Kadhm *et. al.,* Babcock Univ. Med. J.2025 8(2):60-75
https://doi.org/10.38029/babcockuniv.med.j..v8i2.961

BUMJ A Multi-Disciplinary Medical Journal
eISSN: 2756-4657

RESEARCH ARTICLE OPEN ACCESS

Analysis of IL-6 and IL-8 gene polymorphisms and their association with cytokine levels in sinus infections

Kadhm AS[1], Al-Galebi AA[1]ID

[1]*Department of Biology, College of Education, University of Al-Qadisiyah, Iraq*

Submitted: 3rd March 2025
Accepted: 3rd June 2025
Published: 31st December 2025
ID: Orcid ID

Abstract
Objective: Sinusitis is a common inflammatory condition influenced by both genetic predisposition and variations in immune responses. Among the key regulators of inflammation, interleukin-6 (IL-6) and interleukin-8 (IL-8) play pivotal roles in coordinating immune signalling and leukocyte recruitment. This study investigated whether polymorphisms in the IL-6 and IL-8 genes are associated with susceptibility to sinus infections and whether these genetic variants influence circulating cytokine levels.
Methods: A total of 48 patients with sinus infections and 48 matched healthy controls were genotyped for IL-6 (-174 G/C) and IL-8 (-251 A/T) polymorphisms using Amplification Refractory Mutation System-Polymerase Chain Reaction (ARMS-PCR). Serum cytokine levels (IL-10, IL-1α, and IFN-γ) were measured by enzyme-linked immunosorbent assay (ELISA). Statistical comparisons were performed using Chi-square tests, t-tests, and odds ratio analyses.
Results: Significantly elevated levels of IL-10 (2.88 ± 0.69 pg/ml) and IL-1α (12.99 ± 1.03 pg/ml) were observed in patients compared to controls (0.436 ± 0.09 pg/ml and 5.54 ± 2.05 pg/ml, respectively; P = 0.002). The IL-6 GG genotype was present in 75% of patients but only 4.16% of controls, while the IL-8 TT genotype was found exclusively in patients. Protective genotypes (IL-6 GC and IL-8 AT) were more frequent in controls. Although cytokine levels did not differ significantly by genotype, trends suggested a more pro-inflammatory profile among high-risk genotypes.
Conclusion: IL-6 and IL-8 gene polymorphisms may influence susceptibility to sinus infections by modulating host immune responses. These variants may serve as potential biomarkers for identifying individuals at elevated risk for chronic or recurrent sinusitis.

Keywords: IL-6 gene polymorphisms, IL-8 gene polymorphisms, Cytokine levels. Sinus infections, Immune response

Plain English Summary

We investigated the relationship between genetic variations in the IL-6 and IL-8 genes and the risk of sinus infections by comparing patients with healthy individuals (controls) to assess the differences in immune chemical levels and gene types. We discovered that patients had higher levels of inflammatory markers such as IL-10 and IL-1α, and that protective gene variants like IL-6 GC and IL-8 AT were more common in healthy individuals. These findings suggest that IL-6 and IL-8 gene variations may influence immune response and the risk of chronic sinusitis.

Correspondence:
Al-Galebi, Ahlam A
Department of Biology, College of Education,
University of Al-Qadisiyah,
Iraq
+ 9647809732653, ahlam.ali@qu.edu.iq

Introduction

Chronic rhinosinusitis (CRS) is one of the most widespread and persistent inflammatory conditions affecting the paranasal sinuses. Clinically, it is defined by inflammation lasting at least 12 weeks (1). The development of CRS is often driven by a mix of environmental factors, microbial colonisation, and variations in individual immune responses. Over time, this prolonged inflammation can lead to structural damage within the sinuses. While inflammation is a natural protective mechanism, when it becomes chronic or poorly regulated, it may result in tissue dysfunction and remodelling (2). At the centre of this immune process are cytokines—small, active proteins that act as messengers between immune cells. These molecules work through specialised receptors and influence gene activity and cellular behaviour (3). Several cytokines have been closely linked to the pathophysiology of CRS, especially interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-1 alpha (IL-1α), interleukin-10 (IL-10), and interferon-gamma (IFN-γ) (4).

For instance, IL-6 plays a key role in promoting B-cell maturation and antibody production (5), while IL-8 is known for attracting and activating neutrophils, contributing to inflammation in the nasal mucosa (6).

Interestingly, recent studies have highlighted the role of genetic variations, particularly single-nucleotide polymorphisms (SNPs), in influencing cytokine function. These genetic changes can affect how much of a cytokine is produced or how it behaves in the body (7). For example, SNPs in the IL-8 gene promoter have been associated with increased gene expression and a higher risk of chronic respiratory inflammation, including nasal polyps (8). Similarly, the -174 G/C SNP in the IL-6 gene has been linked to altered gene activity and susceptibility to various inflammatory diseases (9, 10). Sinus infections often begin as viral but can progress into bacterial infections, especially in chronic or recurrent cases. Among the most common bacteria found in such cases is Staphylococcus aureus (11). Its continued presence can prolong immune activation, damage epithelial barriers, and worsen inflammation. Notably, not everyone responds to these infections in the same way—some individuals seem more prone to severe or long-lasting inflammation, suggesting a genetic predisposition (12, 13).

These genetic variants, due to their functional importance and the extensive research surrounding cytokine gene regulation, were selected for our study. The IL-6-174 G/C polymorphism is known to impact IL-6 gene transcription and has been linked to various chronic inflammatory diseases, including respiratory infections. Similarly, the IL-8-251 A/T SNP influences promoter activity and is associated with enhanced IL-8 levels, especially during mucosal and respiratory tract inflammation. Previous research has also connected these variants to increased susceptibility to conditions such as asthma, chronic rhinosinusitis, and infections caused by Staphylococcus aureus, a principal pathogen of interest in our research. Therefore, these SNPs are both biologically important and clinically relevant for exploring genetic predisposition to sinus infections within our population.

Understanding cytokine gene polymorphisms may help explain why some individuals develop chronic inflammation while others recover quickly. These genetic markers could also guide diagnostic tools or serve as targets for future therapies (14, 15). In this study, we explored the link between IL-6 and IL-8 gene polymorphisms and serum cytokine levels in individuals diagnosed with sinus infections in Al-Diwaniyah, Iraq. We used allele-specific PCR (ARMS-PCR) to detect IL-6 (-174 G/C) and IL-8 (--251 A/T) variants and measured serum levels of cytokines, including IFN-γ, IL-10, and IL-1α. Our goal was to investigate whether these genetic variations affect immune responses, particularly in cases involving Staphylococcus aureus, and to contribute to a better understanding of the immunogenetic basis of sinusitis.

Our hypothesis suggests that specific single-nucleotide polymorphisms (SNPs) within the IL-6 (-174 G/C) and IL-8 (-251 A/T) genes may influence an individual's susceptibility to sinus infections by affecting how the host's immune system responds through cytokine production. We particularly propose that the IL-6 GG and IL-8 TT genotypes are associated with a heightened pro-inflammatory response, which could increase the risk of developing chronic sinusitis. Conversely, the GC and AT genotypes might promote a more regulated immune environment, potentially offering some degree of protection against persistent inflammation.

Materials and Methods

Study Design

This study was conducted on 100 clinical specimens collected from suspected cases of sinus infections in Al-Diwaniyah Teaching Hospital from November 2023 to May 2024. The samples included both nasal swabs and blood that were processed for different analytical needs. Blood samples were divided into whole blood and serum

aliquots for molecular and immunological testing, respectively. Bacterial pathogens were identified using microbiological culture methods, with Staphylococcus aureus constituting the most frequently isolated organism.

The inclusion criteria for participants encompassed adults aged between 18 and 60 years who had been diagnosed with sinusitis based on clinical evaluation and radiological imaging, with laboratory confirmation of Staphylococcus aureus infection. Exclusion criteria were set to omit individuals who were immunocompromised, had used antibiotics or corticosteroids within the past two weeks, or suffered from chronic widespread inflammatory conditions. The control group consisted of healthy individuals, matched for age and sex, with no history of recurrent sinusitis or chronic respiratory illnesses.

The sample size (48 patients and 48 controls) was based on logistical feasibility and prior studies with similar scope, but a formal power calculation was not performed.

Serum Cytokine Levels Measurement

Serum levels of IFN-γ, IL-10, and IL-1α were measured using an ELISA kit (Elabscience, USA). The procedures were conducted in strict accordance with the manufacturer's protocols. Sandwich ELISA approach was performed, in which the target cytokine is bound to a capture antibody pre-coated on a microplate well. Next, a detection antibody conjugated to an enzyme was added. The colourimetric reaction was read at 450 nm, and cytokine concentrations were determined.

Molecular Analysis: SNP Detection

DNA Extraction

Genomic DNA was extracted from whole blood samples using a commercially available DNA extraction kit (Geneaid, USA), according to the manufacturer's protocol. Spectrophotometric analysis (Nanodrop) was performed for the evaluation of the yield and purity of extracted DNA. IL-6: G allele – 198 bp; C allele – 157 bp; internal control – 407 bp. IL-8: A allele – 203 bp; T allele – 173 bp; internal control – 319 bp. All genotyped samples showed clear internal control bands (407 bp for IL-6, 319 bp for IL-8), confirming assay integrity.

PCR Amplification of Polymorphic Regions

The Amplification Refractory Mutation System-Polymerase Chain Reaction (ARMS-PCR) method was used to genotype selected SNPs located in IL-6 and IL-8 genes. The amplification process was performed on a Thermocycler (Bioneer, Korea) using optimised thermal cycling conditions mentioned below:

Primer design for SNP detection in IL-6 and IL-8 genes

Primer pairs for the SNP detection in Interleukin-6 (IL-6) and Interleukin-8 (IL-8) genes were developed from reference sequences identified at the NCBI GenBank and dbSNP databases. This study addresses SNPs that are recognised as well-established immune response markers in sinus infection patients.

A two-primer approach was used to ensure differential discrimination of the different alleles. This included:

Outer primers, which amplify the whole region with the SNP site. Inner primers for primer binding of either the wild-type or mutant allele, which allow AS-PCR (allele-specific PCR).

All primers were designed using Primer3 Plus software and synthesised from Bioneer (Korea) as shown in Table 1. Further details regarding amplicon sizes and PCR conditions are provided in Tables 2 and 3, respectively.

Table 1: Primer Sequences for IL-6 and IL-8 Amplification

Target Gene	Primer Type	Sequence (5'-3')
IL-6	Outer F	GACTTCAGCTTTACTCTTTGTCAAGACA
	Outer R	GAATGAGCCTCAGACATCTCCAGTCCTA
	Inner F (G allele)	GCACTTTTCCCCCTAGTTGTGTCTTCCG
	Inner R (C allele)	ATTGTGCAATGTGACGTCCTTTAGCTTG
IL-8	Outer F	CATGATAGCATCTGTAATTAACTG
	Outer R	CACAATTTGGTGAATTATCAAA
	Inner F (T allele)	TGTAATCCCAGCAGTTTGGGAGGT
	Inner R (A allele)	CTCATCTTTTCATTATGTCAGAG

Table 2: Amplicon Details and Expected Sizes

Target Gene	Allele	Amplicon Type	Expected Product Size (bp)	Notes
IL-6	G	ARMS-specific band	198	Detected with Inner F (G) primer
IL-6	C	ARMS-specific band	157	Detected with Inner R (C) primer
IL-6	—	Internal control	407	Present in all IL-6 reactions
IL-8	A	ARMS-specific band	203	Detected with Inner R (A) primer
IL-8	T	ARMS-specific band	173	Detected with Inner F (T) primer
IL-8	—	Internal control	319	Present in all IL-8 reactions

Table 3: PCR Conditions

Step	Temperature	Time	Cycles
Initial Denaturation	95°C	3 minutes	1
Denaturation	95°C	30 seconds	
Annealing	58°C	30 seconds	30 cycles
Extension	72°C	1 minute	
Final Extension	72°C	5 minutes	1
Hold	4°C	∞	

Electrophoresis on Agarose Gels

Two per cent agarose gel electrophoresis was used to analyse the amplified PCR products. Agarose gel was prepared by adding 2 grams of agarose powder to 100 millilitres of 1X TBE (Tris-Borate-EDTA) buffer and heating until agarose was completely dissolved. EtBr was added to the gel to visualise DNA bands under ultraviolet (UV) light after cooling down a bit. It was then cast in a casting tray and allowed to solidify. 7 µL of each PCR product, pre-mixed with 2 µL of loading dye, was then added to the wells with a micropipette. A molecular weight DNA ladder was included as a standard to estimate fragment sizes. Then, electrophoresis was conducted using a classical gel electrophoresis chamber at a constant voltage of 100 volts for around 60 minutes. The gel was then placed on a UV transilluminator to visualise DNA bands after the run. Gel images were recorded with a digital imaging system. These band patterns were then compared to the DNA ladder to determine genotypes according to the expected sizes of the amplified fragments.

Statistical Analysis

Statistical analysis was conducted with SPSS, V26. The mean serum cytokine levels (like IL-6, IL-8, IL-10, IL-1, and IFN-γ) were compared between self-reported sinusitis patients and healthy controls using the Independent Samples T-test. Genotype and allele frequency distributions of IL-6 and IL-8 polymorphisms in both groups were evaluated using the Chi-square (χ^2) test. Furthermore, odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were computed to determine the strength of association between individual genotypes/alleles and disease susceptibility. P-values <0.05 were considered statistically significant, and $p < 0.01$ was considered highly significant.

Results

Serum IFN-γ, IL-10 and IL-1α levels

The results of Table 4 and Figures 1, 2, and 3 showed that Cytokines such as IFN-γ, IL-10, and IL-1α are important players involved in regulating the immune response: IFN-γ is a pro-inflammatory mediator that is mainly involved in cellular immunity. IL-10 is a leading anti-inflammatory cytokine, and IL-1α signals as an early pro-inflammatory signal during acute immune activation. IFN-γ mean serum level was significantly higher in patients compared to controls (3.17 ± 0.72 pg/ml vs 2.01 ± 0.71 pg/ml). Although the number of individuals displaying elevated levels of IFN-γ was higher following infection, this difference did not attain statistical significance (P = 0.257), suggesting that while levels of IFN-γ are likely to increase in the infection setting, they are unlikely to be a reliable disease marker in this patient population.

Table 4: Level of serum IFN-γ, IL-10, and IL-1α in patients and controls

Groups	IFN- γ	IL-10	IL-1α
Control	2.01±0.71	0.436±0.09	5.54±2.05
Patients	3.17±0.72	2.88±0.69	12.99±1.03
Calculated T value	1.147	3.500	3.239
Calculated P value	0.257(NS)	0.002(HS)	0.002(HS)

NS: No significant difference at P<0.05; HS: Highly significant difference at P<0.01

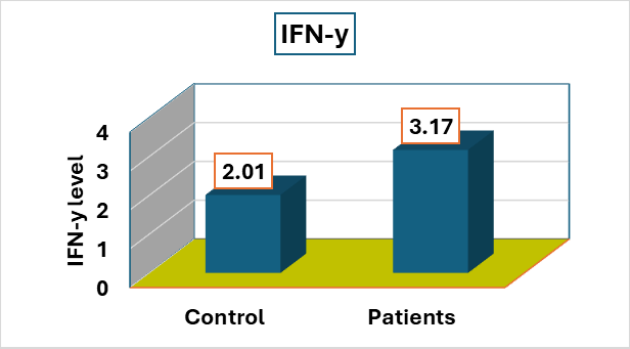

Figure 1: The level of serum IFN-γ in patients compared to the control group

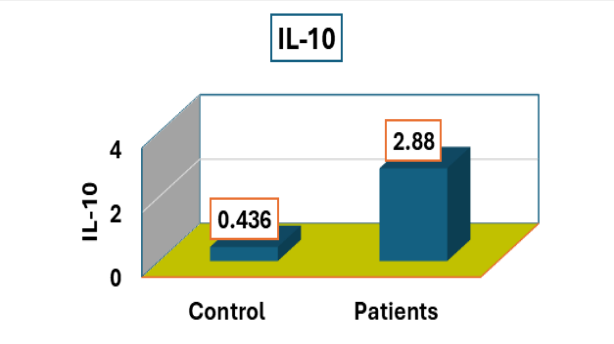

Figure 2: The level of serum IL-10 in patients compared to the control group

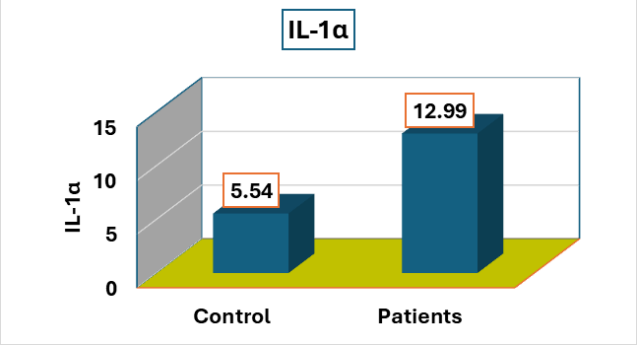

Figure 3: The level of serum IL-1α in patients compared to the control group

On the contrary, the levels of IL-10 were significantly higher in patients (2.88±0.69 pg/ml) than in controls (0.436 ± 0.09 pg/ml, P = 0.002). It is likely that the gradual increases observed at Day 3 and significantly at Day 7 post-infection follow an adaptive inflammatory feedback mechanism to counteract the excess inflammatory response of the immune system during the infection. Considering the well-established function of IL-10 as a key suppressor of excessive immune responses, its elevated levels, particularly in infections caused by Staphylococcus aureus in this study, might, therefore, rather reflect the host's effort to restore immunological homeostasis during sustained inflammation. Likewise, IL-1α was shown to be significantly increased in the patient

group (12.99 ± 1.03 pg/ml) compared to the controls (5.54 ± 2.05 pg/ml), with a P value of 0.002. These findings reinforce the pivotal role played by IL-1α as a central pro-inflammatory cytokine in the innate immune response to the virulence of an active infection. The elevated level of IL-1α in patients coincides with acute inflammation and supports its function in mediating host-protective responses against invading pathogens.

The findings summarised in Table 4 highlight significant changes in cytokines related to sinusitis. The lack of statistical significance of IFN-γ limits its diagnostic quality, although the levels of IFN-γ exhibited a trend toward increase. On the other hand, the major increase of IL-10 and IL-1α levels shows two complementary arms of the immune response; IL-10 as a component of the attempt to limit inflammation, and IL-1α describes the heavy pro-inflammatory response to infection.

Genotype Distribution of IL-8

Table 5 illustrates the distribution of IL-8 gene polymorphisms at position -251 (A/T) genotypes and alleles in sinus infection patients (n=48) and healthy individuals (n=48). This study primarily focuses on evaluating the susceptibility or resistance to sinus infections through genetic variants at the IL-8 promoter region. Genotype homozygous AA was revealed in 16.66% of patients and 8.33% of the control group. Although the AA genotype was more frequent among patients, the difference was not statistically significant (P = 0.217), suggesting that the association between the AA genotype and increased susceptibility for this population was not strong.

Of note, the heterozygous AT genotype was the most prevalent overall but more frequent in the control group (91.66%) than in the patient group (75%). This difference was statistically significant (P = 0.028), with an odds ratio (OR) of 0.2727 (25). These findings may indicate a protective effect of the AT genotype against sinus infection. This genotype is characterised by the presence of both alleles, which may indicate a balanced regulatory mechanism affecting IL-8 expression, leading to a less intense inflammatory response and an overall reduced risk of infection. Conversely, the homozygous TT genotype was detected in 8.33% of patients and was completely missing among controls. This difference was statistically significant (P 0.041), and the calculated odds ratio was particularly high (OR = 9.8090).

These results suggest that this genotype (TT) in individuals may be associated with almost a 10-fold increased susceptibility to sinus infection. This association depicts the TT genotype as a possible genetic influence that could potentially predispose subjects to an overzealous inflammation or reduced immunity to microbial pathogens. The allele frequency distributions were the same for both populations in terms of overall allele frequencies: the A allele accounted for 54.16% and the T allele for 45.83%. This finding is further corroborated by the lack of apparent difference (P = 1) when considering alleles in isolation and concerning disease risk. Instead, the haplotypes, especially TT and AT, dictate modulating susceptibility to sinusitis.

The data in Table 5 support a very strong correlation between IL-8-251 genotypes and the risk of sinusitis. Results indicate that the TT genotype is associated with significantly increased disease risk, whereas the AT genotype may confer some protection. These findings reinforce the idea that polymorphism within the IL-8 locus plays a significant role in determining interindividual variation in immune responsiveness and susceptibility to infection.

Table 5: Distribution of IL-8 (−251 A>T) Genotype and Allele Frequencies in Sinusitis Patients and Controls

Genotype and allele	Control N=48		Patients N=48		Calculated X^2	Calculated P value	Or	Confidence interval 95%
	number	%	number	%				
Genotype								
AA	4	8.33	8	16.66	1.52	0.217(NS)	2.2	0.6152 to 7.8680
AT	44	91.66	36	75	4.8	0.028(S)	0.2727	0.0810 to 0.9185
TT	0	0	4	8.33	4.17	0.041(S)	9.8090	0.5134 to 187.4077
Allele								
A	52	54.16	52	54.16	0	1(NS)	1	0.5668 to 1.7643
T	44	45.83	44	45.83	0	1(NS)	1	0.5668 to 1.7643

NS: No significant difference at P<0.05; S: Significant difference at P<0.05

Genotype Distribution of IL-6

Table 6 presents a comparative assessment of genotype and allele distributions of the IL-6 gene polymorphism (G/C) among patients with sinus infections and a control group of healthy individuals, each comprising 48 subjects. The objective of this analysis is to determine whether specific IL-6 genetic variants are linked to either an increased risk of sinus infection or a potential protective effect. The GG genotype was identified in a remarkably high proportion of patients (75%), whereas it was found in only 4.16% of the control group. This stark difference was statistically highly significant (P < 0.0001), with an odds ratio (OR) of 69.0, indicating an exceptionally strong association between the GG genotype and heightened susceptibility to sinusitis. Carriers of the GG genotype may exhibit a dysregulated or exaggerated IL–6–mediated inflammatory response, thereby increasing their risk of infection. In contrast, the heterozygous GC genotype demonstrated a reverse trend, being present in 79.16% of controls but only 20.83% of patients. This difference also achieved high statistical significance (P < 0.0001), and the odds ratio was notably low (OR = 0.0693), suggesting that individuals with the GC genotype are significantly less likely to develop sinus infections. This protective effect may be attributed to a more balanced production or regulation of IL-6, contributing to a moderated inflammatory response and enhanced immune control. The CC genotype, although less common overall, was observed in 16.66% of the control group and only 4.16% of the patient group. While the statistical significance of this difference was more modest (P = 0.045), the odds ratio (OR = 0.2174) still suggests a possible protective role, albeit weaker than that seen with the GC genotype.

Allelic analysis further emphasised the strength of these associations. The G allele was significantly more prevalent among patients (85.41%) compared to controls (43.75%), while the C allele was dominant in the control group (56.25%) but markedly underrepresented in patients (14.58%). Both differences were highly significant (P < 0.0001). The odds ratio for the G allele was 7.53, confirming its status as a strong genetic risk factor for sinus infections. Conversely, the C allele exhibited an odds ratio of 0.1328, suggesting a robust protective effect.

In summary, the findings presented in Table 6 strongly support a genetic association between the IL-6 G/C polymorphism and susceptibility to sinusitis. The GG genotype and G allele are linked to increased disease risk, potentially through heightened pro-inflammatory activity, while the GC and CC genotypes, along with the C allele, may confer a degree of protection. These findings reinforce the critical role of IL-6 in mediating immune responses and suggest that IL-6 gene variants could serve as valuable biomarkers for predicting individual susceptibility to sinus infections, particularly those involving *Staphylococcus aureus*.

Table :6 **Distribution of IL-6 (-174 G>C) Genotype and Allele Frequencies in Sinusitis Patients and Controls**

Genotype and allele	Control (N=48_		Patients(N=48)		Calculated X^2	Calculated P value	OR	Confidence interval 95%
	number	%	number	%				
Genotype								
GG	2	4.16	36	75	50.35	<0.0001 (HS)	69	14.5107 to 328.1016
GC	38	79.16	10	20.83	32.66	<0.0001 (HS)	0.0693	0.0259 to 0.1855
CC	8	16.66	2	4.16	4.01	0.045(S)	0.2174	0.0436 to 1.0837
Allele								
G	42	43.75	82	85.41	36.43	<0.0001 (HS)	7.5306	3.7561 to 15.0982
C	54	56.25	14	14.58	36.43	<0.0001 (HS)	0.1328	0.0662 to 0.2662

S: Significant difference at P<0.05, HS: Highly significant difference at P<0.01

Relationship between genotype (IL-8) and serum parameters

The association between the IL-8 gene genotypes (AA, AT, TT) elevation of three cytokines, including serum levels of interferon-gamma (IFN-γ), interleukin-10 (IL-10), and interleukin-1 alpha (IL-1α) in patients with sinus infections was examined (n=50), Table 7. Here we investigate whether

genetic variation at the IL-8-251 position modulates the inflammatory and regulatory cytokine profile in response to infection. AA genotype showed the highest mean serum level (3.42 ± 0.65 pg/ml) for IFN-γ, which was closely followed by the AT (3.28 ± 0.64 pg/ml). In contrast, patients with the TT genotype exhibited a significantly decreased level (1.72±0.90 pg/ml). However, regression analysis showed no significant differences between the genotypes (P = 0.693); thus, IL-8 polymorphism may not be a major determinant of IFN-γ expression in this population.

IL-10, a significant cytokine with anti-inflammatory functions, was examined and had the highest mean level in the AA genotype group (3.93 ± 1.20 pg/ml). The TT genotype group was next with a lower level (3.51 ± 1.84 pg/ml), and individuals with the AT genotype had the lowest concentration (2.58 ± 0.56 pg/ml). While this descending trend may suggest some genotype-related regulation of IL-10, differences were not statistically significant (P = 0.560), therefore curbing the strength of this relationship.

For IL-1α, a pro-inflammatory cytokine that plays a significant role in early immune activation, the high level was reported in the TT genotype (7.99 ± 3.77 pg/ml), while the lower level was found in the AA group (6.63 ± 2.87 pg/ml). Lowest levels in the AT genotype group (5.03±1.77 pg/ml). The lack of statistical significance is indicated by the results below the number (P = 0.812).

Finally, despite none of the observed cytokine differences being statistically significant, the trends observed with these cytokines warrant further investigation as they may prove biologically relevant. The TT genotype—previously shown to be associated with increased sinus infection risk—was also associated with higher IL-1α and moderate IL-10 levels, which could be indicative of a strong inflammatory response or, more likely, a dysregulated inflammatory response. In contrast, the AT genotype, previously recognised as possibly protective, was associated with lower levels of IL-10 and IL-1α at sites of infection, suggesting a more controlled immune activation. Although not conclusive, these trends lend support to the hypothesis that genetic variation in IL-8 may have relatively modest modulatory effects on immune responses during sinus infections.

Table 7: Relationship between genotype and serum parameter levels

Genotype	IIFN-γ	IL-10	IL-1α
AA	3.42±0.65	3.93±1.20	6.63±2.87
AT	3.28±0.64	2.58±0.56	5.03±1.77
TT	1.72±0.90	3.51±1.84	7.99±3.77
Calculated F value	0.370	0.587	0.209
Calculated P value	0.693(NS)	0.560(NS)	0.812(NS)

NS: No significant difference at P<0.05

Relationship between genotype (IL-6) and serum parameters

Genotypic variance of the IL-6 gene about serine concentrations of three cytokines, IFN-γ, IL-10, and IL-1α, as mentioned in Table 8, in patients diagnosed with sinus infection. The objective of this part of the analysis is to look at the effects of IL-6 gene polymorphism on systemic immune responses, as evidenced by alterations in circulating levels of cytokines. For IFN-γ, persons with the GC genotype had the highest average serum levels (5.23 ± 1.81 pg/ml), suggesting an elevated pro-inflammatory immune response. Patients belonging to the CC genotype group had moderately increased concentrations of 3.54 ± 0.13 pg/ml, while GG genotype patients presented the lowest concentration of 2.58 ± 0.42 pg/ml. P values indicate no significant differences among genotypes (P = 0.104), suggesting that there was no definitive evidence of genotype-dependent regulation, but that there appeared, at most, to be a trend.

For IL-10, characterised by anti-inflammatory and immunosuppressive properties, the CC genotype group had the highest serum level (5.04 ± 0.21 pg/ml). Individuals with the GC genotype had intermediate levels (3.56 ± 1.11 pg/ml), and the lowest IL-10 concentrations were associated with the GG genotype (2.57 ± 0.56 pg/ml). Though this gradation might represent differences in IL-6 genotype-related immune regulation, the difference did not reach statistical significance (P = 0.475). The biggest differences were found in IL-1α levels, a vital cytokine that plays a role in the start of an inflammatory response. The average level was the highest in the patients with the GC genotype (10.15 ± 5.75 pg/ml), followed by those with the GG genotype (4.54 ± 1.04 pg/ml). In particular, the IL-1α production level of the individuals of the CC genotype was considerably lower (ie, 0.532 ± 0.16 pg/ml). Statistical testing of

the difference among the groups fell short of statistical significance (P = 0.225) despite the substantial numerical differences.

In conclusion, although the differences in cytokine concentrations did not reach statistical significance, the trends have biological relevance. The GC genotype, which was previously associated with a protective effect against sinus infections, showed high levels of IFN-γ and IL-1α, suggesting that there is a strong but regulated immune response. The CC genotype showed the highest IL-10 and lowest IL-1α levels, which may characterise an effective anti-inflammatory control immune profile. By contrast, the GG genotype, previously shown in earlier analysis to correlate with increased susceptibility to infection, was associated with the lowest levels of IFN-γ and IL-10, and a moderate increase in IL-1α, perhaps consistent with a dysregulated or inadequate immune response.

Together, the results were not conclusively statistically significant, yet they provide patterns that could be interpreted as if the IL-6 gene polymorphism role in the cytokine-mediated immunity responses during the sinus infections. Additional studies involving larger cohorts are required to elucidate the functional relevance of these genetic variants and their role in disease pathogenesis and immune regulation.

Table 8**: Relationship between the type of genotype and serum parameter levels**

Genotype	IFN-γ	IL-10	IL-1α
GG	2.58±0.42	2.57±0.56	4.54±1.04
GC	5.23±1.81	3.56±1.11	10.15±5.75
CC	3.54±0.13	5.04±0.21	0.532±0.16
Calculated F value	2.38	0.758	1.54
Calculated P value	0.104(NS)	0.475(NS)	0.225(NS)

NS: No significant difference at P<0.05

Genotype And Allies of IL-8

The picture below shows the ARMS-PCR electrophoretic pattern for the polymorphism corresponding to the single-nucleotide polymorphism (SNP) present at position −251 (A/T) in the promoter region of the IL-8 gene. The assay was developed using allele-specific primers that specifically amplified DNA portions corresponding to the A or T alleles. This system generates a 203-base pair (bp) DNA band from successful amplification of the A allele and a 173 bp band for amplification of the T allele. All reactions were validated with a 319 bp internal control band in all samples to confirm that amplifiable DNA was present and that PCR conditions were appropriate. Samples with the AA homozygous genotype show two separate bands at 203 bp (A allele) and 319 bp (internal control). Samples that are homozygous for the T allele (TT) display bands at 173 bp and 319 bp, by contrast. Heterozygous (AT) individuals show a typical pattern of three bands at 203 bp,173 bp, and 319 bp (well sample 8), indicating the presence of both alleles and the internal control.

In the image (Figure 4) below from electrophoresis, the top row shows samples from patients diagnosed with sinusitis, and the bottom row shows samples from healthy control individuals. Indeed, from the analysis of the banding patterns, which show that the AT genotype is the dominant genotype of both patients as well as controls. But it seems to be much more common in the group of patients. The number of AA genotypes detected was moderate but was higher in the healthy individuals, while the TT genotype was rare but slightly more common in the patient cohort. The data distribution of genotypes observed in the gel following the statistical data in this study concludes that the T allele is more represented in patients suffering sinus infections, especially in heterozygous186. In addition, the high frequency of the AT genotype in the study participants mirrored previous reports from similar studies.

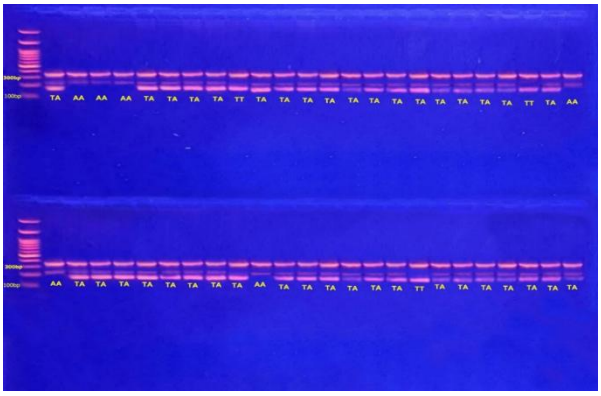

Figure 4: Agarose gel electrophoresis of ARMS-PCR products used to assign genotypes for the IL-8 (−251 A/T) gene polymorphism is shown in Figure 1

A band at 203 bp indicates the presence of the A allele, and a band at 173 bp is indicative of the T allele, while an internal control band at 319 bp serves as an indicator of successful amplification. The banding patterns are read whereby AA homozygous samples have 2 bands at 203 bp and 319 bp, while homozygous TT samples have bands at 173 bp and 319 bp. Heterozygous genotypes are defined by all three bands: 203 bp, 173 bp, and 319 bp. The top row of this gel image is from sinusitis patients, and the bottom row is from healthy controls. The AT genotype, which predominates within both classes of samples, makes up 99% of the total samples. The high frequency of detected heterozygosity at this SNP site in the study population explains this distribution.

Genotype and alleles of IL-6

Figure 5 presents the Agarose gel electrophoresis separation of allelic variants of IL-6 promoter polymorphism. The G allele is visualised as a 198 bp band, the C allele as a 157 bp band. Every reaction contains a 407 bp internal control fragment to confirm PCR amplification. GG homozygotes have two bands at 198 bp and 407 bp, while CC homozygotes have bands at 157 bp and 407 bp. Heterozygous GC specimens showed the three bands (198 bp, 157 bp, and 407 bp), demonstrating that both alleles are present. Samples from sinusitis patients are shown on the top row, while healthy controls are shown in the bottom row of this gel image. Patients show a significantly increased prevalence of the GG genotype and a decreased prevalence of the GC genotype, as can be seen by the banding patterns. In both groups, the CC genotype is relatively rare. This distribution implies a potential relationship between the GG genotype and susceptibility to sinus infections (particularly with Staphylococcus aureus), supporting the statistical data observed in this study.

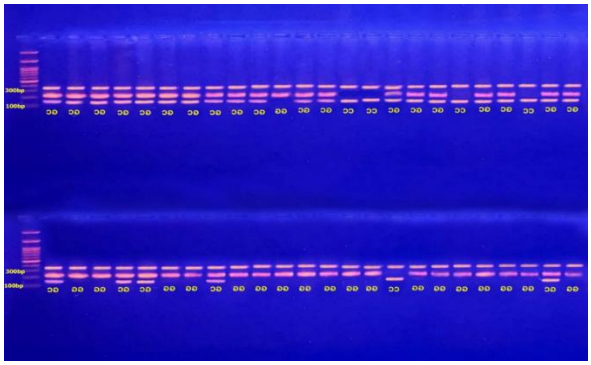

Figure 5: ARMS-PCR products of IL-6 (−174 G/C) gene polymorphism were run on a 3% agarose gel (Figure 2)

The band corresponding to the G G-specific band is at 198 bp, the C C-specific band is at 157 bp, and the internal control is also seen at 407 bp to ensure successful amplification. These samples with the GG genotype are detected at 198 bp and 407 bp, whereas CC genotype samples show bands at 157 bp and 407 bp. GC heterozygous genotypes are recognised with the presence of all

three bands (198 bp, 157 bp, and 407 bp). In the gel above, the patients with sinusitis are on top, and healthy controls are at the bottom. High frequency of a: GG at the beginning of the gel and b: GC genotypes are seen throughout the gel. The GG genotype seems mostly present in the patient samples, but the GC genotype is mostly present in the control samples.

Discussion

Elevated Serum Levels of IFN-γ, IL-10, and IL-1α in Patients and Controls

IFN-γ, IL-10, and IL-1α serum levels highlighted some interesting differences between individuals who experienced sinus infections and healthy controls (Table 3). They found that IL-10 and IL-1α are significantly elevated in the patient group, emphasising that the immune system has a dual response to infection, trying to eradicate pathogens while also reducing tissue injury. IFN-γ levels were elevated in the patients compared with controls, although this difference was not statistically significant. Introduction IFN-γ is a critical cytokine that activates cell-mediated immunity involved in the defence against bacterial infections. Although the modest HLA accumulation in IFN-γ positive patients could suggest an immune attempt to activate such mechanisms and could therefore be related to the opposing outcome of future infection. The lack of statistical significance indicates that IFN-γ is not necessarily a good candidate for distinguishing between infected and non-infected patients in this study. By contrast, IL-10 was significantly elevated in the patient group. It's referred to as a cytokine well-known for its anti-inflammatory effects, which assists in regulating and downregulating the immune response to prevent over-inducing tissue damage. The predominant elevation of IL-10 is probably a sign of the organism's attempts to quell STP-related inflammation (STP: surgical trauma and postoperative) caused by infection, more specifically, due to the especially frequent isolation of Staphylococcus aureus in culture in the study samples.

Patients also had significantly higher levels of IL-1α, a potent pro-inflammatory cytokine. This molecule is usually secreted early in infection and is important for recruiting immune cells and inducing systemic responses such as fever. Its high levels confirm that there is an active inflammatory process within the patients, which is consistent with previous studies that have reported elevated IL-1α expression in patients with chronic rhinosinusitis (12, 13). Overall, both IL-10 and IL-1α are at elevated levels, indicating that the immune system is addressing both an aggressive inflammatory response (IL-1α produced) and activating regulatory mechanisms to minimise damage (IL-10 present). "This dynamic may reflect the body's efforts to contain or resolve persistent or recurrent infection while balancing inflammation and control." These cytokine patterns are then explored further in the context of genetic polymorphisms that may alter immune behaviour during sinus infections in the sections to come.

Association of IL-8 (-251 A/T) Polymorphism with Sinusitis

Similarly, Table 4 examines the IL-8 genotype distribution in patients and healthy subjects. The work points to a significant genetic component to susceptibility to sinus infection. The AT genotype was the predominant genotype, but it occurred more frequently in healthy controls than in patients. This pattern could indicate a protective role in which one copy of each allele may be sufficient to provide balanced levels of IL-8 expression and consequently contribute to better immune control. The TT genotype was detected only in the patient group. Although it was present only in a small number of individuals, its exclusive association among infected patients, along with a high odds ratio, indicates that this genotype could promote sinusitis development. Supernatant for IL-8 Collection and ELISA: IL-8 is a key mediator in attracting neutrophils to sites of infection. However, when IL-8 is released in excess (e.g., in TT genotype carriers), this may promote persistent or uncontrolled inflammation, which can damage the mucosa and lead to chronic symptoms.

The AA genotype was more prevalent in patients compared to controls, although this difference was not statistically significant. And if this is not true -- that is, if the survey or analysis has different sample sizes or other genetic and environmental factors -- it might show a weaker or more complex association. Allelic level: No distinct differences were identified between patients and controls. But whether specific alleles come together into certain genotypes appears to be more important than whether the allele is there. These results demonstrate that it is gene expression control, rather than the mere presence of the gene or genotype (TT versus AT), that shapes the immune response (14). This is per the results of previous studies reporting an association between IL-8 promoter polymorphisms and chronic airway diseases, including asthma and CRS (15, 16, 17, 18, 19). ARMS-PCR genotyping pattern further supports the study, showing clear bands of the three genotypes studied (20, 21, 22), with the

increased prevalence of the AT genotype in the study population. When all the evidence was considered together, it suggested that the IL-8-251 A/T polymorphism might be used to predict how the immune system responds to infection in the sinuses. TT genotype individuals are prone to an excessive inflammatory response, while AT genotype individuals appear to have a more appropriate immune response (23, 24, 25, 26).

Association of IL-6 (-174 G/C) Polymorphism with Sinusitis

Data from Table 5 shows the strong correlation detected between IL-6 gene variations and susceptibility to sinus infections. The GG form was common in patients but rare in controls. This dramatic discrepancy implies that people with the GG genotype may have an exaggerated inflammatory response, raising their susceptibility to sinusitis. It was previously reported that, in other studies, the G allele increases the levels of IL-6 expression and increases immune reaction (27, 28). The strong association of the GG genotype with sinusitis in this study agrees with these findings. People with this genotype could be making more IL-6 and/or making it in a less regulated way, which would upregulate inflammation, and possibly lead to chronic symptoms.

Conversely, the GC genotype was detected more often in healthy controls than in patients. This suggests a potential protective role in which carrying both alleles would lead to a more balanced immune response. Instead of firing off overzealous inflammation, the GC combination may enable a sufficient but controlled response to pathogens. These balanced responses may aid the body in avoiding tissue damage from excess inflammation, leading to chronic infection.

CC genotype was less prevalent overall, but more prevalent in controls than in patients. Although its protective effect is less clear-cut, this pattern is still consistent with the notion that the C allele may help modulate hyperimmune responses. These associations were strengthened by allele-level analysis: the G allele showed greater frequency in patients, and the C allele was more frequent in controls. Such trends emphasise the potential of IL-6 polymorphisms as genetic markers for disease susceptibility. Statistical trends are corroborated by visual validation of genotypes with ARMS-PCR. Patients exhibited GG genotypes more often than GC and CC, which were more prevalent in controls. This distribution fits well with the notion that GG is a risk genotype, while GC/CC are likely protective.

Overall, the IL-6-174 G/C polymorphism appears to be a potential regulator of mucosal inflammatory mediators that may affect the risk for developing sinusitis. In contrast, the GG genotype and G allele seem to confer a risk promoting excessive inflammation (versus the GC and CC genotype that may favour a more controlled immune response). These findings indicate that genetic variants of IL-6 may serve as biomarkers to identify patients more susceptible to chronic/severe sinusitis.

Our observations are consistent with prior research indicating a link between IL-6 (-174 G/C) and IL-8 (-251 A/T) genetic variations and the risk of developing chronic rhinosinusitis (CRS) and other inflammatory conditions of the airway. For example, investigations by Kuran and colleagues and Cergan et al. have emphasised that these IL-6 and IL-8 variants influence mucosal inflammation in CRS cases with nasal polyps (11, 12). Likewise, Ghasemi and associates identified the IL-8 -251 A/T variant as being connected to immune imbalances in both oral and airway inflammatory disorders (13). These similarities reinforce the significance of these single-nucleotide polymorphisms (SNPs) in ongoing mucosal inflammation and emphasise the meaningfulness of our findings in translational research

Genotype–Cytokine Interactions: Linking Genetic Variation to Immune Response

While genotype distributions offered insight into disease susceptibility, Tables 6 and 7 take the analysis a step further by examining whether IL-8 and IL-6 polymorphisms correlate with cytokine levels. Although statistical significance was not achieved, meaningful trends emerged that may reflect how genetic variation influences immune behaviour. In IL-8 genotypes, IFN-γ levels appeared highest in individuals with the AA genotype, slightly lower in AT, and lowest in TT carriers. This downward trend may suggest that the TT genotype is linked to reduced Th1 immune activation. For IL-10, levels were higher in AA and TT genotypes compared to AT, possibly reflecting compensatory regulation in genotypes associated with increased inflammation. Meanwhile, IL-1α levels were highest in TT individuals, reinforcing their potential for a more pro-inflammatory profile.

Similarly, for IL-6 genotypes, GC individuals showed the highest levels of IFN-γ and IL-1α, while GG genotypes showed the lowest IFN-γ and IL-10, but intermediate IL-1α. Interestingly, CC carriers had the highest IL-10 levels and the lowest IL-1α levels, suggesting a strongly regulated immune state with less inflammation. Although these differences did not meet statistical thresholds, they

support the biological hypothesis that specific genotypes contribute to varying immune patterns. The GG and TT genotypes appear to skew the immune system toward inflammation, while GC, CC, and AT may support a more balanced or regulated response. These trends merit further investigation in larger cohorts. Overall, these genotype–cytokine interactions provide a deeper understanding of how IL-6 and IL-8 genetic polymorphisms might influence cytokine dynamics during sinus infections. This insight could prove valuable in developing targeted interventions or personalised approaches to managing chronic sinus inflammation (29).

While several genotype–cytokine associations identified in our study did not reach statistical significance, the observed trends, such as the increased IL-1α levels in individuals carrying the IL-6 GC genotype, may still carry biological importance. The GC genotype, which has been previously associated with a protective effect, appeared to be linked to a more prominent, yet potentially regulated, pro-inflammatory response. This indicates a possible genotype-dependent modulation of cytokine activity that small sample sizes may not fully capture. Consequently, these non-important trends should be interpreted with caution, but they nonetheless support the hypothesis that IL-6 and IL-8 gene polymorphisms can influence immune responses during sinus infections. Further research involving larger, adequately powered cohorts is essential to confirm these findings and to explain their mechanistic implications.

Although there was a discernible trend toward increased levels of IFN-γ among patients, this did not achieve statistical significance. This may be due to the natural variability in IFN-γ secretion and its precise regulation during different phases of inflammation, whether acute or chronic. Besides, given our limited sample size and possible confounders such as individual differences in immune history, our study might not have had enough statistical power to identify a true difference. Nevertheless, the observed pattern suggests that IFN-γ could still be involved in cellular immune responses during sinus infections, which makes it a worthwhile subject for future investigations.

Integration of Genotype Patterns with Electrophoresis Findings

The conclusions drawn from Tables 3 to 7 are further supported by the visual evidence provided through ARMS-PCR gel electrophoresis. The banding patterns observed for both IL-6 and IL-8 genotypes validate the statistical findings by confirming the presence and distribution of each genotype in the study population. For IL-8, all three genotypes, AA, AT, and TT, were distinguishable through their distinct electrophoretic profiles, with the AT genotype being most prevalent. This visual clarity not only underscores the reliability of the genotyping technique but also reinforces the potential protective effect of the AT genotype.

Similarly, for IL-6, the GG genotype appeared dominant among patient samples, while GC and CC genotypes were more common in controls. The presence of internal control bands in all reactions further validates the accuracy and robustness of the ARMS-PCR method used in this study. Altogether, the combination of genetic, immunological, and electrophoretic data builds a cohesive narrative: IL-6 and IL-8 polymorphisms influence the host immune response to Staphylococcus aureus-driven sinus infections. Genotypes associated with higher cytokine imbalance (GG for IL-6 and TT for IL-8) may contribute to prolonged inflammation and tissue damage, while balanced genotypes (GC, CC, and AT) appear to support immune control and resolution.

While several genotype–cytokine associations in this study showed trends toward biological relevance, such as elevated IL-1α in IL-6 GC carriers and reduced IFN-γ in IL-8 TT carriers, these differences did not reach statistical significance. As such, these observations should be interpreted cautiously. Rather than conclusive findings, they serve as preliminary indications of possible immunogenetic patterns that warrant further investigation in larger, well-powered studies. This distinction is important to avoid overinterpretation of results that may reflect sample variability or insufficient statistical power.

These findings point to a promising future in which genotyping may help identify individuals at risk of chronic sinus inflammation, allowing for earlier interventions and personalised treatment strategies aligned with the principles of precision medicine. From a clinical standpoint, recognising IL-6 and IL-8 genetic polymorphisms offers potential in customising treatments for patients with chronic or recurring sinusitis. For instance, individuals with high-risk genotypes like IL-6 GG or IL-8 TT may benefit from early therapies focused on immune modulation or targeted biologic agents that specifically address IL-6 or IL-8-driven inflammation. As biologic drugs targeting these cytokines, such as tocilizumab for IL-6, become more refined, genetic profiling could become an invaluable tool for patient stratification, allowing

more personalised and effective management of persistent airway inflammation

Study limitations
This research does have certain limitations. Firstly, the sample size was relatively small (n=48 per group), which could restrict our ability to detect subtle associations and limit the broader applicability of the results. Larger, multicentre studies are needed to confirm these findings. There is a risk of Type I error due to small sample size and multiple comparisons. This may also account for the high OR of 69.0 for the IL-6 GG genotype. However, due to the exploratory nature of the study and the limited number of comparisons, we did not apply Bonferroni correction. Likewise, due to the relatively small sample size, multivariate analysis was not performed in this study. However, age and sex were matched between groups to reduce confounding. Future studies must apply Bonferroni correction methods and multivariate modelling when using larger datasets. Although we explored linkages between specific SNPs and cytokine concentrations, we did not conduct functional validation experiments, such as luciferase reporter assays, to directly demonstrate how the IL-6 and IL-8 promoter variants influence gene expression. Incorporating such analyses in subsequent work would deepen our understanding of the mechanisms involved and help establish causality.

Conclusion
These findings emphasise the role of IL6 and IL8 polymorphisms in the pathogenesis of sinus infections. The pro-inflammatory alleles (P = 0.0192) phenotype that produced IL-6 (GG) and IL-8 (TT) genotypes was associated with higher risk, while GC and AT genotypes were associated with alternative immune responses or protection. Additionally, the presence of higher levels of IL-1α and IL-10 in patient samples highlights the complex interplay between inflammatory and regulatory pathways activated during infection. The conclusions are further bolstered by a clear electrophoretic representation and the pooling of molecular, immunological, and genotyping data into this single study. These results imply that genotyping IL-6 and IL-8 in combination with cytokine profiling may provide new tools for identifying subjects with a higher risk of developing chronic sinusitis and allow us to target more specific and immunomodulatory therapy.

List of Abbreviations
ARMS-PCR: Amplification Refractory Mutation System-Polymerase Chain Reaction
AS-PCR: allele-specific PCR
CRS: Chronic rhinosinusitis
SNPs: single-nucleotide polymorphisms

Declarations
Ethical considerations and consent to participate
This study was approved by the Ethics Committee of the University of Al-Qadisiyah. Informed consent was obtained from all participants, including both healthy controls and patients, before sample collection. The study followed the ethical guidelines for human research and adhered to the principles outlined in the Declaration of Helsinki.

Data Availability
Datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing Interest
The authors declare no competing interests.

Funding
This work was not supported by any specific funding source.

Author Contributions
AAAS conceived and supervised this study; KAS searched the literature, designed the experiments, performed the experiments, analysed the data, and wrote the manuscript. Both authors reviewed and finalised the manuscript.

Acknowledgment
I would also like to express my sincere gratitude to the personnel of Al-Diwaniyah Teaching Hospital for their kind cooperation during the collection of clinical samples. I would like to thank the Molecular Research Laboratory, Department of Biology, College of Education, University of Al-Qadisiyah, for providing technical assistance with the immunological and molecular analyses.

References
1. Price CP, Guo A, Stevens WW, Cousens L, Vu TH, Suh LA, Erickson KA, Conley D, Grammer LC, Kern RC, Tan BK. Efficacy of an oral CRTH2 antagonist (AZD1981) in the treatment of chronic rhinosinusitis with nasal polyps in adults: a randomized controlled clinical trial. Clinical & Experimental Allergy. 2022 Jul;52(7):859-67. https://doi.org/10.1111/cea.14158
2. Shopen Y, Tsur N, Soudry E. The Long-Term Implications of Rhinitis and Chronic Rhinosinusitis in Young Adults. The

Laryngoscope. 2023 Dec;133(12):3299-303. https://doi.org/10.1002/lary.30685
3. Cavaliere C, Masieri S, Begvarfaj E, Loperfido A, Baroncelli S, Cascone F, Ciofalo A. Long-term perspectives on chronic rhinosinusitis with nasal polyps: evaluating recurrence rates after functional endoscopic sinus surgery in the biologics era—A 5-year follow-up study. Journal of Personalized Medicine. 2024 Mar 10;14(3):297. https://doi.org/10.3390/jpm14030297
4. Yip JQ, Oo A, Ng YL, Chin KL, Tan KK, Chu JJ, AbuBakar S, Zainal N. The role of inflammatory gene polymorphisms in severe COVID-19: a review. Virology Journal. 2024 Dec 20;21(1):327. https://doi.org/10.1186/s12985-024-02597-3
5. Kaliniak S, Fiedoruk K, Spałek J, Piktel E, Durnaś B, Góźdź S, Bucki R, Okła S. Remodeling of paranasal sinuses mucosa functions in response to biofilm-induced inflammation. Journal of Inflammation Research. 2024 Dec 31:1295-323. https://doi.org/10.2147/JIR.S443420
6. Mulder PP, Vlig M, Elgersma A, Rozemeijer L, Mastenbroek LS, Middelkoop E, Joosten I, Koenen HJ, Boekema BK. Monocytes and T cells incorporated in full skin equivalents to study innate or adaptive immune reactions after burn injury. Frontiers in Immunology. 2023 Oct 13;14:1264716.
7. Viksne RJ, Sumeraga G, Pilmane M. Characterization of cytokines and proliferation marker Ki67 in chronic rhinosinusitis with nasal polyps: a pilot study. Medicina. 2021 Jun 11;57(6):607. https://doi.org/10.3390/medicina57060607
8. You, Y.L., Byun, H.J., Chang, Y.B., Kim, H., Lee, H., Suh, H.J., Jeon, J.Y., Kim, B.R., Hwang, J.E., Lee, J.H. and Choi, H.S., 2025. Euglena gracilis-derived β-glucan ameliorates particulate matter (PM2. 5)-induced airway inflammation by modulating nuclear factor kappa B, mitogen-activated protein kinase, and nuclear factor erythroid 2-related factor 2 signaling pathways in A549 cells and BALB/c mice. *International Journal of Biological Macromolecules*, *296*, p.139671. https://doi.org/10.1016/j.ijbiomac.2025.139671
9. Vitucci EC, Simmons AE, Martin EM, McCullough SD. Epithelial MAPK signaling directs endothelial NRF2 signaling and IL-8 secretion in a tri-culture model. Part Fibre Toxicol. 2024;21(1):15. https://doi.org/10.1186/s12989-024-00576-8
10. Li L, Zhang Y, Liu H, Wang T, Li J, Wang X. Exploring causal relationships between inflammatory cytokines and allergic rhinitis, chronic rhinosinusitis, and nasal polyps: a Mendelian randomization study. Frontiers in immunology. 2023 Nov 10;14:1288517. https://doi.org/10.3389/fimmu.2023.1288517
11. Cergan R, Berghi O, Dumitru M, Vrinceanu D, Manole F, Musat GC, Oancea AL, Serboiu C. Interleukin 8 Molecular Interplay in Allergic Rhinitis and Chronic Rhinosinusitis with Nasal Polyps: A Scoping Review. Life. 2025 Mar 15;15(3):469. https://doi.org/10.3390/life15030469
12. Kuran G, Aslan H, Haytoğlu S, Yüreğir ÖÖ, Bozdoğan ST. IL-1RN VNTR, IL-2 (-330), and IL-4 VNTR gene polymorphisms in patients with chronic rhinosinusitis with sinonasal polyposis. Turkish Journal of Medical Sciences. 2019;49(5):1411-7. https://doi.org/10.3906/sag-1710-186
13. Ghasemi H, Mozaffari HR, Kohsari M, Hatami M, Yari K, Marabi MH. Association of interleukin-8 polymorphism (+ 781 C/T) with the risk of oral Lichen Planus disease. BMC Oral Health. 2023 Jun 20;23(1):404. https://doi.org/10.1186/s12903-023-03088-7
14. Kadivnik M, Plečko D, Kralik K, Arvaj N, Wagner J. Role of IL-6, IL-10 and TNFα gene variants in preterm birth. Journal of Clinical Medicine. 2024 Apr 21;13(8):2429. https://doi.org/10.3390/jcm13082429
15. Urinovich KG. FUNDAMENTALS OF THE ETIOPATHOGENESIS, CLINICAL FEATURES AND PATHOMORPHOLOGY OF CAVERNOUS SINUS THROMBOSIS. Multidisciplinary and Multidimensional Journal. 2024 Dec 1;3(10):100-4.
16. Faraj SS, Jalal PJ. IL1β, IL-6, and TNF-α cytokines cooperate to modulate a complicated medical condition among COVID-19 patients: case-control study. Annals of medicine and surgery. 2023 Jun 1;85(6):2291-7. https://doi.org/10.1097/MS9.0000000000000679
17. Watrowski R, Schuster E, Polterauer S, Van Gorp T, Hofstetter G, Fischer MB, Mahner S, Zeillinger R, Obermayr E. Genetic Variants of Interleukin-8 and Interleukin-16 and Their Association with Cervical Cancer Risk. Life. 2025 Jan 21;15(2):135. https://doi.org/10.3390/life15020135
18. Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y, Li Y. Inflammation and tumor progression: signaling pathways and targeted intervention. Signal transduction and targeted therapy. 2021

Jul 12;6(1):263. https://doi.org/10.1038/s41392-021-00658-5
19. Nash D, Hughes MG, Butcher L, Aicheler R, Smith P, Cullen T, Webb R. IL-6 signaling in acute exercise and chronic training: Potential consequences for health and athletic performance. Scandinavian Journal of Medicine & Science in Sports. 2023 Jan;33(1):4-19. https://doi.org/10.1111/sms.14241
20. Tylutka A, Walas Ł, Zembron-Lacny A. Level of IL-6, TNF, and IL-1β and age-related diseases: A systematic review and meta-analysis. Frontiers in Immunology. 2024 Mar 1;15:1330386. https://doi.org/10.3389/fimmu.2024.1330386
21. Zhang Z, Liu J, Xie L, Cao W, Ma F, Zhang Y. Tissue eosinophils and mucous inflammatory cytokines for the evaluation of olfactory recovery after endoscopic sinus surgery in patients with nasal polyposis. American Journal of Otolaryngology. 2022 Sep 1;43(5):103561. https://doi.org/10.1016/j.amjoto.2022.103561
22. Vaitkus J, Vitkauskienė A, Simuntis R, Vaitkus Ž, Šiupšinskienė N, Vaitkus S. Chronic rhinosinusitis with nasal polyps: age and disease severity differences in the levels of inflammatory markers. Medicina. 2021 Mar 18;57(3):282. https://doi.org/10.3390/medicina57030282
23. Viksne RJ, Sumeraga G, Pilmane M. Characterization of cytokines and proliferation marker Ki-67 in chronic rhinosinusitis with recurring nasal polyps. Advances in Respiratory Medicine. 2022 Oct 14;90(5):451-66. https://doi.org/10.3390/arm90050053
24. Lucchinetti E, Lou PH, Chakravarty A, Marcolla CS, Pauline ML, et al. Vegaven lipid emulsion study in piglets. J Nutr. 2025;155(3):703–18. https://doi.org/10.1016/j.tjnut.2024.10.047
25. Smelaya TV, Belopolskaya OB, Smirnova SV, Kuzovlev AN, Moroz VV, Golubev AM, Pabalan NA, Salnikova LE. Genetic dissection of host immune response in pneumonia development and progression. Scientific reports. 2016 Oct 11;6(1):35021. https://doi.org/10.1038/srep35021
26. Michalik M, Krawczyk B. Chronic Rhinosinusitis—Microbiological Etiology, Potential Genetic Markers, and Diagnosis. International Journal of Molecular Sciences. 2024 Mar 11;25(6):3201. https://doi.org/10.3390/ijms25063201
27. Almeida-Santiago C, Quevedo-Abeledo JC, Hernández-Hernández MV, de Vera-González A, González-Delgado A, González-Gay MÁ, Ferraz-Amaro I. Disease activity is more Associated with IL-1 Than with IL-6 in patients with rheumatoid arthritis. Life. 2022 Dec 28;13(1):82. https://doi.org/10.3390/life13010082
28. Piattini F, Sidiropoulos ND, Berest I, Kopf M. IL-6 mediates defense against influenza virus by promoting protective antibody responses but not innate inflammation. Mucosal Immunology. 2025 Feb 18. https://doi.org/10.1016/j.mucimm.2025.02.001
29. Carlini V, Noonan DM, Abdalalem E, Goletti D, Sansone C, Calabrone L, Albini A. The multifaceted nature of IL-10: regulation, role in immunological homeostasis and its relevance to cancer, COVID-19 and post-COVID conditions. Frontiers in immunology. 2023 Jun 8;14:1161067. https://doi.org/10.3389/fimmu.2023.1161067