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# Utility of cytokines to predict neonatal sepsis

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**BACKGROUND:** Sepsis is an important cause of neonatal morbidity and mortality worldwide. Diagnosis and treatment of neonatal sepsis relies on clinical judgment and interpretation of nonspecific laboratory tests. In a prospective cohort, we measured inflammatory cytokines as a potential biomarker for neonatal sepsis.

**METHODS:** Serum inflammatory cytokine levels were evaluated in the early stage of neonatal sepsis and after antimicrobial treatment. Receiver operating characteristic curves assessed the diagnostic value of cytokines. We performed multiple logistic regression analysis to characterize the role of each cytokine independently for infants with culture proven sepsis.

**RESULTS:** C-reactive protein, interleukin (IL)-6, IL-10 and IL-6/IL-10 levels were significantly elevated in neonatal sepsis when compared with the control group and there were 1.4 (95% confidence interval (CI): 1.2–1.5), 4.9 (95% CI: 4.6–5.1), 5.1 (95% CI: 4.5–5.6), and 10.2 (95% CI: 9.2–11.1) fold greater odds, respectively, to predict neonatal sepsis when increased. After effective treatment, median IL-6 (pretreatment value: 263.0 pg/ml and post-treatment value: 7.4 pg/ml) and IL-6/IL-10 levels (pretreatment value: 16.6 and post-treatment value: 1.4) significantly decreased. The areas under the curve for IL-6, IL-10, IL-6/IL-10 and C-reactive protein for differential diagnosis were 0.98, 0.82, 0.90, and 0.88, respectively.

**CONCLUSION:** IL-6 and IL-6/IL-10 outperformed C-reactive protein to diagnose neonatal sepsis. Of the cytokines studied, IL-6 was the most sensitive, whereas IL-6/IL-10 was the most specific predictor of neonatal sepsis.

Despite recent improvements in maternal and child health outcomes, neonatal sepsis remains an important contributor to infant morbidity and mortality worldwide (1,2). Of the estimated 6.3 million deaths of children <5 y of age in 2013, 2.8 million (44%) occurred during the neonatal period, and 0.42 million (95% confidence interval (CI) = 0.27–0.69) neonatal deaths were due to sepsis (1). Currently, differentiating septic from nonseptic infants is based on nonspecific clinical signs. Prior studies have examined various laboratory markers diagnosis of sepsis. The C-reactive protein (CRP) has been most extensively studied and is often used to distinguish between viral and bacterial infections (3). The CRP is a nonspecific marker for sepsis as it is elevated in certain systemic autoimmune diseases, some oncological diseases, in response to trauma or tissue damage, and after surgery (4). Studies have demonstrated that the specificity and sensitivity of procalcitonin are higher than those of CRP; however, procalcitonin is also not entirely specific to sepsis as its level is elevated in patients who have undergone surgery, in those with florid autoimmune disease and in those who have received an OKT3 monoclonal antibody for immunosuppression after solid organ transplantation (5–7). Routine laboratory tests are ineffective for diagnosing sepsis (8), because they are either nonspecific or have a low sensitivity, often resulting in inappropriate antibiotic use or delayed diagnosis. Sepsis is typically associated with a systemic inflammatory response, with the production and release of a variety of inflammatory mediators, including cytokines (9,10). Therefore, this study aimed to investigate the use of cytokines as diagnostic marker for sepsis.

## METHODS

### Participants

This was a prospective study conducted from January 2011 to December 2015. Ethical approval was obtained from the Institutional Review Board of Zhejiang University (approval number: 2010019). Written informed consent was obtained from all guardians on behalf of the minor/child participants involved in the study. Patients with a positive blood culture and compatible clinical features, including respiratory distress, cyanosis, poor perfusion, lethargy, poor feeding, apnea, and bradycardia were enrolled in the study. At the time of onset of clinical symptoms of neonatal sepsis and before the initiation of any antibiotic therapy, blood samples were collected to measure the serum Th1/Th2 cytokine levels. These indexes were tested again after effective treatment. Effective treatment refers to the disappearance of clinical symptoms and the return of the laboratory indexes to normal levels. Neonatal patients with jaundice ($n$ = 140) or enterovirus infection ($n$ = 140) and healthy newborns ($n$ = 140) were included as controls, and they were matched for age, body weight, and gender. Blood samples were also collected from the neonatal patients with jaundice or enterovirus infection at the time of the onset of clinical symptoms and before the initiation of any antibiotic therapy. Blood samples were collected from the healthy newborns when they came to the hospital for physical examination.

### Measurement of Serum Th1/Th2 Cytokine and CRP Levels

The blood samples were centrifuged at 1,000$g$ at 20°C for 20 min after clotting. The serum was carefully harvested, and the Th1/Th2 cytokine levels were measured immediately using 320 flow cytometry. Further, the concentrations of interleukin (IL)-2, IL-4, IL-6, IL-10, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ were

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determined using a CBA kit (BD CBA Human Th1/Th2 Cytokine Kit II; BD Biosciences, San Jose, CA) (11). The minimum limit of detection for all six cytokines was 1 pg/ml, and the maximum was 5,000 pg/ml. CRP concentrations were measured using a QuikRead device and QuikRead go CRP kits (Orion Diagnostica, Finland).

### Statistical Analysis

Multiple regression analysis (logistic regression modeling) was performed to examine the independent role of each cytokine, while controlling for all of the others, with culture-proven sepsis used as the outcome variable. The cytokines were used as continuous variables. The odds ratios indicate the time points at which diagnosis of neonatal sepsis was likely vs. the controls for each cytokine evaluated. Comparisons between the study and control groups were performed using the Mann–Whitney *U*-test for continuous variables. All statistical analyses were conducted using SPSS Version 18.0 (PASW Statistics for Windows, Version 18.0. Chicago: SPSS). A $P < 0.05$ was considered statistically significant. Further, receiver operating characteristic (ROC) curves were used to assess the diagnostic values of the IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, and CRP levels in discriminating neonatal sepsis. The optimal diagnostic threshold was determined according to Youden's *J*-statistic, and the relative sensitivity, specificity, positive and negative predictive values were calculated.

## RESULTS

### Characteristics of Neonatal Sepsis

The study group included 420 patients with neonatal sepsis with a male to female ratio of 1.32:1. The risk factors for neonatal sepsis (in order) were as follows: preterm birth, low birth weight, premature rupture of membrane ≥18 h, meconium-stained amniotic fluid, neonatal asphyxia and intrauterine fetal distress. Of them, the most important risk factors were preterm delivery and low birth weight. In the study group with neonatal sepsis, 31% were premature ($n = 130$), and 30.2% ($n = 127$) had a birth weight of < 2,500 g. Common Clinical manifestations included jaundice, abdominal distension, abnormal temperature, edema, lethargy, apnea, convulsions, and omphalitis. Of these, jaundice (48.1%) and abdominal distension (39.3%) were the most common. Gram-positive bacteria accounted for 52.8% of the pathogenic micro-organisms causing neonatal sepsis, with the main causative organisms being *Staphylococcus epidermidis* ($n = 87$, 20.7%) and *S. haemolyticus* ($n = 37$, 8.8%). In addition, Gram-negative bacteria accounted for 42.2% of the pathogenic micro-organisms, with the main causative organisms being *Escherichia coli* ($n = 87$, 20.7%) and *Klebsiella pneumoniae* ($n = 64$, 15.2%). Further, fungi accounted for 5% of the pathogenic micro-organisms causing neonatal sepsis (**Table 1**).

**Table 1.** The features of neonatal sepsis

| Features | Number |
|---|---|
| Demography | |
| Number | 420 |
| Gender (boys/girls) | 239/181 |
| Gestational age at delivery <37 wk | 130 (31.0%) |
| Birth weight < 2,500 g | 127 (30.2%) |
| Asphyxia neonates | 48 (11.4%) |
| Intrauterine fetal distress | 30 (7.1%) |
| Meconium-stained amniotic fluid | 51(12.1%) |
| Premature rupture of membrane ≥18 h | 60 (14.3%) |
| Clinic manifestation | |
| Abnormal temperature | 126(30.0%) |
| Swelling | 43(10.2%) |
| Lethargy | 142(33.8%) |
| Omphalitis, pustules or burst of the skin | 52(12.4%) |
| Vomiting, abdominal distension | 165(39.3%) |
| Apnea | 60(14.3%) |
| Jaundice | 202(48.1%) |
| Seizures | 81(19.3%) |
| Complication | |
| Septic stock | 19(4.5%) |
| Necrotizing enterocolitis | 25(6.0%) |
| Bacterial meningitis | 61(14.5%) |
| DIC | 2(0.5%) |
| Pathogen | |
| Staphylococcus epidermidis | 87 (20.7%) |
| Staphylococcus haemolyticus | 37 (8.8%) |
| Staphylococcus capitis | 27 (6.4%) |
| Staphylococcus warneri | 18 (4.3%) |
| Staphylococcus aureus | 21 (5.0%) |
| Enterococci | 32 (7.6%) |
| Klebsiella pneumoniae | 64(15.2%) |
| Escherichia coli | 87(20.7%) |
| Acinetobacter baumannii | 26(6.2%) |
| Candida | 21(5.0%) |

### Th1/Th2 Cytokine and CRP Levels in Neonatal Sepsis

There were significant differences in the IL-6, IL-10, IL-6/IL-10, and CRP levels between the study and control groups ($P < 0.001$). However, no difference was found in the IL-2, IL-4, TNF-α or IFN-γ level ($P > 0.05$) (**Figure 1**). The median CRP, IL-6, IL-10, and IL-6/IL-10 levels were significantly elevated in the study group compared with the control group (CRP (mg/ml): 17.0 vs. 4.0, $P < 0.001$; IL-6 (pg/ml): 190.7 vs. 3.8, $P < 0.001$; IL-10: 10.4 vs. 3.6, $P < 0.001$; and IL-6/IL-10: 16.6 vs. 1.0, $P < 0.001$), with odds ratios of 1.4, 4.9, 5.1, and 10.2, respectively, as determined by multiple regression analysis (logistic regression modeling) performed to examine the independent role of each cytokine, while controlling for all of the others, with culture proven sepsis used as the outcome variable. After effective treatment, the median IL-6 and IL-6/IL-10 levels were significantly decreased (IL-6 (pg/ml): 263.0 vs. 7.4, $P < 0.001$; and IL-6/IL-10: 16.6 vs. 1.4, $P < 0.001$) (**Figure 2**). There were significant differences in the IL-10 and IFN-γ levels between early-onset sepsis and late-onset sepsis ($P < 0.05$), but no differences were found in the IL-2, IL-4, IL-6, IL-6/IL-10 or TNF-α level ($P > 0.05$). Further, there were no significant differences in the serum cytokine levels between the neonatal septic patients with Gram-positive bacteria and those with Gram-negative bacteria ($P > 0.05$). Detailed information is provided in **Table 2**.

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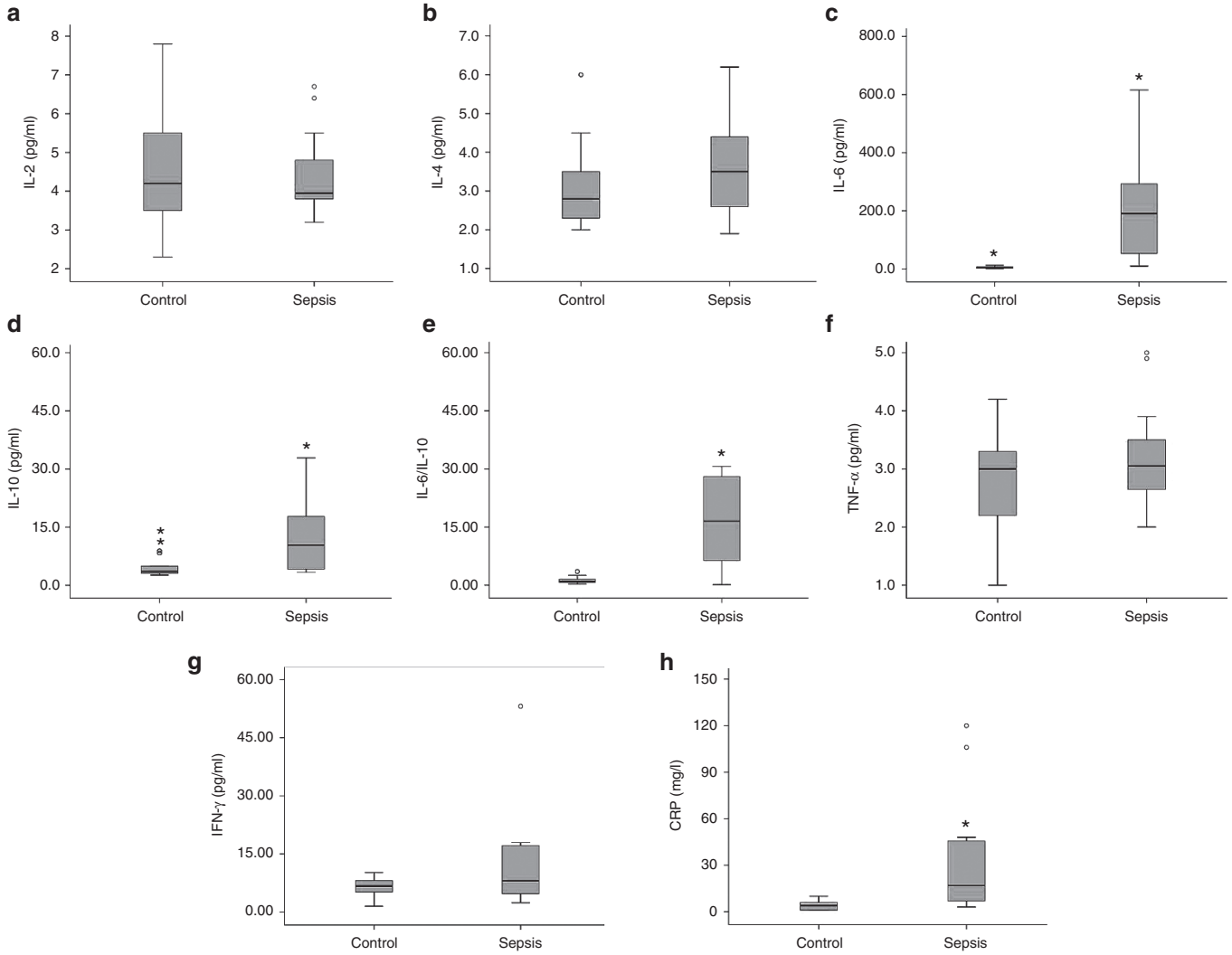


**Figure 1.** Serum concentrations of inflammatory cytokines and C-reactive protein in neonatal sepsis. (**a**) IL-2 level. (**b**) IL-4 level. (**c**) IL-6 level: *$P < 0.001$ vs. control group. (**d**) IL-10 level: *$P < 0.001$ vs. control group. (**e**) IL-6/IL-10 level: *$P < 0.001$ vs. control group. (**f**) TNF-α level. (**g**) IFN-γ level. (**h**) CRP level: *$P < 0.001$ vs. control group. CRP, C-reactive protein; IFN-γ, interferon-γ; IL-2, interleukin; TNF-α, tumor necrosis factor-α.

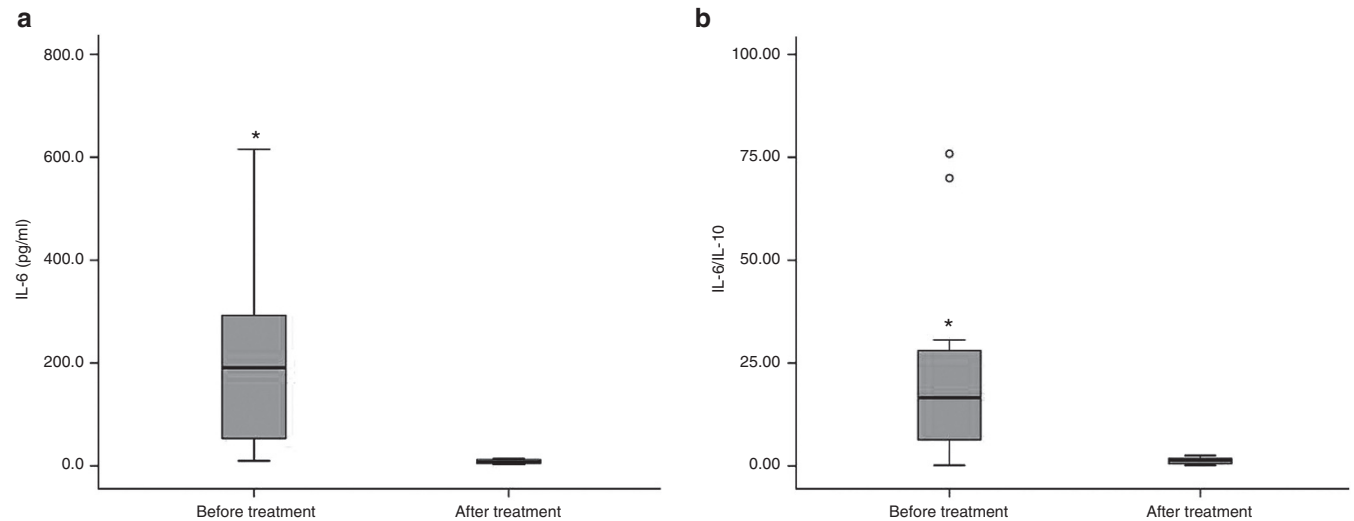


**Figure 2.** Changes in IL-6 level and IL-6/IL-10 ratio before and after effective treatment for neonatal sepsis. (**a**) IL-6 level: *$P < 0.001$ vs. after effective treatment. (**b**) IL-6/IL-10 level: *$P < 0.001$ vs. after effective treatment. IL, interleukin.


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### Using Inflammatory Cytokine Levels to Identify Neonatal Sepsis

The results of this study revealed that the development of sepsis resulted in significant alterations in the CRP, IL-6, IL-10, and IL-6/IL-10 levels, with larger odds ratios compared with other diagnostic indicators; therefore, we evaluated the use of these indicators in the differential diagnosis of neonatal sepsis. For the differential diagnosis of this condition, the areas under the ROC curves were 0.98 for IL-6, 0.82 for IL-10, 0.90 for IL-6/IL-10, and 0.88 for CRP. A serum IL-6 level of >12.5 pg/ml had a sensitivity of 93.75% and a specificity of 94.12% in the differential diagnosis of neonatal sepsis; in addition, a serum IL-10 level of >3.8 pg/ml had a sensitivity of 87.50% and a specificity of 61.76%, and a serum IL-6/IL-10 level of >3.5 had a sensitivity of 81.25% and a specificity of 100%. In addition, at a CRP level of >10.0 mg/l, the diagnostic sensitivity was 62.50%, and the specificity was 100%. Detailed patient information is provided in **Table 3** and **Figure 3**.

## DISCUSSION

The most reliable diagnostic tool for neonatal sepsis, often referred to as the gold standard is a blood culture test for bacteria. While this test is the most reliable diagnostic tool that is currently available, it can take up to 48 h to obtain results, and treatment must often begin before the results are known. An additional complication is that this test can yield negative results for one out of five patients with sepsis (12,13). Therefore, identifying new biomarkers is critically important.

Diagnostic hematological biomarkers, such as CRP, have been previously studied (14), and while they have been shown to be correlated with sepsis, they have been considered to have limited diagnostic potential (15,16). Infectious and noninfectious diseases, such as malignancies and inflammatory diseases can also cause CRP production (17). Sepsis development can begin following the recognition of one or more components of an invading organism, including structural elements, such as Gram-negative endotoxins and secreted exotoxins, which stimulate the local and systemic release of endogenous inflammatory mediators. These inflammatory mediators include cytokines, such as TNF-α, IFN-γ, and IL-6, which promote the migration and activation of immune cells (18,19). Therefore, this study focused on the efficacy of cytokines for the early diagnosis of sepsis. Although IL-2, IL-4, TNF-α, and IFN-γ have been implicated as major mediators of sepsis, no significant differences in their levels were found compared with the control group in this study. Among these cytokines, IL-4 is considered the most relevant for mycoplasma pneumoniae infection, and the IFN-γ level is higher in viral infections (20,21).

Our results showed that IL-6 and IL-6/IL-10 were more effective than CRP in the differential diagnosis of neonatal sepsis.

**Table 2.** Serum cytokine levels in early-onset sepsis, late-onset sepsis and neonatal sepsis patients with gram-positive bacteria or gram-negative bacteria

| Diagnostic indicators | Early-onset sepsis | Late-onset sepsis | Z | *P* | Gram-positive bacteria | Gram-negative bacteria | Z | *P* |
|---|---|---|---|---|---|---|---|---|
| IL-2 (pg/ml) | 3.9 (4.0–5.0) | 4.0 (3.0–7.0) | −0.877 | 0.380 | 4.0 (3.0–6.0) | 5.2 (3.0–7.0) | 0.463 | 0.521 |
| IL-4 (pg/ml) | 4.0 (3.4–4.4) | 3.3 (1.9–6.2) | −0.721 | 0.471 | 3.7 (2.1–4.6) | 2.7 (1.9–6.2) | 0.331 | 0.379 |
| IL-6 (pg/ml) | 2,007.7 (38.0–5,045.0) | 180.6 (9.7–615.5) | −1.277 | 0.201 | 170.4 (9.7–5,045.0) | 219.6 (64.8–615.5) | 0.396 | 0.446 |
| IL-10 (pg/ml) | 4.1 (3.3–11.9) | 11.9 (3.6–213.9) | −2.354 | 0.019 | 8.7 (3.3–80.5) | 20.9 (5.9–213.9) | 0.182 | 0.212 |
| IL-6/IL-10 | 16.9 (11.5–1,230.5) | 16.3 (0.1–75.9) | −0.256 | 0.798 | 16.6 (0.1–1,230.4) | 16.3 (1.2–69.9) | 0.808 | 0.862 |
| TNF-a (pg/ml) | 3.5 (3.0–4.9) | 2.9 (2.0–5.0) | −1.138 | 0.255 | 3.3 (2.0–4.9) | 2.7 (2.5–5.0) | 0.463 | 0.521 |
| IFN-γ (pg/ml) | 9.9 (4.0–109.0) | 6.6 (2.4–305.8) | −2.975 | 0.003 | 9.7 (2.4–305.8) | 6.0 (4.1–16.3) | 0.467 | 0.521 |

IL-1, interleukin-1; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α.

**Table 3.** Performances of inflammatory cytokines in discriminating neonatal sepsis

| Diagnostic indicators | Neonatal sepsis | Control | *P* | AUC | Youden index *J* | Cut off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Odds ratios | 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IL-2 (pg/ml) | 4.0 (3.0–7.0) | 4.2 (2.0–8.0) | 0.925 | 0.50 | 0.081 | >4.0 | 37.50 | 70.59 | 37.5 | 70.6 | 0.9 | 0.8–1.0 |
| IL-4 (pg/ml) | 3.5 (1.9–6.2) | 2.8 (2.0–6.0) | 0.108 | 0.64 | 0.456 | >3.0 | 75.00 | 70.59 | 54.5 | 85.7 | 0.9 | 0.8–1.0 |
| IL-6 (pg/ml) | 190.7 (9.7–5,045.0) | 3.8 (1.1–42.4) | <0.001 | 0.98 | 0.879 | >12.5 | 93.75 | 94.12 | 88.2 | 97.0 | 4.9 | 4.6–5.1 |
| IL-10 (pg/ml) | 10.4 (3.3–213.9) | 3.6 (2.6–12.0) | <0.001 | 0.82 | 0.493 | >3.8 | 87.50 | 61.76 | 51.9 | 91.3 | 5.1 | 4.5–5.6 |
| IL-6/IL-10 | 16.6 (0.1–1,230.5) | 1.0 (0.3–3.5) | <0.001 | 0.90 | 0.813 | >3.5 | 81.25 | 100.00 | 100.0 | 91.9 | 10.2 | 9.2–11.1 |
| TNF-α (pg/ml) | 3.2 (2.0–5.0) | 3.0 (1.0–4.2) | 0.260 | 0.60 | 0.232 | >3.3 | 43.75 | 79.40 | 50.0 | 75.0 | 0.9 | 0.8–1.0 |
| IFN-γ (pg/ml) | 8.1 (2.4–305.8) | 6.7 (1.5–10.2) | 0.197 | 0.61 | 0.471 | >9.3 | 50.00 | 97.10 | 88.9 | 80.5 | 1.2 | 1.1–1.4 |
| CRP (mg/l) | 17.0 (3.0–256.0) | 4.0 (1.0–10.0) | <0.001 | 0.88 | 0.625 | >10.0 | 62.50 | 100.00 | 100.0 | 85.0 | 1.4 | 1.2–1.5 |

AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; IL-1, interleukin-1; IFN-γ, interferon-γ; NPV, negative predictive value; TNF-α, tumor necrosis factor-α; PPV, positive predictive value.In this study, multiple regression analysis (logistic regression modeling) was used to explore the independent role of each cytokine controlling for all the others with culture proven sepsis as the outcome variable. Odds ratios show the time points at which diagnosis of neonatal sepsis was likely vs. the controls for each cytokine evaluated.

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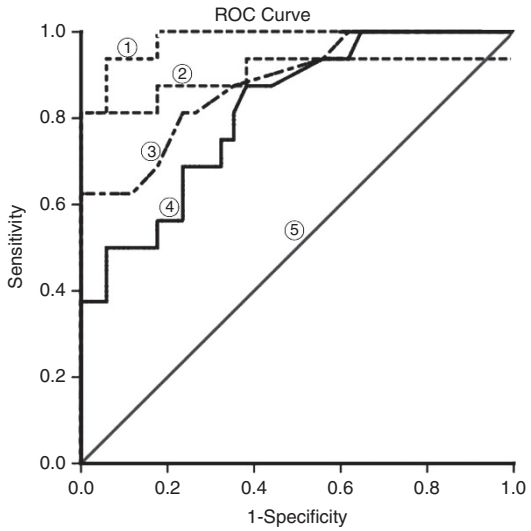


**Figure 3.** Receiver operating characteristic curve analysis evaluating the use of cytokines in discriminating neonatal sepsis. AUC, area under the curve. ① ROC of IL-6, with an AUC of 0.98; ② ROC of IL6/10, with an AUC of 0.90; ③ ROC of CRP, with an AUC of 0.88; ④ ROC of IL-10, with an AUC of 0.82; and ⑤ reference line. CRP, C-reactive protein; IL-6, interleukin-6; ROC, receiver operating characteristic curve.

IL-6 had the highest diagnostic sensitivity, whereas IL-6/IL-10 had the best diagnostic specificity. These findings are consistent with those of previous studies (11,22,23). However, to better simulate the actual clinical situation and increase the relevance of the results, our study included a control group consisting of newborns with neonatal jaundice and intestinal viruses, which are common and can be easily confused with neonatal sepsis. The sample size of this study was also larger than those of previous studies; thus, our findings may be of greater reference value.

IL-6 is a cytokine involved in the early host response to infection preceding the increase in CRP. It is synthesized by endothelial cells, mononuclear phagocytes, fibroblasts, amnion, and trophoblastic cells shortly after stimulation by microbial products (24). As the IL-6 level is higher than the CRP level in early disease stages, IL-6 may be useful for early diagnosis (25). *In vivo* experiments have shown that after lipopolysaccharide injection, the release of IL-6 occurs at 1–2 h, the peak response occurs at 3 h, and then its level decreases to the baseline level at 8 h (26). The half-life of IL-6 is ~100 min (27), and its circulating concentration can drop precipitously following antimicrobial treatment (28). The body's immune response pathway is different in the presence of a viral infection compared with that in the presence of a bacterial infection, although elevations in the IL-6 and CRP levels occur in virally infected children but are generally less pronounced (3). Our findings also showed that after the neonatal sepsis patients received effective treatment, their IL-6 levels dropped significantly, suggesting that IL-6 can be used as a therapeutic monitoring parameter. However, in some cases, such as chorioamnionitis, the passive transfer of IL-6 can result in an elevated IL-6 level after birth, which may lead to a false-positive result. Thus, it is necessary to assess maternal risk factors.

IL-10 is an anti-inflammatory cytokine released by monocytes, macrophages, T and B lymphocytes, neutrophils, and mesangial cells. Because IL-6 and IL-10 are two indicators associated with sepsis, the IL-6/IL-10 ratio has higher specificity in the differential diagnosis of neonatal sepsis. In addition, the appropriate response of IL-10 may have a protective effect on systemic inflammatory response syndrome, and a high IL-6/IL-10 ratio has been observed in patients with a worse prognosis (28).

Flow cytometry is an efficient method for detecting cytokines and may be useful in some medical settings; but is not routinely available in most laboratories. Other cytokine detection methods, such as ELISA, are currently available. The reagent cost associated with ELISA is low, and it does not require the use of expensive instruments; therefore, this technique can be used in hospitals at various levels.

In conclusion, the results of this study demonstrated that levels of IL-6 level and IL-6/IL-10 are more sensitive and specific for diagnosing neonatal sepsis than CRP. IL-6 had the highest diagnostic sensitivity, whereas IL-6/IL-10 had the greatest diagnostic specificity. IL-6/IL-10 may be a marker for effective antimicrobial treatment in neonatal sepsis. Biomarkers do not replace clinical judgment in evaluating and empirically treating neonatal sepsis; rather, analysis of cytokines should serve to support clinical decision-making while awaiting definitive test results.

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