Procalcitonin under Investigation as a Means of Detecting Severe Sepsis, Septic Shock and Bacteremia at Emergency Department, Rajavithi Hospital

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Background: *Severe sepsis, septic shock and bacteremia are critical illnesses, and patients with these conditions require close monitoring and immediate medical treatment. Any delay in diagnosis may lead to an increase in mortality in such critically ill patients. Serum procalcitonin (PCT) has emerged as a highly accurate biomarker for differentiating sepsis from other non-infectious triggers.*

Objective: *In this study, we investigated the effectiveness of PCT in obtaining early diagnosis and efficient prognosis for such patients at the Emergency Department of Rajavithi Hospital.*

Material and Method: *A prospective study was performed of 110 adult patients who attended the emergency service department between August 1 2013 and October 31 2013. The effectiveness of PCT as a specific blood test analysis tool for detecting and classifying the severity of patients with sepsis was investigated, and sensitivity, specificity, negative predictive values (NPV), positive predictive values (PPV) and positive likelihood ratio (LR+) were used to differentiate infected patients.*

Results: *One hundred and ten patients were enrolled and classified into 3 categories as follows: severe sepsis (n = 34, 30.9%), septic shock (n = 13, 11.8%), and bacteremia (n = 23, 20.9%). At a PCT level of ≥2 ng/dL, it was feasible to categorize patients as having severe sepsis (p<0.001; RR 3.58; 95% CI 2.18-5.89), septic shock (p = 0.001; 5.73; 2.06-15.93) or bacteremia (p<0.001; 3.91; 1.98-7.73). Moreover, the PCT value yielded the following diagnostic performances for patients with: severe sepsis (PPV 70.8%; NPV 80.2%; LR+ 5.0; sensitivity 50.0%; specificity 90.8%); septic shock (33.3%; 94.2%; 3.6; 61.5%; 83.5%); and bacteremia (50.0%; 87.2%; 3.7; 52.2%; 86.2%).*

Conclusion: *PCT can be usefully employed as a promising chemical biomarker to differentiate the severity of infections in critically ill patients. Used together with clinical data, the PCT value of ≥2 ng/dL is efficient in categorizing such patients as having severe sepsis, septic shock or bacteremia.*

Keywords: *Procalcitonin, Severe sepsis, Septic shock, Bacteremia, Emergency department*

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Bloodstream infections (BSI) are generally associated with high mortality rates in critically ill patients, especially those who attend emergency departments (ED). Such infections are among the major causes of mortality and morbidity worldwide[1]. Moreover, severe sepsis, septic shock, and multisystem organ dysfunction are associated with BSI, and early diagnosis is required in order to administer appropriate treatment[2]. It is generally accepted that early initiation of effective antibiotic therapy can lead to reduced mortality rates in such patients[3]; however, appropriate antibiotic approaches are necessary to deal with the escalating rates of antibiotic resistance. Over the past two decades, there has been considerable interest in the use of biomarkers to accomplish this goal. Serum procalcitonin (PCT) is an interesting biochemical marker for use with the aim of enhancing the clinical management of bacterial infection[4,5]. The key advantage of PCT compared with other markers is its early and highly specific increase in response to bacterial infections, in particular sepsis[6,7]. Moreover, PCT levels can be measured in less than 1 hour, assisting in the identification of patients at risk of bacteremia and sepsis. This study was designed to determine the clinical usefulness of elevated PCT levels in the early diagnosis of bacteremia and sepsis in adult patients who visited the ED of Rajavithi Hospital,

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Material and Method

One hundred and ten patients, seen in the ED-Rajavithi Hospital between August 1 2013 and October 31 2013, were included in this prospective study. Inclusion criteria were patients who: were at least 20 years old; had not had antibiotic treatments before blood cultures; and displayed symptoms of systemic infections such as sepsis, severe sepsis, or septic shock. Patients were excluded from the study who: had taken any course of antibiotics before blood cultures; had been involved in any accidents; had had any organ transplant; had an autoimmunity or malignancy; were using immunosuppressive drugs; or had returned laboratory findings such as contaminated pathogens, viral or fungal infection.

Laboratory records of included patients were screened for routine blood analysis such as CBC, BUN, Cr, ABG, LFT, UA, BS, CXR, urine culture, sputum culture, 2 specimens of hemoculture and PCT levels. Clinical data were extracted from medical records to complete interview forms suitable for the study, including details of age, sex, SIRS criteria (WBC count, body temperature, blood pressure, and heart rate), basic initial clinical diagnosis, and blood cultures. All patients were analyzed for correlation between increased severity of BSI and a specific PCT level.

The protocol of this research was reviewed and approved by the ethics committee of Rajavithi Hospital. (No. 098/2556), and all patients gave written informed consent.

Statistical analysis

Statistical analysis was performed using the software program SPSS v17.0 (SPSS Inc., Chicago Illinois, US.). Other clinical and laboratory parameters, such as WBC, HR, and BT were interpreted according to SIRS criteria and categories[8]. Each parameter was recorded and examined by categorical analysis, mainly the Chi-square test and Fisher-exact test. A *p*-value of less than 0.050 was considered to imply statistical significance. Also, the procalcitonin cutoff value of 2 ng/dL was taken to indicate that patients were very susceptible to bacteremia[9].

Results

The study was conducted from August 1 2013 to October 31 2013, after its protocol had been reviewed and approved by the ethics committee of Rajavithi Hospital. One hundred and twenty patients were enrolled in the research, in accordance with the standard SIRS criteria and categories in our ED. Ten patients were excluded from the study because they were referred to other hospitals to avail of the privileges of their health benefits; as a result, their subsequent clinical data could not be accessed. Demographics of patients relating to their medical history and records are described in Table 1. Generally, a patient could have more than one underlying disease in his/her medical records, and it is possible that a patient could be diagnosed with more than one disease by the physician.

It is interesting that of the patients with medical history, 26 had hypertension and 20 were diabetic. Forty-two out of the 110 patients (38.3%) in the study group were diagnosed with pneumonia. Causes of infections and their relative contribution to organ failure are shown in Table 2; unfortunately, not all pathogens could not be unequivocally identified. Among infectious organisms associated with patient disorders, bacteremia and genitourinary infections accounted for the majority of the disorders in the infected group. The most common pathogen detected was *E. coli* which is a gram-negative bacillus.

In the study, the infected patients who met the inclusion criteria were classified as follows: severe sepsis (30.9%), septic shock (11.8%) and bacteremia (20.9%). Most of them were diagnosed as having no organ failure (82.7%) and almost 88% of patients survived. Table 3 shows characteristics of infected patients according to the standard SIRS criteria and laboratory reports. Interestingly, the respiratory system was the main area affected in patients with end organ failure, and only one-third of those patients survived. The PCT level of $\geq$2 ng/dL[10] is proposed for evaluating evidence-based utility in identifying various infectious disease conditions. Sensitivity, Specificity, PPV, NPV and Positive Likelihood Ratio (positive LR, LR+) all showed successful outcomes in identifying infected patients, as shown in Table 4.

Using a PCT level of $\geq$2 ng/dL to predict patients' severity of infection such as severe sepsis, septic shock, or bacteremia, it was found that the functional addition of PCT significantly increased the value of diagnostic algorithms for severe sepsis: $p<0.001$, RR 3.583, and 95% CI 2.179-5.891. Similarly, a PCT level of $\geq$2 ng/dL is a significant performance measure for septic shock ($p = 0.001$, RR 5.733, 95%CI 2.064-15.926) and bacteremia ($p<0.001$, RR 3.909, 95%CI 1.977-7.729) when compared to PCT levels of normal patients.

Table 1. Baseline characteristics of overall patients with inclusion criteria

Characteristics	All (110 patients)	Dead (%)	Survived (%)	*p*-value
Age (mean ± SD)	51.70±21.13			
Sex, n (%)				
Male: Female	59 (53.6):51 (46.4)	7 (43.8):9 (56.3)	52 (55.3):42 (44.7)	0.391
Medical history				
Diabetes	20	4 (20.0)	16 (80.0)	0.486
Kidney disease	8	1 (12.5)	7 (87.5)	1.000
Heart disease	5	1 (20.0)	4 (80.0)	0.552
Hypertension	26	3 (11.5)	23 (88.5)	0.758
Liver disease	11	4 (36.4)	7 (63.6)	0.053
Asthma/COPD	3	1 (33.3)	2 (66.7)	0.379
Others*	30	7 (23.3)	23 (76.7)	0.132
No underlying	49	4 (8.2)	45 (91.8)	0.089*
Diagnosis				
Pneumonia	42	10 (23.8)	32 (76.2)	0.030*
Pyelonephritis	27	5 (18.5)	22 (81.5)	0.535
Infectious diarrhea	13	1 (7.7)	12 (92.3)	0.688
Peritonitis	5	0 (0)	5 (100)	1.000
Liver abscess	2	0 (0)	2 (100)	1.000
Others**	18	2 (11.1)	16 (88.9)	1.000

* Others are aplastic anemia, thalassemia, chronic pancreatitis, dyslipidemia, psychosis, old CVA, pulmonary TB, BPH, epilepsy, neurogenic bladder, myoma uteri.
** Others represent acute cholecystitis, infected CAPD, systemic infection, acute tonsillitis, acute pancreatitis, rheumatic heart disease.
* Statistical significance

Table 2. The relative contributions of identifying pathogens and infectious organs in the patients

Infectious organ correlated with disorders	Identifying pathogens (number of patients)
Respiratory (12)	
Pneumonia	*A. baummanii* (MDR) (1), *A. baummanii* (3), *Pseudomonas aeruginosa* (1), *Enterococcus fecalis* (1), *Corynebacterium* spp. (2), *Neisseria* spp. (3), *H. influenza* (non-betalactamase) (1)
Genitourinary (14)	
Pyelonephritis	*E. coli* (6), *E. coli* (ESBL) (2), *Proteus mirabilis* (2), *Klebsella pneumonia* (1), *A. baummanii* (1), *Enterococcus faecium* (1), *Streptococcus agalactiae* (1)
Gastrointestinal (5)	
Infectious diarrhea	*Vibrio parahaemolyticus* (1), *E. coli* (1), *Salmonella* spp. (1), *Plesiomonas shigelloides* (1)
Liver abscess	*Klebsella pneumonia* (1)
Bacteremia (23)	
Bloodstream	*A. baummanii* (MDR) (3), *E. coli* (6), *E. coli* (ESBL) (2), *Proteus mirabilis* (2), *Klebsella pneumonia* (4), *Salmonella* spp. (1), *Vibrio parahaemolyticus* (1), *Streptococcus gallolyticus* (2), *Streptococcus parasanguinis* (1), *Streptococcus agalactiae* (1)

Table 3. Characteristics of infectious patients with inclusion criteria

Characteristics	All (110 patients)	Dead (%)	Survived (%)	*p*-value
Severe Sepsis	34	10 (29.4)	24 (70.6)	0.007*
Septic Shock	13	5 (38.5)	8 (61.5)	0.022*
Bacteremia	23	10 (43.5)	13 (56.5)	<0.001*
End organ failure	19	5 (26.3)	14 (73.7)	0.148
Kidney	11	3 (27.3)	8 (72.7)	0.199
Liver	9	4 (44.4)	5 (55.6)	0.025*
Respiratory system	12	8 (66.7)	4 (33.3)	<0.001*
No organ failure	91	11 (12.1)	80 (87.9)	0.148
PCT level at ≥2 ng/dL	24	7 (29.2)	17 (70.8)	0.043*

* Statistical significance

Table 4. Procalcitonin level at 2 ng/dL for the role of infectious management

Characteristics	RR	95% CI	Sensitivity	Specificity	PPV	NPV	LR+	*p*-value
Severe Sepsis	3.58	2.28-5.89	50.0	90.8	70.8	80.2	5.0	<0.001*
Septic Shock	5.73	2.06-15.93	61.5	83.5	33.3	94.2	3.6	0.001*
Bacteremia	3.91	1.98-7.73	52.2	86.2	50.0	87.2	3.7	<0.001*

* Statistical significance

Moreover, the statistical results show that the PCT level of ≥2 ng/dL is distinct in patients with severe sepsis (PPV 70.8%; NPV 80.2%; LR+ 5.0; sensitivity 50.0%; specificity 90.8%), septic shock (PPV 33.3%; NPV 94.2%; LR+ 3.6; sensitivity 61.5%; specificity 83.5%), and bacteremia (PPV 50.0%; NPV 87.2%; LR+ 3.7, sensitivity 52.2%, specificity 86.2%).

Discussion

Serum PCT levels proved to be the most reliable predictor of blood culture in patients with infections and may help to identify high-risk patients who would benefit from receiving early antibiotic treatment. In fact, the serum levels of PCT of ≥2 ng/dL can be a useful marker in the differentiation of infection severity. The study results show that the patients with severe sepsis (p<0.001, specificity 90.8), septic shock (p = 0.001, specificity 83.5), and bacteremia (p<0.001, specificity 86.2) could be correctly identified by such a PCT level. Several similar results can be found in many other studies[4-7,10-15] which have employed procalcitonin in differentiating between these infections and other aetiologies of critical illnesses. Y. L. Chan, et al[14], for example, reported that a high PCT level (2.6 ng/dL) can be a good marker for prediction of higher severity of infections; however, it may have lower specificity in infected patients.

Conclusion

In conclusion, this study found serum PCT useful as a biomarker in the diagnosis and differentiation of the severity of critically infected patients, especially ED patients. A procalcitonin value of 2 ng/dL or more is indicative of the presence of bacterial organisms. With respect to infection severity, such a procalcitonin level is effective enough to categorize infected patients as having severe sepsis, septic shock or bacteremia. Therefore, if early appropriate treatment such as antibiotics is administered to patients, their survival rates and clinical manifestations can be improved.

What is already known on this topic ?

It is challenging for rapid diagnosis in patients with bloodstream infections at emergency service visit. Recently, serum procalcitonin (PCT) is a promising marker to differentiate between bacterial and viral infections. The PCT level rises above normal values in patients with systemic inflammatory response and sepsis. Many studies suggested the PCT level at various values to rule out such patients in the

emergency service visit. Moreover, only few studies were Thai populations.

What this study adds ?

To achieve rapid diagnosis of bloodstream infections, the PCT cut-off level at 2 ng/dL is considered to differentiate the severity of infections in critically ill patients obtained during the emergency service visit, Rajavithi Hospital. The results confirm that such a PCT level associated with patients' clinical data is suitable for ruling out sepsis and systemic inflammatory response. As a result, high-risk patients can have favor on early receiving of antibiotic treatment leading to a decrease in mortality rates at the emergency room, Rajavithi Hospital.

Potential conflict of interest

None.

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การใช้ Procalcitonin (PCT) เพื่อการตรวจและวิเคราะห์ความรุนแรงของภาวะติดเชื้อ, ช็อกจากการติดเชื้อ และภาวะติดเชื้อในกระแสโลหิตของผู้ป่วยที่เข้ามารับการบริการที่ห้องฉุกเฉินโรงพยาบาลราชวิถี

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ภูมิหลัง: ภาวะติดเชื้อรุนแรง, ภาวะช็อกจากการติดเชื้อ และภาวะติดเชื้อในกระแสโลหิต เป็นภาวะเร่งด่วนที่ต้องได้รับการรักษาที่เหมาะสมและรวดเร็ว ในปัจจุบัน ยังไม่มีตัวชี้ทางชีวภาพตัวใดที่สามารถทำนายความรุนแรงของภาวการณ์เหล่านี้ กับผู้ป่วยที่มีภาวการณ์อักเสบที่เกิดจากภาวะติดเชื้อที่ถูกส่งตัวเข้ารับการรักษาที่ห้องฉุกเฉินได้ตั้งแต่ระยะเริ่มต้นอย่างมีประสิทธิภาพ

วัตถุประสงค์: การศึกษานี้เพื่อแสดงการใช้ procalcitonin (PCT) เป็นตัวชี้วัดร่วมเพื่อการวินิจฉัย และทำนายระดับความรุนแรงเริ่มต้นของภาวะติดเชื้อในผู้ป่วยที่ถูกส่งตัวเข้ามารับการรักษาที่ห้องฉุกเฉินโรงพยาบาลราชวิถีได้อย่างมีประสิทธิภาพ

วัสดุและวิธีการ: เป็นการศึกษาแบบไปข้างหน้าในกลุ่มผู้ป่วยที่สงสัยว่ามีภาวะติดเชื้อ ช็อกจากภาวะติดเชื้อ และภาวะติดเชื้อในกระแสโลหิตที่ถูกส่งตัวเข้ามารับการรักษาที่ห้องฉุกเฉิน โรงพยาบาลราชวิถี ตั้งแต่วันที่ 1 สิงหาคม พ.ศ. 2556 ถึง 31 ตุลาคม พ.ศ. 2556 โดยมีผู้ป่วยในเกณฑ์คัดเข้าทั้งสิ้น 110 ราย จากนั้นทำการเจาะเก็บตัวอย่างเลือดจากผู้ป่วยเพื่อวัดค่าในห้องปฏิบัติการโดยเฉพาะระดับค่า PCT จากนั้นนำผลที่ได้มาหาความสัมพันธ์ทางสถิติโดยการคำนวณค่าความไว ความจำเพาะ NPV, PPV, และ LR+ เพื่อการทำนายความรุนแรงของอาการที่เกิดขึ้นจากภาวะติดเชื้อในกระแสเลือด

ผลการศึกษา: ผู้ป่วยที่มีภาวะติดเชื้อเข้าเกณฑ์การคัดเข้าทั้งสิ้น 110 ราย คัดแยกได้ 3 กลุ่มได้แก่ กลุ่มภาวะติดเชื้อรุนแรงจำนวน 34 ราย (ร้อยละ 30.9) กลุ่มภาวะช็อกจากการติดเชื้อจำนวน 13 ราย (ร้อยละ 11.8) และกลุ่มภาวะติดเชื้อในกระแสโลหิตจำนวน 23 ราย (ร้อยละ 20.9) จากนั้นนำมาวิเคราะห์พบความสัมพันธ์อย่างมีนัยของค่าทางสถิติกับระดับค่าของ PCT ที่มากกว่าหรือเท่ากับ 2 ng/dL ในกลุ่มผู้ป่วยดังนี้ภาวะติดเชื้อรุนแรง (p-value <0.001, RR 3.586, 95%CI 2.179-5.891, sensitivity 50.0%, specificity 90.8%, PPV 70.8%, NPV 80.2% และ LR+ 5.0) กลุ่มผู้ป่วยที่ภาวะช็อกจากการติดเชื้อ (p-value = 0.001, RR 5.733, 95%CI 2.064-15.926, sensitivity 61.5%, specificity 83.5%, PPV 33.3%, NPV 94.2% และ LR+ 3.6) และในกลุ่มผู้ป่วยที่ภาวะติดเชื้อในกระแสเลือด (p-value <0.001, RR 3.909, 95%CI 1.977-7.729, sensitivity 52.2%, specificity 86.2%, PPV 50.0%, NPV 87.2% และ LR+ 3.7)

สรุป: ข้อมูลการศึกษากลุ่มตัวอย่างนี้แสดงให้เห็นว่า PCT เป็นตัวชี้วัดทางชีวภาพในการติดตามระดับอาการความรุนแรงที่เกิดจากภาวการณ์อักเสบที่เกิดจากภาวะติดเชื้อในผู้ป่วยได้ โดยเฉพาะระดับค่า PCT ที่มากกว่าหรือเท่ากับ 2 ng/dL จะมีความสัมพันธ์อย่างมีนัยกับระดับความรุนแรงของโรค ในกลุ่มผู้ป่วยที่มีภาวการณ์อักเสบทั่วร่างกายและสามารถนำมาใช้เป็นเครื่องมือในการช่วยวินิจฉัยและจำแนกผู้ป่วย ในกลุ่มภาวะติดเชื้อรุนแรง กลุ่มที่มีภาวะช็อกจากการติดเชื้อและกลุ่มที่มีภาวะติดเชื้อในกระแสโลหิตได้เป็นอย่างดี