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The Roles of Impulse Oscillometry in Detection of Poorly Controlled Asthma in Adults with Normal Spirometry

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Abstract

Background: Impulse oscillometry (IOS) has been introduced as a method of assessing asthma control. However, the cut-off IOS values for the detection of asthma control in adults are still unclear.

Objective: To assess the diagnostic ability of IOS for distinguishing between poorly controlled and well controlled adult asthmatic subjects with normal spirometry.

Methods: This cross-sectional study was conducted at the Lung Health Center, Chiang Mai, Thailand, between July 2019 and June 2020. IOS and spirometry were performed in all adult asthmatic subjects but only subjects with normal spirometry were enrolled. Poorly controlled asthma was defined in accordance with the Global Initiative for Asthma (GINA) plus an asthma control test (ACT) score ≤ 19 . A Receiver Operating Characteristic (ROC) curve was plotted to detect poorly controlled asthma using the area under the ROC (AuROC) and 95%CI. **Results:** One hundred and forty-two adult asthmatic subjects registering normal spirometry with a mean age of 53.4 ± 15.8 years were enrolled. Eighty-nine (62.7%) subjects were female. IOS parameters including heterogeneity of resistance at 5 Hz and resistance at 20 Hz (R5-R20) and area under reactance (AX) demonstrated excellent detection of poorly controlled asthma with an AuROC of 0.911 and 0.904, respectively. The z-score or absolute value of $R5-R20 \geq 0$ and $1 \text{ cmH}_2\text{O/L/s}$, respectively, represented the highest AuROC of 0.86, with a sensitivity and a specificity of $\geq 80.0\%$ for the detection of poorly controlled asthma. **Conclusion:** IOS is a valuable tool for the detection of poorly controlled asthma in adults with normal spirometry.

Keywords: Asthma; lung function; impulse oscillometry; asthma control; adult; airway resistance

Introduction

Asthma is a chronic inflammatory disease of the airways that causes recurring episodes of wheezing, breathlessness, chest tightness, and coughing [1]. It has a high socioeconomic impact worldwide and its prevalence varies, ranging from 1% to 18% across countries and populations [1].

In 2016 in Chiang Mai, Thailand the prevalence of asthma among adults aged > 40 years old was 10.1% [2].

Achievement and maintenance of the control of the disease at the lowest step and dose of inhaled corticosteroid (ICS) is the goal of asthma care [1]. However, previous studies noted that 36% - 64% of asthma subjects had poorly controlled asthma, despite adherence to prescribed controller therapy [3-5]. Therefore, the guidelines recommend that once the diagnosis of asthma has been made, asthma control should be assessed at every routine visit [1]. In daily practice, evaluation of asthma control is based on physician assessments, questionnaires, and lung function tests. The lung function is mainly assessed by spirometry. However, the Global Initiative for Asthma (GINA) guideline suggests that the use of spirometry results including forced expiratory in the first second (FEV₁), forced vital capacity (FVC), and the average expired flow over the middle half (25%-75%) of the FVC maneuver (FEF_{25-75%}) does not correlate with asthma symptoms in adults [1]. As mentioned before, the assessment of asthma control is an essential part of asthma management. It is important therefore to identify which patients have well controlled asthma and which have poorly controlled asthma in clinical practice [6]. Consequently, reliable and non-invasive measures to assess asthma control in adults are still needed.

Impulse oscillometry (IOS) is a simple, non-invasive measure requiring passive patient cooperation that allows for the evaluation of lung function through the measurement of both airway resistance and airway reactance [7]. Many studies have shown that the IOS was related to asthma symptoms and can be used for the assessment of asthma control [8-17]. Moreover, it could be used in the prediction of future risk of asthmatic attacks [18]. Previous studies have shown that the parameters from IOS could detect the level of asthma control including resistance at 5 Hz (R5), heterogeneity of resistance at 5 Hz and 20 Hz (R5-R20), reactance at 5 Hz (X5), resonant frequency (Fres), and area under reactance curve between 5 Hz and Fres (AX) [8, 9, 12, 15, 17]. However, the cut off values of IOS parameters in these studies have only been derived from children with asthma. Only one study in has taken place in adults and has shown that IOS did not show a discriminative capacity to correctly classify patients according to the degree of asthma control [16]. Thus, more data sets are required to look at the possible predictive value of IOS for the detection of asthma control in adults. Therefore, this study aimed to assess the diagnostic contribution of IOS when distinguishing between poorly controlled and well controlled adult asthmatic subjects with normal spirometric indices.

Materials and Methods

Study procedures

This cross-sectional study was conducted at a single visit in clinically diagnosed asthma subjects whose condition had been stable for more than six weeks. The subjects had been previously diagnosed by a pulmonologist following the GINA guidelines [1], and had normal spirometry results (FEV₁/FVC $\geq$ lower limit of normal (LLN) and FVC $\geq$ LLN [19]. All subjects were treated by their physicians at the Airway Clinic, Lung Health Center, Division of Pulmonary, Critical Care and Allergy, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. All subjects were enrolled between July 2019 and June 2020. The IOS was measured before spirometry in all subjects. All tests were performed by a well-trained therapist. Demographic data including age, sex, body mass index (BMI), co-morbidities, family history of asthma, smoking status, age of disease onset, duration of disease, and medication used were recorded. The asthma control test (ACT) and the level of asthma control were also recorded. The study was approved by the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University [Institutional Review Board (IRB) approval number: MED-2562-06282, date of approval: 28 June 2019 and filed

under Clinical Trials Registry (Study ID: TCTR20190709004, date of approval: 5 July 2019). Written informed consent was obtained from all subjects before enrollment.

Subjects

Two hundred and ten clinically diagnosed asthma subjects were screened for eligibility for enrollment onto the study. The inclusion criteria were as follows: clinically diagnosed asthma subjects aged ≥ 20 years with stable disease status for at least six weeks; a history of clinically diagnosed asthma based on episodic breathlessness, wheezing, cough, and tightness and/or bronchodilator responsiveness ($\geq 12\%$ and 200-milliliter increase in FEV_1 after 400 micrograms of salbutamol [1]; had controller medication for at least 12 weeks; had no history of chronic respiratory diseases other than asthma; and had a history of non-smoking or ex-smoking < 5 packs-year. The exclusion criteria were subjects with abnormal spirometry results including airway obstruction, spirometric restriction, or mixed obstruction and spirometric restriction. The criteria for each pattern were defined as follows: $\%FEV_1/FVC < LLN$ but the $FVC \geq LLN$ for an obstructive defect, $\%FEV_1/FVC$ was $\geq LLN$ but the $FVC < LLN$ for a spirometric restrictive, and both $\%FEV_1/FVC$ and $FVC < LLN$ for a mixed restrictive and obstructive defect [19]. The subjects who were unable to perform acceptable spirometry according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2005 guidelines [20] and were unable to perform the IOS according to the standard recommended by Bickel et al [7] and ERS standard [21] were also excluded.

Definition of poorly controlled asthma

There are several approaches to assess the level of asthma control [22]. The GINA guidelines propose a questionnaire for the assessment of asthma control such as the Asthma Control Test (ACT) [1]. The ACT questionnaire is a multidimensional, standardized, and validated tool for assessing asthma control in asthma subjects age ≥ 12 years [23]. Nowadays, it is a widely used tool for the assessment of asthma control in the clinical setting [24]. The ACT is a patient-centered questionnaire composed of five items including asthma symptoms (daytime and nighttime), rescue medications used, the effect of asthma on working, and patient's perception of asthma control [23]. The score of each item includes five response options corresponding to a 5-point Likert-type rating scale. The sum score of the ACT ranges from 5 (poor asthma control) to 25 (complete asthma control) [23]. According to the latest GINA guidelines [1], a cut-off score of ≤ 19 indicates poorly controlled asthma [23]. As mentioned before, the ACT is a self-assessed questionnaire, so it is open to under- or overestimation. A previous study suggested that there is a minor discrepancy between ACT score and GINA-defined asthma control which is probably due to the different approaches of the two tools in taking into account asthma manifestations [25]. Therefore, poorly controlled asthma was defined using an ACT score ≤ 19 [23] plus the pulmonologists' rating as uncontrolled or partially controlled according to GINA [1] in this study. Pulmonary physicians were blinded to the IOS results.

Impulse Oscillometry (IOS)

All subjects performed pre-bronchodilator (pre-BD) IOS before spirometry to avoid the influence of forced exhalation maneuvers on airway function [26]. The airway resistance (in-phase) and reactance (out phase) were measured using IOS (Master Screen IOS, Viasys GmbH, Hoechberg, Germany). Respiratory resistance (R_{rs}) is the in-phase component of lung impedance. It reflects information about the forward pressure of the conducting airways [7]. The resistance at 5 Hz (R_5), the resistance at 20 Hz (R_{20}), and the difference of the R_{20} from R_5 ($R_5 - R_{20}$) values represent the resistance of the airways. R_5 and R_{20} represent the resistance of total and large airways resistance, respectively. Therefore, the $R_5 - R_{20}$ reflects resistance in the small airways. The reactance is the out-of-phase component of lung impedance. It reflects the capacitive and inertive properties of the

airways [7]. The reactance at 5 Hz (X5), resonant frequency (Fres), and reactance area (AX) are parameters in IOS that represent the reactance of the airways. X5 indicates the elastic recoil of the peripheral airways, Fres indicates the frequency as Xrs crosses zero and the elastic and inertial forces are equal in magnitude and opposite, and AX, the area of the negative reactance between 5 Hz and Fres to the zero lines [7].

All subjects performed tidal breathing for 30-40 seconds via a mouthpiece that was connected to a loudspeaker which generates pressure oscillations made up of multiple frequencies. Subjects were sitting on a chair in an upright position, wore a nose clip, and firmly supported their cheeks with both hands. A minimum of three IOS measurements was performed then the average values from acceptable three IOS measurements were recorded. The IOS parameters including respiratory impedance values at 5 Hz (Z5), R5, R20, R5-R20, X5, Fres, and AX were collected. The z-score of all IOS parameters was calculated using the data from all clinically diagnosed asthma subjects in this study.

Spirometry

Spirometry was performed in all subjects using a spirometer (Vmax Encore 22, Care Fusion, Hoechberg, Germany). Pre-bronchodilator (BD) spirometry was performed in accordance with the ATS/ERS guidelines [21]. Spirometry parameters were collected including FVC, FEV₁, the ratio of FEV₁/FVC, and FEF₂₅₋₇₅%. Global Lung Initiative (GLI) 2012 (Southeast Asian sub-group) reference equations were used for the predicted values of FVC and FEV₁ and were used for z-score calculation [27].

Study size calculation

The study size was calculated based on data from our pilot study using MedCalc Version 18.11.6 [28]. That study consisted of 77 clinically diagnosed asthma patients, 25 poorly controlled and 52 well controlled, the ratio of sample size in negative/positive was 2.08. The lowest area under the receiver operating characteristic (AuROC) curve for detection of poorly controlled asthma was observed in the R20 (AuROC = 0.645). Therefore, at least 142 subjects (46, poorly controlled asthma and 96 well controlled asthma) needed to be included in the investigative study (power = 0.8 with statistical significance < 0.05).

Statistical analysis

Continuous data were expressed as mean $\pm$ standard deviation (SD) or median, interquartile range (IQR) as appropriate. Non-continuous data were expressed as frequencies and percentages. Independent sample t-tests and the Mann-Whitney U Test were used to analyze differences between the two groups for parametric and non-parametric data, respectively. Fisher's exact test was used to compare the categorical data between groups. The receiver operating characteristic (ROC) curve was plotted to detect poorly controlled asthma by the area under the curve (AUC) and 95% confidence interval (CI). Contingency tables were made to calculate the following performance parameters: sensitivity, specificity, positive likelihood ratio (+LR), negative likelihood ratio (-LR), diagnostic odds ratio, and AUC from the various variables of IOS parameters to identify the optimum cut-off point for detection of poorly controlled asthma. The cut-off points with the highest sensitivity, and specificity together with the highest AUC were defined as the best cut-off points of IOS. Statistical significance was accepted at a p-value < 0.05. All statistical analyses were performed using STATA version 15 (StataCorp, College Station, TX, USA).

Results

Two hundred and ten subjects were recruited. After excluding eight subjects due to a history of respiratory diseases other than asthma, 202 clinically diagnosed asthma subjects were enrolled and performed spirometry. Subjects with abnormal spirometry results (n=56) and unacceptable spirometry (n=4) were excluded. Therefore, 142 clinically diagnosed asthma subjects with normal spirometry (46 poorly controlled and 96 well controlled asthma) were included in the analysis. More details are shown in Figure 1.

The baseline demographic data of all subjects included in the two groups are shown in Table 1. There were no significant differences in age, the proportion of female sex, height, and smoking status between the two groups. Bodyweight and BMI were significantly higher in the poorly controlled asthma cohort compared to the well-controlled asthma group. The proportion of patients with a history of asthmatic attacks in the previous year was significantly higher in the poorly controlled group. In addition, the asthma control measured by the ACT score was significantly lower in the poorly controlled group. There were no significant differences in age of disease onset, duration of disease, and atopy between the poorly controlled asthma subjects compared to the well-controlled asthma group. More data including inhaled medication used, any oral medication used, a daily dose of ICS, and co-morbidities are shown in Table 1.

Spirometric data of all subjects are shown in Table 2. There was a significantly lower absolute value, % predicted, and z-score of all parameters of spirometry in the poorly controlled asthma cohort when compared to the well-controlled asthma group except for the ratio of FEV₁/FVC. More details are shown in Table 2.

IOS parameters of subjects are shown in Table 3. In the poorly controlled asthma group, significant increases in z-score and absolute value of IOS parameters including Z5, R5, R20, R5-R20, Fres, and AX were observed in comparison with the well-controlled asthma group. A significant decrease in z-score and absolute value of X5 was recorded in poorly controlled asthma patients compared to the well-controlled asthma group.

The majority of the IOS parameters (z-score and absolute value) including R5-R20, AX, Fres, Z5, R5, and X5 demonstrated good detection of poorly controlled asthma (AuROC > 0.8). The R5-R20 and AX showed excellent detection of poorly controlled asthma with an AuROC of 0.911 and 0.904, respectively (Figure 2).

For spirometry variables, only z-score of FEV₁, %predicted of FEV₁, and z-score of FVC demonstrated acceptable detection of poorly controlled asthma (AuROC > 0.7). (Figure 3).

The following performance parameters: sensitivity, specificity, +LR, -LR, diagnostic odds ratio, and AUC from the various variables of IOS parameters enabling the identification of the optimum cut-off point for detection of poorly controlled asthma are presented in Table 4. The best single parameter was the z-score or absolute value of R5-R20 of which the cut-off level ≥ 0 and ≥ 1 cmH₂O/L/s, respectively showed the highest AUC (0.86), with a sensitivity and specificity $\geq 80\%$, for detection of poorly controlled asthma. Another parameter that could be used for detection of poorly controlled asthma was AX (z-score ≥ -0.04 and absolute value ≥ 9 cmH₂O/L (AUC = 0.84, sensitivity = 80.4% and specificity = 87.5%). The combination of R5-R20 and AX represented an AUC of 0.84, with a sensitivity of 80.4% and specificity of 88.5%, for detection of poorly controlled asthma.

Discussion

To the best of our knowledge, our study is the first study to demonstrate the diagnostic ability of IOS parameters for the detection of poorly controlled asthma in adults with normal spirometry. The current guidelines recommend that once the diagnosis of asthma has been made, asthma control should be assessed at every routine visit [1]. Thus, in clinical practice it is important to identify which patients have well controlled asthma and which have poorly controlled asthma [6]. In this study, we showed that a significant increase in airway resistance and reactance in poorly controlled asthma and the IOS play a potential role in the detection of poorly controlled asthma in adults with normal spirometry.

Our study showed an increase in the majority of IOS parameters for detecting airway resistance especially in the case of small airways resistance (R5-R20) in poorly controlled asthma. Our study results were comparable to those of a previous study, which showed that the R5-R20 was significantly higher in those with partially controlled and uncontrolled asthma than in those with well controlled asthma [16]. Many studies also showed that peripheral airway resistance is associated with asthma control [9, 10, 16, 29]. Thus, in asthma subjects with poorly controlled asthma, airway resistance and airway reactance will be increased [9, 16].

Despite normal spirometry of all subjects in our study, there was a significant difference in respiratory reactance, including AX, Fres, and X5, between the poorly controlled asthma and well controlled asthma groups. Our results are supported by a previous finding which showed that the AX and Fres were significantly higher in asthma which is either partially controlled or uncontrolled (AX ranging from 18.2 to 24.8 cmH₂O/L and Fres ranging from 21.5 to 23.3 Hz) [16]. Our studies showed a decrease in X5 in subjects with poorly controlled asthma which were comparable with the previous findings which indicated that X5 was significantly lower in those with partially controlled and uncontrolled asthma [16].

AuROC was plotted in our study and showed that the IOS provides valuable information regarding peripheral airway function and should be considered as a tool for differentiation of asthma control in adults with normal spirometry. Many variables including R5-R20, AX, Fres, Z5, R5, and X5 could be used to detect poorly controlled asthma with an AuROC greater than 0.8. However, there are two parameters of IOS, namely R5-R20 and AX, which showed excellent AuROC values (0.911 and 0.904, respectively) for the detection of poorly controlled asthma. These two IOS indicators of small airway function were shown to be good parameters of long-term control and treatment response in asthma [8, 13, 30]. Our results were supported by the previous studies which indicated that the R5-R20 and AX showed a good to excellent AuROC for the detection of poorly controlled asthma (AuROC = 0.86-0.91 and 0.84-0.90 for R5-R20 and AX, respectively) [8, 9]. The R5-R20 cut-off values of ≥ 1.0 and ≥ 1.5 cmH₂O/L/s had high sensitivity and specificity for the detection of poorly controlled asthma with a range from 0.813 to 0.820 and 0.840 to 0.842, respectively [8, 9]. The cut-off value of AX ≥ 7.0 and ≥ 9.5 cmH₂O/L had high sensitivity and specificity for the prediction of poorly controlled asthma with a range from 0.860 to 0.875 and 0.840 to 0.921, respectively [8, 9]. However, the AuROC of IOS parameters in these studies were derived from children. Only one study in adults has been carried out and showed poor diagnostic ability of IOS and/or spirometry for discrimination between poorly controlled and well controlled asthma (AuROC = 0.61) [16]. However, this study did not provide the details of each parameter of IOS for the detection of poorly controlled asthma. In our study, the cut-off R5-R20 (z-score ≥ 0 or absolute value ≥ 1 cmH₂O/L/s) showed the highest AuROC (0.86), with a sensitivity and specificity $\geq 80.0\%$ for the detection of poorly controlled asthma. The second parameter that could be used for detection of poorly controlled asthma was AX ≥ 9 cmH₂O/L (AuROC = 0.84, sensitivity = 80.4%, and specificity = 87.5%). However, the combination of R5-R20 and AX, which had an AuROC of 0.84, a sensitivity of 80.4%, and a specificity of 88.5%, was not a more effective single parameter for detection of poorly controlled asthma. Therefore, we suggest that the use of a single parameter gives

adequate information for the detection of poorly controlled asthma. We recommend using R5-R20 at the easy-to-remember cut-off value of R5-R20 as the best single parameter for the detection of poorly controlled asthma because this cut-off resulted in a high level of accuracy together with good diagnostic criteria. A previous study suggested that the +LR between 5 and 10 and -LR between 0.1 and 0.2 indicate good diagnostic criteria [31]. This study therefore adds weight to our findings that the use of R5-R20 was the best tool for the detection of poorly controlled asthma in our population.

Our results showed that the diagnostic ability of IOS parameters (R5-R20 and AX) were superior for detection of poorly controlled asthma when compared to the spirometry variables (FEV₁ and FVC). The AuROC ranged from 0.90 - 0.91 vs 0.71-0.74 for IOS parameters and spirometry variables, respectively. Our results were supported by a previous study indicating that the index of spirometry (FEV₁) did not significantly contribute to health status or asthma control, unlike the indices of IOS [10].

Obesity was found to be associated with poor asthma control and increased risk of exacerbation [9, 32, 33]. Our results showed that BMI was significantly higher in the poorly controlled asthma group in comparison to the well-controlled asthma group ($28.5 \pm 3.9 \text{ kg/m}^2$ vs. $24.8 \pm 4.1 \text{ kg/m}^2$). However, the sample size in this area was limiting as there were only seven obese subjects whose BMI was greater than 35.0 kg/m^2 in this study. Three (3.1%) were in a well controlled asthma group and four (8.7%) in the poorly controlled asthma group. However, a previous study showed that a significant increase in airway resistance and reactance were found in subjects with a BMI greater than 40.0 kg/m^2 [34]. Therefore, the small proportion of subjects with obesity in our study may not affect the results.

Strength and limitations of this study

The strength of our study is its value as the first study that not only confirms the benefits of IOS as a useful test for detection but also identifies the cut-off values of IOS parameters including R5-R20 and AX for diagnosis of poorly controlled asthma in an adult population with normal spirometry. However, this study has some limitations. Firstly, only clinically diagnosed asthmatic subjects with normal spirometry were included. Thus, the cut-off values for the detection of poorly controlled asthma in patients with abnormal spirometry, obstruction and/or restrictions, may be different. Secondly, there are limited data pertinent to the prediction equation of IOS parameters in Southeast Asian, especially in the Thai population. Thus, we used the absolute value of each parameter for the detection of poorly controlled asthma. Previous studies suggested that airway resistance and reactance were correlated with sex, age, height, and weight [9, 35-37]. The diversity of ethnic origins may have resulted in differences in airway resistance and reactance [37]. Therefore, the use of our cut-off point for detection of the level of asthma control in other settings should be interpreted with caution.

Conclusion

Our study indicates that the IOS parameters including R5-R20 and AX showed good detection of poorly controlled asthma in patients with normal spirometry. The z-score or the absolute value of R5-R20 at the cut-off value of ≥ 0 and $\geq 1 \text{ cmH}_2\text{O/L/s}$ is the best parameter for accurate detection. These findings indicate that IOS is a useful tool for the detection of the level of asthma control in adults with normal spirometry.

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Author contributions

Conceptualization, W.C., S.N., C.L., and C.P.; Methodology, W.C., S.N., C.L.; C.P. Software: W.C.; Validation, W.C., S.N., C.L., and C.P.; Formal Analysis, W.C., S.N.; Investigation, W.C., C.L., and C.P.; Resources, W.C., C.L., and C.P.; Data Curation, W.C. and C.P.; Writing – Original Draft Preparation, W.C.; Writing – Review and Editing, W.C., S.N., C.L., and C.P.; Visualization, W.C., S.N., C.L., and C.P.; Supervision, S.N., C.L., and C.P.; Project Administration, W.C., and C.P.; Funding Acquisition, W.C., S.N., and C.P. All authors have read and agreed to the published version of the manuscript.

Disclosure Statement

The authors have no conflict of interest in connection with this work.

List of Abbreviations

ACT	Asthma Control Test
ATS	American Thoracic Society
AUC	Area under the curve
AUROC	Area under the receiver operating characteristic curve
AX	Area under reactance curve between 5 Hz and F_{res}
BD	Bronchodilator
BMI	Body mass index
CI	Confidence interval
ERS	European Respiratory Society
FEF _{25-75%}	Average expired flow over the middle half of the FVC maneuver
FEV ₁	Forced expiratory volume in the first second
FVC	Forced vital capacity

Fres	Resonant frequency
GINA	Global Initiative for Asthma
GLI	Global Lung Initiative
IOS	Impulse oscillometry
IQR	Interquartile range
LLN	Lower limit of normal
LR	Likelihood ratio
R5	Resistance at 5 Hz
R20	Resistance at 20 Hz
R5-R20	Subtraction of the R20 from R5
ROC	Receiver operating characteristic
Rrs	Respiratory resistance
SD	Standard deviation
X5	Reactance at 5 Hz

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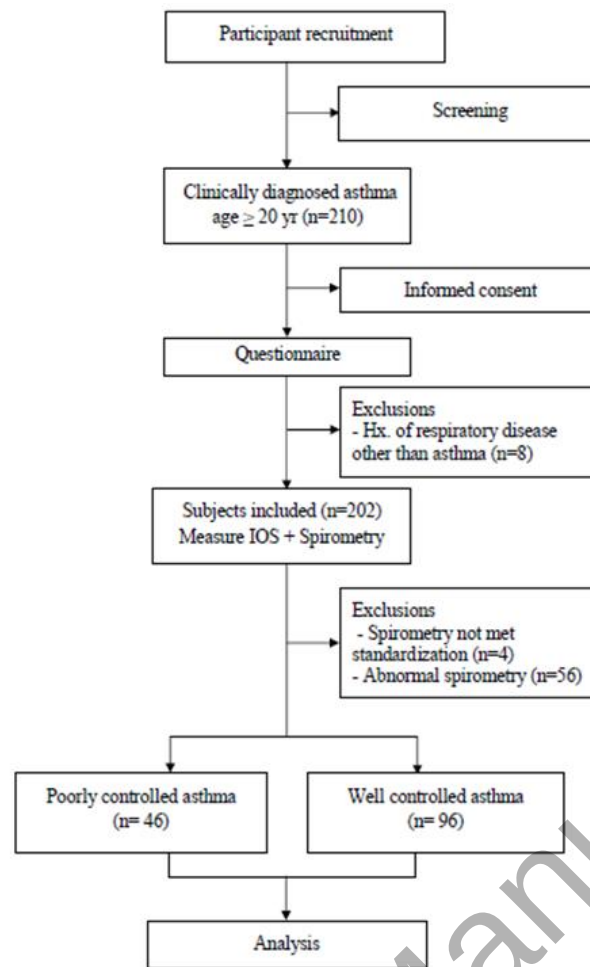


Figure 1. Flow-chart describing the study population

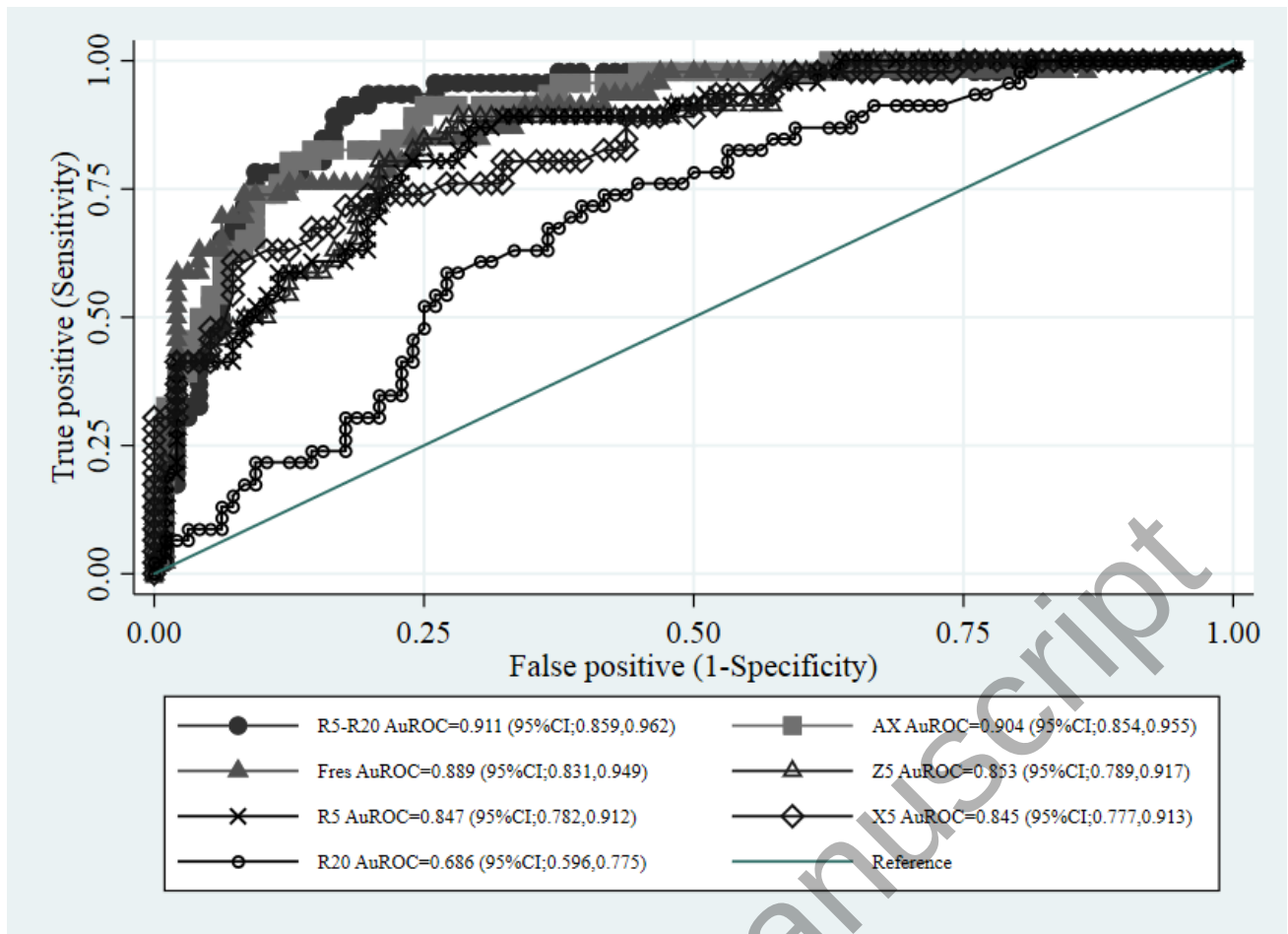


Figure 2. Receiver operating characteristic curves illustrating the performance of z-score and absolute value of IOS variables in the detection of poorly controlled asthma.

Note: AuROC from score based ROC.

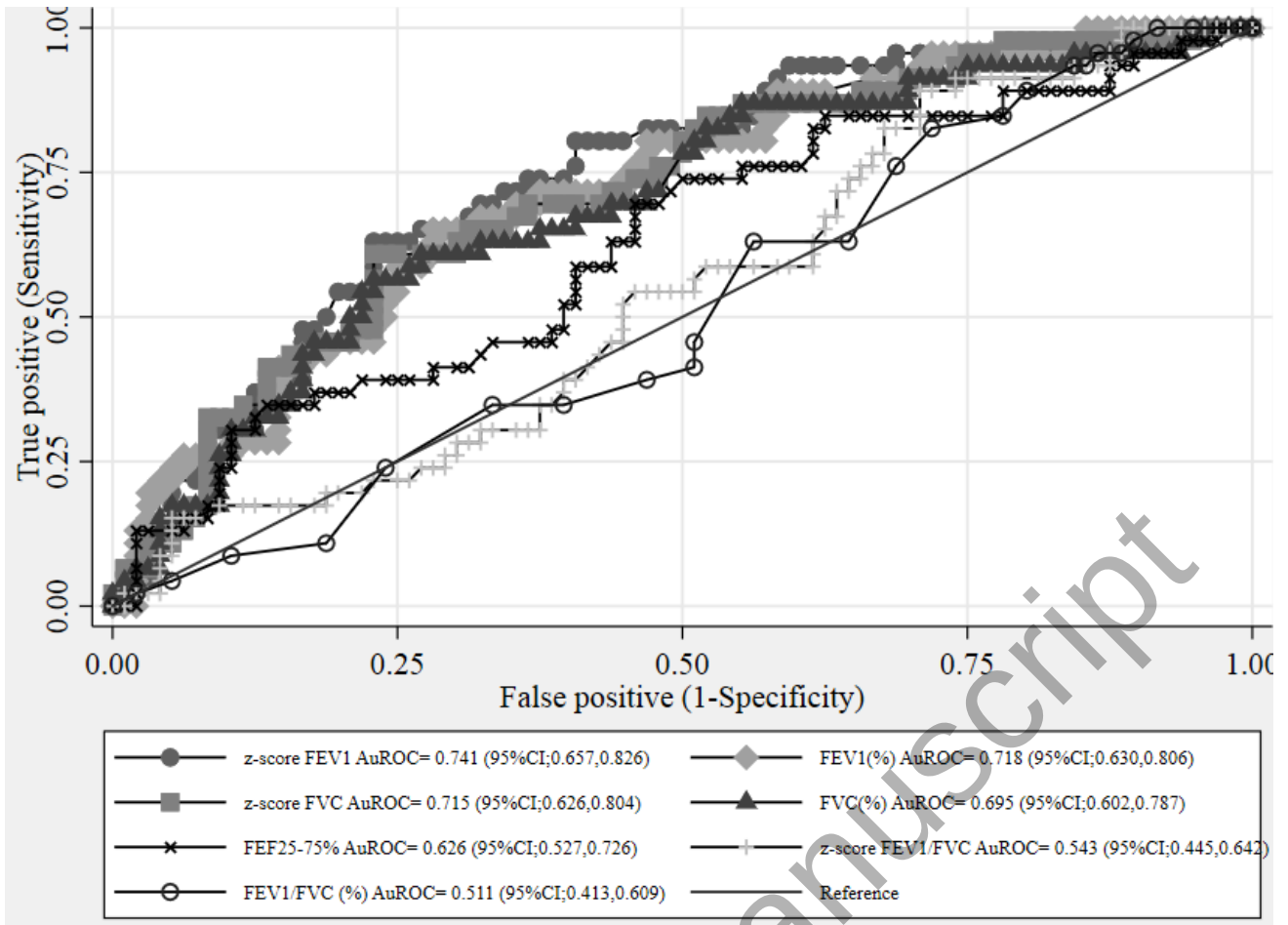


Figure 3. Receiver operating characteristic curves illustrating the performance of z-score, absolute value, and % predicted of spirometry variables in the detection of poorly controlled asthma.

Note: AuROC from score based ROC.

Table 1. Baseline characteristics

Clinical characteristics	Poorly controlled asthma (n=46)	Well controlled asthma (n=96)	p-value
Age (years)	54.9 ± 16.2	53.1 ± 15.9	0.763
Female sex n (%)	33 (71.7)	57 (59.4)	0.193
Height (cm)	153.7 ± 8.1	155.9 ± 8.1	0.242
Body weight (kg) ^a	67.5 ± 12.0	60.4 ± 11.4	0.001
Body mass index (BMI) ^a	28.5 ± 3.9	24.8 ± 4.1	<0.001
Smoking status			0.638
Non-smoker	40 (87.0)	85 (88.6)	
Current-smoker	0 (0.0)	1 (1.0)	
Ex-smoker	6 (13.0)	10 (10.4)	
Hx. of AE asthma in the previous year (yes) ^b	19 (41.3)	11 (11.5)	<0.001
Age of disease onset (year) (median, IQR) ^c	37.5 (27, 55)	37.5 (21, 57)	0.699
Duration of disease (year) (median, IQR) ^c	11 (3, 31)	10.5 (3, 24.5)	0.819
Family history of asthma (yes) ^b	25 (54.4)	56 (58.3)	0.718
ACT score ^a	17.3 ± 3.2	23.0 ± 1.6	<0.001
Inhaled medication used ^b			0.007
ICS	6 (13.0)	9 (9.4)	
ICS + LABA	29 (63.1)	81 (84.4)	
ICS + LABA + LAMA	11 (23.9)	6 (6.2)	
Oral medication used			
Antileukotriene ^b	31 (67.4)	54 (56.3)	0.272
Oral bronchodilator ^b	5 (10.9)	3 (3.1)	0.112
Daily dose of ICS ^b			0.157
Low	20 (43.5)	58 (60.4)	
Medium	22 (47.8)	32 (33.3)	
High	4 (8.7)	6 (6.3)	
Comorbidity n (%)			
Rhinitis ^b	39 (84.8)	81 (84.4)	1.000
Cardiovascular disease ^b	14 (30.4)	26 (27.1)	0.694
Metabolic disease ^b	7 (15.2)	10 (10.4)	0.418
Neuromuscular disease ^b	2 (4.4)	3 (3.1)	0.659

Note: Data are mean ± standard deviation (SD) unless otherwise stated; ^a p-value from t-test comparing poorly controlled asthma and well controlled asthma; ^b , p-value from Fisher's exact test comparing poorly controlled asthma and well controlled asthma; ^c , p-value from Mann-Whitney U test comparing poorly controlled asthma and well controlled asthma.

Abbreviations: AE, acute exacerbation; ACT, asthma control test; IQR, interquartile range; ICS, inhaled corticosteroid; LABA, Long-acting beta2-agonists; LAMA long-acting muscarinic antagonist; NA, not assessed.

Table 2. Absolute value and z-score of spirometric data in all subjects.

Spirometry data (Pre-bronchodilator)	Poorly controlled asthma (n=46)	Well controlled asthma (n=96)	p-value
FEV ₁ (L)	1.86 ± 0.64	2.23 ± 0.62	0.001
%predicted FEV ₁	85.2 ± 11.2	94.8 ± 13.4	<0.001
FVC (L)	2.39 ± 0.72	2.85 ± 0.73	<0.001
%predicted FVC	91.7 ± 12.4	100.5 ± 13.2	<0.001
FEV ₁ /FVC (%)	78.2 ± 5.1	78.9 ± 6.9	0.509
FEF25-75% (L/sec)	1.71 ± 0.87	2.12 ± 1.00	0.019
z-score			
FEV ₁	-1.05 ± 0.73	-0.31 ± 0.94	<0.001
FVC	-0.65 ± 0.85	0.04 ± 0.92	<0.001
FEV ₁ /FVC	-0.90 ± 0.73	-0.69 ± 0.95	0.176
FEF25-75%	N.A.	N.A.	N.A.

Note: Data are mean ± standard deviation (SD); N.A., not available for GLI reference equation

Abbreviations: FVC, forced vital capacity; FEV₁, forced expiratory volume in the first second; FEF25-75%, forced expiratory flow at 25-75% of FVC; L, liter; N.A., not available.

Table 3. Absolute value and z-score of IOS parameters in all subjects.

IOS parameters	Poorly controlled asthma (n=46)	Well controlled asthma (n=96)	p-value
Absolute value			
Z5 (cmH ₂ O/L/s)	6.13 ± 1.74	3.99 ± 1.25	<0.001
R5 (cmH ₂ O/L/s)	5.71 ± 1.56	3.80 ± 1.19	<0.001
R20 (cmH ₂ O/L/s)	3.78 ± 0.87	3.18 ± 0.97	<0.001
R5-R20 (cmH ₂ O/L/s)	1.93 ± 0.88	0.62 ± 0.63	<0.001
X5 (cmH ₂ O/L/s)	-2.16 ± 0.94	-1.14 ± 0.55	<0.001
Fres (Hz)	21.51 ± 4.48	14.62 ± 3.90	<0.001
AX (cmH ₂ O/L)	18.49 ± 11.88	5.32 ± 4.74	<0.001
z-score			
Z5	0.83 ± 1.00	-0.40 ± 0.72	<0.001
R5	0.81 ± 0.98	-0.39 ± 0.75	<0.001
R20	0.41 ± 0.89	-0.20 ± 0.99	<0.001
R5-R20	0.93 ± 0.93	-0.44 ± 0.67	<0.001
X5	-0.82 ± 1.11	0.38 ± 0.65	<0.001
Fres	0.89 ± 0.86	-0.43 ± 0.75	<0.001
AX	0.89 ± 1.19	-0.43 ± 0.48	<0.001

Note: Data are mean ± standard deviation (SD).

Abbreviations: Z5, the impedance at 5 hertz; R5, resistance at 5 Hz; R20, resistance at 20 Hz; R5-R20, heterogeneity of resistance between R5 and R20; Fres, resonant frequency; X5, reactance at 5 Hz; AX, the area under reactance curve between 5 Hz and resonant frequency.

Table 4. Diagnostic performances of IOS parameters to the detection of poorly controlled asthma.

Variable	Cut-off value	Sensitivity	Specificity	+ LR	- LR	Diagnostic odds ratio	AUC
z-score							
R5–R20	≥ 0.00	89.1	83.3	5.35	0.13	41.2	0.86
AX	≥ -0.04	80.4	87.5	6.43	0.22	29.2	0.84
Z5	≥ 0.10	80.4	78.1	3.68	0.25	14.7	0.79
Fres	≥ 0.20	78.3	78.1	2.38	0.16	14.9	0.78
X5	≤ -0.25	71.7	82.3	4.05	0.21	19.3	0.77
R5	≥ 0.00	82.6	71.9	2.94	0.24	12.2	0.77
R20	≥ 0.15	60.9	69.8	1.37	0.38	3.6	0.65
R5–R20 ≥ 0.00 + AX ≥ -0.04		80.4	88.5	7.02	0.22	31.9	0.84
Absolute value							
R5–R20 (cmH ₂ O/L/s)	≥ 1.0	89.1	82.3	5.03	0.13	38.7	0.86
AX (cmH ₂ O/L)	≥ 9.0	80.4	87.5	6.43	0.22	29.2	0.84
Fres (Hz)	≥ 17.5	80.4	76.0	3.36	0.26	12.9	0.78
Z5 (cmH ₂ O/L/s)	≥ 5.0	76.1	79.2	3.65	0.30	12.1	0.78
R5 (cmH ₂ O/L/s)	≥ 4.5	80.4	74.0	3.09	0.26	11.9	0.77
X5 (cmH ₂ O/L/s)	≤ -1.6	73.9	76.0	3.09	0.34	9.1	0.75
R20 (cmH ₂ O/L/s)	≥ 3.5	60.9	69.8	2.01	0.56	3.6	0.65
R5–R20 ≥ 1.0 cmH ₂ O/L/s + AX ≥ 9.0 cmH ₂ O/L		80.4	88.5	7.02	0.22	31.9	0.84

Note: AUC from cut off based ROC.

Abbreviations: Z5, the impedance at 5 hertz; R5, resistance at 5 Hz; R20, resistance at 20 Hz; R5–R20, heterogeneity of resistance between R5 and R20; Fres, resonant frequency; X5, reactance at 5 Hz; AX, area under reactance curve between 5 Hz and resonant frequency; +LR, positive likelihood ratio, -LR, negative likelihood ratio; AUC, area under the curve.