

# Research Advances in the Diagnosis of Neonatal Sepsis

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## Abstract

Neonatal sepsis is one of the most common diseases in newborns, which can lead to multi-system damage. Delayed treatment may result in severe complications, while excessive use of antibiotics can increase bacterial resistance and adversely affect long-term outcomes. Therefore, accurate diagnosis of neonatal sepsis is critical for neonatologists. However, the clinical manifestations of neonatal sepsis are often non-specific, and blood culture—the gold standard for diagnosis—has limitations such as prolonged turnaround time and low positivity rates. Overreliance on blood culture may delay diagnosis and treatment. In clinical practice, we often combine other biomarkers to diagnose, including: White blood cell count (WBC), Neutrophil count, C-reactive protein (CRP), procalcitonin (PCT), serum amyloid A (SAA), interleukins (ILs) and tumor necrosis factor (TNF). This review aims to summarize the laboratory indicators relevant to the diagnosis of neonatal sepsis.

## Keywords

Neonatal Sepsis, Diagnosis, Biomarkers, Research Advances

## 1. Introduction

Neonatal sepsis is one of the important causes of death in newborns, especially in premature infants and low birth weight infants [1]. In clinical practice, neonatal sepsis is classified into early-onset sepsis (EOS) and late-onset sepsis (LOS) based on the timing of onset. Early-onset sepsis refers to neonatal sepsis with an onset age of <72 hours, while late-onset sepsis refers to neonatal sepsis with an onset age of ≥72 hours [2], and there are certain differences in diagnosis between the two [3] [4]. Due to the non-specific and diverse clinical manifestations of neonatal sepsis, its diagnosis is relatively difficult. The gold standard for the diagnosis of neonatal sepsis

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is blood culture, but the positive rate of blood culture is not high and time-consuming. Over-reliance on blood culture results may lead to delayed treatment and serious complications such as shock, disseminated intravascular coagulation, purulent meningitis, neonatal necrotizing enterocolitis, and even death [5]. Both domestically and internationally, neonatal sepsis is often identified through high-risk factors, clinical manifestations, and laboratory indicators [2] [6]. However, this article focuses on laboratory indicators that assist in the diagnosis of neonatal sepsis.

## **2. Hematological Indicators**

Blood samples, as easily obtainable specimens in clinical practice, are often used as the preferred examination. As the gold standard for neonatal sepsis, blood culture not only takes a long time and has a low positive rate, but also the amount and timing of specimen collection can affect the results of blood culture [1]. In order to diagnose neonatal sepsis early and quickly, in addition to classic hematological examination indicators, researchers are constantly exploring new examination indicators.

### **2.1. CBC**

#### **2.1.1. White Blood Cell Count (WBC)**

The neutrophil count and neutrophil to lymphocyte ratio (NLR) in the neonatal sepsis group were significantly higher than those in the control group [7] [8]. The diagnostic significance of neutropenia in neonatal sepsis is higher than that of leukocytosis [1].

#### **2.1.2. Red Cell Distribution Width (RDW)**

Martin *et al.*'s study indicated that RDW levels were higher in neonatal sepsis compared to the control group [9] [10]. A randomized controlled study in China found that there was no statistically significant difference in RDW between the blood culture-negative neonatal sepsis group and the control group [7]. Although there is controversy over the diagnosis of RDW in neonatal sepsis, they unanimously agree that RDW is closely related to the prognosis of neonatal sepsis and has significant diagnostic and therapeutic value in neonatal sepsis. Ellahony also pointed out that RDW has limited value in the diagnosis of neonatal sepsis, but it has important prognostic value, with higher RDW levels indicating a better prognosis [11].

#### **2.1.3. Platelet Count**

Research has shown that platelet count is closely related to sepsis, and regardless of whether LOS or EOS occurs, platelet count decreases significantly compared to the control group [12]. The platelet count in the neonatal sepsis group was significantly lower than that in the common infection group and was negatively correlated with the degree of infection [13].

## **2.2. Acute Reactive Phase Protein**

### **2.2.1. C-Reactive Protein (CRP)**

They found CRP has a sensitivity of 67% (95% Confidence interval (CI) 0.43 - 0.89), a specificity of 79% (95%CI 0.65 - 0.88). Umbilical cord blood CRP has a

better specificity of 90%, 95%CI 0.82 - 0.95 [14]. Whether it is sepsis with positive blood culture or clinically diagnosed sepsis, CRP levels are significantly higher than those in the control group [7] [15]. CRP elevation in the early stages of neonatal sepsis is not sensitive, but continuous monitoring of CRP can help diagnose neonatal sepsis and greatly assist in the course of antibiotic treatment [16]. CRP can also serve as a negative predictor of LOS [17] [18]. The ratio of CRP to platelets and CRP to albumin may be a new indicator for early diagnosis of neonatal sepsis [13] [19]-[21]. Some studies have concluded that there is no statistically significant difference in CRP levels between the neonatal sepsis group and the control group [22], and their study mainly focuses on LOS.

### 2.2.2. Procalcitonin (PCT)

PCT levels may significantly increase in the early stages of neonatal sepsis, but PCT levels are easily influenced by other factors. They found PCT has a sensitivity of 75% (95%CI 0.67 - 0.82) and a specificity of 76% (95%CI 0.66 - 0.87) [14]. The sensitivity of PCT in the diagnosis of neonatal sepsis is higher than that of CRP, but PCT levels may be normal in the early stages of early-onset sepsis, so dynamic monitoring is needed [23].

## 2.3. Interleukin (IL)

### 2.3.1. IL-6

In the diagnosis of neonatal sepsis, most studies are related to IL-6 [1] [3] [14] [22]-[30], and most studies believe that IL-6 has diagnostic significance in neonatal sepsis. They found IL-6 has a sensitivity of 71% (95%CI 0.63 - 0.77), specificity of 76% (95%CI 0.66 - 0.84). Similarly, umbilical cord blood IL-6 has a better sensitivity of 83% (95%CI 0.71 - 0.90), a better specificity of 87% (95%CI 0.78 - 0.93), 14. Some scholars believe that IL-6 in umbilical cord blood can significantly increase in the early stages of neonatal sepsis [14] [21] [22], but due to the short half-life of IL-6, there are also some limitations in practical applications. Combining CRP or PCT levels can greatly improve the accuracy of diagnosing neonatal sepsis [23]. Scholars have also found that compared to EOS, the LOS group showed a more significant increase in IL-6 levels, and IL-6 levels have important diagnostic significance for EOS and premature rupture of membranes sepsis [3]. Studies have shown that IL-6 has better sensitivity and specificity than tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and IL-1 $\beta$  [3] [24]. The diagnostic significance of IL-1, IL-6, and IL-10 in neonatal sepsis may be related to genetic susceptibility [24], and further research is needed.

### 2.3.2. IL-18

IL-18 belongs to the IL-1 family, and its serum levels are significantly elevated in neonatal sepsis patients and are correlated with severity. IL-18 has great value in the diagnosis of neonatal sepsis [20].

### 2.3.3. Other

The genotype TT of the IL-8 gene rs4073 locus is correlated with the occurrence

of neonatal sepsis [26]. The levels of IL-4 and IL-10 were significantly elevated in the LOS group, but no significant difference was observed in EOS. There was no significant statistical difference in IL-1 $\beta$  levels between neonatal sepsis and the control group [3].

#### **2.4. Plasma Amyloid A (SAA)**

The SAA level in the sepsis group was significantly higher than that in the control group, and its diagnostic value in EOS was higher. Combined with other indicators, the effect was better [28]. Studies have also shown that in the effectively treated sepsis group, the SAA level decreased significantly after treatment compared to before treatment, and the difference was statistically significant [31], which fully confirms the role of SAA in sepsis diagnosis and efficacy evaluation.

#### **2.5. Heparin-Binding Protein (HBP)**

HBP is a protein isolated from neutrophils. In the pathogenesis of sepsis, the organism responds to stimulation by inducing hepatocyte production of HBP, thereby initiating a proinflammatory cascade [32]. Recent studies have shown that HBP is associated with many diseases, especially in infectious diseases, the level of HBP is significantly increased. HBP may be a reliable blood biomarker for early prediction of neonatal sepsis and disease severity and also has a guiding role in the clinical application of antibiotics, but still requires a large sample, and multi-center research support [32].

#### **2.6. Other**

##### **2.6.1. Tumor Necrosis Factor $\alpha$ (TNF- $\alpha$ )**

The diagnostic value of TNF- $\alpha$  in neonatal sepsis is similar to PCT, and its synergy with IL-6 can improve the specificity of diagnosing neonatal sepsis. There are studies showing that the level of TNF- $\alpha$  is significantly elevated in the neonatal sepsis group, especially in the LOS group [3].

##### **2.6.2. CD Molecule**

CD64 and CD11 $\beta$  have high sensitivity and specificity in the diagnosis of EOS and LOS, and can significantly increase within minutes after infection, requiring a small sample size [1]. Multiple studies support this conclusion [33]-[35].

##### **2.6.3. Plasma Receptor-Interacting Protein 3 (RIP-3)**

RIP-3 is a key protein in the programmed cell death pathway, and studies have shown its association with various diseases. Feng Zongtai's studies showed that the area under the curve (AUC) of RIP-3 in the diagnosis of neonatal sepsis is 88.8%, and when combined with CRP, PCT, etc., it can reach 93.9%. The AUC in the diagnosis of late-onset neonatal sepsis is 88.4%, indicating that RIP-3 has a high diagnostic value in neonatal sepsis. RIP-3 may be associated with the prognosis of sepsis, and the AUC of RIP3 + high-sensitivity CRP + PLT is higher than that of single-finger elevation [36]-[38].

### 3. Other

#### 3.1. miRNA

In Kosmeri's study, certain miRNAs showed significant upregulation or downregulation in the occurrence of neonatal sepsis [39]. Therefore, the occurrence of neonatal sepsis can be predicted by detecting miRNA expression. However, this study is a small sample, single-center study and may have regional and statistical differences. In some scholars' studies, the decreased expression of miRNA141, miRNA23b, miRNA34a-5P, and miRNA199a-3P, as well as the increased expression of miRNA-16-5P, has clear diagnostic significance in the diagnosis of neonatal sepsis [22] [40]-[42].

#### 3.2. Soluble Triggering Receptor Expressed on Myeloid Cells (sTREM)

TREM, belonging to the immunoglobulin superfamily, serves as a pivotal receptor in inflammatory cascades and exhibits marked upregulation during sepsis [17]. Soluble triggering receptor expressed on myeloid cells (sTREM-1) in urine is of great significance in the early diagnosis of neonatal sepsis and has advantages such as low cost and speed [22]. The plasma sTREM-1 level in the LOS group was significantly higher than that in the control group [43] [44]. Whether in the sepsis group with positive or negative blood cultures (including LOS and EOS), the levels of sTREM-1 in the children's blood were significantly higher than those in the control group, and the increase was more pronounced in the early stages, closely related to mortality [44].

#### 3.3. Molecular Diagnostic Techniques (Including Polymerase Chain Reaction (PCR), Molecular Culture (MC), etc.)

Researchers predict neonatal sepsis by detecting bacterial 16S rRNA or fungal 18S rRNA through PCR [7]. PCR technology has clinical significance for the rapid diagnosis of neonatal sepsis [45]. However, compared to blood culture, PCR technology has a higher false positive rate, is prone to sample contamination, and has no guiding effect on antibiotic treatment for neonatal sepsis [29]. Molecular culture is a novel detection method. Although there is a risk of false positives in molecular culture, Shane pointed out that it has a guiding significance for the diagnosis of EOS and antibiotic use in neonatal sepsis with a history of antibiotic use during pregnancy and negative blood culture [1].

### 4. Clinical Risk Prediction Model

Domestic scholars have established a model by analyzing the clinical manifestations and serological indicators of neonatal sepsis, which improves the diagnosis of neonatal sepsis and reduces the incidence of mortality through early warning scores [39]. Scholars have constructed a four-gene prediction model for early assessment of the risk of early-onset sepsis in newborns by analyzing the mRNA expression profile of newborns with EOS in a gene bank. However, the gene bank is based on

foreign newborns and may have differences in pathogenic bacteria, race, and other aspects. Moreover, the risk prediction model mainly targets EOS bacterial infections, and its significance for LOS, fungal, and viral infections is not yet clear [46].

## 5. Summary

The specificity of conventional hematological monitoring indicators—including white blood cell count, neutrophil count, lymphocyte count, CRP, PCT, and blood culture—for diagnosing neonatal sepsis remains suboptimal. These parameters are susceptible to multiple confounding factors such as gestational age, postnatal age, organ function, and sampling volume [1] [29]. Current studies present divergent conclusions regarding the diagnostic significance of these markers. A majority of researchers suggest that elevated white blood cell count, thrombocytopenia, increased CRP, and raised PCT levels hold diagnostic value for neonatal sepsis, with combined detection or dynamic monitoring offering greater clinical utility [35] [47]-[49]. However, other scholars argue that the negative predictive value of hematological parameters (e.g., cell counts and CRP) outperforms their positive predictive value in this context [1] [49]. Additionally, some studies emphasize that varying cutoff values significantly influence the sensitivity and specificity of sepsis diagnosis [29], necessitating large-scale experiments to establish optimal thresholds. These discrepancies may stem from regional variations, pathogen diversity, sample size limitations, and genetic heterogeneity. Collectively, these findings underscore the need for further multi-center, large-sample studies to validate existing conclusions. Recent research has explored the diagnostic potential of novel biomarkers such as IL, SAA, HBP, RIP-3, and CD molecules. While promising, their clinical application requires additional evidence. Furthermore, composite ratios derived from routine blood parameters—such as red cell distribution width-to-platelet ratio (RPR), CRP-to-platelet ratio (CPR), and CRP-to-albumin ratio—have demonstrated significant elevation in neonatal sepsis cohorts, suggesting their utility as auxiliary diagnostic tools. [10] [13] [19] Clinical risk prediction models represent an emerging diagnostic approach, with personalized models showing potential for improving sepsis diagnosis. However, their generalizability remains limited by etiological, racial, and genetic variability. Consequently, the development of robust, universally applicable models demands ongoing research and validation.

## 6. Limitations

Heterogeneity in testing standards, inconsistent cutoff values, and the limited sample size may affect the generalizability of the conclusion.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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