

## Association Between Serum Level of Interleukin-15 and Severity of Pediatric Asthma

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### Abstract

Background: A chronic inflammatory process of the airways is a common characteristic of asthma, representing a primary health problem. This disease can infect people of all ages, about 3.5-20 % of the population, but it usually begins in childhood.

Objective: To evaluate the relationship between interleukin-15 and pediatric asthma severity.

Methods: The current study is a case-control study that includes 60 asthmatic participants as the patient group and 60 non-asthmatic participants as the control group. Sandwich ELISA using an ELISA kit can be used for the measurement of IL-15 and IgE serum levels.

Results: Elevated serum level of IgE in the patients group compared with a control group with significant ( $P= 0.005$ ) was a result of this study, and there were no significant differences between patients and control about IL-15 serum levels with ( $P= 0.968$ ) in asthmatic children.

Conclusions: According to the present study, there was a non-significant association between the severity of asthma and the serum level of IL-15 in children.

## العلاقة بين مستوى الإنترلوكين ١٥ في مصلى الدم وشدة الربو لدى الأطفال

### الخلاصة

**الخلفية :** يعد الالتهاب المزمن في الشعب الهوائية من الخصائص الشائعة لمرض الربو، والذي يمثل مشكلة صحية أولية، يمكن أن يصاب الناس بهذا المرض في جميع الأعمار بنسبة ٣,٥-٢٠٪ من السكان، لكنه يبدأ عادة في مرحلة الطفولة.

**الهدف :** تقييم العلاقة بين مستوى الإنترلوكين ١٥ وشدة الربو عند الأطفال.

**الطرق :** نوع الدراسة الحالية هو دراسة الحالات والشواهد التي شملت ٦٠ مشاركا من مرضى الربو كمجموعة مرضى و ٦٠ من غير المصابين بالربو كمجموعة سيطرة. يمكن استخدام اختبار الاليزا باستخدام كت الاليزا لقياس مستويات الإنترلوكين ١٥ والامينوكلوبولين E في المصل.

**النتائج :** ارتفاع مستوى الامينوكلوبولين E في مجموعة المرضى مقارنة مع مجموعة السيطرة ذات دلالة احصائية ( $P=0.005$ ) نتيجة لهذه الدراسة. ولم تكن هناك فروق ذات دلالة احصائية ( $P=0.968$ ) بين المرضى ومجموعة السيطرة حول مستوى الإنترلوكين ١٥ في المصل مع في الأطفال المصابين بالربو.

**الاستنتاجات :** كان هناك ارتباط غير معنوي مع شدة الربو لدى الأطفال فيما يتعلق بمستوى مصلى الإنترلوكين ١٥ وفقا لهذه الدراسة.

## 1. Introduction

A chronic inflammatory disorder of the airways is a general characteristic of Asthma, in which mast cells and eosinophils play a vital role. It's the predominant child respiratory disease, affecting 235 million individuals worldwide (1). Childhood and adult-onset asthma share many of the exact causes. The interactions between environmental and other intrinsic factors, such as genetics and atopy, were the primary evidence to potentially cause asthma (Dharmage, Perret and Custovic, 2019). An allergic phenotype is the majority of childhood-onset asthma, while a non-allergic phenotype is predominant in adult-onset asthma. However, both allergic and non-allergic airborne triggers such as animal hair, dander, pollen, tobacco smoke, or other pollutant exposures were associated with allergic and non-allergic asthma (Jacquemin *et al.*, 2012).

Eosinophilic hyper-infiltration, overproduction of mucus in airways, hyper-reactivity, and eventually remodelling of airways were the most characteristic of patients with asthma. T-helper 2 (Th2) cells and their related cytokines, including Interleukins (IL) 4, 5 and 13, are associated with pathological changes in asthma (Larché, Robinson and Kay, 2003). In other asthma phenotypes like severe asthma, in addition to eosinophils, neutrophils can also accumulate in the airways (Louis *et al.*, 2000). Asthma can be classified into four phenotypes depending on the number of different cells in the sputum that are induced by hypertonic saline: eosinophilic asthma, neutrophilic, mixed granulocytic asthma and asthma with normal sputum eosinophil and neutrophil ((Simpson *et al.*, 2006), (Porsbjerg *et al.*, 2009)).

The functioning of several immune and structural cells involved in the pathogenesis of chronic allergic inflammation can be influenced by the complex biological role of IgE. The influence of the cell activity by the effect of IgE is related to the interaction with specific receptors. The prominent cytokine that regards asthma is Interleukin (IL) -15. This protein is structurally similar to a growth factor and modulator of T lymphocytes, which is IL-2, and natural killer (NK) cells; both immune marker levels were increased in bronchoalveolar lavage cells in asthmatic patients, essentially those with steroid-resistant asthma (McInnes and Gracie, 2004).

## 2. Materials and Methods

One hundred twenty participants' blood samples were divided into 60 clinically diagnosed asthmatic cases and 60 non-asthmatic as a control group. These samples were taken from both sexes, aged between 4 months to 14 years old, attending the asthma clinic of Imam AL-Hussein Medical City, Karbala /Iraq, during the period extended from November (2021) to March (2022). Patients' exclusion criteria were autoimmune disease, tumour and chronic obstructive pulmonary disease. One ml of blood was collected from each participant in an EDTA tube and was used for absolute eosinophil count determination. Using Sysmex XN-350, five differential automated haematology analyzers, four ml of venous blood was collected from patients and controlled in gel tubes; serum was separated and stored at -20 C° for subsequent analysis. The immune markers IL-15 and IgE serum levels were determined by classic sandwich-ELISA using kits (Bioassay Technology, China).

Ethical approval for the study was acquired from the Kerbala Health Directorate Committee. Also, verbal approval was obtained from the parents of the children before the sample was taken.

## 3. Statistical Analyses

All statistical tests were calculated using SPSS. A *p-value* less than 0.05 was regarded as statistically significant.

## 4. Results

The current study showed that the ( mean  $\pm$  SE) of eosinophils count were (0.40  $\pm$  0.06) and (2.14  $\pm$  0.24) in patients and control, respectively. There was a significant difference between patients and control in eosinophil counts ( $p = 0.005$ ). Also, this study found that the IgE serum levels were (126.21  $\pm$  14.57) and (37.65  $\pm$  5.14) in patients and control, respectively. There was a significant difference between patients and controls in IgE serum levels ( $p = 0.005$ ). The serum levels of IL-15 were (39.69  $\pm$  8.91) and (39.15  $\pm$  9.89) in patients and control, respectively. There was no significant difference between patients and control in IL-15 serum level ( $p = 0.968$ ), as clarified in Table (1).

**Table 1: Mean Differences of IgE and IL-15 Serum Levels and EOS Count Among the Patients and Control**

Variables	Group				P value
	Patients		Control		
	Mean	SE	Mean	SE	
EOS count	0.40	0.06	2.14	0.24	<b>0.005*</b>
IgE	126.21	14.57	37.65	5.14	<b>0.005*</b>
IL-15	39.69	8.91	39.15	9.89	0.968

\* *p* value is significant ( $P < 0.05$ ), Student's t-test, EOS: Eosinophils

In this study (4.3%) of moderate patients were positive for direct contact with cats, while (100 %) and (95.7%) of both mild and moderate asthmatic patients had negative for direct contact with cats; there were no significant differences between mild and moderate asthma ( $P$  value = 0.427). Also, in the present study (4.3%) of moderate asthma patients were positive for direct contact with dogs. In comparison (100%) and (95.7%) of both mild and moderate asthmatic patients had negative for direct contact with dogs; there were no significant differences between mild and moderate asthma ( $P$  value = 0.585).

In addition, 14.3 % and 10.9% of mild and moderate asthma patients were positive for direct contact with birds. In comparison, 85.7% and 89.1% of both soft and medium asthmatic patients had negative for direct contact with birds; there were no significant differences between mild and moderate asthma ( $P$  value = 0.727).

The study also showed that 64.3 and 30.4 of both mild and moderate asthmatic patients, respectively, were highly aggravated by upper respiratory inflammation, while 35.7% and 69.6% of both soft and medium asthmatic patients, respectively, were not; there were significant differences between mild and moderate asthma regarding aggravating by upper respiratory inflammation ( $P$  value = 0.031).

Regarding aggravated by dust, the study showed that 35.7% and 32.6% of mild and moderate asthmatic patients are favourable. In comparison, 64.3% and 67.4% of both soft and medium asthmatic patients had negative results; there was no significant difference between the severity of asthma and aggravating by dust ( $P$  value = 0.535). Also, this study showed that 64.3% and 50% of both mild and moderate asthmatic patients, respectively, are aggravated by playing or exercising, while 35.7% and 50% of both soft and medium asthmatic patients, respectively, were not; there was no significant difference between the severity of asthma and aggravating by physical activities ( $P$  value = 0.379).

Regarding treatment, 57.1% and 19.6% of the mild and moderate asthmatic patients were under no treatment. 35.7% and 56.5% were taking Montelukast as primary treatment, while 7.1 % and 19.6% were taking inhaled corticosteroids (ICS) as the immediate treatment. Only 4.3 of the moderate were under mixed treatment of ICS and Montelukast. There was a significant difference in treatment between mild and moderate asthmatic patients ( $P$  value = 0.049).

Also, in this study, 42.9 % and 45.7% of mild and moderate asthmatic patients were diagnosed as early wheezier, while 7.1% and 6.5% were diagnosed with allergic asthma. 7.1% and 6.5% of which were diagnosed with non-allergic asthma. 14.3% and 13% were adolescent (obese) asthma, 14.3% and 8.7% of both mild and moderate asthmatic patients, respectively, were diagnosed as late-onset asthma. In comparison, 14.3% and 19.6% of soft and medium

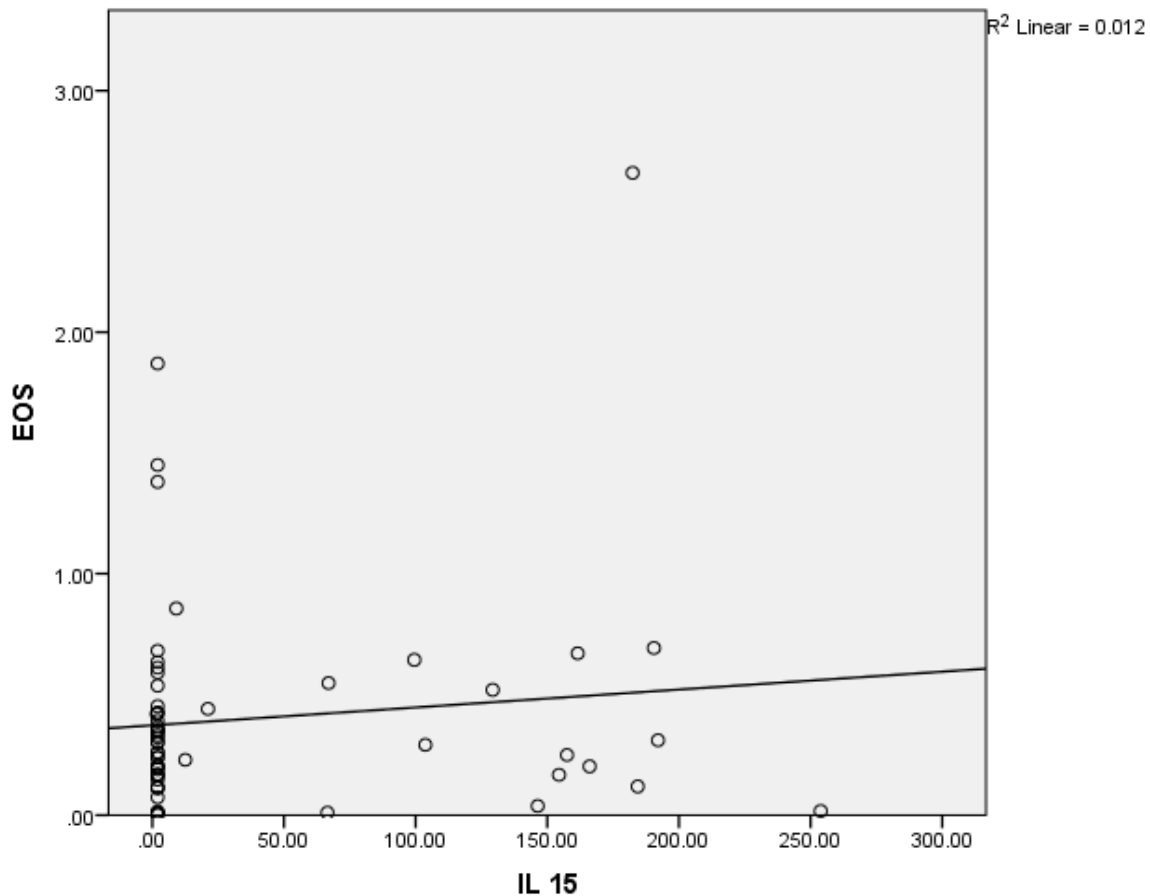
asthmatic patients were diagnosed as persistent wheezier. A non-significant difference regarding the asthma phenotype between mild and moderate asthmatic patients ( $P = 0.991$ ) is demonstrated in Table 2.

**Table 2:**The Relation of Severity with Aggravating Factors, Treatment and Phenotypes in Asthmatic Patients

Variables			Severity				<i>P value</i>
			Mild		Moderate		
			Count	%	Count	%	
Pets	Cats	+ve	0	0.0%	2	4.3%	0.427
		-ve	14	100.0%	44	95.7%	
	Dogs	+ve	0	0.0%	2	4.3%	0.585
		-ve	14	100.0%	44	95.7%	
	Birds	+ve	2	14.3%	5	10.9%	0.727
		-ve	12	85.7%	41	89.1%	
Aggravating by upper respiratory inflammation		+ve	9	64.3%	14	30.4%	<b>0.031*</b>
		-ve	5	35.7%	32	69.6%	
Aggravating by dust		+ve	5	35.7%	15	32.6%	0.535
		-ve	9	64.3%	31	67.4%	
Aggravating by physical activities		+ve	9	64.3%	23	50.0%	0.379
		-ve	5	35.7%	23	50.0%	
Treatment		No treatment	8	57.1%	9	19.6%	<b>0.049*</b>
		Montelukast	5	35.7%	26	56.5%	
		ICS	1	7.1%	9	19.6%	
		Mixed	0	0.0%	2	4.3%	
Asthma phenotypes		Early wheeze	6	42.9%	21	45.7%	0.991
		Allergic asthma	1	7.1%	3	6.5%	
		Non allergic	1	7.1%	3	6.5%	
		Adolescent & obesity	2	14.3%	6	13.0%	
		Late onset	2	14.3%	4	8.7%	
		Persist wheezier	2	14.3%	9	19.6%	

\* *p value* is significant( $P<0.05$ ), Chi-square test, Inhaled Corticosteroids (ICS)

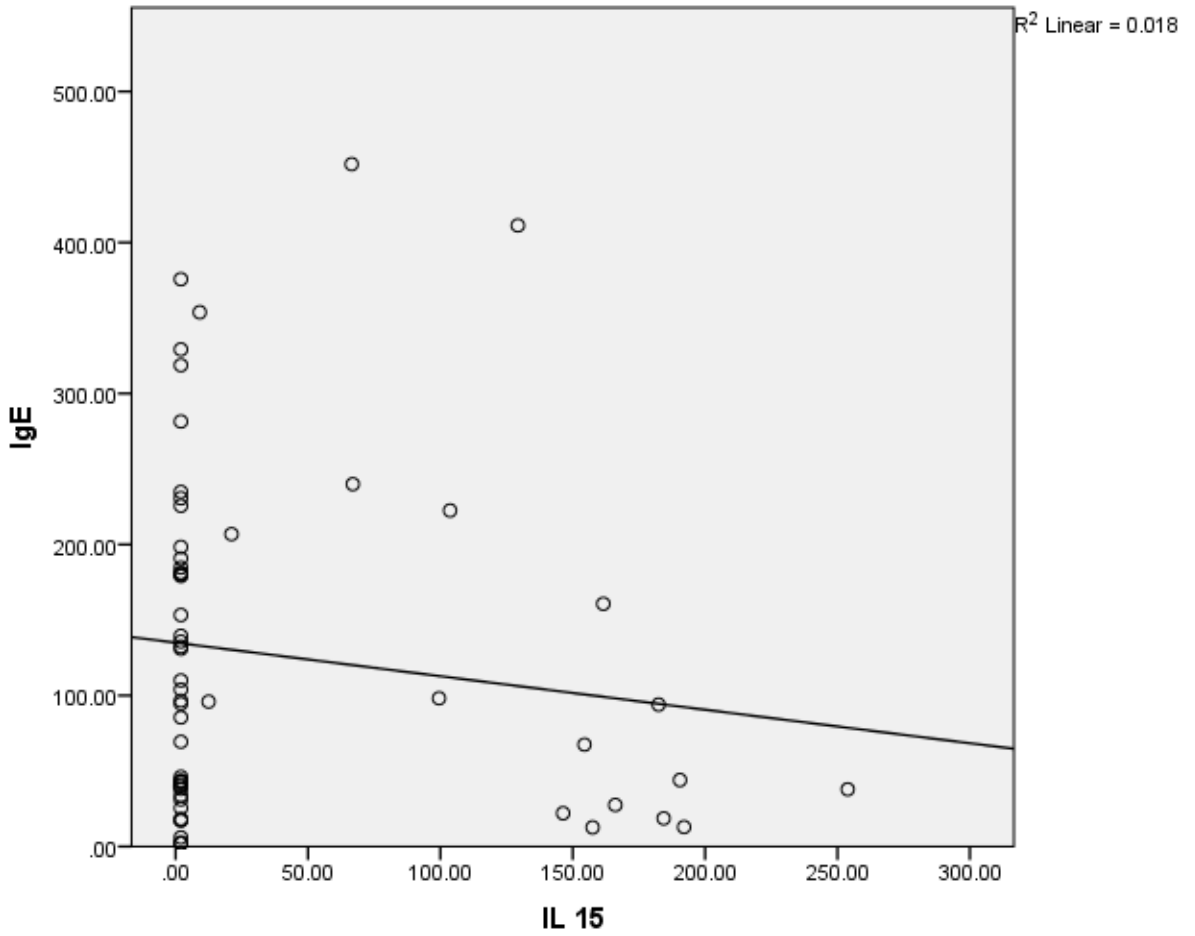
Figure 1 below shows the correlation between the serum IL-15 level and the eosinophil count. No significant positive correlation was found between IL-15 serum level and eosinophil count,  $r = +0.112$  ( $p =$



0.395).

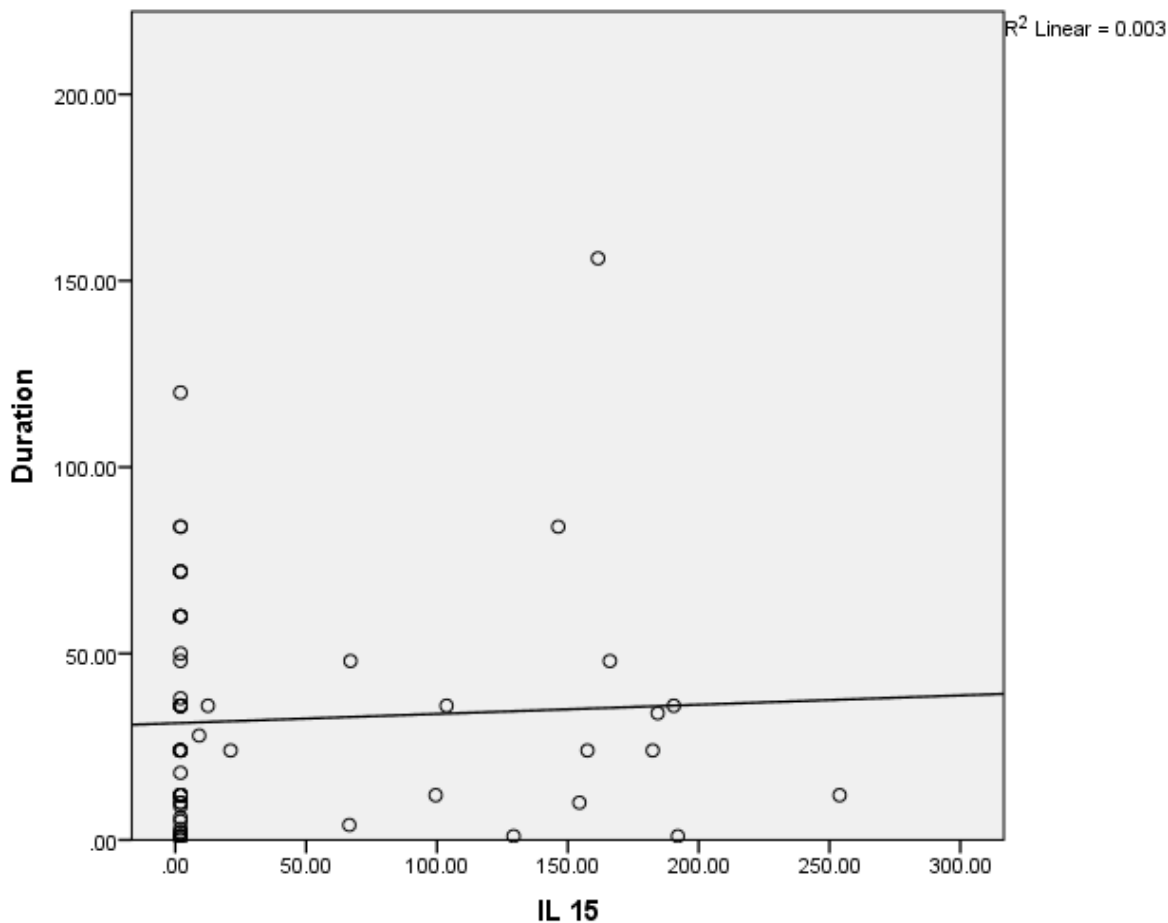
**Figure 1: Correlation of IL-15 Serum Level with The eosinophil Count pg/ml. Pearson Correlation Coefficient:  $r = +0.112$  ( $p = 0.395$ ).**

Figures 2 below showed the correlation between the IL-15 and IgE serum levels. No significant negative correlation were found between IL-15 and IgE serum levels,  $r = -0.136$  ( $p = 0.301$ ).



**Figure 2:** Correlation of IL-15 Serum Level with the Serum IgE pg/ml. Pearson Correlation  
Coefficient:  $r = -0.136$  ( $p = 0.301$ )

**Figure 3** shows the correlation between IL-15 serum level and disease duration in months of asthmatic patients. No significant correlation was found between IL-15 serum level and disease duration,  $r = 0.055$  ( $p = 0.675$ ).



**Figure 3:** Correlation of IL-15 Serum Level with the Duration of Asthma in Months. Pearson Correlation Coefficient:  $r = 0.055$  ( $p = 0.675$ )

The current study showed a non-significant difference in the severity of asthma, regarding the EOS count, IgE and IL-15 levels between the mild and moderate asthmatic children with ( $P$  value = 0.344, 0.391 and 0.283) respectively and mean about (0.30, 154.32 and 57.16) in the mild asthma compared with mean about (0.43, 117.65 and 34.37) in the moderate asthma respectively. At the same time, the present study showed a significant difference ( $P$  value=0.046) in the severity of asthma depending on the duration, which was higher in moderate asthma than the mild asthmatic patients with a mean (of 36.70 ) and (17.86 ) respectively, as clarified in Table (3).



**Table 3:** The Relation of the Studied Markers and Duration with the Severity of Asthma

Variables	Severity				P value
	Mild		Moderate		
	Mean	SE	Mean	SE	
EOS	0.30	0.06	0.43	0.07	0.344
IgE	154.32	38.94	117.65	14.92	0.391
IL 15	57.16	18.94	34.37	10.08	0.283
Duration	17.86	4.34	36.70	4.90	<b>0.046*</b>

\* *p* value is significant ( $P < 0.05$ ), Student's t-test

## 5. Discussion

In the present study, a significant association ( $P = 0.005$ ) existed between eosinophil count in control and asthmatic patients, as shown in (Table). Other studies indicated a non-significant eosinophil count in asthmatic patients, such as a study (Ullmann *et al.*, 2013) that showed that (86%) of asthmatic patients had an average eosinophil count. Also, (Amin *et al.*, 2000) led to low eosinophils in non-atopic asthma. Contrary to the current study, (Foster *et al.*, 2008) revealed that the recruitment of eosinophils has long been recognized as a hallmark of the inflammatory response in asthma. The differences might be due to the small sample size and different procedures.

This study had a significant association ( $P = 0.005$ ) between serum IgE levels in asthmatic patients compared with control. This result is related to previous studies, such as a study (Strømgaard *et al.*, 2011), which found a strong positive relationship between total serum IgE level and asthma in children. Also, a survey (Maneechotesuwan, Sujaritwongsanon and Suthamsmai, 2011) revealed that serum total IgE concentrations were significantly higher in patients with uncontrolled asthma. This aligns with (AN Abood, RI Ghazal and M Al-Musawi, 2013), who mentioned that (48.7%) of asthmatic patients showed positive IgE screening.

Regarding the IL-15 serum level, this study found no significant differences between asthmatic patients and controls ( $P$  value = 0.968). This result agreed with a survey achieved by (Stoner *et al.*, 2019) who showed similar IL-15 responses in exacerbating asthmatics and control. Contrary to this result, a study conducted by (Bierbaum *et al.*, 2006) confirmed the association of IL-15 with asthma by running a genotyping of all IL-15 polymorphisms within the promotor and coding region of IL-15, which were identified by single-strand conformation polymorphism (SSCP) analyses and sequencing in the initial study.

The patients in the present study were classified into mild and moderate groups according to their asthma severity. The number of patients with moderate asthma was higher than those with mild asthma, as shown in Table (2). These results agreed with a previous study conducted by (Hinks *et al.*, 2015), who demonstrated that moderate asthma was more prevalent than mild and severe asthma and a survey conducted by (Dolan *et al.*, 2004), who showed that the percentage of moderate asthma was (48%) more than soft but equal with severe asthma, while other studies reported by ((Jabbar Rahi, 2011), (Fleming *et al.*, 2015), (Abood *et al.*, 2020)) inconsistent with current research. The differences in these results may be because these studies were designed with different methodologies, and the selection of their study population was not randomized.

Regarding aggravating by pets, there were no significant differences between mild and moderate asthmatic patients regarding aggravating by cats ( $p = 0.427$ ); this study was inconsistent with the result of (Simoneti *et al.*, 2018), who demonstrated that exposure to cats was associated with increased asthma risk. Also, this study showed no significant differences ( $P = 0.585$ ) or ( $P = 0.727$ ) between mild and moderate asthmatic patients regarding aggravation by dogs and birds, respectively. This study was incompatible with a survey conducted by (Weber-Chrysochoou *et al.*, 2014), who confirmed that birds may exacerbate asthma severity. This variety may be attributable to the difference in sample group or differences in study geographic location and also socio-cultural variations of study subjects.

This study found a significant association between aggravation by upper respiratory inflammation and mild asthma compared with moderate asthma ( $P=0.031$ ). This study related to (Grissell *et al.*, 2005), who found that respiratory infection can provoke asthma. Along the same line, a study was conducted by (Corne *et al.*, 2002), who confirmed that upper respiratory inflammation causes an extended duration of illness and increased severity of lower respiratory symptoms in individuals with asthma.

In this study, there were no significant differences in the severity of asthma regarding the aggravation by dust between mild and moderate asthma ( $P= 0.535$ ). Contrary to this result, a study achieved by (Cadelis, Tourres and Molinie, 2014) revealed that dust represents a high risk of asthma and increases the severity of asthmatic patients. This discrepancy might be attributed to the differences in sample size between this study and theirs.

In this study, there were no significant differences in the severity of asthma regarding aggravating by physical activities ( $P= 0.379$ ). This study was inconsistent with a study reported by (Paggiaro and Bacci, 2011), which revealed that exercise-induced bronchospasm is frequent in children and young patients with mild asthma.

Regarding the controlling therapy, this study revealed a significant association ( $P = 0.049$ ) between the no treatment administrating and mild asthma compared with moderate asthma and an association between the patients who were controlling their asthma with montelukast and moderate asthma compared with mild asthma. The result of the present study was compatible with a study accomplished by (Paggiaro and Bacci, 2011), who reported that montelukast improved symptoms, rescue medication use and pulmonary function and reduced the rate of exacerbation and the level of blood eosinophils in mild-to-moderate asthmatics not treated with ICS.

Regarding asthma phenotype, there were no significant differences ( $P= 0.991$ ) between asthma phenotype and disease severity. A study by (Fitzpatrick and Moore, 2017) found that despite global differences between severe and non-severe asthma in the Severe Asthma Research Program (SARP), significant heterogeneity was present in both groups, prompting further exploration of phenotypes irrespective of asthma severity definitions.

This study showed no significant association between IL-15 level and EOS count ( $p = 0.395$ ) with a non-significant positive correlation ( $r=0.112$ ); this might be as described by a study conducted by ((Huilan *et al.*, 2010), (Zhu *et al.*, 2011)), which demonstrated that IL-15 activated STAT5 and CD4+ T cells to produce cytokines that act on eosinophils. Also, (Hoontrakoon *et al.*, 2002) found that IL-15 plays an essential role in allergic diseases by inhibiting eosinophil apoptosis. Its anti-apoptotic effects appear to be mediated through autocrine production of GM-CSF and ultimately by NF- $\kappa$ B activation.

In addition, this study showed no significant association between IL-15 level and IgE level ( $p = 0.301$ ) with a non-significant negative correlation ( $r=-0.136$ ). This result was agreed with a study achieved by (Ong *et al.*, 2002), who demonstrated that IL-15 suppressed IgE synthesis. Therefore, a decrease in IL-15 may contribute to the elevation of IgE levels in atopic disease. Also, this study was compatible with a study confirmed by (Huilan *et al.*, 2010), who demonstrated that decreasing the IL-15 serum level induces the increasing expression of IgE produced by B cells.

About IL-15, this result showed no significant association between the IL-15 serum level and duration of asthma ( $p = 0.675$ ), as in Figure 3. This might be because of treatment admission; a study conducted by (Komai-Koma *et al.*, 2001) confirmed that IL-15 production appears to be reciprocally regulated by steroid therapy in asthma patients.

## 6. Conclusion

There was a non-significant association between the IL-15 serum level and the severity of asthma. Therefore, further studies with large sample sizes are needed to confirm the role of this interleukin as an immune marker for the diagnosis of asthma.

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