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Short Communication

PROGNOSTIC VALUE OF INTERLEUKIN 6, PROCALCITONIN, AND C-REACTIVE PROTEIN LEVELS IN INTENSIVE CARE UNIT PATIENTS DURING FIRST INCREASE OF FEVER

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ABSTRACT—To investigate the prognostic value of interleukin 6 (IL-6), procalcitonin (PCT), and C-reactive protein (CRP) in critically ill patients during the first increase of fever, serum levels were measured in 38 patients admitted to intensive care unit of the Department of Medicine, Klinikum Großhadern, University of Munich, immediately after increase of 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 with healthy controls. However, only IL-6 levels were significantly higher ($P < 0.05$) in nonsurvivors (n = 21) compared with survivors. Sensitivity, specificity, positive, and negative predictive values calculated from median levels was higher for IL-6 compared with PCT and CRP. Areas under receiver characteristic operating curves revealed the highest area under the curve for IL-6 in contrast to PCT and CRP. These data suggest that IL-6 rather than PCT or CRP may be an early predictor of mortality in patients with onset of fever and identify patients, who need intensive monitoring to initiate appropriate therapy at an early stage.

KEYWORDS—Cytokines, procalcitonin, fever, infection, sepsis, prognosis

INTRODUCTION

Fever, defined as an increase of a body temperature more than 38.3°C (100.4°F), is often encountered in the intensive care unit (ICU) patient and requires establishing the absence or presence of infection (1). Although prolonged fever is associated with poor outcome (2), the onset of fever may be clinically harmless because many noninfectious disorders are also accompanied by fever. Neutropenic patients developing fever are at high risk for sepsis and require broad-spectrum antibiotic therapy. However, in patients developing fever of unknown origin, caution is necessary not to overtreat them. Therefore, early markers are desirable to identify patients at high risk of sepsis and mortality to initiate immediate adequate therapy.

Among various markers of infection and sepsis, plasma CRP is the most commonly measured acute phase parameter. However, because of its low sensitivity and specificity, it is not a reliable marker to identify patients at high risk in the ICU. Recently, other markers including IL-6 and PCT have been reported to be superior in this respect because elevated levels of these mediators correlate significantly with severity of disease in patients with infection or sepsis (3–7). IL-6 predicts an inflammatory condition before the increase of circulating CRP and clinical signs such as fever (5, 6), whereas PCT has been suggested as a more specific marker for bacterial infections (3, 4). Although the prognostic value of plasma IL-6 concentrations has been established in a number of studies in various diseases, recent studies propose PCT as the most specific and sensitive indicator for high mortality (8). However, it should be mentioned that most of the studies comparing the prognostic value of these inflammatory markers included patients with clinically established infection, systemic inflammatory response syndrome (SIRS), or sepsis. To our knowledge, no study has been reported so far to examine the value of these markers at the onset of fever when course and prognosis is unclear. We therefore prospectively measured PCT, IL-6, and CRP serum levels in 38 ICU patients to evaluate the potential of these markers for prediction of mortality at the early phase of disease.

MATERIAL AND METHODS

Patients

Intensive care unit patients (n = 38) were prospectively included in this study at the onset of fever. Body temperature was measured at least 3 times daily and immediately when clinical signs of fever were suspected. Fever was defined as a body temperature more than 38.3°C (>101°F). All patients fulfilled criteria of SIRS with the onset of fever. In addition to in-house mortality, underlying diseases and subsequent development of sepsis, pneumonia, or noninfectious complications were monitored. SIRS and Sepsis was defined according to the criteria of Bone et al. (9). Pneumonia was diagnosed according to the guidelines of Maschmeyer et al. (10). Healthy controls (n = 10) were also included in the study for comparison. This study was approved by our Institutional Human Use Committee and informed consent was obtained.

Sampling and analysis

At the onset of fever blood was drawn within 1 h, centrifuged, aliquoted, and kept frozen at −70°C for analysis. CRP was measured with routine clinical chemistry methods (Hitachi 911, Roche, Mannheim, Germany). IL-6 and PCT were measured with an automated enzyme-linked immunosorbent assay on CobasCore (Roche, Mannheim, Germany) (12) and immunoluminometric assay LUMItest (Fa Brahms Diagnostica, Berlin, Germany), respectively.

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TABLE 1. **Serum levels of IL-6, PCT, and CRP in ICU patients at the onset of fever**

	IL-6	PCT	CRP
Survivor, pg/mL (n=17)	697 ± 432	27.9 ± 25.9	13.4 ± 4.5
Nonsurvivor, pg/mL (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
Positive predictive value (%)*	78.9	63.2	63.2
Negative predictive value (%)*	68.4	52.6	52.6
P (chi-square test)*	0.003	0.327	0.328

Mean ± 95% confidence interval.
*Calculated using median levels of all patients as cutoffs.

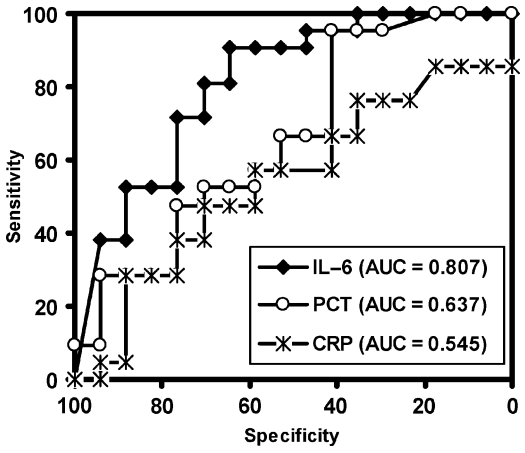
Statistical analysis

The levels of the inflammatory markers are given as medians. Comparisons between survivors and nonsurvivors were based on the Mann-Whitney *U* test. A *P* value less than 0.05 was regarded as statistically significant. The predictive value of IL-6, PCT, and CRP plasma levels was evaluated using receiver operating characteristic (ROC) curves as plots of the sensitivity of a test versus its false-positive rate for all possible cutoff levels. The diagnostic accuracy of IL-6, PCT, and CRP was expressed as the area under the ROC curve (AUC) and the 95% confidence interval (CI). The AUC defines the probability for correct discrimination between survivors and nonsurvivors (11). Median values were taken for calculating sensitivity, specificity, and positive and negative predictive values, and chi-square test was used to evaluate significant differences between sensitivity and false-positive rate (1-specificity).

RESULTS

The median age of 22 male and 16 female patients included in the study was 56 years (range, 19–85 years). Underlying diseases were as follows: lymphoma or leukemia (n = 16), solid tumors (n = 2), liver cirrhosis (n = 8), acute or chronic cardiac disease (n = 10), diabetes (n = 2), renal insufficiency (n = 3), peptic ulcer (n = 3), dermatomyositis (n = 1), mesenteric infarction (n = 1), drug abuse (n = 1), and pulmonary embolism (n = 1). Twenty-eight patients developed sepsis after the increase of fever. In 10 of these septic patients, pneumonia was diagnosed. The remaining patients had local infections (n = 6), myocardial infarction (n = 2), bone marrow rejection (n = 1), or hepatic failure (n = 1). Fifty-five percent of patients (n = 21) did not survive. The causes of deaths were as follows: septic cardiac failure (n = 9), sepsis and pneumonia (n = 3), septic multiorgan failure (n = 4), cardiac failure (n = 3), myocardial infarction (n = 1), and liver failure (n = 1). The onset of fever was accompanied by significantly elevated levels of all 3 markers (median [range]: IL-6: 999.5 [44–2815] pg/mL, PCT: 6.3 [0.3–510.7] ng/mL, CRP 11.4 [0.6–35.0] mg/dL) in comparison with the healthy controls (IL-6: <10 pg/mL, PCT: <1 ng/mL, CRP < 0.5 mg/dL). Among these 3 parameters, only IL-6 levels were significantly higher ($P < 0.05$) in nonsurvivors (n = 21) compared with survivors (n = 17) (Table 1). Sensitivity, specificity, and positive and negative predictive values were also higher for IL-6 in comparison with PCT and CRP.

To compare the diagnostic accuracy of the inflammatory markers, AUC were calculated (Fig. 1). AUC was highest for IL-6 (0.807, [CI, 0.668–0.951]) in comparison with PCT (0.637, [CI, 0.483–0.839]) and CRP (0.545, [CI, 0.362–0.736]), which further supports the diagnostic value of IL-6.



DISCUSSION

Release of proinflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor, play a pivotal role in the onset of fever. Circulating serum levels of IL-6 have been suggested to be downstream mediators of tumor necrosis factor and IL-1 in initiating the acute phase response and the increase of body temperature (13). Previous studies demonstrated a prognostic value of IL-6 in patients with sepsis and infection (5–7). Our data show that IL-6 levels above 1000 pg/mL at the onset of fever may identify high-risk patients in the ICU.

Plasma PCT levels have been reported as markers of infectious disease, septic shock, multi-organ failure, and mortality (3, 4, 14, 15). However, in the present study, this parameter was not as definitive as IL-6 in differentiating survivors from nonsurvivors possibly because of differences in kinetics of elevation and time to attain maximal plasma concentrations. Peak concentrations of circulating IL-6 precede several hours before the rise in circulating levels of CRP. *In vivo* studies show that 2 h after endotoxin administration, PCT levels increase and peak between 6 to 8 h (16). Although we did not monitor follow-up of inflammatory markers in the present study, previous studies have shown that IL-6 levels peak at the onset of fever and then gradually decline (17). Possibly, PCT levels increase at a later stage and remain elevated in circulation because of a longer biologic half-life. Therefore, in patients with established SIRS and sepsis, PCT levels may have a better prognostic value than IL-6 (18).

To our knowledge, this is the first report showing a prognostic value of IL-6 in patients at the onset of fever, who are at high risk to develop inflammatory disease and organ dysfunction and may thus prove useful in initiating appropriate therapeutic measures promptly. Further, prospective studies with larger cohorts of patients are needed to establish, whether elevated circulating levels of IL-6 alone or a combination of IL-6 in the early phase, and PCT at a later phase may improve outcome of ICU patients developing fever.

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