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Use the Lower Limit of Normal, Not 80% Predicted, in Judging Eligibility for Lung Resection

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Key Words

Lung function tests · Preoperative evaluation · Lung resection surgery · Lung cancer

Abstract

Background: Impaired lung function (LF) is a well-known risk factor for perioperative complications in patients qualified for lung resection surgery. The recent European guidelines recommend using values below 80% predicted as indicating abnormal LF rather than the lower limit of normal (LLN). ***Objectives:*** To assess how the choice of a cut-off point (80% predicted vs. LLN at –1.645 SD) affects the incidence of functional disorders and postoperative complications in lung cancer patients referred for lung resection. ***Methods:*** Preoperative spirometry and the transfer factor for carbon monoxide ($T_{L,CO}$) were retrospectively analysed in 851 consecutive lung cancer patients after resectional surgery. ***Results:*** Airway obstruction was diagnosed in 369 (43.4%), and a restrictive pattern in 41 patients (4.8%). The forced expiratory volume in 1 s (FEV_1) or $T_{L,CO}$ was below the LLN in 503 patients (59.1%), whereas the FEV_1 or $T_{L,CO}$ was <80% predicted in 620 patients (72.9%; χ^2 test: $p < 0.0001$). In all, 117 out of 851 patients had LF indices <80% predicted but not below the LLN. Odds ratios (ORs) for perioperative complications were higher in patients with impaired LF indices defined as below the LLN (1.59, $p = 0.0005$) with the exception of large resections (>5 segments). In patients with test results above the LLN and <80% predicted, the OR for perioperative complications was not different (1.14, $p = 0.5$) from that in patients with normal LF. ***Conclusions:*** LF impairments are common in candidates for lung resection. Using the LLN instead of 80% predicted diminishes the prevalence of respiratory impairment by 14% and allows for safe resectional surgery without additional function testing.

Introduction

Pulmonary function tests (PFTs) are indispensable in the preoperative assessment of eligibility for lung resection surgery. This is particularly important in lung cancer patients for whom surgery provides the best chance of radical cure. Preoperative assessment of pulmonary functional reserves is important, as impaired lung function (LF) increases the risk of perioperative complications and early death after surgery [1–4] or may lead to chronic res-

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piratory failure [5]. During recent years, several editorials and recommendations for preoperative functional assessment before radical treatment of lung cancer have been published [6–8], the most recent one being the joint recommendations of the European Respiratory Society and European Society of Thoracic Surgeons (ERS/ESTS) published in 2009 [9]. An important new point in the latter document was the introduction of the transfer factor for carbon monoxide ($T_{L,CO}$) as a mandatory preoperative test, regardless of spirometry test results.

According to the ERS/ESTS guidelines, a value <80% predicted for the forced expiratory volume in 1 s (FEV_1) and/or $T_{L,CO}$ implies impaired LF and necessitates additional investigations before proceeding to surgery. These criteria are at odds with numerous publications [10–13] showing that the use of 80% predicted as a lower limit of normal (LLN) leads to considerable bias in the diagnosis of disease. Indeed, the ATS (1991) [14], the ERS (1993) [15], and the ERS Task Force Global Lung Function Initiative (supported by 6 international respiratory societies; 2012) [16] recommend that the appropriate LLN be at the level of the 5th percentile, corresponding to a value 1.645 standard deviations (SD) below the predicted value.

So far, no studies have looked into the consequences of using an 80% predicted cut-off versus −1.645 SD as an eligibility criterion for resectional surgery without additional exercise or split LF testing. The aims of the present study were: (1) to assess differences in the prevalence of functional disorders when defining the LLN as either 80% predicted or −1.645 SD below the predicted value, and (2) to assess the clinical risk of using the latter lower limit in qualifying patients for surgery without additional tests.

Materials and Methods

We retrospectively analysed the medical records and PFT results of patients surgically treated at the Department of Thoracic Surgery, National Tuberculosis and Lung Disease Research Institute, Warsaw, Poland, between May 2010 and June 2014. Only patients who had undergone major lung resections (lobectomy, bilobectomy, or pneumonectomy) were analysed. Patients were divided into 3 subgroups depending on the extent of lung tissue removal: (a) small resection: 2–3 segments removed (middle lobe or right upper lobe resections); (b) medium resection: 4–5 segments removed (right lower lobe, left upper lobe, or left lower lobe resections, as well as right upper bilobectomy); (c) large resection: >5 segments removed (right lower bilobectomy, left or right pneumonectomy). Perioperative complications and mortality were those occurring within 30 days postoperatively – or later if a patient was still in hospital. The following complications divided in 3 groups were included: (1) surgical complications: prolonged air leak requiring >5 days of postoperative chest tube drainage, bleeding through the chest tubes requiring reoperation or transfusion of ≥3 red blood cell packs; (2) pulmonary complications: respiratory failure requiring mechanical ventilation for >48 h, atelectasis or retention of secretions in the airways requiring bronchoscopy, pneumonia, or death from pulmonary causes; (3) cardiovascular complications: myocardial infarction, symptomatic cardiac arrhythmia requiring medical treatment, cardiac failure, pulmonary embolism, or cardiac death.

In our hospital, PFTs are performed on all patients prior to elective resectional surgery as a standard procedure. Patients with normal LF (FEV_1 and $T_{L,CO}$ ≥LLN) proceed to surgery without further functional testing. In patients with an FEV_1 or $T_{L,CO}$ below the LLN, additional tests (6-min walk test, stair climbing test, and eventually cardiopulmonary exercise test) are performed. The PFTs included spirometry as well as $T_{L,CO}$ measurements using the single-breath method. The tests were performed using a Master-Screen system (software version 4.65; Jaeger, Würzburg, Germany). The ATS/ERS 2005 guidelines [17–19] were followed for all LF measurements. We used reference values from GLI-2012 for spirometry and from the European Coal and Steel Community (ECSC)/ERS 1993 guidelines for lung volumes and $T_{L,CO}$ [15, 16, 20], setting the LLN at the level of −1.645 SD and grading the severity of ventilatory impairment and $T_{L,CO}$ reduction according to the ATS/ERS 2005 guidelines [21].

Descriptive data are expressed as means ± SD. The χ^2 test was used to test for differences in the prevalence of PFT results below the LLN between subgroups. Using the multiple logistic regression technique, odds ratios (ORs) were estimated to evaluate risk factors associated with perioperative complications. The risk factors considered were age, sex, the number of lung segments resected, the level of FEV_1 and $T_{L,CO}$, and the Revised Cardiac Risk Index (RCRI). Statistical analyses were performed using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium). Our study was a retrospective analysis of routinely (not experimentally) obtained, anonymised data, and was accepted by the local ethics committee.

Results

The investigated group comprised 851 patients of whom 326 (38.3%) were female. The mean age was 64.5 ± 9.4 years. The majority of patients (90%) were current or ex-smokers. Cumulated tobacco consumption in the smokers was 37.4 ± 20.5 pack-years (median: 35.0; 95% CI: 30.0–40.0).

Interventions comprised 718 (84.4%) lobectomies, 53 (6.2%) bilobectomies, and 80 (9.4%) pneumonectomies. In 459 patients (53.9%), the spirometry results were within the normal range. The functional abnormalities found among our patients are presented in table 1. The most frequent abnormality in spirometry was airway obstruction [FEV_1/FVC (forced vital capacity) <LLN], occurring in 368 patients (43.2%) with a mean z-score of FEV_1 −1.9 ± 1.0 (69.3 ± 15.5% predicted). A restrictive pattern in spirometry (FEV_1/FVC ≥LLN and FVC <LLN) was found

in 41 patients (4.8%) with mean z-scores of FVC –2.46 ± 0.81 (64.8 ± 8.8% predicted) and FEV_1 –2.50 ± 0.66 (62.1 ± 8.2% predicted).

Table 1 presents the prevalence of ventilatory impairment in 851 patients qualified for lung resection surgery. Of 394 patients with an FEV_1 <80% predicted, the measured value was above the LLN and hence within the normal range in 93 patients (10.9% of the study group). There was not a single case in which the FEV_1 was ≥80% predicted but below the LLN. Technically acceptable $T_{L,CO}$ tests were obtained in 844 patients. Of the 541 patients in whom the $T_{L,CO}$ was <80% predicted, the measured value was above the LLN in 129 cases (15.1%) and hence within the normal range. There was no case in which a $T_{L,CO}$ ≥80% predicted was below the LLN.

$T_{L,CO}$ measurements supplemented spirometry and increased the number of patients with LF impairment, since in 205 cases (24.0%) with an FEV_1 within the normal range, the $T_{L,CO}$ was below the LLN. Conversely, 91 patients (10.6%) with a $T_{L,CO}$ within normal limits had a reduced FEV_1 below the LLN. These differences were statistically significant (χ^2 test: $p < 0.0001$). Figure 1 presents the number of patients with functional disorders depending on the criterion used.

When combining the results of spirometry and gas transfer, the FEV_1 or $T_{L,CO}$ was below the LLN in 506 patients (59.1%), whereas the FEV_1 or $T_{L,CO}$ was <80% predicted in 620 patients (72.9%; χ^2 test: $p < 0.0001$). Hence, 117 patients with LF indices within normal limits were classified as functionally impaired when using 80% predicted as the cut-off level. The OR for having perioperative complications was higher in patients with abnormal LF than in patients with normal LF using either of the cut-offs, i.e. 1.82 (95% CI: 1.34–2.47; p = 0.0001) and 1.78 (95% CI: 1.25–2.52; p = 0.0012) using the LLN and 80% predicted, respectively.

In order to assess the safety of using the LLN instead of 80% predicted, we divided the patients into 3 groups: (1) 'normal LF' (comprising patients with FEV_1 and $T_{L,CO}$ ≥LLN and ≥80% predicted), (2) 'discordant' observations (with FEV_1 and $T_{L,CO}$ ≥LLN but FEV_1 or $T_{L,CO}$ <80% predicted), and (3) 'impaired LF' (with FEV_1 or $T_{L,CO}$ <LLN and <80% predicted). There were 228 patients with normal LF, 506 patients with LF impairment (measurements <LLN), and 117 patients in the 'discordant' group. None of the patients with an FEV_1 and $T_{L,CO}$ above or equal to the LLN with discordant LF (≥LLN and <80% predicted) were rejected for surgery.

Table 2 presents the characteristics of these groups and the numbers of patients with complications in each group.

Table 1. Functional characteristics of the patients

Type of impairment	Number of cases (%)
Ventilatory dysfunction	
FEV_1 <LLN	301/851 (35.7)
FEV_1 <80% predicted	394/851 (46.3)
Airway obstruction	368/851 (43.4)
Mild	174/368 (47.3)
Moderate	89/368 (24.2)
Moderately severe	66/368 (17.9)
Severe and very severe	39/368 (10.6)
FEV_1/FVC ≥LLN and FVC <LLN	41/851 (4.8)
Gas exchange disturbances	
$T_{L,CO}$ <LLN	412/844 (48.8)
Mild (60% predicted to LLN)	228/412 (55.3)
Moderate (40–60% predicted)	174/412 (42.2)
Severe (<40% predicted)	10/412 (2.4)
$T_{L,CO}$ <80% predicted	541/844 (64.1)

Airway obstruction: FEV_1/FVC <LLN; mild: FEV_1 >70% predicted; moderate: FEV_1 60–70% predicted; moderately severe: FEV_1 50–60% predicted; severe and very severe: FEV_1 <50% predicted.

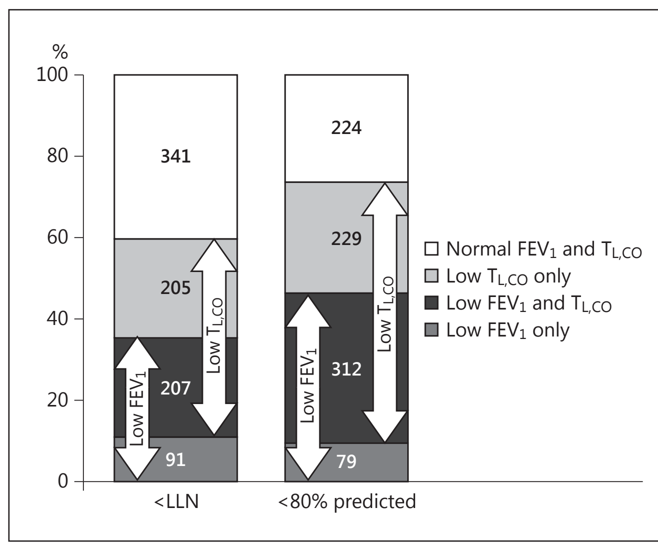

Fig. 1. Numbers of patients with detected abnormalities according to the criterion used (n = 844; both FEV_1 and $T_{L,CO}$ measured).

As expected, the highest number (and percentage) of complications and deaths occurred in patients with impaired LF (187/506; 37%); the OR compared to normal LF was 1.94 (95% CI: 1.36–2.76; p = 0.0003). In the 'discordant' group, we observed complications in 31 patients (26.5%); the OR for perioperative complications was not

Table 2. Characteristics of the patients with normal, impaired, and 'discordant' LF

	Normal LF (n = 228)	'Discordant' LF (n = 117)	Impaired LF (n = 506)
Age, years	64.4±9.07	67.9±8.58*	63.5±9.56*
Sex (F/M), n	85/143	39/78	202/304
FEV_1			
z-score	−0.04±0.80	−0.58±0.92*	−1.72±1.11*
% predicted	99.2±12.2	90.2±14.7*	72.9±17.7*
$T_{L,CO}$			
z-score	−0.40±0.70	−1.23±0.42*	−2.23±0.83*
% predicted	93.7±11.2	79.1±7.1*	64.4±13.0*
FVC			
z-score	0.53±0.80	0.05±0.93*	−0.58±1.09*
% predicted	108.34±12.41	100.92±14.67*	91.50±16.09*
FEV_1/FVC			
Abs.	0.71±0.07	0.69±0.08*	0.62±0.11*
z-score	−0.85±0.82	−1.00±1.00	−1.93±1.19*
Patients with complications, n (%)	53 (23.2)	31 (26.5)	187 (37.0)*
Postoperative deaths, n (%)	1 (0.4)	0 (0)	9 (1.8)

Abs. = Absolute value; z-score = difference between predicted and measured, expressed as the number of SDs. * Significantly different (p < 0.0001) compared with the group with normal LF.

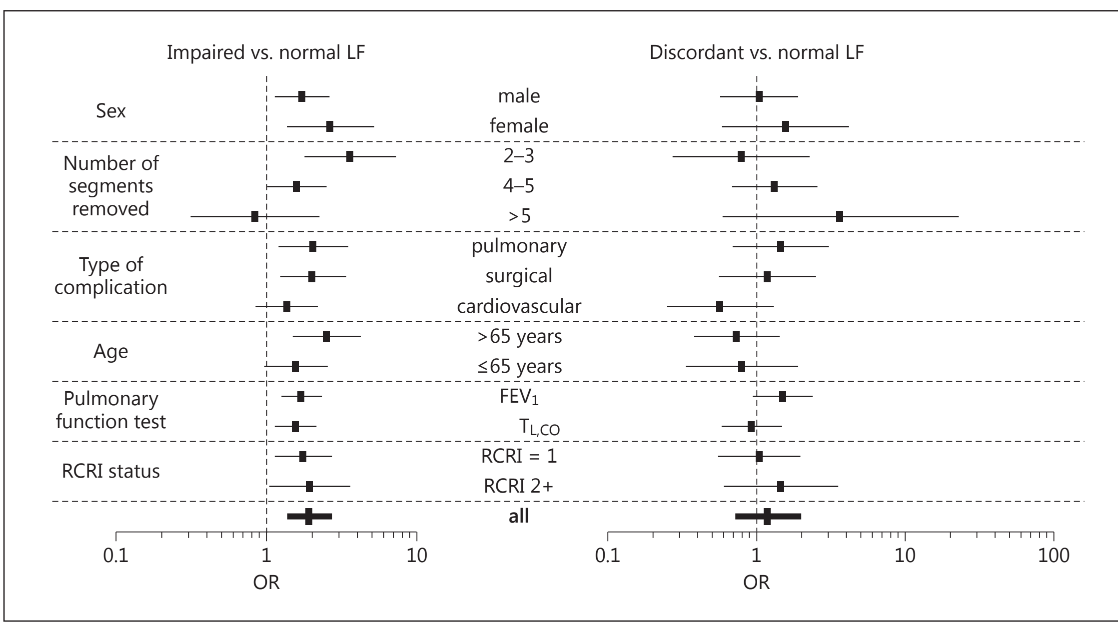

Fig. 2. ORs with 95% CI for having complications after lung cancer surgery.

significantly higher than in the group with normal LF (OR = 1.19; 95% CI: 0.71–1.99; p = 0.5057).

As the rate of complications may be dependent on several factors (e.g. the number of segments removed, age, sex, or RCRI status), we additionally performed some kind of a sensitivity analysis including these factors, and also the type of complication and PFT (fig. 2; table 3).

We observed increased ORs for postoperative complications regardless of age, sex, a small and medium range of resection, pulmonary and surgical complications,

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Table 3. Sensitivity analysis with ORs for having complications after lung cancer surgery depending on sex, age, the number of segments removed, the type of complication, and the PFT used

	Patients[a], n	Abnormal vs. normal			Discordant vs. normal		
		OR	95% CI	p value	OR	95% CI	p value
All patients	851	1.94	1.36–2.76	*0.0003*	1.19	0.71–1.9877	0.5057
Sex							
Male	525	1.74	1.13–2.67	*0.0115*	1.04	0.57–1.91	0.8983
Female	326	2.69	1.37–5.32	*0.0043*	1.57	0.58–4.22	0.3711
Number of segments removed							
2–3	261	3.63	1.80–7.32	*0.0003*	0.79	0.27–2.30	0.6673
4–5	481	1.6	1.00–2.56	*0.0494*	1.32	0.68–2.57	0.4065
>5	109	0.84	0.31–2.25	0.7294	3.67	0.59–12.78	0.1633
Type of complication							
Pulmonary	107	2.06	1.20–3.54	*0.0086*	1.46	0.69–3.09	0.3248
Surgical	115	2.04	1.22–3.42	*0.0067*	1.19	0.56–2.52	0.653
Cardiovascular	110	1.37	0.85–2.21	0.1913	0.57	0.25–1.30	0.1825
Age							
>65 years	387	2.53	1.50–4.26	*0.0005*	1.35	0.70–2.64	0.3729
65 years	464	1.57	0.96–2.57	0.0725	0.80	0.33–1.92	0.6186
PFT							
FEV_1 only	851	1.72	1.26–2.35	*0.0006*	1.51	0.94–2.42	0.0873
$T_{L,CO}$ only	844	1.58	1.14–2.18	*0.0058*	0.93	0.58–1.48	0.7499
RCRI							
1	560	1.77	1.14–2.74	*0.0109*	1.04	0.55–1.97	0.9065
2	291	1.95	1.04–3.67	*0.0371*	1.46	0.60–3.55	0.4034

Italics denote significance. [a] Number of 'exposed' patients in subgroups.

Table 4. ORs for having complications after lung cancer surgery depending on sex, age, the number of segments removed, and the PFT used (multiple regression analysis)

Variable	OR	95% CI	p value
Age ≥65 years (<65 years as reference)	1.89	1.38–2.59	*0.0001*
'Discordant' LF (normal LF as reference)	1.05	0.62–1.78	0.8484
Impaired LF (normal LF as reference)	1.86	1.28–2.69	*0.0010*
4–5 segments removed (<4 segments as reference)	0.93	0.66–1.30	0.6645
>5 segments removed (<4 segments as reference)	1.96	1.20–3.20	*0.0068*
Male sex (female sex as reference)	1.58	1.15–2.18	*0.0048*
RCRI >1 (RCRI = 1 as reference)	1.46	1.06–2.00	*0.0197*

Italics denote significance.

RCRI status, and the type of PFT in patients with abnormal LF in reference to normal LF. There were no significantly increased ORs in patients with 'discordant' LF in relation to normal LF according to any of the factors analysed. Multiple logistic regression revealed that independent factors significantly associated with an increased risk of perioperative complications were: age >65 years, RCRI >1, large-scale surgery, male sex, and impaired LF, but not 'discordant' LF (≥LLN and <80% predicted). See table 4 for ORs.

Discussion

There were two main goals of our study conducted in one of the largest groups of patients referred for lung resection: (1) mapping the prevalence of abnormal LF test results and (2) assessing whether the traditionally used cut-off point for normality at 80% of the predicted value can be replaced by the LLN at 1.645 SD below the predicted value without increasing the perioperative risk to patients referred for resectional surgery, i.e. without additional pre-

operative testing. Our results confirm that LF impairment is often present in lung resection candidates. The most common abnormality was reduced gas exchange, occurring in 48.4% of the patients, followed by airway obstruction in 43.2% of the patients. It is worth noting that when applying the criterion recommended in the GOLD guidelines [22] for COPD detection, 62.9% would be diagnosed with airflow limitation. A restrictive pattern in spirometry was found in only 4.8% of the patients.

The cumulative prevalence of LF impairment differed considerably by the definition used; it was 73.7% if abnormality was defined as a test result <80% predicted, and 59.9% when using the LLN as the criterion for abnormality. Hence, the ERS/ESTS [9] recommendation leads to a 14% overdiagnosis of ventilatory impairment. It is well known that the use of percent predicted leads to significant age-, height-, sex-, and ethnic group-related biases, and hence to misclassification of patients [10–16, 23]. In fact, Sobol and Sobol [11] wrote in 1979: 'It implies that all functions in pulmonary physiology have a variance around the predicted, which is a fixed per cent of predicted. Nowhere else in medicine is such a naive view taken of the limit of normal.' Such misclassification is circumvented by using the LLN, commonly defined as the 5th percentile in a representative population of healthy nonsmokers [12–16], the procedure recommended by the ATS and ERS [16, 21].

In assessing eligibility for resectional surgery, 80% predicted was introduced not so much as the LLN but as a cut-off to ensure that sufficient lung parenchyma would remain after resection. However, comparison of the group of patients with the FEV_1 and $T_{L,CO}$ above or equal to the LLN but <80% predicted with the group of patients with normal LF (≥LLN and ≥80% predicted) revealed a similar incidence of perioperative complications. Therefore, we showed that the LLN can be used instead of 80% predicted without putting patients at an increased risk.

A higher incidence of complications was found when comparing the patients with impaired LF with those with normal LF, with the exception of large resections (pneumonectomy or right lower bilobectomy). It is not surprising that large resections are associated with perioperative complications in patients with normal LF as well as in those with impaired LF. It is well known that the larger the lung resection, the more common perioperative complications [24]. We think that the range of resection was a stronger risk factor than LF in large resections. This is why we did not find a difference in OR between the abnormal and normal LF groups, where perioperative complications occurred with similar frequency. On the other hand, in patients undergoing small resections, functional status played a more important role, and the OR for perioperative complications was higher in patients with abnormal LF.

We also showed that not every type of perioperative complication was associated with LF. Impaired pulmonary function increases the risk of surgical but not of cardiovascular complications. Airway obstruction, a common functional abnormality found in our patients, is associated with damage to alveoli and small airways, which may promote e.g. air leak, bleeding, atelectasis, or retention of airway secretions. Cardiac complications appeared to be independent of LF, and are generally difficult to predict [25]. Comorbid status expressed as an RCRI ≥2 also did not affect results.

The chosen cut-off point directly impacts the number of additional tests required to qualify a patient for surgery, since according to the ERS/ESTS guidelines all patients with abnormal FEV_1 and/or $T_{L,CO}$ require further examinations, such as exercise tests. Adopting the LLN does not put patients at risk and decreases the number of patients referred for additional testing by 14%, reducing the cost and duration of hospitalisation. Nowadays, it should not be a problem to use the LLN, because all modern devices for PFTs show either the number of SDs, percentiles, or directly the lower limit of the predicted value.

Limitations of the Study

A possible limitation of this study may be its retrospective nature. The proportion of cases with impaired LF reflects the current patient population in our surgery department, which may differ from populations in other centres. However, the age distribution and rates of LF impairment among our patients are similar to those reported by other authors. The results might differ when adopting another set of predicted values. We used the recent GLI-2012 predicted values, which have been endorsed by 6 large international respiratory societies and therefore represent a worldwide standard. The number of patients in some of our subgroups (e.g. >5 segments removed) was relatively small, and the results should be interpreted with caution.

Conclusion

The use of 80% predicted leads to an overdiagnosis of ventilatory impairment. Using the clinically valid 5th percentile as the LLN, 14% more patients will qualify for lung resection without additional preoperative tests such as cardiopulmonary exercise testing; this leads to faster clin-

ical decision-making and less medical expenditure. Using the LLN was safe for the patients, as the risk of complications in patients with an FEV_1 and $T_{L,CO}$ above the LLN but <80% predicted was similar to that in patients with an FEV_1 and $T_{L,CO}$ >80% predicted.

Financial Disclosure and Conflicts of Interest

The authors have no conflict of interest related to the subject matter.

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