Discriminative Properties of Two Predictive Indices for Asthma Diagnosis in a Sample of Preschoolers With Recurrent Wheezing

Carlos E. Rodriguez-Martinez, MD, MSc,[1]* Monica P. Sossa-Briceño, MD, MSc,[2] Jose A. Castro-Rodriguez, MD, PhD[3]

Summary. Introduction: It is important to predict if preschool children with recurrent wheezing will suffer from asthma in future years. To aid in this early identification, a number of asthma predictive scores have been reported, such as the asthma predictive index (API) and the PIAMA risk score. However, to the best of our knowledge, their predictive properties have not been evaluated in any lower- to middle-income country. Materials and Methods: A prospective cohort study was carried out including preschoolers aged 1–3 years with recurrent wheezing who came to our Pediatric Pulmonary Unit in Bogota, Colombia. We collected the information required to complete the API index and the PIAMA risk score. At 5–6 years of age, the patients were contacted in order to determine if they were suffering from active asthma. We calculated the sensitivity, specificity, predictive values, and likelihood ratios (LR) of the API and PIAMA risk scores for the presence of active asthma at 5–6 years old. Results: The mean age at recruitment of the 130 included patients was 27.2 $\pm$ 5.9 months. The loose API yielded a sensitivity of 71.4% (95% CI: 50.0–86.2), specificity of 33.3% (95% CI 23.5–44.8), and positive predictive value of 23.8% (95% CI: 15.0–35.6). The stringent API yielded a sensitivity of 42.9% (95% CI: 24.5–63.5), specificity of 79.2% (95% CI 68.4–86.9), positive predictive value of 37.5% (95% CI: 21.2–57.3), and positive LR of 2.06. The PIAMA risk score yielded a sensitivity of 54.5% (95% CI: 42.6–66.0), specificity of 78.9 (95% CI: 66.7–87.5), positive predictive value of 75.0 (95% CI: 61.2–85.1), and positive LR of 2.59. Conclusions: Our results suggest that both indices can be used to predict asthma in preschoolers with recurrent wheezing in the context of a referral hospital. **Pediatr Pulmonol.** © 2011 Wiley-Liss, Inc.

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INTRODUCTION

Childhood asthma is the most common chronic disease among children and a major public health problem in the United States as well as in many other countries, such as Colombia.[1,2] However, it is difficult to determine if preschool children with recurrent wheezing are suffering from asthma or will suffer from asthma in the future. This is because recurrent wheezing is frequently observed in preschool children, many times related to upper respiratory tract infections,[3] and at present it is very difficult to distinguish between the different phenotypes that underlie a similar clinical presentation.[4] Furthermore, neither airflow limitation nor airway inflammation, the main pathologic hallmarks of asthma, can be routinely assessed in this age group.

Identification of symptomatic infants and young children with recurrent wheezing who will go on to develop asthma allows for better targeting of secondary preventive actions and therapeutic strategies for those who are most likely to benefit. Furthermore, it permits doctors

[1]Department of Pediatrics, School of Medicine, Universidad Nacional de Colombia; Department of Pediatric Pulmonology and Pediatric Critical Care Medicine, School of Medicine, Universidad El Bosque, Bogota, Colombia.

[2]Department of Internal Medicine, Clínica Reina Sofía, Bogota, Colombia.

[3]Departments of Pediatrics and Family Medicine, School of Medicine, Pontificia Universidad Catolica de Chile, Santiago, Chile.

*Correspondence to: Carlos E. Rodriguez-Martinez, MD, MSc, Avenida Calle 127 No. 20-78. Bogota, Colombia. E-mail: carlos2671@gmail.com

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to be more cautious when prescribing treatment to those children who probably have transient conditions other than asthma.[5] To aid in the early identification of preschoolers who wheeze and are at high risk of developing persistent asthma symptoms, a number of asthma predictive scores have been reported. One is the ''asthma predictive index'' (API), developed by Castro-Rodriguez et al.,[6] which combines simple and easily measurable clinical and laboratory parameters that can be obtained in any clinical setting. Upon applying this algorithm to a birth cohort (the Tucson Respiratory Study), children with a positive API were 2.6–13 times more likely to have active asthma between ages 6 and 13 than children with a negative API.[6] More recently, Caudri et al., using eight easily obtainable clinical parameters, generated an apparently more accurate although somewhat laborious predictive score called the PIAMA risk score. Upon applying this predictive score to a birth cohort, children scoring 30 or higher had a risk of >40% of having asthma at the age of 7–8 years.[5]

However, there are many reasons for emphasizing the need to test the predictive scoring systems in different populations in order to give clinicians the confidence that these predictive systems are applicable to other populations.[7] First, the predictive ability of the scores (positive and negative predictive values) is dependent on the prevalence of the disease in the population; second, a specific predictive score might miss a factor that is an important predictor in other populations; and lastly there might be important differences in patient characteristics between populations (e.g., ratio of atopic/non-atopic asthma, incomes, settings, etc.).[8] Furthermore, to the best of our knowledge, the discriminative properties of the API and/or PIAMA risk score have not been evaluated in any low- to middle-income country.

Therefore, the aim of the present study was to evaluate the discriminative properties of the API and PIAMA risk scores in a population of preschoolers with recurrent wheezing living in urban Bogota, Colombia.

MATERIAL AND METHODS

Study Population

This prospective cohort study was conducted at Clinica Infantil Colsubsidio, a third-level, multidisciplinary teaching hospital located in Bogota, Colombia.

A screening question that was asked of parents of all children between 1 and 3 years old with recurrent wheezing who attended our outpatient Pediatric Pulmonary Unit between October 2006 and August 2007 was used to select the eligible population.

Patients were included in the study if their parents responded positively to the following question: ''Has your child ever experienced wheezing or whistling in the chest at any time in the past?''; agreed to participate in the study; and signed the informed-consent statement. At the time of enrollment, the parents of participating children completed a questionnaire regarding demographics, frequency of wheezing (scale: 1–5, from ''very rarely'' to ''on most days''), presence of wheezing apart from colds, parental (either father's or mother's) history of a physician's diagnosis of asthma, a physician's diagnosis of eczema and rhinitis, and based on the validated Spanish version of core questionnaires of the International Study of Asthma and Allergies in Childhood (ISAAC), questions regarding clinical signs, symptoms, and previous diagnoses of allergic rhinitis and eczema.

To determine the presence of active asthma, patients were contacted by telephone when they completed 5–6 years of age by an investigator (CR) who was unaware of the child's health status before 3 years of age, and who was blinded to the API classification. During this second assessment, parents provided the following information related to the previous 12 months: presence and number of wheezing episodes, doctor's diagnosis of asthma, and prescription of inhaled steroids by a medical doctor. Likewise, during this second contact, investigators gathered additional information intended to complete the PIAMA risk score (because the study that reports this score was published at a date later than the recruitment of the patients, so not all information required to complete the score was collected at entry), such as antecedents of post-term delivery, medium/low education level by at least one parent, inhalation of medication by at least one parent, and number of serious infections in the 12 months before enrollment (respiratory, throat, nose, and/or ear infections, such as flu, infection of the throat, infection of the middle ear, sinusitis, bronchitis, or pneumonia). The number of serious infections in the 12 months before enrollment was determined through a retrospective review of electronic medical records of all included patients.

In relation to the API, we considered a child as an ''early wheezer'' if his or her chest had ever sounded wheezy; an ''early frequent wheezer'' if the parents reported a value $\geq$3 in the scale for the question regarding frequency of wheezing episodes (scale: 1–5, from ''very rarely'' to ''on most days''); as having ''wheezing apart from colds'' if this symptom was reported in the survey; as having ''MD allergic rhinitis'' if either a physician had diagnosed this condition during the previous year as reported in the survey, or there was a positive response to the following question: ''In the past 12 months, has your child had a problem with sneezing, or a runny or blocked nose when he/she DID NOT have a cold or the flu?''; and as having ''MD

eczema'' if either a physician had diagnosed this condition during the previous year as reported in the survey, or there was a positive response to the following question: ''In the past 12 months, has your child had an itchy rash which has been coming and going for at least 6 months?''. Likewise, we considered the parents as having ''parental MD asthma'' if either the father or the mother had history of a physician's diagnosis of asthma, and the child as having ''eosinophilia'' if circulating eosinophils were $\geq$4% of the total white blood cells. We calculated the proportion of patients with a positive stringent or loose index for the prediction of asthma based on the frequency of wheezing episodes before age 3 and fulfillment of major and minor criteria[6] (Table 1).

In relation to the PIAMA risk score, we considered that at least one of the parents had ''medium/low education'' if either the mother or the father reported primary school or secondary school to the following question ''What was the highest level of education attained by the mother/father? (options: primary school; secondary school; college; university or other form of tertiary education)''; a ''post-term delivery'' when delivery occurred after 42 weeks of gestation; ''inhalation of medication by at least one parent'' if either the mother or the father reported its use in the survey; ''frequent wheezing'' if the parents reported a value $\geq$3 in the scale for the question regarding frequency of wheezing episodes (scale: 1–5, from ''very rarely'' to ''on most days''); ''infrequent wheezing'' if the parents reported a value $<$3 in the scale for the question regarding frequency of wheezing episodes (scale: 1–5, from ''very rarely'' to ''on most days''); ''wheezing/dyspnea apart from colds'' if this symptom was reported in the survey; ''infrequent serious infections'' if the frequency of serious respiratory infections (as previously defined) was 1–2 infections per year; ''frequent serious infections'' if the frequency of serious respiratory infections (as previously defined) was $\geq$3 infections per year; and ''diagnosis eczema and rash present'' if either a physician had diagnosed this condition during the previous year as reported in the survey, or a there was a positive response to the following question: ''In the past 12 months, has your child had an itchy rash which has been coming and going for at least 6 months?'' We calculated the individual PIAMA risk score using the equation reported in the original study[5] (Table 2).

TABLE 1— Asthma Predictive Index (API)[1]

Major criteria	Minor criteria
Parental MD asthma[2]	MD allergic rinitis[4]
MD eczema[3]	Wheezing apart from colds
	Eosinophilia ($\geq$4%)

[1]Loose index for the prediction of asthma: Early wheezer plus at least one of two major criteria or two of three minor criteria. Stringent index for the prediction of asthma: Early frequent wheezer plus at least one of two major criteria or two of three minor criteria.
[2]History of a physician's diagnosis of asthma.
[3]Physician's diagnosis of atopic dermatitis or a positive response to the question ''In the past 12 months, has your child had an itchy rash which has been coming and going for at least 6 months?''.
[4]Physician's diagnosis of allergic rhinitis or a positive response to the question ''In the past 12 months, has your child had a problem with sneezing, or a runny or blocked nose when he/she DID NOT have a cold or the flu?''.

Outcome Measure

At age 5–6 years, a child was considered to have active asthma (case definition of asthma) in the same way reported in the original studies: if he or she had asthma diagnosed by a physician with at least one episode of asthma during the previous year or had more than three episodes of wheezing during the previous year regardless of a diagnosis of asthma (API); and at least one episode of wheezing, or inhaled steroids prescribed by a medical doctor, or a doctor's diagnosis of asthma during the previous 12 months (PIAMA risk score). However, in the present study, we only measured the outcome once instead of in two consecutive years as was done in the original PIAMA study.

Statistical Analyses

Continuous variables were summarized as mean $\pm$ SD or median (interquartile range), whichever was appropriate. Categorical variables were reported as percentages. Differences in categorical variables between patients with and without asthma at 5–6 years old were analyzed using the chi-square test or Fisher's exact test, whichever was appropriate. Differences in continuous variables between patients with and without asthma at 5–6 years old were analyzed using the unpaired *t*-test or Wilcoxon-signed rank test, whichever was appropriate.

We compared the asthma predictive scores and the case definition of asthma using five criteria:[9]

Sensitivity (the probability of a positive asthma predictive score in children with a positive case definition of asthma).

Specificity (the probability of a negative asthma predictive score in children with a negative case definition of asthma).

Positive predictive value (the probability of a positive case definition of asthma in children with a positive asthma predictive score).

Negative predictive value (the probability of a negative case definition of asthma in children with a negative asthma predictive score).

Likelihood ratio (LR, the probability of a positive asthma predictive score in children with a positive case definition of asthma, divided by the probability of a

TABLE 2— Equation Used for Calculating the Individual PIAMA Risk Score

Individual score = 4.6 × Sex (boy = 1, girl = 0) + 7.3 × Post-term delivery (yes = 1, no = 0) + 4.2 × Medium/low education at least 1 parent (yes = 1, no = 0) + 7.7 × Inhalation medication by at least 1 parent (yes = 1, no = 0) + 4.2 × Infrequent wheezing (yes = 1, no = 0) + 9.1 × Frequent wheezing (yes = 1, no = 0) + 7.1 × Wheezing/dyspnea apart from colds (yes = 1, no = 0) + 4.6 × Infrequent serious infections + 6.9 × Frequent serious infections (yes = 1, no = 0) + 8.2 × Diagnosis eczema and rash present (yes = 1, no = 0)

positive asthma predictive score in children with a negative case definition of asthma).

For each result, a 95% confidence interval for a binomial proportion was determined.

The best cutoff threshold value of the PIAMA risk score that discriminates between patients with and without asthma was identified by the value giving the best combination of sensitivity and specificity by plotting receiver operating characteristics (ROC) curves (cut-off value where the sum of sensitivity and specificity was the highest).[10] The area under the curves and 95% confidence intervals were calculated. All statistical tests were two-tailed, and the significance level used was 0.05. The data were analyzed using Stata 10.0 (Stata Corporation, College Station, TX).

All parents provided informed consent prior to enrollment in the study, and the study protocol was approved by the local ethics board.

RESULTS

Of the 130 patients who were enrolled, 123 (94.6%) were able to be contacted at 5–6 years old to assess if they had active asthma. Of these 123 children, in 30 of them (24.4%), the percentage of circulating eosinophils could not be assessed because blood specimens were not obtained for them, so although a total of 123 children had complete information for the variables used to calculate the modified PIAMA risk score, only 93 (75.6%) children had complete information for the variables used to calculate the loose and stringent API. Of these 93 children, 33 (35.5%) were classified as early frequent wheezers, 63 (67.7%) had a positive loose API, and 24 (25.8%) a positive stringent API. The mean age at recruitment was 27.2 ± 5.9 months. Children from whom blood was taken were significantly younger compared to those from whom blood specimens were not obtained [27 (22–31.5) vs. 32 (22–34) months, respectively, $P = 0.04$].

Of the 93 children included in the API analysis, 21 (22.5%) fulfilled the criteria for the definition of active asthma at 5–6 years old. A significantly higher proportion of children with active asthma at 5–6 years old had higher frequency of wheezing episodes at recruitment, medical diagnosis of allergic rhinitis, and medical diagnosis of eczema, when compared with those without active asthma (Table 3). On the other hand, of the 123 children included in the PIAMA risk score analysis, 66 (53.6%) fulfilled the criteria for definition of active asthma at 5–6 years old. A significantly higher proportion of children with active asthma at 5–6 years old were male, had higher frequency of wheezing episodes at recruitment, medical diagnosis of eczema, and parental use of inhaled medications, when compared with those without active asthma (Table 4). Likewise, children with active asthma at 5–6 years old had a

TABLE 3— Frequency of Different Characteristics Used to Develop the Asthma Predictive Index (API), According to the Presence of Asthma at 5–6 Years Old

	Presence of asthma (n = 21)	Absence of asthma (n = 72)	All children (n = 93)
Frequency of wheezing at recruitment			
Very rarely	3 (14.3%)	9 (12.5%)	12 (12.9%)
Rarely	9 (42.9%)	39 (54.2%)	48 (51.6%)
Frequently	6 (28.6%)	24 (33.3%)	30 (32.3%)
Most of the time*	3 (14.3%)	0 (0.0%)	3 (3.2%)
All of the time	0 (0.0%)	0 (0.0%)	0 (0.0%)
Wheezing apart from colds	3 (14.3%)	21 (29.2%)	24 (25.8%)
Sneezing, or a runny nose without the flu[1]	21 (100.0%)	60 (83.3%)	81 (87.1%)
Medical diagnosis of allergic rhinitis*	21 (100.0%)	45 (62.5%)	66 (71.0%)
Itchy rash coming and going for at least 6 months[1]	9 (42.9%)	18 (25.0%)	27 (29.0%)
Medical diagnosis of eczema*	6 (28.6%)	0 (0.0%)	6 (6.5%)
Medical diagnosis of maternal asthma	3 (14.3%)	18 (25.0%)	21 (22.6%)
Medical diagnosis of paternal asthma	0 (0.0%)	3 (4.2%)	3 (3.2%)
Percentage of circulanting eosinophils	3.6 ± 3.1	3.1 ± 2.2	3.2 ± 2.4
Eosinophilia	6 (28.6%)	21 (29.2%)	27 (29.0%)

[1]In the 12 months previous to the recruitment to the study.
*P value < 0.05.

TABLE 4— Frequency of Different Characteristics Used to Calculate the PIAMA Risk Score, According to the Presence of Asthma at 5–6 Years Old

	Presence of asthma (n = 66)	Absence of asthma (n = 57)	All children (n = 123)
Gender, M/F*	54/12	33/24	87/36
Gestational age at birth*	38.8 ± 1.4	39.6 ± 0.9	39.2 ± 1.3
Frequency of wheezing at recruitment			
Very rarely	9 (13.6%)	3 (5.3%)	12 (9.8%)
Rarely*	30 (45.5%)	39 (68.4%)	69 (56.1%)
Frequently*	21 (31.8%)	9 (15.8%)	30 (24.4%)
Most of the time	6 (9.1%)	6 (10.5%)	12 (9.8%)
All of the time	0 (0.0%)	0 (0.0%)	0 (0%)
Wheezing apart from colds	15 (22.7%)	12 (21.1%)	27 (22.0%)
Itchy rash coming and going for at least 6 months[1]	18 (27.3%)	12 (21.1%)	30 (24.4%)
Medical diagnosis of eczema*	6 (9.1%)	0 (0.0%)	6 (4.9%)
Highest level of maternal education			
Primary School	9 (13.6%)	6 (10.5%)	15 (12.2%)
High School	36 (54.5%)	24 (42.1%)	60 (48.8%)
College	21 (31.8%)	27 (47.4%)	48 (39.0%)
Highest level of paternal education			
Primary School	9 (13.6%)	6 (10.5%)	15 (12.2%)
High School	36 (54.5%)	30 (52.6%)	66 (53.6%)
College	21 (31.8%)	21 (36.8%)	42 (34.1%)
Number of serious respiratory infections*[1]	4.4 ± 2.0	3.6 ± 1.7	4.9 ± 1.9
Parental use of inhaled medications*	24 (36.4%)	3 (5.36%)	27 (21.9%)

[1]In the 12 months previous to the recruitment to the study.
*P value < 0.05.

significantly lower gestational age at birth and a significantly greater number of serious respiratory infections in the 12 months previous to the recruitment to the study, when compared to those without active asthma (Table 4).

The PIAMA risk score ranged from 11.1 to 40.7, with a mean of 23.7 ± 7.3. This score was significantly higher in children with active asthma at 5–6 years old compared to children who had not fulfilled the case definition of asthma at this age (26.4 ± 7.1 vs. 20.6 ± 6.2, $P < 0.001$). ROC curve analysis to evaluate the optimal threshold value of the PIAMA risk score to discriminate patients with and without active asthma at 5–6 years old yielded a value of 25.0. For this threshold, sensitivity was 54.5% (95% CI: 42.6–66.0), and specificity was 78.9 (95% CI: 66.7–87.5).

Table 5 shows the sensitivity, specificity, predictive values, and LR tests of the loose and stringent API and PIAMA scores, along with their respective 95% confidence intervals. While the loose API yielded the highest value for sensitivity and stringent API for specificity, PIAMA risk score yielded the highest positive predictive value. Stringent API and PIAMA scores have pretty similar positive LR (Table 5).

DISCUSSION

The present study shows that the discriminative properties of the API and the PIAMA risk score are useful for predicting asthma in preschoolers with recurrent wheezing living in a low- to middle-income country. While our results applying the loose API yielded an acceptable sensitivity, the stringent API and the PIAMA risk score yielded a good specificity and an acceptable positive LR.

Although these indices, especially the API, have been extensively used for years in a clinical setting in Latin America, the findings of the present study will give confidence to physicians in these countries that they can be reliably applied not only for clinical purposes but also in a research context.

When our results of the discriminative properties of these indices are compared with those reported in the original API and PIAMA studies, it can be seen that the

TABLE 5— Sensitivity, Specificity, Predictive Values, Likelihood Ratios, and Their 95% CI of Asthma Predictive Indices (API) and PIAMA Risk Score According to Asthma Diagnosis at 5–6 Years of Age

	Loose API	Stringent API	PIAMA risk score
Sensitivity	71.4 (50.0–86.2)	42.9 (24.5–63.5)	54.5 (42.6–66.0)
Specificity	33.3 (23.5–44.8)	79.2 (68.4–86.9)	78.9 (66.7–87.5)
PPV	23.8 (15.0–35.6)	37.5 (21.2–57.3)	75.0 (61.2–85.1)
NPV	80 (62.7–90.5)	82.6 (72.0–89.8)	60.0 (48.7–70.3)
Positive LR	1.07 (0.78–1.47)	2.06 (1.05–4.01)	2.59 (1.50–4.49)
Negative LR	0.86 (0.40–1.82)	0.72 (0.49–1.06)	0.58 (0.43–0.77)

PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio.

stringent API score yielded higher values for sensitivity and lower for specificity, predictive values, and positive LR, while the PIAMA score yielded lower values for sensitivity and negative predictive value. However, the discriminative properties of our study are not easy to compare to those of the original reports because of differences in methodology, populations and study design. While patients recruited for the API and PIAMA risk score development were screened from the general birth cohort population, the children included in our study were screened from our outpatient pediatric pulmonary unit. Whereas in order to predict the risk of having subsequent asthma patients included in the API study were evaluated with respect to their history of respiratory conditions at 2 and 3 years of age and patients included in the PIAMA study were evaluated at 3 months, 12 months, and yearly thereafter, we evaluated our patients only once, between 1 and 3 years of age. Likewise, whereas the API patients were evaluated at 6–8 years of age for outcome measures (one in a series of evaluations) and the PIAMA patients were evaluated at 7–8 years of age, our patients were evaluated at 5–6 years old. Finally, in the API original study the diagnosis of eczema and rhinitis during the first 3 years of life was based exclusively on a physician's diagnosis, while in the present study parental reports using a standard ISAAC questionnaire were considered.

In addition to these differences, several other factors could be important. The term ''wheezing'' is frequently misunderstood by parents. Often, snoring, upper airway secretions, or rattling sounds reflective of airway secretions are erroneously labeled as wheezing by parents.[11] This misinterpretation of different respiratory sounds could have caused an overestimation of the true prevalence of wheezing in the initial evaluation of the population at 1–3 years old, thereby increasing the sensitivity and lowering the specificity of the API and the PIAMA risk score. This phenomenon could also have caused an overestimation of the true prevalence of asthma during the follow-up evaluation at 5–6 years old. Although this over-reporting of wheezing episodes could have occurred in both the original study and in ours, it is likely to have occurred more often in our study, because there were a smaller number of evaluations, giving the parents less possibility of precisely understanding the meaning of wheezing. Likewise, when analyzing the APIs, the finding of a higher proportion (although not statistically significant) of children with wheezing apart from colds at baseline in those without active asthma at 5–6 years of age compared to those with active asthma was unexpected, and a potential explanation could be the inaccurate report of wheezing by their parents.

Sometimes in Colombia, although a doctor may highly suspect asthma in a pediatric patient, he is reluctant to inform the parents for fear of causing them stress. Furthermore, if the child has never had trouble breathing or episodes of wheezing, the parents may be skeptical of the diagnosis. However, without mentioning the word ''asthma,'' the doctor often advocates the use of inhaled steroids. This fact could explain the higher prevalence of active asthma at 5–6 years old when using PIAMA criteria when compared with API criteria (53.6% vs. 22.5%, respectively), because in the PIAMA study, use of inhaled steroids prescribed by a medical doctor during the previous 12 months was included as one of the criteria in the case definition of asthma during school years, but this criterion was not considered in the API study. Furthermore, the fact that we used only one follow-up evaluation instead of two evaluations in consecutive years, as was done in the original PIAMA study, could have caused a higher estimation of the prevalence of asthma in our study. Therefore, our findings of lower values for positive predictive values for APIs and higher values for PIAMA risk score when compared with those reported in the original studies are probably due to the fact that the prevalence is more important than sensitivity and specificity in determining the predictive values.

When comparing both indices, while the loose API yielded the highest value for sensitivity and stringent API for specificity, PIAMA risk score yielded highest positive predictive value. Stringent API and PIAMA scores have pretty similar positive LR. These results contrast with a recent review comparing the original API versus PIAMA risk score that concluded that API at 6–8 years had higher specificity, positive predictive value and positive LR than PIAMA at 7–8 years; in contrast PIAMA had better sensitivity.[12] In the same way, as has been stated,[6] the decision about which of the three indices should be used in preschool children with recurrent wheezing in order to define a treatment strategy will depend on the efficacy and potential side effects of this treatment. A specific treatment with high efficacy but also with high potential side effects (e.g., inhaled corticosteroids) might be administered to children with a positive PIAMA risk score or a positive stringent API because of its higher specificity and positive predictive value. Conversely, a less effective treatment but also one with little or no side effects (e.g., leukotriene receptor antagonist) might be administered to children with a positive loose API because of its higher sensitivity and negative predictive value. Although the PIAMA risk score can be applied using a single cut-off point, it has the advantage of the possibility of also being used at any cut-off point, indicating a range of probability.

The main limitation of our study comprises the lack of a formal sample size calculation, including only a

small number of preschoolers with recurrent wheezing. This fact could explain the wide confidence intervals around the point estimates calculation of the different parameters. A second limitation comprises the fact that all subjects included were selected from patients at a pediatric pulmonary unit, which might compromise the generalizability of our results because of the higher pretest probability of asthma in this clinical setting. However, although our results may be useful in other pediatric pulmonary units, discriminative properties of the API and the PIAMA might be closer to the properties reported in the original studies when they are tested in the general population because of the lower prevalence of asthma in this population. Another possible limitation of this research concerns the mentioned inaccurate report of wheezing by parents and the lack of exclusive physician diagnosis of eczema and rhinitis for the API index. Therefore, it would be interesting to test if the accuracy of the reporting of this sign improves with subsequent evaluations.

The strengths of this study lie in the design and the setting. The study was a prospective cohort study and the information is collected in the same way as in any clinical setting where doctors have to decide about the prognosis of preschool children with recurrent wheezing. Moreover, to the best of our knowledge, this is the first report of the discriminative properties of these scores in any low- to middle-income country.

In summary, our results suggest that both indices can be confidently used to predict asthma in preschoolers with recurrent wheezing in low- to middle-income countries. Additional research is needed in different countries based on a larger number of patients, and in different settings, with a more representative sample of the general population.

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