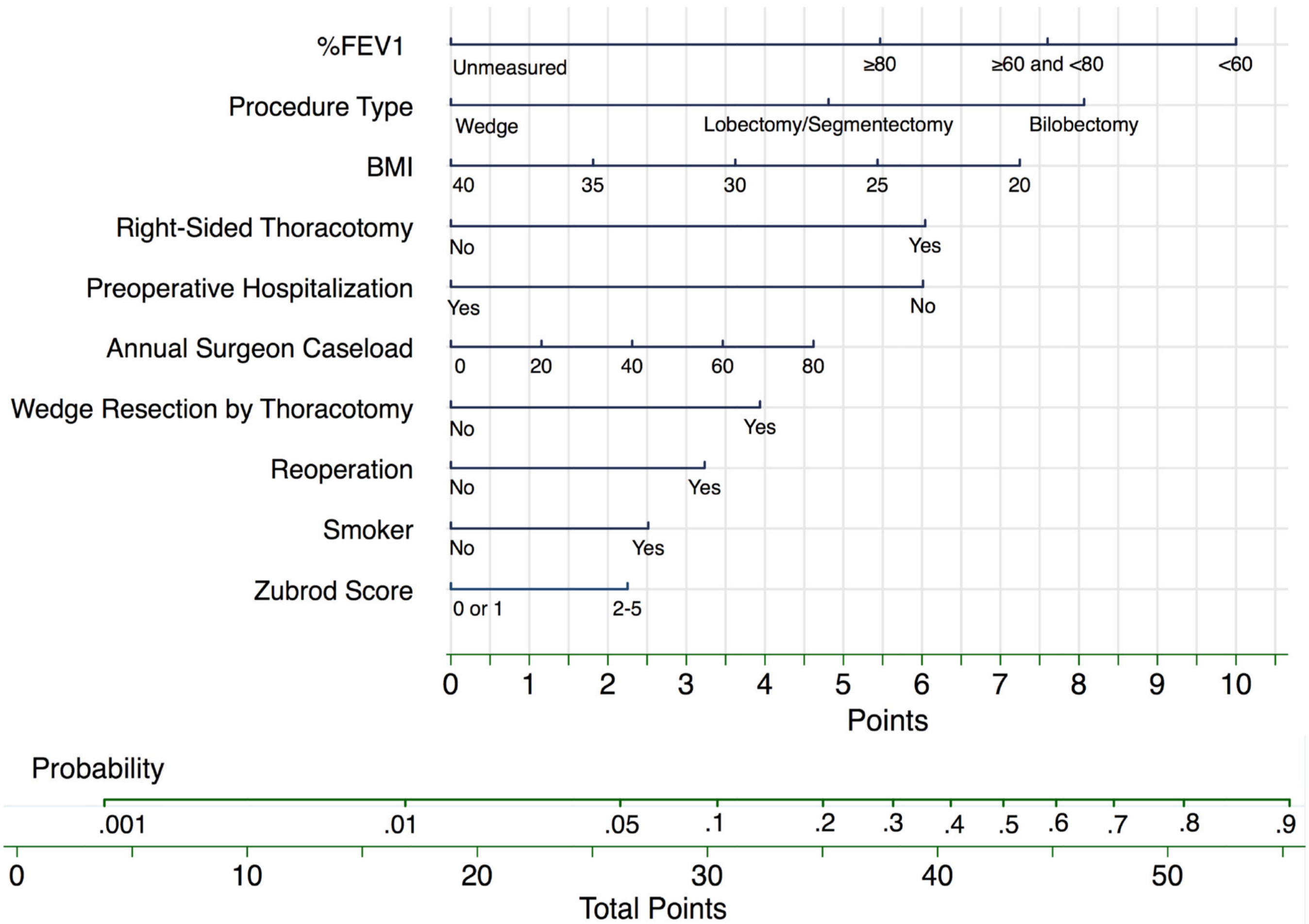


Figure 4. Funnel Plot of Prolonged Air Leak Rate of Operating Surgeons by Case Volume

95% and 99% control limits derived as follows: (θ± z*Sqrt(θ(1- θ)/p), where z is the z-score, θ the study's average PAL rate, and p the total cases of individual surgeons.

Table 1

Population characteristics of patients with or without prolonged air leak

Variables		Total n=2317	Prolonged air leak No n=2117	Prolonged air leak Yes n=200	p-value
Demographics					
Age (mean ± SD)		65 ± 12	65± 12	67 ± 11	0.013
BMI, kg/m (mean ± SD)		28 ± 7	28 ± 7	26 ± 5	<0.001
Sex	Female	1296 (56)	1193 (56)	103 (51)	0.186
	Male	1021 (44)	924 (44)	97 (49)	
Race	White	2168 (94)	1975 (93)	193 (96)	0.288 *
	Black	119 (5)	113 (5)	6 (3)	
	Other	30 (1)	29 (1)	1 (1)	
Treatment Variables					
Surgery Year	2009/10	857 (37)	777 (37)	80 (40)	0.615
	2011/12	886 (38)	815 (38)	71 (35)	
	2013/14	574 (25)	525 (25)	49 (25)	
Hospital Type	Academic	1125 (49)	1030 (49)	95(48)	0.755
	Community	1192 (51)	1087 (51)	105 (52)	
Annual Surgeon Caseload, median [IQR][a]		53 [34–74]	53[34–74]	64 [36–74]	<0.001 †
Disease Category	Malignant cancer	1441 (62)	1290 (61)	151 (76)	<0.001
	Benign/infection	367 (16)	346 (16)	21 (10)	
	Metastatic tumor	509 (22)	481 (23)	28 (14)	
Procedure Type	Lobe/Segment	1500 (65)	1339 (63)	161 (81)	<0.001 *
	Wedge resection	780 (34)	752 (36)	28 (14)	
	Bilobectomy	37 (1)	26 (1)	11 (5)	
Comorbidities					
Smoking History	Never Smoker	684 (30)	655 (31)	29 (14)	<0.001
	Past Smoker	1180 (50)	1058 (50)	122 (61)	
	Current Smoker	453 (20)	404 (19)	49 (25)	

Variables		Total n=2317	No n=2117	Yes n=200	p-value
			Prolonged air leak		
Zubrod Score	0	163 (7)	153 (7)	10 (5)	0.012
	1	1756 (76)	1615 (77)	141 (71)	
	2–5	390 (17)	342 (16)	48 (24)	
ASA Classification	I/II	277 (12)	263 (13)	14 (7)	0.077
	III	1781 (77)	1618 (76)	163 (82)	
	IV	259 (11)	236 (11)	23 (11)	
Weight Loss	≥2kg	1985 (86)	1825 (86)	160 (80)	0.527
	>2kg	113 (5)	102 (5)	11 (5)	
	Missing	219 (9)	190 (9)	29 (15)	
Hypertension		1297 (56)	1192 (56)	105 (53)	0.300
Congestive Heart Failure (24% missing)		76 (4)	67 (4)	9 (6)	0.234
Peripheral Vascular Disease		225 (10)	199 (10)	26 (13)	0.101
Interstitial Fibrosis		27 (1)	23 (1)	4 (2)	0.286 *
Diabetes		419 (18)	392 (19)	27 (14)	0.077
COPD		771 (33)	672 (32)	99 (50)	<0.001
Cerebrovascular Disease		141 (6)	127 (6)	14 (7)	0.574
Preoperative Chemotherapy		470 (20)	433 (21)	37 (19)	0.505
Preoperative Radiation Therapy		314 (14)	282 (13)	32 (16)	0.294
Steroids		127 (5)	112 (5)	15 (8)	0.190
Prior Cardiothoracic Surgery		512 (22)	455 (22)	57 (29)	0.024
Reoperation [b]		289 (13)	249 (12)	40 (20)	0.001
Laboratory					
FEV1, % predicted (12.8% missing; mean ± SD)		83 ± 22	84 ± 21	76 ± 24	<0.001
FEV1, % predicted	>80	1173 (51)	1089 (52)	84 (42)	<0.001
	<60	561 (24)	496 (23)	65 (33)	
	≥60 and <80	285 (12)	238 (11)	47 (23)	
	Unmeasured	297 (13)	293 (14)	4 (2)	
DLCO, % predicted (28% missing; mean ± SD)		71 ± 23	72 ± 23	66 ± 24	0.002

Variables		Prolonged air leak Total n=2317	No n=2117	Yes n=200	p-value
Last Hemoglobin (mean ± SD)		12.1±1.7	12.2±1.7	12.0±1.7	0.152
Last Creatinine, median [IQR]		0.85 [0.7–1]	0.87 [0.7–1]	0.80 [0.7–1]	0.628†
Operative Details					
Status	Elective	2214 (96)	2018 (96)	196 (98)	0.145
	Urgent/Emergent	90 (4)	86 (4)	4 (2)	
Preoperative	<1 day	2157 (93)	1963 (93)	194 (97)	0.025
Hospitalization	≥1 day	158 (7)	152 (7)	6 (3)	
Laterality	Left	915 (40)	854 (40)	61 (30)	0.004
	Right	1377 (59)	1238 (59)	139 (70)	
	Missing	25 (1)	25 (1)	0 (0)	
Robot-Assisted Surgery		82 (3)	79 (4)	3 (2)	0.102
Surgical Approach	Thoracotomy	603 (26)	515 (24)	88 (44)	<0.001
	VATS	1714 (74)	1602 (76)	112 (56)	
OR Blood Transfusion		94 (4)	84 (4)	10 (5)	0.487
Outcomes					
Hospital Stay, median [IQR]		4 [3–7]	4 [3–6]	10 [8–14]	<0.001†
Hospital Death		29 (1)	23 (1)	6 (3)	0.034*

Values n (%), and <1% missing unless indicated otherwise.

[a]average annual cases by patient's operating surgeon in study time period

[b]cardiac or thoracic re-operation that affects operative field

*Fisher's exact

†Wilcoxon rank sum test

BMI, body mass index,%FEV1, percentage of predicted value of forced expiratory volume in 1 second; DLCO, diffusing capacity of carbon monoxide; ASA, American Association of Anesthesiology; COPD, chronic obstructive pulmonary disease; VATS, video-assisted thoracoscopic surgery; SD, standard deviation; OR, operating room; IQR, interquartile range

Table 2

Analysis of potential predictors for prolonged air leak

Variable	Unadjusted		Adjusted			
	Odds Ratio	P-value	Odds Ratio	95% CI	Coefficient	P-value
Intercept[a]			0.043	0.022–0.086	−3.137	
Age (per 1 year increase)	1.017	0.013				
BMI (kg/m^2)	0.936	<0.001	0.938	0.912–0.964	−0.064	<0.001
Sex (Female)	0.822	0.186				
Smoker (vs non-smoker)	2.642	<0.001	1.560	1.013–2.402	0.445	0.043
Zubrod Score 2–5 (vs 0 or 1)	1.643	0.004	1.489	1.015–2.184	0.398	0.042
Diabetes	0.686	0.077				
Steroids	1.451	0.190				
Malignant Cancer	1.665	0.030				
COPD	2.106	<0.001				
Peripheral Vascular Disease	1.431	0.101				
Reoperation[b]	1.877	0.001	1.771	1.183–2.651	0.572	0.005
FEV1, % predicted,		<0.001				
>80	Ref.		Ref.			
≥60 and <80	1.699		1.458	1.016–2.093	0.377	0.041
<60	2.560		2.228	1.467–3.384	0.801	<0.001
Unmeasured	0.177		0.380	0.132–1.096	−0.967	0.073
Preop Hospitalization ≥1 day	0.867	0.025	0.345	0.143–0.833	−1.063	0.018
Annual Surgeon Caseload[c]	1.014	<0.001	1.010	1.003–1.018	0.010	0.009
Resection Type		<0.001				
Lobe/Segment	Ref.		Ref.			
Wedge Resection	0.310		0.427	0.249–0.731	−0.851	0.002
Bilobectomy	3.519		1.778	0.793–3.985	0.575	0.162

	Unadjusted		Adjusted			
Variable	**Odds Ratio**	**P-value**	**Odds Ratio**	**95% CI**	**Coefficient**	**P-value**
Right-sided resection (vs left)	1.571	0.004	1.045	0.697–1.566	0.044	0.832
Thoracotomy (vs VATS)	2.444	<0.001	0.757	0.410–1.398	−0.278	0.370
Interaction terms added to final model						
Right-Sided Thoracotomy			2.910	1.430–5.924	1.068	0.003
Wedge Resection by Thoracotomy			2.006	0.783–5.140	0.696	0.147

[a] intercept of final model used along with regression coefficients to derive nomogram scoring

[b] average annual cases of patient's operating surgeon in study time period

[c] cardiac or thoracic re-operation that affects operative field

BMI, body mass index; %FEV1, percentage of predicted value of forced expiratory volume in 1 second; VATS, video-assisted thoracoscopic surgery; COPD, chronic obstructive pulmonary disease; CI, confidence interval

Table 3

Prolonged Air Leak Risk Classification

Risk Class (Score)	PAL Incidence (n)	Observed Frequency (%)	Predicted Frequency Logistic Model (%)	Odds Ratio (95% CI)
Low (≤25)	938	2.0	2.5	Ref
Intermediate (26–29)	747	8.8	7.7	4.69 (2.79–7.88)
High (≥30)	588	19.2	19.9	11.51 (6.99–18.94)