Research Article

Association Of Interleukin-10 Serum Levels And Rs1800896 Polymorphism With Gram-Negative Sepsis

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Abstract

Early diagnosis and risk stratification of sepsis remain major clinical challenges. Interleukin-10 (IL-10), an anti-inflammatory cytokine, plays an important role in immune regulation during sepsis, and genetic variation in the IL-10 promoter region, particularly the rs1800896 (−1082 A/G) polymorphism, may influence individual susceptibility to severe infection. This study investigated the association between serum IL-10 levels, the IL-10 rs1800896 polymorphism, and susceptibility to gram-negative sepsis.

A case–control study was conducted including 104 adult patients with culture-confirmed gram-negative sepsis and 100 healthy controls. Serum IL-10 concentrations were measured using enzyme-linked immunosorbent assay at three time points among sepsis patients, and genotyping of the rs1800896 polymorphism was performed using allele-specific polymerase chain reaction. Serum IL-10 levels were significantly higher in sepsis patients than in controls ($p < 0.05$) and demonstrated a decreasing trend during follow-up. The rs1800896 GG genotype was significantly more frequent among sepsis patients and was independently associated with increased sepsis risk (adjusted OR = 3.72, 95% CI: 1.31–10.54; $p = 0.014$). Receiver operating characteristic analysis showed moderate discriminatory performance for serum IL-10 (AUC = 0.761), whereas the rs1800896 polymorphism showed poor diagnostic performance (AUC = 0.341). These findings indicate that the IL-10 rs1800896 GG genotype is associated with increased susceptibility to gram-negative sepsis and that serum IL-10 may serve as a complementary biomarker when integrated with clinical assessment tools.

Keywords: Sepsis; Interleukin-10; Gene polymorphism; Gram-negative bacteria; SOFA

1. Introduction

Sepsis is a life-threatening syndrome defined by a dysregulated host response to infection and remains a leading cause of mortality worldwide, accounting for an estimated 11 million deaths annually and representing approximately 20% of all global deaths. Gram-negative bacteria, including *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, are among the most frequent etiological agents of severe sepsis, particularly in hospitalized and immunocompromised individuals [1]. A major challenge in sepsis care is the lack of a reliable diagnostic gold standard. Conventional clinical criteria, such as fever, leukocytosis, and tachycardia, lack sufficient sensitivity and specificity, often resulting in delayed diagnosis and suboptimal outcomes. As a result, there has been increasing emphasis on immunological biomarkers that more accurately reflect host responses and may facilitate earlier, personalized intervention [2].

Interleukin-10 (IL-10) has emerged as a master player in the control of immune homeostasis by counteracting pro-inflammatory signaling and constraining tissue damage. Elevated IL-10 levels have been frequently reported in septic patients and are associated with immune paralysis, secondary infections, and adverse prognosis in the setting of gram-negative infection [1]. Production of IL-10 is induced by pathogen-associated molecular patterns such as lipopolysaccharide (LPS) [3]. Along with circulating cytokine levels, genetic differences in cytokine genes can affect individual susceptibility to sepsis and immune response variability. The IL-10 promoter polymorphism rs1800896 (−1082 A>G) has been associated with altered IL-10 transcriptional activity and cytokine production [1]. Cytokine expression has been shown to be higher in carriers of the G allele [4]. Meta-analytic evidence indicates that individuals carrying this variant exhibit increased susceptibility to sepsis across diverse populations, and next-generation sequencing studies suggest that rs1800896 contributes to variability in immune responses and clinical outcomes. Functionally, these promoter polymorphisms may influence both baseline cytokine expression and dynamic immunological trajectories during critical illness, potentially shaping the course of sepsis and the risk of complications such as secondary infections and organ dysfunction [5].

The present study aimed to investigate the association between serum IL-10 levels, the IL-10 rs1800896 polymorphism, and susceptibility to gram-negative sepsis. By integrating functional cytokine measurements with genetic analysis, this study seeks to clarify the complementary role of immunological and genetic markers in sepsis risk assessment.

2. Materials and Methods

2.1 Study Design and Participants

This study was designed as a case–control study with longitudinal cytokine assessment among cases. Adult patients with culture-confirmed gram-negative sepsis were enrolled as cases, and apparently healthy individuals were recruited as controls. Serial serum IL-10 measurements were performed in sepsis patients at predefined time points to evaluate dynamic cytokine changes during the course of illness.

The study was conducted at Imam Hussein Medical City, Karbala, Iraq, between December 2024 and April 2025. A total of 204 participants were included: 104 adult patients diagnosed with gram-negative sepsis and 100 healthy controls.

2.2 Inclusion Criteria (Cases)

Patients were eligible for inclusion if they met all of the following criteria:

1. Age ≥18 years
2. Hospital admission with a clinical diagnosis of sepsis
3. Evidence of organ dysfunction defined by a Sequential Organ Failure Assessment (SOFA) score ≥2
4. Positive blood culture confirming gram-negative bacterial infection, identified using the Vitek 2 Compact system

2.3 *Exclusion Criteria (Cases)*

Patients were excluded if they had any of the following conditions:

1. Pre-existing chronic inflammatory or autoimmune diseases
2. Known malignancy
3. Chronic thyroid disorders
4. Primary or secondary immunodeficiency
5. Positive blood cultures for gram-positive organisms or mixed infections

2.4 *Sample Size and Power Calculation*

A priori power calculation was carried out by G*Power version 3.1 software. The calculated minimum sample size was 180 individuals (the expected odds ratio for the association between IL-10 polymorphism and sepsis is 2.5, α=0.05, statistical power =80%). Then 204 was deemed a large enough final sample size that statistically significant but not clinically important links would have been detected.

2.5 *Laboratory Analysis*

Venous blood samples were collected from all participants and centrifuged to obtain whole blood for bacteriological and molecular analyses and serum for cytokine measurement. Blood cultures from sepsis patients were processed using BacT/ALERT® FA Plus bottles, and bacterial identification was performed with the Vitek 2 Compact system.

Genomic DNA was extracted from peripheral blood using the FavorGen DNA extraction kit according to the manufacturer's instructions. The IL-10 rs1800896 (−1082 A/G) polymorphism was genotyped in patients and controls using allele-specific polymerase chain reaction (AS-PCR), with primers designed using Primer3Plus (Forward A: 5'-GCAGCGGTAGCAGCAGCG-3'; Forward B: 5'-AGCAGCGGTAGCAGCAGCA-3'; Reverse: 5'-TCCGTGGGATACTGAGACAC-3'). PCR products (258 bp) were visualized on a 1.5% agarose gel.

Serum IL-10 concentrations were measured using a commercial sandwich enzyme-linked immunosorbent assay (ELISA) kit (BT Lab) at three time points in sepsis patients (day 0, day 3, and day 6).

2.6 Statistical Analysis

Statistical analysis was performed using SPSS software version 23. Continuous variables were expressed as mean ± standard deviation. Genotype distributions were assessed for Hardy–Weinberg equilibrium. Logistic regression analysis was used to estimate crude and adjusted odds ratios with corresponding 95% confidence intervals. Receiver operating characteristic (ROC) curve analysis was applied to evaluate diagnostic performance. Due to right-skewed distribution, IL-10 values were interpreted descriptively

3 Results

3.1 Participant Population

A cohort of 204 study participants was involved including 104 adult patients with culture-confirmed gram-negative sepsis and 100 apparently healthy controls. Sepsis patients were enrolled in Imam Hussein Medical City from December 2024 to April 2025 and diagnosed according to clinical assessment, the SOFA scoring system and with positive result of blood culture. All these patients met the criteria for sepsis (SOFA ≥2 points) and showed moderate organ dysfunction with a mean partial SOFA score of 7.88 ± 1.37 respectively, as shown in table 1

Table 1. Baseline demographic and clinical characteristics of the study groups

Variable	Sepsis (n = 104)	Control (n = 100)	P value
Age > 50 years, n (%)	68 (65.4)	38 (38.0)	< 0.001
Male sex, n (%)	68 (65.4)	62 (62.0)	0.675
Partial SOFA score	7.88 ± 1.37	—	—
ICU admission, n (%)	104 (100)	—	—
Baseline IL-10 (pg/mL)	17.64 ± 22.84	12.3 ± 0.3	< 0.05

Continuous variables are presented as mean ± SD.

3.2 Bacterial Profile of Sepsis Patients

A total of 108 gram-negative isolates were identified. *Escherichia coli* was the predominant pathogen (27.8%), followed by *Klebsiella pneumoniae* (20.4%) and *Acinetobacter baumannii* (16.7%). Other isolated species included *Burkholderia cepacia*, *Salmonella typhi*, *Pseudomonas aeruginosa*, and *Proteus mirabilis*. This distribution reflects the classical epidemiological profile of hospital-acquired gram-negative sepsis, as illustrated in Figure 1.

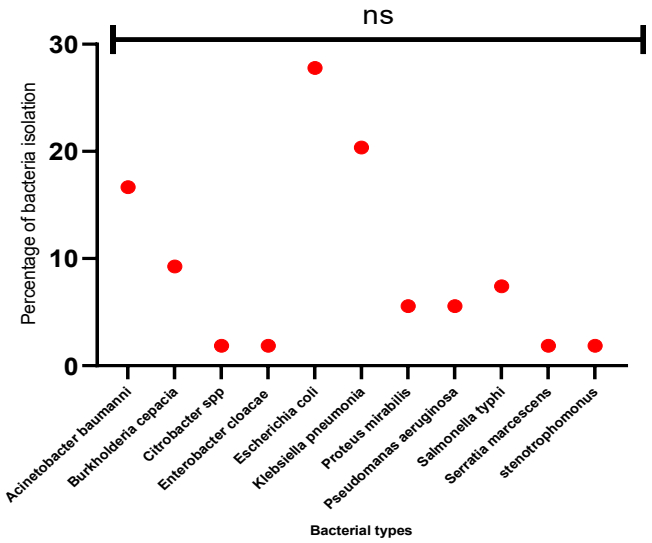

Figure 1. Distribution of gram-negative bacterial isolates recovered from blood cultures of sepsis patients (n = 104).

3.3 Serum IL-10 Levels

Serum IL-10 concentrations were significantly higher in sepsis patients compared with healthy controls at baseline ($p < 0.05$). Among sepsis patients, longitudinal assessment demonstrated a decreasing trend in IL-10 levels over time (day 0, day 3, and day 6). Given the large variability and right-skewed distribution of IL-10 values, results are reported descriptively, and non-parametric comparisons were applied where appropriate (Figure 2).

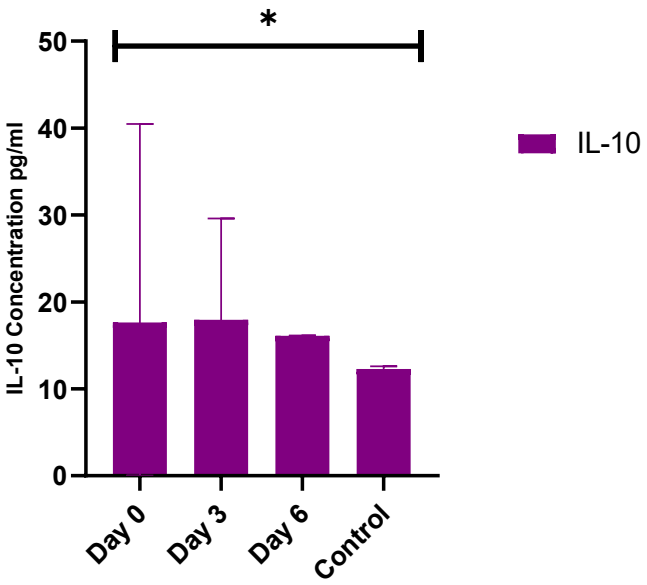

Figure 2. Serum IL-10 concentrations in sepsis patients and controls. Data are presented descriptively; group comparisons were performed using the Mann–Whitney U test. *P < 0.05.

3.4 SOFA Score in Sepsis Patients

Organ dysfunction was estimated using the SOFA score of respiratory (PaO_2/FiO_2), coagulation (platelets) and renal system (creatinine/urea). The mean partial SOFA score was 7.88 ± 1.37, largely influenced by low thrombocytopenia (90.25 ± 90.65 $\times 10^3/\mu L$) and severe renal impairment (creatinine: 6.88 ± 0.27). All the patients fulfilled the criteria of sepsis (SOFA ≥2), thus diagnosing 100% positive cases for sepsis, shown as table 2

Table 2. SOFA score components in sepsis patients

SOFA Component	Clinical / Laboratory Parameter	Value (Mean ± SD)	SOFA Score Contribution
Coagulation	Platelet count ($\times 10^3/\mu L$)	90.25 ± 90.65	2.08 ± 1.38
Renal	Creatinine (mg/dL)	6.88 ± 0.27	4.0 ± 0.0
Renal (supporting)	Urea (mg/dL)	227.65 ± 47.94	Included in renal dysfunction
Total partial SOFA score	Sum of coagulation + renal	—	7.88 ± 1.37
SOFA severity category	Overall assessment	—	Moderate to severe organ dysfunction
Sepsis status	Partial SOFA ≥ 2	—	Confirmed sepsis

3.5 Genotype Distribution of IL-10 rs1800896

The frequency of the IL-10 genotype (rs1800896) was compared between the sepsis and control groups as shown in Table 3. The GG genotype was significantly more prevalent in sepsis patients. Hardy–Weinberg equilibrium was violated in the sepsis group but maintained in controls.

Table 3. Genotype distribution and Hardy–Weinberg equilibrium analysis

Genotype	Sepsis (n = 104)	Control (n = 100)
AA	46	66
AG	22	20
GG	36	14
HWE χ^2	65.79	10.66
HWE p value	< 0.001	0.069

3.6 Logistic Regression Analysis

Multivariate logistic regression adjusted for age and sex demonstrated that the GG genotype remained an independent predictor of sepsis (adjusted OR = 3.72, 95% CI: 1.31–10.54, p = 0.014). Serum IL-10 was not independently associated with sepsis after adjustment.

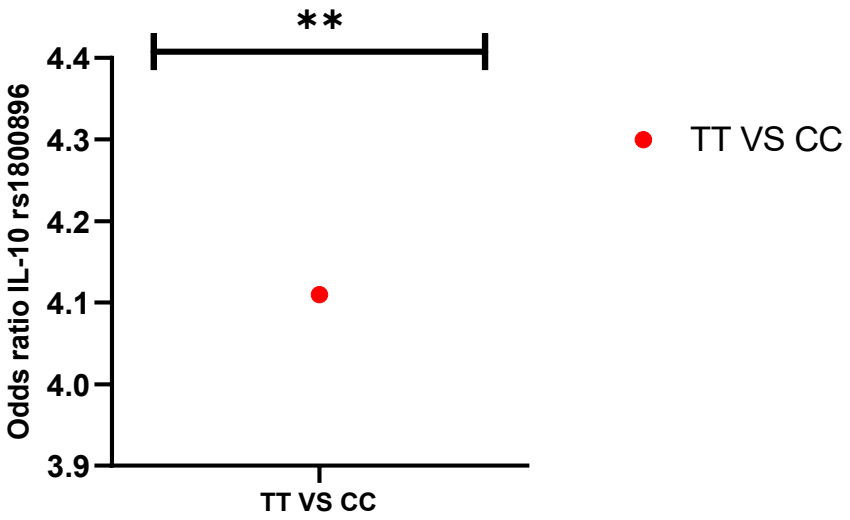

Figure 3. Genotype distribution of the IL-10 rs1800896 polymorphism among sepsis patients and controls. Group comparisons were performed using the χ^2 test.

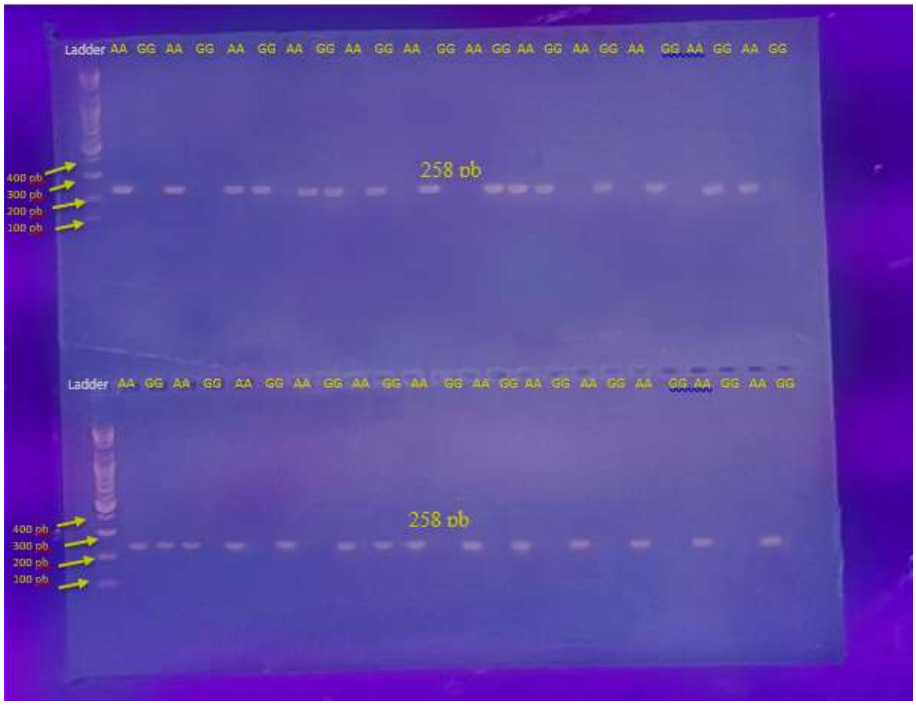

Figure 4. Representative agarose gel electrophoresis (1.5%) showing allele-specific PCR amplification of the IL-10 rs1800896 polymorphism (258 bp).

3.7 ROC Curve Analysis

ROC analysis demonstrated moderate discriminatory performance for serum IL-10 levels (AUC = 0.761). In contrast, the rs1800896 polymorphism showed poor discriminatory ability (AUC = 0.341), indicating that this genetic variant should not be considered a diagnostic marker but rather a susceptibility modifier.

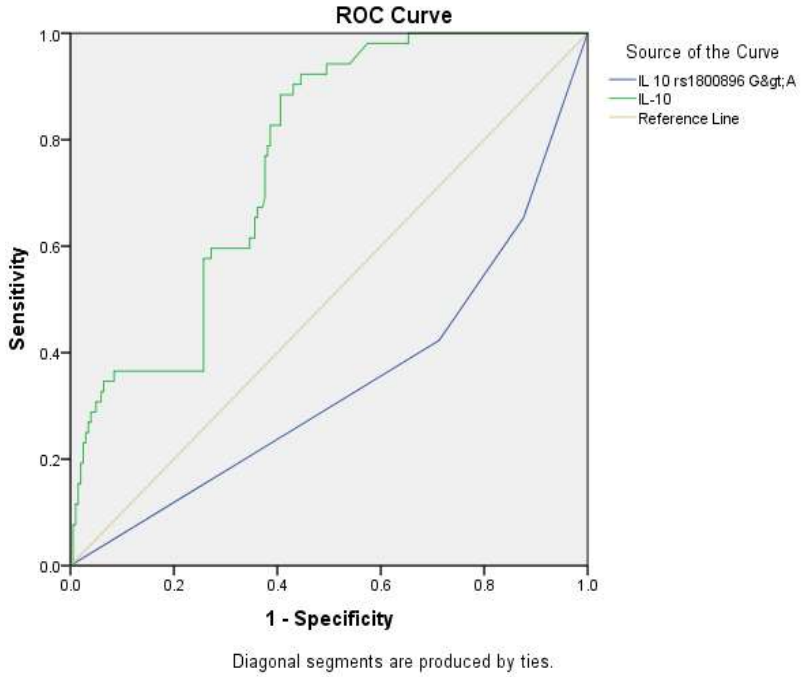

Figure 5. Receiver operating characteristic curves for serum IL-10 levels and IL-10 rs1800896 polymorphism in sepsis patients.

4 Discussion

4.1 Investigation of IL-10 Functional and Genetic Variability in Gram-Negative Sepsis

Sepsis remains a major global health challenge, characterized by a dysregulated host response to infection and subsequent organ dysfunction [6]. A hallmark of sepsis pathophysiology is the imbalance between pro-inflammatory and anti-inflammatory pathways; while early pro-inflammatory signaling aims to control pathogen burden, excessive anti-inflammatory responses contribute to immune suppression and secondary infections [7 , 8]. Interleukin-10 (IL-10) is a pivotal anti-inflammatory cytokine that limits tissue injury by suppressing pro-inflammatory signaling but may paradoxically predispose to immune paralysis in critical illness [9]. In this context, the present study evaluated both functional (serum IL-10 levels) and genetic (IL-10 promoter polymorphism) aspects of immune regulation in gram-negative sepsis.

4.2 Clinical Severity and SOFA Score Interpretation

All patients in this study fulfilled the diagnostic criteria for sepsis, with a mean partial SOFA score of 7.88 ± 1.37, indicating moderate to severe organ dysfunction. Renal and coagulation impairment were the predominant contributors to SOFA elevation, reflecting typical organ involvement in gram-negative sepsis. Previous studies have demonstrated that higher SOFA scores, particularly during early ICU admission, are strongly associated with increased mortality and clinical deterioration [6 , 10]. The elevated SOFA scores observed in this cohort therefore confirm the severity of disease and underscore the clinical relevance of investigating immunological and genetic factors in this population.

4.3 Genetic Association between IL-10 rs1800896 and Sepsis Susceptibility

A key finding of this study was the significant association between the IL-10 promoter polymorphism rs1800896 and susceptibility to gram-negative sepsis. The GG genotype was significantly more frequent among sepsis patients and remained independently associated with disease risk after adjustment for demographic variables. The rs1800896 polymorphism (−1082 A>G) has been shown to influence IL-10 gene transcription, with the G allele associated with higher IL-10 production compared with the A allele [11]. Meta-analyses and genetic association studies have consistently linked this variant to increased sepsis susceptibility and altered clinical outcomes across diverse populations [11 , 12].

Mechanistically, enhanced IL-10 production in GG genotype carriers may suppress protective inflammatory responses during early infection, thereby impairing pathogen clearance and predisposing individuals to persistent infection. This interpretation is consistent with the concept of compensatory anti-inflammatory response syndrome (CARS), in which an exaggerated anti-inflammatory milieu leads to immunoparalysis, increased vulnerability to secondary infections, and multi-organ dysfunction [13 , 14].

4.4 Functional Dynamics of Serum IL-10 Levels

In addition to genetic susceptibility, serum IL-10 concentrations were significantly elevated in sepsis patients compared with healthy controls and demonstrated a declining trend during longitudinal follow-up. This temporal pattern is biologically plausible: the early increase in IL-10 may reflect a compensatory response to excessive inflammation, while the subsequent decrease may indicate immune exhaustion or regulatory imbalance during disease progression [15 , 16]. These findings highlight the limitations of single time-point cytokine measurements and support the value of longitudinal cytokine profiling for a more accurate assessment of immune trajectories in sepsis.

Consistent with these observations, meta-analytic evidence has shown that persistently elevated IL-10 levels are associated with worse clinical outcomes, including increased mortality and cumulative organ dysfunction [17]. Together, these findings reinforce the role of IL-10 as a marker of immune dysregulation rather than a disease-specific diagnostic indicator.

4.5 Translational Implications and Biomarker Integration

Receiver operating characteristic analysis demonstrated moderate discriminatory performance for serum IL-10 levels, while the rs1800896 polymorphism alone showed poor predictive ability. These results suggest that neither functional nor genetic IL-10 markers should be used as standalone diagnostic tools. Instead, IL-10 measurements may provide complementary prognostic information when integrated with established clinical scoring systems such as SOFA. Combining immunological biomarkers with clinical parameters has been proposed as a strategy to improve early risk stratification and support personalized management in sepsis [6 , 18].

4.6 Interpretation of Hardy–Weinberg Disequilibrium

Deviation from Hardy–Weinberg equilibrium (HWE) was observed for the rs1800896 polymorphism in the sepsis group but not in the control group. Such case-specific deviation has been reported in genetic association studies where disease-related selection pressures influence genotype frequencies [19]. The consistency of genotyping procedures across all samples and the conformity to HWE in controls argue against methodological artifacts such as genotyping error or population stratification.

However, deviation from HWE should be interpreted cautiously, as sample size, selection bias, or unmeasured confounders may also contribute to this finding [19 , 20]. Therefore, HWE results should be considered in conjunction with biological plausibility and multivariable association analyses, as applied in this study, to reduce the risk of false-positive conclusions.

4.7 Population Specificity and External Validity

The findings of this study should be interpreted in light of population specificity. The study was conducted at a single center and included participants from a single ethnic background, which may limit generalizability to other populations. Genetic associations, particularly those involving cytokine polymorphisms, may vary across ethnic groups due to differences in allele frequencies and environmental exposures. Consequently, multicenter studies involving diverse populations are required to validate these findings and clarify their broader clinical applicability.

Limitations

This study has several limitations that should be acknowledged. First, it was conducted at a single center and included participants from a single ethnic population, which may limit the generalizability of the findings to other populations. Second, only ICU-admitted patients were enrolled, which may introduce survival or selection bias by excluding patients with milder disease presentations. Third, although serum IL-10 levels were measured, functional IL-10 gene expression was not directly assessed, limiting mechanistic interpretation of the observed genetic associations. Finally, clinical outcome measures such as mortality, length of ICU stay, and long-term prognosis were not analyzed. Future multicenter studies incorporating diverse populations, functional genomic analyses, and outcome-based endpoints are warranted to validate and extend these findings.

Conclusion

In conclusion, the IL-10 rs1800896 GG genotype was significantly associated with increased susceptibility to culture-confirmed gram-negative sepsis in this study population. Elevated serum IL-10 levels demonstrated moderate discriminatory value but should not be considered standalone diagnostic markers. Rather, functional and genetic IL-10 biomarkers may play a complementary role when integrated with established clinical scoring systems such as SOFA. These findings support an association rather than a causal relationship and highlight the need for larger, multicenter studies across diverse populations to confirm clinical utility and translational relevance.

Ethics Approval and Consent to Participate

The Ethics Committee of the Ministry of Health, Karbala Health Department, Imam Hussein Medical City, and the Scientific Affairs Department of the University of Al-Ameed approved the study protocol. Written informed consent was obtained from all participants prior to enrollment, and all data were used exclusively for research purposes.

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Authors' Contributions

All authors contributed equally to the conception and design of the study, data collection, analysis, and manuscript preparation. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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