Procalcitonin as a prognostic marker in non-infected critically ill cardiovascular patients

Judith Koning[a], *Simon Ritter*[b], *Marco Maggiorini*[c]

[a] Institute of Anaesthesiology and Intensive Care Medicine, Hospital Uster, Switzerland
[b] Intensive Care Unit, Department of Internal Medicine, Triemli City Hospital, Zurich, Switzerland
[c] Intensive Care Unit, Department of Internal Medicine, University Hospital Zurich, Switzerland

Summary

Background: Procalcitonin (PCT) is a marker of inflammation in systemic bacterial infections. The aim of this study was to determine the role of PCT as a prognostic marker in cardiovascular intensive care unit (ICU) patients with non-infectious conditions.

Methods: 253 critically ill medical patients were consecutively included during a 4-month period. The highest PCT plasma level during the first 72 hours of ICU stay was taken for analysis, and a level ≥0.5 ng/ml was defined as elevated. Hospital mortality rates stratified by PCT level were compared among the patients without an infection at ICU admission (n = 223) and among a subgroup of non-infected patients with a cardiovascular diagnosis (n = 164).

Results: The non-infected patients with an elevated PCT level had a 38% mortality rate (15/40), whereas a 9% mortality rate was observed among the non-infected patients with a normal PCT (16/183) (p <0.001). The mortality rate was 42% among the subgroup of cardiovascular patients with an elevated PCT level (11/26), whereas it was 4% among the cardiovascular patients with a normal PCT (6/138) (p <0.001). For PCT, the area under the receiver operating characteristic curve for the prediction of mortality was 0.81 (95% confidence interval [CI] 0.74–0.89) in all non-infected patients and 0.90 (95% CI 0.84–0.96) in the cardiovascular subgroup.

Conclusions: In apparently non-infected critically ill medical patients, particularly in cardiovascular patients, elevated PCT plasma levels are associated with an increased hospital mortality. Nevertheless, PCT values should be interpreted carefully in the clinical context.

Key words: procalcitonin; non-infected patients; cardiovascular patients; intensive care unit; prognostic marker; hospital mortality

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Introduction

Procalcitonin (PCT) is a marker of severe systemic infection of bacterial origin [1]. However, various conditions other than infection, such as surgical interventions [2], cardiogenic shock [3], or burn injuries [4] can increase PCT plasma levels. PCT has also been studied as a marker of systemic inflammatory response syndrome (SIRS), severe sepsis and septic shock in intensive care units (ICUs) [5]. In a medical ICU, serum PCT concentrations >1 ng/ml have a high sensitivity and specificity for the diagnosis of sepsis [6], whereas PCT plasma levels of healthy individuals are <0.1 ng/ml. An elevated PCT plasma level >0.5 ng/ml in patients with severe sepsis or septic shock correlates with poor prognosis [6, 7]. A PCT-guided strategy for treating suspected bacterial infections in non-surgical ICU patients can reduce antibiotic exposure without increased mortality [8]. On the basis of the results of this trial, starting of antibiotics is encouraged when PCT concentration is ≥0.5 ng/ml [8]. Cardiosurgical patients with high levels of PCT have been associated with elevated mortality, and higher risk of infection and severe complications early after surgery [9]. Data about PCT as a prognostic marker after acute myocardial infarction have been published recently [10, 11]. However, little is known about PCT as a prognostic marker in unselected non-infected patients. Hence, the aim of the present study was to determine the prognostic value of PCT in a non-selected population of critically ill medical patients with a diagnosis other than infection on ICU admission.

Correspondence:
Simon Ritter, MD
Intensive Care Unit
Department of Internal Medicine
Triemli City Hospital
Birmensdorferstrasse 497
CH-8063 Zurich
Switzerland
simon.ritter[at]zuerich.ch

Methods

Study design

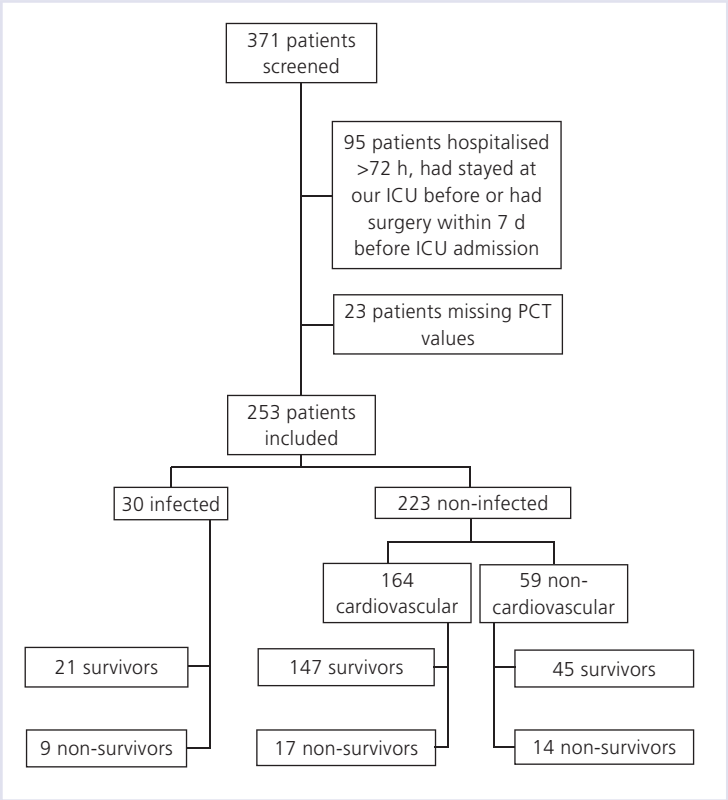
This observational single institution study was performed in the 12-bed medical ICU of the University Hospital Zurich, Switzerland. PCT was measured after routine blood sampling. We retrospectively analysed the data of 371 unselected patients admitted to our ICU during an observation period of 4 months. Data collection was made anonymously. Because of possible confounding factors such as nosocomial infection and postoperative status, patients who had been staying in a different hospital or ward for longer than 72 hours (n = 71), patients who had stayed at our ICU before (n = 23) and patients who underwent a surgical intervention within 7 days prior to ICU admission (n = 1) were excluded from the study. Additionally, 23 patients were excluded because of insufficient material to measure PCT. Finally, 253 patients were included into our analysis (fig. 1).

Patient characteristics

Thirty of the 253 included patients were diagnosed with an infection during the first 72 hours after ICU admission (12%). Infection was diagnosed in the presence of a positive bacterial or fungal culture from sterile body fluids or blood, or evidence of a perforated bowel. New onset of purulent sputum and new or progressive infiltrates or consolidation on chest radiograph was necessary for the diagnosis of pneumonia. Sepsis, severe sepsis and septic shock were diagnosed in accordance with published guidelines [12]. Accordingly, pneumonia with sepsis, severe sepsis or septic shock was diagnosed in 10 patients, and an additional 11 patients fulfilled the criteria for severe sepsis or septic shock. Gram-positive bacteria were isolated in 16 patients, Gram-negative in 5 patients, and combination of both bacteria in another 2 patients. No microorganism could be cultured in 7 patients.

A total of 223 of the included patients were diagnosed as not having an infection during the first 72 hours after ICU admission (88%). Of these 223 non-infected patients, 164 (74%) had a cardiovascular diagnosis (fig. 1). These patients were admitted because of acute myocardial infarction (n = 95), unstable angina pectoris (n = 17), arrhythmia (n = 16), congestive heart failure (n = 11), aortic dissection (n = 13), and other diagnoses (n = 12) such as dilative cardiomyopathy and valvular heart disease. All patients with acute myocardial infarction and unstable angina pectoris were admitted after percutaneous coronary intervention had been performed. The main admission diagnoses of the 59 remaining non-infected patients were related to the central nervous system (CNS) in 26, to the abdomen in 15, to the lung in 6 or to one of the following: intoxication (n = 8), severe heat stroke (n = 1), rhabdomyolysis (n = 1), anaphylactic shock (n = 1) and vasovagal reaction (n = 1).

Figure 1
Flow chart of the study population.
d = days; h = hours; ICU = intensive care unit; PCT = procalcitonin



Monitoring and outcome parameters

In addition to heart rate, mean arterial pressure and temperature, the ratio of partial arterial oxygen pressure (PaO_2) to inspired oxygen fraction (FiO_2) was recorded. The severity of illness was quantified with the Simplified Acute Physiology Score (SAPS II), calculated from the worst values within 24 hours following ICU admission, and associated predicted mortality [13].

Additionally, the following outcome parameters were recorded: need for mechanical ventilation, circulatory shock defined as systolic blood pressure <90 mmHg for at least 1 hour despite adequate fluid resuscitation or need for vasopressors and/or inotropes, prehospital cardiopulmonary resuscitation (CPR) and the number of days in ICU. Patient survival status was recorded at hospital discharge.

Laboratory tests

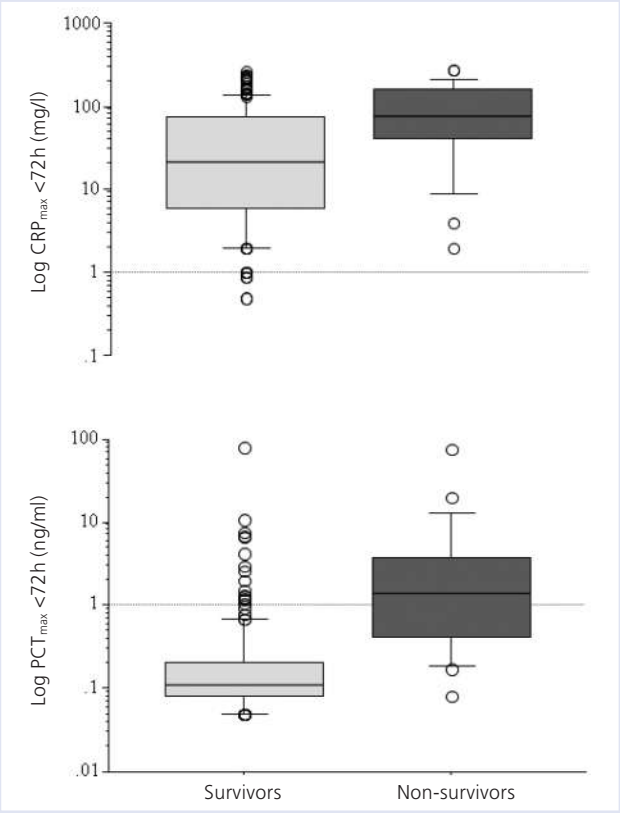
C-reactive protein (CRP) was measured in heparinised plasma using a particle-enhanced turbidimetric immunoassay [14], the lower limit of measurement being 0.1 mg/l and the upper limit of normal <5 mg/l. Plasma PCT levels were determined using the homogeneous immunoassay (Kryptor®, Brahms Diagnostica,

Berlin, Germany) [15] with a limit of detection of 0.06 ng/ml. The normal PCT level was set at <0.5 ng/ml in accordance with previous data [8]. CRP plasma levels were measured in the routine blood sample taken on admission (day 0), and then once daily during the first 3 days (day 1–3) or until ICU discharge, and PCT plasma levels were determined from corresponding blood samples (day 0–3). Blood culture bottles (BacT/ALERT, Biomérieux, Marcy l'Etoile, France) were incubated and evaluated by the Microbial Institute of the University Hospital in Zurich.

Data analysis

Clinical data were collected from the patients' charts, made anonymous and entered into a computerised database. Since the purpose of our study was to determine the prognostic value of PCT in non-infected patients admitted to a medical ICU, we separated the patients with a diagnosis of infection (n = 30). Among the group of patients with no infection (n = 223), a significant proportion (164/223 or 74%) had a diagnosis related to cardiovascular disorders, as mentioned above. Thus, we compared these non-infected patients (subgroup of non-infected cardiovascular patients) with those having a diagnosis that was different from any cardiovascular disorder (subgroup of non-infected non-cardiovascular patients, n = 59) (fig. 1). The highest PCT plasma levels within the first 72 hours of ICU stay (that is from day 0–3) were taken for analysis. PCT cut-off levels were set at 0.25, 0.5, and 1.0 ng/ml. The results obtained for PCT where then compared with the CRP values that were obtained at the same time. CRP cut-off levels were set at 5, 50, and 100 mg/l. The Mann-Whitney U-test, Fischer's exact test and chi-square test were used, as appropriate. All testing was two-tailed, and a p-value below 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves for the prediction of hospital mortality are expressed as the area under the curve (AUC) and the upper and lower bound of an asymptotic 95% confidence interval (CI). Results are expressed as medians, 25th–75th percentiles (interquartile range, IQR) or percentages.

Figure 2
C-reactive protein and procalcitonin plasma levels in non-infected hospital survivors and non-survivors.
Logarithmic distribution of highest CRP and PCT plasma levels measured within the first 72 hours after admission to the intensive care unit in non-infected survivors (n = 192) and non-infected non-survivors (n = 31), p-values for the difference between survivors and non-survivors for PCT <0.001 and for CRP <0.001. CRP = C-reactive protein; h = hours; log = logarithmic; PCT = procalcitonin



Results

Particular characteristics of the study population are summarised in table 1. Infected patients had a higher heart rate, core temperature, SAPS II score and a higher hospital mortality, as compared with non-infected patients. In addition, more patients with infection were in shock and mechanically ventilated. Non-infected patients had a trend to more frequent cardiopulmonary resuscitation during the prehospital phase.

PCT measurements

The median PCT plasma level was 5.82 ng/ml (IQR 2.20–22.07 ng/ml) in infected patients and 0.12 ng/ml (IQR 0.08–0.30 ng/ml) in non-infected patients (p <0.001). All but two of the infected patients had a PCT level ≥0.5 ng/ml (93%). One patient with *Pneumocystis jirovecii* and another with *Micrococcus luteus* infection had a PCT <0.5 ng/ml. Among the patients without infection, 18% had a PCT ≥0.5 ng/ml (40/223). The distribution of PCT plasma levels between non-infected hospital survivors and non-survivors is shown in figure 2.

CRP measurements

The median CRP plasma level was 248 mg/l (IQR 158–303 mg/l) in infected patients and 28 mg/l (IQR 7–82 mg/l) in non-infected patients (p <0.001). All infected patients had a CRP level ≥5 mg/l (n = 30). Among the patients without infection, 81% had a CRP level above normal (180/223). The distribution of CRP plasma levels between non-infected hospital survivors and non-survivors is shown in figure 2.

Outcome

Infected patients had a 30% mortality rate (9/30). The non-infected patients with a PCT level ≥0.5 ng/ml had a 38% mortality rate (15/40). The non-infected patients with a PCT level <0.5 ng/ml had a 9% mortality rate (16/183). A larger proportion of non-infected patients with a PCT ≥0.25, ≥0.5, or ≥1.0 ng/ml died during hospital stay compared with those with a CRP ≥5, ≥50, or ≥100 mg/l (table 2). The same result is found among the subgroup of cardiovascular patients. A significant difference in mortality was found between cardiovascular patients with a PCT <0.5 versus ≥0.5 ng/ml ($p < 0.001$), whereas mortality was not different between cardiovascular patients with a CRP <5 versus ≥5 mg/l

Table 1
Patient characteristics on admission to the intensive care unit.

	Total	Infected	Non-infected	p-value
No. of patients	253	30	223	
Age	60 (50–73)	60 (45–72)	60 (51–73)	0.86
Female gender	72 (28%)	11 (37%)	61 (27%)	0.28
Heart rate (beats/min)	90 (72–105)	110 (100–125)	85 (70–102)	<0.001
MAP (mm Hg)	68 (58–78)	60 (52–70)	70 (58–78)	0.01
Temperature (°C)	37.2 (36.7–37.8)	37.9 (37.3–38.5)	37.1 (36.6–37.7)	0.001
PaO_2/FiO_2 ratio (mm Hg)	188 (140–362)	185 (99–243)	188 (143–414)	0.23
Diagnosis:				
Severe sepsis or septic shock*	11	11	0	
Cardiovascular	168	4	164	
Acute myocardial infarction	96	1	95	
CNS	27	1	26	
Abdomen	18	3	15	
Lung	16	10	6	
Others	13	1	12	
SAPS II score	25 (18–40)	41 (31-58)	24 (16-35)	<0.001
Shock	38 (15%)	11 (37%)	27 (12%)	<0.001
Mechanical ventilation	61 (24%)	17 (57%)	44 (20%)	<0.001
Prehospital CPR	26 (10%)	1 (3%)	25 (11%)	0.18
Days in ICU	2 (2–4)	6.5 (3–16)	2 (2-3)	<0.001
Hospital mortality	40 (16%)	9 (30%)	31 (14%)	0.02

Results are given as numbers (%) or median (interquartile range).
CNS = central nervous system; CPR = cardiopulmonary resuscitation; FiO_2 = inspired oxygen fraction; ICU = intensive care unit; MAP = mean arterial pressure; PaO_2 = partial arterial oxygen pressure; SAPS II = Simplified Acute Physiology Score II.
* Not including 10 patients with pneumonia.
Vital signs include the worst value within the first 24 hours in the ICU. Shock is defined as arterial systolic blood pressure less than 90 mm Hg for at least 1 hour despite adequate fluid resuscitation or need for vasopressors and/or inotropes.

Table 2
Mortality among all infected, all non-infected, and the subgroups of cardiovascular and non-cardiovascular patients according to PCT and CRP cut-off levels.

	Total	PCT ≥0.25 ng/ml		PCT ≥0.5 ng/ml		PCT ≥1.0 ng/ml		CRP ≥5 mg/l		CRP ≥50 mg/l		CRP ≥100 mg/l	
		mortality (%)		mortality (%)		mortality (%)		mortality (%)		mortality (%)		mortality (%)	
Infected	30	9/29	(31)	9/28	(32)	9/28	(32)	9/30	(30)	9/30	(30)	9/25	(36)
Non-infected:	223	23/67	(34)	15/40	(38)	13/28	(46)	27/180	(15)	16/87	(18)	10/44	(23)
Cardiovascular	164	14/42	(33)	11/26	(42)	11/19	(58)	16/134	(12)	11/64	(17)	7/30	(23)
Non-cardiovascular	59	9/25	(36)	4/14	(29)	2/9	(22)	11/46	(24)	5/23	(22)	3/14	(21)

Results are given as numbers and ratios (%).
CRP = C-reactive protein; PCT = procalcitonin.
The subgroup of cardiovascular patients includes: ischaemic heart disease, hypertensive or valvular heart disease, dilative cardiomyopathy, cardiac arrhythmias and arterial dissection.

(p = 0.26). As shown in table 3, the observed mortality in the cardiovascular subgroup with a PCT ≥0.5 ng/ml was higher than the SAPS II predicted mortality. In infected patients, SAPS II predicted mortality was similar to the observed mortality.

Figure 3 illustrates ROC curves for SAPS II and for PCT and CRP plasma levels as markers of mortality. For all non-infected patients the AUC was 0.81 (95% CI 0.74–0.89) for PCT, 0.64 (95% CI 0.53–0.74) for CRP, and 0.92 (95% CI 0.87–0.97) for SAPS II, whereas for the subgroup of non-infected cardiovascular patients AUCs were 0.90 (95% CI 0.84–0.96), 0.72 (95% CI 0.60–0.83) and 0.94 (95% CI 0.89–0.99), respectively.

Figure 3
Prediction of hospital mortality in non-infected critically ill medical patients.
Receiver operator characteristic curves for the prediction of hospital mortality of all non-infected patients (fig. 3A) and the subgroup of non-infected cardiovascular patients (fig. 3B).
CRP = C-reactive protein; CV = cardiovascular; PCT = procalcitonin; SAPS II = Simplified Acute Physiology Score II

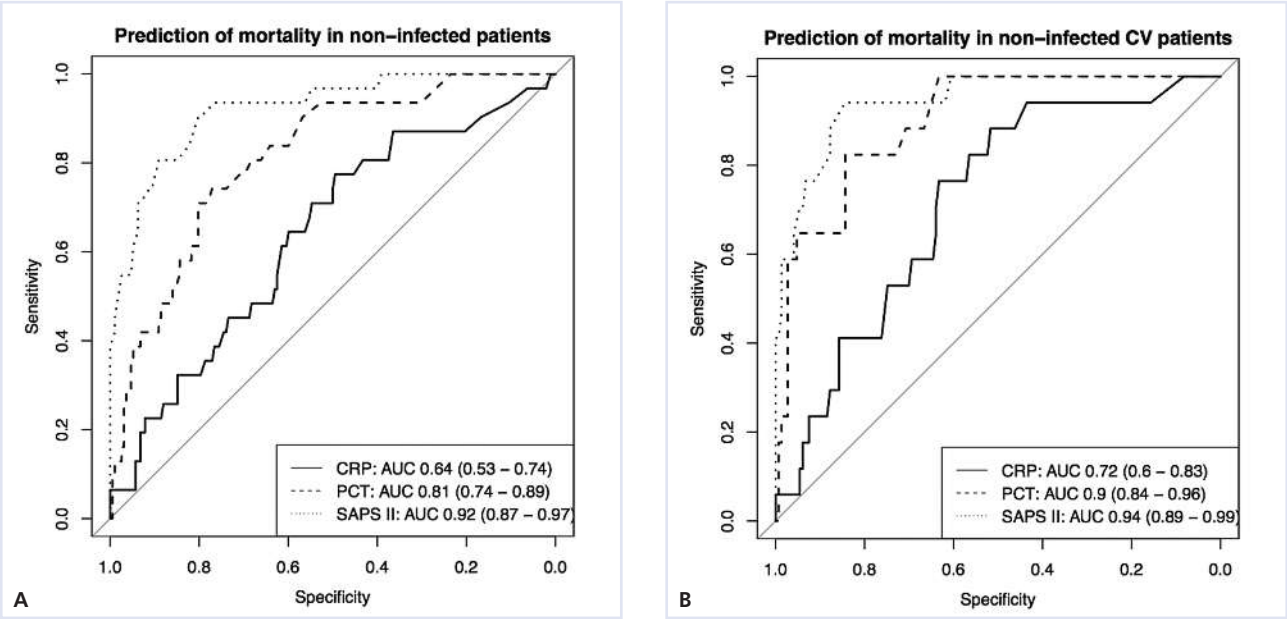


Table 3
SAPS II predicted and observed mortality among all infected, all non-infected, and subgroups of non-infected (cardiovascular and non-cardiovascular) patients.

	PCT (ng/ml)	n	SAPS II score	SAPS II predicted mortality	Observed mortality	p-values for PCT <0.5 versus ≥0.5 ng/ml		
						SAPS II	SAPS II predicted mortality	Observed mortality
Infected	<0.5	2	27 (24–30)	8%	0% (n = 0)			
	≥0.5	28	43 (31–59)	31%	32% (n = 9)	0.11	0.11	NA
Non-infected	<0.5	183	22 (14–30)	5%	9% (n = 16)			
	≥0.5	40	41 (31–59)	26%	38% (n = 15)	<0.001	<0.001	<0.001
Cardiovascular	<0.5	138	21 (13–25)	4%	4% (n = 6)			
	≥0.5	26	43 (29–58)	32%	42% (n = 11)	<0.001	<0.001	<0.001
Non-cardiovascular	<0.5	45	34 (21–50)	15%	22% (n = 10)			
	≥0.5	14	37 (33–62)	20%	29% (n = 4)	0.16	0.16	0.72

Results are given as numbers, median (interquartile range) or percentage.
NA = not applicable; PCT = procalcitonin; SAPS II = Simplified Acute Physiology Score II

Discussion

In this study we found that a relevant proportion of non-infected medical ICU patients (18%) present with PCT plasma levels above normal (≥0.5 ng/ml) during the first 72 hours after ICU admission. These patients have a four-fold higher risk of death than non-infected patients with a normal PCT, and a slightly higher risk of death than patients admitted with a diagnosis of infection. Compared with CRP, PCT had a higher sensitivity and specificity in predicting hospital mortality. The observed hospital mortality in non-infected cardiovascular patients with a PCT ≥0.5 ng/ml was 42% and thus higher than the SAPS II predicted mortality, whereas in infected patients it was similar.

PCT plasma levels in non-infected patients

CRP and PCT are known as markers of SIRS, sepsis, severe sepsis and septic shock in ICU patients [5]. Not only in patients with sepsis, but also in non-infected patients, elevated CRP levels are known to be independent predictors of mortality, for example in patients with acute coronary syndrome [16] and major adverse cardiac events [17]. Elevated plasma PCT levels in primarily non-infected patients have been described after surgical interventions [2], burn injuries [4], trauma [18], myocardial infarction [19, 20] and cardiogenic shock [3]. The results of our study are in line with these studies and suggest that PCT levels exceed the upper limit of 0.5 ng/ml in approximately a fifth of unselected non-infected medical ICU patients.

PCT release is associated with a generalised increase in calcitonin-1 gene expression and a consecutive release of PCT from parenchymal tissues and differentiated cell types throughout the body [21, 22], but not from circulating leucocytes and peripheral mononuclear cells [23]. In coculture experiments, stimulated human macrophages were able to induce calcitonin messenger ribonucleic acid (mRNA) in adipocytes [24]. PCT production is induced by interleukin-(IL-)1β and endotoxin in human mesenchymal stem cells derived mature adipocytes. Several other proinflammatory mediators, such as tumour necrosis factor-α (TNF-α), IL-2 and IL-6, stimulate PCT production [25], which might explain why PCT is elevated in non-infected patients after an insult leading to a systemic inflammatory response such as major surgery [26] and cardiac arrest [27–29].

In cardiogenic shock bacterial translocation, endotoxaemia arising from bowel congestion and ischaemia have been hypothesised as a possible source of elevated inflammatory mediators leading to an increase of both CRP and PCT plasma levels [3, 30]. Patients dying from refractory shock after an out-of-hospital cardiac arrest have higher plasma values of both PCT and the soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) than patients who die from neurological failure [27]. Interestingly, in the same study PCT values measured in patients with refractory cardiogenic shock were comparable to those measured in patients with septic shock [27]. Since sTREM-1 is a member of the immunoglobulin superfamily whose expression on phagocytic cells is up-regulated in the presence of bacteria [31], it is likely that elevated PCT values measured in cardiogenic shock patients are related to gastrointestinal hypoperfusion and ischaemia resulting in bacterial translocation or endotoxaemia. Thus, elevated PCT values found in non-infected patients in the present study may have been caused by a release of proinflammatory mediators from tissue injury in one or more organs leading to a generalised release of PCT from parenchymal tissue and differentiated cell types throughout the body.

PCT as an outcome predictor

Only a few studies have investigated the relationship between PCT and outcome in non-infected patients. In unselected postoperative critically ill patients, PCT was an independent predictor of mortality [2]. After cardiac surgery, PCT was an early prognostic marker [26]. Patients with ST-elevation myocardial infarction had higher PCT levels than those with non-ST-elevation myocardial infarction or unstable angina pectoris [20]. Similarly, elevated PCT plasma levels are reported in patients with complications following acute coronary syndromes and myocardial infarction [3, 10, 32]. The results of these studies suggest that an elevated PCT level in acute myocardial infarction is a marker of large infarct size and/or life-threatening infarct complications. In non-infected medical ICU patients with a PCT ≥0.5 ng/ml we found a mortality rate of 38%, and in the subgroup of cardiovascular patients it was even higher (42%). In these patients PCT was a better outcome predictor than SAPS II or CRP.

Several studies indicate that PCT on admission and during the first ICU days, as well as acute physiological scores (acute physiology, age, chronic health evaluation scores [APACHE II & III], SAPS II) are independent predictors of outcome in patients with severe sepsis and septic shock [33, 34], SIRS [35], multiple-trauma patients [18], and in unselected postoperative ICU patients [2, 36]. In a mixed surgical ICU with predominantly trauma and thoracoabdominal surgery patients, ROC curve AUCs for the prediction of mortality by PCT and APACHE III score on admission were 0.69 and 0.91, respectively [35]. In our study the PCT and SAPS II AUCs for the entire population of non-infected patients were 0.81 and 0.92, respectively. In the subgroup of non-infected cardiovascular patients, PCT ROC curve AUC was 0.90 and close to the AUC for SAPS II, which was 0.94. We showed that in non-infected medical ICU patients measurement of PCT is a valuable predictor of outcome, suggesting high risk of death when elevated.

PCT is a helpful biomarker for early diagnosis of sepsis in critically ill patients [1]. On the basis of our results, elevated PCT levels in non-infected patients are associated with a poor prognosis. This can be assumed to be secondary to major inflammation (SIRS). Compared with CRP, measurement of PCT could enable a severe insult of non-infectious origin to be identified earlier.

There are limitations of the present study. In non-infected medical ICU patients, combining PCT with components of the SAPS II or other markers possibly could have further improved the predictive power. However, we did not address this issue in our study. Whether patients with no documented infection but elevated PCT levels benefit from early antibiotic therapy needs to be studied in a prospective trial. Moreover, we need to be aware that comparisons of various studies are difficult because different assays for PCT measurement were used. Older assays are less sensitive than the one used for this study [25]. In addition, we acknowledge the difficulty of discriminating infected from non-infected patients, especially in the ICU setting.

Conclusions

Apparently non-infected medical ICU patients presenting with PCT plasma levels ≥0.5 ng/ml within the first 72 hours of admission have a high risk of death, particularly if the admission diagnosis is of cardiovascular origin. Our data suggest that PCT is an early marker of inflammation and disease severity. PCT may be helpful for the rapid detection of a severe insult in critically ill cardiovascular patients. Whether PCT plasma elevation in this population was caused by bacterial translocation is not known. These results should be confirmed by additional studies. Clinicians should still interpret PCT values carefully in the clinical context.

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