Early plasma monocyte chemoattractant protein 1 predicts the development of sepsis in trauma patients

A prospective observational study

Yuchang Wang, MD, Qinxin Liu, MM, Tao Liu, MD, Qiang Zheng, MD, Xi’e Xu, MM, Xinghua Liu, MD, Wei Gao, MD, PhD, Zhanfei Li, MD, PhD, Xiangjun Bai, MD, PhD

Abstract
Monocyte chemoattractant protein 1 (MCP-1) is an initiating cytokine of the inflammatory cascade. Extracellular MCP-1 exhibits pro-inflammatory characteristic and plays a central pathogenic role in critical illness. The purpose of the study was to identify the association between plasma MCP-1 levels and the development of sepsis after severe trauma.

The plasma levels of MCP-1 in severe trauma patients were measured by a quantitative enzyme-linked immune sorbent assay and the dynamic release patterns were recorded at three time points during seven days post-trauma. The related factors of prognosis were compared between sepsis and non-sepsis groups and analyzed using multivariate logistic regression analysis. We also used receiver operating characteristic (ROC) curves to assess the values of different variables in predicting sepsis.

A total of 72 patients who met criteria indicative of severe trauma (72.22% of male; mean age, 49.40±14.29 years) were enrolled. Plasma MCP-1 concentrations significantly increased on post-trauma day 1 and that this increase was significantly correlated with the Injury Severity Score (ISS) and interleukin-6 (IL-6). Multivariate logistic regression analysis showed that early MCP-1, ISS, and IL-6 were independent risk factors for sepsis in severe trauma patients. Incorporation of the early MCP-1 into the ISS can increase the discriminative performance for predicting development of sepsis.

Early plasma MCP-1 concentrations can be used to assess the severity of trauma and is correlated with the development of sepsis after severe trauma. The addition of the early MCP-1 levels to the ISS significantly improves its ability to predict development of sepsis.

Keywords: inflammation biomarker, monocyte chemoattractant protein 1, sepsis, trauma

1. Introduction
Sepsis and infectious complications are major contributing factors to trauma-related mortality.[1,2] Timely detection and treatment of emerging infections can allow us to take measures for treatment as early as possible, thereby reducing post-trauma mortality and improving patient outcome. Hence, effective identification of severe trauma patients who have the potential to develop life-threatening infectious complications and are at the risk of death is still an urgent problem.

Severe trauma can induce exacerbation of systemic inflammation, which often progresses to sepsis leading to a lethal outcome.[3] Numerous of evidence has been sought to identify biomarkers to predict patients who are at high-risk of morbidity and mortality. Many biomarkers, such as monocyte human leukocyte antigen-DR (HLA-DR), high mobility group box 1 (HMGB1), and interleukin-6 (IL-6), which are involved in systemic inflammation caused by trauma and relate to the severity of injury, have been assessed as potential markers to predict poor prognosis in critical ill patients.[4-6] Unfortunately, all of these biomarkers lack sufficient specificity.

Monocyte chemo-attractant protein 1 (MCP-1), also referred to as C-C motif chemokine ligand 2 (CCL2), was discovered originally as one of the key chemokines that regulate migration
and infiltration of monocytes/macrophages. It is also an important molecule for regulating leukocyte function and mediating various inflammation-promoting biological activities. A growing body of work has demonstrated that MCP-1 plays a key pathogenic role in the pathogenesis mechanisms of leading sepsis. Therefore, MCP-1 is an interesting candidate biomarker for monitoring patients with severe trauma. However, the changes and significance of MCP-1 in trauma patients have not been well-elucidated. The objective of the present study was to investigate the time course of MCP-1 levels in patients with severe trauma and to determine whether MCP-1 can serve as a biomarker to predict the development of sepsis in trauma patients.

2. Methods

2.1. Study setting, design and patient selection

This prospective study was conducted from October 2016 to March 2017 in the traumatic department of the Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology. The study was strictly observational and did not interfere with the decision-making process and clinical management. The protocol for this study was approved by the Ethical and Protocol Review Committee of the Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, and informed consent was obtained from their next of kin.

The enrolment criteria consisted of a history of trauma (Injury Severity Score [ISS] ≥16), age between 18 and 80 years, admitted to the hospital within 24 hours after injury. Patients with known pre-existing comorbidities such as myocardial infarction, burns, thromboembolic events, and anticoagulant medication were excluded. In addition, patients with inherited or acquired immunodeficiencies and patients receiving immunosuppressive therapy were also excluded from the study. Prophylactic antibiotics were selected and given according to the doctor’s experience and related researches. For comparison, 10 age-matched and sex-matched healthy volunteers who received an annual physical examination and had no clinical evidence of infection were recruited as controls.

2.2. Clinical data collection and evaluation

Demographic characteristics (age and gender), mechanism of injury, ISS, procalcitonin (PCT), IL-6, C-reaction protein (CRP), and days of stay in ICU were collected on admission. Determination of ISS was performed by independent evaluators according to the Abbreviated Injury Scale 2005. In this study, patients were divided into sepsis group and non-sepsis group according to development of sepsis within 28 days post-trauma. According to sepsis-3, sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction was identified as an acute change in total SOFA (Sequential Sepsis-related Organ Failure Assessment) score ≥2 points consequent to the infection. The bloodstream infections were diagnosed according to the isolation of a predominant organism from blood cultures obtained under sterile conditions.

2.3. Blood samples

Venous peripheral blood was drawn from the trauma patients on day 1 (within 24 hours), day 3, day 7 after injury. Samples were collected in potassium ethylenediamine tetra-acetic acid (EDTA) coated bottles and centrifuged at 370 x g for 5 minutes. Plasma samples were obtained and stored at ~80°C until further testing. The plasma levels of MCP-1, IL-6, CRP, PCT were tested by commercially available human ELISA kit (GenWay, San Diego, CA), respectively, according to the manufacturer’s instruction.

2.4. Statistical analysis

Descriptive data were summarized as median (interquartile range), mean ± standard deviation (SD), or frequency (percent-age) as appropriate statistical. Statistical analysis was performed by using the SPSS 19.0 statistical software (SPSS, Chicago, IL). Differences between groups were performed by student t-test for continuous variables and by χ² test or Fisher exact for categorical variables. Correlations between MCP-1 and ISS, IL-6, CRP, as well as PCT were evaluated using scatterplots and Spearman rank-correlation coefficients. Candidate variables were chosen from univariate analyses and significant univariate variables (P < .15) were included in a backwards multivariate model. Logistic regressions were used as odds ratios (ORs) with 95% CI adjusting for MCP-1 levels, ISS and IL-6. Receiver operating characteristic (ROC) curve analysis was used to evaluate the values of different variables to predict sepsis. Statistical significance was defined as a P < .05.

3. Results

3.1. Study population and baseline characteristics

In the study, a total of 72 patients with multiple trauma were recruited and the mean age was 49.40 ± 14.29. 52 patients (72.22%) were male and 20 (27.78%) were female. The mean ISS was 22.63 ± 4.76. Of the patients who were initially evaluated, 9 patients were excluded from the study due to the following reasons: died within 24 hours (n = 4), age younger than 18 years (n = 5). Out of the 72 trauma patients, 45 patients (62.5%) were due to motor vehicle crashes, 9 (12.50%) were caused by falling, and 18 (25.00%) were by other trauma. Thirty-nine patients (54.17%) had brain injury and 45 patients (62.50%) had thoracic injury. Overall, 39 patients (54.17%) developed sepsis, 14 patients (19.44%) died. The length of intensive care unit (ICU) was 7.71 ± 4.04 days (Table 1). Mean SOFA scores were gradually increased and peaked on day 6 in sepsis patients (Supplemental Fig. 1, http://links.lww.com/MD/C186).

3.2. Plasma cytokine levels and ISS in trauma patients

The mean plasma MCP-1 levels in trauma patients on post-trauma day 1 were 659.8 (309.9–1010.0) pg/mL, day 3 527.0 (269.2–784.7) pg/mL, day 7 543.8 (280.2–807.4) pg/mL. The overall patterns of plasma concentrations of MCP-1 were increased and peaked on day 1, decreased but remained elevated on day 3 and 5 days (Fig. 1).

There were no significant differences between the sepsis and non-sepsis groups in the plasma levels of PCT (non-sepsis vs sepsis: 7.52 ± 3.39 vs 5.63 ± 2.18pg/mL), CRP (116.76 ± 79.22 vs 98.64 ± 66.47pg/mL). However, significant differences between the sepsis and non-sepsis groups were found for ISS (23.79 ± 4.52 vs 18.24 ± 4.27), MCP-1 (1013.72 ± 572.43 vs 365.18 ± 226.28pg/mL) and IL-6 (80.94 ± 46.42 vs 47.52 ± 26.34pg/mL) (Table 2).
3.3. Early plasma levels of MCP-1 related with sepsis

Patients in the sepsis group had higher ISS (23.79 ± 4.52 vs 18.24 ± 4.27, *P* < .01) and longer stay in ICU (9.97 ± 3.42 vs 4.26 ± 1.91, *P* < .01) compared with non-sepsis group. We observed that MCP-1 levels statistically significantly higher on post-trauma day 1 in patients who developed sepsis (1013.45 ± 572.17 pg/mL vs 325.28 ± 148.55 pg/mL, *P* = .01), but the levels were not significantly different on day 3 (755.3 ± 591.6 pg/mL vs 334.9 ± 156.6 pg/mL, *P* = .14) and 7 (680.1 ± 643.2 pg/mL vs 329.7 ± 137.8 pg/mL, *P* = .28) between sepsis group and non-sepsis group (Fig. 2).

The association of plasma MCP-1 levels with the risk of sepsis was assessed after adjusting for potential confounding variables in multivariate analyses. Multivariate analyses showed that MCP-1, ISS, and IL-6 on day 1 were independent risk factors for the development of sepsis in severe trauma patients (1.01 [95% CI, 1.00 ∼ 1.02; *P* = .02]; 1.64 [95% CI, 1.17 ∼ 2.31; *P* < .01]; 9.6 [95% CI, 5.72 ∼ 34.8; *P* = .04] respectively) (Table 3).

### Table 1
Demographic and clinical characteristics of the severe trauma patients.

| Variable                | Total (n = 72) | Non sepsis (n = 33) | Sepsis (n = 39) | *P*
|-------------------------|----------------|---------------------|----------------|-----
| Gender                  |                |                     |                |     
| Female, % (n)           | 27.78 (20)     | 27.27 (9)           | 28.21 (11)     | .93 |
| Male, % (n)             | 72.22 (52)     | 72.73 (24)          | 71.79 (28)     |     |
| Age, ys                 | 49.40 ± 14.29  | 49.24 ± 13.47       | 49.68 ± 15.44  | .16 |
| Underlying disease      |                |                     |                |     
| Hypertension, % (n)     | 11.11 (8)      | 9.09 (3)            | 12.82 (5)      | .72 |
| Diabetes, % (n)         | 8.33 (6)       | 9.09 (3)            | 7.69 (3)       | 1.00 |
| Injury mechanism, % (n) |                |                     |                |     
| Motor vehicle collision | 62.50 (45)     | 66.67 (22)          | 58.97 (23)     | .50 |
| Falls                   | 12.50 (9)      | 12.12 (4)           | 15.38 (6)      | .75 |
| Other                   | 25.00 (18)     | 21.21 (7)           | 25.64 (10)     | .66 |
| Brain injury, % (n)     | 54.17 (39)     | (16)                | (23)           | .37 |
| Thoracic injury, % (n)  | 62.50 (45)     | 38.46 (15)          | 48.48 (16)     | .71 |
| Time period of onset of sepsis (d) | – | – | 5.36 ± 2.42 | .01 |
| LOS in ICU, days        | 7.71 ± 4.04    | 4.26 ± 1.91         | 9.97 ± 3.42    | < .01 |

Data are presented as mean ± standard deviation or percentage (%). 
ICU = intensive care unit, ISS = Injury Severity Score, LOS = length of stay.

### Table 2
ISS and plasma cytokine levels (day 1) in severe trauma patients.

| Parameter       | Non-sepsis (n = 33) | Sepsis (n = 39) | *P*
|-----------------|---------------------|-----------------|-----
| ISS             | 18.24 ± 4.27        | 23.79 ± 4.52    | < .01|
| MCP-1 (pg/mL)   | 325.28 ± 148.55     | 1013.45 ± 572.17| .01 |
| IL-6 (pg/mL)    | 47.52 ± 26.34       | 80.94 ± 46.42   | .02 |
| PCT (pg/mL)     | 5.63 ± 2.18         | 7.52 ± 3.39     | .23 |
| CRP (pg/mL)     | 96.64 ± 66.47       | 116.70 ± 79.22  | .18 |

Data are presented as mean ± standard deviation (SD). 
CRP = C-reactive protein, IL-6 = interleukin (IL)-6, ISS = Injury severity score, MCP-1 = monocyte chemoattractant protein-1, PCT = procalcitonin.

![Figure 1. Time course of MCP-1 levels after trauma. Mean MCP-1 levels were gradually increased and peaked on day 1, decreased but remained elevated on day 3 and 5 days. MCP-1: monocyte chemoattractant protein 1.](image1)

![Figure 2. Comparison of MCP-1 levels in patients with sepsis and non-sepsis. MCP-1: monocyte chemoattractant protein 1. *P* < .05.](image2)
3.4. Early plasma levels of MCP-1 related with ISS and IL-6

We analyzed the relationship between MCP-1 expression levels and ISS, PCT, CRP, and IL-6 expression levels on day 1. There was no distinct correlation of the MCP-1 expression level with the PCT or CRP (not shown). However, we found that MCP-1 was significantly correlated with the ISS (r = 0.50, P < .01) and IL-6 (r = 0.66, P < .01) (Fig. 3).

3.5. Predictors of sepsis

In terms of predicting sepsis, AUCs of MCP-1, ISS, IL-6 on day 1 were respectively 0.82 (95% CI 0.71 – 0.93, P < .01), 0.83 (95% CI 0.72 – 0.93, P < .01), and 0.63 (95% CI 0.48 – 0.77, P = .09; respectively). Combined use of the MCP-1 level and ISS score was better than any single indicator alone, with an AUC of 0.87 (95% CI 0.78 – 0.96) (Table 4; Fig. 4).

Optimum cut-off values for prediction of sepsis were determined on the ROC curve with the maximum Youden index [sensitivity-(1-specificity)]. The best thresholds of MCP-1, IL-6, ISS for predicting sepsis were 240.7pg/mL (sensitivity 92.86% and specificity 43.75%), 54.8pg/mL (sensitivity 73.64% and specificity 54.81%), and 21.5 (sensitivity 75.76% and specificity 88.89%), respectively. Sensitivity and specificity of combining use of MCP-1 and ISS for predicting sepsis were 87.88% and 78.96%, respectively. To evaluate the prognosis of patients with trauma, ISS was better than the MCP-1 and IL-6. However, combining the MCP-1 level and ISS had the best prognostic value.

4. Discussion

Dysregulation of the host inflammatory response is central to the mortality of patients with sepsis after trauma, involving the activation of numerous immune cells and inflammatory mediators. Despite innovations in therapy, mortality rates for sepsis remain high.[16,17] Therefore, identifying severe trauma patients who are at a high risk of sepsis is crucial for making appropriate and timely interventions to reduce mortality rates. In the absence of specific clinical signs to predict poor prognosis in trauma patients, early biomarkers of immune dysfunction are clearly highly desirable. In our study, we found that level of plasma

Table 3

| Variable | Odds ratio | 95% CI | P |
|----------|------------|--------|---|
| MCP-1    | 1.01       | 1.00–1.02 | .02 |
| ISS      | 1.64       | 1.17–2.31  | <.01 |
| IL-6     | 9.6        | 5.72–34.8  | .04 |

CI = confidence, IL-6 = interleukin (IL)-6, ISS = injury severity score, MCP-1 = monocyte chemotactic protein-1.

Table 4

| Parameter | AUC   | SE   | P    | 95% CI   |
|-----------|-------|------|------|----------|
| MCP-1 level | 0.82  | 0.06 | <.01 | 0.71–0.93 |
| ISS       | 0.83  | 0.05 | <.01 | 0.72–0.93 |
| IL-6 level | 0.63  | 0.07 | .09  | 0.48–0.77 |
| MCP-1 + ISS | 0.87  | 0.05 | <.01 | 0.78–0.96 |

AUC = area under curve, CI = confidence, IL-6 = interleukin (IL)-6, ISS = injury severity score, MCP-1 = monocyte chemotactic protein-1, SE = standard error.
MCP-1 markedly increased on day 1 after trauma and was a promising biomarker for predicting sepsis in severe trauma patients.

MCP-1 plays an important role in various inflammatory diseases, such as experimental allergic encephalitis, inflammatory bowel disease, allergic asthma, and rheumatoid arthritis. MCP-1 is secreted by many cell types, including monocytes, endothelial cells, smooth muscle cells, and fibroblasts as an initiating cytokine of the inflammatory cascade. Apart from regulating the migration and infiltration of monocytes, memory T lymphocytes, and natural killer (NK) cells, several studies indicate that MCP-1 is also associated with polarized Th2 responses, enhancing the secretion of IL-4 by T cells. Furthermore, accumulating evidence indicated that MCP-1 plays an important role in the pathologic mechanisms leading to sepsis. MCP-1 also regulates inflammatory progression and the production of pro-inflammatory cytokines. Several studies have demonstrated that levels of MCP-1 was markedly increased in sepsis and contributed to systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS). In addition, MCP-1 was positive correlated to sepsis severity and can accurately predict the prognosis of sepsis. Thus, a high level of MCP-1 maybe be associate with poor prognosis in critically ill patients.

Although the ISS and IL-6 score are generally considered to be good biomarkers of trauma prognosis, we demonstrated that combining the MCP-1 level and ISS had the best predictive value. In trauma patients, IL-6 release has been shown to be related to the severity of trauma and complications. Our study demonstrated that MCP-1 was superior to IL-6 in judging the prognosis in the early stage of trauma. Katherine et al. reported that antibody neutralization of MCP-1 in a septic mouse model leads to markedly decreased release of IL-1α, IL-1β, and IL-6. We also found that MCP-1 was correlated with severity of trauma and pro-inflammatory cytokine IL-6. PCT and CPR are sensitive biomarkers of inflammation. Similar to the previous study, we did not find differences in PCT and CRP levels between sepsis and non-sepsis groups. It may be that PCT and CRP act as inflammatory biomarkers, but cannot reflect the injury severity or predict sepsis in trauma patients.

In addition, we found that the plasma MCP-1 level was significantly related with the development of sepsis and a potential biomarker to predict development of sepsis. Recently, accumulating evidences demonstrated that MCP-1 genetic variations within the regulatory regions could make patients susceptible to certain inflammation-related diseases, infection and sepsis by altering MCP-1 expression levels. Furthermore, a number of studies demonstrated that inhibition or specific antagonism of MCP-1 could decrease the septic response and are beneficial to survival in mouse models of sepsis. These results confirmed that MCP-1 played an important role in the pathomechanisms of immune dysregulation and maybe a promising potential therapeutic target for correcting the immune disorder of severe trauma.

There are still some limitations in our study. Firstly, the numbers of patients and controls were relatively small, and the data were collected at a single institution. In addition, sepsis and death could be a cause rather than a consequence of higher substrate levels. Furthermore, there were difficulties in obtaining enough blood samples from these patients, which hindered our investigation into the kinetics of plasma MCP-1 levels in long period.

5. Conclusions
Our study demonstrated that plasma MCP-1 levels were significantly increased in patients with serve trauma. Furthermore, the early plasma MCP-1 was significantly correlated with the severity and development of sepsis in severe trauma patients. Meanwhile, our study revealed that early plasma MCP-1 can improve the performance of ISS to predict sepsis after trauma. In short, our study indicated that MCP-1 might play an important role in the pathogenesis of sepsis after trauma. Further studies are needed to determine whether MCP-1 intervention could prevent the development of poor outcome in patients with severe trauma.

Authors' contributions
Design: Xiangjun Bai
Interpretation: Xiangjun Bai.
Research: Yuchang Wang, Qinxin Liu, Xinghua Liu, Xi’e Xu, Tao Liu
Data collection: Yuchang Wang, Qinxin Liu, Xinghua Liu, Xi’e Xu, Tao Liu
Data Analysis: Yuchang Wang, Qiang Zheng, Wei Gao
Cytokines Test: Yuchang Wang, Qiang Zheng, Wei Gao
Supervision: Zhanfei Li
Drafting: Xiangjun Bai, Zhanfei Li

Acknowledgments
The authors thank all the doctors, nurses, and patients for their dedication in the study. We also thank the medical ethics committee of Tongji Hospital at the Tongji Medical College of Huazhong University of Science and Technology.

References
[1] Frohlich M, Lefering R, Probst C, et al. Epidemiology and risk factors of multiple-organ failure after multiple trauma: an analysis of 31,154 patients from the TraumaRegister DGU. J Trauma Acute Care Surg 2014;76:921–7.
[2] Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. J Trauma 1995;38:185–93.
[3] Namas R, Ghuma A, Hermus L, et al. The acute inflammatory response in trauma hemorrhage and traumatic brain injury: current state and emerging prospects. Libyan J Med 2009;4:97–103.
[4] Wang XW, Karki A, Zhao XJ, et al. High plasma levels of high mobility group box 1 is associated with the risk of sepsis in severe blunt chest trauma patients: a prospective cohort study. J Cardiothorac Surg 2014;9.
[5] Gouel-Cheron A, Aillaouchiche B, Guignant C, et al. Early interleukin-6 and slope of monocyte human leukocyte antigen-DR: a powerful association to predict the development of sepsis after major trauma. PLoS One 2012;7:e33095.
[6] Kraft R, Herndon DN, Fimmett CC, et al. Predictive value of IL-8 for sepsis and severe infections after burn injury: a clinical study. Shock 2015;43:222–7.
[7] Deshmule SL, Kremlev S, Amini S, et al. Monocyte chemoattractant protein-1 (MCP-1): an overview. J Interferon Cytokine Res 2009;29:313–26.
[8] Ziraldo C, Vodovotz Y, Namas RA, et al. Central role for MCP-1/CCL2 in injury-induced inflammation revealed by in vitro, in silico, and clinical studies. PLoS One 2013;8:e79804.
[9] Gerszten RE, Garcia-Zepeda EA, Lim YC, et al. MCP-1 and IL-8 trigger firm adhesion of monocytes to vascular endothelium under flow conditions. Nature 1999;398:718–23.
[10] Zhu TT, Liao XL, Feng T, et al. Plasma monocyte chemoattractant protein-1 as a predictive marker for sepsis prognosis: a prospective cohort study. Tohoku J Exp Med 2017;241:139–47.
[11] Bozza FA, Salluh JI, Japiassu AM, et al. Cytokine profiles as markers of disease severity in sepsis: a multiplex analysis. Crit Care 2007;11.
[12] Tsuda Y, Takakatsu H, Kobayashi M, et al. CCL2, a product of mice early after systemic inflammatory response syndrome (SIRS), induces
alternatively activated macrophages capable of impairing antibacterial resistance of SIRS mice. J Leukoc Biol 2004;76:368–73.

[13] Quinn RH, Wedmore I, Johnson E, et al. Wilderness Medical Society practice guidelines for basic wound management in the austere environment. Wilderness Environ Med 2014;25:295–310.

[14] Lane JC, Malvuure NT, Hindocha S, et al. Current concepts of prophylactic antibiotics in trauma: a review. Open Orthop J 2012;6:511–7.

[15] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801–10.

[16] Annane D, Aegerter P, Jars-Guincestre MC, et al. Current epidemiology of septic shock: the CUB-Rea Network. Am J Respir Crit Care Med 2003;168:165–72.

[17] Christaki E, Opal SM. Is the mortality rate for septic shock really decreasing? Curr Opin Crit Care 2008;14:580–6.

[18] Izikson L, Klein RS, Charo IF, et al. Resistance to experimental resistance of SIRS mice. J Leukoc Biol 2004;76:368–73.

[19] Ip WK, Wong CK, Lam CW. Interleukin (IL)-4 and IL-13 up-regulate alternatively activated macrophages capable of impairing antibacterial resistance of SIRS mice. J Leukoc Biol 2004;76:368–73.

[20] Rantapaa-Dahlqvist S, Boman K, Tarkowski A, et al. Up-regulation of monocyte chemoattractant protein-1 (MCP-1) inhibits the intestinal-like differentiation of monocytes. Clin Exp Immunol 2006;145:190–9.

[21] Karpus WJ, Lukacs NW, Kennedy KJ, et al. Differential CC chemokine receptor (CCR)2. J Exp Med 2000;192:1075.

[22] Gu L, Tseng S, Horner RM, et al. Control of TH2 polarization by the monocyte chemoattractant protein-1. Nature 2000;404:407–11.

[23] Stensballe J, Christiansen M, Tonnesen E, et al. The early IL-6 and IL-10 response in trauma is correlated with injury severity and mortality. Acta Anaesthesiol Scand 2009;53:515–21.

[24] Bossink AW, Paemen L, Jansen PM, et al. Plasma levels of the monocyte chemoattractant protein-1 and -2 are elevated in human sepsis. Blood 1995;86:3841–7.

[25] Matsukawa A, Hogaboam CM, Lukacs NW, et al. Endogenous MCP-1 influences systemic cytokine balance in a murine model of acute septic peritonitis. Exp Mol Pathol 2000;68:77–84.

[26] Han YL, Li YL, Jia LX, et al. Reciprocal Interaction between macrophages and T cells stimulates IFN-gamma and MCP-1 production in Ang II-induced cardiac inflammation and fibrosis. Plos One 2012;7.

[27] Hanemann ALP, Liborio AB, Daher EF, et al. Monocyte Chemotactic Protein-1 (MCP-1) in Patients with Chronic Schistosomiasis Mansoni: Evidences of Subclinical Renal Inflammation. Plos One 2013;8.

[28] Zhang HL, Zhi L, Moohchafa S, et al. Hydrogen sulfide acts as an inflammatory mediator in cecal ligation and puncture-induced sepsis in mice by upregulating the production of cytokines and chemokines via NF-kappa B. Am J Physiol Lung Cell Mol Physiol 2007;292: L960–71.

[29] Ip WK, Wong CK, Lam CW. Interleukin (IL)-4 and IL-13 up-regulate alternatively activated macrophages capable of impairing antibacterial resistance of SIRS mice. J Leukoc Biol 2004;76:368–73.

[30] Labbe K, Danialou G, Gvozdic D, et al. Inhibition of monocyte chemoattractant protein-1 prevents diaphragmatic inflammation and maintainscontractile function during endotoxemia. Crit Care 2010;14:R187.

[31] Rosanova MT, Tramonti N, Taizc M, et al. Assessment of C-reactive protein and procalcitonin levels to predict infection and mortality in burn children. Arch Argent Pediatr 2015;113:41–6.

[32] He JB, Chen YH, Lin Y, et al. Association study of MCP-1 promoter polymorphisms with the susceptibility and progression of sepsis. Plos One 2017;12.

[33] Li YW, Yang CQ, Xiao YL, et al. The-A2518G polymorphism in the MCP-1 gene and in one 2017;12.

[34] Shi GL, Yang L, Sun Y, et al. MCP-1 gene polymorphisms in North Chinese patients with pulmonary tuberculosis. Genet Mol Res 2015;14:4035–40.

[35] Rannath RD, Ng SW, Guglielmotti A, et al. Role of MCP-1 in endotoxemia and sepsis. Int Immunopharmacol 2008;8:810–8.

[36] Shima H, Zhai Y, Youssf NG, et al. Enhanced monocyte chemoattractant protein-1 production in aging mice exaggerates cardiac depression during endotoxemia. Crit Care 2014;18:527.

[37] Speyer CL, Gao H, Rancilio NJ, et al. Novel chemokine responsiveness and mobilization of neutrophils during sepsis. Am J Pathol 2004;165:2187–96.