Procalcitinin and albumin as prognostic biomarkers in elderly patients with a risk of bacterial infection

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Abstract

Aim: This study was performed to investigate serum procalcitonin (PCT) and albumin (Alb) as prognostic biomarkers in elderly patients at risk of bacterial infection.

Methods: Serum PCT was measured in 270 hospitalized patients (mean age, 77.4 years) with suspected bacterial infection. The PCT-negative (<0.5 ng/mL) and PCT-positive (≥0.5 ng/mL) groups comprised 155 and 115 patients, respectively. Logistic regression analysis was performed with various clinical laboratory test values as independent variables and PCT positivity/negativity as the dependent variable.

Results: C-reactive protein (CRP) was the only independent variable significantly associated with PCT positivity/negativity. In the survival analysis, the 30-day in-hospital death rate was significantly higher in the PCT-positive than -negative group. Within the Alb-positive group (>2.5 g/dL), no significant difference in survival was observed between the PCT-positive and -negative groups. However, within the Alb-negative group (<2.5 g/dL), the survival rate was significantly lower in the PCT-positive than -negative group. PCT was strongly associated with CRP and Alb, and having both PCT positivity and Alb negativity was a prognostic factor for elderly people at risk of bacterial infection.

Conclusions: Combined measurement of PCT with Alb is expected to be a valuable tool to assess prognosis in elderly people at risk of bacterial infection.

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Introduction

Himi is a city located in the northwest of Toyama Prefecture, Japan, which has an area of 230 km² and about 50,000 residents. More than 30% of the residents of Himi are elderly people aged ≥65 years, and this proportion of elderly people is growing. Although elderly people often develop infectious disease with fever, they often visit clinics to consult with doctors in a timely manner to avoid a worsening disease state, and their prognosis with general medical treatment has consequently improved. However, elderly people are at risk of developing diseases of various internal organs, such as pneumonia, urinary tract infection, and inflammation of the gallbladder. These underlying diseases in elderly people can become lethal, and as the treatment period becomes longer, disuse worsens and the duration of hospitalization increases. Various surrogate markers have been developed to aid in diagnosis, specifically in the field of infection. Assicot et al. clearly showed that the procalcitonin (PCT) concentration in blood is elevated by systemic infection, especially bacterial infectious disease causing severe illness, but not by local infection. The authors concluded that PCT can be applied for diagnosis of various bacterial infectious diseases. PCT has also been compared with C-reactive protein (CRP) as a useful clinical diagnostic marker for a bacterial infectious disease. However, there is little evidence concerning the relationship of PCT with various vital signs (body temperature, blood pressure, etc.), blood test data (albumin [Alb], blood urea nitrogen [BUN], and CRP), and disease progression and/or death during hospitalization in elderly patients. Therefore, we investigated the clinical correlation between inpatients’ lifetime prognosis and their PCT concentration in blood, which we expected to be a prognostic marker for elderly people at risk of infectious diseases.

Methods

Patient population

The participants in this study were mostly residents of Himi visiting or hospitalized in Himi Municipal Hospital. The study included male and female outpatients and inpatients who underwent blood collection for simultaneous measurement of PCT and CRP because of suspicion of bacterial infection from April 2013 to March 2014. Patients with liver cirrhosis and nephrotic disease were excluded. The patients were divided into a PCT-negative group (<0.5 ng/mL) and PCT-positive group (≥0.5 ng/mL). A patient flow chart is shown in Figure 1. The patients’ disease conditions included organ infection and/or respiratory disease; kidney and/or urinary disease; digestive system disease; pancreatic, biliary tract, and liver disease; circulatory disease, blood or connective tissue disease, and other types of disease.

Data collection

The patients’ electronic health records were viewed, and data on the diagnoses, vital signs, specimen materials, imaging findings,
and other parameters were collected. A B-R·A-H·M-S PCT-Q assay (Thermo Fisher Scientific, Waltham, MA, USA) was used for quick measurement of PCT. The serum PCT concentration was measured by including the PCT measurement option in the routine blood test. According to the classification of the kit, a PCT concentration of $<0.5 \text{ ng/mL}$ was defined as PCT-negative, and a concentration of $\geq 0.5 \text{ ng/mL}$ was defined as PCT-positive.

**Statistical analysis**

A t-test and chi-square test were performed to compare significant differences between the two groups. To evaluate the relationship between PCT positivity/negativity and patients’ background factors, PCT positivity/negativity was set as the dependent variable, and logistic regression analysis in which various clinical and laboratory parameters (e.g., age, CRP concentration) were set as the independent variables was performed. Furthermore, a survival analysis was separately carried out for the PCT-positive and -negative groups. We created Kaplan–Mayer estimated survival curves in which the observation period was defined as 30 days from blood sample collection for PCT and Alb measurement, and the event was defined as death occurred during these 30 days. Significant differences between the two groups were evaluated by the log-rank test, and the overall difference at 30 days between the two groups was evaluated by the hazard ratio and 95% confidence interval by applying a Cox proportional hazards model. EZR was used for all data analyses.

**Ethical considerations**

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and was formally approved by the Clinical Research Ethics Committee of Kanazawa Medical University Himi Municipal Hospital (receipt no. 92). A comprehensive explanation of this clinical study was provided to the patients and their accompanying legal representatives, and all patients provided written informed consent after acknowledging their sufficient understanding.

**Results**

**Demographics**

The patients’ demographics are shown in Table 1. In total, 328 male and female
outpatients and inpatients were assessed for inclusion (215 men aged 73.36 ± 17.40 years and 113 women aged 77.72 ± 17.41 years). After exclusion of 58 outpatients, 270 patients comprised the full analysis set for the main investigation (182 men aged 76.49 ± 15.95 years and 88 women aged 75.44 ± 15.91 years). The PCT-negative and -positive groups comprised 115 and 155 patients, respectively. Organ infection and/or respiratory disease was present in 109 patients; kidney and/or urinary disease in 41; digestive system disease in 36; pluck, biliary tract, and liver disease in 27; circulatory disease in 24; blood or connective tissue disease in 7; and other types of disease in 26.

In total, 18 of 155 patients died in the PCT-negative group and 28 of 115 patients died in the PCT-positive group, revealing a significantly higher mortality rate in the PCT-positive group ($p = 0.015$).

### Logistic regression and survival analyses

The duration of hospitalization in the PCT-negative group was 37.33 ± 32.11 days, and that in the PCT-positive group was 41.21 ± 36.29 days; the difference was not statistically significant. In the PCT-positive

| Variable                        | All n = 270 | PCT < 0.5 ng/mL n = 155 | PCT ≥ 0.5 ng/mL n = 115 | p-value* |
|---------------------------------|------------|-------------------------|-------------------------|----------|
| Age, years                      | 77.4 ± 15.2| 76.5 ± 15.9             | 78.7 ± 15.9             | 0.599    |
| Age of >64 years                | 235 (87.0) | 128 (82.6)              | 107 (93.0)              | 0.011    |
| Female                          | 88 (32.6)  | 53 (34.2)               | 35 (30.4)               | 0.515    |
| CRP, mg/dL                      | 9.6 ± 7.2  | 7.2 ± 6.1               | 12.9 ± 7.4              | <0.001   |
| BP of <90 mmHg                  | 19 (7.2)   | 8 (5.2)                 | 11 (9.8)                | 0.152    |
| HR, beats/min                   | 134 (52.3) | 78 (53.4)               | 56 (50.9)               | 0.690    |
| Abnormal body temperature       | 108 (41.4) | 55 (36.7)               | 53 (47.7)               | 0.072    |
| Abnormal AST                    | 112 (41.5) | 53 (34.2)               | 59 (51.3)               | 0.005    |
| Abnormal ALT                    | 87 (32.2)  | 43 (27.7)               | 44 (38.3)               | 0.067    |
| Abnormal LDH                    | 140 (52.0) | 76 (49.4)               | 64 (55.7)               | 0.306    |
| Abnormal ALP                    | 62 (39.5)  | 35 (40.2)               | 27 (38.6)               | 0.833    |
| Abnormal CK                     | 149 (60.1) | 92 (63.4)               | 57 (55.3)               | 0.199    |
| Abnormal Albumin                | 215 (95.1) | 124 (92.5)              | 91 (98.9)               | 0.030    |
| Abnormal BUN                    | 150 (56.2) | 69 (44.8)               | 81 (71.7)               | <0.001   |
| Abnormal Na⁺                     | 147 (54.4) | 86 (55.5)               | 61 (53.0)               | 0.691    |
| Abnormal K⁺                      | 72 (26.7)  | 40 (25.8)               | 32 (27.8)               | 0.711    |
| Abnormal BNP                    | 45 (52.3)  | 25 (48.1)               | 20 (38.8)               | 0.329    |
| Abnormal glucose                | 137 (77.0) | 89 (80.2)               | 48 (71.6)               | 0.190    |
| Abnormal leukocyte count         | 106 (39.3) | 54 (34.8)               | 52 (45.2)               | 0.084    |
| Abnormal Hb                     | 220 (81.5) | 127 (81.9)              | 93 (80.9)               | 0.824    |
| Death                           | 46 (17.0)  | 18 (11.6)               | 28 (24.3)               | 0.006    |
| Impaired consciousness          | 87 (32.2)  | 46 (29.7)               | 41 (35.7)               | 0.299    |
| Abnormal SpO₂                   | 92 (34.1)  | 49 (31.6)               | 43 (37.4)               | 0.322    |

Data are presented as mean ± standard deviation or n (%).

* t-test (age, CRP); chi-square test (others).

PCT, procalcitonin; CRP, C-reactive protein; BP, blood pressure; HR, heart rate; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CK, creatine kinase; BUN, blood urea nitrogen; Na⁺, sodium; K⁺, potassium; BNP, brain natriuretic peptide; Hb, hemoglobin; SpO₂, blood oxygen saturation.
group, there were no significant differences in the mortality rate among groups of patients with different PCT concentrations: death occurred in 11 of 45 patients with a PCT of 0.5–2 ng/mL, 12 of 38 patients with a PCT of 2–10 ng/mL, and 5 of 32 patients with a PCT of >10 ng/mL. The rates of inpatient death according to underlying disease were as follows: death occurred in 18 of 109 patients with respiratory disease, 0 of 41 patients with kidney and urological disease, 15 of 36 patients with digestive system disease, 3 of 27 patients with gallbladder and liver disease, 5 of 24 patients with circulatory disease, 2 of 7 patients with blood disorders, and 2 of 26 patients with other diseases. (The PCT-positive group showed a lower survival rate than the PCT-negative group; p = 0.00429.) Simultaneous comparison of the CRP and PCT concentrations showed that the mortality rate increased when setting the CRP cutoff value at 5 mg/dL (a cutoff of ≥5 mg/dL was considered positive).

The mean BUN concentration was 22.75 ± 14.32 mg/dL in the PCT-negative group and 35.61 ± 25.89 mg/dL in the PCT-positive group, and this difference was statistically significant (p < 0.001). The mean systolic arterial pressure was 119.47 ± 25.45 mmHg in the PCT-positive group and 129.29 ± 29.95 mmHg in the PCT-negative group. The results of the logistic regression analysis are shown in Table 2. The only significant variable among all independent variables was CRP (p < 0.001). Alb exhibited the largest odds ratio at 1.24 (95% confidence interval, 0.61–2.54). The results of the survival analysis in the PCT-positive and -negative groups are shown in Figure 2. The survival rate was significantly lower in the PCT-positive than -negative group (log-rank test, p = 0.0127). The hazard ratio between the PCT-positive and -negative groups was 0.492 (0.267–0.881) when the Cox proportional hazard model was applied. The results of the survival analysis stratified by Alb positivity (Alb > 2.5 g/dL) and negativity (Alb ≤ 2.5 g/dL) are shown in Figure 3. Within the Alb-positive group, no significant difference in survival was observed.

Table 2. Predictors of PCT positivity/negativity following univariate and multivariate analysis in 270 patients with a risk of bacterial infection

|       | Coefficients | S.E.   | p-value* | Unadjusted odds ratio | 95% CI       | Adjusted odds ratio | 95% CI       |
|-------|--------------|--------|----------|-----------------------|------------|---------------------|------------|
| Age   | −0.010       | 0.019  | 0.068    | 0.991                 | 0.974–1.007| 0.990               | 0.955–1.028|
| CRP   | −0.104       | 0.032  | 0.011    | 0.885                 | 0.850–0.922| 0.901               | 0.846–0.959|
| AST   | −0.002       | 0.010  | 0.032    | 0.995                 | 0.990–1.000| 0.998               | 0.978–1.018|
| ALT   | 0.002        | 0.008  | 0.039    | 0.997                 | 0.992–1.001| 1.002               | 0.986–1.017|
| LDH   | 0.0003       | 0.001  | 0.012    | 0.999                 | 0.998–1.001| 1.000               | 0.998–1.003|
| ALP   | 0.001        | 0.001  | 0.246    | 1.000                 | 0.999–1.001| 1.001               | 0.999–1.003|
| CPK   | 0.001        | 0.001  | 0.256    | 0.999                 | 0.998–1.000| 1.001               | 0.999–1.003|
| Alb   | 0.217        | 0.365  | 0.553    | 1.848                 | 1.207–2.829| 1.242               | 0.607–2.542|
| T-BIL | −0.738       | 0.483  | 0.126    | 0.707                 | 0.487–1.025| 0.478               | 0.186–1.230|
| BUN   | −0.021       | 0.016  | 0.198    | 0.964                 | 0.949–0.980| 0.980               | 0.949–1.011|
| CRE   | −0.150       | 0.118  | 0.203    | 0.834                 | 0.736–0.946| 0.861               | 0.683–1.085|

*p < 0.01 by likelihood ratio chi-square test.

PCT, procalcitonin; S.E., standard error; CI, confidence interval; CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CPK, creatine phosphokinase; Alb, albumin; T-BIL, total bilirubin; BUN, blood urea nitrogen; CRE, creatinine.
between the PCT-positive and -negative groups; the hazard ratio was 0.682 (0.219–2.063) by the Cox regression model. Within the Alb-negative group, however, the survival rate was significantly lower in the PCT-positive than -negative group (log-rank test, p = 0.0354). The hazard ratio was 0.457 (0.204–0.991) by the Cox regression model.

**Figure 2.** Kaplan–Meier survival plot showing proportion of survivors with a risk of bacterial infection. PCT, procalcitonin; CI, confidence interval.

**Figure 3.** Kaplan–Meier plot stratified by albumin concentration with a 2.5-g/dL cutoff level. Alb, albumin; PCT, procalcitonin; CI, confidence interval.
Discussion

Our results have confirmed that a high serum PCT concentration can be a significant risk factor for the survival of hospitalized elderly patients. This study has also revealed an interaction between the PCT and Alb concentrations; i.e., a low Alb concentration with a high PCT concentration can be a significant prognostic factor for elderly patients at risk of infection.

Although PCT is synthesized by thyroid C cells as the precursor of calcitonin, a study performed in 1993 was the first to show that the PCT concentration increases in the blood of patients with infectious disease.5 Inflammatory cytokines such as tumor necrosis factor-alpha are produced by toxic stimulus exposure, and within 3 hours their concentrations begin to increase in response to the stimulus.

The high concentration of PCT continues because its half-life is as long as 22 hours. PCT is produced and increases sharply in patients with infectious diseases affecting the lungs, thyroid gland, kidney, skin, and various other internal organs.11,12 Additionally, although synthesis of CRP is promoted by the liver and synthesis of Alb is inhibited in patients with inflammation, production of PCT by inflamed internal organs occurs and PCT rises more quickly than CRP at an early stage.

In the clinical setting, CRP is frequently used as an index of inflammation and increases in patients with tumors and inflammation. In the present study, we considered that the PCT and CRP levels were correlated as evidenced by the increase in PCT along with the increase in CRP. In a meta-analysis of systemic inflammatory response syndrome, PCT had 77% sensitivity and 79% specificity in differentiation of bacterial and non-bacterial infection.7 In the acute phase, blood collection should be performed for simultaneous measurement of PCT and CRP. If the PCT value is positive (≥0.5 ng/mL), the possibility of bacterial infection is considered to be high, and it may be more desirable to use CRP from the subacute phase to the chronic phase; that is, when initiating time-dependent changes in treatment.

In the present study, the blood pressure was low and BUN was high in the PCT-positive group, indicating that PCT positivity may be a trigger of sepsis and organ failure.

In an animal experiment involving hamsters, Nylen et al.13 reported that inflammation decreased in severity and the mortality rate decreased when the hamsters were administered antiserum reactive to PCT. PCT may affect the whole immunity system and not only act as an inflammation-induced chemical mediator, and its roles in human pathologic conditions and medical treatment are being explored.13 As Zhou and Ho14 reported in 2016, PCT-positive patients showed significantly higher rates of mortality and intensive care unit re-entry.

In the present study, the PCT-positive group had a significantly higher 30-day in-hospital mortality rate than the PCT-negative group (p = 0.0127). However, PCT negativity and positivity did not affect the hospitalization duration. Although this was a retrospective study, patients with suspected bacterial infection who have PCT positivity and a low Alb value are thought to benefit from timely antibiotic administration and whole-body management; intervention of a nutritional support team and early meal restart, nutrition management, and rehabilitation are required thereafter. Although a low Alb concentration must be addressed, a low Alb value at the time of gastrostomy and high CRP value are associated with a significantly increased 30-day mortality rate, and the clinician should identify the ideal corrective strategy for Alb while considering the patient’s overall general medical
The present study suggests that such a strategy leads to a reduction in the mortality rate and a shortened duration of hospitalization. The systolic blood pressure was lower in the PCT-positive than -negative group and was associated with a higher mortality rate, and these patients developed a decline of organ perfusion and more severe dehydration as indicated by a rising BUN level. Therefore, we reaffirmed the need to monitor the blood pressure and correct dehydration in the acute phase of severe sepsis.

The demographics were unbalanced between the PCT-positive and -negative groups. This imbalance was especially apparent in age and BUN and may have served as an underlying confounding factor. However, this was an observational study and not an interventional/randomized study. Therefore, complete adjustment for all confounding factors is impossible. We believe that if these small imbalances reflect the real clinical setting, it would be more effective to compare them without intentional patient selection to avoid selection bias.

Essentially, the PCT value is continuous; however, we set the cutoff value as 0.5 ng/mL and assessed additional dichotomous variables because of the limitation of the semi-quantitative diagnostic procedure. Further studies are required to elucidate the actual cutoff values, which could be near 0.5 g/mL, using qualitative measuring equipment. Because this study was performed in a single institution, its external validity has not been evaluated, and multi-institution studies are necessary. Further investigation involving multiple sampling among several hospitals is necessary to obtain consistent results.

PCT measurement, as well as dual measurement of PCT with Alb, can be a valuable tool to maintain the health and quality of life of hospitalized elderly patients and avoid the risk of infection.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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