

Forced expiratory flow between 25 and 75% of vital capacity might be a predictive factor for bronchial hyperreactivity in children with allergic rhinitis, asthma, or both

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ABSTRACT

Allergic rhinitis and asthma are closely associated. Bronchial hyperreactivity (BHR) is a pathophysiological characteristic of asthma. Forced expiratory flow between 25 and 75% of vital capacity (FEF_{25-75}) has been previously shown to be able to predict BHR in adult patients with allergic rhinitis. Therefore, the aim of this study was (i) to evaluate the presence of BHR in a large group of children with allergic rhinitis, asthma or both and (ii) to confirm whether FEF_{25-75} might be related to BHR and may predict BHR also in a pediatric population. Nine hundred fifty children with allergic rhinitis (350), asthma (300), or both (300) were enrolled. Clinical examination, skin-prick test, spirometry, and methacholine challenge were performed in all patients. Severe BHR was quite frequent in allergic children, mainly in asthmatic patients. FEF_{25-75} values were significantly related to BHR grade, mainly in children with rhinitis ($r = 0.69$). Impaired FEF_{25-75} values (such as $\leq 65\%$ of predicted) constituted a relevant predictive factor for severe BHR, mainly in children with rhinitis (odds ratio, 8.9). In conclusion, this pediatric study confirmed that impaired FEF_{25-75} values might predict severe BHR in children, mainly in those with allergic rhinitis. Therefore, low FEF_{25-75} values could suggest BHR in children.

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Allergic rhinitis and asthma are closely associated.^{1–5} Bronchial obstruction is a paramount characteristic of asthma and can be accurately measured by the forced expiratory volume/1 second (FEV_1).^{6,7} Nevertheless, the forced expiratory flow between 25 and 75% of vital capacity (FEF_{25-75}) has been proposed as a more sensitive indicator of persistent airflow obstruction than FEV_1 mainly in patients suffering from allergic rhinitis.⁸

The World Health Organization document over “the impact of allergic rhinitis on asthma” stressed the concept that allergic rhinitis has to be considered a relevant risk factor for asthma.⁹ In this regard, FEF_{25-75} may be also considered a marker of early bronchial pathology in patients with allergic rhinitis.¹⁰ It has been shown that lower airways may be involved also in patients with recent onset of allergic rhinitis,¹¹ and airway inflammation plays a relevant role in these phenomena.¹² Recently, it has been defined that a FEF_{25-75} value $\leq 65\%$ of predicted should be considered abnormal.¹³

Bronchial hyperreactivity (BHR) characterizes asthma and may be frequently observed also in patients with allergic rhinitis.¹⁴ Patients with allergic rhinitis and BHR may consistently become asthmatic.^{15–17} Furthermore, it has been reported that an absolute difference between FEV_1 and FEF_{25-75} values of >20 may suggest the presence of severe BHR in patients with allergic rhinitis and/or asthma.¹⁸

A very recent study reported that impaired FEF_{25-75} value (such as $\leq 65\%$ of predicted) constitutes a relevant predictive factor (odds ratio [OR], 12.9) for severe BHR in adult patients with allergic rhinitis.¹⁹ Therefore, a new study was designed to evaluate the presence of BHR in a large group of children with allergic rhinitis, asthma, or both and to confirm whether FEF_{25-75} might be related to BHR and may predict it also in a pediatric population.

METHODS

Study Design and Setting

This cross-sectional study included 950 consecutive children (median age, 12 years) with allergic rhinitis (350), asthma (300), or both (300). All of the children were evaluated at the Ave Gratia Plena Hospital for rhinitis and/or asthma. The local review board approved the study and an informed consent was obtained from the parents of each patient.

Detailed clinical history and complete physical examination were performed. The patients were included in the study based on a documented diagnosis of al-

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lergic asthma and/or allergic rhinitis made according to validated criteria (www.ginasthma.com, 9).²⁰ We excluded all of the subjects who met the following criteria: acute or chronic upper respiratory infections; anatomic nasal disorders (*i.e.*, nasal polyps, severe septum deviation, *etc.*); previous or current specific immunotherapy; and use of inhaled, nasal, or oral corticosteroids, nasal or oral vasoconstrictors, long-acting bronchodilators, antileukotrienes, and antihistamines during the previous 4 weeks. All patients were previously treated only on demand with drugs (such as antihistamines or short-acting β_2 -agonist) alone.

Children with rhinitis and BHR were not considered asthmatic if they never suffered from bronchial symptoms (such as wheezing, cough, and difficulty in breathing) and had normal spirometric parameters (such as $FEV_1 \geq 80\%$ of predicted, $FEF_{25-75} \geq 65\%$ of predicted, FEV_1/FVC ratio of >70) and no bronchodilator responsiveness to albuterol. Skin-prick test was performed as stated by the European Academy of Allergy and Clinical Immunology.²¹ The panel consisted of house-dust mites (*Dermatophagoides farinae* and *ptero-myssinus*), cat, dog, grasses mix, *Compositae* mix, *Parietaria officinalis*, birch, hazel, olive tree, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix (Stallergenes, Milan, Italy).

Spirometry

Spirometry was performed by using a computer-assisted spirometer (Pulmolab 435-spiro 235, Morgan Scientific, Haverhill, MA), with optoelectronic whirl flowmeter. It was performed as stated by the European Respiratory Society.^{6,7} FEF_{25-75} was considered impaired if below 65% of predicted.¹³ Because FEF_{25-75} is a parameter with possible variability effort dependent, a session was considered valid after five repeated measurements with a variability $<5\%$.

Methacholine Bronchial Challenge

Methacholine bronchial challenge was performed to evaluate BHR. Aerosol was delivered using a dosimetric computerized supply (Mefar MB3; Mefar, Marcos, Italy). The test was performed following the American Thoracic Society guidelines for methacholine challenge.²² The threshold concentration causing a 20% fall of FEV_1 (provocation concentration causing a 20% fall [PC_{20}]) was calculated.

Degree of BHR Severity

Three categories of BHR were considered based on PC_{20} : severe $PC_{20} < 1$ mg/mL, mild PC_{20} between 1 and 4 mg/mL, and borderline PC_{20} ranging from 4.1 to 16 mg/mL, according to the criteria of the American Thoracic Society guidelines for methacholine challenge.²² Subjects without response to the cumulative

dose of 16 mg/mL were considered having normal bronchial responsiveness.

Statistical Analysis and Data Definitions

Descriptive statistics were first performed and quantitative parameters were reported as medians with quartiles. Qualitative data were reported as frequencies and percentages. Comparison of qualitative data among various groups of patients were made by the chi-square test (or by Fisher's exact test in case of expected frequencies of less than five). Comparison of quantitative variables between the three groups of patients was made by the nonparametric counterpart (Kruskal-Wallis test) whenever the normality assumption was not fulfilled. If the Kruskal-Wallis and/or chi-square tests were positive, a test for pairwise comparison of subgroups was performed according to Conover test.

Linear correlation between pairs of quantitative variables was evaluated by Spearman's correlation coefficient (r). For the purpose of the analysis, correlation coefficients of >0.8 were considered as very strong, from 0.6 to 0.79 were considered as strong, from 0.4 to 0.59 were considered as moderate, from 0.2 to 0.39 were considered as weak, and <0.2 were considered as very weak.

To evaluate the role of different independent variables in the relationship with severe BHR ($PC_{20} < 1$ mg/mL versus $PC_{20} \geq 1$ mg/mL), a multiple logistic regression analysis was performed for each group of patients (patients with rhinitis, patients with asthma, and patients with rhinitis plus asthma). Variables that were statistically significant in the bivariate analysis (sensitization to perennial allergens and duration of pathology) or that were considered *a priori* important (the dichotomized explanatory variable $FEF_{25-75} \leq 65$ of predicted) were entered in the model. Before performing logistic regression, the duration of pathology was dichotomized based on the receiver operating characteristic (ROC) curve analysis; sensitivity and specificity were also calculated. The following predictors were evaluated in the logistic regression model for patients with allergic rhinitis: rhinitis duration (>4 years versus ≤ 4 years), FEF_{25-75} ($\leq 65\%$ of predicted versus $\geq 65\%$ of predicted), and sensitization to perennial allergens (reference category, sensitization to seasonal allergens). For the groups with asthma and asthma plus rhinitis the following were evaluated: the FEF_{25-75} ($\leq 65\%$ of predicted versus $\geq 65\%$ of predicted) and the sensitization to perennial allergens (reference category, sensitization to seasonal allergens). Age of the patient did not enter in the model because of collinearity with pathology duration.

For the multivariate analysis, the step-down strategy was chosen; the effect was expressed in terms of ad-

Table 1 Demographic and clinical characteristics of patients

	Patients with Rhinitis <i>n</i> = 350	Patients with Asthma <i>n</i> = 300	Patients with Asthma and Rhinitis <i>n</i> = 300	<i>p</i> Value
Gender—males, <i>n</i> (%)	217 (62)	172 (57.3)	179 (59.6)	0.2*
Age (yr) median	11	13	12	0.15#
Duration of pathology (yr), median [IQR])	3 [2–5]	6 [3–7]	6 [2–8]	0.001#
FVC, median [IQR]), percent of predicted	94 [89–98]	92 [87–94]	89 [86–93]	0.019*
FEV ₁ , median [IQR]), percent of predicted	85 [83–90]	81 [77–85]	80 [77–85]	<0.001#
FEF _{25–75} , median [IQR], % of predicted	71 [66–81]	67 [60–73]	66.5 [60–72]	<0.001#
FEF _{25–75} ≤ 65% of predicted, <i>n</i> (%)	78 (22.3)	120 (40)	112 (37.3)	0.0001*
FEF _{25–75} > 65% of predicted, <i>n</i> (%)	272 (77.7)	180 (60)	188 (62.7)	0.002*
PC ₂₀ , median [IQR])	4.86 [2.4–7.5]	1.22 [0.6–2.3]	1.32 [0.6–2.3]	<0.001*
BHR ⁺	291 (83.1)	300 (100)	300 (100)	0.09*
Sensitized to perennial allergens pz, <i>n</i> (%)	158 (45.1)	174 (58)	190 (63.3)	0.001*

All percentages in parentheses are calculated over the total number of subjects reported at the top of column. All numbers in brackets represent first to third quartiles.

*Chi-square test.

#Kruskal-Wallis test

BHR = bronchial hyperreactivity; FEF_{25–75} = forced expiratory flow between 25 and 75% of vital capacity; FEV₁ = forced expiratory volume in 1 s; IQR = interquartile range; PC₂₀ = concentration of methacholine required to produce a 20% drop in FEV₁.

justed OR (OR_{Adj}) and 95% confidence interval and was tested by means of the likelihood ratio test. For the analysis, a value of $p < 0.005$ for two-tailed *t*-test was considered significant because of multiple comparison. Otherwise, $p < 0.05$ was considered statistically significant. A statistical software program (StatSoft Italia s.r.l. 2005; Statistica, Vigonza, Italy) was used for all analyses.

RESULTS

Nine hundred fifty children (568 boys and 382 girls) were included in the study. Table 1 shows the demographic and clinical parameters of the patients divided into three groups, according to their pathology: there were 350 patients with allergic rhinitis, 300 patients with allergic asthma, and 300 patients with allergic rhinitis and asthma. Gender did not affect the clinical parameters. All asthmatic children had intermittent asthma. The duration of pathology was significantly shorter in children with rhinitis alone ($p < 0.001$), whereas there was no difference between asthmatic subgroups.

The median forced vital capacity (FVC), FEV₁, and FEF_{25–75} were significantly higher in patients with rhi-

nititis (94, 85, and 71% of predicted, respectively) compared with asthmatic children (92%, 81% and 67% of predicted, respectively) and with children suffering from asthma and rhinitis (89, 80, and 66.5% of predicted, respectively). The difference of median FVC, FEV₁, and FEF_{25–75} were statistically different among the three groups of patients ($p < 0.001$; Kruskal-Wallis test). In particular, children with rhinitis showed the higher values for all spirometric parameters in comparison with the other two subgroups ($p < 0.05$ for both), whereas there was no significant difference between the two asthmatic subgroups.

An FEF_{25–75} ≤ 65% of predicted value was present in 22.3% of patients with rhinitis, in 40% of asthmatic patients and in 37.3% of patients with asthma and rhinitis ($p = 0.0001$; Kruskal-Wallis test). In particular, children with rhinitis had the lower frequency of subjects with impaired FEF_{25–75} values in comparison with the other two subgroups ($p < 0.05$ for both), whereas there was no significant difference between the two asthmatic subgroups.

Children with rhinitis alone had more rarely severe BHR in comparison with the two asthma subgroups ($p < 0.01$), whereas there was no difference between

Table 2 BHR grade distribution in the three subgroups: severe ($PC_{20} < 1$ mg/mL), mild (PC_{20} between 1 and 4 mg/mL), and borderline (PC_{20} ranging from 4.1 to 16 mg/mL)

	$PC_{20} < 1$ mg/mL n (%)	PC_{20} (1–4 mg/dL) n	PC_{20} (4.1–16 mg/dL) n
Patients with rhinitis	47 (13.4)	54 (15.4)	190 (54.2)
Patients with asthma	108 (36)	160 (53.3)	32 (10.6)
Patients with rhinitis and asthma	112 (37.3)	161 (53.6)	27 (9)

BHR = bronchial hyperreactivity; PC_{20} = concentration of methacholine required to produce a 20% drop in FEV_1 ; FEV_1 = forced expiratory volume in 1 s.

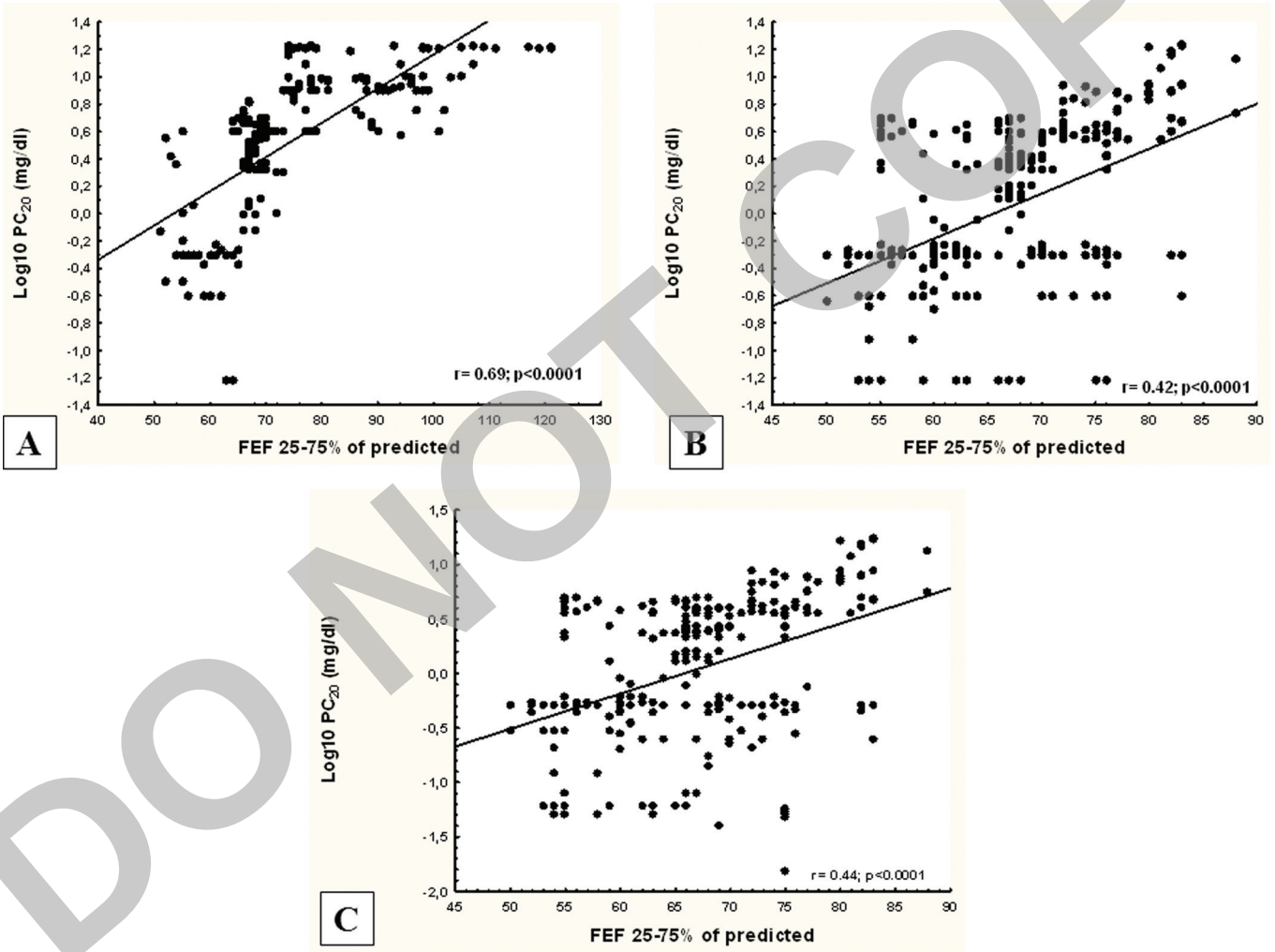


Figure 1. Relationship between forced expiratory flow between 25 and 75% of vital capacity (FEF_{25-75}) values and BHR severity assessed by $\log_{10}$ provocative concentration causing a 20% fall (PC_{20}) in children with (A) allergic rhinitis, (B) asthma, or (C) both.

the two asthma subgroups (Table 2). The FEF_{25-75} values were strongly correlated with BHR severity ($r = 0.69$) in the group of patients with rhinitis and appeared to be moderately related in the groups of patients with asthma and rhinitis and asthma ($r = 0.42$ and 0.44 , respectively) as reported in Fig. 1.

The median and interquartile range of methacholine PC_{20} were higher in children with rhinitis (4.86 mg; 2.4–7.5) than in children with asthma (1.22 mg; 0.6–2.3) and in

children with asthma and rhinitis (1.32 mg; 0.6–2.3). The median PC_{20} was statistically different among the three groups of patients ($p < 0.001$; Kruskal-Wallis test).

For patients suffering from rhinitis, 83.1% had a positive BHR.

The description of sensitizations (seasonal or perennial allergens) in the three groups of patients is shown in Table 1. Significant statistical differences were found between the results ($p < 0.001$; chi-square test): chil-

Table 3 Demographic and clinical parameters in patients with severe BHR ($PC_{20} < 1$ mg/mL) and in patients with BHR of $PC_{20} \geq 1$ mg/mL

	$PC_{20} < 1$ mg/mL	$PC_{20} \geq 1$ mg/mL	<i>p</i> Value
Patients with rhinitis	<i>n</i> = 47	<i>n</i> = 303	
FEF _{25-75%} $\leq$ 65% of predicted	32 (68)	46 (15)	$<0.001^*$
Sensitized to perennial allergens	34 (72.3)	124 (40.9)	0.0001*
Rhinitis duration of ≥ 4 yr	30 (63.8)	55 (18.1)	$<0.001^*$
Gender—males	29 (61.7)	198 (65.3)	NS*
Patients with asthma	<i>n</i> = 108	<i>n</i> = 192	
FEF _{25-75%} $\leq$ 65% of predicted	54 (50)	66 (34.3)	0.008*
Sensitized to perennial allergens	75 (69.4)	99 (51.1)	0.02*
Gender—males	62 (57.4)	110 (57.2)	NS*
Patients with rhinitis and asthma	<i>n</i> = 112	<i>n</i> = 188	
FEF _{25-75%} $\leq$ 65% of predicted	54 (48.2)	60 (31.9)	0.004*
Sensitized to perennial allergens	87 (77.6)	103 (54.7)	0.0001*
Gender—males	67 (59.8)	105 (55.8)	NS*

Values denote *n* (%). All percentages in parentheses are calculated over the total number of subjects reported at top of the column.

*Chi-square test.

BHR = bronchial hyperreactivity; PC_{20} = concentration of methacholine required to produce a 20% drop in FEV₁; FEF₂₅₋₇₅ = forced expiratory flow between 25 and 75% of vital capacity; FEV₁ = forced expiratory volume in 1 s.

dren with rhinitis alone had lower frequency of sensitization to perennial allergens in comparison with the other two groups ($p < 0.05$), whereas there was no difference between the two asthma subgroups. To evaluate possible risk factors for severe BHR, all patients presenting severe BHR (such as $PC_{20} < 1$ mg/mL) for each group of patients were more deeply investigated (Table 3).

Variables, which were statistically significant in the bivariate analysis or that were considered *a priori* important, were entered in the model. Before performing logistic regression, some continuous predictors were dichotomized based on the ROC curve analysis, constructed using the Bamber's criteria.²³ Only the variable duration of rhinitis (≥ 4 years versus < 4 years) for the group of rhinitis patients presented a satisfactory area under the curve (AUC) of 0.79. The following predictors were evaluated in the logistic regression model: rhinitis duration, FEF₂₅₋₇₅ $\leq$ 65% of predicted value, and sensitization to perennial allergens, for rhinitis patients; FEF₂₅₋₇₅ $\leq$ 65% of predicted value and sensitization to perennial allergens, for the other two groups. In the group with rhinitis alone, 68% of patients with severe BHR had an FEF₂₅₋₇₅ $\leq$ 65%, and in the group of patients with asthma, the percentage of subjects with FEF₂₅₋₇₅ $\leq$ 65% and severe BHR was 50%, similar to that of subjects with asthma and rhinitis that found to be 48.2% (Table 3).

Multivariate Logistic Analysis

To evaluate the role of possible predictors for severe BHR ($PC_{20} < 1$ mg/mL), a logistic regression model

was performed for each group of patients (Table 4). Three predictors turned out to be significantly associated with severe BHR for patients with rhinitis: rhinitis duration of > 4 years (OR_{Adj}, 6.4), FEF₂₅₋₇₅ $\leq$ 65% of predicted (OR_{Adj}, 8.9), and sensitization to perennial allergens (OR_{Adj}, 3.2). The model's discriminative ability was very satisfactory (AUC, 0.98).

For the group of patients with asthma and those with asthma and rhinitis, two predictors turned out to be significantly associated with severe BHR: FEF₂₅₋₇₅ $\leq$ 65% of predicted (OR_{Adj}, 1.9 and 2.2, respectively) and sensitization to perennial allergens (OR_{Adj}, 1.5 and 3.1, respectively). The model's discriminative ability was good for both groups (AUC, 0.92 and 0.89, respectively).

DISCUSSION

Allergic rhinitis and asthma may be frequently connected. BHR is a constant physiological characteristic in asthmatic patients and is frequently present also in patients with allergic rhinitis. Allergic inflammation is deeply involved in airways impairment, both in asthma and in allergic rhinitis.^{24,25}

FEF₂₅₋₇₅ measurement may allow detection of early bronchial impairment in patients with allergic rhinitis.²⁶ In this regard, it has been very recently reported that impaired FEF₂₅₋₇₅ value may predict BHR in adults with allergic rhinitis alone.¹⁹ However, this issue has not been considered in children as well as in children with asthma or asthma with allergic rhinitis. Therefore, the present study investigated the possible

Table 4 Best fitting logistic regression models for independent predictors of the presence of severe BHR ($PC_{20} < 1$ mg/mL)

Variables	OR _{Adj}	95% CI	p Value*
Patients with rhinitis			
Rhinitis duration (>4 yr)	6.4	3.3–18.2	<0.005
FEF _{25–75%} ≤65% of predicted	8.9	5.9–17.7	<0.005
Sensitized to perennial allergens	3.2	1.9–6.9	<0.005
			AUC: 0.98
Patients with asthma			
FEF _{25–75%} ≤65% of predicted	1.9	1.3–14.7	<0.005
Sensitized to perennial allergens	1.5	1.2–9.9	<0.005
			AUC: 0.92
Patients with rhinitis and asthma			
FEF _{25–75%} ≤65% of predicted	2.2	1.2–15.7	<0.005
Sensitized to perennial allergens	3.1	1.5–10.9	<0.005
			AUC: 0.89

Outcome variable, severe BHR ($PC_{20} < 1$ mg/mL); AUC of the model, 0.98.

AUC = area under; BHR = bronchial hyperreactivity; CI = confidence interval; FEF_{25–75} = forced expiratory flow between 25 and 75% of vital capacity; OR = odds ratio; PC_{20} = concentration of methacholine required to produce a 20% drop in FEV₁; FEV₁ = forced expiratory volume in 1 s; ROC = receiver operating characteristics.

relationship between FEF_{25–75} and BHR in a large cohort of children with allergic rhinitis, asthma, or both.

First, this study indicated that FVC, FEV₁, and FEF_{25–75} were significantly more impaired in children with allergic asthma and rhinitis than in children with asthma or rhinitis alone. Children with asthma (with or without rhinitis) had more frequently impaired FEF_{25–75} values than children with rhinitis as well as more severe BHR. Interestingly, sensitization to perennial allergens was more frequent in patients with asthma than in children with rhinitis.

Second, some variables were more frequently impaired in children with severe BHR in comparison with other studied children. In particular, lower FEF_{25–75} values and sensitization to perennial allergens (and longer rhinitis duration in children with rhinitis) significantly characterized children with severe BHR.

More interestingly, the logistic regression highlighted that the presence of ≤65% FEF_{25–75} values represented a relevant risk of having severe BHR (OR, 8.9) in children with allergic rhinitis alone. This finding was confirmed by the ROC curve with a fair reliability (AUC, 0.98). Other predictors for severe BHR were rhinitis duration (OR, 6.4) and sensitization to perennial allergens (OR, 3.2).

The predictive role of impaired FEF_{25–75} values for severe BHR was confirmed also in children with asthma, although less significantly: OR, 1.9, in children with asthma and OR, 2.2, in children with asthma and rhinitis. In addition, FEF_{25–75} values were significantly related with the BHR grade, mainly in children with rhinitis. Both findings therefore underline the close link between FEF_{25–75} values and BHR severity.

Therefore, this study substantially confirmed the outcomes of the previous survey¹⁹ conducted on adults with allergic rhinitis, such as the presence of severe BHR may be suspected both in children with asthma and in children with rhinitis if FEF_{25–75} values are ≤65% of predicted. On the other hand, the present study showed that the duration of rhinitis was a more relevant predictive factor for BHR than in adults as well as the presence of sensitization to perennial allergens. These factors might suggest that some difference may exist between childhood allergy and adult allergy. However, additional studies should be conducted to explore this hypothesis.

The findings of this study may be considered robust because the cohort size was large; the BHR prevalence and the impaired lung function confirmed previous studies.^{18,19} The strength of this study is the high OR value; in fact, presence of low FEF_{25–75} values in children with rhinitis constitutes a risk nine times greater of having severe BHR. However, this risk seems slightly inferior in comparison with adult patients.¹⁹ In addition, asthmatic children with impaired FEF_{25–75} values have a double risk for having severe BHR. The clinical relevance of detecting severe BHR allows identifying patients with more serious asthma and, consequently, to adequately treat them.

This study suggests that a simple spirometry may be sufficient to suspect the presence of severe BHR when FEF_{25–75} values are <65% of predicted. The value of this parameter has been recently underlined by a follow-up study that evidenced FEF_{25–75} is the earlier spirometric parameter that worsened in a group of patients with rhinitis alone.²⁷ Thus, FEF_{25–75} values

may predict a possible asthma development and this would be easier and more cost effective than methacholine or other bronchial challenges.

In conclusion, this pediatric study confirmed that impaired FEF₂₅₋₇₅ values might predict severe BHR in children, mainly in those with allergic rhinitis. Therefore, low FEF₂₅₋₇₅ values could suggest BHR in children.

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