

Predictor of recurrent exacerbations in pediatric asthma

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ABSTRACT

BACKGROUND Asthma imposes a heavy morbidity burden during childhood. Severe persistent asthma significantly increases patients' risk of exacerbations, hospital admissions, and mortality and often substantially impairs their quality of life. This study aimed to identify high-risk patients for exacerbation recurrence using spirometric parameters.

METHODS A prospective cohort study involving patients with asthma aged 6–15 years was conducted at the principal children's hospital in Mekong Delta, Vietnam, from June 2020 to June 2022. Demographic, clinical, and lung function characteristics of the patients were collected. Spirometry measurement parameters were utilized as predictive factors for the short-term asthma exacerbation recurrence.

RESULTS Among all patients (mean age of 9.5 years old), 10.4% experienced recurrent exacerbations. FEV₁, FVC, FEV₁/FVC, FEF_{25–75}, FEF_{25–75}/FVC, and PEF, gradually decreased with increasing exacerbation severity ($p < 0.01$). All patients showed a positive bronchodilator responsiveness (BDR), with a mean value of 16.85 (3.00)%, which was significantly different between the severe and non-severe asthma groups (20.53 [2.83] versus 16.00 [2.35], $p < 0.001$). After adjusting in multivariable logistic regression, a BDR $\geq 20\%$ was identified as the sole independent factor associated with an increased risk of asthma exacerbation recurrence (aOR 6.95, 95% CI 1.08–44.75, $p = 0.041$).

CONCLUSIONS A high BDR can serve as a predictor of acute asthma exacerbation recurrence.

KEYWORDS asthma, children, exacerbation, prognosis, spirometry

Asthma, a widespread and chronic condition, impacts an estimated 262 million people globally and significantly contributed to 21.6 million disability-adjusted life years in 2019.¹ This ailment significantly affects global health, reducing the quality of life (QoL) and early mortality across diverse age groups. Asthma is the 34th leading cause of disease burden worldwide and the 24th most common cause of years lived with disability.² In Vietnam, approximately 5% of

the population was affected by asthma in 2010,³ with the prevalence in children ranging from 4–8% and varying by region.⁴ The International Study of Asthma and Allergies in Childhood Phase Three study revealed that the asthma prevalence in Vietnamese children aged 6–7 and 13–14 years was 10–20% and $\geq 20\%$, respectively. Notably, the prevalence of severe asthma was $>7.5\%$ in the 13–14 year age group.⁵ The Global Burden of Disease Study 2019 data indicated that the

prevalence of asthma was highest in countries with a high sociodemographic index (SDI), while mortality rates were higher in low- and middle-SDI countries, with total deaths near 500,000.¹

Asthma exacerbations can significantly increase hospitalization rates, especially in patients with severe disease who do not respond to systemic steroids and beta-2 agonist nebulization, which is a life-threatening condition. Environmental triggers, allergens, infections, and non-compliance with asthma management plans are among the factors leading to asthma exacerbations.^{6,7} Hospitalization rates due to acute asthma episodes vary significantly between and within countries.⁸ Patients with severe persistent asthma ($\leq 10\%$) have increased risks of exacerbations, hospital admissions, and mortality and typically have a markedly reduced QoL.⁹ Approximately, 7.3% of patients with asthma have severe disease. The severity of the condition is underscored by its mortality rate, which ranges from 11.3 to 14.8 per 1,000 person-years and increases to 14.1 to 59.9 per 1,000 person-years following a severe asthma exacerbation.¹⁰ Effective asthma management and disease control is possible through understanding asthma pathophysiology and monitoring of the disease. Achieving ideal disease control, preventing major exacerbations, and preserving lung function are the basic objectives of successful management. Monitoring a patient's condition guarantees disease control. The frequency and severity of symptoms (as reported by the patient, parents, or through specific scores) are considered, while measurable indicators such as spirometry parameters, airway hyperresponsiveness, and inflammatory markers are used for asthma surveillance.¹¹ In low- and middle-income countries with limited access to modern techniques, spirometry is considered the most common and useful test for the diagnosis, prognosis, and management of asthma. It is widely used to evaluate lung function and offers unbiased data for diagnosing respiratory disorders and preserving lung health.¹²

Although primary care physicians and pediatricians underutilize spirometry, it remains a valuable diagnostic and monitoring tool for several pediatric respiratory problems, including asthma. Modern computerized spirometry equipment, updated with current regional reference values, has become increasingly available.¹³ This study aimed to evaluate whether spirometry

parameters can predict short-term recurrences of pediatric asthma exacerbations.

METHODS

Study design and participants

This prospective cohort study included pediatric patients with asthma admitted to the emergency department (ED) of the largest central children's hospital in Mekong Delta, Vietnam, from June 2020 to June 2022. This study included patients aged 6–15 years who required treatment and hospitalization for acute asthma exacerbation. The decision to hospitalize was made based on the patient's clinical condition, lung function, response to medication, current and previous history of exacerbations, and ability to manage the disease at home.⁶

The single proportion estimation formula was used to accurately determine the sample size necessary for estimating the proportion of recurrent asthma exacerbations.¹⁴ This approach used the 5.4% prevalence rate for recurrent exacerbation, as reported in a prior study,¹⁵ and factored in a 5% margin of error with a 95% confidence interval (CI) ($\alpha = 0.05$). Consequently, a sample size of 79 participants was determined to be adequate for estimating the prevalence of recurrent asthma exacerbations using these parameters.

Asthma was defined as having been diagnosed by a pediatrician or at least two previous episodes of flare-up symptoms requiring primary care visits and reliever medication.^{6,7} Patients with any contraindications to reliever medication, pre-existing comorbidities including congenital pneumonia or cardiovascular disease, and those who did not meet the criteria for acceptability and repeatability of spirometry data following the 2019 American Thoracic Society (ATS)/European Respiratory Society (ERS) guidance were excluded from this study.¹²

Data collection

Demographic, clinical, and lung function characteristics of the participants, such as age, sex, severity of asthma exacerbation, history of past ED visits, length of time from admission to initial relief, pediatric asthma score (PAS), and spirometry measurements, were collected. The severity of asthma exacerbations was evaluated at admission following the guidance of Global Initiative for Asthma (GINA) 2019.⁶

The PAS was calculated using five components: respiratory rate, oxygen requirements, auscultation, retractions, and dyspnea. Each component was scored from 0 to 3, and component scores were summed to determine the total PAS.^{16,17} The PAS was used to assess the clinical status of patients during hospitalization, including every hour during the first 12 hours after admission, to determine the time of initial relief from the asthma exacerbation. The term “initial” was used to distinguish it from other subsequent exacerbations (if any). Asthma exacerbations were defined as when the PAS score dropped below four, and reliever medication was administered as needed to provide initial relief.

Data from spirometry measurements were collected within 24 hours of initial relief after withholding the bronchodilator medication. During spirometry, the patient was monitored by a pulmonologist, and reliever medication was available. The PAS was used to determine the best time to perform spirometry without aggravating the patient’s condition. These parameters included forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}), FEF_{25-75} correction for lung volume (FEF_{25-75}/FVC), and peak expiratory flow (PEF). These spirometry measurements used prebronchodilator values. The bronchodilator responsiveness (BDR) was based on the change in FEV_1 from baseline, calculated as $BDR = (\text{postbronchodilator } FEV_1 - \text{prebronchodilator } FEV_1) / (\text{prebronchodilator } FEV_1) \times 100$ (Equation 1). According to GINA 2019, a positive BDR was defined as an increasing $FEV_1 \geq 12\%$ of the predicted value in the pediatric population.⁶ In this study, lung function assessments used the KoKo Sx 1000 Spirometer (nSpire Health, USA). The predicted values for spirometry measurements were derived from the Global Lung Function Initiative 2012, and all pulmonary function test protocols were performed following the ATS and ERS guidelines.¹²

The spirometry measurement parameters were used as predictive factors. There were no published recommendations regarding the abnormal values of these parameters in children with acute asthma after relief from exacerbation. Therefore, standard deviation (SD) values from the mean (normal distribution variable) or the first and third quartiles (non-normal distribution variable) were obtained. The

spirometric parameters were used as “low” when values were less than one SD from the mean or first quartile and “high” when values were at least one SD from the mean or third quartile. For example, a low FEV_1 was an $FEV_1 < 50\%$ of the predicted value, and high BDR was $\geq 20\%$.

The primary outcome was a short-term recurrence of asthma exacerbation. The patients were followed up to determine the binary outcome within 7 days (from the day of admission). During hospitalization, recurrent asthma exacerbation was defined as requiring relief medication for flare-up symptoms and having an acute increase in the PAS score. Patients discharged before Day 7 received consultation and follow-up via phone until Day 7. Asthma exacerbations were defined as unscheduled primary care or emergency facility visits due to flare-up asthma symptoms.

Statistical analysis

Qualitative variables are presented as frequencies and percentages, while quantitative variables conforming to a normal distribution are presented as mean (SD). Quantitative variables not adhering to a normal distribution are presented as median (interquartile range). The associations between qualitative variables were evaluated using the chi-square test. An independent sample t-test was used to compare two normally distributed quantitative variables. Median values were compared using the Wilcoxon test for continuous and non-normally distributed data. Statistical significance was set at $p < 0.05$.

Univariable logistic regression, with specifically defined cut-offs for these spirometry parameters, was used to identify factors associated with recurrent exacerbations. Multivariable logistic regression analysis was applied to identify independent predictors of recurrent asthma exacerbation. Data analysis and processing were performed using R software version 4.1.3.

Ethical approval

This research was approved by the Ethics Committee in Biomedical Research at Can Tho University of Medicine and Pharmacy (ethical approval number: 206/HĐĐĐ-PCT, dated May 28, 2020). Prior to conducting the study, informed consent was gathered for participant enrollment.

RESULTS

Of the 84 eligible patients, 1 had anaphylaxis induced by nebulized salbutamol, 1 had an airway malformation, and 2 had spirometry reports that did not meet the ATS/ERS 2019 standardized measurement methods; these 4 patients were excluded. Among the patients with recurrent exacerbations, 50% had severe initial asthma exacerbations, while 15% of initial exacerbations were severe among those who did not have recurrent exacerbations ($p = 0.037$). Among patients with recurrent exacerbations, 25% presented to the ED at least 2 times. The PAS score at admission was significantly higher in the recurrent group than in the non-recurrent group ($p < 0.001$), accounting for the longer time needed to relieve asthma symptoms in the recurrent group than in the non-recurrent group. The demographics are shown in Table 1.

The pulmonary ventilation function parameters gradually decreased with the severity of the asthma exacerbation ($p < 0.01$), as the values of the parameters were lower in the severe asthma exacerbation group than in the non-severe asthma group. All patients (100%) were positive for BDR. The BDR in the severe asthma exacerbation group was higher than that in the non-severe asthma exacerbation group ($p < 0.001$). Data are presented in Table 2.

In this study, 10% of the patients (95% CI: 3.43–16.57) experienced acute asthma exacerbation recurrence during the follow-up period. Patients with a severe initial asthma exacerbation had the highest recurrence rate (26.7%), followed by those with a moderate initial exacerbation (8.3%). No patients with a mild initial exacerbation had recurrence. The FVC, FEV₁, FEV₁/FVC, and PEF were not significantly different between the recurrent and non-recurrent groups. Meanwhile, there

Table 1. Baseline demographic characteristics of the participants

Characteristics	Overall, n (%) (N = 80)	Recurrence, n (%) (N = 8)	Non-recurrence, n (%) (N = 72)	<i>p</i>
Age (years), mean (SD)	9.5 (1.9)	10.4 (1.7)	9.4 (1.9)	0.177
6–11	69 (86)	6 (75)	63 (88)	0.302
≥12	11 (14)	2 (25)	9 (12)	
Male sex	53 (66)	3 (38)	50 (69)	0.112
Past ED visits*				
≥2 times	15 (19)	2 (25)	13 (18)	0.640
Severe asthma exacerbation	15 (19)	4 (50)	11 (15)	0.037
Admission PAS [†] , mean (SD)	8.5 (1.9)	10.8 (0.9)	8.3 (1.9)	<0.001
Time to relieve (hours), median (IQR)	3 (2–4)	4 (4–5)	2 (2–4)	0.015

ED=emergency department; IQR=interquartile range; PAS=pediatric asthma score; SD=standard deviation

*Past ED visits: history of past ED visits last year; †admission PAS: the score of PAS at admission

Table 2. Spirometry measures across studied groups of asthma exacerbation severity

Parameters	Overall, mean (SD) (N = 80)	Severe, mean (SD) (N = 15)	Non-severe, mean (SD) (N = 65)	<i>p</i>
FEV ₁ (% predicted)	67.45 (18.79)	51.13 (12.37)	71.22 (18.04)	<0.001
FVC (% predicted)	83.21 (19.71)	70.93 (14.91)	86.05 (19.69)	0.003
FEV ₁ /FVC (%)	71.54 (13.80)	63.00 (9.73)	73.51 (13.91)	0.002
FEF _{25–75} (% predicted)	44.95 (20.76)	26.80 (11.85)	49.14 (20.15)	<0.001
FEF _{25–75} /FVC (%)	55.06 (25.36)	38.64 (18.27)	58.85 (25.36)	0.001
PEF (l/s)	1.57 (1.10–2.00)	1.00 (0.86–1.58)	1.63 (1.25–2.07)	0.003
BDR (%)	16.85 (3.00)	20.53 (2.83)	16.00 (2.35)	<0.001

BDR=bronchodilator responsiveness; FEF_{25–75}=forced expiratory flow between 25% and 75% of vital capacity; FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity; PEF=peak expiratory flow; SD=standard deviation

Table 3. Logistic regression of recurrent exacerbation in children with asthma

Variables	Univariable			Multivariable		
	cOR	95% CI	<i>p</i>	aOR	95% CI	<i>p</i>
FEV ₁ <50%	1.51	0.27–8.36	0.635	-	-	-
FEV ₁ /FVC <60%	2.28	0.49–10.64	0.294	-	-	-
FEF _{25–75} <30%	1.17	0.21–6.35	0.858	-	-	-
FEF _{25–75} /FVC <30%	1.51	0.27–8.36	0.635	-	-	-
PEF <1.1 l/s	1.08	0.20–5.85	0.930	-	-	-
BDR ≥20%	13.33	2.67–66.64	0.002	6.95	1.08–44.75	0.041
Severe asthma exacerbation	5.55	1.20–25.54	0.028	2.19	0.39–12.41	0.376

aOR=adjusted odds ratio; BDR=bronchodilator responsiveness; CI=confidence interval; cOR=crude odds ratio; FEF_{25–75}=forced expiratory flow between 25% and 75% of vital capacity; FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity; PEF=peak expiratory flow FEV₁ and FEF_{25–75} variables are presented as percentage of predicted values

were statistically significant differences between the two groups in both the FEF_{25–75} (34.8 [7.6] and 46.1 [21.5], respectively, *p* = 0.005) and BDR (21.3 [3.2] and 16.4 [2.6], respectively, *p*<0.001). Severe asthma exacerbations and a BDR ≥20% were identified as predictors of asthma recurrence in the univariate logistic regression analysis. After adjusting for asthma exacerbation severity in the multivariate analysis, a high BDR was identified as an independent predictor of recurrent exacerbations, with a 6.95-fold increase in the odds of an exacerbation (95% CI for OR = 1.08–44.75, *p* = 0.041) (Table 3).

DISCUSSION

The findings of this study underscore the significant predictive value of spirometry parameters for the short-term recurrence of pediatric asthma exacerbations. In the present study, 66% of the study population was male, which is consistent with previous reports of a higher prevalence of asthma in males (60.2–65%).^{18–20} The male sex is associated with asthma, as boys have a higher likelihood of asthma than girls until puberty. Boys have a smaller airway than girls under 10 years of age, leading to a poorer airway response compared to girls of the same age, height, and weight.²¹ Coverstone et al²² reported that males had greater airflow limitations than females, as indicated by lower FEV₁/FVC ratios before and after performing a bronchodilation test. Additionally, Sorkness et al²³ reported that boys had significantly greater airflow limitations than girls based on FEV₁/FVC values.

In the current study, 19% of the patients had presented to the ED at least 2 times. Tan et al²⁴ reported a significantly different number of prior exacerbations (≥2 times) between the recurrent and non-recurrent exacerbation groups in their study (*p* = 0.021). In this study, spirometry was performed using standard protocols in 80 children with clinically-assessed asthma. Significantly lower values of pulmonary ventilation function parameters were observed among patients with severe exacerbations compared to those with non-severe exacerbations. These findings are consistent with those of previous studies. van Dalen et al²⁵ reported that adolescents with severe asthma had significantly lower median percentages of FEV₁/FVC (84.3% and 83.2%, respectively) and percentages of predicted FEF_{25–75} (90.4% and 86.5%, respectively) than those with mild asthma. Similar to the current study, Schifano et al²⁶ investigated baseline spirometry data and observed a decline in FEV₁% of predicted (*p*<0.001), FVC% of predicted (*p*<0.01), and FEV₁/FVC ratio (*p*<0.001). Additionally, decreased PEF and FEF_{25–75}/FVC ratios were observed as asthma severity increased (*p*<0.01). Fitzpatrick et al²⁷ reported that the predicted lung function values were lower in children with severe asthma than in those with mild-to-moderate asthma. Studies have demonstrated a close association between lung function decline and the severity of asthma exacerbations.^{28–30} Increasing lung function loss is caused by asthma exacerbations and is further affected by the escalation of airway inflammation that occurs during an asthma exacerbation.^{31,32}

In this study, a BDR ≥20% and severe asthma exacerbations were identified as predictors of

recurrent asthma exacerbations. However, only BDR $\geq 20\%$ was identified as an independent predictor of asthma exacerbation. Busse et al³³ determined whether spirometric markers of fixed airflow obstruction (FAO) and the degree of BDR could predict future asthma exacerbations in patients with moderate-to-severe and poorly-controlled disease and reported a significant association between BDR and exacerbation rates ($p = 0.002$). High BDR was the main distinguishing feature of the airway indicating an exacerbation risk. However, the FAO was not associated with the risk of exacerbation, indicating that BDR is a potentially useful predictor of asthma exacerbations.³³ Similarly, Sharma et al³⁴ reported that lower initial prebronchodilator FEV₁ values were associated with consistent BDR (defined as positive BDR at each of the patient's yearly follow-up visits) (OR = 0.71, $p < 0.0001$), which led to more hospital visits ($p = 0.007$). In the current study, the baseline FEV₁ was significantly lower in patients with severe asthma exacerbations than in those with non-severe asthma exacerbations, which is consistent with the findings of previous studies. Furthermore, the recurrence rate in children with severe asthma was significantly higher than that in children with moderate or mild asthma ($p = 0.034$), highlighting airway reversibility as a known risk factor for exacerbation. Although airway reversibility has been identified as a risk factor for exacerbations, few studies have explored the relationship between BDR and the risk of acute asthma recurrence, especially in the pediatric population. The current research contributes to this gap by highlighting a clear relationship between high BDR and an increased likelihood of acute asthma exacerbation recurrence in children; this study is among the first with this focus.

This study had several limitations. The research was performed during the coronavirus 2019 pandemic, which made bias in patient selection inevitable due to several challenges encountered during that time. Furthermore, as this was a single-center, hospital-based investigation, it had a limited scale and sample size, which affected its generalizability. To obtain more objective results, multicenter studies with larger pediatric populations and validated cut-off values are necessary.

To date, few studies have addressed the relationship between BDR and the recurrence of acute asthma exacerbations in pediatric patients. To the best of our knowledge, this is the first study to highlight

a clear association between high BDR and the risk of acute asthma exacerbation recurrence in this population. Spirometry is an easily accessible and highly effective tool for diagnosing and assessing disease severity, managing and categorizing risk factors, and monitoring patients with asthma. A BDR $\geq 20\%$ can be used as an independent risk factor for predicting the possibility of acute asthma exacerbation recurrence. Further research is needed to identify specific markers of future exacerbations, including biomarkers, unique characteristics, and genetic factors, driven by the imperative to predict the future risks for patients.

In conclusion, pulmonary ventilation function parameters gradually decreased with increasing asthma exacerbation severity. High BDR may be used as a predictor of acute asthma exacerbation recurrence.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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