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# *IL-6* rs1800796 Genotype Variants Among Iraqi Patients Suffering from Sepsis

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**Abstract**

Sepsis has a complex genetic background; many genes may directly or indirectly affects its development. Since cytokines control the type, severity, and consequences of pathogenesis, they are also involved in some aspects of sepsis. This research aims to investigate the relationship between *IL-6* gene polymorphism and sepsis. For this research, a total of 75 patients with sepsis disease and another 75 individuals without the disease were taken as the controls for this genetic study. The *IL-6* gene has many high-frequency polymorphisms; these polymorphisms were amplified using well-chosen primers. In the serum of individuals with sepsis (240.42 ± 84.25 pg/mL), *IL-6* was found to be higher compared to the control group (203.58 ± 22.47 pg/mL). Finally, the rs1800796 polymorphism is correlated with the risk of developing sepsis, with the G/A heterozygous variation providing a high level of risk under the dominant inheritance model of the polymorphism. There is no relationship with the recessive model, suggesting that the presence of the GA genotype and the dominant model (GA + AA) had significantly higher chances of sepsis compared with other genotypes (OR = 4.05 and 3.00, respectively; $p < 0.05$). The findings show a clear link between the genetic variation of the *IL-6* gene and the regulation of *IL-6* during sepsis.

**Keywords**
*IL-6*; sepsis patients; polymorphism; genotype

## 1. Introduction

A complex clinical state known as 'sepsis' can develop when the body's immune system reacts negatively to bacteria or their byproducts [1, 2]. The global mortality rate of sepsis patients remains up to 30-60%, despite tremendous improvements in antibiotic therapy and life support. Consequently, there is an immediate need for predictive markers to identify populations at high risk so that preventive therapy and early detection can begin. It has been demonstrated that altered cytokine levels contribute to the development of sepsis, and cytokines play a crucial role in modulating the host immunological response [3]. Improving the results for patients who are susceptible to sepsis should be possible by identifying genetically customised diagnostic and therapeutic approaches that are based on differences in gene expression and related reactions to sepsis [3, 4].

The risk of death is higher in septic shock compared to sepsis alone because of underlying circulatory, cellular, and metabolic problems. Due to their increasing prevalence and high pathophysiology, molecular, genetic, and clinical complexity [5], sepsis and septic shock pose a growing global burden and a challenge for emergency physicians. The processes driving cell damage and immunological responses must be understood to comprehend the course of the disease from asymptomatic to critically severe. Some infected people experience only moderate symptoms, but for others, the sickness can be devastating, if not deadly, according to the research [6]. Sepsis severity is influenced by various variables, including diabetes mellitus, obesity, arterial hypertension, age, and comorbidities [7]. Hyperinflammation and increased levels of proinflammatory cytokines (such as IFN-α, IFN-γ, and *IL-6*) and chemokines, specifically monocyte chemotactic protein-3 (MCP-1/CCL2), are common features of severe outcomes [8]. Furthermore, multiple studies have shown that elevated *IL-6* levels are linked to respiratory failure, shock, and severe symptoms in hospitalised patients, as well as being predictive of mortality [9].

Genetic differences can influence both the innate and adaptive immune responses [10]. Variations in the genes encoding proinflammatory cytokines may influence the development of severe sepsis. Sepsis outcomes may be explained in part by single-nucleotide polymorphisms (SNPs) in the following genes: *TNFA*, *IL-6*, *IL-8*, *IL-10*, *CCL5* and *CXCL6* [11]. This study focused on interleukin-6, a key inflammatory factor in the body's reaction to viral infections. Possible associations between sepsis and/or viraemia severity and *IL-6* gene variation, especially in the promoter region [12]. One of the first proinflammatory cytokines produced in the body's reaction to viral infections is interleukin-6 (*IL-6*), which is encoded by a gene on chromosome 7p15.3. Multiple studies have shown a correlation between circulating *IL-6* levels and the severity of sepsis as well as fatality rates [13]. Some cytokine gene single-nucleotide polymorphisms (SNPs) have been linked to an increased risk of sepsis and its consequences [14, 15]. There is a rising interest in identifying a genetic predisposition associated with sepsis, and recent research has supported the hypothesis that there may be a genetic basis for selecting patients with favourable prospective responses to personalised therapy [16]. At the -174 promoter region, the most researched *IL-6* polymorphism is the G/A

transition, which represents the change from Guanine (G) to Adenine (A). Evidence from in vivo studies showing that the G allele increases inflammatory response through increased cytokine levels in the blood suggests that polymorphisms in the *IL-6* gene's regulatory region may have a role in the onset and progression of sepsis [17]. Although some studies have linked this SNP to an increased risk of sepsis [18], others have shown no such link [19] or have highlighted its significance when combined with other gene polymorphisms [20]; so far, the results in the literature have been ambiguous. Few studies have examined the impact of the G/A transition at the *IL-6*-572 promoter region on sepsis risk and outcome.

Growing evidence confirms that genetic variation in the inflammatory response genes significantly determines susceptibility to sepsis and disease outcome. Functional polymorphisms in cytokines and inflammatory mediators contribute to various changes in the inflammatory response. For example, the IL-27 -964A>G promoter polymorphism induces IL-27 expression and contributes to the inflammatory response during sepsis [21]. The ADAM17 -172A>G promoter polymorphism increases ADAM17 expression and impacts sepsis progression by means of augmented EGR1 binding affinity and inflammatory response, leading to an increased chance of dying from sepsis [22]. The GRK5 rs2230349 G>A mutation (Arg-304-His) protects patients from sepsis because of a decrease in inflammation through the IκB-α/NF-κB pathway [23]. SIRT1 genetic variants (rs4746720 and rs12778366) act as functional predictors of prognosis because the risk allele has a negative effect on SIRT1 expression and increase NF-κB mediated inflammation [24]. Hence, the purpose of this study was to assess the relationships between sepsis outcomes and serum *IL-6* biomarker levels and rs1800796 polymorphisms found in the promoter region of the *IL-6* gene.

## 2. Material and Methods

### *2.1 Study Subjects*

This study used a case-control design and included 75 sepsis patients admitted to hospitals in Babil governorate, from September 2025 to January 2026. The people who took part in the study were between the ages of 10 and 85. The study included 75 participants: 42 men and 33 women. For the cohort of 75 control subjects, the clinicopathological data for both the patient and control groups were derived from their respective hospital records.

The experiments conducted in this study complied with the ethical principles established in the Helsinki Declaration for research involving human subjects. The Institutional Review Board (IRB) at the University of Al-Qasim Green gave the biochemical research with human subjects the go-ahead, with the reference qgec\632026.

We obtained the genomic DNA samples from peripheral blood samples using a Blood/Cell DNA Mini Kit (Cat. No. GB100, Geneaid Co., Taipei, Taiwan). We used standard methods of agarose gel electrophoresis to check the integrity of the isolated genomic DNA.

### *2.2 Inclusion and Exclusion Criteria*

Sepsis was defined based on Sepsis-3 criteria [25]. Patients with an increase in SOFA score by ≥2 points in the presence of suspected or confirmed infection were included. We recruited sepsis patients from the ICU. Exclusion criteria were… patients excluded from the study included those with (i) use of antibiotics before enrollment in the study, (ii) presence of an impaired immune system,

such as those undergoing chemotherapy or HIV/AIDS patients, (iii) an autoimmune disease or any cancerous condition, (iv) being pregnant to avoid possible physiological alterations affecting microbial colonization, and (v) being below the age of ten years. The control group consisted of healthy volunteers who were age-matched and sex-matched and were recruited from the same health screening centre of the hospital where the sepsis patients were recruited.

### *2.3 Genotypic Identification Using ARMS-PCR Amplification*

We used the ARMS-PCR tool to develop PCR-specific primers to amplify specific PCR fragments inside the *IL-6*. The primary goal of the polymerase chain reaction (PCR) design method was to identify a subset of high-frequency SNPs, in this case rs1800796. The length of the DNA pieces that were targeted for this SNP varied, with 231 bp, 133 bp, and 154 bp being the most common (see Figure 1). The PCR oligonucleotide sequences are shown in Table 1. Each amplified fragment was subjected to PCR tests using a 25 ul final volume, and the PCR AccuPower PreMix, a lyophilised product of Promega Co., USA, was utilised. Electrophoresis on agarose gels was used to confirm that the sizes of the PCR products were in agreement with the expected values after PCR assays had been run.

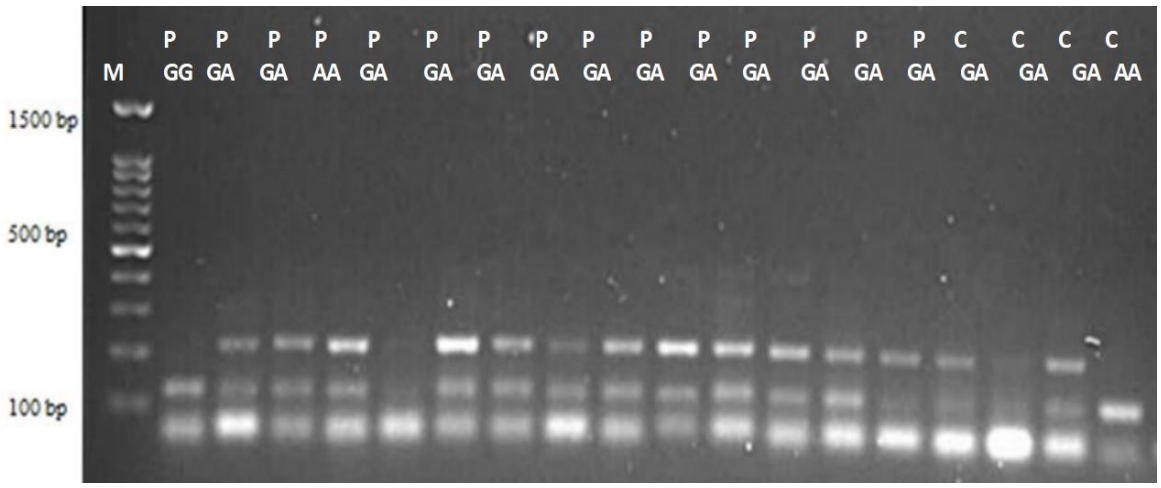


**Figure 1** The present work presents a garose gel electrohphpresis of *IL-6* genotyping through the utilization of the ARMS-PCR approach (Note: P represent patients, C represent control). These primers were designed to amplify DNA fragments of certain lengths, 231 bp, 133 bp, and 154 bp, respectively. Electrophoresis conducted by 1% agarose gel at constant voltage 75 V, current 20 mA and time 120 min. Stained with ethidium bromide in molten agarose gel.

**Table 1** The specific PCR primers designed for the amplification of the *IL-6*-rs1800796 SNP. Primers were designed based on the GenBank accession number NG-011640.01.

| *IL-6*-rs1800796 A\G | 5----------3 | PCR product | Annealing TM |
|---|---|---|---|
| Forward inner primer (G allele) | 5-GGATGGCCAGGCAGTTCTACAACAGACG-3 | 133 bp | 73 |
| Reverse inner primer (A allele) | 5-CTTCTGTGTTCTGGCTCTCCCTGTGCGT-3 | 154 bp | |
| Forward outer primer | 5-GGCTGAAGCAGGTGAAGAAAGTGGCAGA-3 | 231 bp | |
| Reverse outer primer | 5-CTGAGTTTCCTCTGACTCCATCGCAGCC-3 | | |

### *2.4 Statistical and Functional Analysis*

Differences in genotype distribution between healthy controls and patients were evaluated using a Chi-square test. In order to determine the relative risk of sepsis and to investigate the relationships between the single nucleotide polymorphism (SNP) and clinicopathological parameters of persons diagnosed with sepsis, the odds ratio (OR) and 95% confidence interval (CI) were calculated. Values lower than 0.05 were considered to have reached the predetermined level of significance. We used SPSS version 28 to do the statistical analysis.

### *2.5 IL-6 Quantity Assay by ELISA*

Elascience, a Chinese company, supplied the specific ELISA kit that was used to measure the level of human *IL-6* concentration.

## 3. Results

### *3.1 Demographic Characteristics of Study Subjects*

To assess possible correlations between sepsis and several clinical-pathological variables, the researchers compared 75 individuals with sepsis to 75 healthy controls (see Table 2). Since the p-values for gender ($p = 0.74$), age ($p = 0.73$), and residency ($p = 0.39$) were all non-significant, we can conclude that the subjects were evenly distributed across these demographics. Given the lack of statistically significant differences in any demographic variable between the two groups, it is unlikely that these variables would confound the observed correlations.

**Table 2** Clinico-pathologic characteristics of sepsis cases and controls.

| Variable | Subjects n = 75 (100%) | Control n = 75 (100%) | p-value | Chi-square | Odds ratio (95% CI) |
|---|---|---|---|---|---|
| **Gender** | | | | | |
| Male | 42 | 40 | 0.74 | 0.32 | 1.11 (0.58-2.11) |
| Female | 33 | 35 | | | |
| **Living in** | | | | | |
| Urban | 50 | 45 | 0.39 | 0.84 | 1.33 (0.68-2.59) |
| Countryside | 25 | 30 | | | |
| **Education level** | | | | | |
| Up to high school | 30 | 49 | **0.00021*** | 3.07 | 0.35 (0.18-0.68) |
| Beyond high school | 45 | 26 | | | |
| **Age** | | | | | |
| <50 years | 28 | 30 | 0.73 | 0.33 | 0.89 (0.46-1.72) |
| ≥50 years | 47 | 45 | | | |
| **Smoking** | | | | | |
| smoker | 50 | 55 | 0.62 | 0.48 | 1.21 (0.56-2.62) |
| Non-smoker | 25 | 20 | | | |
| **Alcohol consumption** | | | | | |
| Yes | 10 | 20 | **0.044*** | 2.00 | 0.42 (0.18-0.97) |
| No | 65 | 55 | | | |
| **Hypertension** | | | | | |
| Hypertension | 54 | 22 | **<0.00001*** | 4.48 | 5.16 (2.51-10.58) |
| Non-hypertension | 21 | 53 | | | |
| **Diabetes mellitus (DM)** | | | | | |
| With DM | 42 | 26 | **0.009*** | 2.60 | 2.39 (1.24-4.63) |
| Without DM | 33 | 49 | | | |

n: number of subjects, * $p < 0.05$.

### *3.2 Genotyping Analysis*

The most common single nucleotide polymorphisms (SNPs) were selected one by one. In this work, researchers analysed the genetic diversity of the identified single nucleotide polymorphisms in order to estimate the Hardy-Weinberg equilibrium (HWE) of the study population. One such SNP was *IL-6:* rs1800796. We analyzed the results using chi-square tests. Both the control and subject groups confirmed, at a significance level of 0.05 (see Table 3), that the single nucleotide polymorphism (SNP) was incompatible with the Hardy-Weinberg equilibrium (HWE).

**Table 3** Hardy-Weinberg equilibrium (HWE) for the *IL-6*-rs1800796 G\A SNP in patients and control groups.

| SNP | Patients | | Controls | |
|---|---|---|---|---|
| **rs1800796** | **Observed** | **Expected** | **Observed** | **Expected** |
| GG | 25 | 30 | 45 | 40 |
| GA | 45 | 34 | 20 | 29 |
| AA | 5 | 10 | 10 | 5 |
| Chi-square value | 6.38 | | 7.66 | |
| P-value | **0.0115*** | | **0.0059*** | |

The P-value with statistical significance is in bold.

Among the individuals and patients in the study, 5% had the AA allele for the rs1800796 polymorphism and 25% had the GG allele; 45% had the GA allele. For the polymorphic alleles GG, AA, and GA, the healthy control group had frequencies of 45%, 10%, and 20%, respectively, as shown in Table 4.

**Table 4** Genotyping and allele frequencies for polymorphisms between sepsis patients and control groups.

| rs1800796 G\A | Patients (%) | Controls (%) | P-value | Chi-square | OR (95% CI) |
|---|---|---|---|---|---|
| **G\G[a]** | 25 | 45 | 1.00 | | |
| **G\A** | 45 | 20 | **0.0001*** | 3.18 | 4.05 (0.12-5.50) |
| **A\A** | 5 | 10 | 0.86 | 0.17 | 0.90 (0.34-3.61) |
| **Dominant model** | | | | | |
| **G\G[a]** | 25 | 45 | 1.00 | | |
| **G\A + A\A** | 50 | 30 | **0.0012*** | 3.23 | 3.00 (0.17-6.64) |
| **Recessive model** | | | | | |
| **G\G[a] + G\A** | 70 | 65 | 1.00 | | |
| **A\A** | 5 | 10 | 0.18 | 1.33 | 2.15 (0.69-6.63) |
| **Allele frequency** | | | | | |
| **G** | 47.5 | 55 | 1.00 | | |
| **A** | 27.5 | 20 | 0.21 | 0.22 | 0.64 (0.32-1.29) |

The P-value with statistical significance is in bold. CL-confidence interval.

The current investigation evaluated the relationship between polymorphism rs1800796 (G\A) in the interleukin-6 (*IL-6*) gene and risk for developing sepsis. There was a clear difference in the distribution of genotypes and alleles between sepsis patients, compared to healthy controls (p-value < 0.0001) (see Table 4), and showed markers of sepsis risk with patients having substantially more heterozygous G/A genotypes than did healthy controls under a number of specific gene-based models. The analysis using genetic models indicates that the risk factor is largely attributable to the heterozygous GA genotype (OR = 4.05), while the AA genotype has negligible effect (OR = 0.90). The recessive model (AA vs. GA + GG) was also not statistically significant; this implies that the effect of the A allele is not recessive. The observed region of heterozygote dominance may suggest that the

inheritance pattern is complicated and may involve epistatic links to other genetic variations and environmental influences. Alternatively, the low representation of the AA homozygotes (5 cases and 10 controls) may have restricted our statistical power to assess the effect of this genotype. Further studies with larger subject sizes need to be conducted to explain the inheritance pattern. There are significant clinical implications of our results. By finding genetic variations that put someone at risk of sepsis, we could potentially improve risk classification, which would open doors to early therapeutic interventions in high-risk populations. For instance, people with the GA genotype may require enhanced follow-up, early antibiotic treatment, or immune-modulating therapies when infected. In addition, the *IL-6* pathway represents a perfect therapeutic target in sepsis. Our results support the theory that genetic variation in the *IL-6* promoter influences the efficacy of anti-*IL-6* therapies, but future pharmacogenetic studies must verify this.

### *3.3 Serum IL-6 Concentration in the Study Groups*

Table 5 and Table 6 show the measured and recorded levels of *IL-6*, an inflammatory marker. A statistically significant difference in *IL-6* concentration (240.42 ± 84.25 pg/mL vs. 203.58 ± 22.47 pg/mL) was observed between the patient group and the control group, as revealed by an independent-samples t-test on the data from both groups (t = 2.07). Hence, it is highly unlikely that this difference was caused by chance, as evidenced by a p-value less than 0.05.

**Table 5** Estimation of *IL-6* Concentration in Both Study Groups.

| ***IL-6* Concentration (pg/mL)** | **Patients mean ± SD** | **Controls mean ± SD** | **t-test** | **P = value** |
|---|---|---|---|---|
| | 240.42 ± 84.25 | 203.58 ± 22.47 | 2.07 | **0.042*** |

**Table 6** Mean differences in *IL-6* levels and associated with rs1800796 G\A genotype frequencies.

| **Variable** | **(Mean ± SD)** | **Genotype** | **LSD** | **P = value** |
|---|---|---|---|---|
| Patients | 213.4 ± 26.07 | GG | 4.674 | **0.004659*** |
| | 202.2 ± 21.77 | GA | | |
| | 197.66 ± 22.42 | AA | | |
| Control | 179.26 ± 7.40 | GG | | |
| | 154.39 ± 25.06 | GA | | |
| | 167.10 ± 22.49 | AA | | |

Observe the table below for an association between *IL-6* in circulation and the gene polymorphism. Among the patients, there is a discernible gradient in *IL-6* levels that is dependent on genotype. The GG genotype is associated with an average *IL-6* concentration of 213.4 ± 26.07 pg/mL. In contrast, the GA genotype yields a mean concentration of 202.2 ± 21.77 pg/mL, and the AA genotype yields an average concentration of 197.66 ± 22.42 pg/mL. The genotype-specific changes are statistically significant (p = 0.004659) according to an ANOVA with a Least Significant Difference (LSD) post-hoc test. Finally, in this patient group, *IL-6* production is highest in those with the GG genotype and lowest in those with the AA genotype.

## 4. Discussion

The hallmark of sepsis is an infection-induced systemic inflammatory response. In response to microbial invasion, the body releases pro-inflammatory cytokines like *IL-6* in excess, which is a key step in the pathophysiological cascade of sepsis [26]. As an endogenous pyrogen, *IL-6* regulates immunological reactivity and causes fever in infected individuals. It is a multifunctional cytokine. The cytokine levels can vary between individuals due to the rs1800796 G\A polymorphisms in the *IL-6* gene, which are associated with the *IL-6* promoter activity [27]. Although the results have been conflicting, multiple genetic investigations have demonstrated that *IL-6* polymorphisms in the promoter area enhance the risk of sepsis. The difficulty in interpreting these findings is compounded by factors such as diverse ethnic backgrounds, a lack of statistical power, and a small effect size of the polymorphism on sepsis risk [28]. These data need to be reconciled because the number of studies has increased significantly in recent years [29].

We found in the analysis of our rs1800796 polymorphism that there was a strong association between the G/A genotype and risk of developing sepsis using both the codominant model ($p = 0.0001$; OR = 4.05, 95% CI: 0.12-5.50) and dominant model (G/A + A/A vs. G/G: $p = 0.0012$; OR = 3.00, 95% CI: 0.17-4.64) models; suggesting that carrying an expressed copy of the A allele will reduce your chances of acquiring sepsis when compared to those who are homozygous for the G allele. Recessive modeling (A/A vs. G/G and G/A) produced no significant differences ($p = 0.18$; OR = 2.15, 95% CI: 0.69-6.63), and allelic frequency analysis revealed that A allele carriers had no statistically significant protective effect versus non-carriers ($p = 0.21$; OR = 0.64, 95% CI: 0.32-1.29) indicating that protection against sepsis by the rs1800796 G/A genotype is most likely a result of heterozygosity rather than just the presence of the A allele. These results are consistent with previous studies demonstrating that the rs1800796 G allele is associated with increased production of IL-6 and a greater inflammatory response to infection. In contrast, the A allele may decrease expression of *IL-6* and reduce susceptibility to sepsis [29, 30]. Furthermore, we feel that due to the lack of statistical significance for the recessive model, as well as the A allele frequency data, larger, more powerful epidemiologic studies are needed to validate these findings [31].

The observation of heterozygosity providing some level of risk in the current study is interesting. However, there have been a number of studies that have observed the effect of an allele or homozygosity on disease outcomes; it is possible to demonstrate a heterozygote advantage for specific cytokine polymorphisms. An example is the work of Zhang et al. [32], which demonstrated that having the GG genotype resulted in protection from tuberculosis. In contrast, having an AA or GA genotype resulted in an increase in production of *IL-6* following stimulation. While the results of our study demonstrated heterozygote-specific risk, Zhang et al. [33] reported the homozygote effect for the same polymorphism. The differences in our findings as compared to those reported by Zhang et al. [34] could potentially be explained by differences in the pathogenesis of both diseases, population genetics, and/or sample size.

The risk versus protective associations for the rs1800796 location on the *IL-6* gene vary by disease. For example, in the Ghanaian population, Ghalib et al. [30] demonstrated that genotype GA was significantly associated with an increased likelihood of having type 2 diabetes mellitus (OR = 8.67, 95% CI: 4.00-18.90, $p < 0.001$) and that genotype G/A was associated with elevated levels of *IL-6* compared to CC genotypes. In addition, Varpula et al. [35] demonstrated that individuals of Mexican ethnicity who had genotype GC were at a 2.19 times greater risk of having an acute coronary

syndrome than individuals with genotype GG homozygotes. Our study demonstrated a risk association in the G/A heterozygote, suggesting that the function of this polymorphism may vary based on disease and context/setting [36].

Many studies indicated a link between the *IL-6* gene polymorphism rs1800796 and sepsis risk in the meta-analysis. This polymorphism was associated with sepsis in Asians and Africans, but not in Caucasians, according to a subgroup analysis that was stratified by country. First, many studies had small sample sizes, and only two publications focused on Asians and Africans. However, two experiments that included Asian ethnicity did not achieve HWE equilibrium [37]. Nevertheless, there is a lack of comprehensive information in the included research that could shed light on these possible issues. Further validation of these conclusions will require well-designed research with larger sample sizes. This variant was not associated with an increased risk of sepsis in adult, neonatal, or paediatric subjects when analysed in age-specific subgroups [38, 39]. To do the sensitivity analysis, other studies excluded HWE studies that included people of Caucasian ethnicity or the overall population. Despite that, we realize that the deviation in HWE in controls could lead to increased error rates and limited applicability of our findings to the population at large. Therefore, our findings are hypothesis-generating and need replication in a larger sample of ancestry-matched controls before any definitive conclusion can be reached. The rs1800796 polymorphism did not correlate with sepsis risk, and this result persisted even after adjusting for age and ethnicity in later subgroup analyses [40]. Future research should focus on elucidating the complex interplay between sepsis-causing genes and their settings, as is the case with other diseases' development [41].

In addition to statistical significance, there are differences in terms of clinically and biologically important factors. The differences in standard deviations between the two groups are of interest. The control group had a relatively low standard deviation (SD = 22.47), which is characteristic of a relatively consistant baseline *IL-6* for healthy people; this is consistent with the function of *IL-6* being tightly regulated by an individual. On the other hand, the patient group had a much higher standard deviation in *IL-6* levels (SD = 84.25). This substantial amount of variation would support the presence of wide-ranging differences in the expression of *IL-6* among patients with respect to disease severity, disease type, the amount of inflammation, as well as variations at the genetic and/or environmental levels for each patient [42].

The increase in Interleukin-6 in patient samples matches previous studies highlighting that *IL-6* plays a pivotal role in triggering inflammatory and chronic diseases. Conditions such as rheumatoid arthritis, cardiovascular disease, and metabolic syndrome exhibit elevated levels of *IL-6* and are associated with a pro-inflammatory state, acute phase response, and continued progression of disease [42]. Although the average difference of approximately 36.84 pg/mL is statistically significant, its clinical significance depending on the chronic inflammatory disorder being treated. More specifically, elevations of *IL-6*, even in small quantities, are correlated with increased disease activity, fatigue, and an increased risk of negative events occurring in patients with many chronic inflammatory diseases [43]. To conclude, the information detailed throughout the preceding sections provides evidence of a statistically significant and widely variable higher concentration of *IL-6* between patient samples and control samples, thereby supporting existing evidence that *IL-6* may play an important role in the underlying mechanisms of the chronic inflammatory disorder investigated, as well as portraying *IL-6* as a potential biomarker of disease risk or activity, while highlighting the heterogeneous nature of inflammatory response within the chronic inflammatory disorder studied in this group of patients [44].

Comparing patient and control groups with regard to *IL-6* levels in all three genotypes (GG, GA, AA), the findings reveal that patients consistently have significantly higher mean *IL-6* levels than controls across genotypes. This finding supports the previous finding of elevated *IL-6* levels within the entire patient population. Additionally, the findings now indicate that elevated *IL-6* levels within the patient group are influenced by the rs1800796 genotype, whereby the level of inflammation is highest in GG genotype carriers. Given the aforementioned levels of *IL-6* across genotypes, relatively small differences in *IL-6* levels between genotypes may still be significant within the overall patient group [45-47]. These findings may have significant implications for the personalized stratification of patient risk regarding *IL-6*-mediated inflammatory responses, and therefore, may be used as one factor, along with other clinical and biological markers (e.g., CRP), for predicting *IL-6*-mediated inflammatory phenotypes within specific diseases. For example, patients with the AA genotype of rs1800796 may carry a greater risk for enhanced *IL-6*-mediated inflammatory responses, resulting in greater patient severity of disease, less favorable patient prognosis, and/or diminished response to anti-*IL-6* therapy, as reported by He et al. [21]. Thus, genotyping for this SNP may serve as a useful adjunct to the prediction of inflammatory phenotype in some diseases [48].

## Author Contributions

Dr. Zahraa Isam Jameel: formal analysis, wrote and revised the article. Samaa Asaad Hameed: funding the research. Dr. Thikra Adnan Jawad: put the idea of the research.

## Competing Interests

None of the authors has declared a conflict of interest with respect to this work.

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