

Original Article

Standardized IOS Reference Values Define Peripheral Airway Impairment-Associated Uncontrolled Asthma Risk Across Ethnicity in Children

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What is already known about this topic? Peripheral airway impairment has frequently been defined by optimal impulse oscillometry cutoff points determined by best-fit analysis for sensitivity and specificity for clinical outcomes, which can vary by population and specific outcome.

What does this article add to our knowledge? We have shown that peripheral airway impairment, defined by standardized impulse oscillometry reference values based on 95% of the normal population, is a consistent available marker of uncontrolled asthma risk in Hispanic and white children.

How does this study impact current management guidelines? Available standardized impulse oscillometry reference values provide the clinician with a consistent tool to identify the risk of peripheral airway impairment outcomes in children with asthma, which may apply across ethnicity.

BACKGROUND: Although clinically useful in identifying peripheral airway impairment (PAI), impulse oscillometry (IOS) has not received universal acceptance. This may be due to variable cutoff points, and the perception that available standardized reference values may not be clinically relevant in all populations.

OBJECTIVE: To establish the relationship between PAI, based on standardized IOS reference values, and uncontrolled asthma as well as interchangeability between Hispanic and white reference algorithms.

METHODS: IOS reference values were established for upper and lower limits of normal (>95th and <5th percentile, respectively) using published algorithms in Hispanic and white children. Values exceeding normal limits (PAI) were compared in

those uncontrolled and controlled for significance of differences. Probability estimates and odds ratio of uncontrolled asthma were determined for R5, R5-R20, AX, and X5 using adjusted generalized estimating equation analyses. Intraclass correlation coefficients determined interchangeability of Hispanic and white reference algorithm values.

RESULTS: Those with uncontrolled asthma had significantly greater PAI and a higher frequency of PAI than those well controlled ($P < .05$), whereas odds of uncontrolled asthma increased with increasing PAI ($P < .001$) for all IOS measures, particularly for X5, where odds ratios ranged from 2.70 to 11.01. There was good to excellent (>70%) agreement between Hispanic and white algorithms, except for R5-R20 (<70%).

CONCLUSIONS: PAI, defined by IOS reference values, not central airway markers (R20), is consistently related to the risk of uncontrolled asthma. This is true whether using Hispanic or white reference algorithms. Thus, standardized reference values in children offer the clinician readily available IOS cutoff points that are clinically relevant across ethnicity. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Peripheral airway impairment; Impulse oscillometry; Uncontrolled asthma; Reference values; Children; Ethnicity; Resistance; Reactance; Outcomes

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INTRODUCTION

Although current National Asthma Educational and Prevention Program asthma guidelines have proven effective,¹ a considerable number of children experience poor asthma

Abbreviations used

<i>AX</i> -Reactance area
<i>GINA</i> -Global Initiative for Asthma
<i>IOS</i> -Impulse oscillometry
<i>OR</i> -Odds ratio
<i>ROC</i> -Receiver-operator characteristic
<i>R_{rs}</i> -Resistance
<i>R5</i> -Resistance at 5 Hz
<i>R5-R20</i> -Resistance at 5 Hz, minus resistance at 20 Hz
<i>X5</i> -Reactance at 5 Hz
<i>X_{rs}</i> -Reactance

control,² which is associated with increased risk of exacerbations, pulmonary function loss, and increased health care utilization resulting in significant direct and indirect costs.³ One possibility for this observation is the failure to recognize that the peripheral airways are the major sites of airway obstruction⁴ and inflammation,⁵ with overall estimates suggesting that peripheral airway impairment (PAI) affects 50% of adults⁶ and children⁷ with persistent asthma. PAI is clinically important because it has been associated with airway hyperreactivity, nocturnal asthma, exacerbations, steroid-resistant asthma, and fatal asthma.⁸ Impulse oscillometry (IOS), as a tool to assess PAI, has been demonstrated to be a practical in-office procedure that has been validated by several established measures of peripheral airway function.⁹⁻¹¹ This lung function test, which measures impedance, including resistance (R_{rs}) and reactance (X_{rs}), has been shown to be effective in identifying asthma in young children,¹²⁻¹⁴ uncontrolled asthma,¹⁵ as well as a predictor of loss of asthma control,¹⁶ exacerbations,¹⁷ and loss of lung function in adolescence.¹⁸ IOS is effort independent so it can be used in young children and can evaluate both central and peripheral airway function.¹⁹ We have recently shown that PAI is present not only in uncontrolled asthma but also in up to 40% of those considered well controlled by National Institutes of Health guidelines.²⁰ IOS proved to be more sensitive in identifying PAI than the spirometric measure thought to reflect peripheral airways, forced expiratory flow at 25% to 75% of forced vital capacity, in children younger than 18 years.

Although previous studies suggest the clinical usefulness of IOS, the main challenge to universal acceptance of IOS as a standard test for assessing lung function in patients with asthma is the perception of a lack of readily available, standardized cutoff point values that are clinically relevant in different populations.⁸ Our initial studies determined the value of IOS in identifying uncontrolled asthma,¹⁵ and subsequently predicting the loss of control in children with asthma aged 6 to 17 years.¹⁶ Receiver-operator characteristic (ROC) determined optimal cutoff points for our entire cohort of children, not age-specific. However, a similarly designed study in Turkish children reported significantly higher optimal ROC-based cutoff points.²¹ In contrast to these earlier studies that established cutoff points for the entire population of children 6 to 17 years, our recent study established cutoff points by ROC analysis for age-specific cohorts of 4 to 7 years, 8 to 11 years, and 12 years and above.²⁰ We found striking differences in cutoff points by age, particularly in those 12 years and older, which were a much better fit in identifying uncontrolled asthma than values established for the entire cohort aged 6 to 17 years. This makes sense because IOS values as well as spirometry are highly dependent on both age and height.

IOS-based studies have established different cutoff points depending on the type of end point including asthma diagnosis,¹²⁻¹⁴ identification of uncontrolled asthma,^{15,18} prediction of loss of control,¹⁶ and exacerbations,¹⁷ as well as the statistical approach (comparison of mean $\pm$ SD,^{13,14,18} validity measures by ROC analysis,^{15-17,20,21} and population characteristics).^{15,21} Generally, PAI has been determined by ROC analysis for each study by identification of an optimal IOS cutoff point that best correlates with a specific clinical outcome. That makes generalizability of an ROC-defined cutoff point for a specific patient difficult. Although recent American Thoracic Society guidelines for spirometry have defined airway obstruction as values below the lower limits of normal defined by 1.645 SD below the mean,²² there have been few studies that have used normative reference values to identify PAI, defined as exceeding these 1.645 SD criteria, and its clinical relevance.²³⁻²⁵ The reasons might include the perception that there is a lack of ethnic-specific IOS reference values available, as well as the assumption that, despite some evidence to the contrary,⁸ current available commercial values, determined primarily in white children and adults, do not reflect their specific ethnicity.²¹ This suggested to us that a more standardized approach to utilization of clinically relevant IOS cutoff points with normative reference values in children, which would be more accessible to the clinician, was needed.

The primary goals of our study were to establish the relationship between PAI defined by standardized IOS reference values and uncontrolled asthma, and whether normative reference values based on algorithms developed in Hispanic compared with white children produce similar predicted values as measured by intraclass correlation. The secondary goal was to determine whether algorithm-based PAI thresholds are a reliable indicator of ROC PAI thresholds.

METHODS

This retrospective study evaluated 227 children, ages 4 to 18 years, with moderate to severe asthma treated at the Pulmonary Clinic and seen in the Breathmobile Program²⁶ from March 2016 to March 2018. The study was approved by Children's Hospital of Orange County Institutional Review Board. IOS measurements preceded lung function assessment by spirometry. We used the Vmax Encore 20c, which is fully integrated with the IOS system. The IOS requires the subject to breathe normally (tidal breathing) into a mouthpiece, while a loudspeaker generates an impulse-shaped pressure signal into the respiratory system.²⁷ The IOS system was calibrated each day before the measurements, using a 3-L syringe. The IOS measurements were performed in the sitting position, with participants wearing nose clips. Participants tidally breathed into the IOS mouthpiece for 30 seconds, with cheeks supported by the hands of trained technicians. The technicians evaluated the efforts and made sure each observation consisted of at least 3 reproducible maneuvers that did not have artifacts caused by coughing, swallowing, vocalization, or breath holding.²⁷ LabManager Version 4.67.0.1 (CareFusion Germany GmbH, Hoechst, Germany) was used to calculate the pressure-flow relationship and calculate R_{rs} and X_{rs} as a function of oscillation frequency.²⁷ The representative tracing and definitions of the IOS indices, including resistance at 5 Hz ($R5$), resistance at 20 Hz ($R20$), reactance at 5 Hz ($X5$), and reactance area (AX), are reported. Results were acceptable if the coefficient of variation of at least 2 sets of data was less than 10%. Mean values of $R5$, $R20$, $X5$, and AX calculated from the

TABLE I. Description of study population at baseline

Characteristic	Our study (N = 227)
Age (y), mean $\pm$ SD	10.0 $\pm$ 3.2
4-7	22.0%
8-11	53.7%
12-18	24.2%
Sex: female, %	37.9%
Hispanic, %	~67.0%
BMI percentile	
Normal (<85 percentile)	42.3%
Overweight (85%-94%)	21.6%
Obese ($\geq$ 95%)	36.1%
Height (cm), mean $\pm$ SD	141.1 $\pm$ 17.1
Step 3 or higher therapy, %	83.3%
Uncontrolled (NHLBI guidelines), %	30.4%
Spirometry, mean $\pm$ SD	
FEV ₁ % predicted	100.7 $\pm$ 16.9
FVC% predicted	105.4 $\pm$ 16.1
FEV ₁ /FVC%	83.8 $\pm$ 8.6
FEF ₂₅₋₇₅ predicted	92.3 $\pm$ 28.5
IOS metrics, mean $\pm$ SD	
R5 (cmH ₂ O/L/s)	6.5 $\pm$ 2.6
R5-R20 (cmH ₂ O/L/s)	2.6 $\pm$ 1.9
AX (cmH ₂ O/L)	20.3 $\pm$ 14.7
X5 (cmH ₂ O/L/s)	-2.4 $\pm$ 1.2

BMI, Body mass index; FEF₂₅₋₅₀, forced expiratory flow at 25% to 75% of forced vital capacity; FVC, forced vital capacity; NHLBI, National Heart, Lung, and Blood Institute.

R5-R20 restricted to <25 (removed 5 outliers) to assess means.

measurements were used for further analysis. In our initial cohort we did not assess X5 because our previous study showed that resistance at 5 Hz minus resistance at 20 Hz (R5-R20) and AX were superior to X5 in identifying uncontrolled asthma.¹⁵ This was not found in the second cohort.²⁰ Uncontrolled asthma was classified in accordance with 2007 National Asthma Education and Prevention Program guideline criteria¹: day symptoms and short-acting β_2 -agonist use for symptom control more than 2 d/wk, nighttime awakenings more than 1/mo (>2 /mo in adolescents), interference with normal activities, FEV₁ % predicted and FEV₁/forced vital capacity less than 80% (the latter lung function criteria specific to patients younger than 12 years), and 2 or more exacerbations per year requiring oral systemic corticosteroids. All lung function measures were pre-bronchodilator, because our previous study indicated better IOS identification of asthma that was not well controlled than post-bronchodilator values.¹⁵ Short-acting β -agonists were withheld at least 4 hours before the lung function test.

Statistical analysis

Demographic and lung function distributions were described by mean (SD) and percentage with defined trait. Normal random values were generated and plotted by input of mean (SD) of distributions for reference equations and observed values using Vertex42.com simulation "Graphing a Normal Distribution Curve in Excel" by Wittwer.²⁸ Generalized estimating equation repeated-measures analyses determined the significance of difference in IOS distributions and PAI defined by exceedance of the normal reference curve 1.645 SD threshold (IOS abnormal) per normal expectations compared

with our children with well-controlled and uncontrolled asthma. The reference equation value for each patient with asthma served as their within (normal) comparator in the repeated-measures analyses. IOS reference values were calculated and described by upper limits of normal, 95th percentile for each IOS metric (lower limits of normal, 5th percentile for X5) (mean $\pm$ 1.645 SD) using standardized published algorithms in Hispanic²⁹ and white children.^{30,31} SD in calculation was determined for each age group (4-7, 8-11, and $\geq$ 12 years). Clinical relevance of IOS considered probability and odds of uncontrolled asthma when IOS abnormal (high [>99.7 th percentile, mean + 3 SD] and low [>95 th- $\leq$ 99.7th percentile]) versus normal, which were estimated from generalized estimating equation analyses that adjusted for repeat measures across visits, age group, sex, obesity, and National Heart, Lung, and Blood Institute guideline step 3 or higher therapy. X5 value was defined as abnormal high when less than 0.3rd percentile (mean - 3 SD) and abnormal low when greater than or equal to 0.3rd to less than 5th percentile. Age-specific thresholds for each IOS measure (R5, R5-R20, X5, and AX) were then determined from ROC curves using standard criteria (thresholds that maximized the sum of sensitivity and specificity). Reliability of normal reference compared with study-specific ROC thresholds was evaluated by percent agreement and the Kappa statistic. Intraclass correlation coefficients assessed agreement of IOS-predicted values based on reference algorithms developed in Hispanic compared with white children and used a 2-way mixed model procedure that produced similar estimates to Cronbach alpha. Analyses were performed using SPSS v18.0 (SPSS Inc, Chicago, Ill).

RESULTS

In [Table I](#) is the description of the study population at baseline. The average age of patients was 10.0 $\pm$ 3.2 years, and most were male (62.1%), Hispanic (~67.0%), overweight or obese (57.7%), and on step 3 or higher therapy (83.3%). Uncontrolled asthma by National Heart, Lung, and Blood Institute guidelines was indicated in nearly a third of patients (30.4%). For spirometry, average values were all greater than the lower limits of normal. In terms of IOS metrics, greater dispersion around the mean was seen for R5-R20 and AX where the coefficient of variation was approximately 73% compared with 50% for X5 and 40% for R5.

In [Figure 1](#), *A* and *B*, are shown the normal distribution curves for each IOS measure, with marker for upper limits of normal (lower limits of normal for X5) for well-controlled asthma and uncontrolled asthma in the overall population compared with their normal predicted value (expectation in children without asthma). Those with uncontrolled asthma had significantly greater resistance (R5, R5-R20) and reactance (AX, X5) compared with children with well-controlled asthma and expectations in those without asthma ($P < .05$). PAI defined by exceeding normal value expectations of approximately 5% by the 1.645 SD threshold was considerably higher in well-controlled and even higher in uncontrolled patients at baseline, with differentiation more pronounced for reactance measures: (% PAI well controlled, uncontrolled) for R5 (35.4%, 68.1%), R5-R20 (45.6%, 66.7%), AX (38.0%, 73.9%), and X5 (25.7%, 63.8%) ($P < .05$; [Table II](#)).

In [Figure 2](#), *A* and *B*, are the probability and odds ratio (OR) of identifying uncontrolled asthma at the visit level ($n = 508$) (95% CI) related to PAI, defined by abnormal compared with

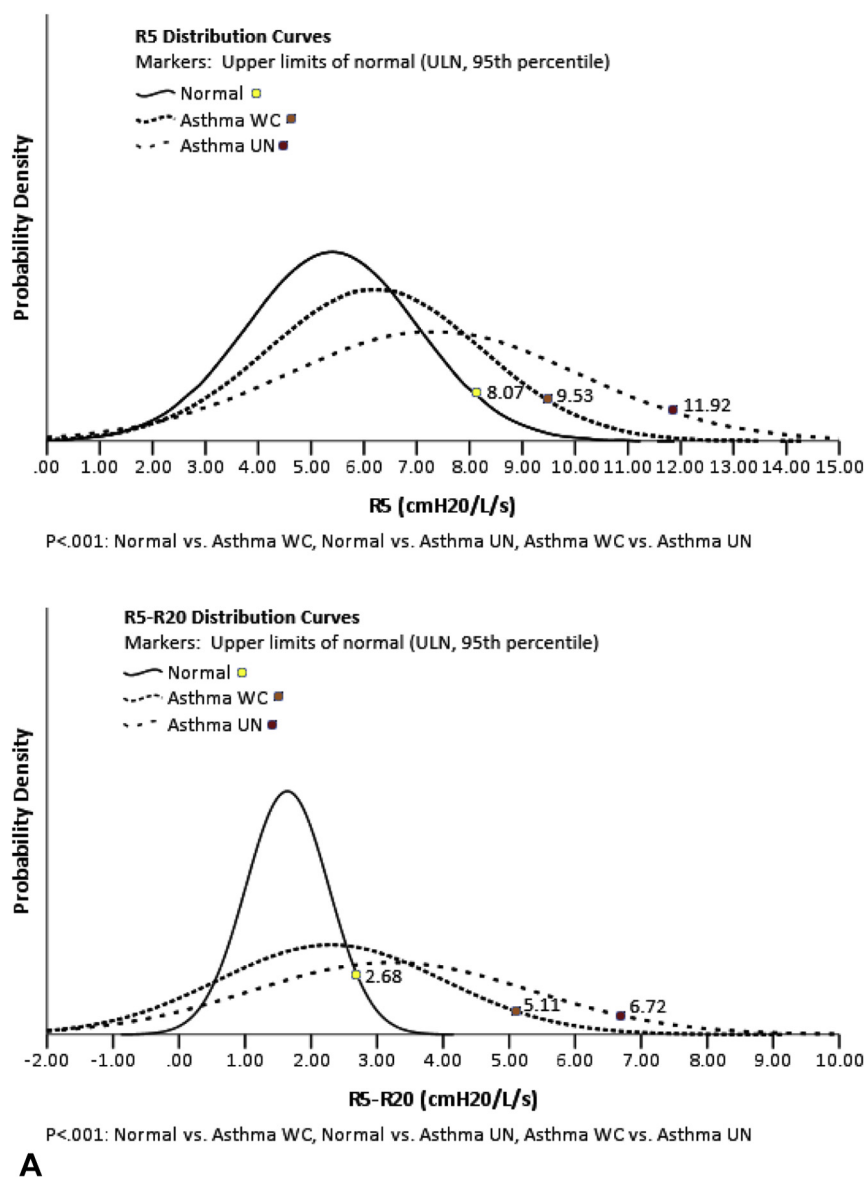
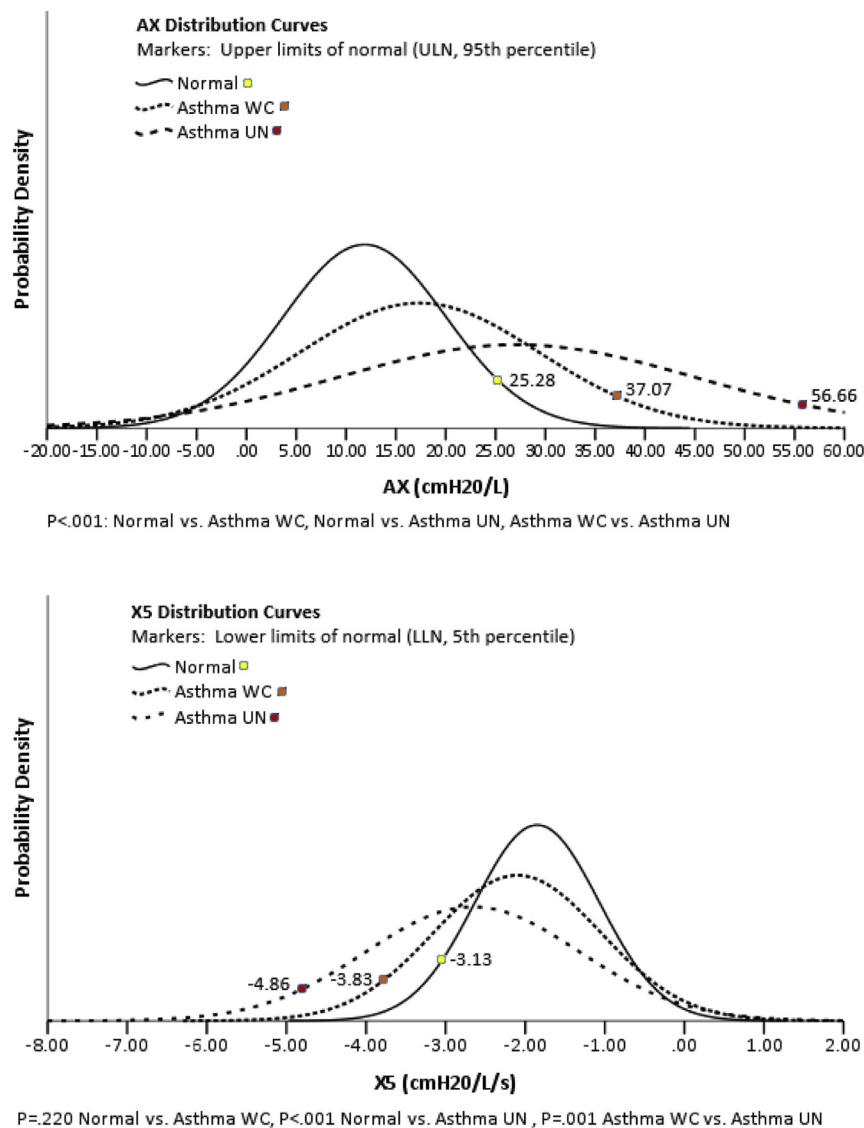


FIGURE 1. (A) Normal distribution simulation plots based on input of mean (SD) for R5 and R5-R20 distributions for actual values in uncontrolled and well-controlled patients with asthma and normal predicted values based on reference algorithms at baseline (Gonchicora-Rangel for R5 and Nowojewska R5-R20). **(B)** Normal distribution simulation plots based on input of mean (SD) for AX and X5 distributions for actual values in uncontrolled and well-controlled patients with asthma and normal predicted values based on reference algorithms at baseline (Gonchicora-Rangel). *GEE*, Generalized estimating equation; *UN*, uncontrolled; *WC*, well controlled. *P* value based on GEE analyses with repeat measures within subject comparing patient's actual value to expectations using normal algorithm reference and then between groups (WC vs UN).

normal reference value range per less than or equal to 95th percentile (≥ 5 th percentile for X5) criteria. The reference categories defining PAI were less than or equal to 95th percentile (normal), greater than 95th to less than or equal to 99.7th percentile (abnormal, lower threshold), and greater than 99.7th percentile (abnormal, higher threshold). The inverse was applicable for X5 because lower values signify more PAI. The pattern shown for IOS metrics R5, R5-R20, AX, and X5 is an increased probability and OR of uncontrolled asthma with increasing PAI compared with normal, adjusted for potential confounding factors. This is best demonstrated by X5 where the probability of

uncontrolled asthma increases from 0.30 in those with normal values to 0.54 with an OR of 2.70 for those with abnormal values, lower threshold ($P = .019$), to a probability of 0.83 and an OR of 11.01 for those with abnormal values, higher threshold ($P < .001$). As expected, the strong relationship between PAI and asthma control was not observed for central airways marker (R20); only in 7 of 519 visits measured (1.3%) did the patient exceed the 95th percentile threshold for R20 (data not shown).

In Table III are reliability estimates of upper limits of normal (95th percentile) for R5, R5-R20, and AX or lower limits of normal (5th percentile) for the X5 threshold



B

FIGURE 1. (CONTINUED).

TABLE II. Abnormal PAI defined by R5*, R5-R20, or AX values >95th percentile or X5 value <5th percentile in well-controlled and uncontrolled asthma ($P < .05$)

IOS Measures	Well controlled (%)	Uncontrolled (%)
R5 (cmH2O/L/s)	35.4	68.1
R5-R20 (cmH2O/L/s)	45.6	66.7
AX (cm H2O/L)	38.0	73.9
X5 (cmH2O/L/s)	25.7	63.8

*R5 reflects total airway resistance.

compared with the optimal IOS thresholds for each age cohort, based on the best sum of sensitivity and specificity determined by ROC analysis. Overall agreement between threshold measures was high across IOS metrics, ranging from 73.7% for R5-R20 to 93.1% for X5. The kappa statistic indicated almost

perfect agreement for X5 (0.86), with substantial agreement for AX (0.74) and R5 (0.66), and moderate agreement for R5-R20 (0.47). The slight differences in agreement statistic across age groups was nonsignificant as indicated by overlap of 95% CI ($P > .05$), with exception of AX where lower agreement was observed for those aged 12 to 18 years compared with those aged 8 to 11 years ($\kappa = 0.58$ vs 0.81, respectively). In summary, clinical relevance and reliability was highest for reactance measure X5.

In Table IV we show the agreement in IOS reference value algorithms established between Hispanic (Gonchicoa-Rangel) and white (Nowowiejska) children. In general, the agreement was excellent (>0.80), except for R5-R20 where the agreement was less than .70. The Nowowiejska algorithm did not provide values in whites for AX, whereas the Frei algorithm allowed AX comparison in those aged 4 to 7 years and 8 to 11 years but did not provide values for those aged 12 to 18 years.

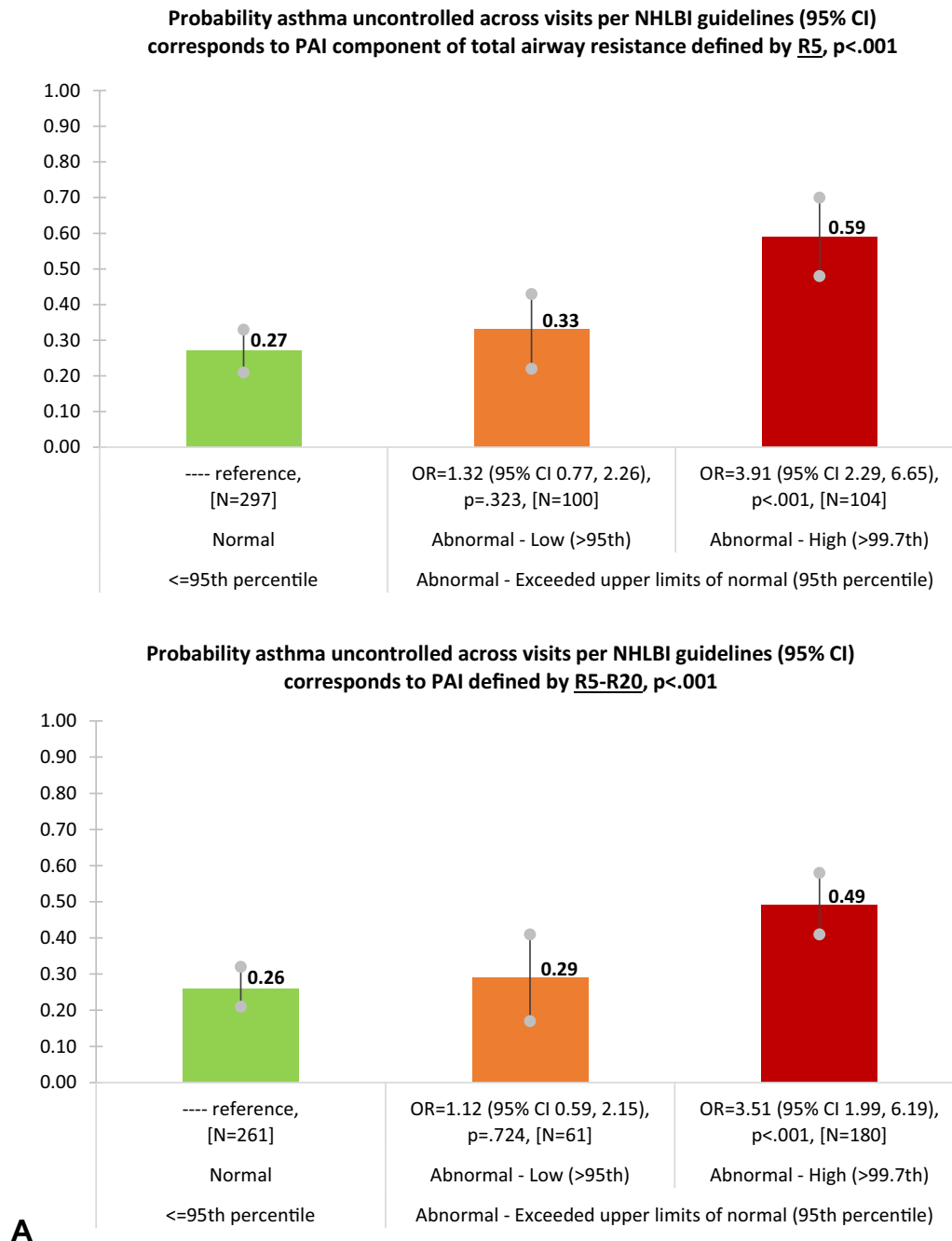


FIGURE 2. Correspondence of PAI for (A) R5* and R5-R20 and (B) AX and X5 to uncontrolled asthma by NHLBI guidelines. GEE analyses with binomial outcome and probabilities calculated at covariate values representative of distributions for adjustment factors: age (4-7, 8-11, 12-18 years), sex (M/F), obesity (nonobese, obese), step 3 or higher therapy (Y/N). F, Female; GEE, generalized estimating equation; M, male; NHLBI, National Heart, Lung, and Blood Institute. *R5 reflects total airway resistance.

DISCUSSION

We have shown by IOS that PAI, defined by resistance and reactance levels that exceed normal reference values (mean $\pm$ 1.645 SD, >95th percentile [$\leq$ 5th percentile for X5]), is associated with the increased risk of uncontrolled asthma. This was shown by our observation that resistance (R5, R5-R20) and reactance (AX, X5) distributions were significantly shifted toward higher values (lower for X5) in well-controlled and even more so in uncontrolled

patients, as well as the greater percentage of PAI in the uncontrolled compared with normal expectations. This was further suggested by showing the increased probability/risk of uncontrolled asthma with increasing PAI thresholds for all IOS measures, particularly for X5 where the ORs ranged from 2.70 to 11.01 for low abnormal to high abnormal PAI thresholds compared with normal. We next looked into the relationship of reference values—defined cutoff points to identify uncontrolled asthma with those established by ROC

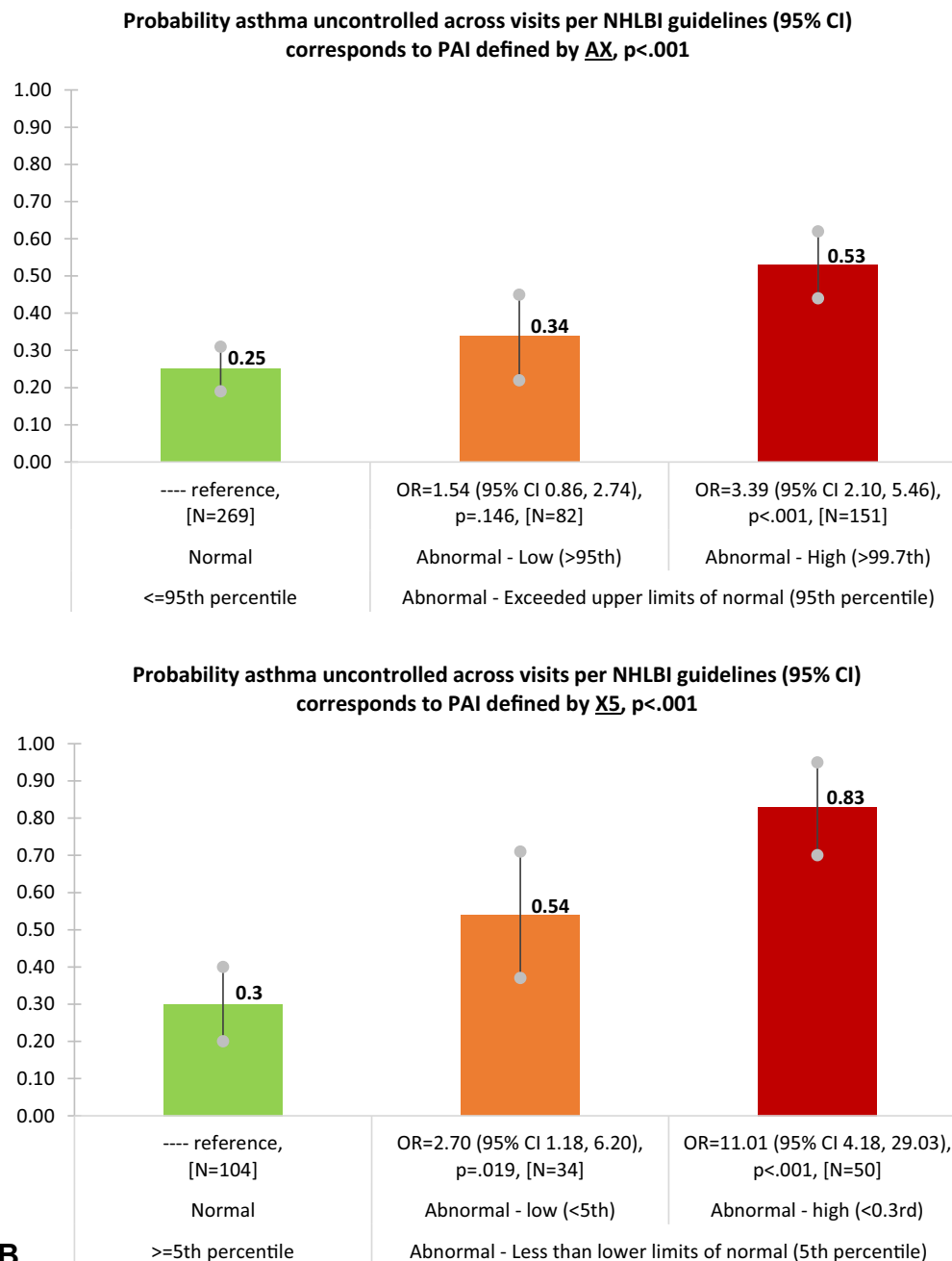


FIGURE 2. (CONTINUED).

analysis, which we and others had used in earlier studies.^{15,16,20} Unlike reference values, which define PAI as IOS values that fall outside the normal range, ROC defines PAI on the basis of best balance between sensitivity and specificity to identify a specific outcome. In general, there was good agreement between the 2 approaches in classification based on defined threshold to identify uncontrolled asthma. We felt this comparison was necessary, because ROC has been shown to be useful in validating the relationship between IOS values and clinical outcomes such as asthma control,¹⁵ loss of control,¹⁶ and exacerbations.¹⁷ However, because studies that use ROC usually evaluate an entire age cohort, and

depend on a specific clinical outcome, IOS cutoff points will vary, limiting its application in the clinical setting. In contrast, the upper and lower limits of normal reference values are available to the clinician assessing the lung function of their patient, similar to spirometry. Finally, there was excellent agreement between the Hispanic and white reference algorithms, except for R5-R20, which may have been due to differences in equations for this metric where the Nowowiecka algorithm³⁰ considered sex and height in the equation compared with sex and age in the Gonchicoa-Rangel algorithm.²⁹ Height recorded in centimeter has more possible values than age in years within our pediatric cohort. The high correlation

TABLE III. Reliability (intrater agreement) of ROC vs algorithm threshold (upper or lower limits of normal based on 1.645 SD for specific age group above/below normal predicted value, 95th or 5th percentile, respectively) in classifying uncontrolled asthma across visits*

ROC vs normal predicted $\pm$ 1.645 SD	R5 (cmH ₂ O/L/s)	R5-R20 (cmH ₂ O/L/s)	AX (cm H ₂ O/L)*	X5 (cmH ₂ O/L/s)
Overall	84.9%, 0.66 (0.59-0.73)	73.7%, 0.47 (0.39-0.54)	87.3%, 0.74 (0.68-0.80)	93.1%, 0.86 (0.79-0.93)
Age group (y)				
4-7	75.6%, 0.48 (0.31-0.65)	73.2%, 0.50 (0.34-0.65)	87.8%, 0.76 (0.62-0.89)	100%, 1.00 (—)
8-11	85.4%, 0.66 (0.56-0.74)	73.2%, 0.46 (0.38-0.54)	90.6%, 0.81 (0.74-0.87)	92.2%, 0.84 (0.73-0.95)
12-18	86.8%, 0.73 (0.62-0.85)	75.2%, 0.53 (0.41-0.66)	79.1%, 0.58 (0.44-0.72)	88.1%, 0.73 (0.52-0.94)

Values are % agree, *k* (95% CI).

*Gochicoa-Rangel (GR) algorithm used to predict values for R5, AX, and X5; Nowowiejska algorithm used to predict R5-R20 due to lack of variation in this parameter with the GR algorithm.

TABLE IV. Reliability (intrater agreement) of algorithm developed in Hispanic compared with white children

Correlation* (95% CI)	R5 (cmH ₂ O/L/s)	R5-R20 (cmH ₂ O/L/s)	AX (cmH ₂ O/L)†	X5 (cmH ₂ O/L/s)
4-7 y	0.90 (0.81-0.94)‡	0.49 (0.10-0.71)‡	0.88 (0.80- 0.93)‡	0.91 (0.81- 0.95)‡
8-11 y	0.93 (0.90- 0.95)‡	0.66 (0.51-0.76)‡	0.83 (0.75- 0.88)‡	0.96 (0.94-0.98)‡
12-18 y	0.93 (0.88- 0.96)‡	0.68 (0.44-0.81)‡	—	0.93 (0.87-0.96)‡

Correlation (ICC*) between Gochicoa-Rangel and Nowowiejska algorithms, respectively, at initial visit, with exception of AX.†

*ICC, Intraclass correlation coefficient (ICC 2-way mixed model producing similar estimate to Cronbach α).

†Frei algorithm compared against Gochicoa-Rangel algorithm (Nowowiejska did not provide algorithm for AX).

‡*P* < .05, *F* test with true value of 0 correlation.

for X5, R5, and AX suggests either algorithm would have given similar results for these metrics. An important observation in our current study was the presence of considerable PAI in those patients considered well controlled by guidelines. The percent PAI value found by reference values for X5 was of similar magnitude to those we previously reported by ROC²⁰ (25.7% vs 26.0%-27.1%, respectively), again supporting the notion that reference values have similar clinical relevance as those derived by ROC. We have also previously reported that those patients considered well controlled who had PAI were at a high risk for loss of control at the 8- to 12-week follow-up visit.¹⁶ This is consistent with the observation that PAI, which reflects ventilation heterogeneity, is associated with the risk of poor asthma control, quality of life, and exacerbations.³² It would therefore be of clinical importance to determine by randomized clinical trials whether this outcome could be prevented in this population by therapeutic intervention, such as the use of extrafine inhaled corticosteroids, which have been shown to reduce exacerbations and improve asthma control.³³

There has been a paucity of studies determining the value of reference thresholds in relationship to clinical outcomes.^{12,23-25} However, recently in a multisite, cross-sectional analysis in adults, the Assessment of Small Airway Involvement in Asthma study, Postma et al²³ reported that PAI, detected by IOS reference values, which exceeded the normal range assessed by reference values, showed the highest correlation with asthma control, severity by Global Initiative for Asthma (GINA) guidelines, quality of life, and exacerbations.²³ For example, the percentage of patients with PAI was approximately 31% for GINA class 1 (mild asthma) compared with 71% for GINA class 5 (severe asthma). This is similar to our current findings in our youngest cohort where X5 was abnormal in 25.7% of those well controlled, 63.8% in those uncontrolled, with a similar pattern across IOS metrics. Spirometric measures indicative of PAI, forced expiratory flow at 25% to 75% of forced vital capacity, forced expiratory flow at 50% of forced vital capacity, and low

forced vital capacity, also showed a significant relationship to these outcomes. The authors concluded that PAI can be present across all GINA severity stages, but the presence of PAI is consistently highest in asthma of the greatest severity.

Foy et al²⁴ evaluated by computational analysis in adults the integration effect of simulated airway narrowing on R5-R20 to confirm its role as marker of peripheral airway function, and its relationship to clinical outcomes. They found that a 40% simulated narrowing of the peripheral, more than central, airways corresponded to an increase in R5-R20 in conjunction with decreased asthma control and poorer quality of life. Furthermore, R5-R20 values above the normal 95th percentile was also related to poorer clinical outcomes including increased exacerbations, even in those with normal spirometry. The fact that clinical outcomes such as asthma control were more related to PAI than central airway obstruction might explain a recent article showing poor correlation between spirometry and validated asthma control metrics.³⁴ This is also similar to our previous findings,^{15,20} and the current study findings, showing a strong relationship between PAI and asthma control, but not central airways marker (R20), possibly on the basis that peripheral airway obstruction is an earlier marker of lung abnormality than central obstruction, which can have clinical consequences. A major concern regarding the use of reference values is the perception that they may be ethnic-specific. However, we have recently reported minimal variation in IOS cutoff point values for R5 and X5 by ethnicity in Asian, European, and North and South American children and adults.⁸ Furthermore, values were comparable to commercially available regression equation-based reference values in primarily white children and adults, suggesting potential application across populations. This is supported by our data finding no significant differences in reference values between white and Hispanic reference algorithms. However, as noted by our comments on Turkish²¹ compared with Hispanic children,¹⁵

more studies are needed to determine whether commercially available reference values are applicable across other ethnicities.

Study limitations

This study is retrospective and observational, which could introduce bias in data selection, although expected to have minimal impact on observed association between PAI and uncontrolled asthma because IOS reference values were determined using standardized algorithms. Because the simulated normal algorithm was used in our population with asthma, anthropomorphic characteristics that could impact the observed relationship between PAI and asthma control were addressed by adjustment for age, sex, obesity, and step 3 or higher step inhaled corticosteroid in our analyses. The population had moderate to severe asthma, predominately on step 3 or higher therapy, and was primarily Hispanic. Although the Hispanic algorithm did not differ significantly from the white algorithm (Table IV), these characteristics could limit generalizability and should be investigated in other populations and settings.

CONCLUSION

PAI, defined by IOS reference values, not central airway markers (R20), is consistently associated with the risk of uncontrolled asthma, even in patients on step 3 or higher inhaled corticosteroid therapy. This is true whether using Hispanic or white reference algorithms. Thus, standardized reference values in children offer the clinician readily available IOS cutoff points that are clinically relevant across the ethnicities we evaluated. Early recognition and treatment of PAI with extrafine inhaled corticosteroids has the potential to reduce the number of children with uncontrolled asthma and frequently associated exacerbations.

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