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The Use of FEF_{25-75} in the Evaluation of Children with Bronchial Asthma at the University of Santo Tomas Hospital

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ABSTRACT

Background: Retrospective studies have shown that asthmatic patients may have ventilatory defects in the presence of a normal FEV_1. Thus, we conducted a prospective cross-sectional study to investigate on the utility of FEF_{25-75}, in the context of having normal FEV_1, in the evaluation of children with bronchial asthma at the University of Santo Tomas Hospital.

Methodology: This is a cross-sectional study of 165 children aged 6 to 18 years diagnosed with bronchial asthma. All patients underwent routine assessment with a questionnaire, allergy skin prick test and spirometry.

Results: Of the 165 asthmatic subjects, 116 (70.3%) had a normal FEV_1. Of these, 103 (88.8%) had an additionally normal FEV_1/FVC and FEF_{25-75}. There were 3 subjects (2.6%) with normal FEV_1 and FEF_{25-75} who also had low FEV_1/FVC; 6 subjects (5.2%) had low FEF_{25-75} alone; and 4 subjects (3.4%) had both low FEV_1/FVC and FEF_{25-75}. A significant number of low FEV_1/FVC group (67%) and low FEF_{25-75} group (50%) had exacerbations within the past 6 months necessitating steroid use. Subjects with low FEF_{25-75} (56.5 ± 8.26 %predicted) had significantly lower mean values even with normal FEV_1 (88.17 ± 4.92) and FVC (92.5 ± 7.09). FEF_{25-75} is directly correlated with FEV_1 (Spearman's rho = 0.693, p<.001) and with FEV_1/FVC (Spearman's rho = 0.653, p<.001) among all children with bronchial asthma.

Conclusion: FEF_{25-75} may be useful in the evaluation of children with bronchial asthma with normal FEV_1. FEF_{25-75} is strongly and directly correlated to FEV_1 and FEV_1/FVC.

Keywords: pediatric bronchial asthma, small airway, spirometry, FEV_1, FEF_{25-75}

INTRODUCTION

An estimated 300 million persons worldwide have asthma, about 50% of whom live in developing countries.[1] In the Philippines, the prevalence of asthma among Filipino children range from 9.2% to 27.4%.[2-4] Childhood asthma can often present diagnostic challenge to the medical professional. Evidence of airway obstruction may not be present on examination, and the clinical history provided by the child and/or parent can be inaccurate.[5,6]

It has long been considered that the middle and large airways are predominantly involved in asthma. In the last years, there has been renewed interest in the role of small airway abnormalities in patients with asthma.[7,8] The small airways are difficult to assess and treat in asthmatic patients.[9] Small airways contribute little to the total respiratory resistance so that extensive damage of small airways may occur before the appearance of any symptoms, and this is the reason why they are characterized as the "silent zone" of airways.[10]

The use of spirometry in the assessment of children with asthma is taking on new importance with the realization that considerable airway obstruction may exist in the absence of clinically detectable abnormalities.[11,12] However, a disadvantage of using spirometry in asthma management is that the forced expiratory volume in 1 second (FEV_1), which is reproducible and an appropriate measure of airway obstruction, is often normal even in children with symptoms of uncontrolled asthma.[13-15] Therefore, it is difficult to utilize this variable both in the clinical setting and in epidemiological and clinical trials.[16]

According to Mc Nulty et al., examination of the midportion of expiratory flow may offer more information on small airway pathology.[17] The forced expiratory flow at 25–75% of the FVC, or commonly known as FEF_{25-75}, is one of the most commonly cited measures of small airways pathology. It is described as more reproducible and more sensitive than FEV_1 to the presence of small airways disease.[18-20] Some studies suggest that the FEF_{25-75} is more sensitive as an indicator of symptomatic asthma than the FEV_1 in children.[11,21,22] Since it does not include flows high in the lung volume, the FEF_{25-75} is theoretically less effort-dependent than the FEV_1 and is believed to be a measurement of small airway patency.[18,19,23]

The guidelines of the American Thoracic Society (ATS) do not suggest that the assessment of the forced expiratory flow between 25-75% of vital capacity (FEF_{25-75}) plays a significant role in the measurement of airflow obstruction.[24,25] However, recent studies have shown that asthmatic patients may have ventilatory defects in the presence of a normal FEV_1.[26,27] The role of a low FEF_{25-75} in the context of normal FEV_1 in predicting asthma morbidity and in designing individualized therapeutic asthma management, remains to be investigated on. Moreover, the contribution of small airways abnormalities in the clinical expression of asthma remained to be assessed, particularly in the cross-sectional manner.[28]

Definition Of Spirometric Indices[24]

FEV_1 – is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration

FVC – is the maximal volume of air exhaled with maximally forced effort from a maximal inspiration, i.e., vital capacity performed with a maximally forced expiratory effort

FEV_1/FVC – ratio of FEV_1 and FVC

FEF_{25-75} – is the mean forced expiratory flow between 25% and 75% of the FVC and has also been known as the maximum mid-expiratory flow; this index is taken from the blow with the largest sum of FEV_1 and FVC

OBJECTIVES

General Objectives

To determine the role of FEF_{25-75} in the clinical evaluation of children aged 6-18 years with bronchial asthma at the University of Santo Tomas Hospital.

Specific Objectives

1. To determine the prevalence of normal FEV_1 among children with bronchial asthma.
2. To determine the distribution of spirometric readings among asthmatic patients with normal FEV_1.
3. To determine the correlation of FEF_{25-75} to FEV_1 and to FEV_1/FVC ratio.

METHODOLOGY

Study Design

A cross-sectional study was conducted for a period of 12 months from December 2016 to November 2017. All patients underwent a thorough history and physical examination, allergy skin prick test and spirometry.

Study Participants

A total of 165 patients with age ranging between 6 and 18 years, diagnosed with bronchial asthma and seen at the University of Santo Tomas Hospital from December 2016 to November 2017 was included in this study. The participants in this study have bronchial asthma that is well-controlled, partly controlled, uncontrolled, or in acute exacerbation.

Sample Size Computation

A minimum of 163 subjects was required for this study based on a level of significance of 5%, a prevalence 88%[14] of patients with normal FEV_1 with a desired width of

confidence interval of 10%, as noted from the reference article by Rao et al.[16]

Inclusion and Exclusion Criteria

The patients with asthma enrolled in this study were those who fulfilled the criteria according to the Global Initiative for Asthma (GINA) 2017 guidelines of having a 1) history of variable respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough; and 2) evidence of variable respiratory airflow limitation.[29] The patients were either well-controlled, partially-controlled, uncontrolled state or in acute exacerbation. Those with concomitant acute or chronic upper respiratory tract infection, with anatomical nasal disorders and were unable to follow the instructions in doing the spirometry test were excluded.
Age, gender, duration of asthma, various morbidity outcomes, FEF_{25-75}, FEV_1 and FEV_1/FVC values and percent predicted were registered for all patients in the analysis.

Spirometry

Spirometry was performed in all patients aged 6 to 18 years. They were asked to breathe in maximally, hold the mouthpiece between their teeth and then apply the lips for an airtight seal, and breathe out as hard and as fast as possible until the lungs are empty. The following spirometric parameters were obtained: forced vital capacity (FVC), forced expiratory volume at 1st second (FEV_1) and forced expiratory flow at 25% and 75% (FEF_{25-75}). The Spiro Lab III was used as the pulmonary function device. At least 3 maneuvers meeting the American Thoracic Society standards were obtained.

Based on the 2007 National Asthma Education and Prevention Program (NAEPP) guidelines, the following values were used to identify normal spirometry values: FEV_1 >80% predicted and FEV_1/FVC >85. Abnormal FEF_{25-75} was defined as <65% predicted.[6]

Patients were grouped as follows: Group A will be referred to as having "normal" spirometry, Group B as "the low FEV_1/FVC" group, Group C as "the low FEF_{25-75}" group, Group D as the "low FEV_1/FVC and low FEF_{25-75}" group. Asthma severity was determined by the primary investigator, documentation in the month during which the spirometry will be obtained. The use of a controller medication, including inhaled corticosteroid, oral leukotriene antagonist, long-acting β-agonist, or combination medication, was recorded. Morbidity outcomes that were included were the following: presence of hospitalization, emergency department (ED) visit, intensive care unit (ICU) admission, asthma exacerbation, and systemic steroid use.

Skin Prick Test (SPT)

Allergy skin prick test was done on all patients. It was performed by placing a small drop of each test extract, positive control solution (histamine) and negative control solution (normal saline solution) on the volar surface of the forearm. The panel consisted of house dust mites *Dermatophagoides farinae* and *pteronyssinus*, cat hair, dog hair, cattle hair, horse hair, cockroach, mosquito, mixed feathers, *Acacia*, *Candida*.

The drops were placed 2 cm or more apart to avoid false-positive reactions. A disposable gauge 25 hypodermic needle was passed through the drop and inserted into the epidermal surface at a low angle with the bevel facing up. The needle tip was then gently lifted upward to elevate a small portion of the epidermis without inducing bleeding and then withdrawn. Reading was done after 15 minutes. A wheal formation of 3 mm or larger was considered positive.

Statistical Analysis

Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables.

One-way ANOVA, Kruskal-Wallis test and Fisher's Exact test was used to determine between-group differences of means, medians, and frequency, respectively.

Spearman's Rank Correlation was used to determine the association between continuous variables.

All valid data was included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 15.0 was used for data analysis.

Safety and Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research involving human subjects, adopted by the general assembly of World Medical Association. Approval of the University of Santo Tomas Hospital Institutional Review Board (IRB) was obtained prior to implementation of the study.

All pediatric patients (age ranging between 6 and 18 years) with bronchial asthma seen in the outpatient department and private clinics of the University of Santo Tomas Hospital were asked to join the study. All of the participants underwent spirometry and skin prick test to inhaled allergens. The study, its primary purpose and procedure were properly explained and discussed with each of the parents/ guardian and the patient. A duly signed regular written informed consent form, both in Filipino and English were obtained from patients aged 18 years and 364 days. A co-sign informed consent form was

duly signed by the patient's parent/s or legal guardian and patients 15 to 18 years. A written assent was also duly signed for children 12 to less than 15 years old and a verbal assent for children 7 to less than 12 years along with parental consent. In cases when the parent agreed to take part in the study, but the child did not want to participate, the child's decision was respected. Participation in this study was voluntary. Parents and patients were not forced to participate.

The subjects were not charged or compensated for participating in this study. The primary investigator also did not receive any monetary incentives for doing this study. All financial expenses were shouldered by the investigator, including the spirometry and skin prick tests.

Risks/Discomfort

In performing spirometry, the children were asked to breathe fast and deep which can result to shortness of breath or lightheadedness. There was no reported incidence of such during the study. Those patients classified under uncontrolled state or those who were in acute exacerbation during the study were closely monitored while doing spirometry and medically treated accordingly.

There were about 3 out of the 165 participants who complained of minimal skin irritation (wheal and flare reaction) after the allergy skin prick test that resolved spontaneously. And there were 2 out of the 165 patients with complaints of persistent itchiness, and medical treatment was provided by the primary investigator for free.

Benefits

The information from this study would directly benefit patients, especially those with normal FEV_1 but with low FEF_{25-75}. Studies have shown that low FEF_{25-75} in the setting of normal FEV_1 is associated with asthma severity, systemic steroid use and asthma exacerbations. Thus FEF_{25-75} should be evaluated in clinical studies of asthma in children to be able to give early intervention.

Results obtained from this study may also be used by clinicians in developing an effective management plan for their patient with asthma. And last, the findings from this study may serve as baseline information for future researchers who will be conducting studies on the same topic.

RESULTS

The average values for FEF_{25-75}, FVC, FEV_1 and FEV_1/FVC are depicted in Table 1 for subjects classified according to level of asthma control. The evidence suggests significant across-group differences in all spirometric parameters (p <0.04). Subjects with uncontrolled asthma significantly had the lowest mean values of FEF_{25-75} (68.78 + 31.06) and with significantly decreased mean values of FEV_1(78.93 + 19.90).

The categorization of subjects according to various spirometric abnormalities is shown in Figure 1. Of the 165 asthmatic subjects, 116 (70.3%) had a normal FEV_1. Of these, 103 (88.8%) had an additionally normal FEV_1/FVC and FEF_{25-75}. There were 3 subjects (2.6%) with normal FEV_1 and FEF_{25-75} who also had low FEV_1/FVC; 6 subjects (5.2%) had low FEF_{25-75} alone; and 4 subjects (3.4%) had both low FEV_1/FVC and FEF_{25-75}.

Selected demographics for all 116 subjects and the 4 subgroups used for analysis are shown in Table 2. The age of the subjects included in the study ranged from

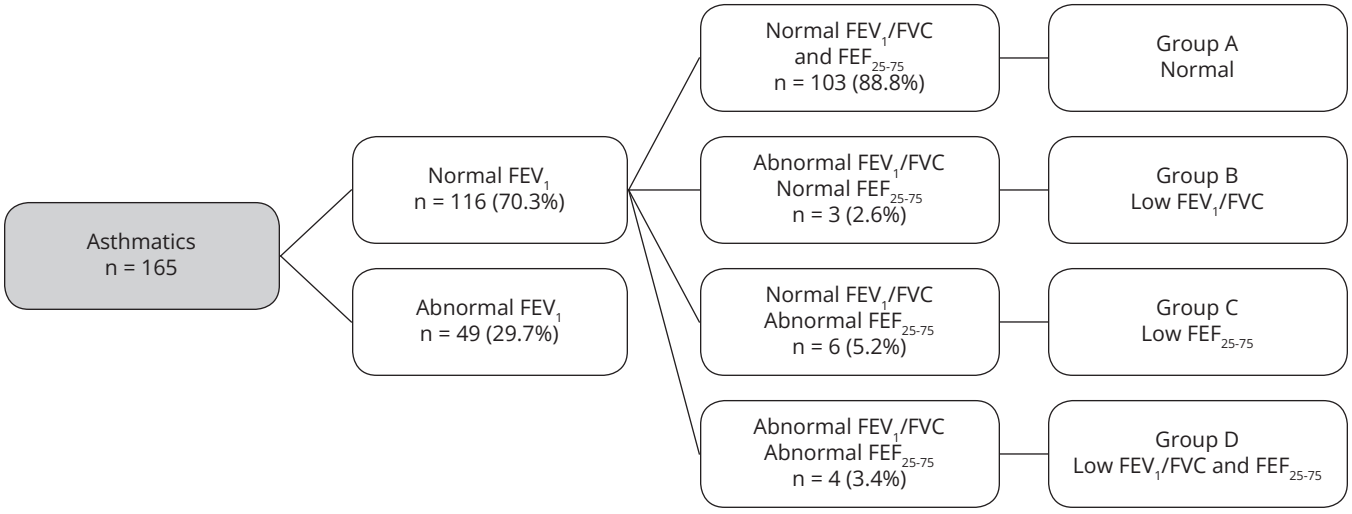

Figure 1. Distribution of subjects according to spirometry readings. (Group A: "Normal Spirometry"; Group B: "Low FEV_1/FVC"; Group C: "Low FEF_{25-75}"; Group D: "Low FEV_1/FVC and Low FEF_{25-75}").

8.67 + 2.08 to 11.28 + 3.42 years. Majority of these subjects was approximately 60.7% male across groups. Patients from the subgroup with normal spirometry were mostly polysensitized (67%) while those having purely low FEF_{25-75} (50%) or both low FEV_1/FVC and FEF_{25-75} (100%) were mostly monosensitized.

The percentages of subjects in the 4 spirometric findings with different morbidity outcomes are shown in Table 3. Majority of subjects with normal spirometry had controlled (69%) and intermittent asthma (59%). Similar findings were noted from the subgroup with both low FEV_1/FVC and FEF_{25-75} (50% controlled; 75% intermittent). On the other hand, all subjects with low FEV_1/FVC had uncontrolled asthma (100%) and had the highest percentage of steroid use (67%) in the past 6 months. Those with low FEF_{25-75} mostly had controlled asthma (67%) and half had mild persistent asthma (50%). A significant number of subjects

Table 1. Mean values of spirometric readings for all subjects according to asthma control expressed in percent predicted (n = 165)

	Controlled (n = 91)	Partly Controlled (n=34)	Uncontrolled (n = 40)	*p*
	Mean ± SD			
FEF_{25-75}	91.64 ± 26.05	75.62 ± 26.85	68.78 ± 31.06	**<0.001**
FVC	94.43 ± 17.92	93.68 ± 12.60	84.38 ± 19.97	**0.009**
FEV_1	94.17 ± 17.02	88.71 ± 16.88	78.93 ± 19.90	**0.0001**
FEV_1/FVC	96.22 ± 12.08	92.38 ± 12.10	90.63 ± 12.44	**0.038**

Statistical test used: One-way ANOVA

Table 2. Characteristics of 116 asthmatic children with normal FEV_1

	Normal Spirometry (n = 103)	Low FEV_1/FVC (n = 3)	Low FEF_{25-75} (n = 6)	Low FEV_1/FVC and FEF_{25-75} (n = 4)	*p*
Age (years)	11.28 ± 3.42	8.67 ± 2.08	9.83 ± 2.04	9.5 ± 2.65	0.302*
	Frequency (%)				
Sex					0.721§
Male	63 (61.17)	1 (33.33)	3 (50)	3 (75)	
Female	40 (38.83)	2 (66.67)	3 (50)	1 (25)	
Sensitization					**0.004§**
None	3 (2.91)	1 (33.33)	1 (16.67)	0	
Monosensitized	31 (30.10)	1 (33.33)	3 (50)	4 (100)	
Polysensitized	69 (66.99)	1 (33.33)	2 (33.33)	0	

*Statistical test used: * – One way ANOVA; ‡ – Kruskal-wallis H test; § – Fisher's exact test*

Table 3. Asthma control, severity and morbidity of subjects with normal FEV_1, low FEV_1/FVC, low FEF_{25-75} and with both low FEV_1/FVC and FEF_{25-75}

	Normal Spirometry (n = 103)	Low FEV_1/FVC (n = 3)	Low FEF_{25-75} (n = 6)	Low FEV_1/FVC and FEF_{25-75} (n = 4)	*p*-value
	Frequency (%)				
Asthma control					**0.007§**
Controlled	71 (68.93)	0	4 (66.67)	2 (50)	
Partly controlled	21 (20.39)	0	0	1 (25)	
Uncontrolled	11 (10.68)	3 (100)	2 (33.33)	1 (25)	
Severity of asthma					0.138§
Intermittent	61 (59.22)	1 (33.33)	2 (33.33)	3 (75)	
Mild persistent	39 (37.86)	1 (33.33)	3 (50)	1 (25)	
Moderate persistent	3 (2.91)	1 (33.33)	1 (16.67)	0	
ER visit due to asthma	4 (3.88)	1 (33.33)	1 (16.67)	0	0.099§
Previous hospitalization due to asthma	1 (0.97)	0	1 (16.67)	0	0.212§
ICU admission	0	0	0	0	–
Steroid use	16 (15.53)	2 (66.67)	3 (50)	1 (25)	**0.020§**
Use of controller	31 (30)	1 (33.33)	3 (50)	2 (50)	0.573§

*Statistical test used: * – One way ANOVA; ‡ – Kruskal-wallis H test; § – Fisher's exact test*

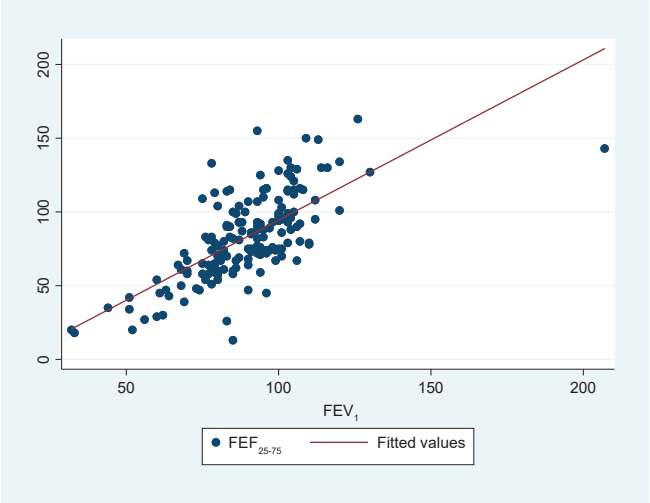

Figure 2. Scatterplot with fitted line of FEF_{25-75} (y-axis) vs. FEV_1 (x-axis) for 165 children with bronchial asthma.

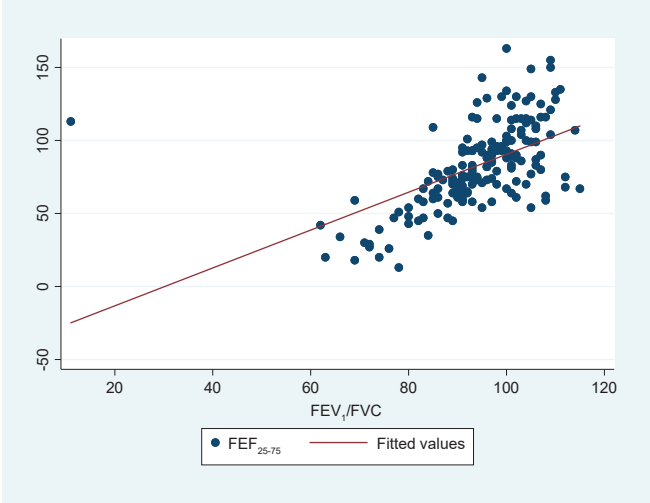

Figure 3. Scatterplot with fitted line of FEF_{25-75} (y-axis) vs. FEV_1/FVC (x-axis) for 165 children with bronchial asthma.

Table 4. Mean values of spirometric readings among asthmatic patients with normal FEV_1 expressed as percent predicted (n = 116)

	Normal Spirometry (n = 103)	Low FEV_1/FVC (n = 3)	Low FEF_{25-75} (n = 6)	Low FEV_1/FVC, Low FEF_{25-75} (n = 4)	*p*-value
	Mean ± SD				
FVC (%predicted)	97.45 ± 16.40	117.67 ± 11.59	92.5 ± 7.09	110 ± 14.81	0.060
FEV_1 (%predicted)	98.31 ±14.83	101.67 ± 7.37	88.17 ± 4.92	86.75 ± 4.92	0.149
FEV_1/FVC	98.67 ± 6.81	84 ± 1	92.33 ± 7.97	76.5 ± 5.80	**<0.001**
FEF_{25-75} (%predicted)	97.41 ± 22.11	72.33 ± 5.51	56.5 ± 8.26	39 ± 23.14	**<0.001**
PEFR (% predicted)	96.64 ± 21.85	82.67 ± 28.92	76.83 ± 10.82	76.75 ± 15.86	**0.038**

Statistical test used: One-way ANOVA

from this subgroup also had exacerbations in the past 6 months necessitating steroid use (50%).

Table 4 shows the mean spirometric values in children according to the 4 spirometric findings. The FVC and FEV_1 parameters were not found to differ significantly across the four patient groups. Subjects with low FEF_{25-75} alone (56.5 ± 8.26 %predicted) had significantly lower mean values even with normal FEV_1 (88.17 ± 4.92) and FVC (92.5 ± 7.09). The remaining group had poor FEV_1/FVC (76.5 ± 5.80) and FEF_{25-75} (39 ± 23.14 liters/sec) but with good FEV_1 (86.75 ± 4.92).

Table 5. Correlations of FEF_{25-75} with FEV_1 and FEV_1/FVC ratio (n = 165)

	Spearman's Correlation Coefficient	Interpretation	*P*-value
FEV_1	0.693	Direct, Strong relationship	**<0.001**
FEV_1/FVC	0.653	Direct, Strong relationship	**<0.001**

FEF_{25-75} is directly and strongly correlated with FEV_1 (Spearman's rho = 0.693, $p<.001$) and FEV_1/FVC (Spearman's rho = 0.653, $p<.001$) among all children surveyed with bronchial asthma as depicted in Table 5, Figures 2 and 3.

DISCUSSION

Our study showed that 70.3% of asthmatic subjects had a normal FEV_1. Of these, 88.8% had an additionally normal FEV_1/FVC and FEF_{25-75}. There were 2.6% with normal FEV_1 and FEF_{25-75} who also had low FEV_1/FVC; 5.2% had low FEF_{25-75} alone; and 3.4% had both low FEV_1/FVC and FEF_{25-75}. Even if almost 67% of those in the low FEF_{25-75} group had controlled asthma and 50% had mild persistent severity of asthma, a significant number had exacerbations in the past 6 months necessitating steroid use (50%). This study showed that subjects with low FEF_{25-75} had significantly lower mean values even with normal FEV_1 and FVC. FEF_{25-75} was found to be strongly and directly correlated with FEV_1 and with FEV_1/FVC among all children surveyed with bronchial asthma.

The finding that having a normal FEV_1 is prevalent among children with asthma was similar to other studies in literature.[9,16,30] This result makes management of asthma in children more difficult for clinicians since they might withhold in giving proper controller medications for patients whose lung function measurements may be within normal limits despite significant burden and medication use.[13,31,32] There is evidence that the magnitude of small airway abnormalities correlates with the severity of the disease.[33] According to Hogg et al., the distal airways are more affected, and that the increased distal lung resistance, in the absence of significant large airway involvement, likely explains the often unimpaired FEV_1 values.[34]

Our study demonstrated that having either a low FEF_{25-75} alone (50%) or a low FEV_1/FVC ratio alone (67%), with normal FEV_1, was significantly associated with systemic steroid use. This could imply that these patients with low FEF_{25-75} or with a low FEV_1/FVC ratio have exacerbations severe enough to warrant the use systemic steroid even if with preserved FEV_1. This is similar to the finding of Rao et al., wherein having both low FEF_{25-75} and FEV_1/FVC ratio was significantly associated with different morbidities, and one of which is steroid use.[16]

In our study, subjects with low FEF_{25-75} had significantly lower mean values even with normal FEV_1 and FVC. This is in accord with the study by Rao et al., wherein subjects with lower FEF_{25-75} had significantly lower mean values for FEV_1, FEV_1/FVC, and FEF_{25-75}.[16] Certainly, there is a small but important subset of asthmatic children with a normal FEV_1 and abnormal FEF_{25-75} who have poor asthma outcomes and likely require close follow-up and more aggressive management.

Our study showed a strong and direct correlation of FEF_{25-75} with FEV_1 and with FEV_1/FVC. This result agrees with the suggestion of several studies saying that FEF_{25-75} percent predicted should be evaluated in clinical studies of asthma in children.[11,21,22] It may have the potential to be an important spirometric index that can be used as a marker of asthma exacerbations in children. Scichilone et al., proposed that physicians should assess peripheral airway function and inflammation in managing cases of 'difficult-to-treat'/uncontrolled asthma in order to detect the involvement of the small airways and to evaluate the possibility of individualized therapeutic decisions.[35]

The strong correlation may also possibly indicate that FEF_{25-75} still cannot stand alone and is dependent on FEV_1 and FVC. The study by Simon et al., showed that the variance of FEF_{25-75} is much higher than that of the FEV_1, thus; even if FEF_{25-75} is more physiologically sensitive, it lacks specificity due to its variability.[30] Therefore, FEF_{25-75} is of limited diagnostic value in detecting abnormality per se, unless a patient is already known to have asthma.[30] In addition, the study of Mc Nulty et al., mentioned that changes in FVC will affect the portion of the flow-volume curve examined.[17] Thus, if FEF_{25-75} is not adjusted for lung volume, there is poor reproducibility.[36]

In the study of Rao et al., the low FEF_{25-75} group had the highest percentage of moderate and severe asthmatics overall.[16] This is in contrast with our results wherein the low FEF_{25-75} group mostly consisted of subjects with controlled asthma and mild persistent severity. In addition, our study showed no significant association of low FEF_{25-75} with other morbidities such as emergency room visit, hospitalization or ICU admission due to asthma. This may be due to higher number of subjects with controlled and intermittent severity of asthma. Another reason could be due to a greater number of subjects have controller medications at that time spirometry was done.

The strength of our study is the prospective, cross-sectional design that could help determine associations with asthma morbidity or poor outcomes. Our findings add to the existing literature by showing that FEF_{25-75} should also be given attention in clinical and epidemiologic studies. Small airway obstruction, as depicted by lower FEF_{25-75} value may take a significant role in asthma management, because children with asthma have more often preserved FEV_1 but might have small airway dysfunctions that are not reflected by FEV_1.[9] As mentioned by Contoli et al., clinicians, and not only researchers, must consider small airways when approaching patients with asthma especially those with 'difficult-to-treat' phenotype.[33] They also said that the identification of subgroups with prominent small airway diseases is not merely speculative and carries pathophysiological and therapeutic implications.[33]

The main limitation of this study is the unevenly distributed subjects. There is a higher number of patients with well controlled and intermittent or mild asthma severity.

Future clinical or epidemiologic studies, with greater number of populations, are recommended to further investigate on the utility of FEF_{25-75}.

CONCLUSION

There is a high prevalence of normal FEV_1 among asthmatic children. A small but important percentage of these children have abnormal FEF_{25-75} and have poor asthma controls. The parameter FEF_{25-75} is strongly and directly correlated to FEV_1 and FEV_1/FVC. Thus, FEF_{25-75} should be given attention in the clinical evaluation of children with bronchial asthma because it is a potentially significant spirometric variable that can be used as a marker of asthma exacerbation necessitating steroid use.

Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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