

# Evaluating the role of high-sensitivity C-reactive protein in asthmatic Iraqi patients and its correlation with parameters of patients' clinical characteristics and pulmonary function tests

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## ABSTRACT

**Aims and Objectives:** To evaluate the relevance of high-sensitivity assays for C-reactive protein (hs-CRP), as a sensitive marker of inflammation in asthmatic Iraqi patients. Additionally, correlations of serum levels of hs-CRP with patients' clinical characteristics and pulmonary function tests (PFTs) will be studied in a cross-sectional design. **Materials and Methods:** A random sample of 58 individuals were divided into a healthy (control) group (n = 12) and two groups of adult patients with chronic stable asthma; (n = 22) patients had been receiving inhaled corticosteroids (inhaled corticosteroid-positive, or ICS + VE group) for the past 2–3 months, and (n = 24) steroid-naïve patients (inhaled corticosteroid-negative, or ICS-VE, group). The selected individuals were subjected to hs-CRP measurement and PFTs. **Results:** The forced expiratory volume in one second (FEV<sub>1</sub>)/forced vital capacity (FVC) was measured in all subjects. In the ICS + VE and the ICS-VE groups, there was a significant correlation between the level of hs-CRP and FEV<sub>1</sub>/FVC with r: -0.891 and a p-value of <0.0005 for both groups. In the ICS-VE group, 78.5% had significant clinical symptoms, whereas only 22.7% of the ICS + VE group had significant clinical symptoms. This difference (for the prevalence of clinical symptoms) was significant with a chi-square value of 19.59, degree of freedom (df) = 1, and p < 0.0005. **Conclusion:** In the ICS-VE group, the level of hs-CRP was significantly higher than in both the ICS + VE group and the control group. The values of the PFTs were significantly lower in the ICS-VE group. The prevalence of clinical features was significantly higher in the ICS-VE group.

**Key words:** High-sensitivity C-reactive protein, Asthma, Obstructive, Corticosteroids, Inflammation, Iraq

## INTRODUCTION

Asthma is a chronic inflammatory disorder that results in recurrent episodes of breathing difficulties, and coughing, mainly at night or in the early morning. Boys are affected more commonly than girls. However, after puberty, females are affected slightly more.<sup>1-6</sup>

### Asthma and C-reactive protein

CRP is an acute-phase protein that can be simply and inexpensively measured to assess systemic inflammation. Standard CRP assays are not sensitive enough. Recently, assays for high-sensitivity C-reactive protein (hs-CRP) have become available. Many studies, concluded that hs-CRP levels are strongly associated with asthma.<sup>7-10</sup>

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## Pathophysiology

The pathologic changes can be patchy, and without an extension to lung parenchyma. A characteristic finding is basement membrane thickening due to the sub epithelial deposition of collagen. Triggering factors, in susceptible patients, induce a hypersensitivity reaction with an early and/or late-phase pulmonary response. Both phases depend on allergen-specific immunoglobulin E (IgE). Bronchospasm in the late phase is mediated by the infiltrating cells' soluble factors.<sup>2,3,5</sup>

## Clinical features

The symptoms are often triggered by exercise, allergen, or viral respiratory infections. The triad of wheezing, chest tightness, and shortness of breath is characteristic of asthma. One or more of these symptoms are reported in 90% of patients. The most characteristic finding of asthma is polyphonic expiratory wheezing, which requires respiratory effort. Over-inflation of the thoracic cage may be obvious.<sup>1,4,11</sup>

## Diagnosis

The diagnosis is largely based on the presence of: characteristic triad of Symptoms; Day-to-day peak flow variability (>15% variability, or reversibility to inhaled beta-2 agonist); and other parameters of pulmonary function tests.<sup>11,12</sup>

## Management

The main drugs for asthma are divided into bronchodilators and controllers.<sup>3</sup>

### Bronchodilator therapy

These are: Beta-2 (B2)-adrenergic agonist, anticholinergics, and theophylline. B2-agonists are the most effective.<sup>3,13-17</sup>

### B2 agonist

#### A. short-acting B2 agonist

These bronchodilators are the most effective in the symptoms of a sudden asthma attack.<sup>3,13-15</sup>

#### B. Long-acting B2 agonist

Long-acting bronchodilators are used in conjunction with inhaled steroids to achieve long-term asthma control; if used alone, they can cause death.<sup>15</sup>

### Anticholinergics

Anticholinergic agents have been used with beta-agonists for the emergency control of acute asthma.<sup>14,16</sup>

### Theophyllines

Theophylline use has now fallen due to its safety profile.<sup>3,17</sup>

### Controller therapies

#### Inhaled corticosteroids

Inhaled corticosteroids are the main therapeutic modality for the long-term control of asthma. Their use has been associated with.<sup>18-20</sup>

### Anti-leukotrienes

Leukotriene (LT) pathway inhibitors may substitute ICS in selected patients with mild asthma in which Steroids are not well-tolerated or not desired by the patient. Furthermore, anti-leukotrienes are useful as steroid-sparing agents in moderate-to-severe asthma.<sup>1,4,6</sup>

### Chromones

They are very effective in trigger-induced asthma. Nedocromil was proven to be effective in children with chronic mild-to-moderate asthma.<sup>4,21</sup>

### Anti-IgE

Omalizumab, a humanized anti-IgE antibody, is very effective in moderate-to-severe asthma by reducing exacerbations, improving lung function, and acting as a steroid-sparing agent.<sup>3,4</sup>

## AIMS OF THE STUDY

1. Evaluation of hs-CRP as a marker of systemic inflammation in asthma.
2. Study the correlation between hs-CRP, clinical characteristics, and the pulmonary function test in asthma.
3. Study the effect of ICS on both PFTs and the level of hs-CRP.

## MATERIALS AND METHODS

### Study sample

A random sample of 58 persons was divided into healthy(control) group (n=12) and two groups of adult patients with chronic stable asthma; 22 (n=22) patients had been receiving ICS(400–600 micrograms per day of chlorofluorocarbon [CFC]-beclomethasone dipropionate) (inhaled corticosteroid-positive, or ICS+VE group) for the past 2-3 months, and 24 (n=24) steroid-naive(inhaled corticosteroid-negative, or ICS-VE) patients had been treated with inhaled short-acting B2agonist (as required). The asthmatic patients were randomly selected from the outpatient clinic of the faculty of internal Medicine at Baghdad Medical City Teaching Complex. Individuals allocated to the control group were randomly selected from the medical and paramedical staff within the same hospital. None of the patients were smokers or had respiratory tract infections or exacerbations of asthma in the month prior to enrolment in the study. Individuals with diabetes mellitus, cardiac disease, malignant status, systemic disorders, or obesity with a body mass index (BMI) equal to or more than 30% and systemic disorders were excluded. The selected individuals were subjected to the measurement of hs-CRP and PFTs. Thorough history and clinical examination was also performed.

## Study design

### A cross-sectional design

#### Diagnostic criteria for asthma

The diagnosis of asthma was considered based on the clinical history of variable and intermittent airway obstruction combined with demonstration of airway variability measured using the reversibility test, which is defined as an increment of more than 12% (or 200 ml) of FEV<sub>1</sub> after 15 minutes of administration of inhaled short-acting B<sub>2</sub>agonist (according to the British guidelines on the management of asthma).

#### Measurement of high-sensitivity C-reactive protein<sup>9,10,22</sup>

Samples of peripheral venous blood were aspirated (5 milliliters), put in a plane tube, and centrifuged at 3000x g at 4 C for 5 minutes. The sera were placed in tightly sealable container and stored at -20 C (repeated freezing and thawing was avoided).

Serum hs-CRP was quantified using a highly sensitive-CRP assay (Cormay CRP U MULTICALIBRATOR), lot 906-21 exp 2011-05, with kit lot no. 909-20 C EXP 2010-12, CE. The reference value was <1mg/dl, with Analytical range of 0.01–32 mg/dl.

#### Pulmonary function test

Pre-bronchodilatory FEV<sub>1</sub> and FEV<sub>1</sub>/forced vital capacity (FVC) were measured using office spirometry in the pulmonary function test/outpatient clinic in Baghdad Teaching Hospital at the Baghdad Medical City Teaching Complex.

#### Statistical analysis

SPSS (Statistical Package for Social Sciences) version 19 was used for data input and analysis. For independent samples, a t-test was used to estimate the significance of difference between two continuous variables. Pearson's correlation coefficient was utilized to estimate the significance of relation between two continuous variables. A p value of less than 0.005 was considered significant.

## RESULTS

Table 1 shows the control group and the two groups of asthmatic patients; the inhaled corticosteroid-positive (ICS+VE) and inhaled corticosteroid-negative (ICS-VE) groups. Demographic parameters are shown together with the PFTs, and serum level of hs-CRP. In the control group, there was an equal sex distribution (6 males, 6 females); in the ICS+VE group, there were 8 males and 14 females, and in the ICS-VE group, there were 11 males and 13 females. Disease duration in the ICS+VE and ICS-VE groups was almost comparable – 15.1±3.9 years and 14.6±4.2 years,

respectively. The FEV<sub>1</sub>/FVC in than ICS+VE group was significantly higher than in the ICS-VE group (73.5± 2.4 for ICS+VE vs. 67.9±2.3 for ICS-VE with p:< 0.0005). The serum hs-CRP in the ICS-VE group was significantly higher than that of the ICS+VE group (2.7±0.3mg/dl for ICS-VE vs. 1.3±0.1mg/dl for ICS+VE with p:< 0.0005, and 0.5± 0.2 mg/dl for the control group with p:< 0.0005). The serum hs-CRP in the ICS+VE group was significantly higher than that of the control group with p<0.05.

Table 2 shows the correlations between serum hs-CRP and other parameters in the ICS+VE and the ICS-VE groups. There was a significant correlation between the serum level of hs-CRP and FEV<sub>1</sub>/FVC, with r: -0.891 and p: <0.0005 for both groups.

Concerning the clinical characteristics, the relation of significant clinical symptoms among the two asthmatic groups; in the ICS-VE group, 78.5% had significant clinical symptoms, whereas only 22.7% of the ICS+VE group had significant clinical symptoms.

Table 3 illustrates the correlation of multiple variables among the ICS+VE group with their corresponding Confidence Interval (CI); the correlation between hs-CRP and FEV<sub>1</sub>/FVC had an inverse relation and was significant with a 99% confidence interval (CI).

**Table 1: Characteristics and outcomes of asthmatics and control group**

	Asthma		Control
	ICS+	ICS-	
Subjects n	22	24	12
Age (years)	45.8±4.9	43.1±6.2	32.0±4.3
Gender (M/F)	8/14	11/13	6/6
Disease duration (years)	15.1±3.9	14.6±4.2 <sup>+</sup>	
FEV <sub>1</sub> /FVC	73.5±2.4	67.9±2.3 <sup>§</sup>	
BMI	25.6±2.4	25.4±2.0	25.8±2.1
hs-CRP mg/dl	1.3±0.1	2.7±0.3 <sup>#</sup>	0.5±0.2 <sup>##</sup>

<sup>+</sup> P>0.05 (not significantly different from ICS+VE, <sup>§</sup>P<0.0005 ICS-VE vs. ICS+VE, <sup>#</sup>P<0.0005 vs. ICS+VE, <sup>##</sup>P<0.0005 vs. ICS-VE and <0.05 for ICS+VE

**Table 2: The correlation between serum high-sensitivity C-reactive protein, demographic parameters, and PFTs in both of the ICS-VE and the ICS+VE groups**

	Serum hs-CRP mg/dl			
	ICS+VE		ICS-VE	
	R	P value	R	P value
Subjects n	22		24	
Age (years)	-0.139	0.537	-0.201	0.347
BMI kg/m <sup>2</sup>	0.18	0.19	0.230	0.280
FEV <sub>1</sub> /FVC	-0.891	<0.0005	-0.891	<0.0005
Disease duration (years)	0.071	0.755	0.016	0.941

ICS+VE correlation significant with FEV<sub>1</sub>/FVC only, ICS-VE correlation significant with FEV<sub>1</sub>/FVC only

Table 4 illustrates the correlation of multiple variables among the ICS-VE group with their corresponding CIs; the correlation between hs-CRP and FEV<sub>1</sub>/FVC had an inverse relation and was significant with a 99% CI. Results of Chi-square tests and group statistics are demonstrated in Tables 5 and 6.

Figure 1 shows the serum levels of hs-CRP among the three groups represented as mean ± standard deviation, 0.5 ±

0.2 mg/dl for control, 1.3 ± 0.1 for the ICS+VE group, and 2.7 ± 0.3 mg/dl for the ICS-VE group.

Figure 2 shows a scattered diagram representing the relation between FEV<sub>1</sub>/FVC and the serum level of hs-CRP in the ICS+VE group; the relationship is an inverse relationship.

Figure 3 shows a scattered diagram representing the relation between FEV<sub>1</sub>/FVC and the serum level of hs-

**Table 3: Illustrating the correlation of multiple variables among the ICS+VE group with their corresponding CIs**

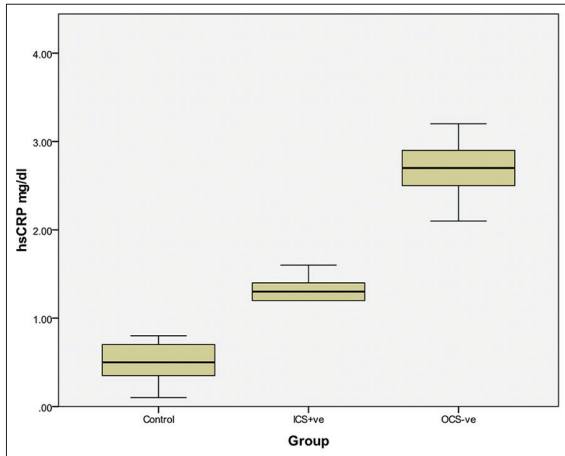
	Age	BMI	hs-CRP	FEV <sub>1</sub> /FVC	Duration
Age					
Pearson correlation	1	0.048	-0.139	0.057	0.649**
Sig. (2-tailed)		0.833	0.537	0.800	0.001
N	22	22	22	22	22
BMI					
Pearson correlation	0.048	1	0.12	-0.13	0.148
Sig. (2-tailed)	0.833		0.16	0.43	0.512
N	22	22	22	22	22
hs-CRP					
Pearson correlation	-0.139	0.18	1	-0.891**	0.071
Sig. (2-tailed)	0.537	0.68		<0.0005	0.755
N	22	22	22	22	22
FEV <sub>1</sub> /FVC					
Pearson correlation	0.057	-0.13	-0.891**	1	-0.065
Sig. (2-tailed)	0.800	0.43	<0.0005		0.774
N	22	22	22	22	22
Duration					
Pearson correlation	0.16	0.148	0.071	-0.065	1
Sig. (2-tailed)	0.64	0.512	0.755	0.774	
N	22	22	22	22	22

\*\*Correlation is significant at the 0.01 level (2-tailed)

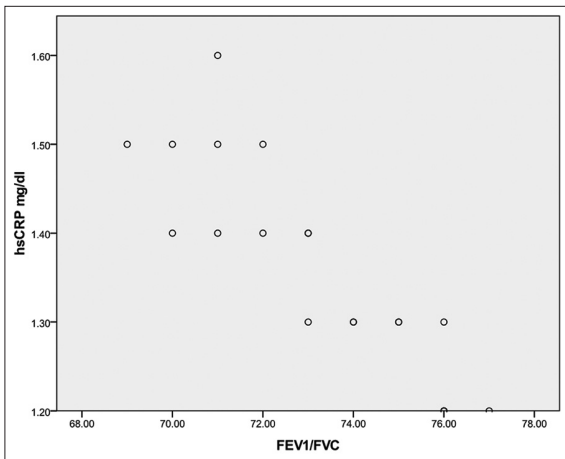
**Table 4: Illustrating the correlation of multiple variables among the ICS-VE group with their corresponding CIs**

	Age	BMI	hs-CRP	FEV <sub>1</sub> /FVC	Duration
Age					
Pearson correlation	1	-0.209	-0.201	0.308	0.12
Sig. (2-tailed)		0.326	0.347	0.144	0.43
N	24	24	24	24	24
BMI					
Pearson correlation	-0.209	1	0.230	-0.402	0.027
Sig. (2-tailed)	0.326		0.280	0.052	0.902
N	24	24	24	24	24
hs-CRP					
Pearson correlation	-0.201	0.230	1	-0.891**	0.016
Sig. (2-tailed)	0.347	0.280		<0.0005	0.941
N	24	24	24	24	24
FEV <sub>1</sub> /FVC					
Pearson correlation	0.308	-0.402	-0.891**	1	-0.151
Sig. (2-tailed)	0.144	0.052	<0.0005		0.481
N	24	24	24	24	24
Duration					
Pearson correlation	0.12	0.027	0.016	-0.151	1
Sig. (2-tailed)	0.43	0.902	0.941	0.481	
N	24	24	24	24	24

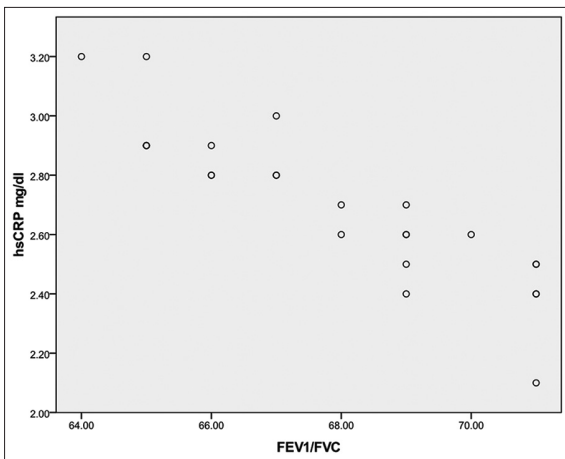
\*\*Correlation is significant at the 0.01 level (2-tailed)



**Figure 1:** Mean and standard deviation of serum hs-CRP among asthmatics and control groups



**Figure 2:** Scattered diagram showing relation between serum hs-CRP and FEV<sub>1</sub>/FVC in ICS+VE group



**Figure 3:** Scattered diagram illustrating relation between serum hs-CRP and FEV<sub>1</sub>/FVC in ICS-VE group

CRP in the ICS-VE group; the relationship is an inverse relationship.

Table 5: Chi-square tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	0.713	2	0.700

Table 6: Group statistics and their independent samples test					
Group statistics					
	Type	N	Mean	Std. deviation	Std. error mean
FEV <sub>1</sub> /FVC	ICS+VE	22	73.4545	2.42462	0.51693
	ICS-VE	24	66.6250	6.30950	1.28792
Duration	ICS+VE	22	15.0909	3.90249	0.83201
	ICS-VE	24	14.5833	4.17983	0.85321

Independent samples test			
t-test for equality of means			
	t	Df	Sig. (2-tailed)
FEV <sub>1</sub> /FVC	4.761	44	<0.0005
Duration	0.425	44	0.673

## DISCUSSION

In this cross-sectional study, the results have high levels of agreement with other studies, including those of: Kony et al.,<sup>8</sup> Shimoda et al.<sup>1,0</sup> Razi et al.,<sup>9</sup> and Kamath et al.<sup>7</sup> However, Ramirez et al.<sup>22</sup> study on patients with asthma, mostly of a mild severity, did not reveal any significant correlation between hs-CRP with asthma, wheezing, National Asthma Education and Prevention Program (NAEPP) control score, forced expiratory volume in one second (FEV<sub>1</sub>), or fractional exhaled nitric oxide (FeNO).<sup>7-10,22</sup>

We studied the validity of hs-CRP in patients with asthma and its relationship to the clinical characteristics and the degree of airway inflammation. In our study, the sample was divided into three groups, the control, the steroid-positive (ICS+VE), and the steroid-negative (ICS-VE) groups. The age in the control group was less than that of the two asthmatic groups, with a value of 32 ± 4.3 years for the control group and 43.1 ± 6.2 years and 45.8 ± 4.9 years for the ICS-VE and ICS+VE groups, respectively. The disease duration in the ICS+VE group was 15.1 ± 3.9 years and 14.6 ± 4.2 in the ICS-VE group. The BMI was almost comparable among the three groups, at 25.6 ± 2.4 kg/m<sup>2</sup>, 25.4 ± 2 kg/m<sup>2</sup>, and 25.8 ± 2.1 kg/m<sup>2</sup> in the ICS+VE, ICS-VE, and control groups, respectively. The BMI did not exceed 30 kg/m<sup>2</sup> because any patient with a BMI of > 30 kg/m<sup>2</sup> had already been excluded from the sample selection.

The FEV<sub>1</sub>/FVC was significantly lower in the ICS-VE group, with a value of 67.9 ± 2.3, in comparison to the higher value



of  $73.5 \pm 2.4$  in the ICS+VE group, with a  $p$  value of  $< 0.0005$ . The level of hs-CRP was significantly more elevated in the ICS-VE group ( $2.7 \pm 0.3$  mg/dl) in comparison to the ICS+VE group ( $1.3 \pm 0.1$ ), with a  $p$  value of  $< 0.0005$ . The level of hs-CRP of the ICS-VE group was also significantly higher than that of the control group ( $0.5 \pm 0.2$  mg/dl), with a  $p$  value of  $< 0.0005$ . The difference between the ICS+VE group and control group was significant, with a  $p$  value of  $< 0.05$ . The relationship between hs-CRP and  $FEV_1/FVC$  in the ICS-VE and ICS+VE groups was an inverse relationship, with  $r = -0.891$  (Pearson correlation) and a significant  $p$  value of  $< 0.0005$ , reflecting a higher degree of airway obstruction in the ICS-VE group due to a lack of inhaled corticosteroid use.

The symptoms of asthma (coughing, wheezing, chest tightness, and early morning awakening) were significantly higher in the ICS-VE group (77.3% with significant symptoms vs. 22.7% without symptoms), while in the ICS+VE group, symptoms were absent in the majority of patients (87.5% without symptoms vs. 12.5% with symptoms). The Pearson Chi-Square of asymptomatic significance (2-sided)  $< 0.0005$  was found.

## CONCLUSION

In inhaled corticosteroid-negative patients (ICS-VE), the level of high-sensitivity C-reactive protein (hs-CRP) was ( $2.7 \pm 0.3$  mg/dl), which is significantly higher than that of both the inhaled corticosteroid-positive patients (ICS+VE) ( $1.3 \pm 0.1$  mg/dl) and the control group ( $0.5 \pm 0.2$  mg/dl), with a  $p$  value of  $< 0.0005$ . The level of hs-CRP in ICS+VE patients was significantly higher than that of the control group, with a  $p$  value of  $< 0.05$ . The values of the PFT ( $FEV_1/FVC$ ) as a measure of the degree of airway obstruction were significantly lower in the ICS-VE group in comparison to the ICS+VE group, correlating inversely with the values of hs-CRP levels. The prevalence of clinical signs and symptoms was significantly higher in the ICS-VE group in comparison to the ICS+VE group.

## RECOMMENDATIONS

1. High-sensitivity CRP can be integrated into the evaluation workup for patients with asthma, especially poorly controlled asthma as a marker of systemic inflammation and for indirectly reflecting the degree of airway inflammation.
2. Emphasizing the important role of inhaled corticosteroids in controlling asthma and reducing disease severity.

3. Further studies are required to better elucidate the clinical significance of the association of high-sensitivity C-reactive protein and asthma, especially its responsiveness to therapeutic protocols.

## ETHICAL STANDARDS

All procedures in this study were in accordance with the ethical standards of the responsible committee on human experimentation in Iraq and the region of the Middle East, and in accordance with the Helsinki Declaration of 1975, as revised in 1983.

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**Authors Contribution:**

**Muhammed Saleh Najdat** - Concept and design of the study, data collection, statistical analysis and data interpretation, preparation of manuscript's initial drafts. **Ahmed Muhammed Lutfi** - Concept and design of the study, Literature review and critical revision of the manuscript.

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