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Comparing spirometry, impulse oscillometry with computed tomography for assessing small airway dysfunction in subjects with and without chronic obstructive pulmonary disease

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Abstract

Background Studies on consistency among spirometry, impulse oscillometry (IOS), and histology for detecting small airway dysfunction (SAD) remain scarce. Considering invasiveness of lung histopathology, we aimed to compare spirometry and IOS with chest computed tomography (CT) for SAD detection, and evaluate clinical characteristics of subjects with SAD assessed by these three techniques.

Methods We collected baseline data from the Early COPD (ECOPD) study. CT-defined SAD was defined as parametric response mapping quantifying SAD (PRM^{fSAD}) ≥ 15%. Spirometry-defined SAD was defined as at least two of maximal mid-expiratory flow (MMEF), forced expiratory flow 50% (FEF50), and forced expiratory flow 75% (FEF75) less than 65% of predicted. IOS-defined SAD was defined as peripheral airway resistance R5 – R20 > 0.07 kPa/L/s. The consistency of spirometry, IOS and CT for diagnosing SAD was assessed using Kappa coefficient. Correlations among the three techniques-measured small airway function parameters were assessed by Spearman correlation analysis.

Results 2055 subjects were included in the final analysis. There was low agreement in SAD assessment between spirometry and CT (Kappa = 0.126, 95% confidence interval [CI]: 0.106 to 0.146, $p < 0.001$), between IOS and CT (Kappa = 0.266, 95% CI: 0.219 to 0.313, $p < 0.001$), as well as among spirometry, IOS, and CT (Kappa = 0.056, 95% CI: 0.029 to 0.082, $p < 0.001$). The correlation was moderate (|r|: 0.5 to 0.7, $p < 0.05$) between spirometry and CT-measured small airway function parameters, and weak (|r|< 0.4, $p < 0.05$) between IOS and CT-measured

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small airway function parameters. Only spirometry-defined SAD group had more lower lung function (FEV_1/FVC: adjusted difference=-10.7%, 95% CI: -13.5% to -7.8%, $p<0.001$) and increased airway wall thickness (Pi 10: adjusted difference = 0.3 mm, 95% CI: 0 to 0.6 mm, $p=0.046$) than only CT-defined SAD group. Only IOS-defined SAD group had better lung function (FEV_1/FVC: adjusted difference = 3.9%, 95% CI: 1.9 to 5.8%, $p<0.001$), less emphysema (inspiratory LAA_{-950}: adjusted difference=-2.1%, 95% CI:-3.1% to -1.1%, $P<0.001$; PRM^{Emph}: adjusted difference=-2.3%, 95% CI: -3.2% to -1.4%, $p<0.001$), and thicker airway wall (Pi 10: adjusted difference = 0.2 mm, 95% CI: 0.1 mm to 0.4 mm, $p=0.005$) than only CT-defined SAD group.

Conclusions There was low consistency in the assessment of SAD between spirometry and CT, between IOS and CT, as well as among spirometry, IOS, and CT.

Clinical trial number Not applicable.

Keywords Computed tomography, Impulse oscillometry, Parametric response mapping, Small airway dysfunction, Spirometry

Introduction

In the small airways, which are defined as peripheral airways with an internal diameter < 2 mm, pathological alterations are difficult to detect [1]. Narrowing and loss of the small airways occurs before emphysema onset in patients with chronic obstructive pulmonary disease (COPD) [2]. A recent study demonstrated a reduction in the number of small airways and airway remodeling in participants without airflow obstruction [3]. Assessment of small airway dysfunction (SAD) provides essential information for the early detection and intervention of COPD [4].

The methods for assessing SAD include lung histology, spirometry, impulse oscillometry (IOS), chest computed tomography (CT), micro-computed tomography, endobronchial optical coherence tomography, body plethysmography, inert gas washout, and hyperpolarized magnetic resonance imaging, amongst others [4]. Lung histology, micro-computed tomography, and endobronchial optical coherence tomography can directly evaluate the histological characteristics of the small airways, such as their number, diameter, and wall thickness. However, the clinical application of these techniques is limited because of their invasiveness [3, 5, 6]. Currently, the routine clinical assessments for SAD include spirometry, IOS, and chest CT, which can be used to indirectly assess changes in small airway function.

Inconsistency in the ability of different examination methods to diagnose SAD affects the assessment of SAD in clinical practice. Previous studies have found that parametric response mapping (PRM)-based CT metrics to quantify functional SAD (PRM^{fSAD}) is closely related to a decrease in the number of terminal bronchioles, luminal narrowing, and occlusion in COPD [7]. However, there are currently no studies comparing the use of spirometry, IOS, and histopathology for SAD detection. And not all patients can undergo spirometry or IOS before obtaining lung tissue samples for histopathology. Hence, in this study, we compared spirometry and IOS with chest CT for SAD detection. We also evaluated the clinical characteristics of subjects with SAD assessed by these three techniques.

Methods

Study design and population

This study is based on the baseline data collected in the Early Chronic Obstructive Pulmonary Disease (ECOPD) cohort study, which is a community-based study conducted in the cities of Guangzhou, Shaoguan, and Heyuan in Guangdong Province, China. The cohort details have been reported previously [8]. Briefly, subjects aged between 40 and 80 years who completed standardized respiratory epidemiology questionnaires, spirometry, IOS, and chest CT that met quality control were included.

Data collection

Questionnaires based on the Chinese epidemiological questionnaire for COPD were done at enrollment [9]. The self-reported severity of chronic respiratory symptoms was assessed according to the COPD Assessment Test (CAT) score and the modified British Medical Research Council (mMRC) questionnaire [10]. Acute respiratory events/exacerbations were defined as the onset or worsening of at least two of the following symptoms: cough, sputum, purulent sputum, wheezing, and dyspnea for at least 48 hours, after excluding cardiac insufficiency, pulmonary embolism, pneumothorax, pleural effusion, and arrhythmia [11, 12]. Spirometry was performed based on the 2005 European Respiratory Society and American Thoracic Society guidelines, and IOS was performed based on the European Respiratory Society standards [13–15]. In addition to maximal mid-expiratory flow (MMEF), forced expiratory flow 50% (FEF50), and forced expiratory flow 75% (FEF75), the 1993 regression equation of the European Community for Steel and Coal was multiplied by the Chinese conversion factor to calculate predicted spirometry values [16, 17]. Chest CT

was performed at full inspiration (total lung capacity) and full expiration (residual volume) using the Siemens Definition AS Plus 128-slice and United-imaging uCT 760 128-slice scanners [8]. We instructed subjects to perform deep inhalation and deep exhalation to ensure that lung volume in the inspiratory phase approached total lung capacity, while lung volume in the expiratory phase approached residual volume. CT scanning was performed only after subjects successfully completed deep breathing training, thereby ensuring the quality of the scans.

Variable definitions

CT-defined SAD was defined as PRM^{fSAD} ≥15%[18]. Spirometry-defined SAD was defined as at least two of MMEF, FEF50, and FEF75 less than 65% of the predicted value [19]. IOS-defined SAD was defined as a difference between resistance at 5 Hz and 20 Hz (R5 – R20) > 0.07 kPa/L/s [20, 21]. Emphysema was defined when the percentage low-attenuation area was below − 950 Hounsfield units on full-inspiration CT (inspiratory LAA_{-950}), and air trapping was defined when the percentage low-attenuation area was below − 856 Hounsfield units on full-expiration CT (expiratory LAA_{-856}) [22]. Pi 10 is the square root of the wall area of a hypothetical airway with 10 mm internal perimeter [23, 24]. PRM based on quantitative inspiratory and expiratory CT measurements was used to assess emphysema (PRM^{Emph}) and functional SAD (PRM^{fSAD}) [25]. Preserved spirometry was defined as postbronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio was ≥ 0.70 [26].

Statistical analysis

Quantitative data are expressed as the mean ± standard deviation, while categorical data are expressed as number (percentage). Group differences were compared using one-way analysis of variance, the χ^2 test, or Fisher's exact test, as appropriate. Bonferroni correction (equal variance assumed) or Tamhane's T2 correction (equal variance not assumed) was applied to adjust for multiple comparisons. Multivariable linear regression analysis was used to compare the chronic respiratory symptom scores, spirometry, IOS, and chest CT continuous variables to adjust for confounders. Adjusted confounders included age, sex, body mass index (BMI), smoking status, smoking index, occupational exposure history, biomass exposure history, and family history of respiratory disease. The Kappa coefficient was used to compare the agreement between spirometry, IOS, and CT for the diagnosis of SAD [27]. Spearman's correlation coefficient was used to evaluate the correlations among the small airway functional parameters measured by spirometry, IOS, and CT. The correlation coefficients were interpreted as follows: 0 <|r| < 0.3 = weak correlation; 0.3 <|r| < 0.7 = moderate correlation; and|r| > 0.7 = strong correlation [28]. To evaluate the robustness of the results, we used expiratory LAA_{-856} ≥15% to replace PRM^{fSAD} ≥15% as the CT diagnostic criterion for SAD to perform the sensitivity analysis, and we performed subgroup analyses in subjects with preserved spirometry. Besides, we used Chinese spirometry reference values to replace reference values of the 1993 regression equation of the European Community for Steel and Coal for spirometry indices to define SAD. All statistical analyses were performed using IBM SPSS V.29.0 software and GraphPad Prism V.8.0 software. A two-tailed p value of < 0.05 was considered statistically significant.

Results

Study sample

Figure 1 showed the study flow chart. 2055 subjects were included in the ECOPD study. Of the 2052 subjects with SAD-related spirometry parameters, 81.9% (1680/2052) subjects met the diagnostic criteria for SAD. Of the 1862 subjects with SAD-related IOS parameters, 32.4% (604/1862) subjects met the IOS diagnostic criteria for SAD.

Consistency among the three techniques for SAD diagnosis

The diagnostic consistency among spirometry, IOS, and CT was shown in Fig. 2. There was a poor level of agreement between spirometry and CT in the assessment of SAD (Kappa = 0.126, 95% confidence interval [CI]: 0.106 to 0.146, $p < 0.001$) (Fig. 2a). Overall, 1,142 subjects (55.7%) were classified as having discordance in the diagnosis of SAD between spirometry and CT. There was a fair level of agreement between IOS and CT in the assessment of SAD (Kappa = 0.266, 95% CI: 0.219 to 0.313, $p < 0.001$) (Fig. 2b). Specifically, 578 subjects (30.0%) demonstrated discordance in the diagnosis of SAD between IOS and CT. The agreement between spirometry, IOS, and CT was very poor (Kappa = 0.056, 95% CI: 0.029 to 0.082, $p < 0.001$) (Fig. 2c).

Correlations among spirometry, IOS, and CT parameters for SAD diagnosis

Figure 3 showed the correlations among spirometry, IOS, and CT-measured small airway function parameters in all subjects. The absolute correlation coefficients between SAD-related spirometry parameters (MMEF, FEF50, and FEF75 as a percentage of the predicted value) and CT parameters (PRM^{fSAD} and expiratory LAA_{-856}) ranged from 0.5 to 0.7 (all $p < 0.05$), while the absolute correlation coefficients between SAD-related IOS parameters (R5 – R20, reactance at 5 Hz (X5), reactance area (AX), and resonant frequency in Hz (Fres)) and CT parameters

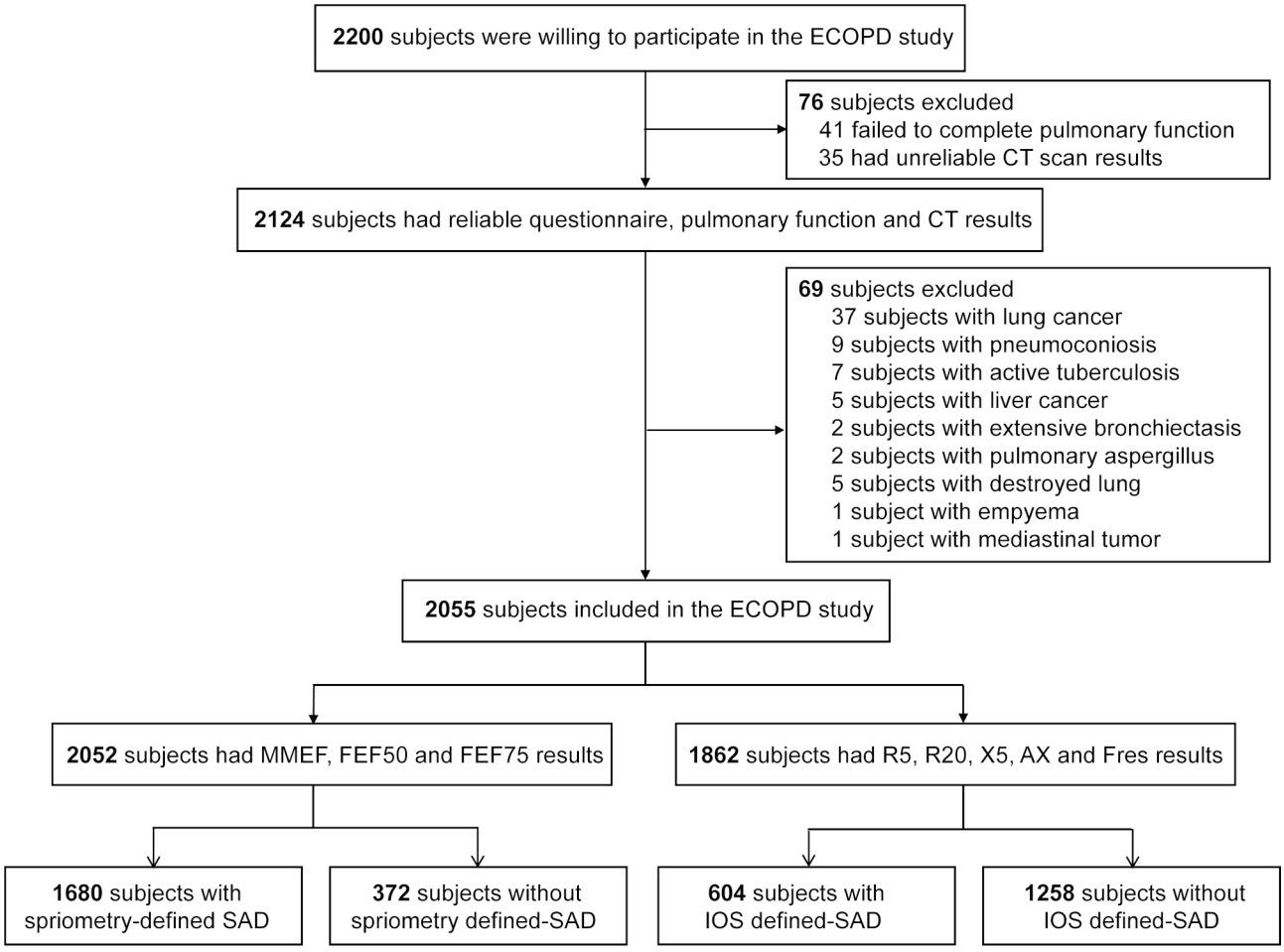

Fig. 1 Study flow chart. Abbreviations: ECOPD, Early Chronic Obstructive Pulmonary Disease; CT, computed tomography; MMEF, maximal mid-expiratory flow; FEF50, forced expiratory flow 50%; FEF75, forced expiratory flow 75%; R5, resistances at 5 Hz; R20, resistances at 20 Hz; X5, reactance at 5 Hz; AX, reactance area; Fres, resonant frequency in Hz; SAD, small airway dysfunction; IOS, impulse oscillometry

(PRM^{fSAD} and expiratory LAA_{-856}) were all less than 0.4 (all $p < 0.05$).

Clinical characteristics of SAD patients defined by spirometry and CT

Table 1 showed characteristics of SAD patients diagnosed by spirometry and CT in 2052 subjects. Only spirometry-defined SAD group was younger (60.3 ± 7.7 years old vs. 64.8 ± 6.9 years old, $p < 0.05$) and had higher BMI (23.4 ± 3.2 kg/m^2 vs. 21.1 ± 2.0 kg/m^2, $p < 0.05$) compared with only CT-defined SAD group. There were no significant differences in smoking status, smoking index, biomass exposure, occupational exposure, family history of respiratory diseases, clinical symptoms and acute respiratory events in the prior year between only spirometry-defined SAD and only CT-defined SAD groups. Compared with no SAD with spirometry and CT group, only CT-defined SAD group was older (64.8 ± 6.9 years old vs. 56.0 ± 7.4 years old, $p < 0.05$) and had lower BMI (21.1 ± 2.0 kg/m^2 vs. 23.9 ± 3.0 kg/m^2, $p < 0.05$).

Table 2 showed chronic respiratory symptoms, spirometry, IOS, and CT results of patients with SAD diagnosed by spirometry and CT in 2052 subjects. The mMRC score and CAT score were not significantly different between only spirometry-defined SAD and only CT-defined SAD groups. Only spirometry-defined SAD group had lower prebronchodilator FEV_1 percentage of predicted value (adjusted difference=-17.6%, 95% CI: -23.4% to -11.8%, $p < 0.001$) and FEV_1/FVC (adjusted difference=-10.7%, 95% CI: -13.5% to -7.8%, $p < 0.001$) compared with only CT-defined SAD group after covariates adjustment. But there was no statistical significance in prebronchodilator FVC percentage of predicted value between only spirometry-defined SAD and only CT-defined SAD groups. Compared with only CT-defined SAD group, the prebronchodilator spirometry parameters of SAD (MMEF, FEF50, and FEF75 as a percentage of the predicted value) were lower (all $p < 0.05$) in only spirometry-defined SAD group after covariates adjustment. Compared with only CT-defined SAD group, Fres was significantly

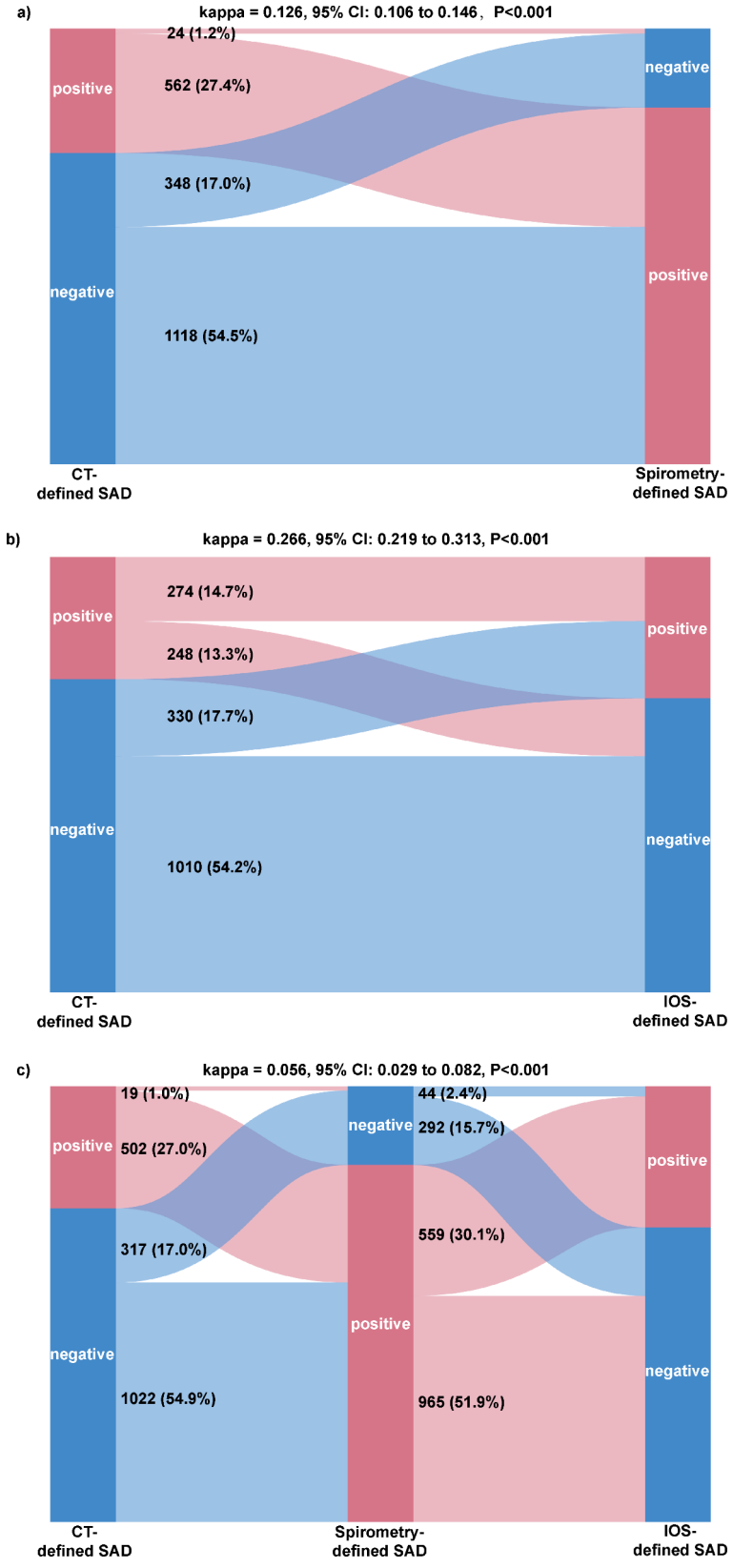

Fig. 2 Comparing consistency of three techniques for diagnosing small airway dysfunction in all subjects. Data are shown as n (%). Abbreviations: CI, confidence interval; CT, computed tomography; SAD, small airway dysfunction; IOS, impulse oscillometry

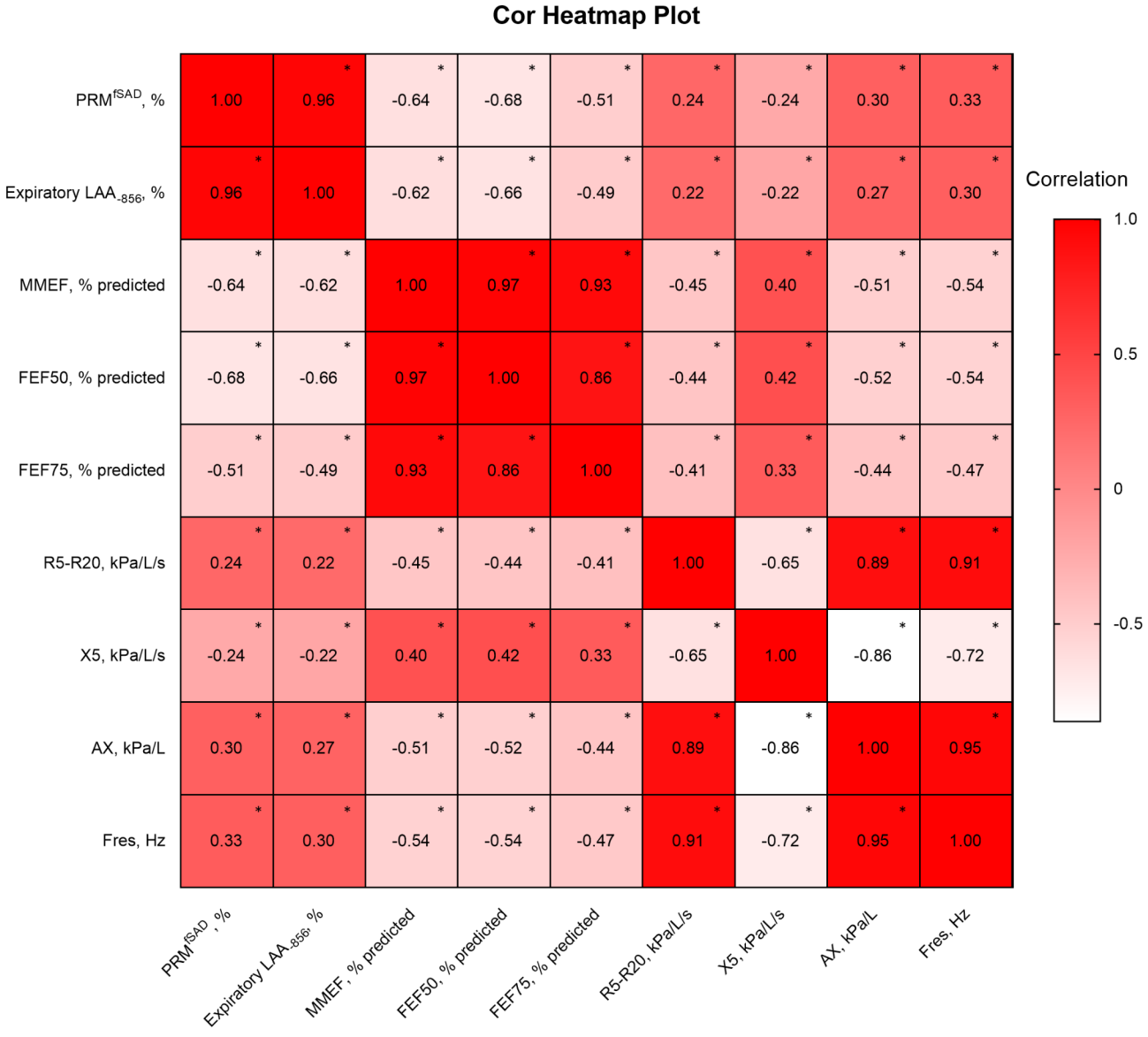

Fig. 3 Spearman correlation coefficients of computed tomography, spirometry, and impulse oscillometry parameters. $^{*}P < 0.05$. Abbreviations: PRM, parametric response mapping; fSAD, functional small airway disease; LAA $_{-856}$, the low-attenuation area below −856 Hounsfield units on full-expiration computed tomography; MMEF, maximal mid-expiratory flow; FEF50, forced expiratory flow 50%; FEF75, forced expiratory flow 75%; R5-R20, resistances at 5 and 20 Hz; X5, reactance at 5 Hz; AX, reactance area; Fres, resonant frequency in Hz

higher (adjusted difference = 2.56 Hz, 95% CI: 0.58 Hz to 4.54 Hz, $p = 0.011$) in only spirometry-defined SAD group but R5 – R20, X5, and AX were not significantly different after covariates adjustment. PRM^{fSAD} (adjusted difference=-22.0%, 95% CI: -23.8% to -20.3%, $p < 0.001$) and expiratory LAA$_{-856}$ (adjusted difference=-22.9%, 95% CI: -25.4% to -20.5%, $p < 0.001$) were significantly lower, but Pi 10 (adjusted difference = 0.3 mm, 95% CI: 0 to 0.6 mm, $p = 0.046$) was significantly higher in only spirometry-defined SAD group than only CT-defined SAD group after covariates adjustment.

Clinical characteristics of SAD patients defined by IOS and CT

Table 3 showed characteristics of SAD patients diagnosed by IOS and CT in 1862 subjects. Only IOS-defined SAD group was younger (61.1 ± 8.3 years old vs. 65.9 ± 6.7 years old, $p < 0.05$) and had a lower proportion of men (56.7% vs. 93.5%, $p < 0.05$), higher BMI (24.6 ± 3.1 kg/m^2 vs. 20.7 ± 2.7 kg/m^2, $p < 0.05$), a lower proportion of current smokers (34.2% vs. 58.5%, $p < 0.05$), lower smoking index (22.1 ± 31.3 pack years vs. 31.8 ± 26.5 pack years, $p < 0.05$), and a lower proportion of chronic cough patients(24.8% vs. 36.3%, $p < 0.05$) than only CT-defined SAD group. There were no significant differences in

Table 1 Characteristics of 2052 subjects stratified by small airway dysfunction status based on spirometry and computed tomography diagnosis

Variable	No SAD with spirometry and CT[§] (*n* = 348)	Combined spirometry and CT-defined SAD[¶] (*n* = 562)	Only spirometry-defined SAD[#] (*n* = 1118)	Only CT-defined SAD[**] (*n* = 24)	*P* value
Age, year	56.0 ± 7.4	66.4 ± 6.6[*]	60.3 ± 7.7[*†]	64.8 ± 6.9[*‡]	**< 0.001**
Male, n (%)	207 (59.5)	516 (91.8)[*]	755 (67.5)[*†]	18 (75.0)[†]	**< 0.001**
BMI, kg/m^2	23.9 ± 3.0	21.0 ± 3.0[*]	23.4 ± 3.2[†]	21.1 ± 2.0[*‡]	**< 0.001**
Smoking status, n (%)					**< 0.001**
Never smoked	201 (57.8)	67 (11.9)[*]	460 (41.1)[*†]	12 (50.0)[†]	
Former smoked	44 (12.6)	198 (35.2)[*]	179 (16.0)[†]	3 (12.5)	
Current smoked	103 (29.6)	297 (52.8)[*]	479 (42.8)[*†]	9 (37.5)	
Smoking index, pack-years	17.5 ± 29.5	37.0 ± 31.2[*]	25.3 ± 31.4[*†]	16.7 ± 21.7[†]	**< 0.001**
Biomass exposure, n (%)	114 (32.8)	218 (38.8)	391 (35.0)	9 (37.5)	0.268
Occupational history of dusts/gases/fumes, n (%)	48 (13.8)	142 (25.3)[*]	217 (19.4)[†]	2 (8.3)	**< 0.001**
Family history of respiratory diseases, n (%)	28 (8.0)	102 (18.1)[*]	139 (12.4)[†]	0 (0.0)	**< 0.001**
Clinical symptoms, n (%)					
Wheeze	15 (4.3)	126 (22.4)[*]	102 (9.1)[*†]	0 (0.0)	**< 0.001**
Cough	61 (17.5)	258 (45.9)[*]	249 (22.3)[†]	1 (4.2)[†]	**< 0.001**
Sputum	97 (27.9)	301 (53.6)[*]	327 (29.2)[†]	7 (29.2)	**< 0.001**
Dyspnea	58 (16.7)	290 (51.6)[*]	277 (24.8)[*†]	4 (16.7)[†]	**< 0.001**
Acute respiratory events in the prior year, n (%)	13 (3.7)	101 (18.0)[*]	96 (8.6)[*†]	2 (8.3)	**< 0.001**

Data are shown as mean ± standard deviation or n (%). [*] Significantly different from No SAD with spirometry and CT ($P < 0.05$). [†] Significantly different from Combined spirometry and CT-defined SAD ($P < 0.05$). [‡] Significantly different from Only spirometry-defined SAD ($P < 0.05$). [§] No SAD diagnosed by both spirometry and CT. [¶] SAD diagnosed by both spirometry and CT. [#] SAD diagnosed by only spirometry but not CT. [**]SAD diagnosed by only CT but not spirometry. Abbreviations: CT, computed tomography; SAD, small airway dysfunction; BMI, body mass index

biomass exposure, occupational exposure, family history of respiratory diseases, and acute respiratory events in the prior year between only IOS-defined SAD and only CT-defined SAD groups. Compared with no SAD with IOS and CT group, only CT-defined SAD group was older (65.9 ± 6.7 years old vs. 58.7 ± 7.6 years old, $p < 0.05$) and had a higher proportion of men (93.5% vs. 69.8%, $p < 0.05$), lower BMI (20.7 ± 2.7 kg/m^2 vs. 23.1 ± 3.0 kg/m^2, $p < 0.05$), a higher proportion of current smokers (58.5% vs. 42.8%, $p < 0.05$), higher smoking index (31.8 ± 26.5 pack years vs. 24.6 ± 31.5 pack years, $p < 0.05$), a higher proportion of chronic respiratory symptoms ($p < 0.05$), and a higher proportion of acute respiratory events in the prior year (12.5% vs. 6.1%, $p < 0.05$).

Table 4 showed chronic respiratory symptoms, spirometry, IOS, and CT results of patients with SAD diagnosed by IOS and CT in 1862 subjects. The mMRC score and CAT score were not significantly different between only IOS-defined SAD and only CT-defined SAD groups. Compared with only CT-defined SAD group, only IOS-defined SAD group had higher prebronchodilator FEV_1/FVC (adjusted difference = 3.9%, 95% CI: 1.9–5.8%, $p < 0.001$) after covariates adjustment. However, no statistical significant difference in the prebronchodilator spirometry parameters of SAD (MMEF, FEF50, and FEF75 as a percentage of the predicted value) was found between only IOS-defined SAD and only CT-defined SAD groups. SAD-related IOS parameters (R5 – R20 [adjusted difference = 0.09 kPa/L/s, 95% CI: 0.08 kPa/L/s to 0.10 kPa/L/s, $p < 0.001$]; X5 [adjusted difference=-0.06 kPa/L/s, 95% CI: -0.07 kPa/L/s to -0.05 kPa/L/s, $P < 0.001$]; AX [adjusted difference = 0.77 kPa/L/s, 95% CI: 0.65 kPa/L/s to 0.89 kPa/L/s, $P < 0.001$]; and Fres [adjusted difference = 6.8 Hz, 95% CI: 6.0 Hz to 7.6 Hz, $p < 0.001$]) were significantly worse in IOS-defined SAD group than CT-defined SAD group after covariates adjustment. The CT parameters of air trapping (expiratory LAA_{-856} [adjusted difference =-24.3%, 95% CI: -26.4% to -22.1%, $p < 0.001$] and PRM^{fSAD} [adjusted difference=-22.6%, 95% CI: -24.5% to -20.7%, $p < 0.001$]) and emphysema (inspiratory LAA_{-950} [adjusted difference=-2.1%, 95% CI: -3.1% to -1.1%, $p < 0.001$] and PRM^{Emph} [adjusted difference =-2.3%, 95% CI: -3.2% to -1.4%, $p < 0.001$]) were significantly lower in only IOS-defined SAD group than only CT-defined SAD group after covariates adjustment. Pi 10 (adjusted difference = 0.2 mm, 95% CI: 0.1 mm to 0.4 mm, $p = 0.005$) was significantly higher in only IOS-defined SAD group compared with only CT-defined SAD group after covariates adjustment.

Sensitivity analysis and subgroup analysis

These results remained robust in both subgroup analysis and sensitivity analysis (Figure S1-4). The Kappa coefficients observed in the subjects with preserved spirometry were 0.010 (95% CI: -0.012 to 0.032, $p = 0.372$), -0.039 (95% CI: -0.084 to 0.006, $p = 0.136$), and – 0.118 (95% CI: -0.153 to -0.083, $p < 0.001$), respectively, between spirometry-defined SAD and CT-defined SAD groups, between IOS-defined SAD and CT-defined SAD groups, and among spirometry-defined SAD, IOS-defined SAD, and CT-defined SAD groups (Figure S1). When expiratory LAA_{-856} ≥15% was used as CT diagnostic criterion for SAD, the Kappa coefficients observed in all subjects were 0.162 (95% CI: 0.138 to 0.186, $p < 0.001$), 0.231 (95% CI: 0.186 to 0.276, $p < 0.001$), and 0.078 (95% CI: 0.052 to 0.104, $p < 0.001$), respectively, between spirometry-defined SAD and CT-defined SAD groups, between IOS-defined SAD and CT-defined SAD groups, and among spirometry-defined SAD, IOS-defined SAD, and CT-defined SAD groups (Figure S2). When using Chinese spirometry reference values for spirometry indices, there was low consistency in the assessment of SAD between spirometry and CT (Kappa = 0.258 95% CI: 0.229 to 0.287, $p < 0.001$), as well as among spirometry, IOS, and CT (Kappa = 0.197, 95% CI: 0.171 to 0.223, $p < 0.001$) (Figure S3). When using Chinese spirometry reference values for spirometry indices, the correlation (|r|: 0.5 to 0.7, $p < 0.05$) between CT parameters and spirometry parameters was moderate (Figure S4).

Discussion

Our study demonstrated that there was a low level of agreement in the diagnosis of SAD between spirometry and CT, between IOS and CT, as well as among spirometry, IOS, and CT. The correlations among spirometry and CT-measured small airway function parameters were moderate, and the correlations among IOS and CT-measured small airway function parameters were weak. The clinical characteristics of subjects with SAD differed between the three methods. These results were robust in the subjects with preserved spirometry and LAA_{-856} ≥15% as the CT diagnostic criterion for SAD. When using Chinese spirometry reference values for spirometry indices to define SAD, these results were similar.

This study is the first to simultaneously compare spirometry and IOS with chest CT for the assessment of SAD, while previous research primarily focused on the consistency of spirometry and IOS in evaluating SAD.

The gold-standard method for evaluating SAD is histopathology, but invasive examinations cannot be used to detect SAD in clinical practice [29–31]. Various noninvasive methods for evaluating SAD are emerging. Therefore, in addition to correlation studies between PRM and histopathological analysis of small airway lesions, studies evaluating the accuracy and consistency of other methods of SAD diagnosis compared with those of histopathological analysis are needed. SAD diagnosed by CT, spirometry, and IOS may not truly reflect the status of

Table 2 Chronic respiratory symptom, spirometry, impulse oscillometry, and computed tomography results of 2052 subjects stratified by small airway dysfunction status based on spirometry and computed tomography diagnosis

Variable	No SAD with spirometry and CT[‡] (*n* = 348)	Combined spirometry and CT-defined SAD[§] (*n* = 562)	Only spirometry-defined SAD[¶] (*n* = 1118)	Only CT-defined SAD[#] (*n* = 24)	Mean difference (95% CI)[*]	*P* value[*]	Adjusted mean difference (95% CI)[*†]	Adjusted *P* value[*†]
Chronic respiratory symptom								
mMRC score	0.20 ± 0.48	0.66 ± 0.75	0.29 ± 0.54	0.17 ± 0.38	0.12 (-0.10 to 0.34)	0.273	0.11 (-0.11 to 0.33)	0.322
CAT score	3.04 ± 3.72	6.04 ± 5.86	3.25 ± 3.93	3.17 ± 4.87	0.08 (-1.52 to 1.68)	0.923	0.02 (-1.59 to 1.64)	0.977
Prebronchodilator spirometry								
FEV_1, % predicted	103.5 ± 12.4	63.7 ± 21.2	85.8 ± 14.6	104.4 ± 12.9	-18.7 (-24.5 to -12.8)	**< 0.001**	-17.6 (-23.4 to -11.8)	**< 0.001**
FVC, % predicted	103.8 ± 14.3	92.5 ± 20.2	99.6 ± 16.4	104.4 ± 15.3	-4.8 (-11.4 to 1.9)	0.159	-4.2 (-10.8 to 2.4)	0.214
FEV_1/FVC, %	81.9 ± 4.9	53.5 ± 11.9	69.8 ± 7.6	80.0 ± 5.9	-10.3 (-13.3 to -7.2)	**< 0.001**	-10.7 (-13.5 to -7.8)	**< 0.001**
MMEF, % predicted	84.6 ± 17.6	22.7 ± 12.9	40.8 ± 13.4	81.5 ± 14.7	-40.7 (-46.1 to -35.3)	**< 0.001**	-40.9 (-46.3 to -35.6)	**< 0.001**
FEF50, % predicted	93.6 ± 18.9	23.6 ± 14.4	47.7 ± 16.3	88.7 ± 18.5	-40.9 (-47.5 to -34.3)	**< 0.001**	-41.7 (-48.2 to -35.2)	**< 0.001**
FEF75, % predicted	68.4 ± 24.6	21.2 ± 13.3	29.7 ± 11.4	71.4 ± 20.2	-41.8 (-46.5 to -37.0)	**< 0.001**	-40.7 (-45.4 to -35.9)	**< 0.001**
Impulse oscillometry								
R5, kPa/L/s	0.31 ± 0.08	0.38 ± 0.13	0.34 ± 0.10	0.27 ± 0.08	0.07 (0.02 to 0.12)	**0.003**	0.04 (0.00 to 0.08)	0.061
R20, kPa/L/s	0.27 ± 0.07	0.27 ± 0.06	0.28 ± 0.07	0.24 ± 0.07	0.04 (0.01 to 0.08)	**0.008**	0.02 (0 to 0.05)	0.088
R5-R20, kPa/L/s	0.04 ± 0.03	0.11 ± 0.10	0.06 ± 0.05	0.03 ± 0.03	0.03 (0 to 0.05)	**0.032**	0.02 (0 to 0.04)	0.205
X5, kPa/L/s	-0.09 ± 0.04	-0.17 ± 0.12	-0.11 ± 0.05	-0.10 ± 0.04	-0.02 (-0.04 to 0.01)	0.143	-0.01 (-0.04 to 0.01)	0.281
AX, kPa/L	0.28 ± 0.21	1.25 ± 1.31	0.53 ± 0.57	0.27 ± 0.21	0.26 (0 to 0.52)	0.050	0.17 (-0.09 to 0.42)	0.192
Fres, Hz	11.8 ± 3.1	18.8 ± 6.9	14.4 ± 4.5	11.3 ± 2.9	3.07 (1.02 to 5.11)	**0.003**	2.56 (0.58 to 4.54)	**0.011**
Computed tomography								
Expiratory LAA_{-856}, %	3.7 ± 4.5	41.2 ± 17.7	7.6 ± 6.4	32.3 ± 14.6	-24.7 (-27.4 to -22.1)	**< 0.001**	-22.9 (-25.4 to -20.5)	**< 0.001**
Inspiratory LAA_{-950}, %	0.5 ± 1.0	7.5 ± 8.8	1.1 ± 2.2	1.5 ± 1.9	-0.3 (-1.2 to 0.5)	0.436	0.0 (-0.9 to 0.8)	0.973
PRM^{fSAD}, %	2.2 ± 3.2	33.5 ± 14.0	4.8 ± 4.2	28.0 ± 14.0	-23.2 (-25.1 to -21.3)	**< 0.001**	-22.0 (-23.8 to -20.3)	**< 0.001**
PRM^{Emph}, %	0.1 ± 0.4	7.0 ± 8.7	0.6 ± 1.6	1.2 ± 1.7	-0.6 (-1.2 to 0.1)	0.080	-0.4 (-1.0 to 0.3)	0.276
Pi 10, mm	3.3 ± 0.6	4.2 ± 0.9	3.8 ± 0.8	3.3 ± 0.8	0.5 (0.2 to 0.8)	**0.003**	0.3 (0 to 0.6)	**0.046**

Data are shown as mean ± standard deviation. [*] Comparing only spirometry-defined SAD with only CT-defined SAD. [†] Adjusted for age, sex, BMI, smoking status, pack-years, biomass exposure, occupation exposure, family history of respiratory diseases. [‡] No SAD diagnosed by both spirometry and CT. [§] SAD diagnosed by both spirometry and CT. [¶] SAD diagnosed by only spirometry but not CT. [#] SAD diagnosed by only CT but not spirometry. Abbreviations: CT, computed tomography; SAD, small airway dysfunction; mMRC, modified Medical Research Council dyspnea score; CAT, chronic obstructive pulmonary disease assessment test; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; FEF50, forced expiratory flow 50%; FEF75, forced expiratory flow 75%; R5, resistances at 5 Hz; R20, resistances at 20 Hz; R5-R20, resistances at 5 and 20 Hz; X5, reactance at 5 Hz; AX, reactance area; Fres, resonant frequency in Hz; LAA_{-856}, the low-attenuation area below −856 Hounsfield units on full-expiration computed tomography; LAA_{-950}, the low-attenuation area below −950 Hounsfield units on full-inspiration computed tomography; PRM, parametric response mapping; fSAD, functional small airway disease; Emph, emphysema; Pi 10, the square root of the airway wall area for a theoretical airway with 10 mm internal perimeter

Table 3 Characteristics of 1862 subjects stratified by small airway dysfunction status based on impulse oscillometry and computed tomography diagnosis

Variable	No SAD with IOS and CT[§] (*n* = 1010)	Combined IOS and CT-defined SAD[¶] (*n* = 274)	Only IOS-defined SAD[#] (*n* = 330)	Only CT-defined SAD[**] (*n* = 248)	*P* value
Age, year	58.7 ± 7.6	66.6 ± 6.5[*]	61.1 ± 8.3[*†]	65.9 ± 6.7[*‡]	**< 0.001**
Male, n (%)	705 (69.8)	252 (92.0)[*]	187 (56.7)[*†]	232 (93.5)[*‡]	**< 0.001**
BMI, kg/m^2	23.1 ± 3.0	21.1 ± 3.2[*]	24.6 ± 3.1[*†]	20.7 ± 2.7[*‡]	**< 0.001**
Smoking status, n (%)					**< 0.001**
Never smoked	424 (42.0)	28 (10.2)[*]	164 (49.7)[†]	34 (13.7)[*‡]	
Former smoked	154 (15.2)	110 (40.1)[*]	53 (16.1)[†]	69 (27.8)[*†‡]	
Current smoked	432 (42.8)	136 (49.6)	113 (34.2)[*†]	145 (58.5)[*‡]	
Smoking index, pack-years	24.6 ± 31.5	40.1 ± 33.4[*]	22.1 ± 31.3[†]	31.8 ± 26.5[*†‡]	**< 0.001**
Biomass exposure, n (%)	343 (34.0)	116 (42.3)	119 (36.1)	87 (35.1)	0.084
Occupational history of dusts/gases/fumes, n (%)	187 (18.5)	75 (27.4)[*]	57 (17.3)[†]	62 (25.0)	**0.001**
Family history of respiratory diseases, n (%)	111 (11.0)	56 (20.4)[*]	40 (12.1)[†]	38 (15.3)	**< 0.001**
Clinical symptoms, n (%)					
Wheeze	61 (6.0)	78 (28.5)[*]	47 (14.2)[*†]	23 (9.3)[†]	**< 0.001**
Cough	200 (19.8)	147 (53.6)[*]	82 (24.8)[†]	90 (36.3)[*†‡]	**< 0.001**
Sputum	263 (26.0)	173 (63.1)[*]	115 (34.8)[*†]	106 (42.7)[*†]	**< 0.001**
Dyspnea	206 (20.4)	174 (63.5)[*]	93 (28.2)[*†]	88 (35.5)[*†]	**< 0.001**
Acute respiratory events in the prior year, n (%)	62 (6.1)	57 (20.8)[*]	35 (10.6)[*†]	31 (12.5)[*]	**< 0.001**

Data are shown as mean ± standard deviation or n (%). [*] Significantly different from No SAD with IOS and CT ($P < 0.05$). [†] Significantly different from Combined IOS and CT-defined SAD ($P < 0.05$). [‡] Significantly different from Only IOS-defined SAD ($P < 0.05$). [§] No SAD diagnosed by both IOS and CT. [¶] SAD diagnosed by both IOS and CT. [#] SAD diagnosed by only IOS but not CT. [**]SAD diagnosed by only CT but not IOS. Abbreviations: IOS, impulse oscillometry; CT, computed tomography; SAD, small airway dysfunction; BMI, body mass index

small airway diseases in the lungs, which seriously affects the usefulness of these methods for clinical decision making in subjects with SAD. Our study showed that spirometry, IOS, and CT produced inconsistent results in terms of SAD diagnosis. This suggests that in clinical practice, we cannot rely on only one of these methods to definitively diagnose SAD.

Our results are supported by some previous literature. For instance, a study found that spirometry and IOS had low consistency for the assessment of SAD in asthma patients [32]. Another study demonstrated that most IOS parameters were not significantly correlated with MMEF indicators in healthy people, COPD patients, and asthma patients [33]. We compared CT with spirometry and IOS and found that they were inconsistent for the diagnosis of SAD. Moreover, the correlations among the parameters measured by these techniques were not strong. This reflects that the diagnosis of SAD will differ in physiology and imaging methods.

The principles of assessing SAD by CT, spirometry, and IOS are significantly different. Currently, chest CT cannot directly perform morphological analysis of terminal bronchioles, and SAD is indirectly assessed by PRM. PRM uses image registration to identify changes in voxel density between inspiration and expiration, thereby explaining functional changes in small airways [34]. PRM^{fSAD} was classified by voxels with values less than − 856 HU on expiratory CT and greater than or equal to − 950 HU on inspiratory CT [7]. The principle of IOS is that impulses are superimposed through large and small airways during tidal respiration. Higher frequencies return from large airways to the mouth, and lower frequencies go deeper into the smaller airways and return to the mouth. The gas flow and pressure signals of inspiration and expiration can be used to quantify the degree of obstruction of the total airway and central airway, respectively [35]. The difference between total and central airway resistance reflects peripheral small airway resistance [36]. Spirometry measures the volume and/or flow of inhaled and exhaled gases to determine airway obstruction [4]. MMEF, as a marker of small airway disease, reflects the condition of peripheral airway airflow, but it has wide variability and is easily affected by FVC [37, 38]. Differences in the principles of SAD measurement may explain the low consistency between these three methods for the assessment of SAD. Further studies are needed to explore the concordance between spirometry and IOS-diagnosed SAD and histopathological small airway lesions.

This study has several limitations. First, we only analyzed the data of participants aged 40–80 years to evaluate the consistency among the three methods of SAD diagnosis. According to the China Pulmonary Health Study, there were 82.6 million people aged 20–39 years with prebronchodilator spirometry-defined SAD in China in 2015 [19]. Since subjects aged 20–39 years were not included, the consistency among the three methods in defining SAD in the young adult population

Table 4 Chronic respiratory symptom, spirometry, impulse oscillometry, and computed tomography results of 1862 subjects stratified by small airway dysfunction status based on impulse oscillometry and computed tomography diagnosis

Variable	No SAD with IOS and CT[‡] (*n* = 1010)	Combined IOS and CT-defined SAD[§] (*n* = 274)	Only IOS-defined SAD[¶] (*n* = 330)	Only CT-defined SAD[#] (*n* = 248)	Mean difference (95% CI)[*]	*P* value[*]	Adjusted mean difference (95% CI)[*†]	Adjusted *P* value[*†]
Chronic respiratory symptom								
mMRC score	0.24 ± 0.51	0.83 ± 0.78	0.33 ± 0.58	0.40 ± 0.59	-0.07 (-0.17 to 0.03)	0.162	-0.04 (-0.16 to 0.09)	0.553
CAT score	3.10 ± 3.76	7.15 ± 6.42	3.73 ± 4.43	4.63 ± 4.71	-0.90 (-1.65 to -0.15)	**0.019**	-0.79 (-1.75 to 0.18)	0.110
Prebronchodilator spirometry								
FEV_1, % predicted	92.9 ± 14.8	53.0 ± 17.6	81.8 ± 16.4	79.9 ± 17.2	2.0 (-0.8 to 4.7)	0.165	-3.7 (-7.1 to -0.4)	**0.030**
FVC, % predicted	102.9 ± 15.7	85.7 ± 18.4	95.3 ± 15.7	102.3 ± 17.4	-7.0 (-9.7 to -4.3)	**< 0.001**	-10.8 (-14.2 to -7.4)	**< 0.001**
FEV_1/FVC, %	73.4 ± 8.2	48.2 ± 10.8	69.8 ± 9.8	61.7 ± 10.2	8.0 (6.4 to 9.7)	**< 0.001**	3.9 (1.9 to 5.8)	**< 0.001**
MMEF, % predicted	54.5 ± 23.5	16.3 ± 9.0	41.2 ± 20.9	34.9 ± 18.5	6.3 (3.0 to 9.6)	**< 0.001**	1.2 (-2.9 to 5.2)	0.574
FEF50, % predicted	62.6 ± 25.3	16.5 ± 9.9	46.9 ± 23.7	37.0 ± 20.3	9.8 (6.2 to 13.5)	**< 0.001**	2.5 (-2.0 to 7.0)	0.268
FEF75, % predicted	41.0 ± 23.1	15.6 ± 8.1	32.0 ± 19.7	31.8 ± 19.9	0.3 (-3.0 to 3.5)	0.876	-0.5 (-4.6 to 3.6)	0.812
Impulse oscillometry								
R5, kPa/L/s	0.30 ± 0.07	0.46 ± 0.11	0.43 ± 0.10	0.28 ± 0.06	0.15 (0.14 to 0.17)	**< 0.001**	0.11 (0.09 to 0.13)	**< 0.001**
R20, kPa/L/s	0.27 ± 0.07	0.29 ± 0.06	0.31 ± 0.07	0.25 ± 0.06	0.06 (0.05 to 0.07)	**< 0.001**	0.02 (0.01 to 0.04)	**< 0.001**
R5-R20, kPa/L/s	0.03 ± 0.02	0.17 ± 0.08	0.12 ± 0.05	0.03 ± 0.03	0.09 (0.09 to 0.10)	**< 0.001**	0.09 (0.08 to 0.10)	**< 0.001**
X5, kPa/L/s	-0.09 ± 0.03	-0.23 ± 0.13	-0.15 ± 0.06	-0.10 ± 0.03	-0.06 (-0.06 to -0.05)	**< 0.001**	-0.06 (-0.07 to -0.05)	**< 0.001**
AX, kPa/L	0.27 ± 0.16	2.04 ± 1.33	1.08 ± 0.73	0.31 ± 0.20	0.77 (0.68 to 0.86)	**< 0.001**	0.77 (0.65 to 0.89)	**< 0.001**
Fres, Hz	12.0 ± 2.8	23.7 ± 4.6	19.2 ± 3.8	12.8 ± 3.9	6.3 (5.7 to 7.0)	**< 0.001**	6.8 (6.0 to 7.6)	**< 0.001**
Computed tomography								
Expiratory LAA_{-856}, %	6.4 ± 6.1	44.7 ± 19.3	7.6 ± 6.6	36.3 ± 14.4	-28.8 (-30.5 to -26.9)	**< 0.001**	-24.3 (-26.4 to -22.1)	**< 0.001**
Inspiratory LAA_{-950}, %	1.0 ± 1.9	9.1 ± 9.7	1.1 ± 2.4	5.1 ± 6.8	-3.9 (-4.7 to -3.1)	**< 0.001**	-2.1 (-3.1 to -1.1)	**< 0.001**
PRM^{fSAD}, %	4.0 ± 4.0	36.3 ± 14.5	5.0 ± 4.4	30.1 ± 13.0	-25.1 (-26.6 to -23.5)	**< 0.001**	-22.6 (-24.5 to -20.7)	**< 0.001**
PRM^{Emph}, %	0.5 ± 1.4	8.8 ± 9.6	0.7 ± 1.8	4.5 ± 6.3	-3.8 (-4.5 to -3.1)	**< 0.001**	-2.3 (-3.2 to -1.4)	**< 0.001**
Pi 10, mm	3.6 ± 0.7	4.4 ± 0.9	4.1 ± 0.8	3.7 ± 0.7	0.4 (0.3 to 0.5)	**< 0.001**	0.2 (0.1 to 0.4)	**0.005**

Data are shown as mean ± standard deviation or median (interquartile range). [*] Comparing Only IOS-defined SAD with Only CT-defined SAD. [†] Adjusted for age, sex, BMI, smoking status, pack-years, biomass exposure, occupation exposure, family history of respiratory diseases. [‡] No SAD diagnosed by both IOS and CT. [§] SAD diagnosed by both IOS and CT. [¶] SAD diagnosed by only IOS but not CT.[#] SAD diagnosed by only CT but not IOS. Abbreviations: IOS, impulse oscillometry; CT, computed tomography; SAD, small airway dysfunction; mMRC, modified Medical Research Council dyspnea score; CAT, chronic obstructive pulmonary disease assessment test; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; MMEF, maximal mid-expiratory flow; FEF50, forced expiratory flow 50%; FEF75, forced expiratory flow 75%; R5, resistances at 5 Hz; R20, resistances at 20 Hz; R5-R20, resistances at 5 and 20 Hz; X5, reactance at 5 Hz; AX, reactance area; Fres, resonant frequency in Hz; LAA_{-856}, the low-attenuation area below −856 Hounsfield units on full-expiration computed tomography; LAA_{-950}, the low-attenuation area below −950 Hounsfield units on full-inspiration computed tomography; PRM, parametric response mapping; fSAD, functional small airway disease; Emph, emphysema; Pi 10, the square root of the airway wall area for a theoretical airway with 10 mm internal perimeter

remains unclear. Second, the study used CT as the reference method to analyze the consistency among spirometry, IOS, and CT for SAD detection. Although previous studies have found that PRM is correlated with small airway lesions in histopathology [7], PRM is not as accurate as histopathology. However, it is not easy to obtain human lung tissue specimens, so it is difficult to compare spirometry and IOS with histopathology. Finally, the ECOPD study included all subjects with $FEV_1/FVC < 0.70$ and a quarter of subjects with $FEV_1/FVC \geq 0.70$ [8]. Therefore, the consistency among these three methods for assessing SAD may be affected by the factors of the included population.

Conclusions

There was low consistency in the assessment of SAD between spirometry and CT, between IOS and CT, as well as among spirometry, IOS, and CT. Among the SAD measurements, the correlation between CT parameters and spirometry parameters was moderate, whereas the correlation with IOS parameters was weak. Moreover, the clinical characteristics of three techniques defined SAD were different. To provide multiple small airway function assessment tools for clinical application, further studies are needed to explore the consistency among spirometry, IOS, and histopathology for SAD diagnosis.

Abbreviations

AX	Reactance area
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CAT	COPD assessment test
ECOPD	Early chronic obstructive pulmonary disease
Emph	Emphysema
fSAD	Functional small airway disease
FEF50	Forced expiratory flow 50%
FEF75	Forced expiratory flow 75%
FEV_1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
Fres	Resonant frequency in Hz
IOS	Impulse oscillometry
LAA_{-856}	The low-attenuation area below −856 hounsfield units on full-expiration computed tomography
LAA_{-950}	The low-attenuation area below −950 hounsfield units on full-inspiration computed tomography
MMEF	Maximal mid-expiratory flow
mMRC	Modified British Medical Research Council
Pi 10	The square root of the airway wall area for a theoretical airway with 10 mm internal perimeter
PRM	Parametric response mapping
R5	Resistances at 5 Hz
R20	Resistances at 20 Hz
R5 – R20	Difference between resistance at 5 Hz and 20 Hz
SAD	Small airway dysfunction
X5	Reactance at 5 Hz

Supplementary Information

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Supplementary Material 1

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Author contributions

S.H., F.W., Y.Z, and P.R. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design—Y.Z., P.R., S.H., and F.W. Acquisition, analysis or interpretation of data—all authors. Statistical analysis—S.H. and F.W. Drafting of the manuscript—S.H., F.W., Z.D., Y.Z, and P.R. Study guarantor—S.H. Critical revision of the manuscript—all authors.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University (No. 2018-53). The participants were made fully aware of the purpose of study, and all subjects have signed the informed consent before the examination. All methods were carried out in accordance with relevant guidelines and regulations. The written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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