# Quantitative CT lung densitometry for the diagnosis of bronchiolitis obliterans in children

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**Abstract**

Background: The purpose of this study was to evaluate the quantitative diagnostic performance of computed tomography (CT) densitometry in pediatric bronchiolitis obliterans (BO) patients. Methods: A retrospective chart review was performed on 109 children under age 18 who underwent 3D chest CT from March 2019 to March 2021. We measured the mean lung density (MLD) and calculated the difference of MLD (MLDD) in expiratory and inspiratory phase, the expiratory to inspiratory ratio of mean lung density (E/I MLD), and the relative volume percentage of lung density at 50 HU intervals (E600 to E950). We calculated the sensitivity, specificity, and diagnostic accuracy of lung density indices for the diagnosis of BO. Results: A total of 81 patients, 51 BO patients and 30 controls, were included in this study (mean age: 12.7 vs 11.4 years). Expiratory (EXP) MLD, MLDD, E/I MLD, and E900 were all statistically significantly worse in the BO group. Multivariate logistic regression analysis showed that MLDD (odds ratio [OR] = 0.98, $p < .001$), E/I MLD (OR = 1.39, $p < .001$), and E850 (OR = 1.54, $p = 0.003$) were significant densitometry parameters for BO diagnosis. In ROC analysis, E900 (cut-off 1.4%; AUC = 0.920), E/I MLD (cut-off 0.87; AUC = 0.887), and MLDD (cut-off 109 HU; AUC = 0.867) showed high accuracy in diagnosis of BO. Conclusion: The quantification of lung density with chest CT complements the diagnosis by providing additional indications of expiratory airflow limitation in pediatric BO patients.

**ORIGINAL ARTICLE**

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**Keywords:** Bronchiolitis obliterans, densitometry, computed tomography, diagnosis

**Running head:** CT densitometry for the diagnosis of pediatric BO

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**Conclusion:** The quantification of lung density with chest CT complements the diagnosis by providing additional indications of expiratory airflow limitation in pediatric BO patients.

## 1 INTRODUCTION

Bronchiolitis obliterans (BO) is a chronic obstructive lung disease that leads to the irreversible obliteration of the small airways[1,2]. BO can occur with various etiologic factors, including infection, allogeneic hematopoietic stem cell transplantation (HSCT), and organ transplantation[3]. Bronchiolar epithelial cell and subepithelial structural damage and inflammation are the major pathogenesis of BO[4].

Early diagnosis of BO in young children is particularly important, as it affects permanent lung function in the future. The diagnosis of BO is generally based on chest computed tomography (CT) images, along with a combination of PFTs or histologic findings. Common CT findings in patients with BO include bronchiectasis, bronchial wall thickening, and air trapping[5]. Conventionally, spirometry and chest CT findings have been suggested as the two most important standards for the diagnosis of BO. However, a clear diagnosis or assessment of the severity of early childhood BO can often be challenging, as the presence of lumen dilatation and bronchial wall thickening may be discrete or absent in the early stages, and poor coordination often makes PFTs difficult to complete. Hence, it is desirable to develop additional tools that can improve the diagnosis of BO among young children.

The purpose of this study was to evaluate the quantitative diagnostic performance of CT in pediatric BO patients by analyzing various lung density indices (LDIs) based on mean lung density (MLD) measured during inspiration and exhalation using the chest CT quantitative method.

## 2 Subjects and Methods

### 2.1 Study Population

We performed a retrospective chart review of 109 pediatric patients under 18 years of age (range, 2-16yrs) who underwent 3D chest CT from March 2019 to March 2021 at the Department of Pediatrics, Seoul St. Mary's Hospital, College of Medicine at the Catholic University of Korea. Inclusion criteria were (a) physician-diagnosed BO (n=51), patients who underwent 3D chest CT with (b) pre-transplant evaluation in the Department of Hemato-oncology without previous lung disease (n=16), or (c) other respiratory complaints without lung disease (calcification, 8; chest pain, 3; GERD, 2; and inhalation burn, 1; total n=14, Table 1). Both (b) and (c) were included in the control group. Patients with asthma, chronic lung disease of

prematurity, or obstructive lung disease other than BO were excluded from the study (n=26). Patient data with poor cooperation of inhalation and exhalation were also excluded (n=2). All chest CT lung densitometry, spirometry, and body plethysmography was performed with written informed consent obtained from the parent or guardian of each participant.

### 2.2. CT and PFTs

Before CT scanning, all patients received instructed training to achieve full-inspiratory and end expiratory breath hold. CT scans during full inspiration and end expiration were obtained craniocaudally in the supine position throughout the entire thorax without intravenous contrast material. All CT examinations were performed using a helical CT scanner (Somatom Force, Siemens Medical Systems, Erlangen, Germany) using a 250–350 mm field of view, a 512×512 reconstruction matrix, 80˜100 kVp, effective mAs (CARE Dose 4D), and a tube rotation time of 0.25 ms. For lung parenchymal analysis, images were reconstructed using the following parameters: 1 mm thickness, no interval, and Br36 kernel. CT attenuation measurements were taken using the CT Pulmo 3D application in a 3D solution program (Syngovia; Siemens). The application calculated the attenuation coefficient for each voxel in the lung and a frequency distribution of voxels with specific attenuation numbers.

All PFTs were performed with a Vmax instrument (Sensor Medics, VIASYS Healthcare, Yorba Linda, CA) according to guidelines from the American Thoracic Society and European Respiratory Society.

### 2.3 Lung Density Index

For each side of the lungs, separated inspiratory and expiratory lung volumes and densities were measured. We obtained the MLD during inspiration and expiration, and the ratio of end expiratory to inspiratory volume (E/I volume) and MLD (E/I MLD) was calculated. To investigate the threshold of pathologic expiratory airflow limitation, we examined the relative volume percentage between -850 and - 950 HU with an interval of 50 HU. Expiratory low attenuation areas (LAA) below -850 HU to -950 HU threshold (E850, E900, and E950) and high attenuation areas (HAA) above -600 HU to -650 HU threshold (E600 and E650) were measured. Figure 1 shows an example of CT results obtained from a representative subject.

### 2.4 Statistical Analysis

The categorical and continuous variables were compared using the $\chi 2$ and Student's t-test, respectively. Wilcoxon's rank-sum test was used for comparisons of lung density indices in CT scans with and without BO. Correlations between the various quantitative lung density indices and PFT parameters were compared using Spearman's rho ($\rho$), due to the heteroscedastic nature of the data. We also tested the association between LDIs and PFTs in linear regression models, with adjustment for age and sex. In multivariate logistic regression, we analyzed the odds ratio (OR) of the diagnosis of BO by lung density and PFT parameters. Stepwise backward elimination and all subset regressions were performed to select the final model in multivariate analysis. The receiver operating characteristic (ROC) method was performed to evaluate the utility of different lung density parameters for predicting physician-diagnosed BO. Areas under the curve (AUCs) and optimal cut-off points based on maximizing the sum of sensitivity and specificity were calculated for each densitometry parameter. P values of $<0.05$ were considered statistically significant; the statistical analyses were performed using R Version 4.0.5 (https://cran.r-project.org/web/packages/maxstat/index.html). This study was approved by the Institutional Review Board of Seoul St. Mary's hospital.

## 3 RESULTS

### 3.1 Patient Characteristics

The demographic and clinical characteristics of the patients are presented in Table 1. A total of 81 patients, including 30 controls and 51 BO patients, were included in this study. Spirometry and body plethysmography, respectively, were performed on 62 (76.5%) and 56 (69.1%) patients; those who failed PFTs were either too young or were unable to do forced inhalation and exhalation due to severe BO.

Of the 51 BO patients, 44 (86.3%) had previously received HSCT, and 7 post-infectious BO patients (13.7%) were included. The mean age of the control and BO groups was 11.4 and 12.7 years, respectively. In the PFTs, FVC, FEV1, FEV1/FVC, FEF25-75%, RV, DLCO, VA, sRaw, and sGaw were statistically significantly worse in the BO group. Raw% (83.4 ± 36.6 vs. 263.6 ± 234.1; p = 0.006) and sRaw% (114.1 ± 46.4 vs. 463.1 ± 488.2; p = 0.008) were significantly higher. Among the MLD parameters, EXP MLD, MLDD, E/I Volume, E/I MLD, E900, E850, E650, and E600 were all statistically significantly worse in the BO group (Table 1, Figure 2). Expiratory MLD was significantly lower in BO (-731.4 ± 69.6) than in the control group (-659.0 ± 61.6; p < 0.001). In the BO group, the expiratory LAA, E900 (7.7 ± 11.3 vs. 0.4 ± 1.0) and E850 (22.6 ± 21.6 vs. 3.9 ± 9.7) were significantly higher than in the control group, and the HAA, E650 (10.9 ± 7.5 vs. 20.7 ± 10.2) and E600 (13.8 ± 9.2 vs. 26.2 ± 13.8) were statistically significantly lower (all p values < 0.001). There was no significant difference in the above indicators during inspiration.

### 3.2 Linear Regression Analysis

In linear regression analysis, the LDIs showed the strongest correlation with conventional PFTs (Table 2). Specifically, the FEV1 and sRaw showed a significant correlation with LDIs. MLDD (p = 0.015), E/I MLD (p = 0.018), and E/I volume (p = 0.004) showed a statistically significant correlation with FEV1. The indicators that showed a correlation with sRaw were E/I Volume (p = 0.025), E850, E900, and E950 (all p < .001). EXP MLD (p = 0.019), E600, and E650 (all p < .001), which are indicators related to air trapping during exhalation, showed statistically significant correlation with RV.

### 3.3 Logistic Regression and ROC Analysis

Multivariate logistic regression showed the OR of the LDIs for the BO diagnosis (Table 3). PFT parameters related to BO diagnosis were low FEV1 (OR = 0.89, p < .001), FEV1/FVC (OR = 0.89, p < .001), FEF25-75 (OR = 0.94, p < .001), and high RV (OR = 1.03, p < .001). MLDD (OR = 0.98, p < .001), E/I MLD (OR = 1.39, p < .001), E/I Volume (OR = 1.11, p < .001), E900 (OR = 1.42, p = 0.036), and E600 (OR = 0.90, p < .001) were statistically significant densitometry parameters for BO diagnosis.

In the ROC analysis, the optimal cut-off values of each MLD and PFT parameter for BO diagnosis were obtained (Figure 3). The sensitivity, specificity, positive predictive value, negative predictive value, and AUC for each cut-off value of LDIs and PFT parameters are presented in Table 4. The parameters showing high AUC for BO diagnosis were FEF 25-75 (cut-off = 56.0%; AUC = 0.961), FEV1 (cut-off 81%; AUC = 0.931), FEV1/FVC (cut-off = 80%, AUC = 0.897) in PFTs, and E900 (cut-off 1.4%; AUC = 0.920), E/I MLD (cut-off 86.9%; AUC = 0.887), and MLDD (109 HU; AUC = 0.867) in MLD parameters, respectively.

## 4 DISCUSSION

Lung densitometry, that is, lung density measurement, is a quantitative CT measurement method capable of measuring structural abnormalities in the lung based on the characteristics of lung tissue that variably attenuate X-rays. Parenchymal abnormalities can typically result in reduced attenuation in emphysema or cystic lung disease or in increased attenuation, as in pulmonary fibrosis[6]. The presence of pathologic air trapping in the expiratory phase on CT scan has been defined as a parameter for detecting diseases in small airways[7]. In particular, in patients with BO, radiologic detection of bronchial dilatation infrequently precedes the clinical diagnosis of disease; air flow limitation in expiratory CT scans has been suggested as the most appropriate indicator for early diagnosis compared to PFTs and transbronchial biopsy[8,9].

Previous studies performed quantitative CT analysis to detect air trapping in adult patients with COPD[10-12], asthma[13], and lung transplantation[14]. Parameters including density mapping, emphysema or air trapping index, MLD, and 15th percentile density index were analyzed. To the best of our knowledge, there have only been a few quantitative densitometry studies in pediatric patients[15-17].

Our results suggest the possibility of quantitative pulmonary function evaluation through CT in pediatric BO patients, as in 19 (23.5%) out of 81 patients, who were unable to complete spirometry measurement. In our experience, in children aged 4–5, who are younger than the age at which spirometry can be performed, the cooperation of 3D CT to control inspiration and expiration was sufficiently possible. LAA from both -850

and -900 HU thresholds showed a statistically significant correlation with specific airway resistance sRaw in multivariate analysis, indicating high OR and high AUC values for BO diagnosis. In previous studies in adult patients, the attenuation threshold range from -856 to -950 HU has been shown to be the most applicable for identifying pathologic air trapping [10,18-22].

According to previous studies regarding lung development, the lung continuously grows in proportion to body size after birth, but the formation of new alveoli stops around the ages of 2–8[23,24]. During the period of formation of new alveoli, lung density is relatively constant. However, the lung density is expected to decrease according to the growth of the lung, following the increased alveoli airspace volume. Robert et al. showed that the lung structure of subjects with larger lungs differs from those with smaller lungs and that larger lungs have a thinner septum and lower parenchymal density as the air volume in the alveoli increases [25]. Interestingly, our study showed that the densitometry expiratory threshold of airflow limitation is similar to or slightly lower than that of adults. This finding is supported by a previous study, where the overall MLD of a group with an average age of 2 was similar to that of adults [26]. It is also consistent with Christian et al.'s suggested -925 to -950 HU threshold in a recent study, which included adolescents with HIV BO patients with mean ages similar to those in our study [15].

The methods frequently used for quantitative analysis of air trapping using CT include (a) the difference or the ratio of the expiratory/inspiratory MLD and (b) the measurement of the percentage of the lung area showing below the threshold HU during exhalation. Pathologic air trapping was defined as a voxel difference of less than 80 to 110 HU between expiration and inspiration within segmented lung parenchyma [14,27,28]. In our study, the MLDD cut-off of BO diagnosis between expiration and inspiration was 109.0, which is consistent with previous studies. In multivariate linear regression analysis, the difference (MLDD) or the ratio of the expiratory/inspiratory MLD (E/I MLD) showed a strong correlation with FEV1, and the -850 to -950 HU threshold method showed a significant correlation with sRaw (Table 2). This indicates that each LDI and PFT parameter can be independently specific to reflect different anatomical areas that are responsible for pathological lung function.

Previous studies on the E/I ratio of MLD have shown a stronger correlation with the spirometric airflow limitation parameters than the density threshold-based method of air trapping [22,29]. E/I MLD showed a strong correlation with FEV1, FEV1/FVC, FEF25-75, and FRC/TLC ratios as well as markers with respiratory morbidities[14,29]. In our study, in contrast, expiratory -900 HU (E900) showed the highest AUC in the ROC analysis for BO diagnosis compared to other LDIs; this was a single factor that consistently showed a significant strong correlation with the PFT parameter in various correlation analyses.

Our study has multiple strengths. This is a study of lung densitometry in pediatric BO patients, and it extensively investigated the correlation between various densitometry and pulmonary function parameters. We suggested an additional role of quantitative CT in evaluating pulmonary function in difficult pediatric BO patients with poor PFT cooperation and a low reliability of test results. The main limitation of our study is that it is a retrospective study using a small sample size of patients. Since young children have varying lung volumes and structures with age, the patients included in our study are likely heterogeneous populations with varying lung densities. Further study is needed to determine whether a fixed lung density threshold can be applied to pediatric BO patients of various ages.

In conclusion, quantification LDIs obtained through chest CT scans have a significant correlation with conventional PFTs. The ratio of the E/I MLD and the LAA below the threshold -900 HU complements the diagnosis of pediatric BO patients by providing additional quantitative indications of progressive expiratory air flow limitation.

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## IMAGE LEGENDS

**Figure 1.** Example of measurement of densitometry parameters by 3D chest CT of a representative subject in the A) expiratory and B) inspiratory phases

**Figure 2.** Comparison of quantitative lung densitometry indices and conventional PFTs according to diagnosis

**Figure 3.** ROC curves of A) conventional PFT parameters and B) quantitative lung densitometry indices for the diagnosis of bronchiolitis obliterans

A)

Intensity Statistics

| | Total | L | R |
|---|---|---|---|
| Vol. [ml] | 2603 | 1496 | 1107 |
| Rel.Vol. [%] | 100.0 | 57.5 | 42.5 |
| MLD [HU] | -733 | -728 | -740 |
| SD [HU] | 223 | 214 | 234 |
| FWHM [HU] | 149 | 149 | 75 |

Subrange -1000 ... -500 HU

Relative Volumes [%]

| [HU] | Total | L | R |
|---|---|---|---|
| -1000...-951 | 3.6 | 3.5 | 3.8 |
| -950...-901 | 10.7 | 7.4 | 15.0 |
| -900...-851 | 20.3 | 16.2 | 25.8 |
| -850...-801 | 16.6 | 20.3 | 11.7 |
| -800...-751 | 10.8 | 13.6 | 7.2 |
| -750...-701 | 6.9 | 8.0 | 5.4 |
| -700...-651 | 5.2 | 5.6 | 4.5 |
| -650...-601 | 4.2 | 4.4 | 3.9 |
| -600...-551 | 3.5 | 3.6 | 3.4 |
| -550...-501 | 2.8 | 2.9 | 2.8 |

B)

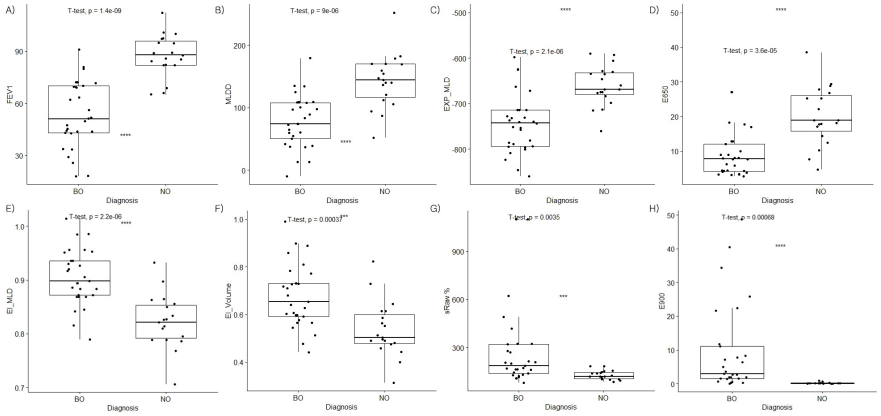
Intensity Statistics

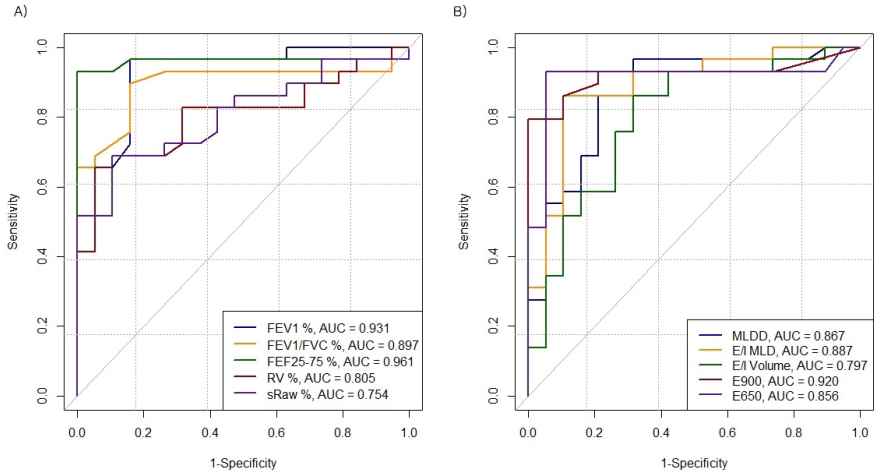
| | Total | L | R |
|---|---|---|---|
| Vol. [ml] | 1418 | 722 | 697 |
| Rel.Vol. [%] | 100.0 | 50.9 | 49.1 |
| MLD [HU] | -598 | -575 | -620 |
| SD [HU] | 233 | 222 | 242 |
| FWHM [HU] | 318 | 377 | 121 |

Subrange -1000 ... -500 HU

Relative Volumes [%]

| [HU] | Total | L | R |
|---|---|---|---|
| -1000...-951 | 2.1 | 1.9 | 2.2 |
| -950...-901 | 1.5 | 1.6 | 1.4 |
| -900...-851 | 3.4 | 4.2 | 2.6 |
| -850...-801 | 9.1 | 6.1 | 12.3 |
| -800...-751 | 12.5 | 6.3 | 18.9 |
| -750...-701 | 9.9 | 7.6 | 12.3 |
| -700...-651 | 9.2 | 10.3 | 8.0 |
| -650...-601 | 8.7 | 11.1 | 6.2 |
| -600...-551 | 8.2 | 10.9 | 5.3 |
| -550...-501 | 6.8 | 9.2 | 4.4 |

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