

# Predicting Respiratory Complications Following Lobectomy Using Quantitative CT Measures of Emphysema

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**Purpose:** In performing surgery for lung cancer, emphysema is a risk factor related to postoperative respiratory complications (PRC). However, few studies have addressed the risk of radiological emphysematous volume affecting PRC. The aim of this study was to investigate the relationship between emphysematous volume as measured on 3-dimensional computed tomography and PRC.

**Patients and Methods:** We reviewed 342 lung cancer patients undergoing lobectomy between 2013 and 2018. The percentage of low attenuation area (LAA%) was defined as the percentage of the lung area showing attenuation of  $-950$  Hounsfield units or lower. Preoperative factors including age, sex, body mass index, smoking index, respiratory function, tumour histology, and LAA% were evaluated. PRC included pneumonia, atelectasis, prolonged air leakage, empyema, hypoxia, ischemic bronchitis, bronchopleural fistula, and exacerbation of interstitial pneumonia. Uni- and multivariable analyses were performed to investigate the relationship between independent clinical variables and postoperative adverse events.

**Results:** Median LAA% was 5.0% (range, 0–40%) and PRC was observed in 50 patients (14.6%). Patients who presented with PRC showed significantly high LAA% compared to those without complications (median: 8.1% vs 3.8%;  $p < 0.001$ ). Based on univariable analysis, age, sex, smoking index, percentage of forced expiratory volume in 1 s ( $FEV_{1.0}$  %), histology, and LAA% were significant predictors for PRC. Multivariable analysis revealed higher LAA% as a significant risk factor for PRC (odds ratio = 1.040; 95% confidence interval, 1.001–1.080;  $p = 0.046$ ).

**Conclusion:** In addition to respiratory function with spirometry, LAA% can be used as a predictor of PRC.

**Keywords:** lung cancer, emphysema, radiology and other imaging, respiratory function tests, thoracic surgery

## Introduction

Despite marked advances in surgical procedures for non-small cell lung cancer (NSCLC), pulmonary resection still carries a risk of postoperative respiratory complications (PRC). Complication rates following lobectomy, which is a standard operative procedure for NSCLC, range from 6% to 34.2%.<sup>1–3</sup> Preoperative risk assessment is generally performed based on detailed algorithms provided by three clinical guidelines (American College of Chest Physicians, European Respiratory Society and European Society of Thoracic Surgery).<sup>4,5</sup> According to these guidelines, several spirometric parameters remain standard for preoperative risk assessment, including forced expiratory volume in 1 s ( $FEV_{1.0}$ ) and diffusing capacity of the lungs for carbon monoxide (DLCO). However, objectivity in

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pulmonary function tests remains lacking due to insufficient respiratory effort, particularly among elderly patients with chronic obstructive pulmonary disease (COPD).<sup>6</sup>

Several recent studies have identified that quantitative computed tomography (CT) assessment using low attenuation area (LAA) correlates well with pulmonary emphysema.<sup>7–9</sup> Previous report revealed that emphysema on CT was associated with significantly increased odds of lung cancer.<sup>10,11</sup> Moreover, the distribution pattern of emphysema may affect both lung cancer risk and tumour location.<sup>12,13</sup> Emphysema is a well-known risk factor for postoperative air leak, as the most frequent adverse event after lung resection.<sup>14</sup> Although increasing evidence seems to demonstrate a link between LAA and pulmonary emphysema, scant information has been published regarding the association between LAA and PRC.<sup>15</sup> Accordingly, combined assessment of the LAA and spirometric parameters has been hypothesized to contribute to the accurate prediction of PRC. The objective of the present study was to analyse the predictive value of LAA in terms of PRC among patients with NSCLC who underwent lobectomy.

## Materials and Methods

### Study Population

Patients who underwent pulmonary lobectomy for primary NSCLC at the University of Tsukuba Hospital between January 2013 and December 2018 were reviewed. Inclusion criteria were as follows: 1) pulmonary lobectomy for primary NSCLC without neoadjuvant chemotherapy or radiotherapy; 2) availability of high-resolution computed tomography for the whole lung with slice intervals  $\leq 2$  mm; and 3) spirometric measurements of lung function conducted before surgical intervention. The medical records of all patients were reviewed to determine age, sex, smoking index, respiratory function on spirometry, and histopathological factors. The study was conducted according to the principles of the Declaration of Helsinki. Ethical approval for the study was obtained from the institutional review board of the University of Tsukuba Hospital (approval number R01-258). All data in this retrospective study were fully anonymized and informed consent from the patients was obtained using the opt-out method with a disclosure document.

### Pulmonary Function Tests

Spirometric variables were obtained within 2 months preoperatively and included forced vital capacity (FVC),

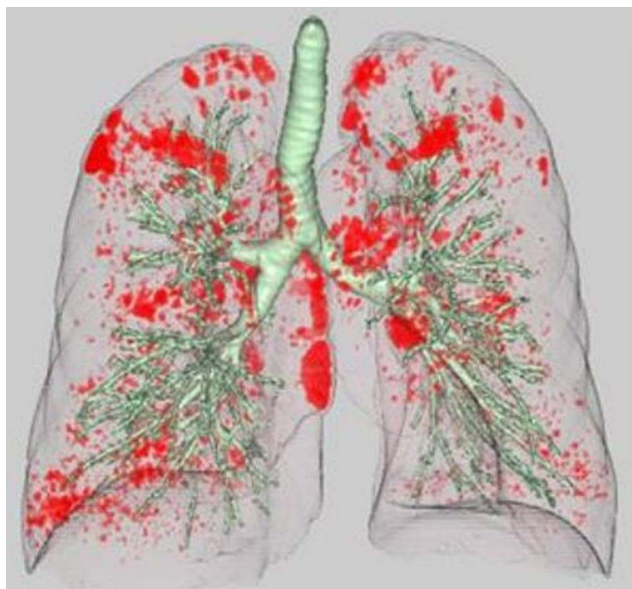
FEV<sub>1.0</sub>, and DLCO. Percentage predicted values were calculated using the age, sex, and height of patients.

## Operative and Perioperative Management

Under single-lung anaesthesia, lobectomy was basically performed by video-assisted thoracic surgery with four incisions without rib spreading. One specific chief surgeon (Y.S) was present for all lung lobectomies and critical portion of each surgical procedure was carefully supervised. All patients were extubated in the operating room. A 24-Fr chest tube with continuous channels was placed in the posterior pleural space via the apical space under continuous suction at  $-7$  cmH<sub>2</sub>O. Rehabilitation was started on postoperative day (POD) 1. Chest X-ray and blood tests were routinely performed on POD 1–4, 7, and on POD 1, 4, and 7, respectively.

## CT Examination and Quantitative Emphysema Measurement

HRCT images were obtained from two multidetector-row CT scanners (Brilliance 64 and Brilliance iCT 256; PHILIPS Electronics, Eindhoven, the Netherlands). A standard contrast-enhanced scanning protocol was performed to evaluate from the lung apex to the diaphragm using the following parameters: 120 kilovoltage peak; 180–280 mAs; resolution, 512×512 pixels, and scanning duration, 0.5 s. Axial images were reconstructed with a slice thickness of 1 or 2 mm. Images were photographed using a window level of  $-500$  to  $-700$  HU with a window width of 1000–2000 HU (lung window setting) and a level of 30–60 HU with a window width of 350–600 HU (mediastinal window setting). All preoperative CT data were transferred to a computer workstation (SYNAPSE VINCENT version 3.0; FUJIFILM, Tokyo, Japan). Threshold limits of  $-600$  to  $-1024$  Hounsfield units (HU) were automatically applied to exclude soft tissue surrounding the lungs as well as large vessels within the lungs. The trachea, main bronchus, and lobar to segmental bronchus were automatically removed from the 3-dimensional model of the whole lung. Lung field area with attenuation values less than  $-950$  HU were considered as LAA, as previously reported.<sup>16</sup> The ratio of the number of voxels with attenuation values lower than  $-950$  HU among the total number of voxels for the whole lung was considered to indicate the percentage of the low attenuation area (LAA%) (Figure 1).



**Figure 1** Representation of a 3-dimensional lung model. Low attenuation area (LAA) is shown in red. The percentage LAA (LAA%) is calculated as: LAA% = volume of LAA/total lung volume  $\times$  100.

## Postoperative Respiratory Complication

In this study, PRC were selected from complications equal to or higher than grade 2 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.<sup>17</sup> PRC included 1) pneumonia (fever with infiltrative shadow on chest radiograph); 2) atelectasis (endobronchial sputum drainage required); 3) prolonged air leakage (air leakage persisting beyond 7 days postoperatively); 4) empyema (pleural effusion with positive bacteriological confirmation); 5) hypoxia (required home oxygen therapy); 6) ischemic bronchitis (defined on capillary hyperplasia, mucosal defect, and ulceration with bronchoscopic inspection); 7) bronchopleural fistula; and 8) exacerbation of interstitial pneumonia.

## Statistical Analysis

According to past reports, radiological emphysema has been defined as being present in more than 10% of the lung.<sup>18,19</sup> In this current study, patients were divided into two groups: a high LAA% group, representing patients with LAA% more than or equal to 10%, and a low LAA% group, representing patients with LAA% less than 10%. Patient characteristics and PRC were evaluated between groups. Data with a normal distribution are expressed as mean  $\pm$  standard deviation (SD), and values for categorical variables are given as

percentages. A  $\chi^2$  test was used to compare categorical variables. Mann–Whitney U testing was used for non-parametric data. Preoperative factors including age, sex, body mass index, smoking index, respiratory function, tumour histology (adenocarcinoma or others), and LAA% were evaluated. Variables showing values of  $p < 0.05$  in univariable analysis were placed into logistic regression multivariable analysis to identify predictors of postoperative respiratory complications. All statistical analyses were performed using SPSS<sup>®</sup> version 25.0 (IBM Corporation, Armonk, NY). Statistical analyses were considered significant for values of  $p < 0.05$ .

## Results

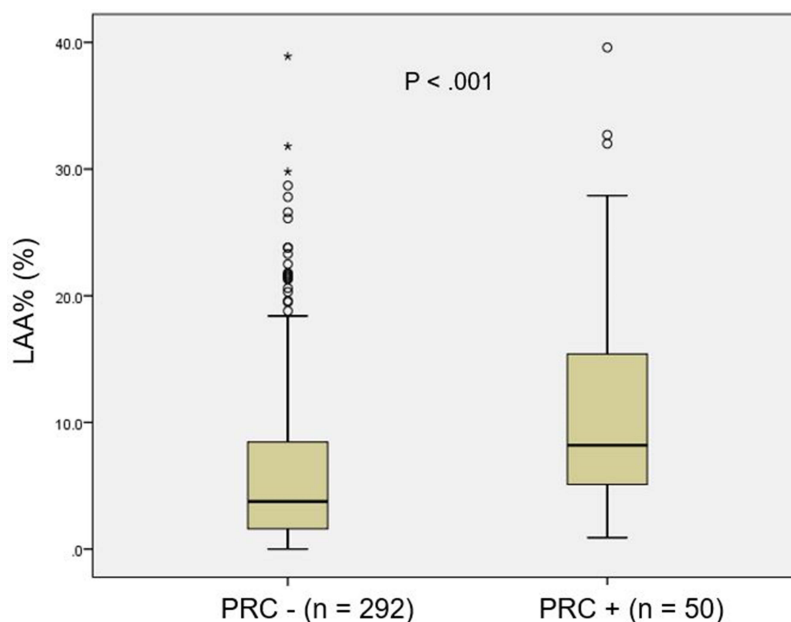
Table 1 summarizes patient and tumour characteristics. The cohort in this study comprised 143 men (41.8%) and 199 women (58.2%). Mean diameter of primary tumours was  $25.5 \pm 14.0$  mm (range, 8–90 mm). Adenocarcinoma constituted the most common pathological subtype ( $n = 272$ , 79.5%), followed by squamous cell carcinoma ( $n =$

**Table 1** Patient Characteristics ( $n = 343$ )

Background Factors		Value
Sex	Male	143 (41.8)
	Female	199 (58.2)
Age, years		$68 \pm 9.5$
Smoking index		$495 \pm 675$
BMI, kg/m <sup>2</sup>		$23.1 \pm 3.4$
PFT, %	FEV <sub>1,0</sub> %	$73.6 \pm 9.4$
	%FVC	$111.4 \pm 17.9$
	%DLCO	$97.8 \pm 25.0$
Whole tumour size, mm		$25.5 \pm 14.0$
Histology	Adenocarcinoma	272 (79.5)
	Squamous cell carcinoma	53 (15.5)
	Others	17 (5.0)
Resected lobes	Upper	195 (57.0)
	Middle	23 (6.7)
	Lower	124 (36.3)
LAA%		$7.0 \pm 7.4$
PRC		50 (14.6)

**Note:** Values are presented as n (%) or mean  $\pm$  standard deviations unless otherwise indicated.

**Abbreviations:** BMI, body mass index; PFT, pulmonary function test; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; DLCO, diffusing capacity of the lungs for carbon monoxide; LAA, low attenuation area; PRC, postoperative respiratory complications.



**Figure 2** Box plot comparing the percentage of low attenuation area (LAA%) between patients with and without postoperative respiratory complications (PRC).

53, 15.5%). Mean and median LAA% were  $7.0 \pm 7.4\%$  (range, 0–39.6%) and 5.0%, respectively. PRC were observed in 50 patients (14.6%). LAA% values for patients who presented with PRC were significantly higher compared to those without PRC (median, 8.1% vs 3.8%;  $p < 0.001$ ) (Figure 2).

PRC in the high LAA% group (LAA%  $\geq 10\%$ ) and low LAA% group (LAA%  $< 10\%$ ) are shown in Table 2. These included pneumonia ( $n = 6$ ), atelectasis ( $n = 8$ ), prolonged air leakage ( $n = 13$ ), empyema ( $n = 4$ ), hypoxia ( $n = 5$ ), ischemic bronchitis ( $n = 3$ ), bronchopleural fistula ( $n = 1$ ), acute exacerbation of interstitial lung disease ( $n = 4$ ), and other adverse events ( $n = 6$ ). The overall PRC rate was significantly greater in the high LAA group (25.0%) than in the low LAA group (11.5%,  $p < 0.05$ ). Of these, patients who developed postoperative pneumonia (5.0%) and hypoxia (5.0%) were significantly higher in high LAA% group ( $p = 0.029$ , 0.012, respectively).

Figure 3 shows the correlation between LAA% and FEV<sub>1.0</sub>%. Only a weak negative correlation between these two variables was identified ( $r = -0.20$ ). Table 3 shows the results of univariable and multivariable analysis for predicting PRC. Based on the univariable analysis, male sex, age, smoking index, tumour histology, FEV<sub>1.0</sub>%, %DLCO, and LAA% were significant predictors for PRC. Conversely, no significant relationships were seen

for BMI, whole tumour size, or %FVC. In order to reduce the impact of confounding variables, both smoking index and tumour histology were excluded from the subsequent multivariable analysis. Male sex (odds ratio [OR] 4.876,  $p < 0.001$ ), %DLCO (OR 0.975,  $p = 0.002$ ), and LAA% (OR 1.040,  $p = 0.046$ ) showed significance predicting PRC after lobectomy.

The ROC curve analysis revealed that the optimal cut-off values of LAA% for predicting PRC was 4.950 (Figure 4). The area under the ROC curves of the LAA% was 0.693. These cut-off values yielded a sensitivity of 0.780 and a specificity of 0.545 for LAA%.

## Discussion

The present study investigated associations between the ratio of emphysematous volume and PRC in patients who underwent lobectomy for primary lung cancer. We found that LAA% had significant impacts on prediction of PRC according to multivariable logistic regression analysis. In general, pulmonary emphysema is pathologically defined as an abnormal enlargement of the airspaces, accompanied by destruction of the alveolar walls.<sup>20</sup> These abnormal changes are observed on chest CT as the relative areas of lung occupied by attenuation values lower than  $-800$  to  $-970$  HU.<sup>21–23</sup> In this study, LAA was defined as areas below  $-950$  HU, because this value had been commonly

**Table 2** Postoperative Respiratory Complications in High and Low LAA% Groups

	Low (LAA% <10%) (n = 262)	High (LAA% ≥10%) (n = 80)	P value
Pneumonia	2 (0.8)	4 (5.0)	0.029
Atelectasis	6 (2.3)	2 (2.5)	1
Prolonged air leakage	7 (2.7)	6 (7.5)	0.086
Empyema	2 (0.8)	2 (2.5)	0.234
Hypoxia	1 (0.4)	4 (5.0)	0.012
Ischemic bronchitis	2 (0.8)	1 (1.3)	0.552
Bronchopleural fistula	1 (0.4)	0 (0)	0.580
IP exacerbation	3 (1.1)	1 (1.3)	0.939
Others	6 (2.3)	0 (0)	0.342
Total	30 (11.5)	20 (25.0)	0.035

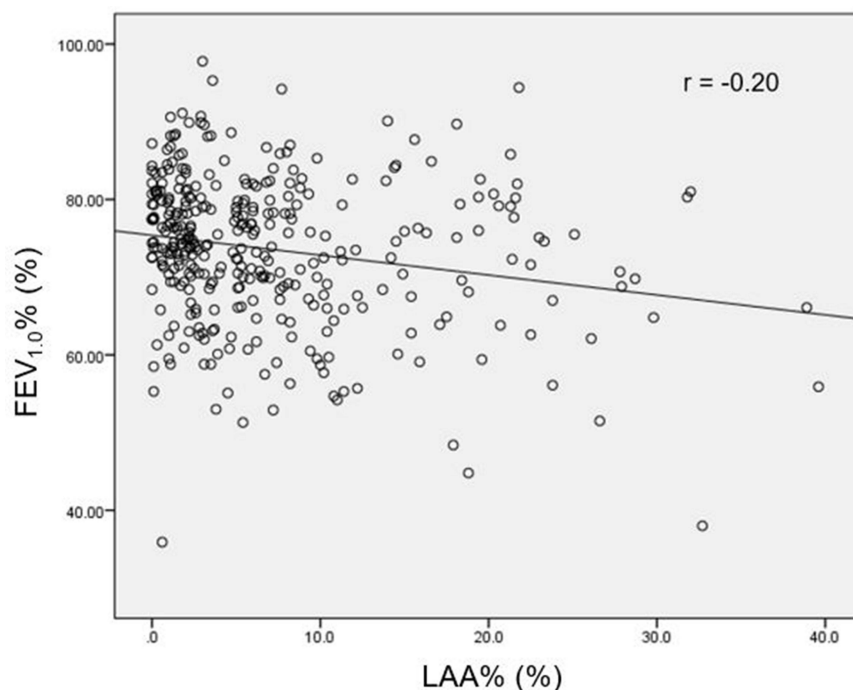
**Note:** Values are n (%) or n.

**Abbreviations:** LAA, low attenuation area; IP, interstitial pneumonia.

used to define radiological emphysema and correlates well with pathological severity of emphysema.<sup>24–26</sup> Since emphysematous lungs comprise fragile lung parenchyma

combined with chronic bronchitis, patients with pulmonary emphysema could reasonably be expected to show higher complication rates after lung surgery. However, preoperative risk assessment has been practically performed only using functional evaluation by pulmonary function testing, cardiopulmonary exercise testing, and maximal exercise O<sub>2</sub> consumption.<sup>27</sup> Radiological evaluation has not yet been established as an appropriate risk indicator, but whether structural emphysematous changes impact the tolerability of lung cancer surgery remains unclear.

Recent studies have addressed the capability of CT to accurately assess the severity of pulmonary emphysema.<sup>28,29</sup> Such findings support the hypothesis that radiological evaluation can be applied for preoperative risk assessment as well as pulmonary function testing. Emphysematous changes on chest CT could be considered to correlate strongly with FEV<sub>1,0</sub>, because cigarette smoking is the common causative factor for both lower pulmonary function and emphysematous changes. However, conflicting results have suggested discrepancies between functional and radiological findings. Ueda et al showed that the extent of emphysema on chest CT did not correlate well with the percentage-predicted FEV<sub>1</sub> ( $r = -0.375$ ).<sup>30</sup>



**Figure 3** Scatter plot showing the relationship between FEV<sub>1,0</sub>% and percentage of low attenuation area (LAA%). The  $r$  value indicates the Pearson correlation coefficient.

**Table 3** Uni- and Multivariable Analysis of Clinical Factors for Predicting PRC

	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Male sex	4.446 (2.294–8.616)	<0.001	4.876 (2.294–8.616)	<0.001
Age	2.438 (1.289–4.609)	0.006	–	–
BMI	0.623 (0.326–1.191)	0.153	–	–
Smoking index	4.357 (2.147–8.843)	<0.001	–	–
Whole tumour size	1.308 (0.710–2.408)	0.389	–	–
Histology	3.227 (1.697–6.135)	<0.001	–	–
FEV <sub>1.0</sub> %	1.978 (1.071–3.654)	0.029	–	–
%FVC	1.031 (0.528–2.011)	0.930	–	–
%DLCO	3.081 (1.252–7.585)	0.014	0.975 (0.960–0.991)	0.002
LAA%	4.239 (2.089–8.601)	<0.001	1.040 (1.001–1.080)	0.046

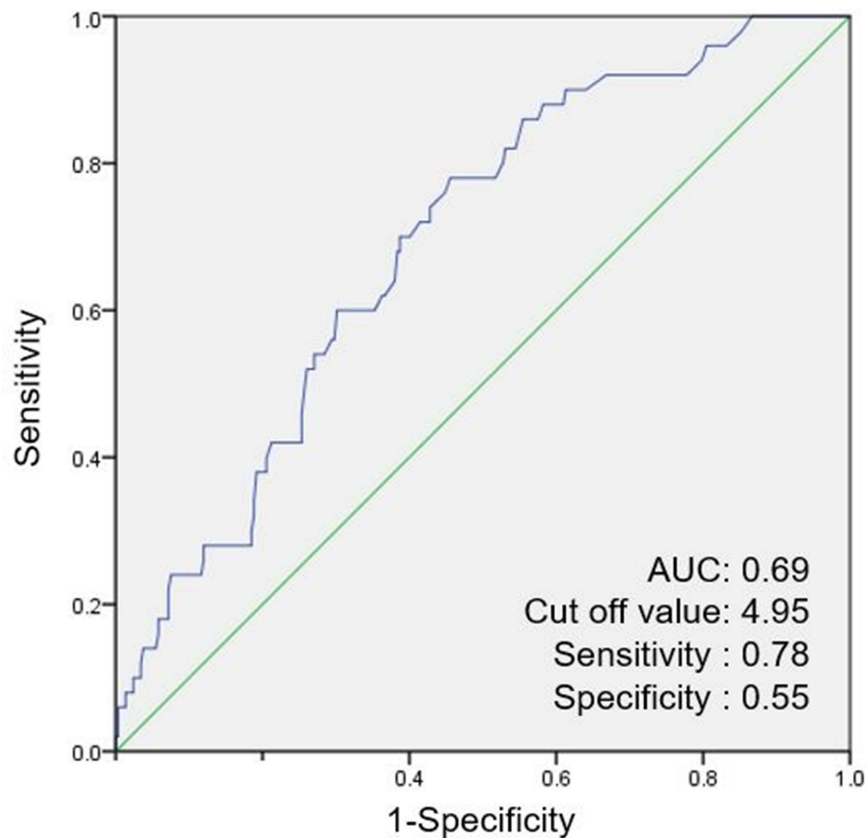
**Abbreviations:** PRC, postoperative respiratory complications; OR, odds ratio; CI, confidence interval; BMI, body mass index; PFT, FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; DLCO, diffusing capacity of the lungs for carbon monoxide; LAA, low attenuation area.

Kim et al also concluded that no strong correlation exists between severity of emphysema and FEV<sub>1.0</sub>% ( $r = -0.216$ ), consistent with our results.<sup>31</sup> Our cohort included patients who showed severe pulmonary emphysematous changes on CT with normal pulmonary functions. One reason explaining the discrepancy is the heterogeneity in smoker responses to tobacco. Studies have reported that smoking-induced tissue damage varies among individuals depending on sex, genetic status, and type of exposure to tobacco smoke.<sup>32–34</sup> Such reports indicate that some populations are more likely to develop radiological emphysema inconsistent with their pulmonary functions. Another possible explanation is that results from pulmonary function testing are commonly affected by several factors including patient effort, cognitive function, and the skill of the examiner. FEV<sub>1.0</sub> obtained by spirometry does not necessarily reflect an objective result, especially in elderly patients. Therefore, in addition to respiratory function with spirometry, objective radiological evaluation seems warranted to achieve accurate preoperative risk assessment.

Quantitative CT analysis is widely accepted as an objective tool to evaluate the severity of pulmonary emphysema. In the present study, patients with high LAA%, defined using the 10% cut-off value, showed a higher PRC than patients with low LAA%. Several microenvironmental factors observed in patients with emphysema may explain the higher rates of inflammatory

complications. Emphysematous changes pathologically involve abnormal, permanent enlargement of the tiniest airspaces including the alveoli and respiratory bronchioles, attributed to colonization with or infection by a potentially pathogenic organism.<sup>35</sup> Moreover, emphysema patients develop small airway stenosis due to the loss of elastic recoil of the lung, resulting in deficient mucociliary clearance.<sup>36</sup> Our study clearly demonstrated that PRC was linked with high LAA% because radiological emphysematous changes might represent disruptions of alveolar structures and surrounding microvessels. These results indicate that the degree of radiological lung parenchymal damage can be used as a predictor of PRC.

In our multivariable analysis, %DLCO was a significant factor for predicting PRC. This result was consistent with previous prospective studies from the Society of Thoracic Surgeons General Thoracic Surgery Database.<sup>37,38</sup> FEV<sub>1.0</sub>%, which is an established prognostic factor for postoperative respiratory adverse events, was not shown to be a significant independent predictor in multivariable modeling. One possible reason to explain these results might be derived from the hypothesis that the presence and severity of emphysema were not directly linked to airflow limitation as measured on spirometry.<sup>39,40</sup> According to previous studies, emphysema and airway wall thickening may already be present in most COPD patients, but some do not yet show airflow limitation.<sup>41</sup> Based on these hypotheses, declines in FEV<sub>1.0</sub> cannot be evident unless the degree of emphysema



**Figure 4** Receiver operating characteristic curve of the low attenuation area (LAA) for postoperative respiratory complications (PRC).

**Abbreviation:** AUC, area under the curve.

reaches a particular threshold. Preoperative risk assessment with quantitative emphysema evaluation may thus allow more accurate prediction of PRC than that with pulmonary function testing alone.

Several potential limitations need to be considered for the present study. First, this investigation was a retrospective study conducted in a single institute and the number of patients with PRC was relatively small. Second, all the CT scans in the current study were performed with contrast and injection rate and time to scan might have been slightly different in each case. This indicates that image acquisition protocol with contrast agents could affect the HU value of the lung parenchyma. However, this was the single-center study and the contrast-enhanced CT scan was performed in the same protocol. Moreover, it is considered that contrast agents do not tend to accumulate on the emphysematous lung and the results would not be different regardless of whether contrast agent was used. Therefore, we consider the effect of contrast-enhanced CT could be neglectable. Third, we measured emphysema severity for global lungs, because

precise lobulation in three-dimensional software was sometimes challenging in patients with incomplete lobulation of the lungs. Further evaluation of the difference in LAA distribution between upper and lower lobes using fissure integrity scores may be ideal.

## Conclusion

LAA% showed a significant correlation with the incidence of PRC after lobectomy. Our findings may have important clinical implications, in that combining radiological assessment of emphysema with functional evaluation by spirometry may facilitate accurate prediction of PRC after lobectomy for NSCLC.

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## Disclosure

The authors report no conflicts of interest in this work.

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