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Pulmonary function characteristics in children with suspected asthma: implications for asthma diagnosis

Mireu Park,[1] Yun Young Roh,[1] Ha Min Kim,[1] Jae Hwa Jung,[1] Soo Yeon Kim,[1] Jong Deok Kim,[1] Yong Ju Lee,[2] Min Jung Kim,[2] Yoon Hee Kim,[3] Kyung Won Kim,[1] Myung Hyun Sohn[1]

Abstract

Background: In children suspected of asthma, diagnosis is confirmed via variable expiratory airflow limitation. However, there is no single gold standard test for diagnosing asthma.

Objective: This study aimed to evaluate the pulmonary function characteristics in children suspected of asthma without bronchodilator response (BDR) and bronchial hyperresponsiveness (BHR).

Methods: We utilized two separate real-world retrospective observational cohorts of children who underwent both spirometry and bronchial provocation testing for asthma. Spirometry parameters were collected and compared between definite asthma, probable asthma, and non-asthma groups. The original cohort comprised 1199 children who visited the Severance Hospital (Seoul, Korea) between January 2017 and December 2019. The external cohort included 105 children who visited the Gangnam Severance Hospital between January 2019 and December 2019.

Results: Probable asthma accounted for 16.8% and 32.4% of the original and external cohorts, respectively. This group showed a significantly higher FeNO level and prevalence of allergic sensitization. Baseline forced expiratory volume in 1 second (FEV_1), FEV_1/forced vital capacity (FVC), forced expiratory flow at 25-75% of FVC (FEF_{25-75}), and FEF_{75} showed stepwise decrements from non-asthma, probable asthma, to definite asthma patients ($P < 0.001$). The probable asthma group showed significantly higher odds of abnormal FEV_1/FVC (OR, 2.24 [95%CI, 1.43-3.52]) and FEF_{25-75} (2.05 [1.13-3.73]) than the non-asthma group and lower odds of abnormal FEV_1 (0.05 [0.01-0.19]), FEV_1/FVC (0.27 [0.18-0.41]), FEF_{25-75} (0.17 [0.11-0.28]), and FEF_{75} (0.14 [0.08-0.24]) compared to the definite asthma group. The external cohort was consistent with the original cohort.

Conclusion: We show evidence of airway dysfunction in children for whom a high clinical suspicion of asthma exists without evidence of BDR and BHR. Repeated pulmonary function tests that closely monitor for subtle lung function impairments and active utilization of additional tests, such as allergic screening and FeNO, should be considered to close the gap in diagnosing asthma.

Key word: asthma, children, diagnosis, paediatric, spirometry

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Affiliations:
[1] Department of Pediatrics, Severance Hospital, Institute of Allergy, Institute for Immunology and Immunological Disease, Brain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, Korea
[2] Department of Pediatrics, Yongin Severance Hospital, Institute of Allergy, Institute for Immunology and Immunological Disease, Brain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, Korea
[3] Department of Pediatrics, Gangnam Severance Hospital, Institute of Allergy, Institute for Immunology and Immunological Disease, Brain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, Korea

Corresponding author:
Soo Yeon Kim
Department of Pediatrics, Institute of Allergy,
Severance Children's Hospital,Yonsei University College of Medicine,
50-1, Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
E-mail: sophi1@yuhs.ac

Abbreviations:

BDR	bronchodilator response
BHR	bronchial hyperresponsiveness
MCT	methacholine challenge test
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
FEF_{25-75}	forced expiratory flow at 25-75% of FVC
FEF_{75}	forced expiratory flow at 75% of FVC
PC_{20}	concentration of methacholine causing a 20% decrease in FEV_1

Introduction

Asthma is one of the most common chronic diseases, with a prevalence of 10-15% in children,[1,2] affecting an estimated 5.5 million children in Europe[3] and 6.1 million in the United States.[4] The substantial impact of this disease is illustrated by 43% children suffering asthma attacks experiencing lost schooldays in Europe. Furthermore, asthma accounts for 3.0% of all paediatric hospital admission and 2.8% of all emergency department visits in the United States.[5-7] Guidelines state that asthma is diagnosed by the history of variable respiratory symptoms, such as cough, wheeze, and shortness of breath, together with confirmed variable expiratory airflow limitation.[8-12] For patients with asthma-like symptoms, the first recommended step for confirming the diagnosis is spirometry with bronchodilator response (BDR) testing, requiring an improvement of ≥ 12% in forced expiratory volume in 1 second (FEV_1).[11,13] If there is an unmet improvement, a confirmatory bronchial provocation test is recommended for bronchial hyperresponsiveness (BHR).[11,13] One recent study found that spirometry with BDR testing was insufficient to rule out asthma by showing a negative predictive value of 57.0%, thus suggesting that the bronchial provocation test is a more reliable tool for asthma diagnosis.[14,15] However, even the BHR threshold in the methacholine challenge test (MCT) for asthma diagnosis is still unclear and not uniformly agreed.

Despite the widespread usage of these objective tests, there is no single gold standard test for diagnosing asthma.[16] In addition, many of these tests do not necessarily exclude asthma, even if their results are normal. This complexity of diagnosis and the variable nature of asthma itself contribute to both over- and under-diagnosis of asthma.[16,17] In a similar context, in some regions of real-world practice, asthma remains a clinical diagnosis based on a patient's history, physical examination, and clinical response to a treatment trial. With such a diagnostic limitation of asthma, it has been reported that even when both spirometry and MCT were used, 12-15% of patients are initially misdiagnosed as false negatives.[2,14] Moreover, even among patients who demonstrated normal baseline spirometry without the evidence of BDR or BHR, a highly suspicious group, who were eventually diagnosed with asthma, could be distinguished based on clinical findings.[11,16]

However, studies focusing on pulmonary function characteristics of this patient population – clinically suspicious children who do not meet objective criteria – are scarce. This study aimed to evaluate the baseline spirometry characteristics in children with asthma symptoms who demonstrated negative BDR and BHR. The primary outcome was whether there are any differences in lung function characteristics among children with 'definite', 'probable', and 'non-asthma'. Here, we focused on children with probable asthma, who were labelled as likely asthmatic despite negative BDR and BHR, with the hypothesis that this group may show distinguishable lung function parameters, as well as clinical characteristics.

Methods

Study population and study design

This study included children aged 4-18 years who were first-time referred to a pulmonary outpatient clinic at Severance Children's Hospital for symptoms suggestive of asthma, without any prior asthma maintenance medication, between January 2017 and December 2019 (**Figure 1**). Respiratory symptoms included cough, wheeze, chest tightness or pain, exercise-induced breathing problems, or dyspnoea. Accordingly, children underwent clinical evaluation, including spirometry with BDR testing and impulse oscillometry. Fractional exhaled nitric oxide (FeNO) measurements were performed for children over 8 years of age. When clinically indicated, children also underwent BHR testing either during the same visit or at a follow-up visit within 1 month. At that point, the clinical diagnosis of definite asthma, probable asthma, and non-asthma was made by experienced paediatric pulmonologists based on medical history, clinical examination, and relevant test results, which were then recorded in the medical charts. Children were excluded from the study if they had a known chronic respiratory disease or respiratory tract infection during the 4 weeks prior to the visit.

Among the subjects who were referred for evaluation of suspected asthma, a total of 1199 children who undertook both spirometry with BDR testing and MCT for asthma diagnosis were identified. Each subject's spirometry and oscillometry indices, with the corresponding initial diagnosis by experienced paediatric pulmonologists, were retrospectively collected by separate clinicians, and the latter was regarded as the reference standard for comparison. The pulmonary function characteristics of children with probable asthma were compared to those of the definite and non-asthma groups. The study flow was shown in **Figure 1**.

For the external cohort, we used a separate dataset provided by Gangnam Severance Hospital (Seoul, Korea). This included 105 children aged 4-18 years who were referred for asthma-like symptoms between January 2019 and December 2019 and who underwent both spirometry and MCT to diagnose asthma. Patients in the external cohort were selected based on the same criteria as those in the original cohort, and an experienced pulmonologist determined their asthma diagnosis at that time. All data were anonymised, and a waiver was obtained from the Institutional Review Board of Yonsei University Health System, Severance Hospital for informed consent (approval No. 4-2020-1452).

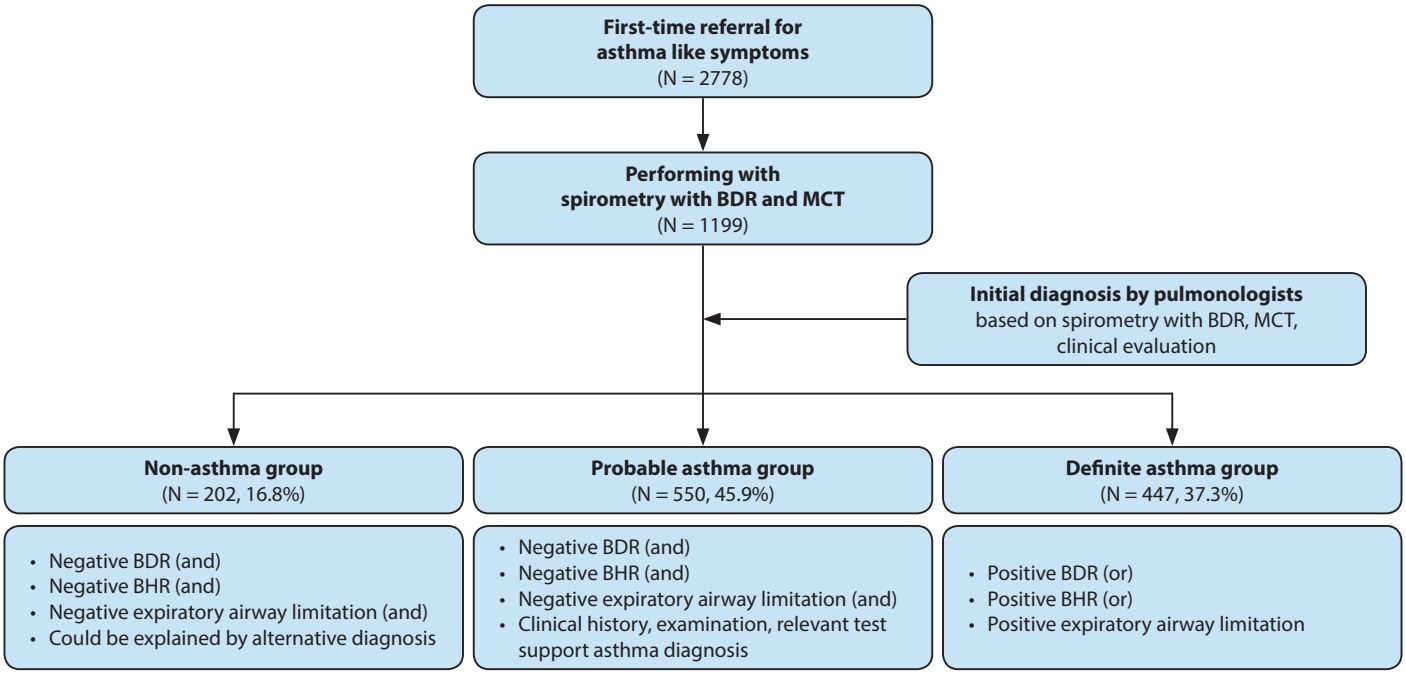

Figure 1. Study flowchart of original cohort.
Expiratory airway limitation defined as reduced $FEV_1/FVC < 0.9$ when FEV_1 < lower limit of normal (z-score < -1.64).
BDR, bronchodilator response; MCT, methacholine challenge test; BHR, bronchial hyperreponsiveness.

Diagnostic tests

1. Spirometry with impulse oscillometry and MCT

Spirometry and MCT were performed with a Jaeger MasterScreen PFT system (Jaeger CO., Würzburg, Germany) according to the American Thoracic Society standards.[18] Pre-bronchodilator spirometry results, including FEV_1, forced vital capacity (FVC), forced expiratory flow at 25–75% of FVC (FEF_{25-75}), and forced expiratory flow at 75% of FVC (FEF_{75}) were expressed as z-scores based on the Global Lung Function Initiative (GLI) 2012 reference standards.[19] For MCT, subjects inhaled increasing doses of methacholine (0.075, 0.15, 0.31, 0.62, 1.25, 2.5, 5, 10, 25, and 50 mg/mL), nebulized by a dosimeter (MB3; Mefar, Brescia, Italy), until FEV1 was reduced by 20% from a post-nebulized saline solution value. The provocative concentration of methacholine that caused a 20% decrease in FEV_1 (PC_{20}) was determined.[20]

Impulse oscillometry was performed with a Jaeger MasterScreen impulse oscillometry system (IOS) (Jaeger CO., Würzburg) in accordance with published guidelines.[21] IOS parameters were recorded, including the mean respiratory resistance at 5 Hz (R5) and 10 Hz (R10), difference between respiratory resistance at 5 and 20 Hz (R5-R20), reactance value at 5 Hz (X5), and reactance area (AX).[22,23]

2. FeNO measurement

FeNO was measured using a CLD 88 analyser (Eco Medics, Durenten, Switzerland) according to standard recommendations.[24] The mean value of the three consecutive measurements was calculated and considered the actual value.

3. Laboratory and allergy screening tests

Complete blood count, including eosinophil count, and total and specific immunoglobulin E (IgE) levels were measured with the ADVIA 2120i haematology system with autoslide (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA) and Pharmacia CAP assay (Uppsala, Sweden), respectively. A specific IgE test was performed for relevant allergens selected by the clinicians. We defined atopy as the presence of at least one positive allergen-specific IgE above the detection threshold (≥ 0.35 KUa/L).

Asthma diagnosis

Following clinical evaluations, including spirometry and MCT, paediatric pulmonologists made an initial diagnosis, according to the criteria below. This clinical diagnosis was regarded as the reference standard.

1. Definite asthma

Subjects were confirmed based on relevant history and physical examination findings with the evidence of variable expiratory airflow limitation demonstrated by one or more of the following:

1.1. Expiratory airflow limitation, defined as reduced $FEV_1/FVC < 0.9$ when FEV_1 < lower limit of normal (z-score < -1.64)[8,25]
1.2. Positive BDR, defined as an increase in FEV_1 of 12% or 200 mL from baseline after bronchodilator inhalation
1.3. Positive BHR, defined as $PC_{20} \leq 16$ mg/mL

2. Probable asthma

This group of patients was such that while the objective criteria mentioned above did not prove variable airflow limitation, the pulmonologists determined that their history, and physical examination findings, and other relevant test results possibly supported asthma diagnosis. The medical history included lower respiratory symptoms including detailed information on wheezing and cough, allergic comorbidity (allergic rhinitis, allergic conjunctivitis, atopic dermatitis, and food allergies), and allergic family history. The relevant test results included allergy screening tests, eosinophil counts, and FeNO measurements, which are associated with atopy.

3. Non-asthma

Subjects without evidence of variable airflow limitation, whose history and examinations did not support asthma diagnosis, and whose symptoms could be explained by alternative diagnosis were labeled as non-asthma. It included cough not due to asthma, including prolonged post-infectious cough and habitual cough, as well as exercise limitation not due to asthma, such as functional symptoms, and allergic rhinoconjunctivitis.

Statistical analysis

Z-scores were calculated and expressed using the Global Lung Function Initiative (GLI) Data Conversion program by the ERS, sourced from the GLI 2012 reference standards. Categorical data were presented as counts and percentages. Continuous data were tested for normality and reported accordingly as the mean (± standard deviations [SDs]). Clinical variables were compared across the classified groups. The Chi-squared test or Fisher's exact test was used to analyse categorical variables, and Student's t-test and ANOVA were adopted for analysing continuous variables. The strength of the associations between the variables was calculated as odds ratios (ORs) and their 95% confidence intervals (CIs) using logistic regression. All statistical analyses were conducted with SPSS Statistics (version 25.0), SAS (version 9.4), and R (version 4.0.1). $P < .05$ was considered statistically significant.

Results

Characteristics of the study population

Of the 1199 children identified, 776 (64.7%) were male, and the mean age was 8.7 years. Asthma was diagnosed in 447 (37.3%) children. In this group, positive BDR was demonstrated in 128 children, positive BHR in 382 children, and expiratory airflow limitation in 78 children. There were 114 patients with both BDR and BHR, 33 patients with BDR and expiratory airway limitation, and 53 patients with BHR and expiratory airflow limitation. Lastly, 28 patients showed both positive BDR and BHR, as well as expiratory airflow limitation. Probable asthma and non-asthma groups accounted for 202 (16.8%) and 550 (45.9%) children, respectively. The demographics and clinical characteristics of each group are depicted in **Table 1**. FeNO measurements and allergy screening tests were performed in 797 (66.4%), and 1175 (97.9%) children, respectively. Compared to those in the probable asthma or definite asthma groups, subjects who belonged to the non-asthma group showed a significantly lower probability of comorbid allergic disease and allergic sensitisations, lower levels of total IgE, as well as blood eosinophils. Across the three groups, PC20 and blood eosinophil count revealed significant stepwise decrement and increment, respectively.

Table 1. Subjects' characteristics from the original cohort (N = 1199).

	Non-asthma (n = 550)	Probable asthma (n = 202)	Definite asthma (n = 447)
Age (years)	9.4 ± 3.2	8.7 ± 3.1*	7.8 ± 2.7†,‡
Sex (% male)	333 (60.5)	140 (69.3)*	303 (67.8)‡
BMI (kg/m^2)	18.4 ± 3.8	18.5 ± 4.2	17.6 ± 3.2†,‡
Presence of comorbid allergic disease, n (%)	297 (53.5)	144 (71.3)*	320 (71.6)‡
Allergic sensitization, n (%)	241 (43.8)	149 (73.8)*	347 (77.6)‡
FeNO (ppb)	13.1 ± 11.5	18.4 ± 17.0*	24.2 ± 21.4‡
MeCh PC_{20} (mg/mL)	48.36 ± 5.82	40.33 ± 12.9*	11.79 ± 13.13†,‡
Total IgE (kU/L)	265.9 ± 442.6	416.4 ± 645.5*	442.2 ± 568.5‡
Blood eosinophil count (cells/μL)	225.0 ± 226.0	335.0 ± 275.0*	416.0 ± 353.0†,‡

Table 1. (Continued)

	Non-asthma (n = 550)	Probable asthma (n = 202)	Definite asthma (n = 447)
Spirometry indices			
FEV_1, z-score	0.39 ± 1.04	0.07 ± 1.00*	-0.47 ± 1.25†,‡
FEV_1, % predicted	104.3 ± 11.6	100.9 ± 11.29*	94.69 ± 14.2†,‡
FEV_1/FVC, z-score	-0.32 ± 1.02	-0.67 ± 1.05*	-1.45 ± 1.16†,‡
FEV_1/FVC, ratio	0.88 ± 0.05	0.86 ± 0.06*	0.82 ± 0.08†,‡
FEF_{25-75}, z-score	-0.04 ± 1.01	-0.45 ± 0.97*	-1.32 ± 1.26†,‡
FEF_{25-75}, % predicted	100.0 ± 21.6	91.3 ± 20.4*	74.3 ± 24.7†,‡
FEF_{75}, z-score	-0.10 ± 1.07	-0.46 ± 0.99*	-1.35 ± 1.33†,‡
FEF_{75}, % predicted	100.4 ± 30.5	90.1 ± 27.2*	70.7 ± 30.0†,‡
Impulse oscillometry parameters			
AX, kPa/L	2.10 ± 1.50	2.54 ± 1.75*	3.29 ± 1.90†,‡
R5-R20, kPa/(L/s)	0.59 ± 0.17	0.63 ± 0.18	0.70 ± 1.78†,‡
R20, % predicted	90.26 ± 19.54	90.12 ± 22.47	91.53 ± 20.04
R5, % predicted	104.87 ± 21.84	108.09 ± 24.88	116.64 ± 25.34†,‡
X5, % predicted	78.90 ± 43.32	83.34 ± 53.46	111.43 ± 54.58†,‡

*Non-asthma vs. Probable asthma: $P < 0.05$.
†Probable asthma vs. Definite asthma: $P < 0.05$.
‡Non asthma vs. Definite asthma: $P < 0.05$.
BMI, Body Mass Index; FeNO, Fractional exhaled Nitric Oxide; MeCh PC_{20}, Provocation concentration of methacholine HCl associated with a 20% decrease in FEV_1; IgE, Immunoglobulin E; AX, Area of reactance; R5, Resistance at 5 Hz; R20, Resistance at 20 Hz; X5, Reactance at 5 Hz

Difference in spirometry indices

Figure 2 represents the distribution of z-scores of each spirometry indices according to classified groups. Parameters, including FEV_1, FEV_1/FVC, FEF_{25-75}, and FEF_{75}, showed a statistically significant gradual decrease in order from non-asthma, probable asthma, to definite asthma. The number of children from the original cohort with abnormal FEV_1/FVC was 53 (9.6%) in the non-asthma group, 39 (19.3%) in the probable asthma group, and 209 (46.8%) in the definite asthma group. Children categorized as having probable asthma evidenced abnormally low values for FEF_{25-75} (9.9%) and FEF_{75} (8.4%). Compared with the probable asthma group, the non-asthma group had a lower proportion of children with abnormal FEF_{25-75} (5.1%) and FEF_{75} (6.5%) values, whereas the definite asthma group showed a higher proportion of children with abnormally low FEF_{25-75} and FEF_{75} values (38.9% and 39.8%, respectively). Subgroup analyses performed in different age groups (4–6, 6–12, and 12–18 years of age), consistently demonstrated stepwise lung function decline.

Consistent findings were shown when the results were analyzed with the lung function indices presented as percent predicted values. All the parameters, including FEV_1, FEV_1/FVC, FEF_{25-75}, and FEF_{75}, showed a significant stepwise decrease from the non-asthma, probable asthma, to definite asthma group (**Figure 2**). The probable asthma group showed significantly higher odds of having abnormal FEV_1, FEV_1/FVC, FEF_{25-75}, and FEF_{75} compared to the non-asthma group, and significantly lower odds of having abnormal FEV_1, FEV_1/FVC, FEF_{25-75}, and FEF_{75} compared to the definite asthma group (**Table 2**).

The strength of associations between abnormal spirometry indices and classified groups is shown in **Figure 3**. Compared to the non-asthma group, the definite asthma group showed significantly higher odds of exhibiting abnormal FEV_1 (OR 9.77, [95%CI, 5.25-18.19]), FVC (2.46, [1.41-4.30]), FEV_1/FVC (8.24, [5.87-11.55]), FEF_{25-75} (11.88 [7.77-18.18]), and FEF_{75} (9.45, [6.41-13.92]). Subjects with probable asthma showed significantly higher odds for having abnormal FEV_1/FVC (2.24, [1.43-3.52]) and FEF_{25-75} (2.05, [1.13-3.73]) than those in the non-asthma group. Moreover, in comparison between probable asthma and definite asthma, the latter group revealed significantly higher odds for abnormal FEV_1 (21.80, [5.30-89.60]), FEV_1/FVC (3.67, [2.47-5.45]), FEF_{25-75} (5.80, [3.52-9.56]), and FEF_{75} (7.20, [4.23-12.25]).

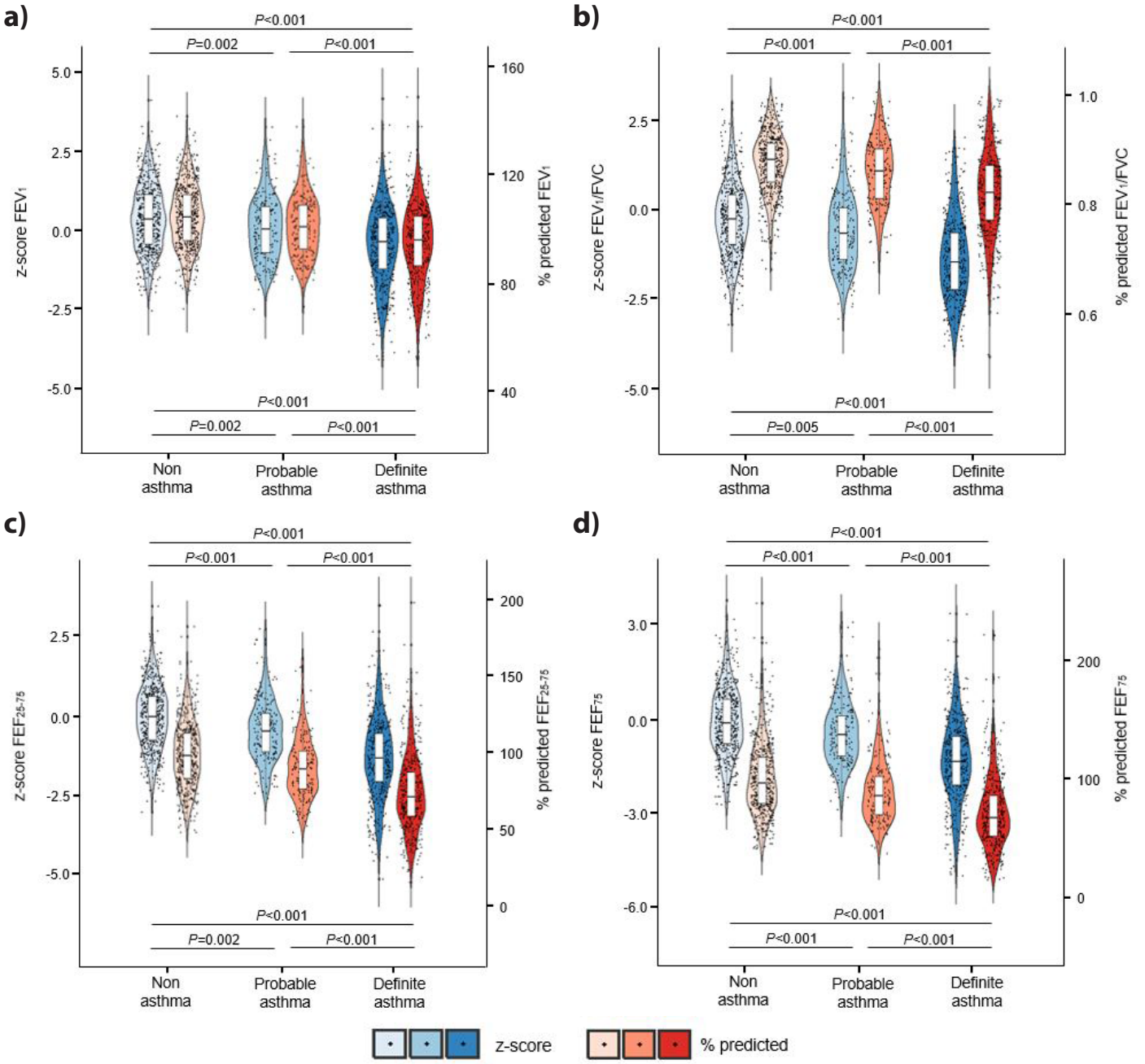

Figure 2. Differences in spirometry indices (original cohort).
Violin plots indicate the median (horizontal line inside the box) and interquartile range (box). The blue colored plots expressed relevant indices as z-score, and the red colored plots as % predicted. *P* values for paired comparisons were obtained with the Kruskal-Wallis/Dunn's test. a) FEV_1, b) FEV_1/FVC, c) FEF_{25-75}, and d) FEF_{75} show a significant stepwise decrease in order from non-asthma, probable asthma, to definite asthma.
Upper row *P* values are for indices of z-score, while lower row *P* values are for % predicted values.
FEV_1, forced expiratory volume in 1s; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow at 25-75% of FVC; FEF_{75} forced expiratory flow at 75% of FVC

Table 2. Risk of abnormal spirometry indices, presented as % predicted (original cohort).

Non-asthma versus Definite asthma	Odds ratio	95%CI	*P* value
FEV_1 < 80% predicted	11.20	5.29-23.71	< 0.001
FEV_1/FVC ratio < 0.8	6.57	4.56-9.48	< 0.001
FEV_1/FVC, ratio < 0.9	3.44	2.51-4.72	< 0.001
FEF_{25-75} < 80% predicted	5.52	4.19-7.27	< 0.001
FEF_{75} < 80% predicted	4.99	3.69-6.75	< 0.001

Table 2. (Continued)

Non-asthma versus Probable asthma	Odds ratio	95%CI	*P* value
FEV_1 < 80% predicted	4.69	1.94-11.35	< 0.001
FEV_1/FVC ratio < 0.8	2.53	1.59-4.02	< 0.001
FEV_1/FVC, ratio < 0.9	1.53	1.09-2.15	0.014
FEF_{25-75} < 80% predicted	2.14	1.55-2.97	< 0.001
FEF_{75} < 80% predicted	2.23	1.60-3.10	< 0.001
Probable asthma versus Definite asthma	**Odds ratio**	**95%CI**	***P* value**
FEV_1 < 80% predicted	9.82	3.53-27.25	< 0.001
FEV_1/FVC ratio < 0.8	3.42	2.22-5.27	< 0.001
FEV_1/FVC, ratio < 0.9	2.65	1.77-3.95	< 0.001
FEF_{25-75} < 80% predicted	3.31	2.34-4.67	< 0.001
FEF_{75} < 80% predicted	2.65	1.81-3.90	< 0.001

FEV_1, forced expiratory volume in 1s; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow at 25-75% of FVC; FEF_{75} forced expiratory flow at 75% of FVC

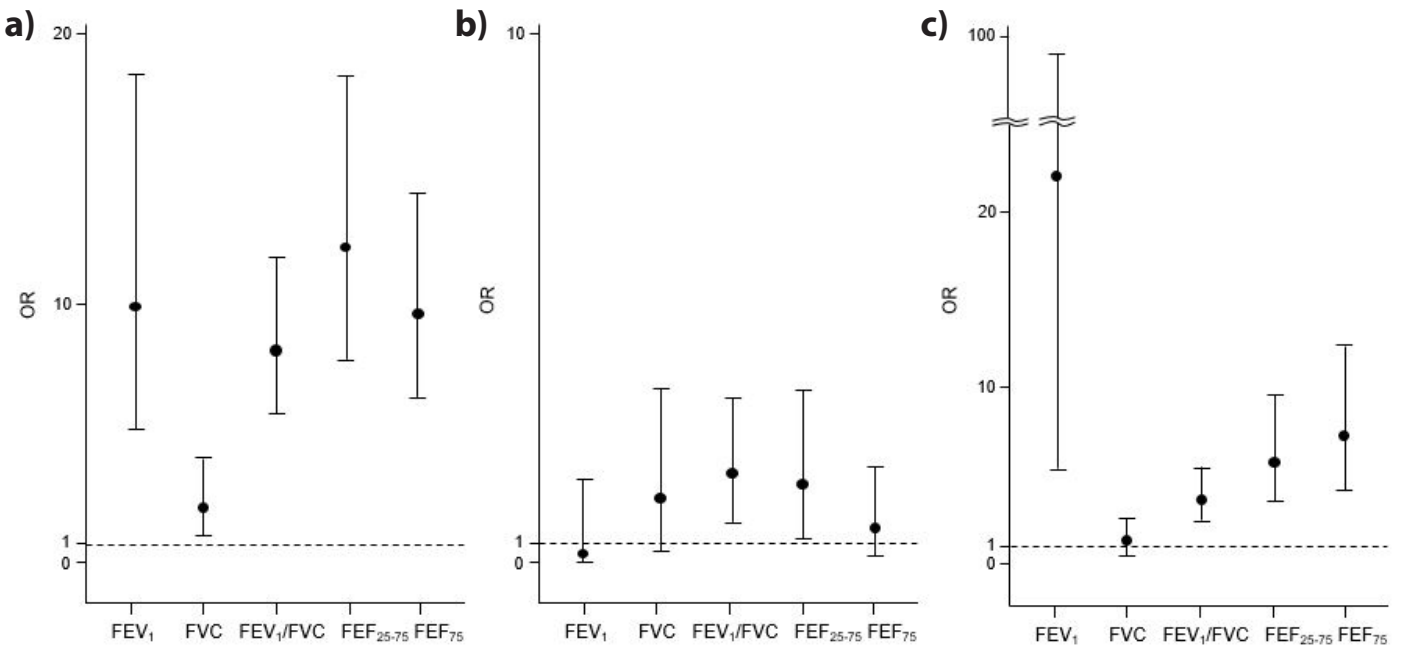

Figure 3. Risk of abnormal spirometry indices (original cohort).
Forest plots indicate the odds ratios (closed circles) for having abnormal spirometry indices less than the lower limit of normal and the whiskers (95% confidence interval).

a) Non-asthma versus Definite asthma
Compared to the non-asthma group, the definite asthma group showed significantly higher odds for having abnormal FEV_1 (OR 9.77, [95%CI, 5.25-18.19]), FVC (2.46, [1.41-4.30]), FEV_1/FVC (8.24, [5.87-11.55]), FEF_{25-75} (11.88 [7.77-18.18]), and FEF_{75} (9.45, [6.41-13.92]).

b) Non-asthma versus Probable asthma
Compared to the non-asthma group, the probable asthma group showed significantly higher odds for having abnormal FEV_1/FVC (2.24, [1.43-3.52]) and FEF_{25-75} (2.05, [1.13-3.73]).

c) Probable asthma versus Definite asthma
Compared to the probable asthma group, the definite asthma group showed significantly higher odds for having abnormal FEV_1 (21.80, [5.30-89.60]), FEV_1/FVC (3.67, [2.47-5.45]), FEF_{25-75} (5.80, [3.52-9.56]), and FEF_{75} (7.20, [4.23-12.25]).

OR, Odds ratio; FEV_1, forced expiratory volume in 1s; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow at 25-75% of FVC; FEF_{75} forced expiratory flow at 75% of FVC

Difference in IOS parameters

Oscillometry parameters for 1188 subjects are presented in **Table 1**. AX showed a positive incremental progression from non-asthma, probable asthma, and definite asthma. Except for R20, which showed no difference among the three groups, R5, R5-R20, and X5 were significantly elevated in the definite asthma group compared to the probable asthma group.

External validation for difference in spirometry indices

From a separate dataset of 105 subjects, 24 (22.8%) were categorized as non-asthma, 34 (32.4%) as probable asthma, and 47 (44.8%) as definite asthma (**Table 3**). The overall presence of comorbid allergic disease and allergic sensitisation was higher in this cohort. When spirometry indices were plotted and compared according to the categorized groups, FEV_1, FEV_1/FVC, FEF_{25-75}, and FEF_{75}

Table 3. Subject's characteristics from the validation cohort (N = 105).

	Non-asthma (n = 24)	Probable asthma (n = 34)	Definite asthma (n = 47)
Age (years)	10.4 (7.6, 14.0)	10.6 (8.5, 13.9)	9.6 (7.6, 13.1)
Male sex, no (%)	17 (70.8)	17 (50.0)	32 (68.1)
BMI, kg/m^2	17.9 (16.1, 19.2)	19.7 (17.3, 21.5)	18.9 (16.1, 21.8)
Presence of comorbid allergic disease, n (%)	20 (83.3)	30 (88.2)	38 (80.9)
Sensitization, no (%)	12 (50.0)	27 (79.4)*	42 (89.4)‡
FeNO, ppb (n = 100)	11.0 (7.0, 17.5)	29.0 (15.0, 56.0)*	27.0 (15.0, 49.0)‡
MeCh PC_{20} (mg/mL)	N/A	N/A	5.9 (2.4, 10.6)†,‡
Total IgE level, kU/L (n = 88)	96.7 (19.0, 326.5)	157.5 (51.0, 634.0)	334.5 (202.0, 811.0)‡
Blood eosinophil count, cells/μL (n = 96)	175.0 (110.0, 230.0)	240.0 (170.0, 450.0)	325.0 (190.0, 465.0)‡

N/A, When a 20% drop in FEV_1 (PC_{20}) did not appear up to 16 mg/mL, methacholine challenge test was stopped, and determinant dose of PC_{20} was not measured in this cohort.
*Non-asthma vs. Probable asthma: $P < 0.05$.
†Probable asthma vs. Definite asthma: $P < 0.05$.
‡Non asthma vs. Definite asthma: $P < 0.05$.
BMI, Body Mass Index; FeNO, Fractional exhaled Nitric Oxide; MeCh PC_{20}, Provocation concentration of methacholine HCl associated with a 20% decrease in FEV_1; IgE, Immunoglobulin E

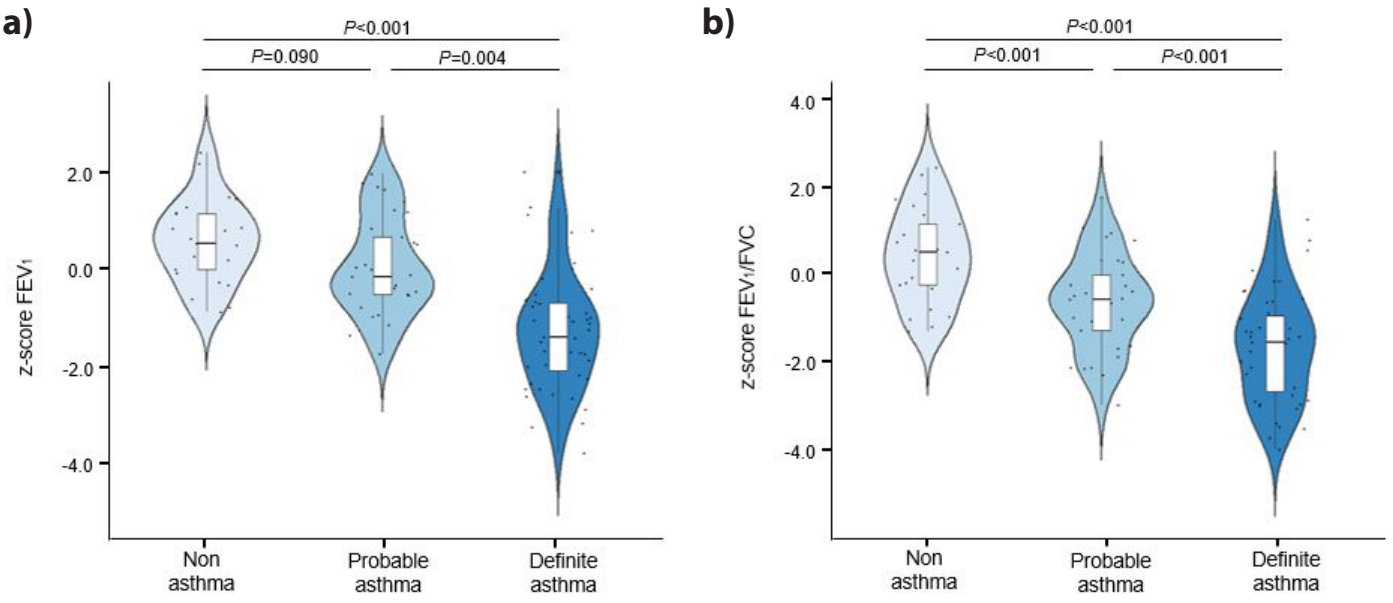

Figure 4. Differences in spirometry indices (validation cohort).
Violin plots indicate the median (horizontal line inside the box) and interquartile range (box). *P* values for paired comparisons were obtained with the Kruskal-Wallis/Dunn's test. a) FEV_1, b) FEV_1/FVC, c) FEF_{25-75}, and d) FEF_{75} show a significant stepwise decrease in order from non-asthma, probable asthma, to definite asthma.
FEV_1, forced expiratory volume in 1s; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow at 25-75% of FVC; FEF_{75} forced expiratory flow at 75% of FVC

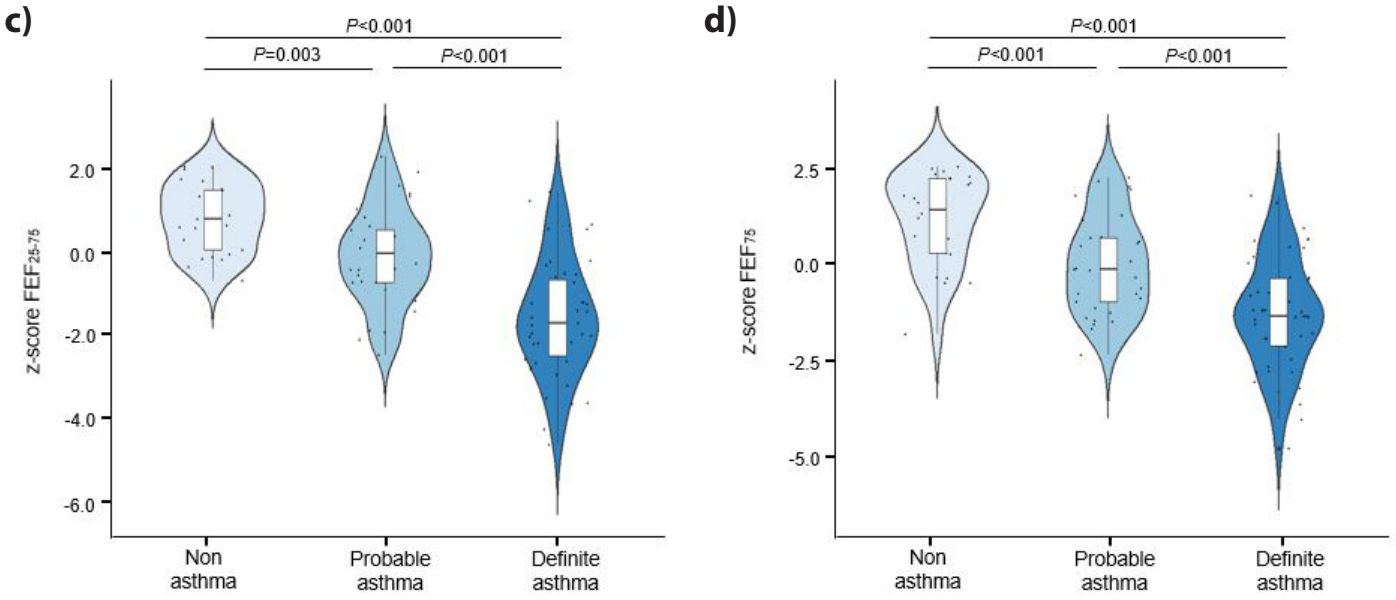

Figure 4. (Continued)

showed a gradually decreasing trend from non-asthma, probable asthma, to definite asthma (**Figure 4**). The number of children with an abnormal FEV_1/FVC ratio was 0 (0%) in the non-asthma group, 7 (21.2%) in the probable asthma group, and 22 (46.8%) in the definite asthma group. In the probable asthma group, abnormally low FEF_{25-75} and FEF_{75} values (12.1% and 9.1%, respectively) were found. Compared with the probable asthma group, a higher proportion of children with abnormal FEF_{25-75} (38.3%) and FEF_{75} (53.2%) values were found in the definite asthma group. No children were identified as abnormal for corresponding values in the non-asthma group.

When the optimal cutoff values were determined to differentiate between the probable and definite asthma groups, the z-score value for FEV_1 was -0.098, as well as for FEV_1/FVC was -1.340, both of which were higher than the lower limit of the normal value. The corresponding area under the curve (AUC) values were 0.566 and 0.666, respectively, from the original cohort, and 0.691 and 0.679, respectively, from the validation cohort. FEV_1 displayed a relatively high sensitivity of 0.851, and FEV_1/FVC showed a relatively high specificity of 0.765 from the validation cohort.

Discussion

This study clearly showed differentiated lung function parameters in subjects with probable asthma, compared to those with definite asthma and non-asthmatics. Spirometry indices, such as FEV_1, FEV_1/FVC, FEF_{25-75}, and FEF_{75} of subjects with probable asthma, were significantly lower than those with non-asthma and higher than those with definite asthma from two separate cohorts. Among IOS parameters, the probable asthma group showed significantly higher AX compared to the non-asthma group and lower AX, R5-R20, and X5 than the definite asthma group.

Diagnosing asthma in children remains challenging, since relevant respiratory symptoms are not specific to asthma and may vary over time.[16] There is no stand-alone diagnostic test, and the interpretation of existing tests is complicated by the temporal variability and phenotypic heterogeneity of asthma.[26] International guidelines advise that asthma diagnosis be based on a characteristic pattern of respiratory symptoms, clinical examination, and demonstration of reversible airway obstruction.[8-12] Recently, diagnosis has been encouraged to encompass more objective tests within the diagnostic process.[8,10,11] However, different national and international diagnostic algorithms still present conflicting advice,[8-12] reflecting ongoing debate concerning optimal diagnostic strategies for childhood asthma.[11,16] The methods and order of the tests and even the criteria to determine variable airflow limitation, which comprise a critical component of asthma, are not consistently standardized among current guidelines.[8-13,16,27] This discrepancy also applies to the need for follow-up tests and their intervals. The role of additional tests, such as FeNO, blood eosinophils, and allergy screening tests, is differently highlighted.[28] In addition, children with physician-diagnosed asthma could be easily made in primary health care, with limited access to the tests mentioned above.[29,30] Accordingly, misdiagnosis of asthma is also known to be common.[1,17,30,31] However, over-diagnosis of asthma leads to unnecessary treatment and a delay in making an alternative diagnosis, while under-diagnosis risks daily symptoms, potentially serious exacerbations, and long-term airway remodelling.[16]

Furthermore, in real practices, we frequently meet some patients under the process of asthma diagnosis, who do not yet meet objective criteria but can be labelled as probable asthma. However, there is little literature focused on these populations, while most publications have adopted a case-control design, comparing children who are already confirmed as having asthma to healthy controls.[32]

A recent observational study by de Jong et al. utilized the Swiss Paediatric Airway Cohort and included children referred to a pulmonary outpatient clinic for evaluation of suspected asthma. They found that 19% of children were categorized as probable cases of asthma by pulmonologists.[33] Here, we reported a similar proportion of probable asthma cases from the two independent cohorts, which accounted for a significant proportion of the children suspected of having asthma.

This study focused on the characteristics of children with probable asthma and found that they already have some degrees of airflow limitation compared to those diagnosed with non-asthma upon first-time referral. While the probable asthma group did not meet any objective criteria of expiratory airflow limitation, BDR, and BHR, their initial spirometry, as well as impulse oscillometry, revealed consistently significant impairment through several indices compared to those in the non-asthma group. Mean z-scores of FEV_1/FVC, FEF_{25-75}, and FEF_{75} were below 0 in the probable asthma group from both independent cohorts. Moreover, the probable asthma group included a significantly large number of children with abnormal spirometry parameters, which can be defined as below -1.64, from the aforementioned indices. For instance, the number of children with abnormal FEV_1/FVC was 53 (9.6%) in the non-asthma group, 39 (19.3%) in the probable asthma group, and 209 (46.8%) in the definite asthma group from the original cohort. Likewise, for FEF_{25-75} and FEF_{75}, 9.9% and 8.4% of children categorized as probable asthma from the original cohort, respectively, showed abnormally low values, which were similar to the validation cohort (12.1% and 9.1%, respectively).

These findings may support the limited usefulness of standard tests, as well as existing arbitrary criteria, in asthma diagnosis. While spirometry with BDR and BHR tests are the two quantitative methods most commonly used to confirm asthma diagnosis, major international guidelines differ in their diagnostic algorithms and thresholds.[8-12] In addition, recent studies have demonstrated that spirometry with BDR testing alone is insufficient to rule out asthma and has documented MCT reliability issues characterized by high false negative rates.[14] Likewise, diagnosing asthma in children is not straightforward, and it partly remains a clinical diagnosis, incorporating a detailed history, examination, physiologic tests, and possibly trials of treatments.[32] In this regard, clinical characteristics and information of children with probable asthma may provide a clue to us. In our study, the probable asthma group showed a higher percentage with the presence of comorbid allergic disease and atopy, higher levels of serum total IgE, blood eosinophils, and FeNO, compared to those with non-asthma from the original cohort. Among them, atopy and FeNO were also significantly elevated in the validation cohort. These results could be interpreted as the distinct characteristics that may differentiate children with probable asthma from those with non-asthma. This finding could also strengthen the value of incorporating additional examinations in diagnosing asthma.[34] Additional examinations such as FeNO and allergy screening tests should be actively incorporated into clinical diagnosis since children with probable asthma in this study were found to already show subtle but significant decreases in lung function compared to those with non-asthma. Moreover, repetitive pulmonary function tests may be needed to overcome the limitations of the current asthma diagnosis mentioned above.

The strength of our study is that the included study population is representative of the daily paediatric clinical practice. All of them were steroid naïve, referred for evaluation of suspect asthma for the first time, and performed a diverse array of diagnostic tests attended by paediatric pulmonologists. This observational design might be suitable for clarifying paediatric patient with highly suspicious symptoms and yet present with unclear asthma diagnoses. In addition, our findings were replicated from the separate independent cohort, which may provide evidence to generalise the high prevalence of children with probable asthma and their discernible clinical and lung function characteristics.

We also acknowledge several fundamental limitations in this study. First, we neither could longitudinally follow the subject and collect the response to treatment trials, nor temporal variations of repeated test results. Some proportion of probable asthma could later be confirmed as asthma, while some may not, and there is a possibility that this group is a mixture of true asthma and non-asthma. Second, due to the limited and unstandardized content of the medical records, we could not delineate the factors that contributed to the clinical judgments of pulmonologists when they categorized the patients as having probable asthma. Individual histories regarding relevant symptoms or findings of physical examinations might affect the clinician's asthma diagnosis in everyday practice, which could not be evaluated due to our retrospective study design.

However, our findings clearly demonstrated that some children who were initially labelled as probable asthma already have distinctively lower lung function parameters and higher levels of FeNO, allergic comorbidity, and atopy, despite not meeting current objective criteria for asthma diagnosis. Therefore, our study contributes to the small body of evidence on the current limitations of asthma diagnosis and highlights the need for taking a more detailed history, careful interpretation of test results, and incorporation of additional tests, such as FeNO and allergy screening tests, to overcome it. For children with probable asthma having atopy and elevated FeNO, repeated pulmonary function tests might have a role in this regard. The next step in the research should be directed to the follow-up progress of this group of children, including their lung function trajectories, which may provide us an opportunity to achieve a more accurate and standardized approach for asthma diagnosis.

Conclusion

In real-world clinical practice, there is a group of children who have a high clinical suspicion of asthma but do not meet the current diagnostic criteria. This study demonstrates that this group, defined as the probable asthma group, does exist and shows objective evidence of airway dysfunction. To close this gap in diagnosing asthma, repeated pulmonary function tests that closely monitor for subtle lung function impairments, as well as active utilization of additional tests, such as allergic screening and FeNO, should be considered.

Author contributions

- Soo Yeon Kim contributed in conceptualization, formal analysis, funding acquisition, project administration, supervision, and writing - review & editing.
- Mireu Park contributed in conceptualisation, data curation, investigation, methodology, writing – original draft, and writing – review & editing.
- Yun Young Roh, Ha Min Kim, and Jae Hwa Jung contributed in data curation, and writing – review & editing.
- Jong Deok Kim, Yong Ju Lee, Min Jung Kim contributed in conceptualization, data curation, and writing - review & editing.
- Yoon Hee Kim contributed in conceptualization, data curation, validation, and writing - review & editing.
- Kyung Won Kim and Myung Hyun Sohn contributed in conceptualisation, data curation, funding acquisition, and writing - review & editing.
- All authors read and approved the final manuscript.

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Conficts of interest

The authors have no financial relationships relevant to this article to disclose and indicate no potential conflict of interests.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical statement

All data were anonymised, and a waiver was obtained from the Institutional Review Board of Yonsei University Health System, Severance Hospital for informed consent (approval No. 4-2020-1452).

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