Plasma Monocyte Chemoattractant Protein 1 as a Predictive Marker for Sepsis Prognosis: A Prospective Cohort Study

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Sepsis is a systemic host response to infection, and patients with sepsis are frequently handled in the intensive care unit. However, mortality related to sepsis remains high throughout the world. In addition, there have been no efficient prognostic biomarkers for sepsis to be employed in clinical practice. We therefore aimed to identify prognostic biomarkers for sepsis using the chemokine/cytokine array. This study included 143 patients with sepsis, who were divided into survivor and nonsurvivor groups according to their 28-day mortality status. The cytokine array analysis was performed with plasma samples from two randomly selected patients in each sepsis group. We thus identified seven cytokines with significantly and consistently different expression levels between nonsurvivors and survivors. The validity of the selected cytokines was then assessed by enzyme-linked immunosorbent assay (ELISA). We finally found monocyte chemoattractant protein 1 (MCP-1) as the most useful biomarker to distinguish the two sepsis groups; namely, non-surviving patients (n = 56) exhibited significantly higher plasma concentrations of MCP-1 compared to survivors (n = 87). MCP-1 is a CC chemokine, a potent chemoattractant that contributes to systemic inflammatory response syndrome. Areas under the receiver operating characteristic curves for prediction of 28-day mortality were 0.763 for MCP-1, 0.680 for the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score, 0.64 for the Sequential Organ Failure Assessment (SOFA) score, 0.621 for procalcitonin, and 0.785 for MCP-1 plus APACHE II score. In conclusion, we propose that plasma MCP-1 is a useful biomarker in predicting outcome of sepsis.

Keywords: biomarker, cytokine; monocyte chemoattractant protein 1 (MCP-1); protein array; sepsis

Introduction

Sepsis is a systemic host response to infection, and cases of sepsis are frequently handled in the intensive care unit (ICU). According to the results of epidemiological investigations in the United States and Europe, severe sepsis is a leading cause of mortality, with mortality rates varying from 30% to 50% depending on the hospital (Levy et al. 2010). Approximately 250,000 sepsis patients die in the United States each year (Gaieski et al. 2013). Sepsis develops very rapidly, even in cases where good monitoring measures and diagnostic technology are used. Moreover, morbidity and mortality related to sepsis remain high throughout the world. It can be difficult to predict the prognosis of patients with sepsis (Becker et al. 2008). Prognostic information is useful for reducing the mortality rate, to ensure the use of timely and effective treatments for patients at a high risk of death (Carlyn et al. 2015).

Dysregulation of the host inflammatory response to infectious agents is central to the mortality of patients with sepsis. Pro- and anti-inflammatory stages of the host immune response to sepsis often occur concurrently (Hotchkiss et al. 2013). Researchers have sought to identify biomarkers to distinguish or predict high-risk patients. Suitable biomarkers should be easily available and inexpensive. Cytokines have been widely assessed as potential biomarkers of sepsis severity. Studied cytokines have included procalcitonin (PCT), C-reactive protein (CRP), and interleukin (IL)-6, which reflect the inflammatory state in sepsis (Assicot et al. 1993; Lobo et al. 2003; Carlyn et al. 2015), as well as soluble triggering receptor expressed on myeloid cells 1 (sTREM-1) (Su et al. 2012) and IL-10 (Matera et al.
2013). Unfortunately, all of these cytokines lack sufficient specificity to enable accurate prognostic judgment.

In this pilot study, we aimed to identify novel cytokines that could be used as valuable plasma biomarkers to predict the risk of death effectively. We performed a series of screening assays and confirmative evaluations to identify differentially expressed proteins between sepsis survivors and nonsurvivors.

**Materials and Methods**

**Subjects and sample collection**

The research protocol was approved by the Institutional Committee for the Protection of Human Subjects, the Institutional Review Board of West China University Hospital, Sichuan University. All patients provided written informed consent before participation.

This study enrolled 143 patients with sepsis who were admitted to ICU of West China University Hospital between March 2014 and September 2015. Sepsis was diagnosed in accordance with the 2001 International Sepsis Definition conference (Levy et al. 2003). Exclusion criteria were as follows: patient age of less than 18 or greater than 80 years; death within less than 24 hours of ICU admission; neutropenia (< 500 neutrophils/mm$^3$) or acquired immunodeficiency syndrome; and refusal to participate. Patients were divided into a survivor group and a nonsurvivor group, on the basis of their 28-day mortality status. Upon admission to the ICU, the following items were recorded for each patient: age, sex, chief complaint for admission, principal diagnosis, vital signs, routine blood test results, blood gas analysis, infection sites, microbiological culture results, PCT, IL-6 and CRP levels, Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score, and Sequential Organ Failure Assessment (SOFA) score for the first 48 hours after admission to the ICU.

Blood samples were collected in EDTA-containing tubes from each patient within the first 48 hours after admission to the ICU. To separate plasma from whole blood, 3 mL of peripheral blood were centrifuged at 3,000 rpm and 37°C for 10 minutes. Then, 500 μL of supernatant (plasma) were aliquoted from each sample, with care taken to avoid contamination by visible blood. Plasma samples were stored at −80°C until being used for the cytokine antibody array or enzyme-linked immunosorbent assay (ELISA).

**Cytokine antibody array**

Blood samples from two dead and two well-recovered patients were randomly selected for cytokine screening with the RayBio Human Cytokine/Chemokine Antibody Array C Series 2000 (RayBiotech, Norcross, GA). This assay simultaneously detects 174 human cytokines and related proteins. Experiments were conducted in accordance with the manufacturer’s suggested procedures.

Array membranes were incubated in 2 mL of blocking buffer at room temperature (RT) for 30 minutes. Blocking buffer was removed, and diluted plasma samples were added and incubated overnight at 4°C. Sample fluid was discarded, and membranes were washed twice with 2 mL of washing buffer. One milliliter of biotin-conjugated detection antibodies was added to the membranes and incubated for 1.5 to 2 hours at RT. Membranes were washed and incubated with horseradish peroxidase-conjugated streptavidin at RT for 2 hours. A chemiluminescence detection mixture was added. Signal intensities for cytokine expression were measured directly with a chemiluminescence imaging system (Molecular Imager ChemiDoc XRS+System, Bio-Rad Laboratories, Hercules, CA). Spots were digitized into pixel densities, which were analyzed by the TotalLabQuant program. Data were exported into EXCEL for further analysis.

**Preliminary screening and confirmatory test by ELISA**

Cytokines showing obviously and consistently different expression profiles between the two groups by cytokine assay were further analyzed by ELISA. Twenty plasma samples from each group were randomly selected for preliminary screening by ELISA. Cytokines that were screened by ELISA included latency-associated protein (LAP), which was detected with the LEGEND MAX$^\text{TM}$ human LAP ELISA kit with precoated plates (BioLegend, San Diego, CA), IL-6, monocyte chemoattractant protein 1 (MCP-1), regulated upon activation normal T cell expressed and secreted (RANTES), epidermal growth factor (EGF), vascular endothelial growth factor receptor 3 (VEGF R3), and macrophage inflammatory protein 1 delta (MIP-1δ), which were detected in duplicate by using commercial kits purchased from RayBiotech, Inc. Cytokines exhibiting differential expression levels between the two groups in the initial ELISAs were submitted to additional confirmatory analysis.

All ELISA experiments were performed in accordance with the manufacturers’ instructions. Briefly, 100 μL of each diluted sample were added to duplicate wells in a 96-well plate and incubated for 2.5 hours at RT with gentle shaking. Plates were washed twice. Then, 100 μL of biotinylated antibody were added to each well and incubated for 1 hour. Next, 100 μL of prepared streptavidin solution were added to each well and incubated for 45 minutes at RT.

Color was developed by adding 100 mL of tetramethylbenzidine substrate solution to each well and incubating for approximately 30 minutes at RT. The reaction was stopped by adding 50 μL of stop solution. Optical absorbance of each microwell was immediately read on a spectrophotometer (Infinite M200, Tecan Trading, Switzerland) at 450 nm. The concentration of each analyte was determined by referring to a standard curve generated simultaneously on the same plate.

**Statistical analysis**

Quantitative data with normal distributions were reported as the mean ± standard deviation (SD) and compared by Student’s $t$ test between survivors and nonsurvivors. Non-normally distributed quantitative data were presented as the median [interquartile range] and compared by the Mann-Whitney U test. Characteristics of survivors versus nonsurvivors were compared by univariate analysis. Receiver operating characteristic (ROC) curves were used to evaluate the prognostic value of the chemokines/cytokines in predicting the 28-day mortality. Correlations between MCP-1 and PCT were analyzed by Spearman’s rank correlation test. Differences with a two-tailed $P$ value less than 0.05 were considered to be statistically significant. Statistical analysis was performed by using the SPSS Statistics 19.0 (SPSS Inc., Chicago, IL) and GraphPad Prism 5 (GraphPad Software, San Diego, CA) software packages.

**Results**

**Patient characteristics**

During the study period, 143 patients (56 nonsurvivors, 87 survivors) with sepsis were included in the analysis. The mean patient age was 58 ± 13 years. There were
no significant differences in age or sex distribution between the survivor and nonsurvivor groups \((P > 0.05)\). APACHE II and SOFA scores of patients in the nonsurvivor group were higher than those of patients in the survivor group \((P = 0.001\) and \(P = 0.004\), respectively; Table 1).

**Screening of plasma samples**

We used a semi-quantitative protein antibody array to detect protein profiles in plasma samples from two patients in each group (Fig. 1). For each spot, the corresponding gray value was analyzed by TotalLabQuant. Five cytokines, RANTES, EGF, VEGF R3, MIP-1\(\delta\), and LAP, showed significant and consistent differences between the two groups and were selected for further analysis. Changes in the MCP-1 and IL-6 expression levels were opposite but obviously different between the two groups, consistent with previous reports (Mera et al. 2011; Li et al. 2014), which demonstrated the value of MCP-1 and IL-6 levels in predicting mortality for patients with sepsis. Therefore, we researched these two cytokines, in addition to the five cytokines mentioned above.

**ELISA**

Plasma samples from 40 randomly selected patients (20 from each group) were subjected to ELISA analysis for the seven selected cytokines (Fig. 2). There were no significant differences between the survivor and nonsurvivor groups in the median plasma expression levels of IL-6 (survivor vs. nonsurvivor: 42.48 vs. 88.64 pg/ml), RANTES (1,392.85 vs. 1,410.25 pg/ml), VEGF R3 (3,473.60 vs. 3,272.04 pg/ml), MIP-1\(\delta\) (23,646.30 vs. 24,908.48 pg/ml), or LAP (13.26 vs. 16.71 ng/ml). However, significant differences in the plasma levels between the groups were found for MCP-1 (75.36 vs. 251.73 pg/ml) and EGF (25.93 vs. 16.78 pg/ml).

We then used ELISAs to confirm the differential plasma levels of MCP-1 and EGF among all 143 sepsis patients (87 survivors and 56 nonsurvivors; Fig. 3). A sig-

Average data are reported as the mean ± SD.

APACHE II score, Acute Physiology, Age, Chronic Health Evaluation II score; SOFA score, sequential organ failure assessment score.

**Screening Study of Prognostic Biomarkers of Sepsis Patients**

\begin{table}[h]
\centering
\begin{tabular}{lccc}
\hline
\textbf{Clinical feature} & \textbf{Survivors} & \textbf{Nonsurvivors} & \textbf{\(P\)} \\
& \textbf{(n = 87)} & \textbf{(n = 56)} & \\
\hline
Average age (years) & 56.63 ± 11.57 & 60.96 ± 15.08 & 0.055 \\
No. of men/women & 38/18 & 50/37 & 0.224 \\
Initial site of infection & & & \\
Lung (%) & 22 & 23 & 0.065 \\
Abdominal (%) & 44 & 24 & 0.395 \\
Skin and soft tissues (%) & 5 & 2 & 0.705 \\
Neurological (%) & 3 & 4 & 0.433 \\
Trauma (%) & 8 & 1 & 0.090 \\
Other (%) & 5 & 3 & 0.921 \\
Organism & & & \\
Gram+ bacterium (%) & 7 & 6 & 0.767 \\
Gram- bacterium (%) & 31 & 18 & 0.720 \\
Fungus (%) & 12 & 15 & 0.079 \\
Mixed (%) & 8 & 4 & 0.765 \\
None detected (%) & 29 & 13 & 0.259 \\
Average APACHE II score & 24.4 ± 7.6 & 19.9 ± 7.4 & 0.001 \\
Average SOFA score & 11.1 ± 4.5 & 9.1 ± 4.0 & 0.004 \\
\hline
\end{tabular}
\caption{Patient characteristics.}
\end{table}

Fig. 1. Human cytokine/chemokine array analysis of plasma samples from sepsis patients. Array results are shown for samples from a nonsurvivor (A1) and a survivor (A2) diagnosed with pneumonia, and those for samples from a nonsurvivor (B1) and a survivor (B2) diagnosed with biliary calculus. Among the positive signals, RANTES (1), MCP-1 (2), MIP-1\(\delta\) (3), IL-6 (4), EGF (5), LAP (6), and VEGF R3 (7) were noticeably different and consistent in direction between the two groups.

A1: a nonsurvivor diagnosed with pneumonia; A2: a survivor diagnosed with pneumonia.
B1: a nonsurvivor diagnosed with biliary calculus; B2: a survivor diagnosed with biliary calculus.
significant difference between the survivor and nonsurvivor groups was observed in the median values of MCP-1 (67.86 vs. 187.05 pg/ml, \(P < 0.05\)), but not of EGF (8.93 vs. 8.04 pg/ml) (Table 2).

Comparison of initial MCP-1, CRP, IL-6, and PCT levels

Plasma levels of MCP-1 (67.86 vs. 187.05 pg/ml) and PCT (1.33 vs. 3.30 pg/ml) in sepsis patients in the nonsurvivor group were significantly higher than those in the survivor group. There were no significant differences in CRP and IL-6 levels between the groups. APACHE II and SOFA scores of the nonsurvivor group were higher than those of the survivor group (APACHE II: 24.4 vs. 19.9, SOFA: 11.1 vs. 9.1; \(P < 0.05\)).

We analyzed the relationship between MCP-1 expression levels and APACHE II scores, SOFA scores, and PCT expression levels. There was no distinct correlation of the MCP-1 expression level with the APACHE II or SOFA.

Fig. 2. ELISA analysis of the plasma levels of the seven differentially expressed cytokines.
The seven cytokines were selected, based on the chemokine/cytokine array (see Fig. 1). Their plasma levels were measured by ELISA in 20 survivors and 20 nonsurvivors of sepsis. Data are expressed as the median, with \(P\) values as follows: RANTES, \(P = 0.653\); MCP-1, \(P = 0.033\); MIP-1\(\alpha\), \(P = 0.292\); IL-6, \(P = 0.285\); EGF, \(P = 0.044\); LAP, \(P = 0.552\); VEGF R3, \(P = 0.787\).

Fig. 3. Plasma levels of MCP-1 and EGF in sepsis patients.
Plasma levels were measured in 87 survivors and 56 nonsurvivors with ELISA (MCP-1, \(P = 0.000\); EGF, \(P = 0.719\)).
However, Spearman correlation analysis revealed a significant association between the expression levels of MCP-1 and PCT (Spearman correlation coefficient = 0.299, \( P = 0.001 \), Fig. 4).

We used multiple logistic regression models to examine the association of prognosis with sex, age, APACHE II score, MCP-1, PCT, and SOFA score. Logistic regression analysis showed that MCP-1 and APACHE II score were independent risk factors for sepsis patients (Table 3, 4). ROC curves for the APACHE II scores, SOFA scores, PCT expression levels, and MCP-1 expression levels for the two groups were constructed based on statistically significant differences (Fig. 5), and areas under the ROC curves (AUCs) were calculated (Table 5). In terms of predicting 28-day mortality, AUCs of MCP-1, APACHE II score, SOFA score, and PCT were 0.766, 0.680, 0.640, and 0.621, respectively. Combined use of the MCP-1 expression level and APACHE II score was better than any single indicator alone, with an AUC of 0.785 (sensitivity = 69.6%, specificity = 76.8%).

Table 2. Plasma cytokine levels and clinical scores in patients with sepsis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Survivors (n = 87)</th>
<th>Nonsurvivors (n = 56)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP-1 (pg/ml)</td>
<td>67.86 [40.20 – 119.94]</td>
<td>187.05 [100.71 – 487.96]</td>
<td>0.000</td>
</tr>
<tr>
<td>CRP (pg/ml)</td>
<td>123.0 [83.5 – 175.0]</td>
<td>143.0 [103.0 – 273.0]</td>
<td>0.116</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>166.9 [47.8 – 525.3]</td>
<td>235.1 [87.81 – 921.9]</td>
<td>0.213</td>
</tr>
<tr>
<td>PCT (pg/ml)</td>
<td>1.33 [0.36 – 11.45]</td>
<td>3.30 [0.59 – 20.60]</td>
<td>0.04</td>
</tr>
<tr>
<td>Initial SOFA score</td>
<td>9.1 ± 4.0</td>
<td>11.1 ± 4.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Initial APACHE II score</td>
<td>19.9 ± 7.4</td>
<td>24.4 ± 7.6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± standard deviation or median [interquartile range].
MCP-1, monocyte chemoattractant protein 1; CRP, C-reactive protein; IL-6, interleukin (IL)-6; PCT, procalcitonin; SOFA score, sequential organ failure assessment score; APACHE II score, Acute Physiology, Age, Chronic Health Evaluation II score.

Fig. 4. Correlation between plasma MCP-1 and PCT levels. Spearman correlation coefficient \((r) = 0.299\) and \( P = 0.001 \) for plasma MCP-1 vs. PCT levels.
### Table 3. The logistic regression analysis about these indicators (Variables in the Equation).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>B</th>
<th>SE</th>
<th>Wals</th>
<th>Df</th>
<th>P</th>
<th>Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II</td>
<td>0.073</td>
<td>0.025</td>
<td>8.324</td>
<td>1</td>
<td>0.004</td>
<td>1.076</td>
</tr>
<tr>
<td>MCP-1</td>
<td>0.010</td>
<td>0.003</td>
<td>12.892</td>
<td>1</td>
<td>0.000</td>
<td>1.010</td>
</tr>
<tr>
<td>Constant</td>
<td>-2.821</td>
<td>0.612</td>
<td>21.286</td>
<td>1</td>
<td>0.000</td>
<td>0.060</td>
</tr>
</tbody>
</table>

**B**, Regression coefficient; **SE**, standard error; **Wals**, wald chi-square; **Df**, Degree of Freedom. **Exp(B)**, OR(odds ratio).

### Table 4. The logistic regression analysis about these indicators (Variables not in the Equation).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
<th>Df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT</td>
<td>2.941</td>
<td>1</td>
<td>0.086</td>
</tr>
<tr>
<td>Sex</td>
<td>0.384</td>
<td>1</td>
<td>0.536</td>
</tr>
<tr>
<td>Age</td>
<td>0.541</td>
<td>1</td>
<td>0.462</td>
</tr>
<tr>
<td>SOFA</td>
<td>0.550</td>
<td>1</td>
<td>0.458</td>
</tr>
<tr>
<td>T</td>
<td>3.974</td>
<td>4</td>
<td>0.410</td>
</tr>
</tbody>
</table>

**Df**, Degree of Freedom.

**Fig. 5.** Receiver operating characteristic curves. Shown are receiver operating characteristic curves for MCP-1 expression, APACHE II score, SOFA score, PCT expression, and MCP-1 expression + APACHE II score for predicting prognosis of sepsis patients.
We used the maximum Youden index to select cut-off values for prediction of death. Sensitivity and specificity for predicting mortality were 76.8% and 71.3%, respectively, for MCP-1 level with a cutoff of 98.92 pg/mL; 76.9% and 58.5%, respectively, for APACHE II score with a cutoff of 21.5; and 62.5% and 67.6%, respectively, for PCT level with a cutoff of 2.68 pg/mL; and 69.6% and 76.8%, respectively, for the combined use of the MCP-1 expression level and APACHE II score. To evaluate the prognosis of patients with sepsis, MCP-1 is better than the APACHE II score, SOFA score, or PCT. Combining the MCP-1 level and APACHE II score has the best prognostic value.

Discussion

Sepsis is a systemic inflammatory response syndrome caused by infection. The occurrence and development of sepsis are associated with infection, inflammation, immune dysfunction, and blood coagulation disorders, involving the activation of numerous cells, inflammatory mediators, and the blood coagulation system. Despite modern antibiotic therapy, mortality rates for septic shock remain high (Annan et al. 2003; Christaki and Opal 2008). Identifying patients who are at an increased risk of death due to sepsis is crucial for making appropriate and timely interventions to reduce mortality rates. In this study, we found that the inflammatory marker MCP-1 was a valuable tool for predicting mortality in sepsis patients. Plasma levels of MCP-1 were significantly higher in the nonsurvivor compared to the survivor group starting from 48 hours of ICU admission. Plasma levels of MCP-1 may be superior to those of EGF, CRP, and IL-6 which showed no significant differential expression between survivors and nonsurvivors, in judging the prognosis of sepsis patients.

Our MCP-1 results are consistent with those reported by Mera et al (2011). Using multiplex cytokine profiling, those authors found that the expression levels of IL-8 and MCP-1 soon after ICU admission were higher in nonsurvivors compared to survivors. MCP-1, also known as small inducible cytokine A2, is a CC chemokine, a potent chemooattractant, and a regulatory mediator involved in various inflammatory diseases. MCP-1 is secreted by monocytes, endothelial cells, smooth muscle cells, and fibroblasts as an initiating cytokine of the inflammatory cascade. Secretion of MCP-1 is induced by IL-1, TNF, and other signaling molecules. MCP-1 shows specific chemotaxis to mononuclear macrophages and lymphocytes, and it possesses various biological functions when combined with its corresponding receptor. MCP-1 induces cells to express carrier molecules and secrete IL-1 and IL-6. It promotes histamine chemokine release by basophils and mast cells (Bilgic et al. 2009). MCP-1 contributes to systemic inflammatory response syndrome (SIRS) and can result in multiple organ dysfunction syndrome (MODS). While detecting various cytokines in sepsis, Assicot et al. (1983) found a positive correlation between the serum level of MCP-1 and sepsis severity. Bozza et al. (2007) reported that MCP-1 can accurately predict the prognosis of sepsis. NF-κB plays a key role in regulating cell transcription factor and adhering to molecules in several diseases, especially MODS (Blackwell and Christman 1996). MCP-1 was activated and released at the early stage of sepsis. The enhanced activity of NF-κB induced MCP-1 gene expression and the release of large amounts of MCP-1, which contributed to the release of a cytokine cascade. These conditions will lead SIRS to progress to MODS. In a previous report, blockade of MCP-1 synthesis protected mice against acute pancreatitis, as evidenced by their attenuated hyperamylasemia, neutrophil sequestration in the pancreas, and pancreatic acinar cell injury/necrosis (Bhatia et al. 2005). Thus, a low level of MCP-1 generally indicates better prognosis in infectious diseases.

Although the PCT level and APACHE II score are generally considered to be good indicators of sepsis prognosis, we found that combining the MCP-1 expression level and APACHE II score had the best predictive value. Multiple studies have shown that PCT not only has diagnostic value in discriminating sepsis from nonspecific systemic inflammatory response syndrome (Uzzan et al. 2006), but also is highly predictive of fatality (Lee et al. 2008).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC</th>
<th>SE</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP-1 level</td>
<td>0.766</td>
<td>0.044</td>
<td>0.000</td>
<td>0.680 – 0.852</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>0.680</td>
<td>0.046</td>
<td>0.000</td>
<td>0.589 – 0.771</td>
</tr>
<tr>
<td>SOFA score</td>
<td>0.640</td>
<td>0.048</td>
<td>0.005</td>
<td>0.546 – 0.734</td>
</tr>
<tr>
<td>PCT level</td>
<td>0.621</td>
<td>0.038</td>
<td>0.015</td>
<td>0.527 – 0.715</td>
</tr>
<tr>
<td>MCP-1 + APACHE II</td>
<td>0.785</td>
<td>0.038</td>
<td>0.000</td>
<td>0.710 – 0.860</td>
</tr>
</tbody>
</table>

AUC, area under the ROC curve; SE, standard error; CI, confidence interval.
However, we found that the prognostic value of PCT was moderate compared to that of MCP-1. The sensitivity and specificity values of PCT (62.5% and 67.7%, respectively) were lower than those of MCP-1 (76.8% and 71.3%, respectively). PCT, which is a sensitive systemic marker of inflammation, especially bacterial infection, has been shown to be useful for predicting mortality in patients with sepsis (Liu et al. 2015). Our result revealed a significant association between the expression levels of MCP-1 and PCT.

Despite its important proinflammatory role in sepsis, we did not find a significant difference in plasma IL-6 levels between the survivor and nonsurvivor groups. This finding is not consistent with research by Suarez-Santamaría et al. (2010), who found that the IL-10 and IL-6 expression levels were the best predictors of survival in sepsis. Similarly, Jekarl et al. (2013) found significantly increased IL-6 levels in nonsurvivors compared to survivors. Our antibody array results also showed a large variation in IL-6 levels between the two groups. Like other markers of sepsis, IL-6 release can enhance the severity of infection. However, although IL-6 plays an important role in sepsis pathophysiology, it remains unclear whether it can be used as a marker of sepsis (Reinhart et al. 2012). Therefore, this cytokine should be researched further.

CRP is an acute-phase protein and a sensitive systemic marker of inflammation and tissue damage. Similar to the previous study (Zhang et al. 2011), we did not find a difference in CRP levels between survivors and nonsurvivors. It may be that CRP acts as an inflammatory biomarker, but cannot reflect the disease severity or predict mortality in sepsis (Zhang et al. 2011).

Our study has some advantages compared to previous analyses of cytokines in sepsis. In this study, we found that the plasma concentration of MCP-1 in patients with sepsis was predictive of mortality. MCP-1 is a potent chemoattractant of mononuclear cells and a regulatory mediator in sepsis. Our study suggests that MCP-1 may play an important immunomodulatory role in controlling the balance between pro- and anti-inflammatory factors in sepsis. Furthermore, the sample size of this study was large.

This study also had some limitations that deserve consideration. First, more than half of our patients developed sepsis at other hospitals and were transferred to our ICU due to poor therapeutic effects. Thus, the measured original MCP-1 levels might not represent the levels at sepsis onset. Second, owing to differences in economic conditions, the patients received different treatments for sepsis. Such differences would directly affect the prognosis of patients. Third, we used a small sample size when screening for potential prognostic biomarkers by chemokine assay. This choice of a smaller sample may bias the results. In addition, we did not perform dynamic analyses of MCP-1 levels, SOFA scores, etc. Such analysis should be the focus of future research. Finally, there are many kinds of chemokines, cytokines, and other biomarkers for sepsis. We measured specific biomarkers due to the limitations of time and funding. It is possible to find a new biomarker that is superior to MCP-1, if we will continue the further efforts.

In conclusion, our results indicate that the plasma levels of MCP-1 were higher in nonsurvivor sepsis patients than in survivors, and that MCP-1 may be superior to several other cytokines for predicting the 28-day mortality status of sepsis patients. Further studies are needed to determine whether plasma MCP-1 may be used as a prognostic biomarker for sepsis severity in a clinical setting.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

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score, procalcitonin, and C-reactive protein in patients with sepsis at the emergency department. *Shock*, 29, 322-327.