Serum Inflammatory Markers in the Elderly: Are They Useful in Differentiating Sepsis from SIRS?

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Abstract- Differentiating sepsis from other noninfectious causes of systemic inflammation is often difficult in the elderly. The aim of this study was to evaluate the ability of C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), procalcitonin (PCT), and Interleukin-6 (IL-6) to identify elderly patients with sepsis. In this single center prospective observational study, we included all consecutive elderly patients admitted with suspected sepsis and systemic inflammatory response syndrome (SIRS) in an emergency department. Blood samples for measuring CRP, PCT, IL-6, ESR and white blood cells (WBC) count were taken at first day of admission. Sensitivity, specificity, positive and negative predictive values were calculated for each inflammatory markers being studied. A total of 150 elderly patients aged 65 and older, 50 with sepsis and 50 with SIRS, and fifty individuals in a normal health status were included. CRP exhibited the greatest sensitivity (98%) and negative predictive value (98.6%) and performed best in differentiating patients with sepsis from those with SIRS. In a receiver operating characteristic curve analysis, IL-6 performed best in distinguishing between SIRS and the control group (AUC 0.75, 95% CI). On the other hand, both CRP and ESR appeared to be a more accurate diagnostic parameter for differentiating sepsis from SIRS among elderly patients.

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Keywords: Sepsis; C-reactive protein; ESR; PCT; IL-6

Introduction

Differentiating sepsis from other noninfectious causes of systemic inflammation is often difficult and common dilemma for the physicians due to the poor sensitivity and specificity of fever and leukocytosis in many clinical settings (1).

The observation in which the serum procalcitonin (PCT) level raised above normal values in patients with sepsis and other clinically significant bacterial infections was first described in 1993 (2). Recent studies have evaluated procalcitonin and some other inflammatory markers such as C-Reactive Protein (CRP), Interleukin-6 (IL-6) and Interleukin-8 (IL-8) as diagnostic tools to define patients with sepsis and systemic inflammatory response syndrome (SIRS) (3,4), of which serum PCT has been found to be the most effective (5).

On the other hand, elderly patients show many atypical features of sepsis which make its early diagnosis difficult. Lai et al. found that PCT levels were significantly higher in elderly patients with bacteremia in comparison with those without (6).

The present study was aimed to assess the usefulness of PCT assay in elderly patients with suspected sepsis in comparison to the other markers such as erythrocyte sedimentation rate (ESR), CRP, IL-6, and white blood cells count (WBC) in order to differentiate the patients with sepsis from those with SIRS.

Materials and Methods

Patients were studied via a prospective method from April 2011 to March 2012 in the emergency department of Rasoul-e-Akram training Hospital. All elderly patients

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(≥65 years) suspected to sepsis and SIRS were enrolled in the study. Patients with an unknown diagnosis and incomplete files and those who have received antibiotics prior to admission were excluded from the study. Patients were divided to two distinct groups of SIRS and sepsis.

According to the standard definition, patients with at least two of the following four criteria were defined as having SIRS: Fever >38°C or <36°C, respiratory rate >20/min, heart rate >90/min, leukocytosis >12000 /μL or a leftward shift >10% of immature granulocyte, or leucopenia <4000 /μL. If SIRS was accompanied with infection as proven by cultures or on clinical grounds, the patient was defined as having sepsis (7).

Another group of 50 elderly patients who were in normal health status and did not experience any diseases were designated as the control group.

Upon admission in an emergency department, age, sex, vital signs, routine blood tests, urinalysis, microbiological cultures and chest radiograph were ordered, and the results were recorded for each patient. A venous blood sample was obtained from each patient before any antibiotic treatment was started at the hospital, in order to measure the serum PCT, IL-6, CRP, ESR levels and WBC count within 24 hours. After centrifuging the sample, plasma was kept at -80°c until assayed.

Serum PCT level was determined by the immunoluminometric assay (LIAISON® BRAHMS PCT®, Germany). Serum IL-6 level was determined by IL-6 ELISA Kit (Sanquin®, the Netherlands). ESR was quantified by an Electra auto-analyzer. CRP was assessed by a semi-quantitative latex agglutination method (Bionik® slide agglutination test kit) measuring the CRP level of 6, 12, 24, 48 and 96 mg/L.

Prior to the study, we chose the following cut off levels, according to the manufacturing company and laboratory references. PCT: 0.5ng/ml; IL-6: 10pg/μL, ESR: 17mm/hr for men and 25mm/hr for women; CRP≥12mg/L and WBC: 12 000 cells/μL. It might be mentioned that the study protocol was approved by the local ethics committee.

Statistical analysis

Statistical analysis was performed using SPSS 15.0 statistical software (SPSS, Chicago IL). Means are expressed as Mean ± Standard deviation (SD). Mann-Whitney U and Chi-square tests were used for analytic comparison. The predictive ability of serum PCT, IL-6, ESR, CRP, and WBC count were expressed as the area under curve -receiver operating characteristic (AUC-ROC). AUC values are reported with the 95% confidence interval (95% CI). $P<0.05$ was considered significant.

Results

One hundred-fifty patients were included in this study, 50 patients in each sepsis, SIRS, and control groups. The overall mean age of the patients was 74.3±0.6 years old.

Septic patients were diagnosed with urosepsis in 25 (50%), pneumonia in 23 (46%) and soft tissue infection in 2 (4%) of the cases. The final diagnosis of patients with SIRS was respiratory diseases in 12 (24%), cerebrovascular accidents in 5 (10%), cardiovascular diseases in 17 (34%), renal diseases in10 (20%) and malignant disorders in 6 (12%) of patients.

The demographic data and the mean values of serum inflammatory marker levels were compared among the three mentioned groups (Table1).

Sensitivity, specificity, positive and negative predictive values (PPV, NPV) of the inflammatory markers are demonstrated in Tables 2-3, and the related AUC-ROC curves are shown in Figures 1-2.

Table 1. Demographic and laboratory data in sepsis, SIRS and control groups

Variables	Sepsis(n=50)	SIRS(n=50)	Control(n=50)	*P*-value
Age (Year)	77.4±1.1	75.2±0.9	74.4±0.8	0.45
Male/Female	24/26	25/25	27/23	0.55
Temperature(°c)	38.2±0.1	37.1±0.05	36.5±0.3	0.001*
Heart Rate (/minute)	100.8±2.1	99.3±3.1	85±20	0.7
Respiratory Rate (/minute)	24.7±0.7	26.8±0.6	22±5	0.054
WBC (cells/μL)	13564±1037	10417.4±652.8	5804±206.2	0.001*
PCT (ng/mL)	74.7±27.8	47.5±22.4	0	0.001*
IL-6 (pg/μL)	64.1±29.3	41.1±20.9	0.7±0.4	0.001*
CRP (mg/L)	58.1±4.5	28.1±4.5	15±5	0.001*
ESR (mm/h)	61.7±3.5	35.2±3.4	8.3±0.6	0.001*

Values are reported as mean ± SD, *P<0.05 is considered as significant
SIRS; Systemic Inflammatory Response Syndrome; WBC, White Blood Cells; PCT, Procalcitonin; IL-6, Interleukin-6; CRP, C-Reactive Protein; ESR, Estimated Sedimentation Rate

Table 2. Sensitivity, Specificity, PPV and NPV of the inflammatory markers to diagnose Sepsis

	Threshold	Sensitivity	Specificity	PPV	NPV	*P* -value	AUC (95% CI)%
CRP (mg/L)	12	98%	72%	63.6%	98.6%	0.00*	0.88 (0.82-0.94)
ESR (mm/h)	Men:17; Women:25	94%	64%	40.8%	91.4%	0.00*	0.87 (0.81-0.93)
PCT (ng/mL)	0.5	88.8%	71.1%	58.8%	93.2%	0.00*	0.80(0.72-0.87)
WBC (cells/µL)	12000	68%	100%	100%	82.6%	0.00*	0.72(0.62-0.81)
IL-6 (pg/µL)	10	38%	78%	46.3%	71.5%	0.00*	0.71(0.63-0.79)

*P<0.05 is considered as significant.
Abbreviations: PPV, Positive Predictive Value; NPV, Negative Predictive Value; AUC, Area Under Curve; CRP, C-Reactive Protein; ESR, Estimated Sedimentation Rate; PCT, Procalcitonin; WBC, White Blood Cells; IL-6, Interleukin-6

Table 3. Sensitivity, specificity, PPV, NPV of the inflammatory markers to diagnose SIRS

	Threshold	Sensitivity	Specificity	PPV	NPV	P-value	AUC (95% CI)%
IL-6 (pg/µL)	10	38%	78%	46.3%	71.5%	0.00*	0.75(0.67-0.83)
WBC (cells/µL)	12000	48%	100%	100%	71.7%	0.00*	0.64(0.54-0.74)
ESR (mm/h)	Men:17; Women:25	62%	52%	39.2%	73.2%	0.05*	0.59(0.50-0.69)
PCT (ng/mL)	0.5	59.5%	57.8%	41.1%	74.3%	0.09	0.58(0.48-0.68)
CRP (mg/L)	12	56%	51%	36.3%	69.8%	0.4	0.53(0.43-0.63)

*P<0.05 is considered as significant.
Abbreviations: PPV, Positive Predictive Value; NPV, Negative Predictive Value; AUC, Area Under Curve; IL-6, Interleukin-6; WBC, White Blood Cells; ESR, Estimated Sedimentation Rate; PCT, Procalcitonin; CRP, C-Reactive Protein

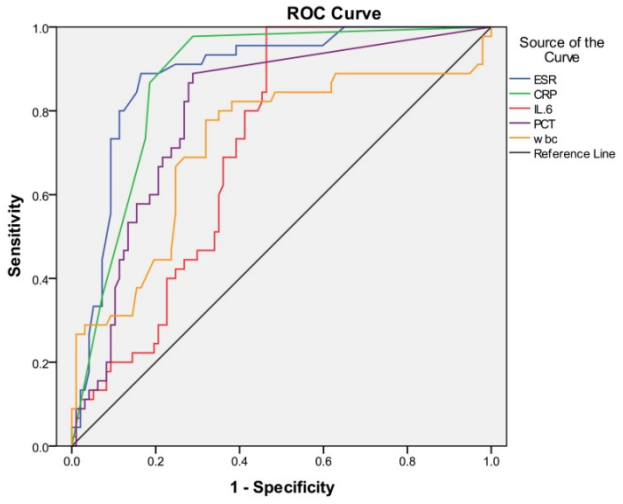

Figure 1. ROC curve in the diagnosis of septic patients

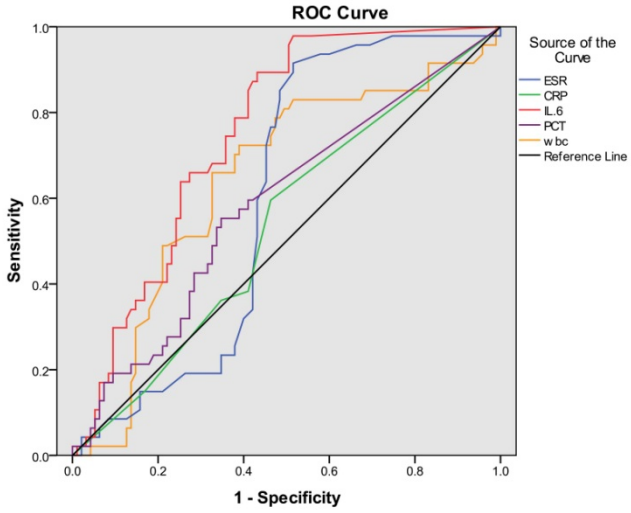

Figure 2. ROC curve in the diagnosis of SIRS patients

Discussion

A number of acute-phase reactants are used in the diagnosis of sepsis, including leukocyte count, ESR, CRP, PCT, IL-6, and IL-8, but the diagnostic role of those in the elderly people is not investigated intensively (8).

The objective of this study was to evaluate the usefulness of measuring a series of inflammatory markers in order to diagnose sepsis in the elderly patients. The results of our study revealed that CRP and ESR were more accurate markers in differentiating sepsis from SIRS in comparison with PCT, WBC count and IL-6.

Determination of ESR is simple and easy to incorporate into daily general practice. However a false negative or positive result may cause a series of potentially harmful policies for the patients (9, 10). We compared the ESR levels in patients with sepsis, SIRS, and healthy control group of elderlies. Our data showed

a significant higher level of ESR in patients with sepsis, which may help the physicians at the time of the initial diagnosis. The ROC curves demonstrated that the ESR had a high sensitivity despite its low specificity, which may show that ESR is a better negative than a positive predictor of sepsis (91.4% vs. 40.8%).

On the other hand, CRP is another acute-phase reactant, produced by the liver in response to inflammation or infection (11). Several studies have focused on the diagnostic test abilities of CRP in diagnosing sepsis (12,13). A few studies showed that plasma CRP level higher than 10 mg/dl predicts bacterial infection which was positively associated with mortality (12,14,15). Sierra et al. showed that the best threshold for C-reactive protein in order to predict sepsis was 8 mg/dl in which the sensitivity was 94.3% and the specificity was 87.3%. The area under the curve for CRP was estimated at 0.94 in the mentioned study (16).

In our study, considering the diagnosis of sepsis, CRP with the sensitivity of 98% and the AUC of 0.88, performed better in comparison with the other inflammatory markers.

Some authors believed higher CRP levels could be observed in older patients (16,17) but the results of our study showed the approximately normal-range CRP levels in healthy elderly group and CRP levels were significantly higher among patients with sepsis than in those with SIRS or the healthy individuals.

Several studies have focused on the diagnostic test abilities of PCT to diagnose sepsis and found PCT to be a better inflammatory marker than CRP (18-20). Although some studies provided a comparison between PCT and CRP markers, and showed that the overall accuracy of PCT is higher than that of CRP markers to differentiate bacterial infections from other non-infective causes of SIRS (13,21-22), some others, consistent with our study, showed that PCT was not a better marker of bacterial infection than CRP (23). Comparing positive and negative predictive values, our data showed that CRP seems to be more useful in excluding sepsis than in diagnosing sepsis while PCT was the second best after CRP and had lower positive and negative predictive values. Conclusively, in agreement with other studies about PCT and infection in elderly patients, PCT performed poorer than CRP in diagnosing infection and in discriminating between sepsis and SIRS (24,25).

Stucker et al. concluded that PCT is useful to identify severely ill elderly patients, but not to discriminate patients with infection from those without (25). We showed that PCT performed a bit better than CRP in discriminating between SIRS and patients in a healthy situation [0.58 vs. 0.53 AUC (95% CI)].

In the agreement with Balc et al. study (26) we found that the IL-6 was a poor predictor of sepsis (AUC = 0.71; CI=95%), although it performed better than other markers for differentiating between patients with SIRS and those in a healthy situation. PCT was superior to IL-6 in other studies (5,19,22,27) this is contrary to Gaini *et al*. study, which found that IL-6 is superior to PCT as a diagnostic marker for infection and sepsis (24).

Some studies support the use of either PCT or IL-6 as an early tool to diagnose sepsis and severe sepsis (20,28,29).

In a prospective study on bacteremic elderly patients WBC counts with or without a left shift performed poorly in the diagnosis of bacteremia, in comparison to PCT (30). The results of our study also revealed that leukocytosis had the best specificity and PPV to diagnose sepsis with a poor AUC of 0.72.

Briefly, in our study CRP yielded the highest discriminative value for differentiating patients with sepsis from those with SIRS followed by ESR and PCT.

On the other hand, both CRP and ESR appeared to be a more accurate diagnostic parameter for differentiating sepsis from SIRS among elderly patients. Although biomarker levels must always be evaluated in the context of a careful clinical and microbiological assessment, CRP, ESR, and PCT and not IL-6, can be used with more precision to diagnose sepsis in the elderly patients.

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