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

Tsuneaki Kenzaka1
Masanobu Okayama2
Shigehiro Kuroki1
Miho Fukui3
Shinsuke Yahata3
Hiroki Hayashi3
Akihito Kitao3
Eiji Kajii2
Masayoshi Hashimoto4

1Division of General Medicine, Center for Community Medicine, Jichi Medical University School of Medicine, Shimotsuke; 2Division of Community and Family Medicine, Center for Community Medicine, Jichi Medical University School of Medicine, Shimotsuke; 3Department of General Medicine, Toyooka Public Hospital, Toyooka; 4Department of Family and Community Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

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 ≥ 2 ng/mL < 10 ng/mL; group C ≥ 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 recommend early diagnosis and treatment of sepsis because any delay may lead to a more serious outcome, ie, fatal organ failure and death. 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. 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. Similarly, many studies
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.\textsuperscript{4-13}
Quantitative procalcitonin concentration is significantly
correlated with both the Sequential Organ Failure Assessment
(SOFA)\textsuperscript{14} score and the Acute Physiology and Chronic
Health Evaluation (APACHE) II\textsuperscript{15} score,\textsuperscript{13,16,17} and significant
differences in quantitative procalcitonin concentrations have
been found between patients with and without septic shock.\textsuperscript{13}
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.\textsuperscript{18}

Due to the cost of procalcitonin analysis, hospitals with
the capability to measure quantitative procalcitonin concen-
trations 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 pro-
calcitonin concentration ranges are well correlated with those
of quantitative procalcitonin measurements.\textsuperscript{19,20} However,
to the best of our knowledge, no study has reported on the
usefulness of a semiquantitative procalcitonin kit for esti-
mating 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.

\section*{Materials and methods}
\textbf{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.\textsuperscript{3} 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 $<36^\circ C$ or $>38^\circ C$,
heart rate $>90$ beats per minute, respiratory rate $>20$
breaths per minute or PaCO$_{2}$ $<32$ Torr (mmHg), and white
blood cell count $>12,000$ cells/mm$^3$, $<4000$ cells/mm$^3$, or
$>10\%$ band forms (immature white blood cells). Sepsis
was diagnosed when patients met criteria for systemic inflam-
matory response syndrome and an infectious source was
documented or strongly suspected on the basis of clinical
appearance.\textsuperscript{3} 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,\textsuperscript{21} 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 inflam-
matory response syndrome, severe sepsis, and septic shock
were diagnosed based on the criteria of the Consensus Con-
ference of the American Society of Chest Physicians/Society
of Critical Care Medicine.\textsuperscript{3} A diagnosis of disseminated
intravascular coagulation (DIC) was based on the diagnostic
criteria established by the Japanese Association for Acute
Medicine.\textsuperscript{22} All patients were followed up for 28 days after
enrollment in the study, and 28-day all-cause mortality was
assessed.

\textbf{Procalcitonin measurement}

Procalcitonin was measured using the semiquantitative Pro-
calcitonin-Q$^\circledR$ test kit (Brahms Ag Diagnostica, Berlin, Ger-
many). Procalcitonin-Q is a rapid immunochromatographic
test performed by pipetting 200 $\mu$L of serum onto a test strip,
with results available in 30 minutes. The manufacturer’s
reference scale categorizes four procalcitonin level intervals,
\textit{i.e.}, $<0.5$ ng/mL, $\geq0.5$ ng/mL and $<2$ ng/mL, $\geq2$ ng/mL and
$<10$ ng/mL, and $\geq10$ 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.\textsuperscript{17,23} It is also suspected that a semiquantitative procalcitonin concentration above 2 ng/mL indicates the presence of bacterially induced systemic inflammatory response syndrome.\textsuperscript{24} 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 $\geq2$ ng/mL and $<10$ ng/mL; and group C had semiquantitative procalcitonin results $\geq10$ 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 $\geq0.5$ and $<2$ ng/mL); group B, 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>
<thead>
<tr>
<th>Table 1 Infection sites in patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection site</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Respiratory system</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Empyema thoracis</td>
</tr>
<tr>
<td>Urinary system</td>
</tr>
<tr>
<td>Pyelonephritis</td>
</tr>
<tr>
<td>Prostatitis</td>
</tr>
<tr>
<td>Hepatobiliary system</td>
</tr>
<tr>
<td>Liver abscesses</td>
</tr>
<tr>
<td>Cholangitis</td>
</tr>
<tr>
<td>Cholecystitis</td>
</tr>
<tr>
<td>Soft tissue system</td>
</tr>
<tr>
<td>Cellulitis</td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
</tr>
<tr>
<td>Colon diverticulitis</td>
</tr>
<tr>
<td>Appendicitis</td>
</tr>
<tr>
<td>Enterocolitis</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Iliopsoas muscle abscess</td>
</tr>
<tr>
<td>Purulent meningitis</td>
</tr>
<tr>
<td>Acute tonsillitis</td>
</tr>
<tr>
<td>Infective endocarditis</td>
</tr>
<tr>
<td>Acute sinusitis</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>PCT level</th>
<th>Group A</th>
<th>Group B $\geq2$, $&lt;10$</th>
<th>Group C $\geq10$</th>
<th>$P$ value $A$ vs $B$</th>
<th>$A$ vs $C$</th>
<th>$B$ vs $C$</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>84</td>
<td>39</td>
<td>83</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>42/42</td>
<td>26/13</td>
<td>38/47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>$75.3 \pm 15.1$</td>
<td>$76.1 \pm 13.4$</td>
<td>$76.4 \pm 12.2$</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>$125.6 \pm 22.6$</td>
<td>$117.2 \pm 23.0$</td>
<td>$102.1 \pm 21.6$</td>
<td>0.049</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>$71.1 \pm 14.6$</td>
<td>$63.1 \pm 14.7$</td>
<td>$57.8 \pm 15.0$</td>
<td>0.03</td>
<td>&lt;0.001</td>
<td>0.049</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>$88.8 \pm 15.2$</td>
<td>$81.1 \pm 16.5$</td>
<td>$72.6 \pm 16.0$</td>
<td>0.014</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory rate (per minute)</td>
<td>$22.6 \pm 4.7$</td>
<td>$23.8 \pm 4.9$</td>
<td>$26.0 \pm 5.9$</td>
<td>0.32</td>
<td>&lt;0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>$92.3 \pm 22.7$</td>
<td>$101.2 \pm 19.5$</td>
<td>$102.8 \pm 21.8$</td>
<td>0.11</td>
<td>&lt;0.001</td>
<td>0.82</td>
</tr>
<tr>
<td>Temperature ($^\circ$C)</td>
<td>$37.9 \pm 1.7$</td>
<td>$38.5 \pm 1.0$</td>
<td>$38.1 \pm 2.1$</td>
<td>0.34</td>
<td>0.51</td>
<td>0.51</td>
</tr>
<tr>
<td>GCS score</td>
<td>$13.8 \pm 2.4$</td>
<td>$13.4 \pm 2.4$</td>
<td>$12.9 \pm 3.1$</td>
<td>0.41</td>
<td>0.08</td>
<td>0.62</td>
</tr>
<tr>
<td>WBC ($&lt;1000$ µL)</td>
<td>$13.1 \pm 6.2$</td>
<td>$14.7 \pm 7.5$</td>
<td>$13.5 \pm 8.1$</td>
<td>0.84</td>
<td>0.85</td>
<td>0.85</td>
</tr>
<tr>
<td>Maximum CRP (mg/dL)</td>
<td>$15.0 \pm 8.5$</td>
<td>$17.8 \pm 7.8$</td>
<td>$19.5 \pm 9.5$</td>
<td>0.25</td>
<td>&lt;0.001</td>
<td>0.03</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>$2.87 \pm 0.55$</td>
<td>$2.65 \pm 0.54$</td>
<td>$2.49 \pm 0.48$</td>
<td>0.09</td>
<td>&lt;0.001</td>
<td>0.14</td>
</tr>
<tr>
<td>AT activity (%)</td>
<td>$82.3 \pm 14.9$</td>
<td>$74.3 \pm 14.5$</td>
<td>$61.7 \pm 16.3$</td>
<td>0.01</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: AT, antithrombin; BP, blood pressure; GCS, Glasgow Coma Scale; WBC, white blood cells; CRP, C-reactive protein; 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 ≥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.25,26 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.13,16,17 Our results show that semiquantitative procalcitonin concentration is an important discriminator that can evaluate sepsis severity as well as quantitative procalcitonin concentration.

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

<table>
<thead>
<tr>
<th>PCT level</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;2</td>
<td>≥2, &lt;10</td>
<td>≥10</td>
<td>A vs B</td>
</tr>
<tr>
<td>DIC score</td>
<td>1.52 ± 1.06</td>
<td>1.80 ± 1.24</td>
<td>2.99 ± 2.19</td>
<td>1.00</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>12.7 ± 6.3</td>
<td>15.7 ± 5.8</td>
<td>20.5 ± 7.8</td>
<td>0.074</td>
</tr>
<tr>
<td>SOFA score</td>
<td>1.9 ± 1.8</td>
<td>3.1 ± 2.3</td>
<td>5.2 ± 3.1</td>
<td>0.057</td>
</tr>
</tbody>
</table>

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

**Figure 1** Comparison of semiquantitative procalcitonin concentrations with rates of severe sepsis and septic shock.
In group C, rates of patients with severe sepsis and septic shock were extremely high. This result using semiquantitative 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. The rate of patients with DIC also showed an upward trend with increasing semiquantitative procalcitonin concentrations. These results strongly suggest that semiquantitative 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. Semiquantitative 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. 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, semiquantitative 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 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.

Acknowledgments
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Disclosure
The authors report no conflicts of interest in this work.

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