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Diagnosis of Sepsis among Adult Patients with AML Using Scd14

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ABSTRACT

Background: Millions of dead cases are reported every year due to sepsis. Sepsis has been estimated in 1-2 % of hospitalized patients especially leukemic patients. The diagnosis of sepsis remains a clinical challenge. Many studies suggest that presepsin plays a role in diagnosing sepsis, but the results remain controversial.

Objective: To evaluate the potential of presepsin as an early biochemical marker of sepsis in adult acute leukemic patients and to assess the correlation between severity of sepsis and level of presepsin. Comparing between presepsin & CRP in diagnosing bacterial infection in critically ill adult leukemic patients.

Patients and Methods: This study was conducted on 24 patients having acute leukemia after receiving chemotherapy and 24 controls at Medical Oncology and Clinical Pathology Departments, Zagazig University Hospitals during the period from June 2018 to August 2019.

Results: There was statistically significant difference between patients and control regarding presepsin levels. The highest levels of presepsin were in patients with septic shock followed by severe sepsis, sepsis, SIRS then control group. There was statistically significant difference between types of sepsis and presepsin (P value = 0.000). There was statistically significant positive correlation between CRP and presepsin (r = 0.658). AT cut off value of 440 the clinical sensitivity of presepsin was 82.5% and its clinical specificity was 90%, AUC was 0.89. On comparing these results with the normal cut off value of CRP level (6), the clinical sensitivity and specificity were 90% & 61% respectively and AUC was 0.70.

Conclusion: Presepsin can be used as a better indicator to the degree of severity of sepsis than CRP in septic adult leukemic patients.

Keywords: Presepsin, Systemic inflammatory response syndrome (SIRS).

INTRODUCTION

Sepsis is the leading cause of death in critically ill patients and requires early goal-directed management to reduce its high burden of mortality and morbidity [(1)]. The evaluation of sepsis severity and outcome is complicated by the lack of gold standard for the diagnosis of sepsis and the variability in its presentation [(2)]. Many scores and biomarkers had been studied in this perspective, with Acute Physiology and Chronic Health Evaluation II (APACHE II) score being traditionally used for this clinical situation [(3)].

Being immunocompromised cancer patients carries the risk of infection with resistant organisms especially those receiving high dose chemotherapy. There is a high risk of neutropenic fever, so the patients′ susceptibility to be infected with resistant organisms increases [(4)]. Survival outcome after infections can be influenced by the capacity of the host immune system in identifying the microbial pathogens and triggering an immediate and effective response [(5)].

The activation of innate immunity responses needs the recognition of the pathogens by different receptors at the cellular surface of immune effector cells particularly monocytes/macrophages [(6)]. Guidelines emphasize that early diagnosis and timely administration of antimicrobial therapy are crucial in reducing morbidity and mortality in sepsis patients. However, no single clinical or biological marker is strictly indicative of sepsis has been adopted totally [(7)].

Research in this direction has paved the way for identification of CD14, which is a glycoprotein expressed on the membrane surface of monocytes and macrophages (Mcd14) and serves as a high-affinity receptor for complexes of lipopolysaccharides (LPSs), a compound from the outer cell wall of Gram-negative bacteria, and LPS-binding proteins (LPB) [(8)]. Presepsin (sCD14-ST) is a soluble N-terminal fragment of the cluster of differentiation (CD) marker protein CD14, which is released into the circulation during monocyte activation upon the recognition of lipopolysaccharide (LPS) from infectious agents [(9)].

Plasma levels of sCD14-ST specifically increase during sepsis and less intensively during SIRS with magnitude correlated to phagocytosis process and to the cleavage with lysosomal enzymes from bacteria and microorganisms [(10)].

Evaluation of the prognostic value of presepsin as an early marker to detect sepsis in adult acute leukemic patients and to assess the correlation between severity of sepsis and level of presepsin. Moreover to determine which marker, presepsin or CRP, is superior in the diagnosis of bacterial infection in critically ill adult leukemic patients.

PATIENTS AND METHODS

This study was held in the Clinical Pathology and Medical Oncology Departments, Faculty of

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Medicine, Zagazig University Hospitals during the period from June 2018 to August 2019.

Sepsis was identified by the presence of SIRS according to the SCCM/ ESICM/ ACCP/ATS/SIS. International Sepsis Definitions Conference [(11)] included two or more of the following signs: (a) temperature of > 38°C or < than 36°C, (b) pulse rate of > than 90 beats/min, (c) respiratory rate of > 20 breaths/min or hyperventilation with a partial pressure of arterial carbon dioxide of < than 32 mmHg, or (d) white blood cell count of > 12 000/mm3 or < than 4000/mm3, or > 10% immature cells in addition to the presence of infection detected by two experts according to the clinical and microbiological criteria of the CDC definitions [(12)].

Routine laboratory investigations:

1. All patients were subjected to thorough history taking, full clinical examination. APACHE II score was performed on patient admission.
2. Complete blood count, bone marrow (BM) aspiration for morphology and cytochemistry.
3. Liver and kidney functions tests, uric acid level, LDH and serum electrolytes.
4. CSF examination was also done in addition to cytogenetics.
5. At least two blood cultures from different sites were collected from each patient on admission. The microorganism's growth on blood cultures were screened by the BacT/ALERT 3D Microbial Detection System (bioMerieux, Marcy l'Etoile, France) with aerobic (BacT/ALERT FA) and anaerobic (BacT/ALERT FN) media.
6. Cultures from any suspected site of infection as wound, sputum, pus or urine were taken on admission.
7. The positive blood culture bottles were confirmed by gram stain.
8. Direct bacterial identification for positive blood cultures using Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) Vitek MS (bioMerieux, Marcy l'Etoile, France), in addition to appropriate antibiotic detection by Vitek were sone.

Specific laboratory investigation:

- Human Presepsin assay by Human PSPN ELISA Kit - SunRed Biotechnology Company. Presepsin level was expressed as pg/ml and its normal value is 60–360 pg/ml.
- Serum quantitative CRP was measured using automated clinical chemistry analyzer Cobas Integra 400 plus (Roche Diagnostics, Deutschland). Normal value is up to 6 mg/l.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value ≤ 0.05 was considered significant.

RESULTS

Forty-eight subjects were included in this study, they were classified into two groups; Control group 24 individuals [13 males (54.2%) & 11 females (45.8%)], their ages ranged from 18 - 56 years with a median age of 46.3 years. Patient group; 24 individuals [17 males (70.8%) & 7 females (29.2%)] with a median age of 34 years ranging from 20 - 57.

Table (1): Distribution of patients' group regarding degree of severity of sepsis

Degree of severity of sepsis	Patients (n=24)	
	No.	%
SIRS	8	33.3
Sepsis	7	29.2
severe sepsis	6	25
septic shock	3	12.5
Total	24	100

Regarding degree of severity of sepsis, Table (1) showed that in patients' group there were 33.3% SIRS, 29.2% sepsis, 25% severe sepsis and 12.5% septic shock.

Table (2): Comparison between control and patients in regard to CRP and Presepsin

		Control (n=24)	Patients (n=24)	T test	P. Value
CRP (mg/L)	Mean ± SD	1.69 ± 0.04	97.36 ± 7.55	6.69	0.001
Presepsin Pg/dl	Mean ± SD	286 ± 15	1310 ± 200	4.14	0.001

Table (2) showed comparison between the studied groups regarding CRP and Presepsin with statistically significant difference regarding both tests (P =0.000).

Table (3): Correlation between Presepsin and CRP

Correlation	Person's correlation	
	R	P
CRP* Presepsin	0.658	0.001

There was statistically significant positive correlation between CRP and Presepsin (r=0.658, P value=0.000) as shown in table (3).

Table (4): Correlation between degree of severity of sepsis and presepsin

Correlation	Pearson's correlation	
	R	P
Degree of severity of sepsis * Presepsin	0.87	0.001

There was statistically significant positive correlation between degree of severity of sepsis and presepsin (r= 0.87, P value = 0.000).

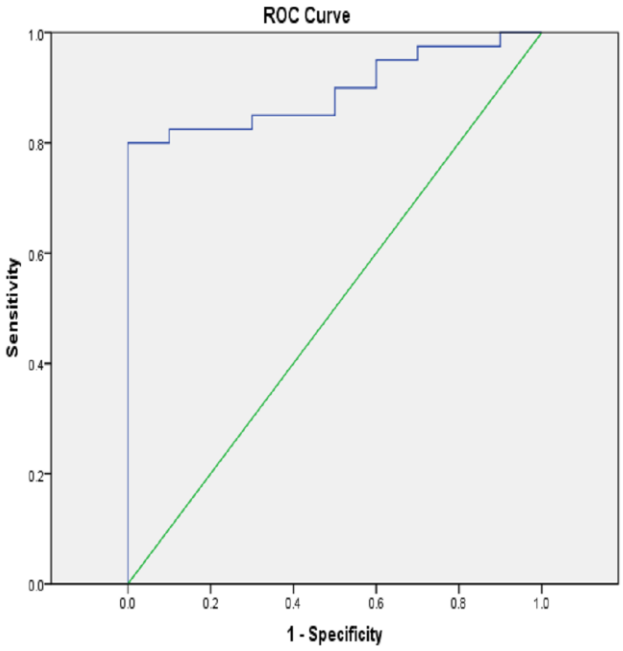

Figure (1): ROC curve to determine the cut off value of presepsin in both patients & control groups

Area Under the Curve (AUC)				
Test Result Variable (s) : Presepsin(pg/ml)				
Area	Asymptotic Sig[b]	Cut off value	Sensitivity	Specificity
0.895	0.000	440	82.5	90.0

The cut off value for normal presepsin level was 440, where its clinical sensitivity was 82.5% and its clinical specificity was 90%. Area under the Curve (AUC) was 0.89.

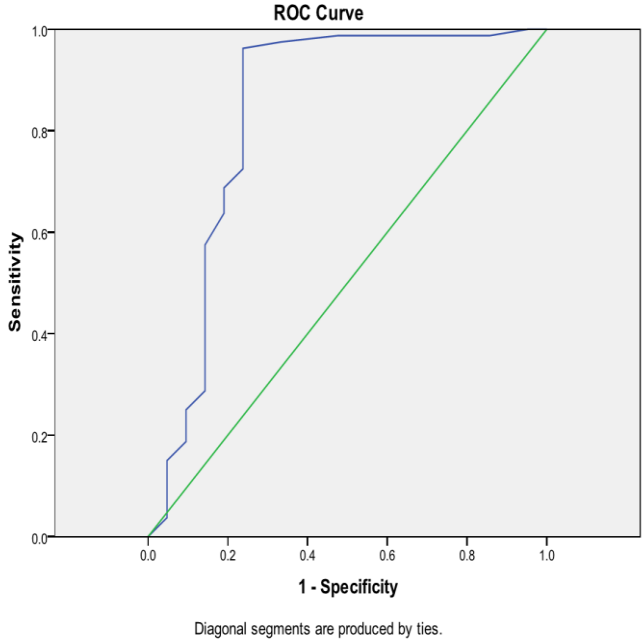

Figure (2): ROC curve to determine the cut off value of CRP in both patients and control

Area Under the Curve				
Test Result Variable(s):CRP(pg/ml)				
Area	Asymptotic Sig.[b]	Cut off value	Sensitivity	Specificity
0.707	0.053	6	90.0	61.0

The cut off value of normal CRP level was 6, with clinical sensitivity of 90% and clinical specificity of 61%. Area under the Curve (AUC) was 0.70

Table (5): The relation between the level of presepsin and the type of sepsis

	Presepsin				F. test	P. value
	Minimum	Maximum	Mean	SD		
Control	100	480	286	115	219.1	0.001
SIRS	180	510	387	111		
Sepsis	730	1150	978	188		
Severe sepsis	1200	1900	1530	293		
Septic shock	3250	4600	4110	752		

The highest level of presepsin was in patients having septic shock and the least was in patients having SIRS. There was no statistically significant difference between control and SIRS group regarding presepsin (P value = 0.277), but there was statistically significant difference between control and other types of sepsis. There was statistically significant difference between the different degrees of sepsis and presepsin (P value = 0.000).

DISCUSSION

Acute leukemia is a clonal hematopoietic tissue characterized by the proliferation of blast cells in the

bone marrow replacing the normal hematopoietic cells [13].

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 [14].

Recent guidelines emphasize that early diagnosis and timely administration of antimicrobial therapy are mandatory in reducing morbidity and mortality in sepsis patients. However, no single clinical or biological marker, which is indicated in sepsis, has been adopted without exceptions [15]. C-reactive protein (CRP) has been used for many years as a biomarker of infection and inflammation. It is one of the acute phase reactants. In spite of its low specificity, which is the primary drawback as being a biomarker of sepsis in adults, it is commonly used for screening as its sensitivity is very high [16].

Presepsin is a novel soluble CD14 molecule, a glycosyl phosphatidyl inositol anchor type bone marrow glycoprotein. CD14 is an important cell surface receptor that binds lipopolysaccharides [17]. The change in its concentration occurred on a much faster time scale than those observed for PCT or CRP [18]. Regarding presepsin mean value in the current study, it was significantly higher among cases than controls (1310 vs 286 respectively) (p =0.000), which goes hand in hand with **Okamura and Yokoi** [19] who investigated 20 sepsis patients and 20 healthy controls and found that the sepsis group had a significantly higher level of presepsin than the healthy group ($p < 0.0001$). In addition, **Ulla *et al.*** [20] reported an elevated concentration of presepsin in septic patients compared to control patients and correlated the values to the severity of disease. Moreover, the level of presepsin typically increases within 2 h and reaches the peak in 3 h after infection [17]. By using the chemiluminescence enzyme immunoassay as detecting tool, the result can be available in 1.5h [18]. The above evidence indicates that presepsin might be a better biomarker for sepsis during the early stage of sepsis than in later stages.

This study showed that, there was statistically significant positive correlation between CRP and presepsin (r=0.658, P value= 0.000). This finding comes in agreement with a study done by **Spanuth *et al.*** [21], who found a significant positive correlation between presepsin and CRP ($P < 0.01$).

Regarding sensitivity and specificity of presepsin in discriminating the sepsis patients from healthy controls, a high specificity, but low sensitivity was reported by most of the studies. In our study, presepsin had a sensitivity lower than that of CRP (82.5% vs 90% respectively), while higher specificity (90% vs 61% respectively). Similar results were reported by **Agilli *et al.*** [22] where presepsin was compared with CRP, IL-6 and PCT. The results showed that presepsin was the best with a sensitivity of 80.1% and a specificity of 81% followed by CRP, IL-6, and PCT. **Kondo *et al.*** [15] showed near results for presepsin sensitivity 84%, but different specificity 73%. They compared their results with PCT (80% & 75%) respectively. **Shozushima *et al.*** [9] found that the concentration of presepsin was 333.5 ± 130.6 pg/mL in the SIRS group & and 1992.9 ± 1509.2 pg/mL in the severe sepsis group. **Spanuth *et al.*** [21] concluded similar results, moreover the concentration of presepsin was positively correlated with APACHE II score and SOFA score.

When ROC curve was used to evaluate the value of the four markers in the diagnosis of sepsis, the AUC of presepsin was 0.845, PCT was 0.652, IL-6 was 0.672, and CRP was 0.815. On comparing these results with ours we found that the AUC of presepsin was 0.895 and that of CRP was 0.707. **Kondo *et al.*** [15] reported 0.84 for procalcitonin and 0.87 for presepsin. In a study done by **Mahmoud *et al.*** [23], the area under the curve (AUC) for presepsin survival prediction was the highest (0.918) compared to PCT (0.84), CRP (0.888), and APACHE II score (0.695), with cutoff value of 1262 pg/ml to be 92.3% sensitive and 81.3% specific for predicting mortality in patients with sepsis. Our results agree with that of **Shigeatsu *et al.*** [24] and **Spanuth *et al.*** [21], who evaluated the significance of presepsin as a diagnostic marker of sepsis. Values of the sepsis patients were found to be significantly higher than in the healthy subjects or in the SIRS patients who did not have infection ($p < 0.0001$). In agreement with our study, **Shozushima *et al.*** [9] conducted a study on 22 normal subjects, 28 with local infection, 41 with SIRS, 87with sepsis, and 14 with severe sepsis using a chemiluminescent enzyme immunoassay. They 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 ($p < 0.05$). In a study conducted by **Nishida *et al.*** [25] they suggested that presepsin values can serve as a parameter that closely reflects the pathology, not only a very useful new biomarker for diagnosis of sepsis, but also useful for monitoring the severity of the disease in the near future.

In summary, different studies have showed that presepsin has a higher sensitivity and specificity in the diagnosis of sepsis as a new biomarker and is a predictor for the prognosis of sepsis. More importantly, presepsin seems to play a main role as a supplemental method in the early diagnosis of sepsis [26].

CONCLUSION

Presepsin can be used as a better indicator to the degree of severity of sepsis than CRP in septic adult leukemic patients.

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