ORIGINAL REPORT

Evaluation of Fibronectin and C-Reactive Protein Levels in Patients with Sepsis: A Case-Control Study

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Abstract- Sepsis is a significant health problem with an estimated 750,000 new cases in the USA annually. It is also the third leading cause of death in developed countries, equaling the number of fatalities from acute myocardial infarction. The high sepsis-related mortalities mean there is an urgent need to improve the diagnosis and management of sepsis patients. The aim of this study was the evaluation of fibronectin and C-reactive protein (CRP) plasma levels in patients with sepsis and other infectious diseases without sepsis. In a case-control study, 90 patients with sepsis and 90 patients with other infectious diseases without sepsis were studied. Serum levels of fibronectin and CRP were measured. The data were analyzed by SPSS version 15. The mean levels of fibronectin in the cases and controls were 288.97±89.10 mg/l and 341.24±110.53 mg/l respectively (P=0.001). The mean levels of CRP in the cases and controls were 89.42±54.05 µg/ml and 27.42±25.89 µg/ml respectively (P<0.001). Concerning the source of infection, the mean CRP levels were significantly higher in septic patients with urinary tract infection, pneumonia, and soft tissue infection (P<0.001). Decreased levels of fibronectin and increased levels of CRP may be considered as reliable diagnostic markers for sepsis. Also, CRP could be a better predictive factor for sepsis than fibronectin.

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Introduction

Sepsis is defined as the systemic response to infection (1,2). It is an increasingly common cause for morbidity and mortality especially in elderly and immune compromised patients (1,3-5). It is also a main cause for mortality and morbidity in the intensive care unit (ICU) (6). The relative risk for sepsis in people older than 65 is 13.1 times higher than those younger than 65 (7).

The rising incidence of sepsis has been related to the increased use of potent antibiotics and immunosuppressive agents as well as the new invasive treatments for inflammatory, infectious, and neoplastic diseases (8,9).

It is known that the frequency of positive blood culture results increases with the severity of the disease. Nevertheless, some studies have shown that in nearly 50% of patients who had sepsis no organism was identified in the blood culture (7). Besides, it is considered that the results of positive blood cultures vary with the infection localization and the different characteristics of organisms (10).

Presence of various non-specific signs and symptoms for sepsis makes its diagnosis and classification very difficult (11). Also, existence of different definitions for terms such as infection, sepsis, septic syndrome, and septic shock makes the diagnosis more complicated (12-14). However, early diagnosis of sepsis and its classification according to the severity of the patient's condition are necessary and lead to better treatment decision and procedures (15,16).

In 1992, the American College of Chest Physicians / Society of Clinical Care Medicine (ACCP/SCCM) presented a set of criteria for the diagnosis of sepsis with the goal of finding a general agreement on the terminology of sepsis as well as providing a practical framework (17, 18). In these criteria, sepsis is defined as systemic response to infection manifested by two or

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more of the following conditions as a result of infection: 1) Temperature > 38°C or < 36°C, 2) Heart rate > 90 beats per minute, 3) Respiratory rate > 20 breaths per minute or PaCO2 < 32 mmHg, 4) White Blood Cell count > 12000/cu mm, or < 4000/cu mm or 10% immature (band) forms.

Also in 2001, the revised ACCP/SCCM criteria published which made the diagnosis of sepsis a potentially difficult situation (11). It also added more fields such as lactate, central venous oxygen saturations, and potential biomarkers to the previous criteria (11). It is believed that biomarkers could have a valuable place in the diagnosis of sepsis especially in the identification of severity (19).

C-reactive protein (CRP) is an acute phase protein and well-known biochemical marker of inflammation (20,21). CRP produced in the liver and its normal plasma concentration is under 10 mg/l but increase several folds after trauma, inflammation and other stimuli that involve tissue damage (20,22).

Bacterial infections are known as potent stimulators for CRP elevation after a few hours and the CRP plasma level evaluation could assist the infection diagnosis (23). It seems that identifying CRP plasma levels could be useful in the diagnosis of sepsis especially when other diagnostic factors are not certain.

Fibronectin is a high molecular weight glycoprotein that found in two distinct forms: an insoluble form in the extracellular matrix of cells and a soluble form which found in plasma. Plasma fibronectin thought to affect wound healing, immunological clearance of injured tissue and antibody coated micro-organisms. Fibronectin also seems to have an important role in mononuclear phagocytosis process. It improves the interaction between phagocytes and antibody opsonised bacteria and increases bactericidal activity in macrophages (24,25).

Fibronectin is present in most of body fluids, and its normal plasma concentration is about 300 mg/l (26). It is proposed that fibronectin plasma level could have diagnostic and prognosis value in patients with sepsis (27-29).

Infection diagnosis procedure is mainly based on the detection of microorganisms in blood cultures that usually take a 6-24 hour period and in 30% of cases the results appeared to be negative. Besides, sepsis could be a result of poisonous factors produced by the infectious agents (27). Thus, it could be very useful to find a suggestive biologic marker for sepsis in addition to clinical markers (27).

There is no certain and gold standard procedure for the detection of sepsis in its early stages which results in a better survival and complication reduction for the patient. Therefore, this study is conducted to evaluate the diagnostic role of fibronectin and CRP for sepsis and its differentiation from other infectious conditions.

Materials and Methods

This case-control study was conducted in Sina hospital located in Hamedan, Iran, in a 2 year period from 2006-2008. The study protocol was approved by the Ethical Committee of Hamedan University of Medical Sciences, Hamedan, Iran, and informed consent obtained from the patients.

Sample size was calculated according to similar studies using their standard deviations as 90 for the sepsis and 90 for the non-sepsis groups.

The sepsis group included all patients who had clinical symptoms of infection in addition to at least two sepsis markers defined by ACCP/SCCM (19,20) as follows:

1- Temperature >38°C or <36°C

2- Heart rate >90 beats per minute

3- Respiratory rate >20 breaths per minute

4- White Blood Cell count >12000/mm^3, or <4000/mm^3

The non-sepsis group included patients who had clinical infection findings but did not fulfill the criteria for sepsis. The clinical infection findings were defined as follows:

Urinary tract infection was defined as urinary symptoms plus pyuria with more than 10 white blood cells/mm^3 and bacteriuria with at least 10^5 bacteria/mL.

Pneumonia was diagnosed according to the following criteria: (1) the presence of a new infiltrate on the chest radiograph consistent with pneumonia; (2) an acute onset of the disease with productive cough, chest pain; or abnormal findings on auscultation characteristic of a pneumonic consolidation.

Soft tissue infection was defined as the presence of symptoms and signs of one of the skin and soft tissue infections including cellulitis, wound infection, subcutaneous abscess, necrotizing fasciitis, or infected decubitus ulcer.

Septic arthritis was defined as the presence of following criteria: (1) acute onset of joint pain and effusion; (2) purulent synovial fluid with a markedly elevated polymorphonuclear cell count; (3) positive smear or culture of synovial fluid for bacteria.

Dysentery was defined according to the following criteria: (1) bloody diarrhea and tenesmus; (2) the presence of fecal leukocytes or isolation of enteropathogenic bacteria from stool culture.

After confirming the diagnosis, blood samples were taken from all patients and the plasma levels of fibronectin and CRP were evaluated. Fibronectin plasma level was measured by employing SRID method and using a commercial kit (Binding Site, Birmingham, UK) and according to the kit protocol. CRP plasma level was measured using ELISA method.

Mean fibronectin and CRP plasma levels obtained for both sepsis and non-sepsis groups and were compared using T-test and one factor ANOVA.

Statistical analysis was performed using SPSS.15.0. $P<0.005$ were assumed as significant.

Also, Receiver-Operator Characteristic (ROC) curves were constructed to select a cut-off point plasma level values for both CRP and fibronectin. A larger area under a ROC curve shows better test performance. One represents 100% sensitivity and specificity and 0.5 shows no discriminatory utility. Besides, sensitivity, specificity, and positive predictive value (PPV) were also calculated for both CRP and fibronectin plasma levels.

Results

A total of 90 patients with sepsis (67.8% males, 32.2% females, mean age: 51.4±22.8) and 90 age and sex matched non-sepsis group (57.8% males, 42.2% females, mean age: 49.7±21.5) were included. Fisher's exact test showed no significant relation between two groups according to their sex ($P=0.109$). The patients mean age was 51.47±22.87 with the median of 50. The mean age of patients in the sepsis group was 53.16±24.14 while the mean age of patients in the non-sepsis group was 49.77 ± 21.51. No significant difference was observed between two groups according to their ages ($P=0.322$).

From the total number of 180 patients in both groups, 56 patients (31.1%) had pneumonia, 49 patients (27.2%) had urinary tract infection, 47 patients (26.1%) had soft tissue infection, 14 patients (7.8%) had GI tract infection, and 14 patients (7.8%) had other forms of infection.

Within the group of sepsis patients, 35 patients (38.9%) had pneumonia, 24 patients (26.7%) had urinary tract infection, 17 patients (18.9%) had soft tissue infection, 7 patients (7.8%) had GI infection, and 7 patients (7.8%) had other infections. In the control group, these statistics were 30 patients (33.3%) with soft tissue infection, 25 patients (27.8%) with urinary tract infection, 21 patients (23.3%) with pneumonia, 7 patients (7.8%) with GI infection, and finally 7 patients (7.8%) had other infections.

Using the chi-square test did not show a statistically significant difference between the two groups ($P=0.130$).

The mean fibronectin plasma level in the sepsis group was significantly lower than the non-sepsis group (288.9±89.1 vs 341.2±110.5 $P=0.001$). Also, the mean CRP plasma level in the sepsis group was significantly higher than in the non-sepsis group (89.4±54 vs 27.4±25.8 $P<0.001$).

ROC curves also produced to obtain optimum cutoff points for both CRP and fibronectin plasma levels as well as determining and comparing the efficiency of both tests in the detection of sepsis.

Comparing the average CRP and fibronectin levels in the sepsis and control groups, based on the source of infection, did not reveal a significant difference for fibronectin; however, for CRP the difference in lung, urinary tract, and soft tissue organs as the source of infection were significant (Table 1).

Table 1. Mean CRP and Fibronectin plasma levels in sepsis and non sepsis groups according to the source of infection.

Biomarker	Sepsis	Non sepsis	P- value
CRP			
Pneumonia	90.2±47.3	21.6±10.4	‹0.001
Urinary tract infection	78.4±47.3	23.5±23.4	‹0.001
Soft tissue infection	97.9±74.1	30.8±25.8	‹0.001
GI tract	89.8±50.8	51.3±55.5	0.139
Fibronectin			
Pneumonia	300.8±89.7	292.6±92.7	0.747
Urinary tract infection	303.7±104.5	344.1±86.7	0.147
Soft tissue infection	271.4±81	352.8±130.6	0.025
GI tract	279.7±66.8	357.4±111.2	0.201

Table 2. Different cut-off points of CRP and Fibronectin and their sensitivity, specificity, and positive predictive value.

Biomarker	cutoff	sensitivity	specificity	positive predictive value
CRP	>=30	88	74	77
	>=40	74	91	89
	>=50	64	92	89
Fibronectin	<=300	66	58	62
	<=350	74	42	56
	<=400	87	23	53

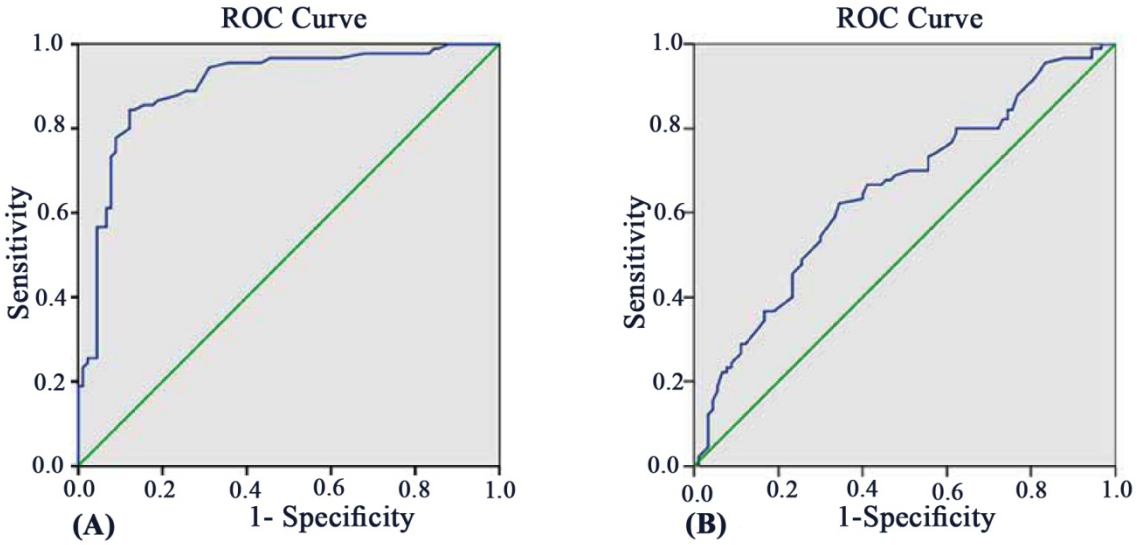

Figure 1. (A) ROC curve for CRP plasma level (B) ROC curve for Fibronectin plasma level. Sensitivity is plotted against 1-spesificity.

Table 2 shows the sensitivity, specificity, and PPV calculated for different fibronectin and CRP cutoff points.

It seems that CRP plasma levels equal to or over 40 mg/l could be a suggestive marker for sepsis with 74% sensitivity, 91% specificity, and 89% PPV. Also, fibronectin plasma levels equal to 300 or lower could be a suggestive marker for sepsis with 66% sensitivity, 58% specificity, and 62% PPV.

Figure 1 shows the ROC curves constructed for both fibronectin and CRP plasma levels. The larger area under the curve shows a better diagnostic performance which is calculated for CRP and fibronectin as 0.91 (95% CI 0.85-0.94) and 0.65 (95% CI 0.57-0.73) respectively. The area under ROC (AUC) curve for CRP appeared to be significantly higher than the AOC for fibronectin (P<0.001).

Discussion

Sepsis is an important health problem and a leading cause of death in developing countries. The diagnosis of sepsis is sometimes very difficult because it is usually common for patients to show some sepsis criteria with no obvious source for the infection, especially in immune compromised patients. Also, the lack of sensitive diagnostic tests for sepsis highlights the role of early sepsis biomarkers.

Various sepsis biomarkers have been proposed in the field of sepsis diagnosis (29). In this study, we aim to compare fibronectin and CRP plasma levels in patients with sepsis and those with other infectious diseases except sepsis.

In our study, the mean fibronectin plasma level was significantly lower in the sepsis group than the non sepsis one. Brodin *et al.*, reported that plasma

fibronectin rise with the clinical improvement of the patients but it remains low in patients with sepsis (30). Also, Eriksen *et al*., found decreased plasma fibronectin concentration in patients with sepsis and DIC (27). O'Connell et al evaluated serial fibronectin plasma level in 66 medical ICU patients and found that the mean values of initial levels were significantly higher in survivors (266±14 mg/l) than non survivors (179±13 mg/l). They also found that patients with minimum fibronectin levels lower than 195 mg/l had a mortality rate up to 65% (31). Ruiz Martin *et al.,* reported that plasma fibronectin acts as a marker for sepsis and patients with sepsis show decreased levels. They proposed that measuring plasma fibronectin level could be used to diagnose sepsis in its early stage and reduce the mortality and morbidity rates (26). They also concluded that plasma fibronectin lower than 120 mg/l could suggest a diagnosis of sepsis (PPV 82.8%), but in our study the cutoff point for fibronectin was calculated as values lower than 300 mg/l (PPV 62%). However, Rubli *et al.,* proposed that although fibronectin showed a significant reduction in patients with sepsis but the predictive potential of this difference could not enhance the diagnosis of sepsis individually (32). Similarly, a couple of studies concluded that although plasma fibronectin may play an important role in the sepsis pathogenesis, but it would not be a useful marker for infection (33,34).

Mean plasma CRP level in our study was 89.42±54.05 mg/l in the sepsis group and 27.42±25.89 mg/l in the non sepsis group which implies that mean CRP plasma level is significantly higher in patients with sepsis. We also suggest 30 mg/l as the cutoff point for CRP plasma level with 88% sensitivity and 74% specificity. Previous studies have shown that CRP could be a very useful marker in the diagnosis of sepsis rather than heart rate or temperature (35). Bentiz *et al.*, concluded that serial CRP measurements are very useful in the diagnosis of sepsis in neonates but the PPV of elevated CRP is not very high. Thus, CRP alone is not sufficient for the therapy decision making (36). Also, Matsen *et al.*, proposed that a 25 % rise in the CRP plasma level is highly suggestive for the infection while other non infective causes of raised CRP such as inflammation, surgery, or tissue injury are absent (37). Also, Povoa *et al.*, surveyed CRP as an indicator of sepsis and suggested CRP plasma level higher than 50 mg/l with 98.5% sensitivity and 75% specificity as a useful predictive factor for sepsis (22). They also concluded that serial measurements of CRP is more useful than other sepsis markers such as body temperature and WBC count in the detection of sepsis in its early stages. Other similar studies reported different results about the diagnostic role of plasma CRP in sepsis and an overall confirmation about the optimum cut-off point for CRP plasma level were not made yet (21,38-41) . Some studies suggested CRP as a diagnostic marker that could differentiate sepsis from other infectious processes (39-41). Keshet *et al.,* also reported the ability of CRP plasma level measurements in the differentiation of bacterial from non-bacterial infections (39).

We also compared the efficiency of both CRP and fibronectin plasma levels in the detection of sepsis by calculating the Area under Curve (AOC) and realized that CRP is more efficient in the prediction of sepsis than fibronectin.

Pierrakos and Vincent conducted a review on sepsis biomarkers on 3370 articles and found that CRP and calcitonin are the most frequent sepsis markers among 178 markers that had been studied yet (29).

According to our results we conclude that CRP and fibronectin levels could enhance the diagnosis of sepsis in its early stages and differentiate the between sepsis and other infections. We also conclude that CRP plasma level is a better biomarker in the detection of sepsis than fibronectin. However, additional studies on sepsis biomarkers and comparing them with other markers of sepsis especially the clinical markers could provide a better understanding of the situation to improve the diagnostic procedures for sepsis.

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