

# Use of a semiquantitative procalcitonin kit for evaluating severity and predicting mortality in patients with sepsis

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**Background:** The aim of this study was to evaluate the clinical usefulness of a semiquantitative procalcitonin kit for assessing severity of sepsis and early determination of mortality in affected patients.

**Methods:** This was a prospective, observational study including 206 septic patients enrolled between June 2008 and August 2009. Disseminated intravascular coagulation (DIC), Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE) II scores were measured, along with semiquantitative procalcitonin concentrations. Patients were divided into three groups based on their semiquantitative procalcitonin concentrations (group A, <2 ng/mL; group B  $\geq$  2 ng/mL < 10 ng/mL; group C  $\geq$  10 ng/mL).

**Results:** A significant difference in DIC, SOFA, and APACHE II scores was found between group A and group C and between group B and group C ( $P < 0.01$ ). Patients with severe sepsis and septic shock had significantly higher procalcitonin concentrations than did patients with less severe disease. The rate of patients with septic shock with high procalcitonin concentrations showed an upward trend. There was a significant ( $P < 0.01$ ) difference between the three groups with regard to numbers of patients and rates of severe sepsis, septic shock, DIC, and mortality.

**Conclusion:** Semiquantitative procalcitonin concentration testing can be helpful for early assessment of disease severity in patients with sepsis. Furthermore, it may also help in predicting early mortality in septic patients. Based on the level of semiquantitative procalcitonin measured in patients with suspected sepsis, a timely decision can be reliably made to transfer them to a tertiary hospital with an intensive care unit for optimal care.

**Keywords:** sepsis, semiquantitative procalcitonin, Sequential Organ Failure Assessment, Acute Physiology and Chronic Health Evaluation II, mortality, procalcitonin

## Introduction

Sepsis is one of the most significant causes of mortality in the intensive care unit. Recent international guidelines for management of severe sepsis and septic shock<sup>1</sup> recommend early diagnosis and treatment of sepsis because any delay may lead to a more serious outcome, ie, fatal organ failure and death.<sup>2</sup> A diagnosis of sepsis is based on evidence of infection along with the presence of systemic inflammatory response syndrome, defined by the presence of two or more of the following: elevated or lowered body temperature, abnormal white blood cell count, elevated heart rate, and high respiratory rate.<sup>3</sup> It has been documented that quantitative evaluation of procalcitonin is useful for discriminating between patients with bacterial infection and those with systemic inflammatory response syndrome caused by another illness.<sup>4-8</sup> Similarly, many studies

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have reported that quantitative procalcitonin values may help to discriminate between patients with severe sepsis infection and septic shock and those with less severe conditions.<sup>4–13</sup> Quantitative procalcitonin concentration is significantly correlated with both the Sequential Organ Failure Assessment (SOFA)<sup>14</sup> score and the Acute Physiology and Chronic Health Evaluation (APACHE) II<sup>15</sup> score,<sup>13,16,17</sup> and significant differences in quantitative procalcitonin concentrations have been found between patients with and without septic shock.<sup>13</sup> A quantitative procalcitonin concentration is also useful as an early prognostic indicator; among patients with septic shock, those who died in the intensive care unit had significantly higher quantitative procalcitonin concentrations at all assay time points than those who survived to be discharged from an intensive care unit.<sup>18</sup>

Due to the cost of procalcitonin analysis, hospitals with the capability to measure quantitative procalcitonin concentrations are limited to larger facilities with intensive care units. However, in hospitals and medical clinics without intensive care units, it is important to diagnose sepsis early and to make an estimate of severity in support of an early decision to transfer patients to a hospital with an intensive care unit so that they may receive optimal care. Therefore, semiquantitative procalcitonin measurement may benefit patients in hospitals and medical clinics without intensive care units.

A semiquantitative procalcitonin test kit is easy to use at the bedside. Research indicates that semiquantitative procalcitonin concentration ranges are well correlated with those of quantitative procalcitonin measurements.<sup>19,20</sup> However, to the best of our knowledge, no study has reported on the usefulness of a semiquantitative procalcitonin kit for estimating severity and determining the prognosis of sepsis. Therefore, the aim of this study was to evaluate the clinical usefulness of a semiquantitative procalcitonin kit for assessing severity of sepsis and early determination of mortality in affected patients.

## Materials and methods

### Study population

This prospective observational study was conducted in the Department of General Medicine and Emergency Department of Toyooka Public Hospital, Hyogo, Japan, a 500-bed teaching hospital that has been designated as the major emergency center of the North Hyogo province by the Japanese government. The local ethics committee approved the study and waived the requirement for written informed consent. Patients were evaluated for the presence of systemic

inflammatory response syndrome and sepsis as defined by American College of Chest Physicians/Society of Critical Care Medicine guidelines.<sup>3</sup> Systemic inflammatory response syndrome was defined as a systemic inflammatory response to an unspecified stimulus manifested by the presence of two or more of the following: body temperature  $< 36^{\circ}\text{C}$  or  $> 38^{\circ}\text{C}$ , heart rate  $> 90$  beats per minute, respiratory rate  $> 20$  breaths per minute or  $\text{PaCO}_2 < 32$  Torr (mmHg), and white blood cell count  $> 12,000$  cells/mm<sup>3</sup>,  $< 4000$  cells/mm<sup>3</sup>, or  $> 10\%$  band forms (immature white blood cells). Sepsis was diagnosed when patients met criteria for systemic inflammatory response syndrome and an infectious source was documented or strongly suspected on the basis of clinical appearance.<sup>3</sup> We excluded patients younger than 18 years of age as well as patients with do not resuscitate status, those with liver cirrhosis, those receiving warfarin, and individuals with evidence of traumatic injury. The patients included were consecutively enrolled from June 2008 to August 2009. Semiquantitative procalcitonin concentrations and C-reactive protein were measured on admission. SOFA and APACHE II scores were determined on the day of admission. Blood pressure, body temperature, pulse rate, respiratory rate, white blood cell count, Glasgow Coma Scale,<sup>21</sup> serum albumin level, and antithrombin activity level were also measured. The maximum C-reactive protein value was defined as the highest level recorded during the first 48 hours of hospital admission.

The final diagnosis was determined by the physician based on clinical course in the hospital. Systemic inflammatory response syndrome, severe sepsis, and septic shock were diagnosed based on the criteria of the Consensus Conference of the American Society of Chest Physicians/Society of Critical Care Medicine.<sup>3</sup> A diagnosis of disseminated intravascular coagulation (DIC) was based on the diagnostic criteria established by the Japanese Association for Acute Medicine.<sup>22</sup> All patients were followed up for 28 days after enrollment in the study, and 28-day all-cause mortality was assessed.

### Procalcitonin measurement

Procalcitonin was measured using the semiquantitative Procalcitonin-Q<sup>®</sup> test kit (Brahms Ag Diagnostica, Berlin, Germany). Procalcitonin-Q is a rapid immunochromatographic test performed by pipetting 200  $\mu\text{L}$  of serum onto a test strip, with results available in 30 minutes. The manufacturer's reference scale categorizes four procalcitonin level intervals, ie,  $< 0.5$  ng/mL,  $\geq 0.5$  ng/mL and  $< 2$  ng/mL,  $\geq 2$  ng/mL and  $< 10$  ng/mL, and  $\geq 10$  ng/mL.

Previous reports have shown that quantitative procalcitonin concentrations above 2 ng/mL discriminate between patients with systemic inflammatory response syndrome, severe bacterial infections, and sepsis, and patients with systemic inflammatory response syndrome, sepsis, and organ failure.<sup>17,23</sup> It is also suspected that a semiquantitative procalcitonin concentration above 2 ng/mL indicates the presence of bacterially induced systemic inflammatory response syndrome.<sup>24</sup> Therefore, patients were divided into three groups based on semiquantitative procalcitonin concentrations: group A comprised patients showing semiquantitative procalcitonin results < 2 ng/mL; group B had semiquantitative procalcitonin results  $\geq$  2 ng/mL and <10 ng/mL; and group C had semiquantitative procalcitonin results  $\geq$  10 ng/mL.

## Statistical analysis

The statistical significance of differences were determined using the analysis of variance or the Chi-square test. Calculations were performed with R, version 2.12.1 (R Foundation for Statistical Computing, Vienna, Austria), and *P* values < 0.05 were considered to be statistically significant.

## Results

A total of 206 patients were enrolled in the study, were of mean age  $75.8 \pm 13.5$  (range 23–103) years, and had a male-to-female ratio of 113:93. Table 1 shows the infection sites in the 206 patients. The enrolled patients were divided into three groups as follows: group A, comprising 84 patients (46 with a procalcitonin concentration < 0.5 ng/mL and 38 with procalcitonin  $\geq$ 0.5 and <2 ng/mL); group B,

**Table 1** Infection sites in patients

Infection site	Patients (n)
Respiratory system	
Pneumonia	104
Empyema thoracis	3
Urinary system	
Pyelonephritis	64
Prostatitis	1
Hepatobiliary system	
Liver abscesses	3
Cholangitis	3
Cholecystitis	2
Soft tissue system	
Cellulitis	5
Necrotizing fasciitis	5
Gastrointestinal system	
Colon diverticulitis	3
Appendicitis	3
Enterocolitis	2
Others	
Iliopsoas muscle abscess	2
Purulent meningitis	2
Acute tonsillitis	2
Infective endocarditis	1
Acute sinusitis	1

including 39 patients; and group C with 83 patients. The clinical data for each group are shown in Table 2. Systolic blood pressure and mean blood pressure significantly decreased in groups B and C as compared with group A. Furthermore, group C patients showed increased respiratory rates compared with groups A and B. The antithrombin activity level was significantly decreased in groups B and C as compared with group A. Table 3 shows mean DIC, SOFA,

**Table 2** Clinical data for study patient groups according to procalcitonin level

	PCT level			P value		
	Group A <2	Group B $\geq$ 2, <10	Group C $\geq$ 10	A vs B	A vs C	B vs C
n	84	39	83			
Gender (male/female)	42/42	26/13	38/47			
Age (years)	75.3 $\pm$ 15.1	76.1 $\pm$ 13.4	76.4 $\pm$ 12.2	1.00	1.00	1.00
Systolic BP (mmHg)	125.6 $\pm$ 22.6	117.2 $\pm$ 23.0	102.1 $\pm$ 21.6	0.049	<0.001	0.001
Diastolic BP (mmHg)	71.1 $\pm$ 14.6	63.1 $\pm$ 14.7	57.8 $\pm$ 15.0	0.03	<0.001	0.049
Mean BP (mmHg)	88.8 $\pm$ 15.2	81.1 $\pm$ 16.5	72.6 $\pm$ 16.0	0.014	0.001	<0.001
Respiratory rate (per minute)	22.6 $\pm$ 4.7	23.8 $\pm$ 4.9	26.0 $\pm$ 5.9	0.32	<0.001	0.05
Heart rate (beats per minute)	92.3 $\pm$ 22.7	101.2 $\pm$ 19.5	102.8 $\pm$ 21.8	0.11	<0.001	0.82
Temperature ( $^{\circ}$ C)	37.9 $\pm$ 1.7	38.5 $\pm$ 1.0	38.1 $\pm$ 2.1	0.34	0.51	0.51
GCS score	13.8 $\pm$ 2.4	13.4 $\pm$ 2.4	12.9 $\pm$ 3.1	0.41	0.08	0.62
WBC ( $\times$ 1000/ $\mu$ L)	13.1 $\pm$ 6.2	14.7 $\pm$ 7.5	13.5 $\pm$ 8.1	0.84	0.85	0.85
Maximum CRP (mg/dL)	15.0 $\pm$ 8.5	17.8 $\pm$ 7.8	19.5 $\pm$ 9.5	0.25	0.001	0.33
Albumin (g/dL)	2.87 $\pm$ 0.55	2.65 $\pm$ 0.54	2.49 $\pm$ 0.48	0.09	<0.001	0.14
AT activity (%)	82.3 $\pm$ 14.9	74.3 $\pm$ 14.5	61.7 $\pm$ 16.3	0.01	<0.001	<0.001

**Abbreviations:** AT, antithrombin; BP, blood pressure; GCS, Glasgow Coma Scale; WBC, white blood cells; CRP, C-reactive protein; vs, versus.

**Table 3** DIC score, SOFA score, and APACHE II score for each group divided by procalcitonin level

	PCT level			P value		
	Group A <2	Group B ≥2, <10	Group C ≥10	A vs B	A vs C	B vs C
DIC score	1.52 ± 1.06	1.80 ± 1.24	2.99 ± 2.19	1.00	<0.001	0.001
APACHE II score	12.7 ± 6.3	15.7 ± 5.8	20.5 ± 7.8	0.074	<0.001	0.001
SOFA score	1.9 ± 1.8	3.1 ± 2.3	5.2 ± 3.1	0.057	<0.001	<0.001

**Abbreviations:** DIC, disseminated intravascular coagulation; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; vs, versus.

and APACHE II scores in each procalcitonin group. A significant difference in DIC, SOFA, and APACHE II scores was found between group A and group C and between group B and group C. Figure 1 shows a comparison of semiquantitative procalcitonin concentration with the rate of severe sepsis and septic shock. In group C, the rates of patients with severe sepsis and septic shock were extremely high, at 76% and 51%, respectively. Figure 2 shows a comparison of semiquantitative procalcitonin concentration with the rate of DIC and 28-day all-cause mortality. The mortality rate, at 13% in group C, is obviously high.

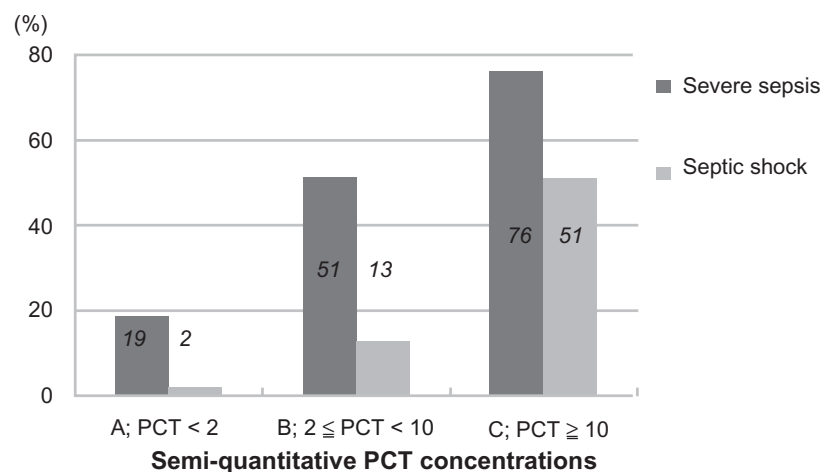
Table 4 shows the numbers of patients and rates of severe sepsis, septic shock, DIC, and mortality in each procalcitonin group. The results were significantly different between three groups. For numbers of patients and rates of severe sepsis, septic shock, DIC, and mortality, the value in group C was higher than expected and the value in group A was lower than expected from the adjusted residual error. All mortality was due to infection. No other cause of death was documented. Almost all patients with septic shock were in group C (procalcitonin  $\geq 10$ ). Approximately 60% of patients with DIC were in group C, and there were few patients with DIC in group A. Moreover, the mortality

rate was highest in group C, which also had the highest procalcitonin level.

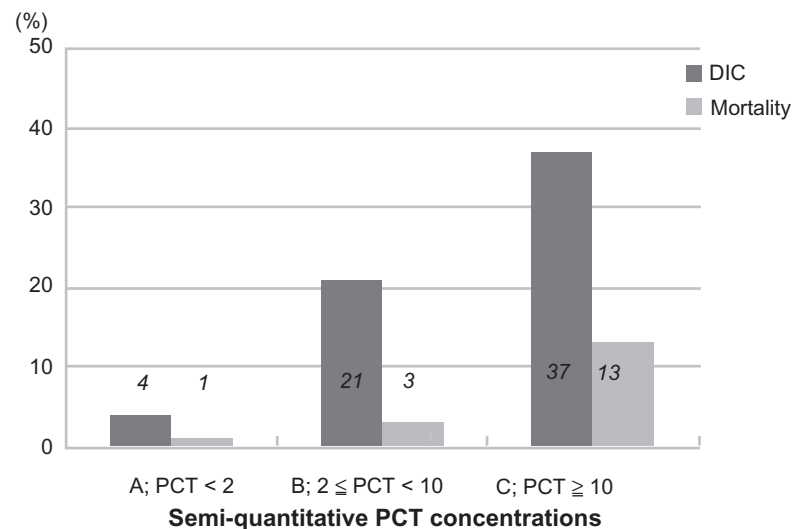
## Discussion

Our results show that semiquantitative procalcitonin concentration is an important discriminator for severity of sepsis. Furthermore, it may help in predicting early mortality in patients with sepsis. The results for systolic blood pressure, mean blood pressure, and respiratory rates may reflect severity of circulatory failure and respiratory failure. Antithrombin activity levels have been reported to be of prognostic value for the prediction of death in patients with severe sepsis or septic shock.<sup>25,26</sup> Our results suggest that the semiquantitative procalcitonin concentration is indirectly a predictor of death in these patients.

In the present study, SOFA and APACHE II scores were significantly increased in group C as compared with groups A and B. Higher SOFA and APACHE II scores have been associated with significantly higher quantitative procalcitonin concentrations in several previous studies.<sup>13,16,17</sup> Our results show that semiquantitative procalcitonin concentration is an important discriminator that can evaluate sepsis severity as well as quantitative procalcitonin concentration.



**Figure 1** Comparison of semi-quantitative procalcitonin concentrations with rates of severe sepsis and septic shock.



**Figure 2** Comparison of semi-quantitative procalcitonin concentrations with rate of disseminated intravascular coagulation and mortality.  
**Abbreviations:** DIC, disseminated intravascular coagulation.

In group C, rates of patients with severe sepsis and septic shock were extremely high. This result using semi-quantitative procalcitonin measurement is similar to that found with quantitative procalcitonin measurement, where significant differences are apparent in quantitative procalcitonin concentrations between patients with and without septic shock.<sup>13</sup> The rate of patients with DIC also showed an upward trend with increasing semi-quantitative procalcitonin concentrations. These results strongly suggest that semi-quantitative procalcitonin concentration is a predictor of severity in patients with sepsis. While septic shock is a clinical diagnosis, severe sepsis (sepsis with acute organ failure) is a complicated diagnosis that can utilize several different organ failure assessments. The procalcitonin assay correlates with the presence of severe sepsis and can be helpful in the early triage of this patient population.

The mortality rate, which was 13% in group C, is obviously high. Also, the value in group C was higher than expected. Semi-quantitative procalcitonin concentration may be of great initial prognostic value. In hospitals and medical

clinics without intensive care units, it is important to diagnose sepsis early and to make an estimate of severity in support of an early decision to transport patients to a hospital with an intensive care unit so they may receive optimal care. Our study may contribute to making a timely decision to transfer them to a tertiary hospital with an intensive care unit.

This study had several limitations. First, the timing of onset of infection was not considered, although it is known that serum procalcitonin begins to rise within 2–4 hours and shows peak levels at 6 hours.<sup>27</sup> Therefore some patients may have been measured before procalcitonin began to rise. Second, because we used clinical and microbiological evidence, it might have been difficult to ascertain the precise cause of sepsis in all patients, and this might have introduced some misclassification bias. Finally, the conduct of this study was confined to departments in single centers, so case numbers were limited, and multicenter validation would have increased the generalizability of such findings.

In conclusion, semi-quantitative procalcitonin concentration testing can be helpful for early assessment of disease severity in patients with sepsis. Furthermore, it may help in predicting early mortality in patients with sepsis. Based on the level of semi-quantitative procalcitonin measured in patients with suspected sepsis, a timely decision can be reliably made to transfer them to a tertiary hospital with an intensive care unit for optimal care.

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**Table 4** Numbers of patients and rates of severe sepsis, septic shock, disseminated intravascular coagulation, and mortality for each group according to procalcitonin level

	PCT level			P value
	Group A <2	Group B ≥2, <10	Group C ≥10	
Severe sepsis	15 (19%)	20 (51%)	63 (76%)	<0.0001
Septic shock	2 (2%)	5 (13%)	42 (51%)	<0.0001
DIC	3 (4%)	8 (21%)	31 (37%)	<0.0001
Mortality	1 (1%)	1 (3%)	11 (13%)	0.003

**Abbreviations:** DIC, disseminated intravascular coagulation; PCT, procalcitonin.

## Disclosure

The authors report no conflicts of interest in this work.

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