

Research Article

# Estimation of IL-6 and IL-17A Levels in Bacterial Isolates from Sinusitis Patients attending a hospital in Iraq

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## I N F O

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## A B S T R A C T

**Background:** Sinusitis are highly prevalent diseases and significantly impair life of patients. Viral and bacterial acute sinusitis are common occurrence with morbidity and serious complications.

**Methods:** The study involved collection of 150 nasal swabs and blood specimens from patients of both genders with different age groups attending Balad General Hospital and primary health centres from November 2022 to June 2023 in Iraq. The diagnosis relied on differential mediator for bacterial identification, biochemical tests, and Vitek device. Elisa technique was used to estimate the immune marker; all data were analysed using SPSS and presented with tables and figures indicating statistical association at 5% error.

**Results:** Sample showed *Escherchia coli*, *Staphylococcus haemolyticus*, *Klebsiella pneumoniae*, *Yersinia enterocolitica*, *Providencia stuartii*, *Staphylococcus epidermidis*, *Pseudomonas oryzihabitans*, *Leuconostoc pseudomesenteroides*, and *Burkholderia cepacia*. Age groups of 21-30 and 31-40 years showed high prevalence of sinusitis. Levels of interleukins IL-6 and IL-17A were also measured. Mean levels of IL-6 and IL-17A were higher in patients ( $88.08 \pm 33.00$  and  $231.62 \pm 101.00$ ) than in controls ( $40.46 \pm 13.27$  and  $127.35 \pm 52.00$ ). respectively. The comparison of IL-6 and IL-17A with respect to bacterial species showed a significant difference between IL-6 and *E. coli* obtained from the same patient, as compared to patients without this isolate.

**Conclusion:** Despite the isolation of uncommon bacterial pathogens; *Staphylococci* spp. remains the predominant bacteria. the results revealed that IL-17A showed high sensitivity and specificity in examining patients with sinusitis as compared to IL-6, which showed moderate sensitivity and specificity. However, further studies are needed to confirm these findings.

**Keywords:** Sinusitis, Interleukin-6, Interleukin-17A

## Introduction

Chronic sinusitis with sinonasal polyposis is a disease with a complex pathophysiology and complicated treatment. There are multiple theories that seek to explain its pathogenesis, among which the superantigen theory,<sup>1</sup> the biofilm theory,<sup>2</sup> and alterations in the sinonasal microbiota<sup>3</sup> stand out. In all cases, *Staphylococcus aureus* (*S. aureus*) appears to have an important role in creating a state of persistent inflammation. In a systematic review with meta-analysis published in 2014 involving colonisation of *S. aureus*, the existence of specific IgE for bacterial exotoxins and the detection of exotoxins derived from *S. aureus* were found to be independent risk factors associated with chronic rhinosinusitis with sinonasal polyposis.<sup>4</sup> Though chronic rhinosinusitis with allergic rhinitis is a nasal inflammatory disease similar to chronic sinusitis with sinonasal polyposis, the former has a particular aetiology and pathophysiological mechanisms, which involve the differentiation of T lymphocytes and inflammatory cytokines.<sup>5</sup>

Cytokines are important modulating proteins in cell signalling that are produced and released by a large number of cells, including macrophages, mast cells, and B and T lymphocytes, in addition to epithelial and endothelial cells and fibroblasts. They trigger several immunological mechanisms involved in allergy, inflammation and autoimmune diseases.<sup>6</sup> T helper (Th) lymphocytes are responsible for defence against microorganisms, inducing inflammation. Classically, they were divided into T helper 1 (Th1) and T helper 2 (Th2), based on their cytokine profile. The Th1 response is characterised by the production of interleukin 12 (IL-12) and interferon-gamma (IFN $\gamma$ ), promoting defence against intracellular agents. The Th2 response, characterised by the production of interleukin 4 (IL-4), interleukin 5 (IL-5) and interleukin 13 (IL-13), is important in the defence against parasites and is associated with asthma and allergy.<sup>7</sup> This division was revised when regulatory T cell (Treg), which secrete interleukin 10 (IL-10) and transforming growth factor-beta (TGF- $\beta$ ), mediators of immunosuppression and associated with autoimmune diseases, were discovered, followed by T helper 17 (Th17), producers of interleukin 17 (IL-17) and active in combating extracellular bacteria. More recently, T helper 9 (Th9) and T helper 21 (Th21) have also been described.<sup>8</sup>

This study was conducted to isolate and identify bacterial causative agents and assess specific immunological parameters in patients with sinusitis.

## Materials and Methods

### Study Design

The study was conducted in Salah al-Din Governorate in the city of Balad in Balad General Hospital and Balad

Healthcare Sector in the period from November 11, 2022 to June 1, 2023. Nasal swabs and blood samples were collected from individuals of both genders belonging to different age groups patients with chronic diseases and/or having immune suppression. Patients taking medical drugs were excluded from the current study. A total of 150 samples were collected from 90 individuals, among whom 60 were patients, and 30 constituted the control group.

The Ethics and Research Committee of the hospital gave its approval for this study, as well as all participants gave their consent to be sampled. By Resolution No. 11 dated 4/4/2023

### Preparation of Culture Media & Sterilisation Process<sup>9</sup>

All media were prepared according to the instructions of the manufacturer. The culture media and solutions prepared for this study were sterilised using an autoclave at 121 °C at a pressure of 15 pounds/inch for a period of 15 minutes and then dispensed into sterile Petri dishes or tubes as required and stored at 4 °C until use. The solutions, sensitive to high temperatures, were sterilised using Millipore filters with a diameter of 0.22  $\mu$ m, while the glassware was sterilised in the electric oven at 180 °C for two hours.<sup>9</sup>

### Culture Identification<sup>10</sup>

The colonies growing on the media were identified according to colour, shape, size, edge, and height. The colonies were grown more than once on the following culture media to obtain single pure cultures, and the morphological characteristics of the growing colonies were established:

- **Blood Agar:** The morphological characteristics and colours of growing colonies were established based on the bacterial production of the haemolysin enzyme.
- **MacConkey Agar:** This medium was used to study the morphological characteristics of the colonies and to separate the lactose-fermenting bacteria from the non-fermenting ones, as the lactose-fermented colonies appear red or pink in colour on the surface of the medium, and the other colonies appear pale or yellow (Figure 1).

**Mannitol Salt Agar:** This medium was used to investigate the ability of the bacteria to ferment mannitol sugar, indicated by a change in the colour of the medium from pink to yellow, as shown in Figure 2 and 3

### Microbial Identification using the Vitek System

The identification of the isolated species was performed using the Vitek 2 technology. A novel automatic method for detecting bacterial and selection tests using fluorescence-based technologies is the VITEK 2 method.<sup>11</sup>



Figure 1. E. coli on MacConkey Agar



Figure 2. Staphylococcus haemolyticus on Mannitol Salt Agar



Figure 3. Staphylococcus epidermidis on Mannitol Salt Agar

The bacteria were isolated using the streak technique and were cultivated in nutrient agar and incubated for 24 hours at 37 °C. The testing tube was fitted with normal sterile saline (3.0 mL). Pure culture colonies were isolated and suspended in normal saline using a sterile stick or swab. The McFarland standard was adjusted to a turbidity of 0.5–0.63, and the DensiChek™ turbidity meter was used. The outcomes were noted after 4 hours.

### Determination of Immunological Parameters (Human Interleukin-6 (IL-6) & Interleukin-17A (IL-17A))

This kit was designed for the purpose of conducting an enzyme-linked immunosorbent assay test (ELISA). The interleukin levels were determined according to the instructions provided by the company BT LAB, China,<sup>12</sup> as shown in Figure 4.

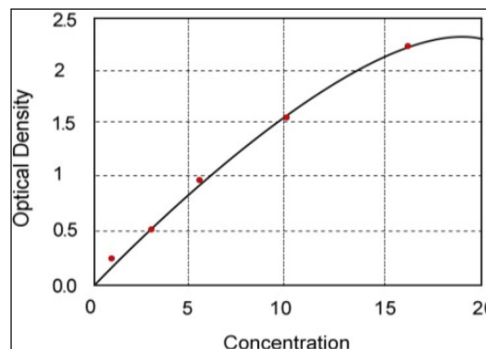


Figure 4(a). Standard Curve for IL-6

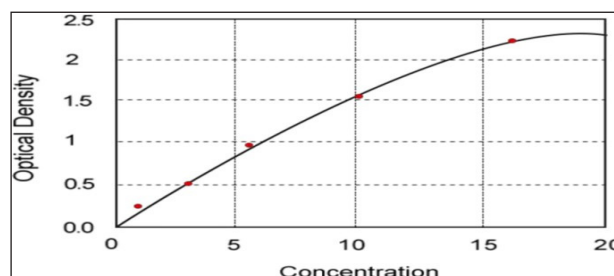


Figure 4(b). Standard Curve for IL-17A

### Statistical Analysis

The levels of all markers were first tested for normality using the Kolmogorov–Smirnov test and the Shapiro–Wilk test. The mean  $\pm$  SD values were recorded, and significant differences between means were assessed using Student's t-test. Other parameters were given as percentages and frequencies, and significant differences between frequencies were assessed using Pearson's chi-square test. The Statistical Package for the Social Sciences (SPSS) version 25.0 and GraphPad Prism version 6 were employed to carry out these analyses.

### Results and Discussion

The results of the present study showed that there was no significant difference ( $p > 0.05$ ) between the study groups on the basis of age and sex, as shown in Table 1.

The findings of the current research revealed that the individuals belonging to the age categories of 21–30 and 31–40 years exhibited a significantly higher prevalence of sinusitis. These findings were consistent with the results reported in a previous study by Shoib and Viswanatha.<sup>13</sup> A similar study done in the Kingdom of Saudi Arabia (KSA) revealed that those below the age of 40 years had a higher propensity for sinusitis.<sup>14</sup> However, another study conducted in India found that those aged 21–30 years were most commonly affected<sup>13,5</sup>

Wu et al. reported that 65.7% of the patients diagnosed with chronic sinusitis were male, while 34.3% were female.<sup>14</sup> However, these findings are inconsistent with the results of the current study, which indicated that 55.0% of the patients were male and 45.0% were female. However,

When looking at age adjusted data from the National Health Interview Survey, it was shown that Sinusitis was more prevalent in woman (63% vs.45%).<sup>15</sup>

On the others contrary, research conducted in Europe, Korea, and Taiwan did not detect any difference in sinusitis prevalence based on sex.<sup>16</sup>

The potential explanation for the observed variations in the incidence of sinusitis as per age and sex is dependent on the differences in the rates of seeking medical assistance and reporting symptoms. Furthermore, the prevalence of other

potential risk factors for sinusitis may differ according to gender.<sup>17</sup> The variation in the prevalence of sinusitis across different age groups and sexes may also be attributed to factors such as sample size, organ dysfunction, poor immunological state, and chronic disorders.

The results of the present study showed significant differences ( $p < 0.05$ ) between the levels of IL-6 and IL-17A in both groups, as shown in Table 2. The mean levels of these interleukins (IL-6 and IL-17A) were higher in patients ( $88.08 \pm 33.00$  and  $231.62 \pm 101.00$ , respectively) than in controls ( $40.46 \pm 13.27$  and  $127.35 \pm 52.00$ , respectively).

**Table 1. Comparison between Study Groups on the Basis of Age and Sex**

Variable	Value	-	Groups		Total	p Value
			Patients (N = 60)	Controls (N = 30)		
Age groups (years)	1–10	n	9	2	11	> 0.05
		%	15.0	6.7	12.2	
	11–20	n	12	10	22	
		%	20.0	33.3	24.4	
	21–30	n	18	9	27	
		%	30.0	30.0	30.0	
	31–40	n	15	8	23	
		%	25.0	26.7	25.6	
	41–50	n	4	1	5	
		%	6.7	3.3	5.6	
Sex	Male	n	33	16	49	> 0.05
		%	55.0	53.3	54.4	
	Female	n	27	14	41	
		%	45.0	46.7	45.6	

**Table 2. Comparison of Levels of IL-6 and IL-17A between Study Groups**

Groups	-	N	Mean	SD	p Value
IL-6	Patients	60	88.08	33.00	< 0.001***
	Controls	30	40.46	13.27	
IL-17A	Patients	60	231.62	101.00	p < 0.001***
	Controls	30	127.35	52.00	

\*\*\*means Highly statistically significant at  $p < 0.001$

The present study showed increased levels of IL-6 in patients than in controls, and these results were similar to the results of a previous study by Kubota et al.<sup>18</sup> IL-6 is produced by numerous types of cells, including T-cells, B-cells, monocytes, fibroblasts, epithelial and endothelial cells, and tumour cells in response to microorganisms or other cytokines (IL-1 and TNF- $\beta$ ). IL-6 is a pleiotropic cytokine, well-known as a regulator of inflammation, classically

described as inducing B-cell proliferation and activation and neutrophil recruitment.<sup>19</sup> Ryu et al. showed higher levels of IL-17A in patients with sinusitis than in controls, and these results were consistent with those of the present study.<sup>20</sup> There is a possibility that IL-17A plays a part in the pathophysiology of chronic rhinosinusitis with nasal polyps (CRSwNP), with M1 macrophages being the primary cellular source occurring in nasopharyngeal tissues. It

has been suggested by Ryu et al. that a viable treatment method for CRSwNP might include targeting IL-17A, either directly or indirectly.<sup>20</sup> It was found that the determination of pro- and anti-inflammatory cytokines in the blood serum of the subjects provided sufficient information for early diagnosis and management of patients in the dynamics of the course of the disease, as well as for predicting the outcome of various diseases, including inflammatory diseases of the paranasal sinuses (IDPS). This involves determining the content of pro- and anti-inflammatory

cytokines when assessing the immune status in sick individuals.<sup>21</sup>

The result of the present study showed statistically significant associations ( $p < 0.05$ ) between IL-6 and positivity of *E. coli*. The level of the interleukin was found to be lower in patients with *E. coli* infection ( $68.41 \pm 33.02$ ) than in patients with no *E. coli* infection. IL-17A was found to be lower in patients with *Staphylococcus epidermidis* ( $170.42 \pm 68.66$ ) as compared to patients without this isolate, and the association was found to be significant ( $p < 0.05$ ) (Table 3).

**Table 3. Comparison of the Levels of Interleukins IL-6 and IL-17A with respect to the Microbial Isolates**

Microbial Isolates.	Result	IL-6		IL-17A	
		Mean	SD	Mean	SD
E.Coli	eNegatives	91.11	61.24	237.44	138.15
	Positive	68.41	33.02	193.84	98.80
	p value.	< 0.05*		> 0.05	
Staphylococcus haemolyticus	Negative	85.99	59.39	233.57	129.12
	Positive	< 0.05*	84.42	216.90	176.16
	p value	> 0.05		> 0.05	
Klebsiella pneumoniae	Negative	88.60	62.88	227.48	130.80
	Positive	84.72	61.40	258.57	158.39
	p value	> 0.05		> 0.05	
Yersinia enterocolitica	Negative	88.15	61.81	228.40	129.58
	Positive	87.28	73.92	267.11	187.89
	p value	> 0.05		> 0.05	
Providencia stuartii	Negative	86.38	64.05	228.70	135.91
	Positive	106.80	34.47	263.83	113.69
	p value	> 0.05		> 0.05	
Staphylococcus epidermidis	Negative	91.79	65.00	245.36	141.22
	Positive	71.57	46.56	170.42	68.66
	p value	> 0.05		< 0.05*	
Pseudomonas oryzihabitans	Negative	89.18	65.57	233.53	135.88
	Positive	81.85	40.03	220.84	127.67
	p value	> 0.05		> 0.05	
cLeuconostoc Pseudomonsenteroides	Negative	82.99	59.50	218.35	132.16
	Positive	113.53	72.21	297.99	127.42
	P value	>5.05		<0.05*	

\*means significant  $p < 0.05$



A previous study demonstrated that the functional activities of Innate lymphoid cells (ILCs) are strongly influenced by the microenvironment. Plasticity permits tissue resident ILCs to adapt to changing conditions and may also change their migratory properties. Consequently, ILCs' transdifferentiation will facilitate the eradication of invading pathogens that require different types of immune responses or pathogens that colonise multiple niches along their life cycle. Henceforward, on disease remission, ILCs might undergo cell reprogramming to avoid excessive mucosal damage, restore the mucosal tissue, and re-establish a beneficial interplay with commensal flora.<sup>22</sup> The increased levels of interleukins in patients with sinusitis that infected with some bacterial infections compared to other bacteria refer to variation in pathogenicity of bacteria that stimulate huge immune response.<sup>23</sup>

### Correlation Relationship among Interleukins

The results of the present study showed that there is a positive correlation between IL-6 and IL-17A ( $R^2 = 0.389$ ) (Figure)(5)

Cao et al. showed a positive correlation between IL-6 and IL-17A in patients with sinusitis, and these results are similar to those of the present study.<sup>24</sup> These interleukins are pro-inflammatory cytokines that increase with inflammation progression in patients with sinusitis.

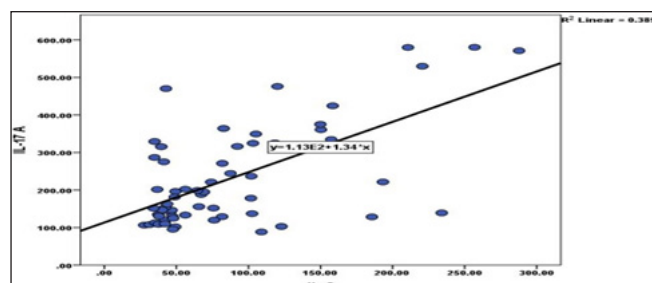


Figure 5. Correlation between IL-17A and IL-6 in Patients with Sinusitis

### Sensitivity and Specificity of Interleukins

The results of the present study showed that IL-17A showed high sensitivity (83%) and a specificity of 60% with a significant difference ( $p < 0.05$ ) in screening patients with sinusitis, as compared to IL-6, which showed moderate sensitivity (73%) and a specificity of 61% (Table 4).

Table 4. Sensitivity and Specificity of Interleukin

Variables	AUC	SEM	p Value	Cut-Off	Sensitivity (%)	Specificity(%)
IL-6	0.792	0.046	< 0.0001***	> 42	73	61
IL-17A	0.829	0.047	< 0.001***	> 115	83	60

AUC= Area Under the Curve

PLS-SEM=partial Least Squares Structural Equation Modeling

\*\*\* means Highly statistically significant at  $p < 0.001$

### Conclusion

Despite the isolation of uncommon bacterial pathogens, Staphylococci remained the predominant bacteria in younger age group with sinusitis. The results revealed that IL-17A showed high sensitivity and specificity in examining patients with sinusitis, as compared to IL-6, which showed moderate sensitivity and specificity.

**Conflict of Interest:** None

**Source of Funding:** None

**Declaration of Generative AI and AI-Assisted Technologies in the Writing Process:** None

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