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Usefulness of procalcitonin for diagnosis of sepsis in the intensive care unit

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Abstract

Introduction The diagnosis of sepsis in critically ill patients is challenging because traditional markers of infection are often misleading. The present study was conducted to determine the procalcitonin level at early diagnosis (and differentiation) in patients with systemic inflammatory response syndrome (SIRS) and sepsis, in comparison with C-reactive protein, IL-2, IL-6, IL-8 and tumour necrosis factor-α.
Method Thirty-three intensive care unit patients were diagnosed with SIRS, sepsis or septic shock, in accordance with the American College of Chest Physicians/Society of Critical Care Medicine consensus criteria. Blood samples were taken on the first and second day of hospitalization, and on the day of discharge or on the day of death. For multiple group comparisons one-way analysis of variance was applied, with *post hoc* comparison. Sensitivity, specificity and predictive values for PCT and each cytokine studied were calculated.
Results PCT, IL-2 and IL-8 levels increased in parallel with the severity of the clinical condition of the patient. PCT exhibited a greatest sensitivity (85%) and specificity (91%) in differentiating patients with SIRS from those with sepsis. With respect to positive and negative predictive values, PCT markedly exceeded other variables.
Discussion In the present study PCT was found to be a more accurate diagnostic parameter for differentiating SIRS and sepsis, and therefore daily determinations of PCT may be helpful in the follow up of critically ill patients.

Keywords C-reactive protein, cytokine, diagnosis, procalcitonin, sepsis

Introduction

The term 'sepsis' is used to define the systemic inflammatory response to an infectious agent (i.e. bacterial, viral, fungal or parasitic). Despite the use of new treatment modalities, improvements in technology and increased experience, mortality rates in sepsis remain high [1,2]. Critical care physicians have at their disposal a variety of data to serve as a guide in discriminating infectious from noninfectious conditions in newly admitted patients. In a number of newly admitted patients the diagnosis of sepsis becomes clear after taking the medical history and completing the physical examination

APACHE = Acute Physiology and Chronic Health Evaluation; AUC = area under the receiver operating characteristic curve; CRP = C-reactive protein; ICU = intensive care unit; IL = interleukin; PCT = procalcitonin; SIRS = systemic inflammatory response syndrome; TNF = tumour necrosis factor.

[3]. In other cases, in which noninfectious insults are responsible for systemic inflammatory response syndrome (SIRS; e.g. trauma, burns, haemorrhages, hypothermia, pancreatitis and surgery) or in comatose patients, the diagnosis of sepsis remains difficult.

Prompt diagnosis and treatment with appropriate antimicrobial chemotherapy is of the utmost importance in reducing the morbidity and mortality associated with sepsis. The lack of specific early markers of infection may be responsible in part for withholding of, or delaying or unnecessary antimicrobial treatment in critically ill patients [4]. Thus, there is an unmet need for clinical or laboratory tools that can distinguish between SIRS and sepsis. Various markers of sepsis, including C-reactive protein (CRP), tumour necrosis factor (TNF)-α, IL-1β, IL-6 and IL-8, have all been studied for their ability to differentiate SIRS from sepsis [4–7]. Several investigators have questioned the diagnostic accuracy of procalcitonin (PCT) measurement, results with which have been inconsistent and variable [4,6–10]. Thus, it may not be easy to discriminate between SIRS and sepsis, even with the use of PCT.

The present study was conducted to determine the PCT level at early diagnosis (and differentiation) in patients with SIRS and sepsis, in comparison with CRP, IL-2, IL-6, IL-8 and TNF-α in an unselected population of patients suffering from a broad range of diseases in an intensive care unit (ICU).

Method

The study was approved by the Institutional Ethics Committees of the Pamukkale University Medical School. Written informed consent was obtained from all patients or their relatives before enrollment. Over a 6-month period, all patients staying for more than 24 hours in the ICU were consecutively enrolled in the study. Patients who had chronic organ failure, thyroid cancer or pancreatitis; who had received massive blood transfusion; or whose anticipated duration of stay was under 24 hours were excluded from the study.

At admission, the patient's age, sex, height and weight were recorded. Also, data were collected at admission, on day 2, and on the day of discharge or on the day of death. These data included the following: clinical status (SIRS, sepsis or septic shock); Acute Physiology and Chronic Health Evaluation (APACHE)-II score; temperature; heart rate; respiratory rate; blood pressure; central venous pressure; laboratory analysis (complete blood count, blood urea nitrogen, blood sugar, serum sodium, potassium and calcium, aspartate aminotransferase, alanine aminotransferase, prothrombin time, activated partial thromboplastin time, albumin, transferrin and CRP); and arterial blood gas analysis. The final determination of the patient's status was done retrospectively, without knowledge of plasma cytokine and PCT levels, on the basis of the complete patient charts, results of microbiological cultures, chest radiographs and ultrasound, when available.

Blood samples were centrifuged at 1500 ***g*** for 5 min (Rotina 35; Cheftich Zentrifugen, Hennigsdorf, Berlin, Germany), and serum for cytokine and PCT determination was collected in sterile tubes. Serum samples were stored at −30°C until assayed in Nu-6511E (Nuare, Tokyo, Japan). The treating clinicians were blinded to the PCT results, and those performing the PCT assays were blinded to the clinical status of the patient. The PCT results were not available during the study period. Routine cultures of blood and urine, and of samples from trachea and suspected sites were obtained to identify the organisms present and determine the degree of antibiotic resistance.

We attempted to maintain the patients' haemoglobin level at 10–12 g/dl and central venous pressure at 8–12 mmHg in the ICU. If needed, blood products, intravascular fluid replacement, and inotropic and/or vasopressor agents were administered.

The American College of Chest Physicians/Society of Critical Care Medicine consensus classification was used for diagnosis of SIRS, sepsis and septic shock [11]. Patients were assessed for the presence of infection at admission, on day 2, and on the day of discharge or on the day of death. Clinical assessment was the first step in diagnosing infection. Cultures of urine, blood and tracheal aspirates were taken for diagnosis. Respiratory tract infection was assessed according to chest radiography and the presence or absence purulent tracheal aspirates containing micro-organisms. Intra-abdominal infection was suspected in the presence of contaminated or dirty surgical sites, and wound swabs were taken and ultrasound performed in such cases. Colonization was defined as microbiological evidence with no host response.

Laboratory measurements

CRP was measured using a routine turbidimetry assay (ILAD-900; Instrumentation Laboratory, Milan, Italy); a value greater than 10 mg/l was considered to be abnormally elevated. TNF-α, and IL-2, IL-6 and IL-8 were measured using commercially available cheluminescence kits (Immulite-One; DTC, Los Angeles, CA, USA). All cytokine samples were analyzed in duplicate. PCT levels (normal range 0–0.5 ng/l) were determined by means of a specific and ultrasensitive immunoluminometric assay (LUMI test PCT; Brahms Ag, Hennigsdorf/Berlin, Germany).

Statistical analysis

For multiple group comparisons of CRP, ILs and PCT, one-way analysis of variance was applied, with least squares difference for *post hoc* comparison. The best cutoff value of parameters for the diagnosis of sepsis was determined according to the Youden's index method. The ability of PCT to predict sepsis was evaluated by performing receiver operating characteristic analyses to compare SIRS versus sepsis patients [12]. Furthermore, the areas under the receiver operative characteristic curve (AUCs) were determined, as well as

Table 1

Clinical diagnoses of the patients

Diagnosis	Number of patients
Medical	13
Respiratory insufficiency	6
Neurological disease	5
HELLP syndrome	1
Gastrointestinal haemorrhage	1
Surgical	20
Gastrointestinal surgery	12
Polytrauma	2
Orthopaedic surgery	4
Thoracic surgery	1
Urological surgery	1

HELLP, haemolysis–elevated liver enzymes–low platelets.

the positive/negative predictive values. Positive predictive values and negative predictive values indicate the proportion of patients with a cytokine level greater than or below the chosen cutoff point. Test effectiveness is the sum of the positive predictive values and negative predictive values. Thus, the maximum score is 2, which represents perfect prediction, both positive and negative [13]. The septic shock group was not included in this analysis because of insufficient data. Statistical analyses were conducted using the Statistical Program for Social Science (SPSS, Chicago, IL, USA). $P < 0.05$ was considered statistically significant. Data in the text are shown as mean ± standard error, or as median and percentiles (10%/25%/75%/90%).

Results

A total of 33 patients (17 men and 16 women) were included in the study. The median age of the patients was 58 ± 16 years. The duration of stay of the patients in the ICU was 7.4 ± 6.78 days. The final, retrospectively confirmed diagnoses of all patients are shown in Table 1.

For each of the time points assessed in the present study, patients were categorized into the three groups, namely SIRS, sepsis and septic shock. No severely septic patients were identified. Ten patients died on the second day following admission to the ICU, and those patients underwent only two assessments. Thus, a total of 89 assessments of the patients' clinical status were conducted (referred to hereafter as 'conditions'), 48 of which indicated SIRS (53% of all patients), 35 sepsis (39% of all patients) and 6 septic shock (7% of all patients).

Of the 41 conditions of sepsis and septic shock, 24 (58%) involved pneumonia, 8 (20%) urogenital infection, 2 (5%) intraperitoneal abscess and 5 (12%) wound infection. In three patients no infectious focus could be found, but blood cultures were positive. Infections were microbiologically proven in 36 (88%) conditions, with 51% being Gram-negative, 41% Gram-positive and 8% mixed infections. Of the five conditions with SIRS, tracheal cultures were positive but did not exhibit any host response; they were therefore considered colonization. Eight patients did not receive antimicrobial treatment in any of the study periods. Five of the patients who died (5/6 [83%]) were in septic shock group and the other five patients who died (5/35 [14%]) were in the sepsis group.

APACHE-II scores did not differ between groups. No correlation was found between PCT concentrations and APACHE-II scores ($r = 0.23$). Serum concentrations of CRP, TNF-α and IL-6 were not statistically different between SIRS, sepsis and septic shock groups. IL-2, IL-8 and PCT levels were different between groups. Septic shock patients had the highest level of IL-2, IL-8 and PCT concentrations. Median and percentiles (10/25/75/90%) for all parameters and APACHE-II scores in patients with SIRS, sepsis and septic shock are presented in Table 2.

Because only six septic shock conditions were identified, we employed only SIRS and sepsis conditions for statistical analysis of diagnostic reliability of serum PCT and cytokines. Using Youden's Index, the best cutoff value for PCT was 2.415 ng/ml. The best cutoff value and AUC for all markers are shown in Table 3. The AUC was highest for PCT. Table 4 summarizes the predictive accuracy of the laboratory variables for the specific diagnoses of SIRS and sepsis. With a cutoff point of 2.415 ng/ml, serum PCT concentration was found to be the most discriminatory laboratory variable, the predictive accuracy of which exceeded those of CRP, TNF-α, IL-2, IL-6 and IL-8. With regard to positive and negative predictive values, we found that PCT markedly exceeds the values calculated for other variables. The test effectiveness was 1.84 for PCT in predicting sepsis, whereas the other variables reached values between 0.96 and 1.22.

Discussion

We analyzed the plasma concentrations of various biochemical markers with respect to their potential use in differentiating between patients suffering from SIRS and those suffering from sepsis. This assessment is of potential interest because systemic inflammation is a common problem in the ICU, which often leads to shock and death. The diagnostic repertoire for identifying SIRS is poor. Verification of infection site, and even the presence of infection, remains problematic in sepsis. In 20–30% of patients, the infection site is never identified. Neither imaging studies nor blood culture analysis can rule out the presence of infection [14]. Moreover, there are classes of patients with unconfirmed infection, or for whom cultures are negative yet who develop similar symptoms, rates of organ failure and survival outcomes as do those patients in whom infection is confirmed. The availability of lab-

Table 2

Median and percentiles for all parameters and APACHE-II scores in patients with SIRS, sepsis and septic shock

Parameter	SIRS ($n = 48$)	Sepsis ($n = 35$)	Septic shock ($n = 6$)
CRP (mg/dl)	22.5 (9.9/13.3/40/80)	50 (15/30/90/130)	45 (18/37/85/160)
TNF-α (pg/ml)	60 (5/10/110/336)	80 (13.5/39/142.5/290)	105 (7/46.8/407/1210)
IL-2 (pg/ml)	2194 (832/1098.3/4075/10256)	1780 (1060/1340/4320/13068)*	5931 (1590/1897/10417/15570)*†
IL-6 (pg/ml)	145 (17.6/61.8/557.8/1389)	320 (44/80/1000/2266)	800 (13/64.8/3250/10000)
IL-8 (pg/ml)	122 (16.9/31/332.5/792)	240 (23.6/66/470/1418)*	444 (190/212.5/1205.3/2061)*†
PCT (ng/ml)	56.5 (10.9/26/124.5/198.4)	395 (33.2/147/801/2627)*	460.1 (237/341.2/858.5/1000)*†
APACHE-II	18 (7/10/25/29)	19 (8/13/24/32)	21 (12/25/26/33)

Data are expressed as means (10%/25%/75%/90% percentiles). *$P < 0.05$, versus SIRS; †$P < 0.05$, versus sepsis. APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; PCT, procalcitonin; SIRS, systemic inflammatory response syndrome; TNF, tumour necrosis factor.

Table 3

Best cutoff and AUC value of laboratory parameters in predicting of sepsis

Parameter	Best cutoff	AUC (mean ± SE)	*P* value
CRP (mg/dl)	14.5	0.554 ± 0.062	0.378
TNF-α (pg/ml)	11.5	0.607 ± 0.06	0.085
IL-2 (pg/ml)	1288.5	0.641 ± 0.058	0.022
IL-6 (pg/ml)	68.5	0.515 ± 0.62	0.805
IL-8 (pg/ml)	31.5	0.663 ± 0.057	0.008
PCT (ng/ml)	2.415	0.969 ± 0.016	0.000

P values are for AUC as a predictor of sepsis. AUC, area under the receiver operating characteristic curve; CRP, C-reactive protein; PCT, procalcitonin; TNF, tumour necrosis factor.

Table 4

Sensitivity, specificity, and negative and positive predictive value of laboratory parameters in predicting sepsis

Parameter	CRP	TNF-α	IL-2	IL-6	IL-8	PCT
Sensitivity (%)	58	55	63	51	68	85
Specificity (%)	58	66	55	53	57	91
Negative predictive value (%)	68	65	65	56	69	95
Positive predictive value (%)	53	54	50	42	53	89

CRP, C-reactive protein; PCT, procalcitonin; TNF, tumour necrosis factor.

oratory tests for accurate and rapid identification of septic patients by isolation of micro-organisms from body fluid specimens would be of considerable value. Thus, there is a clear need for a reliable diagnostic procedure that allows early discrimination between patients suffering from SIRS and those with sepsis. A relatively new marker that has been associated with inflammation and sepsis is PCT, a 116-amino-acid protein that is the precursor to calcitonin. The PCT plasma level in healthy individuals is low, usually below 0.1 ng/ml [15]. That PCT concentration is significantly elevated in patients with organ dysfunction is undoubted. However, the difference in PCT between patients with SIRS and those with sepsis may be small. Reports of the usefulness of PCT for discriminating between SIRS and sepsis are conflicting [4,6–10]. Therefore, we selected several cytokines as well as PCT for early diagnosis (and differentiation) of patients with SIRS and sepsis.

High serum PCT concentrations were first described by Assicot and coworkers [16] in children with severe bacterial infections, and were suggested to be a specific marker for bacterial infection. Al-Nawas and coworkers [17] reported

higher PCT levels in patients with clinically documented infection than in those fulfilling the criteria for SIRS.

Two studies compared PCT and CRP in ICU patients and found that PCT had poorer sensitivity, specificity and AUC than did CRP as a marker of sepsis [8,10]. In order to assess the diagnostic utility of PCT and CRP in a medical ICU, prospective measurements were conducted in 101 consecutive patients with acute SIRS or sepsis. PCT did not clearly discriminate SIRS from sepsis [8]. Another group from Germany reported average PCT concentrations of 0.4 ± 3.0 ng/ml for SIRS, 0.5 ± 2.9 ng/ml for sepsis and 6.9 ± 3.9 ng/ml for severe sepsis. On the basis of their findings, the investigators concluded that PCT, CRP, white blood cell and body temperature does not discriminate SIRS from sepsis, and PCT was the only parameter to discriminate between sepsis and severe sepsis [9].

Muller and colleagues [4] investigated 101 patients admitted to a medical ICU and suggested that PCT is a more reliable marker of sepsis than is CRP, IL-6 and lactate levels. To assess the diagnostic value of PCT, IL-6, IL-8 and standard measures for identifying critically ill patients with SIRS and suspected sepsis, prospective measurements were taken in 78 consecutive patients admitted with acute SIRS and suspected infection. PCT yielded the highest discriminative value for differentiating patients with SIRS from those with sepsis, followed by IL-6 and IL-8 [6]. Selberg and coworkers [7] studied discrimination of sepsis and SIRS by determination of circulating plasma concentrations of PCT, IL-6 and C3a in a medical ICU. Their data indicated that of PCT, IL-6 and C3a concentrations are more reliable parameter for differentiating between septic and SIRS patients than are CRP and elastase.

Mechanical trauma causes elevated PCT levels, the degree of which depends on the severity of the injury. Levels peak on days 1–3 and fall thereafter. High concentrations of circulating PCT during the first 3 days after injury discriminate between patients at risk for SIRS, sepsis and multiple organ dysfunctions in the early and late post-traumatic course [18].

Previous studies compared CRP, IL-2, IL-6, and TNF-α and PCT separately for differentiating SIRS from sepsis; in the present study, all of the available biochemical markers were measured at the same time [4,7–10]. PCT had the highest sensitivity and specificity for differentiating SIRS from sepsis, followed by IL-2 and IL-8. Thus, in agreement with previous studies [6,7], PCT was a more reliable marker in the diagnosis of sepsis than other measures.

The present study included consecutive unselected patients who were representative of an ICU population, with baseline characteristics similar those reported in the literature, and strict objective criteria for the diagnosis of infection were employed [19]. However, several criticisms of the study should be addressed. First, PCT was not monitored every day, and a shorter monitoring interval may improve its performance as an aid for diagnosis and follow up of sepsis. Second, with the use of clinical criteria and microbiological evidence, it might have been difficult to ascertain the exact aetiology of SIRS in all patients. This may have introduced some misclassification bias, because investigators who were blinded to the cytokine results performed the case ascertainment; however, we do not believe this lack of an important standard compromised our study conclusions. Third, antimicrobial therapy may have an impact on PCT values. Our study design did not allow us to explain the exact relationship between antimicrobial therapy and PCT values. The temporal relationship between PCT and antibiotic treatment should be assessed in further studies.

Key message

- PCT appears to be a useful early marker for discriminating between SIRS and sepsis

Conclusion

In the present study, PCT appeared to be a more accurate diagnostic parameter for differentiating between patients suffering from SIRS and those with sepsis. Routine determination of PCT may improve management of patients, for example by preventing the use of unnecessary antibiotics that are known to select resistance strains. Further studies of the early phases of sepsis are necessary to define the role of PCT in possible therapeutic strategies, such as antimicrobial and immunological therapies, and cost implications.

Competing interests

None declared.

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