Original Article

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Presepsin (Scd14) as a Marker of Serious Bacterial Infections in Chemotherapy Induced Severe Neutropenia

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Abstract

Objective: Timely detection of serious bacterial infections or prediction of sepsis and death is of paramount importance in neutropenic patients especially in oncology settings. The aim of this study was to determine a rapid and secure predictor of sepsis in severe neutropenic cancer children.

Methods: In addition to blood culture, we have evaluated serum soluble CD14 on this role and measured it in 39 neutropenic episodes in Mahak pediatric oncology center from September 2012 to January 2013. Fifteen episodes had positive bacterial cultures and 18 had fever. The mean sCD14 values were compared in the presence or absence of fever, positive blood culture and other clinical conditions. Also, mean levels compared in different white cell counts and different four combination settings of fever and blood culture.

Findings: It was statistically higher in febrile episodes, in the presence of oral mucositis, indwelling catheter infection, otitis media, and post toxic epidermal necrolysis sepsis and in instances of death within 15 days. Leukocyte count did not affect sCD14 level and in combinations of fever and blood culture, mean sCD14 values were ranked as follow: febrile culture negatives, febrile culture positives, afebrile culture positives and afebrile culture negatives.

Conclusion: Although sCD14 was not sensitive in detection of bacteremia, in the absence of clinically detectable source of infection, it was significantly higher in culture positives.

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Key Words: Soluble CD14; Cancer; Neutropenia; Infection; Pediatrics

Introduction

Infection is one of the most important causes of death in the field of pediatric oncology. Immuno-suppression, neutropenia and destruction of anatomic barriers will prone cancer patients to infections. Rapid diagnostic approach is the mainstay of sepsis prevention, but proving of microbiologic evidences with blood culture as a gold standard for its diagnosis is time-consuming and has remarkable false negative results. Finding a rapid and sensitive marker to detect infections, or predict a critical course in a febrile neutropenic patient would be lifesaving.

Principally, immunity against bacterial endotoxins is mediated by either membranous or soluble CD14, which is a human monocyte differentiation antigen. In a more declared pathway, lipopolysaccharide (LPS) binds to membranous CD14 on myeloid cells; this binding stimulates associated signal transducer, toll-like receptor-4 (TLR4) and TLR4 mediates microbial

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endocytosis. Soluble CD14 (sCD14 or presepsin) circulates as a soluble plasma protein and is required for activation of endothelial and epithelial cells by LPS[1-4]. In addition to granulocytes and monocyte-macrophage cell rows, hepatocytes in the liver are important sources of sCD14 production[5]. Immunological role of sCD14 has been investigated in the endothelium and epithelial barrier of buccal mucosa, proximal convoluted tubules and intestine[6-11]. The aim of this study was to investigate the utility of sCD14 level to detect serious bacterial infections in chemotherapy induced neutropenia. Despite studies which have introduced sCD14 as a valuable marker in detection of severe sepsis in neonates and other age groups[12-14], there isn't any study on this biomarker in neutropenic patients especially in oncology settings to predict sepsis (unlike studies on other biomarkers such as C-reactive protein (CRP), procalcitonin (PCT) and proinflammatory cytokines)[15-20]. Some studies have suggested that sCD14 is even more valuable than other investigated biomarkers to detect serious bacterial infections[21-22].

Subjects and Methods

Severely neutropenic patients with hematologic or solid malignancies whose age was less than 19 years, randomly entered this prospective study after written informed consent obtained from their parents or legal guardian in MAHAK highly specialized cancer hospital & research center, Tehran, Iran. In our study, we supposed severe neutropenia to be present when absolute neutrophil count was equal to or less than 500 cells/mm^3 and fever, axillary temperature more than 37.3°C, persisted for more than 2 hours (oral and rectal temperature were not allowed). Patients who met the criteria were admitted and blood culture was obtained in the first day of admission. Their fever had started in the last 48 hours. The blood cultures were obtained under aseptic conditions; the site of venipuncture was cleaned with 70% isopropyl alcohol swabs. 5 ml of blood was taken and poured into thioglycollate broth bottles. The cultures were monitored for 7 days. Positive cases were sub-cultured on agar plates to isolate the pathogenic organisms. The isolated organisms were identified by standard methods and antibiotic susceptibility was assessed by disk diffusion method. All mixed culture-positive cases were supposed as contamination and excluded from the study. We allowed double neutropenic encounter from the same patient enter the primary sample if it had occurred more than 5 days from the first episode. For each severe neutropenic episode, one blood culture and one serum sample to be frozen at -20°C to measure serum soluble CD14, were taken. Finally, samples from 78 episodes of severe neutropenia observed in 39 patients were collected during a period of 5 months from September 2012 to January 2013. Thirty episodes had positive blood culture and 48 episodes were culture negative. There were also seven episodes of mixed culture positive (3 samples with mixed gram positive and negative, 3 samples with mixed gram positive, one sample with mixed gram negative) which are excluded. Soluble CD14 was measured in all positive and negative blood culture episodes. We stratified culture positive and negative groups into febrile and afebrile strata (Fig 1). Patients' mortality was assessed during the next 60 days of sampling.

Enzyme linked immunoassay (ELISA) research kit (CUSABIO Co, Wuhan, Hubei/China) which had been pre-coated by antibody specific for sCD14, was used to measure serum sCD14. Two milliliters blood sample was taken from patients and held in a serum separator tube at room temperature for 2 hours to clot before centrifugation. After centrifugation for 15 minutes at 1000×g (units of gravity) separated serum was removed and stored at a temperature lower than =20°C. Then standards and sample tubes were pipetted into the wells. By removing any unbound substances,

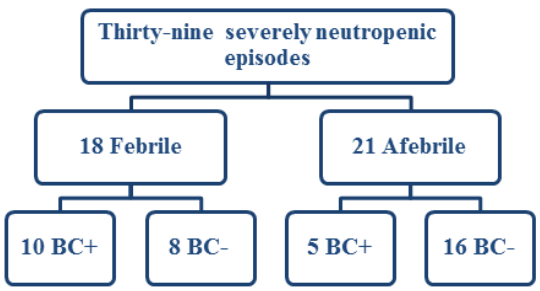

Fig. 1: Diagram shows sampling method and stratification of samples.
BC+: positive blood culture; BC-: negative blood culture.

biotin-conjugated antibody specific for sCD14, avidin conjugated horseradish peroxidase (HRP), avidin-enzyme reagent and tetramethylbenzidine (TMB) substrates were added respectively and washed out. In proportion to the amount of sCD14 in each well, color change was measured by microplate reader (ASYS Hitech Expert 96, Eugendorf, Austria) capable to measure absorbance at 450 nm, with the correction wavelength set at 540 or 570 nm. The normal range of sCD14 for this kit was 0.156-10 ng/ml and the lowest detectable level was 0.039 ng/ml. Data was analyzed by SPSS 18 software (IBM Corporation, New York, USA, 2009), and evaluated with descriptive statistical methods and comparisons of the mean values of sCD14 in different categories were done by one-way ANOVA or independent samples t-test. Receiver-operating characteristic (ROC) curves were calculated to evaluate the sensitivity and specificity of sCD14 to detect bacteremia.

Findings

We evaluated 71 neutropenic episodes occurred in 39 patients. Acute (lymphoblastic and myelogenous) leukemia was the most common malignancy leading to severe neutropenic episodes (56.4%), followed by non-Hodgkin lymphoma. The demographic characteristics are summarized in Table 1. There was no source of inflammation in 35.9% of episodes (14 cases of 39 evaluated episodes). Inflammatory/infectious sources are listed in Table 2.

Some cases had two or more sites of inflammation. Gram-negative bacteria especially *pseudomonas* and *klebsiella* were the most common isolated bacteria (Table 3). The mean values of sCD14 in different subsets of fever, blood culture and leukocyte levels are shown in Fig 2, Table 4. Mean difference of sCD14 level between febrile and afebrile groups was 0.277 ng/ml (95% CI: 0.483-0.505 ng/ml). This difference was also not statistically significant between positive and negative blood culture groups (P<0.05). In the absence of other clinically detectable sources of inflammation, mean sCD14 level was significantly higher in blood culture positives (P< 0.05). The mean value of sCD14 was as low as -0.317 ng/ml in febrile blood culture positive episodes in contrast to febrile culture negatives (95% CI: -0.631 to -0.004), but in afebrile group, such a difference was not statistically significant.

Mean difference in four subsets of fever and blood culture combinations and in different WBC levels was analyzed, which showed a significant difference between mean sCD14 levels in subsets of fever and blood culture combinations (P< 0.05). By exclusion of mixed culture episodes this difference was more statistically reliable (P=0.01) but the randeking for mean sCD14 values changed as is obvious in Fig 2. Box-plot graphs are also shown in Fig 3. There was no statistically significant difference in sCD14 levels in different leukocyte groups (P<0.05).

Table 1: Demographic characteristics of the patients

Characteristic		No. of patients (%)
Age (years)		9 (1-19)
Sex	**Male/Female (percent)**	12/27 (30.8/69.2)
Diagnosis	**Acute lymphoblastic leukemia**	12 (30.8%)
	Acute myeloblastic leukemia	10 (25.6%)
	Non-Hodgkin Lymphoma	3 (7.7%)
	Osteosarcoma	3 (7.7%)
	Neuroblastoma	2 (5.1%)
	Rhabdomyosarcoma	2 (5.1%)
	Retinoblastoma	2 (5.1%)
	Ewing sarcoma	2 (5.1%)
	Hodgkin's Lymphoma	1 (2.6%)
	Wilms tumor	1 (2.6%)
	Ependymoma	1 (2.6%)
	Total	39 (100%)

Table 2: Sources of infection/inflammation and mean sCD14 in presence of each clinical condition

Infectious/Inflammatory sources	Different combinations of fever and blood culture					sCD14 Mean value (±SD), ng/ml
	Total	Febrile & BC +	Afebrile & BC +	Febrile & BC -	Afebrile & BC -	
No source	14	5	0	0	9	0.471 (0.266)
Oral ulcer/mucositis	8	4	0	3	1	0.761 (0.377)
Indwelling catheter infection	6	1	1	1	1	0.827 (0.359)
Pneumonia	6	0	1	4	1	0.647 (0.514)
Cellulitis	4	1	1	1	1	0.459 (0.408)
Gastroenteritis	3	0	0	2	1	0.798 (0.613)
Urinary tract infection	2	0	1	0	1	0.100 (0.000)
Otitis media	2	1	0	1	0	0.851 (0.685)
Sinusitis	1	0	0	1	0	0.100
Anal abscess	1	0	0	0	1	0.050
Mucormycosis	1	1	0	0	0	0.100
Toxic epidermal necrolysis	1	0	0	1	0	1.250
Anal ulcer	1	1	0	0	0	0.880
Hepatitis B	1	0	0	0	1	0.490

BC+: positive blood culture; BC-: negative blood culture; sCD14: soluble subset of cluster of differentiation antigen-14; SD: standard deviation.

Linear regression analysis did not show any linear relationship between leukocyte and sCD14 levels. The difference in mean values of sCD14 in the different inflammatory/infectious episodes compared by independent samples t-test delineated a significant rise in the presence of oral mucositis, culture positive indwelling catheter infection and otitis media in contrast to their absence (P<0.05). A significant rise in sCD14 was seen in one clinically septic blood culture negative patient, suspicious to toxic epidermal necrolysis (TEN). Two clinically suspicious to urinary tract infection patients who received antibiotic therapy, had mixed microbial growth, one of them also had a positive blood culture with *Escherichia coli*. The mean value of sCD14 in both of them was significantly low (P<0.05). During 60 days of observation, eight (20.5%) mortalities occurred in 39 neutropenic patients, five (12.8%) after 30 days and the remaining three (7%) during the first 15 days of sampling. The mean sCD14 values were significantly higher in patients who died during the first 15 days, but the difference was not high in five patients who died after 30 and 60 days (Fig 2).

There was no significant difference between the mean values of sCD14 in each bacterial species except for *pseudomonas*.

The mean values of sCD14 in these patients were significantly higher by 0.208 ng/ml (95% CI: 0.048-0.369 ng/ml). Most gram positive bacteria isolated from mixed growth were supposed as contamination, even if they were assumed as real

Table 3: Bacterial species isolated from blood cultures and mean sCD14 value in each case

Bacteria	No. of episodes	sCD14 mean value (SD), ng/ml
No bacterial growth	24	0.517 (0.376)
Mixed gram positive & gram negative bacteria	3	0.368 (0.238)
Mixed gram positive cocci	3	0.878 (0.519)
Klebsiella species	2	0.362 (0.371)
Pseudomonas species	2	0.727 (0.053)
Escherichia coli	1	0.100
Salmonella species	1	0.880
Stenotrophomonas maltophilia	1	0.100
Staphylococcus saprophyticus	1	0.899
Mixed gram negative bacilli	1	0.312

SD: standard deviation; sCD14: soluble subset of cluster of differentiation antigen-14

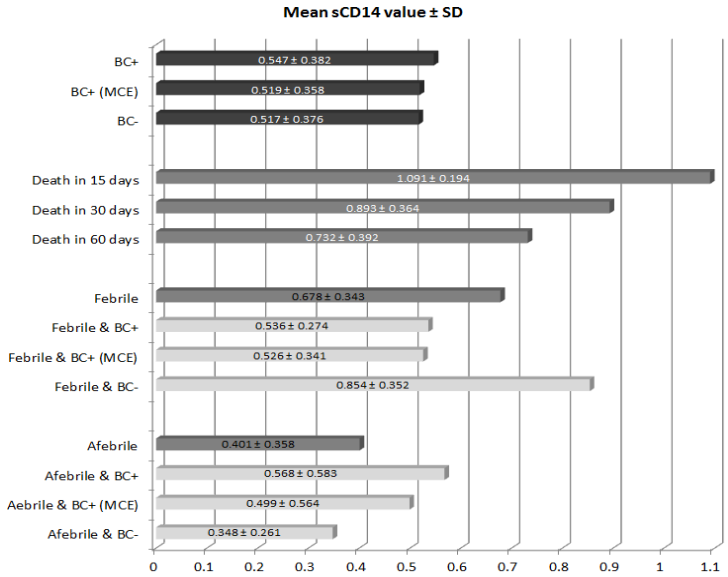

Fig. 2: Mean soluble subset of cluster of differentiation-14 values in presence or absence of fever, blood culture positivity and combinations of fever and blood culture and death within 15, 30 and 60 days after sampling.
BC+: positive blood culture; BC-: negative blood culture; MCE: mixed culture excluded

infection. The difference between mean sCD14 in gram positives and gram negatives was not statistically significant (Fig 3).

Sensitivity and specificity of sCD14 in detection of bacteremia was evaluated by ROC curves, by supposing blood culture positive as bacteremic and afebrile culture negative cases as non-bacteremic cases. This calculation was done in two occasions, by including and excluding mixed cultures, the results were not statistically significant: Area under the curve (AUC) was 0.563 in the first and 0.633 in the second case.

Discussion

This study showed that sCD14 level would increase in the presence of fever. As Endo's study, presepsin levels were not significantly higher in blood culture positive cases[21]. However, by excluding other infectious/inflammatory sources, sCD14 was significantly higher in culture positives. To omit the possible effect of fever on sCD14, samples were classified into 4 groups: febrile blood culture positives, afebrile blood culture positives, febrile blood culture negatives and afebrile blood culture negatives (Fig 1). The study showed that in febrile patients, sCD14 level was lower in blood culture positives, and in overall (includes febrile and afebrile cases) the highest levels were observed in febrile patients with negative cultures. Due to low sensitivity of blood culture as a gold standard test in detection of serious bacterial infections, absence of sCD14 increment in all documented bacteremic cases (positive blood culture) is not equal to low capability of sCD14 in detection of sepsis. These results support the hypothesis that in higher

Table 4: Mean values of sCD14 in different WBC counts

Total WBC count (with ANC≤500 cell/mm³)	No. of cases	Mean (SD) ng/ml
WBC ≤ 500	21	0.587 (0.418)
500 < WBC ≤ 1000	14	0.459 (0.328)
WBC ≥ 1000	4	0.460 (0.284)

WBC: white blood cell; ANC: absolute neutrophil count; SD: standard deviation; sCD14: soluble subset of cluster of differentiation antigen-14.

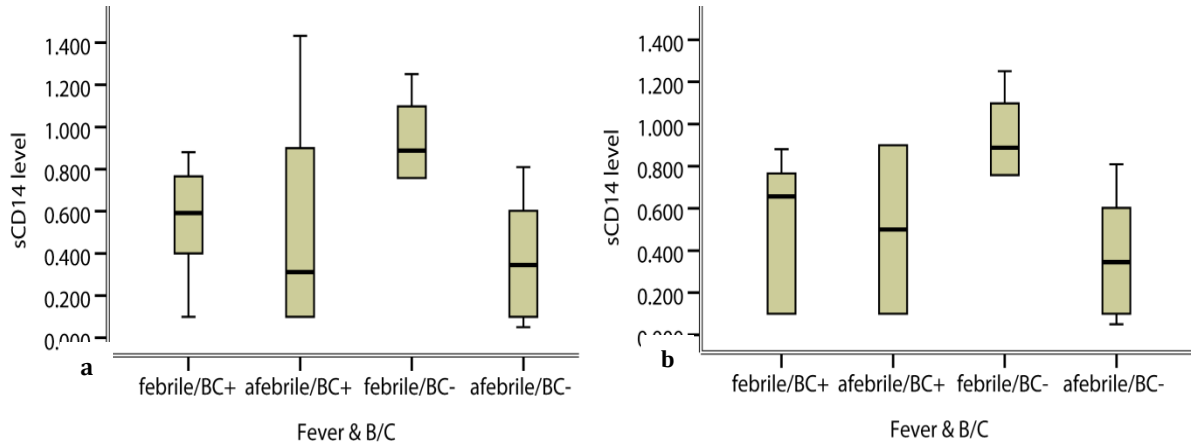

Fig. 3: Box-plot graph showing soluble CD14 levels in different blood culture results. sCD14: soluble subset of cluster of differentiation-14.

sCD14 producers, bacteremia detection would be made earlier and bacterial clearance occur more effective. In addition, higher levels of sCD14 in blood culture positive patients who did not have a clinically detectable source of infection, could be a sign of its capability to screen serious bacterial infections in the absence of detectable sources and differentiate it from false blood culture negative results. This finding has also been observed by Koh and collagenous, who reported that sCd14 increment directly correlate with severity of sepsis[23].

Significant rise in sCD14 levels occurred in patients with oral mucositis, indwelling catheter infection and otitis media. One suspicious patient to TEN (not confirmed by biopsy), who was septic and died in the first week of sampling, had significantly higher levels of sCD14. The interesting result was meaningful lower levels of sCD14 in two patients suspicious to UTI. No significant change was seen in the presepsin levels in patients with cellulitis, pneumonia, sinusitis, gastroenteritis, mucormycosis, anal ulcer and acute hepatitis B cases. However, because of the scarcity in these conditions, the results could not be generalized. Among different bacterial species, *pseudomonas* caused a significant rise in sCD14 levels. Rise in sCD14 values in buccal mucositis is compatible with studies in the field of periodontal inflammations[7,24]. Mucositis in a neutropenic patient was equivalent to higher sCD14 level, which could only be a trigger for higher mucosal presepsin production or inversely, a sign of more serious course of infection to produce more presepsin with inflammatory effects on the mucosa. Among cutaneous disorders, sCD14 was higher in psoriasis and Kawasaki diseases[25-26]. Presepsin level increased in chronic hepatitis B infection and is inversely related to hepatitis B surface antigen (HBsAg) levels although in Meuleman's study, hepatocytes did not increase sCD14 secretion after hepatitis B or C infections[5,27]. According to Endo's published study, there was no significant difference between the mean values of sCD14 in gram positive and negative blood culture positive patients[21].

According to the present study, sCD14 values in neutropenic patients are independent from leukocyte level, and there is also non-circulating source of sCD14 production in neutropenic patients. Although presepsin values in this study were within the lower normal range, statistically meaningful differences between various groups were detected. Lower levels of sCD14 in these patients, may be explained by inhibitory effects of chemotherapeutic agents on main sources of its production. Defining a different normal range for this population of patients or measuring a baseline sCD14 value for each patient, who is in his/her normal clinical condition after an arbitrary time passed, chemotherapy may be rational. On the other hand, although the total sCD14 value is lower in those who received chemotherapy, its changes in response to infection will not be affected by leukocyte levels.

Higher level of sCD14 in neutropenic cancer patients who died in the next 15 days of sampling was considered significant statistically. This correlates well with the other studies, which denoted that at the end stage of sepsis, sCD14

increments is more pronounced[28]. Aalto et al found that sCD14 could predict 28-day mortality rate in community-acquired infections, and Palmiere et al revealed that sCD14 is valuable for postmortem evaluation of sepsis related fatality[29,30]. According to Gluck et al's published data, patients with sepsis survived by 28th day, have significantly higher sCD14 levels as compared to non-survivors, so higher sCD14 levels may be potentially beneficial in sepsis patients[31].

It has been shown that soluble CD14 (sCD14) is directly correlated with the severity of sepsis. Therapeutic effect of recombinant sCD14 has been evaluated in animal models and has been effective in reduction of sepsis mortality[32].

In summary, comparing to other studies, increasing sCD14 level correlates directly with the severity of infection[21,22], this new method in sepsis prediction is also confirmed by our experiment.

Conclusion

Although sCD14 was not sensitive in detection of bacteremia, in the absence of clinically detectable source of infection, it was significantly higher in culture positives. It is highly recommended to perform more extensive larger scale studies in this regard to establish a more precise conclusion.

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Authors' Contribution

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All authors approved final version of the Article.

Conflict of Interest: None

References

1. Zanoni I, Ostuni R, Marek LR, et al. CD14 controls the LPS-induced endocytosis of Toll-like receptor 4. *Cell* 2011; 147(4):868-80.
2. Kelley SL, Lukk T, Nair SK, et al. The crystal structure of human soluble CD14 reveals a bent solenoid with a hydrophobic amino-terminal pocket. *J Immunol* 2013; 190(3):1304-11.
3. Moreno C, Merino J, Ramirez N, et al. Lipopolysaccharide needs soluble CD14 to interact with TLR4 in human monocytes depleted of membrane CD14. *Microbes Infect* 2004; 6(11):990-5.
4. Nomura S, Inamori K, Muta T, et al. Purification and characterization of human soluble CD14 expressed in Pichia pastoris. *Protein Expr Purif* 2003; 28(2):310-20.
5. Meuleman P, Steyaert S, Libbrecht L, et al. Human hepatocytes secrete soluble CD14, a process not directly influenced by HBV and HCV infection. *Clin Chim Acta* 2006; 366(1-2):156-62.
6. Feghali K, Tanabe S, Grenier D. Soluble CD14 induces cytokine release by human oral epithelial cells. *J Periodontal Res* 2011; 46(1):147-52.
7. Nicu EA, Laine ML, Morre SA, et al. Soluble CD14 in periodontitis. *Innate Immun* 2009; 15(2):121-8.
8. Bergandi L, Defabianis P, Re F, et al. Absence of soluble CD14 in saliva of young patients with dental caries. *Eur J Oral Sci* 2007; 115(2):93-6.
9. Bussolati B, David S, Cambi V, et al. Urinary soluble CD14 mediates human proximal tubular epithelial cell injury induced by LPS. *Int J Mol Med* 2002; 10(4): 441-9.
10. Spencer WJ, Binette A, Ward TL, et al. Alpha-lactalbumin in human milk alters the proteolytic degradation of soluble CD14 by forming a complex. *Pediatr Res* 2010; 68(6):490-3.
11. Mo H, Liu S, Zhou Z, et al. Change of serum soluble CD14 level in newly diagnosed type 2 diabetes and its significance. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2010; 35(7):699-704.
12. Mussap M, Noto A, Fravega M, Fanos V. Soluble CD14 subtype presepsin (sCD14-ST) and lipopolysaccharide binding protein (LBP) in neonatal sepsis: new clinical and analytical perspectives for two old biomarkers. *J Matern Fetal Neona* 2011;24(Suppl 2):12-4.
13. Berner R, Furll B, Stelter F, et al. Elevated levels of lipopolysaccharide-binding protein and soluble CD14 in plasma in neonatal early-onset sepsis. *Clin Diagn Lab Immunol* 2002; 9(2):440-5.
14. Yaegashi Y, Shirakawa K, Sato N, et al. Evaluation of a newly identified soluble CD14 subtype as a marker for sepsis. *J Infect Chemother* 2005; 11(5):234-8.
15. Martinez-Albarran M, Perez-Molina Jde J, Gallegos-Castorena S, et al. Procalcitonin and C-reactive protein serum levels as markers of infection in a pediatric population with febrile neutropenia and cancer. *Pediatr Hematol Oncol* 2009; 26(6):414-25.

16. Secmeer G, Devrim I, Kara A, et al. Role of procalcitonin and CRP in differentiating a stable from a deteriorating clinical course in pediatric febrile neutropenia. *J Pediatr Hematol Oncol* 2007; 29(2): 107-11.

17. Dornbusch HJ, Strenger V, Sovinz P, et al. Non-infectious causes of elevated procalcitonin and C-reactive protein serum levels in pediatric patients with hematologic and oncologic disorders. *Support Care Cancer* 2008; 16(9):1035-40.

18. Persson L, Soderquist B, Engervall P, et al. Assessment of systemic inflammation markers to differentiate a stable from a deteriorating clinical course in patients with febrile neutropenia. *Eur J Haematol* 2005; 74(4): 297-303.

19. Sakr Y, Sponholz C, Tuche F, et al. The role of procalcitonin in febrile neutropenic patients: review of the literature. *Infection* 2008; 36(5):396-407.

20. von Lilienfeld-Toal M, Dietrich MP, Glasmacher A, et al. Markers of bacteremia in febrile neutropenic patients with hematological malignancies: procalcitonin and IL-6 are more reliable than C-reactive protein. *Eur J Clin Microbiol Infect Dis* 2004; 23(7):539-44.

21. Endo S, Suzuki Y, Takahashi G, et al. Usefulness of presepsin in the diagnosis of sepsis in a multicenter prospective study. *J Infect Chemother* 2012; 18(6): 891-7.

22. Shozushima T, Takahashi G, Matsumoto N, et al. Usefulness of presepsin (sCD14-ST) measurements as a marker for the diagnosis and severity of sepsis that satisfied diagnostic criteria of systemic inflammatory response syndrome. *J Infect Chemother* 2011; 17(6):764-9.

23. Koh H, Nakamae H, Aimoto M, et al. Diagnostic value of serum level of soluble cd14-subtype in febrile neutropenia in patients with hematologic disorders. *Blood* 2013; 122(21):4718.

24. Hayashi J, Masaka T, Ishikawa I. Increased levels of soluble CD14 in sera of periodontitis patients. *Infect Immun* 1999; 67(1):417-20.

25. Schopf RE, Dobmeyer J, Dobmeyer T, et al. Soluble CD14 monocyte antigen in suction blister fluid and serum of patients with psoriasis. *Dermatology* 1993; 186(1):45-9.

26. Takeshita S, Nakatani K, Tsujimoto H, et al. Increased levels of circulating soluble CD14 in Kawasaki disease. *Clin Exp Immunol* 2000; 119(2):376-81.

27. Steyaert S, Vanlandschoot P, Van Vlierberghe H, et al. Soluble CD14 levels are increased and inversely correlated with the levels of hepatitis B surface antigen in chronic hepatitis B patients. *J Med Virol* 2003; 71(2):188-94.

28. Endo S, Inada K, Kasai T, et al. Soluble CD14 (sCD14) levels in patients with multiple organ failure (MOF). *Res Commun Chem Pathol Pharmacol* 1994; 84(1):17-25.

29. Aalto H, Takala A, Kautiainen H, et al. Monocyte CD14 and soluble CD14 in predicting mortality of patients with severe community acquired infection. *Scand J Infect Dis* 2007;39(6-7): 596-603.

30. Palmiere C, Mussap M, Bardy D, et al. Diagnostic value of soluble CD14 subtype (sCD14-ST) presepsin for the postmortem diagnosis of sepsis-related fatalities. *Int J Legal Med* 2013; 127(4):799-808.

31. Gluck T, Silver J, Epstein M, et al. Parameters influencing membrane CD14 expression and soluble CD14 levels in sepsis. *Eur J Med Res* 2001; 6(8):351-8.

32. Lee JW, Paape MJ, Zhao X. Recombinant bovine soluble CD14 reduces severity of experimental Escherichia coli mastitis in mice. *Vet Res* 2003; 34(3): 307-1.