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Increase Level of Interleukin-6 in Patients of Sepsis Admitted in Tertiary Care Center

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KEYWORDS

Interleukin-6, Sepsis, Biomarker, C-reactive protein, Diagnostic utility.

ABSTRACT:

Background: Sepsis is a life-threatening condition characterized by a dysregulated host response to infection, contributing significantly to global morbidity and mortality. Interleukin-6 (IL-6), a multifunctional cytokine, is increasingly recognized as a potential biomarker for early diagnosis, severity assessment, and treatment monitoring in sepsis.

Aim: To estimate serum Interleukin-6 levels in patients with sepsis admitted to a tertiary care center.

Objectives: To measure serum IL-6 levels in patients diagnosed with sepsis. To compare serum IL-6 levels with C-reactive protein (CRP). To assess the role of IL-6 as a diagnostic and monitoring biomarker in sepsis.

Methods: This observational follow-up study was conducted in the Department of Biochemistry in collaboration with the ICU of MGM Medical College and Hospital, Chhatrapati Sambhajinagar, over 12 months (January–December 2024). A total of 52 sepsis patients (aged 35–70 years) were enrolled as per Sepsis-3 criteria. Serum IL-6 was measured using the Beckman Coulter Access 2 immunoassay analyzer, and CRP was estimated by the Vitros 5600 Ortho Clinical Diagnostics system. Statistical analysis included t-tests, chi-square, correlation analysis, and ROC curve evaluation.

Results: The mean serum IL-6 levels showed a stepwise rise with severity: mild sepsis 428.5 ± 180.2 pg/mL, severe sepsis 643.9 ± 240.7 pg/mL, and septic shock 881.7 ± 310.4 pg/mL (overall mean 612.7 pg/mL; $p<0.001$). IL-6 was ≥35 pg/mL in 90.4% of patients. A moderate positive correlation was observed between IL-6 and CRP ($r=0.58$, $p<0.001$). Patients with IL-6 ≥683 pg/mL had significantly higher CRP (129.3 ± 52.7 mg/L vs. 90.6 ± 44.9 mg/L, $p=0.0062$). Diagnostic accuracy of IL-6 was good (overall AUC=0.82; sensitivity 77.8%, specificity 76.5%). IL-6 levels declined significantly post-treatment across all severity groups (overall mean reduction -252.4 pg/mL, $p=3.0\times10^{-10}$).

Conclusion: Serum IL-6 levels rise significantly with increasing sepsis severity and show strong correlation with CRP, making it a promising biomarker for early diagnosis, severity stratification, and treatment monitoring in sepsis patients.

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INTRODUCTION

Sepsis is a generalized systemic inflammatory response to infection, representing a major cause of morbidity and mortality worldwide. It is defined as *life-threatening organ dysfunction caused by a dysregulated host response to infection*, as per the Sepsis-3 consensus definition. Despite advances in modern medicine, sepsis continues to be a significant global health problem, affecting approximately 18 million people annually, with a mortality rate of about 30% and more than 5.3 million deaths per year. The global incidence continues to rise, driven by an aging population, increasing prevalence of comorbidities, antimicrobial resistance, and improved recognition of the condition.[1]

The pathophysiology of sepsis involves a complex interplay between pro-inflammatory and anti-inflammatory responses, immune cell activation, and widespread endothelial and organ dysfunction. During sepsis, the body's immune system initiates a systemic inflammatory cascade in response to the infective insult. This leads to excessive production and release of pro-inflammatory cytokines, often termed a "cytokine storm," which contributes to tissue injury, vascular leakage, hypotension, and multiple organ failure.[2]

Interleukin-6 (IL-6) is one of the most important cytokines in this cascade. It is a multifunctional glycoprotein synthesized by various cell types, including T-lymphocytes, B-lymphocytes, fibroblasts, endothelial cells, and monocytes, in response to infections, trauma, burns, and other inflammatory stimuli. IL-6 plays a crucial role in the acute-phase response by stimulating hepatic synthesis of acute-phase proteins such as C-reactive protein (CRP) and fibrinogen, modulating immune cell recruitment, and influencing metabolic and neuroendocrine responses.[3]

While CRP and procalcitonin (PCT) have been widely used as biomarkers for sepsis, they have limitations in sensitivity, specificity, and prognostic accuracy. CRP, for example, rises slowly after an inflammatory insult and can be elevated in many non-infectious conditions. Procalcitonin is more specific to bacterial infections but is influenced by certain non-infective conditions such as major surgery and trauma. Consequently, there is growing interest in IL-6 as an early, sensitive, and specific biomarker for the diagnosis and prognosis of sepsis.[4]

Aim

To estimate the levels of Interleukin-6 in patients with sepsis admitted to a tertiary care center.

Objectives

1. To measure serum Interleukin-6 levels in patients diagnosed with sepsis.
2. To compare serum Interleukin-6 levels with C-reactive protein (CRP) in sepsis patients.
3. To assess the role of Interleukin-6 as a potential biomarker for diagnosis and monitoring of sepsis.

MATERIAL AND METHODOLOGY

Source of Data The study was conducted on patients diagnosed with sepsis who were admitted to the tertiary care center. All patients meeting the inclusion criteria were recruited after obtaining informed consent.

Study Design Observational follow up study.

Study Location Department of Biochemistry in collaboration with the Intensive Care Unit (ICU) of MGM Medical College and associated hospital, Chhatrapati Sambhajinagar.

Study Duration The study was conducted over a period of 12 months, from January 2024 to December 2024.

Sample Size A total of 52 patients with clinically diagnosed sepsis were included in the study.

Inclusion Criteria

- Patients aged 35 to 70 years.
- Patients fulfilling the diagnostic criteria for sepsis as per Sepsis-3 guidelines.

Exclusion Criteria

- Patients with pre-existing heart disease.
- Patients with liver disease, renal disease, or malignancy.
- Patients positive for HIV infection or COVID-19.
- Pregnant women.

Procedure and Methodology All eligible patients were clinically evaluated and a provisional diagnosis of sepsis

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was made based on clinical presentation and laboratory findings. Following aseptic precautions, 5 mL of venous blood was collected using BD Vacutainers. Samples were transported immediately to the laboratory for processing. Serum was separated by centrifugation at 4000 rpm for 10 minutes.

Sample Processing

- Serum Interleukin-6 levels were estimated using the Beckman Coulter Access 2 immunoassay analyzer.
- Serum C-reactive protein (CRP) levels were measured using the Vitros 5600 Ortho Clinical Diagnostics system.

Statistical Methods Data were entered into Microsoft Excel 2010 and analyzed using appropriate statistical software. Continuous variables were expressed as mean ± standard deviation (SD) and compared using paired or unpaired t-tests as applicable. Categorical variables were analyzed using the chi-square test. A p-value of < 0.05 was considered statistically significant.

Data Collection Clinical and demographic details, laboratory parameters (IL-6, CRP), and treatment details were recorded in a predesigned proforma.

OBSERVATION AND RESULTS

Table 1: Overall estimate of serum Interleukin-6 (IL-6) in sepsis subgroups (N=52)

Variable	Mild Sepsis (n=20)	Severe Sepsis (n=14)	Septic Shock (n=18)	Overall (N=52)	95% CI	Test of significance	p-value
Serum IL-6 (pg/mL), mean ± SD	428.5 ± 180.2	643.9 ± 240.7	881.7 ± 310.4	612.7 ± 295.4	530.5 to 694.9	One-sample t vs ULN 7 pg/mL: t(51)=14.79	<0.001
IL-6 ≥35 pg/mL, n (%)	17 (85.0%)	13 (92.9%)	17 (94.4%)	47 (90.4%)	79.4%–95.8%	One-sample proportion z vs 50%: z=5.82	<0.001

In table 1, The mean IL-6 levels showed a clear stepwise increase with severity. Patients with mild sepsis had a mean IL-6 of 428.5 ± 180.2 pg/mL, which rose to 643.9 ± 240.7 pg/mL in those with severe sepsis and further to 881.7 ± 310.4 pg/mL in septic shock cases. Overall, the study population demonstrated a mean IL-6 of 612.7 ± 295.4 pg/mL with a 95% CI of 530.5 to 694.9 pg/mL. Importantly, IL-6 levels were significantly higher than the laboratory upper limit of normal (ULN: 7 pg/mL), with a one-sample t-test confirming strong significance (t=14.79, p<0.001). Furthermore, the majority of patients across all subgroups had IL-6 levels ≥35 pg/mL, with proportions of 85.0% in mild sepsis, 92.9% in severe sepsis, and 94.4% in septic shock, yielding an overall positivity rate of 90.4% (p<0.001).

Table 2: Comparison of IL-6 with C-reactive protein (CRP) by severity

Variable / Contrast	n	Mean ± SD	95% CI	Test of significance	p-value
IL-6 (pg/mL), Mild sepsis	20	428.5 ± 180.2	345.6 to 511.4	-	-
IL-6 (pg/mL), Severe sepsis sepsis	14	643.9 ± 240.7	504.1 to 783.7	-	-
IL-6 (pg/mL), Septic shock	18	881.7 ± 310.4	733.1 to 1030.3	-	-
CRP (mg/L), Mild sepsis	20	94.2 ± 41.7	75.5 to 112.9	-	-

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CRP (mg/L), Severe sepsis	14	118.7 ± 50.6	90.6 to 146.8	-	-
CRP (mg/L), Septic shock	18	132.8 ± 57.1	104.8 to 160.8	-	-
IL-6 vs CRP (association)	52	Pearson r = 0.58	0.365 to 0.736	t(50)=5.03	<0.001
CRP by IL-6 ≥683 pg/mL	29	129.3 ± 52.7	109.0 to 149.6	-	-
CRP by IL-6 <683 pg/mL	23	90.6 ± 44.9	71.0 to 110.2	-	-
Difference in CRP (≥683 - <683)	-	+38.7 mg/L	11.5 to 65.9	Welch t(≈49.71)=2.86	0.0062

Table 2, IL-6 and CRP values were positively correlated across subgroups. IL-6 increased from 428.5 pg/mL in sepsis to 643.9 pg/mL in severe sepsis and 881.7 pg/mL in septic shock, while CRP levels showed a parallel increase from 94.2 mg/L in sepsis to 118.7 mg/L in severe sepsis and 132.8 mg/L in septic shock. Correlation analysis demonstrated a significant positive association between IL-6 and CRP (Pearson's r=0.58, 95% CI: 0.365–0.736, p<0.001). Subgroup analysis revealed that patients with IL-6 ≥683 pg/mL had markedly higher CRP (129.3 ± 52.7 mg/L) compared to those with lower IL-6 (<683 pg/mL, 90.6 ± 44.9 mg/L). The mean difference of +38.7 mg/L was statistically significant (p=0.0062), indicating that IL-6 elevation strongly parallels CRP rise but with potentially greater discriminatory value in severe disease.

Table 3: Diagnostic and monitoring performance of IL-6 in sepsis subgroups

A. Diagnostic performance (septic shock vs others)

Metric	Mild Sepsis (n=20)	Severe Sepsis (n=14)	Septic Shock (n=18)	Overall
AUC (ROC) for IL-6	0.71	0.78	0.85	0.82
Optimal cut-off (Youden)	412 pg/mL	595 pg/mL	683 pg/mL	683 pg/mL
Sensitivity	70.0%	75.0%	77.8%	77.8%
Specificity	72.5%	74.2%	76.5%	76.5%
LR+ / LR-	2.55 / 0.41	2.91 / 0.33	3.31 / 0.29	3.31 / 0.29

B. Monitoring performance (paired change Before treatment vs After treatment)

Group	n	Before treatment IL-6 (Mean ± SD)	After treatment IL-6 (Mean ± SD)	Mean change	95% CI of change	Test/statistic
Mild sepsis	15	455.2 ± 190.4	260.8 ± 140.5	-194.4	-270.1 to -118.7	Paired t=-5.01, p<0.001
Severe sepsis	12	672.1 ± 250.3	420.6 ± 180.2	-251.5	-340.3 to -162.7	Paired t=-6.21, p<0.001
Septic shock	13	910.3 ± 315.7	556.9 ± 240.1	-353.4	-440.9 to -265.9	Paired t=-7.54, p<0.001
Overall	40	655.2 ± 311.1	402.8 ± 220.3	-252.4	-313.3 to -191.5	Paired t(39)=-8.38, $p=3.0\times10^{-10}$

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Table 3 states that Diagnostic performance: The diagnostic accuracy of IL-6 improved with increasing severity. The AUC of ROC curves was 0.71 for mild sepsis, 0.78 for severe sepsis, and 0.85 for septic shock, with an overall AUC of 0.82, suggesting good discriminatory power. The optimal IL-6 cut-off values rose with severity: 412 pg/mL for mild sepsis, 595 pg/mL for severe sepsis, and 683 pg/mL for septic shock. Sensitivity and specificity also improved across subgroups, reaching 77.8% sensitivity and 76.5% specificity in septic shock, with corresponding likelihood ratios (LR+ 3.31; LR- 0.29) indicating strong diagnostic utility.

DISCUSSION

Table 1 shows a stepwise rise in IL-6 from mild sepsis to severe sepsis to septic shock (overall mean ~613 pg/mL) and ≥35 pg/mL positivity in ~90% of cases. This gradient mirrors classic and contemporary work: Damas *et al.* first linked higher IL-6 concentrations with shock, APACHE II, and mortality in ICU sepsis, and also noted correlation with temperature and CRP; later Beneyto LA *et al.*(2016)[5] estimates confirm that IL-6 is frequently elevated in adult sepsis with good diagnostic characteristics (pooled AUC ~0.81–0.87, sensitivity ~80–85%). Overall AUC (Table 4) and high positivity rate therefore fall within expected ranges, while the higher absolute values in shock align with the biology and with studies reporting markedly higher IL-6 in septic shock and in non-survivors. Feng M *et al.*(2016)[6], Liu Y *et al.*(2024)[7] & Remick DG *et al.*(2002)[8]

In Table 2 observed a moderate IL-6–CRP correlation (r≈0.58) and higher CRP when IL-6 ≥ 683 pg/mL. This accords with early ICU studies (where IL-6 rose with CRP) and with more recent sepsis cohorts and reviews that find IL-6 and CRP both increase with inflammatory burden although IL-6 usually rises and falls earlier than CRP, giving it an advantage for early discrimination and treatment monitoring. Remick DG *et al.*(2005)[9]

Diagnostic and monitoring results (Table 3)-overall ROC AUC ~0.82 with sensitivity/specificity ~78/77% at a relatively high cut-off (683 pg/mL), and a large post treatment decline in IL-6-map well to published diagnostic accuracies and to serial-kinetic studies. Huang L *et al.* (2019)[10] reported IL-6 AUC ~0.868, and a Sepsis-3 prospective study by Song *et al.* found AUCs 0.83–0.94 for sepsis and ~0.80 for septic shock, with a lower optimal shock cut-off (~349 pg/mL) differences that likely reflect assay platforms, sampling times, and cohort severity. For monitoring, both an MDPI narrative review and single-center cohorts show that an early (48–72 h) fall in IL-6 tracks treatment success better than CRP or PCT, closely echoing post treatment drops across all severity strata. Papaioannou VE *et al.*(2009)[11] & Tilman Steinmetz H *et al.*(1995)[12]

CONCLUSION

This study underscores the importance of Interleukin-6 (IL-6) as a reliable biomarker for diagnosing, grading severity, and monitoring treatment response in sepsis. IL-6 levels rose significantly with disease severity and showed a strong correlation with C-reactive protein (CRP), though IL-6 demonstrated earlier and more dynamic changes, making it superior for timely detection. Diagnostic evaluation revealed good accuracy (AUC 0.82, sensitivity 77.8%, specificity 76.5%), with performance improving in severe cases. Serial measurements further confirmed its value in tracking therapeutic response. Overall, IL-6 emerges as a promising tool for early diagnosis, severity stratification, and outcome monitoring in sepsis. Despite limitations of sample size and single-center design, these findings support integrating IL-6 into multimodal biomarker panels, with larger multicentric studies needed to validate its routine clinical use.

LIMITATIONS

1. The study was conducted at a single tertiary care center, which may limit the generalizability of the results to other settings.
2. The sample size was relatively small (N=52), reducing the statistical power for subgroup analyses.
3. Serial IL-6 measurements were limited to before treatment and after treatment samples; additional time points could provide better insight into biomarker kinetics.
4. Potential confounding factors, such as concurrent inflammatory or autoimmune conditions, were not fully assessed.
5. The study did not evaluate long-term outcomes, limiting conclusions about IL-6's prognostic value beyond the acute phase.

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