Diagnostic value of ventilation/perfusion single-photon emission computed tomography/computed tomography for bronchiolitis obliterans syndrome in patients after lung transplantation

Short title: Bronchiolitis obliterans syndrome after lung transplantation

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Abstract

Objective

To evaluate the diagnostic value of function volume/morphological volume ratio calculated from ventilation/perfusion single-photon emission computed tomography/computed tomography in distinguishing the lungs with bronchiolitis obliterans syndrome from the lungs without this syndrome after lung transplantation, and to assess its relationship with spirometry parameters.

Methods

We retrospectively identified 84 consecutive lung transplant recipients and 13 donors who underwent ventilation/perfusion single-photon emission computed tomography/computed tomography. Differences in the function volume/morphological volume ratio of unilateral lungs were tested for significance between the lungs with and without bronchiolitis obliterans syndrome. Receiver operating characteristics and correlations between function volume/morphological volume ratios of bilateral lungs and forced expiratory volume in 1 second, forced vital capacity, and total lung capacity were analysed.

Results

The function volume/morphological volume ratios of ventilation and perfusion images of unilateral lungs were significantly lower in lungs with bronchiolitis obliterans syndrome (each $P < 0.0001$). The area under the curve values of ventilation and perfusion images were 0.97 and 0.99, respectively.

Significant correlations were identified between the function volume/morphological volume ratios of ventilation and perfusion images and forced expiratory volume in 1 second ($r = 0.54$, $P < 0.0001$ and $r = 0.45$, $P < 0.0001$, respectively). The function volume/morphological volume ratio of ventilation image had a significantly weak correlation with forced vital capacity.

Conclusions

The function volume/morphological volume ratio enables a semi-quantitative assessment of ventilation and perfusion lung functions and is useful for diagnosing bronchiolitis obliterans syndrome after lung transplantation.

Keywords

Bronchiolitis obliterans syndrome, Lung transplantation, Forced expiratory volume

Morphological volume, Function volume

Introduction

Lung transplantation is a valuable treatment option for patients with end-stage lung disease, resulting in an improvement in short-term survival. However, bronchiolitis obliterans syndrome (BOS), a major complication resulting in morbidity and mortality, limits the long-term survival of lung transplant recipients [1]. For lung transplant patients with BOS, early azithromycin therapy slows the progression of BOS and is associated with decreased mortality in some patients [2,3]. Therefore, accurate diagnosis of BOS and early intervention are important.

In clinical practice, BOS is defined as a 20% decrease in forced expiratory volume in 1 second (FEV_1) from baseline values after lung transplantation [4]. High-resolution computed tomography (HRCT) is generally used for the diagnosis of BOS by morphological lung imaging [5]. Shinya et al. reported that ^{133}Xe washout imaging is more useful than CT for early detection of BOS [6]. However, in Japan, ^{133}Xe ventilation scintigraphy was not being performed because of discontinued production. Additionally, ^{81m}Kr ventilation/ ^{99m}Tc-macro aggregated human albumin (MAA) perfusion scintigraphy has also served as functional lung imaging for the diagnoses of obstructive pulmonary disease, pulmonary embolism, and detection of bronchiolitis obliterans (BO) [7]. Ouwens et al [8] reported that ^{81m}Kr ventilation scintigraphy was useful in the early diagnosis of

BOS in lung transplant recipients [8]. However, there have been no previous studies quantitatively or semi-quantitatively evaluating the diagnostic capacity of ^{81m}Kr ventilation/ ^{99m}Tc-MAA perfusion scintigraphy in patients with BOS after lung transplantation.

We thus speculated that the semi-quantitative analyses of ventilation/perfusion (V/P) single-photon emission computed tomography/computed tomography (SPECT/CT) images enables the calculation of functional lung volume in BOS and non-BOS lungs and could be a potential tool for clinical diagnosis of BOS after lung transplantation.

The primary aim of this retrospective study was to evaluate the diagnostic value of semi-quantitative analysis based on functional lung volume to morphological lung volume (F/M) ratio in V/P SPECT/CT images for distinguishing BOS lungs from non-BOS lungs after transplantation. An additional aim was to examine the relationship between the parameters of spirometry and F/M ratio.

Material and methods

Study population

In this retrospective observational study, we enrolled 84 consecutive patients after lung transplantation (30 men and 54 women; mean age 42.5 years; range, 11–68 years) and 13 donor patients (four men and nine women; mean age 38.4 years; range, 21–59 years), who underwent V/P SPECT/CT between August 2016 and September 2017 at our institution. The patient characteristics are shown in Table 1. The median duration from lung transplantation to V/P SPECT/CT was 1600 days (range 101- 6622 days). All patients underwent chest CT and spirometry around 0.69 days (range 0 – 13 days) and 0.75 days (range 0 – 13 days) after V/P SPECT/CT, respectively. BOS was diagnosed according to the published standards from the International Society for Heart and Lung Transplantation as a decrease of ≥20% from baseline FEV_1 [4]. We identified BOS lungs based on follow-up CT (4 unilateral lungs) or ^{133}Xe imaging performed a year before V/P SPECT/CT (13 unilateral lungs). We identified air trapping on expiratory CT [4] and prolonged mean transit time on ^{133}Xe images [7] of BOS lungs. When BOS was suspected bilaterally, the F/M ratios of unilateral lungs were adopted as separate image entities. We then classified the images into 17 of BOS lungs and 138 of non-BOS lungs (Fig. 1). The mean duration from the diagnosis of BOS to V/P SPECT/CT imaging was 5.01 years (rang 0 – 14 years). The F/M ratios of 13 donors were adopted for the normal data (donor lungs). Study approval was obtained from our institutional review board (No. 1711-022).

Ventilation/Perfusion single-photon emission computed tomography/computed tomography

Images were acquired using a dual-head hybrid SPECT/CT system (Symbia T16, Siemens AG, Erlangen, Germany) equipped with a low- and medium- energy general-purpose collimator and diagnostic multi-detector spiral CT. SPECT acquisition was performed in a 128 × 128 matrix with a pixel size of 4.8 mm, zoom of 1.0, and noncircular orbit (auto contour) with continuous mode through 360° rotation at 90 angular views. The total acquisition time was 10 min with 1 min/cycle by 10 repeats. The photo-peak window of ^{99m}Tc was 140 keV ± 10%, and scatter window as upper and lower sides of the photo-peak window was 7%. ^{81m}Kr was set at 192 keV ± 10%. After intravenous injection of ^{99m}Tc-MAA 185 MBq in the supine position, ^{81m}Kr gas (185 MBq) was eluted from the ^{81m}Kr generator (Nihon Medi-Physics Co. Ltd., Japan) using humidified oxygen at 2 L/min. The patient continuously breathed ^{81m}Kr gas using a mouth mask. After SPECT scan, low-dose CT scan was performed with shallow free breathing. The CT scan conditions were tube voltage 130 kV, effective 60 mAs with activated adaptive dose modulation CARE Dose4D (Siemens AG, Erlangen, Germany), and 5 mm slice thickness. SPECT data were reconstructed by using an iterative method based on an ordered subset expectation maximization algorithm; subset 10 iteration 15, using resolution correction and CT-based attenuation correction. Post-processing filter using a 3D Gaussian filter full width at half maximum (FWHM) = 14.8 mm (^{81m}Kr gas), 12.5 mm (^{99m}Tc-MAA).

Image data analysis

Morphological lung volumetry

Using CT raw data obtained by SPECT/CT, image reconstruction was performed with a thickness of 1.0 mm and a slice thickness of 0.8 mm. The data was transferred to volumetric analysis of chest 3D computed tomography scan using SYNAPSE VINCENT imaging software (Fuji Film Medical, Tokyo, Japan), and the morphological lung volume of the left and right lungs were automatically calculated.

Function lung volumetry

In the analysis of ventilation SPECT/CT, the bronchus was automatically extracted from the CT image using the VINCENT imaging software, and the CT value range was changed from 0 to 255 by mask processing (Fig. 2a). The matrix size was then changed to 128 × 128 using Syngo MI Applications (Siemens AG, Erlangen, Germany), and the region with the CT value of 100 or more was visualized (Fig. 2b). Subtraction processing was performed on the reconstructed SPECT image (Fig. 2c), SPECT images with bronchi removed were prepared (Fig. 2d). Each of the ventilation SPECT and perfusion SPECT images were used to create a fusion of the SPECT image and CT image. On the fusion image, the region of interest (ROI) was manually set in the right and left lung areas (Fig. 3a). We performed the processes on all the transverse slices of the lungs and semi-automatically calculated the function lung volume using the contour extraction method from the threshold of the maximum voxel count value in the ROI of each slice (Fig. 3b). The threshold was 33% for ventilation SPECT and 18% for perfusion SPECT. These thresholds were determined on the basis of morphological volumes calculated from the SPECT/CT images of donor patients.

Calculations of functional lung volume/morphological lung volume ratios

Using the calculated ventilation/perfusion functional lung volume and morphological lung volume, F/M ratio was calculated as follows:

$$\% F/M = FLV/MLV \times 100\%$$

where FLV represents the functional lung volume of ventilation SPECT and perfusion SPECT, respectively, and MLV is morphological lung volume.

Statistical analysis

In 155 unilateral lungs, the differences in the F/M ratio of ventilation SPECT/CT and perfusion SPECT/CT images between BOS lungs and non-BOS lungs, and between non-BOS and donor lungs, were significant using the Mann-Whitney U-test. We performed a receiver operating characteristic (ROC) analysis to evaluate the diagnostic performance of F/M ratio in ventilation SPECT/CT and perfusion SPECT/CT images. The cut-off value was determined from the point where sensitivity and specificity are nearest to 1 on the ROC curve. Significance was tested using Delong's test for the two AUCs determined from the ROC curve. A value of $P < 0.05$ was considered significant.

In all 84 patients, the relationship between the mean F/M ratio of bilateral lungs and FEV_1, forced vital capacity (FVC), and total lung capacity (TLC) was evaluated for ventilation SPECT/CT and perfusion SPECT/CT images using the Pearson correlation coefficient. All statistical analyses were performed with EZR, which is a graphical user interface for R [9].

Results

Differences in the functional lung volume/morphological lung volume ratios

In the ventilation SPECT/CT images, the mean and standard deviation (SD) of the unilateral F/M ratio was 95.9 ± 16.2 for non-BOS lungs, 43.0 ± 25.0 for BOS lungs, and 99 ± 11.9 for donor lungs; on perfusion SPECT/CT images, these values were 96.3 ± 15.0 for non-BOS lungs, 51.7 ± 19.9 for BOS lungs, and 100.7 ± 9.55 for donor lungs. The unilateral F/M ratio was significantly lower in the BOS lung than in the non-BOS lung on both ventilation SPECT/CT and perfusion SPECT/CT images (ventilation: P <0.001; perfusion: P <0.001) (Fig. 4a, b). However, no significant differences could be identified between the F/M ratio of non-BOS lungs and donor lungs on both ventilation SPECT/CT and perfusion SPECT/CT images (ventilation: P = 0.596; perfusion: P = 0.056).

Receiver operating characteristic analysis of functional lung volume/morphological lung volume ratios

Fig. 5 show the ROC analysis for BOS in unilateral F/M ratio on ventilation SPECT/CT and perfusion SPECT/CT images. The AUC values were 0.97 (95% confidence interval (CI); 0.939 – 1.000) for ventilation SPECT/CT and 0.99 (95% CI; 0.977 – 1.000) for perfusion SPECT/CT images. The optimal cut-off value for F/M ratio with ventilation SPECT/CT was 79.0, yielding a sensitivity 0.855 and specificity of 0.941, and the optimal cut-off value for F/M ratio with perfusion SPECT/CT was 74.1, yielding a sensitivity 0.949 and specificity of 1.000. Delong’s test showed no significant difference in AUCs between ventilation SPECT/CT and perfusion SPECT/CT images ($P = 0.18$).

Functional lung volume/morphological lung volume ratio and the spirometry parameters

The F/M ratio and FEV_1 showed a significant correlation in both ventilation SPECT/CT and perfusion SPECT/CT images (ventilation: $r = 0.54$, $P < 0.001$; perfusion: $r = 0.45$, $P < 0.001$) (Table 2). The ventilation SPECT/CT images showed a significant correlation with FVC; there was no significant correlation observed between FVC and the perfusion SPECT/CT images (Table 2). The F/M ratio and TLC showed no significant correlation in both ventilation SPECT/CT and perfusion SPECT/CT images (Table 2).

Representative case

Representative V/P SPECT/CT images of BOS are shown in Fig. 6. A 42-year-old woman underwent bilateral living-donor lobar lung transplantation for bronchiectasis. A decrease in FEV_1 was observed four years after lung transplantation and she was diagnosed with BOS. A reduction in the accumulation of lung ventilation and perfusion is observed in the left lung (Fig. 6a, b). The F/M ratios of ventilation and perfusion were 113.68% and 110.62%, respectively, in the right lung, and 30.15% and 39.97%, respectively in the left lung.

Discussion

In the present study, we calculated the functional volume obtained from V/P SPECT/CT and the morphological volume obtained from CT images. Moreover, we demonstrated the diagnostic value of F/M ratio, a novel imaging parameter, obtained from V/P SPECT/CT for distinguishing BOS lungs from non-BOS lungs after lung transplantation. We demonstrated that the F/M ratio of the BOS lungs was significantly lower than that of the non-BOS lungs in both ventilation SPECT/CT and perfusion SPECT/CT images. In addition, no significant difference in the F/M ratio between non-BOS lungs and donor lungs was detected in both ventilation SPECT/CT and perfusion SPECT/CT images. The AUC of perfusion SPECT/CT image was slightly higher than that of ventilation SPECT/CT image according to the ROC analysis, with no significant difference. Furthermore, the relationship between the F/M ratio and FEV_1 showed a significant correlation in both ventilation SPECT/CT and perfusion SPECT/CT images. The F/M ratio of ventilation and FVC had a significantly weak correlation; no significant correlation observed between the F/M ratio of perfusion and FVC. In addition, no significant difference was detected in the correlations between the F/M ratio and TLC in both ventilation SPECT/CT and perfusion SPECT/CT images.

BOS is an obstructive pulmonary disease in which small airways are obstructed by inflammation and fibrosis [10]. In BOS lungs, a decrease in accumulation of lung ventilation is observed using ^{81m}Kr gas [8]. Accumulation decline is observed with V/P scintigraphy in patients with BO [6]. Using both ventilation SPECT/CT and perfusion SPECT/CT images, we demonstrated that F/M ratio of the unilateral BOS lungs was significantly lower than that of non-BOS lungs. Furthermore, the F/M ratio showed an extremely high diagnostic performance. We considered that stenosis of the airway decreases volume of ventilation and pulmonary perfusion due to hypoxic pulmonary vasoconstriction (HPV). HPV is fundamental physiological mechanism to optimize the ventilation perfusion matching [11]. In the present study, the F/M ratio correlated with the decreased accumulation on ventilation SPECT/CT and perfusion SPECT/CT images. Furthermore, the F / M ratio was significantly correlated with FEV1, which is a parameter of obstructive ventilatory impairment. These results suggest that, on ventilation SPECT/CT and perfusion SPECT/CT images, the F/M ratio may be a useful tool for differentiating a BOS lung from a non-BOS lung after lung transplantation and for the evaluation of the lung function.

Previous studies have shown a correlation between semi-quantitative values of ^{81m}Kr lung ventilation scintigraphy and FEV_1 in chronic obstructive pulmonary disease (COPD) [12]. The semi-quantitative values of ^{99m}Tc lung perfusion scintigraphy have been reported to significantly correlate with the pulmonary function and severity of COPD [13]. We demonstrated that the FEV_1, a parameter used for the diagnosis of obstructive pulmonary disease after lung transplantation, demonstrated a significant correlation with the F/M ratio of ventilation SPECT/CT and perfusion SPECT/CT images. FVC, a parameter of restrictive ventilatory impairment, was significantly correlated with the F/M ratio of ventilation SPECT/CT image, but the correlation was weak. There was no correlation between the F/M ratio and TLC, a parameter of restrictive ventilatory impairment, in both ventilation SPECT/CT and perfusion SPECT/CT images. These findings suggest that the semi-quantitative analyses in ventilation SPECT/CT and perfusion SPECT/CT studies enable the assessment of lung function and may be a potential tool for the diagnosis of BOS and the semi-quantitative evaluation for the obstructive lung diseases after lung transplantation. In addition, the F/M ratio is a parameter for an obstructive ventilatory impairment rather than a restrictive ventilatory impairment, and may be a potential tool for diagnosing other obstructive pulmonary diseases.

Lung transplants may be single or bilateral. Living-donor lobar lung transplantation especially requires two donor lobar lungs of different origins; BOS may develop in the unilateral or bilateral lobes, and the development of BOS is predominant in unilateral lungs than in bilateral lungs [14]. When the unilateral lung is affected with BOS, the potential ability of the unaffected lobes to maintain lung function may mask the decline in FEV_1% of the affected lung [14], which evaluates the ventilation function of bilateral lungs. The F/M ratio on V/P SPECT/CT images provides selective information on separate graft function, which would be useful for clinical evaluation of the obstructive lung disease including BOS following lung transplants.

In V/P SPECT/CT performed in clinical settings, misregistration between the SPECT image and CT image may occur due to respiratory lung motion. Therefore, we performed V/P SPECT/CT during shallow free breathing. In this study, the F/M ratio of ventilation SPECT/CT and perfusion SPECT/CT was significantly correlated with FEV_1%, and high AUC was obtained. We speculated that misregistration could be reduced by performing SPECT and CT with shallow free breathing using the SPECT/CT system [15]. The studies by Suga et al [16-18] reported that using a respiratory gating technique and breath-hold reduced the effects of respiratory lung motion and improved the accuracy of the fusion of SPECT/CT images [16-18]. Therefore, using a respiratory gating technique and breath-hold may have the potential to improve the diagnostic accuracy of the F/M ratio.

Our results confirm a high diagnostic performance of F/M ratio on ventilation

SPECT/CT and perfusion SPECT/CT images for BOS lungs. In addition, no significant difference in AUCs between ventilation SPECT/CT and perfusion SPECT/CT images was observed. The results demonstrated that BOS can be diagnosed with either ventilation SPECT/CT or perfusion SPECT/CT. However, since the F/M ratio of perfusion SPECT/CT also decreases with pulmonary vascular lesions, F/M ratio of perfusion SPECT/CT alone is not suitable for diagnosing BOS, especially when pulmonary vascular disease cannot be excluded as a possible diagnosis. In addition, the effective dose of ^{81m}Kr gas is lower than that of ^{99m}Tc-MAA [19] and the ^{81m}Kr gas ventilation SPECT/CT could reduce the patient radiation exposure when compared to V/P SPECT/CT and ^{99m}Tc-MAA perfusion SPECT/CT. Therefore, we consider that the BOS can be sufficiently diagnosed only using ventilation SPECT/CT after lung transplantation in clinical practice.

Our study has several limitations. First, the number of subjects was relatively small. Second, selection of BOS lungs was based on follow-up CT, or ^{133}Xe washout imaging performed a year before undergoing V/P SPECT/CT, without pathological findings. Third, pulmonary vascular lesions could not be excluded because of lack of pathological diagnosis. However, transbronchial lung biopsy or video-assisted thoracoscopic surgery after lung transplantation for the detection of BOS, is invasive and may not provide an adequate sample. Examination of a larger number of patients in a prospective study comparing ventilation and perfusion SPECT/CT in BOS and non-BOS lungs would be useful in evaluating the lung function after lung transplantation. However, despite these limitations, our results suggest that F/M ratio is a useful semi-quantitative index for BOS lungs and may have the potential to diagnose drug-induced BOS and other obstructive pulmonary diseases. In addition, there is a possibility that it is useful for identifying the position of the target when performing biopsy.

Conclusion

We examined the diagnostic value of the F/M ratio, a semi-quantitative parameter calculated using V/P SPECT/CT. The results of this study suggested that the F/M ratio allows semi-quantitative evaluation, and could distinguish BOS lungs from non-BOS lungs after lung transplantation with a high diagnostic accuracy. Furthermore, the F/M ratio correlated with FEV_1 and therefore, it could selectively provide information on lung ventilation and perfusion.

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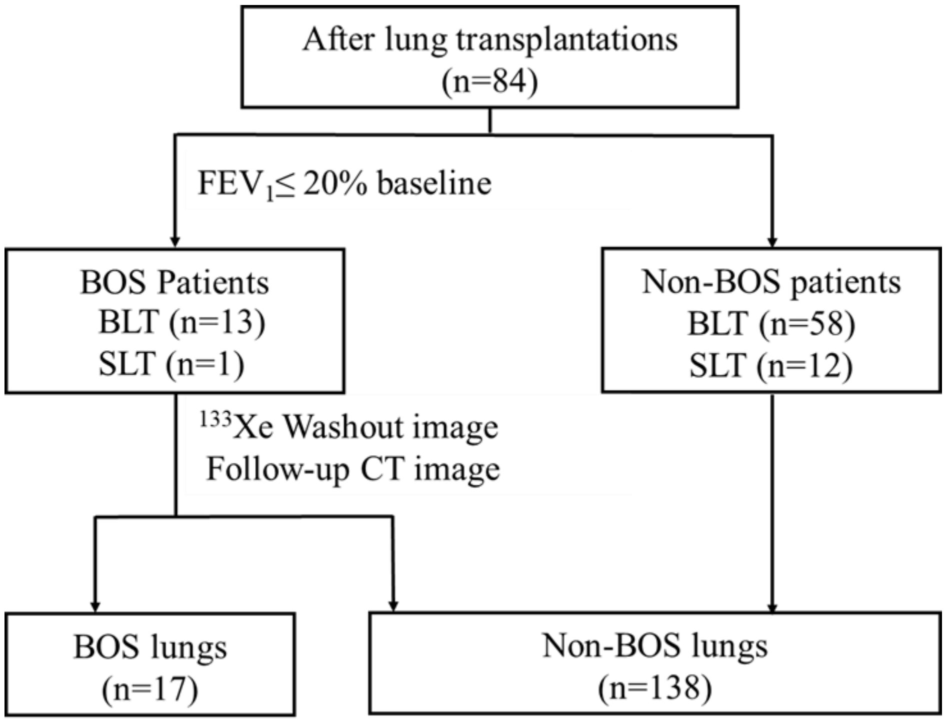

After lung transplantations
(n=84)
FEV1≤ 20% baseline
BOS Patients
BLT (n=13)
SLT (n=1)
Non-BOS patients
BLT (n=58)
SLT (n=12)
133Xe Washout image
Follow-up CT image
BOS lungs
(n=17)
Non-BOS lungs
(n=138)

Fig. 1

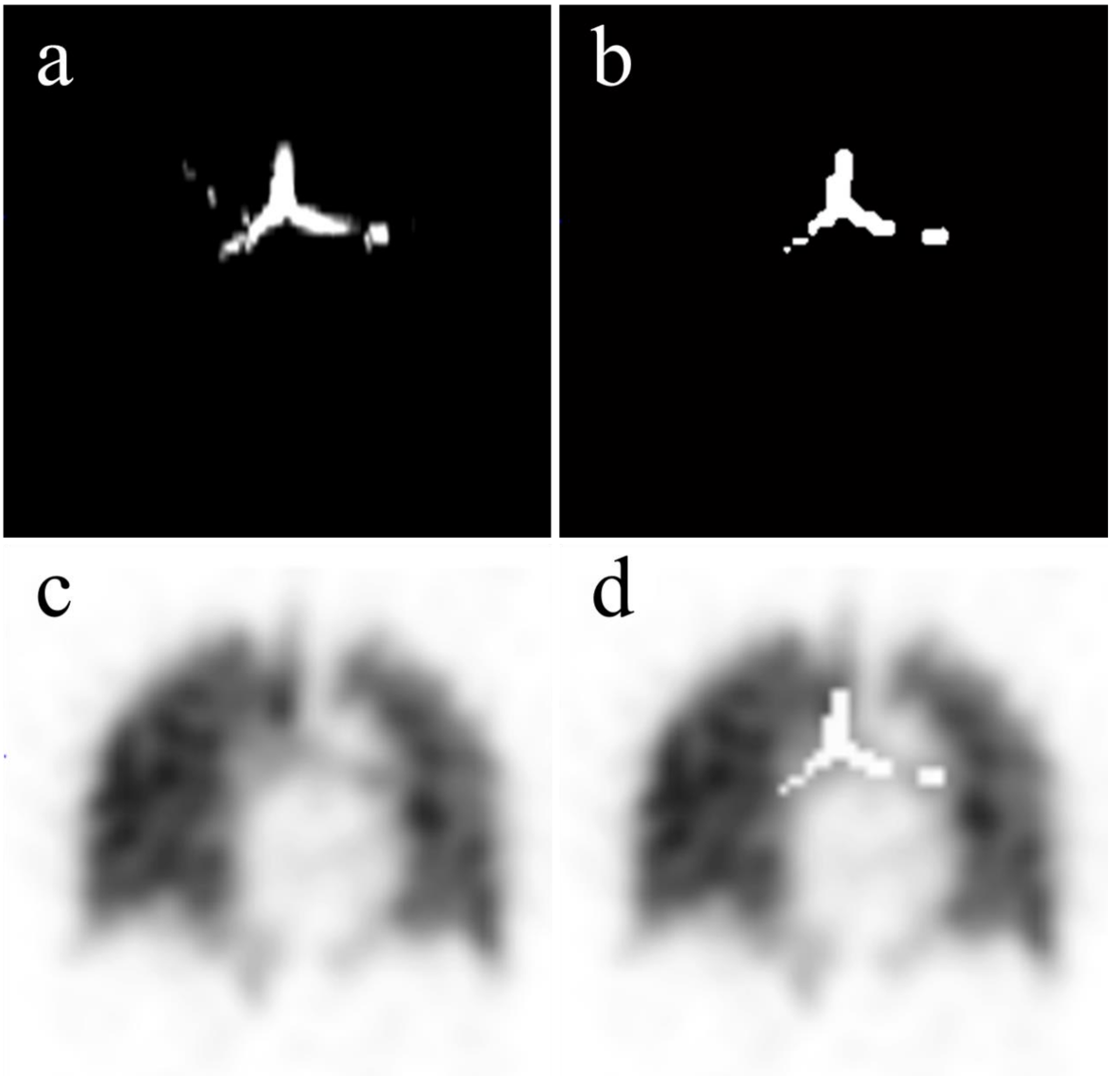


Fig. 2

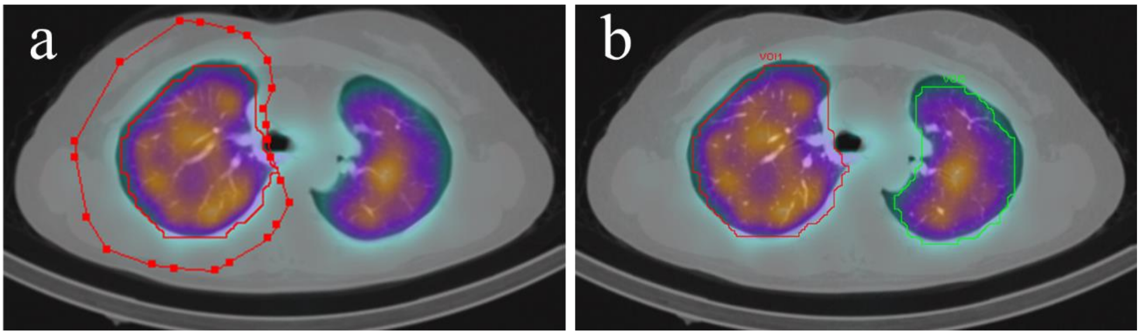
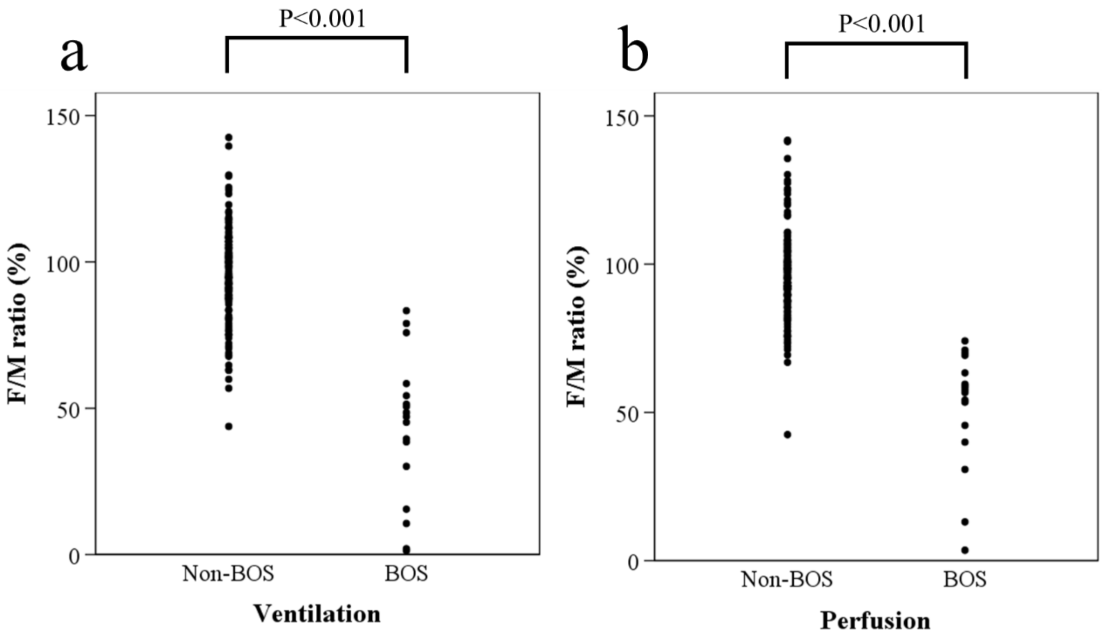


Fig. 3


a
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F/M ratio (%)
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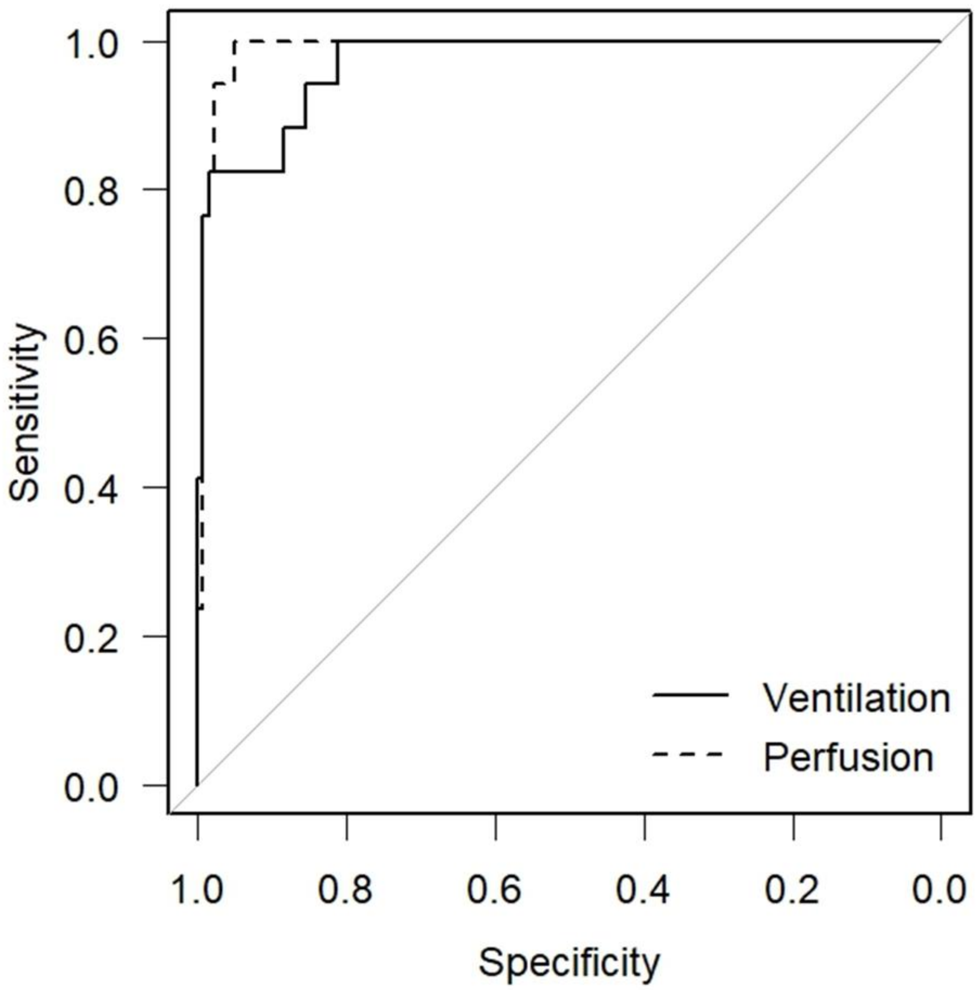
50
0
F/M ratio (%)
Non-BOS
BOS
Perfusion

Fig. 4


1.0
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Specificity

Fig. 5

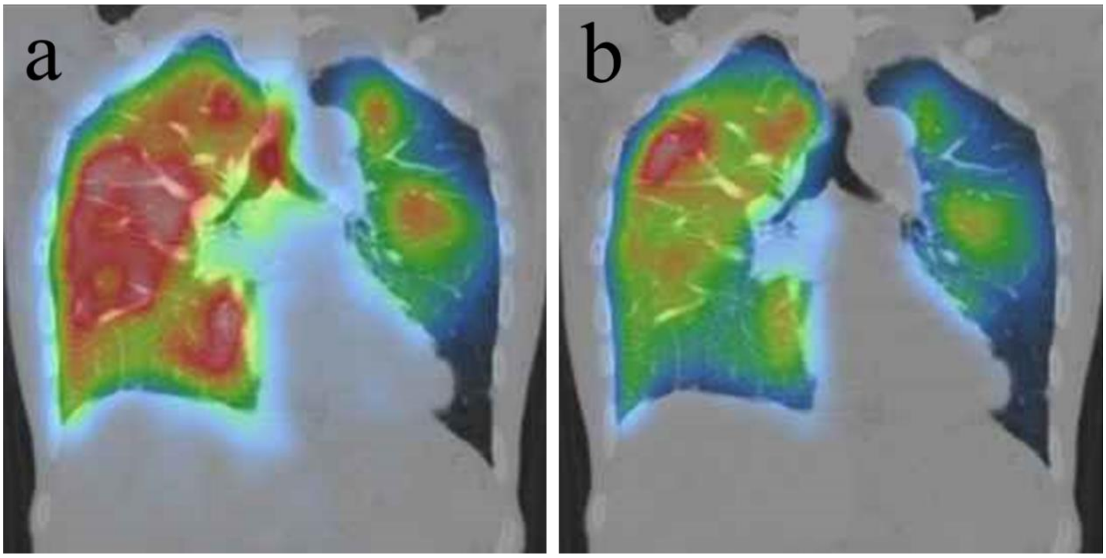

Fig. 6

Table 1 Patient characteristics

	All patients	BOS patients	Non-BOS patients	Donor patients
Number of Patients	84	14	70	13
Age in years (mean ± SD)	41.61 ± 14.45	41.71 ± 10.99	41.59 ± 15.05	38.38 ± 7.48
Gender (male/female)	30/54	6/8	24/46	4/9
Tx Type (BLT/SLT)	71/13	13/1	58/12	
Tx Graft (CLT/LDLLT/ both)	47/34/3	6/8/1	41/29/2	
Number of subject lungs	155	17	138	26

BOS: bronchiolitis obliterans syndrome, SD: standard deviation, Tx: transplant, BLT: bilateral lung transplant, SLT: single-lung transplant, CLT: cadaveric lung transplantation, LDLLT: living-donor lobar lung transplantation

Table 2 Correlation analysis of the functional volume/morphological volume ratios and the parameters of spirometry

	F/M ratio of ventilation		F/M ratio of perfusion	
	R (95% CI)	P value	r (95% CI)	P value
FEV_1 (L)	0.542 (0.370 - 0.677)	P <0.0001*	0.446 (0.256 - 0.603)	P <0.0001*
FVC (L)	0.284 (0.0741 - 0.470)	P = 0.009*	0.159 (-0.057 - 0.361)	P = 0.148
TLC (L)	0.00717 (-0.145 - 0.282)	P = 0.517	0.00355(0.256 - 0.211)	P = 0.974

* P <0.05, significant correlation; F/M: functional volume/morphological volume; R: correlation coefficient, CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity; L: litre

Figure Legends

Fig. 1 Overview of study population distribution. This study included 84 patients.

FEV_1: forced expiratory volume in 1 second; BOS: bronchiolitis obliterans syndrome, BLT: bilateral lung transplant, SLT: single lung transplant; CT: computed tomography.

Fig. 2 Ventilation image processing method. a. A computed tomography (CT) image of the bronchus. b. A CT image of the bronchus with a matrix size of 128 × 128. c. A single-photon emission computed tomography (SPECT) image of ventilation. D. A SPECT image of ventilation after mask processing.

Fig. 3 Function lung volume analysis method. a. On the fusion image (ventilation single-photon emission computed tomography/computed tomography image), the external region of interest (ROI) was manually set to the right lung area, and the internal ROI was set by the threshold method (33%). b. Right and left ROIs are set for all transverse lung slices.

Fig. 4 Comparison of the functional volume/morphological volume (F/M) ratio between bronchiolitis obliterans syndrome (BOS) and non-BOS lungs. a. The F/M ratio of ventilation single-photon emission computed tomography/computed tomography (SPECT/CT). b. The F/M ratio of perfusion SPECT/CT.

Fig. 5 Receiver operating characteristic curve for differentiation of bronchiolitis obliterans syndrome (BOS) and non-BOS lungs using functional volume/morphological volume ratio. The area under the curve for ventilation single-photon emission computed tomography/computed tomography (SPECT/CT) and perfusion SPECT/CT were 0.97 and 0.99, respectively.

Fig. 6 Representative ventilation/perfusion single-photon emission computed tomography/computed tomography (SPECT/CT) images of a 42-year-old woman with bronchiolitis obliterans syndrome. a. Ventilation SPECT/CT fused image. b. Perfusion SPECT/CT fused image. A reduction in the accumulation of lung ventilation and perfusion is observed in the left lung.