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C-reactive protein, procalcitonin and interleukin-8 in the primary diagnosis of infections in cancer patients

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Abstract

The diagnostic utility of C-reactive protein (CRP), procalcitonin (PCT) and interleukin-8 (IL-8) were studied in 66 cancer patients with suspected infection (39 with definite foci of infection, 17 with antibiotic responses without foci and 10 with neoplastic fever without infection) and 26 patients scheduled for chemotherapy. The infection group ($n=56$) had higher median CRP (91 versus 19 mg/l, $P<0.001$), PCT (0.28 versus 0.12 ng/ml, $P<0.001$) and IL-8 values (27.7 versus 16.9 pg/ml, $P=0.032$) than the non-infection group ($n=36$). In patients with suspected infection, only PCT was a good marker to discriminate bacteraemia with an area under the receiver operating characteristics curve of 0.92 (95% confidence interval (CI), 0.77–1.0), but even PCT was less well able to differentiate between non-bacteraemic infections and neoplastic fever (0.56; 95% CI, 0.35–0.77). In conclusion, PCT was a good indicator for bacteraemia, but none of the three markers were reliable indicators for minor infections in non-neutropenic cancer patients.

Keywords: Cancer; Infection; C-reactive protein; Procalcitonin; Interleukin-8

1. Introduction

Procalcitonin (PCT), a 116 amino acid propeptide of calcitonin, has been proposed as a new diagnostic marker of severe infections [1], such as neonatal infections [2,3], septic shock [4,5] and bacterial meningitis [6] as well as pyelonephritis amongst children [7]. In normal individuals, calcitonin and PCT are produced by C-cells of the thyroid gland, but the reason for increased PCT secretion in patients with severe infections is not known [1]. Enhanced production of calcitonin-like peptides or calcitonin-precursor peptides is also seen in patients with different malignancies [8] PCT has been shown to be a promising indicator for bacteraemia, even in neutropenic patients with haematological malignancies [9–11].

Interleukin-8 (IL-8) is an important chemotactic regulator of neutrophil function *in vivo* [12,13]. Its concentration increases during different infections, such as bacteraemia [14] and meningococcal disease [15]. High IL-8 concentrations have also been demonstrated in association with malignancies [16,17]. In neutropenic patients, enhanced IL-8 production has been demonstrated comparable with PCT in predicting bacteraemia [11].

C-reactive protein (CRP) is the most widely used marker of ongoing infection in clinical practice [18,19]. The use of CRP values to diagnose infection in cancer patients is often difficult, because the underlying malignancy also induces CRP production in hepatocytes [19,20]. Actually, the activation of an acute-phase response is regarded as prognostic in oncology [21–23].

The purpose of our prospective study was to assess whether PCT and IL-8 are more useful than CRP to identify infection in non-neutropenic cancer patients, which would help to avoid unnecessary antibiotic treatment as well as hospitalisation.

2. Patients and methods

2.1. Study design for the identification of study groups

The study protocol was approved by the Ethics Review Committee of the Medical Faculty of the

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University of Oulu, Oulu, Finland. Between September 1996 and March 1998, 92 consecutive cancer patients with suspected infection and Karnofsky performance scores higher than 40 were enrolled in this prospective study at the Department of Oncology and Radiotherapy, Oulu University Hospital, Finland. When the oncologist in charge suspected infection, oral and written informed consent was obtained from the patient, and serum samples were obtained on admission and stored at −70°C until analysis. Only one suspected episode of infection per patient was accepted into this study.

The pretreatment evaluation of the 92 study patients included a medical history, a physical examination, two blood cultures obtained from different sites for aerobic and anaerobic bacteria and fungi (BacT/Alert©), Organon Teknika Corporation, Durham, NC, USA), a bacterial culture of urine ($n=86$) and chest X-rays ($n=88$). Other radiological examinations were made individually if clinically indicated, including radiography of the paranasal sinuses ($n=69$), ultrasonography ($n=19$), computed tomography ($n=11$) and magnetic resonance examination ($n=3$). After the inclusion of the patient in this study, treatment and follow-up were made as a matter of routine by the oncologists working on the ward. The patient data were later analysed by an oncologist and an infectious disease physician by using the following definitions.

2.2. Definitions of the study groups

2.2.1. Infection group

A patient was considered to have bacteraemia if he or she had a clinical infection and a positive blood culture. The diagnosis of urinary tract infection required both symptoms and significant growth of bacteria 10^{4-5} cfu/ml in urine culture. The diagnosis of pneumonia was based on both respiratory symptoms and a pneumonic infiltrate that disappeared during the antibiotic treatment whilst the patient recovered. For other foci, distinct radiological or microbiological documentation of the foci and recovery during the antimicrobial treatment were required. In addition, the patients who had a clinical picture of infection and showed an unequivocal antibiotic response with defervescence and decreasing CRP values during the follow-up were considered to have an infection, although no foci of infection could be demonstrated.

2.2.2. Non-infection group

The patients were considered to have neoplastic fever if they did not have any evidence of infection clinically or in the examinations performed. Moreover, these patients did not respond to empirical antibiotic treatments, but typically showed a response to steroids, anti-inflammatory analgesics or radiotherapy. In addition, the non-infection group included voluntary patients with different types of malignancy without clinical infection, who were randomly selected before their first course of chemotherapy.

2.3. Serum analyses

The serum PCT concentrations were measured as duplicates using a chemoluminescent immunoassay kit (LUMItest PCT, B.R.A.H.M.S. Diagnostica GMBH, Berlin, Germany) with a lower detection limit of 0.1 ng/ml [1]. The IL-8 concentrations were determined as duplicates using a commercially available enzyme linked immunosorbent assay (ELISA) kit (Duoset, Genzyme Diagnostics, Cambridge, MA, USA) according to the manufacturer's instructions. The lower detection limit of IL-8 was 15 pg/ml. The serum CRP concentration was assessed in our hospital laboratory using an automated system (Technicon H1™, Tarrytown, NY, USA).

2.4. Statistical analyses

The statistical analysis was performed using the SPSS software (SPSS Inc. Chicago, IL, USA) and the confidence intervals were calculated with the CIA program [24]. The calculations for continuous variables were performed with the Mann–Whitney U-test and those for non-continuous variables with the Pearson χ^2-test (or Fisher's exact test when appropriate). The diagnostic applicability of serum CRP, PCT and IL-8 was evaluated for 66 patients with suspected infection using the area under a receiver operating characteristic (ROC) curve [25]. The optimal cut-off values for serum CRP, PCT and IL-8 in identifying infections were determined using the Youden index based on sensitivity and specificity [26]. For PCT, the cut-off value of $\geqslant 0.5$ ng/ml recommended by the manufacturer was also used.

3. Results

26 of the 92 patients (28%) with suspected infection did not meet the abovementioned classification criteria. In these cases, simultaneous antibiotic and cancer treatments did not allow classification, and these 26 patients were therefore excluded from the study. From the remaining 66 cancer patients, 56 had the following infections: 8 had bacteraemia (3 had *Staphylococcus aureus*, and 1 each *Escherichia coli*, *Pasteurella multocida*, *Clostridium bifermentans*, another gram-negative anaerobic rod and mixed bacteraemia) and 15 had pneumonia. The other foci were as follows: 7 cases of urinary tract infection, 2 cases of sinusitis, 1 case each of infection at the insertion site of a central venous catheter, cholangitis, perirectal abscess, mediastinitis, pulmonary tuberculosis, erysipelas and *Herpes zoster* infection. In

Table 1
Demographic data and underlying cancer and their stages in infection and non-infection groups of cancer patients

Variable	Infection group ($n=56$) n (%)	Non-infection group ($n=36$) n (%)	P value
Gender			NS
Male	35 (63)	23 (64)	
Female	21 (38)	13 (36)	
Mean age (S.D.)	57 (16)	57 (13)	NS
Tumour type			NS
Lymphoma	23 (41)	11 (31)	
Lung cancer	7 (13)	13 (36)	
Breast cancer	6 (11)	3 (8)	
Gastrointestinal tract	7 (13)	3 (8)	
Urinary tract	4 (7)	1 (3)	
Other cancer	9 (16)	5 (14)	
Stage[a]			NS
I	4 (8)	0	
II	7 (13)	5 (14)	
III	12 (23)	9 (25)	
IV	30 (57)	22 (61)	

NS, not-significant.
[a] 3 cases with glioblastoma multiforme (not staged) in the infection group.

addition, 17 patients had a clinical infection and showed an unequivocal antibiotic response. The remaining 10 patients with suspected infection proved to have neoplastic fever. These and 26 chemotherapy-naïve patients comprised the non-infection control group. Gender and age did not differ statistically between the infection and non-infection groups (Table 1). In the former group, lymphoma (41%) was the most common underlying cancer, whilst lung cancer was the most common (36%) in the non-infection group. However, the types or stages of underlying cancer did not differ statistically between the two study groups. Only 7 (11%) of the 66 patients with suspected infection had a leucocyte count lower than 1.0×10^9/l.

The CRP, PCT and IL-8 concentrations were significantly higher in the infection group than in the non-infection group (Table 2). After a division of patients into those with local disease (stages I and II) and those with advanced disease (stages III and IV), the difference in CRP values between the infection and non-infection groups remained significant in both local and advanced diseases (Fig. 1). The median PCT values were statistically higher in the infection group amongst the patients with advanced disease ($P<0.001$) and also tended to be higher in the infection group with local disease, but the difference did not reach statistical significance ($P<0.07$), probably due to the small number of cases (Fig. 1). For IL-8, the statistical differences disappeared after the subdivision of the groups.

Table 2
Median levels of C-reactive protein (CRP), procalcitonin (PGT) and interleukin-8 (IL-8) in infection and non-infection groups of cancer patients

Variable	Infection group	Non-infection group	P value
CRP (mg/l)	91 (40–191)[a]	19 (10–98)	<0.001
PCT (ng/ml)	0.28 (0.16–0.57)	0.12 (0.02–0.23)	<0.001
IL-8 (pg/ml)	27.7 (12.4–86.3)	16.9 (6.2–47.3)	0.032

[a] Interquartile range (25th to 75th percentile).

The discriminatory power of the three markers for infection in 66 cancer patients was evaluated in terms of the area under ROC curves (AUC). Amongst the cancer patients, of whom 89% were non-neutropenic, the discriminatory power of CRP, PCT and IL-8 was low with an AUC value of 0.42 (95% CI, 0.28–0.57) for CRP, 0.61 (95% CI, 0.42–0.81) for PCT and 0.51 (95% CI, 0.34–0.69) for IL-8. As shown in Fig. 2(a), PCT was the best discriminator for bacteraemia, (AUC value 0.92; 95% CI, 0.77–1.0), whilst CRP and IL-8 were less powerful (0.52; 95% CI, 0.25–0.79 and 0.62; 95% CI, 0.36–0.87). PCT also showed poor discriminatory power 0.56 (95% CI, 0.35–0.77) for other infections versus neoplastic fever, falling between CRP and IL-8 (0.42; 95% CI, 0.26–0.58 and 0.49; 95% CI, 0.31–0.67, respectively, Fig. 2b).

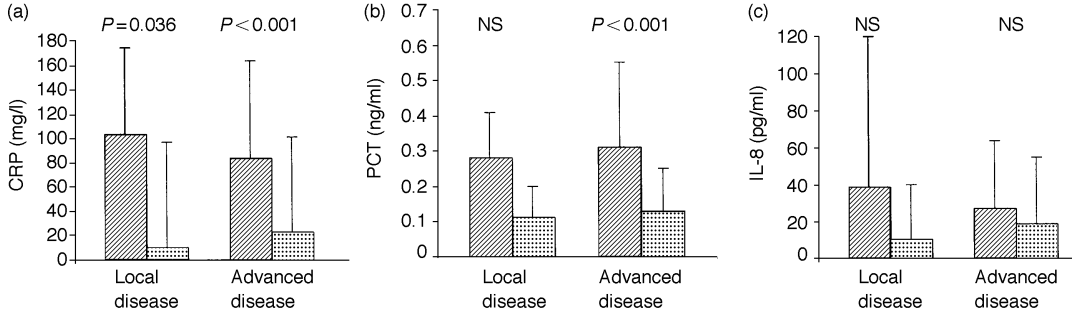

Fig. 1. (a) Admission C-reactive protein (CRP); (b) procalcitonin (PCT) and (c) IL-8 median concentrations and upper quartiles in the infection (▨; $n=56$) and non-infection groups (⊡; $n=36$) with local (stages I and II) and advanced cancer (stages III and IV). NS, not significant.

Table 3
Utility of admission C-reactive protein (CRP), procalcitonin (PCT) and interleukin-8 (IL-8) in identifying infections in 66 cancer patients with a suspicion of infection

Variable	Sensitivity	Specificity	PPV	NPV	Accuracy
CRP $\geqslant$ 140 mg/l[a]	39 (27–53)[b]	70 (35–93)	88 (69–98)	17 (7–32)	44 (32–57)
PCT $\geqslant$ 0.24 ng/ml	59 (45–72)	70 (35–93)	92 (78–98)	23 (10–42)	61 (48–72)
PCT $\geqslant$ 0.5 ng/ml	29 (17–42)	80 (44–98)	89 (65–99)	17 (8–30)	36 (25–49)
IL-8 $\geqslant$ 60 pg/ml	32 (20–46)	90 (56–100)	95 (74–100)	19 (9–33)	41 (29–54)

PPV, $\frac{\text{true positives}}{\text{true positives+false positives}}$; NPV, $\frac{\text{true negatives}}{\text{true negatives+false negatives}}$.
[a] The cut-off values were selected using the Youden index.
[b] 95% Confidence interval.

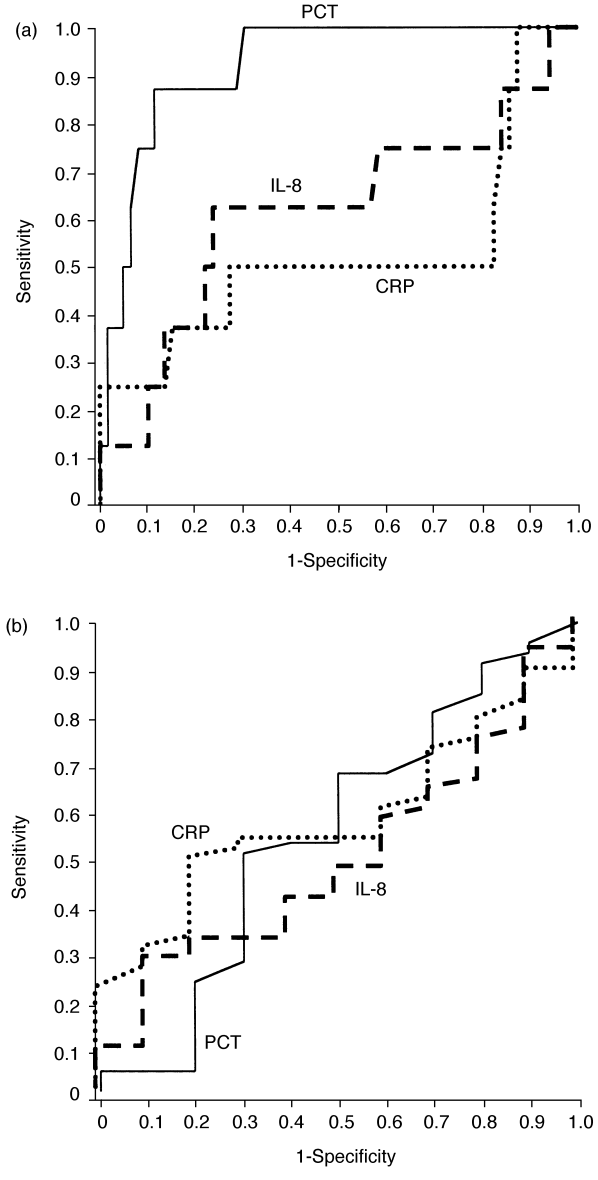

Fig. 2. Comparison of area under ROC curves for CRP, PCT and IL-8 in the prediction of infection in 66 cancer patients with suspected infection. (a) Discrimination of bacteraemic ($n=8$) from other patients ($n=58$). (b) Discrimination of non-bacteraemic infections ($n=48$) from neoplastic fever without infection ($n=10$).

The optimal cut-off values with sensitivity and specificity were identified using the Youden index and were as follows: CRP $\geqslant$ 140 mg/l, PCT $\geqslant$ 0.24 ng/ml and IL-8 $\geqslant$ 60 pg/ml. The sensitivity, specificity, positive and negative predictive values as well as diagnostic accuracy are presented in Table 3. In this series, the cut-off value of PCT determined by the Youden index identified infection better than the cut-off value suggested by the manufacturer (Table 3). All the test characteristics had relatively high positive but low negative predictive values. The accuracy of PCT was highest with a cut-off value of 0.24 ng/ml and clearly lower when a cut-off value of 0.5 ng/ml was used (Table 3). The discriminatory power of PCT for infection was clearly lower in our series than in the previous studies [9–11], where the subjects have been neutropenic (Table 4).

When the abovementioned cut-off values were used, both CRP and PCT were statistically more often positive in the infection group than in non-infection group, whilst the IL-8 levels did not differ between the groups (Fig. 3). When the infection group was subdivided into bacteraemia and other infections, PCT with a cut-off value of $\geqslant$0.50 ng/ml was statistically more often positive during bacteraemia (88%) than minor infections (19%), whilst the CRP and IL-8 values did not differ between bacteraemia and other infections (Fig. 4). When the results of 7 neutropenic patients were analysed, IL-8 was positive in 6, PCT ($\geqslant$0.50 ng/ml) in 1 and CRP in 2 cases (1 patient with three and 1 with two positive findings).

Table 4
Comparison of procalcitonin (PCT) results in infections with neutropenia and the current series with solid tumours

Author [Ref.]	PCT, ng/ml	Sensitivity	Specificity	PPV	NPV
Bernard [9]	$\geqslant$0.50	60	100	100	70
Lestin [10]	$\geqslant$0.50	77	96	91	89
Engel [11]	$\geqslant$0.51	51	89	87	57
Current study	$\geqslant$0.50	29	80	89	17

PPV, positive predictive value; NPV, negative predictive value.

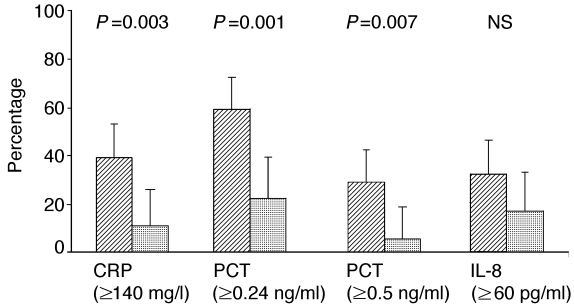

Fig. 3. Proportion of positive C-reactive protein (CRP), procalcitonin (PCT) and interleukin-8 (IL-8) values with the upper 95% confidence intervals in the infection (▨, $n=56$) and non-infection groups (⊠; $n=36$). NS, not significant.

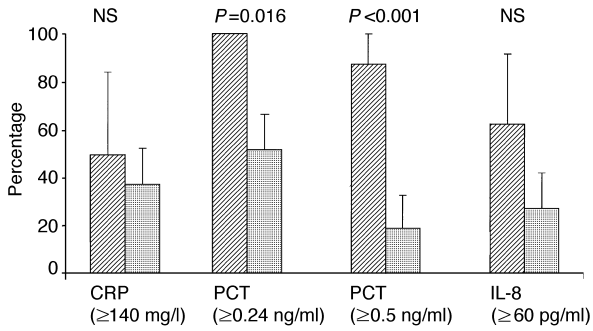

Fig. 4. Proportion of positive C-reactive protein (CRP), procalcitonin (PCT) and interleukin-8 (IL-8) values with the upper 95% confidence intervals on admission within the infection group ($n=56$): bacteraemia (▨, $n=8$) and other infections (⊠; $n=48$). NS, not significant.

4. Discussion

Our results show that the discriminatory power of PCT amongst cancer patients was best for bacteraemia with an AUC value of 0.92, whilst its ability to discriminate minor infections from neoplastic fever was less good with an AUC value of 0.56. In contrast, the AUCs of CRP and IL-8 were poor for both bacteraemia and other infections in this population with solid tumours, of whom most were non-neutropenic and non-bacteraemic. Thus, our study population differs from those previously reported, where the diagnostic value of PCT or IL-8 has been evaluated for infection in neutropenic cancer patients with haematological malignancies [9–11].

PCT has been previously described as a powerful predictor for bacteraemia in patients with or without neutropenia [4,5,9–11,27]. This was also seen in our study, where the admission PCT was found to be positive ($\geqslant 0.5$ ng/ml) in 88% of the patients with bacteraemia with an AUC value of 0.92, but in a clearly smaller proportion (19%) of other infections with AUC values of 0.56. In addition, the poor discriminatory power of PCT in infections milder than bacteraemia in this cancer population was reflected in its clearly lower sensitivity and negative predictive values compared with those reported for neutropenic infections (Table 4). In cancer patients, the utility of PCT for the diagnosis of infection may be impaired due to the influence of the tumour, as has been reported in patients with medullary C-cell carcinoma of the thyroid and small cell carcinoma of the lung [8]. In our study, 2 patients with advanced pulmonary cancer had a positive PCT value without infection (a false-positive rate of 6%; 2 out of 36). Thus, the underlying cancer was not a major problem for the diagnostic use of PCT in this series.

The diagnostic value of IL-8 has previously been reported to be relatively good (AUC value 0.78) in patients with neutropenic bacteraemia [11]. In our series, the corresponding AUC value for bacteraemia was lower (0.62) and even less powerful (0.49) for the demonstration of other infections. 6 of our 7 neutropenic patients also had an increased concentration of IL-8. If we had excluded these neutropenic patients, the AUC values for IL-8 would have been even poorer (data not shown). The underlying cancer has recently been shown to increase IL-8 secretion in patients with prostate cancer [17], suggesting that at least solid tumours may interfere with the diagnostic use of IL-8 to identify infection. In haematological malignancies, the underlying cancer does not seem to interfere with the diagnostic use of IL-8 [11].

According to our results, admission CRP had a low AUC value (0.57) for the demonstration of infection in cancer patients. Many of the patients had superficial infections less severe than bacteraemia, which may be associated with only a marginal increase in CRP values and result in a low sensitivity in the CRP analyses. In contrast, activated CRP production has been linked with advanced cancer [20,28]. In our study, all patients with neoplastic fever had advanced cancer, which may partly explain the low specificity of CRP in comparison with a recent study with neutropenic infections [29].

In conclusion, CRP, PCT and IL-8 have obvious drawbacks in the practical diagnosis of infections in non-neutropenic cancer patients. These differences may be due to several things. The infections in patients with solid tumours are frequently milder than sepsis and are often associated with tumour necrosis and obstructive problems. Although the underlying cancer seems to disturb all three markers, there may be quantitative differences. PCT was found to be a good marker for bacteraemia even in this series, though it was seldom positive in other infections, which are, however, the most common problem in everyday practice. In contrast, both CRP and IL-8 seemed to be poor markers even for sepsis, possibly due to the influence of the tumour load. These markers did not help to identify infections in the primary evaluation of cancer patients and hence to avoid unnecessary antibiotic treatments as well as hospitalisation.

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