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Interleukin 6, procalcitonin and CRP levels during first increase of fever in intensive care patients[1)]

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Abstract

Serum levels of interleukin 6 (IL-6), procalcitonin (PCT), and C-reactive protein (CRP) were measured in 38 critically ill patients immediately after an increase in body temperature above 38.3°C. Ten healthy controls were also included for comparison. The onset of fever was accompanied by elevated circulating levels of all the 3 markers in comparison to healthy control subjects. However, only IL-6 levels were significantly higher ($p < 0.05$) in nonsurvivors compared with survivors. Sensitivity, specificity, positive, and negative predictive values for survival were higher for IL-6 in comparison to levels of PCT and CRP. Areas under receiver characteristic operating curves revealed the highest area under the curve for IL-6 compared to PCT and CRP. These data suggest that IL-6 rather than PCT or CRP may be an early predictor of prognosis and mortality in patients with the onset of fever.

Keywords: cytokines; fever; infection; procalcitonin; prognosis; sepsis.

Introduction

An increase of body temperature (>38.3°C), one of the first signs of an incipient complication in critically ill intensive care patients, is associated with increased mortality [1, 2]. While the first onset of fever may be the result of an uncritically elevated temperature, the possibility of a serious infectious complication cannot be ruled out. In neutropenic patients, fever is associated with a particularly high risk of sepsis development, and intensive antibiotic treatment is usually required. The assessment of sepsis risk at the onset of fever is therefore often a helpful tool which may not only allow early anti-infective therapy, but also avoid overtreatment of patients. It is the goal of the present study to identify and evaluate early biomarkers for the assessment of sepsis risk.

One of the most commonly measured laboratory inflammation markers is C-reactive protein (CRP). CRP is, however, not suitable for early identification of high risk patients, due to its low sensitivity and specificity in the prediction of infection or sepsis. Numerous studies have shown that other more recently identified markers, such as interleukin 6 (IL-6) and procalcitonin (PCT), are also elevated in patients with inflammatory diseases and more suitable tools for the diagnosis of sepsis [3–7]. While PCT is a more specific indicator of bacterial infections, SIRS, or sepsis, than CRP [3, 4], IL-6 concentrations increase very early, well before any clinical signs of inflammation, and before CRP levels increase [5, 6]. In patients diagnosed with sepsis, a correlation was shown between both elevated IL-6 and PCT concentrations and mortality [8].

To evaluate the potential of IL-6 and PCT levels for the identification of high risk patients in ICU units in comparison with CRP, this study prospectively measured all three biomarkers in 38 ICU patients at the onset of fever and analyzed their correlation with mortality.

Materials and methods

Patients

Thirty-eight intensive care unit patients were prospectively included in this study as soon as an onset of fever could be detected. The mean age of patients (22 men, 16 women) was 56 years (19–85 years). The underlying diseases were as follows: Lymphoma/leukemia (n=16), solid tumor (n=2), liver cirrhosis (n=8), acute or chronic cardiac disease (n=10), diabetes (n=2), renal insufficiency (n=3), stomach ulcer (n=3), dermatomyositis (n=1), mesenteric infarction (n=1), drug dependency (n=1), and lung embolism (n=1).

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Measurements of body temperature were taken three times daily. Fever was defined as elevated body temperature >38.3°C. Hospital mortality, underlying disease, and signs of developing sepsis, pneumonia, and non-infectious complications in patients were documented. Sepsis was defined according to the criteria of Bone [9]. Pneumonia was diagnosed according to the guidelines of Maschmeyer et al. [10]. Ten healthy controls were included as comparisons.

Sampling of blood and analysis

Venous blood was drawn at the first onset of fever (38.3°C). Following centrifugation, aliquots of serum were frozen at −70°C until analyzed. For the turbidimetric measurement of CRP, a Hitachi 911 (Roche, Mannheim, Germany) was used. IL-6 was measured using an automated ELISA assay on a CobasCore® (Roche, Mannheim, Germany) [11]. PCT levels were obtained using an immunoluminometric test (LUMItest, Brahms Diagnostica, Berlin, Germany).

Statistical analysis

Statistical comparisons between surviving patients and non-survivors were based on the Mann-Whitney *U*-test. p-Values <0.05 were considered statistically significant. Predictive values of the biomarkers were determined for each test using ROC-(receiver operating characteristic) analysis as plots of sensitivity versus false-positive rate for all possible cutoff levels. The diagnostic accuracy of IL-6, PCT, and CRP was expressed as AUC (the area under the ROC curve) with the 95% confidence interval. χ^2-Tests were used to evaluate sensitivity, specificity, negative and positive predictive values for the median, first and third quartiles of data for all patients.

Results

Ten patients developed sepsis following the onset of fever, and 8 patients developed pneumonia. In the remaining patients, fever was caused by either local infections (n=6), myocardial infarction (n=2), bone marrow rejection (n=1), or hepatic failure (n=1). Twenty-one of all 38 patients (55%) passed away while admitted to the hospital.

The fever correlated with a significant increase in serum concentrations of all three biomarkers (IL-6: 1000 (44–2815) pg/mL; PCT: 6.3 (0.3–510.7) ng/mL; CRP 11.4 (0.6–35.0) mg/dL), compared to the healthy normal subjects (IL-6: <10 pg/mL; PCT: <1 ng/mL; CRP <0.5 mg/dL). Compared with survivors, only IL-6 levels were significantly higher ($p<0.05$) in non-surviving patients. PCT and CRP concentrations were not significantly different in these two patient groups. Sensitivity, specificity, as well as negative and positive predictive values were also higher for IL-6 than for PCT and CRP (Table 1).

To compare the diagnostic value of IL-6, PCT, and CRP, the AUC (area under the curve) was calculated using ROC analysis (Figure 1). The AUC for IL-6 levels was 0.807 (confidence interval 0.668–0.951) and higher than the AUC of PCT levels (0.637, confidence interval 0.483–0.839), and the AUC of CRP levels (0.545, confidence interval 0.362–0.736).

Discussion

Experimental in vivo studies have shown that TNF and IL-1, and subsequently IL-6, are released only minutes following the triggering of an inflammatory reaction. All three cytokines play a pivotal role in the initiation of the acute phase reaction which is accompanied by fever [12]. While TNF and IL-1 are frequently released intermittently, circulating levels of IL-6 are detectable for a longer period of time, due to its longer biological half-life. Furthermore, a correlation between IL-6 concentrations and prognosis was established [5–7]. This prognostic relevance was confirmed by the results of this study. At the onset of fever, IL-6 concentrations of >1000 pg/L in particular, were associated with high mortality rates.

Contrary to pro-inflammatory cytokines, very little is known about the pathophysiological relevance of PCT. Elevated PCT levels were detected in various inflammatory diseases, such as bacterial infections and sepsis. Particularly in patients suffering from severe inflammatory diseases, a correlation was also shown between PCT levels and disease severity [3, 4, 13]. However, the present study shows that IL-6 concentrations at the onset of

Table 1 IL-6, PCT, and CRP concentrations in intensive care patients at the onset of fever (>38.3°C).

	IL-6 [pg/mL]	PCT [ng/mL]	CRP [mg/dL]
Survivors (n=17)	697±432	27.9±25.9	13.4±4.5
Non-Survivors (n=21)	1706±420	59.7±48.7	15.4±4.2
P (Kruskal-Wallis test)	0.001	0.091	0.607
Sensitivity*	71.4%	57.1%	57.1%
Specificity*	76.5%	58.8%	58.8%
Pos. predictive value*	78.9%	63.2%	63.2%
Neg. predictive value*	68.4%	52.6%	52.6%

Mean±95% confidence interval.
*Calculated using the median of all patients as threshold value (with permission, [17]).

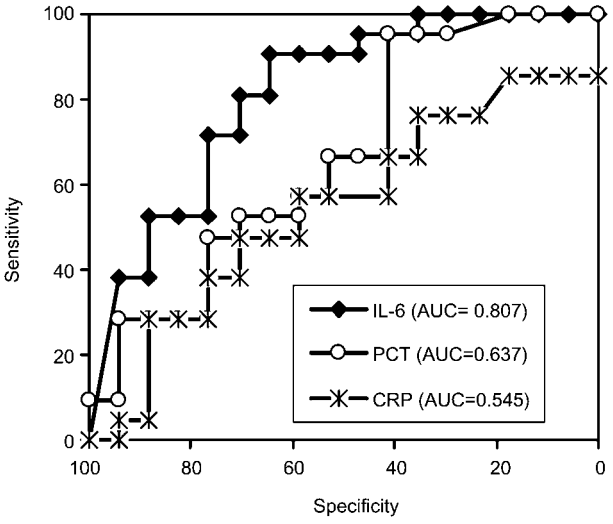

Figure 1 ROC-analysis for the assessment of survival using IL-6, PCT, and CRP concentrations at the onset of fever (with permission, [17]).

fever were better prognostic markers than PCT and CRP. This may be due to differences in time dependent release patterns between IL-6, PCT, and CRP. Based on in vivo studies, circulating levels of IL-6 are detectable only minutes following endotoxin administration, whereas serum PCT concentrations increase only 2 h later, and CRP concentrations as late as 6 h later [14]. Although no concentration/time data were obtained for the present study, previous studies [15] have shown that IL-6 concentrations peak at the onset of fever and then decline gradually. Serum PCT levels increase a little later, but can be detected significantly longer than those of IL-6, due to PCT's longer biological half-life. This may explain why at the early onset of fever, IL-6 is superior as prognostic marker, whereas in patients diagnosed with sepsis, PCT levels are better markers of severity [16].

In summary, the present study demonstrated the suitability of IL-6 as marker for the identification of high risk patients at the early onset of fever. Further prospective studies are needed to establish if early IL-6 measurements may improve prognosis of intensive care patients with increasing fever by initiating early targeted anti-infective therapy.

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