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Value of Total Serum Immunoglobulin-E (IgE) as Predictor of Asthma in Children with Recurrent Wheezing

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Original Article

Abstract

Background: *Early detection of asthma in children is challenging, especially those with a history of asthma or allergies. Serum IgE levels help understand allergy mechanisms, create diagnostic tool, and establish allergen extract consistency.*

Objective: *To evaluate the role of total serum IgE level in predicting asthma in wheezy children .*

Methods: *A cross-sectional study included 100 wheezy children, IgE level measured by Diagnostics ELISA kit, results were read with microtiter plate reader at optical density 450 nm. Validity of IgE as predictor of asthma assessed using receiver operating characteristics (ROC) curve analysis. Estimation of risk factors for elevated IgE more than 100 IU/ml was assessed using odds ratio and appropriate statistical analysis with the statistical package for social sciences (SPSS) version 25 at a level of significance ≤ 0.05.*

Results: *A study found that children aged 12 months or older, had significantly higher levels of IgE than those aged < 12 months. Males were more likely to have higher IgE levels than females, (P<0.05). A positive family history of asthma, bottle feeding, higher number of wheeze attacks and presence of two or more criteria of atopy were significantly associated with more frequent elevated IgE levels > 100 IU/ml. IgE was a strong predictor of asthma at a cutoff value of > 100 IU/ml. A binary regression analysis showed that family history of asthma, presence of more than one Atopy criteria, wheeze attacks of ≥ 3, eosinophil ≥ 5%, and bottle feeding were stronger predictors of elevated IgE levels. Breast feeding was associated with lower IgE levels, reflecting a protective effect.*

Conclusions: *High proportion of wheezy children were asthmatic. IgE was a strong predictor of asthma at a cutoff value of > 100 IU/ml*

Keywords: *Childhood asthma, Wheezing, predictors, Immunoglobulin-E,*

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1. INTRODUCTION

Childhood asthma is a heterogeneous inflammatory disease with different phenotypes that depend on age, gender, genetic background and environmental exposure, and that follow a common pathway characterized by recurrent symptoms of airway obstruction Most cases of asthma begin in the first years of life, so identifying children at high risk of developing the disease is a public health priority (1). In some countries, consultations for bronchial obstruction in primary care constitute 23% of morbidity care in children under15 years of age and, according to data from the Ministry of Health, they generate 16% of all consultations in the group between 5 and 14 years of age. The presence of recurrent wheeze in the first years of life occurs in approximately 40% of children, although only 30% of children with recurrent wheeze will have asthma by six years of age (2). Studies carried out in different developed countries reveal a sustained increase in the prevalence of asthma and atopy, in the last 5 years it had been estimated that the overall prevalence of paediatric patients with symptoms of asthma were about 10% globally. In the quest to predict whether a wheezing patient will suffer from asthma, predictive indices have been developed (3). Asthma, the most common long-term illness in children, typically begins before the age of 5. However, it remains challenging for doctors to accurately diagnose this condition in infants and preschoolers. This can be attributed to the fact that in this age group, the clinical features of asthma are diverse and less specific compared to adult because some other conditions that may cause wheezing can be also present. Moreover, in young children it is not possible to routinely investigate and assess the limitation in the airflow and airway inflammation which are the main characteristics of asthma in paediatric patients. However, it is important to note that not all instances of wheezing and coughing are attributable to asthma, hence it is crucial to deal with wheezing cases with caution to avoid inappropriate prolonged unnecessary asthma treatment (4). Unfortunately, there is a group of children who experience wheezing and later acquire asthma. This group exists alongside another group of infants who have recurring wheezing, but their symptoms are temporary and typically diminish during their early school years. Differentiating between these categories in infancy and early childhood only based on clinical presentation is a difficult task and. currently, there are no precise screening tests like genetic or high accurate biomarker to identify which recurrent wheezy child at high risk of developing asthma the risk of developing

asthma among wheezy children. Several studies investigated and evaluated both invasive and non-invasive approaches for early diagnosis of asthma or to predict it. From other point of view, studies that assess responsiveness of air ways in young children yielded conflicting results in prediction of asthma in school age (5.6). Therefore, the management of pediatric asthma mainly depend on the clinical assessment and observation by the pediatricians which rely on subjective evaluation. Furthermore, incidence of wheezing in the early childhood age, particularly below the age of 3 is not an accurate or effective indicator for asthma. Conversely, the presence of atopy during early stages of life was a more reliable predictor of future respiratory conditions (4). Recurrent wheezing is a very common problem in the first years of life. Worldwide, up to 40% of young children present have at least one episode of asthmatic symptoms (wheezing, dyspnoea or persistent cough) in this age group. However, only 30% of children with wheeze will persist with these symptoms and diagnosed as asthma at the age of 6 years of age. From a clinical point of view, it would be very useful to have a "risk index", combining history with clinical or laboratory findings, which would allow to identify those children with a greater probability of developing persistent asthma over time. However, in children with symptoms and a high risk of persistence, it is recommended to start pharmacological treatment to reduce morbidity (7). With the aim of helping the clinician identify children who will continue to wheeze, several prediction models or clinical risk indicators have been studied. These models have used various risk factors associated with the development of asthma in epidemiological studies, such as family history of allergic sensitization and asthma, history of wheezing, atopic disease in the child, immunoglobulin E (IgE) levels, and cytosine secretion profiles. When the asthma guide was published in 2005, different other indices were available, nonetheless, some of these indices have showed applicability problems since they were not validated in populations other than the original ones (8). Several research in the literature have attempted to validate the current predictive indices. However, there is no definitive test considered as the most reliable for diagnosing asthma. Practically, a diagnosis should be determined by analyzing unique symptom patterns, observing fluctuations in airflow restriction alongside airway inflammation, considering the possibility of alternative diagnoses, and evaluating the response to treatment (9). Recurrent wheezing in early childhood can be categorized according to its pattern or duration; according

to duration it can be categorized into :

Infrequent or never, include children who are never wheeze or having one wheezing episode in their life. Early / transient wheezing; recurrent wheezing in the first 3 years of life, Late-onset and persistent wheezing, According to pattern, it classified as episodic and multitrigger wheezing (REF: classification scholar) (10). Identifying children who are at risk for developing asthma at an early stage is challenging, particularly in children who are also at risk for atopy. However, positive history of allergies, rhinitis, eczema, family history of asthma, have shown to be significantly associated with asthma or wheeze. Therefore, they require careful and regular clinical monitoring. The identification of serum IgE levels has facilitated comprehension of the mechanisms behind allergic reactions. Furthermore, it has resulted in the creation of diagnostic instruments, as well as the examination and uniformity of allergen extracts. Immunoglobulin E (IgE) has been demonstrated to be a significant causative element in the emergence of bronchial hyperresponsiveness in asthma. An increase in the levels of IgE in the blood is a contributing factor to asthma and is regarded a strong indicator of the likelihood of developing asthma. Multiple population studies have demonstrated a correlation between the occurrence of asthma or bronchial hyper-responsiveness and the overall levels of IgE in the bloodstream. This correlation exists regardless of specific response to common allergens or allergy symptoms. Additionally, a strong link between the levels of IgE in the blood and the asthma was widely documented (11). However, the validity of total IgE in prediction of childhood asthma in wheezy children is still not well clarified, hence we tried to assess the role of total IgE as predictor of childhood asthma in wheezy children in Karbala city

2. PATIENTS and METHODS

This was a prospective study conducted during a period of 16 months (2022-2023), in Karbala city 100 children who were presented with recurrent wheezing episodes

Study population and eligibility:

The study included a total of 50 wheezy children as cases in whom the prevalence of asthma was estimated and reported. As control group we included 50 children who were apparently healthy and they were almost matched to wheezy children.

We included children who were presented with recurrent wheezing episodes of both genders

We excluded children who had one or more of the following; other confirmed respiratory diseases like cystic fibrosis, bronchopulmonary dysplasia, severe comorbidities, malignant diseases, hematological diseases, autoimmune disease, using immunosuppressant medications, and those who were currently at active infection status. Children with missed data for laboratory tests and those whose parents\ guardians did not provide consents for their participation were also excluded.

Study tools and Data collection:

A pre-constructed data collection sheet (Questionnaire) was used for data collection. Data were collected through direct interview with the child's parents who were asked to answer about the questionnaire's items. Their responses were reported.

Family history and demographic variables of the children and their parents were all reported. Additionally, clinical data were collected through a thorough physical examination and full-history taking.

Full investigations were performed for all participated children accordingly such as imaging, hematological investigations and other necessary laboratory tests were also performed when needed to confirm the diagnosis.

Total Immunoglobulin E (IgE) concentration was assessed in both cases and control groups using a quantitative enzyme immunoassay is used to determine the content of immunoglobulin E (IgE) in serum. Individuals suffering from atopic allergy conditions, such as atopic asthma, atopic dermatitis, and hay fever, have been observed to display elevated amounts of Immunoglobulin E (IgE) in their bloodstream.IgE, which stands for Immunoglobulin E, is commonly referred to as the reaginic antibody. Typically, higher levels of IgE suggest a greater likelihood of an IgE-mediated hypersensitivity, which is responsible for causing allergic reactions. The level of IgE is directly correlated with the degree of color intensity observed in the test sample. The DRG IgE ELISA is a fast, sensitive, and dependable test for measuring the total amount of IgE in the blood serum. A pair of meticulously chosen IgE antibodies is employed to ascertain a minimal concentration of IgE at 5.0 IU/mL (12).

Statistical analysis:

Data were entered, managed and processed using statistical software; the statistical package for social sciences version 28 (SPSS28) for windows. Microsoft Excel program version 2020, Epi-calc 2000 software were also utilized. Appropriate statistical tests were applied according to the type of variables. For scale variables, Student's t test and ANOVA tests were used to compare means. Chi-square test and Fisher's exact test were used to compare qualitative (categorical) variables. Bivariate correlation analysis used to assess the correlation between variables. Receiver Operating characteristics (ROC) curve used to assess the validity and the optimal cutoff concentration of IgE that can predict asthma. ROC curve is a statistical graph that plot the true positive rate versus false positive rate. Area under the ROC curve (AUC) was calculated which is an estimator of validity of a test; AUC of larger values close to one indicates high performance of a test. All statistical procedures in our study performed at a level of significance (P. value) of ≤ 0.05.

3. RESULTS

There were 100 wheezy children enrolled in this study of them 52 aged less than 12 months, 55 were males, 72 residents in urban areas, 59 had positive family history of asthma and parental smoking reported in 54 of patients. Breast feeding documented in 22 patients, bottle feeding in 31, mixed feeding in 27 while 20 children had table feeding. The IgE was > 100 IU/ml in 68 patients and <100 IU/ml in the remaining 32 patients (**Figure 1**). Comparison of baseline characteristics of the studied group across the levels of IgE revealed that level of IgE > 100 IU/ml was significantly more frequent in children of age ≥ 12 months compared to those < 12 months of age, 85.4% vs. 51.9%, respectively, (P=0.001). IgE > 100 IU/ml was significantly more frequent in males (81.8%) than females (51.1%), (P=0.002). No significant association was found between level of IgE and residence of wheezy children, (P>0.05). Children with positive family history of asthma had significantly higher frequency of higher IgE level of >100 IU/ml, compared to those with negative family history, 88.1% vs. 39%, respectively, (P<0.001). Among children whose fathers were smokers, 79.6% had IgE level of >100 IU/ml while 54.3% of those whose fathers were non-smokers, with significant difference, (P=0.013). Type of feeding was significantly associated with elevated IgE levels; the proportion of

children who had IgE level of >100 IU/ml was significantly higher among those on bottle feeding, (93.5%), while the least proportion, (18.2%) among those on breast feeding, (P<0.001), all these findings are demonstrated in (**Table 1**). Among the studied group, 33 had their first wheeze attack, 26 had their second attack while 41 had history 3 or more attacks. Atopy criteria were not reported in 31 patients, one criteria present in 39 patients, two criteria in 18 and three criteria reported in 12 patients. Eosinophil percent was ≥ 5% in 34 patients. Cross-tabulation revealed that frequency of IgE level of > 100 IU/ml was significantly increased with higher number of wheeze attacks, (P<0.001). Patients who had two or more criteria of atopy had significantly more frequent IgE of > 100 IU/ml, (P<0.001). Eosinophil percent of ≥ 5% was significantly associated with elevated IgE of > 100 IU/ml, (P<0.001), (**Table 2**). Further analysis was performed to assess the validity of IgE in prediction of asthma among the 100 wheezy children. We used receiver operating characteristics (ROC) curve which revealed that IgE was a strong predictor of asthma at a cutoff value of > 100 IU/ml. It produced an area under the curve (AUC) of 0.984, a sensitivity of98.3%, specificity of 98%, accuracy 98.6%, positive predictive value of 98.2% and a negative predictive value of 98.4%, (**Figure 2 and Table 3**). Furthermore, to estimate the risk variation of higher IgE and the relationship with different variables, a binary regression analysis using IgE as dependent variable and other variables as independent variables, results of this analysis is demonstrated in (Table 4). All patients' characteristics except residence and table feeding that showed non-significant association with IgE levels, in both comparisons, P. value > 0.05. According to the odds ratio (OR) values and confidence interval, family history of asthma, presence of more than one criteria of Atopy, wheeze attacks of ≥ 3 , eosinophil ≥ 5 % and bottle feeding were stronger predictor of elevated IgE levels where the odds ratio values were 9.61, 9.36, 8.22, 8.1 and 7.18, respectively. Followed by age ≥ 12 months and male sex with an OR of 5.42 and 4.30, respectively. From other point of view, breast feeding was significantly associated with lower IgE levels where the OR was below one (OR = 0.05), reflecting a protective effect for breast feeding., (**Table 4**).

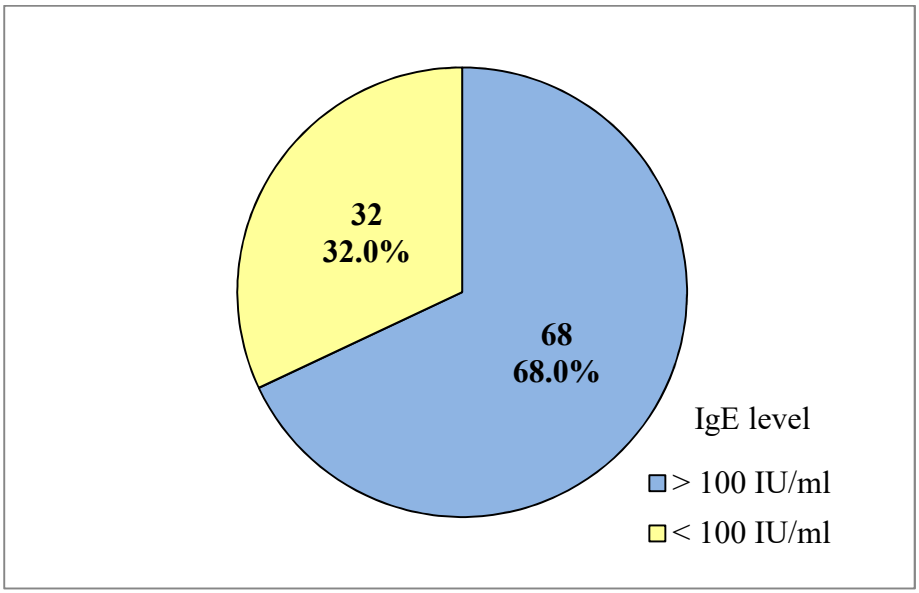

Figure 1. Distribution of 100 wheezy children according to IgE levels

Table 1. Cross-tabulation for the relationship between IgE levels and baseline characteristics of the studied group

Variable		IgE level				Total	P. value
		> 100 IU/ml (N=68)		< 100 IU/ml (N=32)			
		No.	%	No.	%		
Age (months)	≥ 12	41	85.4	7	14.6	48	0.001 sig
	< 12	27	51.9	25	48.1	52	
Sex	Male	45	81.8	10	18.2	55	0.002 sig
	Female	23	51.1	22	48.9	45	
Residence	Urban	49	68.1	23	31.9	72	0.873 ns
	Rural	19	67.9	9	32.1	28	
Family history of asthma	Yes	52	88.1	7	11.9	59	<0.001 sig
	No	16	39.0	25	61.0	41	
Paternal smoking	Yes	43	79.6	11	20.4	54	0.013 sig
	No	25	54.3	21	45.7	46	
Type of feeding	Breast feeding	4	18.2	18	81.8	22	<0.001 sig
	Bottle feeding	29	93.5	2	6.5	31	
	Mixed feeding	23	85.2	4	14.8	27	
	Table feeding	12	60.0	8	40.0	20	

Table 2. Cross-tabulation for the relationship of IgE levels with Wheeze Attacks , atopy criteria and Eosinophil percent of the studied group

Variable		IgE level				Total	P. value
		> 100 IU/ml (N=68)		< 100 IU/ml (N=32)			
		No.	%	No.	%		
Wheeze attacks	First	11	33.3	22	66.7	33	<0.001 sig
	Second	18	69.2	8	30.8	26	
	Third / more	38	92.7	3	7.3	41	
Atopy criteria	None	6	19.4	25	80.6	31	<0.001 sig
	One	32	82.1	7	17.9	39	
	Two	18	100.0	0	0.0	18	
	Three	12	100.0	0	0.0	12	
Eosinophil percent	≥ 5%	31	91.2	3	8.8	34	<0.001 sig
	< 5 %	37	56.1	29	43.9	66	

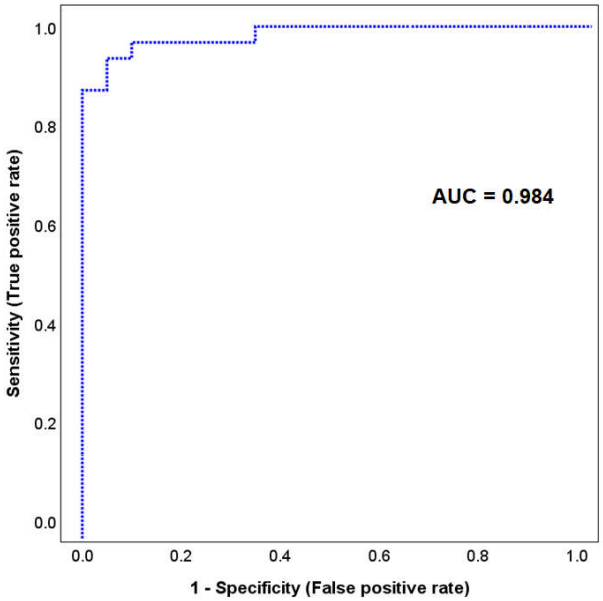

Figure 2. Receiver operating characteristics (ROC) curve for the validity of IgE as predictor of asthma in 100 wheezy children (AUC: area under the curve)

Table 3. Validity parameters of IgE > 100 IU/ml in prediction of Asthma

Validity parameter	Value
Cutoff value	> 100 IU/ml
AUC	0.984
Sensitivity	98.30%
Specificity	98.00%
Accuracy	98.60%
PPV	98.20%
NPV	98.40%

AUC: Area under the ROC curve, PPV: positive predictive value, NPV: negative predictive value

Table 4. Results of binary regression analysis for the correlation between IgE > 100 IU/ml and other variables

Independent Variable		OR	95% CI of OR	P. value
Age ≥ 12 months		5.42	2.06 - 14.29	0.001 sig
Sex (male)		4.30	1.75 - 7.59	<0.001 sig
Residence		1.01	0.40 - 2.57	0.826 ns
Family history of asthma		9.61	4.24 - 13.81	<0.001 sig
Paternal smoking		3.28	1.36 - 7.92	0.013 sig
Type of feeding	Breast feeding	0.05	0.01 - 0.17	< 0.001 sig
	Bottle feeding	7.18	2.46 - 12.49	< 0.001 sig
	Mixed feeding	3.58	1.12 - 11.43	0.025 sig
	Table feeding	0.64	0.23 - 1.77	0.557 ns
Wheeze Attacks ≥ 3		8.22	3.40 - 11.10	<0.001 sig
Atopy criteria > one		9.36	5.28 - 12.73	<0.001 sig
Eosinophil ≥ 5 %		8.10	2.25 - 13.16	<0.001 sig

OR: odds ratio, 95% CI: 95% confidence interval

4. DISCUSSION

Identifying children who are at risk for developing asthma at an early stage is challenging, particularly in children who are also at risk for atopy. Delayed diagnosis leads to a higher likelihood of long-term health issues and other complications, in contrast to individuals who were early diagnosed and receive proper treatments (13). Wheezing, as a prominent characteristic of asthma, is quite prevalent among preschool children, with a reported occurrence rate of 30% to 50%. Nevertheless, the diagnostic value of wheezing in identifying childhood asthma is a subject of contention due to its inconsistent progression during early years. It had been widely postulated that children who have a family history of asthma or allergies and experience frequent early wheezing are at a significantly higher risk of developing asthma. Therefore, they should receive thorough clinical monitoring (14).

There are different standardized screening methods aiming for early detection of high risk group who may develop persistent symptoms of asthma and required additional healthcare services. Nonetheless, sometimes, invasiveness of these methods limiting their applicability (14),therefore, searching for new , practical and cost-effective test and techniques is continued and necessarily required for early detection of asthma and prevention of its related adverse sequela. The quantification of IgE is an essential component of evaluating patients who are being studied for allergy disorders. Since its discovery in 1966, IgE has been widely regarded as the primary biological target for treating allergy and asthma (15). The diagnostic efficacy of IgE was initially observed in extrinsic bronchial asthma since 1980s where a population based study showed a strong correlation between IgE levels and asthma (16). The identification of serum IgE levels has facilitated comprehension of the mechanisms behind allergies. Currently, testing for IgE represents the key diagnostic tool for assessing patients with suspected allergic conditions (17).

In our present study the primary aim was to assess the precision of predicting the likelihood of developing asthma in a sample of 100 wheezy children. This study holds significant implications for strategies targeting early intervention in individuals with an increased risk of developing asthma. There is a hypothesis suggesting that administering anti-inflammatory medications at an early stage could alter the course of the disease and prevent exacerbation of symptoms, however, little evidence supported their use (18).

In our study, out of the 100 children, 68% showed elevated total serum IgE levels of > 100 IU/ml, suggesting that it can serve as a reliable indicator for asthma.

Among the studied group, males were relatively dominant, 55%, we found that males had significantly more frequent elevated IgE levels than females, where 81.8% of males and 51.1% of females had elevated IgE > 100 IU/ml, ($P<0.05$). These findings consistent with that reported by Satwani et al. who found that IgE levels were raised in bronchial asthma and in male children (19). In a systematic review, Strina et al. reported that serum IgE had a significant explanatory value for the mechanism of allergy that mediated asthma (20)

Regarding the age, we found that older children had significantly higher levels of IgE compared to younger children < 12 months. Conversely, Kartasamita et al. from Indonesia found that IgE levels were not related to age (21). So as, Satwani et al. (19) found no significant association between age and elevated serum IgE levels among children at any age group. On the other hand Satwani et al. (19) found no difference between males and females regarding the IgE levels, however, some previous studies documented higher levels in males than females (22–24).

In the present study positive family history of asthma have been associated with increased level of IgE , since IgE level is closely related to asthma, with the risk of development of asthma is subsequently increased . Another study had shown no influence of family history on IgE level, Lopez N et al. (25).

We found none of the mothers were smoker and that raised IgE significantly associated with paternal smoking. It is well-known that parental and passive smoking are strongly established risk factors of childhood asthma (26,27). Satwani et al. stated that passive smoking is a stronger environmental risk factor associated with higher levels of total serum IgE (19). Nonetheless, the precise contribution of passive smoking to the development of asthma is still unclear, there is increasing evidence linking it to the worsening of asthma symptoms in children (28). Therefore, Paediatricians should caution parents that smoking can have harmful consequences for their children who have asthma.

We documented that formula and mixed feeding associated with higher levels of IgE, this might give a clue that early introduction of formula milk may increase the risk of subsequent development of allergic disorder including asthma since cow's milk protein is considered as

foreign protein. From the above data, we find that exclusive breast feeding in the 1st six months of life can prevent subsequent development of asthma. Silva et al. concluded that allergic sensitization and formula feeding were independent risk factors for persistent wheezing while breast feeding was a protective factor. Additionally, in the same study, Silva et al. found a stronger association in the younger children (29).

In the present study positive family history of asthma have been associated with increased level of IgE. In contrast, Lopez et al. found no significant effect of family history on IgE levels (25).

In our investigation, we observed that eosinophilia, accompanied by elevated blood IgE levels, served as a notable indicator of allergies. Peripheral blood eosinophil counts are commonly employed in clinical practice to establish the allergic origin of an illness, track its clinical progression, and guide treatment decision (19). Hence, the measurement of eosinophils in peripheral blood can serve as a valuable tool for examining the correlation between host variables and environmental determinants as markers of the incidence of allergies (19). An association was found between the frequency of wheezing attacks and the raised serum total IgE levels which were not only raised but also correlated well with the severity of bronchial asthma, in our series patients with more frequent attacks of wheezing had higher levels of IgE. This study corroborates the findings shown by previous studies (19).

From other popint of view, it has been suggested that high total serum IgE level could itself be a marker of air way inflammation in asthmatic patients (30) . All patients with multiple atopic conditions in our study showed serum IgE levels more than 100 IU , while 10 % of patients with single criteria have IgE less than 100 IU , supported by Kerkhof M et al and Ahmed et al studies (24,30).

In our study we assessed the validity of total serum IgE as predictor of asthma among the 100 wheezy children. We found that IgE was a strong predictor of asthma at a cutoff value of > 100 IU/ml it had a sensitivity of 98.3%, specificity of 98% and an accuracy of 98.6%.

A previous Iraqi study conducted in Ninevah , north of Iraq, by Haitham Bader Fathi found that IgE at a cutoff value of 100IU/ml had moderate accuracy in diagnosing various allergic diseases. However, Fathi stated that this cutoff value was the best useful classifier and that total serum IgE can be used as a useful screening test rather than as a confirmatory test (31)

Cárdenas et al. (32) found that total serum IgE was able to predict clinical allergy to cat dander

in asthmatic patients good, it showed a good performance with an AUC of 0.838, sensitivity of 94%, specificity of 97.5% and accuracy of 96%.

Tu et al. established that the serum total IgE ability to accurately diagnose asthma, rhinitis, and eczema was generally moderate, but in certain instances, it was inadequate, with a range of 49.0% to 78.3%. However, what is noteworthy is the remarkably high negative predictive values (NPVs) ranging from 84.2% to 97.9% for total IgE levels when the threshold is set at 77.7 KU/L for these three allergic conditions (33). This suggests that lower levels of total IgE in children might potentially utilized with ambiguous symptoms to rule out the possibility of allergic disorders. The disparity in the findings between our study and that of Tu et al. could be attributed to the differences in the studied population and inclusion of other diseases like rhinitis and eczema in addition to asthmatic patients who were represented only a small proportion (4.5%) of the total study population of 1321 patients. Also they used higher cutoff value of total serum IgE (33).

5. CONCLUSIONS

High proportion of wheezy children were asthmatic. IgE was a strong predictor of asthma at a cutoff value of > 100 IU/ml. Children aged 12 months or older, male gender, positive family history of asthma, bottle feeding, higher number of wheeze attacks and presence of two or more criteria of atopy were significantly associated with elevated IgE levels.

Ethical Clearance:

Ethical issues were taken from the local research ethics committee. Informed consent was obtained from each participant. Data collection was in accordance with the World Medical Association (WMA) declaration of Helsinki for the Ethical Principles for Medical Research Involving Human Subjects, 2013 and all information and privacy of participants were kept confidentially.

Conflict of interest: Authors declared none

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