Research

Procalcitonin as a marker of bacterial infection in the emergency department: an observational study

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Abstract

Introduction Procalcitonin (PCT) has been proposed as a marker of infection in critically ill patients; its level is related to the severity of infection. We evaluated the value of PCT as a marker of bacterial infection for emergency department patients.

Methods This prospective observational study consecutively enrolled 120 adult atraumatic patients admitted through the emergency department of a 3000-bed tertiary university hospital in May 2001. Fifty-eight patients were infected and 49 patients were not infected. The white blood cell counts, the serum C-reactive protein (CRP) level (mg/l), and the PCT level (ng/ml) were compared between the infected and noninfected groups of patients.

Results A white blood cell count >12,000/mm^3 or <4000/mm^3 was present in 36.2% of the infected patients and in 18.4% of the noninfected patients. The best cut-off serum levels for PCT and CRP, identified using the Youden's Index, were 0.6 ng/ml and 60 mg/l, respectively. Compared with CRP, PCT had a comparable sensitivity (69.5% versus 67.2%), a lower specificity (64.6% versus 93.9%), and a lower area under the receiver operating characteristic curve (0.689 versus 0.879). PCT levels, but not CRP levels, were significantly higher in bacteremic and septic shock patients. Multivariate logistic regression identified that a PCT level ≥2.6 ng/ml was independently associated with the development of septic shock (odds ratio, 38.3; 95% confidence interval, 5.6–263.5; $P < 0.001$).

Conclusions PCT is not a better marker of bacterial infection than CRP for adult emergency department patients, but it is a useful marker of the severity of infection.

Keywords bacterial infection, C-reactive protein, emergency department, procalcitonin, sepsis

Introduction

Bacterial infection can cause sepsis [1]. Sepsis with acute organ dysfunction, namely severe sepsis [1], is a major threat to life [2]. Early institution of an appropriate antimicrobial regimen in infected patients is associated with a better outcome [3], and hence early diagnosis of bacterial infection is of primary importance. However, some patients with an infection have minimal or even no symptoms or signs. Not all patients who appear septic demonstrate an infection, and the widespread administration of antibiotics to all these patients

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APACHE = Acute Physiology and Chronic Health Evaluation; AUC = area under the receiver operating characteristic curve; BT = body temperature; CRP = C-reactive protein; ED = emergency department; IL = interleukin; NPV = negative predictive value; PCT = procalcitonin; PPV = positive predictive value; SIRS = systemic inflammatory response syndrome; TNF-α = tumor necrosis factor alpha; WBC, white blood cell.

carries problems of antibiotic resistance, of drug toxicity, and of increased medical costs. There is a need for an effective and accurate biochemical marker to support, or exclude, the diagnosis of infection.

The host response to bacterial infection involves the activation of complex immune mechanisms and the release of a wide array of inflammatory mediators [4], which has led to the suggestion that some of these mediators could be used as markers of infection or its severity [5]. Previous studies addressed the use of tumor necrosis factor alpha (TNF-α), IL-6 [5,6], and C-reactive protein (CRP) [7,8] to identify infection and to predict the presence of bacteremia, the severity of disease, and mortality. The common problem for these mediators is their nonspecific nature, and the correlation between CRP and the severity of disease is not always clear [9,10].

Procalcitonin (PCT) has recently been proposed as a marker of bacterial infection in critically ill patients [10,11]. PCT is a 116 amino acid peptide with a sequence identical to that of the prohormone of calcitonin [12], but PCT itself has no known hormonal activity. Under normal metabolic conditions, PCT is only present in the C cell of the thyroid gland. In bacterial infection and sepsis, however, intact PCT is found in the blood and, more importantly, its level is related to the severity of sepsis [10,11,13]. We evaluated the value of PCT as a marker of bacterial infection in emergency department (ED) patients. We hypothesized that, for ED patients, PCT is a more sensitive and specific marker of bacterial infection compared with CRP and the white blood cell (WBC) count. We also hypothesized that the PCT level is related to the severity of infection.

Materials and methods

Study design

The present study was a prospective observational study using a consecutive sample of adult atraumatic patients admitted through the ED of a tertiary university hospital. The primary outcome was the infection status of the patients. The study was approved by the Institutional Review Board of the hospital, and informed consent was waived in view of the lack of need for additional blood sampling.

Study population and setting

The study was performed from 16 to 20 May 2001 in the ED of a 3000-bed tertiary university hospital with about 150,000 visits annually. All adult atraumatic patients admitted through the ED of the hospital, except for those who were dead on arrival and those who were referred from a ward or an intensive care unit of other hospitals, were included in the study.

Study protocols

All patients were examined for signs and symptoms of infection on ED admission. Samples were collected for cultures of blood and of other body fluids, depending on the clinical symptoms. There were no protocol-driven decisions regarding disposition from the ED or specimen collections other

than phlebotomy for the study proteins. Three groups of patients were defined based on clinical findings, on laboratory findings, and on bacteriologic findings throughout the admission course. The WBC count and the serum CRP and the serum PCT levels were compared between infected and noninfected patients [14].

Infected patients

Patients had a definable source of infection and/or positive blood cultures and received antibiotic treatment. A patient was considered to have bacteremia if he/she had a clinical infection and a positive blood culture. The diagnosis of urinary tract infection required the presence of symptoms such as urinary frequency, dysuria, costovertebral angle tenderness, and a significant growth of 10^{4-5} cfu/ml bacteria in urine culture. The diagnosis of pneumonia was based on both respiratory symptoms such as a productive cough, dyspnea and chest pain, and a pneumonic infiltrate that disappeared during the antibiotic treatment while the patient recovered. For other foci, distinct radiological or microbiological documentation of the foci and recovery during the antimicrobial treatment were required.

Noninfected patients

Noninfected patients were those who, throughout their course of admission to the hospital or in the examinations performed, had no evidence of infection clinically. The patients did not receive antibiotic therapy.

Possibly infected patients

Thirteen patients had an uncertain diagnosis of infection. Two patients suffered from cholecystitis, two patients suffered from hollow organ perforation, and one patient suffered from appendicitis. These patients' blood cultures were either negative or unchecked, and none had an ascites culture. Three female patients had asymptomatic urinary tract infection, along with other diagnoses that became their principal reason for admission. All three patients had negative blood culture, and none received antibiotic therapy. Two patients had suspicious nosocomial infection. Eleven patients had systemic inflammatory response syndrome (SIRS) [1]. Since the diagnosis of infection in this group was doubtful, all 13 patients were excluded from analysis.

Measurements

All data were collected by two of the authors (YLC and SSC) themselves. The clinical and laboratory data collected included age, sex, admission diagnosis, patient disposition, body temperature (BT), WBC count, CRP levels, and other available information required for the calculation of the Acute Physiology and Chronic Health Evaluation (APACHE II) score [15].

The American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions of sepsis [1] were used to identify patients with sepsis, with severe sepsis, and with septic shock in the infected group, and to

identify SIRS in the noninfected group of patients. The infectious status of the patients, the presence of bacteremia, the development of severe sepsis or septic shock, and the mortality were documented by chart review.

The serum CRP level was measured by laser immunonephelometry (Wako Pure Chemical Industries, Osaka, Japan). Serum samples for PCT determination were collected and stored at −20°C for less than 2 weeks before assay. The PCT level was measured by immunoluminometric assay (Brahms Diagnostica, Berlin, Germany). The detection limit of this test is 0.5 ng/ml. The serum samples were processed by the same person without prior knowledge of the patient outcome and miscellaneous laboratory data. All samples were tested in duplicate.

Data analysis

The best cut-off value was chosen using Youden's Index [16]. The Mann–Whitney *U* test was used to compare independent samples, and the chi-square test (or Fisher's exact test when appropriate) was used to compare proportions. All variables were expressed as the median. All tests were two-sided, and $P < 0.05$ was considered significant. The receiver operating characteristic curve and the respective areas under the curve (AUCs) [17] were calculated. The correlations between age, APACHE II score, BT, WBC count, and serum CRP and PCT levels were tested using the Spearman correlation coefficients.

A multiple logistic regression model [18] was used to identify variables (age, gender, APACHE II score, BT, WBC count, serum CRP and PCT levels, the presence of SIRS, a BT or a WBC count that fulfilled the SIRS criteria [1], and a CRP or a PCT level that was higher than the cut-off value for identifying infection and predicting the development of septic shock) independently associated with outcome variables; namely, the presence of bacterial infection, the development of septic shock, and mortality. For all models, both forward and backward selection procedures were employed. The model of best fit was determined by the log-likelihood estimate. Variables with $P \leq 0.15$ were included in the model. Data were computed with the Statistical Program for Social Science (SPSS, Chicago, IL, USA).

Results

Admission diagnoses of the 107 patients included in the analysis are presented in Table 1. The age ranged from 19 to 90 years (median, 66 years), and 59.8% ($n = 64$) of the patients were male. The median APACHE II score was 10. Six patients died, giving a crude mortality rate of 5.6%. Fifty-eight (54.2%) of the 107 patients were infected and 49 patients (45.8%) were not infected (Table 2). In the 58 infected patients, 45 patients (77.6%) had an identified etiological microorganism, and 11 patients (19.0%) had bacteremia. The commonest site of infection was the urinary tract, followed by the lung, wounds and soft tissue, and the

Table 1

Clinical diagnoses of the patients

	Number of patients[a]	%
Infected ($n = 58$)		
Urinary tract infection	26	44.8
Pneumonia, empyema, and lung abscess	17	29.3
Wound and soft tissue infection	11	19.0
Biliary tract infection and cholecystitis	5	8.6
Bacteremia	2	3.4
Epiglottitis	1	1.7
Appendicitis, with positive ascites culture	1	1.7
Central venous catheter	1	1.7
Perianal abscess	1	1.7
Noninfected		
Cerebrovascular accident	11	22.4
Malignancy	8	16.3
Gastrointestinal bleeding	7	14.3
Liver cirrhosis	5	10.2
Chronic renal insufficiency and end stage renal disease	4	8.2
Congestive heart failure	3	6.1
Ischemic heart disease	3	6.1
Chronic lung disease	3	6.1
Diabetic ketoacidosis and nonketotic hyperosmolar syndrome	2	4.1
Miscellaneous	3	6.1

[a] Seven patients had more than one site of infection.

biliary system (Tables 1 and 3). Seven patients had more than one infection site, and 18 patients had more than one kind of infected microorganisms (Table 3). Seventeen (29.3%) patients had severe sepsis, and 11 patients (19.0%) developed septic shock.

SIRS was present in 82.8% of the infected patients and in 42.9% of the noninfected patients ($P < 0.001$). A WBC count $>12,000/mm^3$ or $<4000/mm^3$, fulfilling the SIRS criteria, was present in 36.2% of the infected patients and in 18.4% of the noninfected patients ($P < 0.001$) (Table 4). In patients with SIRS ($n = 69$), there was no difference in the proportion fulfilling the WBC count criteria between infected and noninfected patients ($P = 0.661$).

Using Youden's Index, the best cut-off values for CRP and PCT levels were 60 mg/l and 0.6 ng/ml, respectively. CRP levels were ≥ 60 mg/l in 67.2% of the infected patients, and in only 6.1% of the noninfected patients ($P < 0.001$). PCT

Table 2

Median age, sex, median Acute Physiology and Chronic Health Evaluation (APACHE) II score, mortality, median white blood cell count, C-reactive protein level and procalcitonin level for each group

	Infected ($n = 58$)	Noninfected ($n = 49$)	P value
Age (years)	66.5 (42.8–75.3)[a]	65.0 (46.5–70.5)[a]	0.812
Sex (male/female)	30/28	34/15	0.063
APACHE II score	13.0 (7.4–18.6)[a]	10.0 (6.8–18.0)[a]	0.045
Mortality	5 (8.6%)	1 (2.0%)	0.216
White blood cell count (/mm^3)	10,650 (7375–12,700)[a]	8,100 (6,250–10,150)	0.024
C-reactive protein level (mg/l)	102.75 (32.35–169.63)[a]	5.30 (2.00–17.65)[a]	< 0.001
Procalcitonin level (ng/ml)	0.93 (0.48–2.45)	0.47 (0.29–0.92)	< 0.001

[a] Data presented as median (interquartile range).

Table 3

Site of infection and microbiology

Site of infection	Microbiology
Urinary tract ($n = 26$)	*Escherichia coli* (7), *Pseudomonas aeruginosa* (4), *Enterococcus faecalis* (3), *Staphylococcus aureus* (2), *Serratia marcescens* (2), *Klebsiella pneumoniae* (1), *Proteus mirabilis* (1), *Citrobacter diversus* (1), *Pseudomonas* species (1), *Candida albicans* (1), unknown (4)
Lung ($n = 17$)	*Staphylococcus aureus* (6), *Pseudomonas aeruginosa* (5), *Streptococcus pneumoniae* (2), *Klebsiella pneumoniae* (2), *Acinetobacter baumanii* (2), *Hemophilus influenzae* (1), *Escherichia coli* (1), *Proteus mirabilis* (1), *Serratia* marcescens (1), unknown (5)
Wound and soft tissue ($n = 10$)	*Staphylococcus aureus* (2), *Viridans streptococcus* (2), *Prevotella* species (2), *Escherichia coli* (1), *Klebsiella pneumoniae* (1), *Proteus vulgaris* (1), *Bacteroides species* (1), *Peptostreptococcus* (1), unknown (1)
Abdominal (gastrointestinal tract and biliary system) ($n = 5$)	*Escherichia coli* (4), *Proteus vulgaris* (2), *Citrobacter freundii* (2), *Enterococcus faecalis* (2), *Morganella morganii* (1), *Klebsiella oxytoca* (1), *Pseudomonas aeruginosa* (1), *Enterococcus avium* (1), *Clostridium perfringens* (1), *Gemella mor*billirum (1), *Viridans streptococcus* (1), unknown (1)
Bacteremia ($n = 2$)	*Viridans streptococcus* (1), *Aeromonas caviae* (1)
Miscellaneous	
Central venous catheter ($n = 1$)	*Staphylococcus aureus*
Perianal abscess ($n = 1$)	*Staphylococcus aureus*
Unknown ($n = 2$)	

levels were ≥0.6 ng/ml in 69.5% of the infected patients, but also in 35.3% of the noninfected patients ($P < 0.001$). The median serum CRP and PCT concentrations in infected and noninfected patients were 102.75 and 5.30 mg/l ($P < 0.001$) and 0.93 and 0.47 ng/ml ($P = 0.001$), respectively (Fig. 1). There was no relationship between the serum CRP and PCT levels and the type of infecting bacteria (data not shown). A serum PCT level >2 ng/ml is 100% specific for infection in patients with SIRS ($n = 69$), but only 35.4% patients reached such a high level. The negative predictive value (NPV) for CRP in this group of patients was only 50.9%, and that for PCT was only 50.0% (Table 4). The BT and the CRP level

($r = 0.37$, $P < 0.001$), the WBC count and the CRP level ($r = 0.32$, $P = 0.001$), and the CRP and PCT levels ($r = 0.38$, $P < 0.001$) were significantly correlated.

Figure 2 shows the receiver operating characteristic curves predicting the presence of bacterial infection and the development of septic shock. The AUC for infection identification was greatest for CRP, followed by PCT and then WBC (0.879 versus 0.689 versus 0.627; all $P < 0.05$). In predicting the development of septic shock, the AUC for PCT was greater than that for CRP (0.911 versus 0.767; both $P < 0.05$).

Table 4

Clinical parameters, serum C-reactive protein and procalcitonin levels for diagnosing adult infection in an emergency department (%)

Parameter	Sensitivity	Specificity	Positive predictive value	Negative predictive value
SIRS	82.8 (48/58)	57.1 (28/49)	69.6 (48/69)	73.7 (28/38)
White blood cell count >12,000/mm³ or <4000/mm³	36.2 (21/58)	81.6 (40/49)	70.0 (21/30)	51.9 (40/77)
C-reactive protein (cut-off 60 mg/l)				
All	67.2 (39/58)	93.9 (46/49)	92.9 (39/42)	70.8 (46/65)
SIRS	68.8 (33/48)	90.5 (19/21)	94.3 (33/35)	50.9 (19/34)
No SIRS	60.0 (6/10)	96.4 (27/28)	85.7 (6/7)	87.1 (27/31)
Procalcitonin (cut-off 0.6 ng/ml)				
All	70.7 (41/58)	63.3 (31/49)	69.5 (41/59)	64.6 (31/48)
SIRS	70.8 (34/48)	66.7 (14/21)	82.9 (34/41)	50.0 (14/28)
No SIRS	70.0 (7/10)	60.7 (17/28)	38.9 (7/18)	85.0 (17/20)

Numbers in parentheses indicate patient numbers. SIRS, systemic inflammatory response syndrome.

The median PCT levels were 0.50 ng/ml in noninfected patients without SIRS, 0.47 ng/ml in noninfected patients with SIRS, 0.67 ng/ml in septic patients, and 3.13 ng/ml in septic shock patients. The PCT levels in the septic shock patients were significantly higher than in the sepsis subgroup ($P < 0.001$). The median CRP levels in each group were 3.20, 9.70, 75.60, and 106.35 mg/l, respectively. The CRP levels in the sepsis subgroup were significantly higher than in the noninfected SIRS subgroup ($P < 0.001$) (Fig. 3). In infected patients ($n = 58$), the best cut-off value of PCT levels predicting the development of septic shock was 2.6 ng/ml (sensitivity, 72.7%; specificity, 91.5%; positive predictive value [PPV], 66.7%; NPV, 93.5%; $P < 0.001$), and that for CRP was 142 mg/l ($P = 0.151$). The median PCT level of the bacteremic and nonbacteremic groups was 2.51 and 0.70 ng/ml, respectively ($P = 0.006$), and the median CRP level for each group was 84.1 and 114.0 mg/l, respectively ($P = 0.613$) (Fig. 3). Using Youden's Index, the best cut-off level for PCT to predict the presence of bacteremia was 1 ng/ml. The specificity was only 63.8%, but the NPV was 96.8% ($P = 0.001$).

Multivariate logistic regression identified a BT that fulfills the SIRS criteria [1] (odds ratio, 11.9; 95% confidence interval, 3.2–44.5; $P < 0.001$), a CRP level ≥60 mg/l (odds ratio, 27.3; 95% confidence interval, 6.7–110.6; $P < 0.001$) and a PCT level ≥0.6 ng/m (odds ratio, 3.5; 95% confidence interval, 1.1–11.1; $P = 0.033$), were independently associated with the presence of bacterial infection. The APACHE II score (odds ratio, 1.1; 95% confidence interval, 1.0–1.3; $P = 0.058$) and a PCT level ≥2.6 ng/ml (odds ratio, 38.3, 95% confidence interval, 5.6–263.5; $P < 0.001$) were independently associated with the development of septic shock. The APACHE II score (odds ratio, 1.2; 95% confidence inter-

val 1.0–1.4; $P = 0.04$) was the only variable independently associated with mortality.

Discussion

The diagnosis of bacterial infection in acutely ill patients is not always straightforward. Infection, in contrast with colonization, involves some degree of host response. It is the manifestations of the host response that cause us to presume a patient has an infection and to proceed to search for the infection focus and administer antimicrobial agents. In some elderly patients, neonate patients, and immunosuppressed patients, however, the manifestations may be absent, and these patients turn out to be most vulnerable to the complicated courses of infection. Similar manifestations, on the contrary, may be induced by stimuli other than bacterial infection (e.g. trauma, pancreatitis, burn, etc.).

Routine laboratory tests in patients presenting with SIRS frequently lack both sensitivity and specificity in differentiating which patients should receive antibiotics, and most confirmatory microbiological tests results are not immediately available. In today's climate of escalating medical costs and increasing antibiotic resistance, it is perhaps even more important to be able to identify those patients in whom an antimicrobial agent is likely to be of benefit. Many rapid diagnostic methods for detecting infection have been developed in recent years [9], and much effort has gone into finding biochemical markers of infection; for example, finding markers like cardiac troponin used as the marker of myocardial injury. The ideal biochemical marker of bacterial infection, if any, should be sensitive enough to detect the presence of infection in patients with minimal or even no host response, should be specific enough to discriminate infection from other stimuli that may induce SIRS, should be present early in the course
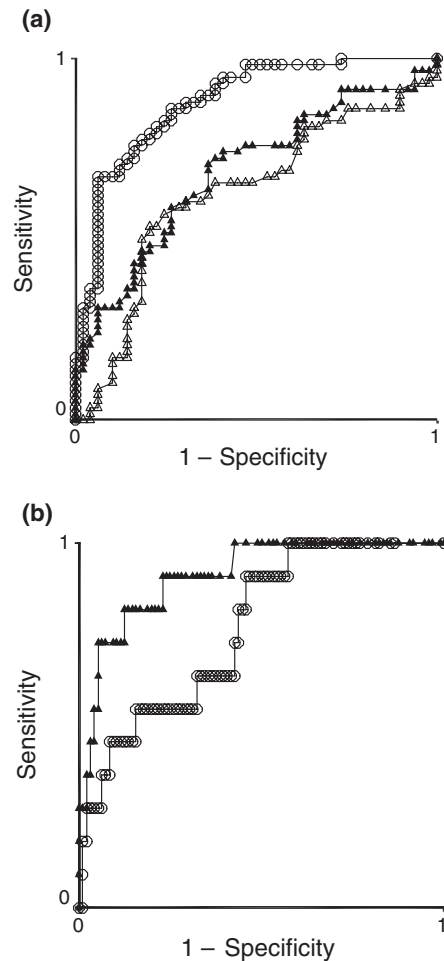
Figure 1
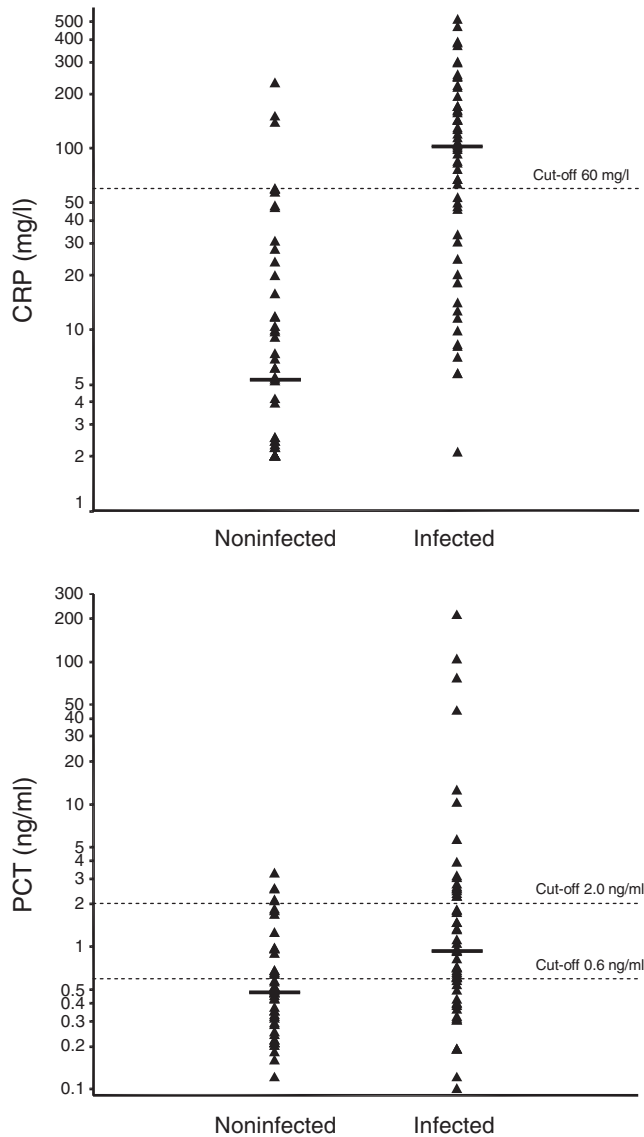
C-reactive protein (CRP) and procalcitonin (PCT) concentrations in infected and noninfected patients. Bar represents the median.

Figure 2

Receiver operating characteristic curves of C-reactive protein (open circle), of procalcitonin (solid triangle), and of the white blood cell count (open triangle) in **(a)** the diagnosis of infection and **(b)** predicting septic shock.

of the disease, should be rapidly and conveniently measured, and should be of prognostic significance.

TNF-α and IL-6 have been studied as markers of bacterial infection for ED patients [4,5]. Moscovitz and colleagues [5] collected 100 patients admitted through the ED with signs of infection and reported that plasma IL-6 concentrations were able to predict bacteremia and death from infection. A plasma IL-6 concentration ≥ 2.0 ng/ml detected bacteremia with a sensitivity of 42.1%, with a specificity of 96.7%, and with a PPV of 72.7%. Plasma TNF-α concentrations predicted mortality from all causes. The results just reflected the nonspecific nature of TNF-α for identifying infection, and disclosed

the potential usefulness of IL-6 as a marker of severe infection. A cut-off level of 2.0 ng/ml, however, is too high to be clinically useful.

Terregino and colleagues [6] collected 180 ED patients with SIRS and reported TNF-α to be a more important predictor of disease progression to severe sepsis than IL-6. Both cytokines had low PPVs but high NPVs for severe sepsis, for bacteremia, and for death at various cut-off levels. The cut-off values of the two mediators for diagnosing infection were not reported. In their study 108 patients were presumed infectious and were admitted, but only 33 (30.6%) had recovery of organisms from sites. Could it be that some patients with high TNF-α and IL-6 levels had SIRS caused by stimuli other than bacterial infection, and certainly did not progress to severe sepsis, bacteremia, and death, thus giving rise to low PPVs? If this was the case, then again it reflected the non-

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Figure 3
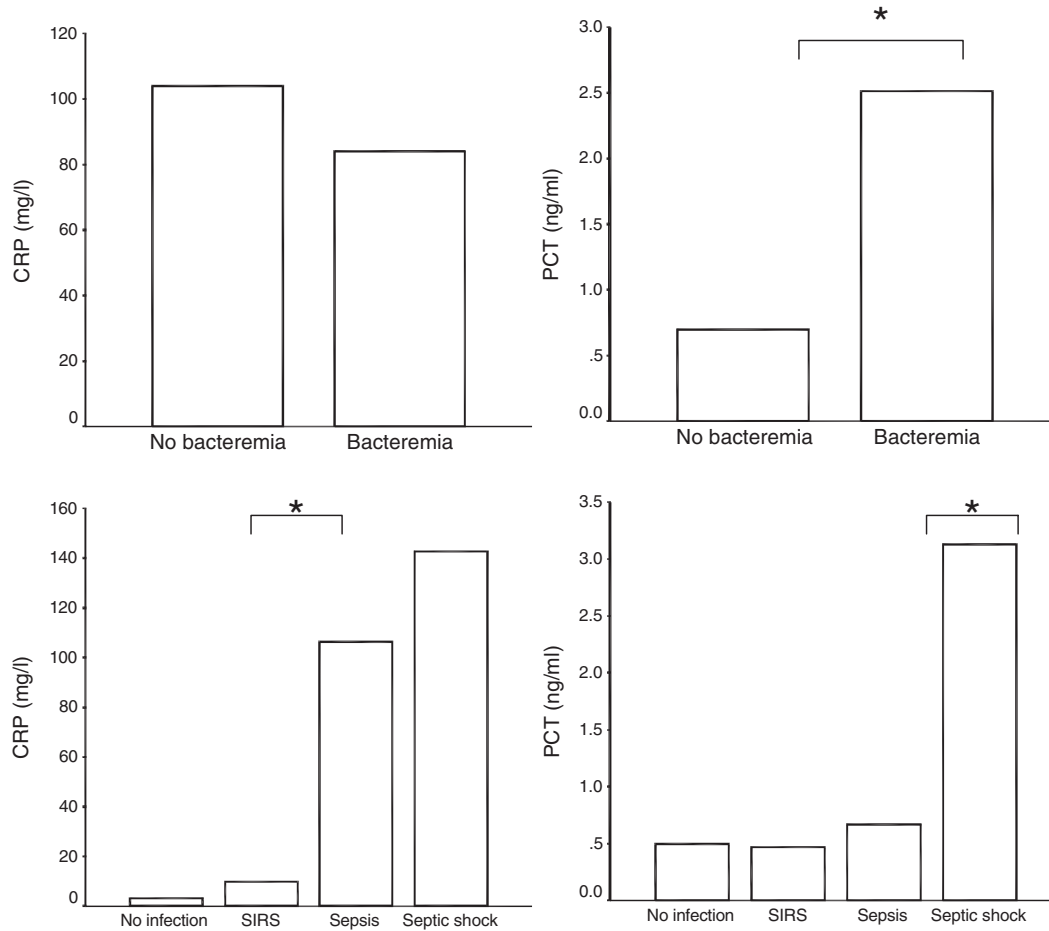
Median C-reactive protein (CRP) and procalcitonin (PCT) concentrations in bacteremic patients, nonbacteremic patients, noninfected patients, systemic inflammatory response syndrome (SIRS) patients, sepsis patients, and septic shock patients. * $P < 0.001$.

specific nature of the two mediators to be used as markers of infection.

CRP is an acute phase protein [19]. In contrast to most acute phase proteins for which there are wide plasma level variations (which depend on synthesis, consumption, and catabolic rates), CRP has a plasma half-life that is constant under almost all conditions [20]. Its plasma level is determined exclusively by its rate of synthesis, which reflects the presence and extent of disease activity. CRP has been widely used clinically as a diagnostic tool for infection identification [7,8,21]. Some authors even advocate using CRP as one of the criteria of sepsis [22]. Our results showed that CRP is a good marker of bacterial infection in adult atraumatic ED patients. This is in contrast to the results from the study by Ugarte and colleagues [10], who investigated 190 critically ill patients and reported a sensitivity of 71.8% and a specificity of 66.6% for infection identification at the cut-off CRP level of 79 mg/l. There was a comparable sensitivity (67.2%) but a

much higher specificity (93.9%) according to our data. The difference in specificity between the two studies is reasonable because critically ill patients generally maintained higher 'normal' CRP levels than did the ED patients, which is immediately evident by the marked difference in median CRP levels (56 mg/l versus 5.3 mg/l) between noninfected patients of the two studies. CRP does have shortcomings. Our data showed that CRP is unable to discriminate bacteremic and septic shock patients, and the low NPV, especially in patients with SIRS, limited its use as a means to exclude the presence of infection.

Remarkably little is known about the process by which PCT is released in sepsis; even the source of its generation during bacterial infection is not well defined. Plasma concentrations of PCT are substantially below 0.1 ng/ml in healthy individuals. The most potent stimulator for PCT induction under experimental conditions is the systemic effect of bacterial endotoxins [23]. Viral and localized bacterial infections have

lower plasma PCT levels than patients with systemic infections [24]. Autoimmune diseases [25] and neoplastic disorders [26] do not induce PCT. If systemic infection is present in immunosuppressed patients, PCT remains elevated [27]. Plasma PCT is very stable and is not degraded to hormonally active calcitonin [28].

The actual pathophysiologic role of PCT is still under investigation, and it was speculated that PCT might also be an acute phase protein [29]. Our data showed that PCT might be used not just as a marker of infection, but, more importantly, that it is a good marker of the severity of infection. Our results were comparable with those from the study by Ugarte and colleagues [10]; at a cut-off value of 0.6 ng/ml, PCT had a sensitivity of 67.6%, a specificity of 61.3%, a PPV of 71.0%, and a NPV of 57.5%. In patients with SIRS, our data showed a NPV for PCT that is too low to be safely used to exclude the presence of infection.

Hausfater and colleagues [30] collected 195 ED patients with suspected infectious or inflammatory disease and found that 24 (35%) of 68 patients with systemic infection had serum PCT levels >0.5 ng/ml (specificity, 99%; PPV, 96%; NPV, 74%). The mean PCT level was 5.3 ng/ml (range 0.5–98.5 ng/ml) for infected patients and 0.09 ng/ml for non-infected patients ($P<0.001$), and the mean CRP level for each group was 88 mg/l and 80 mg/l, respectively ($P=0.9$). The mean APACHE II score of the study subjects and the number of patients progressing to septic shock were not reported. Our study subjects had a higher value (mean ± standard deviation, 8.98 ± 32.02 ng/ml in infected patients and 0.75 ± 0.73 ng/ml in noninfected patients) and a broader range (0.10–210.55 ng/ml) of PCT levels; the ability of PCT in discriminating the presence of infection was lower.

The subjects of the present study were patients admitted to the hospital through the ED, and theoretically the mean PCT level should be lower compared with that of Hausfater and colleagues (indeed, the median PCT level of infected patients was lower than that from Ugarte and colleagues [10]). Whether the overall PCT levels in our study subjects were significantly higher, and whether the differences were related to patient characteristics, disease courses, and severity, other factors such as racial difference remain uncertain.

Guven and colleagues [31] collected 34 patients with SIRS and reported an AUC for predictive accuracy of sepsis for a PCT level, a WBC count and a CRP level of 0.88, 0.44 and 0.34, respectively. So is CRP good or bad? How about PCT? We believe the performance of each marker in different studies is closely related to the characteristics of the study subjects. In most studies the levels of the inflammatory mediators produced are far higher when the initial trigger is infectious, and it seems obvious that, although the same pathway is probably involved, there is a clear quantitative difference in the activation of the inflammatory network for septic versus nonseptic insult [9]. Our study subjects were heterogeneous ED patients, in which the average inflammatory status was less severe than critically ill patients and the most frequent cause of acute inflammation was ultimately infection. It might be that elevated CRP levels in ED patients are most frequently induced by an infection, and thus CRP becomes a good marker of infection in ED. However, many other stimuli also cause inflammation. An elevated serum CRP level in individual patients should hence be interpreted with caution, and an underlying cause of inflammation other than infection should always be considered. It seems that PCT is more specific to infectious stimuli compared with CRP [13,23,24]. We recommend that in patients with elevated CRP levels, PCT may be used as a measure to further support the diagnosis of infection, and as a marker of disease severity.

There were limitations with the present study. The first limitation is that patients who were directly discharged from the ED were not included. The effects may be twofold. Certain patients were not enrolled, especially those with elevated CRP levels induced by stimuli other than bacterial infection. This might result in an overestimation of the specificity of CRP, and a possible underestimation of the specificity of PCT if the serum levels of these patients were within the normal range. The subjects in the present study, on the contrary, were all admitted patients who might have more serious diseases and higher 'normal' CRP levels than the general ED patient population. This might result in an underestimation of both the specificity and the PPV of CRP. Which effect predominated is difficult to predict. Further studies of larger sample size to recruit all ED patients are needed to obtain more convincing results.

A second limitation is that some authors advocated close follow-ups of the PCT levels in infected patients, as the peak level correlated best with prognosis [32]. The present study used only a single PCT level on admission to the ED, and the correlation with the outcomes may be suboptimal.

The final limitation of the study is that the number of patients at risk of having infection without developing SIRS is limited. PCT levels were reported to elevate normally in infected immunosuppressed patients [27]. Failure to recruit these patients may lead to an underestimation of sensitivity. Now that PCT showed convincing results in detecting infection in immunosuppressed and leukopenic patients, shall we assay PCT routinely in all these patients? Further studies with a special focus to the immunosuppressed patients are needed.

Conclusions

PCT is not a better marker of bacterial infection than CRP in adult ED patients, but it is a useful marker of the severity of infection. An elevated CRP level in ED patients has a high PPV for infection, but the absence of CRP elevation cannot be used safely to exclude the presence of infection, especially in patients with SIRS. In patients with elevated serum

> **Key messages**
>
> - Using a cut-off level chosen by Youden's Index, PCT is not a better marker of bacterial infection than CRP for adult emergency department patients. Yet high serum PCT level is highly specific for infection
>
> - A low serum CRP or PCT level cannot be used safely to exclude the presence of infection, especially in patients with SIRS
>
> - In patients with elevated serum CRP levels, PCT may be used as a measure to further support the diagnosis of infection, and as a marker of disease severity

CRP levels, PCT might be used to further support the presence of infection and to predict the disease severity.

Competing interests

None declared.

Acknowledgements

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