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Original Article

The elevated blood CD74 mRNA associated with prognosis in septic shock patients

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Abstract: The hyperinflammation and immunosuppression were activated together in sepsis and septic shock patients by different inflammatory mediators or cytokines, such as CD74 and macrophage inhibitory factor (MIF), to kill bacteria and control infections in intensive care unit (ICU). In total, 88 cases (40 for sepsis and 28 for septic shock, 20 for healthy control) were enrolled in this study. Blood samples were collected at admission and Day 2, Day 4 after ICU admission. The level of serum CD74 was detected by ELISA kits. The blood CD74 mRNA was detected by real-time PCR. We found that serum CD74 levels were increased on day 2 after admission, and decreased on day 4 after admission to ICU in sepsis and septic shock patients. And blood CD74 mRNA kept the trend consistently with serum CD74, increasing at admission and Day 2, and then decreasing on day 4. But the level of serum CD74 and CD74 mRNA expression in both patients was markedly higher compared to healthy control cases. Meanwhile, we found that the concentration of serum CD74 was positive correlated with CD74 gene expression levels, at admission or on day 2, day 4. In consequence, the level of CD74 was higher in sepsis patients than in septic shock patients during ICU admission days, both for serum CD74 and blood CD74 mRNA. And multivariate analysis also revealed that blood CD74 mRNA was associated with prognostic factors for septic shock. These results implied that CD74 may play an important role in septic shock, and blood CD74 mRNA level was suitable to predict septic shock with disease severity after ICU admission.

Keywords: CD74, sepsis, septic shock

Introduction

Sepsis means a kind of clinical organ dysfunction due to the host response to infection [1]. Now the epidemiology of sepsis is various for global different regions, because of variation of risk factors, case definitions, socioeconomic status and race [2]. Sepsis still remains a significant financial burden and contributes to more than 5 million deaths annually, although followed by increased incidence and decreased mortality due to appropriately evaluate and new therapies [3]. Sepsis may be characterized as apparent paradox pathophysiologic process, which involves hyperinflammation activation of the innate immune system and immunosuppression by dysregulation of proinflammatory and anti-inflammatory responses, such as IL-1, IL-6, IL-8, IL-12, and macrophage inhibitory factor (MIF) et al [4]. The activation of host immune response results in the activation of numerous cytokines and chemokines, which kills bacteria and controls infectious [5]. Meanwhile, the mortality and incidence of sepsis remains incompletely understand.

The dysfunction of host response to infection is a severe clinical syndrome related to sepsis, which will lead to the cytokine storm [6]. As an MHC class II chaperoneis, CD74 is mainly expressed on antigen-presenting cells. CD74 serves as a cytokine receptor and transmembrane protein binding to MIF in the intracytoplasmic domain on many cell types [7]. CD74 could down-regulate cytokines expression on the monocyte cell surface by binding to MIF,

and enhance secretion of proinflammatory cytokines and anti-inflammatory activity [8]. The research indicated that the expressions of CD74 mRNA were significantly associated with intensive care unit-acquired infections at different time-points, independent of sepsis and shock status at admission. CD74 could be considered as a relevant marker for high risk of secondary infections in general ICU population [9].

During sepsis, many kinds of inflammatory cytokines could be increased, such as TNF-α, IL-1β and IL-6. Especially, as a response to a proinflammatory stimulus in the short time from stimulus to induction in sepsis, procalcitonin (PCT) is the only biomarker implemented in clinical sepsis guidelines [10]. But information on the level of CD74 protein, as a biomarker of sepsis, remains limited. There is no recommendation and evaluation related to its concentration in the blood for disease phase and clinical outcome.

The purpose of this study was to measure circulating concentrations of CD74 in ICU patients with sepsis and severe sepsis. It could be helpful to know more about sepsis patients which may contribute to decrease the mortality in intensive care units.

Materials and methods

Patients

We enrolled 68 individuals (>18 years old) and 20 healthy volunteers from October 2016 to October 2017 in Suzhou science & technology town hospital in the study. They were hospitalized in the ICU with sepsis admission. According to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), all adult patients were defined as sepsis (40 cases) and septic shock (28 cases) [11]. Patients were eligible for enrollment with an onset of sepsis syndrome and by standard treatment. All of related clinical data were collected by the treating physicians. The first blood draw was also performed within 24 hours after admission. And the second, the third blood samples were drew within 48 and 96 hours after the diagnosis of sepsis. All blood samples were stored at -80°C before detected. The information of related patients, such as Clinical data, and laboratory parameters were collected at admission and during the course of disease. This study was approved by the local ethics committee of Suzhou Science & Technology Town Hospital, China. All patients and healthy cases signed written informed consent.

Quantitative CD74 mRNA level

We extracted total RNA from blood sample by the PAXgene Blood RNA System (PreAnalytix, Hombrechtikon, Switzerland). cDNA was generated using a first strand cDNA synthesis kit (Invitrogen, China) and was synthesized from 2 μg of total RNA. The levels of CD74 mRNA were performed by Real-time PCR. Primer sequences of CD74 for reverse transcription-PCR (RT-PCR) reaction were forward (5'-CAT GGA TGA CCA ACG CGA C-3') and reverse (5'-TGT ACAGAG CTC CAC GGC TG-3') [12]. RT-PCR was carried out by using the Mx3000P QPCR System (Stratagene, CA, USA). The cDNA was then used for qPCR in a 20 μl SYBR Premix Ex Taq. Reaction mixtures for CD74 mRNA were carried out by conditions: 40 cycles of 35 seconds at 95°C, 35 seconds at 48°C, and 50 seconds at 72°C. The expression of β-actin mRNA was amplified from the same cDNA samples as an internal control for qPCR. The relative expression of CD74 mRNA was determined with the comparative CT method, using average CT values for CD74 and β-actin.

Quantification of serum CD74 protein in blood

The level of serum CD74 protein was detected by the ELISA kit for "RayBio® Human CD 74 ELISA Kit" (Cat. No. ELH-CD74, RayBiotech, Inc., GA, USA) following the manufacturer's indications. After treatment and balance buffers, the protein concentration of serum was quantified with TaKaRa Bradford Protein Assay Kit (Code No. T9310A, Takara Co., Beijing, China).

Laboratory assays

The 5 ml blood sample was collected from each patient and stored at -80°C for the blood analysis. Clinical laboratory assays were routinely detected in our hospitals by cobas® 6000 analyzer series using commercial kits, such as Serum C-reactive protein, Procalcitonin, et al.

Statistical analysis

Statistical analyses were done using SPSS 18.0 software. Data comparison among groups

Table 1. Clinical characteristic of sepsis and septic shock patients

Characteristic	Sepsis (N = 40)	Septic shock (N = 28)	*P*
Age (years)*	75.5 (16.25)	67.00 (13.25)	0.690
Gender (male vs. female)	22 v.s. 18	21 v.s.7	0.090
Source of infection, *n* (%)			n.a
Abdomen	5 (12.5)	1 (3.57)	
Respiratory tract	25 (62.5)	14 (50.0)	
Urinary tract	2 (5.0)	1 (3.57)	
Surgical site	4 (10.0)	6 (21.43)	
Other	4 (10.0)	6 (21.43)	
Type of admission, *n* (%)			n.a
Medical	17 (42.5)	10 (35.71)	
Elective surgery	7 (17.5)	4 (14.29)	
Emergency surgery	5 (12.5)	9 (32.14)	
Trauma	4 (10.0)	2 (7.14)	
Other	7 (17.5)	3 (10.71)	
Microbiological type, *n* (%)			n.a
Gram(-) bacteria	14 (35.0)	8 (28.57)	
Gram(+) bacteria	16 (40.0)	12 (42.86)	
Mixed infections	4 (10.0)	3 (10.71)	
Not documented	6 (15.0)	5 (17.86)	
White Blood cells (cells/mm^3)* at admission	11.82 (5.87)	13.75 (16.02)	0.097
CRP (mg/L) at admission*	78 (112.55)	115 (169.75)	0.492
Procalcitonin (ng/mL) at admission*	1.19 (2.43)	11.10 (52.33)	0.183
Length of ICU (days)*	5 (9)	7 (16)	0.026

*, Data are median (interquartile range, IQR); CRP, C reactive protein; n.a: not applicable. Data comparison among groups was assessed using paired or unpaired *t* test.

was assessed using paired or unpaired *t* test. The risk of septic shock associated with CD74 expression was assessed using logistic regression analyses. Statistical comparisons of the correlation results were performed using linear regression. Receiver operating characteristic curve analysis was carried out for blood CD74 mRNA levels to predict septic shock. Statistical significance was defined as $P < 0.05$.

Results

Serum CD74 mRNA expression was up-regulated in sepsis and septic shock patients

There were 68 patients enrolled in our medical ICU, including 40 cases with the main diagnosis of sepsis and 28 cases with septic shock. 43 cases were male, and 25 cases were female (the median age: 73 years; range 18-90 years). There were no significant differences existed among the sepsis and septic shock groups for age and gender (**Table 1**). And respiratory tract and surgery were identified as main origins of infection.

The levels of serum CD74 and blood CD74 mRNA expressions were measured in 68 medical ICU patients and 20 healthy volunteers served as controls. Serum CD74 levels were significantly higher in sepsis patients after admission (ng/ml, mean ± SD, Day 1: 1.34 ± 0.48, Day 2: 1.88 ± 0.40, Day 4: 1.58 ± 0.36, respectively) as compared to healthy groups (ng/ml, mean ± SD, 0.41 ± 0.28, $P < 0.0001$, **Figure 1A**). And there was a significantly difference between days. The levels of serum CD74 also were increased in septic shock group compared to healthy ($P < 0.0001$, **Figure 1B**). There was a significantly difference between day 1 (ng/ml, mean ± SD, 3.82 ± 1.63) and day 2 (ng/ml, mean ± SD, 4.94 ± 1.87, $P < 0.0001$), and between day 2 and day 4 (ng/ml, mean ± SD, 4.35 ± 1.43, $P = 0.038$).

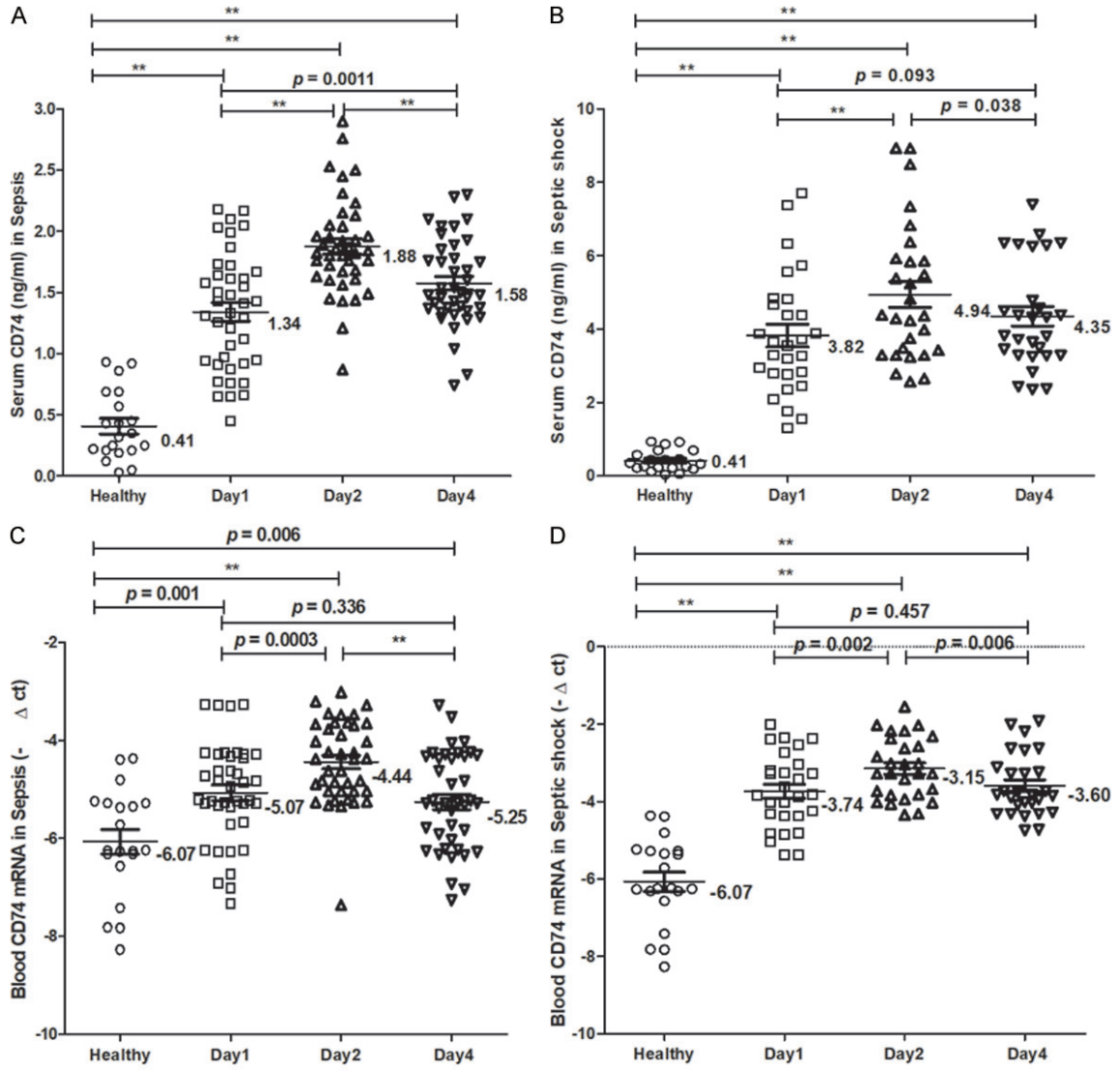

Figure 1. Serum CD74 and blood CD74 mRNA in patients. A. The level of serum CD74 in sepsis. B. The level of serum CD74 in septic shock. C. The level of blood CD74 mRNA in sepsis. D. The level of blood CD74 mRNA in septic shock. Unpaired *t* test were for healthy group and others groups; paired *t* test were for Day 1, Day 2 and Day 4 group. **, $P < 0.0001$.

For blood CD74 mRNA expression, we found a significantly higher level in sepsis patients after admission (-Δct, mean ± SD, Day 1: -5.07 ± 1.02, Day 2: -4.44 ± 0.84, Day 4: -5.25 ± 0.99, respectively) as compared to healthy groups (-Δct, mean ± SD, -6.07 ± 1.12, P < 0.05, **Figure 1C**). And there was a significant difference between day 1 and day 2 (P = 0.0003), between day 2 and day 4 (P < 0.0001). For septic shock cases, blood CD74 mRNA expression also was increased compared to healthy (P < 0.0001, **Figure 1D**). There was a significant difference between day 1 (-Δct, mean ± SD, -3.74 ± 0.96) and day 2 (-Δct, mean ± SD, -3.15 ± 0.78, P = 0.002), and between day 2 and day 4 (-Δct, mean ± SD, -3.60 ± 0.79, P = 0.006).

The elevated CD74 expression after ICU admission in sepsis and septic shock patients

The next, we want to know the change of CD74 expression after ICU admission. We found that whatever days after admission, there was a significant difference between sepsis and septic shock group, and the serum CD74 level was higher in septic shock group than sepsis group (P < 0.0001, **Figure 2A**). For blood CD74

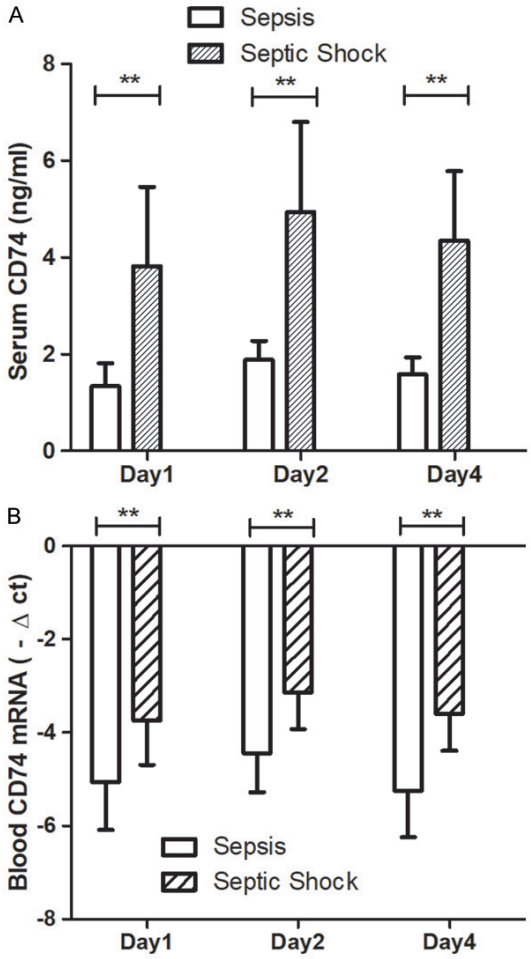

Figure 2. The level of serum CD74 and blood CD74 mRNA after admission in patients. A. Serum CD74 had a significant difference between sepsis and septic shock patients. B. Blood CD74 mRNA had a significant difference between sepsis and septic shock patients. Statistical comparisons of the results were using unpaired s *t* test. **, $P < 0.0001$.

mRNA expressions, an elevated level was found in septic shock patients than sepsis patients ($P < 0.0001$, **Figure 2B**).

Meanwhile, we found that the ratio of serum CD74 Day 2/1 and Day 4/2 after ICU admission had no significant difference between sepsis (mean ± SD, 1.53 ± 0.44; 0.84 ± 0.14, respectively, **Figure 3**) and septic shock patients (mean ± SD, 1.40 ± 0.47; 0.95 ± 0.31, respectively). And the ratio of blood CD74 mRNA had no significant difference between sepsis (mean ± SD, 0.90 ± 0.20; 1.21 ± 0.27, respectively) and septic shock patients (mean ± SD, 0.87 ± 0.25; 1.19 ± 0.31, respectively).

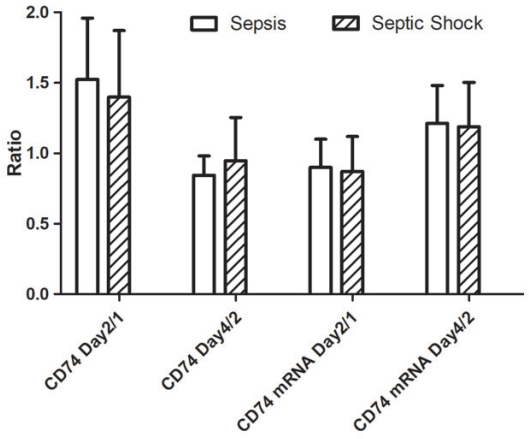

Figure 3. The ratio of serum CD74 and blood CD74 mRNA after admission in patients. The ratio of serum CD74 Day 2/1 and Day 4/2 had no significant difference between sepsis and septic shock patients. And the ratio of blood CD74 mRNA had no significant difference between sepsis and septic shock patients. Statistical comparisons of the results were using unpaired s *t* test.

The correlation between serum CD74 and blood CD74 mRNA in patients

We evaluated the correlation between the serum CD74 and blood CD74 mRNA in sepsis and septic shock patients after ICU admission. The analysis demonstrated there were significant correlations between the levels of serum CD74 and blood CD74 mRNA in sepsis patients after ICU admission (Day 1: $R^2 = 0.242$; Day 2: $R^2 = 0.434$; Day 4: $R^2 = 0.474$; respectively, $P < 0.01$), and in septic shock patients (Day 1: $R^2 = 0.594$; Day 2: $R^2 = 0.743$; Day 4: $R^2 = 0.825$; respectively, $P < 0.0001$). The scatter plots for these correlations were presented in **Figure 4**.

Elevation of CD74 mRNA levels predicts prognosis of septic shock

In order to demonstrate significant role of CD74 gene expression in septic shock, multivariate analysis was carried out between clinical characteristics at admission and concentration of CD74 in 68 patients. The results of the Cox regression analysis for prognostic factors associated with septic shock are summarized in **Table 2**. Multivariate analysis revealed that blood CD74 mRNA and serum CD74 were associated with septic shock. Each incremental elevation of -1Δct CD74 mRNA increased the

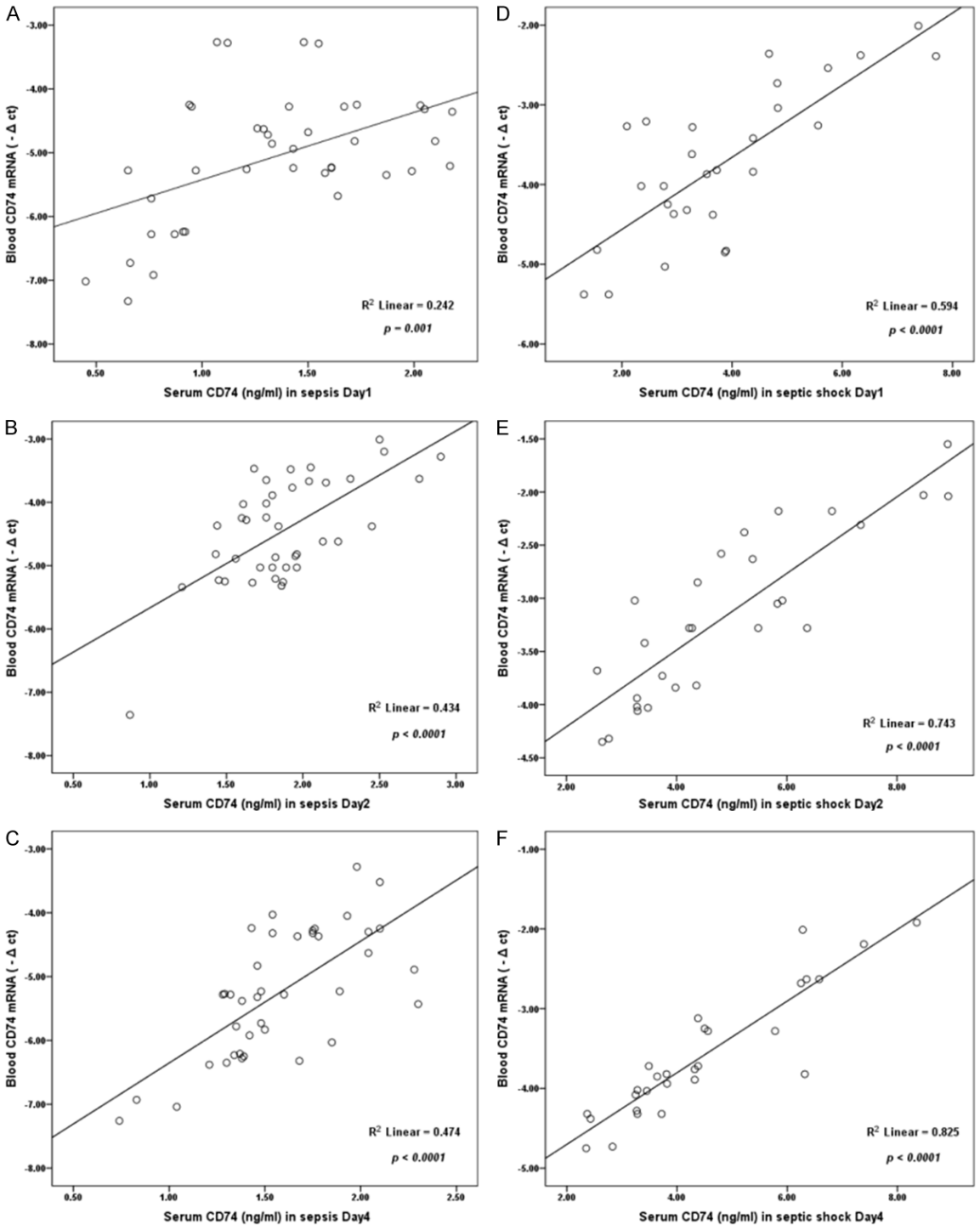

Figure 4. The correlation between serum CD74 and blood CD74 mRNA in patients. A-C. Serum CD74 was associated with blood CD74 mRNA in sepsis patients. D-F. Serum CD74 was associated with blood CD74 mRNA in septic shock patients. Statistical comparisons of the results were using linear regression.

risk of septic shock by a factor of 5.499 (95% CI 2.075-14.573; P = 0.001), for 1 ng/ml serum CD74 with HR 2.356 (95% CI 1.423-10.863; P = 0.018), and for 1 ng/ml procalcitonin with HR 1.050 (95% CI 1.013-1.089; P = 0.008). But the other factors, such as age, CRP, and length of ICU were not significant prognostic factors for septic shock. These results

Table 2. Results of Cox regression analysis of prognostic factors for septic shock

Factor	β	SE	Hazard ratio (95% CI)	*P*
Age	0.001	0.024	1.001 (0.955, 1.050)	0.952
White Blood cells (cells/mm^3)	0.083	0.042	1.086 (1.000, 1.180)	0.051
CRP (mg/L)	0.001	0.005	1.001 (0.992, 1.010)	0.836
Procalcitonin (ng/mL)	0.049	0.018	1.050 (1.013, 1.089)	0.008
Length of ICU (days)	0.051	0.039	1.053 (0.974, 1.137)	0.194
Blood CD74 mRNA (Day 1)	1.705	0.497	5.499 (2.075, 14.573)	0.001
Serum CD74 (ng/ml, Day 1)	1.036	0.256	2.356 (1.423, 10.863)	0.018

CI: confidence interval; CRP: C reactive protein.

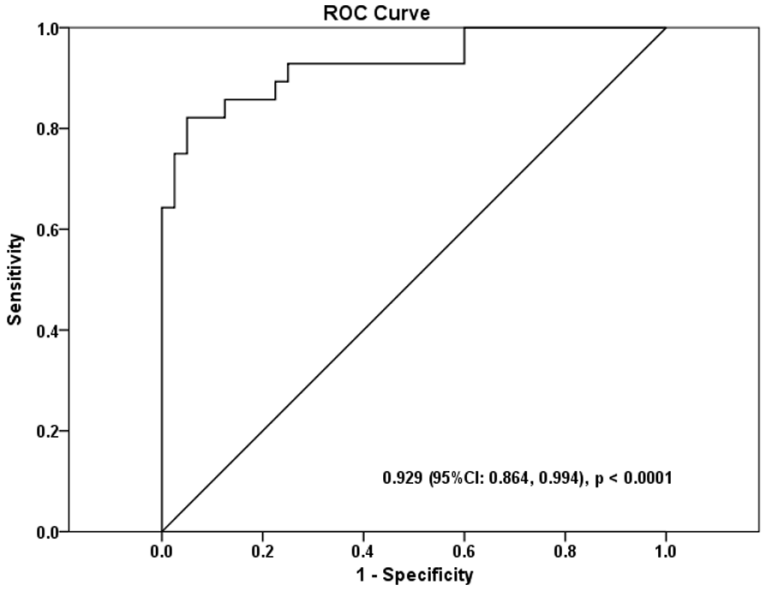

Figure 5. Receiver operating characteristic (ROC) curve analysis of blood CD74 mRNA levels to predict septic shock. ROCs were constructed to assess the sensitivity and specificity of blood CD74 mRNA levels for predicting septic shock. Areas under the curve (AUC) were calculated. Data are presented as ACU (95% confidence interval).

implied that the level of blood CD74 mRNA was the most significant factor leading to septic shock. Then we assessed the sensitivity and specificity of blood CD74 mRNA levels for predicting septic shock. We found that the blood CD74 mRNA level was suitable to predict septic shock with the highest specificity and sensitivity (AUC, 0.929; 95% CI, 0.864-0.994, P < 0.0001, **Figure 5**).

Discussion

Sepsis remains a major cause of morbidity and mortality due to increasing aging population worldwide. But for biological syndrome of sepsis, we still have an incomplete understanding [13]. It is helpful to distinguish organ dysfunction between infectious and non-infectious causes. And septic shock is defined as a subset of sepsis with sequential organ dysfunction enough to substantially increase the risk of mortality [14].

Previously research had found that several risk factors, such as older age, burden of chronic diseases, immobility, vision impairment, nursing, et al. were associated with poor long-term functional outcomes in ICU [15]. But there were no routinely used markers to predict prognosis for sepsis and septic shock. Increased researches have confirmed a large number of inflammatory factors involved in sepsis. There are many biomarkers used in sepsis patients for risk assessment and clinical care, such as procalcitonin, CRP, WBC, et al. [16]. But these biomarkers have some limitations for diagnosis and prognostication of sepsis and septic shock. Therefore, a better biomarker will be more important for effective treatment, especially for sepsis and septic shock patients after ICU ad-mission.

There are many proinflammatory cytokines, such as IL-1, IL-6, IL-8, and MIF, et al., that function as mediators in sepsis and septic shock. And the cytokines (IL-4, IL-6 and IL-10) could play a role in anti-inflammatory effects [4]. CD74 as a membrane protein of MHC class II on cell surface was identified in blood of some types of patients, such as diabetes, tumors, burn, hepatitis, stroke, and rheumatoid arthritis [17-21].

Pachot et al. firstly confirmed that the expression of CD74 was decreased at the early phase of septic shock [22]. And then Didier Payen found that the increased expression of CD74 gene was significantly correlated with HLA-DR monocyte expression in the recovery period of the septic shock [23]. Meanwhile, a decreased CD74 mRNA level had a predictive value for 28-day mortality after septic shock [24]. However, these studies did not investigate predictive value of serum CD74 protein in regard to sepsis patients.

In this study, serum CD74 levels was increased on day 2 after admission, and decreased on day 4 after admission during the study period in both patients. And blood CD74 mRNA kept the trend consistently with serum CD74, increasing at admission, and then decreasing on day 4. But the level of CD74 in both patients was markedly higher compared to healthy control cases.

Meanwhile, we found that the concentration of serum CD74 was positive correlated with CD74 gene expression levels, either at admission or on day 2, day 4. In consequence, the level of CD74 was higher in sepsis patients than in septic shock patients during ICU admission days, both for serum CD74 and blood CD74 mRNA. And multivariate analysis also revealed that blood CD74 mRNA was associated with prognostic factors for septic shock. These results implied that blood CD74 mRNA level was suitable to predict septic shock with disease severity after ICU admission.

Many studies have supported that MIF/CD74 coupling could lead to activation of inflammation and immunity. Wu, et al. reported the elevated levels of serum CD74 in ALI/ARDS and positive correlation with lung inflammation in reflecting severity of ALI/ARDS on Day 3 after admission [12]. Blood CD74 mRNA could be a molecular marker of inflammation to monitor sepsis patients' physiology. In addition, there is more research for specifically investigating the mechanisms of post-translational regulation mechanisms for CD74 gene in the future in sepsis patients.

In summary, these data indicated that CD74 mRNA and serum CD74 were elevated in septic shock and that CD74 is an independent prognostic factor. It is needed to determine the relationship of serum CD74 and mRNA in larger groups of septic shock patients, and then have a better understand of the role of CD74 in sepsis and septic shock.

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Disclosure of conflict of interest

None.

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