The impact of marginal lung function on outcomes in the era of minimally invasive thoracic surgery

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Background: The effect of marginal lung function on outcomes after lung resection has traditionally been studied in the context of open thoracic surgery. Its impact on postoperative outcomes in the era of minimally invasive lung resection is unclear.

Methods: In this retrospective cohort study, we included adult patients who underwent minimally invasive lung resection at our institution between January 2017 and May 2020 for known malignancy or lung nodule. Marginal lung function was defined as pre-operative forced expiratory volume in 1 second (FEV1) and/or diffusion lung capacity of carbon monoxide <60% of predicted. Our outcomes included a composite outcome of pulmonary morbidity and/or 30- and 90-day mortality, and hospital length of stay. We used multivariable logistic and Poisson regression models to identify associations with outcomes, and Kaplan-Meier and Cox models to estimate survival.

Results: Of 300 patients, 88 (29%) had marginal lung function. Patients in the marginal group were more likely to be female (69% *vs.* 56%; P=0.028), and more likely to have: hypertension (HTN) (83% *vs.* 71%; P=0.028), chronic obstructive pulmonary disease (COPD) (38% *vs.* 12%; P<0.001), interstitial lung disease (ILD) (9% *vs.* 3%; P<0.019), and ischemic heart disease (28% *vs.* 18%; P=0.033). Patients were similar in terms of age (68±8 *vs.* 68±10 years; P=0.932), and other comorbidities. Anatomic lung resection comprised 56.8% of the marginal group *vs.* 74% in the non-marginal group (P=0.003). The most common complication was prolonged air leak (18.2% *vs.* 11.8%; P=0.479). Marginal lung function had a trend toward increased composite respiratory complications (22.7% *vs.* 15.1%; P=0.112) and 90-day mortality (5.7% *vs.* 4.2%; P=0.591), although they did not reach statistical significance. There was a statistically significant 1-day average increase in length of stay in the marginal lung function cohort (4.6 *vs.* 3.4 days; P<0.015) with a stronger association with diffusion lung capacity of carbon monoxide than FEV1. Survival was similar (marginal function HR =1.0; P=0.994).

Conclusions: In the era of minimally invasive thoracic surgery, lung resection in patients with marginal lung function may be considered in select patients. These findings aid in the selection consideration and counseling of this patient population.

Keywords: Minimally invasive thoracic surgery; marginal lung function; robotic-assisted thoracic surgery (RATS)

Introduction

Pre-operative pulmonary lung function tests have long been utilized to predict post-operative outcomes following lung resection. Specifically, low percent predicted values for forced expiratory volume in 1 second (FEV1) and diffusion lung capacity of carbon monoxide (DLCO) have been shown to be associated with increased morbidity and mortality (1-4). Thus, some patients with marginal lung function are traditionally viewed as high risk operative candidates and often get referred to alternative non-surgical methods of treatment such as stereotactic body radiation therapy (SBRT) or radiofrequency ablation (RFA) (5-11). It is important to note that the impact of marginal lung function is based mainly on studies on patients undergoing open thoracotomy and lung resection.

However, with the advent of minimally invasive surgery, many studies have compared the minimally invasive approach [e.g., video-assisted thoracic surgery (VATS) or robotic-assisted thoracic surgery (RATS)] to open thoracotomy, and demonstrated lower perioperative complications overall (12-22). Since current guidelines are based on studies of patients who underwent thoracotomy, the impact of marginal lung function on patients undergoing VATS or RATS lung resection is unclear. Granular data on outcomes following minimally invasive lung resection in patients with marginal lung function are limited.

In this context, we studied the impact of marginal lung function on patients undergoing minimally invasive surgery at a single tertiary center where nearly all lung resections are performed in a minimally invasive fashion. Specifically, we analyzed morbidity, length of stay, perioperative mortality and long-term survival relative to marginal lung function. The findings can help with shared decision making in this patient population in the era of minimally invasive thoracic surgery.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/jtd-21-1382).

Methods

Patient population

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of Loyola University Medical Center (No. 211663: the registration number of ethics board) and individual consent for this retrospective analysis was waived. We used our institutional database to identify all patients who underwent pulmonary resection via VATS or RATS between January 2017 to May 2020. We included all adult patients (age >18 years old) who underwent lobectomy, segmentectomy or wedge resection for known or suspected malignancy. We did not include patients undergoing open surgery, those who underwent pneumonectomy, or those who underwent a wedge lung biopsy.

Independent variables

Preoperative clinical and demographic characteristics included age at presentation, gender, and pre-existing comorbid conditions including: hypertension (HTN), coronary artery disease (CAD), diabetes mellitus (DM), cerebral vascular disease, pulmonary hypertension (pHTN), smoking history, chronic obstructive pulmonary disease (COPD), co-existing cancer, venous thromboembolism (VTE), interstitial lung disease (ILD), myocardial infarction (MI), peripheral vascular disease (PVD), congestive heart failure (CHF), liver dysfunction, atrial fibrillation (afib), and Zubrod score. Zubrod score was defined as 0 for asymptomatic patients, 1 for symptomatic but completely ambulatory patients, 2 for symptomatic but <50% in bed during the day, 3 for symptomatic and in bed >50% of the time but not bedbound, and 4 for bedbound patients. Tumor pathology including tumor size, location, clinical TNM stage, and tissue histology were collected. Lung resection was defined as either anatomic (segmentectomy or lobectomy) or non-anatomic (wedge resection). Surgical resection was performed by two surgeons and the technique for VATS and RATS was consistent throughout the study. VATS was performed with 4 ports for anatomic resections and 3 ports for wedge resections. RATS was performed using 4 robotic ports or a 5th port for a robotic stapler for anatomic resections and 4 robotic ports for wedge resections. Missing data in categoric variables were modeled as a separate "unknown" category.

Exposure variables and outcomes

The main exposure variable was marginal lung function *vs.* normal lung function. Marginal lung function was defined as preoperative FEV1 and/or DLCO <60% (1,2). The primary outcomes were the occurrence of composite pulmonary complication within 30 days and/or 30- and 90-day mortality as a composite variable. Pulmonary

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complications were defined as prolonged air leak >5 days, pneumonia, acute pulmonary embolism, pneumothorax requiring chest tube replacement, and ventilator dependence for >48 h. Intervention for prolonged air leak was defined as mechanical or chemical pleurodesis, endobronchial valve placement, or operative resection. Our secondary outcomes included hospital length of stay measured in days. Lastly, overall survival data was collected from the date of last follow-up and/or phone calls to each individual patient if the last follow-up date was not in the past year.

Statistical analysis

Clinical and demographic variables for patients with preoperative marginal or normal lung function were analyzed using χ^2 tests for categorical variables and Student *t*-tests for continuous variables, as indicated.

Independent variables with P values <0.200 were then entered into a multivariable logistic regression model predicting the binary composite outcome of morbidity and mortality. From this model, the beta-coefficients were used to calculate the predicted probability of the composite at deciles of each lung function metric. All other variables were held as observed. A separate Poisson regression model was used to predict hospital length of stay in days and identify associations with outcomes. Poisson models were used given the skewed distribution. Similar to the previous model, the beta coefficients were used to calculate the predicted length of stay in days per decile of pulmonary function metric, while holding all other variables as observed. This methodology allows for identifying the specific contribution of the pulmonary function values while adjusting for other important variables.

Finally, Kaplan-Meier survival analyses were then performed and differences assessed using the log-rank test. All tests were two-sided, with significance set at a P value of less than 0.05. The statistical analyses were conducted using Stata 13.1 software (StataCorp., College Station, TX, USA).

Results

Of 300 patients who underwent minimally invasive thoracic surgery, 88 (29%) had marginal lung function. Patients in the marginal lung function group were more likely to be female (69% *vs.* 56%; P=0.028), and more likely to have: COPD (38% *vs.* 12%; P<0.001) and ILD (9% *vs.* 3%;

P<0.019). In these patients, the incidence of ischemic heart disease (28% *vs.* 18%; P=0.033) and HTN (83% *vs.* 71%; P=0.028) were also higher. Patients were similar in terms of their age (68±8 *vs.* 68±10 years; P=0.932), and their other comorbidities, as shown in *Table 1*. Anatomic lung resection was less commonly performed in the marginal lung function group, but still comprised 56.8% of lung resections, compared to 74.1% in the non-marginal group (P=0.003). Of the patients that underwent anatomic lung resections, the use of segmentectomy was significantly higher in the marginal lung function group compared to normal lung function (13.6% *vs.* 9.4%; P=0.003) (*Table 1*).

The pre-operative FEV1 in patients with marginal lung function ranged from 28–59% with a median of 50%, and pre-operative DLCO ranged from 18–59% with a median of 54%. In contrast, pre-operative FEV1 and DLCO of normal lung function ranged from 60–137% with a median of 86% for FEV1 and 82% for DLCO (*Table 1*).

The most common complication in the marginal lung function cohort was prolonged air leak (18.2% *vs.* 11.8%; P=0.142), as shown in *Table 2*. The majority of patients that had prolonged air leak underwent conservative management with continuation of a chest tube; 1/16 (6.3%) of marginal lung function patients with an air leak underwent intervention with chemical pleurodesis and 2/25 (8.0%) patients with normal lung function underwent intervention (P>0.999), one patient with chemical pleurodesis and one patient with endobronchial valve placement. Overall, marginal lung function was associated with a trend toward increased composite respiratory complications (22.7% *vs.* 15.1%; P=0.112) (*Figure 1*), 90-day mortality (5.7% *vs.* 4.2%; P=0.591), and the composite outcome of respiratory morbidity and/or 90-day mortality (27.2% *vs.* 17.9%; P=0.069), although none of these outcomes reached statistical significance, as shown in *Table 3*.

However, there was a 1-day average increase in length of stay in the marginal lung function cohort (4.6 *vs.* 3.4 days; P<0.015). On multivariable analysis, this increased length of stay association is noted across deciles of FEV1 and DLCO (*Figure 1*), with a stronger association with DLCO than FEV1. There was an increasing trend toward an association between individual lung function metrics with the composite respiratory outcome, although this did not reach statistical significance.

Lastly, median follow-up was 699 days. On Kaplan-Meier analysis, long term overall survival was similar between the two cohorts, as shown in *Figure 2* (P=0.994).

Table 1 Baseline characteristics and types of surgical resection between patients with marginal lung function and normal lung function

Characteristics	Marginal lung function (n=88)	Normal lung function (n=212)	P value
Age	67.8±10.2	67.9±7.7	0.932
Gender			0.028
Female	61 (69.3%)	118 (55.7%)	
Male	27 (30.7%)	94 (44.3%)	
HTN	73 (83%)	150 (70.8%)	0.028
DM type 2	16 (18.2%)	44 (20.8%)	0.612
Lung cancer	75 (85.2%)	168 (79.2%)	0.229
COPD	33 (37.5%)	26 (12.3%)	0.000
ILD	8 (9.1%)	6 (2.8%)	0.019
pHTN	0 (0%)	2 (0.9%)	0.361
MI	0 (0%)	6 (2.8%)	0.111
CAD	25 (28.4%)	37 (17.5%)	0.033
afib	3 (3.4%)	8 (3.8%)	0.878
CHF	5 (5.7%)	11 (5.2%)	0.863
VTE	3 (3.4%)	11 (5.2%)	0.506
CVA	6 (6.8%)	7 (3.3%)	0.173
Co-existing cancer	6 (6.8%)	31 (14.6%)	0.061
PVD	6 (6.8%)	13 (6.1%)	0.824
Liver dysfunction	0 (0%)	1 (0.5%)	0.519
Pre-operative PFTs			
FEV1—range (median)	28–59% (50%)	60–137% (86%)	
DLCO—range (median)	18–59% (54%)	60–137% (82%)	
Type of resection			0.003
Lobectomy	38 (43.2%)	137 (64.6%)	
Segmentectomy	12 (13.6%)	20 (9.4%)	
Wedge	38 (43.2%)	55 (26%)	

HTN, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; pHTN, pulmonary hypertension; MI, myocardial infarction; CAD, coronary artery disease; afib, atrial fibrillation; CHF, congestive heart failure; VTE, venous thromboembolism; CVA, cerebral vascular accident; PVD, peripheral vascular disease; PFTs, pulmonary function tests; FEV1, forced expiratory volume in 1 second; DLCO, diffusion lung capacity of carbon monoxide.

Discussion

In this contemporary, single-institution observational study of 300 patients who underwent minimally invasive lung resection for lung cancer or pulmonary nodules, we found that: (I) nearly 1 in 3 of our patients had marginal lung function and half of those underwent anatomic lung resection; (II) there was a trend toward increased morbidity and 90-day mortality in marginal lung function group although this did not reach statistical significance; and (III) there was a 1-day on average increased length of stay in patients with marginal lung function.

With the advent of minimally invasive surgery, patients with marginal lung function are increasingly undergoing surgical resection for lung cancer. Previous guidelines by

Table 2 Thirty-day respiratory complications

Thirty-day respiratory complications	Marginal lung function (n=88)	Normal lung function (n=212)	P value
Prolonged air leak	16 (18.2%)	25 (11.8%)	0.142
Intervention for prolonged air leak	1/16 (6.3%)	2/25 (8.0%)	0.999
Pneumothorax	4 (10.5%)	9 (12.7%)	0.741
Pneumonia	2 (5.3%)	5 (7%)	0.718
Pleural effusion	0 (0%)	1 (1.4%)	0.462
Tracheostomy	0 (0%)	2 (2.8%)	0.296
Pulmonary embolus	1 (2.6%)	1 (1.4%)	0.955
Ventilator support >48 h	0 (0%)	1 (1.4%)	0.462
Respiratory failure	2 (5.3%)	1 (1.4%)	0.241
Other pulmonary events	1 (2.6%)	1 (1.4%)	0.650
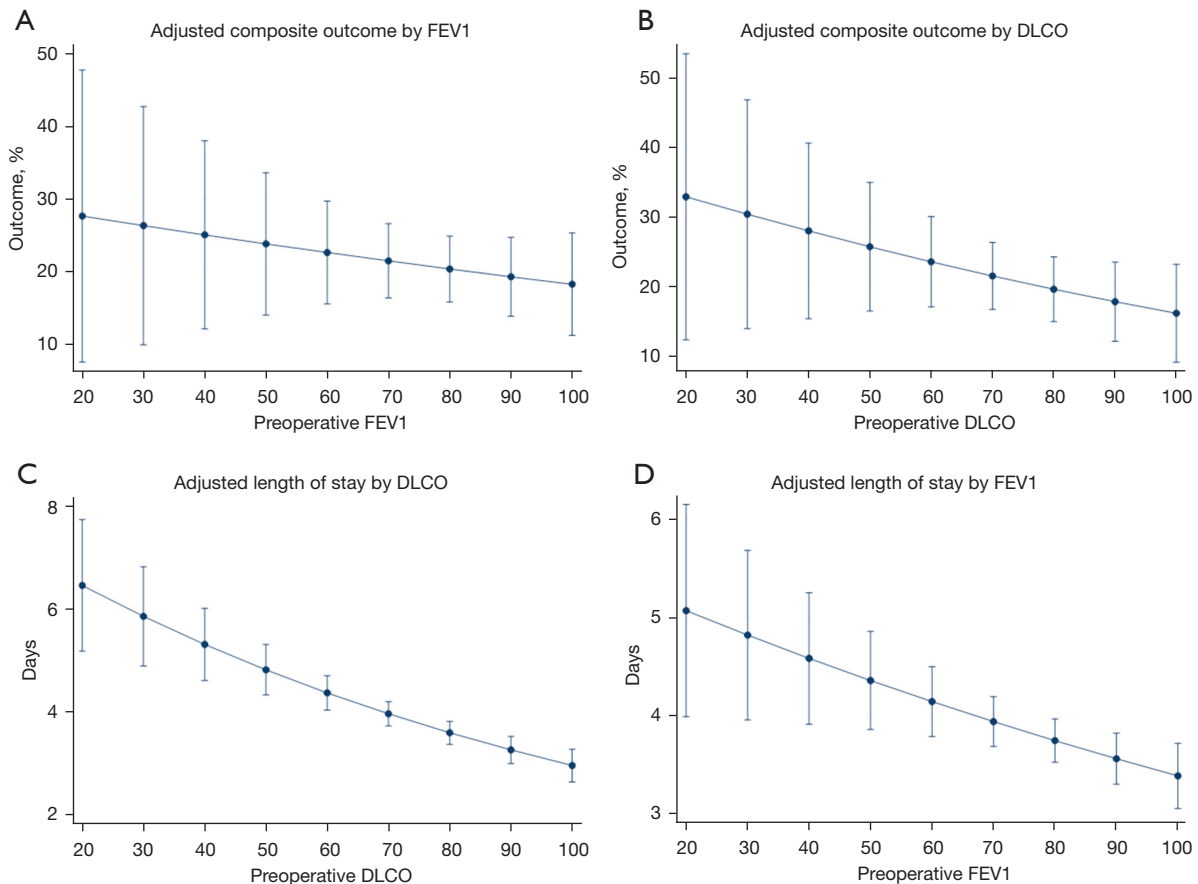
Figure 1 Adjusted composite outcome and length of stay by FEV1 and DLCO. (A) Ninety-day composite respiratory outcome by deciles of FEV1. (B) Ninety-day composite respiratory outcome by deciles of DLCO. (C) Adjusted length of stay by deciles of DLCO. (D) Adjusted length of stay by deciles of FEV1. Note that FEV1 and DLCO are not significantly associated with the composite outcome, but are associated with length of stay. DLCO has a stronger association than FEV1. FEV1, forced expiratory volume in 1 second; DLCO, diffusion lung capacity of carbon monoxide.

Table 3 Thirty- and 90-day mortality, composite respiratory outcomes, and composite respiratory and 90-day mortality

| Composite outcomes	Marginal lung function	Normal lung function	P value
Thirty-day mortality	1 (0.9%)	3 (1.1%)	0.878
Ninety-day mortality	5 (5.7%)	9 (4.2%)	0.591
Respiratory complications	20 (22.7%)	32 (15.1%)	0.112
Composite respiratory and 90-day mortality	24 (27.2%)	38 (17.9%)	0.069
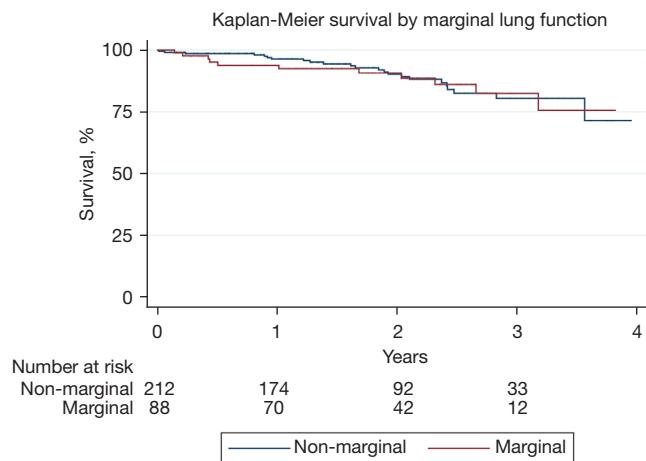
Figure 2 No significant difference in overall survival on Kaplan-Meier curve.

American College of Chest Physicians (ACCP), European Respiratory Society (ERS)/European Society of Thoracic Surgeons (ESTS), and British Thoracic Society (BTS) emphasized limitations of surgical resection in patients that were deemed high risk for surgery based on pulmonary function tests (PFTs) and patient co-morbidities (1-3). Patients deemed too high risk for surgical resection with early stage I lung cancer are referred for stereotactic body radiation therapy (SBRT) or radiofrequency ablation (RFA) based on American Society for Radiation Oncology (ASRO) guidelines (5). SBRT has been successful in local control with recurrence rates reported as low as 10% in short-term follow-up (6-9). Short-comings of SBRT include difficulty in surveilling tumors via imaging due to radiation-induced lung injury and omission of invasive lymph node staging prior to treatment, causing reportedly higher distant recurrence rates (9). RFA has been reported to have high recurrence rate and may be limited in efficacy in larger tumor sizes >3 cm (10,11). A 2015 analysis of the Surveillance, Epidemiology, and End Results (SEER) database comparing SBRT to surgical resection for stage I

non-small cell lung cancer found a lower 90-day mortality rate in the SBRT group compared to surgery (2.2% *vs.* 6.1%; P=0.005); however, this outcome was reversed by 1 year, with a significantly higher mortality for SBRT compared to surgery (40.1% *vs.* 22.3%; P<0.001) (12). To stratify out any underlying co-morbid conditions that are inherently higher in patients selected for SBRT, a large National Cancer Database analysis comparing propensity-matched SBRT to lobectomy for operable stage I lung cancer found a significant difference in 5-year overall survival (29% SBRT *vs.* 59% lobectomy; P<0.001) (13). Due to limitations in non-surgical approaches as well as data suggesting higher overall survival in the surgical cohort in long-term follow-up, expanding criteria for surgical resection in poor lung function candidates should be considered, particularly in patients with longer life expectancy.

Updated guidelines by ACCP in 2013 includes grade 1c evidence for consideration of minimally invasive surgery in patients deemed surgically high risk (14). Indeed, our overall composite respiratory complications and 30-day mortality were similar to previous studies (15-22). Our 90-day mortality of 5.7% and 4.2% for marginal lung and normal lung function, respectively, are similar to 90-day mortality of 6.1% following lung resection from the SEER database (12). The 90-day mortality is not frequently reported in literature but we included it in our study to report the trend. Berry *et al.* (17) demonstrated that marginal lung function patients had significantly lower respiratory complications and mortality when undergoing thoracoscopic surgery compared to thoracotomy. Reported 30-day mortality for marginal lung function patients who underwent VATS ranged from 1–3% and similar to our reported 30-day mortality of 1% (17,20). Similar associations were made when comparing RATS to open approach for marginal lung function patients (20-22). These results are postulated to be related to decreased post-operative pain from elimination of rib spreading and preserving chest wall anatomy as well as reduced manipulation of lung parenchyma (17,22-25).

Our study was unique in that we compared marginal lung function patients to normal lung function patients who had all undergone minimally invasive surgery. Although there was no significant difference demonstrated in composite respiratory outcome and mortality, however, the groups in this study were not powered to detect this difference. Future studies with a larger patient population or a multicenter study may help elucidate these differences. Our data is a contemporary study that used the most recent data available at our institution, thus we had limited long-term follow-up data for the more recent surgical patients. Notwithstanding this limitation, the increasing trend in composite respiratory outcome was not associated with overall survival on the Kaplan-Meier analysis.

Although our marginal lung function cohort had a significantly lower rate of anatomic lung resection, this was not associated with increased mortality in these patients after 90-day or decreased overall survival. Lobectomy is currently the gold standard therapy for resectable lung cancer based on a landmark randomized control trial by the Lung Cancer Study Group in 1995 (26). Old paradigms have been challenged by recent advancements in preoperative imaging, staging modalities, and minimally invasive surgery (27). There has been an increase in anatomic segmentectomies in patients undergoing minimally invasive surgery for early lung cancer, likely related to worse pulmonary function in this patient cohort; however, no associated difference in overall morbidity or mortality have been observed (20-25,28). The recently reported JCOG0802/ WJOG4607L phase III randomized control trial compared segmentectomy and lobectomy for stage Ia peripheral non-small cell lung cancer ≤2 cm in diameter (29). They found a significant difference in post-operative air leak in patients who underwent segmentectomy compared to lobectomy; this difference was attributed to increased technical surgical complexity of segmentectomy compared to lobectomy although these findings did not result in any differences in morbidity or mortality (29). It is possible that the increased air leak in the marginal lung function group in our study may be due to higher incidence of segmentectomy among these patients. Furthermore, updated data presented at the American Association for Thoracic Surgery 101st annual meeting demonstrated superiority in 5-year overall survival of segmentectomy compared to lobectomy (94.3% *vs.* 91.1%; P=0.0082), albeit a higher loco-regional recurrence (12.1% *vs.* 7.9%; P=0.0214) (30). Compared to lobectomies, segmentectomies preserve more lung parenchyma and subsequently pulmonary physiology, thus contributing to the

improved perioperative respiratory outcome (27-29). Non-anatomical resection, especially in early stage cancer, related to composite outcomes warrant further investigation. In addition, there have been limited studies assessing the appropriate "cutoff" value in FEV1 or DLCO for minimally invasive lung resection and the appropriate surgical procedure for each marginal or "high risk" patient based on pre-operative lung function values. Larger studies to power for each range of FEV1 and DLCO can help delineate these differences.

In this study, marginal lung function was associated with increased hospital length of stay although the overall length of stay is short in both groups. Reported median length of stay of patients undergoing minimally invasive surgery for lung resection ranged from 2 to 5 days although these studies did not stratify length of stay based on lung function (17,20,25,28). In our patient population, marginal lung function patients had significantly elevated co-morbid conditions that could contribute to this finding, although the length of stay is similar to reported median length of stay in similar studies. Furthermore, the longer length of stay had a stronger association with patients with DLCO <60% compared to FEV1 <60% or normal lung function. Consistent with our findings, there have been multiple reports demonstrating DLCO as an independent risk factor for patients undergoing lung resection (31-34). The stepwise increase in length of stay for every 10 percentage points decrease demonstrates the strength of this association. The absence of such a relationship with overall survival on the other hand, suggests that in the minimally invasive approach to lung resection, those effects are largely blunted.

Our findings in this study indicate that surgical resection with a minimally invasive approach should be considered in patients with marginal lung function. However, it's important to emphasize the importance of surgeon judgement and patient selection in this patient population. Although PFTs are helpful adjuncts in predicting outcome after lung resection, patient co-morbid conditions, social factors, and type of surgical resection need to be considered prior to offering surgery. Important discussions regarding outcome of surgical intervention are respiratory complications, especially prolonged air leak that potentially require intervention, and increased hospitalization days should be included in the shared decision-making with patients.

This study has several limitations. First, this is an observational study subject to inherent selection bias and

confounding. We included all consecutive lung resection patients at our institution to mitigate this; however, we do not have data on patients with marginal lung function who were deemed poor operative candidates. Although this is a major limitation, it does highlight the importance of the surgeon's judgment at the preoperative visit. Second, the type of surgical resection that was performed, namely lobectomy, segmentectomy, or wedge resection, were determined by surgeon judgement based on patient baseline parameters and preoperative lung function. More objective guidelines for determining the surgical approach based on patient lung function is a target for further studies. Finally, these surgical results are from a single center and the sample size was small, thus, the results might not be generalizable. The small sample limited the ability to propensity match between the marginal lung function and normal lung function group to assess composite outcome and survival. Although propensity match was not performed due to small sample size, a logistic regression model was used to adjust for important confounders. Notwithstanding these limitations, we believe the findings are contemporary, relevant, and reflect modern thoracic surgical practice. The finding of increased length of stay in patient with marginal lung function help in patient counseling and can identify targets for quality improvement.

In conclusion, select patients with marginal lung function can safely undergo lung resection utilizing minimally invasive approaches albeit an increased trend in composite respiratory outcome and 90-day mortality. Larger studies are warranted to statistically power for any significant associations. Hospital length of stay is short overall, but those with marginal lung function should be expected to stay 1 day longer on average. In summary, this information should be considered in shared decision-making with the patients and multi-disciplinary team.

Footnote

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