

# Usefulness of Presepsin (Soluble CD14 Subtype) as a Diagnostic Marker of Sepsis in Egyptian Patients with Acute Myeloid Leukemia

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## Abstract

**Background:** Systemic inflammatory response syndrome (SIRS) is a systemic inflammatory response to a variety of insults. Presepsin; the soluble CD14 subtype is a novel soluble CD14 molecule that is useful for diagnosing sepsis. It plays an important role in modulating the immune response to endotoxin *in vitro* and *vivo*. The aim: Of the study was to evaluate the usefulness of presepsin as a diagnostic marker of sepsis in acute leukemia. **Methods:** The current study was carried out on 40 adult patients with acute myeloid leukemia after receiving chemotherapy. 10 clinically normal individuals were included in the study to measure the level of presepsin. **Results:** This study was conducted on 50 individuals divided into 2 groups. Group I included 40 adult AML patients who fulfilled at least two of the diagnostic criteria for SIRS and Group II were 10 healthy adult persons as a control group. In Group I there were 11 patients (27.5%) having SIRS, 8 (20%) having sepsis, 9 (22.5%) having severe sepsis and 12 (30%) having septic shock. Data indicate that presepsin level was significantly higher in patients than control  $P = 0.017$ . Our results showed that the level of presepsin has a significantly positive correlation to the degree of severity of sepsis with  $P$  value 0.0001. Using the ROC curve, we found that presepsin was more specific than CRP in detection of sepsis. **Conclusion:** sCD14-ST (presepsin) is a new important marker for diagnosis and prognosis of sepsis. Its level increases in the first six hours after the onset of sepsis. Our data demonstrated that the concentration of presepsin is specifically increased during sepsis and is directly proportional to the degree of sepsis. Regarding sensitivity and specificity of presepsin in the discrimination of sepsis patients from healthy controls, a high specificity but low sensitivity was reported by most of the studies.

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## Keywords

**AML, SIRS, Presepsin, CRP**

### 1. Introduction

Acute leukemia is a clonal hematopoietic tissue that originates from hematopoietic stem or progenitor cells. It is characterized by the proliferation of blast cells in the bone marrow replacing the normal hematopoietic cells [1] [2].

Severe Neutropenia is defined as an absolute neutrophil count (ANC) < 500 cells/cmm [3].

The risk of infection in the neutropenic patient is related to the virulence of the pathogen, the immunologic impairment of the host, and the disruption of skin and mucosal barriers [4].

Systemic inflammatory response syndrome (SIRS) is a systemic inflammatory response to a variety of insults (ischemia, inflammation, trauma). The response is manifested by two or more of the following conditions: temperature > 38°C or <36°C, heart rate > 90 beats per minute, respiratory rate > 20 breaths per minute or PaCO<sub>2</sub> < 32 mmHg and white blood cell count > 14,000 cells/cmm or <4,000 cells/cmm [5] [6]. Sepsis is a SIRS in the presence of a confirmed or suspected infection. Severe sepsis is sepsis associated with organ dysfunction, hypoperfusion or hypotension. Septic shock is sepsis induced hypotension despite adequate fluid resuscitation. Presepsin; the soluble CD14 subtype is a novel soluble CD14 molecule that is useful for diagnosing sepsis [7]. CD14 is a glycosyl phosphatidyl inositol anchor type bone marrow glycoprotein. CD14 is an important cell surface receptor that binds lipopolysaccharide [8]. It is expressed by cells of the myeloid lineage, B cells, liver parenchymal cells, gingival fibroblasts and microglial cells [9]-[13]. It plays an important role in modulating the immune response to endotoxin *in vitro* and *vivo* [14]-[17]. sCD14 ± LPS complexes can activate cells which do not themselves express CD14 as endothelial cells leading to release of proinflammatory mediators. In addition, sCD14 may act as a shuttle molecule like LBP (lipopolysaccharide binding protein) to transfer LPS to HDL (high density lipoprotein), thus neutralizing its toxic effects [18].

Presepsin is superior to other humoral factors in terms of its diagnostic power for sepsis [19] [20]. Measuring presepsin is also useful for evaluating the efficacy of treatment [21]-[23]. Significant correlations have been found between presepsin values and both acute physiology and chronic health evaluation II score (APACHE II score) and sequential organ failure assessment score (SOFA score). The insult of sepsis also seems capable of being inferred by making sequential observations. CRP and IL6 increase 1 - 2 days later and a slight time lapse develops between their rises and the changes in APACHE II.

The aim of the study was to evaluate the usefulness of presepsin as a diagnostic marker of sepsis in acute leukemia.

### 2. Subjects and Methods

The current study was carried out on 40 adult patients with acute myeloid leukemia (AML) after receiving chemotherapy. All patients were presented to the hematology department of Alexandria Main University Hospital during the period between July 2012 and March 2013.

The criteria used to include patients were the manifestations of sepsis in AML patients receiving chemotherapy. Patients with diabetes, chronic heart failure, HIV, TB, chronic inflammatory disease (Rheumatoid arthritis or systemic lupus erythematosus), on dialysis and surgical invasive procedures were excluded.

For normal control, 10 clinically and hematologically normal individuals of matched age and sex were included in the study to measure the level of presepsin. A written informed consent was obtained from all subjects before enrollment in the study.

#### 2.1. All Patients in the Present Study Were Subjected to the Following

- 1) Full history taking and complete clinical examination.
- 2) Complete blood count: performed on 3 part differential automated cell counter Sysmex KX-21N (Sysmex, Kobe, Japan) [24].
- 3) ALT, AST, BUN, Serum creatinine, and uric acid: performed using DADE BEHRING Dimension RxL

- clinical chemistry auto-analyzer [25] [26].
- 4) Bone marrow aspirate: Using Klima needle from the sternum or iliac spine [27].
  - 5) Immunophenotyping by flowcytometry for the diagnosis of AML [28]:
    - Primary panel: CD2, CD7, CD10, CD13, CD14, CD33, CD34, CD45, CD19 and HLA-DR;
    - Secondary panel: cyt CD22, cyt IgM, cyt-MPO.
  - 6) Measurement of the level of C-reactive protein (CRP) [29].
  - 7) Measurement of presepsin:
    - Principle: It is based on a non-competitive chemiluminescent enzyme immunoassay (CLEIA) combined with MAGTRATION technology. The presepsin binds to (ALP) labelled polyclonal Abs and monoclonal Abs coated magnetic particles.

## 2.2. Measurement Method

- 1) 100 µl whole blood were dispensed into the wells of the reagent cartridge.
- 2) To 25 µl of the specimen, 25 µl dilution solution, 50 µl magnetic latex reagent & 50 µl labelled Ab reagent were added and allowed to react at 37°C for 5 min. Then washing was done three times with the wash solution provided.
- 3) 100 µl luminescent substrates were added. The luminescence intensity generated was related to presepsin concentration in the sample.
- 4) The presepsin concentration was measured by comparison with the amount of luminescence of a calibration agent (CAL-1 & CAL-2) that has been subjected to the same procedure as the sample.
- 5) The steps from (2) to (4) were automatically processed with an immunoassay analyzer (PATHFAST: Mitsubishi Chemical Medicine Corporation, Japan) [30].

## 2.3. Statistical Analysis

- The data were collected and entered into the personal computer. Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 20) software.
- The statistical tests used were as follow: Arithmetic mean, standard deviation, for categorized parameters Chi square test was used. While for two groups ANOVA-test was used for parametric data.
- ROC curve was done to determine the best cut off value of the marker to determine the highest value of sensitivity and specificity on this point.
- The level of significance was 0.05.

## 3. Results

This study was conducted on 50 individuals divided into 2 groups: Group I included 40 adult AML patients who fulfilled at least two of the diagnostic criteria for SIRS and Group II were 10 healthy adult persons as a control group.

Group I included 27 male patients (67.5%) and 13 female patients (32.5%) whose ages ranged from 16 - 67 years with a mean  $\pm$  SD 44.82  $\pm$  33.4 years. Group II included 5 males and 5 females whose ages ranged from 22 - 52 years with a mean  $\pm$  SD 33.4  $\pm$  10.98 years.

In Group I there were 11 patients (27.5%) having SIRS, 8 (20%) having sepsis, 9 (22.5%) having severe sepsis and 12 (30%) having septic shock.

In the study we noticed that the presepsin levels in the 10 control healthy subjects were <210 pg/ml while that of CRP levels were <5 mg/l. In the patients, the range was between 73.3 - 4550 pg/ml for the presepsin while that of the CRP was between 12.0 - 809 mg/l. These data indicate that presepsin levels as well as the CRP levels were significantly higher in the patients than the control group ( $P = 0.017$ ,  $P = 0.004$  respectively) (See **Table 1**).

In normal subjects presepsin level ranged from 73 - 209 pg/ml with a mean  $\pm$  SD 132.5  $\pm$  50.6, in SIRS patients presepsin level range from 73.3 - 254 pg/ml with a mean  $\pm$  SD 157.4  $\pm$  66.5, in sepsis patients it was from 269 - 536 pg/ml with a mean  $\pm$  SD 440  $\pm$  106.4, in severe sepsis patients the level ranged from 609 - 773 pg/ml with a mean  $\pm$  SD 693.3  $\pm$  58.9 and in septic shock patients the level ranged from 861 - 4550 pg/ml with a mean  $\pm$  SD 1882.3  $\pm$  1076.4. Our results showed that the level of presepsin has significantly increased in relation to the severity of sepsis with  $P$  value 0.0001 (See **Table 2**).

**Table 1.** Comparison between patients and controls regarding presepsin and CRP levels.

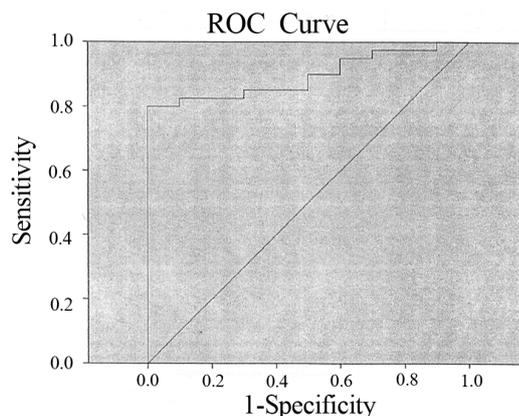
	Patients	Control	Test P
<b>Presepsin (pg/ml)</b>			
Range	73.3 - 4550.0	73.0 - 209.0	6.107
Mean	852.0	132.5	0.017*
SD	913.3	50.6	
<b>CRP (mg/l)</b>			
Range	12.0 - 809.0	0.7 - 4.2	9.022
Mean	165.0	2.3	0.004*
SD	170.0	1.2	

\*P < 0.05 is statistically significant.

**Table 2.** The relation between the level of presepsin and the type of sepsis.

Presepsin (pg/ml)	Mean	SD	Min	Max	F	Sig
Normal	132.5	50.6	73.0	209.0	20.701	0.0001*
SIRS	157.4	66.5	73.3	254.0		
Sepsis	440.0	106.4	269.0	536.0		
Severe sepsis	693.3	58.9	609.0	773.0		
Septic shock	1882.3	1076.4	861.0	4550.0		

\*P < 0.05 is statistically significant.



Area	Cut off value	Sensitivity	Specificity
0.895	198.00	82.5	90%

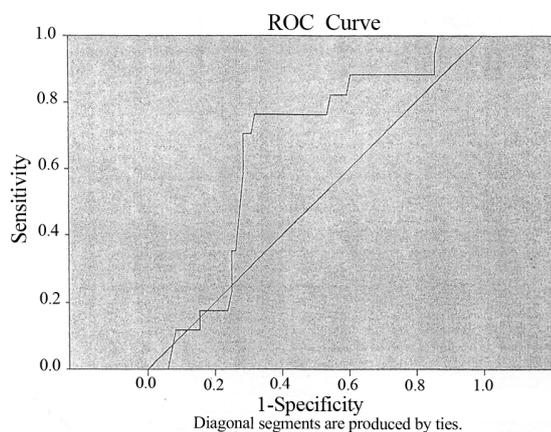
**Figure 1.** ROC curve to determine the cut off value of presepsin.

**Figure 1** the roc curve to determine the cut off value of presepsin in detection of patients and control.

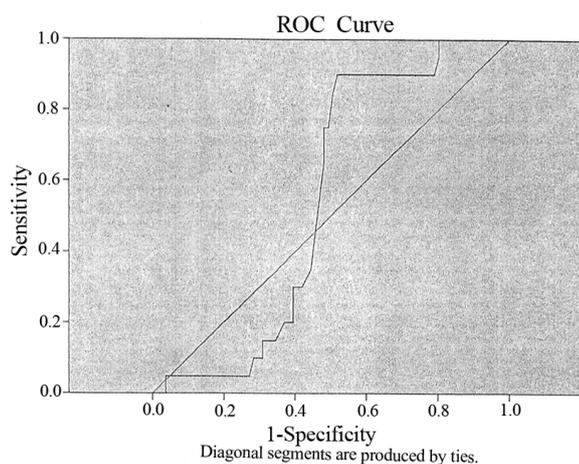
The area under the curve (AUC) calculated from the ROC curve was 0.895 for presepsin and 0.707 for CRP. When the cut off value of presepsin was 198 pg/ml, its clinical sensitivity was 82.5% and its clinical specificity was 90% suggesting its usefulness as a diagnostic marker of sepsis. While for CRP, when the cut off value was 96 mg/l its clinical sensitivity was 90% and its clinical specificity was 61%. Thus we found that presepsin was more specific than CRP in the detection of sepsis.

**Figure 2** and **Figure 3** the ROC curves for the sepsis diagnostic markers (presepsin and CRP), in the SIRS, sepsis, severe sepsis and the septic shock groups.

When the cut of value of presepsin was 198 pg/ml (SIRS), its clinical sensitivity was 95% and its clinical specificity was 55%, when the cut of value of presepsin was 272 pg/ml (sepsis), its clinical sensitivity was 90% and



**Figure 2.** ROC curve to detect the level of presepsin in each type of sepsis.



**Figure 3.** ROC curve to detect the level of CRP in each type of sepsis.

its clinical specificity was 70%, when the cut of value of presepsin was 529 pg/ml (severe sepsis) its clinical sensitivity was 90% and its clinical specificity was 84%, and when the cut of value of presepsin was 1043 pg/ml (septic shock), its clinical sensitivity was 85% and its clinical specificity was 100%.

When the cut off value of CRP was 85 mg/l (SIRS), its clinical sensitivity was 51% and its clinical specificity was 66.7%, when the cut off value of CRP was 123.5 mg/l (sepsis), its clinical sensitivity was 62% and its clinical specificity was 46.2%. When the cut off value of CRP was 147.1 mg/l (severe sepsis), its clinical sensitivity was 42% and its clinical specificity was 15.4%.

Better results were obtained with presepsin; so we can conclude that presepsin can be used as an indicator to the degree of severity of sepsis in comparison with CRP.

#### 4. Discussion

The severity of sepsis varies considerably and early diagnosis is important to perform the specific treatment early. It is difficult to diagnose infection on the basis of the clinical findings alone as patients with non-infectious inflammation sometimes exhibit similar signs and symptoms.

C-reactive protein (CRP) has been used for many years as a biomarker of infection and inflammation although it has low specificity, it is commonly used to screen for early onset sepsis because its sensitivity is considered to be very high [31] [32].

Procalcitonin (PCT) has been proposed as a more specific [33] and has better prognostic marker than CRP, although its value has also been challenged [34].

sCD14-ST (presepsin) is a new important marker for diagnosis and prognosis of sepsis. Its level increases in the first six hours after the onset of sepsis [35].

The aim of our study was to test the potential of presepsin as an early biochemical marker to detect sepsis. In our data, a significant correlation was found between presepsin level and CRP ( $P = 0.001$ ), similarly E. Spanuth, H. Ebelt *et al.* [30] conducted a study on 146 patients presenting with sepsis to assess the diagnostic and prognostic value of presepsin in emergency patients with early sepsis and found a significant correlation between presepsin and other markers including CRP ( $P < 0.01$ ).

We measured presepsin levels in healthy individuals, SIRS, sepsis, severe sepsis and septic shock patients and its level was  $132.5 \pm 50.6$  pg/ml,  $157.4 \pm 66.5$  pg/ml,  $440 \pm 106.4$  pg/ml,  $693.3 \pm 58.9$  pg/ml and  $1882.3 \pm 1076.4$  pg/ml respectively. Although we found a small elevation of presepsin in the SIRS group, the levels of presepsin in patients (sepsis, severe sepsis and septic shock) were significantly higher than those in patients with SIRS or the healthy control subjects ( $P = 0.0001$ ). These data demonstrated that the concentration of presepsin is specifically increased during sepsis and is directly proportional to the degree of sepsis. Our results were in agreement with that of Shigeatsu Endo *et al.* [36], who examined the significance of presepsin as a diagnostic marker of sepsis in a study including 46 sepsis patients. He found that presepsin values of the sepsis patients were found to be significantly higher than in the healthy subjects and in the SIRS who did not have source of infection ( $P < 0.0001$ ). Spanuth *et al.* [30] in his study found that presepsin values differed significantly between patients with sepsis and severe sepsis or septic shock ( $P < 0.0001$ ).

In agreement with our study Tatsuyori Shozushima *et al.* [37] found that the patients with local infection or sepsis had significantly higher presepsin levels than the patients who did not have infection as a complication. In addition, the presepsin levels in SIRS that was not complicated by infection were significantly lower than in sepsis ( $P < 0.05$ ).

Regarding sensitivity and specificity of presepsin in the discrimination of sepsis patients from healthy controls, a high specificity but low sensitivity was reported by most of the studies.

These findings were confirmed by receiver operator characteristics (ROC) curves plotted for presepsin and CRP.

The area under the curve for presepsin and CRP were 0.895 and 0.707 respectively.

In our study, presepsin had a sensitivity (82.5%), lower than that of CRP (90%) and a specificity (90%) higher than that of CRP (61%) at a cut-off value 198 pg/ml for presepsin and 96 mg/l for CRP.

Similar results were obtained by T. Nishida *et al.* [38] who found that presepsin was able to discriminate between patients with and without sepsis with a sensitivity and specificity of 92.9%, and 83.3% respectively at a cut off value 647 pg/ml (AUC: 0.92 for presepsin and 0.83 for CRP).

Regarding sensitivity and specificity of presepsin in different types of sepsis, in our study, presepsin had a sensitivity (95%) in SIRS, 90% in sepsis and severe sepsis which was higher than its sensitivity in septic shock (85%), and a specificity (55%) in SIRS, (70%) in sepsis, (84%) in severe sepsis and (100%) in septic shock. This means that the more the degree of severity of sepsis, the more is the level of presepsin and the more is its specificity in the diagnosis of sepsis. In our study, the results of presepsin were significantly higher than those of CRP, which had a lower sensitivity (51% in SIRS, 62% in sepsis, 42% in severe sepsis and 44% in septic shock) and a lower specificity (66.7% in SIRS, 46.2% in sepsis, 30.8% in severe sepsis and 15.4% in septic shock). In general we found a higher specificity and sensitivity for presepsin than for CRP in different types of sepsis.

Similar results were reported in the study conducted by Tatsuyoni Shozushima *et al.* [37] who found that presepsin had a specificity of 81% at high level compared to 78.5% at low level, but its sensitivity was more or less the same in different levels (80.3% and 80.1%).

T. Nishida *et al.* [38] concluded that the ROC analysis at a cut-off value of 647 pg/ml, presepsin may be able to discriminate between patients with and without sepsis with a sensitivity and specificity of 92.9% and 83.3% respectively. And the presepsin values were significantly higher in the patients with the more severe septic condition.

## 5. Conclusion

As a marker of sepsis, sCD14-ST (presepsin) is a good discriminator between healthy and septic conditions with evidence of infection. It is expected to be widely used in clinical settings near future.

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