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Novel predictors of airway hyperresponsiveness in children with respiratory symptoms without obstructive pattern

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Abstract

Background: Methacholine challenge (MCC) is the most common method to detect airway hyperresponsiveness (AHR). Although MCC is accepted as safe diagnostic tool, it is time consuming and could be exhausting for patients. Thus, it might be helpful to identify predictive factors for AHR. We aimed to develop a diagnostic tool for predicting AHR in children with respiratory symptoms without obstructive pattern. Methods: Data from children who had undergone MCC were analyzed retrospectively. The demographic features of patients along with laboratory results were collected. Results: A total of 123 children with a median age of 10.5 years were enrolled. AHR was detected in 81 children (65.8%). The age of the children with AHR was significantly younger. The prevalences of aeroallergen sensitization, nocturnal cough, wheezing and a baseline forced expiratory flow at 75% of vital capacity (FEF75) <65% were significantly more frequent in children with AHR. Multivariate logistic regression analysis revealed age, ever wheezing, nocturnal cough, tree pollen allergy and FEF75<65% as independent predictors of the AHR. A weighted clinical risk score was developed (range, 0-75 points). At a cutoff point of 35 the presence of AHR is predicted with a specificity of 90.5% and a positive predictive value (PPV) of 91.5%. Conclusion: In children suspected of having asthma, but without an obstructive pattern, combining independent predictors, which can be easily obtained in clinical practice, in a novel prediction rule might be used to identify children with AHR.

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Methods: Data from children who had undergone MCC were analyzed retrospectively. The demographic features of patients along with laboratory results were collected.

Results: A total of 123 children with a median age of 10.5 years were enrolled. AHR was detected in 81 children (65.8%). The age of the children with AHR was significantly younger.

The prevalences of aeroallergen sensitization, nocturnal cough, wheezing and a baseline forced expiratory flow at 75% of vital capacity (FEF_{75}) <65% were significantly more frequent in children with AHR. Multivariate logistic regression analysis revealed age, ever wheezing, nocturnal cough, tree pollen allergy and FEF_{75}<65% as independent predictors of the AHR. A weighted clinical risk score was developed (range, 0-75 points). At

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a cutoff point of 35 the presence of AHR is predicted with a specificity of 90.5% and a positive predictive value (PPV) of 91.5%.

Conclusion: In children suspected of having asthma, but without an obstructive pattern, combining independent predictors, which can be easily obtained in clinical practice, in a novel prediction rule might be used to identify children with AHR.

Keywords: airway hyperresponsiveness, children, FEF_{75}, methacholine challenge, nocturnal cough, predictive score, tree pollen allergy,

Main Text

Introduction

Asthma is a chronic disease with a high prevalence which is characterized by chronic airway inflammation and variable expiratory airflow limitations. Apart from airway obstruction, the presence of airway hyperresponsiveness (AHR) is accepted as one of the important key factors in asthma pathogenesis(1), and severe AHR predicts asthma with a high sensitivity(2).

The diagnostic performances of various bronchoprovocation tests are under discussion, but the direct methacholine challenge (MCC) is still the most common method to detect and quantify AHR, and the response to methacholine correlates with the severity of AHR(3). There is evidence that the MCC has a quite low specificity compared to indirect bronchoprovocation tests(2). Thus, indirect tests are suggested as the best screening tool to detect asthma. However, in patients suffering from asthma-related symptoms without an obstructive pattern in spirometry and without a positive reaction to indirect bronchoprovocation, there is a diagnostic dilemma in reaching the correct diagnosis, particularly as the absence of AHR confirmed by a negative MCC is considered in this patient subgroup as the "gold standard" in being able to exclude the presence of asthma with reasonable certainty(4).

Although the MCC is accepted as a safe diagnostic tool, it is time consuming and could be exhausting for patients(4). The aim of this study was to identify the predictive factors which allow for a reliable identification of patients with a high probability of AHR who would thus benefit from a validation by the MCC. This can prevent the mental stress and even other aggravating effects induced by the performance of the MCC in a pediatric population when it might not be necessary. Therefore, we have developed a prediction model combining factors that best predict AHR and can be easily obtained in practice. The diagnostic performance of this novel prediction model was also investigated.

Methods

Study participants

We analyzed the data from children who had undergone the MCC at the Department of Pediatric Allergy at the Children's Hospital, University of Bonn between January 2009 and December 2018. From an initial population of 939 children, patients with an obstructive pattern, that is baseline forced expiratory volume in one second (FEV_1) and/or FEV_1/forced vital capacity (FVC) ratio $< 80\%$ predicted, or relevant ([?]200 mL or [?]12%) reversibility in executed spirometry (n = 712), were not included. Furthermore, according to the established protocol in our department, children with primarily exercise-induced symptoms underwent exercise challenge testing before the MCC and those children who had exercise-induced bronchoconstriction in the exercise challenge testing were also excluded (n = 104). The data from 123 children were analyzed (Fig.1).

Definitions

Admission symptoms were investigated at the patient's first visit by a standardized list of questions based on the International Study of Asthma and Allergies in Childhood (ISAAC)(5) using the German questionnaire developed by Duhme et al. (1998)(6). Additional questions were used as have been previously described in detail elsewhere(7). *Wheezing not associated with colds* was defined as a positive response to the question:

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"Has your child had wheezing or whistling in their chest in the past twelve months without a cold". *Wheezing associated with colds* had the same definition as the clinical evidence of a viral cold(8). *Ever had wheezing* was defined as a positive response to the question: "Has your child ever had wheezing or whistling in their chest at any time in the past"(5). All symptoms were reported by the children and confirmed by the parents or by a physician. Children with at least one positive answer were declared as having asthma-like symptoms.

Skin prick tests

All children underwent skin prick testing to common aeroallergens for our region (ALK-abelló, Hamburg) including house-dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), grass pollen mix (*Phleum pratense* , *Poa pratensis* , *Dactylis glomerata* , *Lolium perenne* ,*Festuca pratensis* and *Avena eliator*), grain pollen mix (*Secale cereale* and *Triticum aestivum*), weed pollen mix (*Artemisia vulgaris* , *Plantago lanceolate* and*Ambrosia artemisiifolia*), tree pollen mix (*Alnus glutinosa* , *Corylus avellane* , *Betula verrucosa* , and*Quercus petraea*), molds (*Alternaria alternata* and*Aspergillus fumigatus*), and animal dander (cat and dog). Histamine (10 mg/mL of histamine phosphate) and 0.9% saline were used as positive and negative controls respectively. Weal 3 mm greater than the negative control was considered a positive reaction.

Blood Eosinophil Counts and Serum Total Immunoglobulin E Levels

Blood eosinophil counts were determined by Coulter Counter (Beckman Coulter, Fullerton CA) leukocyte measurements. The serum total immunoglobulin E (IgE) level was measured with the ImmunoCAP system (Phadia AB, Uppsala, Sweden).

Bronchial Provocation Tests

To guarantee a meaningful performance of the MCC, patients had to follow the preparation guidelines(3, 9). The administration of the MCC was largely automated according to the 1-concentration-4-step dosimeter protocol(10) which promises advantages in dosing accuracy and handling. Briefly, spirometry was performed at baseline as a first step, followed by four steps, each with the inhalation of methacholine and subsequent spirometry two minutes after inhalation. With each step the inhaled methacholine dose was raised, starting from 15 µg and increasing to a maximum of 720 µg. The exact dose inhaled at each step was determined by measuring the effective nebulization time at inspiration and referring it to the drug concentration and nebulizer power. The complete procedure was realized with the MasterScreen^{TM} Body system (CareFusion, Höchberg, Germany) powered by the Sentry Suite software (Version 2.17.66, Hotfix Package 4) with automated control, providing a real-time visualization of the dose administration and breathing pattern. To optimize the inhalation process, patients could control their breathing themselves by a visual computer graphic imitating their breathing to attain an airflow of 0.5 L/s and to guarantee an inspiration time of 3 seconds during inhalation. The aerosol for inhalation was generated directly by the flow-triggered nebulization of a solution with a constant methacholine concentration (16 mg per mL isotonic saline(11)) through a mouthpiece of an APSpro jet-type nebulizer (240 mg/min performance; Medic Aid pro; Sidestream Care Fusion).

The current, as well as the cumulative, methacholine dose (PD20) which caused a decrease of FEV_1 by more than 20% was calculated by logarithmic interpolation. The end-of-test criterion was met if either FEV_1 decreased by more than 20% or the maximum cumulative methacholine dose of 960 µg had been inhaled. The result of the MCC was assessed as positive if PD20 was lower than 960 µg.

Statistical Analysis

The median and interquartile range were computed for continuous parameters, and counts and percentage for categorical variables. Group comparisons were carried out using the Mann–Whitney test and the χ^2 test as appropriate. Independent predictors of AHR were identified by multivariate logistic regression modeling entering parameters with $P < .05$ in a univariate analysis in a block. Odds ratios with their 95% confidence intervals and regression coefficients were computed. In order to create a weighted multivariate prediction score, points were assigned to each of the elected predictors based on the respective regression coefficient

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multiplied by ten and rounded up or down to the next integer number. An individual score value was calculated for each child by summing the weighted points of all the predictors. For each predictor, as well as for the multivariate score, sensitivity, specificity, a positive predictive value (PPV), and a negative predictive value (NPV) were determined at respective cutoff values, and receiver operating characteristics (ROC) curves were constructed. The SPSS software package 25 (IBM Armonk, New York, USA) was used for all calculations. P values $< .05$ were considered significant.

Results

The study population included 123 children (5-18 years) of which 64 (52%) were male. The MCC was positive in 81 (65.9%) children indicating the presence of AHR. In Table 1, the characteristics of the study population are summarized according to the presence of AHR. The median age of children with AHR was significantly younger at the time of diagnosis compared to those without AHR (9.7 vs 12.3 years; P = .001). The prevalence of aeroallergen sensitization in the skin prick test was significantly higher in children with AHR when compared to those without AHR (35.7% vs 58.0%; P = .019). Subclassification according to individual allergen groups revealed for AHR positive children an elevated incidence of allergy to tree pollen (11.9% vs 37.0%; P = .003), animal dander (9.5% vs 27.2%; P = .023) and house dust allergy (21.4% vs 44.4%; P = .012). With regard to admission symptoms,*nocturnal cough* (9.5% vs 30.9%; P = .008), *wheezing not associated with colds* (4.8% vs 22.2%; P = .013) and *wheezing associated with colds* (35.7% vs 58.0%; P = .019) were observed significantly more frequently in AHR positive children compared to children without AHR. Combining wheezing symptoms (*ever wheezing*) resulted in an improved significance (40.5% vs 66.7%; P = .005), while significance was reduced for combinations of *nocturnal cough* with*exercise-induced cough* . However, *dyspnea* and*exercise-induced dyspnea* , even in combination with other parameters, did not reach significance. For the spirometry items, only a baseline forced expiratory flow at 75% of vital capacity (FEF_{75}) <65% was found significantly more frequently in AHR positive children compared to the group without AHR (14.3% vs 30.9%; P = .045). The diagnostic value of significant parameters in the univariate analysis is shown in Table 2.

A comparison of laboratory parameters reveals that the percentage of children with a blood eosinophilia count over 500/ µL was significantly elevated in the AHR positive group compared with children without AHR (22.8% vs 2.4%; P = .002; N = 80). Also, the median of the percentage of blood eosinophilia was significantly higher in AHR positive children compared with the group without AHR (5.6% vs 2.8%; P = .004; N = 93).

Multivariate logistic regression including age, *ever wheezing* ,*nocturnal cough* , tree pollen allergy and FEF_{75}<65% confirmed that all parameters chosen are independent predictors of the occurrence of AHR. In Table 3, the results of multivariate analysis are summarized. Multivariate prediction score values, weighted as described in the methods section, were calculated for each child as follows: individual score value = 14 x tree pollen allergy (yes = 1, no = 0) + 11 x ever wheezing (yes = 1, no = 0) + 13 x nocturnal cough (yes = 1, no = 0) + 11 x FEF_{75}<65% (yes = 1, no = 0) – 2 x age (5 – 18 years) + 36. The last summand was added to get only positive score values ranging from 0 to 75 points. The individual score values calculated for our patients ranged from 3 to 61 with a median (interquartile range) of 32 (19-41). The risk of the occurrence of AHR increased with the score value. In Table 4, the test characteristics of the multivariate score at various cutoff points are summarized. At a cutoff point of 35 the presence of AHR is predicted with a specificity of 90.5% and a PPV of 91.5%. The ROC curve displaying sensitivity and specificity of score with ascending cutoff points is shown in Figure 2. The area under the curve (AUC) was 0.813.

Discussion

In the present study, we identified several factors associated with the occurrence of AHR in children. With five of these factors, we constructed a weighted multivariate score to predict the presence of AHR in children suspected of having asthma but without an obstructive pattern.

Association of allergy, atopic history and eosinophilia with AHR

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Several studies have identified a personal history of having an allergy to various antigens as a risk factor for AHR(3, 12-14). Tree pollen, especially, has been described as an important allergen in this context(15), while no association could be verified in relation to mold sensitization(15, 16). In accordance with previous studies, we found an association of AHR with general skin test positivity as well as with sensitization to most aeroallergens, except mold, and where tree pollen sensitization reached the highest significance level. This high significance might be due to the specific local environment. The birch tree is widely spread in Germany and has emerged as a common allergen in children with allergic rhinitis and asthma(17).

In contrast, in an earlier study including children who were also without an obstructive pattern, no significant relationship between personal allergy and the presence of AHR was detectable(7). However, unlike the earlier study, in the present study patients with predominantly exercise-induced symptoms were excluded. The symptoms of the patients in our study group occurred mainly when they were at rest and were frequently triggered by allergens. Thus, it can be assumed that in the present study there are more patients with allergies, supported by the higher percentage of sensitized children compared with the previous study (51.2% vs 43.6%). Correspondingly, a stronger association between allergy and AHR can be expected. Especially in atopic patients, the MCC is accepted as a highly sensitive tool to detect AHR(18).

A family history of atopy has also been described by some authors as associated with AHR(19, 20), while others could not confirm such a relationship(21). Although our data did not show a significant relationship of atopic family history with AHR, co-existence of two or more atopic diseases in the family nearly reached significance. In general, it is difficult to evaluate the influence of a genetic history because subjective measures might lead to overestimating the risk from family history. So it can be assumed that parents suffering from respiratory symptoms would be more likely to recognize symptoms in their children and consult a physician(21, 22).

In accordance with the results of previous studies, we identified an association between high eosinophilia counts and AHR(7, 14, 23). Unfortunately, our database of eosinophilia was incomplete, therefore it was not included in the multivariate analysis.

Association of asthma-like symptoms with AHR

Wheezing was identified in several studies as the most sensitive single symptom for asthma(12, 20) and was also included in many scores developed for the prediction of asthma(24). An interrelation between wheezing associated with colds, AHR and asthma has been reported(19, 25). Likewise, several studies reported that cough, and especially nocturnal cough, is related to severity as well as to a worse prognosis of asthma (26).

Nocturnal cough is highly prevalent in adult patients with asthma(27) and a high frequency of nocturnal cough is shown to be significantly related to the presence of AHR(28). While our findings confirm the importance of wheezing and nocturnal cough as predictors of AHR, Yavuz et al.(7) found that, in spite of a quite similar patient selection, there is neither a significant association of AHR with wheezing nor with nocturnal cough. They observed significance only for the co-existence of nocturnal and exercise-induced cough, a combination with reduced significance in our study.

Several studies have reported a negative association between AHR and dyspnea which might be due to a worse perception of breathlessness(7, 29). The prevalence of dyspnea was also more frequent in children without AHR, however without reaching significance. Nevertheless, findings reported in the literature for single admission symptoms related to AHR and asthma seem to be inconsistent, probably due to a wide variability.

Association of spirometry findings with AHR

FEV_1 reflects mainly the functioning of the large and medium airways(30), whereas FEF represents the functioning of the medium-sized and small airways(30-32). There are several studies observing the important role of FEV_1 in predicting AHR(12, 14, 33). After excluding children with an obstructive pattern, FEF becomes more important, and FEV_1 has been reported to lose its significance(7, 32). Thus, FEF might have a possible role in the prediction of AHR, particularly in patients with a normal FEV_1 and FEV_1/FVC

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ratio(31),(32). However, the predictive value of FEF for AHR is controversial. While some authors found a significant association of FEF values, especially of a forced mid-expiratory flow between 25% and 75% of vital capacity ($FEF_{25-75\%}$), with AHR in patients with normal FEV_1(31, 32, 34), others did not(35, 36). This inconsistency may be due, at least, to the fact that some studies also included other diseases like cystic fibrosis(35, 36). In our population, none of the spirometry variables recorded at baseline were significantly associated with AHR. However, after dichotomizing the FEF values at a cutoff of 65%, as proposed by others(31),(32), the role of $FEF_{75} < 65\%$ in predicting AHR became significant.

Association of age with AHR

In this study we found a negative association between age at time of diagnosis and presence of AHR. Also, in multivariate analysis, age remained a strong predictor of AHR. Our results were in accordance with several studies that report a relationship between age and AHR in children(14, 34, 37). But the relationship with age seems to be multifaceted. Obviously pathophysiologic processes determining AHR alter with age(33) as well as with the duration of disease(38), and the predictive value of some variables changes depending on age(14). An additional influence of age might be due to the considerable growth rate of children leading to the application of a larger dose in young children related to body size(34).

Prediction of AHR by a multivariate score

Admission symptoms related to AHR and asthma have a wide variability, and the diagnostic role of a single symptom is limited. The combination of single items can improve the power of prediction(7, 24). We combined the five items, extracted by multivariate analysis as independent predictive factors, to construct a weighted multivariate score which reached an AUC > 0.7 which is acceptable for a prognostic model(39). To our knowledge, we generated a novel algorithm to predict AHR in children without an obstructive pattern. In contrast to the previously established predictive scores like the asthma predictive index (API), we aimed for the diagnosis of current asthma and not for the prediction of the development of asthma in later life(24). This algorithm could allow a reliable identification of those patients with an increased probability of AHR, and where an extended diagnostic using MCC might be helpful, against those patients who are less likely to have AHR and so prevent the mental stress and even the exhaustion of such patients caused by the severe symptoms induced by the performance of the MCC.

Limitations

The comparability of our study population recruited from a specialized tertiary center for pediatric allergy is limited. We included only children with asthma-like symptoms and without obstructive patterns. We also excluded patients with exercise-related leading symptoms. Due to these exclusion criteria, only patients with certain conditions could be recruited onto the study. However, our findings are extracted from a real-life setting and it represents the routine diagnostic procedures. The large sample size is another strength of our study.

Conclusion

We identified tree pollen allergy, nocturnal cough, wheezing, a $FEF_{75} < 65\%$ and a younger age as significant predictors of AHR. Combining these predictors in a weighted multivariate score improved the diagnostic value. This novel score might be used in children suspected of having asthma, but without an obstructive pattern, to identify those who probably will show a positive response to the MCC as well as to substantiate the result of the MCC. Further prospective studies may help to demonstrate the predictive value of this score.

Impact Statement

Methacholine challenge is the most common method to detect airway hyperresponsiveness in children. However, it is time consuming and could be exhausting for patients. We aimed to develop a diagnostic tool for predicting AHR in children with respiratory symptoms without obstructive pattern. We identified tree pollen allergy, nocturnal cough, wheezing, a $FEF_{75} < 65\%$ and a younger age as significant predictors of

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AHR. This novel predictive tool might be used in children suspected of having asthma, but without an obstructive pattern, and it may decrease the need for bronchial provocation tests.

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Table 1. Comparison of Demographic and Laboratory data according to presence of AHR

	Study Population (n = 123)	**AHR Positive (n = 81)**	**AHR Negative (n = 42)**	**p-value**
Demographic data				
Male sex	64 (52.0)	42 (51.9)	22 (52.4)	0.96
Age at time of diagnosis, years	10.5 (8.0-13.0)	9.7 (7.1-12.0)	12.3 (9.7-14.0)	0.001
Family history of allergic disease	38 (30.9)	24 (29.6)	14 (33.3)	0.67
Family history of asthma	18 (14.6)	12 (14.8)	6 (14.3)	0.94
Family history of hay fever	25 (20.3)	13 (16.0)	12 (28.6)	0.10
Family history of eczema	6 (4.9)	4 (4.9)	2 (4.8)	0.97
Co-existence of 2 or more atopic diseases in family	10 (8.1)	4 (4.9)	6 (14.3)	0.07
Aeroallergen sensitization	62 (50.0)	47 (58.0)	15 (35.7)	0.019
-Tree pollen	35 (28.5)	30 (37.0)	5 (11.9)	0.003
-Grass pollen	48 (39.0)	36 (44.4)	12 (28.6)	0.09
-Animal dander	26 (21.1)	22 (27.2)	4 (9.5)	0.023
-Mold	7 (5.7)	5 (6.2)	2 (4.8)	0.75
-House dust mite	45 (36.6)	36 (44.4)	9 (21.4)	0.012
Accompanying eczema	25 (20.3)	17 (21.0)	8 (19.0)	0.80
Accompanying allergic rhinitis/conjuntivitis	38 (30.9)	27 (33.3)	11 (26.2)	0.42
Pet ownership	51 (41.5)	36 (44.4)	15 (35.7)	0.35
Smoke exposition at home	13 (10.6)	10 (12.3)	3 (7.1)	0.37
Admission symptoms				
Daytime cough	67 (54.5)	49 (60.5)	18 (42.9)	0.06

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Nocturnal cough	29 (23.6)	25 (30.9)	4 (9.5)	0.008
Exercise-induced cough	30 (24.4)	23 (28.4)	7 (16.7)	0.15
Co-existence of nocturnal and exercise-induced cough	12 (9.8)	11 (13.6)	1 (2.4)	0.047
Dyspnea	39 (31.7)	28 (34.6)	11 (26.2)	0.34
Exercise-induced dyspnea	60 (48.8)	36 (44.4)	24 (57.1)	0.18
Daytime cough and/or dyspnea	84 (68.3)	60 (74.1)	24 (57.1)	0.06
Exercise-induced cough and/or exercise-induced dyspnea	78 (63.4)	50 (61.7)	28 (66.7)	0.59
Ever wheezing	71 (57.7)	54 (66.7)	17 (40.5)	0.005
Wheezing not associated to colds	20 (16.3)	18 (22.2)	2 (4.8)	0.013
Wheezing associated to colds	62 (50.4)	47 (58.0)	15 (35.7)	0.019
Laboratory parameters [a]				
Peripheral blood eosinophilia count $> 500/\mu L$	19 (15.4)	18 (22.2)	1 (2.4)	0.002
Peripheral blood eosinophilia	4.0 (2.5-7.0)	5.6 (2.8-8.9)	2.8 (2.2-4.2)	0.004
Serum total IgE	123 (30-355)	150 (36-489)	77 (18-295)	0.07
Spirometry parameters				
Baseline FEV_1, %	100 (90-109)	100 (90-109)	101 (92-111)	0.49
Baseline FVC, %	93 (85-105)	93 (82-105)	93 (85-105)	0.84
Baseline FEV_1/FVC ratio, %	100 (89-112)	100 (89-111)	102 (89-117)	0.56
Baseline FEF_{25}, %	87 (77-98)	87 (77-95)	89 (75-99)	0.70
Baseline FEF_{50}, %	84 (75-98)	83 (74-97)	89 (80-104)	0.13
Baseline FEF_{75}, %	78 (64-103)	77 (61-99)	86 (69-110)	0.08
Baseline FEF_{25} <65%	13 (10.6)	7 (8.6)	6 (14.3)	0.33
Baseline FEF_{50} <65%	12 (9.8)	10 (12.3)	2 (4.8)	0.18
Baseline FEF_{75} <65%	31 (25.2)	25 (30.9)	6 (14.3)	0.045

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Data are presented as count (%) or median (interquartile range). Abbreviations: AHR, airway hyperresponsiveness; IgE, immunoglobulin E; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{xx}, forced expiratory flow at XX percent of vital capacity. [a] Laboratory parameters were available in the study population (AHR+/AHR-) only from 80 (52/28), 93 (61/32), and 95 (62/33) children for peripheral blood eosinophilia count>500/µL), peripheral blood eosinophilia % and serum total IgE, respectively.

Data are presented as count (%) or median (interquartile range). Abbreviations: AHR, airway hyperresponsiveness; IgE, immunoglobulin E; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{xx}, forced expiratory flow at XX percent of vital capacity. [a] Laboratory parameters were available in the study population (AHR+/AHR-) only from 80 (52/28), 93 (61/32), and 95 (62/33) children for peripheral blood eosinophilia count>500/µL), peripheral blood eosinophilia % and serum total IgE, respectively.

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Table 2. Diagnostic performances of variables elected by univariate analyses

Tree pollen allergy
Ever wheezing
Nocturnal cough
$FEF_{75} < 65\%$

Abbreviations: FEF_{75}, forced expiratory flow at 75 percent of vital capacity; NPV, negative predictive value; PPV, positive

Table 3. Results of multivariate analysis

Age at time of diagnosis

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Tree pollen allergy
Ever wheezing
Nocturnal cough
FEF_{75} < 65%
Abbreviations: FEF_{75}, forced expiratory flow at 75 percent of vital capacity. Odds ratio is presented with 95% confidence i

Table 4. Test characteristics of multivariate prediction score at various cutoff points

Cutoff point	**Sensitivity, %**
>15	91.4
>25	80.2
>35	53.1
>45	24.7
Abbreviations: NPV, negative predictive value; PPV, positive predictive value	Abbreviations: NPV, negative predictive v

Figure Legends

Figure 1. Patient selection

Figure 2. Receiver operating characteristic curve of multivariate prediction score for the presence of AHR. The area under the receiver operating characteristic curve was 0.813

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