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impulse oscillometry registry

Xiaolin Liang¹, Jinping Zheng¹, Yi Gao¹, Zhe Zhang¹, Wen Han², Jing Du³, Yong Lu⁴,
Li Chen⁵, Tao Wang⁶, Jinming Liu⁷, Gang Huang⁸, Bingrong Zhao⁹, Guihua Zhao¹⁰,
Xuhua Zhang¹¹, Yi Peng¹², Xin Chen¹³, Ning Zhou¹⁴

¹ National Clinical Research Center for Respiratory Disease, State Key Laboratory of
Respiratory Disease, Guangzhou Institute of Respiratory Health, First Affiliated
Hospital of Guangzhou Medical University, Guangzhou, China;
² Department of Respiratory and Critical Care Medicine, Shanxi Bethune Hospital,
Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of
Shanxi Medical University, Taiyuan, China;
³ Department of Respiratory and Critical Care, West China Hospital, Sichuan
University, Chengdu, China;
⁴ Department of Respiratory and Critical Care Medicine, Beijing Institute of
Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University,
Beijing, China;
⁵ Department of Respiratory Medicine, The First Affiliated Hospital of Fujian
Medical University, Fuzhou, China;
⁶ Department of Respiratory and Critical Care Medicine, Tongji Hospital, Tongji
Medical College, Huazhong University of Science and Technology, Wuhan, China;

7 Department of Pulmonary Circulation, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China;

8 Key Laboratory of Respiratory Disease of Zhejiang Province, Department of Respiratory and Critical Care Medicine, Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China;

9 Department of Respiratory Medicine, National Key Clinical Specialty, Branch of National Clinical Research Center for Respiratory Disease, Xiangya Hospital, Central South University, Changsha, China;

10 Department of Cardiopulmonary function, Henan Provincial People’s Hospital, Zhengzhou, China;

11 Department of Pulmonary Function Test, Ningxia Medical University General Hospital, Yinchuan, China;

12 Department of Respiratory Medicine, Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China;

13 Department of Respiratory and Critical Care Medicine, Zhujiang Hospital of Southern Medical University, Guangzhou, China;

14 Department of Respiratory and Critical Care Medicine, Tianjin Medical University General Hospital, Tianjin, China.

Corresponding author:

Yi Gao, misstall2@163.com, The First Affiliated Hospital of Guangzhou Medical
Take-Home Message: This multicenter registry of impulse oscillometry revealed that respiratory oscillometry is more suitable to be a tool of evaluation instead of diagnosing for respiratory diseases. A severity grading system of oscillometry was developed.

Abstract

Background: Respiratory oscillometry is a promising complement to the traditional pulmonary function tests for its simplicity. The usefulness of oscillometry in adult clinical practice has not been clarified. This study aimed to analyse the characteristics and diagnostic performance of oscillometry in respiratory diseases, and explore the cut-offs of oscillometric parameters for severity grading.

Methods: In this multicentre registry of impulse oscillometry (IOS), IOS and spirometric data of healthy individuals and patients with respiratory diseases were collected and analysed. Linear mixed model analysis was performed to explore the effects of disease and FEV$_1$ on oscillometric parameters.

Results: The study included 567 healthy subjects, 781 asthmatic patients, 688 patients with chronic obstructive pulmonary disease (COPD), 109 patients with bronchiectasis, 40 patients with upper airway obstruction (UAO), and 274 patients with interstitial lung disease (ILD) in the analysis. Compared at the same FEV$_1$ level, asthma, COPD, bronchiectasis, UAO, and ILD displayed different oscillometric characteristics. The
z-score of resistance at 5 Hz ($R_5$) was the best variable to identify respiratory diseases with a sensitivity of 62.4%-66.7% and a specificity of 81.5%-90.3%. With reference to the severity grading cut-offs of FEV$_1$, the $R_5$ z-score of 2.5 and 4 were defined as the cut-off values of moderate and severe increased $R_5$.

**Conclusion:** Respiratory oscillometry is more appropriate to be a tool of evaluation instead of diagnosing for respiratory diseases. A Severity grading system of oscillometric parameters was developed to help the interpretation of oscillometry in clinical practice.

**Keywords:** respiratory oscillometry, asthma, COPD, bronchiectasis, interstitial lung disease, upper airway obstruction

**Introduction**

Pulmonary function tests (PFTs) play an essential role in the diagnosis and management of respiratory diseases. For instance, spirometry, the prominent test of PFTs, is acknowledged as the gold standard for assessing airflow limitation in guidelines [1–3]. Despite its wide range of use, spirometry is sometimes hard to fulfil in practice, due to its requirements of rigorous and forceful breathing manoeuvres during the measurements, which is challenging for the very young, old or weak. For those who cannot co-operate with or is contra-indicated to the traditional PFTs, alternative tools to provide lung function information is necessary for diagnosing and monitoring diseases.
Respiratory oscillometry is a non-invasive technique for measuring respiratory resistance and compliance of the respiratory system during quiet tidal breathing [4]. The impulse oscillometry system (IOS), a common device of respiratory oscillometry, can measure respiratory mechanics of different airway sites by imposing multiple-frequency sound waves over normal breathings [5, 6]. Resistance ($R_{5}$) measured at 5 Hz ($R_{5}$) and 20 Hz ($R_{20}$) mainly reflect the total respiratory resistance and the central airway resistance, respectively, while reactance at 5 Hz ($X_{5}$) represents the elastance (i.e., the compliance) of the respiratory system. The frequency dependence of $R_{5}$, determined by the difference between $R_{5}$ and $R_{20}$ ($R_{5} - R_{20}$), is considered to primarily be sensitive to heterogeneous narrowing in the peripheral airways, although it may also be affected by the heterogeneity of more central airways and time constants, and the upper airway shunt flow [6][7]. These technical features allow oscillometry to provide additional information to the traditional PFTs. Coupled with its minimal demand for the co-operation of the patient, respiratory oscillometry is expected to be a potential complementary tool for traditional PFTs, especially for those who cannot perform spirometry [8][9].

Despite its promising potential, oscillometry is currently more of a research tool than a routine test in practice, especially in adult clinical practice. The main hindrances of oscillometry to be routinely applied lie in the uncertainty of its usefulness and the difficulty in the interpretation in routine clinical practice. Although prior studies have reported oscillometric data on respiratory diseases [10–14], most of these observations focused on one specific disease and its comparison of the raw
oscillometric data with healthy individuals, without taking the effects of anthropometrics and the severity of the disease into consideration. Also, data concerning comparisons among multiple respiratory diseases is lacking. Thus, the characteristics and usefulness of oscillometry about respiratory diseases in adult clinical practice have not been clearly clarified. More importantly, there is a lack of standardized cut-offs to determine the abnormality or severity of the oscillometric results, leading to the difficulty of the interpretation of oscillometry.

Based on the multicentre registry of impulse oscillometry, the present study aimed to: 1) clarify oscillometric characteristics of the common respiratory diseases; 2) analyse the diagnostic performance of oscillometry in respiratory diseases; 3) explore the cut-offs of oscillometric parameters for severity grading.

**Methods**

**Study design and participants**

The multicentre study of impulse oscillometry in China is a registry that collected data on impulse oscillometry from healthy individuals and patients with respiratory diseases, conducted in 20 hospitals across China from 2016 to 2018. In brief, ≥18-year-old healthy subjects and patients with a physician-assigned diagnosis or suspected diagnosis of asthma, stable chronic obstructive pulmonary disease (COPD), bronchiectasis, upper airway obstruction (UAO), and interstitial lung disease (ILD) were enrolled through the lung function laboratories. The inclusion criteria of the healthy subjects and the details of study sites were published previously [15].
The study was conducted in accordance with the Helsinki Declaration and approved by the relevant institutional review boards and ethics committees. All participants provided written informed consent.

More information regarding the Methods was provided in the online supplementary material.

**Measurements**

Oscillometry measurements were performed using the MasterScreen Impulse Oscillometry System (CareFusion, Hochberg, Germany) according to the European Respiratory Society (ERS) 2003 guideline [16]. Impedance verification was performed daily and a criterion of error $\leq 10\%$ or $0.01 \text{kPa} \cdot \text{s} \cdot \text{L}^{-1}$ was adopted. Briefly, participants were required to normally breathe 30-60s with nose clipped and the cheek supported by hands. The average values of three technically acceptable measurements under the requirements of the ERS 2020 guideline [4] were used in the analysis. Oscillometric parameters analysed in the study included $R_5$, $R_{20}$, $R_5-R_{20}$, $X_5$, resonant frequency ($f_{res}$), and the area of reactance (AX).

Spirometry measurements were made using a spirometer (CareFusion, Hochberg, Germany) under the recommendations of ERS/American Thoracic Society guideline [17]. Spirometric parameters analysed were forced expiratory volume in the first second ($\text{FEV}_1$), forced vital capacity ($\text{FVC}$), $\text{FEV}_1/\text{FVC}$, maximum mid-expiratory flow ($\text{MMEF}$), and peak expiratory flow ($\text{PEF}$).

**Statistical analysis**
Data were presented as mean ± standard deviation (SD), median (interquartile range), or number (percentage), as appropriate. Between-group differences in oscillometric parameters were compared using the Kruskal-Wallis test. Significance for multiple testing was adjusted by the Bonferroni method.

To exclude the influences of anthropometrics, standardized z-scores were applied in the analysis. References values and z-scores of oscillometric parameters and spirometric parameters were derived from the previous reports [15, 18]. The effects of diseases and FEV₁ to oscillometric parameters were analysed using a linear mixed model in which disease, FEV₁ z-score and their interaction as the fixed effects, centre and its interaction with FEV₁ z-score as the random effects. As the z-scores of oscillometric parameters exhibited skewed distribution and contained negative values, oscillometric data were analysed in linear mixed models after logarithmic transformations: \( \ln(5+R_{ns}) \) or \( \ln(42+X_5) \). Estimates of the fixed effects in the linear mixed model were used to establish the equations of the oscillometric z-scores predicted by the FEV₁ z-score. Diagnostic performances of the oscillometry were evaluated by the receiver operating characteristic (ROC) curves analysis, using the MedCalc application (version 15.8). Other analysis was performed using R software (version 4.0.5).

**Results**

**Anthropometrics and spirometry**

Between December 2016 and September 2018, a total number of 4189 adult
participants were enrolled. After the eligibility assessment, 567 healthy subjects, 781 patients with asthma, 688 patients with COPD, 109 patients with bronchiectasis, 40 patients with UAO, and 274 patients with ILD were included in the analysis (Figure 1).

The anthropometric and spirometric parameters of the analysed population were shown in Table 1. The FEV₁ z-score (mean±SD) of healthy group, asthma group, COPD group, bronchiectasis group, UAO group, and ILD group was 0.291±0.914, -1.784±1.902, -4.12±1.796, -2.506±1.942, -2.034±2.34, and -1.766±1.664.

**Oscillometric parameters in respiratory diseases**

As shown in Figure 2, $R_5$ z-scores, $R_{20}$ z-scores, $R_5-R_{20}$ z-scores, $f_{res}$ z-scores, and AX z-scores of the five disease groups (except for the $R_{20}$ z-score of ILD) were all significantly higher than those of the healthy group ($P < 0.05$), while $X_5$ z-scores of the disease groups were more negative than that of the healthy group ($P < 0.05$). Moderate to high correlations were shown between oscillometric z-scores and FEV₁ z-score (supplementary Figure S1 and S2). Estimates of the functional relationships between oscillometric z-scores and FEV₁ z-score analysed by the linear mixed model were displayed in Table 2, where the intercepts represented the oscillometric z-score values when FEV₁ z-score=0 and the slopes reflected the changes of oscillometric z-scores with FEV₁ z-score. There was no significant difference between the healthy group and the ILD group in the intercepts and slopes, except for the slope of the $R_5-R_{20}$ z-score. For the $R_{20}$ z-score, asthma was the only disease group that presented a significantly different intercept and slope from the healthy group. With the estimates of intercepts
and slopes, equations of the z-scores of oscillometric parameters predicted by the FEV\textsubscript{1} z-score were established by different diseases and displayed in Figure 3. Among the disease groups, UAO exhibited the highest z-scores of $R_5$ and $R_{20}$. For asthma, COPD and bronchiectasis, COPD presented higher mean z-scores of $R_5$, $R_{20}$, and $R_5-R_{20}$ along with a more negative mean $X_5$ z-score than asthma or bronchiectasis (Figure 2). However, when compared at the same FEV\textsubscript{1} z-score level with FEV\textsubscript{1} z-score < lower limit of normal (LLN) (Figure 3), $R_5$ z-score and $R_{20}$ z-score of asthma were higher than those of COPD or bronchiectasis, $R_5-R_{20}$ z-score of COPD was higher than that of asthma or bronchiectasis, $X_5$ z-score were similar in these three groups. For ILD, $R_5$ z-score began to exceed the upper limit of normal (ULN) when FEV\textsubscript{1} z-score was approximately < -3.5, while $R_5-R_{20}$ z-score and $X_5$ z-score tended to exceed the ULN or LLN when FEV\textsubscript{1} z-score was approximately < LLN, $R_{20}$ z-score remained within the ULN at any FEV\textsubscript{1} z-score level (Figure 3).

**Diagnostic values of oscillometric parameters**

Among the analysed oscillometric parameters, $R_5$ z-score was the best parameter to identify respiratory diseases (all disease groups) and obstructive airway diseases (disease groups except for ILD) with sensitivities of 62.4 and 66.7%, and specificities of 81.5 and 90.3%. However, compared with spirometry, oscillometric parameters showed lower diagnostic values than the FEV\textsubscript{1} z-score or FEV\textsubscript{i}/FVC z-score (Table 3 and Figure 4).

For identifying specific respiratory disease, the highest discriminative capacity existed in using $R_{20}$ z-score to diagnose UAO, of which the sensitivity and specificity reached
87.5% and 78.9% (supplementary Table S1 and Figure S3), presenting a superior diagnostic value than the z-score of FEV₁, FEV₁/FVC or PEF (Table 3 and supplementary Figure S4).

**Severity grading cut-offs of oscillometric parameters**

According to the equations of oscillometric z-scores predicted by the FEV₁ z-score, z-score values of oscillometric parameters corresponded to the spirometric severity grading cut-offs (-2.5 and -4 of FEV₁ z-score) proposed by the ATS/ERS[19] were derived (Table 4). As the corresponding z-score values of \( R_5 \), \( R_5-R_{20} \), and \( X_5 \) of asthma, COPD, and bronchiectasis were relatively similar, the average values of these three groups were applied as the grading cut-offs of the z-scores of \( R_5 \), \( R_5-R_{20} \), and \( X_5 \), taking account of the generalization of the cut-offs. No cut-off of \( R_{20} \) was derived as the corresponding \( R_{20} \) z-score values of different diseases varied and most were within the ULN.

**Discussion**

Based on the multicentre, large-sample oscillometric data of healthy subjects and patients with respiratory disease, this study presented an overview of oscillometric characteristics in asthma, COPD, bronchiectasis, UAO, and ILD. ROC curves analysis revealed that oscillometry displayed a lower diagnostic value than spirometry in identifying respiratory diseases and obstructive airway diseases with high specificity and moderate sensitivity. According to the equations of oscillometric z-scores predicted by the FEV₁ z-score, severity grading cut-offs of oscillometric
parameters were developed: for $R_5$ and $R_5-R_{20}$, $z$-scores $\leq 1.645$ are normal, $1.645 < R_5$ $z$-scores $\leq 2.5$ or $1.645 < R_5-R_{20}$ $z$-scores $\leq 3$ are mild increased, $2.5 < R_5$ $z$-scores $\leq 4$ or $3 < R_5-R_{20}$ $z$-scores $\leq 5$ are moderate increased, and $R_5$ $z$-scores $> 4$ or $R_5-R_{20}$ $z$-scores $> 5$ are severe increased; for $X_5$, $z$-scores $\geq -1.645$ are normal, $-1.645 < z$-scores $\leq -4.5$ are mild decreased, $-1.645 < z$-scores $\leq -8.5$ are moderate decreased, and $z$-scores $> -8.5$ are severe decreased.

**Characteristics of oscillometry in asthma, COPD, bronchiectasis, UAO, and ILD**

Increased airway resistance is a hallmark of obstructive airway diseases. The present study showed that although the total respiratory resistance assessed by oscillometry ($R_5$) of asthma, COPD and bronchiectasis were all increased (compared with the healthy subjects), when compared at the same FEV$_1$ level, asthma presented a higher $R_5$ than COPD or bronchiectasis, mainly owing to a higher central airway resistance ($R_{20}$). In contrast, COPD displayed a higher peripheral airways resistance (assessed by $R_5-R_{20}$) than asthma or bronchiectasis at the same FEV$_1$ level. These characteristics are consistent with the underlying pathophysiology of the diseases, as the airflow limitation manifested in asthma is a result of the pathological changes of both the large and small airways [20], while the airflow limitation of COPD largely refers to the pathological changes of the peripheral lung and airways[2]. These findings also indicate that oscillometry can offer more detailed information on the pathophysiology of obstructive airway diseases than spirometry, suggesting its potential usefulness in clinical evaluation.

Although ILD is recognized as a group of disorders that primarily affects the lung
interstitium instead of the airways, $R_5$ was found to be mildly increased when $\text{FEV}_1$ z-score was approximately $<-3.5$ in the present study, and this increase of $R_5$ was mostly due to the increase of the $R_5 - R_{20}$. This finding is in keeping with the report of van Noord et al. [13] in which $R_n$ presented a negative frequency dependence in diffuse ILD patients with total lung capacity (TLC) $<80\%\text{Pred}$, and a small increase at low frequencies as well as a more marked frequency dependence of $R_n$ was found in those with TLC $<50\%\text{Pred}$. The manifestation of frequency dependence of $R_n$ in ILD patients may be owing to the occurrence of small airways dysfunction in some ILD patients [21][22]. Although $X_5$ is defined as an indicator for the dynamic compliance of the respiratory system, which is basically determined by the lung elasticity and the airway resistance [4, 5], this study demonstrated that at the same $\text{FEV}_1$ level with $\text{FEV}_1<\text{LLN}$, the $X_5$ of ILD (i.e., an $X_5$ determined by the lung elasticity) was less negative than the $X_5$ of the airway obstructive diseases. This indicates that $X_5$ is more sensitive to the changes of airway obstruction rather than lung elasticity.

As the resistance of the central airway accounts for most of the total airway resistance [23], it is reasonable that upper airway obstruction exhibited the highest $R_5$ and $R_{20}$ among the obstructive airway diseases. This distinct oscillometric characteristic enables oscillometry to discriminate UAO from other respiratory diseases with relatively high sensitivity and specificity, suggesting that oscillometry may be an easy screening tool for UAO in clinical practice.

**Diagnostic performance of oscillometry**

The present study showed that oscillometry had a lower diagnostic value than
spirometry in identifying patients with respiratory diseases with high specificity but moderate sensitivity. The reason for the low sensitivity may be due to the overlap in oscillometric parameters between healthy subjects and disease patients (Figure 2). Since COPD was diagnosed with the criteria of $\text{FEV}_1/\text{FVC}<0.70$, it may increase the diagnostic value of spirometry to identify respiratory diseases in this study. Except for UAO, the capacity of oscillometry to diagnose other respiratory diseases was less than satisfactory. Sensitivities and specificities of oscillometric parameters in diagnosing COPD in the present study were lower than those of the previous studies [24, 25]. This may be attributed to the different analysed populations, as the present study included not only healthy subjects and patients with COPD, but also patients with other respiratory diseases in the ROC analysis, which we believe to be more in agreement with the practical situation in lung function laboratories. The present findings suggest that oscillometry may be not suitable to apply as a diagnostic tool in laboratories given its unsatisfied sensitivity. However, it does offer valuable information for those with airway obstruction as its high specificity. Thus, oscillometry may be served as an alternative when spirometric information is not available.

**Cut-offs for defining abnormality and grading severity of oscillometric parameters**

The lack of relevant cut-offs in the interpretation of respiratory oscillometry is an unsolved problem in clinical practice. For IOS, H.J. Smith proposed to use 150% of predicted $R_5$ as the cut-off of abnormality, and 200% and 300% of predicted $R_5$ as the
moderate and severe grading cut-offs [26]. Our previous report has shown that the ULN of $R_{rs}$ derived from the reference equations were lower than the 150% of predicted $R_{rs}$ [15]. What’s more, the latest ATS/ERS technical standard recommended using z-scores but not percent of the predicted values for the severity grading of lung function impairment, as the latter is influenced by sex and age[19]. This indicates that the previous cut-offs may be inappropriate to be adopted in clinical practice. The present study developed a grading system of oscillometry in the form of z-scores with reference to the grading cut-offs of spirometry. The drawback of this method lies in the limited consistency of oscillometry and spirometry. Ideal cut-offs ought to be based on the own distribution of oscillometric parameters but not the reference to spirometry, and are supposed to be relevant to the prognosis of patients for guiding the clinical practice [19]. However, in this aspect, various cut-offs may be derived concerning different clinical outcomes of different diseases. The present study was designed to provide generalized grading criteria that could be applied to the majority of respiratory diseases. Considering spirometry is currently recognized as and may still remain to be the gold standard of airflow limitation in the foreseeable future, oscillometric cut-offs developed by referring to spirometry could offer reference information for physicians in clinical decision making. This is of particular importance in those who cannot perform spirometry. Further studies are needed to prospectively validate the grading cut-offs developed in the present study, taking account of the possible device-dependent difference, or to develop oscillometric cut-offs that are more associated with the clinical outcomes.
Strengths and limitations

The strength of this study is the large-sample and broad-scale oscillometric data of multiple diseases, which we believe can cover the common spectrum of oscillometric data encountered in routine clinical practice. However, limitations exist for the lack of data on those who are in the pre-disease stage, such as symptomatic individuals, severe smokers, or those with occupational exposure. This may bias the analysed sensitivity of oscillometry in the study when compared with the actual situation in laboratories. Also, the number of patients with UAO was relatively small, thus the data on UAO in this study may be less representative for the whole population of UAO. Lastly, longitudinal oscillometric data or data regarding the bronchodilator and bronchoconstrictor responses were lacking, these data may offer additional insights into the disease characteristics or clinical application of oscillometry.

Conclusions

This multicentre registry of impulse oscillometry on adult patients with respiratory diseases revealed that under the same level of FEV₁, asthma, COPD, bronchiectasis, UAO, and ILD display different characteristics of oscillometry. Respiratory oscillometry can offer more detailed information on the pathophysiology of obstructive airway diseases than spirometry. Instead of being a diagnostic tool, oscillometry is more appropriate to be a tool for clinical evaluation, especially when spirometric data is unavailable. Severity grading cut-offs of oscillometric parameters were developed, which may be helpful for the interpretation of oscillometry in clinical practice. Further researches are needed for the validation of these cut-offs, and to
explore more potential application value of oscillometry in clinical evaluation.

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This study is registered at ClinicalTrials.gov with identifier number NCT03467880. The data of the study are available from the corresponding author on reasonable request.

Author contributions: All authors contributed to the conception and design of the work. Y Gao and J Zheng contributed to the funding acquisition. XL Liang, W Han, J Du, Y Lu, L Chen, T Wang, J Liu, G Huang, B Zhao, G Zhao G Zhao, X Zhang, Y Peng, X Chen, and N Zhou contributed to the data acquisition. X Liang and Z Zhang contributed to the data analysis. All authors contributed substantially to the interpretation of the data results and the writing of the manuscript. All authors read and approved this study before submission.
Conflicts of Interest: The authors declare that they have no conflicts of interest.

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Table 1 Anthropometrics and spirometric parameters of the analysed population

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>ILD</th>
<th>Asthma</th>
<th>COPD</th>
<th>Bronchiectasis</th>
<th>UAO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, N</td>
<td>567</td>
<td>274</td>
<td>781</td>
<td>688</td>
<td>109</td>
<td>40</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>300 (52.9)</td>
<td>441 (45.3)</td>
<td>58 (56.5)</td>
<td>124 (8.4)</td>
<td>66 (60.6)</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td>Age, years</td>
<td>38.3±14.3</td>
<td>57.4±11.6</td>
<td>45.9±12.9</td>
<td>63.2±8.6</td>
<td>52.9±11.1</td>
<td>54.5±14.9</td>
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<tr>
<td>Height, cm</td>
<td>164.3±8.3</td>
<td>161.6±8.0</td>
<td>162.2±8.2</td>
<td>165.2±7.0</td>
<td>160.0±8.4</td>
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<td>Weight, kg</td>
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<td>64.8±10.9</td>
<td>63.7±12.5</td>
<td>62.7±11.5</td>
<td>58.0±12.1</td>
<td>61.7±10.7</td>
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<tr>
<td>BMI, kg/m²</td>
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<td>24.7±3.3</td>
<td>24.1±3.7</td>
<td>22.9±3.6</td>
<td>22.5±3.7</td>
<td>23.8±3.3</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, L #</td>
<td>3.32±0.72</td>
<td>2.15±0.64</td>
<td>2.39±0.83</td>
<td>1.5±0.64</td>
<td>1.93±0.74</td>
<td>2.11±0.85</td>
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<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; z-score #</td>
<td>0.291±0.914</td>
<td>-1.766±1.664</td>
<td>-1.784±1.902</td>
<td>-4.12±1.796</td>
<td>-2.506±1.942</td>
<td>-2.034±2.34</td>
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<tr>
<td>FVC, L #</td>
<td>3.96±0.87</td>
<td>2.71±0.84</td>
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<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC #</td>
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<td>MMEF, L/s ¶</td>
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<td>0.59±0.39</td>
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<td>-0.904±1.347</td>
<td>-1.917±1.172</td>
<td>-2.901±0.552</td>
<td>-2.094±1.304</td>
<td>-1.399±1.067</td>
</tr>
<tr>
<td>PEF, L/s #</td>
<td>8.02±1.93</td>
<td>5.12±2.19</td>
<td>6.08±1.98</td>
<td>4.00±2.21</td>
<td>7.03±1.94</td>
<td>4.08±2.27</td>
</tr>
<tr>
<td>PEF z-score #</td>
<td>0.378±0.995</td>
<td>-1.212±1.537</td>
<td>-2.653±1.311</td>
<td>-0.233±1.349</td>
<td>-1.623±1.464</td>
<td>-2.658±1.661</td>
</tr>
</tbody>
</table>

Data are presented as N, N (%) or mean±SD. #: 11 data were missing in this analysis. ¶: 177 data were missing in this analysis.
Table 2: Intercepts and slopes of the predictive equations of oscillometric parameters (ln z-scores) estimated by the linear mixed model analysis

<table>
<thead>
<tr>
<th></th>
<th>Ln (5 + R₂ z-score)</th>
<th>Ln (5 + R₂₀ z-score)</th>
<th>Ln (5 + R₂₀ z-score)</th>
<th>Ln (42 + X₅ z-score)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (95%CI) P#</td>
<td>Estimate (95%CI) P#</td>
<td>Estimate (95%CI) P#</td>
<td>Estimate (95%CI) P#</td>
</tr>
<tr>
<td><strong>Intercept</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>1.67 (1.60, 1.73)</td>
<td>&lt;0.001</td>
<td>1.66 (1.59, 1.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ILD</td>
<td>1.68 (1.63, 1.74)</td>
<td>0.555</td>
<td>1.64 (1.59, 1.69)</td>
<td>0.463</td>
</tr>
<tr>
<td>Asthma</td>
<td>1.71 (1.68, 1.75)</td>
<td>0.014</td>
<td>1.70 (1.67, 1.73)</td>
<td>0.008</td>
</tr>
<tr>
<td>COPD</td>
<td>1.66 (1.61, 1.72)</td>
<td>0.933</td>
<td>1.74 (1.69, 1.79)</td>
<td>0.001</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>1.61 (1.52, 1.70)</td>
<td>0.182</td>
<td>1.59 (1.51, 1.67)</td>
<td>0.091</td>
</tr>
<tr>
<td>UAO</td>
<td>2.29 (2.17, 2.42)</td>
<td>&lt;0.001</td>
<td>2.08 (1.97, 2.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Slope (against FEV₁ z-score)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>-0.0514</td>
<td>&lt;0.001</td>
<td>-0.0309</td>
<td>0.006</td>
</tr>
<tr>
<td>ILD</td>
<td>(-0.0788, -0.0240)</td>
<td>(-0.0532, -0.0086)</td>
<td>(-0.0956, -0.0282)</td>
<td>(-0.0039, 0.0390)</td>
</tr>
<tr>
<td>Asthma</td>
<td>-0.0639</td>
<td>0.439</td>
<td>0.0159</td>
<td>0.292</td>
</tr>
<tr>
<td>COPD</td>
<td>(-0.0956, -0.0322)</td>
<td>(-0.0438, 0.0121)</td>
<td>(-0.1364, -0.0648)</td>
<td>(-0.0019, 0.0447)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>-0.1391</td>
<td>&lt;0.001</td>
<td>-0.0672</td>
<td>0.003</td>
</tr>
<tr>
<td>UAO</td>
<td>(-0.1661, -0.1121)</td>
<td>(-0.0909, -0.0435)</td>
<td>(-0.1734, -0.1121)</td>
<td>(0.0440, 0.0837)</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

# : P values of the healthy groups were derived from the comparisons with zero, P values of disease groups were derived from the comparisons with the healthy group. 95%CI: 95% confidential interval.
**Table 3** Comparisons of the diagnostic values between $R_5$ and spirometric parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC (95% CI)</th>
<th>$P$</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory diseases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$R_5$ z-score</td>
<td>0.807 (0.790, 0.824)</td>
<td>&lt;0.01</td>
<td>&gt;1.426</td>
<td>62.4</td>
<td>90.3</td>
</tr>
<tr>
<td>FEV$_1$ z-score</td>
<td>0.900 (0.888, 0.912)</td>
<td>&lt;0.01</td>
<td>≤-1.112</td>
<td>74.0</td>
<td>95.4</td>
</tr>
<tr>
<td>FEV$_1$/FVC z-score</td>
<td>0.861 (0.847, 0.875)</td>
<td>&lt;0.01</td>
<td>≤-1.410</td>
<td>70.5</td>
<td>97.4</td>
</tr>
<tr>
<td><strong>Obstructive airway diseases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$R_5$ z-score</td>
<td>0.788 (0.770, 0.806)</td>
<td>&lt;0.01</td>
<td>&gt;1.426</td>
<td>66.7</td>
<td>81.5</td>
</tr>
<tr>
<td>FEV$_1$ z-score</td>
<td>0.820 (0.803, 0.837)</td>
<td>&lt;0.01</td>
<td>≤-1.069</td>
<td>76.2</td>
<td>75.2</td>
</tr>
<tr>
<td>FEV$_1$/FVC z-score</td>
<td>0.922 (0.912, 0.933)</td>
<td>&lt;0.01</td>
<td>≤-1.401</td>
<td>80.72</td>
<td>94.5</td>
</tr>
<tr>
<td><strong>UAO</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$R_{20}$ z-score</td>
<td>0.895 (0.852, 0.938)</td>
<td>&lt;0.01</td>
<td>&gt;2.300</td>
<td>87.5</td>
<td>79.0</td>
</tr>
<tr>
<td>FEV$_1$ z-score</td>
<td>0.509 (0.420, 0.598)</td>
<td>0.84</td>
<td>≤-0.230</td>
<td>82.1</td>
<td>26.6</td>
</tr>
<tr>
<td>FEV$_1$/FVC z-score</td>
<td>0.557 (0.473, 0.640)</td>
<td>0.18</td>
<td>≤-0.595</td>
<td>87.2</td>
<td>32.2</td>
</tr>
<tr>
<td>PEF z-score</td>
<td>0.728 (0.657, 0.799)</td>
<td>&lt;0.01</td>
<td>≤-0.835</td>
<td>89.47</td>
<td>47.87</td>
</tr>
</tbody>
</table>

AUC: area under the curve; 95%CI: 95% confidential interval. Respiratory diseases: ILD + asthma + COPD + bronchiectasis + UAO V.S. healthy. Obstructive airway diseases: asthma + COPD + bronchiectasis + UAO V.S. healthy + ILD.
<table>
<thead>
<tr>
<th>FEV\textsubscript{1} z-score</th>
<th>( R_5 ) z-score</th>
<th>( R_{20} ) z-score</th>
<th>( R_5 - R_{20} ) z-score</th>
<th>( X_5 ) z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>1.024</td>
<td>1.506</td>
<td>0.656</td>
<td>0.925</td>
</tr>
<tr>
<td>ILD</td>
<td>2.859</td>
<td>4.682</td>
<td>1.475</td>
<td>2.162</td>
</tr>
<tr>
<td>Asthma</td>
<td>2.374</td>
<td>4.006</td>
<td>1.196</td>
<td>1.518</td>
</tr>
<tr>
<td>COPD</td>
<td>1.318</td>
<td>1.954</td>
<td>0.35</td>
<td>0.479</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>2.022</td>
<td>3.624</td>
<td>0.632</td>
<td>1.129</td>
</tr>
<tr>
<td>Average of As+Co+Br #</td>
<td>2.418</td>
<td>4.104</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\#: the average values of asthma, COPD and bronchiectasis.
References:


23. Green, M. How big are the bronchioles. *St Thomas Hosp Gaz* 1965; 63: 136–139.


4189 adult participants assessed for eligibility

752 were excluded, including:
- 190 with unclear diagnosis
- 183 combined with other respiratory/cardiovascular/systematic diseases
- 348 did not meet inclusion criteria of healthy subjects
- 31 for missing data of oscillometry

3437 subjects assessed for eligibility of analysis

978 Oscillometry data did not meet the quality control requirements of the ERS 2020 technical standard [4]

2459 subjects included in analysis

Figure 1 Study flowchart
Figure 2 Comparisons of the z-scores of oscillometric parameters between different groups NS: non-significant between-group difference (P>0.05), other between-group differences without this notation were all significant (P<0.05). ULN: upper limits of normal=1.645. LLN: lower limits of normal=-1.645.
Figure 3 Equations of the z-scores of oscillometric parameters predicted by the FEV1 z-score. The solid line and the around area indicated the mean and the 95% confidential interval.
Figure 4 Diagnostic performances of oscillometric and spirometric parameters in diagnosing respiratory diseases and airway obstructive diseases. Respiratory diseases: ILD + asthma + COPD + bronchiectasis + UAO versus healthy. Obstructive airway diseases: asthma + COPD + bronchiectasis + UAO versus healthy + ILD.
Supplementary materials

Methods

Study participants

Patients were excluded with the following criteria: 1) the diagnosis was not supported by the relevant medical records; 2) combined other respiratory diseases (except for UAO combined lung tumour); 3) combined severe cardiovascular diseases or systematic diseases.

Procedures

Through a case report form, physicians or technicians at the laboratory recorded the basic demographics; smoking history; allergies; occupational exposures history; comorbidities; respiratory symptoms; exacerbations; medications, and examinations (chest radiography, electrocardiography, echocardiography, bronchoscopy, or histopathological examination) of the participants. COPD patients and asthmatic patients were required to respectively fulfil the modified Medical Research Council (mMRC) [1] dyspnoea grade as well as the COPD Assessment Test (CAT) [2], and the Asthma Control Test (ACT) [3].
Results

Figure S1 Scatter plots between z-scores of oscillometric parameters and FEV₁ z-score

**Figure S2** Correlation between the oscillometric parameters and spirometry parameters

The correlation coefficients were derived from the Spearman correlation analysis, $P$ all <0.05.

**Figure S3** The best oscillometric parameters in diagnosing each respiratory disease
**Figure S4** Comparisons of the diagnostic performances between $R_{20}$ and spirometric parameters in identifying upper airway obstruction.

**Table S1** Diagnostic values of the best oscillometric parameters in diagnosing specific respiratory disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC (95% CI)</th>
<th>$P$</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAO</td>
<td>$R_{20}$ z-score</td>
<td>0.895 (0.852, 0.938)</td>
<td>&lt;0.01</td>
<td>&gt;2.300</td>
<td>87.5</td>
</tr>
<tr>
<td>COPD</td>
<td>$f_{\text{res}}$ z-score</td>
<td>0.807 (0.789, 0.826)</td>
<td>&lt;0.01</td>
<td>&gt;2.590</td>
<td>70.6</td>
</tr>
<tr>
<td>Asthma</td>
<td>$R_{20}$</td>
<td>0.620 (0.596, 0.645)</td>
<td>&lt;0.01</td>
<td>&gt;0.346</td>
<td>39.7</td>
</tr>
<tr>
<td>ILD</td>
<td>$R_5$</td>
<td>0.580 (0.549, 0.612)</td>
<td>&lt;0.01</td>
<td>$\leq$0.450</td>
<td>88.0</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>$R_5$</td>
<td>0.536 (0.482, 0.590)</td>
<td>0.148</td>
<td>&gt;0.335</td>
<td>67.9</td>
</tr>
</tbody>
</table>

AUC: area under the curve; 95%CI: 95% confidential interval.
References:

