Minimal clinically important difference for impulse oscillometry in adults with asthma

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Shareable abstract (@ERSpublications)
In patients with asthma, small airway function is a distinguished end-point that can be feasibly quantified using the proposed minimal clinically important difference for impulse oscillometry measures https://bit.ly/3YjwZkp

Abstract

Background Impulse oscillometry (IOS) allows an effort-independent evaluation of small airway function in asthma. Unfortunately, well-determined minimal clinically important differences (MCIDs) for IOS measures are lacking. Here, we provide MCIDs for frequently used IOS measures, namely frequency dependence of resistance (FDR) and area of reactance (AX), in patients with asthma.

Methods We performed IOS at baseline and 1 year later in adult patients with mild-to-severe asthma (n=235). In a two-step approach, we first applied a distribution-based method to statistically determine the MCID. Next, we validated the proposed MCID according to patient-reported outcome measures (PROMs): Asthma Quality of Life Questionnaire (AQLQ), Asthma Control Questionnaire-7 (ACQ-7) and Asthma Control Test (ACT). We used multivariable analyses to investigate the proposed MCIDs as predictors for improvements in PROMs compared with the established MCID of forced expiratory volume in 1 s (FEV_1).

Results The proposed MCID was a decline of $\geqslant 0.06$ $kPa \cdot L^{-1} \cdot s^{-1}$ and $\geqslant 0.65$ $kPa \cdot L^{-1}$ for FDR and AX, respectively. Patients who had changes beyond the MCIDs for both FDR and AX showed greater improvements in all PROMs than those who had not. The mean improvements in PROMs were beyond the established MCIDs for ACQ-7 and AQLQ, and approximated the MCID for ACT. Multivariable analyses demonstrated the MCIDs for both FDR and AX as independent predictors for the MCIDs of all PROMs. The MCID for FDR was a stronger predictor of all PROMs than the MCID for FEV_1.

Conclusions This study provides MCIDs for IOS-derived measures in adult patients with asthma and emphasises that small airway function is a distinguished end-point beyond the conventional measure of FEV_1.

Introduction

Impulse oscillometry (IOS) is the most widely used variant of the forced oscillation technique for assessment of lung function [1]. The fundamental principle of this noninvasive tool is to passively measure

the physiological properties of the lung through superimposing sound waves on normal tidal breathing [1]. As a consequence, IOS has the unique advantage of providing lung function testing unconstrained by forced expiratory manoeuvres in children, poorly cooperative or frail subjects, or in patients with respiratory muscle dysfunction. Additionally, recent clinical and lung computational data have demonstrated that IOS measures of airway resistance (fall of airway resistance from 5 to 20 Hz (R5–R20)) and low-frequency reactance, such as reactance at 5 Hz, might be sensitive to small airway dysfunction in asthma [2, 3]. Owing to these distinctive features, IOS has increasingly gained great attention as a reliable tool that allows identifying and quantifying functional alterations in the small airways, which in turn has enriched our understanding of the nature of small airway dysfunction and its great clinical significance in patients with asthma [4, 5]. Using IOS, recent clinical studies have demonstrated the high prevalence of small airway dysfunction in patients with asthma and its association with distinct disease phenotypes and clinical outcomes [6]. IOS might also reveal lung function impairments in patients with normal conventional lung function testing according to spirometry [7]. Moreover, IOS might detect longitudinal changes in the small airways in patients with relatively stable spirometry; in association with alterations in airway inflammatory phenotypes [8] or in those who are receiving anti-eosinophil biological therapy [9].

Although IOS appears to be a sensitive and easily reproducible lung function test, its use in routine clinical practice is still limited, especially in adult patients with airway diseases such as asthma. A part of this limitation can be attributed to a lack of standardisation, including clearly determined minimal clinically important differences (MCIDs) for the distinct IOS parameters. For the purpose of this study, the MCID might be defined as the least change in small airway function parameters that conveys clinically significant improvements in health status and quality of life from the patients' perspective [10]. A clear-cut MCID might help optimising asthma therapy and identifying unmet needs in asthma management [11]. In this multicentre study, we sought to determine the MCIDs for frequently used measures of IOS and validate the proposed values based on patient-reported outcome measures (PROMs) for asthma control and quality of life.

Methods

Study design

Eligible subjects were adult asthma patients who participated in the multicentre All Age Asthma Cohort (ALLIANCE), a longitudinal observational cohort study of paediatric and adult asthma patients, initiated by the German Center for Lung Research (DZL). The study was approved by the ethics committee at the University of Lübeck School of Medicine (Lübeck, Germany; Az.21-215) and is registered at ClinicalTrials.gov (adult arm: NCT02419274). Written informed consent was obtained before enrolment. This longitudinal analysis included adult patients with mild-to-severe asthma who underwent a pulmonary function test, using IOS, at baseline and after 1-year follow-up. The participants had to have stable disease at the time of assessment, *i.e.* absence of acute exacerbations or respiratory tract infections within 4 weeks prior to study visit. Detailed information on recruitment, inclusion and exclusion criteria of the ALLIANCE cohort are as previously described [12].

Lung physiology characteristics

Lung function testing was performed in the morning and patients were allowed to receive their controller medication as usual. We performed IOS (MasterScreen IOS; Vyaire Medical, Höchberg, Germany) according to current European Respiratory Society (ERS) recommendations [13, 14]. A routine calibration of the IOS system was done based on the manufacturer's protocol [15]. Throughout the test, patients were seated in an upright posture with a very slight chin-up position, and were instructed to breathe as normal with their lips around the mouthpiece and their tongue below. We also asked the patients to support their cheeks with their fingers or palms, to avoid swallowing, and to use a nasal clip. During tidal breathing, two to three acquisitions each for 20–40 s were performed [14]. Measures of total and proximal airway resistance were obtained at 5 and 20 Hz (R5 and R20 ($kPa \cdot L^{-1} \cdot s^{-1}$)), respectively. Consequently, the fall of airway resistance from 5 to 20 Hz (R5–R20) was expressed as the frequency dependence of resistance (FDR ($kPa \cdot L^{-1} \cdot s^{-1}$)) and considered as an index for the resistance in small airways [2]. A further measure was the area of reactance (AX ($kPa \cdot L^{-1}$)), a well-established composite measure of airway reactance at lower frequencies that reflects the airway compliance and hence its increase is considered a surrogate for peripheral airway obstruction [16, 17]. Following IOS, the patients underwent forced spirometry according to ERS recommendations [18]. Regarding the MCID for FEV_1, recent ERS/American Thoracic Society recommendations have proposed that over a 1-year period, an improvement of $\geqslant 15\%$ in the FEV_1 is with high confidence clinically meaningful [11].

PROMs for asthma control and quality of life

We used validated PROMs for asthma control and quality of life to evaluate the clinical utility of the proposed MCIDs for both FDR and AX. These measures were the Asthma Quality of Life Questionnaire

(AQLQ), Asthma Control Questionnaire 7 (ACQ-7) and Asthma Control Test (ACT). The MCIDs for PROMs has been determined as 0.5 point for AQLQ [19], 0.5 point for ACQ-7 [20, 21] and 3.0 points for ACT [22].

Statistical approach to determine the MCID

The MCID is the smallest value of benefit to patients' health that can be determined using an expert consensus, the anchor or distribution-based methods [23]. Here, we applied a two-step approach that has allowed the clinical validation of statistically proposed minimal detectable changes.

First, we used the effect size, a distribution-based method, to calculate the minimal detectable change, which is the lowest change beyond random error that roughly approximates the MCID [24]. The effect size is a standardised measure of change that depends on the distribution of population-based scores and thus allows to detect changes in these scores through statistical indices [11]. It can be obtained by dividing the difference in scores from baseline to follow-up by the standard deviation of baseline scores [11, 25]. The correspondent result is an effect size of <0.20, 0.20–0.49, 0.50–0.79 or ⩾0.80, which reflects the occurrence of a negligible, small, moderate or large change, respectively [11]. An effect size between 0.30 and 0.50 is the most frequently acceptable surrogate for the MCID [26, 27]. In our study, we set an arbitrary effect size threshold of 0.40 to calculate the MCIDs for the 1-year change in FDR and AX. The proposed statistical approach to do this is to multiply the effect size by the standard deviation of the baseline measures [28]. To confirm the outcome of this approach, we further stratified the patients into three groups: 1) patients with improved FDR or AX were those with an effect size of ⩽−0.40 (where the minus sign denotes a decline in small airway resistance), 2) patients with worsened FDR or AX were those with an effect size increase of ⩾0.40, while 3) patients with an effect size between −0.39 and 0.39 were considered to have no change. Subsequently, the minimal change, *i.e.* the least decline in FDR or AX in patients who had improved, was set as the MCID.

Since the effect size method is purely based on statistical calculations [23], in a second step we investigated the clinical utility of the proposed MCIDs for both FDR and AX. We used one-way ANOVA and Tukey's post-hoc test to compare the 1-year change in PROMs between patients who were stratified based on effect size. Eventually, we used PROMs as an anchor and investigated the proposed MCIDs of FDR and AX as predictors for the 1-year change in PROMs using multivariable linear models. The outcome variables of these models were the absolute 1-year change or the incidence of improvement beyond the MCIDs of PROMs. Independent predictors were a change beyond the proposed MCID for FDR or AX, the 1-year change of FEV_1 or a change beyond the MCID of FEV_1, treatment with anti-type 2 (T2) biologics, systemic corticosteroid therapy and the dose if inhaled corticosteroids. The models were adjusted for age, sex and body mass index. Multivariable regression models for the newly proposed MCIDs allow illustrating their clinical relevance with respect to well-established patients' health and quality of life measures [27]. Statistical analyses were performed using R version 1.4.1106 (R Foundation, Vienna, Austria). An α error of <5% was considered statistically significant.

Results

We recruited 294 adult asthma patients, of whom 246 patients attended their follow-up visit at 1 year. After 11 patients were excluded due to missing baseline or follow-up IOS measures, 235 patients were eligible for analysis. Patient age ranged from 19 to 79 years; they showed a roughly similar sex distribution and half of them had severe asthma (table 1). Overall, the patients had poor symptom control and a high exacerbation frequency, which were improved at 1-year follow-up. Detailed baseline and follow-up patient characteristics are presented in table 1.

Initially, patients were stratified based on the magnitude of change in IOS measures, indicated by the standardised measure of effect size (table 2). Here, we observed an association between the magnitude of change in IOS measures and the corresponding changes in PROMs. Patients with large improvements in FDR or AX demonstrated significant improvements in their reported outcome measures compared with those who had worsening, negligible or even small improvements in their FDR or AX and showed poor improvements in their outcome measures (table 2).

The result of multiplying the predefined effect size of 0.40 by the standard deviation of baseline FDR (0.13) was 0.052, indicating that the statistical approximation of MCID is a change beyond 0.052 kPa·L^{-1}·s^{-1}. The stratification of patients based on the predefined effect size showed that the minimal decline in patients who improved their FDR (n=48) was −0.06 kPa·L^{-1}·s^{-1} (mean±SD change −0.13±0.09) *versus* a minimal increase of 0.06 kPa·L^{-1}·s^{-1} (mean±SD change 0.12±0.07) in patients who had worsened FDR (n=40), while patients without significant change (n=146) who had an effect size

TABLE 1 Baseline and follow-up patient characteristics (n=235)

	Baseline	Follow-up
Male	44	
Age at baseline (years)	51.1±14	
Severe asthma[#]	50	
Body mass index (kg·m^{-2})	27.7±5.7	27.6±5.3
Controller ICS use	85	88
ICS dose (µg fluticasone-equivalent)	500 (250–1000)	500 (250–1000)
High-dose ICS	35	35
Maintenance OCS use	22	19
Biological therapy	12	14
FVC (% pred)	102±17	103±16
Pre-BD FEV$_1$ (% pred)	80±21	80±20
Pre-BD FEV$_1$/FVC	64±12	64±12
Frequency dependence of resistance (kPa·L^{-1}·s^{-1})	0.15±0.13	0.14±0.12
Area of reactance (kPa·L^{-1})	1.33±1.59	1.17±1.33
ACT score	17.9±5.4	18.9±4.9
ACQ-7 score	1.86±2.2	1.59±1.1
AQLQ score	5.1±1.2	5.4±1.2
Severe exacerbation[¶]	57	38

Data are presented as %, mean±SD or median (interquartile range). ICS: inhaled corticosteroids; OCS: oral corticosteroids; BD: bronchodilation (400 µg salbutamol); FVC: forced vital capacity; FEV$_1$: forced expiratory volume in 1 s; ACT: Asthma Control Test; ACQ-7: Asthma Control Questionnaire-7; AQLQ: Asthma Quality of Life Questionnaire. [#]: severe asthma was defined based on European Respiratory Society/American Thoracic Society guidelines [35] (severe asthma patients had high-dose ICS and a second controller or systemic steroids or steroid-sparing biological therapy to prevent asthma from becoming uncontrolled); [¶]: ⩾1 severe exacerbations within 12 months before study visit.

between −0.39 and 0.39 demonstrated FDR changes between −0.05 and 0.05 kPa·L^{-1}·s^{-1} (mean±SD change 0.00±0.03). Using the same approach for a standard deviation of 1.59 for baseline AX, the statistical approximation of MCID is a change beyond 0.64 kPa·L^{-1}. The stratification of patients (with available AX measures, total n=231) based on the predefined effect size showed that the minimal decline in patients who improved their AX (n=43) was −0.65 kPa·L^{-1} (mean±SD change −1.98±1.46) *versus* a minimal increase of 0.63 kPa·L^{-1} (mean±SD change 1.5±0.93) in patients who had worsened AX (n=39). Patients without significant change (n=149) who had an effect size between −0.39 and 0.39 had AX changes between −0.59 and 0.57 kPa·L^{-1} (mean±SD change −0.03±0.26). Consequently, the proposed

TABLE 2 Change in patient-reported outcome measures according to the effect size of impulse oscillometry

	Relative size							p-value
	Large improvement	Moderate improvement	Small improvement	No change	Small worsening	Moderate worsening	Large worsening	
Effect size of FDR								
Patients	22	16	45	74	42	17	19	
ΔFDR (kPa·L^{-1}·s^{-1})	−0.19±0.12	−0.08±0.01[#]	−0.04±0.02[#,¶]	0±0.01[#,¶]	0.04±0.01[#,¶]	0.08±0.01[#,¶]	0.17±0.07[#,¶]	<0.001
ΔACT score	3.82±4.27	1.5±2.83	0.61±3.29[#]	0.45±3.24[#]	0.63 3.67[#]	0.29±0.84[#]	0.2±0.7[#]	<0.01
ΔACQ-7 score	−1.1±0.93	−0.25±0.72[#]	−0.17±0.75[#]	−0.07±0.7[#]	−0.1±0.68[#]	0.08±1.03[#]	0.06±0.56[#]	<0.001
ΔAQLQ score	1.11±0.79	0.41±0.51	0.22±0.7[#]	0.17±0.64[#]	0.36±0.76[#]	0.29±0.84[#]	0.2±0.76[#]	<0.001
Effect size of AX								
Patients	21	12	27	114	28	12	17	
ΔAX (kPa·L^{-1})	−3.0±1.20	−1.05±0.14[#]	−0.52±0.16[#]	−0.03±0.14[#,¶]	0.54±0.14[#,¶]	1.03±0.16[#,¶]	2.13±0.93[#,¶]	<0.001
ΔACT score	4.0±4.2	0.34±2.0	1.3±4.0	0.53±3.18[#]	0.0±3.95[#]	2.91±3.7	−0.71±3.1[#]	<0.01
ΔACQ-7 score	−1.12±0.9	−0.41±0.59	−0.32±0.80[#]	−0.11±0.69[#]	0.05±0.83[#]	−0.03±0.8[#]	0.22±0.66[#]	<0.001
ΔAQLQ score	1.11±0.72	0.3±0.81	0.26±0.70[#]	0.22±0.63[#]	0.39±0.92[#]	0.47±0.93	0.08±0.63[#]	<0.001

Data are presented as n or mean±SD, unless otherwise stated. FDR: frequency dependence of resistance; ACT: Asthma Control Test; ACQ-7: Asthma Control Questionnaire-7; AQLQ: Asthma Quality of Life Questionnaire; AX: area of reactance. Post-hoc pairwise comparisons. [#]: significantly different (p<0.05) from patients with large improvement; [¶]: significantly different (p<0.05) from patients with moderate improvement.

MCID cut-off values are a decline of $\geqslant 0.06$ kPa·L^{-1}·s^{-1} and $\geqslant 0.65$ kPa·L^{-1} for FDR and AX, respectively.

Using these proposed MCID cut-offs, we found that patients with improvements beyond the MCIDs for both FDR and AX had greater improvements in their PROMs compared with those with unchanged or worsened FDR or AX (figure 1). Additionally, in these patients with improved FDR and AX the mean improvements in PROMs were beyond the established MCIDs for ACQ and AQLQ, and also approximated the MCID for ACT (figure 1).

IOS MCID versus FEV$_1$ MCID as predictors for PROMs

Finally, multivariable linear regressions indicated that improvements beyond the proposed MCIDs for both FDR (table 3) and AX (table 4) are independent predictors for both the 1-year change in PROM scores and for improvements beyond their established MCIDs. Even after including the change in FEV$_1$ as a predictor for PROMs, the proposed MCIDs, particularly for FDR, remained the strongest predictors for the changes in PROMs (tables 3 and 4).

Discussion

IOS has been increasingly recognised as a reliable lung function tool in patients with obstructive lung diseases. However, there are currently no precisely determined MCIDs for IOS measures in patients with asthma. In this study, we proposed MCIDs for FDR and AX, which both are well-established measures of small airway function. Moreover, we validated the proposed MCID values based on PROMs for asthma
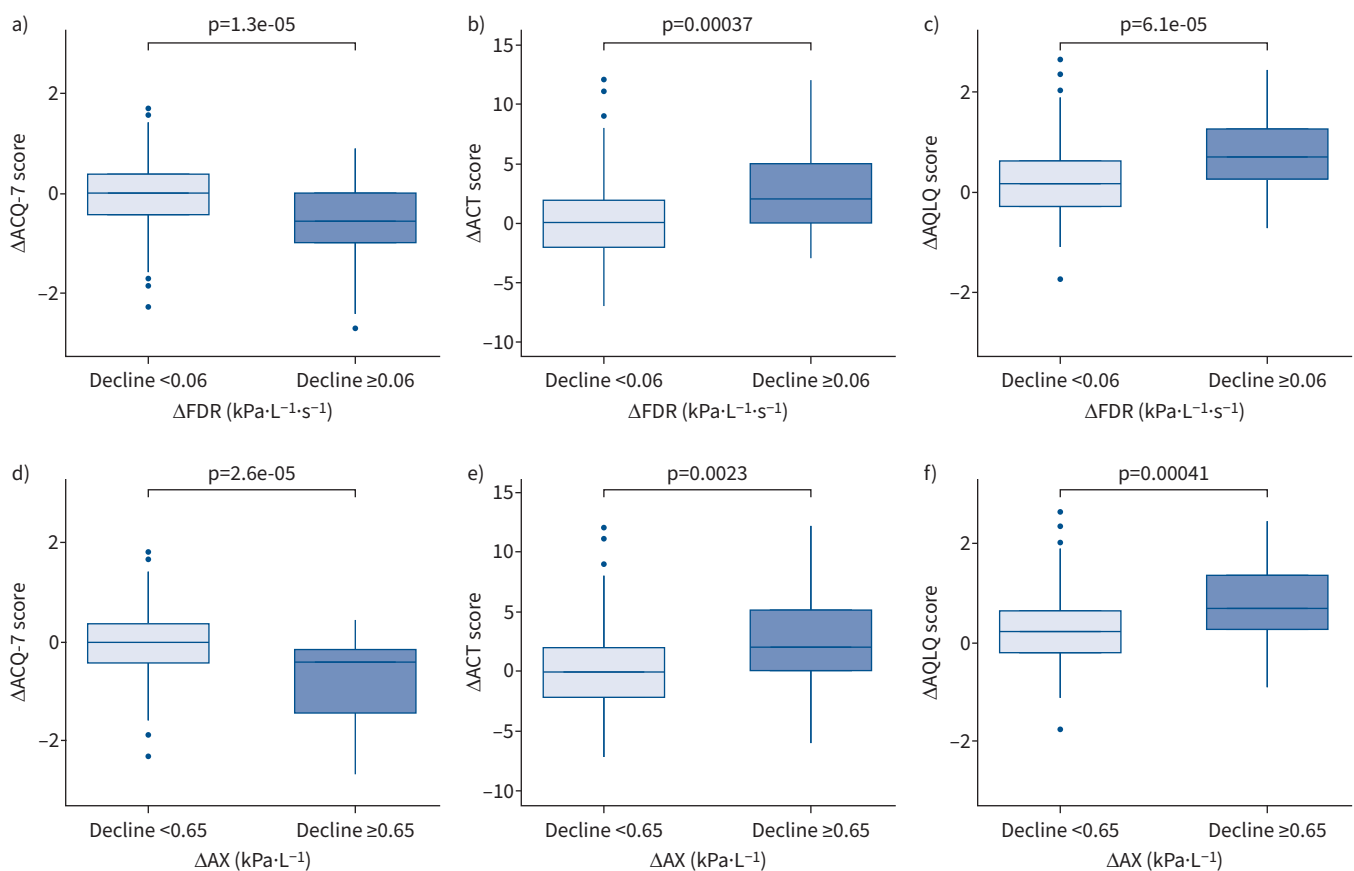
FIGURE 1 Box plots demonstrating the improvements in patient-reported outcome measures of asthma control and quality of life based on improvements beyond the minimal clinically important differences (MCIDs) for a–c) frequency dependence of resistance (FDR (kPa·L^{-1}·s^{-1})) and d–e) area of reactance (AX (kPa·L^{-1})). Patients (n=48) with improvements in FDR beyond the proposed MCID ($\geqslant 0.06$ kPa·L^{-1}·s^{-1}) had mean±SD improvements of −0.71±0.89, 2.70±3.79 and 0.74±0.72 for Asthma Control Questionnaire 7 (ACQ-7), Asthma Control Test (ACT) and Asthma Quality of Life Questionnaire (AQLQ) scores, respectively. Patients (n=43) with improvements in AX beyond the proposed MCID ($\geqslant 0.65$ kPa·L^{-1}) had mean±SD improvements of −0.79±0.93, 2.53±4.0 and 0.72±0.81 for ACQ-7, ACT and AQLQ scores, respectively. Boxes represent median and interquartile range (IQR); whiskers represent minimum and maximum values. If there are outliers, whiskers are then by default 1.5×IQR.

TABLE 3 Frequency dependence of resistance (FDR) minimal clinically important difference (MCID) as predictor for patient-reported outcome measures (PROMs)

	Standardised estimate (FDR MCID)	Standard error (FDR MCID)	p-value (FDR MCID predictor)	Standard estimate (FEV$_1$ predictor)	R^2
ΔACQ-7[#]	−0.322	0.060	<0.0001		0.173
MCID ACQ-7[#]	0.289	0.062	<0.0001		0.168
MCID ACQ-7 adjusted for ΔFEV$_1$[#]	0.214	0.064	0.001	0.203	0.210
MCID ACQ-7 adjusted for FEV$_1$ MCID[#]	0.224	0.064	<0.001	0.190	0.194
ΔAQLQ[#]	0.295	0.068	<0.0001		0.102
MCID AQLQ	0.261	0.068	<0.001		0.083
MCID AQLQ adjusted for ΔFEV$_1$	0.200	0.070	0.005	0.199	0.12
MCID AQLQ adjusted for FEV$_1$ MCID	0.202	0.069	0.004	0.259	0.130
ΔACT[#]	0.257	0.065	<0.001		0.102
MCID ACT	0.210	0.065	0.001		0.080
MCID ACT adjusted for ΔFEV$_1$	0.135	0.068	0.049	0.213	0.116
MCID ACT adjusted for FEV$_1$ MCID	0.171	0.068	0.012	0.080	0.073

FEV$_1$: forced expiratory volume in 1 s; ACQ-7: Asthma Control Questionnaire-7; AQLQ: Asthma Quality of Life Questionnaire; ACT: Asthma Control Test. Multivariable linear regressions were adjusted for age, sex and body mass index. Predictors for PROMs were FDR MCID, inhaled corticosteroid dose (fluticasone-equivalent) and therapy with systemic corticosteroids for at least 6 months during the follow-up year or anti-type 2 (T2) biological therapy. Δ represents the absolute 1-year change in PROM. MCID was defined as 0.06 kPa·L^{-1}·s^{-1} decrease in FDR, 0.5 point decrease in ACQ-7 score, 0.5 point increase in AQLQ score, 3.0 points increase in ACT score and 15% increase in FEV$_1$. The outcome variable indicates a change beyond the MCID. [#]: anti-T2 biological therapy is a significant independent predictor.

control and quality of life. We also report that IOS measures predict significant improvements in asthma control and quality of life independent from the conventional measure of FEV$_1$. Given the broad range of asthma patients in terms of age and disease severity, this study provides reference MCID values for routine clinical use and especially for clinical trials where improvement in small airway function might be desired as a clinical end-point.

The notion of the MCID originated from the need for defining clinically relevant changes in treatment outcomes that are tangible for patients [29]. The MCID is hence different from mere statistically significant changes in clinical measures in the sense that changes beyond this threshold are clinically meaningful. Therefore, it is recommended to consider both statistical significance and clinical relevance for the interpretation of changes in clinical measures [29]. Correspondingly, our two-step approach has allowed linking the statistically proposed MCID to frequently reported patient outcome measures from routine

TABLE 4 Area of reactance (AX) minimal clinically important difference (MCID) as predictor for patient-reported outcome measures (PROMs)

	Standardised estimate (AX MCID)	Standard error (AX MCID)	p-value (AX MCID predictor)	Standard estimate (FEV$_1$ predictor)	R^2
ΔACQ-7[#]	−0.376	0.072	<0.0001		0.202
MCID ACQ-7[#]	0.226	0.074	0.002		0.13
MCID ACQ-7 adjusted for ΔFEV$_1$[#]	0.112	0.079	0.16	0.216	0.18
MCID ACQ-7 adjusted for FEV$_1$ MCID	0.143	0.077	0.067	0.197	0.169
ΔAQLQ	0.321	0.077	<0.0001		0.109
MCID AQLQ	0.316	0.075	<0.0001		0.115
MCID AQLQ adjusted for ΔFEV$_1$	0.250	0.083	0.003	0.152	0.140
MCID AQLQ adjusted for FEV$_1$ MCID	0.257	0.079	0.001	0.242	0.166
ΔACT	0.281	0.071	0.001		0.106
MCID ACT	0.256	0.074	<0.001		0.85
MCID ACT adjusted for ΔFEV$_1$	0.158	0.080	0.051	0.203	0.121
MCID ACT adjusted for FEV$_1$ MCID	0.196	0.079	0.014	0.060	0.066

FEV$_1$: forced expiratory volume in 1 s; ACQ-7: Asthma Control Questionnaire-7; AQLQ: Asthma Quality of Life Questionnaire; ACT: Asthma Control Test. Multivariable linear regressions were adjusted for age, sex and body mass index. Predictors for PROMs were AX MCID, inhaled corticosteroid dose (fluticasone-equivalent) and therapy with systemic corticosteroids for at least 6 months during the follow-up year or anti-type 2 (T2) biological therapy. Δ represents the absolute 1-year change in PROM. MCID was defined as 0.65 kPa·L^{-1} decrease in AX, 0.5 point decrease in ACQ-7 score, 0.5 point increase in AQLQ score, 3.0 points increase in ACT score and 15% increase in FEV$_1$. [#]: anti-T2 biological therapy is a significant independent predictor.

clinical practice. Furthermore, to calculate the MCID we applied the effect size, which is a standardised measure of change that depends on the distribution of scores and is appropriate for paired longitudinal data with intra-individual differences. The adapted effect size of 0.40 represents a crude mean guideline measure of the MCID [26].

To the best of our knowledge, this is the first study to provide clear MCID cut-offs for IOS in patients with asthma. Recent studies have demonstrated good medium- and long-term repeatability, *i.e.* an acceptable within-subject variability of oscillometry measures, in patients with asthma [30, 31]. Good test repeatability is essential for identifying the MCID, which reflects changes beyond the natural variability of the test [31]. The MCID cut-offs proposed in our study exceed the medium-term variability values for FDR $(0.04 \text{ kPa·L}^{-1}\text{·s}^{-1})$ and for AX $(0.39 \text{ kPa·L}^{-1}\text{·s}^{-1})$ that have been recently reported in a cohort of severe asthma patients (n=42) [30]. Moreover, FDR values >0.03 or >0.07 $\text{kPa·L}^{-1}\text{·s}^{-1}$ are frequently used for the diagnosis of IOS-defined small airway dysfunction in patients with asthma [7, 32]. The proposed MCID for FDR compares to these cut-offs, which also indicate small airway dysfunction in subjects with respiratory symptoms and preserved spirometry, supporting their plausibility in objectifying patients' symptoms [7].

Furthermore, MCIDs for both FDR and AX demonstrated great potential as predictors for changes in disease-specific symptom control and quality of life scores, even after adjustment for asthma therapy and confounders. It is noteworthy that both IOS measures were independent predictors above and beyond the conventional measure of FEV_1. This finding is particularly important because it emphasises that the impact of small airway dysfunction on patients' symptoms [7, 33] and asthma treatment outcomes [9] can be distinguished from the impact of classical lung function measures of airflow obstruction. Subsequently, considering IOS in the assessment of lung function might solve, even partially, the uncoupling between patients' symptoms and conventional lung function testing as dynamic IOS-defined changes in the small airways may exist despite relatively stable FEV_1 [8].

We acknowledge that small airway dysfunction is an umbrella term that comprises a spectrum of diverse abnormalities in the small airways and some are beyond the scope of IOS [34]. We also recognise that this analysis provides MCIDs based on long-term (1-year) change observations only. However, this is the first study to propose MCIDs for important IOS-derived small airway function measures in patients with asthma.

In conclusion, this study provides MCIDs for IOS-derived measures of small airway function in asthma. The MCIDs were determined based on a statistical approach and validated according to PROMs for symptom control and quality of life. We also report that small airway dysfunction is an independent predictor of asthma outcomes that can be distinguished from conventional spirometry measures of airflow obstruction. Therefore, we suggest including IOS-derived measures of small airway dysfunction as potential end-points in future clinical trials and in routine clinical care.

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