

## QUANTIFICATION OF PREDICTIVE VALUES OF CERTAIN PARAMETERS INCLUDING THE EXPIRATORY VARIABILITY INDEX IN THE FOLLOW-UP OF CHILDREN WITH RECURRENT BRONCHIAL OBSTRUCTIONS

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### Abstract

This study shows the quantification of predictive values of certain parameters including measurements with the Ventica-system. This new device has recently started to be used in the Balkans with results being used as relevant values in monitoring lung function in young children.

Objective: usage of this method as one of the standards for monitoring lung function in preschool children. Over a 2 year period we performed measurements on 52 children aged 1-6 years who have recurrent bronchitis. Inclusion criteria: at least 3 lower respiratory infections or exacerbation in the previous year with the need for treatment in intensive care, or at least two broncho-obstructive episodes. Exclusion criteria: tracheomalacia and bronchopulmonary dysplasia. Ventica system by the Finnish company Revenio Research Oy, was used. The measurement is based on continuous impedance pneumography in which the machine calculates the appropriate values and gives the results in the form of an EVI (Expiratory Variability Index). In determining the significance of the contribution to the prediction of recurrent bronchitis it was found that increasing EVI per unit value reduces the risk of chronic bronchitis by 15.10%  $p > 0.05$  ( $p = 0.258$ ). In this study the increasing of EVI values did not show statistical significance with the reduction of broncho-obstruction in chronic bronchitis. Nevertheless, more extensive studies show the undoubted benefits in using this method. Thus, more investigation are needed in this field to objectify the usage of one of the non-invasive lung function monitor.

**Key words:** preschool children, recurrent bronchitis, lung function, Ventica-system

### Introduction

The most common diseases in children, regardless of their age, are the diseases of respiratory organs. The younger the child, the incidence and the clinical picture of these diseases are more prominent. Etiopathogenetic causes include not only the undoubted influence of the external agents, but also the peculiarities in the anatomy and physiology of the respiratory system in childhood, and not the least, the immune system which in the pediatric population is immature and still in development.

In general all respiratory diseases can be divided into two large groups: acute and chronic diseases of the upper and lower respiratory organs. In this research the project of interest were children under 6 years of age with chronic lower respiratory tract involvement. By definition, recurrent obstructive bronchitis is a disease when a child has three or more episodes of acute obstructive bronchitis over the course of a year, between each episode is symptom-free and in good general condition. The Chronic bronchitis in children includes: 1. Recurrent bronchitis in children younger than 5 years of age (usually triggered by viral infections and/or allergic diathesis), 2. Asthma in childhood, 3. Bronchiectasis, 4. Ciliary dyskinesia, 5. Cystic fibrosis. [1,2]

Monitoring children with chronic lung disease requires exceptional dedication not only by highly professional medical staff, but also by parents, in order to regulate and properly administer the necessary therapy, in order to prevent or reduce additional complications that would arise from the underlying condition. In addition to regular clinical, laboratory, microbiological, and imaging examinations, regular assessment of the lung function is required. In our conditions, spirometry is still the golden standard, and it

can be implemented in children who have a higher level of communication, i.e. children over 5 years of age. Worldwide, there are devices for monitoring lung function in infant age, however with a more invasive approach not suitable for widespread use [3, 17-22]

One option for non-invasive monitoring of lung function in children aged 1–6 years is the Ventica system. This new device has recently begun to be used in countries abroad, but also in the Balkans (Croatia), with results, which are used as relevant values in monitoring lung function in children over one year of age. Several studies have been published in relevant medical journals involving children under 6 years of age who have used this device. The results were compared with a control group of healthy children, and it was found that the results obtained using the Ventica system provided good insight into the incidence of bronchial obstruction in children during sleep, and correlated with the assessment of regular reception of therapy [7-15]

### **Material and methods**

This prospective research lasted two years, from 2023 to 2025, and it involved 52 children aged 1–6 years of age who were admitted to our consultation clinic in this period with the diagnosis of recurrent lung disease, or wherein the process of being diagnosed. All the research respondents that were included in the study had pre-signed consent from the parent or the legal guardian. Inclusion and exclusion criteria are as followed: Inclusion criteria include In the previous year at least 3 lower respiratory infections, or exacerbation requiring treatment in intensive care, or at least two broncho-obstructive episodes. This study will not include children with Tracheomalacia, and Bronchopulmonary dysplasia.

For monitoring the lung function we used Ventica- system. This device is from the Finnish company Revenio Research Oy and it consists of: small portable system - basic unit, four electrodes, four matching cables, two AAA batteries and, stretch T-shirt for children (Figure 1.)



**Figure 1.** Components of Ventica-system

The placement is done before the child falls asleep. Electrodes are placed on the volar sides of the left and right upper arm and on the left and right upper rib cage, respectively. The corresponding cables, which are of different colors, are connected to the base unit and plugged in. The child is dressed in the given stretch shirt, with the basic unit inserted into a separate pocket, thus achieving safe usage of the system. There are two different ways of recording: automatic or manual mode. In automatic mode, the recording lasts for 12 hours after which the device switches off on its own.

This system is a new test that tracks the occurrence of broncho obstructive seizures that occur during deep sleep. The measurement is based on continuous impedance pneumography, in which the machine calculates the appropriate values, annuls any artifacts that may occur during the child's sleep (agitation, sneezing, crying, coughing), and gives the results in the form of an EVI (Expiratory Variability Index).

Healthy children have high sleep expiratory curve variability and have a normal EVI greater than 14.0 ( $EVI > 14.0$ ). When bronchial obstruction occurs, the variability of the expiratory curve is small and the EVI is less than 14 ( $EVI < 14.0$ ).

Lung function measurements were performed once a week, at the University Clinic for Respiratory Diseases in children-Kozle.

Other than the Ventica system, also we included some of the regular diagnostic methods for chronic bronchitis in children: tot IgE (total Immunoglobulin E), SPT (Skin Prick Test), Eosinophilia in the nose smear/sputum, family allergy predisposition.

### **Results:**

We observed the influence of several parameters, including the values of EVI measured by Ventica, in predicting the outcome of recurrent bronchitis in preschool children. The parameters observed are as followed:

- I. Gender and Age,
- II. Diagnosis,
- III. Duration of recording time with Ventica,
- IV. Values of EVI,
- V. Allergy diagnostic procedures (IgE, SPT, Eosinophilia in sputum/nasal smear),
- VI. Family history for atopy,
- VII. Previous topic steroid,
- VIII. Acute exacerbation, and
- IX. Diagnosis of recurrent bronchitis.

Statistical data processing was performed in statistical program Statistica 7.1 and SPSS 23

The following statistical methods were used:

1. For a series of attributive traits (Gender, Diagnosis, Ige, SPT, Eo, Family allergy predisposition, Previous topic steroid, Acute exacerbation, Chronic bronchitis) percentages of structure (%);
2. For the series with numerical features (Age, Record duration, EVI), descriptive statistics (Mean  $\pm$ Std.Dev., median, minimum, maximum);
3. Quantification of the predictive values of Gender, Age, EVI, Family allergy predisposition, Previous topic steroid, Acute exacerbation, for Chronic bronchitis was determined using Binary Logistic Regression Analysis (Wald, Exp (B) / 95.0% CI for Exp (B)/(p)/ Enter method.

The significance is given  $p < 0.05$ .

The data are tabulated and graphically displayed.

I). Gender and age: Out of a total of 52 children, 26(50,0%) were female and 26(50,0%) were male. Age of patients with lower respiratory infection varied in the range of  $3.84 \pm 1.54$  years;  $\pm 95,00\%$  CI: 3,41-4,27; median 4 years; The minimum age was 1 year and the maximum age 6 years.

II). Diagnosis: According to the diagnosis of the patients included in the study, the largest number had 37(71.15%) recurrent bronchitis, 9(17.31%) were diagnosed with acute bronchitis, 3(5.77%) had allergic rhinitis, 1(1.92%) had GER (Gastro esophageal reflux), 1(1.92%) had chronic urticaria, and 1(1.92%) had chronic laryngitis. (table 1.)

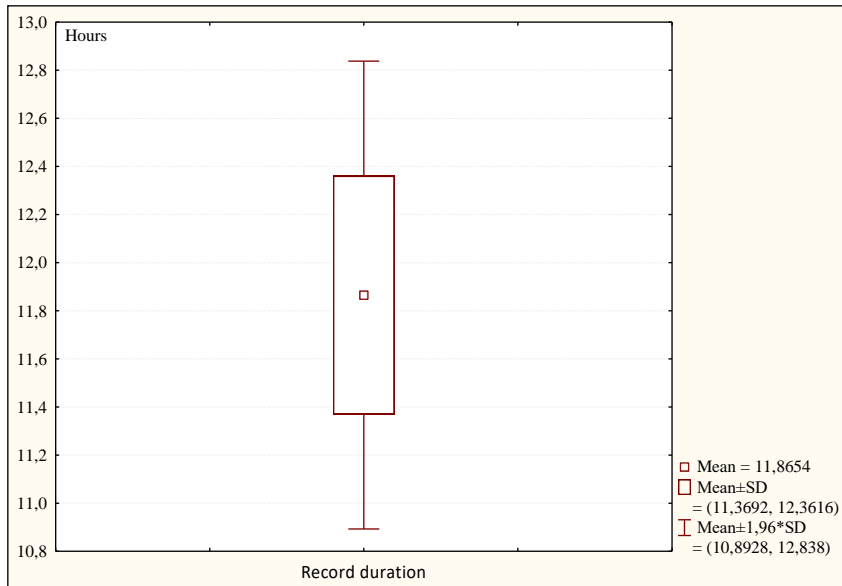
**Table 1.** Diagnosis

Category	Count	Cumulative Count	Percent	Cumulative Percent
Rhinitis allergica	3	3	5,77	5,77
Bronch rec obstr	37	40	71,15	76,92
Bronchobstr ac	9	49	17,31	94,23
Bronch rec obstr, GER	1	50	1,92	96,15
Urticaria rec	1	51	1,92	98,08
Laryng rec	1	52	1,92	100,00
Missing	0	52	0,00	100,00

III). Duration of recording: The mean value of Recording time with Ventica system was 11,73 hours showed in Table 2 and Figure 2.

**Table 2.** Recording time

Variable	Valid N	Mean	Confidence -95,00%	Confidence +95,00%	Median	Minimum	Maximum	Std. Dev.
Record duration	52	11,87	11,73	12,00	12,00	10,50	13,00	0,50

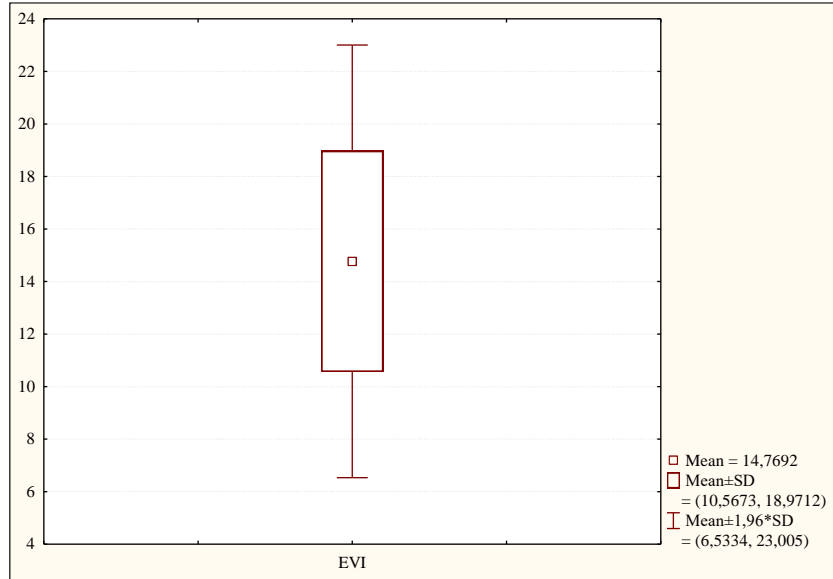


**Figure 2.** Recording time

IV). EVI values: Descriptive statistics of the EVI (Expiratory Variability Index) showed that in this study value of the EVI varied in the range of  $14.77 \pm 4.20$ ;  $\pm 95,00\% \text{CI}: 13,60-15,94$ ; median 15.60; The minimum value was 4.80 and the maximum value was 22.00. (Table 3. and Figure 3.)

**Table 3.** EVI (Expiratory Variability Index)

Variable	Valid N	Mean	Confidence -95,00%	Confidence +95,00%	Median	Minimum	Maximum	Std. Dev.
EVI	52	14,77	13,60	15,94	15,60	4,80	22,00	4,20

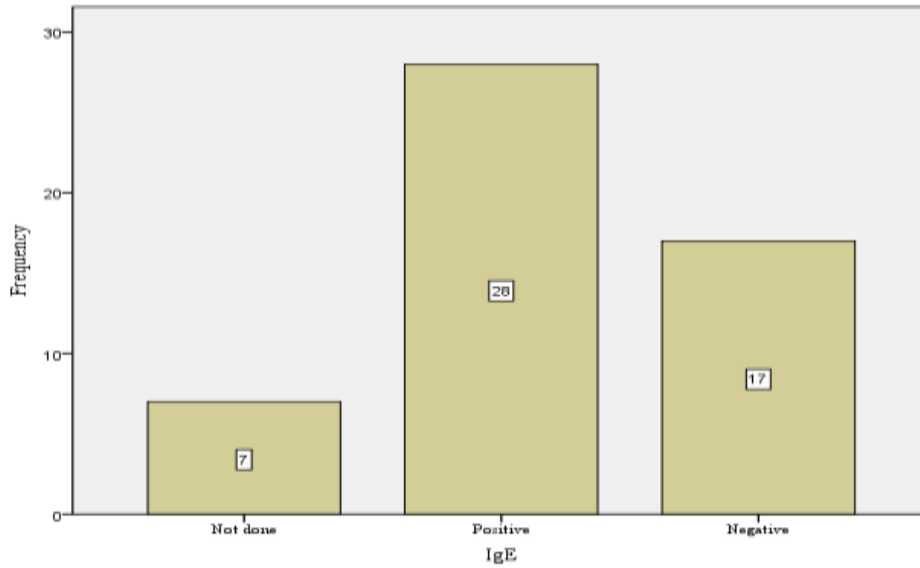


**Figure 3.** EVI (Expiratory Variability Index)

V). Allergy diagnostic procedures: The results that refer to the allergy diagnostic procedures show that out of the 52 children 28 (53,8%) had positive IgE (Table 4. Figure 4), 16 (30,8%) had positive SPT (Table 5. Figure 5) and 24 (46,2%) had eosinophilia in nasal smear/sputum (Table 6. Figure 6).

**Table 4.** IgE

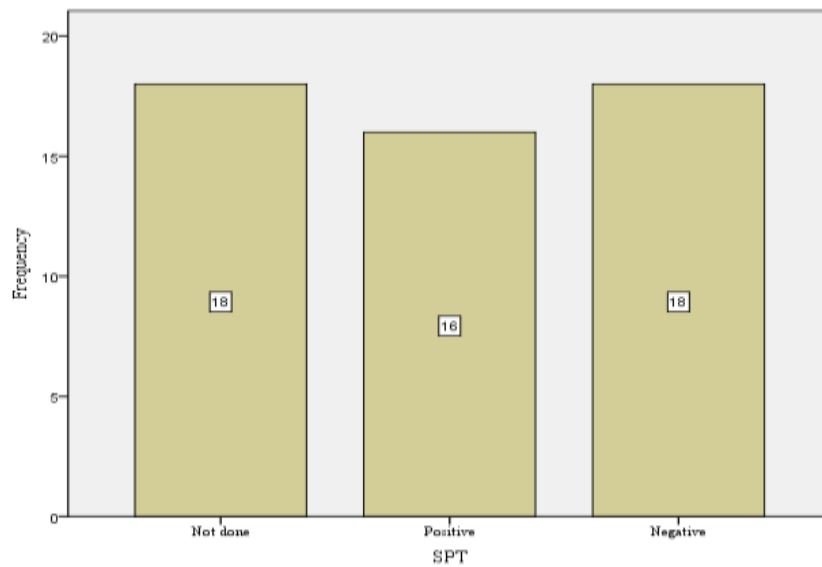
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Not done	7	13,5	13,5	13,5
	Positive	28	53,8	53,8	67,3
	Negative	17	32,7	32,7	100,0
	Total	52	100,0	100,0	



**Figure 4.** IgE

**Table 5.** SPT (Skin Prick Test)

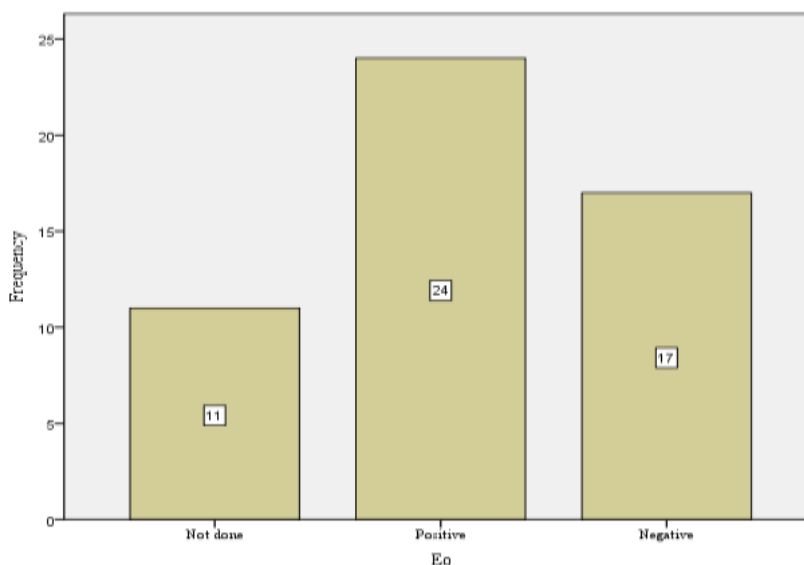
	Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Not done	18	34,6	34,6
	Positive	16	30,8	65,4
	Negative	18	34,6	100,0
	Total	52	100,0	100,0



**Figure 5.** SPT (Skin Prick Test)

**Table 6.** Eosinophils in nasal secret/sputum

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Not done	11	21,2	21,2
	Positive	24	46,2	67,3
	Negative	17	32,7	100,0
	Total	52	100,0	100,0

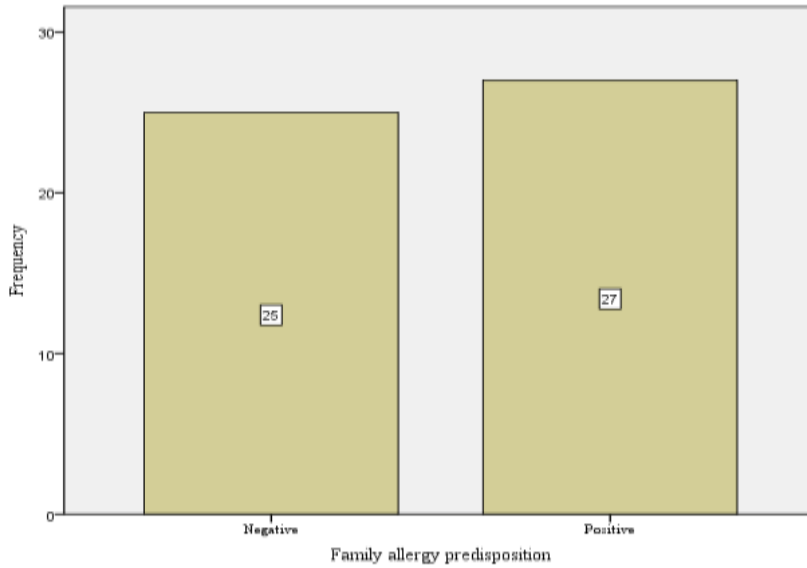


**Figure 6.** Eosinophils in nasal secret/sputum)

VI). Family history of atopy: Of the 52 patients (children), 25 (48.1%) had a negative family history and 27 (51.9%) had a positive family history (Table 7 and Figure 7).

**Table 7.** Family allergy predisposition

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Negative	25	48,1	48,1
	Positive	27	51,9	100,0
	Total	52	100,0	100,0

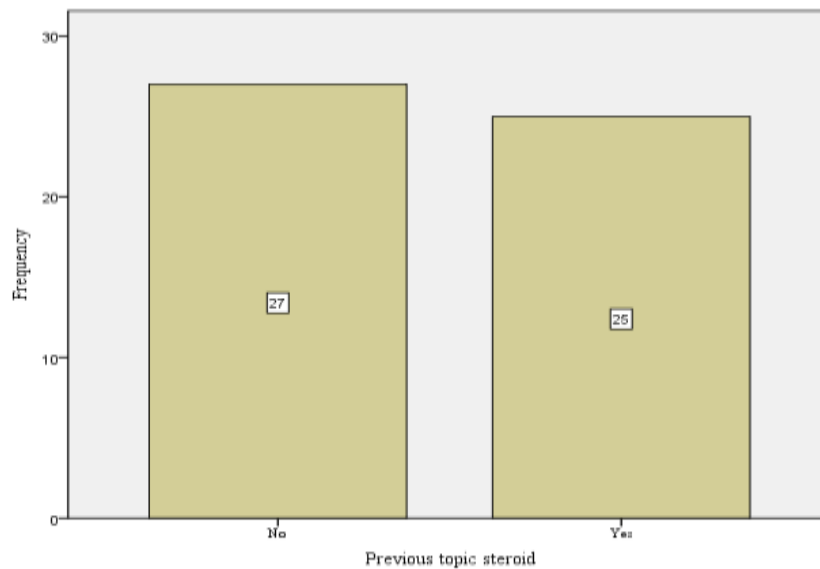


**Figure 7.** Family allergy predisposition

VII). Previous therapy with topic steroid: Of the 52 patients (children), 27 (51.9%) did not receive previous therapy with a topic steroid and 25 (48.1%) received previous therapy with a topical steroid (Table 8 and Figure 8).

**Table 8.** Previous topic steroid

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	27	51,9	51,9	51,9
	Yes	25	48,1	48,1	100,0
	Total	52	100,0	100,0	

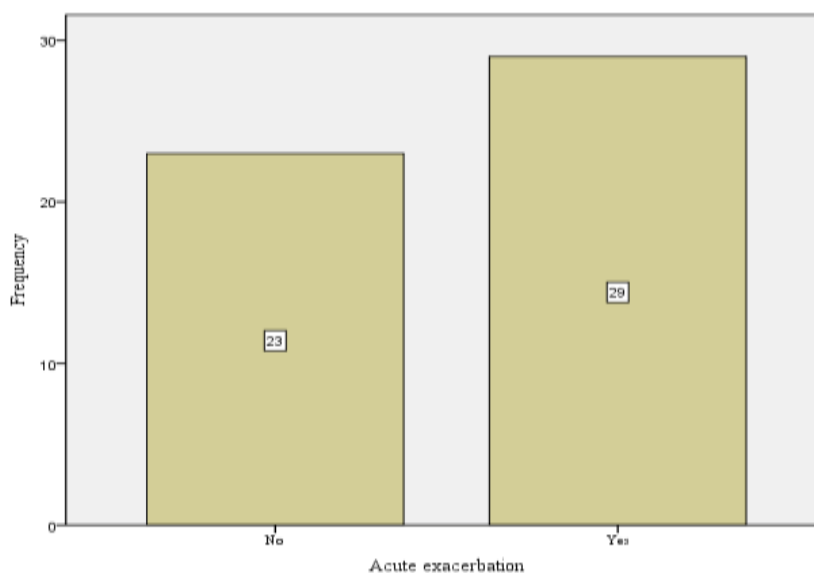


**Figure 8.** Previous topic steroid

VIII). Acute exacerbation: Of the total 52 patients (children), 23 (44.2%) did not have acute exacerbation and 29 (55.8%) had acute exacerbation (Table 9 and Figure 9).

**Table 9.** Acute exacerbation

	Frequency	Percent	ValidPercent	CumulativePercent
No	23	44,2	44,2	44,2
Valid Yes	29	55,8	55,8	100,0
Total	52	100,0	100,0	

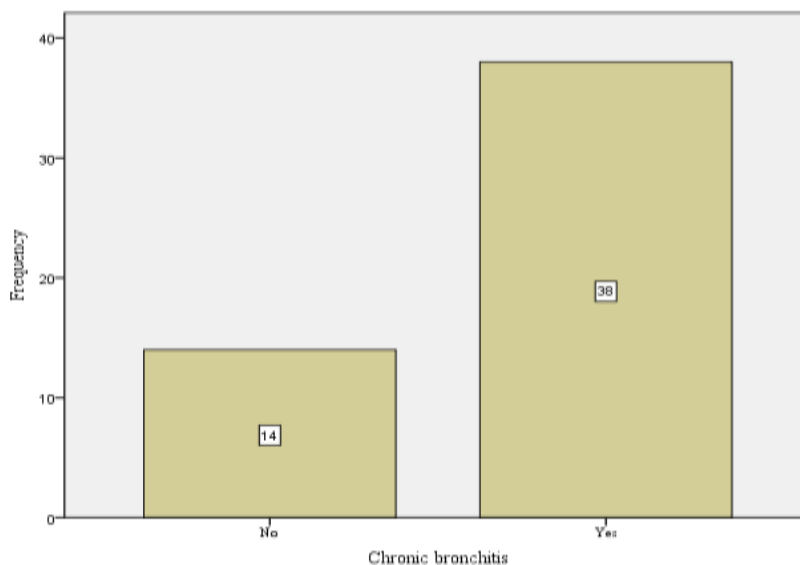


**Figure 9.** Acute exacerbation

IX). Diagnosis of recurrent bronchitis: From the 52 patients (children), 14 (26.9%) did not have recurrent bronchitis and 38 (73.1%) had recurrent bronchitis (Table 10 and Figure 10).

**Table 10.** Recurrent bronchitis

	Frequency	Percent	Valid Percent	Cumulative Percent
No	14	26,9	26,9	26,9
Valid Yes	38	73,1	73,1	100,0
Total	52	100,0	100,0	



**Figure 10.** Recurrent bronchitis

### Prediction of Recurrent Bronchitis

When determining the predictive values of Gender (1), Age, EVI, Family allergy predisposition (1), Previous topic steroid (1), Acute exacerbation (1), for chronic bronchitis the enter method was used.

The global accuracy of this model to predict Chronic bronchitis is 86.50%. Sensitivity is 97.40% and specificity is 57.10% (Table 11).

**Table 11.** Predictive values of age, occupational groups by type of work, education, total work experience / Pattern of discrimination

Observed			Predicted		
			Chronic bronchitis		Percentage Correct
			No	Yes	
Step 1	Chronic bronchitis	No	8	6	57,1
		Yes	1	37	97,4
Overall Percentage					86,5

a) The cut value is ,500

In determining the significance of the contribution to the prediction of Recurrent bronchitis, it was found that the greatest influence was Previous topic steroid (1) (Wald=9.191 /  $p < 0.01$  ( $p = 0.002$ )), then Acute exacerbation (1) (Wald=3.512 /  $p > 0.05$  ( $p = 0.061$ )), EVI (Wald=1.280 /  $p > 0.05$  ( $p = 0.258$ )), Age (Wald=0.870 /  $p > 0.05$  ( $p = 0,351$ )), Family allergy predisposition (1) (Wald=0.233 /  $p > 0.05$  ( $p = 0.629$ )) and the weakest influence is Gender (1) (Wald=0.005 /  $p > 0.05$  ( $p = 0.943$ )).

Patients (children) who have previously received therapy with a topical steroid (1) / by 60,801 times ( $\text{Exp}(B) = 60,801$ ) / have a higher risk of chronic bronchitis than patients (children) who have not previously received therapy with a topical steroid, 95% C.I. for  $\text{EXP}(B)$  / 4,272 – 865,331 /, significant for  $p < 0.01$  ( $p = 0.002$ ).

Patients (children) who had Acute exacerbation (1) by 10,871 times (Exp(B) = 10,871) had a higher risk of Chronic bronchitis than patients (children) who did not previously have Acute exacerbation, 95% C.I. for EXP(B) / 0.897–131,827/, non-significant for  $p > 0.05$  ( $p = 0.061$ ).

Increasing EVI per unit reduced the risk of chronic bronchitis by 15.10% (Exp(B)=0.849) / 95% C.I. for EXP(B) / 0.639 – 1.128/, non-significant for  $p > 0.05$  ( $p = 0.258$ ).

Increasing Age per unit value (1 year) reduced the risk of Chronic bronchitis by 26.50% (Exp(B)=0.735) / 95% C.I. for EXP(B) / 0.385 – 1.404/, non-significant by  $p > 0.05$  ( $p = 0.351$ ).

Patients (children) who had Familial allergy predisposition (1) by 1,559 times (Exp(B) = 1.559) had a higher risk of Chronic bronchitis than patients (children) who had no prior Family allergy predisposition, 95% C.I. for EXP(B) / 0.257 – 9.464/, not significant for  $p > 0.05$  ( $p = 0.629$ ).

Male patients (children)/Gender(1) by 0.934 times (Exp(B) = 0.934) have a lower risk of Chronic bronchitis than female patients (children), 95% C.I. for EXP(B) / 0.143 – 6.098/, non-significant for  $p > 0.05$  ( $p = 0.943$ ).

**Table 11.1.** Binary Logistic Regression Analysis for Prediction of Chronic bronchitis

Step 1 <sup>a</sup>	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Gender(1)	(,068)	,957	,005	1	,943	,934	,143	6,098
Age	(,308)	,330	,870	1	,351	,735	,385	1,404
EVI	(,164)	,145	1,280	1	,258	,849	,639	1,128
Family allergy predisposition (1)	,444	,920	,233	1	,629	1,559	,257	9,464
Previous topic cortico (1)	4,108	1,355	9,191	1	<b>,002</b>	60,801	4,272	865,331
Acute exacerb (1)	2,386	1,273	3,512	1	,061	10,871	,897	131,827
Constant	1,929	2,863	,454	1	,500	6,882		

a. Variable(s) entered on step 1: Gender(1), Age, EVI, Family allergy predisposition(1), Previous topic cortico(1), Acute exacerb(1).

The ROC area is 0.891, meaning that in 89.10% / 95% CI: 0.785–0.996/  $p < 0.001$  ( $p = 0.000$ ) / of all possible pairs in which one has Chronic bronchitis and the other does not have Chronic bronchitis, this model will determine a higher probability of Chronic bronchitis (Figure 11).

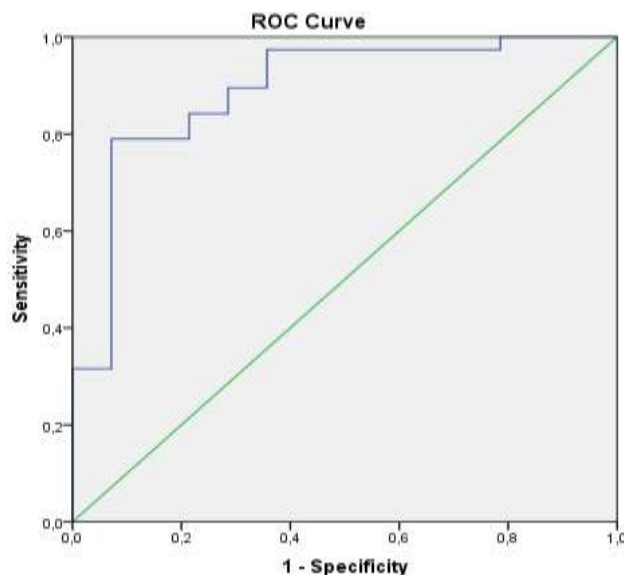


Figure 11. Area Under the Curve

### Discussion

In this study we assessed the influence of different variables in diagnosing and outcome of recurrent bronchitis in preschool children. According to the Diagnosis, the largest number of our patients had recurrent bronchitis (37 children, or 71,15%), and 29 (55,8%) had acute exacerbation.

Out of all 52 children, 25 (48.1%) received previous therapy with a topical steroid. 27 (51,9%) of the children had positive family history for atopy, and as far as the diagnostic allergy procedures are concerned, 53,8% had positive IgE, 46,2% had eosinophilia in nasal smear/sputum and 30,8% had positive SPT. For assessment of the lung function all of the children surpassed measurement with Ventica system, for which all of the parents did give their written consent.

The measurements were carried out in hospital conditions on one occasion, and in all of 52 children the recordings were successful. EVI values were given by the software accordingly. Mean value of duration of recording time was 11,73 hours. The values of EVI varied from 4,80 up to 22, with median 15,60.

Our research in determining the significance of the contribution to the prediction of recurrent bronchitis showed that the greatest influence had previous therapy with topic steroid (Wald=9.191 /  $p < 0.01$  ( $p = 0.002$ )), followed by acute exacerbation (Wald=3.512 /  $p > 0.05$  ( $p = 0.061$ )). Value of EVI analyzed as contributor of prediction of recurrent bronchitis showed (Wald=1.280 /  $p > 0.05$  ( $p = 0.258$ )). Increasing EVI per unit reduced the risk of chronic bronchitis by 15.10% (Exp(B)=0.849) / 95% C.I. for EXP(B) / 0.639 – 1.128/, non-significant for  $p > 0.05$  ( $p = 0.258$ )).

Based upon clinical trials in older children, early introduction of ICS in the treatment of asthma has been recommended [4-5]. In a cohort study in Oslo published 2004a cohort of 3,754 newborn children were analyzed of which 306 children had documented recurrent bronchitis by age 2 yrs. Two tidal flow/volume measurements were taken, one at presentation of disease (children were steroid naïve) and one at 2 yrs of age (mean age 11.2 and 25.6 months, respectively), from: 21 cases who subsequently received ICS (ICS+); 33 who did not (ICS-); and in 15 controls. The mean±sd duration of ICS treatment was 10.3±6.5 months.

The main outcomes were treatment with ICS and baseline ratio of time to peak expiratory flow/total expiratory time ( $t_{PEF}/t_E$ ). This study demonstrated that one-fifth of young children with recurrent bronchial obstruction had received inhaled corticosteroids, and that early inhaled corticosteroid treatment improved lung function by age 2 yrs, mostly in those with the longest duration of treatment [6]. Several studies have

been published in relevant medical journals involving children under 6 years of age who have used the Ventica device for assessing the lung function [7–16].

A 2020 paper published in Pediatric Allergy and Immunology analyzed 68 children (aged 1.0-5.6) and 40 healthy controls (aged 1.0-5.9 years). The patients were prescribed a three-month inhaled corticosteroid (ICS) treatment due to recurrent obstructive bronchitis. They measured EVI using IP at home at the end of the treatment (0W) and 2 (2W) and 4 (4W) weeks after ICS withdrawal.

EVI was higher in controls than in patients, and significant within-patient reduction occurred at 4W as compared to 2W or 0W. Area under curve of the ROC curve (controls vs all patients) at 4W was 0.78 (95% CI 0.70-0.85). Children who were administered bronchodilator by parental decision had lower EVI than those without bronchodilator need at 4W, but not at 0W or 2W. Patients with parent-reported airway infection, but no bronchodilator need, had normal EVI. Measurement success rate was 94% [13].

In another paper, also from 2020, the association of EVI values with the severity of bronchoobstructive attacks was being analyzed. In this research EVI was measured using a wearable IP system (Ventica®) during sleep in 40 healthy controls (aged 1.5-5.9 years) and 30 patients hospitalized due to acute bronchoobstruction (aged 1.3-5.3 years). In healthy controls, EVI was measured for 1-3 nights at their homes. Patients were measured for several nights during hospitalization, as practically feasible, and at home 2 and 4 weeks post-discharge. Compared to controls, EVI was significantly lower during hospitalization ( $P < .0001$ ) having significant correlation with number of days to discharge ( $r = -.38$ ,  $P = .004$ ). At 2 or 4 weeks post-discharge, EVI was not significantly different from the controls ( $P = .14$ ,  $P = .49$ , respectively). EVI was significantly associated with chest auscultation findings ( $P = .0001$ ) being 17.5 (4.9) (median, IQR) with normal auscultation, 15.6 (7.4) in those with prolonged expiration and 11.4 (6.8) in those with wheeze and/or rales and crackles [14].

A 2021 papers published in Pediatric Pulmonology showed that EVI value correlates with the severity of acute bronchoobstructive attacks in preschool age. Between January 2014 and May 2017 they followed 43 infants referred for infant lung function testing because of recurrent respiratory symptoms such as wheeze, cough and/or laborious breathing. Children were classified by asthma risk by using loose criteria of the modified Asthma Predictive Index (mAPI).

Children with a history of multiple episodes of wheeze (at least two) and who fulfilled one of the major criteria (parental history of asthma, atopic dermatitis, sensitisation to respiratory allergens), were considered to have a high risk of asthma. Children who did not have a history of wheeze or did not fulfil any of the major criteria above were considered to have low risk. Infants who fell between the criteria of high and low risk were considered to have an intermediate risk.

Children with current respiratory infection were excluded. Lung function was determined by measuring the maximal flow at functional residual capacity using rapid thoracic compression under sedation, and expressed as z-scores, adjusting for weight, length, and/or sex. Fractional exhaled nitric oxide ( $F_{ENO}$ ) was measured with the tidal online technique. After lung function tests, an IP device (university-developed prototype) was installed on the subjects for overnight recording at home. EVI was different between asthma risk categories (ANOVA linear trend test  $p=0.022$ ), being lowest in the high asthma risk children. Children with prolonged expiration or wheeze as the main symptom had lower EVI than those with only cough ( $t$ -test  $p=0.044$ ).

EVI showed positive correlation with  $V'_{max}FRC$  (Pearson correlation  $r=0.52$ ,  $p=0.002$ ). EVI values from children with nasal congestion were not statistically different from those without congestion. In overnight recordings, EVI was not significantly associated with AHR ( $p=0.70$ ), nor with atopic eczema (Mann–Whitney U-test  $p=0.40$ ), skin prick test ( $t$ -test  $p=0.49$ ) or  $F_{ENO}$ . They concluded that lower values of EVI were observed as the asthma risk in the children increased [15,16].

The results were compared with a control group of healthy children, and it was found that the results obtained using the Ventica system provided good insight into the incidence of bronchial obstruction in children during sleep, and correlated with the assessment of regular reception of therapy. Children who are stable on anti-inflammatory therapy would have a normal EVI, which would indicate that they may be discontinued from starting therapy.

## Conclusion

There are several studies published in relevant scientific papers that confirm the usage of Ventica-system as non invasive lung function monitoring system in children aged 1-6 years. In our research the increasing of EVI values did not show statistical significance with the reduction of broncho-obstruction in recurrent bronchitis. We must emphasize that in this study the number of sampled children is relatively small and the measurements were carried out on one occasion in hospital conditions. Thus, more profound investigations with larger number of samples, as well as increasing number of consecutive measurements are needed in this field to objectify the usage of one of the non-invasive lung function monitoring in preschool children.

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