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The Clinical Significance of Interleukin-6, C-Reactive Protein, and Procalcitonin in the Early Recognition of Nosocomial Infections in Preterm Infants

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Research Article

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ABSTRACT

Aim: This study assessed the clinical value of interleukin-6 (IL-6), C-Reactive Protein (CRP), and Procalcitonin (PCT) for early recognition of nosocomial infections in preterm infants.

Methods: 120 neonates were finally analyzed, 89 with sepsis were compared with 31 noninfected controls. IL-6, CRP and PCT were measured at certain stages. Receiver-Operating Characteristic (ROC) curve analysis was used to determine the best cutoff values of IL-6, CRP, and PCT for diagnosing sepsis.

Results: IL-6 peaked 6 hours after the infection onset and dropped to normal 24–48 hours after the infection was controlled. The best cutoff values of IL-6, CRP, and PCT were >99.6 pg/mL, >9.27 mg/L, and >2.33 ng/mL, respectively. The areas under the ROC curves were 0.888, 0.823, and 0.953, respectively. When PCT was combined with IL-6 or with both IL-6 and CRP, the sensitivity and specificity were >85%.

Conclusion: IL-6, CRP, and PCT are reliable indicators for early diagnosis of nosocomial infections in preterm infants. When PCT was combined with IL-6 or with both IL-6 and CRP, the accuracy of clinical diagnosis could be improved.

INTRODUCTION

Neonatal sepsis is a systemic infectious disease caused by pathogens such as bacteria, fungi, and viruses that invade the circulation, grow and multiply, and produce toxins within 28 days after birth. According to the onset time (before or after 3 days of age), it can be divided into Early-Onset Sepsis (EOS) and late-onset sepsis [1]. The incidence is 1-8/1,000 live births. The lower the birth weight, the higher the incidence of neonatal sepsis. The incidence of neonatal sepsis in infants with very low birth weights may reach 164/1000, and the incidence of long-term hospitalization may reach 300/1000 [2]. The clinical signs of neonatal sepsis are atypical: It often manifests as respiratory distress, tachycardia or bradycardia, poor perfusion, feeding intolerance, jaundice, and abnormal body temperature. The nonspecific clinical signs increase the difficulty in diagnosing neonatal sepsis. Therefore, clinical diagnosis is an unreliable early indicator of sepsis [3].

The risk of developing sepsis is higher in neonates due to their immature immune systems, low leukocyte phagocytic activity, low cytokine production, poor humoral immunity, weak skin barrier, and the use of invasive procedures such as mechanical ventilation, central venous catheterization, and lumbar puncture [4,5]. In 2013, the World Health Organization announced the results of an assessment of the causes of death of 2.8 million neonates worldwide. There were an estimated 420,000 neonatal deaths caused by sepsis per year, accounting for 15.0% of neonatal deaths [6]. The onset of neonatal sepsis is relatively insidious. However, it progresses rapidly and is often accompanied by severe complications, such as shock and multiple organ dysfunctions. Therefore, early diagnosis is essential to reducing the mortality of neonatal sepsis and improving the prognosis. At present, the laboratory tests that are used for the diagnosis of sepsis include bacterial culture, white blood cell counts, platelet counts, cell surface antigen and bacterial gene detection. However, because of unclear diagnostic thresholds, complex detection methods, false-negative results, and other reasons, there is no ideal indicator for the early diagnosis of neonatal sepsis. The gold standard for the diagnosis of sepsis is blood culture, but the reporting of results may take 24-48 hours. Therefore, testing methods with good accuracy, high sensitivity and specificity, and quick results are urgently needed to guide the clinical diagnosis and treatment of neonatal sepsis. Many conventional hematological tests such as CRP, PCT and “Potential biomarkers” such as IL-6 have been used for the diagnosis of sepsis while the diagnostic threshold for IL-6 remains unclear [7]. This study assessed the best cutoff value of IL-6, the diagnostic accuracy of CRP, IL-6, PCT, singly and in combination, for the early diagnosis of nosocomial infections in preterm infants.

MATERIALS AND METHODS

Participants

This study was conducted among preterm infants admitted to the Department of Neonatology, Shengjing Hospital of China Medical University, from July 2019 to July 2020. The inclusion criteria included an age >3 days in preterm infants whose gestational age was ≥ 30 and ≤ 34 weeks at birth, with stable vital signs and hemodynamic parameters. The exclusion criteria included the mother’s use of glucocorticoids before delivery; diagnosis with a community-acquired infection; incomplete clinical records; antibiotic use before the first blood collection; and a suspicion that the infant had inherited metabolic diseases, congenital malformations, or prenatal or intrapartum asphyxia.

This study was approved by the Ethics Committee of Shengjing Hospital of China Medical University. Informed consent was obtained from the guardians of the study participants, and sample collection was performed in accordance with the standards of diagnosis and treatment.

Study design

Participants were assigned to groups according to a 2019 expert consensus on the diagnosis and treatment of neonatal sepsis. In the sepsis group, 1 mL of venous blood was drawn to measure the IL-6 level when the infection was first clinically suspected (before the administration of antibiotics); 6 hours and 12 hours after infection onset; and 24-48 hours, 3 days, and 7 days after infection control. Another 1 mL of venous blood was drawn to measure the CRP and PCT levels at infection onset (before the administration of antibiotics) and 7 days after infection control. Additionally, 1 mL of blood was drawn for bacterial culture before the administration of antibiotics [8]. In the control group, according to the admission routine, 2 mL of venous blood was drawn after admission for measurement of IL-6, CRP, and PCT.

Index and methods

IL-6 was measured by enzyme-linked immunosorbent assay with a reagent provided by Xiamen Huijia Biotechnology Co, Ltd. (Xiamen, China), and ≥ 96.52 pg/mL was considered positive [9]. CRP was measured by immune scattering turbidimetry with a reagent provided by Shanghai Jiemen Biotechnology Co, Ltd. (Shanghai, China), and ≥ 8 mg/L was considered positive. PCT was quantitatively measured by enzyme-linked fluorescence assay with a reagent produced by BRAHMS Co. (Hennigsdorf, Germany), and ≥ 0.5 ng/mL was considered positive.

Definitions and diagnostic criteria

A confirmed sepsis diagnosis was defined as clinical manifestations of sepsis and a positive blood or cerebrospinal fluid (or other sterile body cavity fluid) culture. A clinical sepsis diagnosis was defined as clinical manifestations of sepsis with any of the following: more than two positive nonspecific blood detection indicators (total leukocyte count, platelet count, CRP, PCT), cerebrospinal fluid showing signs of purulent meningitis; or the detection of pathogenic bacterial DNA in the blood. A nosocomial infection was defined as an infection occurring ≥ 48 hours after hospital admission, including infections occurring during hospitalization and those occurring after discharge, as a result of hospital exposure to pathogens [10].

Statistical analysis

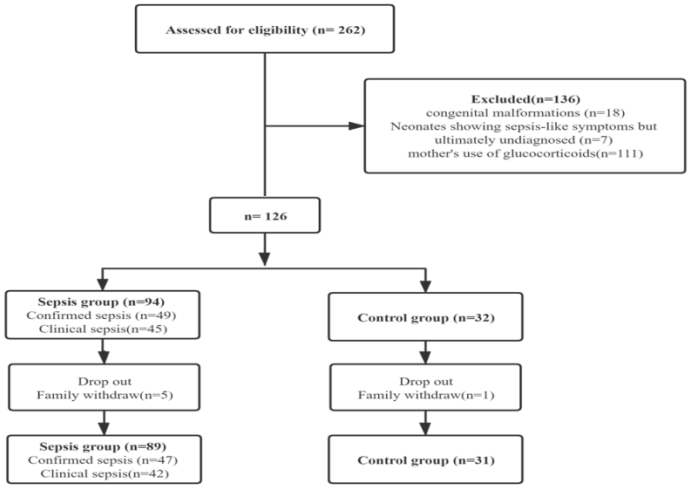
SPSS 22.0 (IBM Corp, Armonk, NY, USA) was used for the statistical analysis of the data. Continuous data were expressed as means ± standard deviations, and t-tests were used for comparisons between groups. Discrete data were expressed as frequencies, and chi-square tests were used for comparisons between groups. The best cutoff values of IL-6, CRP, and PCT were determined using Receiver-Operating Characteristic (ROC) curve analysis. The sensitivity, specificity, Positive Predictive Values (PPVs), Negative Predictive Values (NPVs), and Areas Under the ROC Curves (AUCs) of the three inflammatory marker levels were calculated singly and in combination. The correlation analysis used single-factor regression analysis, with the levels of the indicators as independent variables. A P value of <0.05 indicated that the difference was statistically significant. This study was retrospectively registered in the China Clinical Trials.

RESULTS

Participant characteristics

A total of 262 cases were enrolled in the study. Among these infants, 136 were excluded. In all, 126 infants enrolled in the study; 5 infants in sepsis group and 1 infant in control group dropped out of the programme because of parent's wish to withdraw from the trial. Finally, 89 cases of sepsis (47 cases of confirmed sepsis and 42 cases of clinical sepsis) and 31 controls (noninfected neonates hospitalized during the same period) could be analyzed. There were 12 cases of low birth weight, 8 cases of neonatal hyperbilirubinemia, 4 cases of neonatal anemia, 4 cases of gastrointestinal bleeding, and 3 cases of arrhythmia in control group (Figure 1).

Figure 1. Flow chart of the study.



Participant characteristics according to group there were no statistically significant differences in gestational age, age, sex, Apgar score, or birth weight between the neonates in the three groups (Table 1).

Table 1. Participant characteristics according to group.

Group	Confirmed sepsis group	Clinical sepsis group	Control group
N	47	42	31
Sex (male/female)	25/22[a]	21/21[a]	17/14
Gestational age (weeks)	33.55 ± 3.02[a]	33.71 ± 2.51[a]	33.66 ± 2.33
Age (days)	14.32 ± 9.74[a]	13.50 ± 8.92[a]	11.58 ± 7.42
5 min Apgar score	9.31 ± 0.84[a]	9.29 ± 0.82[a]	9.30 ± 0.83
Birth weight (g)	1784 ± 677.6[a]	1918 ± 666.1[a]	1913 ± 626.7
Note. [a] P>0.05 compared to the control group.			

Blood culture: A total of 47 neonates in the sepsis group had positive blood cultures, and the distribution of pathogens was as follows: 23 cases of gram-negative bacilli (48.9%), 20 cases of gram-positive cocci (42.5%), and four cases of fungi (8.6%) (Table 2).

Table 2. Pathogens identified in neonates with sepsis.

Pathogen classification	Cases (n)	Proportion of cases (%)
Gram-negative bacilli	**23**	**48.9**
Klebsiella pneumoniae	16	34
Escherichia coli	6	12.8
Acinetobacter baumannii	1	2.1
Gram-positive cocci	**20**	**42.5**
Staphylococcus epidermidis	10	21.3
Staphylococcus aureus	5	10.6
Enterococcus faecium	4	8.5
Streptococcus agalactiae	1	2.1
Fungus	**4**	**8.6**
Candida albicans	2	4.3
Candida parapsilosis	2	4.3

IL-6, CRP, and PCT levels: Before antibiotic treatment, the levels of IL-6, CRP, and PCT in the sepsis group were significantly higher than those in the control group. After effective infection control (7 days), the levels of IL-6, CRP, and PCT in the sepsis group were significantly reduced (Table 3).

Table 3. Mean interleukin-6, C-reactive protein, and procalcitonin levels according to group.

Group	Confirmed sepsis group		Clinical sepsis group		Control group
N	47		42		31
	Pretreatment	Post treatment (7 days)	Pretreatment	Post treatment (7 days)	
IL-6 (pg/mL)	393.8 ± 213.4[a,b]	27.11 ± 14.20	375.5 ± 192.1[a,b]	21.55 ± 6.44	41.87 ± 24.30
CRP (mg/L)	26.51 ± 28.83[a,b]	5.61 ± 3.00	20.22 ± 18.19[a,b]	5.36 ± 3.01	5.00 ± 2.84
PCT (ng/mL)	8.70 ± 10.63[a,b]	0.37 ± 0.66	6.93 ± 6.87[a,b]	0.31 ± 0.18	0.32 ± 0.45

Note: [a] $P<0.05$ compared to the control group; [b] $P<0.05$ compared to the same group after treatment.

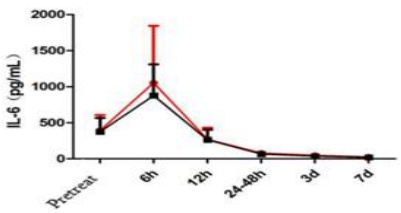
Abbreviations: CRP: C-Reactive Protein; IL-6: Interleukin 6; PCT: Procalcitonin.

IL-6 at each stage of infection: Previous studies have clarified the dynamic trends of CRP and PCT [11]. The IL-6 levels peaked at 6 hours after the onset of infection and decreased to normal levels 24–48 hours after the infection was effectively controlled (Table 4, Figure 2).

Table 4. Mean interleukin 5 levels at each stage of infection in the sepsis group.

Group	IL-6 (pg/mL) (mean ± SD)
Sepsis group	
Confirmed sepsis (N=47)	
Pretreatment	393.8 ± 213.4
Post treatment (6 hours)	1052 ± 791.4
Post treatment (12 hours)	270.6 ± 160.8
Post treatment (24-48 hours)	80.62 ± 28.51
Post treatment (3 days)	49.03 ± 18.85
Post treatment (7 days)	27.11 ± 14.20
Clinical sepsis (N=42)	
Pretreatment	375.5 ± 192.1
Post treatment (6 hours)	877.2 ± 431.4
Post treatment (12 hours)	264.2 ± 140.1
Post treatment (24-48 hours)	67.95 ± 16.89
Post treatment (3 days)	37.49 ± 9.40
Post treatment (7 days)	21.55 ± 6.44
Abbreviations: IL-6: Interleukin 6; SD: Standard Deviation.	

Figure 2. Mean interleukin 6 levels in the neonates with sepsis according to time since the infection onset IL-6, interleukin 6. **Note.** Confirmed sepsis group; Clinical sepsis group.



Comparison of the diagnostic values of IL-6, CRP, PCT, and combined testing: The ROC curves revealed that the best cutoff values of IL-6, CRP, and PCT were >99.6 pg/mL, >9.27 mg/L, and >2.33 ng/mL, respectively (Figures 3 and 4).

Figure 3. Receiver-operating characteristic curves for diagnosing neonatal sepsis according to the mean interleukin 6, C-reactive protein, and procalcitonin values. All tests were performed on admission to hospital. CRP, C-reactive protein; IL-6, interleukin 6; PCT, procalcitonin. **Note.** CRP; PCT; IL-6.

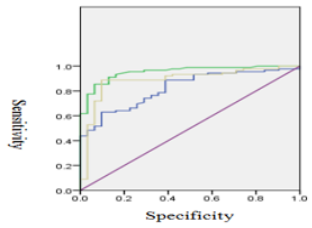
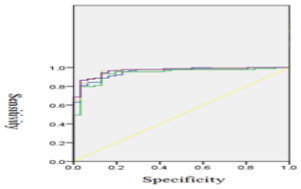


Figure 4. Receiver-operating characteristic curves for diagnosing neonatal sepsis according to the combinations of interleukin 6, C-reactive protein, and procalcitonin values. All tests were performed on admission to hospital. CRP, C-reactive protein; IL-6, interleukin 6; PCT, procalcitonin. **Note.** CRP and PCT; CRP and IL-6; PCT and IL-6; PCT and IL-6 and CRP.



PCT had a high sensitivity, specificity, PPV, NPV, and AUC value, making it an ideal single index for the early identification of nosocomial infection in preterm infants. When combining PCT and IL-6 or using a combination of CRP, IL-6, and PCT for testing, the sensitivity and specificity values were over 85%, and the predictive values were high (Table 5).

Table 5. The diagnostic accuracy of interleukin 6, C-reactive protein, and procalcitonin, singly and in combination, for making the diagnosis of sepsis.

Inflammatory marker	Cutoff value	AUC	95% CI of AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
IL-6	99.6	0.888	0.815-0.960	87.6	91.3	96.3	71.8
CRP	9.27	0.823	0.746-0.900	62.9	87.1	93.3	45
PCT	2.33	0.953	0.916-0.990	84	97.8	98.3	78.4
CRP+PCT	-	0.954	0.919-0.990	91	83.9	98.2	77.7
CRP+IL-6	-	0.939	0.893-0.985	93.3	83.1	94.9	45.9
PCT+IL-6	-	0.966	0.936-0.997	96.6	87.1	98.3	78.4
CRP+PCT+IL-6	-	0.965	0.934-0.996	86.5	96.8	98.2	77.6

Note. All tests were performed before the administration of antibiotics.

Abbreviations: AUC: Area Under The Curve; CI: Confidence Interval; CRP: C-Reactive Protein; IL-6: Interleukin 6; NPV: Negative Predictive Value; PCT: Procalcitonin, PPV: Positive Predictive Value.

DISCUSSION

Cytokines are proteins or small molecular polypeptides secreted by cells. Among them, the proinflammatory cytokine IL-6 is currently a focus of research [12]. IL-6 is a multi-effect proinflammatory factor. Under normal circumstances, the body's IL-6 content is extremely low (<10 pg/mL). After pathogens invade the body, lymphocytes, monocytes-macrophages, and fibroblasts are stimulated and a large amount of IL-6 is produced. The

IL-6 then stimulates the production of other inflammatory factors and acute phase response proteins [13]. Newborns with a gestational age less than 30 weeks or whose mothers used glucocorticoids before delivery have significantly reduced IL-6 levels [14]. In addition, IL-6 can also be markedly increased due to certain tumors, autoimmune diseases, and transplant rejection. The half-life of IL-6 is about 100 minutes, and it decreases significantly 24–48 hours after the appearance of clinical signs, which means that it can be used for the effective diagnosis of bacterial infections and can be used to accurately judge the severity and prognosis of the infection [15-17]. Moreover, a prospective, randomized control study showed that IL-6 levels increase significantly 2 days before the onset of signs of bacterial infection, which is before other laboratory indicators indicated positive results [18]. The IL-6 level was negatively correlated with the time of blood collection, and the timing of its peak after infection was earlier than that of PCT. Combined with the finding that it had no physiological peak, the IL-6 level could be regarded as a sensitive indicator for the early diagnosis of neonatal sepsis. However, there are certain limitations to using IL-6 for guiding the empiric administration of antibiotics. IL-6 has a short half-life and peaks early. If the blood sample is not collected in time, the test may provide false-negative results. Moreover, the IL-6 level can return to normal while infection still persists [19]. The IL-6 levels in cord blood in 109 newborns who were born prematurely due to the premature rupture of membranes [20]. The results showed that when the cutoff value of IL-6 was 108.5 pg/mL, the sensitivity for diagnosis of sepsis was 95% and the specificity was 100%, suggesting that IL-6 levels in the cord blood of neonates with a high risk of neonatal sepsis could help predict EOS. So far, the diagnostic threshold for IL-6 was unclear. The cut-off range was 3.6 to 300 pg/mL in a meta-analysis [21]. In this study, the best cutoff value of IL-6 was 99.6 pg/mL. The IL-6 level peaked at 6 hours after infection, which was much earlier than the levels of CRP and PCT, and returned to normal 24–48 hours after the onset of infection and showed the highest sensitivity. It is released 4-6 hours after the onset of infection, reaches its peak in 24-48 hours, and has a half-life of about 24 hours [22,23]. CRP increases with the increase of inflammatory factors and decreases after infection control. Therefore, a significant increase can be used as an early sign of bacterial sepsis. However, some non-infectious factors, such as neonatal asphyxia, traumatic tissue damage, immunization, and hemolysis, could also cause an increase in CRP, resulting in low specificity of CRP as an indicator of sepsis [24]. A retrospective analysis by showed that CRP peaked 24-48 hours after infection occurred and returned to normal 7 days after the infection was effectively controlled, indicating its dynamic trend is of great significance in guiding the rational administration of antibiotics and monitoring of clinical efficacy. In this study, the level of CRP before treatment in the sepsis group was significantly higher than that in the control group, indicating that CRP could be used for the diagnosis of neonatal sepsis. The ROC curve analysis found that the best cutoff value of CRP was 9.27 mg/L. Compared with PCT and IL-6, CRP had lower sensitivity and specificity; therefore, it should not be used as an independent marker for the early diagnosis of nosocomial infection in preterm infants.

In bacterial infections, the PCT level increases under the stimulation of endotoxin and proinflammatory factors (IL-6, TNF-α, and IL-1β). However, in viral infections, interferon gamma inhibits the synthesis and release of PCT [25]. PCT is not affected by factors such as stress and is only related to the extent of bacterial infection. The level of PCT in healthy people is extremely low (<0.1 ng/mL). When the body is infected, a level ≥ 0.5 ng/mL is defined as abnormal. A study by showed that PCT started to increase 4 hours after the onset of infection and remained at the peak level for 8–24 hours [26]. After control of the infection, the PCT level decreased by 50% per day. However, found that PCT peaked 12 hours after the onset of infection and returned to normal within 3 days after infection control. This study found that in the sepsis group, the serum PCT level before the initiation of antibiotic treatment was significantly higher than that after treatment and was higher than the level in the control group, suggesting

that the PCT level was positively correlated with the severity of infection [27]. Conducted a prospective, controlled study and found that the serum PCT levels of neonates with sepsis were significantly higher than those of healthy neonates, with the best cutoff value of 2.4 ng/mL. In this study, the best cutoff value of PCT was 2.33 ng/mL, with a sensitivity of 84.0%, specificity of 97.8%. Therefore, serum PCT is of higher value for the early diagnosis of nosocomial infection in preterm infants, and the administration of antibiotics can be determined in the early stage of infection. However, there is a physiological increase of PCT after birth. It peaks after 24 hours, and drops to below 0.1 ng/mL within 72 hours. This physiological pattern limits the diagnostic accuracy of serum PCT for the diagnosis of EOS [28]. Moreover, a retrospective analysis by showed that the average cord blood PCT level of neonates with EOS was 3.03 ng/mL, which was significantly higher than the 0.16 ng/mL of noninfected neonates [29]. With the cutoff value of cord blood PCT as 0.6 ng/mL, the NPV of PCT was 99%, which made it an useful indicator for diagnosing EOS. This study found that when the PCT was combined with the IL-6 or with both IL-6 and CRP, the sensitivity, specificity, PPVs, NPVs, and AUC values were high. These two combinations could both improve the accuracy of PCT for the early diagnosis of nosocomial infection in preterm infants. The results of this study showed that gram-negative bacteria were isolated significantly more frequently than gram-positive bacteria in the blood cultures of the neonates with sepsis, and that *Klebsiella pneumoniae* was the dominant bacteria, which is consistent with the results [30].

CONCLUSION

In summary, IL-6, CRP, and PCT could be used as reliable indicators for the early identification of nosocomial infections in preterm infants. IL-6 levels peaked 6 hours after the onset of infection. The ROC curve analysis revealed that the best cutoff values of IL-6, CRP, and PCT were >99.60 pg/mL, >9.27 mg/L, and >2.33 ng/mL, respectively. In single-marker measurements, the sensitivity, specificity, PPVs, NPVs, and AUC values of PCT were high, making PCT an ideal index for the early identification of nosocomial infections in preterm infants. Combined testing using PCT combined with IL-6 or with both CRP and IL-6 could improve the accuracy of clinical identification of nosocomial infections in preterm infants. Testing these markers is fast and convenient and is conducive to early diagnosis and treatment.

CONFLICTS OF INTEREST STATEMENT

The authors have no conflicts of interest to declare that are relevant to the content of this article.

DATA AVAILABILITY STATEMENT

The data sets generated and analyzed during the current study are available in the Harvard Dataverse repository.

FUNDING

None.

DECLARATIONS OF INTEREST

None.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Medical Ethics Committee of Shengjing Hospital of China Medical University.

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