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A SYSTEMATIC REVIEW OF THE EVALUATION OF NEONATAL SEPSIS DIAGNOSIS USING INTERLEUKINS

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Abstract

Background:

Aim: *This study aims to summarize and evaluate the diagnostic potential and accuracy of interleukins (ILs) level as a diagnostic marker for neonatal sepsis.*

Methods: *A systematic search strategy was conducted across several electronic reference databases (PubMed, Cochrane Library, Google Scholar) and included articles published between 2019–2023. Duplicate publications, review articles, and incomplete articles were excluded.*

Results: *Database searches identified a total of 19553 articles. Of these, 100 articles passed the screening process, resulting in 20 articles for full-text assessment. Among them, 11 articles did not evaluate the outcome of interest. Hence, we found 9 appropriate studies included. The ILs reported include IL-6, IL-10, IL-18, and IL-27, with the most common reported was IL-6.*

Conclusion: *Current evidences supports the potential predictive utility of ILs level, especially IL-6, as a potential diagnostic marker for detecting neonatal sepsis. To determine the precise predictive efficacy of the marker, well-designed prospective studies had to be conducted due to the methodological variability and variation of the implemented thresholds.*

Keywords: *Neonatal sepsis, Diagnostic marker, Interleukin level*

INTRODUCTION

Sepsis is a dysregulated host response to infection that results in organ dysfunction that is life-threatening.[1] Neonatal sepsis is a clinical syndrome that may include systemic symptoms of infection, circulatory shock, and multisystem organ failure diagnosed in infants less than 28 days old. Early-onset neonatal sepsis (EONS) and late-onset neonatal sepsis (LONS) are the two subtypes of neonatal sepsis. EONS is typically defined as infections and sepsis occurring within the first 24 to 7 days of life. LONS has been designated as after 24 hours or after the initial week of life, up to 28 days or 1 month.[2] In the overall time frame, the incidence of neonatal sepsis was 2,824 cases per 100 000 live births, with an estimated 17.6% mortality rate of 9. In the overall time frame, early-onset neonatal sepsis cases had a higher estimated incidence and mortality rate than late-onset cases.[3] Another study established that in high-income countries, the incidence of neonatal sepsis ranges from 1 to 4 cases per 1000 live births, whereas in low- and middle-income countries, the incidence ranges from 49 to 170 cases, with a case fatality rate of up to 24%.[4] Despite advances in neonatal medicine, sepsis is still a leading cause of morbidity and mortality in newborns.[5,6]

Conventional microbiologic culture procedures, which can be time-consuming, are the gold standard for the diagnosis of neonatal sepsis.[7] Despite the excellent sensitivity in identifying low bacterial loads (1-4 colony-forming unit (CFU)/mL), when a sick infant is presented, many healthcare professionals are skeptical about negative blood cultures. With evidence of unintended consequences, such as increased risk for necrotizing enterocolitis, fungal infections, bronchopulmonary dysplasia, and death, the diagnostic "culture-negative" sepsis or "clinical sepsis" has caused a 10-fold increase in antibiotic use in newborns.[4,8]

In order to aid in the prompt detection and precise diagnosis of sepsis, more modern molecular approaches and nonculture-based techniques are required. Due to their low sensitivity and shifting normal ranges during the newborn period, the current biomarkers and auxiliary hematological indices utilized in ordinary clinical practice have limited utility and are challenging to interpret.[9] Sensitivity, negative predictive value (NPV), and positive predictive value (PPV) should all be above 85% for a perfect marker. There are no biomarkers or biomarker combinations with sufficient diagnostic accuracies to be employed consistently in the diagnosis of newborn sepsis.[4] Here, we aim to systematically review the diagnostic potential and accuracy of interleukins (ILs) level as a diagnostic marker for neonatal sepsis.

Method

Search Strategy

This study is a qualitative systematic review. The data is obtained through electronic database search in Medline (PubMed), Cochrane Library, and Google Scholar. The keywords used are “Interleukin level” AND “Diagnosis” AND “Neonatal sepsis”. The selected articles are based on inclusion and exclusion criteria.

Table 1. Literature search strategy

Database	Keywords	Results
PubMed	“Interleukin level” AND “Diagnosis” AND “Neonatal sepsis”	55
Cochrane Library	“Interleukin level” AND “Diagnosis” AND “Neonatal sepsis”	3
Google Scholar	“Interleukin level” AND “Diagnosis” AND “Neonatal sepsis”	18000

Eligibility Criteria

All studies were assessed for eligibility. The inclusion criteria of the included studies were original articles (observational studies including cohort, case control, cross-sectional) published in the last 5 years between 2019 and 2023, full-text articles available, published in English, and studied the diagnostic accuracy or the role of ILs as a diagnostic marker of neonatal sepsis. The exclusion criteria of the studies are articles that are not indexed by Scopus, editorials, reviews, and articles that did not evaluate the diagnostic accuracy or the role of ILs as a diagnostic marker for neonatal sepsis. The research selection was carried out in three successive phases. The titles and abstracts of all search results were initially screened and evaluated for relevance. Second, all potentially eligible studies were accessed in their entirety. Finally, the studies that met our inclusion criteria were included in the systematic review. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline is used for the selection.

Data Extraction and Parameter Measured

All the authors extracted the data from the articles. The following datas are collected: Author, year of publication, study design, number of subjects and groups, definition of neonatal sepsis applied for subjects, age of the patients, Ils being measured, samples for measurement, methods for measurement of the sample, and diagnostic accuracy regarding the use of ILs as a diagnostic marker for neonatal sepsis. All disagreements regarding the methodology, article retrieval, and statistical analysis were resolved by consensus among the authors.

Results

The databases search identified a total of 18.058 articles (Table 1). Of these, 100 articles passed the screening process, resulting in 20 articles for full-text assessment. Among them, 11 articles did not evaluate the outcome of interest. Hence, we found 9 appropriate studies included (Figure 1). The summary of the main findings of the selected studies is presented in Table 1.

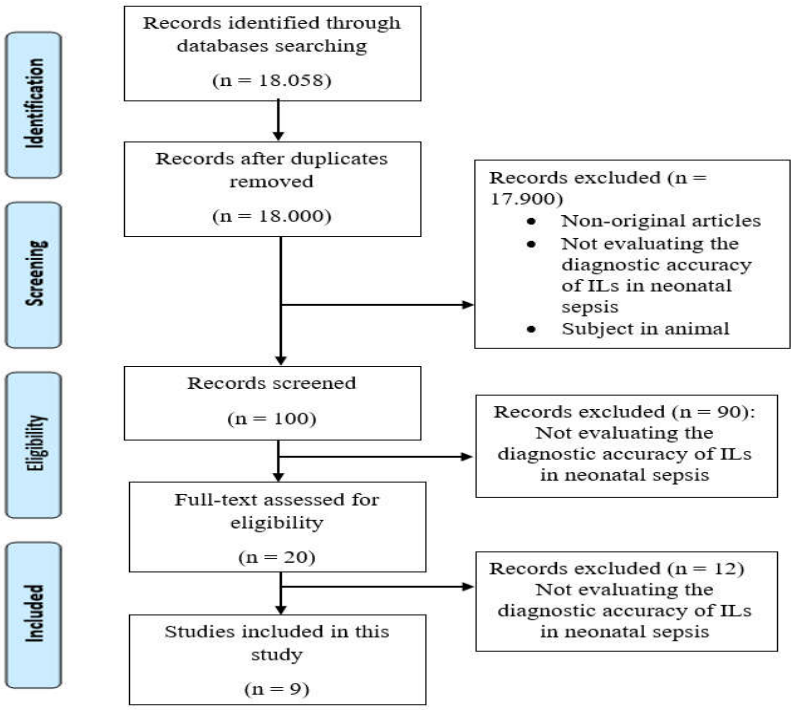

Figure1. PRISMA flow diagram

Table 1. Summary of included studies

Author (Year)	Study design	No. of subjects	Group	Definition of sepsis	Age	IL measured	Samples	Volume of sample	Methods of IL measurement	Diagnostic Accuracy of IL
Barekatain et al. 2019[10]	Cross-sectional	89	Septic: 49 Healthy: 40	Positive blood culture	Mean GA: • Septic: 34.64±1.43 weeks • Healthy: 38±1.66 weeks	IL-18	Saliva	1 mL	Not reported	Salivary IL-18 is insignificant for diagnostic marker of neonatal sepsis (P = 0.37).
Chinedu et al. 2019[11]	Case control	182	EOS: 67 Withous EOS: 115	EOS: positive blood culture or a CRP elevation ≥5 mg/l within the first 72 hours of life together with the presence of two or more of the following clinical signs: temperature instability, respiratory symptoms, cardiovascular symptoms (hypotension, tachycardia, brachycardia), neurological symptoms (seizures, hypotonia, lethargy) or abdominal symptoms (vomiting, poor feeding, abdominal distension).	Median GA: 29.5 weeks (range: 23.9-35.8 weeks)	IL-6	Blood	NR	ECLIA	• Specificity: 72.8% • Sensitivity: 75.0% • AUC: 0.804 • Optimal cut-off: 40 ng/l.
Morad et al. 2020[12]	Cross-sectional	50	-	Positive blood culture	Mean postnatal age: 6 ± 2.4 days	IL-6	Blood	2 mL	ELISA	• Sensitivity: 82.9% • Specificity: 66.7% • PPV: 91.9% • NPV: 46.2% • Accuracy: 80%
Tessema et al. 2020[13]	Cross-sectional	899	• Culture proven sepsis:104 • Clinical sepsis: 160 • Control: 625	• Proven sepsis: CRP > 10 mg/L in at least one of the five serial measurements and positive blood culture. • Clinical: CRP > 10 mg/L in at least one of the five serial measurements and negative blood culture.	Mean postnatal age: • Proven-sepsis: 11.4 ± 7.3 days • Clinical sepsis: 7.2 ± 8.6 days • Controls: 2.5 ± 5.0 days	IL-6	Blood	0.5–1 mL	ECLIA	• Sensitivity: 73.1% • Specificity: 80.2% • PPV: 37.6% • NPV: 94.8% • Optimal cut-off value: 313.5 pg/mL

Cortés et al. 2021[14]	Case control	93	Sepsis: 31 Controls: 62	NR	Mean postnatal age • Sepsis: 1(1–23) days • Control: 1 (1–30)	IL-6	Blood	1–2 mL	ELISA	NS group: • AUC: 0.6572 • Optimal cutoff: 2.38 pg/mL • Sensitivity: 85% • Specificity: 48% • PPV: 62% • NPV: 76% EONS group: • AUC: 0.6869 • Optimal cutoff: 17.75 pg/mL • Sensitivity: 64% • Specificity: 78% • PPV: 74% • NPV: 68%
Omran et al. 2021[15]	Case control	70	LOS: 35 Control: 35	The presence of three or more of the following categories of clinical signs (Clinical sepsis score by Töllner): (1) temperature instability (hyperthermia and hypothermia); (2) cardiovascular alterations (tachycardia, bradycardia, poor perfusion, and hypotension); (3) respira-tory alterations (tachypnea, grunting, intercostal retractions, cyanosis, and apnea); (4) gastrointestinal alterations (abdom- inal distension and feeding intolerance); and (5) neurologic alterations (lethargy, hypotonia, and seizures).	Mean postnatal age: Sepsis: 13 ± 6 days Controls: 11 ± 2 days	IL-10	Saliva, Blood	Saliva: NR Blood: 2 mL	ELISA	Salivary IL-10: • Cut-off: >31 pg/ml • Sensitivity: 97.1% Specificity: 94.3% • AUC: 0.994 Serum IL-10: • Cutoff: ≥33.6 pg/ml • Sensitivity: 97.1% • Specificity: 80%. • AUC: 0.97
Shoukry et al. 2021	Case control	60	Septic: 30 Healthy: 30	NR	Post natal age: • Septic: ≤ 7 days (n = 23); 8–30 days (n = 7) • Control: ≤ 7 days (n = 22); 8–30 days (n = 8)	IL-6	Blood	2 mL	ELISA	Sensitivity: 100% Specificity: 90.32% PPV: 90.63% NPV: 100% Accuracy: 95.16%
Li et al. 2022[16]	Case control	122	Septic: 91 Non-septic: 31	At least two or more of the subsequent four situations, one of which must be aberrant body temperature or leukocyte count: (1) core body temperature of > 38.5°C or < 36°C; (2) tachycardia or bradycardia, (3) average respiratory rate > 2 SD above normal for age or in the presence of mechanical ventilation, and (4) abnormal leukocyte count or >10% immature neutrophils.	Mean postnatal age: Septic: 7 (5–14) days Non-septic: 9 (4–16) days	IL-18	Blood	NR	ELISA	Prediction of neonatal sepsis: • AUC: 0.77 • Cut-off: 0.85 ng/mL • Sensitivity: 60% • Specificity: 84% Prediction of mortality: • AUC: 0.80 • Cut-off: 1.49 ng/mL • Sensitivity: 78% • Specificity: 79%
Wu et al. 2022[17]	Case control	160	Case: 90 Control: 70	The patient has signs and symptoms of an inflammatory reaction, an infection with hypothermia (rectal temperature <35.0°C) or fever (rectal temperature >38.5°C), signs of tachycardia, changes in consciousness, hypoxemia, hyper-lactatemia, or a jumpy pulse.	Mean postnatal age: Case: 7.21 ± 2.44 days Control: 7.34 ± 2.50 days	IL-6, IL-10, IL-27	Blood	NR	ELISA	• Patients with sepsis showed higher levels of IL-27, IL-6, IL-10 (P< 0.05). • The levels of IL-27, IL-6, and IL-10 were increased on day 1 and day 3 but decreased on day 7 (P< 0.05).

Note: AUC: Area under the curve; ECLIA: Electrochemiluminescent immunoassay; ELISA: Enzyme-linked immunosorbent assay; EONS: Early-onset neonatal sepsis; GA: Gestational age; LOS: late-onset sepsis; NR: Not reported; NS: Neonatal sepsis

Discussion

Blood culture is still the gold standard for diagnosing newborn sepsis, but its lengthy turnaround time, high risk of false-negative results, and low culture positive rates make it difficult to use. About 100% sensitivity (infected newborns get a positive test) and NPV (a negative test clearly rules out infection) are desired in a diagnostic marker. A diagnostic marker must also have a decent PPV (infection is present when the test is positive) and a reasonable level of specificity, ideally better than 85%, in order to reduce the overuse of antibiotics in false-positive cases.[4,13]

In this systematic review, we found nine studies published in the last five years evaluating the diagnostic accuracy and potential of ILs as a diagnostic marker for neonatal sepsis. The ILs reported include IL-6, IL-10, IL-18, and IL-27, with the most common reported was IL-6. Several biochemical and immunological markers, including elevated CRP, IL-6, TNF-α, procalcitonin, and E-selectin, rise in the plasma during newborn sepsis. The most used tests for diagnosing newborn sepsis are IL-6 and CRP.[5] A key player in the early host response to infection is the cytokine IL-6. The ideal cut-off values of IL-6 have been determined inconsistently across many studies, and their diagnostic efficacy for detecting neonatal sepsis differs.[13] In our study, there are five studies reporting the optimal cut-off value for IL-6 as a diagnostic marker for neonatal sepsis.

As a cytokine, IL-6 governs immunological reactions and is intimately linked to the development and cell differentiation of numerous types of cells. The body's immunological and inflammatory responses are significantly influenced by IL-27. IL-27 acts immediately and directly on the initial CD4+ T cells after the formation of activated dendritic cells and monocytes, increasing the cellular immune response and defending the body from excessive harm, while IL-10 is markedly up-regulated and maintained for a considerable amount of time.[17]

To the best of our knowledge, this is the first systematic review evaluating ILs level as a diagnostic marker for neonatal sepsis. This systematic review serves as a usefull tool for diagnosis of neonatal sepsis. However, there are several limitations in our study. First, the included studies have heterogenity in the definition of neonatal sepsis. Second, not all studies included reporting the diagnostic accuracy parameter in the form of sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), area under the curve (AUC), accuracy, and cut-off value. Among nine studies included, two studies did not report the diagnostic accuracy parameters previously stated. However, these two studies provide another indicator that signify the diagnostic potential of ILs level as a marker for neonatal sepsis. Third, the methods used for measurement of ILs level was varied and not all studies clearly defined the methods used for measurement of ILs level and thus we did not know if the authors are using the standardize methods. Future large-scale prospective studies will be required due to the significant level of inter-study heterogeneity. In this regard, the current evaluation may work as a pilot study, informing future investigations into the ideal cutoff values and any potential confounding variables that might affect ILs measurements.

Conclusion

Current evidences showed that ILs level is a potential diagnostic marker for detecting neonatal sepsis given that high values of this parameter were associated with the diagnosis of newborn sepsis. This study supports the potential predictive utility of ILs level, especially IL-6, in neonates at risk of developing neonatal sepsis. To determine the precise predictive efficacy of the marker, well-designed prospective studies had to be conducted due to the methodological variability and variation of the implemented thresholds.

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