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Early Diagnosis of Neonatal Septicemia: Current Status and Prospects of Inflammatory Markers and Detection Technologies

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Abstract: ***Early-onset sepsis (EOS) is a common and severe infectious disease in neonatal intensive care units, and early diagnosis is crucial for improving patient outcomes. This review systematically summarizes the application of inflammatory biomarkers and detection methods in the early diagnosis of neonatal EOS. Due to the atypical early symptoms of EOS and the limitations of traditional blood culture—such as long turnaround time and limited sensitivity—inflammatory biomarkers including IL-6, CRP, and PCT have demonstrated certain value in early diagnosis. Combined detection and dynamic monitoring can help improve diagnostic accuracy. Detection methods include traditional laboratory techniques such as ELISA and CLIA, as well as novel molecular technologies and POCT, including PCR, T2MR, and miRNA assays. These new technologies have improved detection speed and convenience, but their clinical effectiveness requires further validation. Standardization of detection methods and proper blood sampling procedures are also essential to ensure the accuracy and comparability of results. This review aims to provide a reference for clinicians in selecting appropriate inflammatory biomarkers and detection methods, thereby promoting advances in the early diagnosis and management of neonatal EOS.***

Keywords: Neonatal early-onset sepsis, Early diagnosis, Inflammatory biomarkers, Cytokines, Acute phase proteins**.**

1. Introduction

Neonatal sepsis remains one of the major challenges in neonatal medicine, with persistently high morbidity and mortality rates [1]. Epidemiological data indicate that approximately 3 million infants worldwide are affected by neonatal sepsis each year, with a mortality rate of up to 17% [2]. Notably, the incidence of neonatal sepsis is significantly higher in low- and middle-income countries compared to high-income countries [3]. Based on the time of onset, neonatal sepsis can be classified into early-onset sepsis (EOS) and late-onset sepsis (LOS) [4]. EOS specifically refers to sepsis occurring within 72 hours after birth, mainly resulting from transplacental or ascending infection through the cervix. The most common pathogens are group B Streptococcus (GBS) and Escherichia coli, which colonize the maternal genitourinary tract and are transmitted to the neonate during delivery [5]. Prematurity, low birth weight, premature rupture of membranes, and maternal perinatal infection are recognized high-risk factors that increase the incidence of EOS.

The clinical manifestations of early-onset neonatal sepsis (EOS) are non-specific, and early symptoms are often atypical, such as temperature instability, respiratory distress, feeding difficulties, lethargy, or irritability. As the disease progresses, affected infants may develop severe complications such as shock and multiple organ dysfunction syndrome [6]. Due to the immature immune system and weak immune defense mechanisms in neonates, especially preterm infants, infection can progress rapidly, with a mortality rate as high as 20–30%. Even among survivors, neurological sequelae may persist, significantly affecting quality of life. Therefore, early diagnosis is crucial for improving the prognosis of EOS. Timely identification and confirmation of EOS enable affected infants to receive targeted antibiotic therapy as early as possible, reducing the risk of progression to multiple organ dysfunction and death. Early diagnosis also helps avoid unnecessary use of broad-spectrum antibiotics, thereby decreasing the emergence of resistant strains and the incidence of nosocomial infections, ultimately optimizing antimicrobial stewardship and infection control [7]. However, traditional diagnostic methods such as blood culture, although highly specific, are limited by long turnaround times and low sensitivity, making it difficult to guide clinical decision-making promptly. Consequently, the search for rapid and accurate early diagnostic methods has become a major focus of current clinical research

Inflammatory biomarkers play a crucial role in the early diagnosis of neonatal early-onset sepsis (EOS). Upon invasion by pathogens, an inflammatory response is triggered, leading to changes in the levels of various inflammatory biomarkers, such as cytokines (IL-6, TNF-α) and acute-phase proteins (CRP, PCT) [8]. Compared with traditional blood culture, the detection of inflammatory biomarkers offers advantages of rapidity, simplicity, and good reproducibility. Dynamic monitoring of these biomarkers enables earlier detection of infection and provides timely evidence for clinical decision-making [9]. In addition, several biomarkers, including presepsin and alpha-fetoprotein, have demonstrated significant clinical value in the early diagnosis and risk stratification of neonatal sepsis, facilitating the early identification of high-risk infants and improving prognosis [10]. It is noteworthy that changes in the levels of inflammatory biomarkers are closely related not only to disease severity and prognosis, but also assist in disease assessment and therapeutic guidance. Therefore, in-depth

research on the application of inflammatory biomarkers in the early diagnosis of EOS is of great significance for improving diagnostic accuracy and patient outcomes.

2. Commonly Used Inflammatory Biomarkers in the Diagnosis of Neonatal Early-Onset Sepsis

The diagnosis of neonatal early-onset sepsis relies on the detection of various inflammatory biomarkers, which can be categorized into three major groups: cytokines, acute-phase proteins, and other inflammatory biomarkers.

Among cytokine biomarkers, interleukin-6 (IL-6) is one of the most valuable indicators for diagnosis. As a representative pro-inflammatory cytokine, IL-6 increases within 2–4 hours after infection, and its level is closely related to the severity of infection [11]. The chemokine interleukin-8 (IL-8) functions by regulating the recruitment and activation of neutrophils, and is characterized by a rapid response (1–3 hours) and a short half-life (<4 hours). Its diagnostic accuracy is reflected by a sensitivity of 0.78 and a specificity of 0.84 [12]. Tumor necrosis factor-alpha (TNF-α), another important pro-inflammatory cytokine, is not affected by gestational age or postnatal age [13]. Interleukin-1β (IL-1β) activates immune signaling pathways by binding to its receptor, playing a pivotal role in initiating and amplifying the early immune response [14]. In contrast, changes in the level of the anti-inflammatory cytokine IL-10 reflect the body's ability to regulate inflammation. The reference ranges for umbilical cord blood IL-6 (<10.2 pg/mL) and IL-8 (<14.1 pg/mL) established by Barug et al. provide important clinical standards for the early diagnosis of neonatal early-onset sepsis [15].

As products of the hepatic response to inflammatory stimuli, acute-phase proteins play an important role in the diagnosis of neonatal sepsis, with C-reactive protein (CRP) and procalcitonin (PCT) being the most representative. CRP, as a traditional biomarker, begins to increase 10–12 hours after infection and peaks at 36–48 hours. A CRP level exceeding 10 mg/L is of significant diagnostic value for early-onset sepsis [16]. PCT, as a novel biomarker, offers the advantages of a more rapid response (3–6 hours) and higher specificity, particularly in distinguishing between bacterial and viral infections [17]. A diagnostic threshold of 2–2.5 ng/mL for PCT demonstrates moderate accuracy for systemic inflammatory response syndrome (SIRS) or suspected sepsis; however, its use in differentiating early-onset from late-onset sepsis still requires careful evaluation [18]. It is noteworthy that although a PCT concentration greater than 0.5 ng/mL suggests infection, its level may be influenced by non-infectious factors and may exhibit physiological elevation. Therefore, dynamic monitoring is recommended in clinical practice to better guide antibiotic therapy.

Hematological indicators each have distinct characteristics in the diagnosis of neonatal sepsis. White blood cell count (WBC) demonstrates high specificity but low sensitivity. Absolute neutrophil count (ANC) and the immature-to-total neutrophil ratio (I:T), with the latter being the most sensitive indicator, are both influenced by gestational age, sampling time, and perinatal factors, and may remain within normal ranges during the early stage of infection [19]. Red cell distribution width (RDW) is mainly associated with mortality, while thrombocytopenia and increased mean platelet volume (MPV) also provide important diagnostic references [20]. In recent years, the neutrophil-to-lymphocyte ratio (NLR) has attracted attention as a novel inflammatory marker due to its ease of calculation and its value in infection diagnosis and prognosis assessment [21].

Each of these inflammatory biomarkers has its own characteristics, and the diagnostic value of a single marker is limited; combined detection can improve diagnostic accuracy [22]. Studies have shown that the diagnostic performance of IL-6 combined with PCT is superior to that of a single marker, and integrating clinical manifestations with other laboratory tests can further enhance diagnostic precision. In addition, the dynamic changes of these biomarkers are of great value in assessing disease progression and prognosis, and continuous monitoring can help guide clinical decision-making [23]

3. Application of Inflammatory Biomarkers in the Early Diagnosis of Neonatal Early-Onset Sepsis

In the early diagnosis of neonatal early-onset sepsis, the application strategy of inflammatory biomarkers requires comprehensive consideration of the characteristics of individual markers, the advantages of combined detection, the value of dynamic monitoring, and integration with clinical manifestations.

The diagnostic value of individual biomarkers varies according to their specific characteristics. A study by Janec et al. found that nine miRNAs, including miRNA-142-5p and miRNA-223-3p, were significantly upregulated in the peripheral blood of neonates with early-onset sepsis. Although the sample size in these studies was limited, these miRNAs, which are associated with inflammation and innate immune regulation, provide important research directions for the development of novel diagnostic biomarkers [24]. A prospective controlled study by Ahmed et al. confirmed that presepsin is the most promising early diagnostic biomarker for neonatal early-onset sepsis (AUC 0.934, sensitivity 88.9%, specificity 85.7%). The authors also recommend combining presepsin with PCT and IL-8/IL-6 to further improve diagnostic accuracy [25]. S100A8/A9 serves as an important biomarker for the diagnosis of EOS, with significantly elevated serum levels observed in patients with EOS. It enables early identification of severe cases and prediction of poor outcomes. Multiple studies have shown that S100A8/A9 exhibits higher specificity and sensitivity than traditional markers (such as CRP and PCT) in diagnosing sepsis and related organ injury, with specificity reaching up to 83%, and its elevation is closely associated with 30-day mortality. Therefore, S100A8/A9 not only facilitates early diagnosis and risk stratification of sepsis, but also serves as an effective predictor of disease severity and prognosis [26]. However, each individual biomarker has its limitations, such as stringent requirements for sampling timing, insufficient specificity, and susceptibility to various influencing factors, making it difficult to fully meet the needs of early clinical diagnosis.

Combined detection of biomarkers can significantly improve

diagnostic accuracy. A study by Hesse et al. demonstrated that the combination of IL-6 with other perinatal factors can enhance the sensitivity (75.0–92.2%) or specificity (82.4–100%) for the diagnosis of EOS in preterm infants. However, due to the trade-off between sensitivity and specificity, such a combination is more suitable as an adjunct tool for individualized clinical decision-making [27]. A study by Eichberger et al. indicated that IL-6 appears to be an ideal biomarker within the first 12 hours, with a median sensitivity and specificity of 83% and 83.3%, respectively, for the diagnosis of EOS. Its performance is optimal in preterm infants and umbilical cord blood samples, and the earlier the sampling, the greater its diagnostic value. Furthermore, when combined with CRP after this period, the sensitivity can reach as high as 100% [28]. As an early infection biomarker, IL-6 can improve the diagnostic accuracy of EOS in term neonates. Combined detection with CRP further enhances both sensitivity and specificity. However, routine blood screening is not recommended for neonates who have only maternal risk factors but no clinical symptoms, in order to reduce unnecessary treatment [29]. The selection of biomarker combinations should take into account factors such as testing cost, accessibility, and turnaround time, so as to develop combination strategies suitable for different healthcare settings.

Dynamic monitoring of inflammatory biomarkers is of great significance for disease management. A study by Varga et al. demonstrated that dynamic monitoring of IL-6 provides a more comprehensive and real-time reflection of disease progression in sepsis patients than a single baseline measurement, offering important value for risk stratification, individualized treatment, and efficacy assessment [30]. By continuously tracking changes in IL-6 levels, clinicians can detect fluctuations in the inflammatory response and patient reactions to therapy earlier and more sensitively, promptly identify disease deterioration, and scientifically adjust treatment plans to achieve personalized management. Dynamic monitoring not only helps evaluate treatment effectiveness, but also identifies high-risk patients, optimizes resource allocation, and improves patient survival rates.

A retrospective study by Berka et al. involving 445 extremely preterm infants further confirmed the clinical value of dynamic IL-6 monitoring. The study showed that the peak IL-6 level within 24 hours after birth has high diagnostic value for neonatal early-onset sepsis (EOS): when the IL-6 peak exceeds 200 ng/L, the sensitivity for diagnosing EOS is 89%, specificity is 77%, negative predictive value reaches 98%, and the area under the ROC curve (AUC) is 0.92, which is significantly superior to a single early measurement (AUC of 0.73 within 2 hours). In addition, elevated IL-6 levels were closely associated with adverse outcomes such as hypotension, intraventricular hemorrhage, and death. The study suggests that sequential monitoring of IL-6 peaks helps to rule out EOS early, reduce unnecessary antibiotic use, and provides a reliable biomarker basis for the clinical management of extremely preterm infants [31].

In recent years, machine learning (ML) technologies have introduced new approaches for the early detection of infectious diseases such as neonatal sepsis by integrating multiple data sources and analytical methods [32]. ML models can dynamically analyze various inflammatory biomarkers—including IL-6, procalcitonin, C-reactive protein, and lactate—as well as patient-specific characteristics, to establish multidimensional risk assessment systems. This helps identify high-risk patients, allocate medical resources more efficiently, improve patient survival rates, and assist clinicians in evaluating treatment efficacy. However, ML models require rigorous validation before clinical application, with attention to false positive rates and user acceptance, and must be continuously optimized and evaluated in clinical practice. In the future, with advances in detection technologies and artificial intelligence, dynamic monitoring of inflammatory biomarkers such as IL-6 combined with machine learning is expected to support precision medicine, helping to improve the prognosis and quality of life for patients with sepsis.

The comprehensive assessment of clinical manifestations is of great significance. Since the clinical symptoms of neonatal sepsis are mostly non-specific, relying solely on laboratory indicators makes it difficult to identify infections in a timely and accurate manner. Clinical manifestations not only provide a basis for early screening and assessment of disease progression, but also serve as important references for formulating diagnostic and therapeutic strategies. Studies have shown that hematological parameters (such as white blood cell count, neutrophils, platelets) and biomarkers (such as C-reactive protein [CRP], procalcitonin [PCT]) have certain value in early diagnosis; however, their sensitivity and specificity are limited, necessitating a comprehensive judgment in combination with clinical manifestations [33]. For example, in neonates with high-risk factors, even if clinical manifestations are atypical, elevated inflammatory markers should prompt consideration of possible infection; conversely, in patients with typical clinical manifestations but normal inflammatory markers, other diseases should be considered. The severity of clinical manifestations is correlated with the dynamic changes of inflammatory markers, which provides a certain reference for evaluating disease severity and prognosis. Therefore, establishing a comprehensive scoring system that combines clinical manifestations and inflammatory markers may help improve the accuracy of early diagnosis and clinical management of neonatal sepsis.

In summary, the application of inflammatory biomarkers in the early diagnosis of neonatal early-onset sepsis requires a comprehensive strategy. This involves integrating the characteristics of individual biomarkers, the advantages of biomarker combinations, the value of dynamic monitoring, and the incorporation of clinical manifestations to achieve early and accurate diagnosis, thereby ensuring timely treatment and improved prognosis.

4. Detection Methods for Neonatal Inflammatory Biomarkers

The detection methods for neonatal inflammatory biomarkers are continuously evolving, ranging from traditional laboratory assays to novel rapid detection technologies, thus providing more options for clinical diagnosis.

The traditional detection methods for neonatal inflammatory

biomarkers mainly include enzyme-linked immunosorbent assay (ELISA), chemiluminescence immunoassay (CLIA), and radioimmunoassay (RIA). Among these, ELISA is currently the most widely used method, offering advantages such as ease of operation and relatively low cost; however, it requires a longer detection time (typically 2–4 hours) and is susceptible to operational factors [34]. CLIA provides high sensitivity, good specificity, and a broad detection range, but the equipment is expensive and requires operation by specialized personnel [35]. Although RIA is highly sensitive, it has gradually been replaced by other methods due to the risk of radioactive contamination [36]. Overall, these traditional detection methods are technically mature and yield reliable results, but their relatively long turnaround times make it difficult to meet the clinical demand for rapid diagnosis of neonatal inflammatory biomarkers.

The emergence of novel detection technologies, such as quantitative PCR, 16S/23S rRNA PCR, and multiplex molecular PCR, offers higher sensitivity (up to 0.98) and specificity (up to 0.94) for neonatal sepsis diagnosis compared to traditional methods, but they cannot yet fully replace blood culture and require further clinical validation [37]. T2MR technology can efficiently and specifically detect bloodstream infection pathogens in children and neonates directly from whole blood samples without the need for blood culture. Its sensitivity and specificity are both superior to those of traditional blood culture; however, its clinical value still requires further validation through large-scale prospective studies [38]. Multiple studies have shown that miRNA technology demonstrates high accuracy in the diagnosis of neonatal sepsis, with a pooled sensitivity of 0.83 and specificity of 0.76. Specific miRNAs such as miR-15a, miR-16, miR-26a, and miR-223 can serve as effective biomarkers; however, larger sample sizes and multicenter prospective studies are needed for further validation [39]. In contrast, genomic sequencing is currently not suitable for widespread use in routine diagnosis due to the high cost associated with complex data analysis, the need for technical optimization, and the reliance on expertise in bioinformatics and statistics [40].

Point-of-care testing (POCT) technology provides a new approach for the early diagnosis of neonatal early-onset sepsis. Immunochromatographic assays, a commonly used POCT technique, are characterized by ease of operation, short detection time (15–30 minutes), and no requirement for specialized equipment, making them suitable for use in primary healthcare settings. Microfluidic chip technology integrates sample processing, reaction, and detection on a single chip, enabling an automated “sample-in, result-out” workflow. Relevant studies have shown that POCT methods can reduce the diagnostic time from 24–48 hours with traditional blood culture to just tens of minutes, facilitating earlier initiation of anti-infective therapy and shortening the duration of antibiotic use [41]. Although the sensitivity and specificity of POCT (e.g., PCT POCT sensitivity 81%–85%, specificity 54%–79%) are slightly lower than those of laboratory-based methods, the rapidity and convenience of POCT offer practical value in clinical settings, especially in situations requiring rapid decision-making and in resource-limited environments [42].

In summary, the standardization of detection methods is crucial for ensuring the accuracy and comparability of neonatal inflammatory biomarker test results. Unified testing standards and operating procedures should be established to regulate all aspects of sample collection, processing, storage, and analysis, with regular implementation of quality control and proficiency testing to ensure result reliability. At the same time, appropriate reference intervals should be developed for neonates of different gestational and postnatal ages, and the performance characteristics of detection methods should be validated. The selection of detection methods should comprehensively consider clinical needs, technical conditions, and cost-effectiveness, with rational application of traditional methods, novel technologies, and POCT. Standardized testing procedures and proper blood sampling are fundamental to guaranteeing test quality. With ongoing technological advancements, more rapid, accurate, and convenient detection methods will continue to emerge, providing stronger technical support for the early diagnosis of neonatal early-onset sepsis in clinical practice.

5. Summary and Outlook

Neonatal early-onset sepsis (EOS) remains a major challenge in the field of neonatology due to its high incidence and mortality rates. Inflammatory biomarkers play a crucial role in the early diagnosis of EOS, providing timely and effective diagnostic evidence for clinical practice. With continuous advancements in detection technologies, a wide range of methods—from traditional laboratory assays to novel molecular diagnostics, miRNA detection, T2MR, and point-of-care testing (POCT)—have greatly expanded clinical options. Studies have shown that the combined detection and dynamic monitoring of inflammatory biomarkers can significantly improve diagnostic sensitivity and specificity, optimize antimicrobial management, reduce unnecessary antibiotic use, and lower the risk of antimicrobial resistance. However, current detection methods still face challenges such as long turnaround times, high costs, technical complexity, and lack of standardization. In the future, it is essential to further promote the standardization of detection methods, establish unified operating procedures and reference intervals, and enhance the accuracy and comparability of test results. Meanwhile, with the application of emerging technologies such as artificial intelligence and machine learning, dynamic monitoring of inflammatory biomarkers and multidimensional data integration are expected to enable more precise risk assessment and individualized treatment. Looking ahead, ongoing innovation in detection technologies and in-depth clinical research will undoubtedly lead to the development of faster, more accurate, and more convenient diagnostic methods for the early detection of EOS, thereby providing strong technical support for improving neonatal outcomes and quality of life.

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