International Journal of Medical Toxicology & Legal Medicine **Volume 27, No. 4S, 2024**
e-ISSN: 0974-4614
p-ISSN: 0972-0448
https://doi.org/10.47059/ijmtlm/V27I4S/100

The role of aryl hydrocarbon receptor in correlation to IL-17 level in non-allergic asthma

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Received: 15.09.2024 Revised: 13.10.2024 Accepted: 20.11.2024

ABSTRACT
Asthma is a heterogenic chronic disease of the airways. It also classified as allergic and non-allergic asthma, which its mechanism based on the action of Th17 cell and affected by other risk factors such as body mass index (BMI). The aryl hydrocarbon receptor (Ahr) is a xenobiotic agent which activated by exogenous and endogenous ligands, and it has been considered to be a regulator of both toxic and carcinogenic responses to environmental pollutants. Recently, it has been linked to several immune disorders including asthma. The aim of the study the role of Ahr in correlation to IL-17 non-allergic asthma.Blood from non-allergic asthma patients and aged matched healthy controls were collected, complete blood count (CBC) was performed on each sample and the serum level of IL-17 and Ahr were estimated by enzyme linked immunosorbent assay (ELISA). The majority of AS patients were obese (34.3%). The current findings of the present study revealed a significant elevation (p=0.00001) of IL-17 level in AS group in compare to HC group(22.59±3.7 and 3.14±0.4 ul/ml, respectively).The level of Ahr showed a significant elevation (p=0.025) in AS group in compare to HC group (46.91±5.9 and 21.58± 4.2 ul/ml, respectively).A strong significant and positive correlation was found betweenIL-17 and AhR level in asthma patients (R2 = 0.75, p=0.00) in compare to no correlation found between them in healthy controls (R2 = -0.5, p=0.054).The results of the receiver operating characteristic (ROC) curve for the two parameters in the present study showed that IL-17 gave an excellent performance in the ROC with AUC =0.961 followed by the Ahr with AUC= 0.704.In conclusion, in non-allergic asthma, Ahr correlates positively with IL-17 suggesting a significant role of Ahr in non-allergic asthma and the possibility of a new therapeutic agent to treat non-allergic asthma.

Keywords: non allergic Asthma, IL-17,AhR, Basrah

INTRODUCTION

Asthma is a diverse chronic disease of the airways characterized by inflammation, airway hyperresponsiveness and constrict that product from airway smooth muscle (ASM) contraction and airway restoration (James et al., 2009; Asher et al., 2020). Patientswith asthma have episodes of wheezing, shortness of breath, tightness in the chest, and coughing as clinical symptoms (Maslan and Mims, 2014).In Iraq, dust and a diet of spicy foods considered to be the primary risk factors for atopic individuals, while, seasonal allergies, chest infections, and perfumes considered as the most prevalent risk factors of asthma; indicating a variety of causes that can cause an asthma attack (Sherhan,2018).

Asthma can be allergic or non-allergic. In the non-allergic form of asthma, eosinophils are transported into the airway by production of IL-5 from innate lymphoid cells' (ILC2) (Jonckheere et al., 2019). When cells like Th1 and Th17 release the cytokines like IFN-γ and IL-17, it can cause non-eosinophilic neutrophilic asthma. This promotes the activation of macrophages, and the release of neutrophil chemokines (Papi et al., 2018).

Interleukin 17 (IL-17) cytokines are key inflammatory mediators in numerous diseases such as autoimmunity, allergy, and infection (McGeachy et al.,2019).The first and best characterized IL-17 cytokine is IL-17A, which was originally described as being released by T helper 17 (Th17) cells during an adaptive immune response. Subsequently, five additional members (IL-17B, IL-17-C, IL-17-D, IL-17-E, and IL-17-F) is identified(Song et al.,2016).IL-17A-mediated the recruitment of inflammatory cells such as neutrophils likely contributes to lung damage in severe pneumonia and acute respiratory distress syndrome (ARDS) (Ritchie et al., 2018; Wonnenberg et al.,2016; Muir et al.,2016). The expression and production of IL-17A and IL-17F is enhanced in patients with

asthma. Thus, increased levels of these cytokines have been observed in sputum, serum, bronchial, and nasal biopsies (Zheng et al.,2021).

The aryl hydrocarbon receptor (AhR) is a ligand-mediated transcription factor implicated in the biological detoxification of ligands (Forman and Finch ,2018). It is activated by exogenous and endogenous ligands, and it has been considered to be a regulator of both toxic and carcinogenic responses to environmental pollutants such as 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) or (dioxin) (Xue, 2018; Vacher et al., 2018).AhR may play an important a role in preventing the onset of allergic asthma, according to recent research (Jeong et al., 2012; Chang et al., 2020) Numerous studies have demonstrated how AhR functions in a variety of physiological and pathological processes, including those involving the immune system, autoimmune disorders, cancer, and gastrointestinal function (Kawajiri and Fujii-kuriyama, 2017; Kolluri, et al., 2017). Although historically, The AhR has primarily been connected to the hazardous xenobiotic metabolism, it has demonstrated that the AhR inhibits the progression of chronic obstructive pulmonary disease (COPD) (Guerrina et al., 2021), an obstruction of the lungs brought on primarily by smoking cigarettes. Additionally, in reaction to tobacco smoke, the AhR inhibits neutrophil migration to the lungs (De Souza et al., 2014; Rico De Souza et al., 2021). Numerous immune cell types that participate in the asthmatic response express AhR, and their simultaneous activation by AhR ligands may be regulated when the response develops. Among asthma phenotypes, the most common is the type 2 phenotype triggered by allergen stimulation (Kuruvilla et al.,2019). The aim of the study is to study the role of aryl hydrocarbon receptor in correlation to IL-17 level in non-allergic asthma

Methods

Adult subjects aged 18 years and above from both sexes were eligible for the study. The study subjects (n=150) including Asthmatic Patients (AS group, n=75) and aged matched and randomly collected Healthy Controls (HC group, n=75). All patients with asthma attended a private allergy clinic in Basrah, and diagnosed with asthma by a specialist physician. All participant filled a related questionnaire including information regarding age, sex, symptoms and body mass index (BMI) of participants and signed a consent form.

Blood samples (5 ml) were withdrawn from the study subjects. Each samplewas separated into two parts: the first part of 4 ml part placed in an SST tube with gel for the serological study. The serum was separated by centrifugation at 3000 RPM for 20 min., 4 aliquots of serum was made for each sample and all serum samples kept in -20 ℃ until further analysis. The second part of 1 ml was placed in an EDTA tube for Physiological study including CBC. The level of serum total IL-17 andAhR in the study subjects using ELISA kits, Human IL-17 ELISA Kit and Human AhR ELISA Kit (Shanghai YL Biont, China). The data underwent statistical analysis using a normality test at beginning followed by non-parametric test (Mann-Whitney U test) and Spearman and ANOVA test were applied to the related experiments using SPSS software. In addition, ROC curve analysis was performed on the study parameters

RESULT

The result showed that the majority of AS patients were Obese 23 (34.3%) over weigh comes in second place in AS patients 19 (28.40%) then normal weight comes in third place 14 (20.9%) then AS patients with Extremely obese 11 (16.40%). The number and percentages of the distribution of study subject according to BMI is demonstrated in Table 1and figure 1

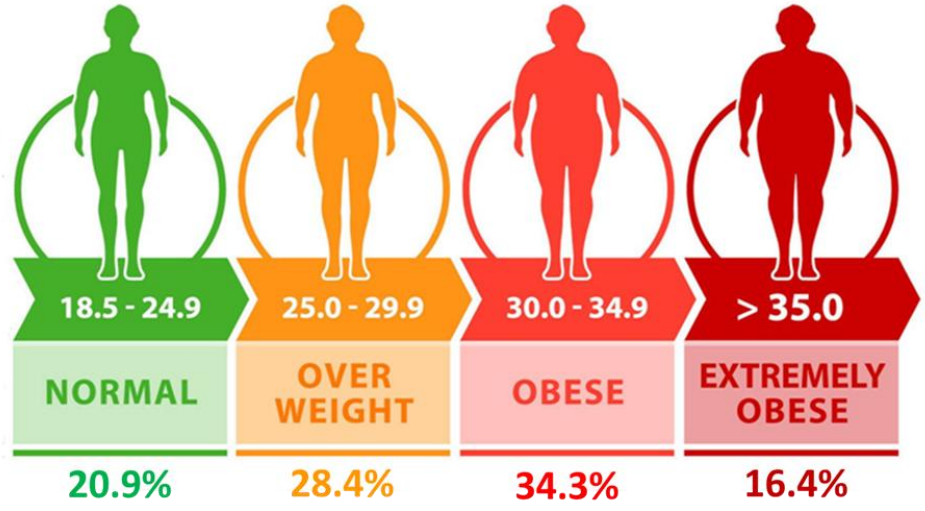

Figure 1: The distribution of asthma patients according to BMI

Table 1: The distribution of AS groups according to BMI and sex

BMI categories	Total		Females		Males	
	No.	%	No.	%	No.	%
Normal weight	14	20.90	9	64.28	5	35.71
Over weight	19	28.40	12	63.15	7	36.84
Obese	23	34.30	15	65.21	8	34.78
Extremely obese	11	16.40	11	100	0	0

The CBC results regarding the total WBC, neutrophils and eosinophils in AS patients showed that the mean of total WBC count 9.61±0.44, the mean of neutrophils count was 6.12±0.39 while the eosinophils count was 0.33±0.12. Moreover, the obese asthma patients shoed elevated count of eosinophiles while no difference found in the total WBC count and the neutrophils count among the BMI groups as shown in Table 2

Table 2: CBC results in asthma patient according to their BMI

BMI categories	NO.	Total WBC	Neutrophil count	Eosinophil count
Normal weight	14	9.49	6.38	0.24
Over weight	19	9.79	6.27	0.27
Obese	23	9.83	6.31	0.54
Extremely obese	11	9.03	5.24	0.16

The current findings of the present study revealed a significant elevation (p=0.00001) of IL-17 level in AS group (22.59±3.7) in compare to HC group (3.14±0.4) as shown in Figure 2
The current findings of the present study revealed a significant elevation (p=0.025) of AhR level in AS group (46.91±5.9) in compare to HC group (21.58±4.2) as shown in Figure 3.

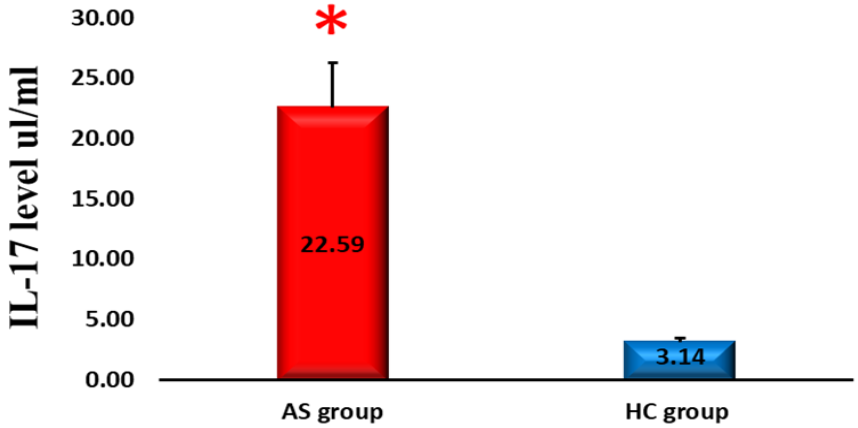

Figure 2: Serum IL-17 level in Asthma group and HC group.There is a significant elevation of IL-17 in asthma patients

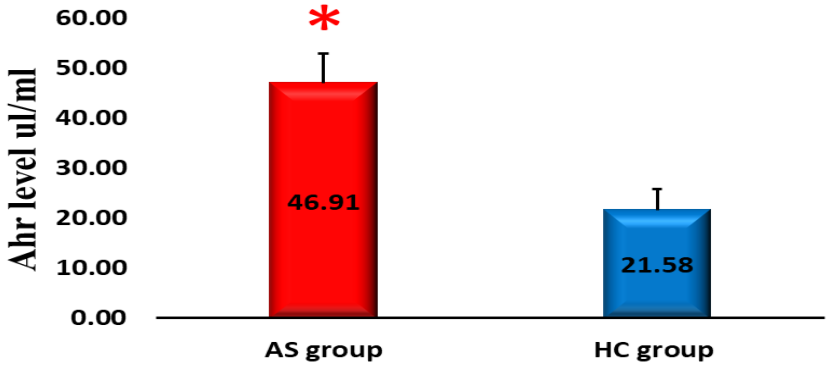

Figure 3: Serum AhR level in Asthma group and HC group.There is a significant elevation of AhR in asthma patients

Spearman correlation results among the various parameters of the present study showed a very positive and significant correlation between the IL-17 level and Ahr levels in AS group (R2 = 0.75, p=0.00), while no significant correlation was found between the two parameters in HC group (R2 = -0.5, p=0.054) as shown in Figure 4A & B.

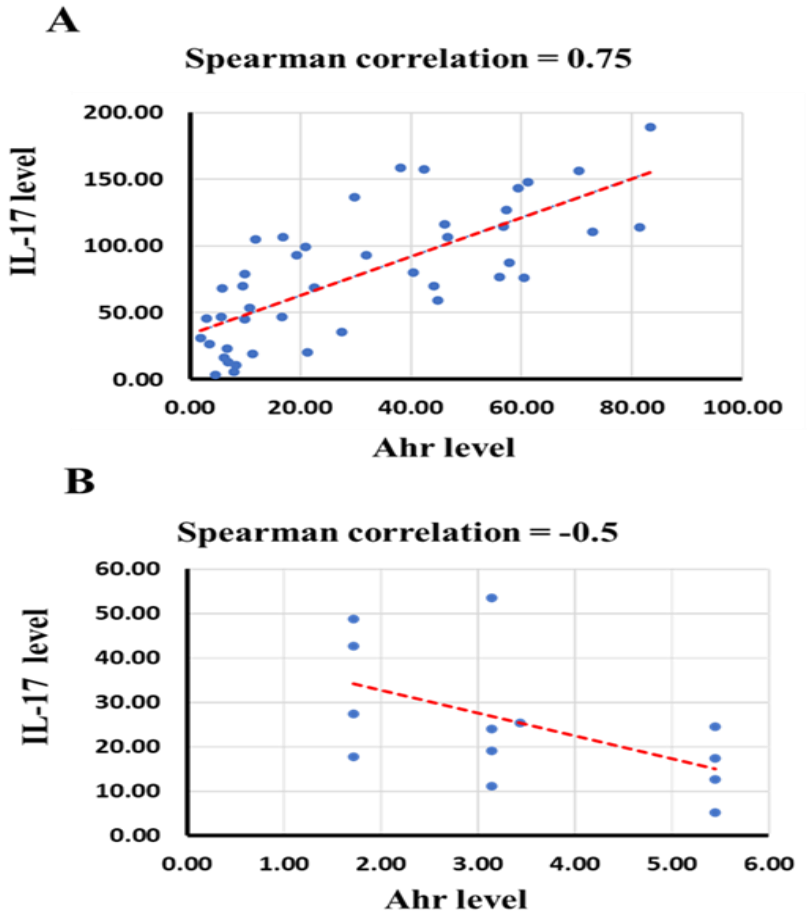

Figure 4: Spearman correlation between IL-17 and Ahr in study groups. A. Spearman correlation between IL-17 and Ahr in AS group. B. Spearman correlation between IL-17 and Ahr in HC group

The receiver operating characteristic (ROC) curve for IL-17 and Ahr is shown in Figure 5 A & B.The area under the curve (AUC) values for the level IL-17 in AS and HC groups were 0.961(Figure 5 A), indicating an excellent overall performance IL-17. The area under the curve (AUC) values for the level Ahr in AS and HC groups were 0.704 (Figure 5 D), indicating good overall performance of Ahr.

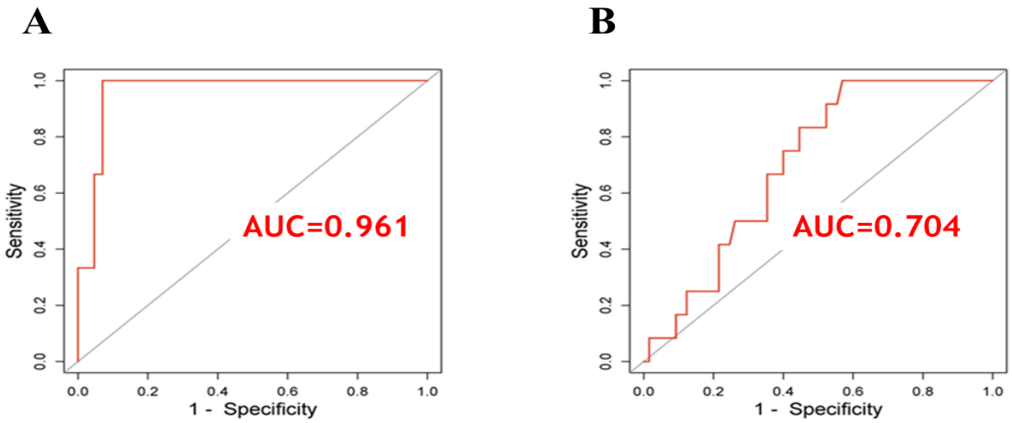

Figure 5: The receiver operating characteristic (ROC) curve of the four study parameters. A. ROC curve for IL-17. B. ROC curve for Ahr.

DISCUSSION

The present results showed that the majority of asthma patients were obese followed by over-weight patients. Gomez-Llorente et al., (2017) showed the prevalence of asthma is higher in obese individuals which agree with the present study. Also, the present study agrees with Saadon et al., (2018) who found that asthma is higher in obese individuals.Furthermore, genetic and lifestyle factors such as diet, exercise and physical activity and early exposure to microorganisms are vital factors that might contribute to the escalating prevalence of asthma as well as obesity. In Iraq and particularly in Basrah, asthma has been included in many studies that delt with several aspect of asthma such as the involvement of cytokines and risk factors such as smoking cigarettes (Hashim et al., 2022; Al-Ali, 2020)

In obesity, factors including the infiltration of adipose tissue by macrophages M1 and the increased expression of multiple mediators that magnify and propagate inflammation, are considered as the culprit of obesity-related inflammation. In general, adipose tissue is the main source of adipokines such as pro-inflammatory leptin which is produced in excessively during obesity. Additionally, another mediator called adiponectin which have anti-inflammatory effects have a reduced production rate (Nguyen, 2020).

Along with other pro-inflammatory cytokines including TNF, TGF, IL-1, and IL-6, the inflammatory process also involves their production. It was discovered that these pro-inflammatory cytokines also aided in the etiology of asthma. Pro-inflammatory cytokines that are produced during asthma, like IL-4, IL-5, IL-13, and IL-33, help to keep the body slim, which has an impact on the immunomodulatory pathways that underlie both obesity and asthma. It is one of the numerous processes that have been proposed to explain why obesity raises both the risk and severity of asthma (Bantulà et al., 2021).

The present study showed higher neutrophils count and white blood cell but lower eosinophils count in patients presenting the patients as patients with neutrophilic asthma. Increased airway CD4+ and IL-17F+ cells were also present in patients with high bronchial neutrophilia, and there was a strong correlation between the values of neutrophil counts, serum IgE, IL-17F+, and CD4+ cells. These findings suggest that IL-17 and neutrophils may play a role in allergic mechanisms in this disease phenotype, consistent with a Th2/Th17 dual T-helper cell immune response (Irvin et al.,2014).Also, the study of Tashiro et al., (2020), noted that compared to asthma patients who are not overweight, patients with overweight asthma have a much lower eosinophil percentage and count, and there is a significant negative correlation between the eosinophil percentage and BMI.Regarding to IL-17 which showed a great elevation in asthma patients compared with healthy control.

The results of the present study agree with Kenawy and colleagues (2017). Interleukin-17 (IL-17) is considered as an early trigger of the T lymphocyte-induced inflammatory response and can generate and activate the recruitment of neutrophils to the respiratory tract, which explains the rise. IL-17 also plays a role in asthma (Qu et al., 2013) and it also enhances T-helper 2 (Th2) cell mediated eosinophilic airway inflammation in asthma (Park et al., 2010).Alsaimary and Mezban (2021) thought that the amounts of IL-17 may have an impact on allergic asthma. About the relationship between age and IL-17. It has been discovered that increasing airway neutrophilia may be the reason of older asthmatic patients' elevated IL-17 levels. This finding suggests that IL-17 may be a target for asthma medication, particularly in individuals with severe asthma (Dunn et al., 2018).

The present study showed that AhR level increased in asthma patients in compared with a healthy control group. In asthma, AhR serves as a mediator between the external environment and internal molecular pathways, which can have both positive and negative effects. It stops airway inflammation in bronchial epithelial cells and inhibits the production of pro-inflammatory T cells in dendritic cells. At the cellular level, it inhibits Th2 differentiation, regulates T cell activation, and causes macrophages to adopt an anti-inflammatory M2 phenotype.

On the other hand, AhR's detrimental method of action causes asthma by dysregulating antigen-presenting cells and pathogenic T cells and stimulating lung epithelial cells and fibroblasts (Guerrina et al.,2018).According to a different study, smoking activates the aryl hydrocarbon receptor pathway, which is critical for the metabolism of environmental pollutants. Numerous illnesses, particularly inflammatory ones like arthritis, might be brought on by Ahr activation since it directly promotes Th17 growth (Talbot et al.,2018).Another study by Ahmadi and colleagues (2023) showed that while some ligands, like FICZ, stimulate Th17 cell differentiation, others, like AhR binding, may encourage naïve T cell differentiation to regulatory T cells, such as TCDD (Ahmadi et al.,2023).

Additionally, Li and colleagues (2016) showed that through promoting Treg differentiation and IL-10 production and inhibiting Th17 differentiation and IL-17 expression, TCDD-induced AhR activation decreased non-eosinophilic airway inflammation (Li et al.,2016).

In conclusion, the finding of the current study suggests the Ahr as a possible target for asthma therapy.

Ethics approval

This is an observational study. The Research Ethics Committee has confirmed that no ethical approval is required**.**

Conflict of interest
The authors confirmed there is no conflict of interest.

Author contributions
Contributors:Aliaa Abood was responsible for material preparation and data collection,
Shereen Al-Ali contributed to design the study, analysis of the collected data, and writing the draft Iqbal Abdul Aziz contributed to write the manuscript.Ziad T. Malgoth contributed to the diagnosis and collection of samples.

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