

Diagnostic value of ESR, CRP, and PLT in comparison to PCT and C3 in septic ICU casesReza Imani Rastabi^{1*}, Ghorbanali Shahabi² and Ali Fazeli³¹Department of Infectious & Tropical Diseases, Shahrekord University of Medical Sciences, Shahrekord, Iran²Department of Immunology, Shahrekord University of Medical Sciences, Shahrekord, Iran.³Shahrekord University of Medical Sciences, Shahrekord, Iran***Corresponding author:** Reza Imani Rastabi

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Abstract: Sepsis is one of the most common reasons worldwide for death among intensive care unit patients because of diagnostic procedures' limitations. Despite new supportive treatments and administration of high potent antibiotics, sepsis remains fatal and reduces survivors' life quality. To measure Procalcitonin (PCT) and Complement C3 (C3) and their association with Blood Sedimentation (ESR), C-Reactive Protein (CRP), and Leukocytes (WBC) in suspected sepsis patients in Intensive Care Unit (ICU), and use changes in ESR, CRP, and WBC as simple and less expensive tests to diagnose and/or follow up sepsis patients. For this descriptive analytical study, 30 patients with suspected sepsis at ICU were enrolled. ESR, CRP, PLT, and WBC measurements were performed in three stages: admission time (pre-sepsis), in case of onset of possible sepsis indications (peri-sepsis), and prior to discharge (post-sepsis). Serum level of PCT was measured by immunochromatography and C3 determined by SRID. The data was analyzed by repeated measure and Pearson correlation coefficient (SPSS 11). ESR, CRP, PLT, and WBC in peri-sepsis were significantly higher than those in pre- and post sepsis ($p < 0.05$). Comparing PCT mean level in peri- and post-sepsis (lowest level) showed a significant difference, while no significant difference was seen between pre- and peri sepsis ($p < 0.05$). C3 biomarker was also significantly higher in peri-sepsis than pre- and post sepsis ($p < 0.05$). Although changes in PCT and C3 have a high diagnostic value in early stages of sepsis and are used as guides for antibiotic therapy in suspected sepsis cases, regarding the significant difference in ESR, CRP, and WBC in peri-sepsis compared to pre- and post-sepsis in our study, these tests could be offered as simpler and less expensive tests, having moderate diagnostic value for the diagnosis of sepsis on ICU admission.

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Introduction

Sepsis is defined as the body's systemic response to invading microorganisms, *e. g.* bacteria and/or fungus (1), and one of diseases affecting critically ill patients (2). Sepsis is the second most prevalent cause of mortality in non coronary Intensive Care Unit (ICU) and among the top 10 reasons for death among all hospitalized patients (3). In ICU patients, sepsis occurrence ranges widely (4-7), and their

mortality rates vary from 20% for sepsis, to 40% for severe sepsis, to 60% for septic shock (8).

Distinguishing sepsis from non infectious conditions in the early stage may be difficult in critically ill or comatose patients and diagnosis, treatment, and outcomes are considerably different between patients with and without sepsis (9). In addition, there is an unsatisfied need for clinical or laboratory tools distinguishing SIRS from sepsis (10). Although several biomarkers including Tumor Necrosis

Factor-alfa (TNF- α), Interleukin-8 (IL-8), Interleukin-6 (IL-6), Platelet (PLT), and Procalcitonin (PCT) have been suggested for sepsis diagnosis and studied repeatedly, White Blood Cell (WBC), Erythrocyte Sedimentation Rate (ESR), and C-Reactive Protein (CRP) are still emphasized in medical references (11).

CRP is measured routinely in hospitalized patients and is more sensitive and more rapid compared to ESR. In addition, CRP returns to normal values after recovery more quickly but CRP is not a specific test for sepsis (12).

Traditional markers of infection such as body temperature and WBC count may have inadequate specificity (13, 14). CRP with anti- and pro-inflammatory features does not increase significantly until 24–48 h after onset of inflammation, with low specificity and positive predictive value (15–18). The ESR is a common but not specific test, often used as a marker of active disease. ESR has been found more helpful compared to the leukocyte count in discriminating between inflammatory diseases and harmless and self-limiting conditions (19). PCT is a 116-amino acid prohormone of calcitonin (20) which is found without changes in the total amount of calcitonin in the bloodstream (21). The expression of PCT is stimulated by inflammatory cytokines, e. g. TNF- α and IL-6 (22). Recent studies on PCT have focused on patients with confirmed or suspected bacterial infections, and the duration of antibiotic treatment was guided through lowering PCT concentrations (23–25). Vicnent et al. indicated measurement of PCT levels accompanied with CRP could be a very useful index for sepsis diagnosis (26). The other biomarker that can help us make the diagnosis of sepsis in early stages is C3 (27). For example, systemic inflammatory response caused a 40-fold increase in C3 (28).

Considering high rate of sepsis-related mortality the present study aims to compare PCT and C3 and their association with ESR, CRP, and WBC in suspected sepsis patients in ICU, and use changes in ESR, CRP, and WBC as simple and less expensive tests to diagnose and/or follow up sepsis patients.

Material and methods

This descriptive-analytical study was conducted in 2009 lasting for 6 month. Blood samples of patients hospitalized at intense care unit (ICU) of Kashani Hospital, Shahrekord, Iran were drawn from venous lines for measurement of ESR, CRP, PLC and WBC levels in three

stages: The first and second stages were admission time (pre-sepsis) and when possible sepsis indications, e.g. tachycardia, tachypnea, fever, hypothermia, leukocytosis, or leukopenia, started, i.e., suspected sepsis (peri-sepsis); finally a sample population of 30 patients with a suspected diagnosis of sepsis was enrolled. The third stage was prior to discharge (post-sepsis). Before blood collection, a questionnaire for patients' demographic characteristics and test results was developed based on an infectious diseases specialist's comments, sepsis indicators, and predisposing factors.

In addition to positive bacterial culture, incidence of sepsis was confirmed if at least two of the following signs (as SIRS cases) would be detected:

1. A temperature of less than 36°C (Hypothermia) or higher than 38°C (Fever)
2. A heart rate of more than 90 (beats/minute) (Tachycardia)
3. A respiratory rate of more than 20 (breaths/minute) or a paCO_2 of less than 32 mmHg (Tachypnoea)
4. WBC of more than 12000 (Leukocytosis) or less than 4000 cells/mm³ (Leukopenia) or 10% immature (Band) forms.

The blood samples were centrifuged at 3500 g for 5 minute and serum samples were stored at -20°C. While collecting samples for performing given tests, a 3 cc serum was also obtained for serum level measurement of quantitative PCT. PCT was characterized by immunochromatography method (PCT-Q B.R.A.H.M.S. Aktiengesellschaft, Neuendorfstr 25, D-16761 Hennigsdor). CRP levels were measured using an immunoturbidometric assay with a cut-off level of 50mg/L. ESR was quantified by an Electa autoanalyser and WBC and PLT count calculated by Sysmec (Kolbe, Japan) SE 9000 analyzer. The amount of C3 in the plasma was determined according to SRID.

Statistical analysis

The data analysis was performed by means of repeated measure and pearson correlation coefficient (SPSS 11.5) and the difference was considered significant at $p < 0.05$.

Results

Mean age of 30 subjects (28 males and 2 females) studied in the present study was 24.9 ± 11.3 years. As mentioned above, three serum samples were taken from each patient.

The comparison of the samples' results for PCT, C3, CRP, ESR, WBC, and PLT for three stages is shown in table 1. In this table, the first and second P values, respectively, correspond to the first comparison (between pre- and peri-sepsis) and the second comparison (between peri- and post-sepsis).

As demonstrated in table 1, the highest rate of ESR, CRP, and WBC was observed in mean levels obtained in peri-sepsis stage compared to those measured in pre- and post-sepsis stages, with a significant difference between these stages ($p < 0.05$). The lowest level of PLT was seen in peri-sepsis (145.4 ± 54.8) significantly different compared to other stages (pre- and post-sepsis) ($p < 0.05$). Given PCT, there was no significant difference in mean levels between pre- and peri-sepsis ($p > 0.05$) and the highest level of PCT was seen in pre- and peri sepsis stages (2.5 ± 1 ng/mL). Comparing mean PCT levels in peri- and post-sepsis stages indicated a significant difference ($p < 0.05$). Finally, a statistically significant difference in C3 levels was observed between pre- and peri-sepsis stages ($p < 0.05$) as well as peri- and post-sepsis ($p < 0.05$), with the highest level of 100.9 ± 46.5 ng/mL in peri-sepsis. The associations between PCT and C3 on the one hand and ESR, CRP, WBC, and PLT on the other hand was examined, indicating an indirect linear relationship between PLT and C3 in the second stage (peri-sepsis). The same relationship was applicable to ESR and PCT levels at peri-sepsis, i.e., acute sepsis phase.

Discussion

In the present study we investigated PCT and C3 utility at early diagnosis of sepsis in ICU patients, in comparison with clinically informative values of WBC, ESR, and CRP. PCT and CRP have long been used in hospital settings for diagnosis and monitoring treatment of sepsis in critically ill patients (29) but ESR has been used clinically for almost 90 years (30). Tsalik et al. observed biomarkers such as PCT, IL-6, and CRP were strongly associated with infection, sepsis severity, and septicemia (31). Ucar et al. found that neonates with bacterial sepsis reduced thrombocyte count (32). In this study the lowest level of PLT, in comparison to other stages, was in peri-sepsis stage.

Miynaar et al. studied the usefulness of serum PCT, IL-6, LBP, and CRP levels in differentiating between SIRS and sepsis in critically ill patients. CRP, PCT, IL-6, and LBP levels were significantly higher in patients with sepsis as compared to SIRS. With PCT levels of

< 2 ng/mL in the first 24 h after ICU admission sepsis was virtually excluded. With PCT > 10 ng/mL sepsis with bacterial infection was very likely. This study showed that PCT is more useful than LBP, CRP and IL-6 in differentiating sepsis from SIRS (18).

In a study in Iran, serum levels of PCT, CRP, ESR, and WBC were compared among 60 burn cases, with and without infection, to find which one is better for sepsis diagnosis. The PCT level in the septic patients and non-survivors was significantly higher compared to the non septic and survivors, respectively. In this regard no significant difference was found in CRP, WBC, and ESR (33). Suarez-Santamaria et al. offered PCT, associated with positive blood cultures, as better at discriminating between non complicated and more severe forms of sepsis compared to CRP (34). In Charles et al.'s study PCT was less reliable for the diagnosis of sepsis in critically ill patients with secondary sepsis (35). Laboratory signs of sepsis were leukocytosis, leukopenia, immature leukocyte count less than 10%, and high CRP levels (36).

In this study C3 and PCT seem to increase during sepsis acute phase and they could be considered as rapid tests for sepsis diagnosis. Furthermore, PCT contributes to early diagnosis, follow-up, and prognosis of patients with sepsis and septic shock; therefore, it could be employed as a laboratory test with rapid diagnostic efficiency and utility of treatment response follow-up of sepsis cases. Because the final diagnosis of sepsis is made by taking blood culture that is usually time-consuming, it is recommended that biochemical markers be examined for quick diagnosis. In addition, PCT and C3 are more rapid diagnostic markers and could be proposed for sepsis diagnosis and subsequently starting antibiotic therapy.

In suspected patients with PCT $\leq 0/5$ ng/ml, it is suggested that PCT be successively measured because it is possible that PCT measurement has already done immediately after the beginning of infection. Sustained increase in plasma PCT to higher than 2 ng/ml indicates the lack of control over the infection process, and undesirable prognosis; therefore, change in treatment and type of antibiotic administered should be done for better patients' care.

Although PCT could be the best marker to differentiate between sepsis and SIRS, the decision should not be made based on only PCT. Rather, the diagnosis should be confirmed based on a series of clinical and laboratory information. Therefore, it is suggested that PCT be used for

the initial diagnosis to start treatment; then, final diagnosis could be made through blood culture and the special treatment started. However, other markers including CRP, because of high expenditures of PCT imposed on both patients and health systems, may be utilized for seeking and hence achieving a more cost-effective treatment as well.

In this study, the highest levels of ESR, CRP, and WBC were in peri-sepsis stage and these laboratory routine simple tests could be chosen over PCT and C3 for diagnosis of sepsis. In addition, PCT is not an easily available test in less developed countries and more expensive than other tests for sepsis diagnosis.

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Table 1: Comparison of mean PCT, WBC, PLT, CRP, ESR, and C3 in three stages of serum collection

		mean±SD*	min.	max.	P value
ESR (mm/h)	pre-sepsis	16.4±13.5	3	72	0.00
	peri-sepsis	41.7±21.2	18	90	
	post-sepsis	17.1±5.3	5	32	0.00
CRP (mg/dL)	pre-sepsis	40.6±33.9	90	118	0.00
	peri-sepsis	173.6±171	15	756	0.00
	post-sepsis	24.1± 22.1	2	122.4	0.00
WBC(cells/μL)	pre-sepsis	9.8±2.7	5900	14000	0.00
	peri-sepsis	12.4±3.5	9000	27000	
	post-sepsis	9.4 ±1.4	6000	12000	0.00
PLT (cells/μL)	pre-sepsis	148.9±55.2	93000	300000	0.04
	peri-sepsis	145.4 ±54.8	73000	286000	
	post-sepsis	158 ±57.2	110000	300000	0.01
PCT (ng/mL)	pre-sepsis	2.5±1	0	10	0.95
	peri-sepsis	2.5±1	0	10	
	post-sepsis	0.5±0.2	0	2	0.04
C3 (mg/dL)	pre-sepsis	78.3 ±21.3	50	120	0.02
	peri-sepsis	100.9±46.5	36	270	
	post-sepsis	87.2 ±31.3	51	205	0.04