Prediction of postoperative DL_{CO} in lung cancer patients after lobectomy. Comparison between quantitative CT and the anatomic method

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ABSTRACT

BACKGROUND: Prediction of postoperative DL_{CO} has a key role in the preoperative evaluation of lung resection candidates. The aim of the study is to evaluate the role of quantitative CT to predict postoperative DL_{CO} in lung cancer patients undergoing lobectomy, comparing it with the anatomic method of segment counting. **METHODS:** DL_{CO} was measured preoperatively and 3 months postoperatively in 16 lung cancer patients undergoing lobectomy. Predicted postoperative values estimated with quantitative CT and the anatomic method were correlated to the actual postoperative measurements. **RESULTS:** Pearson's r was 0.81 for quantitative CT vs 0.75 for the anatomic method. The limits of agreement between predicted and actually measured postoperative DL_{CO} were narrower for quantitative CT vs the anatomic method (-0.4±2.4 vs -0.45±2.8mmol/min/kPa respectively). Focusing on 8 patients with abnormal preoperative DL_{CO} values, higher correlation and smaller mean difference was observed when using quantitative CT. **CONCLUSION:** Quantitative CT is more accurate than the anatomic method of functional segment counting for the prediction of postoperative DL_{CO} in lobectomy candidates.
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Key words:
- Quantitative CT
- Predicted postoperative DL_{CO}
- Lobectomy

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1. INTRODUCTION

Lung resection is the mainstay of treatment in patients with early stage non-small cell lung cancer. However, most patients suffer from comorbidities that impair the cardiorespiratory reserve, leading to increased risk of perioperative and postoperative complications. Lung function testing has a key role in the preoperative evaluation of lung resection candidates. According to current guidelines, forced expiratory volume in 1 second (FEV_1) and diffusing capacity of the lung for carbon monoxide (DL_{CO}) should be routinely measured in all patients. Additionally, predicted postoperative (ppo) FEV_1 and DL_{CO} values should be calculated in all patients, a recommendation added in the latest guidelines which highlights the key role of the prediction of postoperative lung function, since it should be performed even in cases with normal values of preoperative lung function[1].

Perfusion radionuclide lung scanning is the most widespread radiological method to predict postoperative lung function. $PpoFEV_1$ and $ppoDL_{CO}$ are estimated by reducing the preoperative values by the fraction of the regional radioactivity counts of the part to be resected to total radioactivity counts of both lungs[2-4]. A simpler approach is the anatomic method which is based on the formula ppo FEV_1= preoperative FEV_1 x (1-y/z), where y is the functional or unobstructed (based on bronchoscopy and CT findings) lung segments to be removed and z is the total functional segments. The total number of segments for both lungs is nineteen, 10 in the right lung (3, 2, 5 in the upper, middle, lower lobe, respectively) and 9 in the left lung (5 in the upper and 4 in the lower lobe)[5]. Current guidelines recommend the use of lung scanning for the prediction of postoperative lung function in case of pneumonectomy, while the anatomic method is proposed in case of lobectomy. If both $ppoFEV_1$ and $ppoDL_{CO}$ are >60% predicted, no further testing is required and resection up to calculated extent can be performed. Otherwise, depending on the ppo values, a low technology exercise test (stair climb or shuttle walk test) and/or a formal cardiopulmonary exercise test may be required in order to stratify patients on the risk for perioperative death and cardiopulmonary complications prior to lung surgery. In case preoperative maximal oxygen consumption (VO_2max) is <10 ml/kg/min or <35%predicted the risk is high, thus major anatomic resection should be avoided and other treatment modalities should be chosen[1].

Apart from perfusion scintigraphy, quantitative CT has been widely tested in order to evaluate its capability to predict postoperative FEV_1[5-10]. Quantitative CT predicts postoperative lung function by processing the already available data of the chest CT (which is in any case performed for staging) using the system's software. Volumetric analysis is technically simple and fast and estimates the volume of each lobe in order to predict postoperative lung function by reducing the preoperative values by the fraction that the part to be resected contributes to the total volume of both lungs[11]. The capability of quantitative CT to predict postoperative FEV_1 has been well established, with superior accuracy when compared to the anatomic method[8-10]. However, studies regarding its capability to predict postoperative DL_{CO} are lacking, especially in case of abnormal (<80%predicted) preoperative values.

The aim of our study is to investigate the capability of quantitative CT to predict postoperative DL_{CO} in lung cancer patients undergoing lobectomy. The recommended procedure to predict postoperative lung function in lobectomy candidates is the anatomic method, so we focused on this group of patients to compare the two methods, with special reference to the subgroup with abnormal preoperative DL_{CO} values.

2. MATERIALS AND METHODS

2.1. Patients

Twenty consecutive patients referred to our respiratory function laboratory for assessment of their respiratory reserves prior to lobectomy were enrolled. All patients met the following inclusion criteria: 1) histologically confirmed non-small cell lung cancer, 2) stage of disease Ia or Ib, 3) patient suitable for lobectomy, 4) low cardiovascular risk or with an optimized cardiovascular treatment, 5) no other severe comorbidity that prohibits surgery.

All patients met the eligibility criteria and were included in the study. Pulmonary function tests (PFTs) and chest CT scans were performed preoperatively. One patient was submitted to pneumonectomy due to local extension of tumor and three patients were lost to follow up. Sixteen patients were finally evaluated (6 Right Upper Lobectomies, 1 Right Upper-Middle Bilobectomy, 1 Right Middle-Lower Bilobectomy, 2 Right Lower lobectomies, 5 Left Upper lobectomies, 1 Left lower lobectomy). The study was approved by our institutional ethical review board and all patients gave their informed consent. Patient characteristics are summarized in table 1.

2.2. Pulmonary Function Testing

Pulmonary function testing was performed with our institution's Benchmark PFT System (PK Morgan, Rainham, Kent, UK). Spirometry, measurement of total lung capacity with the helium dilution method and DL_{CO} calculation with the single breath method were performed in all patients, according to the joint European Respiratory Society/American Thoracic Society clinical practice guidelines[12,13].

2.3. Prediction of postoperative DLCO

2.3.1. Anatomic method of segment counting

Prediction of postoperative lung function with the

TABLE 1. Anthropometric characteristics and preoperative routine respiratory function data.

Age (years)	61 (50-79)
Gender (M/F)	14/2
BMI (kg/m2)	30 (20-37)
FEV1	96±19
FVC	101±15
TLC	94±13
DLCO	81±19

Values are means ± SD for normally distributed data and medians (range) for not normally distributed data. Unless otherwise specified, values are expressed as % of predicted. Explanation of abbreviations: M: male; F: female; BMI: Body mass index; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; TLC: total lung capacity; DLCO: diffusing capacity for carbon monoxide.

anatomic method was performed using the formula developed by Bolliger et al[5]: $ppoDL_{CO}$=preoperative DL_{CO} x(1-y/z), where y is the number of functional segments to be removed and z is the total number of functional segments, according to bronchoscopy and CT findings. This formula is currently proposed to be the method of choice to predict postoperative lung function in case of lobectomy[1].

2.3.2. Quantitative CT analysis

All patients underwent a chest CT scan for tumor staging in our institution's Somatom Emotion Unit (Siemens, Erlangen, Germany). Scanning was performed at full inspiration from the lung apex to the diaphragm using the following parameters: 110-130 kVp, 40 effective mAs, pitch 2 with 5mm slice width and 3mm reconstruction increment. Contrast medium was administered in order to delineate the boundaries of the tumor and the mediastinal structures for accurate staging. Functional lung volume was estimated using the system's software (Volume, Siemens), as described elsewhere in detail[5,6]. Briefly, lung parenchyma is segmented in three areas according to the attenuation of each voxel, using the dual threshold of -500 to -910 Hounsfield Units (HU). Attenuation levels <-910HU indicate emphysema, areas >-500HU denote tumor, postobstructive atelectasis or pneumonitis, whereas areas between -500 and -910 HU correspond to functional lung parenchyma,which is auto-

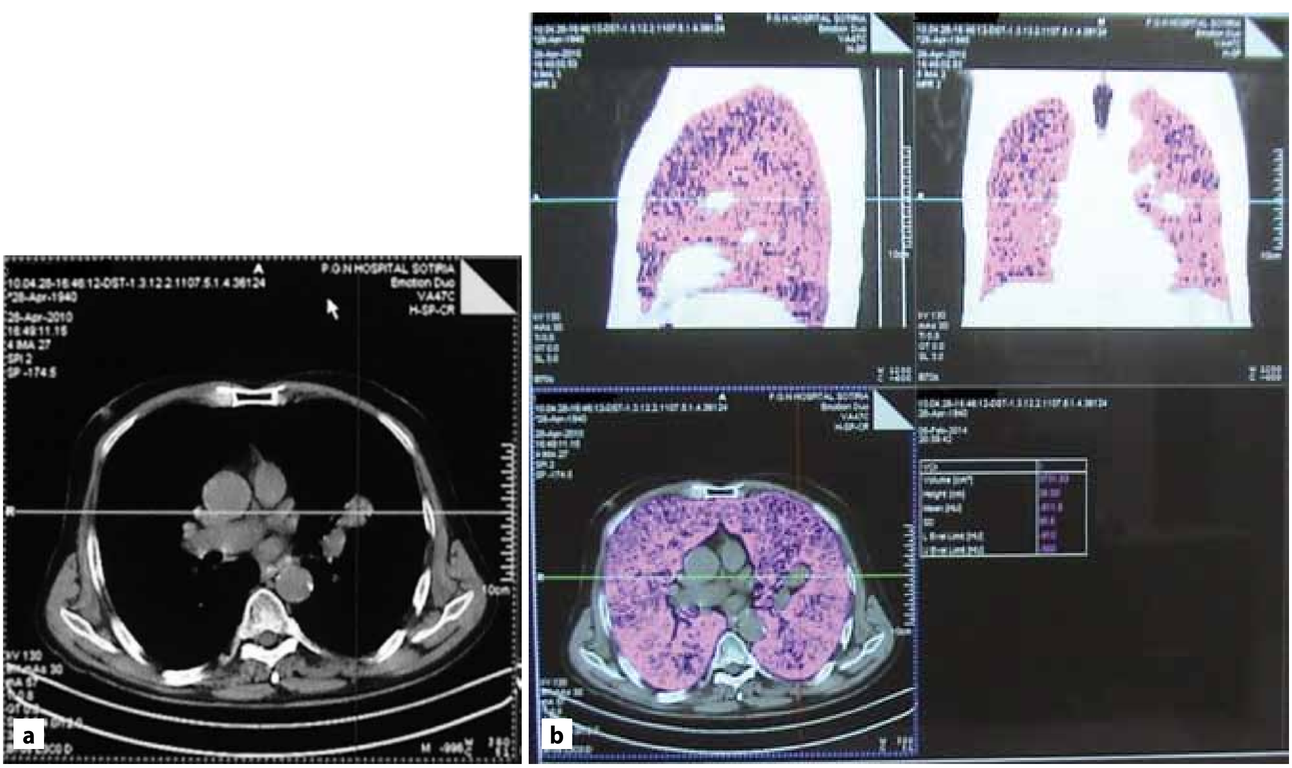

FIGURE 1. Quantitative CT volume estimations (a) Chest CT scan of a patient with a tumor in the left upper lobe, (b) Quantitative analysis of functional lung parenchyma of both lungs, using the dual threshold of -500 to -910 HU. Areas in purple correspond to voxels within these attenuation limits. Total functional lung volume of both lungs is estimated to be 3731ml.

matically calculated (Figure 1). Additionally, guided by the fissures between the different lobes and by delineating the region of interest (that is the boundaries of the lobe to be resected) in every slice, functional lung volume of the lobe can be estimated (Figure 2). Postoperative lung function can be predicted by using the following formulas:

$$ppoDL_{CO} = \text{preoperative } DL_{CO} \times (1\text{-predicted volume loss})$$

$$\text{predicted volume loss} = \frac{\text{regional functional lung volume of the part to be resected}}{\text{total functional lung volume of both lungs}}$$

2.4. Procedure

Patients scheduled for lobectomy underwent pulmonary function testing and chest CT scan with volumetric analysis within a week prior to surgery, which was performed in our institution through a posterolateral thoracotomy. The postoperative course of evaluated patients was uneventful, with mean duration of hospital stay 7±2 days. Pulmonary function tests were repeated 3 months after surgery, using the same equipment. All patients were in stable condition, had no sign of recurrence or metastasis of the neoplasm and since negative surgical margins and N0 status was pathologically confirmed, no adjuvant treatment was administered.

2.5. Statistical analysis

Variables are reported as mean±SD for normally distributed data and as median (range) for not normally distributed data. Pearson correlation coefficient with linear regression analysis was used to estimate correlations between predicted and actual postoperative measurements. The limits of agreement were analyzed by means of Bland-Altman analysis. A p value less than 0.05 was considered significant. Statistical analysis was performed using SigmaStat V3.5 and SigmaPlot V10.0 statistical software (Jandel Scientific, CA, USA).

3. RESULTS

Significant correlations between predicted and actually measured postoperative values of DL_{CO} were observed

FIGURE 2. Volumetric analysis of the resected lobe (same patient as in figure 1) (a) Fissure identification between left upper and lower lobe, (b) Delineation of the region of interest (limits of the lobe to be resected) with the cursor, in all transaxial images, (c) Volumetric analysis of the left upper lobe. Regional functional lung volume is estimated to be 868mL

with both methods of prediction (Figure 3a). Pearson's r was 0.81 using quantitative CT (p=0.0001) compared to r=0.75 (p=0.0007) using the anatomic method. The limits of agreement between predicted and actual measurements for each method are depicted in figure 4a. Quantitative CT limits ranged from -2.8 to 2mmol/min/kPa while the

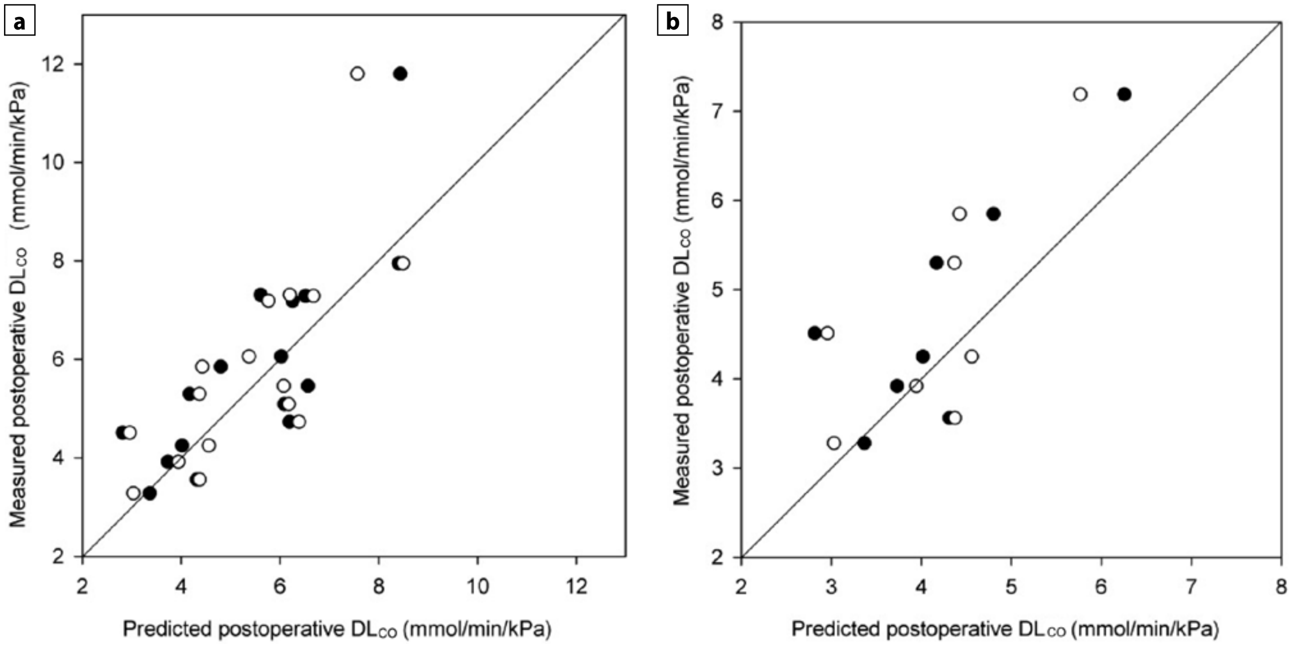

FIGURE 3. (a) Correlations between predicted and measured postoperative values of DL_{CO} in all evaluated patients with line of equality. Quantitative CT: r=0.81 p=0.0001, Anatomic method: r=0.75 p=0.0007. (b) Correlations between predicted and measured postoperative values of DL_{CO} in the subgroup with abnormal preoperative DLCO. Quantitative CT: r=0.8 p=0.017, Anatomic method: r=0.72 p=0.04. Linear regression equation and corresponding Pearson's correlation coefficient for all patients are shown.
(●): Quantitative CT (○): Anatomic method.
DL_{CO}: Diffusion lung capacity for carbon monoxide.

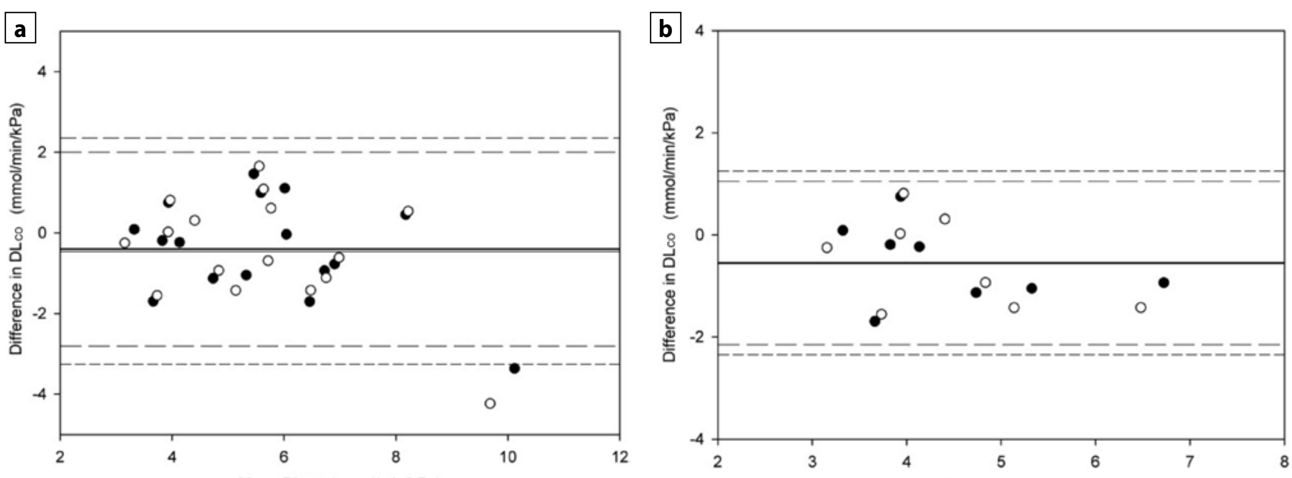

FIGURE 4. (a) Agreement between predicted and measured postoperative values of DL_{CO} in all evaluated patients. The limits of agreement for quantitative CT are -0.4±2.4mmol/min/kPa (long dashes) and -0.45±2.8mmol/min/kPa for the anatomic method (short dashes). (b): Agreement between predicted and measured postoperative values of DL_{CO} in the subgroup with abnormal preoperative DL_{CO}. The limits of agreement for quantitative CT are -0.55±1.6mmol/min/kPa (long dashes) and -0.55±1.8mmol/min/kPa for the anatomic method (short dashes).
(●): Quantitative CT (○): Anatomic method.

anatomic method limits of agreement ranged from -3.25 to 2.35mmol/min/kPa.

Similar differences were observed when we focused on the subgroup with abnormal preoperative DL_{CO} values. Eight patients with preoperative DL_{CO} <80% predicted were analyzed with both methods of prediction. Significant correlations were observed both for quantitative CT (r=0.8, p=0.017) and for the anatomic method (r=0.72, p=0.04) (Figure 3b). Additionally, the limits of agreement of the anatomic method were wider, ranging from -2.35 to 1.25mmol/min/kPa versus -2.15 to 1.05mmol/min/kPa of quantitative CT (Figure 4b).

4. DISCUSSION

The main finding of this study is that quantitative CT predicts postoperative DL_{CO} more accurately than the anatomic method, in lobectomy candidates. The correlation between predicted postoperative DL_{CO} values and the actual postoperative measurements is higher and the limits of agreement narrower when quantitative CT is used, in comparison to the anatomic method. This finding is consistent even when patients with abnormal preoperative DL_{CO} are evaluated. However, given the small differences that were observed, the anatomic method could be a reliable first-step tool to predict postoperative DL_{CO}, reserving the use of quantitative CT only in cases with marginal ppo values.

Measurement of DL_{CO} prior to surgery improved risk stratification in lung resection candidates, since DL_{CO} is an important predictor of postoperative morbidity even in patients with normal spirometry[14,15]. Current guidelines propose the routine measurement of DL_{CO} during the physiologic evaluation of lung cancer patients who are considered for resectional surgery[1]. Additionally, predicted postoperative DL_{CO} should be calculated in all patients, since it has been shown that ppo values are strongly associated with the risk of pulmonary complications and mortality following lung resection[16,17]. The anatomic method of functional segment counting is currently the proposed method to predict postoperative lung function in lobectomy candidates[1]. It is a simple approach that enables a rapid estimation of $ppoFEV_1$ and $ppoDL_{CO}$ in the outpatient clinic[18]. However, calculation of $ppoFEV_1$ has been extensively studied, since traditionally FEV_1 was the sole index that was preoperatively evaluated, and has been shown that it can be more accurately estimated using quantitative CT. Ueda et al demonstrated that CT volumetric analysis was better for estimating the functional contribution of a specific lobe compared to segment counting, especially in cases of heterogeneously distributed diseases, such as pulmonary emphysema or fibrosis[8]. Ohno et al. demonstrated that the correlation coefficient was lower and the limits of agreement between predicted and measured postoperative FEV_1 were larger when the anatomic method was used instead of quantitative CT[9]. In the study of Yoshimoto et al., the segment counting method was proven inferior to quantitative CT for predicting postoperative FEV_1 after lobectomy[10]. These studies verified the superiority of quantitative CT for the prediction of postoperative FEV_1 in lobectomy candidates, and that is why European guidelines on fitness for lung resection propose quantitative CT to be the method of choice in patients with borderline lung function scheduled for lobectomy[19].

However, studies that compare different methods of predicting postoperative DL_{CO} are lacking and the anatomic method is systematically used to calculate $ppoDL_{CO}$ in lobectomy candidates. Based on FEV_1 findings and on the fact that prediction of postoperative DL_{CO} is based on the same principle, that postoperative loss proportionately approximates the regional lung function contributed by the resected lobe, calculating $ppoDL_{CO}$ via the functional segment counting may not be the optimal method[20]. The research of Bolliger et al. is the only study that evaluated the efficacy of quantitative CT compared to the anatomic method, in estimating $ppoDL_{CO}$[5]. In this study, the limits of agreement between ppo and actual postoperative DL_{CO} values had the same range for both methods (-2.92 to 1.7 mmol/min/kPa vs -2.78 to 1.83 mmol/min/kPa for quantitative CT vs the anatomic method respectively). The correlation coefficients were also identical (r=0.84 for both methods). This finding was particularly observed in case of lobectomy (r=0.85 for both methods) and for that reason the authors proposed the anatomic method as a simple and accurate way to predict with confidence the postoperative lung function in resections not exceeding one lobe. In our study, quantitative CT appears to be more accurate than segment counting. The correlation coefficient and the limits of agreement between predicted and actually measured postoperative DL_{CO} favor the use of quantitative CT. Pearson's r and the range of agreement observed in our study are similar to the findings of Bolliger et al (r=0.81 vs r=0.85 and range of limits of agreement 4.8 vs 4.62 mmol/min/kPa in our study vs Bolliger et al). However, the predictive capability of the anatomic method in our study was inferior to that reported by Bolliger et al (r=0.75 vs r=0.85 and range of limits of agreement 5.6 vs 4.62mmol/min/kPa). A possible explanation for this discrepancy is that in the study of Bolliger et al, all patients had normal preoperative DL_{CO} values, while in our study half of the evaluated patients had mild to moderate decrease in preoperative DL_{CO}. The subanalysis of this group revealed that quantitative CT reserved its predictive capability, whereas the anatomic method yielded less accurate results. Additionally, the limits of agreement remained larger when compared to quantitative CT. This could be explained by the fact that low preoperative DL_{CO} values may associate with subclinical emphysema which can be heterogeneously distributed. In this case, the use of quantitative CT over segment counting is obviously advantageous, because of its ability to accurately identify not functional emphysematous areas instead of hypothesizing that every segment equally contributes to global lung function.

To our knowledge, this is the first study that compared the capability of quantitative CT versus the anatomic method to predict postoperative DL_{CO} in lobectomy candidates with abnormal preoperative DL_{CO} values. Current guidelines propose the routine calculation of ppoDLCO in all resection candidates, so it is particularly important to evaluate the available methods of prediction in order to determine the optimal procedure. In our study we focused on lobectomy candidates, comparing functional segment counting [the method of choice in ACCP guidelines[1]] to quantitative CT [proposed in ERS/ESTS guidelines[19]]. Our findings support the use of the latter, especially in cases with abnormal preoperative DL_{CO} that results in marginal ppo values.

A limitation of our study is the small number of evaluated patients. Another limitation is that patients with severe emphysema or fibrosis were not evaluated, so we could not verify the potential advantage of quantitative CT, which provides a detailed mapping of lung parenchyma and assesses regional contribution excluding emphysematous or fibrotic areas, a procedure which could further corroborate its utility against the anatomic segment counting. Further studies should evaluate the accuracy of different methods of prediction in large series of resection candidates, focusing especially on patients with abnormal preoperative lung function or with underlying lung diseases.

In conclusion, volumetric analysis via quantitative CT imaging is a simple and accurate method to predict postoperative DL_{CO} by analyzing the already existing data of the chest CT scan, without adding to the discomfort of the patient or increasing the radiation exposure. The anatomic method of segment counting provides the ability to rapidly calculate ppo values, however it appears to be less accurate than quantitative CT, especially in patients with marginal lung function. We propose that quantitative CT is the method of choice to predict postoperative lung function in lobectomy candidates.

Conflict of interest: None declared.

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