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Inflammatory markers in patients with severe burn injury What is the best indicator of sepsis?

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ABSTRACT

Objective: To estimate the diagnostic value of serum PCT, CRP, leukocyte count and temperature as markers of sepsis in critically ill ICU burn patients.
Design and setting: Prospective, observational study in a four bed Burn Intensive Care Unit.
Patients: Forty-three patients admitted in a Burn ICU were included in our study.
Measurements and results: Serum PCT, CRP concentrations, WCC (white cell count), neutrophils and temperature were measured within the first 24 h after-burn and daily thereafter. Severity of organ failure was estimated by sequential organ failure assessment (SOFA) score. Every day we classified all patients in one of the following three categories: non-systemic inflammatory condition (non-SIRS), SIRS non-infected and SIRS 2 infected or sepsis. Patients with infected SIRS differ significantly from non-infected SIRS in PCT (11.8 ± 15.8 versus $0.63 \pm 0.0.43$, respectively, $p < 0.001$). On the other hand, WCC, temperature and neurtophils did not differ significantly between patients with SIRS non-infected and infected SIRS. CRP was elevated in all three groups but didn't differ significantly between SIRS non-infected and septic patients. Area under receiver operating curves was 0.975 and showed reasonable discriminative power ($p = 0.002$, 95% CI, 0.91–1.035) in predicting of sepsis only for PCT.
Conclusions: Serum procalcitonin levels can be used as an early indicator of septic complication in patients with severe burn injury

1. Introduction

Sepsis, clinically defined as the systemic inflammatory response syndrome (SIRS) secondary to infection [1–3], is a common complication in Burn Intensive Care Unit and delayed diagnosis is associated with increased morbidity, mortality and cost in the ICU [1]. A classification scheme for sepsis (PIRO) [2] was recently developed. Clinical and laboratory signs of systemic inflammation including changes in body temperature, leucocytosis and tachycardia are used for diagnosis of sepsis. However they are neither specific nor sensitive for sepsis, and can be misleading because critically ill burn patients often manifest a systemic inflammatory response syndrome (SIRS) without infection [2–4]. This phenomenon might be in part responsible for withholding, delaying, or overutilizing antimicrobial treatment in critically ill burn patients [5,6]. Thus, diagnosis of sepsis is frequently difficult. A marker that is able to distinguish inflammatory response to infection from other types of inflammation would be useful in clinical practice [7].

C-reactive protein (CRP) is a commonly used marker of an acute inflammatory response, and its plasma concentration has been reported to be related to the clinical course of infection [8]. CRP plasma concentration >8 mg/dl have been reported to distinguish the inflammatory response to infection from other types of inflammation [9].

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Recent investigations suggest that infection diagnosis may be better achieved by monitoring of procalcitonin (PCT) plasma concentration, which is closely related to the severity and evolution of infection [10,11]. Moreover, recent reports demonstrated that PCT plasma concentrations in septic patients are correlated to organ failure [12,13]. However, other authors still discuss the clinical value of monitoring of PCT concentrations [14,15]. Several studies showed an association between serum PCT and septic complications in patients with burns [18–20].

In our study, we attempt to assess fluctuations of inflammatory markers in burn ICU patients and compare their clinical informative value for sepsis diagnosis. Moreover we tried to compare plasma levels of inflammatory markers to severity of organ dysfunction as estimated by SOFA score.

2. Materials and methods

This prospective study was conducted between 2002 and 2004 and performed at the Burn Unit of ''G. Papanikolaou'' General Hospital in Thessaloniki. The study protocol was approved by the local ethic committee.

2.1. Patients

We prospectively investigated 43 patients (11 female, 32 male), mean age 45.6 ± 20.1 mean burn size (total of second and third degree burns) 41.4 ± 22% of total body surface area (TBSA), admitted to our four bed burn ICU. Each patient was examined for signs and symptoms of infection at the time of admission and daily until they discharged from the ICU or death. Every day we classified all patients in one of the following three categories: non-systemic inflammatory condition, non-infected SIRS and infected SIRS or sepsis [2]. All patients were evaluated on admission by acute physiology and chronic health evaluation II (APACHE II) score, total burn surface area (TBSA) and SOFA score. SOFA score was also evaluated daily until discharge from ICU. The severity of organ dysfunction was compared to the values of PCT and CRP in three increasing SOFA score groups (I = 1–4; II = 5–8; III ≥ 9). In all three groups PCT and CRP plasma concentrations were measured daily during ICU stay (first sample was performed within the first 24 h from admission).

2.2. Laboratory measurement

Blood samples from patients were drawn from indwelling arterial lines for measurement of CRP, PCT and routine laboratory tests including WCC. Serum PCT levels were determined by immunoluminometric assay (Lumitest PCT, Brahms Diagnostica, Berlin, Germany). The lower detection limit was 0.08 ng/ml. The CRP concentration was measured by a Boehringer Mannheim (BM)/Hitachi automated immunoturbidimetric (Tuna-quant, BM, Germany) technique. The lower detection limit was set at 0.2 mg/dl. Other parameters and blood counts were assessed by routine laboratory procedures.

Table 1 – Patient's characteristics

Age (years)	45.6 ± 20.1
Admission APACHE II	9.3 ± 3.2
Admission SOFA	4 ± 2.1
Admission SAPS II	32.8 ± 9
TBSA (%)	41.4 ± 22
LOS (days)	23.2 ± 18
Mortality (%)	20.9

2.3. Statistical analysis

Values are presented as mean ± S.D. Statistical Program for Social Science for Windows (release 12 standard version, SPSS Inc.) was used. Analysis of variance (one-way ANOVA) was performed in order to compare parametric variables in the three patients groups and Bonferroni post-hock test was used in order to investigate differences within groups. Correlations between different inflammation markers in each patient group were studied using Pearson bivariate correlation coefficient. The null hypothesis was rejected when p-value was <0.05. The predictive ability regarding sepsis of PCT, CRP, WCC, neutrophils and temperature was expressed as the area under the receiver operating characteristics curve (AUC-ROC).

3. Results

Clinical characteristics of the 43 patients included in the study are presented in Table 1.

Patients were classified in two groups according to TBSA. Laboratory parameters are represented in Table 2.

A statistically significant higher SOFA score was observed in patients with TBSA > 60% compared to those with TBSA < 60% (6 ± 1.8 versus 3.5 ± 1.5, respectively, $p < 0.01$ unpaired t-test). Additionally, patients with TBSA > 60% had statistically significantly elevated PCT levels compared to those with TBSA < 60% (2.6 ± 2.4 ng/ml versus 0.54 ± 0.4 ng/ml, respectively, $p < 0.001$, unpaired t-test).

Table 2 – PCT, CRP and routine inflammation markers in patients with different burn size on admission

Parameter	TBSA < 60% (30.3 ± 7.8), N = 34	TBSA > 60% (76.9 ± 10.9), N = 9	p-Value
SOFA score	3.5 ± 1.5	6 ± 1.8	<0.01
PCT (ng/ml)	0.54 ± 0.4	2.6 ± 2.4	<0.001
CRP (mg/dl)	16.2 ± 8.3	15.1 ± 6.3	0.23
WCC ($\times 10^9$ l^{-1})	16.7 ± 7.9	19.4 ± 8.9	0.3
Neutrophils (%)	78 ± 9.3	81.7 ± 4.9	0.18
Temperature (°C)	37.8 ± 1	36.2 ± 1.8	0.15

Table 3 – Inflammation markers in the three diagnostic classes

Diagnostic classes	PCT (ng/ml)	CRP (mg/dl)	WBC ($\times 10^9\ l^{-1}$)	Neutrophils (%)	Temperature (°C)
Negative	0.62 ± 0.5	14.29 ± 7.5	12.96 ± 8.91	77.6 ± 9.7	37.4 ± 1.2
SIRS	$0.63 \pm 0.0.4$	18.43 ± 6.3	14.05 ± 7.9	78.28 ± 9.1	$38.6 \pm 1.19^{\#}$
Sepsis (infected SIRS)	$11.8 \pm 15.8^{*}$	21.39 ± 10.3	16.72 ± 10.4	83.5 ± 9.1	38 ± 1.8

Analysis of variance (ANOVA), d.f. = 2, Bonferroni post-hock test.
* $p < 0.001$ difference between SIRS and sepsis.
# $p < 0.05$ between SIRS and negative.

Table 4 – Sensitivity and specificity of PCT in different cut-off points

	Cut-off		
	1.5 ng/ml	2 ng/ml	2.5 ng/ml
Sensitivity (%)	82	66.6	66.6
Specificity (%)	91.2	96.8	97.6
Positive predictive value (%)	71	84.6	88

No other differences were observed in CRP, WCC, neutrophils and temperature between these two groups of patients.

A total of 934 days in ICU staying of all 43 patients was evaluated and classified into three diagnostic groups:

1. negative (non-inflammatory condition), $n = 553$ (days);
2. SIRS (non-infected), $n = 267$ (days);
3. sepsis (infected SIRS), $n = 114$ (days).

Both PCT and CRP plasma concentrations were statistically significant higher among patients with sepsis compared to SIRS (non-infected) and negative patients (Table 3).

We tested several cut-off values of PCT between 1.5 and 2.5 ng/ml that would potentially allow the discrimination of non-infectious SIRS and sepsis. The corresponding sensitivity, specificity are shown in Table 4.

The predictive ability regarding sepsis of PCT, CRP, WCC, neutrophils and temperature was expressed as the area under the receiver operating characteristics curve (AUC-ROC). The results are shown in Table 5.

The patients were assigned to three groups depending on the maximum SOFA score Table 6.

A rise in SOFA score group was related to a higher mean value of PCT. CRP concentrations did not differ at low SOFA scores and had significantly higher levels only in patients with SOFA score ≥ 9. Patients with high SOFA score also developed hypothermia or had showed statistically significant decrease in temperature. Statistically significant difference was not observed in WBC and neutrophils among three SOFA groups.

From 43 patients, 9 died from sepsis related multiple organ failure. Time course of median PCT of survivors and non-survivors from infected SIRS (sepsis) were analyzed in Fig. 1.

PCT concentration that exceeded 15 ng/ml was observed in four patients. Three of them died, in one survived patient with a prolonged sepsis course three consecutive PCT values of more than 30ng/ml were observed with a peak level of 80 ng/ml.

Table 5 – Area under the ROC curve differentiates sepsis from SIRS according to inflammatory markers

Variable	Area under the curve	S.E.	Significance	95% Confidence interval
PCT	0.975	0.031	0.002	0.91 to 1.035
CRP	0.463	0.156	0.8	0.156 to 0.469
Neutrophils	0.794	0.099	0.052	0.6 to 0.987
WBC	0.531	0.150	0.83	0.237 to 0.826
Temperature	0.281	0.172	0.14	−0.056 to 0.619

Table 6 – Inflammation markers in different maximum SOFA score groups

SOFA group	SOFA score	PCT (ng/ml)	CRP (mg/dl)	WBC ($\times 10^9\ l^{-1}$)	Neutrophils (%)	Temperature (°C)
I	1–4 (2.4 ± 1.3)	0.53 ± 0.4	14.4 ± 7.4	12.5 ± 8.9	76.4 ± 10.2	37.7 ± 1.5
II	5–8 (6.2 ± 1)	$3.9 \pm 6.9^{*}$	16.5 ± 6.9	15.7 ± 7.8	84.1 ± 5.6	37.5 ± 1.6
III	≥ 9 (10.5 ± 1.6)	$11.5 \pm 7.6^{*}$	$26.1 \pm 15.5^{\#}$	12.9 ± 5.5	86.9 ± 5	$35.7 \pm 1^{\#}$

* Differences among three SOFA groups ($p < 0.05$).
# Difference between groups II and III.

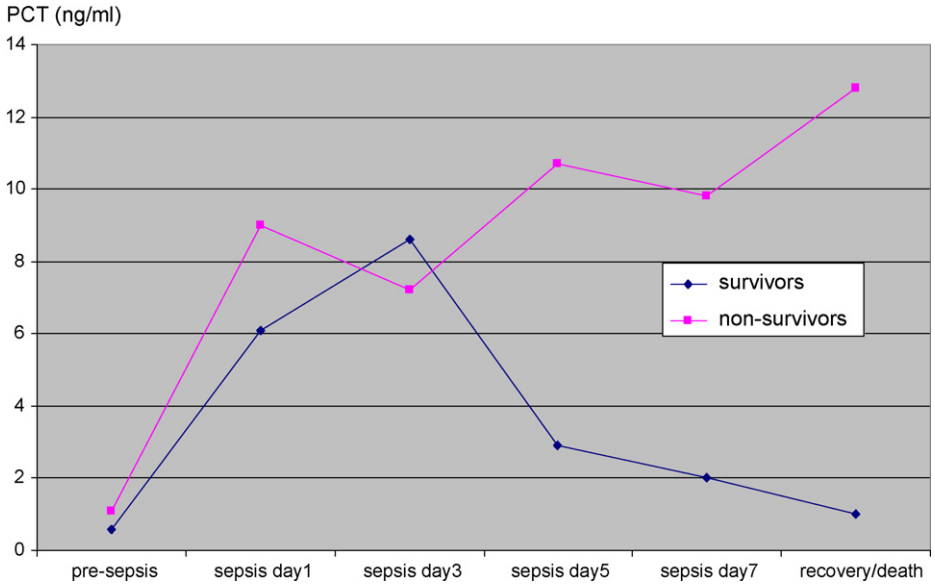

Fig. 1 – Time trend of PCT levels in survivors and non-survivors from sepsis.

4. Discussion

As sepsis remains an important cause of morbidity and mortality in burn patients, rapid diagnosis and treatment of septic complications is essential. The aim of our study was to analyze the value of inflammatory markers as an early diagnostic tool of sepsis in burn ICU patients.

The classic markers of inflammation are fever and leukocytosis. Although easy to measure, body temperature is a specific, but not a sensitive marker of infection [8]. Infection is frequently not the cause of fever in febrile critically ill burn patients [17,33]. High fever can be associated with minor infections, while normal temperature or even hypothermia is possible in very severe situations. In fact, in our study patients with extremely high SOFA score (≥9) developed profound hypothermia. The WCC is routinely performed in almost every ICU and it could be a criterion of sepsis. However, it is influenced by many non-infectious factors [8,21]. The value of leucocytosis in the diagnosis of infection and sepsis was very poor in our study. Neutrophil count but not WCC, showed greater accuracy in differentiation of sepsis from SIRS (area under ROC curve 0.794, 95% CI, 0.6–0.987).

The efficacy of PCT and CRP levels in differentiation of sepsis (infected SIRS) from non-infected SIRS is a matter of discussion in literature [22–25,29,30,32,35]. Additionally, in burn septic patients, PCT and CRP value remains controversial in the diagnosis of sepsis [17,19,20,33,34]. Procalcitonin has been proposed as a marker of infection [10,16] in a variety of clinical conditions. PCT as an acute phase protein is secreted in response to severe bacterial infections, sepsis and multiple organ failure. Localized bacterial infections are responsible for minor PCT increases. On the contrary, systemic bacterial infections caused marked PCT elevation. Administration of Escherichia coli endotoxin to healthy volunteers induces a rapid and short-lived peak of TNF-α and IL-6 followed by an increase of PCT level. After an inflammatory stimulus, PCT is detectable 3–4 h later, peaks at 14 h, remains elevated for 24 h and has a half-life in serum of 22–35 h [10]. However there are several non-infectious inflammatory diseases, such as trauma, burn and surgery which are also associated with PCT elevations. The value of PCT to diagnose septic complications in burn patients was investigated by a small number of trials [17–20,34]. Dehne et al. [17] investigated the PCT and CRP levels in 24 severely burned patients with different sizes of TBSA and observed that CRP levels were constantly elevated. On the other hand, levels of PCT were decreased in patients with uncomplicated burn course after thirteen day of thermal trauma. However, Ulrich et al. [34] could not be able to find any association between PCT and endotoxin levels in burn patients. Other investigators suggested that PCT is a highly efficient laboratory parameter for the diagnosis of severe infectious complications after burn injury [19,20,33].

CRP induction is mediated by interleukin-6 (IL-6) and either IL-1 or tumor necrosis factor-α (TNF-α). Therefore, CRP synthesis and secretion usually reflects proinflummatory cytokine production and may be considered as surrogate marker. CRP secretion begins within 4–6 h after stimulus, is doubling every 8 h and is peaked at 36–50 h. CRP has a half-life of 19 h, so after stimulus cessation, it falls rapidly [9]. If the underlying cause of the elevation persists, CRP can remain elevated for a long period. Elevation in serum CRP is present in most invasive infections. In addition to infection, there are several other conditions that commonly lead to substantial changes in CRP concentration, such as trauma, burns, tissue necrosis and immunologically mediated inflammatory diseases. CRP cannot be used as a unique diagnostic tool for infection as it is not specific. So the diagnostic value of CRP remains controversial. Increase CRP levels in association with infections and sepsis have been described in many studies [8,9,21,25]. Some of these studies proposed CRP as a biological marker of infection and as a diagnostic criterion for sepsis, but other have drown attention to its limitations such as slow kinetics and poor diagnostic specificity. It is not yet clear

whether the increase of CRP in burn patients is related to the presence of septic complications or is an effect of thermal trauma itself. Several investigators reported persistently high levels of CRP in burn patients and the absence of changes in septic complications [17,19].

Some researchers have rejected an association between CRP levels and severity of organ dysfunction [26,27,35]. Other authors have found a relationship between organ dysfunction and CRP levels [8,9,21,28,31]. In agreement with that, high SOFA score patients (SOFA ≥ 9) in our study showed a statistically significant increase of CRP levels. We were unable to find any difference in CRP levels in those with low SOFA score. A statistically significant difference in PCT levels was detected among three different SOFA score groups.

Serum PCT levels on admission are significantly higher in patients with TBSA $> 60\%$ compared to those with TBSA $< 60\%$. This is not an issue in CRP. These results are in agreement with Sachse et al. [19] who observed a moderately statistically significant correlation between burn size and plasma PCT during the first week after burn, and not during the second week, but Neely et al. rejected an association between PCT and burn size in pediatric patients [18].

Wanner et al. suggest a threshold of 1.5 ng/ml as a value that discriminate trauma patients at risk for septic complications [12]. von Heimburg et al. found a cut-off value of 3 ng/ml reliable to indicate severe bacterial infection in burn patients [20]. We tested different cut-off values of PCT. and we found specificity to rise from cut-off 1.5 to 2.5 ng/ml, and sensitivity to drop. A cut-off value of 1.5 ng/ml seems to have an acceptable value that distinguish burn patients at risk for septic complications.

In addition to the absolute PCT, time course was also of diagnostic value. Procalcitonin was significantly elevated in 1st septic day compared to presepsis period and declines in patients who survived progressively from third to seventh day. On the other hand a sustained elevation of PCT was observed in nine patients who died in ICU from multiple organ failure induced by sepsis.

5. Conclusion

The verification of an episode of infection using culture is a time consuming process in diagnosis of sepsis and so the initiation of appropriate antibiotic treatment may be delayed. Our study supports the option that PCT is a better marker of sepsis than other inflammatory markers and the area under ROC curve has an acceptable accuracy. Daily PCT determination offers a unique opportunity to burn intensive care specialists to make an early decision of any changes in the antimicrobial regimen as well as in monitoring of the response to therapy.

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