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Diagnostic value of impulse oscillometry in chronic obstructive pulmonary disease: a multicentre, retrospective, observational study

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ABSTRACT

Objectives Diagnosis and assessment of chronic obstructive pulmonary disease (COPD) rely extensively on spirometry, which necessitates patient cooperation. The clinical value of impulse oscillometry (IOS) as a non-volitional method in patients with COPD remains uncertain.

Design This retrospective observational study was conducted using patient data from between January 2014 and December 2015.

Setting Five public hospitals in China: West China Hospital, Nuclear Industry 416 Hospital, Suining Central Hospital, Affiliated Hospital, Medical College of Chengdu University and 363 Hospital.

Participants The study included 6307 participants aged>40 years, comprising 2109 COPD patients and 4198 general non-COPD individuals, according to the Global Initiative for Obstructive Lung Disease (GOLD) spirometry standard. Participants with lung cancer, pulmonary tuberculosis, pneumonia or those who underwent lung resection were excluded from the study.

Outcome measures and analysis Demographic data, spirometry results and IOS results were collected. Spearman's correlation analysis was used to examine the correlation between the IOS and spirometry parameters. Receiver operating characteristic curve analysis was used to evaluate the IOS performance in COPD diagnosis and severity staging.

Results Patients with COPD exhibited significant increases in Z5, R5, R20, R5–R20, Fres and Rp, but a decrease in X5 compared with non-COPD subjects (p<0.0001). IOS parameters, including Z5, R5–R20, Fres, Rp and X5, varied with the GOLD stages, with mild-to-moderate correlations with $MMEF_{25\%–75\%}$, forced expiratory volume in one second (FEV_1)/forced vital capacity and $FEV_{1\%}$, respectively. However, the combination of these five IOS parameters did not exhibit ideal performance in diagnosing COPD (area under the curve (AUC) 0.78; sensitivity 63.68%; specificity 80.09%), differentiating GOLD stage 1 patients from the general non-COPD population (AUC 0.71; sensitivity 54.71%; specificity 77.49%) or identifying GOLD stages 3 and 4 patients among those with COPD (AUC 0.75; sensitivity 69.51%; specificity 70.32%).

Conclusion IOS parameters, while showing good correlation with spirometry in patients with COPD, did not perfectly substitute for spirometry in diagnosing COPD, especially in the early and advanced stages of the disease.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ One of the strengths of this study was its multicentre design and large sample size, which augmented the reliability and generalisability of our evaluation of the diagnostic efficacy of impulse oscillometry (IOS) for chronic obstructive pulmonary disease (COPD).
⇒ This retrospective study was limited to recruiting high-risk subjects with COPD and performing a comprehensive analysis of the IOS parameters.
⇒ The absence of a gold standard for small airway obstruction impeded the evaluation of the value of IOS in the detection of early-stage COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) affects 10.1% of all adults aged at least 40 years worldwide, while the rate in China is 13.7%.[1] COPD is the third leading cause of death worldwide.[2] Spirometry is the most widely used method and the gold standard for diagnosing and assessing COPD and is widely accepted for its practicality and reliability.[3] Moreover, the current COPD treatment guidelines provide both pharmacological and non-pharmacological recommendations based principally on forced expiratory volume in one second (FEV_1). However, spirometry may not fully delineate the extent of small airway disease in COPD and demands considerable patient cooperation, with variable sensitivity and accuracy across different subjects,[4] which restricts its application among specific populations such as children, critically ill patients, geriatric patients and those with cognitive or motor impairments or breathing difficulties. A previous study indicated that approximately

18% of older COPD patients were unable to undergo adequate spirometry.[5] Conversely, the geriatric population aged 70 years and older exhibited a COPD prevalence as high as 35.5%.[1] Peak expiratory flow metre (PEFM) is a simple and portable device that measures the maximum flow rate during forced exhalation. It is useful for monitoring asthma and can easily be used for daily peak flow variability assessments. Although PEFM is easy to use, it yields variable results and is less sensitive than spirometry to subtle changes in lung function. Furthermore, it is more commonly associated with asthma, which may limit its application in patients with COPD. Therefore, a stable technique that is independent of patient effort in COPD is required.

Impulse oscillometry (IOS) can measure respiratory mechanical properties during quiet tidal breathing and may be an alternative method for evaluating lung function. It stimulates the respiratory system with slight sinusoidal pressure variations at frequencies higher than the normal breathing frequency, measures the resulting flow response and does not require active patient participation such as forced expiration. This means that it is easier and more readily available to be conducted among specific populations that may have difficulty undergoing traditional spirometry. Significant correlations have been demonstrated between IOS and spirometry parameters, and IOS can be used for COPD detection.[6 7] Studies have reported that IOS is more sensitive than spirometry for detecting small airway obstructions in patients with COPD.[8–10] However, Liang *et al* proposed that the IOS may not be appropriate as a diagnostic tool for COPD, given its unsatisfactory sensitivity.[11] Another study indicated poor correlations ($r \leq 0.16$) between IOS parameters and the percentage of low attenuation areas on CT, an indicator the extent of emphysema, suggesting that IOS was limited in evaluating the disease progression in COPD.[12] Although a multitude of studies have been conducted to evaluate whether IOS can be used as an alternative for the diagnosis of COPD, the results have been inconsistent, and the interpretation of IOS results requires specialised knowledge. Furthermore, while the IOS has its advantages, most of the research has been conducted in single centres and recent reports have indicated that there may be ethnic variations in IOS results.[13] For a technology to be useful, it is necessary for it to be reproducible and valid across multiple centres. Therefore, the clinical significance of the IOS in the diagnosis and assessment of COPD remains unclear.

In this multicentre retrospective study, we aimed to elucidate the clinical application value of IOS in patients with COPD by exploring the correlations between IOS and spirometry parameters and evaluating the performance of IOS in the diagnosis and detection of the severity of airflow limitation in COPD patients.

METHODS

Study design and subjects

This was a retrospective study and included patients older than 40 years from West China Hospital, Nuclear Industry 416 Hospital, Suining Central Hospital, Affiliated Hospital, Medical College of Chengdu University and 363 Hospital from 1 January 2014 to 31 December 2015. Patients diagnosed with lung cancer, pulmonary tuberculosis, pneumonia or restrictive lung diseases, including large pleural effusion, extensive pleural thickening, severe thoracic deformity, severe thoracic deformity and interstitial lung disease, were excluded. Demographic and baseline characteristics including age, sex, body mass index, spirometry and IOS parameters were collected from all study participants.

Spirometry and IOS test

Respiratory impedance was measured using a commercial IOS device (Jager, German, MS-IOS, V.5.72) as described.[14] Briefly, the patient was asked to sit upright in a neutral head position and breathe via a mouthpiece attached to a pneumotach. The patient was asked to breathe normally. The nose was closed using a nose clip. During the examination, the patient was asked to place his hands against his cheeks and stabilise the cheek, tongue position and chin to minimise upper airway shunting. If the patient's breathing was stable (breathing baseline), the measured values were recorded. After the recommended recording time of at least 30 s, the measurements were completed manually. Oscillometric procedures are so-called 'the principles of external current', which determine important parameters based on external stimulus. Here, the respiratory flow (tidal breathing) was overlaid by short-term test impulses. The mathematical transformation of the measured flow signal created by the impulse and the resulting pressure response of the pulmothoracic system yields the required respiratory impedance. Several parameters were recorded: impedance at 5 Hz (Z5), an indicator of the sum of all forces that oppose the generated impulse, respiratory resistance at 5 Hz (R5) and 20 Hz (R20), the difference between R5 and R20 (R5–R20), reactance at 5 Hz (X5), resonant frequency (Fres) and peripheral resistance (Rp). The measurements were repeated at least three times. These oscillatory parameters were measured during the entire breath cycle and inspiratory and expiratory phases.

Spirometry was performed by two technicians according to the American Thoracic Society criteria.[15] Spirometry was performed immediately after IOS and before and after bronchodilator administration. FEV_1, forced vital capacity (FVC), FEV_1/FVC and forced expiratory flow at 25%–75% of FVC ($MMEF_{25\%–75\%}$) were determined. During the examination, maximal inspiration, a 'blast' of expiration, continued complete expiration for a maximum of 15 s, and inspiration at maximal flow back to maximum lung volume are required for the patients. COPD was diagnosed based on a FEV1/FVC ratio less than 70% following bronchodilator spirometry,

according to the Global Initiative for Obstructive Lung Disease (GOLD) guidelines.[16] These measurements were performed in duplicate or triplicate to evaluate repeatability.

Statistical analysis

The data are assessed by the mean and SD or as the median and IQR after evaluation of normality. An independent samples t-test was employed to evaluate normally distributed data, and the Mann-Whitney test was used to evaluate non-normally distributed data when comparing two groups. Spearman correlation analysis was adopted to determine correlations among variables. We used area under the receiver operating characteristic curve (ROC) to evaluate the prognostic value of the subject properties and evaluated the ability of five IOS parameters together with the methods recommended by Creaney *et al*.[17 18] All analyses were performed using SPSS V.26.0 and figures were drawn with GraphPad Prism V.9.3.1 (GraphPad Software, La Jolla, California, USA). A two-sided p value<0.05 was considered statistically significant.

Patient and public involvement

None.

RESULTS

Baseline characteristics and IOS parameters

The study included 6307 participants (mean age, 61.23±12.67 years), approximately half of whom (3035, 48.12%) were men. According to the GOLD spirometry standard, 2109 (33.43%) patients fulfilled the criteria for COPD diagnosis. Table 1 summarises the baseline characteristics, spirometry results and IOS results. Compared with general non-COPD subjects defined spirometrically, patients with COPD were older and showed significantly higher Z5 (7.20±3.09 $cmH_2O/(L/s)$ vs 5.68±2.34 $cmH_2O/(L/s)$, p<0.0001), Fres (23.18±6.64 L/s vs 17.76±5.31 L/s, p<0.0001), R5 (6.36±2.48 $cmH_2O/(L/s)$ vs 5.34±2.10 $cmH_2O/(L/s)$, p<0.0001), R20 (3.99±1.35 $cmH_2O/(L/s)$ vs 3.86±1.29 $cmH_2O/(L/s)$, p<0.0001), R5–R20 (2.37±1.50 $cmH_2O/(L/s)$ vs 1.48±1.15 $cmH_2O/(L/s)$, p<0.0001), Rp (6.34±3.74 $cmH_2O/(L/s)$ vs 4.14±2.59 $cmH_2O/(L/s)$, p<0.0001) and lower X5 (−3.07±2.24 $cmH_2O/(L/s)$ vs −1.80±1.26 $cmH_2O/(L/s)$, p<0.0001) than general non-COPD subjects in table 1. According to the GOLD criteria, 222 patients (10.53%) were classified as GOLD stage 1, 1018 (48.27%) as stage 2, 659 (31.25%) as stage 3 and 210 (9.96%) as stage 4 among 2109 COPD patients. Figure 1 shows a comparison of the IOS measurements according to the GOLD stage. Z5,

Table 1 Baseline characteristics, spirometry and IOS measurements in the full study population

Variable	Non-COPD (n=4198)	COPD (n=2109)	Total (n=6307)	P value
Demographics				
Age (year)	57.80±11.92	68.07±11.26	61.23±12.67	<0.0001
Male	1700 (40.50)	1335 (63.30)	3035 (48.12)	<0.0001
BMI	23.94 (21.64–26.22)	22.77 (20.45–25.18)	23.50 (21.23–25.89)	<0.0001
Spirometry				
FVC (L)	2.60 (2.13–3.14)	2.01 (1.54–2.56)	2.43 (1.89–2.98)	<0.0001
FEV_1 (L)	2.18 (1.76–2.65)	1.08 (0.80–1.47)	1.86 (1.25–2.41)	<0.0001
FEV_1/FVC (%)	83.80±7.22	55.40±10.08	74.30±15.75	<0.0001
FEV_1 (%predicted)	96.30 (84.20–108.30)	54.60 (40.30–69.65)	85.90 (64.10–102.00)	<0.0001
MMEF (L/s)	2.23±1.04	0.58±0.32	1.68±1.17	<0.0001
$MMEF_{25\%–75\%}$ (%predicted)	73.23±28.43	21.51±10.51	55.93±34.21	<0.0001
IOS				
Z5 ($cmH_2O/(L/s)$)	5.68±2.34	7.20±3.09	6.19±2.71	<0.0001
Fres (Hz)	17.76±5.31	23.18±6.64	19.57±6.33	<0.0001
R5 ($cmH_2O/(L/s)$)	5.34±2.10	6.36±2.48	5.68±2.29	<0.0001
R20 ($cmH_2O/(L/s)$)	3.86±1.29	3.99±1.35	3.90±1.31	<0.0001
R5–R20 ($cmH_2O/(L/s)$)	1.48±1.15	2.37±1.50	1.78±1.34	<0.0001
Rp ($cmH_2O/(L/s)$)	4.14±2.59	6.34±3.74	4.87±3.20	<0.0001
X5 ($cmH_2O/(L/s)$)	−1.80±1.26	−3.07±2.24	−2.22±1.76	<0.0001

All data are presented as the mean±SD or as the median (IQR). P values less than 0.05 were considered statistically significant.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; Fres, resonant frequency; FVC, forced vital capacity; IOS, impulse oscillometry system; MMEF, maximal mid-expiratory flow; R5, respiratory resistance at 5 Hz; R20, respiratory resistance at 20 Hz; Rp, peripheral resistance; R5–R20, the value of R5 minus R20; X5, respiratory reactance at 5 Hz; Z5, respiratory impedance at 5 Hz.

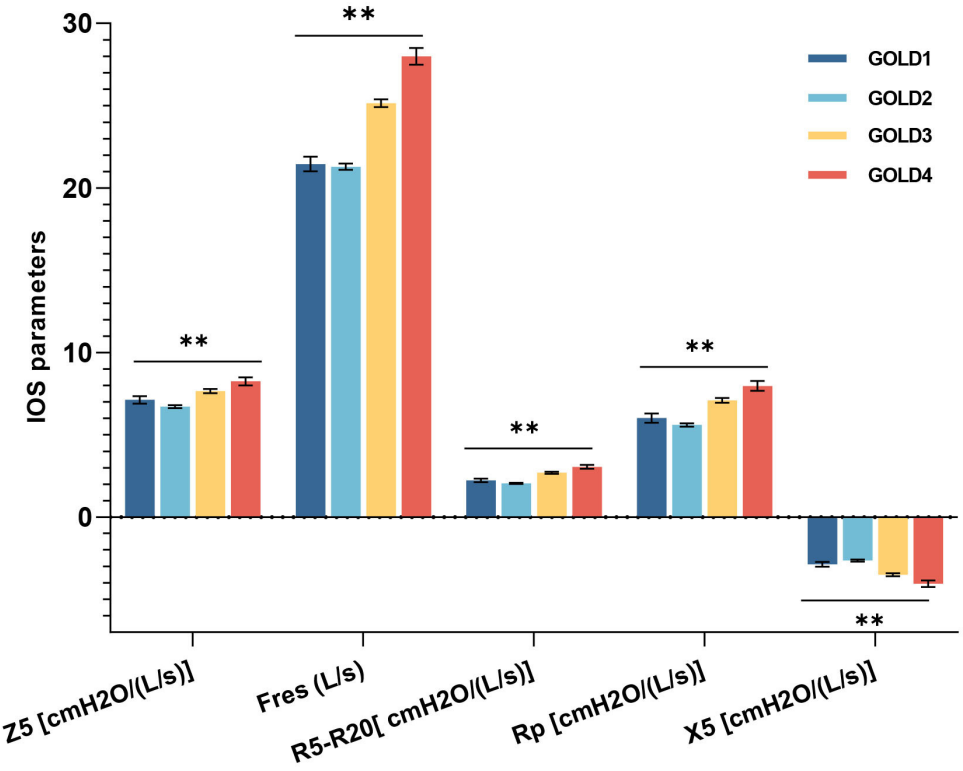

Figure 1 IOS measurements in all subjects stratified by GOLD stage. Z5, R5–R20, Fres and Rp showed an increasing trend along with the GOLD stage, whereas X5 showed a decreasing trend. Fres, resonant frequency; GOLD, Global Initiative for Obstructive Lung Disease; IOS, impulse oscillometry system; R5, respiratory resistance at 5 Hz; R20, respiratory resistance at 20 Hz; Rp, peripheral resistance; R5–R20, the value of R5 minus R20; X5, respiratory reactance at 5 Hz; Z5, respiratory impedance at 5 Hz. *p<0.05, **p<0.0001 among the groups.

R5–R20, Fres and Rp showed an increasing trend with GOLD stage, whereas X5 showed a decreasing trend.

Association of IOS and spirometry parameters

Spearman correlation analysis was used to detect correlations between the IOS and spirometry parameters, as summarised in table 2. In the entire population, IOS parameters, including Z5, Fres, R5–R20 and Rp, were all negatively correlated with FEV_1/FVC, $FEV_{1\%}$ and $MMEF_{25\%–75\%}$. In addition, X5 was positively correlated with FEV_1/FVC, $FEV_{1\%}$ and $MMEF_{25\%–75\%}$. Among these IOS parameters, Fres had the highest correlation with FEV_1/FVC (rho = −0.46, p<0.0001) and $FEV_{1\%}$ (rho = −0.46, p<0.0001) and $MMEF_{25\%–75\%}$ (rho = −0.54, p<0.0001).

Ability of IOS in diagnosing patients with COPD

Given the correlation between IOS and spirometry, we assessed IOS's ability to differentiate COPD patients from spirometrically normal individuals (online supplemental table 1). All the five IOS parameters showed certain values in recognising COPD, and Fres showed the best diagnostic performance for detecting COPD among single

Table 2 IOS parameters correlated with FEV_1/FVC, $FEV_{1\%}$ and $MMEF_{25\%–75\%}$ in all subjects

	Spearman's Rank (95% CI)		
IOS parameters	**FEV_1/FVC**	**$FEV_{1\%}$**	**$MMEF_{25\%–75\%}$**
Z5(cmH_2O/(L/s))	−0.32(−0.34 to −0.30)**	−0.30 (−0.32 to −0.28)**	−0.41 (−0.43 to −0.39)**
Fres (L/s)	−0.46 (−0.48 to −0.44)**	−0.46 (−0.48 to −0.44)**	−0.54 (−0.55 to −0.52)**
R5–R20 (cmH_2O/(L/s))	−0.39 (−0.42 to −0.37)**	−0.39 (−0.41 to −0.37)**	−0.49 (−0.51 to −0.47)**
Rp (cmH_2O/(L/s))	−0.39 (−0.41 to −0.37)**	−0.38 (−0.40 to −0.36)**	−0.48 (−0.50 to −0.46)**
X5 (cmH_2O/(L/s))	0.41 (0.39 to 0.43)**	0.39 (0.37 to 0.41)**	0.50 (0.48 to 0.51)**

P values less than 0.05 were considered statistically significant.
*p<0.05.
**p<0.0001.
FEV_1, forced expiratory volume in one second; Fres, resonant frequency; FVC, forced vital capacity; IOS, impulse oscillometry system; MMEF, maximal mid-expiratory flow; R5, respiratory resistance at 5 Hz; R20, respiratory resistance at 20 Hz; Rp, peripheral resistance; R5–R20, the value of R5 minus R20; X5, respiratory reactance at 5 Hz; Z5, respiratory impedance at 5 Hz.

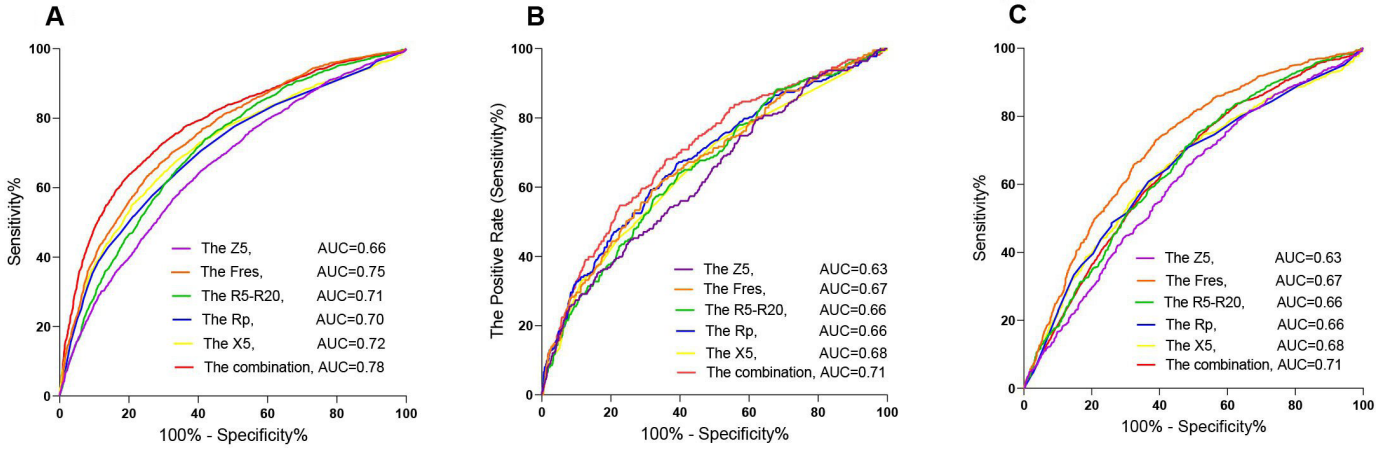

Figure 2 The diagnostic ability of IOS parameters. Receiver operating curve analysis was used to identify the ability of the IOS parameters detecting COPD patients from all subjects (A), detecting GOLD stage 1 from general non-COPD patients (B) and diagnosing GOLD stage 3 and 4 among COPD patients (C). AUC, area under the curve; COM, combination of Z5, Fres, R5–R20, X5 and Rp; Fres, resonant frequency; GOLD, Global Initiative for Obstructive Lung Disease; IOS, impulse oscillometry system; R5, respiratory resistance at 5 Hz; R20, respiratory resistance at 20 Hz; Rp, peripheral resistance; R5–R20, the value of R5 minus R20; X5, respiratory reactance at 5 Hz; Z5, respiratory impedance at 5 Hz.

IOS parameters, with an area under the curve (AUC) of 0.75 (95% CI: 0.74 to 0.76, p<0.0001, figure 2A), selectivity of 63.30%, specificity of 74.77% and cut-off value of 20.44 L/s. The overall best diagnostic performance was obtained using a combination of five parameters (Z5, R5–R20, Fres, Rp and X5), which yielded an AUC of 0.78 (95% CI: 0.77 to 0.79, p<0.0001), selectivity of 63.68% and specificity of 80.09% in figure 2A.

Ability of IOS in detecting GOLD stage 1 COPD

As early-stage COPD, GOLD stage 1 patients are receiving increasing attention. Thus, the ability of the IOS to differentiate COPD patients with GOLD stage 1 from those with normal FEV_1/FVC was explored using ROC analysis (figure 2B and online supplemental table 2). All the five IOS parameters showed certain values in recognising stage 1 COPD, and X5 yielded the highest AUC of 0.68 (95% CI: 0.66 to 0.69, selectivity: 66.82%, specificity: 60.89%, p<0.0001, cut-off value: −1.73 cmH_2O/(L/s), figure 2B). A combination of five parameters (Z5, R5–R20, Fres, Rp and X5) suggested the best predictive ability, giving an AUC of 0.71 (95% CI: 0.69 to 0.72, p<0.0001), selectivity of 54.71% and specificity of 77.49% (figure 2B).

Ability of IOS in identifying GOLD stages 3 and 4 COPD

To further explore the value of IOS in detecting moderate and severe COPD patients, we performed ROC analysis to predict the ability of the five IOS parameters in recognising COPD patients with GOLD stages 3 and 4 among patients with FEV_1/FVC<70% and found that Fres had the highest AUC of 0.71 (95% CI: 0.69 to 0.73, p<0.0001, online supplemental table 3, figure 2C), with a cut-off value of 21.93 L/s obtaining with sensitivity of 73.07% and specificity of 61.21%. Similarly, combination with five IOS parameters (Z5, R5–R20, Fres, Rp and X5) minorly increased the AUC from 0.71 to 0.75 (95% CI: 0.73 to 0.77, selectivity: 69.51%, specificity: 70.32%, p<0.0001, online supplemental table 3 and figure 2C).

DISCUSSION

In this study, we conducted a multicentre, large sample-sized, retrospective analysis to explore the diagnostic and assessment capabilities of the IOS in the Chinese population aged at least 40 years regarding COPD severity. Overall, our results showed that IOS indicators (Z5, Fres, R5–R20, X5 and Rp) were correlated with spirometry parameters (FEV_1/FVC, $FEV_{1\%}$ and $MMEF_{25\%-75\%}$). Furthermore, ROC curve analyses revealed that the combination of these five IOS parameters could distinguish COPD patients from the control population with an AUC of 0.78 (selectivity of 63.68% and specificity of 80.09%); differentiate COPD patients in GOLD stage 1 from general non-COPD subjects with an AUC of 0.71 (with a selectivity of 54.71% and specificity of 77.49%) and identify GOLD stages 3 and 4 patients among COPD patients with an AUC of 0.75 (with a selectivity of 69.51% and specificity of 70.32%). These findings imply that, although other studies have reported higher AUC values for individual IOS parameters in the diagnosis of COPD patients,[6 19] these values seem to overestimate the corresponding predictabilities of IOS in real-world clinical practice.

Previous studies have assumed that IOS can provide the total mechanical properties of the respiratory system[6 20 21] and augmented airway resistance constitutes a distinctive feature of obstructive airway diseases. IOS resistance parameters have been reported to possess good long-term repeatability in both asthma and COPD and exhibit superior repeatability compared with spirometry parameters across different GOLD stages.[22] Our study demonstrated an increase in the total respiratory resistance (R5,

R20) and peripheral airway resistance (R5–R20 and Rp), which is consistent with the underlying pathophysiological mechanisms of the COPD, as the airflow limitation of COPD largely refers to the pathological changes of the peripheral lung and airways.[2] R5–R20 refers to the frequency range (5–20 Hz) within which the resistance is measured and is considered to optimally represent the behaviour of the peripheral airways. Rp represents the resistance to airflow in the airways beyond the central airways, particularly in the peripheral airways, and can be affected by the frequency of oscillations.[23] Respiratory reactance comprises inertance and elastance.[21 24 25] X5 is delineated as an indicator of the dynamic compliance of the respiratory system, which is essentially determined by lung elasticity and airway resistance.[21] Our results indicated a significant decrease in X5 in patients with COPD, which can reflect the elastic and viscous resistance of peripheral small airways.[26] Fres is the point at which the magnitudes of the compliance and inertial reactance are equivalent and opposite, respectively. We also observed significantly elevated Fres levels in patients with COPD. Fres and X5 are both related to the degree of airflow obstruction (measured by FEV_1). Hence, these findings indicate that IOS can provide more detailed information on the pathophysiology of COPD than spirometry.

Although some researchers substantiated favourable correlations between the IOS and spirometry parameters,[7 27] we observed mild-to-moderate relationships (all r values for these associations were <0.55) between IOS (Z5, Fres, R5–R20, Rp and X5) and spirometry ($MMEF_{25\%–75\%}$, $FEV_{1\%}$ and FEV_1/FVC) parameters in all individuals. It has been previously proposed that abnormalities in $MMEF_{25\%–75\%}$ may be indicative of small airways disease.[28] However, the variability in the measurements was considerable, with an average CV of 25%.[29] Additionally, previous studies have suggested that many IOS variables, including Z5, Fres, X5 and R5–R20, can predict COPD.[6 30] Fres and X5 manifested a high AUC (0.90 and 0.85, respectively) for the detection of COPD in a previous study.[6] Nevertheless, our results demonstrated that the IOS parameters had a lower precision for the diagnosis of COPD, with AUC ranging from 0.66 to 0.78. A previous study suggested that Fres was the optimal IOS parameter for the detection of COPD with an AUC of 0.905 (sensitivity of 78.9%, specificity of 93.1%) for the diagnosis of COPD,[6] we also found that Fres performed best among single IOS parameters for the detection of COPD with an AUC of 0.75 (sensitivity of 58.99% and specificity of 65.29%). The combination of these five parameters slightly increased the AUC from 0.75 to 0.78 (sensitivity of 63.68%, specificity of 80.09%). Generally, an AUC range from 0.7 to 0.8 and 0.8 to 0.9 are regarded as acceptable and excellent diagnostic tests, respectively.[31] Our results suggest that IOS parameters demonstrate acceptable accuracy in the diagnosis of COPD. The sensitivities and specificities of the IOS parameters for diagnosing COPD in the present study were lower than those reported in previous studies.[6 19 32] Therefore, the present findings suggest that IOS might not be suitable as a diagnostic tool because of its unsatisfactory sensitivity and specificity.

Early intervention for COPD is essential for preventing a rapid decline in lung function[33–35] and pharmacological intervention in the early stages of COPD may be effective in improving prognosis,[34 36] preserving quality of life and reducing the frequency of acute exacerbations.[36] Nevertheless, patients with early-stage COPD rarely complain of respiratory symptoms. It has been concluded that Fres, R5–R20 and X5 denote small airway lesions in early-stage COPD.[37–39] In this study, subgroup analysis indicated that IOS parameters varied in accordance with GOLD stage, implying that airway elastic resistance and peripheral airway resistance increased with the extent of airflow limitation. To demonstrate the ability of the IOS to detect early-stage COPD more directly, we measured its performance in differentiating between GOLD stage 1 subjects and general non-COPD controls. We found that a combination of five IOS parameters (Z5, Rp, R5–R20, X5 and Fres) displayed diagnostic accuracy with an AUC of 0.71, sensitivity of 54.71% and specificity of 77.49%. Although a previous study suggested that IOS might be more sensitive than spirometry in the diagnosis of small airway dysfunction in the early stage of diseases,[10 40] we observed a low sensitivity in detecting early-stage COPD. In addition, our study demonstrated that a combination of these five IOS parameters could detect GOLD stages 3 and 4 subjects who were at a higher risk of AECOPD with an AUC of 0.75 (sensitivity of 69.51% and specificity of 70.32%), which was less than satisfactory. The low sensitivity may be attributed to the overlap in IOS parameters between healthy subjects and patients with COPD. Because GOLD stages were identified using the criterion of $FEV_{1\%}$, it may enhance the evaluation performance of spirometry in COPD. This study explored the diagnostic and evaluation abilities of the IOS based on the grading cut-offs of spirometry. The drawback of this approach is the limited congruence between IOS and spirometry. The ideal diagnostic accuracy should be based on the distribution of IOS parameters without reference to spirometry and should be related to the prognosis of COPD patients to guide clinical decision-making. Considering that spirometry is currently recognised as and might remain the gold standard for airflow obstruction in the foreseeable future, IOS cut-off values referred to as spirometry can merely provide physicians with complementary information in clinical practice. Furthermore, respiratory impedance appears to vary slightly, and intraindividual variability has been reported, either within the same day or from day to day.[41 42] Thus, further prospective investigations are required to explore the clinical value of IOS.

As a retrospective study, a limitation exists in that our data collection was restricted to the period from 2014 to 2015, as a result of limited financial resources. However, the diagnostic and grading standards for COPD remain unchanged, and we believe that they can offer insights into the value of IOS in the diagnosis and assessment of COPD. However, because of the retrospective nature of

data collection, we did not specifically enrol high-risk subjects for COPD who were suffering from respiratory symptoms with a smoking history but without FEV_1/FVC impairment (GOLD 0 subjects), thereby restricting insights into the progression to COPD and informing early intervention strategies. Second, the capacity of the IOS to detect airflow limitations in the small airways could be further enhanced by conducting specialised tests for small airway function, such as paired inspiratory/expiratory CT. Moreover, we did not incorporate IOS parameters such as X19 and X11, which may have the potential to diagnose COPD. Last, the evaluation of IOS measurements in patients with COPD during exacerbations and the assessment of changes in IOS parameters over longer periods should be modified in further studies.

CONCLUSION

Although in previous studies, IOS has been regarded as an appropriate approach for the evaluation of COPD, requiring less patient participation than spirometry, the present findings indicate that IOS might not be ideal for application as a screening and evaluation tool for COPD given its unsatisfactory sensitivity and specificity. However, it provides complementary information on respiratory mechanics, which is beneficial for physicians in clinical decision-making, particularly for patients who are unable to undergo traditional pulmonary function tests.

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