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**Title:**

# Impact of serial measurements of lysophosphatidylcholine on 28-day mortality prediction in patients admitted to the intensive care unit with severe sepsis or septic shock

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**Abstract**

Purpose: To investigat the effect of serial lysophosphatidylcholine (LPC) measurement on 28-day mortality prediction in patients with severe sepsis or septic shock admitted to the medical intensive care unit (ICU).

Methods: Prospective observational study of 74 ICU patients in a tertiary hospital. Serum LPC, white blood cell, C-reactive protein and procalcitonin levels were measured at baseline (day 1 of enrollment) and day 7. LPC concentrations were compared with inflammatory markers using their absolute levels and relative changes.

Results: The LPC concentration on day 7 was significantly lower in non-survivors than in survivors (68.45 ± 42.36 μmol/L and 99.76 ± 73.65 μmol/L; P= 0.04). A decreased LPC concentration on day 7 to its baseline, as well as a sustained high concentration of procalcitonin on day 7 at more than 50 % of its baseline value, was useful for predicting the 28-day mortality. Prognostic utility was substantially improved when combined LPC and procalcitonin criteria were applied to 28-day mortality outcome predictions. Further, LPC concentrations increased over time in patients with appropriate antibiotics, but not in those with inappropriate antibiotics.

Conclusions: Serial measurements of LPC help in the prediction of 28-day mortality in ICU patients with severe sepsis or septic shock.

Key word: lysophosphatidylcholine;mortality;severe sepsis;septic shock;intensive care unit

## Introduction

Sepsis, the leading cause of death in intensive care unit (ICU) patients, shows a severity-related hospital mortality rate ranging from 25% to 60% [1]. Dysregulation of the host immune response plays an important role in the pathogenesis of sepsis. Recently, the systemic effects of pro-inflammatory and anti-inflammatory cytokines and mediators have been closely linked to mortality in patients with sepsis [2]. Several inflammatory lipid mediators derived from the metabolism of membrane phospholipids have been established as regulatory factors in several inflammatory states including sepsis [3].

Recent data suggested that lysophosphatidylcholine (LPC) may be an important mediator in the septic process [4]. LPC, which is generated by the action of phospholipase A2 on phosphatidylcholine (PC), has a potent pro-inflammatory effect that is mediated by the upregulation of endothelial cell adhesion molecules, growth factors, and various immune cells [5-7]. LPC is also implicated in various inflammatory processes such as atherosclerosis and systemic autoimmune disease [8, 9]. However, evidence suggests that LPC may also have immunosuppressive functions. Previous studies indicate that LPC has a high affinity for immunoregulatory receptor G2A [4], and that G2A-deficient mice develop an autoimmune syndrome with the activation of lymphocytes and hyper-responsive T cells [10]. Furthermore, decreased LPC concentrations may enhance lysophosphatidic acid production by the activation of lysophospholipase D [11]. Lysophosphatidic acid subsequently induces an immune response by activating various immune cells, such as T and B cells, and macrophages [12]. Hence, LPC depletion may be closely related to the development of sepsis by promoting excessive immune responses.

Previous reports have showed that LPC levels might be useful for discriminating patients with sepsis from those without sepsis [13, 14]. However, we have recently suggested that a single measurement of LPC concentrations at baseline was insufficient to predict mortality [13]. Because the prognostic utility of LPC measurement in patients with sepsis remains to be elucidated, the aim of the present study was to evaluate whether serial measurements of LPC improved prediction of 28-day mortality in ICU patients with severe sepsis or septic shock.

## Materials and Methods

### Study population

We conducted a prospective observational study on medical ICU patients at the Asan Medical Center of Ulsan

University, Seoul, South Korea, from September 2007 to November 2010. The inclusion criteria for the study were age above 18 years, and the presence of severe sepsis or septic shock within the first 24 h of ICU admission. Severe sepsis was defined as the presence of sepsis associated with any organ dysfunction and septic shock was defined as sepsis with requirement of vasopressor support or with hypotension despite fluid resuscitation according to the Consensus Conference Criteria [15]. Patients were excluded in cases of clearly irreversible conditions, advanced cancer, withdrawal of life support, and immunosuppression. They were observed for at least 28 days from enrollment or until death or discharge from the hospital. Patients were classified as either survivors or non-survivors according to the 28-day postenrollment outcome. Informed consent was obtained from all patients or their relatives before enrollment and the study protocol was approved by the institutional review board of Asan Medical Center.

**Study protocol**

At time of enrollment, all included patients had to have a microbiologically confirmed or definite clinical relevance of infections, and fulfillment of at least two criteria of systemic inflammatory response syndrome within the first 24 h of ICU admission. Microbiological cultures were performed as previously described [13]. We recorded variables including age, sex, Charlson comorbidity index, patient location before ICU admission, infection source, microbiological culture results, adequacy of initial antibiotics on admission, and ICU stay management. The Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scoring systems were used to determined the severity of the patient's condition at baseline (day 1 of enrollment), and SOFA was also measured on day 7. Patients were treated with the standard therapy for severe sepsis and septic shock, according to international guidelines [16]. We encouraged that the measurement of inflammatory markers, including white blood cell (WBC) count, C-reactive protein (CRP), procalcitonin (PCT), and serum LPC concentrations of all enrolled patients on days 1 and 7 be performed at the same time. All clinicians participating in the study were blinded to the LPC results.

**Measurements of inflammatory markers and LPC**

We identified 74 consecutive patients with severe sepsis or septic shock. Serum LPC concentrations, WBCs, CRP were measured in all enrolled patients, and PCT was measured in 54 patients on day 1. On day 7, measurements of LPC concentrations and WBC were repeated in all enrolled patients. Among 74 enrolled

patients, on day 7, measurements of CRP and PCT were repeated in 69 and 43 consecutive patients, respectively. All blood samples were immediately delivered to a central laboratory and centrifuged plasma was stored at -80 °C within 2 h of withdrawal. PCT was measured by immunoassay (ADVIA Centaur XP, Siemens Healthcare Diagnostics GmbH, Eschborn, Germany) and CRP by immunoturbidimetric latex CRP assay (Cobas 8000, Roche-Diagnostics, Basel, Switzerland). The values of PCT <0.5 ng/mL and CRP levels <0.6 mg/dL were considered to be within normal reference ranges, according to the manufacturer's instructions. LPC concentrations were measured with an enzyme-linked immunosorbent assay (ELISA) kit (ANZWELL LPC Assay Kit: Alfresa Pharma Corporation, Osaka, Japan) [17].

**Statistical analysis**

We used SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA) for all statistical analyses after testing for a normal distribution using the Kolmogorov-Smirnov test. Continuous variables were compared with the *t* test or Mann–Whitney nonparametric *U*-test and categorical variables were compared with the chi-square ($\chi^2$) or Fisher's exact tests. All nominal variables were expressed as frequencies. Continuous variables were expressed as means ± standard deviations, if normally distributed. Repeated-measures ANOVA were performed to investigate the difference in the time course of various markers between survivors and non-survivors. We compared the patient characteristics between survivors and non-survivors using univariate analysis and estimated receiver operating characteristics (ROC) curves to evaluate the predictive ability of LPC and inflammatory markers for 28-day mortality.

In addition to absolute levels on days 1 and 7, we compared LPC concentrations with other inflammatory markers using their relative changes between days 1 and 7. Serum levels of CRP, PCT, and LPC on day 7 were normalized to their baseline values (i.e. divided by the values on day 1, then multiplied by 100) and were expressed as percentage of baseline (POB). LPC concentrations in patients with sepsis were significantly lower than those without sepsis [13]. And we hypothesized that persistent LPC depletion could be related to poor outcome. To simplify the variation of relative changes in LPC, we predefined five criteria of LPC-POB (≤50%, ≤75%, ≤100%, ≤125%, ≤150%). In contrast, pre-existing inflammatory markers such as CRP and PCT were increased as the infection became more severe. Therefore, we predefined the criteria as ≥50%, ≥75%, ≥100%, ≥125% and ≥150%. The POBs with the highest predictive power were determined from the predefined criteria, using the area under the ROC curve. From all these analysis, variables with *P*-values < 0.05 in univariate

analysis were subjected to multivariate logistic regression analysis to identify the independent predictors of 28-day mortality and their adjusted odds ratios (ORs) with 95% confidence intervals (CIs). In all tests, $P < 0.05$ was considered significant.

## Results

### Clinical characteristics of the study population

This study comprised 74 patients (mean age, 69.1 ± 10.8 years; 60 men) meeting the definitions of severe sepsis or septic shock. The baseline characteristics of the patients are listed in Table 1. On day 28, sepsis-related mortality in this group was 27.0% and the mortality rate by sepsis severity was 24.3 % in severe sepsis, and 29.7 % in septic shock groups. The mean SOFA, APACHE II, and Charlson comorbidity index were 9.39 ± 3.43, 23.46 ± 5.52, and 2.98 ± 1.99 in survivors and 11.35 ± 3.66, 26.45 ± 5.92, and 4.25 ± 2.27 in non-survivors, respectively ($P = 0.035$, $P = 0.046$, and $P = 0.022$, respectively; Table 1). The most common source of infection was pulmonary. Of all infections, 21 (28.4%) were caused by gram-positive bacteria and 17 (23.0%) by gram-negative bacteria. No pathogens were identified in 26 patients (35.1%). 48 patients had documented infection. Appropriate antibiotics were administered to 40 patients (83.3 %) and 8 (16.7 %) were given inappropriate antibiotics on ICU admission. There were no significant differences in ICU management between survivors and non-survivors.

### Absolute levels of WBCs, CRP, PCT, and LPC as prognostic markers

No inflammatory biomarker showed a satisfactory 28-day mortality predictive ability on day 1 (Fig 1). On day 7, high levels of LPC concentrations were only predictive of 28-day mortality. LPC concentrations showed a significantly upward trend in survivors over time, which was not observed in non-survivors ($P = 0.014$, Fig 1A). On day 7, LPC concentrations in non-survivors were significantly lower than those in survivors. The LPC concentrations on day 7 were 68.45 ± 42.36 μmol/L in non-survivors and 99.76 ± 73.65 μmol/L in survivors ($P = 0.04$, Fig. 1A). In contrast, the trend of other inflammatory markers did not show any significant differences between non-survivors and survivors. The mean CRP levels on day 7 in non-survivors (10.83 ± 6.92 mg/dL) were not significantly higher than those of survivors (8.32 ± 8.19 mg/dL; $P = 0.071$; Fig. 1B). The mean PCT levels on day 7 in non-survivors were 4.89 ± 5.42 ng/mL, which was not significantly higher than those of survivors (3.35 ± 8.83 ng/mL; $P = 0.091$; Fig. 1C). No significant difference in WBC counts was observed

between survivors and non-survivors (Fig. 1D).

**POB in WBCs, CRP, PCT, and LPC as a prognostic marker**

All baseline values of biomarkers in patients were higher than normal reference ranges. The most suitable criteria for each marker are indicated in Table 2. A decreased LPC concentration on day 7 to its baseline was useful for predicting 28-day mortality (LPC-POB on day 7 ≤100%; $P = 0.023$). An increase in the PCT value on day 7 at more than 50% of its baseline predicted 28-day mortality with a sensitivity of 76.5% and specificity of 69.2% (PCT-POB on day 7 ≥50%; $P = 0.012$).

**Combined use of PCT and LPC in POB as a prognostic marker**

Outcome prediction considerably improved when LPC-POB and PCT-POB were combined. Using this predictive rule, the positive predictive value (PPV) to 28-day mortality increased to 81.8% in patients with LPC-POB ≤100% and PCT-POB ≥ 50% on day 7. Although the sensitivity in combined criteria was relatively low, more than 90% of severe sepsis patients who finally survived on day 28 could be identified (specificity 92.3%). Accordingly, patients with LPC-POB ≤100% and PCT-POB ≥50% on day 7 showed a high 28-day mortality of 72.7%. In contrast, patient in which only one of these two criteria was fulfilled showed a lower mortality rate of 42.9% (Fig. 2).

**Multivariate comparisons of LPC and clinical severity scores**

On day 1, the Charlson comorbidity index, APACHE II, and SOFA scores were significantly different between survivors and non-survivors in univariate analysis (Table 1). There was a significant difference in LPC concentrations on day 7 between survivors and non-survivors. We entered these variables into a logistic regression model for 28-day mortality prediction. Among these variables, a high Charlson comorbidity index remained independently associated with 28-day mortality. A 1-point increase in the Charlson comorbidity index resulted in a 1.332 OR of dying (95% CI, 1.035-1.713; $P = 0.026$). Based on univariate association between 28-day mortality and the concurrent use of both LPC-POB and PCT-POB criteria, we substituted LPC concentrations on day 7 with these two criteria in multivariate logistic regression model. Consequently, the Charlson comorbidity index was still independently associated with 28-day mortality (OR, 1.589, 95% CI, 1.029-2.452; $P = 0.027$). Furthermore, use of both LPC-POB ≤100% and PCT-POB ≥50% on day 7 was a strong

independent 28-day mortality predictor (OR, 10.487, 95% CI, 1.568-70.159; $P = 0.015$).

**LPC concentrations and other associations**

To evaluate the utility of LPC concentrations in predicting the outcome, we assessed the associations between LPC concentration and clinical severity scores (APACHE II and SOFA). Among inflammatory markers, PCT levels on day 1 had a significant association with SOFA scores on day 1 ($r = -0.385$, $P = 0.004$). However, there was no significant associations between LPC concentrations on day 1 and clinical severity scores including APACHE II and SOFA scores on day 1 ($r = 0.051$, $P = 0.666$; and $r = -0.106$, $P = 0.369$, respectively). LPC-POB on day 7 was negatively correlated with the differences between SOFA scores on days 7 and 1, but there was no significant difference ($r = -0.182$, $P = 0.121$). In addition, there was no correlation between LPC concentrations on day 1 and sepsis severity. The mean LPC concentration on day 1 was 61.92 ± 36.93 μmol/L in patients with severe sepsis and 58.26 ± 34.89 μmol/L in patients with septic shock ($P = 0.758$).

We performed a subgroup analysis to investigate whether serial LPC measurements would correlate with appropriateness of antibiotic use. LPC concentrations showed a significantly increasing trend in patients with appropriate antibiotics over time, but not in those with inappropriate antibiotics ($P = 0.046$, Fig. 3). On day 7, the mean LPC concentrations were 85.00 ± 54.76 μmol/L in the former and 54.19 ± 23.44 μmol/L in the latter group ($P = 0.016$, Fig. 3).

To assess the potential role of LPC as an inflammatory marker, we calculated the correlation between the levels of LPC and inflammatory markers. Significant inverse correlation was found between LPC concentrations and CRP and PCT levels, although significance was weak (r = -0.285, $P = 0.014$, and r = -0.290, $P = 0.034$, respectively; Fig. 4).

**Discussions**

We have shown here that LPC concentrations on day 7 were significantly lower in non-survivors than in survivors, although there was no difference in baseline LPC concentrations between survivors and non-survivors in ICU patients with severe sepsis or septic shock. A decreased concentration of LPC on day 7 to its baseline value, as well as a sustained high concentration of PCT on day 7 at more than 50% of its baseline value, was useful for predicting 28-day mortality. Prognostic utility was substantially improved when combined criteria of

LPC and PCT were applied to outcome prediction for 28-day mortality. Further, LPC concentrations increased between days 1 and 7 in patients with appropriate antibiotics, but not in those with inappropriate antibiotics.

Similar to our study, Drobnik et al. [14] conducted clinical research in patients with sepsis. They demonstrated in their published material that LPC-PC ratios, not absolute LPC concentrations, were significantly lower in non-survivors on day 4 and 11. This is the first study to use absolute concentrations of LPC and demonstrate that relative changes of LPC were predictive of 28-day mortality. We also confirmed the clinical utility of commercial ELISA kits for the prediction of 28-day mortality in sepsis patients. This could help physicians apply LPC measurements in clinical fields. Drobnik et al. explored LPC concentrations using tandem mass spectrometry, which is time-consuming and complicated [17]. In addition, we compared LPC concentrations, as a prognostic marker, along with commonly used inflammatory markers such as CRP and PCT. We considered various clinical factors that affect sepsis-related mortality, including comorbidity, management of ICU stay, and severity of sepsis. These are the main features of this study that deserve to be highlighted as they differentiate it from the study by Drobnik et al.

In the present study, no significant difference was observed between survivors and non-survivors in the absolute levels of inflammatory markers on day 1, even in LPC concentrations. Several studies have shown that sepsis patients with unfavorable outcomes usually have higher CRP and PCT levels at ICU admission or onset of sepsis than those with favorable outcomes, even after several days [18, 19]. However, some studies suggested no significant differences in the initial levels of both markers between survivors and non-survivors [20-22], which were consistent with our findings. To improve the efficacy of outcome predictions, repeated periodical measurements of markers have been used in several studies [20-22]. We analyzed the predictive value of LPC and other inflammatory markers expressed in POB during the first week of severe sepsis or septic shock for the mortality to day 28. PCT has been known as a diagnostic and prognostic marker in patient with severe sepsis and septic shock [18]. Using PCT-POB on day 7 exceeding 50% of its baseline value (PCT-POB on day 7 $\geq$50%) as prediction rule, the criterion had a moderate sensitivity of 76.5%, moderate specificity of 69.2%, and a PPV of 61.9% for predicting 28-day mortality. The PPV of patients to die to day 28 was substantially improved to 81.8% with high specificity (92.3%), when a decrease in LPC on day 7 to its baseline (LPC-POB on day 7 $\leq$100%) was additionally taken into account (Table 2). Along with these data, fulfillment of combined criteria also has a significant impact on 28-day mortality in enrolled subjects. The patients showing LPC-POB $\leq$100% and PCT-POB $\geq$50% on day 7 had a higher mortality of 72.7% compared with patients who fulfill only one of

this combined criteria (42.9%; Fig 3). These findings are in line with the results of multivariate logistic regression analysis. We found this prediction rule using combined criteria were predictive of 28-day mortality in patients with severe sepsis or septic shock.

Interestingly, the LPC concentrations in patients with appropriate antibiotics significantly increased over time, but not in those with inappropriate antibiotics. In management of sepsis, prompt initiation of appropriate antibiotic therapy is imperative. A body of evidences showed that inadequate antibiotic therapy is an important determinant of poor outcome [23]. Decreasing levels of biomarkers, such as PCT, after institution of antibiotics correlate well with adequacy of antibiotics and controlled infection [24]. Recent literatures suggested that guidance of antibiotics by PCT may help reduce antibiotic exposure in the critical care setting [25]. Although our study intervals have limited value for application to clinical strategy, our results indicate that increased levels of LPC might help confirm the effect of instituting adequate antibiotics. Therefore, monitoring of LPC could be a helpful tool to guide antibiotic treatment in ICU patients with sepsis.

Recent studies that evaluated the prognostic utility of serial measurement of inflammatory markers have shown that early changes of markers (less than 4 days) are more likely to be predictive of outcome in critically ill patients with sepsis [18, 26]. In contrast, one study by Claeys et al. [27] noted that CRP and PCT measurements during 5 days of treatment could not discriminate survivors from non-survivors in patients with septic shock. Another study showed that the predictive power of PCT for fatal outcome was the highest on day 6 in specific groups of septic shock patients [28]. In a previous report [14], measurements of LPC-PC ratios were repeated on day 4 and 11. The authors reported that significantly lower levels of LPC-PC ratios were observed on days 4 and 11 in non-survivors of sepsis, with the highest reduction on day 11, compared to survivors. Thus, we deduced that a time point between days 4 and 11 may be optimal, and finally selected 6 days as the appropriate time interval to assess relative changes in LPC concentrations when we designed this study. Our results showed that the relative changes of LPC on day 7 could predict 28-day mortality. However, considering the dramatic clinical course of severe sepsis and septic shock, LPC measurements over a shorter time period were recommended to improve clinical significance and outcome prediction.

We evaluated the potential role of LPC as an inflammatory marker, and found that LPC concentrations at baseline were significantly negatively correlated with those of CRP and PCT. This might reflect the potential of using LPC as an inflammatory marker. However, there was no significant correlation found between LPC concentrations and APACHE II and SOFA scores within 24 hr in our study. These findings might be related to

the mechanism of LPC, which acts on immunologically relevant cells and modulates immune responses in the pathophysiology of sepsis [5, 12]. The actual immunologic or inflammatory status of the septic process could be closely related to the LPC concentrations. On the other hand, current outcome prediction models (such as APACHE II scores) and organ failure scores (such as SOFA scores), calculating the prediction on values within 24 hr of ICU stay, could have a restricted value in reflecting ongoing immunologic and inflammatory status of sepsis patients, which are the critical determinants of organ damage and death. To overcome the limitation of clinical severity scores, it has been suggested to utilize serial monitoring of SOFA scores [29] and other methodology including inflammatory cytokines [30]. In this study, persistent LPC depletion may represent severe immunologic response in the septic process. These are consistent with our results showing negative correlation of the changes of LPC concentrations with differences of SOFA scores between days 1 and 7, although there was no significant difference.

Certain limitations to this observational study should be addressed. First, we only measured concentration of LPC on days 1 and 7. Relative changes of LPC concentrations at earlier time point, such as day 3 or 5, could provide better prediction of outcome and offer the clinician a greater opportunity to take appropriate actions during the drastic course of severe sepsis or septic shock. Further studies with more serial samples are required to elucidate the association between LPC dynamics and mortality. Second, our study was limited by its relatively small sample size, which influenced the prognostic power of the inflammatory markers to differentiate non-survivors from survivors. Third, we used a commercial LPC assay kit that analyzed the total LPC concentration and did not measure the specific forms of 12 different LPC species. Although this method is simple and can be applied conveniently in various clinical settings, accurate LPC assays such as tandem mass spectrometry are required to determine the effect of individual LPC species on mortality prediction. Fourth, it is difficult to apply our data to patients with sepsis not requiring ICU treatment or those in the surgical ICU.

In summary, we have demonstrated that serial LPC measurements help to predict 28-day mortality in sepsis cases. As a commonly used inflammatory biomarker, PCT is still useful in predicting outcome, and using combined criteria of serial LPC and PCT improves mortality prediction in patients with severe sepsis or septic shock.

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**Conflicts of interest**

none

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Figure Legends

Figure 1. Time course of WBC, CRP, PCT, and LPC levels in survivors versus nonsurvivors. White boxes depict survivors and gray boxes depict nonsurvivors. Box plots represent the 25$^{th}$ and 75$^{th}$ percentiles, with the internal horizontal line showing the median and the T bars showing the 10$^{th}$ and 90$^{th}$ percentiles. *$P$ < 0.05 for comparisons between groups on the same day using an independent $t$-test or Mann-Whitney $U$ test. $^{\dagger}P$ value refers to the difference in the time course of inflammatory markers between survivors and nonsurvivors using repeated-measures ANOVA. WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; LPC, lysophosphatidylcholine.

Figure 2. Combining trends in LPC and procalcitonin levels between days 1 and 7 to predict 28-day mortality. PCT, procalcitonin; LPC, lysophosphatidylcholine; POB, percentage of baseline.

Figure 3. Time course of LPC levels in patients with appropriate antibiotics and those with inappropriate antibiotics. White boxes depict patients with appropriate antibiotics and gray boxes depict patients with inappropriate antibiotics. Box plots represent the 25th and 75th percentiles, with the internal horizontal line showing the median and the T bars showing the 10th and 90th percentiles. *$P$ < 0.05 for comparisons between groups on the same day using an independent $t$-test. †$P$ value refers to the difference in the time course of LPC levels between patients with appropriate antibiotics and those with inappropriate antibiotics using repeated-measures ANOVA. LPC, lysophosphatidylcholine.

Figure 4. Correlation between the LPC concentration and inflammatory biomarkers (including C-reactive protein and procalcitonin) on day 1. LPC, lysophosphatidylcholine.

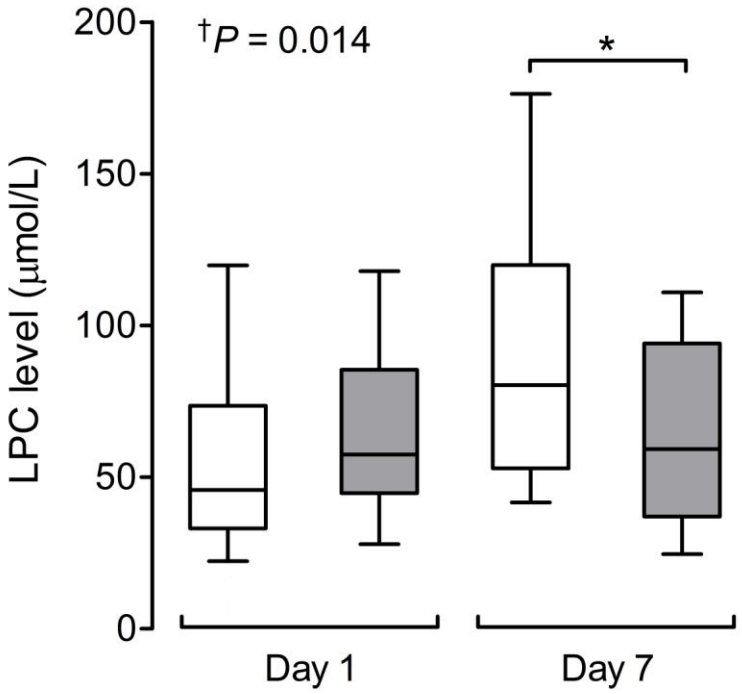


Figure 1A

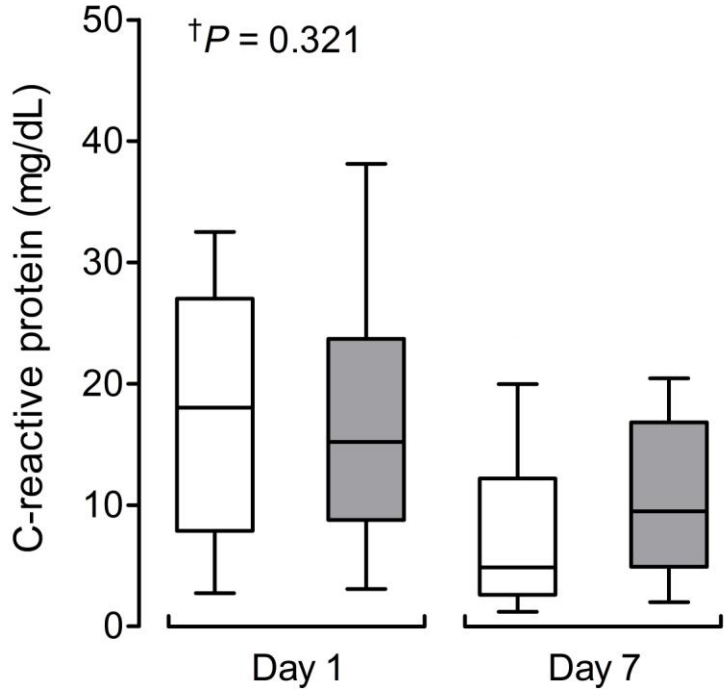


Figure 1B

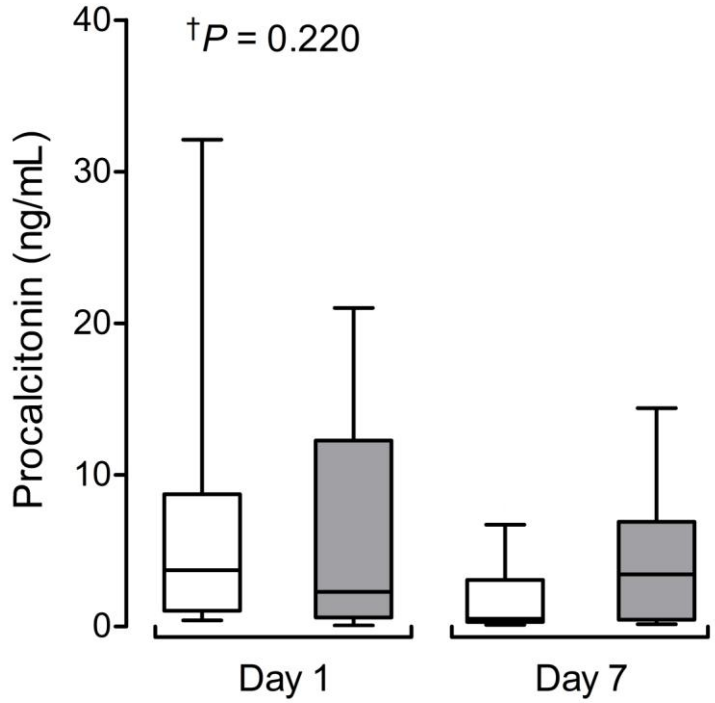


Figure 1C

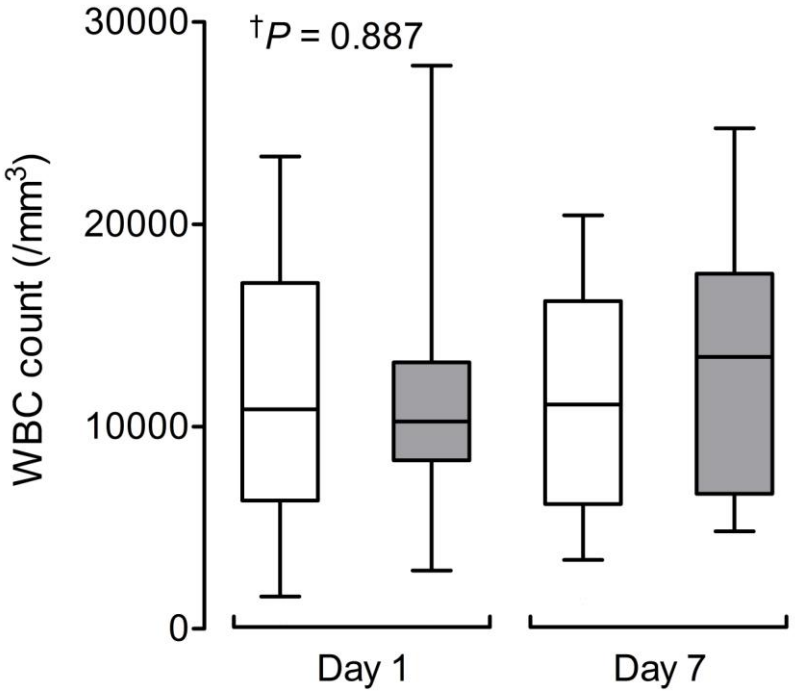


Figure 1D

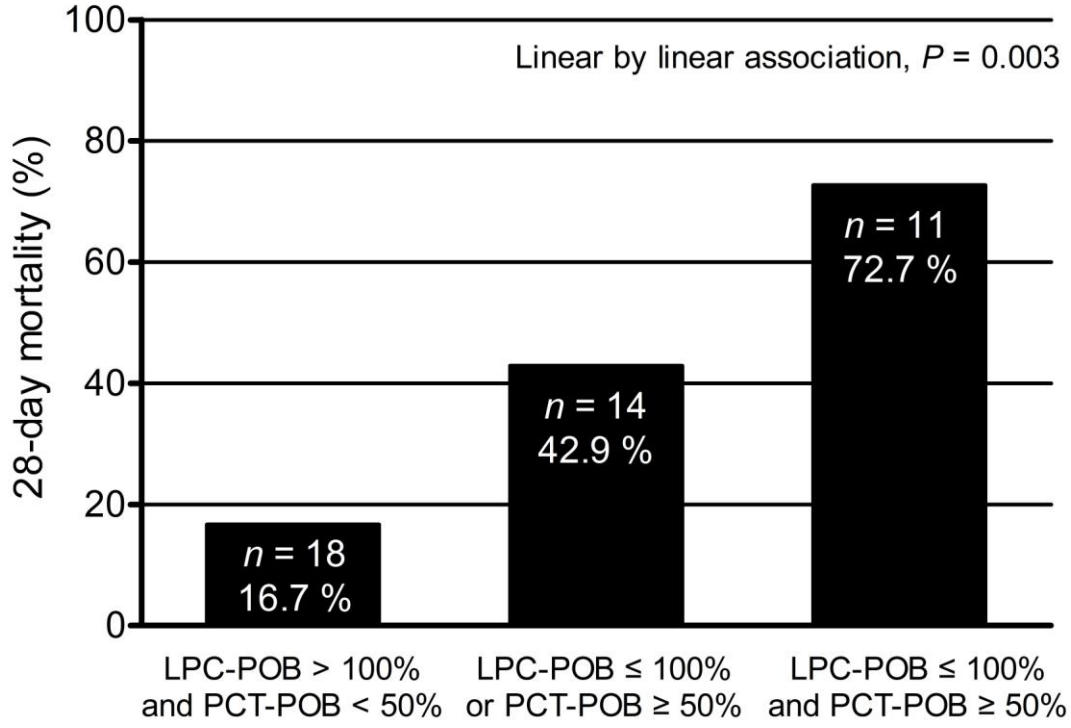


Figure 2

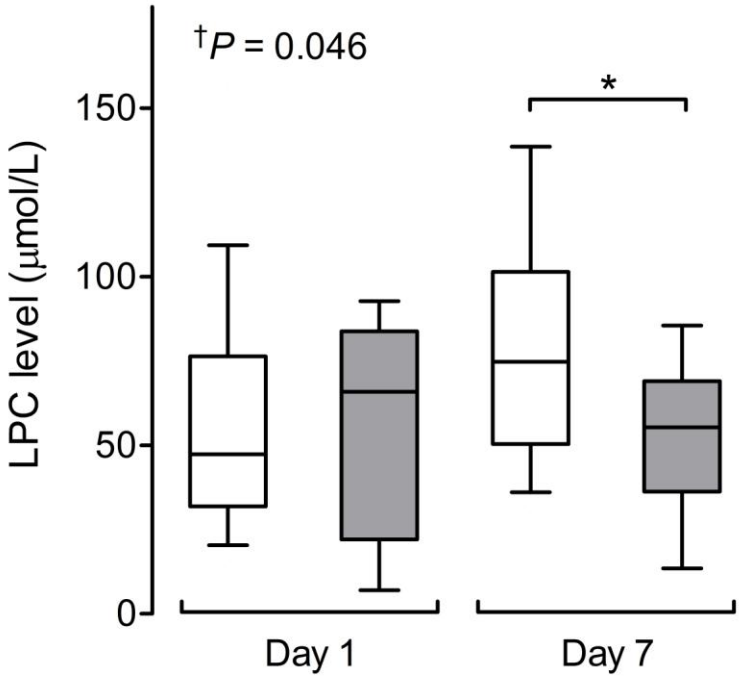


Figure 3

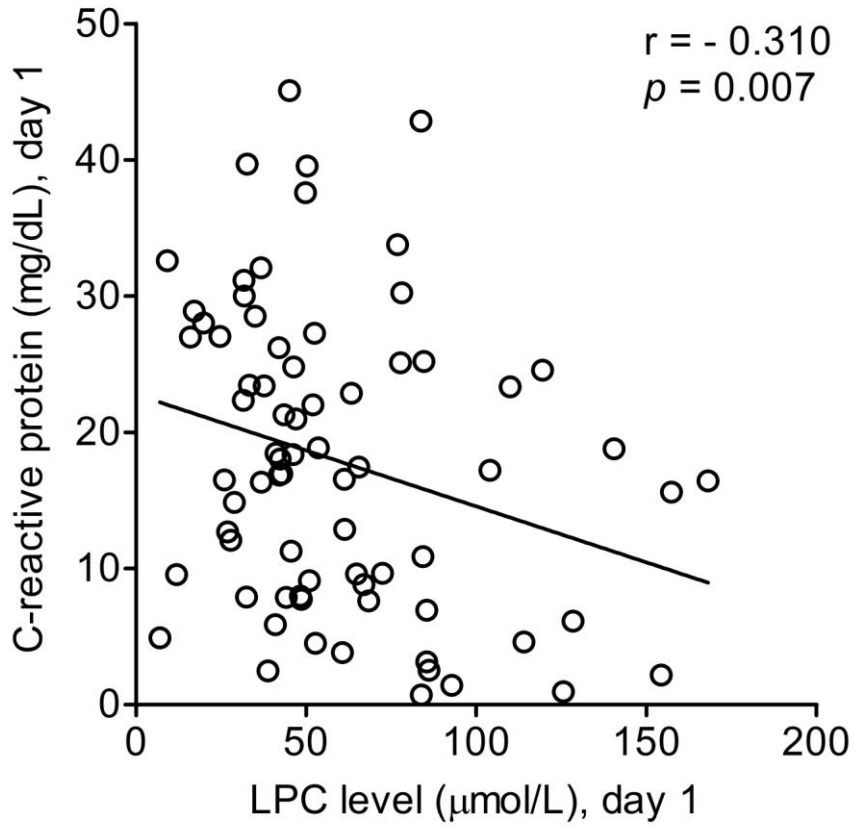


Figure 4A

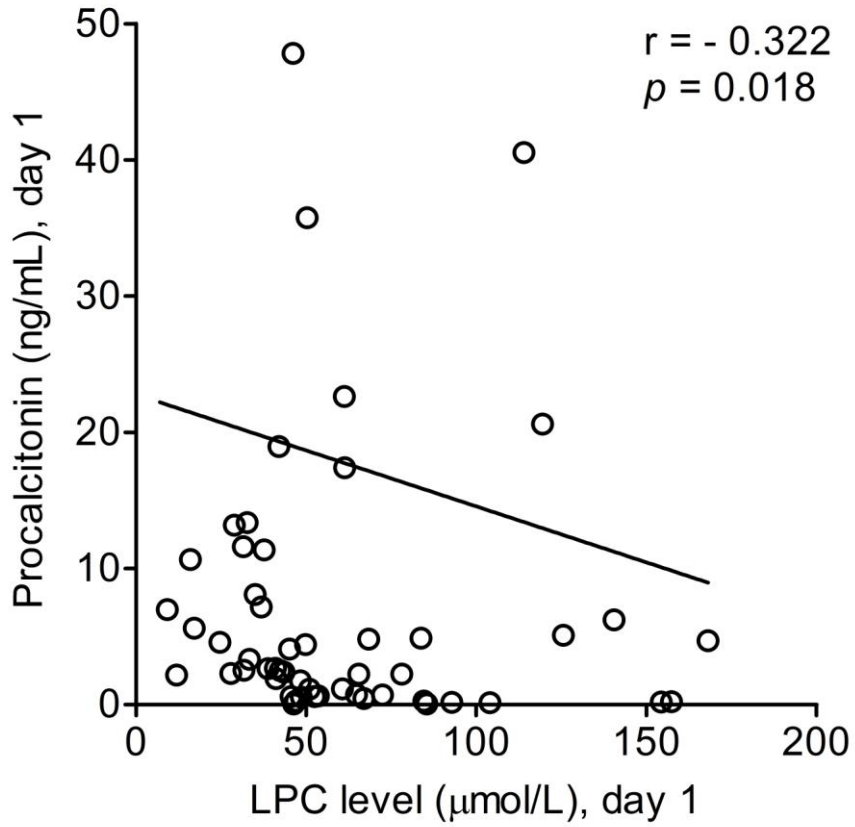


Figure 4B

Table 1 Clinical characteristics of the study patients with severe sepsis and septic shock admitted to the ICU

| Variable | All patients ($n$ = 74) | Survivors ($n$ = 54) | Non-survivors ($n$ = 20) |
|---|---|---|---|
| Age (years) | 69.1 ± 10.8 | 68.2 ± 11.9 | 71.5 ± 7.1 |
| Male | 60 (81.1) | 46 (85.2) | 14 (70.0) |
| Charlson comorbidity index | 3.32 ± 2.13 | 2.98 ± 1.99 | 4.25 ± 2.27* |
| Clinical severity score, day 1 | | | |
| SOFA score | 9.92 ± 3.57 | 9.39 ± 3.43 | 11.35 ± 3.66* |
| APACHE II score | 24.27 ± 5.75 | 23.46 ± 5.52 | 26.45 ± 5.92* |
| LOS, ICU (day) | 22.3 ± 20.6 | 25.0 ± 23.3 | 15.2 ± 5.8* |
| LOS, Hospital (day) | 62.5 ± 118.3 | 78.4 ± 135.3 | 19.5 ± 7.6* |
| ED at diagnosis | 49 (66.2) | 33 (61.1) | 16 (80.0) |
| Severe sepsis | 37 (50.0) | 28 (51.9) | 9 (45.0) |
| Septic shock | 37 (50.0) | 26 (48.1) | 11 (55.0) |
| Source of infection | | | |
| Pulmonary | 55 (74.3) | 42 (77.8) | 13 (65.0) |
| Urinary tract | 3 (4.1) | 2 (3.7) | 1 (5.0) |
| Skin and soft tissue | 3 (4.1) | 2 (3.7) | 1 (5.0) |
| GI & hepatobiliary | 4 (5.5) | 3 (5.6) | 1 (5.0) |
| Primary bacteremia | 3 (4.1) | 2 (3.7) | 1 (5.0) |
| Others[a] | 4 (5.5) | 3 (5.6) | 1 (5.0) |
| Unknown | 2 (2.7) | 0 (0.0) | 2 (10.0) |
| Positive culture, n (%) | | | |
| Gram-positive | 21 (28.4) | 17 (31.5) | 4 (20.0) |
| Gram-negative | 17 (23.0) | 12 (22.2) | 5 (25.0) |
| Others[b] | 12 (16.2) | 8 (14.8) | 4 (20.0) |
| Culture not obtained | 26 (35.1) | 18 (33.3) | 8 (40.0) |
| Management during ICU stay | | | |
| Appropriateness of antibiotics | 40 (83.3) | 30 (83.3) | 10 (83.3) |
| Vasoactive agent | 64 (86.5) | 46 (85.2) | 18 (90.0) |
| Norepinephrine | 61 (95.3) | 43 (93.5) | 18 (100.0) |
| Dopamine | 10 (15.6) | 9 (19.6) | 1 (5.6) |
| Vasopressor | 12 (18.8) | 7 (15.2) | 5 (27.8) |
| Number of vasopressors | 1.32 ± 0.47 | 1.33 ± 0.47 | 1.32 ± 0.48 |
| Inotropics (dobutamine) | 30 (41.1) | 24 (45.3) | 6 (30.0) |
| MV duration | 14.4 ± 8.4 | 14.6 ± 9.0 | 13.8 ± 7.0 |

Values are given as means ± standard deviations

*$P$ < 0.05

[a]Others : rickettsia, tsutsugamushi, osteomyelitis, encephalitis

[b]Others : rickettsia, tsutsugamushi, mycobacteria, fungus, viruses, mycoplasma, legionella

APACHE II, acute physiology and chronic health evaluation II; ED, emergency department; GI, gastrointestinal; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; SOFA, sequential organ failure assessment.

Table 2 Changes in the levels of inflammatory markers between day 1 and 7 as predictors of 28-day mortality using receiver operating characteristics (ROC) curves

| Inflammatory marker | AUC* | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | *P*-value |
|---|---|---|---|---|---|---|
| WBC-POB ≥ 100% | 0.569 | 60.0 | 53.7 | 32.4 | 78.4 | 0.368 |
| CRP-POB ≥ 50% | 0.619 | 61.1 | 62.7 | 36.7 | 82.1 | 0.135 |
| PCT-POB ≥ 50% | 0.729 | 76.5 | 69.2 | 61.9 | 81.8 | 0.012 |
| LPC-POB ≤ 100% | 0.673 | 55.0 | 79.6 | 50.0 | 82.7 | 0.023 |
| LPC-POB ≤ 100% and PCT-POB ≥ 50% | 0.707 | 52.9 | 92.3 | 81.8 | 75.0 | 0.013 |

*Based on ROC curves.

AUC, area under the receiver operating characteristic curve; POB, percentage of baseline; PPV, positive predictive value; NPV, negative predictive value; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; LPC, lysophosphatidylcholine.