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Full Length Research paper

Rapid detection of procalcitonin as an early marker of sepsis in intensive care unit in a tertiary hospital

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This study investigated the usefulness of procalcitonin (PCT) as an early marker of sepsis, its relation to infection severity and its prognostic value. A total of 109 consecutive systemic inflammatory response syndrome (SIRS) patients admitted to the intensive care unit were included: 68 with infectious SIRS (33 with sepsis, 20 with severe sepsis and 15 with septic shock) and 41 patients with non infectious SIRS. Within the admission day, serum PCT concentrations were measured using the PCT- Q assay. Elevated PCT concentrations were detected at a significantly higher frequency among infectious than non infectious SIRS patients [(54.4% versus 34.1%, P = 0. 04) with 54.4% sensitivity and 65.9% specificity], among severe sepsis /septic shock patients compared to those with sepsis (74.3% versus 33.3%, P < 0.001 at cut off point of ≥ 0.5 ng/ ml and 45.7% versus 12.1%, P < 0.002 at cut off point of ≥ 2.0) and within infectious SIRS patients, among non survivors than survivors (76.0% versus 41.9%, P = 0.006). PCT was not an accurate diagnostic marker for sepsis; however, it appears to be useful in early assessment of infection severity which may improve the management and consequently the survival of severe sepsis and septic shock patients. The results of the PCT-Q assay should be interpreted taking into consideration that sensitivity and specificity are imperfect.

Key words: Procalcitonin, sepsis, systemic inflammatory response syndrome, intensive care unit.

INTRODUCTION

Severe infection and sepsis are common causes of morbidity and mortality in intensive care units (ICUs). (Garrouste-Orgeas et al., 2006). An early detection and specific clinical intervention has been shown to be crucial for the improved outcome of patients with sepsis.

However, the diagnosis of bacterial infection in the critically ill patients remains notoriously difficult, particularly in the presence of other non- infectious conditions that can generate a systemic inflammatory response e.g. trauma, major surgery and burns (Schneider and Lam, 2007).

The diagnostic repertoire for identifying systemic inflammatory response syndrome (SIRS) is poor. Verification of infection site and even the presence of infection remains problematic in sepsis (Giamarellos et al., 2004; McGee and Baumann, 2009). The lack of specific early markers of infection may be responsible in part for withholding, delaying or unnecessary antimicrobial treatment in critically ill patients (Ghorbani, 2009). Therefore, there is an unmet need for clinical or laboratory tools that can distinguish SIRS from sepsis for two reasons; a) early diagnosis and appropriate management of sepsis has been shown to reduce mortality and b) inappropriate antibiotic prescriptions, which carries with it problems of cost and emerging antibiotic resistance, may be minimized.

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Abbreviations: ACCP/ SCCM criteria, American College of Chest Physicians/Society of Critical Care Medicine criteria; **ICU,** Intensive care unit; **IL,** Interleukin; **NPV,** Negative predictive value; **PCT,** Procalcitonin; **PPV,** Positive predictive value; **SAPS,** Simplified acute physiology scoring; **SIRS,** Systemic inflammatory response syndrome.

During the past few years, several variables have been examined as suitable markers of sepsis. High blood concentrations of C- reactive protein, Procalcitonin (PCT), interleukin (IL)-6, IL-8, (Castelli et al., 2004; Harbarth et al., 2001) and IL-10 (van Dissel et al., 1998) and a high IL-10/ tumor necrosis factor-α (TNF-α) ratio (Gogos et al., 2000) were positively correlated with the severity of the infective process and the occurrence of septic shock and multiorgan failure and in general, signified a poorer prognosis.. Among the potentially useful sepsis markers, IL-6, IL-8 and PCT have been proposed to be the most promising candidates (Becker et al., 2008; Ventetuolo and Levy, 2008).

Procalcitonin, the precursor of calcitonin is a protein with growing acceptance in the diagnosis of infection (Santuz et al., 2008). The synthesis of PCT is regulated by the *Calc-1* gene located on chromosome 11. In healthy individuals production of PCT and subsequently calcitonin is restricted to the thyroid C-cells (Assicot et al., 1993). In systemic inflammatory conditions, inflammatory mediators trigger ubiquitous production of PCT by non-neuroendocrine cells throughout the body. Induction of *Calc-1* transcription and expression of calcitonin mRNA has been demonstrated in extra-thyroidal tissues, including liver, kidney, pancreas, adipose and white blood cells. The stimulus for gene transcription and PCT secretion appears to be both directly via microbial toxins and indirectly via inflammatory mediators, such as IL-1, IL-6 and TNF-α (Becker et al., 2008; McGee and Baumann, 2009; Schneider and Lam, 2007).

Normally, all PCT is cleaved and none is released into the blood stream, therefore, PCT levels are undetectable (< 0.1 ng/ml) in healthy individuals (Whicher et al., 2001). However, a significant increase in plasma concentrations of PCT has been detected during severe infections with systemic manifestations (Christ- Crain and Muller, 2005). In contrast to the short half life of calcitonin (10 min), PCT has a long half-life of 25 - 30 hours in serum (Assicot et al., 1993). One major advantage of PCT compared to other parameters is its early and highly specific rise that can be observed 3-6 h after exposure to an infection (Fioretto et al., 2007).

Procalcitonin has been proposed as an indicator of severe generalized infections or sepsis (Christ- Crain and Muller, 2005). It has been documented that PCT levels elevate with increasing the severity of the inflammatory response to infection (Mitaka, 2005). Moreover, serum PCT level seems to correlate with patient outcome (Clec'h et al., 2004; Jensen et al., 2006). Despite the previous information, reports of the usefulness of PCT for discriminating SIRS from sepsis are conflicting (Brunkhorst et al., 2000; Castelli et al., 2004; Jones et al., 2007; Ruokonen et al., 2002; Tang et al., 2007; Ugarte et al., 1999; Uzzan et al., 2006); therefore, this issue needs to be further elucidated.

This prospective study was designed to test the usefulness of PCT as an early marker of sepsis, to correlate this marker with infection severity and to state its prognostic value in septic patients.

MATERIALS AND METHODS

Patients

Over a 12- month period, all consecutive patients admitted to the adult medico-surgical ICU of a tertiary hospital in Eastern Saudi Arabia with clinical evidence of SIRS, as defined by the attending physician, were recruited into this prospective study. Patients diagnosed as SIRS had to fulfill at least two of its criteria which are; fever or hypothermia, tachypnea (> 20 /min), tachycardia (> 90 /min), leukocytosis or leukopenia and more than 10% band cell (Rangel et al., 1995). Written informed consent was obtained from all patients or their relatives before enrollment.

Every effort was done to identify patients with suspected infection as early as possible after admission. Clinical assessment was the first step in diagnosing infection. Data collected for each patient included; age, sex and clinical diagnosis. Temperature, heart rate, blood pressure, central venous pressure and respiratory parameters were recorded. Laboratory tests routinely scheduled in the management of infection including; leukocytic count, C-reactive protein, platelet count and the immature to total neutrophil ratio were performed and results were recorded. Arterial blood-gas analysis, renal function and liver function tests results were also recorded. Routine blood cultures and culture of other specimens from suspected sites, as clinically indicated, were performed. Available data on the primary site of infection and the causative microorganisms were recorded.

Retrospectively, after analysis of all diagnostic criteria (clinical, laboratory and microbiological findings), the study population was divided into two groups. The first group is the infectious SIRS group which included patients who developed clinical signs of SIRS (Rangel et al., 1995) determined by a definable source of infection (microbiologically confirmed) and/or positive blood cultures. Those patients were further divided into sepsis, severe sepsis and septic shock according to American College of Chest Physicians/Society of Critical Care Medicine criteria(ACCP/ SCCM criteria) (Bone et al., 1992). The other group comprised patients with non infectious SIRS, who developed clinical signs of SIRS but had no defined source of infection as proved by negative cultures. Collected data regarding the groups were double blinded to the results of serum PCT levels. The severity of the patients' condition, including complications and the severity of organ dysfunction, was clinically assessed and measured according to the simplified acute physiology scoring (SAPS) II system (Le Gall et al., 1993). Survival or death in the ICU was assessed during a follow-up.

Measurement of PCT serum levels

During the first 24 h after admission and study entry, a venous blood sample was drawn from each patient. Serum was separated by centrifugation, aliquoted and stored at - 70° C until used for assaying PCT. Serum PCT levels were measured in duplicates using a commercial semi-quantitative immunochromatographic test; PCT- Q, according to the manufacturer's protocol (PCT- Q, Brahms Diagnostica GmbH, Berlin, Germany). The test is performed with 0.2 ml serum and results are available after 30 min incubation at room temperature. No instrument or calibration is needed. According to the manufacturer's recommendations, PCT values were expressed as; < 0.5 ng/ml (sepsis is not likely), ≥ 0.5 - < 2.0 ng/ml (sepsis is possible with moderate risk for progression to severe sepsis), ≥ 2.0 - < 10.0 ng/ml (sepsis is likely with high risk for progression to severe sepsis) and ≥ 10.0 ng/ml (high likelihood of severe sepsis or septic shock).

Table 1. Procalcitonin concentrations in infectious and non-infectious systemic inflammatory response syndrome.

SIRS Status	PCT concentration (ng/ml)			Significance (Chi-square test)
	< 0.5No. (%)	≥ 0.5 No. (%)	Total No. (%)	
Infectious	31 (45.6)	37 (54.4)	68 (100.0)	
Non-infectious	27 (65.9)	14 (34.1)	41 (100.0)	P = 0.04 *
Total	58 (53.2)	51 (46.8)	109 (100.0)	

Note. SIRS, systemic inflammatory response syndrome; PCT, procalcitonin.
*p value < 0.05 was considered as indicative of statistical significance.

Statistical analysis

Data was entered in a personal computer incorporating the statistical Package for Social Sciences SPSS-PC Version 16.0. Frequency distributions were generated and presented in tabular form. The T- test, Chi-square test, odds ratio were used to assess the significance of relations with categorical variables. In case of sparse data, the Fisher's exact probability was used as indicated. Level of significance was set to be < 0.05 throughout the study. The sensitivity and specificity of PCT-Q in determining sepsis were calculated. The sensitivity of the test was defined as the proportion of cases with sepsis and were correctly identified by the test, while the specificity was defined as the proportion of cases without sepsis and were correctly identified by the test.

RESULTS

From June 2007 to May 2008, all SIRS patients consecutively admitted to the ICU were studied. We evaluated a total of 109 patients, of whom, 68 had microbiological evidence of infection and thus fulfilling the criteria of infectious SIRS. Those patients were categorized into; sepsis (n = 33), severe sepsis (n = 20) and septic shock (n = 15). The remaining 41 patients were classified as non infectious SIRS, with no defined source of infection as proved by negative cultures. The mean age of the study population (45 males and 64 females) was 49.8 ± 20.9 years. The clinical diagnosis included; infection with varying degrees of sepsis (68), trauma (12), respiratory failure (ten), post surgical (seven), non infective complications requiring ICU (five), heart failure (three), sickle cell with crisis (three) and seizure disorder (one). Infections were microbiologically proven in 68 patients, of whom, 25 (36.8%) had pneumonia, ten (14.7%) urinary tract infection, nine (13.2%) wound infection, two (3.0%) bed sores infection, one (1.5%) meningitis, one (1.5%) peritonitis, six (8.8%) both respiratory and urinary infections and three (4.4%) both respiratory and wound infections. In 11 patients (16.2%), no infectious focus could be detected, but blood cultures were positive. Among the 68 septic patients, bacteremia was detected in only 24 (35.3%). Recovered pathogens were; Gram-negative bacteria in 55.9% of cases (38/68), Gram-positive in 17.6% (12/68), mixed Gram positive and Gram negative in 17.6% (12/68), fungi in 4.4% (3/68, two *Candida* isolates and one *Aspergillus*) and mixed bacteria and fungi in 4.4% (3/68). The mean SAPS II score among the study population was 38.1 ± 21.6 (mean ± 1 SD). Thirty patients died with a mortality rate of 27.5% (15 patients with severe sepsis, six with septic shock, four with sepsis and five patients with non infectious SIRS). Within infected patients (n = 68), 25 died while 43 discharged.

Using culture results as the gold standard for infection, the usefulness of PCT in predicting infection was evaluated. Table 1 shows that elevated PCT concentrations (≥ 0.5 ng/ml) were detected in a significantly higher proportion of patients with infectious compared to those with non infectious SIRS (P = 0.04 using Chi-square test). However, the discriminative power was poor. At a cutoff point of ≥ 0.5 ng/ml, PCT demonstrated 54.4% sensitivity 65.9% specificity, 72.5% positive predictive value (PPV) and 46.6% negative predictive value (NPV) in discriminating infectious from non infectious SIRS. On the other hand at a cutoff point of ≥ 2.0 ng/ml there was no significant difference between both groups (P = 0.062).

Among patients with infectious SIRS (n = 68), with increasing infection severity from sepsis through severe sepsis and septic shock, there was a significant parallel increase in the proportion of cases with high PCT concentrations at different cutoff points (Table 2). The relationship between PCT concentrations and the degree of sepsis was found to be statistically significant (P = 0.007 using Fisher's Exact test). This indicates a significant association between PCT level and the severity of sepsis.

On comparing PCT concentrations in sepsis versus severe sepsis and septic shock, elevated PCT concentrations were detected at a significantly higher frequency among patients with severe sepsis/ septic shock compared to those with sepsis (74.3% versus 33.3% at a cutoff point of ≥ 0.5, P < 0.001, sensitivity = 74.3% , specificity = 66.7%, PPV = 70.3%, NPV = 71.0%) and (45.7% versus 12.1% at a cutoff point of ≥ 2.0, P < 0.002, sensitivity = 45.7% , specificity = 87.9%, PPV = 80.0%, NPV = 60. 4%).

Among infected patients, elevated PCT concentrations (≥ 0.5 ng/ml) were detected in 7/12 (58.3%) of Gram positive and 13/38 (34.2%) of Gram negative infections (statistically non significant, P = 0.141 using Fisher's Exact test). A significantly higher proportion of patients with mixed Gram positive and Gram negative infections [11/12(91.7%)] demonstrated raised PCT values (≥ 0.5

Table 2. Relation between procalcitonin concentration and infection severity.

Infection severity	PCT concentration (ng/ml)					Significance (Fisher's Exact test)
	< 0.5 No. (%)	≥ 0.5 - < 2.0 No. (%)	≥ 2.0 - < 10.0 No. (%)	≥ 10.0 No. (%)	Total No. (%)	
Sepsis	22 (66.7)	7 (21.2)	4 (12.1)	0 (0.0)	33 (100.0)	P = 0.007 *
Severe sepsis	6 (30.0)	6 (30.0)	7 (35.0)	1 (5.0)	20 (100.0)	
Septic shock	3 (20.0)	4 (26.7)	8 (53.3)	0 (0.0)	15 (100.0)	
Total	31	17	19	1	68	

Note. PCT, procalcitonin.
*p value < 0.05 was considered as indicative of statistical significance.

Table 3. Relation between procalcitonin concentration and outcome of septic patients.

Outcome	PCT concentration (ng/ml)			Significance (Chi-square test)
	<0.5 No. (%)	≥0.5 No. (%)	Total No. (%)	
Survivors	25 (58.1)	18 (41.9)	43 (100.0)	P = 0.006*
Non survivors	6 (24.0)	19 (76.0)	25 (100.0)	
Total	31 (45.6)	37 (54.4)	68 (100.0)	

Note. PCT, procalcitonin.
* p value < 0.05 was considered as indicative of statistical significance.

ng/ml) compared to those with either of the two infections (P < 0.001 using Fisher Exact test). All three patients with fungal infections, as well as two out of three (66.7%) with mixed bacterial and fungal infections displayed raised PCT values.

The mean values of SAPSII scores were significantly higher in patients with elevated PCT concentrations compared to those with concentrations of < 0.5 ng/ml (45.2 ± 22.6 versus 31.9 ± 18.8, P < 0.001 using T-test).

Among patients with infectious SIRS (n= 68), 25 died and 43 survived. A significantly higher proportion of non survivors demonstrated raised PCT concentrations (≥ 0.5 ng/ ml) as compared to those who were alive at ICU discharge (Table 3). The difference was found to be statistically significant, P = 0.006 using Chi-square test, (odds ratio, 1.658; 95% confidence intervals, 1.141 - 2.408). This indicates that patients having PCT concentration of ≥ 0.5 ng/ ml have 1.67 times more likely to be non survivors as compared to those with PCT concentration of < 0.5 ng/ ml. A cut off point of ≥ 0.5, separated patients who died from those who survived with 76.0% sensitivity and 58.1% specificity. The PPV and NPV were 51.4 and 80.6% respectively.

DISCUSSION

Despite the use of new treatment modalities, improvements in technology and increased experience, mortality of patients with sepsis, severe sepsis, septic shock and sepsis-induced multiorgan failure remains high (Larosa and Opal, 2008). Such unfavorable prognosis of patients with sepsis is partly due to delayed diagnosis. Disclosure of severe infections is hampered by low sensitivity and specificity of the laboratory tests and by non-specificity of clinical signs (McGee and Baumann, 2009).

In the present study we analyzed the plasma concentrations of PCT with respect to its potential use as a marker of sepsis. Although elevated PCT concentrations (≥ 0.5 ng/ml) were detected at a significantly higher frequency among patients with infectious compared to those with non infectious SIRS, PCT was not sufficiently reliable as a marker of sepsis since the discriminative power was relatively low. Similar results were obtained by other investigators (Tang et al., 2007). Another group from Germany reached the same conclusion; however, they found that PCT is a useful parameter to discriminate between sepsis and severe sepsis (Brunkhorst et al., 2000).

The role of PCT in discriminating SIRS from sepsis is equivocal, although the majority of studies indicate higher values in patients with sepsis (Giamarellos et al., 2004; Jones et al., 2007; Uzzan et al., 2006). In contrast, some investigators reported that PCT is not very accurate in differentiating infection from inflammation in critically ill patients, where no significant difference was observed (Castelli et al., 2004; Ruokonen et al., 2002; Tang et al., 2007). One of the causes of such ambiguous conclusions is the lack of a gold standard for infection. In the present study, culture results were used as a gold standard for infection. This could be partly responsible for the poor specificity we got (65.9%), since potentially infected patients with negative cultures would be misclassified into the non infectious SIRS group. Furthermore, it has been

documented that microbiology is not sensitive enough in sepsis diagnosis (De La Rosa et al., 2008). Another contributing factor for the low specificity is the multifactorial nature of PCT induction (Schneider and Lam, 2007).

In this study, we got a negative predictive value for PCT that is too low (46.6%) to be safely used to exclude the presence of infection. This finding is in consistent with others (Ugarte et al., 1999). Our results agreed with earlier findings which demonstrated that PCT alone does not possess a good discriminative value between septic and non septic ICU patients especially in a heterogeneous mix of diseases (Castelli et al., 2004). However, it may be useful together with full clinical assessment including signs of sepsis and bacteriological data.

The results of this study showed that, in a significant number of patients, PCT was a good indicator of severe sepsis and septic shock. We observed a significant increase in the proportion of cases with high PCT concentration in parallel with the degree of sepsis suggesting that PCT might be used not just as a marker of infection, but, more importantly, that it is a useful marker of infection severity. Increasing PCT concentrations during severe sepsis and septic shock were previously reported by many investigators (Chan et al., 2004; Ghorbani, 2009; Jensen et al., 2006). Brunkhorst and co workers found that PCT demonstrated significant differences between sepsis, severe sepsis and septic shock on the first day after admission to the ICU or at the onset of inflammatory symptoms (Brunkhorst et al., 2000). Some studies reported poor sensitivity and specificity of PCT in diagnosis of infection despite a high discriminative power for diagnosis of sepsis, severe sepsis or septic shock (Chan et al., 2004; Mitaka, 2005; Muller et al., 2004; Ruokonen et al., 2002). Since there is a stepwise increase in mortality rates from SIRS to septic shock (Rangel et al., 1995), it might be important that PCT could help to differentiate, early, between sepsis and severe sepsis or septic shock.

Only one patient in this study demonstrated severely elevated PCT concentration (> 10.0) and he had severe sepsis. This finding is in agreement with other investigators who suggested that in patients with, even, severe infections, but still without remote organ dysfunction, PCT is only moderately increased (Brunkhorst et al., 2000).

Low PCT concentrations in patients with septic shock have been reported previously but are rather unusual (Clec'h et al., 2004; Muller and Becker, 2001). The low concentrations of PCT observed in six patients with severe sepsis and three with septic shock in this study may be explained by the technique used. Despite The attractiveness of a simple assay for rapid decision-making, its reliability remains unconvincing. In a study performed on neonates with sepsis, the PCT-Q test kit demonstrated moderate sensitivity but poor specificity for early diagnosis of neonatal sepsis and it was recommended that commencement of antibiotics in newborn infants should still be based on clinical features, rather than on PCT-Q results alone (Boo et al., 2008). Furthermore, Manzano and co workers demonstrated a moderate agreement between PCT measured semi-quantitatively and quantitatively which is probably due to a subjective interpretation of the assay result (Manzano et al., 2009). According to Pelinka et al, the semiquantitative PCT-Q test is far less sensitive than the quantitative assay since normal PCT readings by the PCT-Q test are often incorrectly low, whereas moderately (0.5 - 2 ng/ml) and highly increased (> 2 ng/ml) readings are usually correct (Pelinka et al. , 2003). Korczowski et al. reported that PCT-Q test is useful as a screening method in patients suspected of systemic bacterial infection. However, they recommended the verification of the results with the luminometric assay in doubtful cases as well as for monitoring of treatment (Korczowski et al., 2003). Similarly, Schneider and Lam recommended the quantitative assay, as the preferred option, for the purpose of monitoring of daily PCT concentrations (Schneider and Lam, 2007).

Other investigators, however, reported a good correlation of PCT- Q test with the quantitative values of the marker (Fernández et al., 2003; Stefanowicz et al., 2008). Gómez-Rivera and co workers documented that PCT-Q is a useful tool for the early detection of patients with bacterial sepsis. Additionally, they found a correlation between persistently high levels (≥ 10 ng/ml) and the severity of illness and death (Gómez-Rivera et al., 2006). In Kordek's study, PCT-Q revealed satisfactory concordance with the quantitative method when results in the next category are included to account for readout error. The authors reported that semiquantitative test is rapid, easy to use and helpful as a supportive test when the quantitative assay is not available (Kordek et al., 2006).

The data showed a significant relationship between PCT plasma concentrations and the severity of the patients' condition, including complications and the severity of organ dysfunction, as assessed by the SAPAII system. This finding agreed with previous investigators (Castelli et al., 2004).

In this study, we found evidence that PCT may be an early prognostic marker in patients with sepsis since those who ultimately died demonstrated a significantly higher frequency of elevated PCT concentrations, on admission, than those who were alive at ICU discharge. This is in agreement with other studies (Clec'h et al., 2004; Maskin et al., 2003), where higher PCT levels were demonstrated in patients with poor prognosis as early as the first day of the disease. However, other studies documented that the course of PCT concentrations rather than the initial height plays a major role for prognosis (Jensen et al., 2006; Meisner et al., 1999). The prognostic value of the initial PCT concentration on admission still remains to be clarified. In a recent study using PCT level to guide therapy in septic patients, PCT guidance resulted in a 4-day reduction in the duration of antibiotic therapy and a smaller overall antibiotic exposure. A 2-day

shorter intensive care unit stay was also observed. The authors concluded that a protocol based on serial PCT measurement allows reducing antibiotic treatment duration and exposure in patients with severe sepsis and septic shock without apparent harm (Nobre et al., 2008).

A significantly higher proportion of patients with mixed Gram positive and Gram-negative infection demonstrated raised PCT levels compared to those with either of the two infections. It was not certain what underlying mechanisms were responsible for this difference. Further studies are required to confirm this finding and to determine the underlying mechanisms. Moreover, elevated PCT concentrations were detected in the three patients with fungal infection. This finding is in agreement with others (Clec'h et al., 2004). Yet, no conclusion could be drawn since only few cases were involved. This issue needs further investigation.

One limitation of this study was the semi- quantitative way in which the assay of PCT was performed, as it did not help us in monitoring the daily PCT concentrations during clinical course of illness, which may improve its performance as an aid for diagnosis and follow up of sepsis. Second, antimicrobial therapy may have an impact on PCT values but our study design did not allow us to investigate this issue which needs to be further assessed. Third limitation could be the wide range of patients who suffered from many different diseases that may have different influences on PCT.

Conclusion

Although PCT was not perfect in differentiating between infectious and non-infectious SIRS, it appears to be a useful early marker of infection severity, since its concentrations increased significantly in parallel with the degree of sepsis. PCT–Q assay is simple and quick. It can be used for the early assessment of infection severity which may improve the management and consequently, the survival of severe sepsis and septic shock patients. However, based on the data of this study, the results of the assay should be interpreted taking into consideration that sensitivity and specificity are imperfect.

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