ORIGINAL ARTICLE

Investigation of IgA, IL-9, IL-13, and hs-CRP Levels Among Asthmatic Patients with Recurrent Respiratory Tract Infections in Southern Regions of Iraq

[1]Hussian Y. Uoda*, [1]Nibras S. Al-Ammar, [2]Ali N. Salman, [3]Hermann Kreyenberg, [4]Peter Bader

[1]Microbiology Department, College of Medicine, University of Basrah
[2]Biology Department, College of Pure Sciences, University of Thi Qar
[3]Head of Chimarism Laboratory, Goethe University Hospital, Frankfurt, Germany
[4]Head of Division of Stem Cell Transplantation and Immunology, Goethe University Hospital, Frankfurt, Germany

Key words:
Asthma, IgA, IL-9, IL-13, hs-CRP

Corresponding Author:
Hussian Younis Uoda
Microbiology Department/College of Medicine/University of Basrah
mustafafadil837@gmail.com

ABSTRACT

Background: *Asthma is a chronic inflammatory condition causes chest tightness, wheezing, coughing, and shortness of breath.* ***Objectives:*** *To assess the levels of IL-9, IL-13, and hs-C-reactive protein in asthmatic patients and controls and assessing level of IgA in all studied cases to investigate presence of IgA deficiency if present.* ***Methodology:*** *A case control study was carried out during (October-April 2024). Out of 380 randomly selected cases with age range (7-80 years), 250 were asthmatic patients and 130 healthy controls. Immunological tests were done by using ELISA to measure levels of IgA, IL-9, IL-13 and hs-CRP.* ***Results:*** *IgA, IL-9 and hs-CRP levels were increased significantly in patients with recurrent respiratory tract infection (RTI) at p-value<0.05. Levels of IgA, IL-9 and IL-13 were increased non-significantly in atopy patient, except hs-CRP. Weak negative correlation between age group and both IL-9 and hs-CRP, IgA scored a moderate positive correlation with IL-9, and moderate positive correlation with both IL-13 and hs-CRP. IL-9 scored moderate positive correlation with IL-13 and weak positive correlation with hs-CRP. IL-13 scored very weak positive correlation with hs-CRP.* ***Conclusion:*** *Receiver Operating Characteristic (ROC) test indicated that all patients have positive results compared with control group, 77% of patients with IgA level were more than or within average of control group, and 23% were less the average of control group. Regarding to IL-9 and IL-13, more than 60% of patients have cytokines mean more than or within the mean of control group. Regarding hs-CRP, it was less specific indicator than other parameters.*

INTRODUCTION

Asthma is considered a heterogeneous disease with chronic airway, demographically distinct locations and pathophysiological features[1,2]. Asthma is classified regarding to etiology and triggers to allergic, non-allergic, occupational, exercise-induced bronchoconstriction and aspirin-exacerbated respiratory disease[3]. Additionally it can be classified regarding to severity and control into intermittent, persistent, and severe persistent[4].

Moreover, it can be classified regarding to inflammatory phenotype into type2 (T2) low, T2-high allergic, and T2-high non allergic asthma[5]. Regarding to Iraq, numerous researches have been done to recognize the prevalence of asthma[6]. Pandemic-related items may for the time being a decrease asthma rate[7]. A meta-analysis research through 2016 figured that the Eastern Mediterranean regions have insufficient analysis and details in the zones of asthma and chronic obstructive pulmonary disease. Further attempts and proper work are needed to recognize the prevalence and concern of these diseases[8].

Asthma is characterized by reversible, episodic constriction of the airways and inflammation in reaction to environmental allergens, irritants, and infections. It is a multifaceted, immune-mediated, and intricate process that manifests as a range of clinical manifestations[9]. Coughing, wheezing, shortness of breath, and chest tightness are signs of asthma, a chronic inflammatory disease of the airways that is triggered by inflammation of the airways, which causes mucus production, remodeling of the airway wall, and bronchial hyper responsiveness (BHR), which is the propensity of smooth muscle cells to respond to non-specific stimuli like cold air[10]. Some asthmatic patients suffer from respiratory tract infections, some are viral but most are bacterial infections[11]. Recent documentations exhibit that wheezing episodes at the first years of life that resulted from some viral infections give probability for later asthma[12].

Many studies have been done to approximate the connection between allergic respiratory diseases and the development of repeated respiratory infection[13]. The risk items such as elevated body mass index, family history of atopy, exposure to house mite, history of allergic diseases, gastroesophageal reflex disease, allergic sinusitis and allergic rhinitis are mostly described by asthmatics[14]. Extensive works looks over the main role of cellular and humoral immunity that conduct to customize treatment choice for asthma. Humoral immunity set out twofold tasks of direct pathogen neutralization and improvement of leukocytes function. Production of antibody subclasses is turn on by antigen and the evolved antibodies can come up with disease pathogenesis and host defense[15]. Humoral and cellular immunity are considered as the players that function in protection mechanisms against pathogens. Immunoglobulins serve in defense mechanism by neutralizing the pathogen, in addition to involvement of interleukins in defense mechanisms during asthma[15].

Regarding to healthy individuals, humoral responses comprise principally little amount of IgG1, IgG4 and secretory IgA antibodies to allergens in the presence or absence of low levels of IgE[16-18]. Respiratory mucosa is very important in keeping homeostasis and driving disease, one of its main players is immunoglobulin A (IgA)[19]. Allergic asthma, inflammation that results from allergen is influenced by Th2 cells and IgE molecules, also boost with Th17 cells in severe asthma[20]. A reduced immature B-cell populations are shown in patients with severe asthma while memory B-cells significantly expand in contrast with both mild, moderate asthmatic patients and healthy individuals. Besides, rising of IgA^+ memory B-cells are related to lessen lung role and particularly with variables representative for elevation of resistance in the peripheral airways[21].

Interleukine-9 (IL-9) is considered as a pleiotropic cytokine in mucosal environment and it can inhibit alveolar macrophage development and stimulates recruitment of monocytes[22]. Many studies showed increasing levels of IL-9 in asthma patients[23]. IL-13 is essential for IL-9 to increase expression of eotaxin which attracts eosinophil in the lung. A study showed that IL-9 can boost asthma through IL-13 in an independent pathway[24]. C-reactive protein is considered as a non-specific plasma protein indicator for inflammation. Its level gives a clear picture for the development of inflammatory process. It is an acute phase protein produced by hepatocytes[25]. The aim of our study assess the levels of IL-9, IL-13, and hs-C-reactive protein in asthmatic patients and controls. Assessing level of IgA in all studied cases to investigate presence of IgA deficiency if present.

METHODOLOGY

A case control study was carried out during the period between October 2024 and April 2024. Out of 380 randomly selected cases with age range (7-80 years), 250 were asthmatic patients and 130 were healthy controls. Among asthmatic patients, 126 have recurrent respiratory tract infections (RTI). All patients have been diagnosed by specialized clinician, patient's data were collected using specially designed questionnaire. Immunological tests were done by using ELISA to measure levels of IgA, IL-9, IL-13 and hs-CRP.

Inclusion criteria

Diagnosed asthmatic patients, asthmatic patients who have recurrent respiratory tract infections, in addition to patients with any abnormal laboratory parameters (severe lymphopenia, neutropenia, and eosinophilia) were included in the current study.

Exclusion criteria

Patients under treatment with immunosuppressive drugs, patients infected with HIV, in addition to patients with immunodeficiency secondary to any disease (nephrotic syndrome, protein losing enteropathy or severe malnutrition) were excluded from the current study.

Blood samples collection

Blood samples were collected from patients and controls in the gel tube and left at room temperature for about 30 minutes for clotting, then serum was isolated by centrifugation at 3000 rpm for 5 minutes, and kept at -20 °C for further use for immunological biomarkers (IgA, IL-9, IL13 and hs-CRP).

ELISA Kits

The ELISA kits used in the current study were Human IgA (SunLong Biotech Co., LTD/SL0912Hu), Human IL-9 (SunLong Biotech Co., LTD/SL1005Hu), Quick Step Human IL-13 (SunLong Biotech Co., LTD/CQS0974Hu) and Human high sensitivity hs-CRP (SunLong Biotech Co., LTD/SL0881Hu).

ELISA procedure and standard curves

Procedures of ELISA and obtaining of standard curves for all the four parameters were done according to instruction of the kits, (Figures 1-4) indicated the standard curves for IgA, IL-9, IL-13 and hs-CRP.

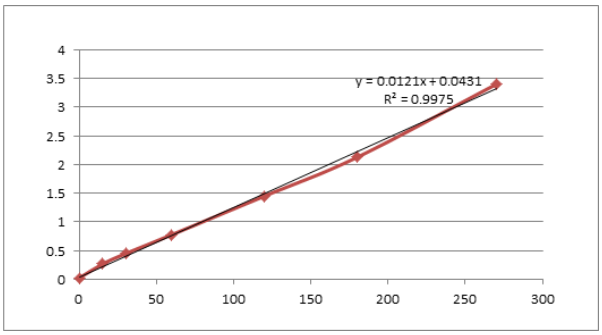

Fig. 1: Standard curve of IgA

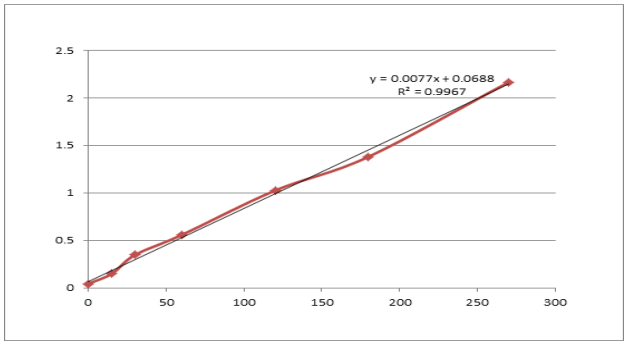

Fig. 2: Standard curve of IL- 9

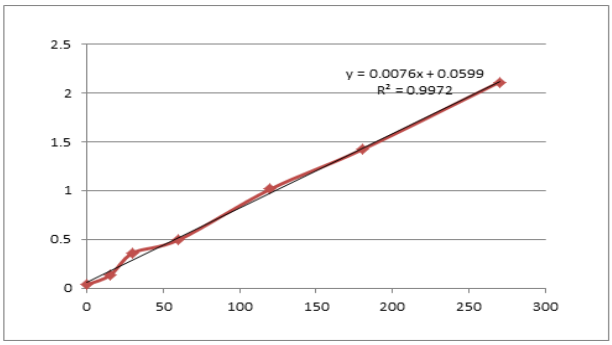

Fig. 3: Standard curve of IL-13

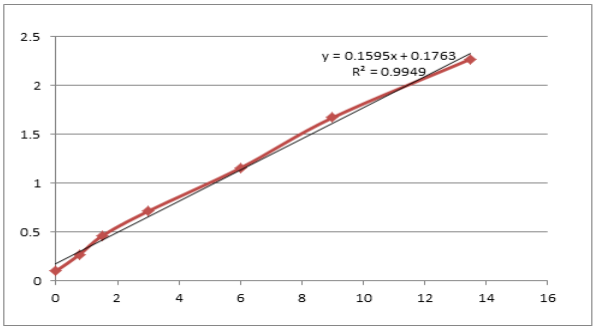

Fig. 4: Standard curve of hs-CRP

Statistical Analysis

The data of this study was statistically analyzed using SPSS version 26, using chi-square and descriptive statistic for mean and range, independent sample t test, one way ANOVA for variance, person for correlation, and ROC test analysis at *p*-value<0.05. Each *p*-value has two stars that indicate a high significant at *p*-value 0.01, *p*-value has one star indicate significant at 0.05, while *p*-value without star indicates a non-significant difference. Similar small letters above the means indicate the non-significant differences, while different letters indicate the significant differences. Sometimes the ANOVA did not give a significant difference, but the post hoc, such as LSD, showed that there were differences.

RESULTS

The current results indicated a significant difference between asthmatic patients and controls at *p*-value<0.05, in the levels of immune parameters, IgA, IL-9, and IL-13 were increased significantly in patients than controls (Table 1).

Table 1: Evaluation of immune parameters in asthma patient compared to control group

Immune Parameters	Patients No. 250	Control No. 130	*p*-value
	Mean ± S. D		
IgA g/L	2.92 ± 0.77	2.19 ± 0.65	<0.01**
IL-9 pg/dl	31.5 ± 9.48	27.4 ± 8.11	<0.01**
IL-13 pg/dl	30.2 ± 7.57	27.0 ± 6.18	<0.01**
Hs-CRP pg/dl	1.23 ± 0.40	1.32 ± 0.51	0.054

The level of IgA was increased significantly in female group than male group at *p*-value <0.05 while levels of IL-9 and hs-CRP were increased non-significantly in female group, IL-13 level was increased non-significantly in male group than female group (Table 2).

Table 2: Immune parameters in asthma patient according to sex

Immune Parameters	Male No. 122	Female No. 128	*p*-value
	Mean ± S. D		
IgA g/L	2.77 ± 0.82	3.06 ± 0.70	<0.01**
IL-9 pg/dl	31.2 ± 9.60	31.7 ± 9.40	0.674
IL-13 pg/dl	30.5 ± 8.41	30.0 ± 6.69	0.609
Hs-CRP pg/dl	1.22 ± 0.38	1.23 ± 0.43	0.829

The IgA level was increased significantly in patients with recurrent respiratory tract infection (RTI) at *p*-value<0.05, increased levels of IL-9 and hs-CRP in recurrent RTI patient group, and the level of IL-13 was increased non-significantly in non-recurrent RTI patient group (Table 3).

Table 3: Evaluation of immune parameters in asthma patient according to disease recurrence

Immune Parameters	Recurrent RTI No. 126	Non recurrent No. 124	*p*-value
	Mean ± S. D		
IgA g/L	3.07 ± 0.74	2.77 ± 0.78	<0.01**
IL-9 pg/dl	31.7 ± 10.0	31.2 ± 9.88	0.705
IL-13 pg/dl	29.6 ± 7.18	30.9 ± 7.92	0.163
Hs-CRP pg/dl	1.26 ± 0.49	1.19 ± 0.30	0.168

The result noted a non-significant difference in all immune parameters according to the duration of disease at *p*-value<0.05, the levels of IgA and hs-CRP were increased non-significantly with increasing disease duration, while other parameters were increased non-significantly in patients who had disease ≤ 1 year as in (Table 4).

Table 4: Evaluation of immune parameters in asthma patient according to duration of disease

Immune Parameters	≤ 1 year No. 217	≥ 1 years No. 33	*p*-value
	Mean ± S. D		
IgA g/L	2.91 ± 0.77	3.02 ± 0.79	0.445
IL-9 pg/dl	31.8 ± 10.6	29.4 ± 8.83	0.223
IL-13 pg/dl	30.5 ± 7.49	28.3 ± 7.93	0.111
Hs-CRP pg/dl	1.21 ± 0.39	1.35 ± 0.47	0.058

All the studied cases; asthmatic patients and controls did not record a history of primary immune deficiency. The result noted non-significant difference in all immune parameters according to family history of asthma at *p*-value <0.05 except hs-CRP, the levels of IgA, IL-9 and IL-13 were increased non-significantly in atopy patient, while hs-CRP increased significantly in atopy patient as in (Table 5).

Table 5: Evaluation of immune parameters according to family history

Family History of asthma	IgA	IL-9	IL-13	Hs-CRP
	Mean ± S. D			
Asthma 68	2.84 ± 0.70	32.0 ± 10.1	30.5 ± 8.02	1.24 ± 0.45
Atopy 53	2.97 ± 0.96	33.6 ± 10.5	31.9 ± 7.93	1.28 ± 0.42
Non-FH 129	2.91 ± 0.74	31.3 ± 9.46	29.9 ± 8.03	1.15 ± 0.29
***p*-value**	0.640	0.443	0.322	0.120 0.040[2-3*]

Evaluation of immune parameters in patients with asthma according to their order between sibs noted a non-significant difference in all immune parameters according to order of sibs at *p*-value <0.05 except IL-13 which indicated increased levels while IgA and hs-CRP levels were high non-significantly in third sibs patient, while IL-13 increased significantly in second sibs patient (Table 6).

Table 6: Evaluation of immune parameters in asthma patient according to sibs orders

Order of sibs	IgA	IL-9	IL-13	Hs-CRP
	Mean ± S. D			
1st 44	2.86 ± 0.67	31.6 ± 9.97	28.0 ± 6.72	1.21 ± 0.44
2nd 72	3.00 ± 0.80	31.1 ± 9.07	30.8 ± 6.84	1.28 ± 0.41
3rd 134	2.90 ± 0.79	31.6 ± 9.60	30.7 ± 8.10	1.21 ± 0.33
***p*-value**	0.558	0.951	0.098 0.043[1-2*]	0.422

Patients were divided according to five age groups. The result showed a significant difference in the level of IL-9 and Hs-CRP at *p*-value<0.05, levels of IL-9 and hs-CRP were increased significantly in age group (7-14), and decreased in the age group (50-69) in IL-9 and (≥ 70**)** in hs-CRP, also, the level of IgA and IL-13 were increased non-significantly in age group (7-14) (Table 7).

The present study recorded a weak negative correlation between age group and both IL-9 and hs-CRP, IgA scored a moderate positive correlation with IL-9, and moderate positive correlation with both IL-13 and hs-CRP. IL-9 scored moderate positive correlation with IL-13 and weak positive correlation with hs-CRP. In addition, IL-13 scored very weak positive correlation with hs-CRP (Table 8).

Table 7: Evaluation of immune parameters in asthma patient according to age groups

Age Groups	IgA	IL-9	IL-13	hs-CRP
	Mean ± S. D			
7-9 years 14	3.15 ± 0.96	40.5 ± 12.4[a]	31.5 ± 7.01	1.37 ± 0.27[a]
10-29 years 77	3.01 ± 0.81	32.1 ± 10.3[b]	29.6 ± 7.08	1.33 ± 0.37[ab]
30-49 years 63	2.89 ± 0.76	30.8 ± 9.80[bc]	30.3 ± 7.68	1.23 ± 0.39[b]
50-69 years 70	2.78 ± 0.61	28.6 ± 7.28[c]	30.3 ± 7.81	1.12 ± 0.25[c]
≥ 70 years 24	3.06 ± 0.66	33.8 ± 9.34[b]	31.1 ± 8.67	1.11 ± 0.25[c]
***p*-value**	0.200	<0.01[**]	0.859	<0.01[**]

Table 8: Person correlation between immune parameters

		IgA	IL-9	IL-13	Hs-CRP
Age	r. value	-.059	-.148*	.043	-.196**
	p-value	.351	.019	.499	.002
IgA	r. value		.513**	.320**	.223**
	p-value		.000	.000	.000
IL-9	r. value			.452**	.216**
	p-value			.000	.001
IL-13	r. value				.159*
	p-value				.012

According to ROC test, it showed that all patients have positive results compared with control group, the study also recorded that 77% of patients with IgA level more than or within average of control group, and 23% were less than the average of control group. IL-9 and IL-13, showed that more than 60% of patients have cytokines mean more than or within the mean of the control group. According to hs-CRP, it was less specific indicator than other parameters (Table 9), and (Figure 1).

Table 9: ROC Curve of immune parameters

Variable	Cut point	Sensitivity	Specificity	Area	S. E	*p*-value	Asymptotic 95% CI	
							Lower Bound	Upper Bound
IgA	1.01	0.99	0.94	0.778	0.025	0.000	0.730	0.826
IL-9	15.6	0.99	0.98	0.627	0.030	0.000	0.568	0.686
IL-13	14.7	1.00	0.96	0.604	0.030	0.001	0.545	0.663
Hs-CRP	0.59	1.00	0.90	0.394	0.033	0.001	0.329	0.459

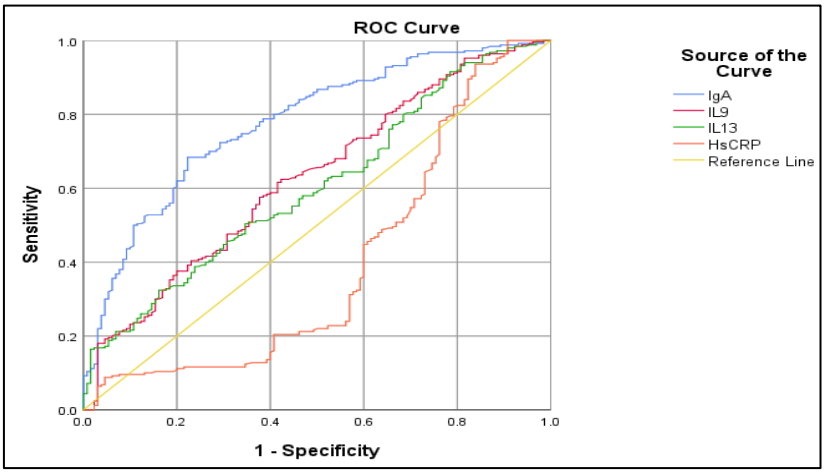

Fig. 5: ROC Curve of immune parameters

DISCUSSION

Asthma is marked by reversible, serial tightness of the airways and inflammation in reaction to environmental allergens, irritants, and infections. It is a sophisticated, immune-mediated and complex process that displays a range of clinical signs[9]. A dominant starting point of illness in adults affecting large number of children and adults worldwide[26]. The immune responses are generated in the course of the pathogenesis of diseases such as asthma are complex and assume the activation of several cells of immune system and their mediators. Immunoglobulins that are produced by; plasma cells that have been developed from activated B-cells, antibodies secreted by plasma cell take part in human health to attenuate infectious microbes [27].

In the current study asthmatic patients and controls indicated a significant difference regarding to immune

parameters levels, including IgA that indicates the role of humoral immunity as an important player in immune response in asthma. A study done on Diyala patients indicated a significant increased IgA levels in asthmatic patients compared to controls[28]. Interleukin-9 level was increased in asthmatic patients when compared to controls, it is expressed by many cells including mast cell and T helper cell subsets. This interleukin has twofold role as pro-inflammatory and anti-inflammatory. IL-13 high levels in asthmatic patients suggested its role in the pathogenesis of asthma. Many works showed that it is an important cytokine in chronic airway inflammation. It is implicated in Th2 inflammation and was spotted as achievable therapeutic target for asthma. Blocking IL-13 signaling, seems to enhance lung function[29]. The correlation between IgA and IL-9 was moderate positive as well as with IL-13 and hs-CRP. Correlation of IL-9 and both IL-13 and hs-CRP scored moderate positive correlation with IL-13 while it was weak positive with hs-CRP. IL-13 scored very weak positive correlation with hs-CRP. IL-9 directly stimulates asthma via IL-13 independent pathway by expansion of mast cells, eosinophils, and B-cells, also through initiation of making IL-13 by hemopoietic cells[24].

A study done by Obaidi *et al.*,[30] indicated that CRP was significantly higher in asthmatic patients in comparison to controls. High sensitive CRP is correlated with asthma[31]. Level of IgA was increased significantly in females than males at p-value<0.05. In a comparison between asthmatic patients with recurrent respiratory infections and those without recurrent respiratory infections the levels of the studied parameters were significantly high in asthmatic patients who complained from recurrent respiratory infections. Actually, recurrent infections lead to elevated levels of immunoglobulins as a part of humoral defense mechanism and increased amount of interleukins secreted from immune cells that have been activated through the course of repeated inflammation. Duration of asthma did not indicate any differences in levels of the studied parameters, although some of these parameters as IgA and hs-CRP levels were increased non-significantly.

Levels of IgA, IL-9 and IL-13 were increased non-significantly in atopy patient, while hs-CRP increased significantly in atopy patient. Evaluation of immune parameters in patients with asthma according to order of sibs noted a non-significant difference in all immune parameters according to the order of asthmatic patient between sibs at p-value<0.05 except IL-13 that indicated increased levels while IgA and hs-CRP levels were high non-significantly in third sibs patient, while IL-13 increased significantly in second sibs patient. One of the main goals behind the current study was to investigate presence of IgA immunodeficiency, all the studied cases did not record a family history of primary immunodeficiency including IgA immunodeficiency. It is possible to find at least one single case if the sample size is more than one thousand. In addition there was no differences in parameters levels regarding to family history of asthma.

CONCLUSION

Receiver Operating Characteristic **(**ROC) test indicated that all patients have positive results compared with control group, 77% of patients with IgA level were more than or within average of control group, and 23% were less than the average of control group. Regarding to IL-9 and IL-13, more than 60% of patients have cytokines mean more than or within the mean of control group and hs-CRP was less specific indicator than other parameters.

Ethical Approval

The study was approved by the Research Ethics Committee at the College of Medicine, University of Basra, in accordance with Protocol No. 98, dated March 18, 2024. Verbal consent was obtained from all patients during the study.

Conflict of Interest

All authors declare that they have no conflict of interest.

Funding

None

REFERENCES

1. Asher MI, Garcia-Marcos I, Pearce NE, Strachan DP. Trends in worldwide asthma prevalence. Eur Respir J 2020;56(6):1-14.
2. Venkatesan P. GINA report for asthma. Lancet Respir Med 2023;11(7):589.
3. Lommatzch M. Modern asthma management. Dtsch Med Wochenschr 2024;149(13):764-770.
4. Holguin F, Cardt J, Chung K, Diver S, Ferreira D, *et al.*, Management of severe asthma: a European Respiratory Society/American Society guideline. Eur Respir J 2020;55(1): 1900588.
5. Ricciardolo F, Sprio A, Baroso A, Gallo F, Riccardi E. Characterization of T2-Low and T2-High Asthma Phenotypes in Real-Life. Biomed 2021;9(11):1684-1699.
6. Alsajri AH, Al-Qerem W, Mohamed Noor D. Asthma prevalence among Iraqi children. Al-Salam J for Med Sci 2024;3(1):17-21.
7. Zheng Y, Lan L, Lu G, Gao Y. Patterns and trends in asthma incidence rates in main Asian and Western countries and their prediction to 2030. Chinese Med J Pulm and Crit Care Med 2024;2(3):188-196.

8. Masjedi M, Ainy E, Zayeri F, Paydar R Assessing the prevalence and Incidence of Asthma and Chronic Obstructive Pulmonary Disease in the Eastern Mediterranean Region. Turk Thorac J 2018;19:56-60.
9. Patel SJ, Teach SJ. Randomized Trial of a Portable HEPA air cleaner. Asthma. Pediatr Rev 2019;40(11):549-67.
10. Hamida H, Lambrecht N. The basic Immunology of Asthma. Cell 2021;184(6):1469-1985.
11. Juhn YJ, Kita H, Yawn BP, Boyce TG, Yoo KH, McGree ME, Weaver AL, *et al.*, Increased risk of serious pneumococcal disease in patients with asthma. Aller Cli Immunol 2008; 122(4):719-723.
12. Busse WW, Lemanske RF, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. Lancet 2010;376(9743):826-834.
13. Oliveira TB, Klering EA, da Veiga ABG. Is recurrent respiratory infection associated with allergic respiratory disease?. J Asthma 2019;56(2):160-166.
14. Muhammed SM, Sultan KM, Abdulrazaq MY. Asthma in Adults; Epidemiology, Risk factor and Patterns of Presentation: A cross Sectional, Questionnaire Based Study in Baghdad Teaching Hospital. Karbala J Med 2012;5(1):1255-1261.
15. Doorley LA, LeMessurier KS, Iverson AR, Palipane M, Samarsinghe AE. Humoral immune response during asthma and influenza comorbidity in mice. Immunobiol 2017; 222(12):1064-1073.
16. Platts-Mills TAE, Woodfolk JA, Allergens and their role in the allergic immune response. Immunol Rev 2011;242(1):51-68.
17. Akdis M. Immune tolerance in allergy. Curr Opin in Immunol 2009;21(6):700-707.
18. Barberi S, Villa MP, Pajino GB *et al.*, Immune response to sublingual immunotherapy in children allergic to mites. J of Bio Reg Homeo Agents 2011;25(4):627-634.
19. Montalvo AS, Gohy S, Rombaux Ph, Pilette Ch, Hox V. The role of IgA in chronic upper airway disease: Friend or Foe?. Front in Aller 2022;3:1-15.
20. Gloudemans AK, Lambrecht BN, Smits HH. Potential of Immunoglobulin A to prevent Allergic Asthma. Clin and Develop Immunol 2013;2013(1):1-12.
21. Habener A, Grychtol R, Gaedcke S, DeLuce D, Dittrich A. *et al.*, IgA^+ memory B-cells are significantly increased in patients with asthma and small airway dysfunction. Eur Res J 2022;60(5):1-15.
22. Fu Y, Wang J, Zhou B, Pajulas A, Gao H, *et al.*, An IL-9-pulmonary macrophage axis defines the allergic lung inflammatory environment. Sci Immunol 2022;7(68),eabi9768.
23. Shimbara AP, Christodoulopoulos A, Soussi-Gouni R, Olivenstein Y, Nakamura R, Livitt N, *et al.*, IL-9 and its receptor in allergic and non-allergic lung disease, J Aller Clin Immunol 2000;105(1):108-115.
24. Steenwinckel V, Louahed J, Orabona C, Huaux F, Warnier G, *et al.*, IL-13 mediates in vivo IL-9 activities on lung epithelial cells but not on hematopoietic cells. The J of Immunol 2007;178(5):3244-3251.
25. Allam MH, Said AF, Omran AA, El-Reheim DM, Kasem AH. High sensitivity C-reactive protein: its correlation with sputum cell counts in bronchial asthma. Res Med 2009;103(12):1878-1884.
26. Urm S, Yun H, Fenta Y, Yoo K, Abraham R, *et al.*, Asthma and risk of selective IgA deficiency or common variable immunodeficiency: a population-based case-control study. Mayo Clin Proc 2013;88(8):813-821.
27. Holgate ST. Innate and adaptive immune responses in asthma. Nat Med 2012;18(5):673-683.
28. Ali OM, Hasan MI, Ahmed AR. Serological evaluation of IgA and IgE antibodies in asthmatic patients in Diyala governorate: Implications for oncology patients. Oncol and Radiother 2024;18(2):1-4.
29. Marone G, Granata F, Pucino V, Pecorao A, Heffler E, *et al.*, The intriguing role of interleukin 13 in the pathophysiology of asthma. Front Pharmacol 2019;10:1387.
30. Al-Obaidi AH, Al-Samarai AM, Jawad AY, Al-Janabi JM. Association between C reactive protein and asthma. Tur Toraks Der 2010;11(3):98-104.
31. Athari AH, Aldhalmi AK, Al-Hindy HM. Association of High-sensitivity C-reactive protein and vitamin D with Bronchial Asthma. J Med Sci 2022;10(B):931-936.