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Original Article

Soluble CD14 subtype (sCD14-ST) is a biomarker for neonatal sepsis

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Abstract: This prospective observational study evaluated soluble CD14 subtype (sCD14-ST) as an early diagnosis and monitoring biomarker for neonatal sepsis in controls, patients with sepsis, or systemic inflammatory response syndrome (SIRS). sCD14-ST, procalcitonin (PCT), C-reactive protein (CRP), white blood cell (WBC), and acute physiology and chronic health evaluation II (APACHE-II) score were evaluated before and after therapy. sCD14-ST levels were significantly higher in sepsis than in SIRS, and higher in SIRS than controls. Treatment significantly decreased sCD14-ST, APACHE-II, PCT, CRP, and WBC. sCD14-ST levels correlated with APACHE-II before and after therapy, and with PCT before therapy (r=0.201, P=0.05). The receiver operating characteristic area under the curve of sCD14-ST was 0.958. A 304.5 pg/mL cutoff value was associated with 95.8% sensitivity and 84.9% specificity. sCD14-ST had superior diagnostic power for neonatal sepsis than the other indicators. In conclusion, sCD14-ST is a potential biomarker for the early diagnosis and monitoring of neonatal sepsis.

Keywords: Sepsis, soluble CD14 subtype, newborn, systemic inflammatory response syndrome

Introduction

Neonatal sepsis is a systemic inflammatory response syndrome (SIRS) with suspected or diagnosed infection during the neonatal period [1]. Due to their immature immune system, newborns may be infected with many pathogenic bacteria from amniotic fluid aspiration, birth canal, and the umbilical cord during labor, leading to sepsis. If SIRS is not found or treated in a timely manner, the disease will develop quickly, readily causing septic shock, or even multiple organ failure with a high fatality rate [2]. The occurrence of SIRS is much more common in premature infants, and it can severely affect the development of the central nervous system, resulting in pulmonary diseases and other problems [3, 4]. Therefore, seeking a simple, accurate, and rapid early laboratory biomarker for diagnosis and prognosis of neonatal sepsis is currently an important area of research.

To date, 178 sepsis markers have been found, most of which are intermediate inflammatory products and pro-inflammatory cytokines [5]. However, whether early laboratory indicators can accurately diagnose and predict severe sepsis and septic shock remains controversial [6]. Cluster of differentiation 14 (CD14) is a glycoprotein expressed on the surface of monocytes and macrophages, and it is also a receptor for the lipopolysaccharide (LPS)/LPS binding protein (LBP) complex, which activates a series of signal transduction pathways and inflammatory responses and leads to SIRS [7]. CD14 can be divided into soluble CD14 (sCD14) and membrane CD14 (mCD14). sCD14 subtype (sCD14-ST) is generated from sCD14 by presepsin [8, 9].

Many studies have found that sCD14-ST could be used as an indicator for early stage sepsis [10-15]. When sCD14-ST was combined with acute physiology and chronic health evaluation II (APACHE-II) it was found to be superior to APACHE-II alone for the prognosis of sepsis patients [16]. Currently, studies are mainly focused on adults and children, and reports on neonatal sepsis are limited.

Therefore, the aim of the present study was to evaluate the usefulness of sCD14-ST as an early diagnosis and monitoring biomarker for neonatal sepsis, compared with procalcitonin (PCT), C-reactive protein (CRP), and white blood cells (WBC). This study could help fill the knowledge gap about appropriate biomarkers for sepsis in neonates.

Materials and methods

Study design and patients

This was a prospective observational study of newborns admitted to the Neonatology Department of Longyan First Hospital between August 2013 and March 2015. During the study period, 140 SIRS patients were consecutively treated and enrolled.

The diagnostic criteria for neonates with SIRS were according to the criteria of the International Pediatric Sepsis Consensus Conference [17]: two or more of the following conditions (one of which must be abnormal temperature or leukocyte count): i) body temperature >38°C or <36°C; ii) tachycardia (heart rate >180 bpm) or bradycardia (heart rate <100 bpm); iii) abnormal respiratory rate (0 days to 1 week: respiratory rate >50 breaths/min; 1 week to 1 month: respiratory rate >40 breaths/min); and iv) elevated or depressed leukocyte count for age (not secondary to chemotherapy-induced leukopenia) or >10% immature neutrophils.

EOS was defined as newborns with symptoms of SIRS within 72 h of birth. They were the ones who had a definite systemic infection or septic shock, or who had positive results for pathogens cultured from blood. The neonates of SIRS caused by hypovolemic shock or hypoxemia etc. were involved in non-infectious SIRS group. There were 96 cases of early-onset sepsis (EOS) and 44 cases of non-infectious SIRS. Based on the results of blood culture, the patients with EOS were divided into bacterial SIRS (42 cases) and non-bacterial SIRS (54 cases). All infants with EOS received anti-infection treatment, and non-infectious SIRS newborns were treated with respiratory support, circulatory support, timely blood transfusion, and infection prophylaxis.

During the same study period, 53 newborns hospitalized for other reasons (such as hyperbilirubinemia, non-infectious diarrhea, or swallowing syndrome) were included as controls. The inclusion criteria were: 1) no clinical signs or symptoms of infection; 2) negative infection index; and 3) without significant deformity.

The exclusion criteria for SIRS and control subjects were: 1) autoimmune diseases, tumor, chronic renal failure, extensive burns, severe trauma, or immunodeficiency; 2) immunosuppressive therapy; 3) fetal congenital malformations or chromosomal abnormalities; or 4) received antibiotics before hospitalization.

This study was approved by the ethics committee of the Longyan First Affiliated Hospital of Fujian Medical University (Longyan, China). Written informed parental consent was obtained for all patients.

Sample collection

All patients with EOS were tested before treatment and 3 and 5 days after beginning treatment. SIRS and control patients were routinely tested. Venous blood samples were collected in EDTA anti-coagulation tubes (2 mL) and separation gel pro-coagulation tubes (5 mL) from all of the subjects. Plasma and serum samples were obtained by centrifugation at 3500×g for 10 min at 4°C. All analyses were completed within 2 h of collection.

sCD14-ST and inflammatory markers

EDTA-Na_2 anticoagulated whole blood was used for sCD14-ST measurement using the sCD14-ST PATHFAST kit on a PATHFAST cardiac marker immune analyzer (Mitsubishi Chemical Corporation, Tokyo, Japan), which is a chemiluminescence immunoassay. PCT, CRP, and WBC were measured by immunochromatography using a HR201 detector (Highcreation, Shenzhen, China), nephelometry with an AU2700 analyzer (Olympus, Tokyo, Japan), and electric resistance with a XE-5000 analyzer (Sysmex, Tokyo, Japan), respectively. All samples were randomly numbered for blind testing.

Bacterial testing

A BACTEC FX (BD Diagnostics, Sparks, MD, USA) fully automated blood culture instrument was used for detecting the potential bacteria. Susceptibility to antibiotics was tested with a Phoenix-100 automatic system (BD Diagnostics, Sparks, MD, USA).

Table 1. Baseline characteristics of the SIRS newborns and controls

	Early-onset sepsis group	Non-infective SIRS group	Healthy control group	P
Case number	96	44	53	
Age (hours)	48 (24-72)	48 (24-96)	24 (24-60)	0.466
Male, n (%)	50 (52.1)	23 (52.27)	28 (52.83)	0.996
Gestational age (weeks) [M (P_{25}-P_{75})]	38.00 (38.00-39.08)[a,b]	39.10 (38.00-40.00)	39.10 (38.00-39.95)	0.013
Premature birth (28-37 weeks), n (%)	17 (17.7)	2 (4.5)	-	
Full-term >37 weeks, n (%)	79 (82.3)	42 (95.5)	53 (100)	
Birth weight (g) [mean ± SD]	3008.33±596.64[a]	3316.25±753.06	3093.77±585.58	0.030
<1500 g, n (%)	1 (1.0)	2 (4.5)	1 (1.9)	
<2000 g, n (%)	7 (7.3)	-	1 (1.9)	
<2500 g, n (%)	9 (9.4)	1 (2.3)	5 (9.4)	
≥2500 g, n (%)	79 (82.3)	41 (93.1)	46 (86.8)	
Delivery method, n (%)				
Natural labor	56 (58.3)	30 (68.2)	37 (69.8)	
Cesarean	40 (41.7)	14 (31.8)	16 (30.2)	0.296
APGAR score Mean [min-max]	9.53 [7-10][a,b]	9.93 [9-10]	9.94 [9-10]	<0.001
4-7 scores, n (%)	2 (2.1)	-	-	
8-10 scores, n (%)	94 (97.9)	44 (100)	53 (100)	

Notes: P_{25}-P_{75} = first and third quartile. Classified variables were expressed as %. [a]P<0.05 compared with non-infective SIRS group; [b]P<0.05 compared with the healthy control group.

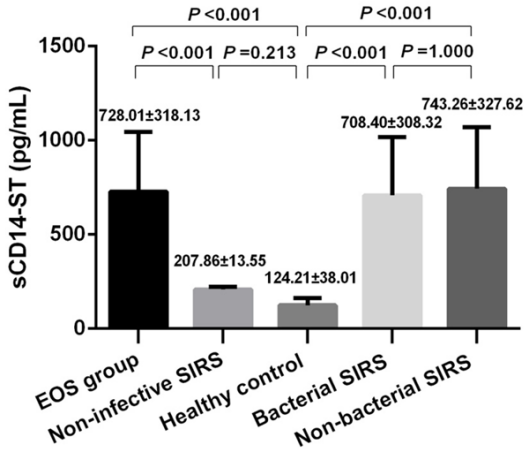

Figure 1. sCD14-ST levels in the early-onset sepsis (EOS), bacterial SIRS, non-bacterial SIRS, non-infective SIRS, and healthy control groups before treatment.

Data collection

Gender, age, disease history, blood tests, and biochemical indexes were recorded. The EOS group was scored by APACHE-II [16].

Statistical analysis

SPSS 19.0 (IBM, Armonk, NY, USA) was used for data analysis. Data was analyzed by the Kolmogorov-Smirnov test for normality. Normally distributed data was represented as mean ± standard. Analysis of variance (ANOVA) was used for comparison between several groups with the Bonferroni post-hoc test. Skewed data was represented as median (quartiles) [M (P_{25}-P_{75})]. Comparisons among groups were analyzed by the Kruskal Wallis H test, and comparison between groups was analyzed by the Mann-Whitney U test. Categorical data was expressed as frequencies and percentages. Comparison among groups was analyzed by the chi-square test. Test performance was evaluated using the receiver operating characteristic (ROC) method. Comparisons between ROC areas under curve (AUC) were analyzed by the Z test. Correlation analysis was analyzed by the Pearson test. Two-sided P<0.05 was considered statistically significant.

Results

Characteristics of the patients

Table 1 presents the characteristics of the subjects. Gestational age, birth weight, and APGAR score were significantly different among the three groups (P=0.013, P=0.030, and P<0.001, respectively); but gender and delivery method were not significantly different (both P>0.05).

Table 2. Indicator changes of 96 sepsis newborns before and after therapy [M (P_{25}-P_{75}) or mean ± SD]

Time point	Before therapy	Day 3 after therapy	Day 5 after therapy	P
N	96	96	96	
sCD14-ST (pg/mL)	728.01±318.13	545.01±400.89	330.53±208.65	<0.001
APACHE-II	34.72±15.29	19.92±7.89	13.39±3.88	<0.001
PCT (ng/mL)	12.28±6.85	5.09±4.41[a]	3.99±3.53	<0.001
CRP (mg/L)	15.27 (10.03-31.34)	3.50 (0.96-9.23)[a]	5.31 (2.38-10.19)	<0.001
WBC (×10^9/L)	13.01±6.02	10.60±4.08[a]	9.08±3.36	<0.001

Abbreviations: CD14-ST, soluble cluster of differentiation 14 subtype; PCT, procalcitonin; CRP, C-reactive protein, WBC, white blood cells. [a]P>0.05 compared with day 5 after therapy.

Table 3. ROC analyses of four indicators between newborns in the sepsis and control groups

Indicator	Cut-off value	Youden index	Sensitivity (%)	Specificity (%)	AUC	P	95% CI
sCD14-ST	304.5 pg/mL	0.807	95.8 (92/96)[a]	84.9 (45/53)[b]	0.964[c]	<0.001	0.939-0.989
PCT	6.815 ng/mL	0.653	82.3 (79/96)	83 (44/53)	0.838	<0.001	0.772-0.904
CRP	8.9 mg/L	0.592	78.1 (75/96)	81.1 (43/53)	0.823	<0.001	0.755-0.891
WBC	8.81×10^9/L	0.57	74.0 (71/96)	83 (44/53)	0.816	<0.001	0.749-0.884

Compared with PCT, WBC and CRP, [a]P<0.01, [b]P>0.05, [c]P<0.01. P was represented as the area under the curve compared to 0.5 (ROC curve of diagnostic test with no diagnostic value was the area under the curve). Abbreviations: ROC, receiver operating characteristic; sCD14-ST, soluble cluster of differentiation 14 subtype; PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cells; AUC, area under curve; CI, confidence interval.

Gestational age and APGAR score of the EOS groups were significantly lower than in the non-infective SIRS and healthy control groups (P<0.05), and birth weight was significantly lower than that of the non-infective SIRS group (P=0.008), but not significantly different from the healthy control group (P=0.431). In the non-infective SIRS and healthy control groups, gestational age, birth weight, and APGAR score were not significantly different (P=0.844, P=0.086, and P=0.815, respectively).

sCD14-ST levels before therapy

sCD14-ST levels in the EOS group newborns were significantly higher than in the non-infective SIRS and control groups (728.01±318.13 vs. 207.86±13.55 and 124.21±38.01, P<0.01) (**Figure 1**). sCD14-ST levels in the non-infective SIRS group were higher than that of the control group (207.86±13.55 vs. 124.21±38.01, P<0.01) (**Figure 1**). When the EOS group was further divided into bacterial and non-bacterial SIRS, sCD14-ST levels in the bacterial SIRS group were significantly higher than in controls (708.40±308.32 vs. 124.21±38.01, P<0.01), but not when compared with the non-bacterial SIRS group (708.40±308.32 *vs.* 743.26± 327.62 P=0.687) (**Figure 1**).

Changes in inflammatory markers after therapy

sCD14-ST, APACHE-II, PCT, CRP, and WBC were significantly decreased (all P<0.001, **Table 2**). sCD14-ST had a positive linear correlation with APACHE-II before and at days 3 and 5 after therapy (r=0.239, 0.363, and 0.478, respectively; all P<0.01), but it only had a positive linear correlation with PCT before therapy (r= 0.201, P=0.05).

Diagnostic value of sCD14-ST with PCT, CRP, and WBC for sepsis

For differentiating EOS from healthy controls, AUC of sCD14-ST was the highest (P<0.01 vs. that of PCT, CRP, and WBC) (**Table 3**). Using a cut-off of 304.5 pg/mL, sCD14-ST had 95.8% sensitivity (P<0.01 vs. that of PCT, CRP, and WBC) and 84.9% specificity (P>0.05 vs. that of PCT, CRP, and WBC) (**Table 3**).

For differentiating EOS from non-infectious SIRS, AUC of sCD14-ST was the highest (P<0.01 vs. that of PCT, CRP, and WBC) (**Table 4**). Using a cut-off of 300.5 pg/mL, sCD14-ST had 95.8% sensitivity (P<0.01 vs. that of PCT, CRP, and WBC) and 88.6% specificity (P>0.05 vs. that of PCT, CRP, and WBC) (**Table 4**).

Table 4. ROC analyses of four indicators between newborns in the sepsis and non-infectious SIRS groups

Indicator	Cut-off value	Youden index	Sensitivity (%)	Specificity (%)	AUC	P	95% CI
sCD14-ST	300.5 pg/mL	0.844	95.8 (92/96)[a]	88.6 (39/44)[b]	0.959[c]	<0.001	0.924-0.993
PCT	3.35 ng/mL	0.718	85.4 (82/96)	86.4 (38/44)	0.887	<0.001	0.832-0.942
CRP	9.915 mg/L	0.657	77.1 (74/96)	88.6 (39/44)	0.806	<0.001	0.733-0.880
WBC	6.355×10^9/L	0.760	89.6 (86/96)	86.4 (38/44)	0.849	<0.001	0.766-0.932

Compared with PCT, WBC and CRP, [a]P<0.01, [b]P>0.05, [c]P<0.01. P was represented as the area under the curve compared to 0.5 (ROC curve of diagnostic test with no diagnostic value was the area under the curve). Abbreviations: SIRS, systemic inflammatory response syndrome; ROC, receiver operating characteristic; sCD14-ST, soluble cluster of differentiation 14 subtype; PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cells; AUC, area under curve; CI, confidence interval.

Discussion

The clinical manifestations of neonatal sepsis are various, and laboratory diagnostic indicators with high specificity and sensitivity are lacking [18]. Early diagnosis of neonatal sepsis is vital to prevent septic shock or even multiple organ failure, which develop quickly and is associated with a high mortality [2]. As a potential biomarker, sCD14-ST plays a very important role in bacterial infection [19]. Increased serum sCD14-ST level is a marker for systemic inflammatory response, and sCD14-ST levels are significantly increased in adult sepsis patients [10-15]. sCD14-ST is also closely related to the development of some infective diseases, and changes in sCD14-ST levels are also related with disease severity and prognosis, especially for sepsis combined with multiple organ failure [17, 20]. The role of sCD14-ST in neonatal sepsis has been less reported. The present study suggest that whole blood sCD14-ST levels in neonatal sepsis were significantly higher than that of the non-infective SIRS and normal control groups, suggesting that it could be an indicator for identifying infective and non-infective SIRS.

As a receptor for LPS, sCD14 can combine with bacterial LPS during infection. Furthermore, it activates the MyD88-dependent and TRIF-dependent signaling pathways, promotes multi-inflammatory cells to release inflammatory medium, and mediates the immune reaction, especially in SIRS caused by Gram-negative bacteria [21]. In the present study, the levels of sCD14-ST in bacterial and non-bacterial SIRS groups were significantly higher compared with the control group, but there was no significant difference between the two SIRS groups, which is in line with a previous study on sCD14-ST in premature and full-term critically ill newborns with sepsis and SIRS [22]. Currently, studies into sCD14-ST differences in bacterial and non-bacterial SIRS patients are limited, and whether it can identify bacterial or non-bacterial SIRS still needs further study.

Due to the rapid development of neonatal sepsis, the markers were evaluated at different time points in order to evaluate their changes during therapy. APACHE II is currently the most authoritative severity evaluation system and a good indicator for disease assessment [23]. It was found that sCD14-ST in adults showed a positive correlation with APACHE II [11]. In terms of determining the prognosis of sepsis patients, the predicting significance of sCD14-ST combined with APACHE-II was previously found to be superior to APACHE-II only [10-12, 16]. In the present study, sCD14-ST was correlated with APACHE II before and at days 3 and 5 of therapy. As the patients were getting better, sCD14-ST was significantly decreased. Therefore, sCD14-ST possessed an important clinical value in the fast evaluation, monitoring, and prognosis of neonatal sepsis.

PCT can be considered to be a diagnostic marker for bacterial sepsis, but its accuracy is not high (70% sensitivity and 80% specificity). PCT levels in severe trauma and burn patients are also increased, which will lead to false positive in sepsis patients [24, 25]. In this study, ROC curve analysis between the EOS group and either the healthy control group or non-infectious SIRS group showed that the sensitivity of sCD14-ST for the diagnosis of neonatal sepsis was similar to the specificity, with values of 95.8% and 84.9%, and 95.8% and 88.6%, respectively, which were much higher than for PCT, CRP, and WBC. Thus, the diagnostic value of sCD14-ST in neonatal sepsis was superior to other conventional indicators. sCD14-ST was

significantly correlated with PCT before treatment, but not with CRP and WBC. sCD14-ST was decreased significantly before treatment, and on days 3 and 5 after beginning treatment, whereas CRP and WBC were not significantly decreased from day 3 to 5. Thus, sCD14-ST levels play an important role in rapid assessment and prognosis for neonatal sepsis.

Based on the ROC analyses, it was shown that the detection efficiency of sCD14-ST in neonatal sepsis was superior to other indicators. AUC of sCD14-ST was 0.964 and 0.959, respectively, and it was higher than that of PCT (0.838 /0.887), CRP (0.823/0.806), WBC (0.816/ 0.849), which was roughly similar to results from adult sepsis [26]. The best cut-off value of sCD14-ST was 304.5 pg/mL and 300.5 pg/ml, respectively, lower than reported values [27, 28]. The possible reason for this was probably because newborns were studied, and their immune systems were not mature. Furthermore, some research did not exclude cases with factors leading to false positive results of sCD14-ST and PCT, such as patients with chronic renal failure, burn, and severe trauma.

The study indicated that sCD14-ST played a very important role in the early diagnosis, evaluation of severity, and the prognosis of sepsis [29, 30]. Liu et al. [28] reported that sCD14-ST was significantly different between 28-day survivors and non-survivors. Kweon et al. [26] found that sCD14-ST was not correlated with the 30-day mortality rate of sepsis patients, and there was no significant difference between survivors and non-survivors. The sCD14-ST showed significant differences between the EOS and severe sepsis groups, but PCT did not. In the present study, the correlations of sCD14-ST with severity and 30 day-fatality were not studied due to limited cases; therefore, the ability for sCD14-ST to predict survival in neonates needs further exploration.

As a study from a single center, the limitations of this study include the small sample size, which prevented any survival analysis and may have introduced some selection bias. Data from multiple centers would improve the sample size and provide more evidence for these findings.

In conclusion, sCD14-ST levels were significantly correlated with APACHE II, and it was also an effective indicator for quickly evaluating neonatal sepsis. Furthermore, sCD14-ST in the EOS group was significantly higher than that in the non-infective SIRS group, and its diagnostic value was superior to other clinical indicators such as PCT and CRP. sCD14-ST was also a marker for early diagnosis and monitoring the efficacy of treatment of neonatal sepsis.

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Disclosure of conflict of interest

None.

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