



## Role of Interleukin-6 and Interleukin-8 Cytokines as Early Diagnostic Markers of Sepsis

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### Abstract

**Background:** Rapid diagnosis is essential for effective therapy among the patients with sepsis. **Objectives:** The purpose of the present study was to determine the relationship of serum levels of IL-6, IL-8 in patients with various stages of sepsis. **Methodology:** This case control study was conducted in the Department of Immunology at Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka from January 2015 to December 2015 for a period of one (01) year. All patients had been selected from the ICU of BIRDEM General Hospital with known clinicopathological parameters of sepsis. Serum levels of IL-6 and IL-8 were assessed using Enzyme Linked Immunosorbent Assay (ELISA) method. **Results:** In this study, a total of 80 subjects was enrolled of which 60 patients were with at least 2 SIRS criteria and 20 healthy age matched controls without SIRS. Significant difference was found in IL-6 and IL-8 values in the patients with bacteriological culture positive and negative group ( $p < 0.05$ ). AUC for IL-6 was 0.710 (95% CI 0.580-0.840), sensitivity 54.16%, specificity 59.09%, PPV 74.28% and NPV 52% with cutoff value  $>177$ pg/ml. **Conclusion:** Elevated levels of serum IL-6 and IL-8 is found in the patients with sepsis. [Bangladesh Journal of Infectious Diseases, December 2019; 6(2):34-38]

**Keywords:** Interleukin-6; Interleukin-8; Microbiological culture; Systemic inflammatory response syndrome (SIRS); Sepsis; Intensive care unit (ICU)

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## Introduction

The term 'sepsis' is used to define the systemic inflammatory response syndrome (SIRS) to an infectious agent. It is complicated to differentiate sepsis from other noninfectious conditions in critically ill patients admitted with systemic inflammatory response syndrome. Though we have new treatment modalities, advanced laboratory technique and clinical experience, mortality rates in sepsis are still higher<sup>1</sup>. Hospital mortality in ICU patients of Bangladesh suffering from severe sepsis was 49.2% which is very higher than other country<sup>2</sup>. The critically ill patient frequently presents with similar clinical pictures in infection, SIRS, various severities of sepsis and organ dysfunction. This issue is of paramount importance given that therapies and outcomes greatly differ between patients with and those without sepsis. Thus, there is an unmet need for laboratory tools to determine SIRS and the various forms of sepsis early.

The incidence of sepsis and the number of sepsis-related deaths are increasing day by day and among hospitalized patients by 8.7% per year<sup>3</sup>. Early diagnosis and appropriate therapy of sepsis is a daily challenge in intensive care units (ICU). An international prospective cohort study done among patients admitted to the 28 participating units in eight countries between May 1997 and May 1998 were followed until hospital discharge and overall 3034 infectious episodes (incidence: 21.1%) were recorded at ICU admission<sup>4</sup>.

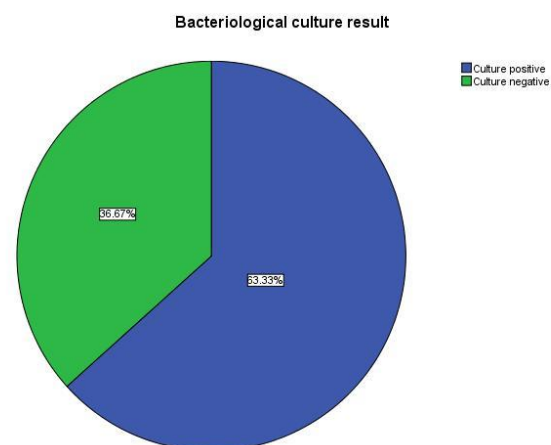
## Methodology:

This case control study conducted at Department of Immunology, BIRDEM General Hospital, Dhaka in collaboration with Intensive Care Unit of BIRDEM General Hospital, Dhaka for a period of one year from 1st January 2015 to 31st December 2015. The study includes 80 subjects and purposive sampling done. Here 60 patients (Case) were chosen with at least 2 SIRS criteria and 20 age matched healthy control. All of them were above 18 years and after taking full medical history all of them examined properly and all medical data were reviewed. Selected patients under study were diagnosed as various stages of sepsis patient with different age group. Basic haematological, biochemical, microbiological laboratory data were recorded from laboratory report. IL-6 was measured by Enzyme linked Immunosorbent Assay (ELISA); IL-8 was measured by Sandwich Immunoassay. All patients were classified into SIRS, sepsis, severe sepsis, septic shock and MODS

according to ACCP/SCCM definition which is now widely used. All data was checked and reviewed after collection. From the primary data obtained, tables and graph were made and interpreted. Levels of IL-6 and IL-8 were expressed as the means  $\pm$  SD or median  $\pm$  interquartile range. A p value of  $<0.05$  was considered to be statistically significant. A nonparametric levene's test was used to verify the equality of variance in the samples data. The quantitative variables were analyzed by Mann Whitney U test. Data was applied in the SPSS version 16 for statistical analysis. Their diagnostic utilities were compared using ROC curves.

## Results

The study was performed in Intensive care unit (ICU), BIRDEM General Hospital, Dhaka. On admission all patients were examined and selected on the basis of SIRS criteria. All past and present data were reviewed carefully to conduct the study. A total of 80 subjects were include in the study, 60 of them were patients with at least 2 SIRS criteria and their mean age was  $51.90 \pm 9.89$  years and 20 healthy controls with mean age of  $49.65 \pm 9.58$  years. Among study population male were 51.2% (41) and female were 48.8% (39) in number. Commonest age range in patients was 51-60 years (40%).



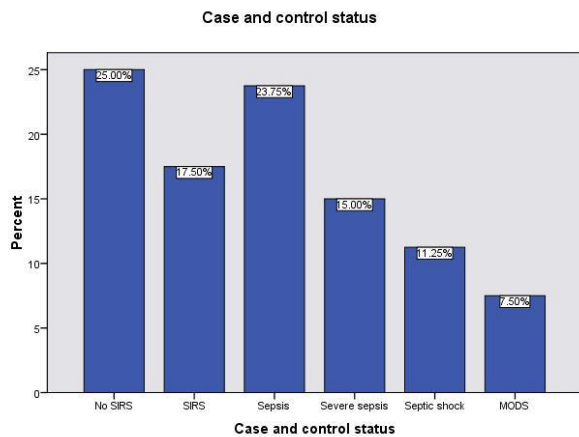
**Figure I: Percentage of bacteriological culture result**

All of the patients had at least 2 SIRS criteria and they were diagnosed clinically at various stages of sepsis. But SIRS criteria may appear in non-inflammatory condition and without bacterial infection also. The gold standard method to prove sepsis is positive bacteriological culture. In this study 38 (63.33%) patients were bacteriological

culture positive and 22 (36.67%) patients were bacteriological culture negative.

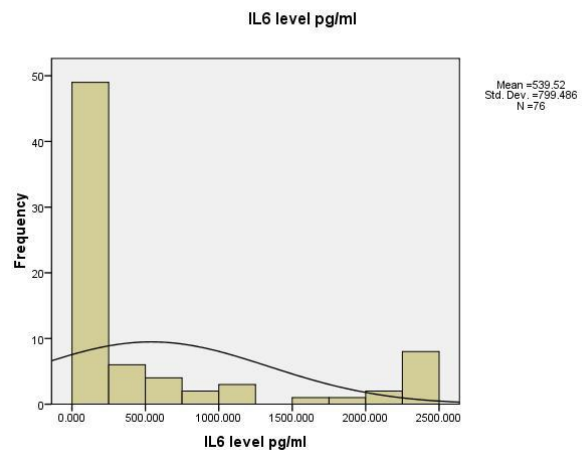
(ESBL) (10.53%) and Staphylococcus aureus (5.26%).

**Staging of healthy individuals and patients according to clinicopathological parameter:** In this study 20 (25%) healthy individual were taken as control (No SIRS) and 60 (75%) patients were categorized into SIRS, sepsis, severe sepsis, septic shock and MODS according to ACCP/SCCM guideline



**Figure II: Staging of sepsis**

**Distribution of organism pattern in sepsis:** Among bacterial growth, the commonest organism was Klebsiella (28.95%) followed by Escherichia coli (15.79%), Acinetobacter (15.79%), Pseudomonas aeruginosa (13.16%), Enterococcus (10.53%), Extended spectrum beta lactamases



**Figure III: Distribution of IL-6 data**

**The difference of IL-6 and IL-8 values between the patients and control:** The sample data were not approximately normally distributed. A nonparametric levene’s test was used to verify the equality of variance in the samples data (p<0.05) which confirmed the non-homogeneity of the distribution. Because of the nonhomogeneity, nonparametric Mann-Whitney U test was used to see the difference between the groups. On Mann-Whitney U test, statistically significant difference was found in between the IL-6 and IL-8 values in the study subject and control population where p<0.05 in all four biomarkers.

**Table I: Significance of serum IL-6 and IL-8 values in patient and control.**

Biomarkers	Study group	Median	Interquartile range	P value
IL6 level pg/ml	Case	202.55	957.93	0.000
	Control	4.43	8.03	
IL-8 level pg/ml	Case	29.31	168.10	0.002
	Control	16.34	15.39	

**The difference of IL-6 and IL-8 in between bacteriological culture positive and negative:** The sample data were also not approximately normally distributed in bacteriological culture positive and negative patients. A nonparametric levene’s test was used to verify the equality of variance in the samples data (p<0.05) which confirmed the non-homogeneity of the distribution. Because of no homogeneity, nonparametric

Mann-Whitney U test was used to see the difference between the groups. On Mann-Whitney U test, statistically significant difference was found in the IL-6, and IL-8 values in the bacteriological culture positive and negative group (p<0.05).

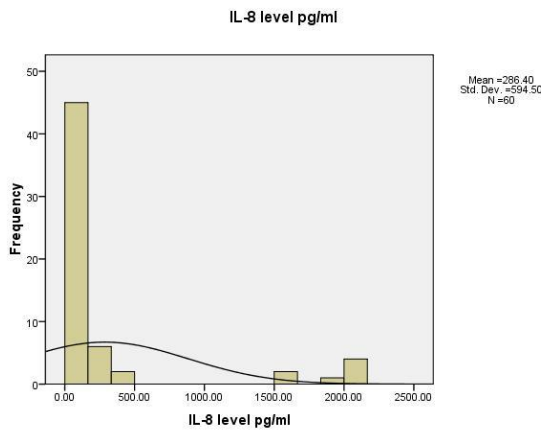


Figure IV: Distribution of IL-8 data

Table II: Diagnostic performance of IL-6, IL-8 to determine sepsis.

Validity test	IL-6	IL-8
Cutoff value	177pg/ml	20pg/ml
Sensitivity	54.16%	76%
Specificity	59.09%	50%
PPV	74.28%	72.5%
NPV	52%	55%
Accuracy	65%	66.66%
AUC	.710	.681

**Discussion**

In a cross-sectional point-prevalence study done over 454 ICUs in Germany in 2003 prevalence was 12.4% (95% CI, 10.9–13.8%) for sepsis and 11.0% (95% CI, 9.7–12.2%) for severe sepsis including septic shock<sup>5</sup>. Despite the enormous investment in critical care resources, sepsis mortality ranges from 25% to 80%<sup>6</sup>. Moreover, cases of severe sepsis are expected to rise for several reasons, including: increasing numbers of immunocompromised patients and aged population; wider use of invasive procedures; more resistant microorganisms. In point prevalence study 32.8% of 895 patients in ICUs had sepsis on a single day<sup>7</sup>. Physicians use various clinical and laboratory data to differentiate infectious from noninfectious conditions in newly admitted patients. But no single clinical or biological indicator of sepsis has gained unanimous acceptance.

Though blood culture is the gold standard and has higher sensitivity and specificity over the hematological value and cytokine but this highly sensitive microbiological parameter is not available in our community health situation and it is time consuming also. In these cases, several indicators have been proposed as new diagnostic tests to assess various stages of sepsis in critically ill patients.

Several attempts have been made to correlate cytokines levels with sepsis and patient prognosis. Among the cytokines, IL-6 and IL-8 are important mediator of host response to bacterial infection and has important role in inflammatory pathogenesis. These cytokines also stimulate release of acute-phase reactants such as CRP and PCT. These cytokines and acute phase proteins have been proposed to be the most promising candidates for diagnosis of sepsis in early stage. Few studies abroad showed combinatorial use of these markers as early diagnosis and prognosis of sepsis in ICU patients. As far best of our knowledge, no studies focusing on the significance of combinatorial use of these markers in sepsis patients of Bangladesh have been reported. In view of these conflicting findings and the utmost importance of the timely diagnosis of sepsis at time of admission in ICU, the present study was undertaken to prospectively investigate the diagnostic value of IL-6 and IL-8 in a group of severely ill patients admitted with sign of systemic inflammatory response syndrome in ICU.

**Conclusion**

Elevated levels of serum IL-6 and IL-8 is found in the patients with sepsis. These will help clinicians to make their decision in diagnosis of sepsis along with other systemic manifestation.

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