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Assessment of IL-27 as a Predictive Biomarker for Immune Response in Asthmatic Patients in Diyala Governorate

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Abstract **— Asthma is a persistent inflammatory respiratory disease characterized by coughing, wheezing, and intermittent dyspnea, as well as a sensation of chest tightness. The relationship between interleukin-27 (IL-27) and asthma is not precisely known yet. This study attempted to estimate the serum level of IL-27 and its relationship with immunological and inflammatory markers in patients suffering from asthma. The demographic characteristics of this study were analyzed statistically. The serum levels of IL-27 were evaluated by Enzyme-linked immunosorbent assay (ELISA). CRP and Total IgE were evaluated by Cobas C111 and Cobas E411, respectively. The study showed a highly significant difference in IL-27, CRP, and total IgE when we compared between the patient group (62.12 ± 16.58 pg/ml, 11.2 ± 6.29 mg/l, and 297.26 ± 86.6 IU/ml), and the healthy control group (39.32 ± 3.576 pg/ml, 2.49 ± 1.1 mg/l, and 93 ± 18.3 IU/ml) respectively. ROC analysis of the studied biomarkers showed high sensitivity and specificity. That observation of elevation in all studied biomarker levels in asthma patients indicates a strong evidence in the diagnosis of asthma, as well as in the differentiation between acute and chronic cases, and in determining the severity of asthma.**

Keywords— **Allergy, Asthma, IL-27, CRP, Total IgE.**

I. INTRODUCTION

Asthma is a heterogeneous chronic disease with an extreme condition diagnosed by bronchial obstruction that is resolving spontaneously or by using medication, hyperresponsiveness of the bronchial system, and decline in respiratory function that may result into chronic airway obstruction [1]. Clinically, it presents as coughing, wheezing, dyspnea, and a tightness in the chest; the severity of these symptoms varies according to the degree of bronchial blockage and the patient's perception of it. There are a lot of processes play a significant role in the pathogenesis of asthma, such as alterations in the inflammatory cells (infiltration), airway remodeling, and releasing of mediators [2]. The immunological condition known as asthma is believed to be mediated by T helper 2 (Th2) cells. More airway inflammation and bronchial hyperreactivity result from the mediators and cytokines released in the early stages of an immune response to an instigating allergen, which also causes a more inflammatory reaction known as the late-phase asthmatic response. Interleukin-4 (IL-4), IL-5, and IL-13, which are primarily released by activated Th2 cells and type 2 innate lymphoid cells (ILC2), can mediate type 2 immunity. [3]. The pleiotropic controversial cytokine IL-27 belongs to the IL-12 family that regulates Th1 responses, also has anti-inflammatory actions via altering the effector activities of CD4+ and CD8+ T cells. Epstein-Barr virus (EBV)-induced gene 3 (Ebi3) and IL-27p28 make up IL-27. IL-27 binds to either gp130 or IL-27rα, depending on its function, and regulate the downstream cascade [4]. The production of IL-27 is significantly influenced by the Toll-like receptor (TLR) and signaling pathways linked to interferon receptors. IL-27 promotes the generation of naive CD4+ T cells and triggers both pro-inflammatory and anti-inflammatory reactions. According to some authors, it is a representative biomarker for sepsis [5]. Higher concentrations of C-reactive protein, which are synthesized in the liver, are associated with disrupted lung function and respiratory hyperresponsiveness. In asthma, as the Asthma Predictive Index, there is a rapid C- reactive protein production which acts as a universal foraging molecule as well as aids in processes of opsonization, phagocytosis, and have toxic effects on cells. Therefore, it is very important to investigate whether there is a connection between blood concentrations of CRP and asthma (an inflammatory state) [6]. Immunoglobulin E (IgE), produced by B cells, is another inflammatory marker for airway inflammation [7]. It mediates its effects through binding to high-affinity cell surface receptors that are expressed on mast cells and

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basophils (FcεRI), as well as low-affinity receptors that are found on B cells (FcεRII) [8]. IgE levels against environmental allergens and eosinophil recruitment are significant mediators of lung symptoms in this kind of inflammation. [9].

II. Materials and Methods

A. Study design

This case-control study included 80 patients (37 males and 43 females) ranging from 15 to more than 65 years old, and 40 as healthy controls (20 males and 20 females) with the same age range. Patient and data (Questionnaire) were collected from Baquba Teaching Hospital Consulting Clinic and Consultation clinic for chest and respiratory diseases in Diyala governorate, Iraq, within the period between November 2024 - February 2025. Specialized physicians diagnose patients with asthma based on the Global Initiative for Asthma (GINA) by investigating their symptoms, medical history, and X-ray pictures [10].

B. Method

Venous blood samples were withdrawn from asthmatic patients and a healthy control group using a disposable syringe, allowed to clot at room temperature for 10 minutes. We used the centrifuge at 4000 round per minute (RPM) for 10 minutes to obtain serum. The study protocol involved quantitative measurement of IL-27 by Enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocol of Sunlong Biotech Company, China. In addition, the quantitative measurement of CRP and Total IgE was done using Cobas C111 and Cobas E411 (Roche/Hitachi, Germany), respectively.

C. Statistical Analysis

The results were analyzed using the statistical system SPSS version 26 and MedCalc version 23.1.7. A chi-square test was used to compare the percentages. T-test were used to make comparisons of the means between the studied groups. Receiver operating curve analysis (ROC) was used to determine the best cut-off value to identify the sensitivity and specificity of biomarkers used in this study. ($P \leq 0.05$) was considered as a significant difference, and ($P \leq 0.01$) was considered a highly significant difference.

III. Results

A. Demographics of the study groups

A Total of 80 asthmatic patients were included in this study. 46% of the patients were males, while 54% of them were females. The control subjects included 40 healthy individuals; 50% of them were males, and 50% of them were female. Sex and Residency have no significant differences between the studied groups. BMI and family history have significant differences between the patient and the control groups at ($P<0.01$) as shown in Table I. In this study, patients with age range between (15-34) and (45-54) showed the highest prevalence of asthma in this study. However, the family history and Body Mass Index (BMI) showed a highly significant difference between the studied groups at ($P<0.01$), as shown in Table I.

B. Concentration of studied biomarkers in study groups

The study showed a highly significant difference in IL-27, CRP, and total IgE when we compare between the patient group (62.12 ± 16.58 pg/ml, 11.2 ± 6.29 mg/l, 297.26 ± 86.6 IU/ml), and the healthy control group (39.32 ± 3.576 pg/ml, 2.49 ± 1.1 mg/l, 93 ± 18.3 IU/ml) respectively, as shown in Table II.

Table I. Demographic characteristics of the study groups

Parameters		**Patients n=80 No. (%)**	**Controls n= 40 No. (%)**	**Tests**	***P* value**
Age	15-34	19 (23.75)	11 (27.50	$\chi^2 = 0.930$	0.920 NS
	35-44	12 (15)	8 (20)		
	45-54	19 (23.75)	8 (20)		
	55-64	17 (21.25)	7 (17.5)		
	≥ 65	13 (16.25)	6 (15)		
Sex	Male	37 (46)	20 (50)	$\chi^2 = 0.150$	0.698 NS
	Female	43 (54)	20 (50)		
Residency	Urban	60 (75)	20(50)	$\chi^2 = 3.214$	0.07 NS
	Rural	20(25)	20(50)		
Family history	Yes	43 (54)	0 (0)	$\chi^2 = 32.506$	0.001**HS
	No	37 (46)	40 (100)		
BMI	Normal	28(35)	31(77.5)	T-test = 3.247	0.002**HS
	Overweight	19(23.75)	9(22.5)		
	Obese	33(41.25)	0(0)		
	Mean ± SD	29.3 ± 6.3	24.65 ±1.1		

** (HS): Highly significance at $P \leq 0.01$; *(S): Significance at $P \leq 0.05$;(NS): No Significance; No: number; (%): percentage; BMI: Body Mass Index; χ^2: Chi-square, SD: Standard deviation.

Table II. shows concentration of studied biomarkers in the study groups

Biomarkers	Mean ± SD		*P* value
	Patient	Control	
IL-2 (pg/ml)	62.12±16.58	39.32±3.576	0.0001**
CRP (mg/l)	11.2±6.29	2.49±1.1	0.0001**
Total IgE (IU/ml)	297.26±86.6	93±18.3	0.0001**

SD: Standard Deviation; ** (HS): High significance difference at *P* ≤0.01

C. ROC analysis for the studied Biomarkers

The results presented in Table III for the asthmatic patients, illustrate the concentrations of biomarkers IL-27, CRP, and total IgE with their best cut-off value along with specificity and sensitivity as shown in Figure I.

Table III. ROC analysis for the studied Biomarkers

Biomarker	Cut-off	AUC	Sig.	Specificity	Sensitivity
IL-27	>43.53	0.982	0.001** HS	100	94.43
CRP	>4.24	0.989	0.001** HS	100	91.43
Total IgE	>142	1.000	0.001** HS	100	100

AUC: Area Under Curve, **(HS): Highly Significance at *P* ≤0.01

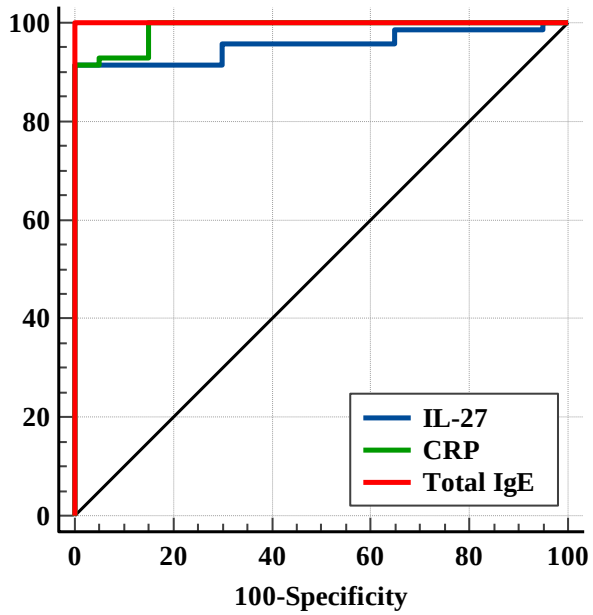

Fig. I. ROC analysis for biomarkers among the study groups

D. Person's correlation coefficients of biomarkers

The results represented in Table IV. showed that IL-27, CRP, and total IgE had a highly significant correlation between their levels in the studied groups. This result refers to a moderate positive correlation between the concentrations of IL-27 and CRP (r= 0.579, *P* ≤0.0001), and a strong positive correlation between IL-27 and total IgE (r=0.621, *P* ≤0.0001), as well as a strong positive correlation between CRP and Total IgE (r=0.633, *P* ≤0.0001).

Table IV. Association between biomarkers in asthmatic patients

Biomarkers		IL-27	CRP	Total IgE
IL-27	r	1	0.579	0.621
	P-value		0.000*	0.000**
CRP	r	0.579	1	0.633
	P-value	0.000**		0.000**
Total IgE	r	0.621	0.633	1
	P-value	0.000**	0.000**	

r.: correlation coefficient, **: Highly significance at *P* ≤0.01

IV. DISCUSSION

Bronchial asthma is a chronic, heterogeneous disease with complex immunopathology [11]. Genetic susceptibility and environmental exposures are involved in the pathogenesis of asthma [12]. According to the result of this study, obese patients with high Body Mass Index (BMI) are associated with increased risk in development of airway hyperresponsiveness in asthmatic patients compared to the healthy individuals, and this result agrees with a study was done by Abbas *et al* [13]. The positive family history in asthma patients enrolled in this study is considered a strong determinant, and it is consistent with the result of a study was done by Patil *et al* [14].

The present study elucidated that asthmatic patient expressed higher serum levels of IL-27, CRP, and total IgE compared to healthy control groups. Patients with elevated serum IL-27 concentration have a greater likelihood of chronic oral corticosteroid use. Activated dendritic cells and lung macrophages are good sources to produce IL-27, which acts on helper T cells and regulates their differentiation and growth. In patients with bronchial asthma, the accurate role of IL-27 is not completely known and understood.

Allergen stimulation can lead to an inflammatory response in the body that subsequently leads to an overexpression of IL-27, thereby inducing the expression of CXCL10 and CXCL9, and then intense the inflammation of the bronchial airway. This may be one of the mechanisms through which IL-27 is included in bronchial asthma [15]. Elevated blood IL-27 concentrations in asthmatic patients showed that the level of IL-27 synthesis can play a varied function on various cells, altering the development of allergy-related inflammatory responses. IL-27 encourages monocytes to differentiate into macrophages, stimulates the production of nitric oxide by macrophages, and causes monocyte-derived DCs to express IL-8, IL-27, CXCL10, chemokine

receptor (CCR1), and IFN-stimulated genes [16]. Our study has compatible results in serum IL-27 levels with a study was done by Xie *et al* and Liu *et al* [15, 17], as these studies also showed an increase in IL-27 levels in the patients compared to healthy controls.

A broad biomarker of systemic and vaso-inflammation, C-reactive protein is an acute-phase reactant produced by the liver cells in response to inflammatory events [18]. The results of this study indicated significantly higher serum CRP concentration in patients with asthma than in healthy controls. These results agree with Al-Hindy *et al* and Mohany *et al* [18, 19].

Immunoglobulin E (IgE) is a protein produced by activated plasma cells, and it is one of the major causes of the allergic inflammation process [20]. Total IgE level, as expected, has a high significant difference between asthma patients and the healthy control group, and this result is consistent with the findings of Jebur and Saud, Shaban and Brakhas [21, 22].

The ROC curve demonstrates that IL-27, CRP, and total IgE have 100% specificity, and the sensitivity was 94.43%, 91.43%, and 100%, respectively, and this result is compatible with Liu *et al*, Shareef, and Al-Athari *et al* [15, 23, 24], respectively. This result is important and has diagnostic value in the diagnosis of asthma and in the differentiation between acute and patients with chronic asthma.

V. CONCLUSION

The combined elevation of IL-27, CRP, and total IgE levels in patients with chronic asthma indicates an ongoing inflammatory process in these patients, and poor asthma control or more severe active asthma attacks, requiring close observation and preventive management. However, the high level of these biomarkers and their high specificity and sensitivity have strong evidence in the diagnosis of asthma, as well as in the differentiation between acute and chronic cases, and in determining the severity of asthma.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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