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Patient Reported Outcomes and Their Relationship with Lung Cancer Surgery Outcomes

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Abstract

Patient Reported Outcomes and Their Relationship with Lung Cancer Surgery Outcomes

By Onkar V. Khullar

Introduction: Patient quality of life (QOL) is a critical outcomes measure in lung cancer surgery. Patient reported outcomes (PRO) are an ideal method for measurement of pre- and post-operative QOL, and physical functioning. There is little understanding of the relationship between PRO, clinical comorbidities and post-operative outcomes after lung cancer surgery. We hypothesize that age and poor pulmonary function will predict worse postoperative PRO. Additionally, we hypothesize that worse higher preoperative physical function PRO will be associated with greater risk of postoperative complication and prolonged length of stay (LOS).

Methods: PRO surveys assessing multiple domains including physical function and pain intensity were generated using instruments from the NIH Patient Reported Outcome Measurement Information System (PROMIS). PRO surveys were administered to patients undergoing minimally-invasive lung cancer resections at the preoperative, one and six month postoperative time points. Data were collected and merged with our institutional Society of Thoracic Surgeons database for clinical data. Mixed-effects regression models were created to assess the impact of clinical variables on changes in PRO scores from baseline to one and six months postoperative. Poisson regression models were constructed to estimate the association between the LOS and PROMIS physical function, adjusting for procedure, age, gender, and race.

Results: A total of 123 patients underwent a thoracoscopic lung resection for cancer. When comparing clinical variables with changes in PRO after surgery, lower diffusing capacity of the lung for carbon monoxide (DLCO) was associated with significantly worse physical function ($p<0.01$) and greater pain intensity scores ($p<0.01$) at 6 months. No other clinical factor was associated with significant differences in postoperative pain or physical function scores. Among patients who had a post-operative complication, a lower preoperative physical function T-score was associated with progressively increasing LOS (p-value=0.006). LOS increased by 18% for every 10-point decrease in physical function T-score. Among patients without complications, T-score was not associated with LOS (p=0.86).

Conclusions: These results can be of significant utility in preoperative counseling for patients with low DLCO and physical function scores. These findings can be used to identify patients who may experience greater declines in QOL after surgery, greater resource utilization, and who may benefit from further risk-reduction measures.

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Introduction:

Patient reported outcomes (PROs) are direct assessments of health-related outcomes and quality of life obtained directly from the patient, rather than the clinical provider. PRO can provide a more accurate assessment of a patient's quality of life, as they are not subject to the interpretation of a health care provider. As greater emphasis is placed on the delivery of high quality, patient-centered care, the importance of PRO has become widely accepted. Patient-centered care, ultimately, is the delivery of treatment focused on what matters most to the patient. Measuring success in this effort through objective provider-driven measures would be inadequate. PROs are increasingly viewed as the optimal measurement for the quality of patient-centered care. As a result, several major national organizations are promoting PRO research and utilization, including the Center for Medicare and Medicaid Services, National Quality Forum (NQF), National Institute for Health (NIH), National Cancer Institute (NCI), the United States Food and Drug Administration, American College of Surgeons, European Agency for Evaluation of Medical Products, among others. (1)

Often in thoracic surgery research, we focus our efforts and analyses on more objective measurements. Most existing thoracic surgery literature focuses on traditional surgery endpoints, such as perioperative complications and mortality rates. Undoubtedly, these results are of vital importance as they form the basis of any treatment evaluation and, particularly in relation to oncologic care, they predominate our research endeavors. There is the commonly accepted belief, particularly in regard to cancer treatment, that the best therapy is the one that provides the longest survival. Further, results such as survival, perioperative mortality, and complication rates are objective and relatively easy to measure. However, focusing on such outcomes provides a narrow view of the patient experience, and lacks insight into the quality of life outcomes that are often of equal importance to the patient.

Lung cancer is one of the most careful studied thoracic diseases as it is the second most common cancer in the United States with an estimated 180,000 new cases yearly. Approximately 35% of patients will present with localized disease. (2) In patients with limited disease, surgical resection provides the

best opportunity for cure. While overall survival in patients in lung cancer is quite poor, patients with early stage disease exhibit 5-year survival rates are over 90% after curative resection.(3) As discussed, most studies of lung cancer surgery focus on these more objective measures that are relatively straightforward to quantify, such as peri-operative mortality, long-term survival, and rates of complications.

Thoracic surgeons typically do not routinely gather and examine data from the most important resource – the patient. At this time we are still unable to effectively counsel patients regarding the changes and differences in QOL that directly reflects a patient's experience. The full extent to which PROs can be utilized in thoracic surgical clinical practice remains to be determined as PROs are not routinely assessed, analyzed, or researched - a critical knowledge gap. Ultimately, to deliver true patient-centered care, it will be necessary to universally gather PROs prospectively, including them in routine patient care, clinical registries, and clinical trials.

The existing thoracic surgical literature contains several retrospective and observation studies focused on describing longitudinal patterns and variance in post-operative PROs measuring pain, functional status, and dyspnea, however these studies lack quality comparative data. The few studies that do aim to perform CER utilizing PROs again typically do so in an observational manner with minimal inclusion of or correlation with patient risk factors.(4-8) Moreover, we still do not routinely use PROs in clinical practice and risk prediction. At Emory University, we have previously completed a prospective trial to gather patient reported physical function, pain, and emotional well-being scores from 150 patients undergoing lung cancer surgery using the prospectively validated, NIH-sponsored Patient Reported Outcomes Measurement Information System (PROMIS). (9) The purpose of this initial pilot study was to link this PRO data with clinical data from our institutional Society of Thoracic Surgeons General Thoracic Surgery Database (STS-GTSD). Results of this analysis showed significant worsening in physical function and pain scores in the first month after surgery, with return to preoperative levels at 6 months (Figure 1).

For these analyses, we utilized this existing dataset to examine the relationship between PROs and post-operative outcomes in patients undergoing lung cancer surgery. Clinical outcomes data was obtained from our institutional retrospective general thoracic surgery database from the Society of Thoracic Surgeons (STS-GTSD) after linking to the PRO database with a unique study identifier. These results will provide insight into the impact and importance of patient reported health status and function on results of surgery, which can potentially be used in predictive algorithms and treatment guidelines. The primary aims of this study were to determine whether traditionally viewed clinical high risk criteria are predictive of greater decline in patient reported outcomes after surgery and whether lower preoperative patient-reported physical function scores are predictive of postoperative outcomes.

Background:

A number of PRO based studies have been conducted on surgical treatment of lung cancer. (4-17) However, most of these are observational studies regarding quality of life after surgery meant to analyze what surgical factors result in greater decline in quality of life. None of these studies examine the predictive value of preoperative measurement of PRO. The findings of these studies in total describe a common theme – a decrease in physical function, dyspnea, and quality of life scores after surgery. Most studies describe a return to baseline within 6 months to a year.

Most of these studies are either retrospective or prospective observational studies of limited sample size. However, in one of the few studies with a large enough sample size to perform an adjusted analysis, Yun, et al., conducted surveys of over 800 patients undergoing lung cancer surgery using the EORTC QLQ-C30 and QLQ–LC13 questionnaires, examining the relationship between PROs and long-term survival. After adjusting for independent demographic and clinical predictors of survival, they found QOL measures for post-operative physical function, dyspnea, personal strength, and anxiety were all independent predictors of long-term survival. (6) In another recently published series including 60 patients evaluated with the MD Anderson Symptom Inventory, Fagundes, et al., administered the survey to patients daily for the first week after surgery followed by weekly for 3 months. (4) The authors found fatigue, pain, shortness of breath, disturbed sleep, and drowsiness to be the postoperative symptoms to be most significantly affected. Symptom severity peaked 3 to 5 days after surgery. By 3 months all of these symptoms had returned to preoperative levels. To date, this represents the only study to survey patients immediately after surgery while still in the hospital, providing valuable information regarding the immediate postoperative impact on HR-QOL.

Results from analysis of QOL in the ACOSOG Z4032 study cohort showed significantly worse scores in regards to postoperative shortness of breath in patients treated with a thoracotomy (a surgical approach requiring an approximately 10cm long incision on the lateral chest wall in order to open the thoracic cavity), when compared with minimally invasive techniques completed with a camera and

smaller incisions (often referred to as video-assisted thoracic surgery, or VATS). (15) Similarly, in a prospective observational study using the SF-36 questionnaire, Zhao, et al., found pain, energy and physical role functioning all to be worse after thoracotomy, when compared with minimally invasive surgical approaches. (16)

Not surprisingly, it does appear that a greater extent of pulmonary resection, particularly pneumonectomy, can have a significantly detrimental impact on postoperative HR-QOL. Sartipy, et al., performed a prospective comparison of patients undergoing lobectomy (n = 101) versus pneumonectomy (n = 16) using the SF-36 questionnaire. Results from their analysis found a significantly greater decrease in physical function scores after pneumonectomy. (7) Balduyck, et al., found similar to results when comparing sleeve lobectomy with pneumonectomy. (12) Physical functioning, role functioning, cognitive functioning, and shoulder dysfunction were all significantly worse than sleeve lobectomy.

The initial goal of our pilot study was to successfully gather PROs from patients undergoing lung cancer surgery and link these data with clinical results from our institutional Society of Thoracic Surgeons General Thoracic Surgery Database (STS-GTSD). The second aim was to use these results for treatment comparison. (9) To accomplish this, a HR-QOL questionnaire pertaining to patients undergoing lung cancer surgery was generated using the PROMIS system. PROMIS® is a well validated system of measures of PROs which include a variety of questionnaires that span multiple physical, mental and social health domains. (18) PROMIS instruments utilize a variety of short form modules across all health domains, surveys can be customized to the patient population and disease process of interest. PROMIS questionnaires and instruments use item response theory and computer adaptive testing to adapt to the specific symptoms of a patient. Because of its versatility and advantages, it has been recommended by the Center for Medical Technology Policy as one of their preferred PRO measures for cancer clinical research and has been used in a variety of fields including oncology, orthopedics, cardiothoracic surgery, transplantation, and pediatrics. (19) PROMIS questionnaires can be easily administered from via the website Assessment Center^{SM}. Assessment Center contains a library of PROMIS tools as described above,

thereby allowing investigators to create a study-specific website with PROMIS instruments of their choosing. Additionally, it allows for near real-time scoring of PROMIS tools using a t-score distribution normalized to responses from the general population, which can be used to track changes in an instrument of choice with a quantifiable score.

Results from this initial analysis of 127 patients showed significant increase in pain intensity, pain interference, and fatigue, along with significant declines in physical function at the initial post-operative visit (Figure 1). Patient reported levels for each of these instruments returned to near-baseline levels by 6 months. Comparative analysis of physical function in patients treated with minimally-invasive video-assisted approaches versus thoracotomy revealed significantly lower levels in patients treated with thoracotomy at the initial post-operative visit (Figure 2). Interestingly, at the 6-month follow-up visit no difference was identified between the two groups. These results confirmed the feasibility of collecting PRO data from lung cancer surgery patients and the value in integrating the results into a clinical surgical database.

The majority of the aforementioned studies focused on describing changes in QOL over time after surgery. There remains a poor understanding of the relationship between patient-reported outcomes, clinical comorbidities and post-operative surgical outcomes/complications in lung cancer surgery patients. For example, which patients are at risk for greatest decline in QOL surgery, or whether poor QOL and functional status prior to surgery is predictive of postoperative complications? For example, an age greater than 75, forced expiratory volume in 1 second (FEV1) > 50% of predicted, and diffusing capacity for carbon monoxide (DLCO) < 50% of predicted are generally considered to be high risk criteria for peri-operative complication after lung cancer surgery. (15, 20) There has been little investigation into whether these criteria correlate with quality of life. The goal of this analysis was to better understand and explain this complex relationship.

Specific Aims:

Aim 1: To determine which baseline (pre-surgical) clinical factors and medical conditions correlate with worse pre-operative patient-reported physical function and pain intensity.

Hypothesis: Advanced age (age ≥ 75, diminished pulmonary function (FEV1 ≤ 50%, DLCO ≤ 50%), and presence of cardiac conditions such as CHF will be associated with lower preoperative reported levels of physical function (1^0 endpoint), and no difference in pain intensity.

Aim 2: To compare long term post-operative changes in patient-reported physical function and pain intensity after minimally-invasive lung cancer surgery between patients considered standard vs high-risk for post-operative morbidity (defined as FEV1 ≤ 50%, DLCO ≤ 50%, or age ≥ 75).

Hypothesis: Patients at high risk for pulmonary surgery will have greater decline in post-operative patient reported physical function (1^0 endpoint), and greater increase in pain intensity scores, when compared with standard risk patients.

Aim 3: To examine the impact of baseline patient-reported physical function on the occurrence of complications and post-operative length of stay, as reported in the Emory institutional Society of Thoracic Surgeons General Thoracic Surgery Database.

Hypothesis: We hypothesize that patients with lower baseline reported physical function will be at higher risk for any complication and prolonged length of stay.

Methods:

Study Population

The Emory University Division of Cardiothoracic Surgery previously completed a prospective cohort study to demonstrate the feasibility of obtaining PRO results and integrating these into our institutional STS-GTSD in patients undergoing lung cancer surgery. The current study is a secondary analysis of this. Approval to conduct this study was granted by the institutional review board at the Emory University School of Medicine (IRB #76320). From November 2014 through January 2017 patients were identified in the thoracic surgical clinic and enrolled with written informed consent. Eligibility criteria included patients 18 years of age or older, undergoing surgery for primary lung cancer, and who could read and understand English. Details of surgical approach, including extent of resection, was left to the discretion of the treating surgeon and was based on the extent of disease, pulmonary and physical function, and pre-existing comorbidities. Patients with a final pathologic diagnosis other than primary lung cancer following resection were excluded from subsequent analysis.

All patients were given PRO surveys (described below) at three time points: before a pre-surgery baseline assessment, at their initial postoperative visit (typically within 1 month of surgery) to assess the acute impact of surgery on PRO results, and at 6 months after surgery to assess longer-term impact and recovery. A total of 209 patients were consented for the trial (Figure 4). There were 51 screen failures. A total of 152 patients completed the initial postoperative survey, 128 completed the final follow up survey. Preliminary data showed surgical approach (VATS versus thoracotomy) was associated with significant differences in PRO results at the baseline and 1 month time points (Figure 2). (9) Therefore, in order to avoid any confounding by surgical approach, these current analyses was restricted to patients treated with video-assisted, minimally invasive approaches (n=123).

PROMIS Survey

We developed a PRO survey using validated instruments from PROMIS developed by the National Institutes of Health (NIH). (21, 22) Selection of instruments for inclusion in the survey was performed empirically after review by the thoracic surgeons at out institution. Ten PROMIS instruments assessing several health domains were selected. Seven fixed length (short form) PROMIS instruments were selected: pain intensity, anxiety, depression, sleep related impairment, ability to participate in social roles and activities, informational support, and emotional support. These short forms range from 4-10 questions in length. In addition, three Computer Adaptive Test (CAT) instruments were selected as well: cancer-fatigue, cancer-pain interference, and cancer-physical function and mobility. Dyspnea-related questions were included within physical function. Financial-related questions were not included. CATs utilize Item Response Theory to produce scores for replies to each question that allow selection of the most appropriate follow-up question. Each CAT contained between 4-12 questions, depending on the response pattern. The entire survey ranged between 63 to 87 questions with five ordinal response options. (23)

Researchers from the Interactive Media Technology Center at the Georgia Institute of Technology created a customized PRO survey on the Assessment Center^{SM} website incorporating the PROMIS instruments named above. The Assessment Center^{SM}, available through the NIH, allows investigators to create study-specific websites for secure, electronic remote data capture online of PRO assessments using PROMIS instruments. (24) Eligible patients were enrolled on the Assessment Center website and then completed the PRO survey in the clinic via a touch-screen tablet device. The clinical research nurse was available for assistance as needed. Patients who did not complete the survey in clinic were contacted and completed the survey over the phone with the assistance of a research nurse. PRO data and results were then exported from the Assessment Center and electronically merged with the STS-GTSD. Linkage of the two data sources was accomplished with an encrypted identifier generated at the time of patient enrollment.

Total scores were calculated for each PROMIS domain for each patient assessment on the Assessment Center website. These scores were then calibrated to a weighted distribution of scores from the United States general population using a T-score algorithm. (25) T-scores are calibrated such that the general population mean is 50 with a standard deviation of 10. Therefore, a patient with a T-score of 60 has a score that is one standard deviation greater than the general population mean. Higher scores reflect "more" of a given domain, thus better functioning (physical function, support) but worse symptoms (pain, depression, fatigue).

Statistical Analysis

Preoperative clinical variables were summarized as counts (proportions) for categorical variables or mean (standard deviation) for quantitative variables. Baseline variables and mean PRO T-scores were compared using student's T-test and analysis of variance for categorical variables. Age, % predicted FEV1, and % predicted DLCO were categorized by established high risk criteria as follows, age=75, FEV1 = 50%, and DLCO = 50%. (15, 26) Mixed-effects regression models were utilized for comparing baseline variables with baseline, initial postoperative, and 6 month postoperative T-scores in order to control for correlation between T-scores. These models controlled for age, gender, and race for all variables except % predicted FEV1 and DLCO, as theses variables are already adjusted for when calculating these measures. Poisson regression models were constructed to estimate the association between complications, PROMIS physical function T-score and length of stay given the discrete values of LOS (days) and non-normal distribution of LOS. Covariates in the model included: extent of resection (lobectomy versus sublobar), age, gender, and race. All tests of hypotheses were two-sided and performed at the 0.05 level of significance. All data analysis was performed using SAS 9.4 (Cary, NC).

Results:

Baseline Demographics and Study Characteristics

A total of 209 patients were enrolled in the study, 152 completed survey 2, 128 completed survey 3 (Figure 2). The analysis was restricted to 123 patients treated with minimally invasive surgical approaches to avoid confounding by surgical approach. All patients completed the preoperative and initial postoperative surveys. 117 patients (95.1%) completed all three surveys, including the final 6 month survey. Baseline characteristics of the study population are summarized in Table 1. Mean age of the cohort was 67±9.6, 35% were male, and 65% were Caucasian. 75% of treated patients were stage 1. 71.5% of patients were treated with VATS lobectomy, with the remainder treated with VATS segmentectomy or wedge resection. Zubrod score, also known as ECOG score/status, is a measurement of physical function commonly used in oncology studies. A score of 0 means an asymptomatic, fully active individual. A score of 1 corresponds to a symptomatic but still fully ambulatory individual who is restricted in physically strenuous activity. A score of 2 or 3 corresponds to an individual who is in bed for < 50% or > 50% of the day, respectively, and capable of limited self-care. All enrolled patients had a Zubrod score of 0 (48.8%) or 1 (51.2%).

41.5% of patients had chronic obstructive pulmonary disease (COPD) and 15.5% of patients had coronary artery disease (CAD). FEV1 and DLCO are commonly utilized measurements of lung function, and are expressed as a percentage of the predicted value given a patients demographics. Values below 80% are indicative of diminished pulmonary function, below 50% are considered high risk for lung surgery. The mean FEV1 in this study was 85.1% (±21.6), and mean DLCO was 70.8% (± 20.9). The presence of comorbidities are further listed in Table 1.

Aim 1: To determine which baseline (pre-surgical) clinical factors and medical conditions correlate with worse pre-operative patient-reported physical function and pain intensity.

The association of baseline characteristics with physical function PROMIS T-scores at the baseline survey is shown in Table 2. Generally accepted high risk criteria for lung cancer surgery include age > 75, preoperative predicted FEV1 less than 50%, and preoperative predicted DLCO less than 50%. Age and DLCO were associated with significant differences in physical function scores. The difference in physical function T-score among patients with age above and below 75 was 4.0 (p=0.04) and DLCO above and below 50% predicted was 5.7 (p=0.002). It should be noted that prior study has shown the minimal clinically important difference in PROMIS T-score in cancer patients to be between 4 and 6. (27) No difference was identified in patients with FEV1 above and below 50%, though it should be noted that only 10 patients had an FEV1 less than 50%, as this is a standard relative exclusion criteria for lung cancer surgery.

Other significant differences at baseline were noted by smoking status in active smokers (difference of 6.7, p = 0.03), presence of COPD (difference of 5.7, p < 0.001), and presence of CAD (difference of 6.2, p = 0.004). As would be expected, Zubrod score of 1 was associated with lower physical function scores at baseline by a mean T-score difference of 3.9 (p = 0.01), compared with Zubrod score of 0, validating the PROMIS physical function instrument in this cohort.

The association of baseline characteristics with pain intensity PROMIS T-scores at the baseline survey is shown in Table 3. Only race was associated with a statistically significant difference, with non-Caucasians (vs. Caucasians) reportingd higher pain intensity (difference of 4.4, p = 0.01) prior to surgery. While potentially clinically meaningful differences were noted among active smokers (difference of 5, p = 0.06), this did not achieve statistical significance.

Aim 2: To compare long term post-operative changes in patient-reported physical function and pain intensity after minimally-invasive lung cancer surgery between patients considered standard vs high-risk for post-operative morbidity (defined as FEV1 ≤ 50%, DLCO ≤ 50%, or age ≥ 75).

As discussed, patients with age > 75, FEV1 < 50% of predicted, or DLCO < 50% of predicted are generally considered to be at high risk for surgical perioperative complication after lung surgery. The goal of Aim 2 was to determine if such patients noted greater declines in physical function and worse pain intensity as measured with PROMIS PRO T-scores. Mixed effects regression models were generated, to compare longitudinal changes in T-scores with demographics and clinical comorbidities, given the repeated measurements of T-score over time.

Among these three criteria, lower DLCO (< 50% predicted), in particular, was associated with significantly worse physical function at 6 months after surgery (mean difference in T-score of 6.7, 95% CI 2.7-10.7, Table 4). However, no difference was seen at 1 month, where both groups declined to similar levels (Figure 4). No other clinical factor, including age (Figure 5), FEV1 (Figure 6), Zubrod score (Figure 7), diabetes, CAD, and body mass index, were predictive of significant differences in postoperative physical function after controlling for age, gender, race, and procedure type (Tables 4 & 5).

In regards to pain intensity, patients with DLCO < 50% reported higher pain intensity scores at 6 months (mean difference of 5.1, 95% CI 0.3-10.1, Table 5, Figure 4), again with no difference at 1 month. Interestingly, younger age (<75) was associated with higher reported pain intensity at 1 month (mean difference of 7.8, 95% CI 4.3-11.4, Table 5, Figure 5). However, no difference was seen at 6 months. No other factor was associated with a difference at 1 month. Non-Caucasian race was also associated with higher reported pain intensity at 6 months, similar to the difference seen at baseline.

Further examination shows a linear relationship between DLCO and postoperative patient-reported physical function and pain intensity at 6 months after surgery, as shown in Figures 8 and 9. For every 10% increase in DLCO, 6-month physical function T-scores increased by 1.4 (SE=0.4) (Figure 8). 6-month pain scores decreased by 1.7 (SE=0.4) points for every 10% increase in DLCO (Figure 9).

Aim 3: To examine the impact of baseline patient-reported physical function on the occurrence of complications and post-operative length of stay.

The incidence of complications is shown in Table 6. 38% of patients had a complication (n=47). The most common complication was an "other pulmonary event" (19.5%), defined by the STS-GTSD as a pulmonary event not otherwise characterized as pneumonia or respiratory failure. The next most common complication was urinary retention (9.8%). The other complications frequently seen were persistent air leak (4.8%), atrial arrhythmia (4%), and chylothorax requiring intervention (3.2%). Length of stay, a commonly used measure of resource utilization, was significantly extended in patients who suffered a complication by 93% (95% CI: 1.60 - 2.32), after controlling for procedure, age, gender, and race (Table 7). The unadjusted incidence of complications by each decile of preoperative physical function T-score is shown in Figure 10. After controlling for age, gender, race, and type of procedure in a logistic regression analysis, the OR for a complication for every 10-point decrease in T-score was 1.57 (95% CI 0.97 - 2.52).

The association between the baseline PROMIS Physical Function T-Score and the predicted mean length of stay (LOS) and is shown in Table 8. As mentioned, complication status was a significant effect modifier on the relationship between baseline physical function score and LOS, as complication status was directly associated with length of stay. Therefore, a Poisson regression model was constructed, stratifying the analysis by the presence/absence of any complication. In patients with a complication, there was a significant decrease in predicted LOS as the preoperative physical function T-score improved. The mean LOS ratio for a patient with a T-score of 50 was 0.54, compared with a patient with a T-score of 30. In other words, the predicted LOS for the former was nearly half that of the later. For example, in a mean aged (67 years old) male Caucasian undergoing lobectomy with a T-score of 30, the predicted LOS was 8.47 days. This is in comparison to 4.61days for a similar patient with a T-score of 60 (Table 8). For each 10-point improvement in T-score, there was a 13 to 18% decrease in LOS, among patients who had a

complication (Figure 11A). On the other hand, when no complication occurred, there was no association identified between preoperative physical function T-score and the length of stay (Figure 11B).

Discussion

In this secondary analysis of a prospective observation cohort study, we found that PRO to be closely related with clinical comorbidities, specifically COPD and low DLCO, and that PRO can be used to identify patients at risk for increased postoperative length of stay. Results from this analysis showed that traditionally accepted high risk surgical criteria, such as advanced age, DLOC < 50%, and the presence of coronary artery disease correlated with low preoperative physical function scores. Only non-Caucasian race was associated with worse pain intensity scores. On the other hand, the only clinical variable to predict a statistically significant, as well as clinically meaningful, difference in both physical function and pain intensity scores at 6 months after surgery was a preoperative DLCO < 50% of predicted. No other clinical parameters, including age, Zubrod score, and FEV1, were predictive. Interestingly, no parameters were associated with a significant difference at 30 days postoperatively, with the exception of younger age and pain intensity. All groups showed worsened scores to similar levels at this time point.

We then examined the predictive capacity of PRO prior to surgery. Here, we found that preoperative physical function was associated with longer post-operative LOS, among patients who had a complication. In patients without complication, there was no correlation between T-score and LOS. These findings suggest that our frailest patients take longer to recover from a complication, when compared with the standard patient. Further, the odds ratio for complication were significantly higher in patients were lower physical function (OR = 1.5 for each 10 point decrease in T-score), though this result did not reach statistical significance (95% CI 0.97 - 2.52). Thus, routine measurement of patient-reported physical function scores can help identify such patients at risk for longer length of stay and potentially complications.

The clinical importance of PRO is increasingly recognized in the current era of medicine, with numerous specialties examining and endorsing their uses. (28, 29) PRO reflect the true patient experience and often reflect what is most important to the patient. Accordingly, patient reported physical function

measurement has been endorsed by the Centers for Medicare and Medicaid Services as a quality metric. (1) These measures are particularly salient in surgical oncology patients who generally feel well prior to surgery, after which they often experience significant declines in physical function and increases in pain intensity.

Results from this study show that after minimally invasive lung cancer surgery, mean postoperative patient-reported physical function and pain intensity T-scores were nearly 10 points worse than the population mean. In prior analysis of the PROMIS instruments, the minimal clinically significant difference for the physical function and pain intensity T-score measurements was 4-6. (27) It should be noted, that lower physical function scores reflect worse physical function, whereas higher pain intensity scores reflect worse pain. While there is considerable recovery at 6 months, mean scores still remain slightly worse than baseline, on average (Figure 1).

We have previously reported the initial results of a pilot study to measure PRO in thoracic surgery cancer patients and link this data with clinical data from the STS database, as a model for widespread incorporation of PRO measures into the STS database. (9) In that study, we showed that physical function scores were significantly worse at 30 days for patients treated with thoracotomy when compared with minimally-invasive techniques. In the current analysis we identified a low DLCO to be a significant predictor of greater decline in physical function and increases in pain intensity after surgery. Additionally, we found that lower preoperative physical function scores can be predictive of longer postoperative length of stay.

Prior research into health-related quality of life using PRO after lung cancer surgery has typically focused on describing patterns of change after surgery. (8) Several studies have shown considerable initial declines in physical function and dyspnea after surgery, with recovery to baseline within 3 months to 1 year. (4, 7, 9, 13, 15) Few of these studies, however, examined which patients are at risk for greatest declines in quality of life. In on analysis, Schulte, et al., found that older patients (age > 70), experience similar initial declines in physical function compared with younger patients, however take longer to

recover. (30) This is contrary to our findings, in which we found no correlation between age and PRO after surgery. Rather, we found that the only reliable predictor of greater decline in PRO after lung surgery was a DLCO < 50% of predicted. Previous studies have established that postoperative clinical outcomes are clearly associated with pulmonary function. In an analysis of over 850 patients, Ferguson, et al., identified that DLCO was an independent predictor of long-term survival. (31) Taken together, these results are of considerable importance when discussing surgical options in patients with marginal pulmonary function as they are at greater risk for decline after surgery.

Most importantly, this study represents the first to examine the utility of PRO measures to identify patients at risk for prolonged LOS after surgery for lung cancer. There are several inherent advantages to using a patient reported outcome measure over individual clinical measures. The first is that physical function scores potentially represent a useful composite measure of a patient's clinical status. More importantly, these measures come directly from the patient and are not subject to the inherent biases of a clinical provider. On the other hand, they may be influenced a patients perception of their medical and functional status, rather than reality. For that reason, it is important to choose a well validated, prospectively studied measure like PROMIS.

The association between length of stay and resource utilization has been previously studied. In several studies, including general inpatient and cardiac surgery, there were significant increases in hospital costs associated with increased duration of hospital stay. (20, 32-34) Previously published studies have shown that in thoracic surgical units, the most significant contributors to hospital cost after minimally invasive lung surgery were floor charges that relate directly to the duration of stay in the hospital. An addition of even a single complication increased the cost associated with a minimally invasive lobectomy by over $6,000. (32) Ultimately, these studies all underscore the importance of identifying patients who may be likely to have an increased length of stay.

In the current study, we have demonstrated that a patient's self-reported measure of physical function can be used to identify patients who are at high risk for increased resource utilization through

longer LOS. This quantifiable preoperative physical function score can be used to identify patients who are at risk for longer postoperative LOS. In a recent study from a large tertiary academic medical center, factors identified to predict length of stay were age > 75, COPD, Medicare payer status, and low hospital volume. (35) Similarly, another study with 366 patients who underwent a pulmonary lobectomy found that age, FEV1, DLCO, and surgeon involved in the case were predictive of LOS. (36) Several other publications have examined predictors of LOS with similar results. (37-39)

The primary challenge in identifying predictors of prolonged LOS after minimally invasive lung operations is the relatively short LOS and low incidence of complications. Not surprisingly, LOS was longer in patients who had a complication. Therefore, we stratified our analysis of the relationship between preoperative physical function and LOS by complication status. Among patients who did not have a complication, we did not identify a difference in LOS related to physical function score. However, in the subset of patients who did have a complication, the preoperative physical function was able to parse out the differences in the length of stay even when the differences in the length of stay between these groups were small. In this regard, the physical function domain of the PROMIS instrument therefore appears well suited for this task.

Interestingly, a 10-point decrease in physical function score was associated with an odds ratio of 1.57 for having a complication, though the confidence interval ranged from 0.97 to 2.52, thus not reaching statistical significance. It is possible, and likely, that this secondary analysis lacked sufficient sample size to fully evaluate the relationship between physical function score and risk for a complication. 38% of patients in this study had a complication. However the majority of these were in the category of "other pulmonary event" (19.5%), defined by the STS-GTSD as a pulmonary event not otherwise characterized as pneumonia, or respiratory failure. Further study on this topic, particularly with larger samples, will be needed to clarify the predictive ability of PRO for adverse outcomes/events.

However, at the very least, PRO scores can identify patients at risk for greater resource utilization when a complication occurs. Early preoperative identification of such patients may allow for better

counseling and mobilization of additional resources. Such resources could include early involvement of physical and occupational therapy, goal directed ambulation, additional nursing resources, intensive use of supportive measures that may include more aggressive respiratory care, or social work to identify specialized rehabilitation placement options that may be able to better care for this subset of patients upon discharge.

Such patients may also benefit from risk-reduction measures that are instituted at the time of the preoperative visit. This practice of prehabilitation has been used for patients undergoing major abdominal operations with significantly improved postoperative infection rates, and reduced in-hospital morbidity. (40) There has also been discussion of prehabilitation prior to major lung resections; however, these have had mixed results so far. (41, 42) The most significant challenge remains to identify the highest risk population of patients that would derive the most benefit from these measures. Patients with low physical function T-scores may be an ideal population to study such measures in.

Limitations

There are several limitations to this analysis that must be considered. Given that it is a secondary analysis of an observation cohort study, it may be subject to confounding by unknown variables. Additionally, 6 of the 123 patients did not complete the final time point survey at 6 months. This could potentially effect the long term follow up results. Lastly, given the sample size of 123 there were relatively few major complications in the study. As mentioned, the most common complication was an "other pulmonary event". This may bias the results. However, one would expect this to bias the results towards finding no correlation between T-score and post-operative outcomes, and may be why the relationship between T-score and complication status did not reach statistical significance. Despite this, we still found a significant correlation between physical function scores and length of stay in patients with a complication.

Additionally, as this was originally intended as a pilot study to show the feasibility of gathering and incorporating PRO into clinical practice, this study may be limited in its ability to identify subtle differences in PRO scores. As patient selection was at the discretion of the surgeon, marginal surgical patients may not be fully represented in this study. On the other hand, this study cohort is likely a more realistic, pragmatic example of patients undergoing lung cancer surgery. In other words, the more marginal patients are unlikely to be undergoing lobectomy and are more accurately represented in an observational study such as this.

Future Directions

There is considerable potential for the future use of PRO. Since completion of this study we have moved to routine collection of PRO in all thoracic surgical patients. This will allow for a more robust analysis of the utility of PRO data after surgery. Additionally, it will allow us to determine the true clinical value of PRO in routine surgical care, outside of the research setting. The Society of Thoracic Surgeons has implemented a task force to begin nationwide integration of PRO into their database, in large part due to the results of this analysis. Future studies within thoracic surgery will also focus on comparative research of esophagectomy approaches and robotic versus minimally invasive techniques, and how PRO are impacted by these differences in operative techniques.

Conclusions

In summary, pre-operative DLCO was associated with significant decreases in PRO following minimally-invasive lung cancer surgery. DLCO may be of utility in predicting patients who experience greater decline in QOL after surgery and for guiding surgical decision-making. Additionally, patient-reported physical function, measured by PROMIS, was associated with increased LOS in patients who had a complication. We conclude that routine administration and collection of PRO prior to and after surgery can aide surgeons in identifying patients at greater risk for postoperative decline and adverse events. Ongoing longitudinal collection of PRO data in lung cancer surgery patients will be necessary to continue to inform how patient and procedural risk factors impact optimal post-operative quality of life. Patients with lower preoperative PRO scores may benefit from additional preoperative counseling and various risk reduction strategies. Lastly, future thoracic surgery studies should strongly consider inclusion of PRO measures and endpoints to further understand the complex relationship between patient-reported and clinical measures.

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Figures

Figure 1: Patient reported outcomes measured using PROMIS from our initial pilot study of 123 patients, including pain intensity, pain interference, physical function, and ability to participate in social roles, in patients undergoing lung cancer surgery. From: Khullar, et al. 2017 (9)

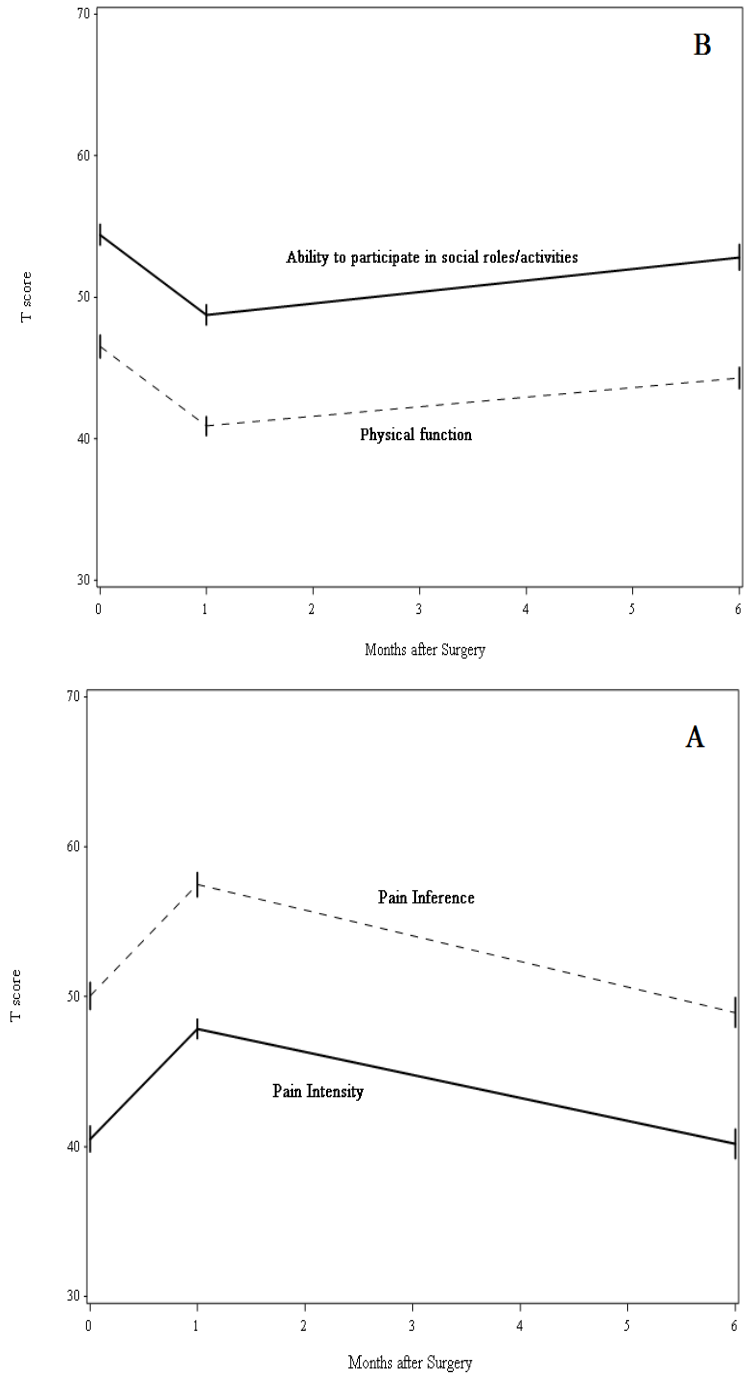


Figure 2: Patient reported physical function, from our initial pilot study of 123 patients, in patients treated with video-assisted thoracic surgery versus open thoracotomy. From: Khullar, et al. 2017 (9)

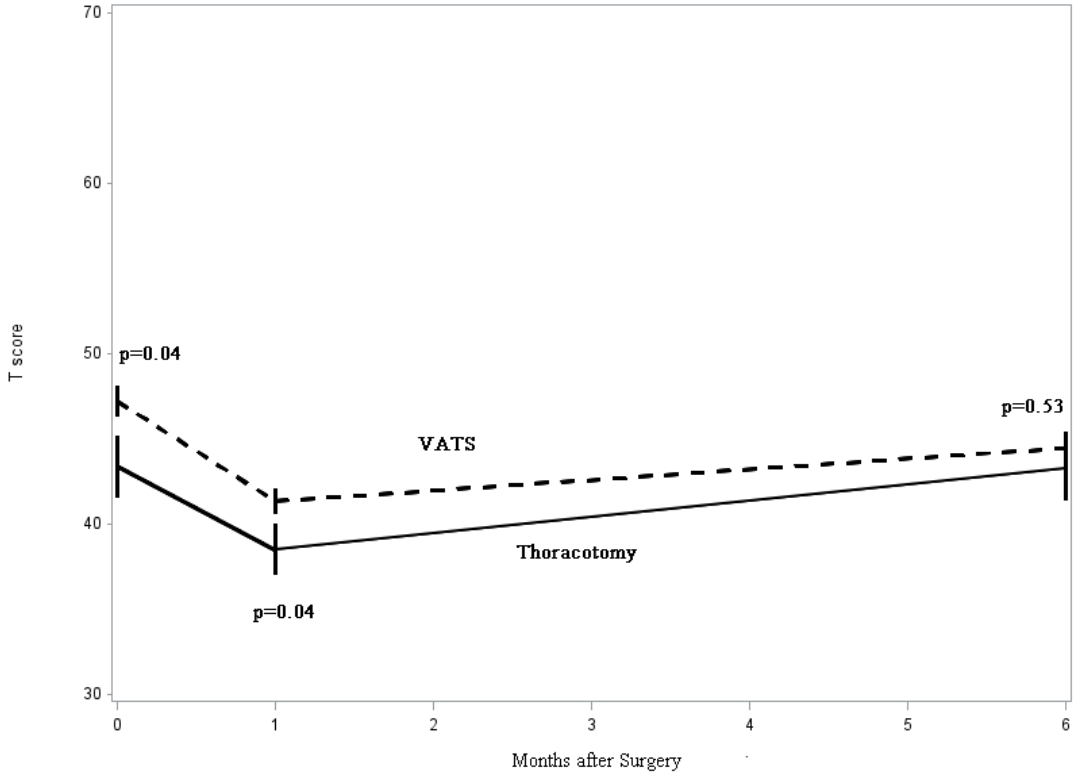


Figure 3: CONSORT Flow diagram detailing patient enrollment

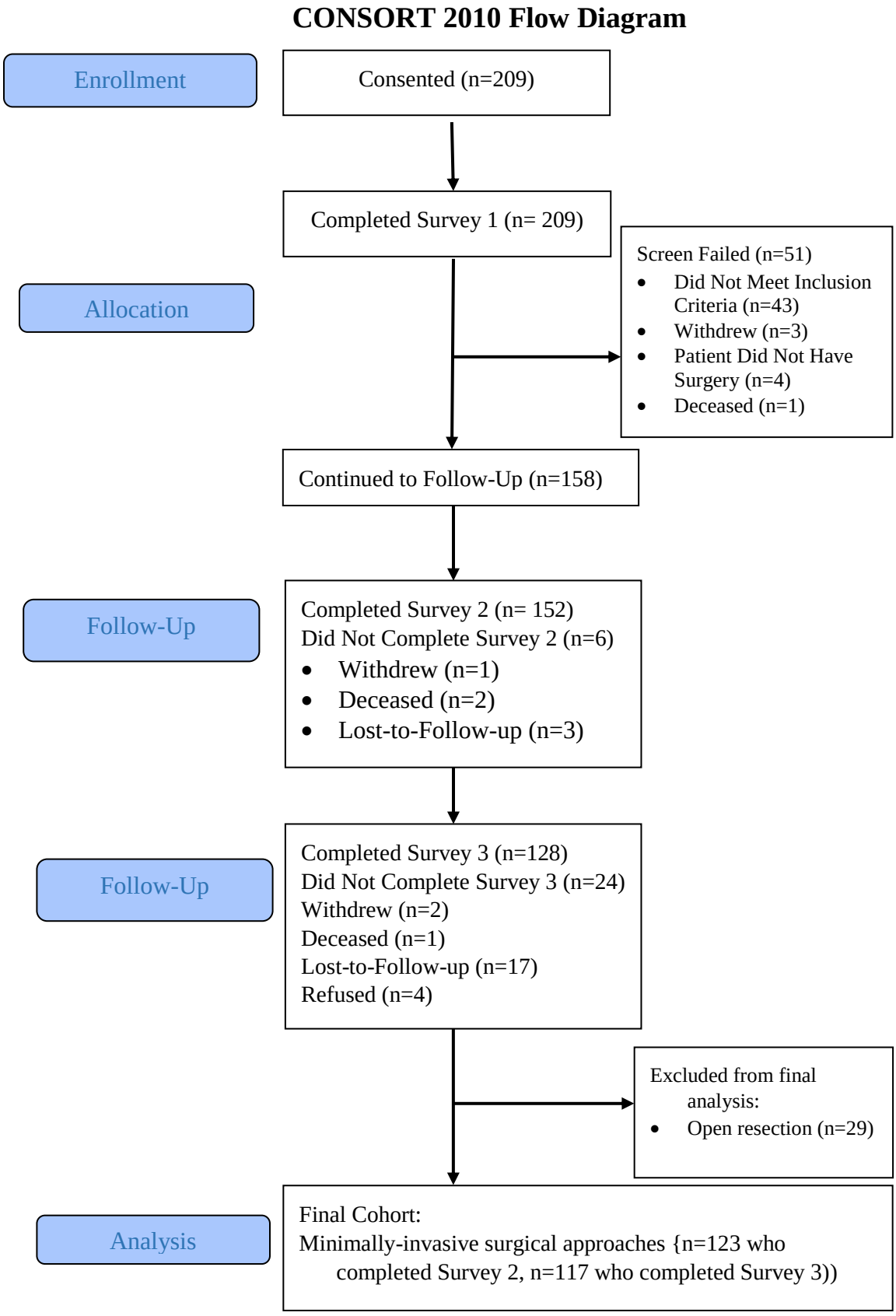


Figure 4: Patient-reported physical function and pain scores by DLCO above and below 50%, as measured by PROMIS. DLCO below 50% was associated with significantly worse physical function and pain intensity scores at the preoperative and 6 month postoperative visits.

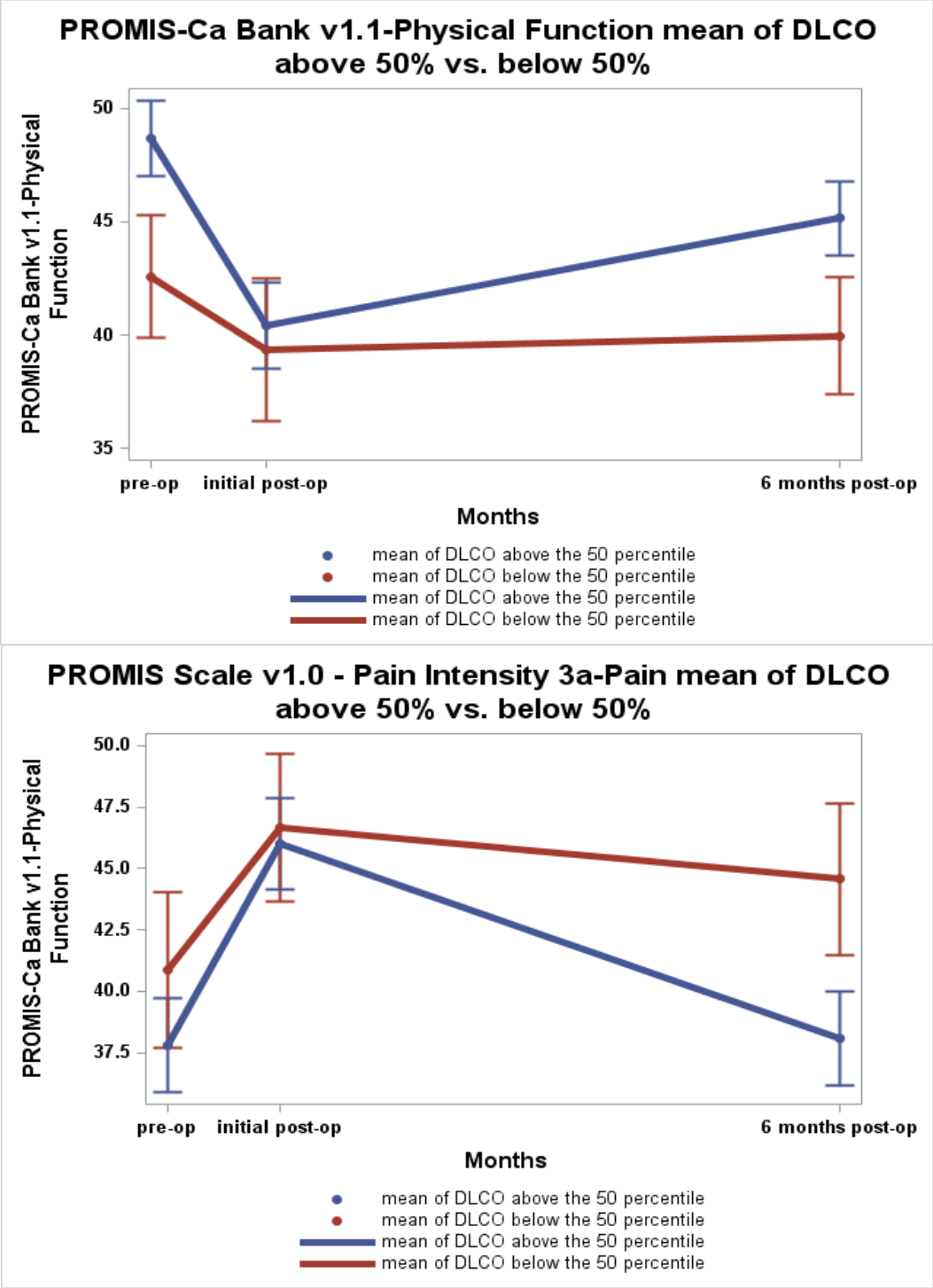
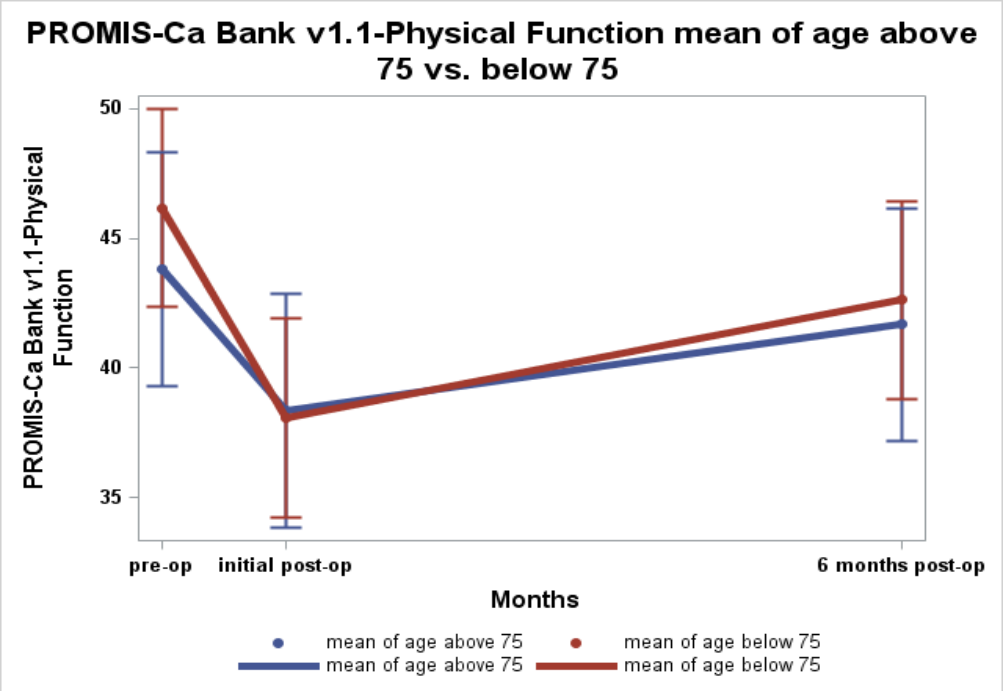


Figure 5: Patient-reported physical function and pain scores by age above and below 75, as measured by PROMIS. Age was not associated with differences in physical function or pain at any time point.



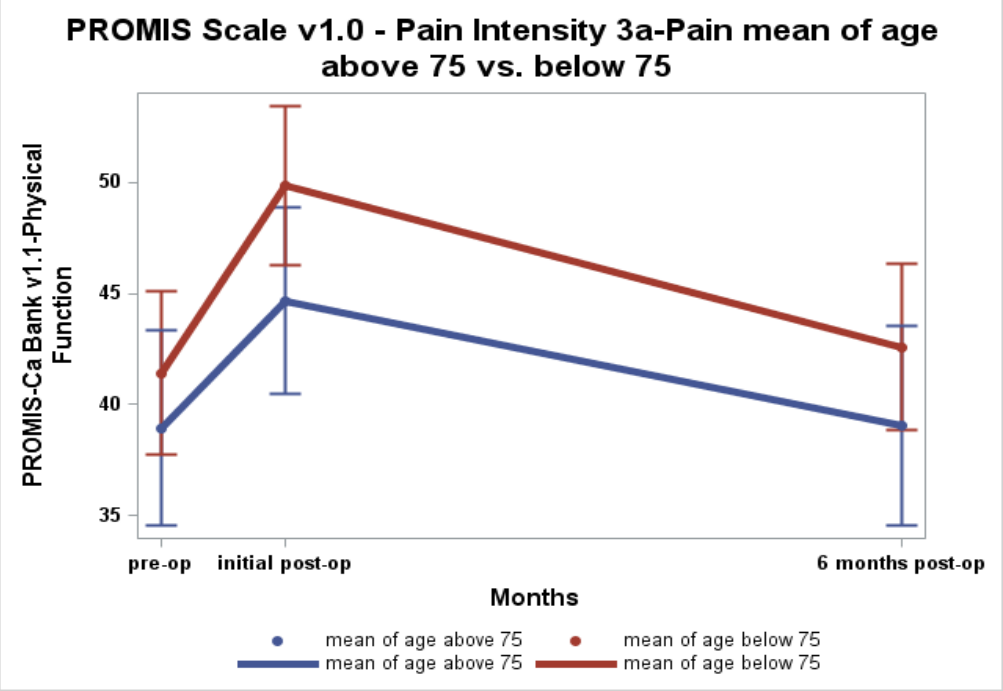
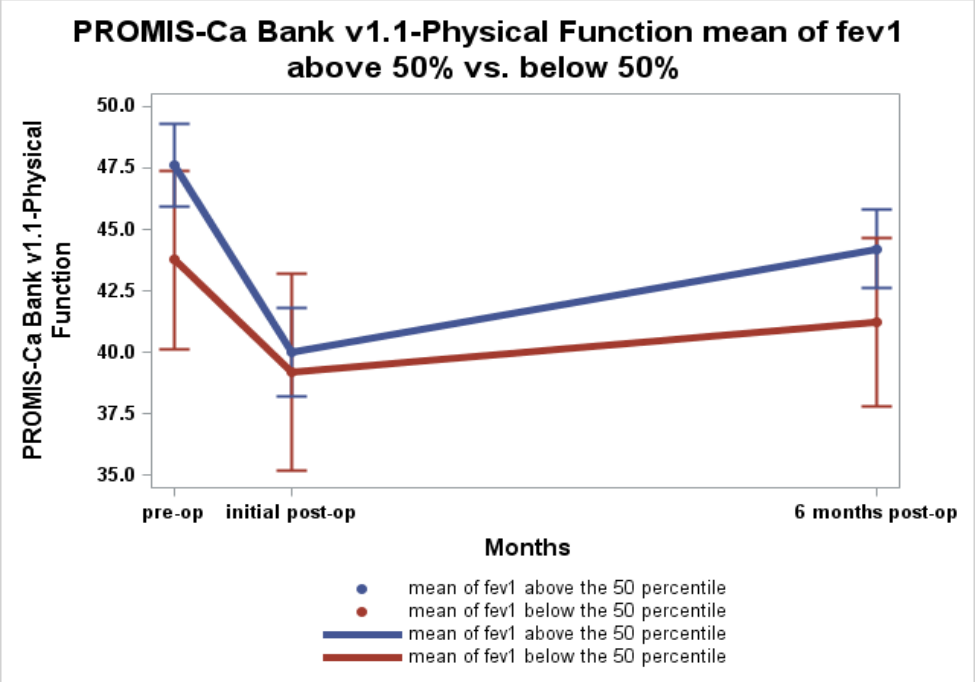


Figure 6: Patient-reported physical function and pain scores by FEV1 above and below 50%, as measured by PROMIS. FEV1 was not associated with differences in physical function or pain at any time point.



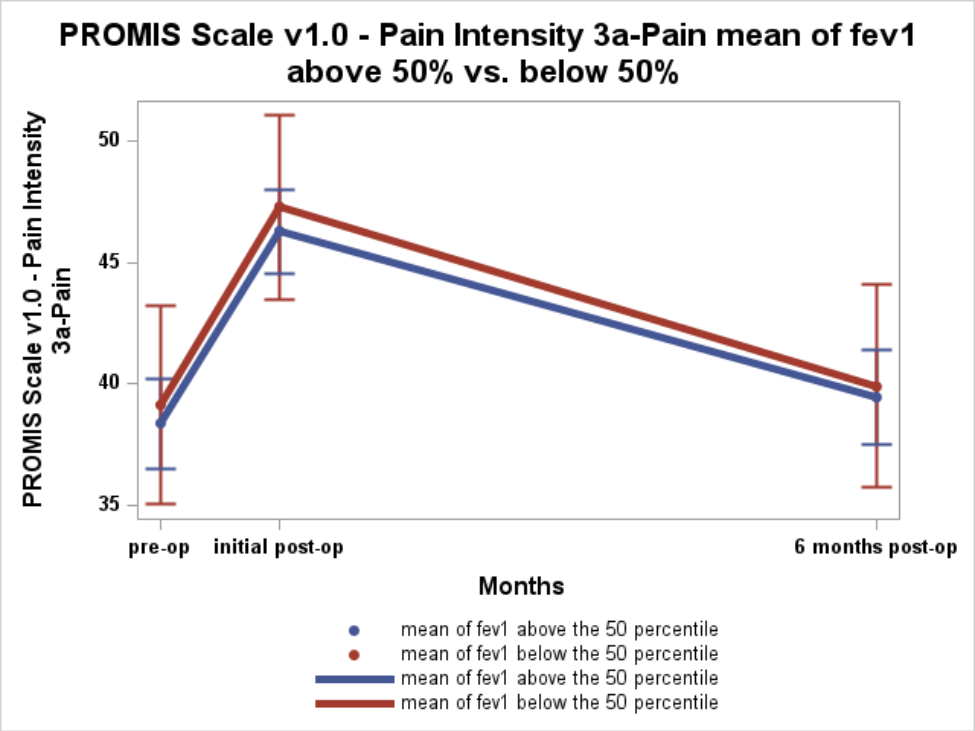


Figure 7: Patient-reported physical function and pain scores by Zubrod score of 0 or 1, as measured by PROMIS. Zubrod score is a measurement of physical activity used commonly in oncology clinical care and research. 0 means fully active with no limitations and 1 means restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. Zubrod score was not associated with differences in physical function or pain at any time point.

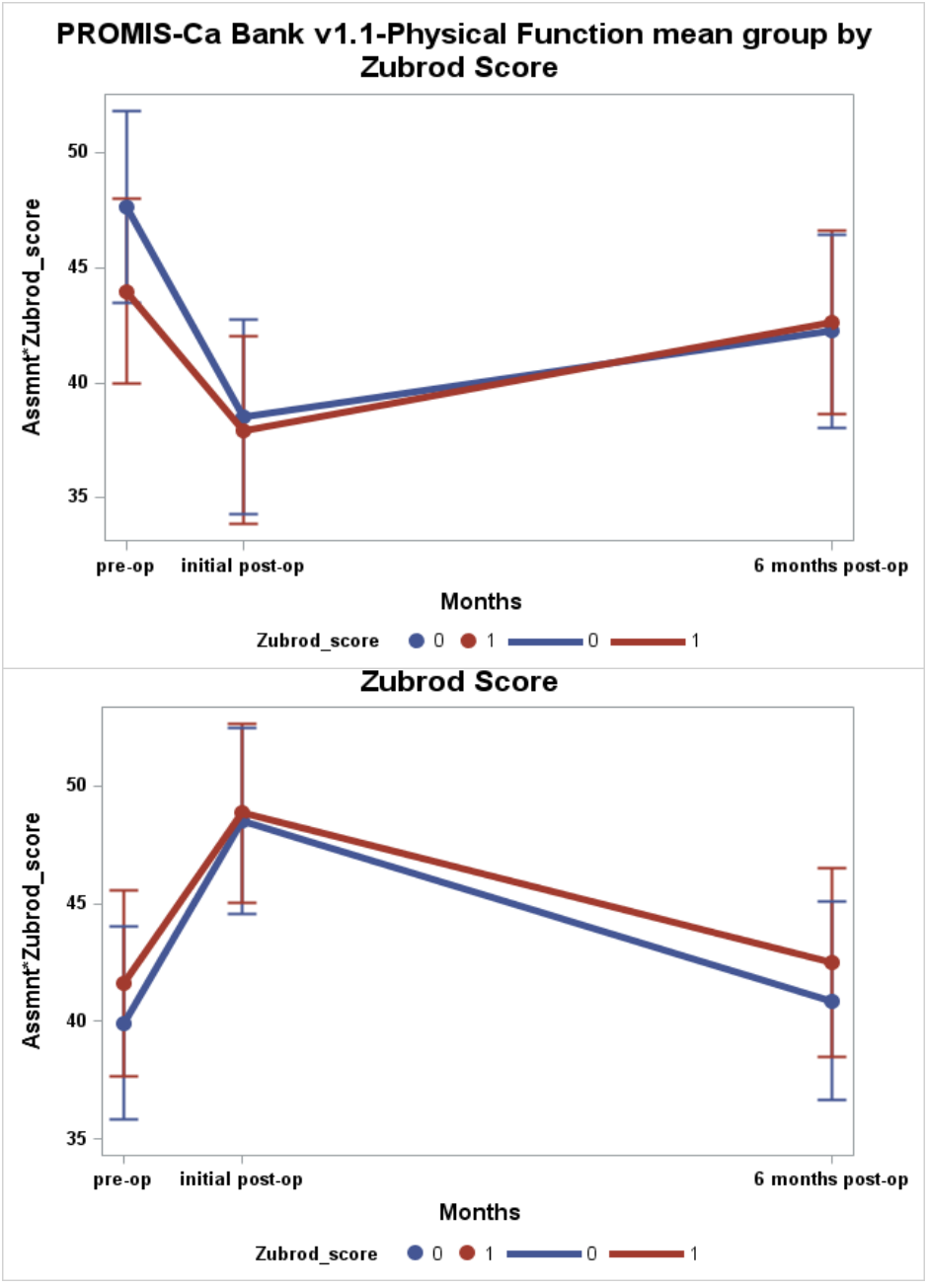


Figure 8: Scatter plot of correlation between diffusing capacity of the lungs for carbon monoxide (DLCO) with physical function T-scores as measured using PROMIS, 6 months after lung surgery, via mixed effects regression modeling (blue). For every 10% increase in DLCO, 6-month physical function T scores were 1.4 (SE=0.4) points higher.

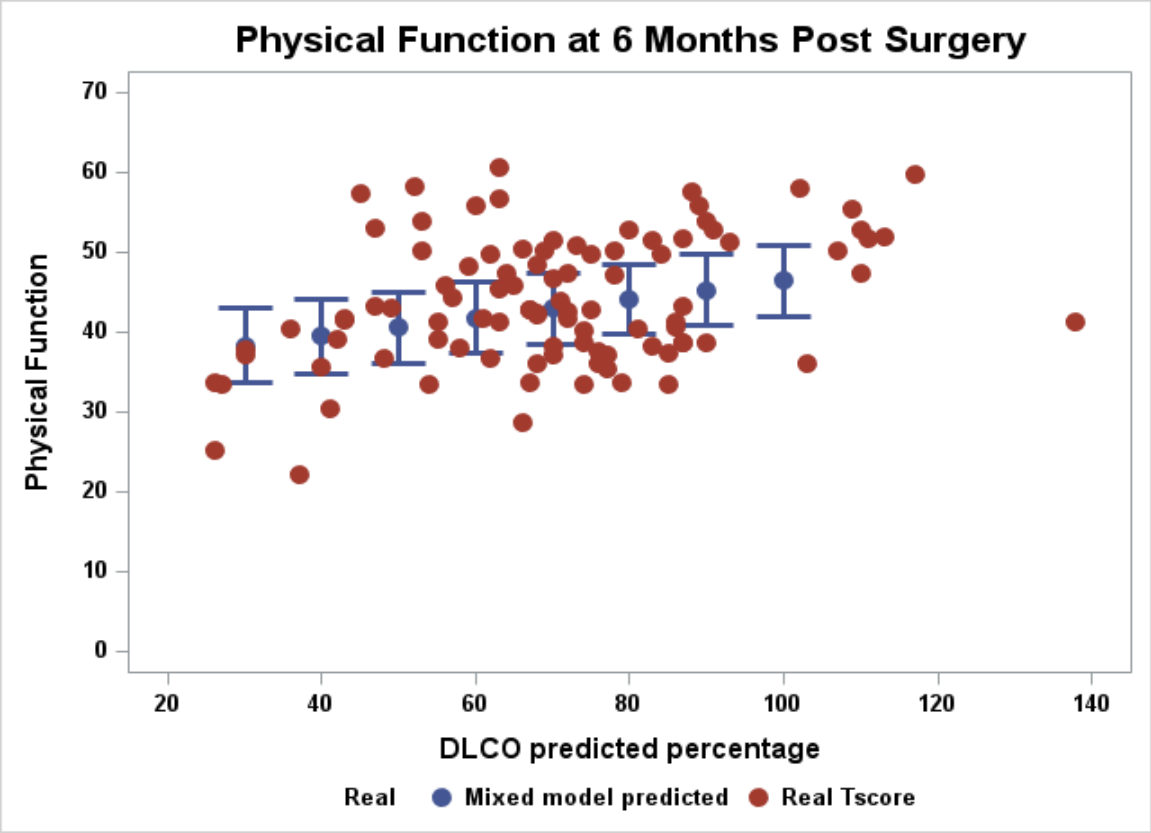


Figure 9: Scatter plot of correlation between diffusing capacity of the lungs for carbon monoxide (DLCO) with pain intensity T-scores as measured using PROMIS, 6 months after lung surgery, via mixed effects regression modeling (blue). For every 10% increase in DLCO, 6-month pain intensity T scores decreased by 1.5 (SE=0.4).

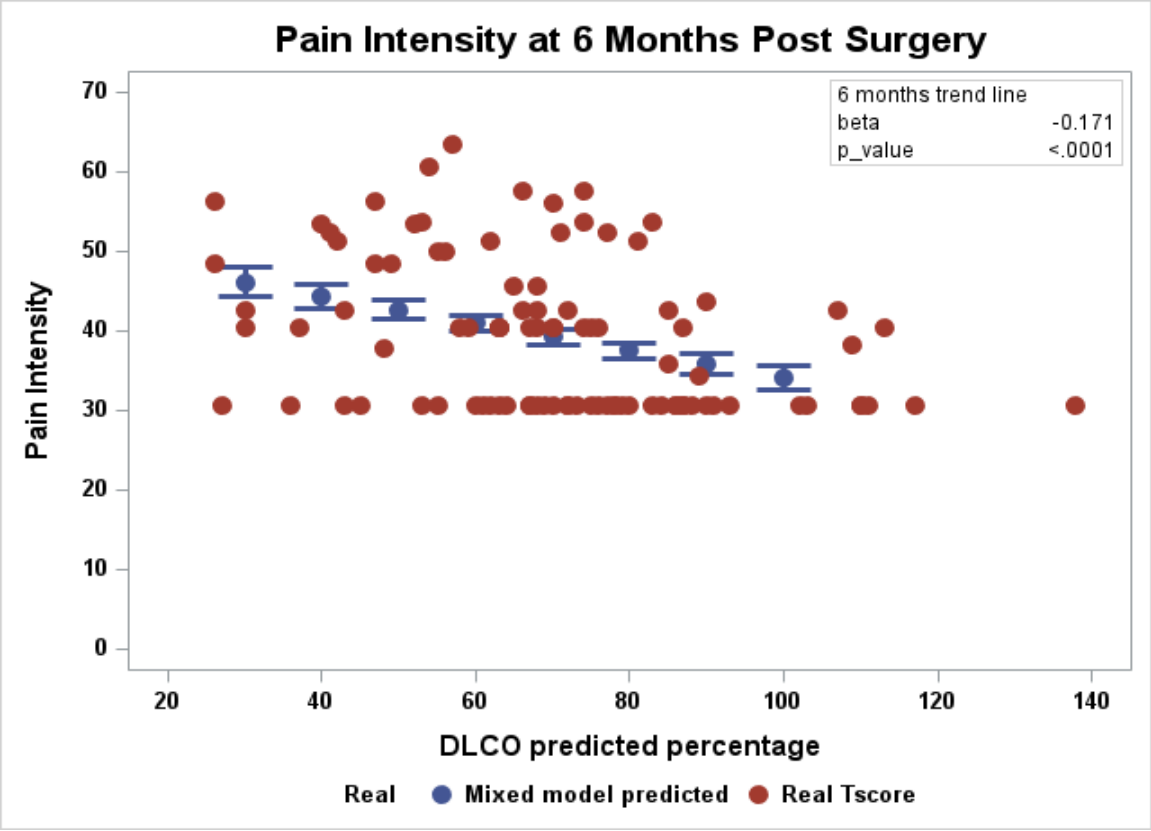
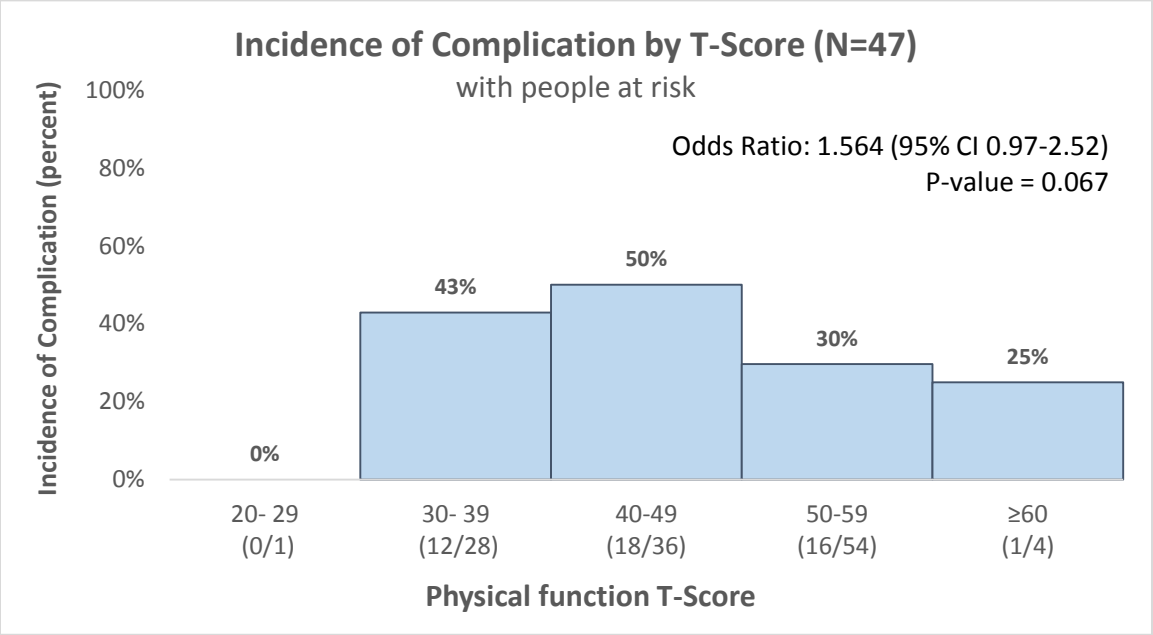
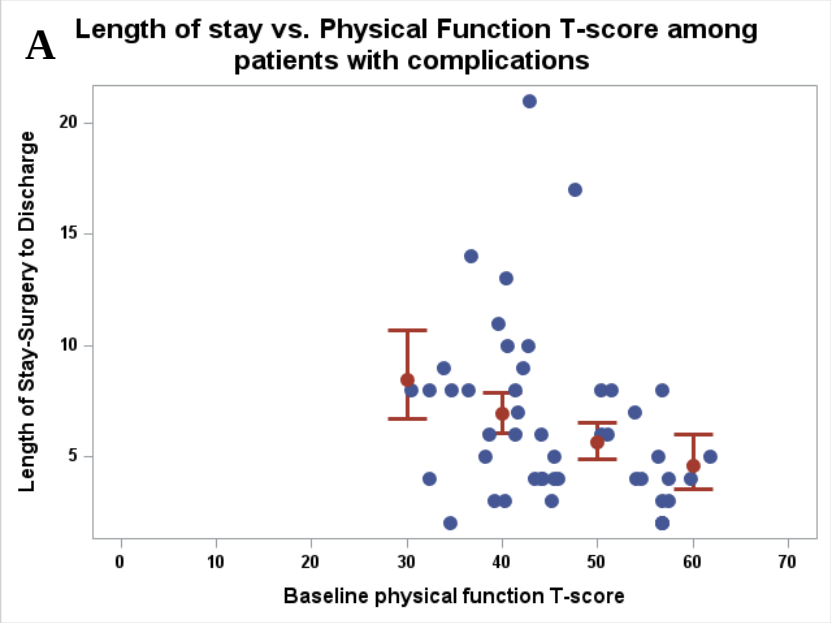


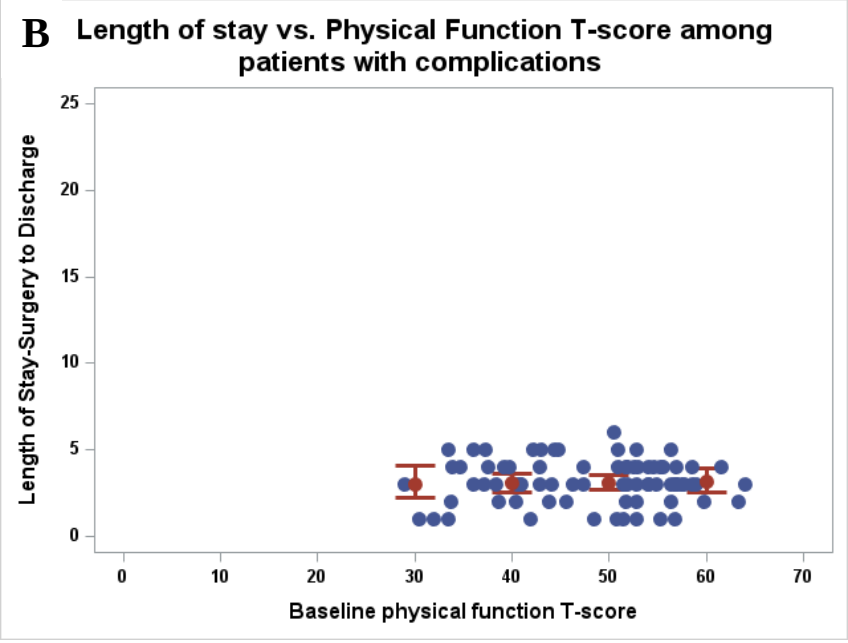
Figure 10: Frequency distribution table showing the incidence of complications (Y-axis) by decile of preoperative physical function T-score (X-axis). Odds of complication for each 10 point increase in T-score was 1.564, 95% CI 0.97-2.52.*



*Logistic regression analysis, adjusted for age, sex, race, and procedure type (lobectomy versus sublobar resection).

Figure 11: The correlation between preoperative physical function T-score (X-axis) and the length of stay (Y-axis). Panel A shows the correlation in patients with any complication, with significant decrease in the length of stay with increasing (improving) physical function T-score (p=0.002, see Table 9). In patients with no complication (1B) there was no correlation between length of stay and preoperative physical function T-score and the length of stay.





Tables

Table 1: Baseline Study Population Characteristics (n=123)

Baseline Characteristic	**Mean (SD) or N (%)**
Mean Age (SD)	67.1 (9.6)
Mean BMI (SD)	28.0 (6.1)
Male	43 (35.0%)
Race Caucasian	80(65.0%)
Smoking Status:	
Current smoker	18 (14.6%)
Former smoker*	77 (62.6%)
Never smoker	28 (22.8%)
Zubrod Score 0	60 (48.8%)
1	63 (51.2%)
Cerebrovascular History	
No CVD History	113 (91.9%)
Transient Ischemic Attack	4 (3.3%)
Cerebrovascular Accident	6 (4.9%)
COPD	51 (41.5%)
Coronary Artery Disease	19 (15.5%)
Diabetes	25 (20.3%)
Hypertension	85 (69.1%)
Mean FEV1 % predicted (SD)**	85.1% (21.6)
Mean DLCO % predicted (SD)**	70.8% (20.9)
Pathologic Stage	
IA	63 (51.22%)
IB	30 (24.39%)
IIA	12 (9.76%)
IIB	11 (8.94%)
IIIA	6 (4.88%)
IV	1 (0.81%)
Neoadjuvant Chemotherapy	2 (1.6%)
Neoadjuvant Radiation	5 (4.1%)
Surgery Performed	
VATS Wedge Resection	19 (15.5%)
VATS Lobectomy	88 (71.5%)
VATS Segmentectomy	16 (13.0%)

*: Stopped > 1 month prior to operation

**: FEV1 missing on 4 patients, DLCO missing on 8 patients, stage missing on 3 patients

CVD: cerebrovascular disease; COPD: chronic obstructive pulmonary disease; FEV1: Forced Expiratory Volume 1 Second; DLCO: Diffusion capacity of the lung for carbon monoxide

Table 2: The association of baseline characteristics with preoperative PROMIS physical function T-score

Baseline Characteristic	Mean Preoperative Physical Function T-score (SD)	Difference	p-value*
Age: < 75 (n=98)	47.9 (8.9)		
≥ 75 (n=25)	43.9 (7.2)	**-4**	**0.04**
Gender: Male	48.9 (8.6)		
Female	46.2 (8.7)	-2.7	0.10
Race: Non-Caucasian	45.9 (9.3)		
Caucasian	47.8 (8.4)	1.9	0.24
Smoking Status:			
Never smoker	49.3 (8.5)		
Former smoker	47.4 (8.7)	**-1.9**	
Current smoker	42.6 (7.9)	**-6.7**	**0.03**
Zubrod Score: 0	49.1 (8.3)		
1	45.2 (8.8)	**-3.9**	**0.01**
COPD: No	49.5 (8.1)		
Yes	43.8 (8.6)	**-5.7**	**< 0.001**
FEV1 % predicted:			
≥ 50% (n=113)	47.3 (8.7)		
< 50% (n=10)	45.6 (8.9)	-1.7	0.55
DLCO % predicted:			
≥ 50% (n=96)	48.4 (8.6)		
< 50% (n=27)	42.7 (7.7)	**-5.7**	**0.002**
Coronary Artery Disease:			
No	48.1 (8.4)		
Yes	41.9 (9.1)	**-6.2**	**0.004**
Cerebrovascular Disease History			
No CVD History	47.6 (8.7)		
Transient Ischemic Attack	42.0 (7.3)	-5.6	
Cerebrovascular Accident	40.8 (8.2)	-6.8	0.08
Diabetes: No	47.7 (8.7)		
Yes	44.7 (8.6)	3.0	0.13
Hypertension: No	47.6 (9.3)		
Yes	46.9 (8.5)	-0.7	0.67
Pathologic stage:			
IA	46.3 (8.1)		0.66
IB	47.3 (10.3)	1.0	
IIA	50.3 (9.2)	4.0	
IIB	47.6 (8.8)	1.3	
IIIA	46.6 (8.7)	0.3	
IV	37.2 (-)	-8.9	

*: Students T-test or one-way ANOVA

Table 3: Association of baseline characteristics with preoperative pain intensity PROMIS T-score

Baseline Characteristic	Mean Preop. Pain Intensity T-score (SD)	Difference in mean T-score	p-value*
Age: < 75 (n=97)	39.5 (10.0)		
: ≥ 75 (n=25)	36.4 (7.3)	-3.1	0.16
Gender: Female	39.9 (9.5)		
Male	36.8 (9.4)	-3.1	0.08
Race: Non-Caucasian	41.7 (9.8)		
Caucasian	37.3 (9.1)	**-4.4**	**0.01**
Smoking Status:			
Never smoker	38.7 (8.3)		
Former smoker	37.8 (9.2)	-0.9	
Current smoker	43.7 (11.8)	5	0.06
Zubrod Score: 0	37.9 (9.3)		
1	39.7 (9.8)	1.8	0.3
COPD: No	38.4 (9.7)		
Yes	39.5 (9.4)	1.1	0.5
FEV1 % predicted: ≥ 50% (n=112)	39.0 (9.7)		
< 50% (n=10)	36.5 (7.5)	-2.5	0.4
DLCO % predicted: ≥ 50% (n=95)	39.2 (10.0)		
< 50% (n=27)	37.5 (7.7)	-1.7	0.4
Coronary Artery Disease: No	39.1 (9.7)		
Yes	37.6 (8.6)	-1.5	0.5
Cerebrovascular history:			
No CVD history	38.5 (9.6)		
Transient Ischemic Attack (TIA)	44.8 (9.7)	6.3	
Cerebrovascular Accident (CVA)	41.2 (7.0)	2.7	0.4
Diabetes: No	38.4 (9.5)		
Yes	40.5 (9.9)	2.1	0.3
Hypertension: No	39.1 (10.3)		
Yes	38.7 (9.3)	-0.4	0.9
Pathologic stage: IA	39.6 (10.0)		0.1
IB	38.9 (9.6)	-0.7	
IIA	32.5 (4.2)	-7.1	
IIB	39.4 (9.5)	-0.2	
IIIA	39.7 (8.9)	0.1	
IV	53.7 (-)	14.1	

*: Students T-test or one-way ANOVA

Table 4: Longitudinal analysis of changes in patient-reported physical function after surgery compared with baseline patient characteristics and comorbidities.*

	Variables	Mean T-score at 1 Month	SE/CI	Mean T-score at 6 Month	SE/CI
Age	< 75 (n=98)	39.6	1.0	44.4	0.9
	>= 75 (n=25)	41.3	1.8	43.4	1.7
	Difference	-1.7	(-5.8, 2.4)	1.1	(-2.7, 4.8)
Smoke Status:	Never smoker	37.8	1.8	45.1	1.6
	Former smoker	40.6	1.0	44.4	1.0
	Current smoker	40.3	2.2	42.3	2.2
	Former vs Never	-2.8	(-6.9, 1.3)	0.7	(-3, 4.4)
	Current vs Never	-2.5	(-8.2, 3.2)	2.8	(-2.6, 8.3)
	Current vs Former	0.3	(-4.6, 5.2)	2.1	(-2.7, 6.9)
Zubrod Score:	0	40.5	1.2	44.2	1.2
	1	39.5	1.2	44.2	1.1
	Difference	1.0	(-2.3, 4.4)	0.1	(-3.1, 3.2)
COPD:	No	40.6	1.2	45.9	1.1
	Yes	39.7	1.3	42.4	1.2
	Difference	0.9	(-2.5, 4.3)	**3.5**	**(0.4, 6.7)**
Coronary Artery Disease:	No	40.3	1.0	44.8	0.9
	Yes	38.6	2.1	42.0	1.9
	Difference	1.8	(-2.9, 6.4)	2.7	(-1.5, 7.0)
FEV1 % predicted	>= 50% (n=113)	40.4	0.9	44.5	0.8
	< 50% (n=10)	33.9	3.9	38.1	3.2
	Difference	6.6	(-1.5, 14.6)	6.4	(-0.2, 13)
DLCO % predicted	>= 50% (n=96)	40.3	1.0	45.4	0.9
	< 50% (n=27)	39.8	2.2	38.7	1.8
	Difference	0.5	(-4.3, 5.3)	**6.7**	**(2.7, 10.7)**

Not significant: BMI, Gender, Race, Cerebrovascular history, Diabetes, Hypertension, Pathologic stage

* Mixed-effects regression models were utilized for comparing baseline variables with T-scores, in order to address correlation between T-score measurements. Covariates included age, gender, and race for all variables except % predicted FEV1 and DLCO, as theses variables are already adjusted for when calculating these measures. Procedure type was controlled for with all variables.

Table 5: Longitudinal analysis of changes in patient-reported pain intensity after surgery compared with baseline patient characteristics and comorbidities.*

	Variables	Mean T-score at 1 Month	SE/CI	Mean T-score at 6 Month	SE/CI
Age	< 75 (n=98)	47.9	0.9	40.0	1.1
	>= 75 (n=25)	40.1	1.6	36.9	1.9
	Difference	7.8	(4.3, 11.4)	3.1	(-1.3, 7.5)
Race	Non- Caucasian	48.2	1.3	42.3	1.5
	Caucasian	45.1	1.0	37.5	1.1
	Difference	3.1	(-0.1, 6.4)	**4.8**	**(1.2, 8.4)**
Smoke Status:	Never smoker	47.8	1.7	37.3	1.9
	Former smoker	44.7	1.0	38.9	1.1
	Current smoker	50.7	2.1	44.0	2.6
	Former vs Never	3.1	(-0.7, 6.9)	-1.6	(-5.9, 2.7)
	Current vs Never	-2.9	(-8.2, 2.5)	**-6.7**	**(-13, -0.5)**
	Current vs Former	**-6.0**	**(-10.5, -1.5)**	-5.1	(-10.7, 0.5)
Zubrod Score:	0	45.9	1.2	38.2	1.4
	1	46.4	1.1	40.2	1.3
	Difference	-0.5	(-3.7, 2.7)	-2.0	(-5.7, 1.6)
COPD:	No	46.7	1.1	38.0	1.2
	Yes	45.4	1.2	41.0	1.4
	Difference	1.3	(-2.0, 4.5)	-3.0	(-6.8, 0.7)
Coronary Artery Disease:	No	46.3	0.9	39.6	1.0
	Yes	46.1	2.0	38.0	2.3
	Difference	0.1	(-4.3, 4.6)	1.5	(-3.4, 6.5)
FEV1 % predicted	>= 50% (n=113)	46.3	0.9	39.7	1.0
	< 50% (n=10)	47.7	3.7	36.3	3.9
	Difference	-1.4	(-9.1, 6.3)	3.4	(-4.7, 11.4)
DLCO % predicted	>= 50% (n=96)	46.4	1.0	38.5	1.1
	< 50% (n=27)	45.4	2.1	43.6	2.2
	Difference	1.1	(-3.5, 5.6)	**-5.1**	**(-10.1, -0.3)**

Not significant: BMI, Gender, Cerebrovascular history, Diabetes, Hypertension, Pathologic stage

* Mixed-effects regression models were utilized for comparing baseline variables with T-scores, in order to address correlation between T-score measurements. Covariates included age, gender, and race for all variables except % predicted FEV1 and DLCO, as theses variables are already adjusted for when calculating these measures. Procedure type was controlled for with all variables.

Table 6: Incidence of complications

Complication	Incidence, n,%
Any Complication	47 (38.21%)
Other Pulmonary Event[1,2]	24 (19.51%)
Urinary Retention	12 (9.76%)
Other cardiovascular event[1, 3]	7 (5.69%)
Air Leak Greater Than Five Days	6 (4.88%)
Atrial arrhythmia needing treatment	5 (4.07%)
Chylothorax needing intervention	4 (3.25%)
Other events requiring OR with general anesthesia	3 (2.44%)
Delirium	2 (1.63%)
Post-operative PRBC tranfusion	2 (1.63%)
Bronchopleural Fistula	1 (0.81%)
Clostridium Difficile Infection	1 (0.81%)
Pneumonia	1 (0.81%)
Respiratory Failure	1 (0.81%)
Surgical Site Infections	0, (0%)

1. General Thoracic Surgery Database version 2.41 (https://www.sts.org/sites/default/files/GTSD_TrainingManual_V2.41_August2019.pdf)

2. Other pulmonary event: pulmonary event not otherwise characterized as pneumonia, or respiratory failure

3. Other cardiovascular event: Cardiovascular events other arrhythmia or myocardial infarction, that extend the length of stay or affected the patient's outcome. Example: Pericardial effusion, pericarditis, etc.

Table 7: Association of length of stay (LOS) and complication status

Complication	Predicted Mean LOS[1]	95% CI	Mean LOS Ratio	95% CI
No	3.09	(2.72, 3.53)	ref	
Yes	5.96	(5.24, 6.78)	**1.93**	**(1.60, 2.32)**

[1] Poisson regression analysis to account for the non-normal distribution of length of stay, adjusted for procedure type (lobectomy vs. sublobar resection), age, gender, and race

Table 8: Association of mean length of stay (days) and baseline preoperative PROMIS physical function T-Score, stratified by complication status

	With Complication			**Without Complication**		
T-score	Predicted Mean LOS (days)[1]	Mean LOS ratio	95% CI	Predicted mean LOS (days)[1]	Mean LOS ratio	95% CI
T = 30	8.47	**ref**		3.03	ref	
T = 40	6.91	**0.82**	(0.71, 0.94)	3.07	1.01	(0.87, 1.17)
T = 50	5.64	**0.67**	(0.50, 0.89)	3.11	1.03	(0.77, 1.38)
T = 60	4.61	**0.54**	(0.35, 0.84)	3.15	1.04	(0.67, 1.62)
P Value[2]		**0.002**			0.90	

[1] Poisson regression analysis to account for the non-normal distribution of length of stay, adjusted for procedure type (lobectomy vs. sublobar resection), age, gender, and race

[2] P-value here indicates the significance of the association between increasing physical function score and decreasing mean LOS for patients within each complication status