ORIGINAL ARTICLE

Diagnostic and prognostic value of procalcitonin in patients with sepsis

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ABSTRACT

Aim To investigate predictive value of procalcitonin in diagnosis of sepsis in predicting positive blood culture, and possibility to predict final outcome in septic patients.

Method This prospective study involved 106 hospitalized patients who met two or more criteria for systemic inflammatory response syndrome (SIRS). In comparison to Sepsis Related Organ Failure Assessment score (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II score procalcitonin (PCT), C-reactive protein and lactate levels were used to predict final outcome in septic patients (recorded as 28-day survival or non-survival). Using Receiver operating characteristic (ROC) curve the area under the curve (AUC) was calculated for diagnostic value and accuracy of different parameters with the best sensitivity and specificity for given cut-off values.

Result Fifty-two out of 82 patients with documented sepsis had positive blood culture. Procalcitonin showed the best predictive value for both diagnosis of sepsis and bacteraemia with the cut-off value of 0.57 ng/mL (AUC 0.99) and 4.68 ng/mL (AUC 0.94), respectively. Serum lactate level showed the best 28-day mortality predictive value with the cut-off value of 3.25 mmol/L (AUC 0.95), and procalcitonin with the cut-off value of 15.05 ng/mL (AUC 0.92), followed by SOFA (AUC 0.92), CRP (AUC 0.84) and APACHE II score (AUC 0.83).

Conclusion Monitoring of PCT in SIRS-positive patients raises possibility to distinguish between patients with sepsis and those with non-infectious SIRS. A significant correlation between PCT and SOFA, and APACHE II score in non-surviving septic patients indicates that PTC combined with clinical score could be useful for assessing severity of infection.

Key words: SIRS, severity of sepsis, lactate, C-reactive protein, APACHE II, SOFA score

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INTRODUCTION

Sepsis is defined as the presence (probable or documented) of infection together with systemic inflammatory response to infection. It is a life-threatening disease which causes millions of deaths globally each year (1). Sepsis is caused by immune systemic response to a serious infection, most commonly bacteria, but also fungi, viruses and parasites.

It is difficult to recognize patients with sepsis because there is a lack of specific clinical signs (2). Bacterial cultures are considered as the gold standard method for definitive detection of bacterial infection, but microbiological cultures require time. They do not reflect the host systemic inflammatory response and may not be positive in septic patients who have been receiving antibiotics (3). Despite the improvement in diagnostic capability to detect disease, patients with sepsis are a heterogeneous group and their condition is very often difficult to recognize especially in the early stages of the disease (4). The definition of sepsis which involves SIRS + proof or suspicion of infection, could be very broad and it includes a large number of patients who do not have to develop sepsis (2). At the same time, the transition from SIRS and sepsis to severe sepsis develops over time differently in various patients so that even the progression of serious disease could be unrecognized until it reaches the late stage (2). In comparison to numerous biological markers, which have been examined in sepsis, procalcitonin has the best diagnostic value (5). Procalcitonin plasma concentration rises very rapidly (6-12h) after infection, which had caused systemic response (6). Besides that, PCT plasma concentration level is indirectly related to the severity of sepsis and the systemic inflammatory reaction, and PCT plasma elimination half-life of about day gives indications of the course of the disease and the success of therapy (7).

Literature emphasizes the importance and a role of biochemical markers, especially procalcitonin levels for early detection of infectious process in critically ill patients, which is very important (8). Even that, procalcitonin is not routinely used in Intensive Care Units at University Clinical Centre Tuzla in evaluation of septic patients.

The aim of this study was to investigate the importance and role of procalcitonin in early diagnosis of sepsis in critically ill patients, possibility to distinguish between patients with sepsis and those with non-infectious systemic inflammatory response syndrome (SIRS), in comparison to severity of sepsis, and the possibility to predict fatal outcome in patients with sepsis.

PATIENTS AND METHODS

Patients and study design

In the prospective study, during the period betwee July 2013 and June 2014, 106 patients hospitalized in the University Clinical Centre Tuzla, Bosnia and Herzegovina, were enrolled. According to the ACCP/SCCM (American College of Chest Physicians/Society of Critical Care Medicine) (2), in all patients who met two or more criteria for systemic inflammatory response syndrome (SIRS) (body temperature >38 or <36 ºC, heart rate >90 beats/min, respiratory rate >20 breath/min or pCO_2<4.3 kPa, white blood cell count >12.0 x 10^9/L or <4.0 x 10^9/L, or >10% immature forms) predictive value of procalcitonin in sepsis was analysed.

In total of 82 (out of 106; 77.36%) patients infection was proved (sepsis group), and in 24 (22.64%) patients the source of infection was not identified (the group of non-infectious SIRS). Fifty-two (63.41%) patients with sepsis had a positive blood culture (BC+) and 30 (36.59%) patients had a negative blood culture (BC-). Twenty-four (22.64%) patients were with SIRS, 43 (45.58%) patients had sepsis (SIRS+proof of infection), 31 (32.86%) patients had organ dysfunction with severe sepsis, and eight (8.06%) patients were diagnosed with septic shock (sepsis-associated hypotension that is associated with lactic acidosis or organ hypoperfusion and cannot be reversed by the administration of intravenous fluids). Thirty-nine patients had an organ dysfunction (47.56%), and 16 (19.51%) patients were succumbed to sepsis.

Exclusion criteria were: patients with malignancy or haematological disorders, patients on antitumor drug therapy, patients with any kind of transplantation, and patients after a surgery treatment (less than 48h).

The research was done respecting ethical standards of the Declaration of Helsinki. The study approval was obtained from the Ethics Committee of University Clinical Centre Tuzla.

Methods

Procalcitonin (0.05-0.1 ng/mL) and C-reactive protein (CRP) (0.0-3.0 mg/L) concentration was measured in sera samples, and lactate concentration (<2.0 mmol/L) in capillary blood samples. Procalcitonin level was measured in sera via the automatic analyser VIDAS (B.R.A.H.M.S. PCT assay) (bioMérieux, Marcy L'Etoile, France). The lower limit of detection of the assay sensitivity was 0.05 ng/mL, and the functional assay sensitivity was 0.09 ng/mL (VIDAS B.R.A.H.M.S. PCT package insert; bioMérieux). The values between SIRS-positive non-infected patients (n=24) and patients with documented sepsis (n=82), as well as between septic patients with positive blood culture (n=52) and those with negative blood culture (n=30) were compared.

Sepsis Related Organ Failure Assessment score (SOFA) (9) and Acute Physiology and Chronic Health Evaluation (APACHE) II score (10) were obtained from all patients at the same time and compared to procalcitonin concentration.

The SOFA score has been developed by European Society of Critical Care Medicine (ESCCM) in 1994, as a system for measuring the status of the patients in the intensive care unit (ICU). SOFA score is based on six different scores, one of each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological system. According to SOFA score criteria (9) different variables and parameters (pO_2/FiO_2, platelets count, bilirubin concentration, creatinine concentration, mean arterial pressure or vasopressors required, Glasgow coma score) are included in each of the organ system and a definite score is given to that state varying from 0-4, all of which are later added to calculate the SOFA score (out of maximum 24).

According to APACHE II score criteria (10) 12 different variables (temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, pH or HCO_3, sodium, potassium, creatinine, haematocrit, white blood count, Glasgow coma score) are included, and a definitive score is given to that state varying 0-4 of all, which is later added to age points (0-6), chronic health points (0-5), and then final APACHE II score (out of maximum 59) is calculated.

Statistical analysis

Procalcitonin concentration, C-reactive protein concentration and lactate level in comparison to SOFA and APACHE II score were used to predict final outcome in septic patients (recorded as 28-days survival or non-survival).

Normality of the data distribution influenced the decision of whether to apply mean±standard deviation or median with interquartile range in descriptive statistics. The non-parametric Mann-Whitney test or Student's t-test was used to compare continuous variables and the $\chi 2$ or Fisher's exact tests was used to compare categorical variables. Binominal logistic regression, stratified on the presence or absence of death, was performed to adjust for potential confounding variable, to assess independent relationship between investigated parameters and final outcome in patients with sepsis. Spearman's non-parametric correlation coefficient was used for calculating correlation between procalcitonin and severity of sepsis and correlations between procalcitonin, C-reactive protein, lactate, SOFA and APACHE II scores with fatal outcome. One way ANOVA test was used to analyse procalcitonin concentration with different stage severity of sepsis. Using Receiver operating characteristic (ROC) curve the area under the curve (AUC) for diagnostic value and accuracy of different used parameters with the best sensitivity and specificity for given cut-off values was calculated. Positive and negative predictive values were calculated using recommended cut-off values. The $p<0.05$ was considered as statistically significant.

RESULTS

A total of 52 (63.41%) out of 82 patients with sepsis had a positive blood culture. The most common sources of infection were urinary tract (24/82; 29.3%), abdomen and digestive system (24/82; 29.3%), respiratory system (19/82; 23.2%), skin and soft tissue (12/82; 15%), and other (2.4%).

Etiology of infections provided by blood cultures were: Gram-negative bacterial infections in 31 (60%), Gram-positive infections in 21 (40%) patients, and in 30 (36.59%) patients blood cultures were negative. Presented Gram-negative bacterial species were *Escherichia coli*, in 13 (25%), *Acinetobacter baumannii*, in nine (17.31%), *Klebsiella pneumoniae*, in three (5.77%), *Proteus mirabilis* in two (3.85%) patients, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Salmonella enteritidis* and *Serratia* in one (1.92%) case each. The most

Table 1. Receiver operating characteristic (ROC) for procalcitonin (PCT), C-reactive protein (CRP) and lactate for prediction of sepsis and positive blood culture

	Sepsis			BC(+)		
	Procalcitonin	**CRP**	**Lactate**	**Procalcitonin**	**CRP**	**Lactate**
Cut off	0.57 ng/mL	165.0 mg/L	2.05 mmol/L	4.68 ng/mL	239.7 mg/L	2.35 mmol/L
AUC	0.99±0.001	0.98±0.01	0.87±0.04	0.94±0.02	0.76±0.05	0.79±0.06
p	<0.0001	<.0001	<.0001	<0.001	0.0001	<0.0001
95% CI	0.99 -1.0	0.96 - 0.1	0.79 - 0.94	0.9 - 0.99	0.65 - 0.86	0.68 - 0.91
Sensitivity (%)	97.56	84.15	73.13	73.08	67.31	65.22
Specificity (%)	95.83	95.83	100.00	96.67	76.67	76.19
PPV (%)	98.76	85.7	100.00	97.44	83.33	85.71
NPV (%)	92.00	63.89	57.14	67.44	57.5	50.0
Accuracy (%)	97.17	86.79	79.31	81.71	70.73	68.56

BC(+), blood positive culture; AUC, area under curve; CI, confidence interval; PPV, positive predictive value ; NPV, negative predictive value

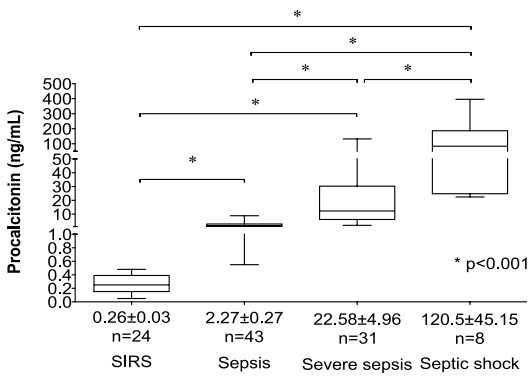

Figure 1. Procalcitonin concentration (ng/mL) during various stages of sepsis; SIRS, systemic inflammatory response syndrome;

common species of Gram-positive bacteria were *Staphylococcus aureus*, in nine (17.31%), coagulasa-negative *Staphylococcus*, in eight (15.38%), *Enterococcus*, in two (3.85%), *Bacillus* and *Streptococcus* in one (1.92%) case each.

There was a significant difference in procalcitonin concentrations between SIRS positive non-infected patients, 0.25 ng/mL (range 0.05-0.58) and patients with documented sepsis, 3.495 ng/mL (range 0.55-395.6) (p<0.001), as well as between patients with sepsis who had positive blood culture (BC+), 9.915 ng/mL (range 1.2-395.6) and those with negative blood culture (BC-), 1.295 ng/mL (range 0.55-4.81) (p<0.01). Procalcitonin level was increased by high severity of sepsis (r=0.91; p<0.0001) (Figure1).

Procalcitonin showed the best predictive value in the diagnosis of sepsis with the cut-off value of 0.57 ng/mL (AUC 0.99), with positive predictive value of 98.76%, negative predictive value of 92.0%, and the accuracy of 97.1%. Procalcitonin also showed the best predictive value in predicting bacteremia with the cut-off value of 4.68 ng/mL (AUC 0.94), positive predictive value of 97.44%, negative predictive value of 67.44%, and with the accuracy of 81.71% (Table1).

When considering the outcome, the non-survivors had higher SOFA scores (p<0.0001), and APACHE II scores (p<0.01) in comparison to survivors (Table 2). The SOFA score >7 was associated with higher mortality (11/21; 52.38%) in comparison to lower SOFA score (4/58; 6.89%) with fatal outcome. Patients with APACHE II score ≤ 9 had lower mortality in comparison to patients with APACHE II score 10-19 (8/36; 12.22%) as well as the patients with APACHE score >20 (7/16; 43.75%) (p<0.01).

There was strong positive correlation between procalcitonin, CRP, lactate concentration, SOFA and APACHE II scores with fatal outcome (p<0.0001 for all; Spearman coefficient of correlation: procalcitonin 0.57; 95% CI: 0.3952-0.6996; CRP 0.46; 95% CI: 0.2637-0.6160; lactatee 0.66; 95% CI: 0.4910-0.7787; SOFA score 0.58; 95% CI: 0.4006-0.7101; APACHE II score 0.45; 95% CI: 0.2486-0.6150). Serum lactate concentration showed the best predictive value in predicting 28-day mortality with the cut-off value of 3.25 mmol/L (AUC 0.95). Procalcitonin was on the second place with the cut-off value of 15.05 ng/mL (AUC 0.92), followed by SOFA

Table 2. Biochemical parameters, sepsis related organ failure assessment (SOFA) score and acute physiology and chronic health evaluation (APACHE) II scores in septic patients with fatal outcome

Parameter	**Non-survival**	**Survival**	
	Median (range)	**Median (range)**	**p**
Procalcitonin (ng/mL)	17.22 (2.01-209.5)	1.105 (0.05-16.35)	0.0126
CRP (mg/L)	269.5 (168-500.7)	164.95 (13.6-433)	<0.0001
Lactate (mmol/L)	3.5 (2.2-14.5)	1.7 (1.0-3.7)	0.0059
SOFA score	9 (6-17)	4 (1-9)	<0.0001
APACHE II score	19 (12-38)	11 (1-25)	0.0003

CRP, C-reactive protein;

Table 3. Receiver operating characteristic (ROC) for procalcitonin (PCT), C-reactive protein (CRP), lactate, sepsis related organ failure assessment (SOFA) score and acute physiology and chronic health evaluation (APACHE) II score for prediction of fatal outcome in sepsis

	Death				
	PCT	**CRP**	**Lactate**	**SOFA score**	**APACHE II score**
Cut-off	15.05 ng/mL	294.7 mg/L	3.25 mmol/L	6.5	17.5
AUC	0.92± 0.03	0.84±0.05	0.95±0.02	0.92±0.03	0.83±0.05
p	<0.0001	<0,0001	< 0.0001	< 0.0001	< 0.0001
95% CI	0.85 - 0.98	0.74 - 0.93	0.91 - 0.99	0.86 - 0.98	0.74 - 0.92
Sensitivity (%)	50.0	43.75	60.0	73.33	66.67
Specificity (%)	98.53	89.71	98.08	84.38	81.25
PPV (%)	88.89	50.0	90.0	52.38	45.45
NPV (%)	89.33	87.14	89.47	93.1	91.23
Accuracy (%)	89.29	80.95	89.55	82.28	78.48

AUC, area under curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value

Table 4. Multivariate analysis for sepsis, positive blood culture, and fatal outcome in sepsis

	Sepsis			**BC (+)**			**Death**		
	K	p	OR	K	p	OR	K	p	OR
Procalcitonin	0.058	0.001	1.060	0.059	0.002	1.061	0.055	0.049	1.056
CRP	-0.004	0.827	0.996	-0.012	0.520	0.988	-.0018	0.602	0.982
Lactate	-0.143	0.828	0.867	-0.222	0.753	0.801	4.533	0.079	93.071
Constant	-3.143	0.007	0.043	-2.157	0.080	0.116	-72.06	0.030	0.000

BC (+), positive blood culture; K, Coefficient of regression; OR, odds ratio; CRP, C-reactive protein;

score (AUC 0.92), CRP (AUC 0.84) and APACHE II score (AUC 0.83) (Table 3).

In multiple variance model, procalcitonin was the only independent predictor for sepsis, bacteremia and 28-day mortality in patients with sepsis (Table 4).

DISCUSSION

The ability to diagnose or exclude suspected sepsis is vitally important for patients' outcomes. It has been proven that prompt diagnosis of sepsis and adequate and early initiated therapy lead to better outcome and decrease mortality caused by sepsis (11).

Acute phase protein, C-reactive protein is a widely known marker of inflammatory response. Because the level of CRP rises much more significantly during acute inflammation then the level of other acute phase reactant, the test has been used for decades to indicate the presence of significant inflammatory or infectious disease (12). Although its low specificity may be primary drawback as biomarker of sepsis in adults, it is commonly used to screen for early onset sepsis because its sensitivity is generally considered to be very high in this settings (13).

In septic patients, the CRP levels often are already increased to a certain limit, which often will not or cannot be exceeded if the condition becomes more severe since this limit is the upper range of concentrations usually induced (14). Besides statistically significant distinction of this parameter in differentiating between SIRS and sepsis (15,16), a great number of studies have confirmed a significant predictive CRP value in the early diagnosis of sepsis, and in predicting positive blood culture results (17-20). Better predictive CRP value obtained in our study could be explained by the fact that the marginal CRP value (165.0 mg/L) was higher and that leads to higher sensitivity (84.15%) and specificity (95.83%) of this parameter in diagnosis of sepsis. Lower, but still significant predictive CRP value, as it was the case in our study, was found in the prediction of positive blood culture results in the research of Patil et al. (19); they have found that marginal value of CRP (150 mg/L) had sensitivity of 69.6 % and specificity of 52.9 % (AUC 0.64). The results of this study suggest that CRP with very high values may point to bacteraemia (cut off 239.7 mg/L; AUC 0.76)

Procalcitonin was first described as a sepsis induced protein detectable in the plasma of patients with sepsis and infection in the early 1990s (21). Since then procalcitonin has been evaluated in multiple clinical settings as a tool to distinguish bacterial infection from other inflammatory states and infectious processes (22). The diagnostic capacity of PCT is superior to that of other parameters of infection and inflammation in certain indications due to the close correlation

between the PCT concentration and the severity of systemic inflammation, the preferential induction of PCT during inflammation of bacterial origin, PCT's high concentration range, especially during the severe stages of sepsis and systemic inflammation (8). PCT is considered a good biomarker of sepsis that correlates with extent and severity of infection (23) and a reliable test to rule out or predict bacteraemia in patients with acute fever (24, 25). The predictive significance of procalcitonin in diagnosis of sepsis (15-18) and bacteraemia (15-20, 26-28) has been examined at different marginal values to obtained best sensitivity and specificity. We also found the significant differences in PCT between SIRS positive non-infected and SIRS positive patients with documented sepsis, and between blood culture positive and blood culture negative sepsis. The possible differences in the median absolute value for PCT in our study, and between some other studies (15-18, 26-28), occur because there has been a large time interval between obtained results and because of an inclusion of the patients whose results had extremely high values. It has resulted in some higher marginal values (cut off: for sepsis 0.57ng/mL; for bacteraemia 4.68ng/mL), but predictive significance was noticeably better due to higher marginal value. The rise in PCT concentration in patients with severe sepsis is much greater than in those with SIRS or sepsis alone, as was confirmed in a number of studies (2,29). In our study the PCT concentrations also correlated with the severity of organ dysfunction defined by SOFA and APACHE II scores indicating that this biomarker, combined with a clinical score, could be useful for assessing the severity of infection. The results of randomized study of Jansen et al. (30) showed that monitoring of PCT, unlike many other inflammatory markers, especially CRP, correlates better with clinical scoring systems for evaluation of disease severity and some organ damages in sepsis (SOFA), especially later in the course of the disease, which makes it more effective in recognizing and treating severe sepsis in comparison to those parameters. Anand et al. (31) found a correlation of PCT values with the level of SOFA score, and the PCT concentration was much higher in patients with fatal outcome (89.3%) indicating that PCT is in relation to the severity of the disease and organic dysfunction and that it could be useful for prediction of fatal outcome in patients with sepsis. In the study of Zhang et al. (32) PCT has correlated well with SOFA score (r=0.406), and positive predictive value in comparison to fatal outcome in patients with sepsis (AUC 0.81) was found. Clech et al. (33) have found sensitivity of 87.5% and specificity of 45% in the prediction of fatal outcome on the first day of septic shock at the marginal value of 6 ng/mL.

Besides the fact that PTC is a marker of sepsis, it could contribute to decreased survival in cases of patients with sepsis due to toxic proinflammatory effects on leukocytes and cytokine production. The researchers have treated the animals with experimental sepsis with antibodies against PCT and have shown significant improvement in survival. This effect was evident after the diagnosis of sepsis and in the early stage of disease when immune neutralization was implemented, which shows that early treatment could be effective (34).

Blood lactate level is used as a marker for tissue hypoperfusion in shock patients, adequate post-shock resuscitation, prognostic index after resuscitation, and prognostic factor in the case of severe disease (35). Shapiro et al. (36) have confirmed that, based on lactate level, patients could be stratified into groups related to the specific rate of mortality: the lactate level 0-2.4 mmol/L was related to the mortality rate of 4.9 %, 2.5-3.9 mmol/L with 9.0% and ≥4 mmol/L with 28.4% mortality rate. Mikkelsen et al. (37) have shown that the initial lactate value and the highest recorded one, regardless of the presence of organic dysfunction and cardiogenic shock and hypoperfusion, were related to fatal outcome in patients with severe sepsis in the emergency departments. Kim et al. (38) have found in cases of children with septic shock, 0h, 24h, and 24-hour clearance of lactate meet great predictive significance (AUC 0.828). Chen and Li (39) have also found significant predictive lactate value in comparison to SOFA and APACE II scores in the prediction of fatal outcome in cases of patients with sepsis (AUC: lactate 0.79, SOFA 0.75, APACHE II 0.74), as the results of our research have shown (AUC: lactate 0.95, SOFA 0.92, APACHE II 0.83). The difference in clinical utility between lactate and PCT is that PCT may be a good early predictor of sepsis prior to progression to severe sepsis.

The small sample size and heterogeneous groups of patients are considered as two important limitations of this study.

In conclusion, there are many changes of clinical findings and laboratory parameters during sepsis. Monitoring of PCT increase in SIRS-positive patients, raises the possibility to distinguish between patients with sepsis and those with non-infectious SIRS. Absolute concentration of procalcitonin and monitoring of PCT elevation reveal the severity of sepsis and it could also predict fatal outcome in patients with sepsis.

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