Combination of Procalcitonin Value on Hospital Admission and Its Subsequent Change in Value Is Associated With the Prognosis of Sepsis

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OBJECTIVES: To evaluate the relationship between the procalcitonin value in blood on hospital admission and its subsequent change and prognosis among sepsis patients.

DESIGN: A single-center, retrospective, observational study.

SETTING: Critical care center in Japan.

PATIENTS: Sepsis patients 18 years old or older admitted from January 1, 2015, to March 31, 2018.

INTERVENTIONS: None.

MEASUREMENT AND MAIN RESULTS: Among 173 sepsis patients enrolled, the median age was 74 years old (interquartile range, 64–79 yr old), and there were 102 men. The median value of procalcitonin in blood on hospital admission was 14.8 ng/mL (interquartile range, 3.5–78.4 ng/mL), and the median change in serum procalcitonin value between hospital admission and the next day was 0 ng/mL (interquartile range, −4.5 to 5.2 ng/mL). Mortality at 28 days after hospital admission was 5.8% (10/173). In univariate logistic regression analysis, elderly (crude odds ratio, 5.314; 95% CI, 1.094–25.806; $p = 0.044$), procalcitonin value of less than 33.2 ng/mL on hospital admission ($p = 0.007$), and change in serum procalcitonin of less than 0.0 ng/mL (crude odds ratio, 5.056; 95% CI, 1.041–24.545; $p = 0.046$) were associated with mortality at 28 days after hospital admission. The mortality of patients with a procalcitonin value of less than 33.2 ng/mL on hospital admission and change in serum procalcitonin of less than 0.0 ng/mL was 18.6% (8/43) and was significantly higher than that of other patients ($p < 0.001$).

CONCLUSIONS: Our study showed the sepsis patients with a procalcitonin value in blood of less than 33.2 ng/mL on hospital admission and change in serum procalcitonin of less than 0.0 ng/mL had high mortality at 28 days after hospital admission.

KEY WORDS: change of procalcitonin; elderly; infection; mortality; procalcitonin; sepsis

S epsis is a global health problem from which more than 110,000 people die worldwide every year (1). In recent years, although the mortality rate of sepsis has been improved by several strategies for sepsis such as the Surviving Sepsis Campaign Guidelines (SSCG), it remains high. Especially in sepsis patients with shock, the risk of death increases by 7.6% every hour after the start of antibiotic treatment is delayed (2, 3). Therefore, early detection

and treatment of sepsis are important and may lead to an improved prognosis. The quick Sequential Organ Failure Assessment (qSOFA) score is used for the early detection of severe sepsis. However, it is possible for qSOFA to be false positive in patients with hypotension or severe dementia, and the score is associated with predicting inhospital mortality only in patients who do not require intensive care (4). It remains unclear whether qSOFA is associated with the prediction of prognosis in sepsis patients.

Procalcitonin, which is the prohormone of calcitonin, is synthesized by the C cells of the thyroid gland and is not usually released into the blood. Once inflammatory cytokines such as tumor necrosis factor (TNF)-α are produced in systemic bacterial infection, procalcitonin is produced by these inflammatory cytokines not only in the thyroid gland but also in extrathyroidal organs such as lung, kidney, liver, adipocyte, and muscle. As procalcitonin secreted from these organs is not degraded to calcitonin (5), the measurement of procalcitonin is weakly recommended as an adjunct test for the diagnosis of infection in the SSCG guidelines (6). In addition, the procalcitonin value in blood is reported to increase within 6 hours after the onset of sepsis and peaks from 12 to 48 hours later (7). Therefore, the procalcitonin value in blood and its change may lead to the early recognition of severe sepsis.

Several previous studies have examined the relationship between changes of the procalcitonin value in blood during the acute phase and the prognosis of sepsis (8, 9). However, the relationship between the change of procalcitonin value and the prognosis of sepsis has not been fully revealed.

The purpose of this study was to evaluate the relationship between the procalcitonin value in blood on hospital admission and its subsequent change and the prognosis of sepsis patients.

MATERIALS AND METHODS

Study Design and Patients

This study was a single-center, retrospective, observational study with a study period of 39 months from January 1, 2015, to March 31, 2018. In this study, we included the septic patients 18 years old or older who were admitted to the Department of Emergency and Critical Care Medicine, Kansai Medical University Hospital. We diagnosed them as septic patients according to Sepsis-3

criteria that the Sequential Organ Failure Assessment (SOFA) score increases of 2 points or more among patients with suspected infections (10). We extracted the septic patients according to disease names recorded in electronic medical records. And we excluded the patients who were not willing to be treated, in cardiopulmonary arrest on hospital arrival, died within 24 hours after hospital admission, and did not have procalcitonin value on next day in this study. We defined patients 18–74 years old as adults and those 75 years and older as elderly. We have measured procalcitonin in all patients with suspected infection at our institution during study period. We measured the procalcitonin value in blood in sepsis patients on hospital admission and the next day. We divided the foci of infection into abdomen, urinary tract, soft tissue, lungs, and others. We evaluated the severity of sepsis with the SOFA score (11). To measure the procalcitonin value in blood in sepsis patients, we used the commercially available Elecsys BRAHMS Procalcitonin electrochemiluminescence immunoassay device (Roche Diagnostics, Indianapolis, IN). The analytical measurement range of this device was 0.5–100 ng/mL. When the procalcitonin value in blood was greater than 100 ng/mL, we defined the value as 100 ng/mL. We also calculated the change in serum procalcitonin (ΔPCT) value in blood from the difference between the procalcitonin value on hospital admission and that measured the next day and defined it as ΔPCT. We defined the patients whose systolic blood pressure was less than 90 mm Hg on hospital admission as having hypotension. We diagnosed patients with a disseminated intravascular coagulation (DIC) score of 4 or higher as having DIC (12). We collected blood from two different sites for blood culture. A positive blood culture was defined as the presence of bacteria in both sets of blood cultures (13). The study protocol was approved by the Institutional Review Board of Kansai Medical University (Approval Number: 2018239), which waived the need to obtain patient written informed consent because of the observational nature of the study.

Outcome

The outcome of this study was mortality at 28 days after hospital admission.
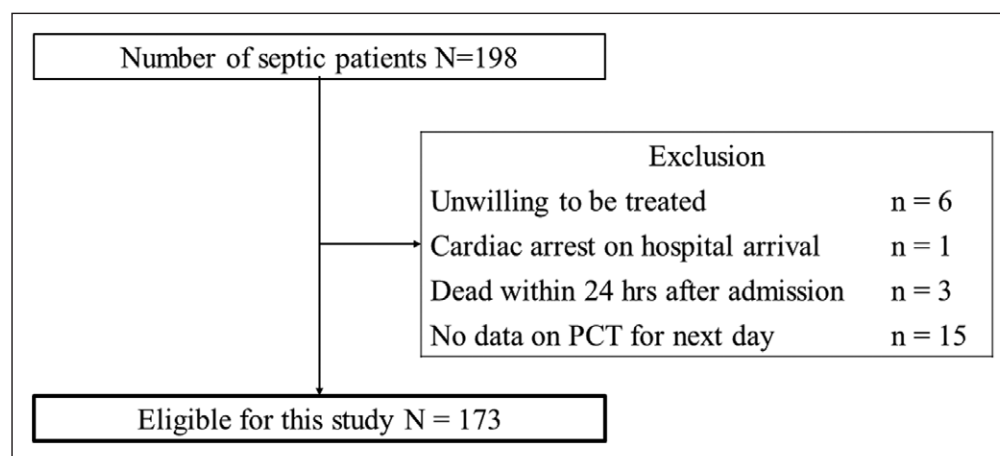
Statistical Analysis

Continuous variables are presented as the median and interquartile range (IQR) and categorical variables as

counts and percentages. We assessed the relationship between variables and outcome with univariate logistic regression analysis and calculated the crude odds ratio (OR) and 95% CI. The variables that we assessed were age group, sex, cause of sepsis, hypotension, systemic inflammatory response syndrome, DIC, blood culture, and procalcitonin value on hospital admission. We used the receiver operating characteristic (ROC) analysis and regression tree analysis (14) to define the cutoff value of procalcitonin on hospital admission. In the ROC analysis, we evaluated the relationship between procalcitonin value on hospital admission and the outcome. In regression tree analysis, we used the items to be found at admission; DIC, SOFA score, procalcitonin value on hospital admission, and ΔPCT as variables. In this classification and regression tree analysis, we determined the bifurcation based on the likelihood ratio chi-square of each variable. We then evaluated the relationship with the outcome. All tests were two-tailed, and p values of less than 0.05 were considered statistically significant. All statistical analyses were performed with the use of JMP 14 (SAS Institute, Cary, NC).

This article was written based on the Strengthening the Reporting of Observational Studies in Epidemiology statement to assess the reporting of cohort and cross-sectional studies (15).

RESULTS

Figure 1 shows the patient flow in this study. In total, 198 patients were diagnosed as having sepsis. We excluded six patients who were not willing to be treated, one patient with cardiac arrest on hospital arrival, three patients dead within 24 hours after hospital admission, and 15 patients who had no data on procalcitonin values in blood on the next day. We thus included 173 patients in this study.

Table 1 shows the baseline characteristics in the sepsis patients in this study. The median age was 74 years old (IQR, 64–79 yr old), and there were 102 men (59.0%). The most common focus of sepsis was the abdomen in 74 patients (42.8%), followed by the urinary tract in 36 patients (20.8%). The number of patients with hypotension was 66 (38.2%) and that with DIC was 69 (39.9%). The median procalcitonin value in blood on hospital admission was 14.8 ng/mL (IQR, 3.5–78.4 ng/mL), and the median ΔPCT was 0.0 ng/mL (IQR, –4.5 to 5.2 ng/mL). The mortality rate at 28 days after hospital admission was 5.8% (10 patients died).

In ROC analysis, the cutoff value of procalcitonin on hospital admission was 31.6 ng/mL (area under the curve, 0.65). In regression tree analysis, the cutoff value of procalcitonin on hospital admission was 33.2 ng/mL and that of ΔPCT was 0.0 ng/mL. The cutoff value of procalcitonin on hospital admission was almost the same between the two analyses. Because we focused on not only the procalcitonin value on hospital admission but also ΔPCT, we used the result of regression tree analysis as the cutoff value in our study (Fig. 2).

Table 2 shows the results of univariate logistic regression analysis. Elderly (crude OR, 5.314; 95% CI, 1.094–25.806; p = 0.044), procalcitonin value in blood of less than 33.2 ng/mL on hospital admission (p = 0.007), and ΔPCT of less than 0.0 ng/mL (crude OR, 5.056; 95% CI, 1.041–24.545; p = 0.046) were associated with mortality at 28 days after hospital admission in this study.

Figure 3 shows a scatter plot of the relationship between the procalcitonin value in blood on hospital admission and ΔPCT. Among the patients with a procalcitonin value in blood of less than 33.2 ng/mL on hospital admission, we classified those with ΔPCT of less than 0.0 ng/

Figure 1. Patient flow in this study. One-hundred ninety-eight patients were diagnosed as sepsis during study periods. We excluded six patients with unwilling to be treated, one patient with cardiac arrest on hospital arrival, three patients with dead within 24 hr after admission, and 15 patients with no data on procalcitonin (PCT) for next day. We finally included 173 patients in this study.

TABLE 1.
Baseline Characteristics of the Patients With Sepsis in This Study

Variables	All Patients (n = 173)	Survival Patients (n = 163)	Nonsurvival Patients (n = 10)	p
Age, yr, median (IQR)	74 (64–79)	73 (63–79)	82 (75–90)	0.007
Male, n (%)	102 (59.0)	96 (58.9)	6 (60.0)	1.000
Focus of sepsis, n (%)				0.397
Abdomen	74 (42.8)	68 (41.7)	6 (60.0)	
Urinary tract	36 (20.8)	26 (20.0)	0 (0.0)	
Soft tissue	20 (11.6)	19 (11.7)	1 (10.0)	
Respiratory system	17 (9.8)	15 (9.2)	2 (20.0)	
Others	26 (15.0)	35 (21.5)	1 (10.0)	
Hypotension, n (%)	66 (38.2)	60 (36.8)	6 (60.0)	0.184
Disseminated intravascular coagulation, n (%)	69 (39.9)	65 (39.9)	4 (40.0)	1.000
Blood culture (positive), n (%)	57 (32.9)	53 (32.5)	4 (40.0)	0.731
Lactate level[a] (mg/dL), median (IQR)	23.0 (15.0–47.5)	23.0 (15.0–47.0)	40.0 (16.8–72.8)	0.189
Procalcitonin level on hospital admission (ng/mL), median (IQR)	14.8 (3.5–78.4)	15.6 (3.9–81.2)	8.7 (1.4–23.8)	0.124
Change in serum procalcitonin[b] (ng/mL), median (IQR)	0.0 (−4.5 to 5.2)	0.0 (−4.3 to 5.6)	−1.9 (−5.9 to 0.4)	0.507
Sequential Organ Failure Assessment score, median (IQR)	7 (4–9)	7 (4–9)	8 (6–12)	0.217
Mortality on 28 d after hospital admission, n (%)	10 (5.8)			

IQR = interquartile range.
[a]Date of lactate levels in four patients were missing.
[b]Change in procalcitonin value in blood between hospital admission and the next day.

mL as group A1 and those with ΔPCT of greater than or equal to 0.0 ng/mL as group A2. In the patients with a procalcitonin value in blood of greater than or equal to 33.2 ng/mL on hospital admission, we classified those with a ΔPCT of 0.0 ng/mL as group B1 and those with a ΔPCT of greater than or equal to 0.0 ng/mL as group B2.

The mortality rate of group A1 was 18.6% (8/43) and that of group A2 was 3.2% (2/62). In contrast, the mortality rate of group B1 and that of group B2 were both 0.0%. The patients in group A1 had significantly higher mortality than the other patients (p < 0.001) (Figs. 2 and 3).

DISCUSSION

Our results suggested that the procalcitonin value in blood on hospital admission and the change in the procalcitonin value on the next day may be useful as an indicator of the necessity for early therapeutic intervention for sepsis and could lead to improvement in the prognosis of sepsis patients.

In our study, a procalcitonin value in blood of less than 33.2 ng/mL on hospital admission was associated with mortality at 28 days after hospital admission. The following three mechanisms may be responsible for this result. First, severe sepsis patients may not be able to produce inflammatory cytokines including TNF-α
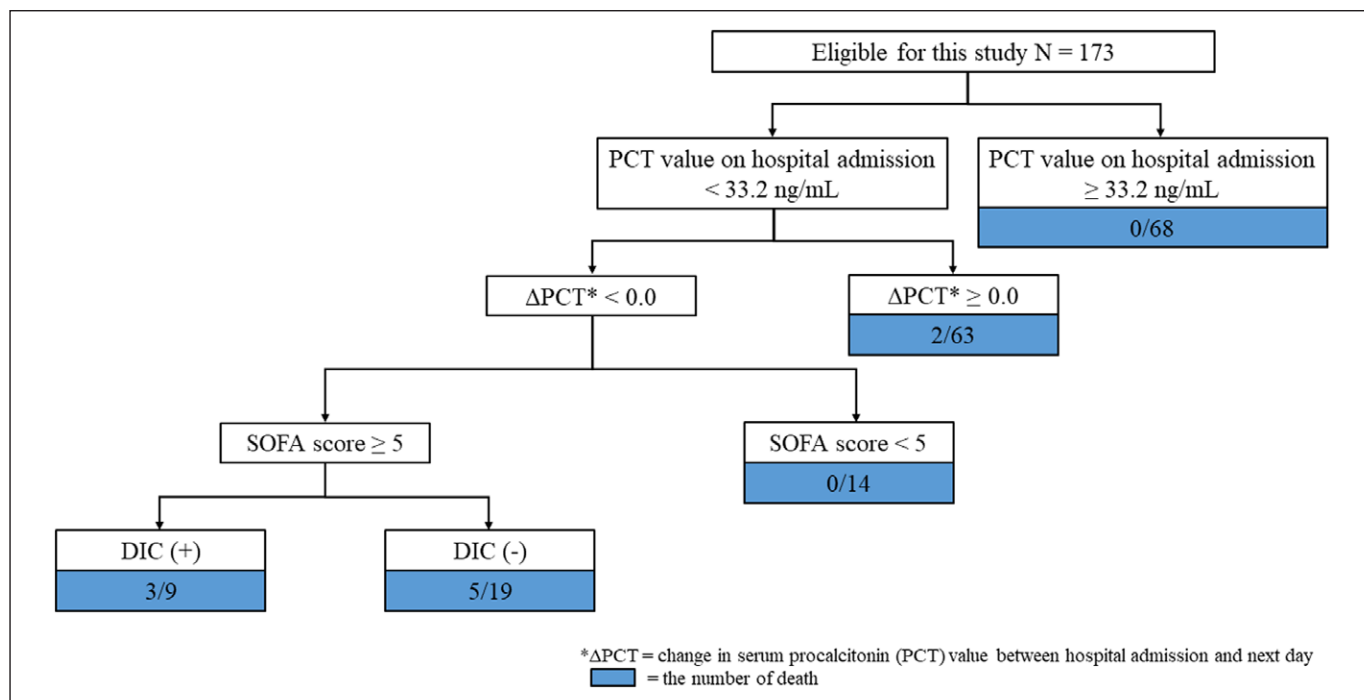
Figure 2. Result of regression tree analysis. DIC = disseminated intravascular coagulation, PCT = procalcitonin, SOFA = Sequential Organ Failure Assessment, ΔPCT = change in serum procalcitonin.

despite the expression of Toll-like receptor (TLR) and to produce procalcitonin. Antigen-presenting cells such as macrophages recognize pathogen-associated molecular patterns and damage-associated molecular patterns via TLR in systemic bacterial infection, and antigen-presenting cells produce inflammatory cytokines such as TNF-α. However, a previous study showed that the expression of TLRs was not necessarily associated with the synthesis of proteins such as cytokines in sepsis patients (16). Particularly, the production of inflammatory cytokines by monocytes in severe sepsis patients was significantly lower than that in healthy patients (17). Second, some sepsis patients in our study may have been complicated with organ dysfunction that affected the production of inflammatory cytokines such as TNF-α. As a result, the patients whose procalcitonin value in blood on hospital admission was less than 33.0 ng/mL might have organ dysfunction and higher mortality. Finally, in these patients, severe sepsis may lead to excessive production of anti-inflammatory cytokines including interleukin (IL)-10, which may be suppressed immune function and damaged some organs. Indeed, when the inflammatory response persists, IL-10 is produced by not only type-II T-helper cells but also some type-I T-helper cells that acquire the ability to produce IL-10 (18).

This causes an immunosuppressive status and the prolongation of infection, and the complication of another new infection could lead to progressive organ dysfunction (19).

Some previous studies reported that the high procalcitonin value on hospital admission was associated with poor outcome among septic patients (20–25). There is a reason why our result differed from these previous studies. The reason was the cause of sepsis in our study differed from that in previous studies. Respiratory infections were the most common in previous studies, but most of the diseases were abdominal and urinary tract infections in our study. Differences in mortality of septic patients depending on the focus of infection have been reported previously (26–30). Esper et al (28) reported that septic patients with respiratory infection had higher rates of acute organ dysfunction and higher mortality rates compared with other sources of infection. The median of SOFA score among the patients with respiratory infection was higher than other sources of infection in this study. Therefore, the mortality rate of patients with respiratory infection may have higher than that of the patients with other sources of infection (**Supplemental Table 1**, http://links.lww.com/CCX/A452). On the other hand, a previous study showed the patients with urinary tract

TABLE 2.
Factors Associated With Mortality at 28 Days After Hospital Admission in the Patients With Sepsis

Variables	Mortality Rate, % (n/n)	Crude OR (95% CI)	p
Age group, n (%)			
16–74 yr old	2.1 (2/95)	Reference	
≥ 75 yr old	10.3 (8/78)	5.314 (1.094–25.806)	0.044
Gender, n (%)			
Male	5.9 (6/102)	1.047 (0.284–3.853)	1.000
Female	5.6 (4/71)	Reference	
Cause of sepsis, n (%)			
Abdomen	8.1 (6/74)	0.324 (0.037–2.796)	0.250
Urinary tract	2.8 (1/36)	Reference	
Soft tissue	5.0 (1/20)	0.543 (0.032–9.176)	0.674
Respiratory system	11.8 (2/17)	0.214 (0.018–2.547)	0.206
Others	0.0 (0/26)	NA	0.990
Hypotension, n (%)			
Hypotension (+)	9.1 (6/66)	2.575 (0.699–9.492)	0.184
Hypotension (−)	3.7 (4/107)	Reference	
DIC, n (%)			
DIC (+)	5.8 (4/69)	1.005 (0.273–3.701)	1.000
DIC (−)	5.8 (6/104)	Reference	
Blood culture, n (%)			
Blood culture (+)	7.0 (4/57)	1.384 (0.374–5.112)	0.731
Blood culture (−)	5.2 (6/116)	Reference	
Procalcitonin value on hospital admission, n (%)			
Procalcitonin value < 33.2 ng/mL	9.5 (10/105)	NA	0.007
Procalcitonin value 33.2 ng/mL	0.0 (0/68)		
ΔPCT[a], n (%)			
ΔPCT < 0.0 ng/mL	10.0 (8/80)	5.056 (1.041–24.545)	0.046
ΔPCT ≥ 0.0 ng/mL	2.2 (2/93)	Reference	

DIC = disseminated intravascular coagulation, NA = not applicable, OR = odds ratio, ΔPCT = change in serum procalcitonin.

[a]Change in procalcitonin value in blood between hospital admission and the next day.
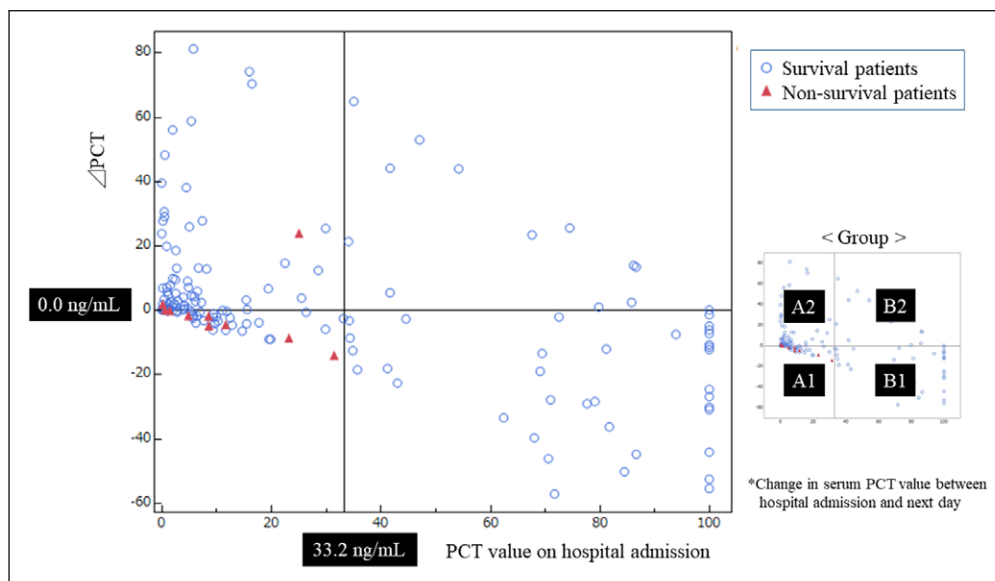
Figure 3. Scatter plot of the relationship between procalcitonin (PCT) value in blood on hospital admission (*horizontal axis*) and change in serum procalcitonin (ΔPCT) (*vertical axis*). *Circles* indicate survival patients, and *triangles* indicate nonsurvival patients.

infection had a better prognosis than patients with other sources of infection (29). The anatomic structure of the genitourinary tract or the washout by urinary excretion of the patients may prevent bacterial invasion and limit absorption of microbes and bacterial toxins (30). Patients with abdominal infection were often performed surgical treatment including drainage for the site of infection. The treatment may affect the mortality rate by preventing bacterial invasion and limiting absorption of microbes and bacterial toxins.

In the subgroup analysis, the prognosis of the patients in group B was better than that of those in group A. In the subgroup analysis of patients in group A, the prognosis of the patients with an increase of ΔPCT (group A2) was better than that of those with a decrease of ΔPCT (group A1). The patients in group B would have had to be in relatively good general condition to produce procalcitonin. However, there may have been a mixture of patients with relatively mild sepsis and those with severe sepsis in group A. The procalcitonin value in blood increased along with the exacerbation of sepsis in the patients with relatively mild sepsis. However, in the severe sepsis patients who were too ill to produce procalcitonin, the procalcitonin value in blood on hospital admission was low and may not have been able to increase thereafter.

The relationship between the procalcitonin value in blood on hospital admission and the subsequent changes in procalcitonin value and the prognosis of

sepsis patients has not been revealed. However, a previous study reported that the procalcitonin value in blood on hospital admission did not correlate with the severity of sepsis (21), but there may have been mixture of patients with mild and with extremely severe sepsis in the group of the patients with low procalcitonin value on hospital admission. Thus, our results indicate that the combination of procalcitonin value in blood on hospital admission and the subsequent change of procalcitonin value may reflect the severity of sepsis and may potentially contribute to improvement of the prognosis of sepsis patients.

This study has some limitations. First, this study was a single-center retrospective observational study and the number of participants in this study was not many. Therefore, the general validity of these results was low, and so a multicenter, prospective cohort study is needed to validate the results of this article. Second, we could not investigate the relationship between the production of inflammatory cytokines and procalcitonin values. Inflammatory cytokines are involved in procalcitonin production, and further studies may be needed to determine the prognostic relationship between these and sepsis patients. Third, because the limit of measurement of procalcitonin value in blood was 100 ng/mL, it is unclear about the relationship between procalcitonin overproduction and the prognosis of patients with sepsis. Fourth, we were not able to put past medical history into the decision tree analysis because we did not have the data about patient's past medical history. Last, this study was a retrospective observational study, and there may be unknown confounding factors in this study.

CONCLUSIONS

Our study showed that sepsis patients with a procalcitonin value in blood of less than 33.2 ng/mL on hospital

admission and a ΔPCT of less than 0.0 ng/mL on the next day had high mortality at 28 days after hospital admission. The combination of procalcitonin value on hospital admission and subsequent change in the procalcitonin value may be associated with the prognosis of sepsis.

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