ORIGINAL SCIENTIFIC ARTICLE

C REACTIVE PROTEIN AND PROCALCITONIN AS DIAGNOSTIC MARKERS IN CRITICALLY ILL PATIENTS WITH SUSPECTED SEPSIS

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ABSTRACT

The primary aim of this retrospective study was to estimate significance of determining C-reactive protein and procalcitonin for a diagnosis of sepsis in adult patients in early triage. Also, the aim of this study was to measure the sensitivity of the SIRS criteria, PCT and CRP levels and sepsis definitions to identify the most serious sepsis cases in the prehospital setting and at the Emergency Department (ED) triage. All patients were divided into two groups according to specific criteria for defining sepsis. First group (SIRS+ group) of patients were patients with clinically and/or laboratory confirmed sepsis (or systemic inflammatory response syndrome (SIRS) to bacterial infection with different localization). For confirmation of the SIRS we consider positive two or more clinical criteria (≥2 clinical criteria). The SIRS criteria use the clinical criteria of the Surviving Sepsis Campaign (SSC) for the SIRS, comprising at least two of the following criteria: HR > 90/min, RR > 20/min and temperature < 36° or ≥ 38.3°C and the next laboratory parameters such as leucocytosis > 15x109/L, leucopenia < 4x109/L, > 10% immature leucocytes. Second group of patients were patients with the SIRS negative criteria as a diagnostic tool (SIRS- group). We have founded that the CRP showed high sensitivity but no specificity in patients with sepsis, but on the other side, the PCT as a diagnostic marker showed a high sensitivity and high specificity in these patients. Also, the PCT is in positive correlation with the SIRS criteria, which could be of a clinical significance in early diagnosis of septic infections.

Keywords: *sepsis, C-reactive protein, procalcitonin, early diagnostic markers.*

INTRODUCTION

Patients hospitalized in the Intensive Care Units have a high risk of developing different complications. Infection is one of the most common and most serious complications. Infection is defined as "a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms" (1, 2).

In critically ill patients the intensity of infections is difficult to estimate especially in the initial stages of the disease. The diversity of a clinical picture of the underlying disease can often lead to an altered clinical presentation of the infection. In some cases, infection can be associated with an inadequate or inappropriate host response, and when this results in the development of organ dysfunction, the term "sepsis" is used (2, 3). Because of the complexity of reactions that are simultaneously triggered in the body and at various levels of homeostatic mechanisms of sepsis in patients, the intensity of the infection itself may vary from local infection to the development of sepsis with multiple organ failure (MOF) (4-7).

The incidence of sepsis is increasing at global level. Approximately 2% of hospitalized patients are under suspicion of sepsis. At the same time, the mortality rate remains high despite current progress in understanding pathophysiological mechanisms, diagnosis and therapy (8, 9). Sepsis and its various adverse sequelae, such as septic shock, the Acute Respiratory Distress Syndrome (ARDS), and Multiple Organ Dysfunction (MODS) continue to be among the most common causes of death in the non-coronary Intensive Care Unit (10).

For the past thirty years, a great deal of attention has been paid to the concept of sepsis as better as possible, to determine clinical and laboratory parameters for its rapid diagnosis and to improve the treatment of sepsis.

The importance of rapid identification of a patient with a suspicion on sepsis as well as the microorganisms of causative agents of severe infections is a crucial for the patient survival and a choice of antibiotic therapy (11). Guidelines for sepsis therapy are recommended by intravenous the use of wide-spectrum antibiotics within 1 h of the recognition of severe sepsis and septic shock. The delay in antibiotic therapy is associated with a significant increase in mortality (12).

In addition to the recommended clinical tests in the rapid identification of septic patients, with hemocultures that represent the "gold standard", numerous biomarkers from the blood and body fluids of the patient are used. An inflammatory markers, such as leukocyte (white blood cells - WBC) count in complete blood picture, C-reactive protein (CRP), and procalcitonin (PCT), have been applied in the diagnosis of the inflammation and infection.

White blood cells (WBC) or leucocytes produce, transport and distribute antibodies as a part of the human immune system response. Normal values of white blood cells are $4\text{-}10x10^9$ in adult. Number of leukocytes is an unspecified and insensitive indicator, but if it is elevated it can indicate the occurrence of a local or systemic infection (12, 13). Neutrophils and monocytes are also activated during sepsis. A poor prognosis is associated with lower expression of activation markers on monocytes and neutrophils, which indicates that poor outcome in these patients is due to a compensatory anti-inflammatory response (14).

In physiological conditions, the PCT concentrations are low (<0.15 ng/ml). Cytokines caused by the infection promote the production of extrathyroide by increasing the PCT level after 3-4 hours and reaching maximum values after 6 h. This level is maintained for the next 24-48 h. PCT is less than 0.5 ng/ml, indicating localized bacterial infection. Values of 0.5-2 ng/ml for the possible systemic infection. Values of 2-10 ng/ml and more for the safe systemic infection (15). PCT is a good marker of the bacterial infection in patients with systemic autoimmune diseases, even when they are being treated with corticosteroids and immunosuppressive agents. In such patients they rarely exceed the limit of 5 ng/ml (15).

The primary aim of this retrospective study was to estimate significance of determining C-reactive protein and procalcitonin for the diagnosis of sepsis in adult patients in early triage. Also, the aim of this study was to measure the sensitivity of the SIRS criteria, PCT and CRP levels and sepsis definitions to identify the most serious sepsis cases in the prehospital setting and at the Emergency Department (ED) triage.

PATIENTS AND METHODS

Study design and setting

This retrospective cross sectional clinical study included 55 patients which were admitted between May 2018 and August 2018 in the Health Center Valjevo in Serbia. This study was performed under the Good Clinical Practice guidelines and according to the Declaration of Helsinki.

Population and data sources

All patients with age above 18 and suspected or proven infection were included. Patients <18 years old, prisoners, pregnant women, patients in cardio-respiratory arrest, severe trauma victims, malignancies and epileptic seizure cases were excluded.

All patients were divided into two groups according to specific criteria for defining sepsis. First group (SIRS+ group) of patients were patients with clinically and/or laboratory confirmed sepsis (or systemic inflammatory response syndrome (SIRS) to bacterial infection with different localization). For confirmation of the SIRS we consider positive two or more clinical criteria (≥2 clinical criteria). The SIRS criteria use the clinical criteria of the Surviving Sepsis Campaign (SSC) for SIRS (16), comprising at least two of the following criteria: HR > 90/min, RR > 20/min and temperature

<36° or ≥ 38.3°C and the next laboratory parameters such as leucocytosis > $15x10^9$/L, leucopenia < $4x10^9$/L, > 10% immature leucocytes. Second group of patients were patients with the SIRS negative criteria as a diagnostic tool (SIRS-group).

During the period of three months, we observed the anamnestic and clinical data from medical history such as demographic characteristics (sex, age), comorbidities and previous diseases, reason of hospitalization, levels of procalcitonin and C reactive protein in serum samples, biological characteristics (laboratory values, microbiological data of blood and urine samples), therapy interventions (surgical intervention), as well as the SIRS criteria (positive or negative) and outcome for each patient.

Statistical analysis

Simple descriptive statistics were used to analyze population characteristics. We described data using percentages or medians with the Interquartile Range (IQR). To evaluate the differences between means we used Mann Whitney (Z test) and Spearman correlation (Rho coefficient) to evaluate associations between categorical and continual variables. Sensitivities, specifies (ROC curve), medians, averages and percentages were calculated using the SPSS 22.0, statistical software.

RESULTS

Demograhic characteristics of study population

In all, 34 (61.8%) patients were male, the mean age was 67.18±1.95 years (range: 31-90), and 29 (52.7%) were selected for surgical intervention (Table 1). Following the SIRS criteria, 42 (76.36%) patients were classified in the SIRS+ group and 13 (23.64%) in the SIRS- group (Table 1). Hemoculture test was positive in 24 cases in SIRS+ group and in 2 cases in SIRS negative group. Urine culture test was positive in 16 patients in SIRS+ positive group and in 2 patients in SIRS- group (Table 1). Also, negative outcome was present in 21 patients in SIRS+ group (Table 1).

Table 1. Study group characteristics

	All patients	**SIRS+ group**	**SIRS- group**
N (cases)	55 (100%)	42 (76.36%)	13 (23.64%)
Sex *	M 34 (61.8%) F 21 (38.2%)	M 24 (57.14 %) F 18 (45.86%)	M 10 (76.9%) F 3 (23.1%)
Mean age (years)	67.17±1.95	68.48±2.05	65.85±5.14
Surgical intervention	No 29 (52.7%) Yes 26 (47.3%)	No 26 (61.9%) Yes 16 (38.1%)	No 3 (23.07%) Yes 10 (76.93%)
Hemoculture test	No 29 (52.7%) Yes 26 (47.3%)	No 18 (42.85%) Yes 24 (57.15%)	No 11 (84.6%) Yes 2 (15.4%)
Urine Culture Test	No 37 (67.3%) Yes 18 (32.7%)	No 26 (61.9%) Yes 16 (38.1%)	No 11 (84.6%) Yes 2 (15.4%)
Outcomes (Mortality)	No 34 (61.8%) Yes 21 (38.2%)	No 21 (50%) Yes 21 (50%)	No 13 (100%) Yes 0 (0%)

According to the localization of infection, in all patients gastrointestinal tracts is the most common with 26 (47.27%) patients. In SIRS+ group is 17 patients (40.47%) and SIRS-9 (69%) patients the cause of gastrointestinal tract infections. Respiratory infection was present in 9 (16.36%) patients where 8 (19.36%) in SIRS+ group and 1 in SIRS-group (Table 2). Genito-urinary, Skin/Joint and Central nervous system represented by 3 (5.45%) patients. 1 patient in genito-urinary tract in SIRS- group. Other in SIRS+ genito-urinary 2 (5.45%), Skin/Joint 3 (7.14%) and Central nervous system 3 (7.14%) patients. Also, 2 patients (4.76%) unknown focus of infection in SIRS+ group 4.76%.

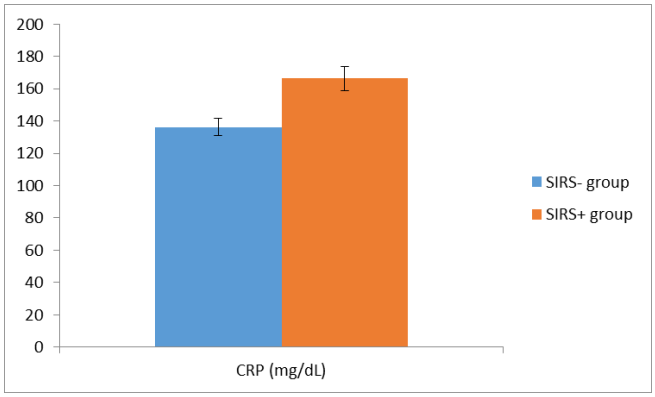
Table 2. Focus of infection in study population

Focus of infection	All patients	SIRS+ group	SIRS- group
N (cases)	55 (100%)	42 (76.36%)	13 (23.64%)
Respiratory (%)	9 (16.36%)	8 (19.04%)	1 (7.69%)
Genito-urinary (%)	3 (5.45%)	2 (4.76%)	1 (7.69%)
Gastrointestinal (%)	26 (47.27%)	17 (40.47%)	9 (69.23%)
Skin/joint (%)	3 (5.45%)	3 (7.14%)	0 (%)
Central nervous system (%)	3 (5.45%)	3 (7.14%)	0 (%)
Cardiovascular (%)	9 (16.36%)	7 (16.66%)	2 (15.38%)
Unknown (%)	2 (9.09%)	2 (4.76%)	0 (%)

Sensitivity of C reactive protein in SIRS+ and SIRS- groups

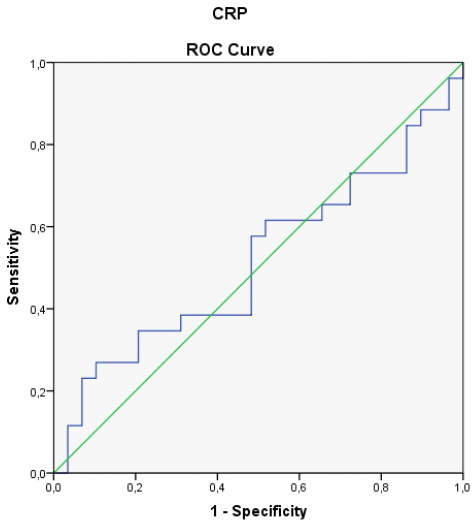
Mean value of the CRP in SIRS+ was 166.386 mg/dL and in SIRS- group was 136.21 mg/dl. Levels of the CRP in SIRS+ and SIRS- groups were very similar and without a statistically significant difference (p= 0.276) (Figure 1) but with slightly higher levels of this diagnostic marker in a group of patients with positive criteria for the systemic inflammatory response syndrome. Furthermore, we evaluated the sensitivity of the CRP in diagnosing sepsis by statistical methods (Figure 2). The area under ROC curve for C-reactive protein was 0.516. Cut-off value for C reactive protein was 1.685 mg/dl (sensitivity 96.2%, specificity 100.0%) (Figure 2).

Figure 1. Levels of CRP (mg/dl) in all groups of patients



Values are presented as mean±standard deviations. Asterisks (*) presents statistical significant differences (p<0.05) between means in SIRS+ and SIRS- groups confirmed by Mann Whitney test Z test.

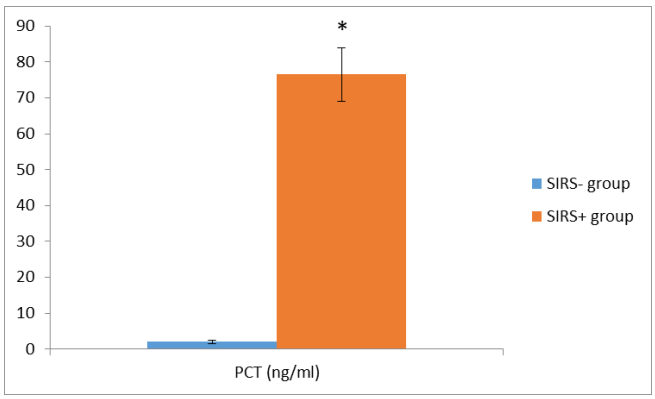
Figure 2. ROC curve for CRP



Sensitivity of procalcitonin in SIRS+ and SIRS- groups

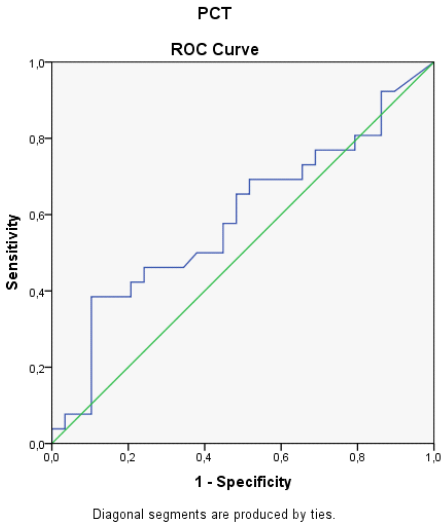
Mean value of the PCT in SIRS+ was 76.489 ng/mL and in SIRS- group was 2.085 ng/ml. Levels of the PCT in SIRS+ and SIRS- groups were different and with a statistical significant difference (p= 0.023) (Figure 3). Values of the PCT was significantly higher in group of patients with positive criteria for systemic inflammatory response syndrome. Also, we evaluated the sensitivity of the PCT in diagnosing of sepsis by statistical methods (Figure 4). The area under ROC curve for procalcitonin was 0.590. Cut-off value for PCT was 0.060 mg/dl (sensitivity 92.3%, specificity 82.7%) (Figure 4).

Figure 3. Levels of the PCT (ng/ml) in all groups of patients



Values are presented as mean±standard deviations. Asterisks (*) presents statistical significant differences ($p<0.05$) between means in SIRS+ and SIRS- groups confirmed by Mann Whitney test Z test.

Figure 4. ROC curve for the PCT



Correlation between CRP and PCT in study population

Procalcitonin and C reactive protein are in moderate positive correlation ($p=0.024$, $Rho=0.305$) in study group. Separately, the CRP was not in association with theSIRS criteria ($p=0.280$, $Rho=0.148$) while levels of the PCT were in moderate positive correlation with SIRS criteria ($p=0.021$, $Rho=0.310$) in study group (Table 3).

Table 3. Correlation between diagnostic parameters and SIRS tools in patients with and without sepsis. Results are presented as p values (p) and Spearman correlation coefficient (Rho).

Correlations

			PCT	CRP	SIRS_criteria
Spearman's rho	PCT	Correlation Coefficient	1,000	,305*	,310*
		Sig. (2-tailed)	.	,024	,021
		N	55	55	55
	CRP	Correlation Coefficient	,305*	1,000	,148
		Sig. (2-tailed)	,024	.	,280
		N	55	55	55
	SIRS_criteria	Correlation Coefficient	,310*	,148	1,000
		Sig. (2-tailed)	,021	,280	.
		N	55	55	55

*. Correlation is significant at the 0.05 level (2-tailed).

DISCUSSION

The primary aim of this retrospective study was to estimate significance of determining C-reactive protein and procalcitonin for the diagnosis of sepsis in adult patients in early triage. Also, the aim of this study was to measure the sensitivity of the SIRS criteria, PCT and CRP levels and sepsis definitions to identify the most serious sepsis cases in the prehospital setting and at the Emergency Department (ED) triage.

C-reactive protein (CRP) is an acute-phase reactant, synthesized by the liver and adipocytes mainly in response to IL-6. IL-6 is a cytokine that generates an initial response to injury or infection; its levels rise significantly during early sepsis, and therefore it is used to diagnose sepsis and predict the outcome of the patient's treatment (17). Synthesis of C-reactive protein begins in hepatocytes. After a latent period of about 6h, the serum level is doubled every 8h, and the highest concentration reaches 36-48h from the duration of the inflammatory process. When administered with an adequate

antibiotic therapy, the CRP decreases in the first two days to 50%. The normal C-reactive protein serum concentration is 0.8 mg/l. The level above this value indicates abnormalities and indicates a disease (12).

In our study, mean value of the CRP in SIRS + was 166.386 mg/dL and in SIRS- group was 136.21 mg/dl. Levels of the CRP in SIRS+ and SIRS- groups were very similar and without a statistically significant difference (p=0.276) (Figure 1) but with slightly higher levels of this diagnostic marker in group of patients with positive criteria for systemic inflammatory response syndrome. Furthermore, we evaluated the sensitivity of CRP in diagnosing of sepsis by statistical methods (Figure 2). The area under ROC curve for C-reactive protein was 0.516. Cut-off value for C reactive protein was 1.685 mg/dl (sensitivity 96.2%, specificity 100.0%) (Figure 2).

Meta analyses conducted by Shabuj et al, evaluated a role of the CRP as prognostic factors in neonatal sepsis. Meta-analysis showed that the CRP had a moderate accuracy (AUC=0.8535) for the diagnosis of NS. CRP is a helpful biomarker for diagnosis of NS. However, authors should combine the results with clinical symptoms and signs, laboratory and microbial results (18). On the other hand, Ticinesi et al measured the CRP in geriatric patients hospitalized for acute infection. C-reactive protein (CRP) is the most used biomarker of inflammation, and a substantial amount of the reference has demonstrated its importance and clinical usefulness in adult subjects. They concluded that the CRP dosage at hospital admission is helpful to detect acute infection, and particularly sepsis, in geriatric patients, and that CRP elevation may provide valuable short-term prognostic information. Also, at the current state of art, serial CRP measurements are instead not indicated to monitor disease course and plan hospital discharge in this setting (19).

Definitely, the clinical significance of serum CRP determination has not been completely clarified in older subjects with an acute infection, especially in the light of the age-related rearrangements in immunity and cytokine production.

Procalcitonin (PCT) is considered a relatively innovative and highly specific biomarker for the diagnosis of clinically relevant bacterial infections and sepsis; therefore it is increasingly recognized as an important diagnostic tool in clinical practice (20, 21). Procalcitonin is a prohormone calcitonine with secretory protein properties, which, in normal metabolic conditions, is only produced in C cells of the thyroid gland. After proteolytic digestion, only hormone activated calcitonin is secreted. For this reason, the blood of healthy people has the level of PCT very low or immeasurable (22). In patients with bacterial infection in the blood, high concentrations of intact PCT were detected. High circulation levels of PCT do not flow from the thyroid gland. An increased PCT concentration in patients with infection is secreted in the extratiroide tissue, they are the predominantly macrophage-monocytic system of various organs particularly lungs, liver and intestinal tract (23).

Furthermore, in our study mean value of the PCT in SIRS+ was 76.489 ng/mL and in SIRS- group was 2.085 ng/ml. Levels of the PCT in SIRS+ and SIRS- groups were different and with a statistically significant difference (p=0.023) (Figure 3). Values of the PCT was significantly higher in the group of patients with positive criteria for the systemic inflammatory response syndrome. Also, we evaluated the sensitivity of PCT in diagnosing of sepsis by statistical methods (Figure 4). The area under ROC curve for procalcitonin was 0.590. Cut-off value for PCT was 0.060 mg/dl (sensitivity 92.3%, specificity 82.7%) (Figure 4).

Prompt and accurate diagnosis of sepsis is of the high importance for clinicians. Procalcitonin (PCT) and C-reactive protein (CRP) have been proposed as markers for this purpose. Beqja-Lika et al examined the serum PCT levels in diagnosing of sepsis as an early diagnostic marker (24). Levels of the PCT and CRP were taken from 60 patients with sepsis criteria and 39 patients with the SIRS symptoms. Sensitivity, specificity and predictive values for the PCT and CRP were calculated. They found that PCT and CRP levels were increased in parallel with the severity of the clinical conditions of patients. The mean PCT level in patients with sepsis was 11.28 ng/ml versus 0.272 ng/ml in patients with the SIRS symptoms, with a sensitivity of 97.4% and a specificity of 96.6% for PCT >0.5 ng/ml. The mean CRP level in septic patients was 146.58 mg/l vs. 34.4 mg/l in patients with SIRS, with a sensitivity of 98.6% for sepsis and a specificity of 75% for CRP > 11mg/l. They concluded that the PCT and CRP values are useful markers to determine an early diagnosis and severity of an infection and the PCT was found to be a more accurate diagnostic parameter for differentiating SIRS from sepsis and may be helpful in the follow-up of critically ill patients (24).

Procalcitonin as a diagnosis and prognosis marker for sepsis: Many studies have demonstrated that serum PCT levels are increased in patients with sepsis, and the high levels of PCT correlate with the outcome of the disease. PCT can be used for differential diagnosis, prognosis, and follow-up of critically sick patients. However, it cannot be recommended as the single definitive test for sepsis diagnosis but rather it must be interpreted in context with information from clinical data (25, 26).

CONCLUSION

We can conclude that the CRP showed a high sensitivity but no specificity in patients with sepsis, but on the other side, the PCT as a diagnostic marker showed high sensitivity and high specificity in these patients. Also, the PCT is in positive correlation with SIRS criteria, which could be of a clinical significance in early diagnosis of septic infections. Further the cohort prospective clinical study is necessary to confirm our assumptions.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2013. Voluntary written and informed consent was obtained from each participant prior to enrollment in the study

COMPETING INTERESTS

There are no conflicts of interest.

FUNDING

None.

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