ORIGINAL ARTICLE

AL-ANBAR MEDICAL JOURNAL
Anb. Med. J. 21(4): 255–262, 2025

Biomarkers of Sepsis Severity: A Comparative Evaluation of Immunological and Biochemical Parameters

Rusul A.A. Alshammary,[1] Maha M. Khadim,[1] Abdullah Salim Al-Karawi,[1,*]
Ali Saad Kadhim,[2] Haider Yousif Ahmed,[1] Ali R. Laftah,[1] and Giuseppe Lippi[3]

[1] *Department of Microbiology, College of Science, Mustansiriyah University, Baghdad, Iraq.*
[2] *Branch of Biology, Department of Science, College of Basic Education, Wasit University, Wasit, Iraq.*
[3] *Section of Clinical Biochemistry, University of Verona, Verona, Italy.*
(Received : 30 April 2025; Accepted : 4 August 2025; First published online: 1 October 2025)

ABSTRACT

Background: Sepsis is a significant health concern characterized by high mortality rates, further complicated by diagnostic challenges and the absence of reliable prognostic biomarkers.
Objectives: To investigate the clinical value of specific immunological parameters along with liver and kidney function tests in individuals with sepsis and their relationship to disease severity.
Materials and methods: In this research, we included 300 participants (100 healthy individuals as the control group and 200 patients in the sepsis group, including 100 with non-severe sepsis and 100 with severe sepsis). Serum levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), C-X-C motif chemokine ligand 9 (CXCL9), C-C motif chemokine ligand 12 (CCL12), soluble urokinase plasminogen activator receptor (suPARIII), and monocyte chemoattractant protein-1 (MCP-1), creatinine (S-Cr), High-sensitive C-reactive protein (hs-CRP), platelet counts (PLT), and the PaO2/FiO2 ratio were measured for each participant.
Results: Our results showed significantly increased (P-value < 0.05) levels of IL-6 and TNF-α in patients with non-severe sepsis and severe sepsis compared to the control group. The levels of CXCL9, CCL12, suPARIII, and MCP-1 were also significantly elevated in both non-severe sepsis and severe sepsis patients compared with the control group. Significantly higher levels of TSB, hs-CRP, and S-Cr were observed in the severe sepsis group compared to the control group. Conversely, platelet counts were markedly reduced in both non-severe and severe sepsis patients relative to controls.
Conclusion: The study identified several critical immunological and biochemical markers that demonstrated a significant positive correlation with sepsis severity. Elevated levels of these immune response markers were consistently associated with more severe clinical presentations, underscoring their potential utility as early diagnostic and prognostic indicators in sepsis management.
Keywords: Sepsis; Interlukin-6; Chemokines; Monocyte chemoattractant protein-1; Soluble urokinase plasminogen activator receptor.

DOI: 10.33091/amj.2025.159680.2222

INTRODUCTION

Sepsis is a global health concern, accounting for approximately 20% of all annual deaths, and has been recognized by the World Health Organization (WHO) as a critical public health priority [1]. Sepsis is typically considered a life-threatening acute (multiple) organ dysfunction caused by dysregulated host response to infections or other triggers [2–4]. Epidemiological studies found that sepsis impacts 48.9 million people yearly and leads to 11 million worldwide deaths each year, thus emphasizing its significant morbidity and mortality rates [5, 6]. The clinical symptoms mostly include: Body temperature exceeding 38°C or falling below 36°C, tachycardia with a heart rate greater than 100 beats/min, a respiratory rate over 20 breaths/min, an arterial partial pressure of carbon dioxide (PaCO2) of less than 32 mmHg, and abnormal white blood cell counts [7]. Gram-negative bacteria produce endotoxin, often referred to

* Corresponding author:
E-mail: abdullah.s.shaker@uomustansiriyah.edu.iq

as lipopolysaccharide bacterium, a potent mediator of microorganism that contributes to the pathophysiology of sepsis by triggering the creation and release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Chronic inflammation impairs tissue perfusion, which impacts the liver and kidneys, among other organs [8, 9]. Long-term immunosuppression, immunological collapse, and even physical limitations are characteristics of sepsis, sometimes referred to as persistent inflammation, immunosuppression, and catabolism syndrome. Notably, other serious conditions, such as significant trauma, pancreatitis, and cardiopulmonary bypass, that are brought on by sterile insults, can also result in sepsis [10].

Sepsis pathophysiology is characterized by intricate interactions among inflammatory, coagulation, and endothelial processes in response to infection. At the onset, pathogens activate the innate immune system via pattern recognition receptors (PRRs), prompting the secretion of cytokines and the mobilization of immune cells, including neutrophils and macrophages. This cascade generates a cytokine storm, marked by the simultaneous presence of both pro-inflammatory and anti-inflammatory mediators, ultimately driving widespread systemic inflammation. In severe cases, this immune suppression becomes more pronounced, leading to phenomena like lymphocyte exhaustion and apoptosis, particularly affecting T cells. Elevated levels of regulatory T cells, which inhibit immune responses, contribute to immunoparalysis, impeding pathogen clearance and worsening organ dysfunction [11, 12]. Multiple mechanisms appear to frame this distinctive microcirculatory derangement, including endothelial dysfunction, impaired red blood cell (RBC) deformability, thinning and damage to the glycocalyx layer, increased leukocyte activation and recruitment, and activation of the coagulation cascade. Importantly, these variations in microcirculatory flow and endothelial function are expected to directly contribute to the development of multiple organ dysfunction through several mechanisms. The generation of microvascular shunts has been suggested to separate microcirculatory blood flow distribution from metabolic demand, resulting in regions of hypoperfusion and hypoxia [13]. At the same time, activation of the complement system enhances leukocyte recruitment and intensifies the inflammatory response. Upon activation, the endothelium releases von Willebrand factor (VWF) and expresses tissue factor (TF), thereby triggering the extrinsic coagulation pathway. These events result in increased thrombin production and fibrin deposition, which contribute to the development of microvascular thrombosis and subsequent endothelial dysfunction [14, 15].

In sepsis, the kidneys are particularly vulnerable due to the interplay of inflammation, endothelial dysfunction, and coagulation abnormalities. The systemic inflammatory response the release of cytokines, which damage the renal endothelial cells and disrupts the glomerular filtration barrier. Endothelial injury in the kidney leads to increased vascular permeability and the promotion of micro-thrombosis. Additionally, sepsis-associated renal dysfunction involves alterations in renal blood flow regulation, with vasodilation and hypotension reducing perfusion pressure. These changes compromise microcirculatory flow, hindering effective oxygen delivery to tissues. Neutrophils contribute to the process by releasing neutrophil extracellular traps (NETs), which enhance platelet aggregation and further stimulate the coagulation cascade [16–18].

Despite its critical impact on sepsis, current clinical tools are insufficient for timely and accurate assessment of sepsis severity, which limits effective treatment and prognosis. Therefore, our study aimed to evaluate the clinical value of specific immunological biomarkers such as IL-6, TNF-α, CXCL9, CCL12, suPARIII, and MCP-1, alongside liver and kidney function tests in patients with sepsis. The purpose is to determine the relationship between these biochemical and immunological parameters and the severity of sepsis, as well as to improve early diagnosis and prognostication of the disease.

MATERIALS AND METHODS

This comparative cross-sectional study included 300 participants recruited from the Intensive Care Units (ICUs) of Baghdad Teaching Hospital, Al-Kindi Teaching Hospital, Al-Yarmouk Teaching Hospital, and Ibn Al-Nafees Hospital in Baghdad, Iraq, between July and October 2024. This study received approval from the Ethical Clearance Committee at the College of Basic Education, Wasit University, as per administrative order number 23/7-9-2024. The participants were divided into three groups; First group: Healthy controls (n=100: First group, healthy controls (n = 100), aged 19-50 years. Second group: Non-severe sepsis patients (n=100), aged 18–65 years. Third group: patients with severe sepsis (n=100), aged 19–52 years. Sepsis was defined according to the Systemic Inflammatory Response Syndrome (SIRS) criteria associated with confirmed infection without organ dysfunction [7]. Severe sepsis was defined by the presence of infection-induced organ dysfunction, identified through clinical assessments and supported by laboratory markers such as elevated lactate levels and pro-inflammatory cytokines [7].

Adult patients aged 18–65 years admitted to the ICU with a diagnosis of non-severe sepsis or severe sepsis were included, provided they gave informed consent. The healthy control group consisted of adults aged 19–50 years recruited from hospital staff, blood donors, or individuals attending routine health check-ups. All controls were free of infectious diseases, chronic illnesses, or any use of immunosuppressive or anti-inflammatory therapies. While the exclusion criteria for the sepsis groups included: Immunosuppressive disorders, active malignancy, end-stage renal or hepatic disease, pregnancy, and those who declined to participate. For the healthy control group, exclusion criteria were any acute illness or infection within the past month, chronic medical conditions (e.g., diabetes, hypertension), autoimmune diseases, malignancy, organ dysfunction, pregnancy, use of immunosuppressive or anti-inflammatory medications, and those who declined to participate.

All participants underwent laboratory tests, which included: Biochemical and immunological tests [TSB, S-Cr, hs-Crp and PLT—] and immunological tests (IL-6, TNF-α, CXCL9, CCL12, suPARIII, and MCP-1). The ratio of PaO2/FiO2 was compared with the Sequential Organ Failure Assessment (SOFA). The SOFA score could accurately predict clinical outcomes in patients with non-severe sepsis and severe sepsis. It is a method for determining the extent of damage to a patient's vital organs in sepsis. It gauges how well the body's six essential organs (the respiratory system, nervous system, liver, heart, and circulatory system, kidneys, and coagulation system) are functioning. Each function is scored from 0 to 4, with a higher score indicating a worsening condition.

Figure 1 shows the flow chart of the 300 participants.

http://doi.org/10.33091/amj.2025.159680.2222

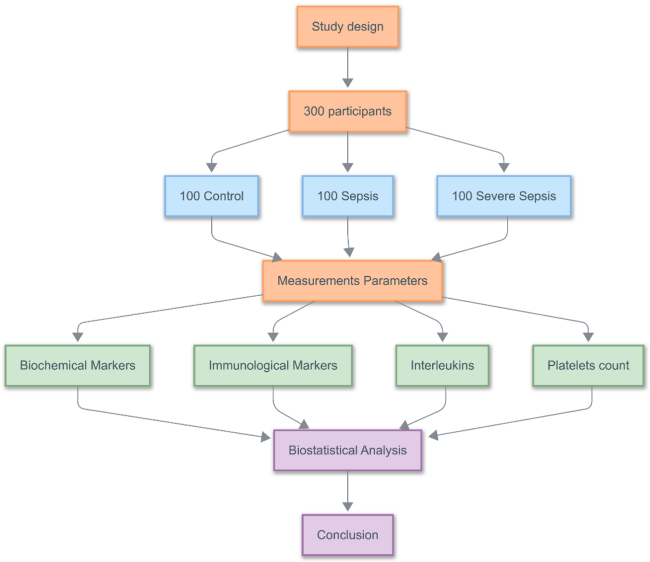

Figure 1. Flowchart representing the progression of participant selection and grouping.

Five milliliters of blood were drawn by venipuncture from each subject. Patient's blood samples were drawn upon arrival at the emergency room. Two and a half milliliters were collected into an anticoagulated tube containing K2-EDTA for the PLT count. The remaining 2.5 ml were collected into a gel activator tube to obtain serum for biochemical and immunological tests. Serum was transferred into plain tubes and refrigerated at –20°C until measurement. IL-6, TNF-α, CXCL9, CCL12, suPARIII, and MCP-1 were assayed with sandwich enzyme-linked immunosorbent assay (ELISA) provided by Melsin – china (No.111125MBL). TSB, hs-CRP, and S-Cr were measured on the Cobas C111 analyzer Roche Diagnostics (No.1126RSH). The PLT count was performed using the hematology analyzer Pentra 80 (ABX Horiba Group, Minami-ku, Kyoto, Japan). Additionally, the PaO_2/FiO_2 ratio was calculated by dividing arterial oxygen partial pressure-PaO_2 mmHg by the fraction of inspired oxygen (FiO_2). This ratio was used to assess the degree of hypoxemia and organ dysfunction in accordance with critical care guidelines.

The sample size was calculated using G*Power software for a one-way ANOVA comparing three groups, with an effect size of 0.25, α level of 0.05, and power of 0.95. The calculation indicated a minimum total sample size of 252 participants (Approximately 84 per group). Our study recruited 100 participants per group to ensure adequate power and to account for potential 10% dropouts (Figure 2).

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) Statistics version 28 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA). Continuous variables were tested for normality using the Shapiro-Wilk test and expressed as the mean ± standard error (SE) or mean ± standard deviation (SD) as appropriate. Comparisons among the three groups (healthy controls, non-severe sepsis, and severe sepsis) were conducted using a one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test for pairwise comparisons. Pearson correlation analysis was used to assess relationships between immunological and biochemical parameters. A P-value less than 0.05 was considered statistically significant. Effect sizes were calculated using Cohen's d and Glass's delta to quantify the magnitude of differences between groups. The equation for Cohen's d is

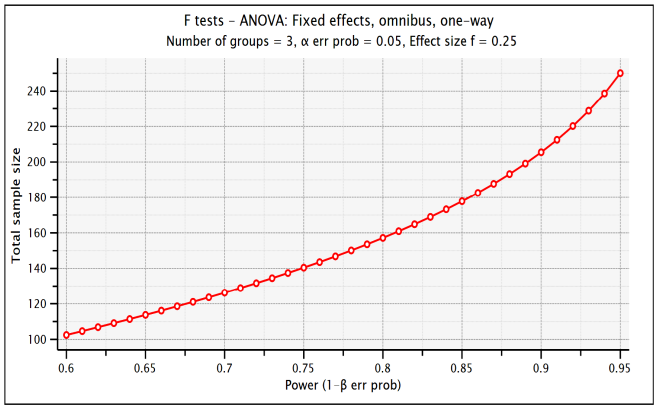

Figure 2. Sample size estimation using G*Power for one-way ANOVA with effect size 0.25, α level = 0.05, power = 0.95, and 3 groups.

$$d = 2t\sqrt{n_1 + n_2} \quad ,$$

this approach is used when the n's between conditions are equal. Effect sizes for the primary comparisons ranged from moderate to large (Cohen's d between 0.5 and 0.9), indicating a substantial magnitude of difference in biomarker levels between groups.

RESULTS

Table 1 summarizes the demographic characteristics of the study participants. The mean age of the healthy control group was 34.5 ± 7.8 years, while the non-severe sepsis and severe sepsis groups had mean ages of 41.5 ± 11.8 and 35.5 ± 8.3 years, respectively. Sex distribution was relatively balanced across groups, with a slight male predominance in the control and non-severe sepsis groups, and a slight female predominance in the severe sepsis group.

Table 2 shows significantly increased (P-value < 0.05) levels of TSB and hs-CRP in patients with non-severe sepsis and severe sepsis compared with the control group. A significant increase (P-value < 0.05) in S-Cr was also observed in non-severe sepsis and severe sepsis patients compared with the control group. The PLT count was significantly decreased in non-severe sepsis and severe sepsis patients compared with the control group. The level of PaO2/FiO2 ratio was significantly (P-value < 0.05) decreased in patients with non-severe sepsis and severe sepsis compared with the control group.

The data in Figure 3 shows significantly increased (P-value < 0.05) serum levels of IL-6, TNF-α, CXCL9, and CCL12 in severe sepsis patients and non-severe sepsis patients in compared to healthy control group. The levels of these biomarkers were also significantly higher in patients with severe sepsis than in the non-severe sepsis group.

The data in Figure 3 shows significantly increased (P-value < 0.05) serum levels of IL-6, TNF-α, CXCL9, and CCL12 in severe sepsis patients and non-severe sepsis patients in compared to healthy control group. The levels of these biomarkers were also significantly higher in patients with severe sepsis than in the non-severe sepsis group.

Table 1. Demographic and clinical characteristics of the 300 participants. ICU: Intensive care unit. NA: Not applicable.

Characteristic	Healthy controls (n=100)	Non-severe sepsis (n=100)	Severe sepsis (n=100)	P-value (Healthy vs. Non-severe)	P-value (Healthy vs. Severe)	P-value (Non-severe vs. Severe)
Age (years)	34.5 ± 7.8	41.5 ± 11.8	40.1 ± 8.3	0.001	~ 0.004	0.45
Sex (Male/Female)	57 / 43	54 / 46	45 / 55	0.75	0.12	0.18
ICU admission time	0	Within 24 hours	Within 24 hours	NA	NA	NA

Table 2. Comparative analysis of biomarkers (TSB, S. Cr, hs-CRP, platelets, and PaO2/FiO2 Ratio) among severe sepsis, non-severe sepsis, and healthy control groups. Values in the same row that do not share the same superscript letter (a, b, c) are significantly different (P-value < 0.05)*.

Biomarkers	Mean ± standard error					P-value
	Non-severe sepsis group	SOFA score	Severe sepsis group	SOFA score	Healthy control	
TSB (ng/ml)	$^{b}2.6 \pm 0.5$	2	$^{a}5.9 \pm 1.0$	1	$^{c}0.9 \pm 0.01$	0.008
S. Cr (ng/ml)	$^{c}2.0 \pm 0.4$	2	$^{a}4.6 \pm 1.0$	3	0.62 ± 0.06	0.019
hs-CRP (ng/ml)	$^{b}9.6 \pm 0.6$	–	$^{a}55.6 \pm 2.6$	–	$^{c}1.2 \pm 0.3$	0.002
Platelets ($\times 10^9$/L)	$^{a}110 \pm 5.9$	1	$^{a}48.0 \pm 1.6$	3	$^{a}350 \pm 5.9$	0.001
PaO_2/FiO_2 ratio (mmHg)	$^{b}290.3 \pm 10.9$	2	155.5 ± 2.6	3	$^{a}400.9 \pm 10.6$	0.001

* TSB: Total serum bilirubin, S. Cr: Serum creatinine, hs-CRP: Highly sensitive C-reactive protein, PaO2/FiO::Oxygen partial pressure/fraction of inspired oxygen, SOFA: Sequential Organ Failure Assessment.

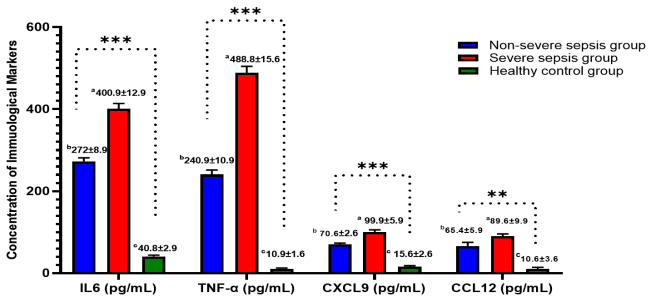

Figure 3. Comparison of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), C-X-C motif chemokine ligand 9 (CXCL9), C-C motif chemokine ligand 12 (CCL12) between severe sepsis patients, sepsis patients and healthy controls. Data are presented as mean ± SD. The statistical analysis was performed using one-way ANOVA. Significant differences are indicated P-value< 0.05 . The letters (a, b, c) above the bars indicate statistically significant differences among the groups, as determined by multiple comparisons. Different letters mean the groups are significantly different from each other at a defined significance level (usually P-value < 0.05). Bars sharing the same letter are not significantly different. The asterisks (***) in the figure indicate the level of statistical significance between groups..

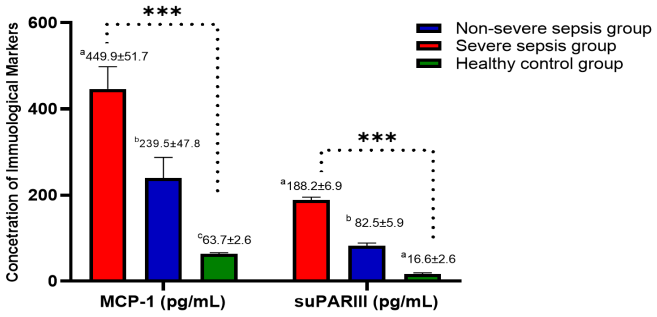

Figure 4. Comparison of monocyte chemoattractant protein-1 (MCP-1) and soluble urokinase plasminogen activator receptor (suPARIII) between severe sepsis, non-severe sepsis patients, and healthy control groups. The asterisks (***) in the figure indicate the level of statistical significance between groups.

Figure 4 shows a significantly increased (P-value < 0.05) level of MCP-1 and suPAR111 in patients with severe and non-severe sepsis compared to the control group.

A significant positive (P-value < 0.05) correlation was observed between IL-6 and TNF-α, as well as between IL6 and CCL12. Similarly, MCP-I exhibited a strong correlation (P-value < 0.05) with TNF-α and CCL12. Furthermore, suPARIII was significantly correlated with TNF-α. These correlations demonstrate a potential association (P-value < 0.05) between proinflammatory cytokines and chemokines in non-severe sepsis and severe sepsis (Figure 5).

DISCUSSION

Sepsis remains a critical global health challenge due to its complex pathophysiology, high mortality rates, and difficulties in early diagnosis and prognosis. The current study reveals that some common biomarkers (e.g., TSB, hs-Crp, and S-Cr) are significantly increased in the serum of patients with sepsis compared to the control group, with severe sepsis showing the highest levels. Furthermore, according to our research, sepsis patients who have acute kidney injury due to hypoperfusion and inflammation may also be at risk for damage to

http://doi.org/10.33091/amj.2025.159680.2222

Characteristic											
IL6	1										
TNF-α	0.610	0.001*	1								
CXCL9	0.549	0.001*	0.561	0.001*	1						
CCL12	0.633	0.001*	0.510	0.001*	0.681	0.001*	1				
SUPARIII	0.53	0.001*	0.59	0.001*	0.56	0.001*	0.66	0.001*	1		
MCPI	0.44	0.002*	0.66	0.003*	0.44	0.006*	0.68	0.003*	0.86	0.001*	1

Figure 5. Heatmap Pearson's correlation between immunological parameters in patients with non-severe sepsis and severe sepsis*.

* Pearson correlation coefficient (r) and their corresponding P-values are shown for immunological markers, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), C-X-C motif chemokine ligand 9 (CXCL9), C-C motif chemokine ligand 2 (CCL12), soluble urokinase plasminogen activator receptor domain III (suPARIII), and monocyte chemoattractant protein-1 (MCPI).

other organs, including the liver. Since organ damage during sepsis may increase the hepatic release of bilirubin, the increase in bilirubin levels may be related to liver dysfunction, which is frequently seen in patients with sepsis. S-Cr levels were significantly increased in severe sepsis patients, suggesting the presence of renal impairment, which is also a frequent complication in septic patients due to reduced renal perfusion and acute kidney injury (AKI) [19, 20].

The PaO2/FiO2 ratio and PLT were significantly decreased in the severe sepsis cohort compared to non-severe sepsis patients and controls. The PLT count decreased dramatically in the severe sepsis group compared to the non-severe sepsis group. A more recent study found a drop in PLT count levels in non-severe sepsis patients and suggested that PLT loss may be caused by increased consumption for PLT incorporation into disseminated thrombi, generation of PLT-leukocytes aggregates, and reduced PLT synthesis due to impaired bone marrow function [21, 22]. In another study, a low ratio of PaO2/FiO2 was seen in non-severe sepsis patients compared with a control group, and a high or low PaO2/FiO2 ratio was related to an increased risk of 28-day death; this reduction has been attributed to impaired gas exchange, suggestive of acute respiratory distress, a common complication in septic patients [23].

The results of our study agreed with those of previous studies, showing a statistically significant increase in the levels of IL-6 and TNF-α in non-severe sepsis patients [24, 25]. Another previous study found increased levels of IL-6 and IL-10 in non-severe sepsis patients [26], and this latter finding may be suggestive of immunosuppression in patients with sepsis, which may then lead to more severe clinical progression [26]. In the early stages of inflammation, IL-6 and TNF-α are pro-inflammatory cytokines that cause cells to produce and release other acute-phase proteins. They stimulate the development and activation of neutrophils, the growth and differentiation of B and T cells, and the synthesis of immunoglobulins during infection [25].

Furthermore, pro-inflammatory cytokines were the most significant inflammatory agents during the early stages of SIRS. The elevation of IL-6 is a critical cytokine in the inflammatory cascade during sepsis, reflecting an acute response to infection and tissue injury. TNF-α is known for its role in mediating inflammation and apoptosis, and its elevated levels correlate with disease severity, suggesting that it may contribute to the pathophysiology of septic shock. TNF-α, IL-1β, and IL-6 mediate the innate early reaction of the immune system to damage or infection, and are primarily responsible for the risk of developing SIRS [27].

Additionally, as expected, the levels of CXCL9 and CCL12 in the serum of patients with severe sepsis were higher than in all other groups. Our study suggests that the observed elevation in the levels of cytokines and chemokines in non-severe sepsis patients reflects an amplified proinflammatory state and dysregulation of the immune response. Furthermore, their upregulation contributes to systemic inflammation, vascular permeability, and subsequent organ dysfunction, underscoring their potential as biomarkers of sepsis severity and therapeutic targets. These results are in line with those of a previous study, which also demonstrated an increased level of CXCL9 in sepsis patients compared to healthy controls [28]. The expression of chemokines is thought to increase in severe inflammatory diseases as a result of the humoral immune response against bacteria [18]. CXCL9 plays a crucial role in attracting immune cells to the sites of infection, thereby amplifying the inflammatory response. CCL12 is also involved in monocyte recruitment and has been implicated in

the development of sepsis-related complications. The significant increases in IL-6, TNF-α, CXCL9, and CCL12 observed in our study among severe sepsis patients would hence reflect heightened immune activation and inflammation, reinforcing the concept that a robust inflammatory response is both a hallmark and a contributing factor in determining the severity of sepsis. These immunological markers can hence serve as potential targets for therapeutic intervention, but may also aid in monitoring disease progression and response to treatment.

SuPARIII has recently been investigated as a novel inflammatory biomarker with significant regulatory roles in various immunological processes. Our study suggests that suPARIII enhances immune cell migration. Additionally, MCP-1 facilitates leukocyte recruitment to sites of infection, further amplifying immune cell migration. Together, they contribute to the immune dysregulation seen in sepsis and may serve as useful biomarkers and therapeutic targets. The immune system is activated, thus resulting in an enhanced production of suPARIII during inflammation or other illnesses [29]. This is confirmed by our findings, which show that the levels of suPARIII are associated with the severity of sepsis. MCP-1, a proinflammatory cytokine that plays a crucial role in various inflammatory diseases, is released by a range of cell types, including fibroblasts, endothelial cells, smooth muscle cells, and monocytes. Our study reported that the levels of this cytokine were considerably elevated in sepsis patients, confirming previous findings of elevated MCP-1 levels in sepsis patients compared with controls [30].

Reliable biomarkers for both diagnosing and assessing the severity of sepsis are critical. An optimal sepsis biomarker should be analytically easy to detect, highly sensitive and specific, cost-effective, and readily available for clinical use. Thus, this is one of the few studies that have assessed the diagnostic utility of a large number of sepsis biomarkers to the best of our knowledge. The levels of IL-6, TNF-α, CXCL9, CCL12, suPARIII, MCP-1, and hs-CRP were then evaluated alongside sepsis scoring systems, such as SOFA, which may serve as valuable indicators for monitoring sepsis progression and identifying cases with a poor prognosis. Moreover, these immunological parameters may have potential in assessing the immune status of patients with sepsis.

Our study has several limitations. Firstly, the cross-sectional design limits the ability to establish causality relationships between the biomarkers and sepsis severity. Secondly, the study was performed in the ICUs of selected hospitals in Baghdad, which may restrict the generalizability of the findings to broader populations. Finally, although multiple immunological and biochemical markers were evaluated, other potentially relevant biomarkers and clinical variables may have been excluded. Future prospective studies with larger sample sizes and prospective designs are needed to validate and extend these findings.

CONCLUSION

This study highlights the prognostic value of specific immunological and biochemical markers in sepsis. Elevated baseline levels of IL-6 and TNF-α emerged as robust indicators of disease severity, while serum suPARIII and MCP-1 demonstrated potential utility in tracking disease progression. Furthermore, elevated TSB and S. Cr levels were associated with hepatic and renal dysfunction, and reduced PLT counts correlated strongly with the risk of septic shock and progression to disseminated intravascular coagulation. These findings suggest a multi-marker approach may enhance early stratification and clinical decision-making in sepsis. Future research should focus on validating these markers in larger, multi-center cohorts and exploring their integration into rapid point-of-care diagnostic tools. Additionally, longitudinal studies assessing biomarker kinetics in response to therapeutic interventions may offer insights into personalized treatment strategies for sepsis management.

ETHICAL DECLARATIONS

Acknowledgments

We express our gratitude to the management of Wasit University and Mustansiriyah University for their support in facilitating our study.

Ethics Approval and Consent to Participate

This study received approval from the Ethical Clearance Committee of Wasit University, as Administrative Order No. 23/7-9-2024. Informed consent was obtained from all participants included in the current study.

Consent for Publication

Not applicable (no individual personal data included).

Availability of Data and Material

Data generated during this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that there is no conflict of interest.

Funding

No funding.

Authors' Contributions

Al-Karawi AS designed the study protocol, supervised all aspects of the research process, and played a key role in data interpretation and manuscript revisions. Alshammary RAA conducted the literature review and performed data analysis. Khadim MM assisted in participant recruitment and laboratory analyses. Kadhim AS analyzed serum samples for immunological markers. Ahmed HY managed the statistical analysis, while Laftah AR provided feedback on the study design and helped coordinate the research team. Lippi G critically reviewed the manuscript drafts, provided expert feedback to enhance the quality of the writing. All authors read and approved the final version of the manuscript.

http://doi.org/10.33091/amj.2025.159680.2222

REFERENCES

[1] J. E. Avila, J. E. De Frías, and L. J. Olivero. Role of preventive measures in sepsis. In *The Sepsis Codex*, pages 287–295. Elsevier, 2023.

[2] L. La Via, G. Sangiorgio, S. Stefani, A. Marino, G. Nunnari, S. Cocuzza, I. La Mantia, B. Cacopardo, S. Stracquadanio, S. Spampinato, and S. Lavalle. The global burden of sepsis and septic shock. *Epidemiologia*, 5(3):456–478, 2024.

[3] N. R. Kumar, T. A. Balraj, S. N. Kempegowda, and A. Prashant. Multidrug-resistant sepsis: A critical healthcare challenge. *Antibiotics*, 13(1):46, 2024.

[4] R. E. Hancock, A. An, C. C. dos Santos, and A. H. Lee. Deciphering sepsis: transforming diagnosis and treatment through systems immunology. *Frontiers in Science*, 2:1469417, 2025.

[5] M. Leone, I. Lakbar, and J. L. Vincent. Sepsis: Actual numbers and uncertainties. *Revue d'Épidémiologie et de Santé Publique*, 71(6):102176, 2023.

[6] R. Markwart, H. Saito, T. Harder, S. Tomczyk, A. Cassini, C. Fleischmann-Struzek, F. Reichert, T. Eckmanns, and B. Allegranzi. Epidemiology and burden of sepsis acquired in hospitals and intensive care units: a systematic review and meta-analysis. *Intensive Care Medicine*, 46(8):1536–1551, 2020.

[7] R. S. Hotchkiss, L. L. Moldawer, S. M. Opal, K. Reinhart, I. R. Turnbull, and J. L. Vincent. Sepsis and septic shock. *Nature Reviews Disease Primers*, 2(1):1–21, 2016.

[8] M. Wang, J. Feng, D. Zhou, and J. Wang. Bacterial lipopolysaccharide-induced endothelial activation and dysfunction: a new predictive and therapeutic paradigm for sepsis. *European Journal of Medical Research*, 28(1):339, 2023.

[9] T. Srdić *et al.* From molecular mechanisms to clinical therapy: understanding sepsis-induced multiple organ dysfunction. *International Journal of Molecular Sciences*, 25(14):7770, 2024.

[10] D. Jarczak, S. Kluge, and A. Nierhaus. Sepsis—pathophysiology and therapeutic concepts. *Frontiers in Medicine*, 8:628302, 2021.

[11] J. Arora, A. A. Mendelson, and A. Fox-Robichaud. Sepsis: network pathophysiology and implications for early diagnosis. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 324(5):R613–R624, 2023.

[12] W. Wu, W. Lan, X. Jiao, K. Wang, Y. Deng, R. Chen, R. Zeng, and J. Li. Pyroptosis in sepsis-associated acute kidney injury: mechanisms and therapeutic perspectives. *Critical Care*, 29(1):168, 2025.

[13] G. Alebachew, B. Teka, M. Endris, Y. Shiferaw, and B. Tessema. Etiologic agents of bacterial sepsis and their antibiotic susceptibility patterns among patients living with human immunodeficiency virus at gondar university teaching hospital, northwest ethiopia. *BioMed Research International*, 2016(1):5371875, 2016.

[14] A. B. Liu, B. Tan, P. Yang, N. Tian, J. K. Li, S. C. Wang, L. S. Yang, L. Ma, and J. F. Zhang. The role of inflammatory response and metabolic reprogramming in sepsis-associated acute kidney injury: mechanistic insights and therapeutic potential. *Frontiers in Immunology*, 15:1487576, 2024.

[15] T. Pais, S. Jorge, and J. A. Lopes. Acute kidney injury in sepsis. *International Journal of Molecular Sciences*, 25(11):5924, 2024.

[16] W. Miao, Y. Yan, X. Xinyu, B. Jiawei, M. Chengtai, and D. Xianjin. Effect of endothelial responses on sepsis-associated organ dysfunction. *Chinese Medical Journal*, 137(23):2782–2792, 2024.

[17] T. Iba, J. Helms, C. L. Maier, M. Levi, E. Scarlatescu, and J. H. Levy. The role of thromboinflammation in acute kidney injury among patients with septic coagulopathy. *Journal of Thrombosis and Haemostasis*, 22(6):1530–1540, 2024.

[18] Y. Peng, Q. Wang, F. Jin, T. Tao, and Q. Qin. Assessment of urine ccl2 as a potential diagnostic biomarker for acute kidney injury and septic acute kidney injury in intensive care unit patients. *Renal Failure*, 46(1):2313171, 2024.

[19] Y. R. Shah, D. S. Dahiya, P. Chitagi, and L. G. Rabinowitz. Hyperbilirubinemia in a patient with sepsis: A diagnostic challenge. *ACG Case Reports Journal*, 10(6):e01076, 2023.

[20] B. Khwannimit, R. Bhurayanontachai, and V. Vattanavanit. Ability of a modified sequential organ failure assessment score to predict mortality among sepsis patients in a resource-limited setting. *Acute and Critical Care*, 37(3):363, 2022.

[21] A. Setarehaseman, A. Mohammadi, and R. W. Maitta. Thrombocytopenia in sepsis. *Life*, 15(2):274, 2025.

[22] A. Dewitte, S. Lepreux, J. Villeneuve, C. Rigothier, C. Combe, A. Ouattara, and J. Ripoche. Blood platelets and sepsis pathophysiology: a new therapeutic prospect in critical ill patients? *Annals of Intensive Care*, 7(1):115, 2017.

[23] H. Bi, X. Liu, C. Chen, L. Chen, X. Liu, J. Zhong, and Y. Tang. The pao2/fio2 is independently associated with 28-day mortality in patients with sepsis: a retrospective analysis from mimic-iv database. *BMC Pulmonary Medicine*, 23(1):187, 2023.

[24] M. S. Mostafa, E. W. ELshourbagy, and A. Shahat. Association between interleukin-6 promoter polymorphism (-174 g/c), serum interleukin-6 levels and severity of sepsis. *Egyptian Journal of Medical Microbiology*, 31(3):77–81, 2022.

[25] B. Yu, M. Chen, Y. Zhang, Y. Cao, J. Yang, B. Wei, and J. Wang. Diagnostic and prognostic value of interleukin-6 in emergency department sepsis patients. *Infection and Drug Resistance*, 15:5557–5566, 2022.

[26] Y. Zhang, B. Li, and B. Ning. Evaluating il-6 and il-10 as rapid diagnostic tools for gram-negative bacteria and as disease severity predictors in pediatric sepsis patients in the intensive care unit. *Frontiers in Immunology*, 13:1043968, 2022.

[27] X. Y. Li, M. Liu, Y. J. Fu, Y. J. Jiang, and Z. N. Zhang. Alterations in levels of cytokine following treatment to predict outcome of sepsis: A meta-analysis. *Cytokine*, 161:156056, 2023.

[28] E. J. Giamarellos-Bourboulis, M. Antonelli, F. Bloos, I. Kotsamidi, C. Psarrakis, K. Dakou, D. Thomas-Rüddel, L. Montini, J. Briegel, G. Damoraki, and P. Koufargyris. Interferon-gamma driven elevation of cxcl9: a

new sepsis endotype independently associated with mortality. *EBioMedicine*, 109:105414, 2024.

[29] Q. Huang, H. Xiong, P. Yan, T. Shuai, J. Liu, L. Zhu, J. Lu, K. Yang, and J. Liu. The diagnostic and prognostic value of supar in patients with sepsis: a systematic review and meta-analysis. *Shock*, 53(4):416–425, 2020.

[30] Z. Chen, C. Li, and J. Yu. Monocyte chemoattractant protein-1 as a potential marker for patients with sepsis: a systematic review and meta-analysis. *Frontiers in Medicine*, 10:1217784, 2023.

http://doi.org/10.33091/amj.2025.159680.2222