Observational Study

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

A prospective observational study

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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.

Abbreviations: AUC = area under curve, CCL2 = C-C motif chemokine ligand 2, CI = confidence interval, CRP = C-reaction protein, ELISA = enzyme-linked immune sorbent assay, HLA-DR = human leukocyte antigen-DR, HMGB1 = high mobility group box 1, ICU = intensive care unit, IL = interleukin, ISS = Injury Severity Score, LOS = length of stay, MCP-1 = monocyte chemotactic protein-1, MODS = multiple organ dysfunction syndrome, ORs = odds ratios, PCT = procalcitonin, ROC = receiver operating characteristic, SIRS = systemic inflammatory response syndrome, SOFA = Sequential Organ Failure Assessment.

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

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and infiltration of monocytes/macrophages.[7,8] It is also an important molecule for regulating leukocyte function and mediating various inflammation-promoting biological activities.[7–9] A growing body of work has demonstrated that MCP-1 plays a key pathogenic role in the pathogenesis mechanisms of leading sepsis.[10–12] 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 concomitant acute 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.[13,14] 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,[15] 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 × 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 (percentage) 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 χ^2 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 serve 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).

Table 1

Demographic and clinical characteristics of the severe trauma patients.

Variable	Total (n = 72)	Non sepsis (n = 33)	Sepsis (n = 39)	P
Gender				.93
Female, % (n)	27.78 (20)	27.27 (9)	28.21 (11)	
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	–
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.

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).

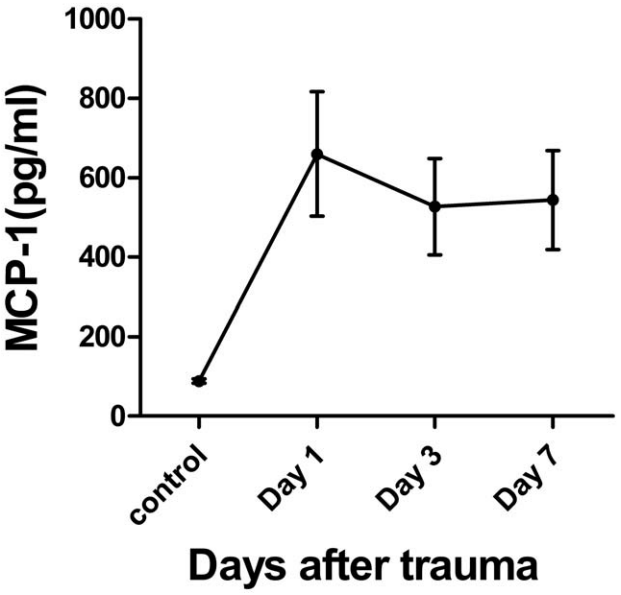

Figure 1. Time course of MCP-1 levels after trauma. Mean MCP-1 levels were gradually were increased and peaked on day 1, decreased but remained elevated on day 3 and 5 days. MCP-1: monocyte chemoattractant protein 1.

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)	98.64 ± 66.47	116.76 ± 79.22	.18

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

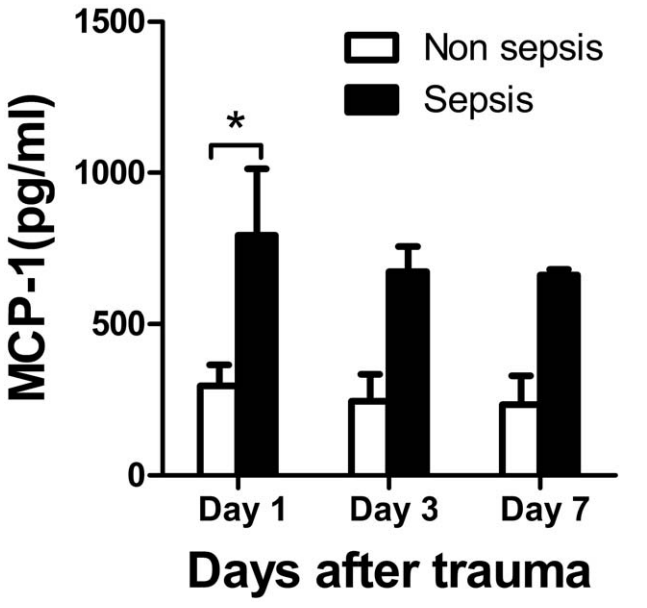

Figure 2. Comparison of MCP-1 levels in patients with sepsis and non-sepsis. MCP-1: monocyte chemoattractant protein 1. *$P < .05$.

Table 3

Multiple logistic regression models of independent risk factorsfor sepsis of severe trauma patients (day 1).

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

Area under the ROC curve for predicting sepsis in trauma patients (day 1).

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.

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, $P < .01$) (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-seecificity)]. The best thresholds of MCP-1, IL-6, ISS for predicting sepsis were 240.7 pg/mL (sensitivity 92.86% and specificity 43.75%), 54.8 pg/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.

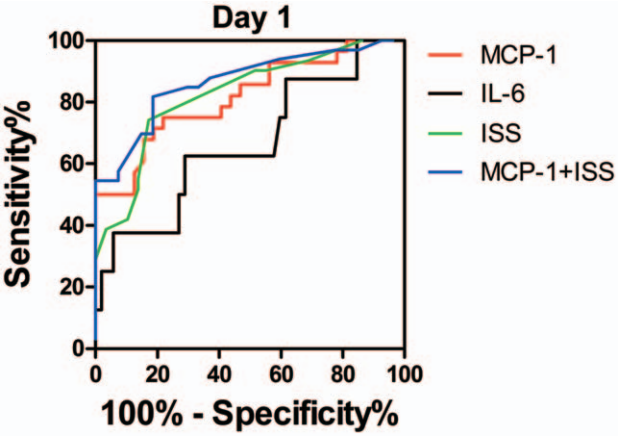

Figure 4. The ROC curves of MCP-1, ISS, IL-6 and ISS+MCP-1 for predicting sepsis after severe trauma (day 1).

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

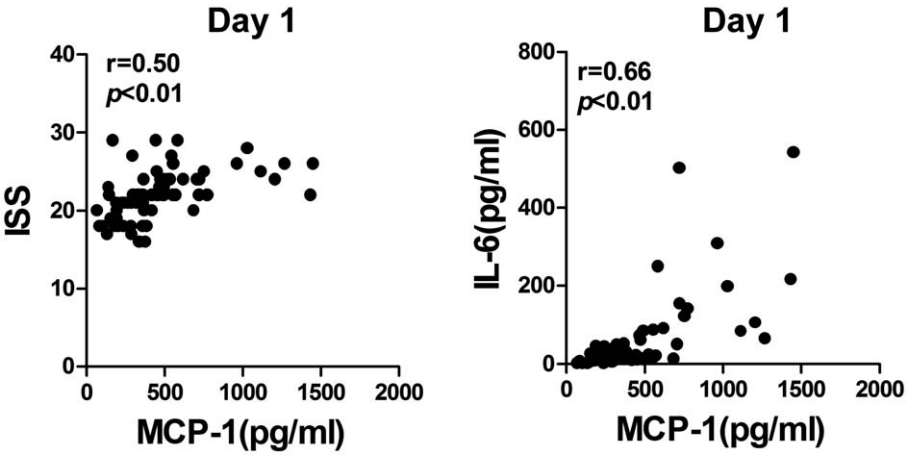

Figure 3. The correlations between MCP-1 levels and ISS as well as IL-6 on day 1. MCP-1 was associated with the ISS and IL-6 ($r = 0.50$, $P < .01$; and $r = 0.66$, $P < .01$, respectively). ISS: Injury Severity Score; MCP-1: monocyte chemoattractant protein 1.

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,[18] inflammatory bowel disease,[19] allergic asthma,[20] and rheumatoid arthritis.[21] 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.[7] 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 associate with polarized Th_2 responses,[22] enhancing the secretion of IL-4 by T cells.[23] Furthermore, accumulating evidence indicated that MCP-1 plays an important role in the pathogenic mechanisms leading to sepsis.[11,24,25] MCP-1 also regulated inflammatory progression and the production of pro-inflammatory cytokines.[26,27] 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).[12,25,28] In addition, MCP-1 was positive correlate to sepsis severity and can accurately predict the prognosis of sepsis.[11] 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.[5,29] 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.[30] 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,[31] 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.[32–34] 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.[35–37] 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

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Drafting: Xiangjun Bai, Zhanfei Li

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