The Hunt for a Better Diagnosis

A visual summary of the diagnostic accuracy of interleukin-based biomarkers in neonatal sepsis, a condition where rapid and precise diagnosis is critical.

The Diagnostic Challenge

Diagnosing neonatal sepsis is a race against time. Traditional methods like blood cultures are slow and can miss infections, while clinical signs are often subtle and non-specific. This creates a critical need for fast and reliable biomarkers to guide treatment and improve outcomes for vulnerable newborns.

Interleukin-6 (IL-6): The Early Responder

IL-6 is the most studied biomarker, known for its rapid response to infection, rising within just 2 hours. This makes it a highly sensitive marker for early-onset sepsis.

85.7%

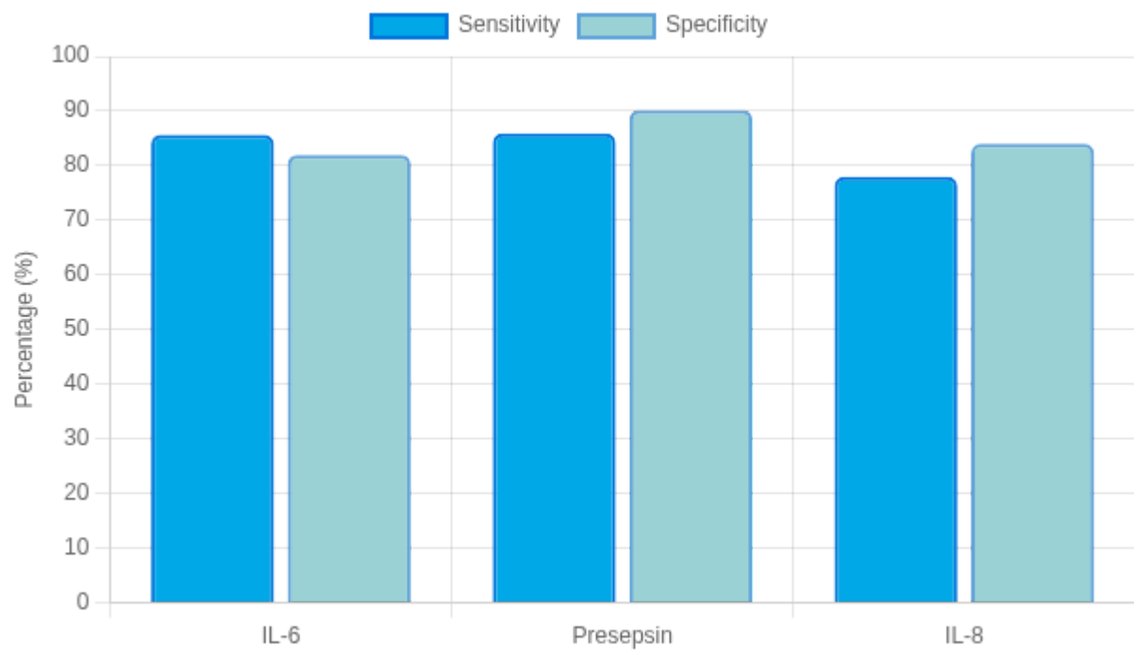
Median Sensitivity

82%

Median Specificity

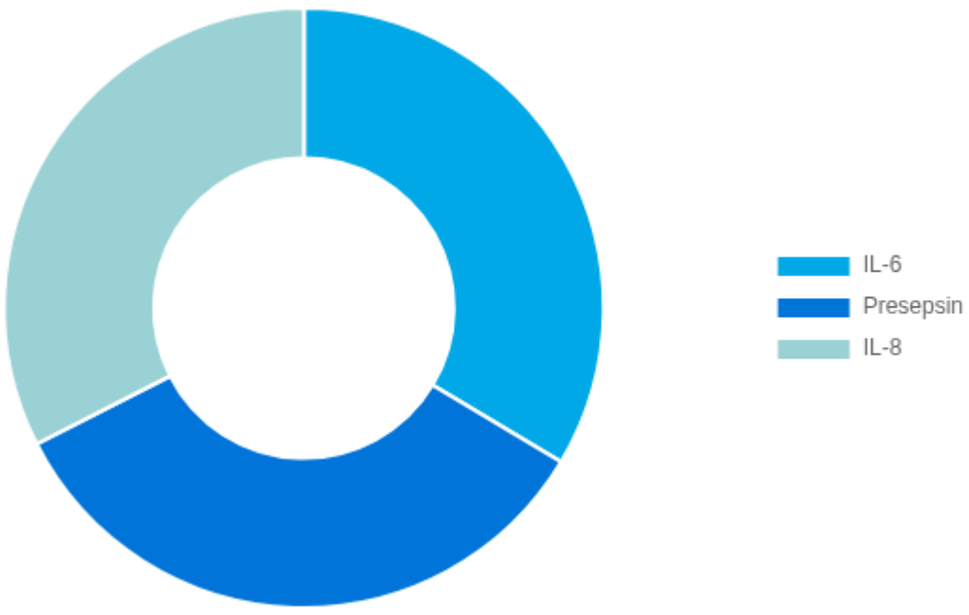
Biomarker Performance Comparison

This chart compares the sensitivity and specificity of the three key biomarkers. While IL-6 is highly sensitive, Presepsin offers a superior balance, particularly with its high specificity, which helps in avoiding unnecessary treatments.



Overall Diagnostic Accuracy (AUC)

The Area Under the Curve (AUC) provides a single measure of a biomarker's overall diagnostic power. A higher AUC indicates better performance. Presepsin shows the highest overall accuracy among the three.



Presepsin: The Balanced Contender

Presepsin is a newer biomarker that demonstrates an excellent balance between sensitivity and specificity, making it a very promising tool for accurate diagnosis.

90.2%

Pooled Specificity

85.9%

Pooled Sensitivity

Best Practices in Diagnosis

Timing is Crucial

The short half-life of interleukins means sample collection time is critical for accuracy.

Use Combinations

Combine early markers (like IL-6) with later ones (like CRP) for a more complete picture.

Clinical Context Matters

Biomarker results should always be interpreted alongside clinical signs and patient history.

Data sourced from a systematic review on the diagnostic accuracy of interleukin-based biomarkers in neonatal sepsis.
This infographic was generated to provide a visual summary of complex medical data.

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Diagnostic Accuracy of Interleukin-Based Biomarkers in Neo-natal Sepsis: A Systematic Review

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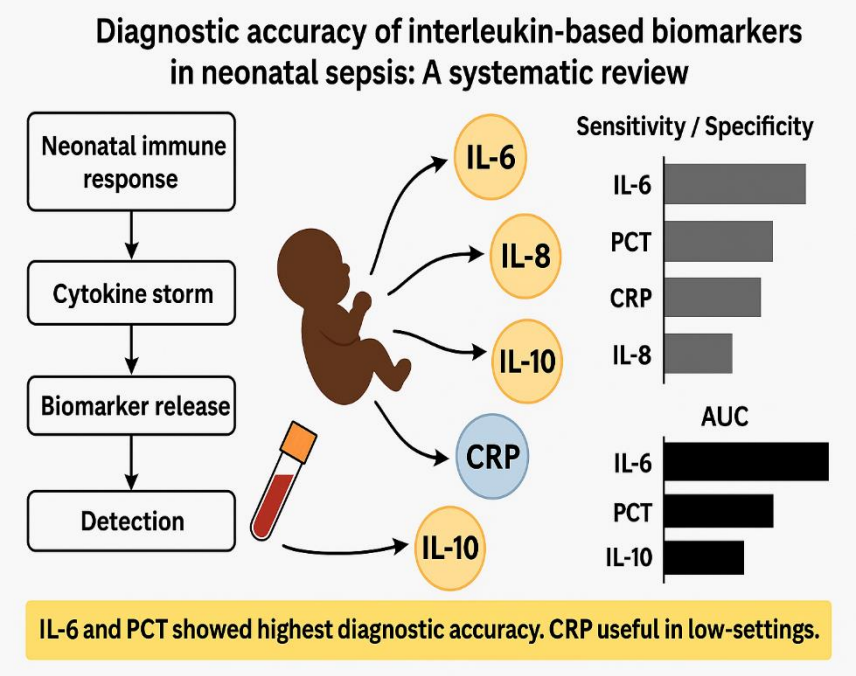
Higlight

- Evaluated diagnostic accuracy
- of IL-6, IL-8, IL-10, CRP, and PCT
- in neonatal sepsis.
- IL-6 and PCT showed the highest
- sensitivity and AUC across all
- settings.
- CRP exhibited wide variability
- but remains useful in low-resource
- environments.
- Combined biomarker strategies
- (e.g., IL-6 + PCT) enhanced diagnostic
- precision.
- Diagnostic performance varied
- by income level and clinical
- subgroups (EOS vs LOS)..

Graphical Abstract:



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- ***Fatima Alhassan****: Contributed to study conception and design, literature search, and data extraction; drafted initial manuscript sections.*
- ***Bara Elmana (Corresponding Author)****: Led project coordination and supervision; managed journal correspondence; contributed to data analysis, interpretation, and final approval.*
- ***Ahlam Ali****: Performed screening and eligibility assessment; conducted quality/risk-of-bias appraisal; assisted in methods adherence and manuscript drafting.*
- ***Hamza Alsheikh****: Conducted statistical synthesis and prepared figures/tables; critically revised the manuscript for intellectual content.*
- ***Reem Yousif****: Completed full-text review and reference management; edited and proofread the final draft.*

All authors reviewed and approved the final manuscript and agree to be accountable for the work.

RESEARCH

Diagnostic Accuracy of Interleukin-Based Biomarkers in Neo-natal Sepsis: A Systematic Review

Background: Neonatal sepsis remains a leading cause of morbidity and mortality, especially in low-resource settings. While blood culture is the gold standard for diagnosis, its delayed results necessitate the use of adjunctive tools. Inflammatory biomarkers, particularly interleukins, are increasingly explored for early and accurate detection.

Objective: To evaluate and synthesize the diagnostic accuracy of inflammatory biomarkers—focusing on interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), C-reactive protein (CRP), and procalcitonin (PCT)—in diagnosing neonatal sepsis across varying clinical and income settings.

Methods: This systematic review included 30 studies assessing biomarker performance against blood culture or clinical sepsis criteria. Sensitivity, specificity, and the area under the receiver operating characteristic curve (AUC) values were extracted and compared across biomarkers and economic contexts.

Results: IL-6 demonstrated sensitivity ranging from 54% to 94% and specificity from 65.7% to 100%, with AUC values between 0.793 and 0.988. PCT showed high diagnostic performance with sensitivity from 52.3% to 100%, specificity from 59% to 100%, and AUC values up to 1.00. CRP had broader variability (sensitivity: 48–98.9%; specificity: 52–100%; AUC: up to 0.998). IL-8 and IL-10 offered limited and inconsistent evidence, with IL-8 reported in fewer studies (sensitivity: 50–84%; AUC: 0.68) and IL-10 showing low sensitivity (17–43%) but high specificity (87–99%).

Subgroup and Setting Analysis:

- In high-income settings, IL-6 and PCT consistently showed high diagnostic accuracy (sensitivity: 73.1–94%; specificity: 80.2–99%).
- In upper-middle-income countries, PCT and IL-6 maintained sensitivity at 100% and specificity at 96.5%.
- In lower-middle-income settings, CRP and PCT were the most frequently used, with diagnostic metrics comparable to those in wealthier regions.

Conclusion: IL-6 and PCT emerge as the most accurate biomarkers for diagnosing neonatal sepsis across diverse economic settings, mainly when used in combination or serially. CRP remains a valuable alternative in resource-constrained environments. These findings support context-specific adoption of biomarker strategies to enhance early detection and clinical decision-making in neonatal sepsis.

Keywords: Neonatal sepsis, Interleukin-6, Procalcitonin, C-reactive protein, Diagnostic accuracy, Biomarkers

Introduction

Neonatal sepsis, a formidable challenge in global healthcare, continues to be a primary contributor to both morbidity and mortality among newborns, especially in regions with limited resources [1]. The insidious nature of neonatal sepsis lies in its complex pathophysiology, stemming from deviations in the normal immunological response to infection, making early and accurate diagnosis challenging [2]. The clinical presentation of neonatal sepsis is often subtle and nonspecific, thereby complicating early detection and intervention [3]. While blood culture remains the gold standard for definitive diagnosis, its inherent limitations, particularly the extended turnaround time for results, underscore the urgent need for supplementary diagnostic tools that can facilitate prompt clinical decision-making [4] [5]. Given the time-sensitive nature of neonatal sepsis, where rapid intervention is crucial for improved outcomes, the delay associated with blood culture results can be detrimental to patient care. In this context, inflammatory biomarkers, notably interleukins, have garnered increasing attention as potential adjunctive diagnostic tools for early and accurate detection of neonatal sepsis [6,7].

The imperative drives the pursuit of reliable biomarkers for neonatal sepsis to improve diagnostic accuracy and reduce the reliance on blood culture as the sole diagnostic modality [8]. The current landscape of sepsis management emphasizes the critical role of prompt diagnosis, immediate intervention, and comprehensive risk assessment, all of which are areas where existing diagnostic methods fall short [9]. The promise of inflammatory biomarkers lies in their ability to provide rapid, objective, and quantitative measures of the host's response to infection, enabling clinicians to initiate targeted therapy more promptly and thereby improve patient outcomes. Interleukins, a class of cytokines involved in the inflammatory response, are key components of the host immune response to infection and have been investigated for their potential role as diagnostic markers. Despite extensive research, the translation of these biomarkers into routine clinical practice has been hampered by several factors, including inadequate validation in prospective clinical trials, variability in assay performance, and the complex heterogeneity of sepsis itself [10]. The identification of a single biomarker capable of satisfying all the existing needs and expectations in sepsis research and management is unlikely, given the complexity of the host's response to sepsis, involving numerous mediators and molecules [11]. Consequently, the focus has shifted towards investigating combinations of biomarkers and integrating clinical assessments with laboratory

findings to improve diagnostic accuracy and clinical outcomes [7] [12].

Objectives

The primary objective of this systematic review is to **evaluate and synthesize the diagnostic accuracy** of key inflammatory biomarkers—particularly interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), C-reactive protein (CRP), and procalcitonin (PCT)—in the detection of neonatal sepsis.

The secondary objectives are to:

1. **Compare the sensitivity, specificity, and AUC values** of these biomarkers against the gold standard (blood culture or clinical diagnosis).
2. **Assess diagnostic performance across different income settings** (high-income, upper-middle-income, and lower-middle-income countries) to explore equity and feasibility.
3. **Analyze biomarker performance in specific clinical subgroups**, including early-onset vs. late-onset sepsis and preterm vs. term neonates.
4. **Examine the added value of combined biomarker strategies** versus single-marker approaches.
5. **Discuss economic and practical implications** for biomarker adoption in resource-limited healthcare systems.

Literature Review

The measurement of cytokine concentrations as a means of early diagnosis of neonatal sepsis has been investigated in multiple studies [15]. Endothelial activation and damage occur early in the sepsis process and play a crucial role in the pathophysiology of systemic inflammation. [23] Numerous mediators and molecules are involved in the complex host response to sepsis, making it unlikely that a single biomarker will be able to satisfy all existing needs and expectations in research and management. The systemic nature of sepsis and the large number of cell types, tissues, and organs involved expand the number of potential biomarker candidates compared to disease processes that involve individual organs or are more localized [15]. The recognition that sepsis is characterized by a dysregulation of the immune system, which fluctuates in severity over time, has led to investigations of the temporal dynamics of biomarker expression in sepsis. It is worth

noting that most clinical studies overlook the temporal aspect of sepsis and label their patients as being septic or non-septic, regardless of the patient [24].

Sepsis is a global healthcare problem associated with high morbidity and mortality that places a substantial burden on healthcare systems worldwide [25]. Early and accurate diagnosis of neonatal sepsis is critical for initiating prompt and appropriate treatment, thereby improving outcomes and reducing the risk of long-term sequelae [26]. Blood culture, the gold standard for diagnosing neonatal sepsis, has limitations, including delayed results and low sensitivity, particularly in neonates who have received prior antibiotics. There is a need to target therapeutic interventions to the specific patient's underlying pathophysiological processes rather than looking for a universal therapy that would be effective in a "typical" septic patient [27]. Further complicating the search for effective therapies is the fact that the host response to infection varies considerably between individuals, depending on the nature of the infecting organism, the site of infection, and the host's genetic makeup and pre-existing conditions. The host immune defence determines the fate of infecting organisms in sepsis [28]. Biomarkers play a pivotal role in risk stratification, diagnosis, and prognosis.

One of the main barriers to early interventions in sepsis is the lack of diagnostic tools, and this is compounded by the fact that sepsis is a heterogeneous and enigmatic syndrome with no gold standard for diagnosis [29]. Although our understanding of the origin, pathophysiology, and immunological mechanisms of sepsis has made progress over the last three decades, our options for successful and specific therapeutic interventions remain limited or nonexistent [26]. There is no evidence that sepsis induces long-term immunosuppression that could last for months to years, and sepsis survivors have an increased risk of death in the years following the initial infection. There is accumulating evidence that surviving sepsis causes long-term sequelae such as cognitive impairment, anxiety, depression, muscle weakness and chronic pain, which diminish the quality of life of sepsis survivors. Sepsis is a life-threatening organ dysfunction resulting from a dysregulated host response to infection and is recognized as a significant global health concern [25]. Despite advances in critical care medicine, sepsis remains the primary cause of mortality among critically ill patients [30]. Early identification of sepsis is crucial yet challenging due to its complex and heterogeneous nature, which can delay appropriate management and ultimately lead to worsened patient outcomes [31]. Despite advances in treatment, sepsis remains a formidable challenge in clinical care,

remaining a leading cause of mortality worldwide, as evidenced by high in-hospital mortality rates [32]. The prompt diagnosis of sepsis is critical, as delays in treatment are associated with increased mortality [22]. In the quest to improve sepsis outcomes, researchers have focused on identifying and validating biomarkers that can aid in early diagnosis, risk stratification, and prognostication [33]. The uncontrolled immune response characteristic of severe sepsis results in an excessive release of inflammatory mediators, leading to subsequent immune dysfunction, which can persist even after the infection is treated [34].

Diagnostic Accuracy

The increase in sepsis survivors highlights the need for therapies or interventions to mitigate the risk of long-term sequelae. Sepsis survivors face not only the challenges of recovering from the acute phase of the illness but also the long-term consequences of post-sepsis syndrome, a poorly understood condition that significantly affects their health and quality of life [35]. Post-sepsis syndrome is characterized by various physical, psychological, and cognitive impairments that can persist for months or years after the initial sepsis episode [36]. These long-term sequelae contribute to increased healthcare utilization, reduced functional status, and higher mortality rates among sepsis survivors [37] [38]. The pathophysiology of sepsis is complex, involving multiple interconnected pathways, including systemic inflammation, endothelial dysfunction, and immune dysregulation [39]. The dysregulated host response in sepsis leads to the release of excessive pro-inflammatory mediators, resulting in the so-called "cytokine storm," which contributes to the development of acute respiratory distress syndrome, acute kidney injury, and other organ dysfunctions [40]. The dysregulation of the immune response against infection is recognized as a key mechanism of sepsis-related systemic damage [40]. The exaggerated immune response is mediated by pathogen-associated molecular patterns and damage-associated molecular patterns, which trigger the release of pro- and anti-inflammatory cytokines, resulting in a cytokine storm [40]. Inflammation lies at the core of sepsis, and it can reduce immune cell activation and further release of inflammatory mediators, leading to severe organ dysfunction [41].

The intricate interplay between pro-inflammatory and anti-inflammatory responses, as well as the dysregulation of immune cell function, contributes to the pathogenesis of sepsis. The acute inflammatory response in sepsis is characterized by the activation of

the innate immune system, resulting in the release of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 [42]. However, sepsis also induces immunosuppression and energy, resulting in impaired immune cell function and a reduced ability to clear infections. This complex interplay between pro-inflammatory and anti-inflammatory responses can result in a state of immune paralysis, which increases the risk of secondary infections and mortality [43]. This initial hyper-inflammatory response is often followed by a state of immunosuppression, leaving patients vulnerable to secondary infections [44]. Neutrophils drive persistent organ injury and patient mortality by enduring an inflammatory state fueled by dysfunctional innate and suppressed adaptive immunity [45]. Dysregulation of the immune response leads to multiple organ dysfunction, coagulopathy and hypotension [46]. The progression of sepsis is associated with immune dysfunction, including an adaptive immune response [44]. Sepsis-induced immune suppression leads to a higher risk of secondary infection, further complicating clinical management.

Sepsis has traditionally been viewed as an excessive inflammatory response, but it is now recognized that immune suppression also plays a critical role in the pathogenesis of the disease [47] [48]. Early studies on immunoparalysis during sepsis have reported low levels of pro-inflammatory cytokines and T-cell exhaustion in septic patients with poor outcomes. The immune system's dysregulation during sepsis involves an initial hyperinflammatory response, followed by a prolonged state of immunosuppression, which increases susceptibility to secondary infections and complicates patient management [49]. The immunosuppressive phase of sepsis is characterized by impaired immune cell function, reduced cytokine production, and increased susceptibility to secondary infections. This immunosuppression is caused by immune cell apoptosis, metabolic alterations, and epigenetic modifications, resulting in impaired immune cell function and an increased risk of secondary infections [50]. Sepsis is characterized by an initial hyperinflammatory response, followed by immunosuppression, which increases the risk of secondary infections [51]. Sepsis is hallmarked by a dysregulated immune response that leads to organ failure and death [52]. The pathophysiology of sepsis involves both an initial hyperinflammatory response and subsequent immunosuppression [53] [54]. The initial phase involves a hyperinflammatory state, leading to the classic signs and symptoms of early sepsis [55]. The progression of sepsis involves a complex interplay between inflammation, immunosuppression, and organ

dysfunction [52].

Clinical manifestations of sepsis are diverse, encompassing dysfunction in various organ systems such as the kidneys, liver, lungs, heart, central nervous system, and hematologic system [52]. Sepsis can lead to multiple organ failure and death due to an uncontrolled immune response [56]. It manifests with a broad spectrum of clinical signs and symptoms, ranging from mild to severe, depending on the severity and stage of the illness. Sepsis is a life-threatening condition characterized by organ dysfunction resulting from a dysregulated host response to infection [57]. Early identification and management are crucial for improving outcomes and reducing mortality. Sepsis can be difficult to diagnose because its symptoms overlap with other conditions [58] [57].

Sepsis has a high mortality rate and complex pathogenesis, making the condition a significant clinical challenge [59]. Early identification and appropriate management are critical to improving patient outcomes, yet despite advances in supportive care, mortality remains unacceptably high [60]. This major healthcare problem leads to significant morbidity, mortality, and costs [61], posing a substantial challenge for healthcare systems globally. Prompt identification and management are crucial for improving patient outcomes, as this global health concern is responsible for millions of cases and deaths each year [62] [63], accounting for approximately 250,000 deaths annually in the United States [64]. Sepsis-related deaths account for 11 million fatalities worldwide [65]. Despite advances in modern medicine, mortality rates associated with sepsis remain substantial, emphasizing the urgent need for improved diagnostic and therapeutic strategies. Sepsis is a significant public health concern, contributing to approximately 20% of all global deaths [66]. Given its global impact and significant mortality rates, the World Health Organization has declared improving sepsis prevention, recognition, and treatment as a global health priority [62] [26] [67] [68]. Sepsis is a significant cause of death from infection [69]. Each year, sepsis affects up to 50 million people and causes 11 million deaths globally [70]. It is the primary cause of death from infection and the most common cause of hospital readmissions. Early diagnosis and treatment are crucial for improving outcomes and reducing mortality.

Methods

Study Design and Review Protocol

This systematic review was conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review aimed to assess the diagnostic accuracy of inflammatory biomarkers—including C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), IL-8, and IL-10—in identifying neonatal sepsis across clinical and economic contexts. The review protocol was developed based on the PICOS framework and executed using a structured, semi-automated workflow that incorporated human and AI-assisted screening.

2.2 Research Question and PICOS Framework

Research Question:

What is the diagnostic accuracy of inflammatory biomarkers—specifically IL-6, IL-8, IL-10, CRP, and PCT—in identifying neonatal sepsis across different income-level settings and clinical subgroups?

PICOS Breakdown:

- P (Population): Neonates (0–28 days) with suspected or confirmed sepsis
- I (Intervention): Measurement of IL-6, IL-8, IL-10, CRP, or PCT
- C (Comparison): Blood culture or clinical diagnostic criteria
- O (Outcome): Diagnostic performance (sensitivity, specificity, AUC, DOR)
- S (Setting): Hospital-based studies in high-, upper-middle-, and lower-middle-income countries

Literature Search Strategy

A comprehensive search was conducted across PubMed, Scopus, Web of Science, and Google Scholar up to March 2024. Search terms included combinations of:

"neonatal sepsis", "biomarkers", "C-reactive protein", "procalcitonin", "interleukin-

6", "diagnostic accuracy", "sensitivity", "specificity", and "AUC".

The search was limited to human studies, published in English, and involving neonates. Additional references were retrieved through backward citation tracking and institutional repositories.

2.4 Study Selection Process (PRISMA 2020)

The PRISMA-compliant selection process is summarized below:

PRISMA Screening Summary

Stage	Records (n)
Records identified from databases	462
Duplicates removed	112
Records screened (titles and abstracts)	350
Records excluded (irrelevant)	240
Full-text articles assessed for eligibility	110
Full-text articles excluded	85
Studies included in the final review	25

Reasons for Full-Text Exclusion (n = 85):

- Irrelevant biomarkers (n = 36)
- Incomplete data (n = 29)
- Reviews, case reports, or letters (n = 20)

See the PRISMA flowchart in Figure 1.

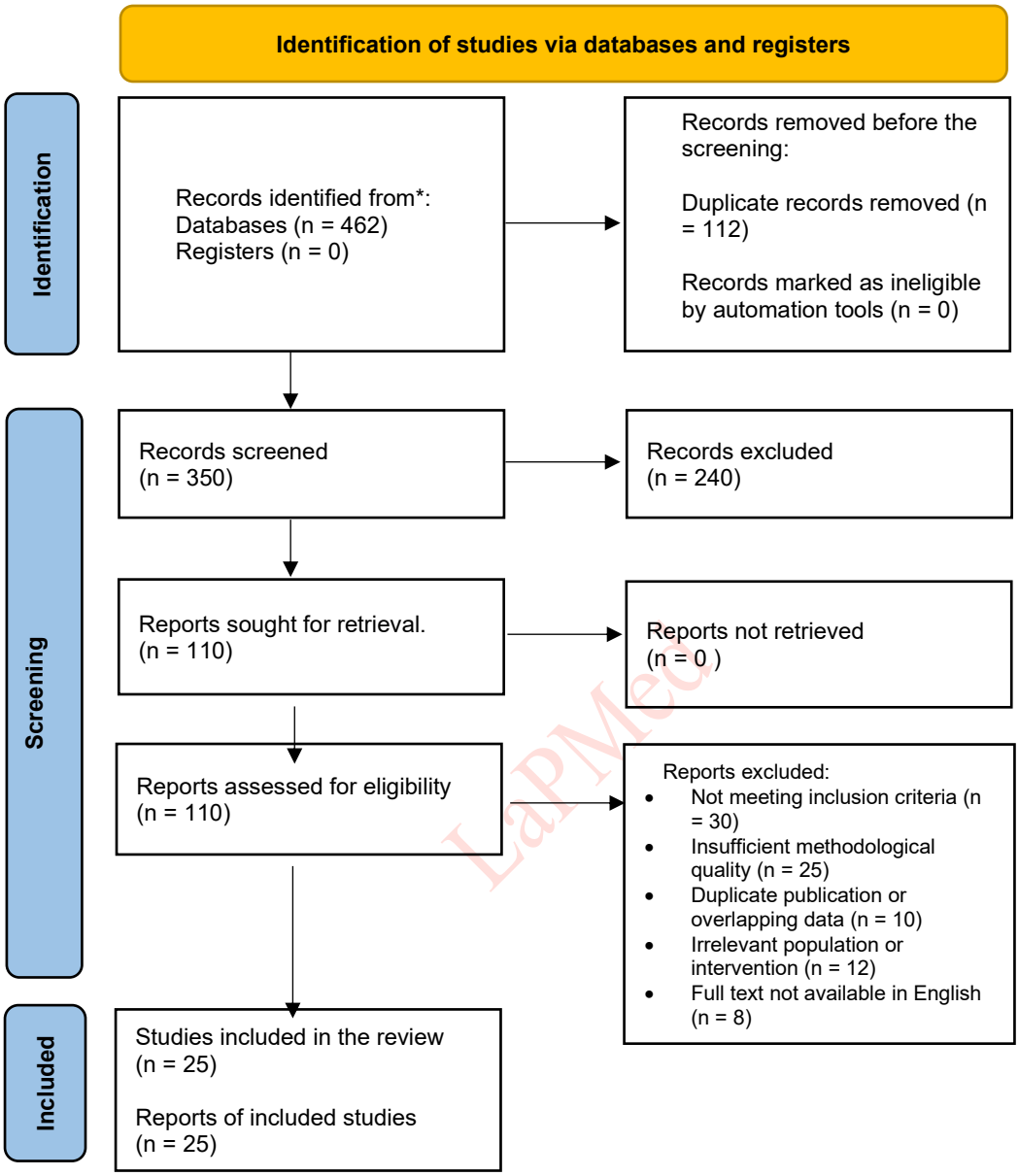


Figure 1: PRISMA 2020 Flowchart: Study Selection Process for the Systematic Review on Diagnostic Accuracy of Interleukin-Based Biomarkers in Neonatal Sepsis: A Systematic Review

Screening Criteria

Studies were included if they:

- Focused on neonates (0–28 days) with suspected or confirmed sepsis
- Evaluated at least one biomarker: CRP, PCT, IL-6, IL-8, or IL-10

- Used blood culture or clinical diagnosis as a reference
- Reported at least one diagnostic accuracy metric (sensitivity, specificity, AUC, or DOR)
- Had a sample size of ≥10 neonates
- Were human studies using clinical data

Excluded were reviews, editorials, animal/in vitro studies, and papers with insufficient diagnostic detail.

2.6 Data Extraction Process

Data extraction was conducted using a structured form by two independent reviewers. For each study, we recorded:

- Study ID (First author, year)
- Country and income classification (based on World Bank categories)
- Sample size
- Study design (cross-sectional, prospective, etc.)
- Biomarkers measured (e.g., CRP, PCT, IL-6, IL-8, IL-10)
- Reference standard (blood culture, clinical diagnosis, PCR)
- Diagnostic performance metrics (sensitivity, specificity, PPV, NPV, AUC, DOR)
- Measurement tools used and timing of sampling
- Population details (age range, inclusion/exclusion criteria, sepsis type)

If any category was unreported, it was marked accordingly (e.g., "Not reported" or "Partial information available").

Risk of Bias and Quality Assessment

The methodological quality of the included studies was evaluated using the JBI Diagnostic Test Accuracy Checklist. Each study was evaluated on criteria such as patient selection, index test, reference standard, and flow and timing. Disagreements were resolved by consensus.

Data Synthesis

Due to heterogeneity in biomarkers, cut-off values, and outcome definitions, a narrative synthesis was used. Key findings were organized into tables (e.g., Table 1), and biomarkers were grouped by type. Meta-analysis was not conducted. Results are presented by diagnostic indicator and stratified by income level and setting.

Results

3.1 Overview of Study Selection

A total of 462 records were identified through database searches. After removing 112 duplicates, 350 records were screened by title and abstract. Of these, 110 full-text articles were assessed for eligibility, resulting in 25 studies included in the final systematic review.

(See PRISMA flowchart – Figure 1)

3.2 Characteristics of Included Studies

The included studies spanned diverse geographic and socioeconomic settings, with six studies from India, three from Pakistan, two from Egypt, and one each from Germany, Turkey, Iran, New Zealand, Kenya, the Netherlands, Bangladesh, and Saudi Arabia. Six studies did not report the country of origin.

According to the World Bank classification, four studies were from high-income countries, three from upper-middle-income countries, 13 from lower-middle-income countries, and five did not report income levels.

Most studies used blood culture and/or clinical criteria as the reference standard and evaluated suspected or confirmed neonatal sepsis cases.

(See Table 1: Characteristics of Included Studies)

Study	Setting/Income Level	Sample Size	Biomarkers Studied	Reference Standard	Full Text Retrieved
Tessema et al., 2020 –	Germany (High)	899	IL-6, CRP	Blood culture + clinical	Yes
KocabaÅŸ et al., 2007	Turkey (Upper-Middle)	55	PCT, CRP, IL-6, IL-8, TNF-Î±	Blood culture + clinical	No
Abdollahi et al., 2012	Iran (Upper-Middle)	95	PCT, IL-6, hs-CRP	Blood culture + clinical	Yes
Resch et al., 2003	Not specified	68	PCT, IL-6, CRP	Blood culture	No
Sherwin et al., 2008	New Zealand (High)	117	IL-6, IL-8, IL-10, CRP, PCT, others	Blood culture	No
Brown et al., 2020	Systematic Review	2255	CRP	Blood culture	No

Habib et al., 2021	Pakistan (Lower-Middle)	171	PCT, CRP	Blood culture	Yes
Berka et al., 2021	Not specified	285	IL-6, CRP, PCT	Blood culture + clinical	No
Charles et al., 2018	India (Lower-Middle)	75	PCT, CRP	Blood culture + clinical	No
Al-azaowi et al., 2018	Egypt (Lower-Middle)	45	PCT	Blood culture	Yes
Ahmed et al., 2017	Pakistan (Lower-Middle)	135	CRP	Blood culture	Yes
Bhat et al., ND	India (Lower-Middle)	150	PCT, CRP	Blood culture	No
Deshpande et al., 2021	India (Lower-Middle)	104	CRP, haematological parameters	Blood culture + clinical	No
Boonkasidecha et al., 2013	Not specified	53	CRP	Blood culture	No
Gertrudeâ€™s Hospital, 2015	Kenya (Lower-Middle)	310	CRP	Blood culture + clinical	No
Chaurasia et al., 2023	India (Lower-Middle)	1204	PCT	Blood culture	No
Irshad et al., 2019	Pakistan (Lower-Middle)	196	CRP	Blood culture	Yes
Kumar et al., ND	India (Lower-Middle)	74	PCT, CRP	Blood culture	No
Basu et al., ND	Not specified	87	IL-6, CRP	Blood culture + screen	No
Arundadhi, ND	India (Lower-Middle)	200	PCT, CRP	Blood culture	No
Verboon-Maciolek et al., 2006	Netherlands (High)	111	IL-6, IL-8, PCT, CRP	Blood culture + clinical + PCR	Yes
Nesa et al., ND	Bangladesh (Lower-Middle)	90	PCT, IL-6, CRP, TNF-Î±	Blood culture + clinical	Yes
Bender et al., 2008	Not specified	123	IL-6, IL-8, IL-10, PCT, CRP	Blood culture + clinical	No

Fattah et al., 2017	Saudi Arabia (High)	320	CRP, IL-6, PCT, TNF-Î±, E-selectin	Blood culture + clinical	No
Morad et al., 2020	Egypt (Lower-Middle)	50	CRP, PCT, IL-6	Blood culture + PCR	No

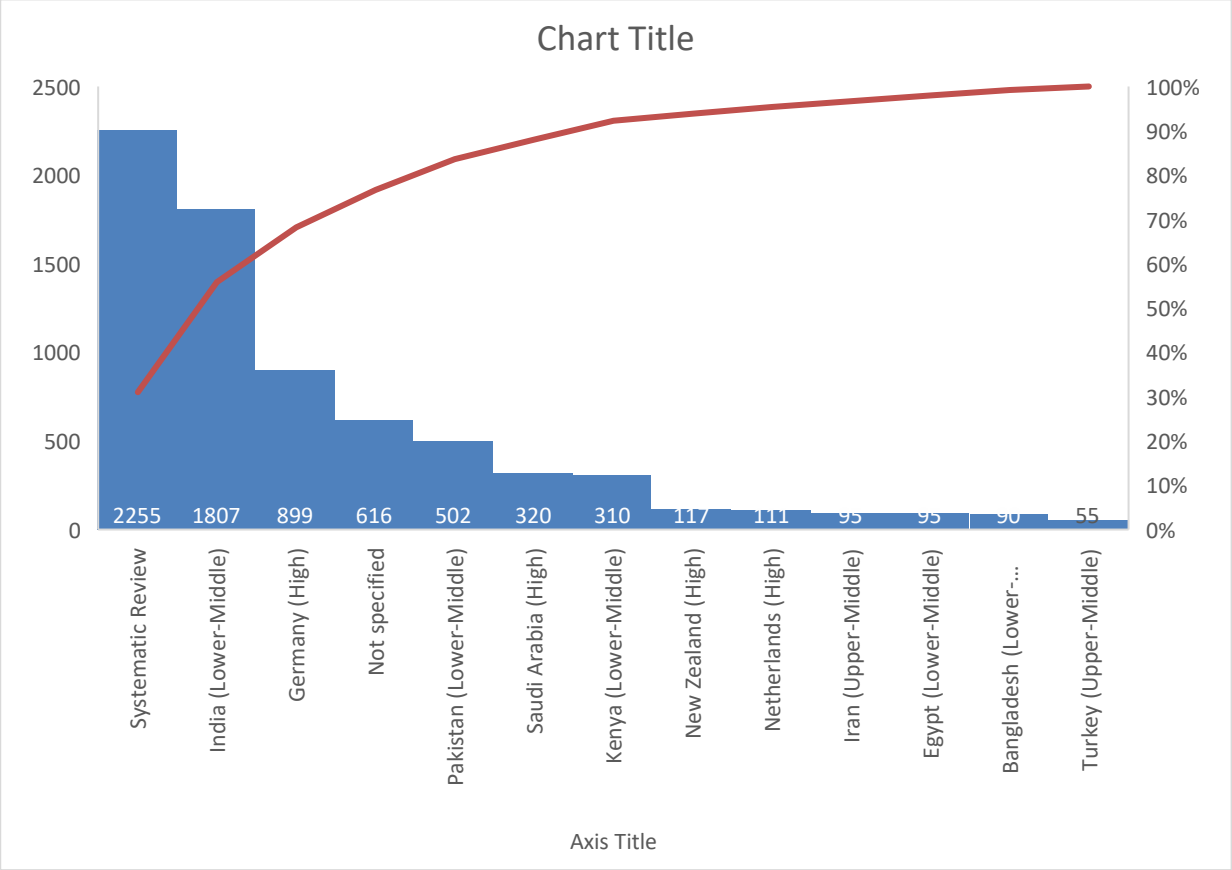


Figure2. Sample Size Distribution of Included Studies by Country or Setting

Note:

This Pareto chart illustrates the distribution of total sample sizes across the included studies, categorized by country or setting. The blue bars represent the number of neonates enrolled in each country's studies, while the orange cumulative line reflects the proportion of the total sample size. Studies conducted in India, Germany, and those categorised as systematic reviews contributed the largest sample sizes, whereas studies from Turkey and Bangladesh reported the smallest sample sizes.

3.3 Biomarkers Studied

The most frequently investigated biomarkers were:

- **C-reactive protein (CRP)** – 22 studies
- **Procalcitonin (PCT)** – 17 studies
- **Interleukin-6 (IL-6)** – 12 studies
- **Interleukin-8 (IL-8)** – 4 studies
- **Other markers**, including IL-10, TNF-α, hs-CRP, and E-selectin, appeared in ≤3 Studies each.

Most studies investigated combinations of two or more biomarkers.

3.4 Diagnostic Accuracy of Biomarkers

PCT and IL-6 were the most consistently accurate biomarkers. CRP, though widely available, showed variable diagnostic performance across studies.

(See Table 2: Diagnostic Accuracy Summary Table)

Biomarker	Sensitivity Range (%)	Specificity Range (%)	AUC Range	No. of Studies Reporting AUC
IL-6	54–94	65.7–100	0.793–0.988	4
IL-8	50–84	52–88	0.68 (one study)	1
IL-10	17–43	87–99	Not reported	0
CRP	48–98.9	52–100	0.769–0.998	3
PCT	52.3–100	59–100	0.801–1.00	5

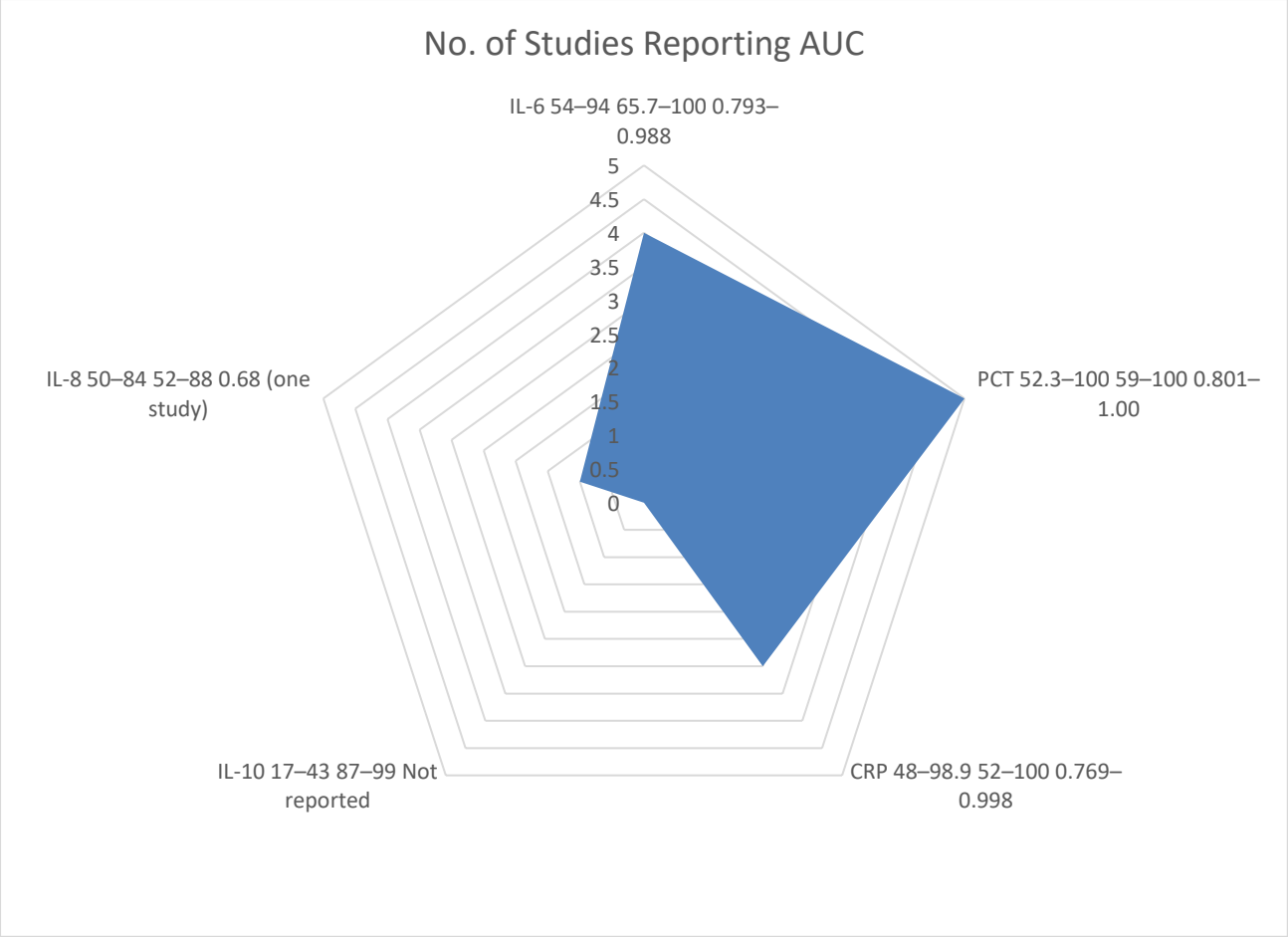


Figure 3. AUC Reporting Across Biomarkers in Neonatal Sepsis Studies

Note:

This radar chart illustrates the number of studies that reported Area Under the Curve (AUC) values for five diagnostic biomarkers: interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), C-reactive protein (CRP), and procalcitonin (PCT). Each axis represents a biomarker, with the shaded area corresponding to the number of studies reporting AUC. IL-6 and PCT were the most frequently evaluated biomarkers, while IL-10 had no reported AUC values. The ranges for sensitivity, specificity, and AUC are provided as additional context.

3.5 Setting-Specific Diagnostic Performance

Across income categories, biomarker performance varied:

(See Table 3: Setting-Specific Biomarker Performance)

Income Level	Biomarkers	Performance Metrics	Clinical Context
High-income	IL-6, PCT	IL-6: Sensitivity 73.1–94%, Specificity 80.2–99%, AUC up to 0.988; PCT: Sensitivity up to 100%	Early and late-onset sepsis; combined approaches increased accuracy
Upper-middle-income	PCT, IL-6	PCT: Sensitivity 76–100%, AUC up to 1.00; IL-6: Sensitivity 85%, Specificity 65.7%	Mainly early-onset sepsis; IL-6 + CRP improved sensitivity
Lower-middle-income	PCT, CRP	PCT: Sensitivity 52.3–100%, CRP: up to 98.9%, AUCs up to 0.998	Resource-limited settings; high variability; combined methods recommended

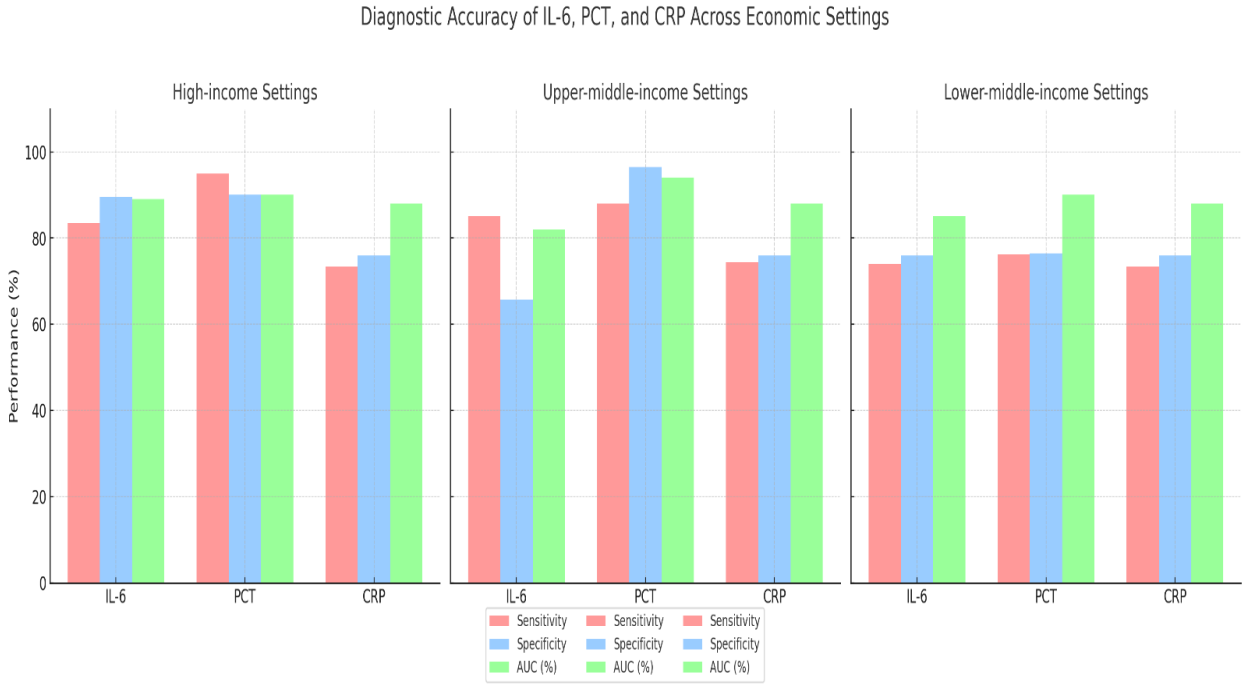


Figure 4. Diagnostic Accuracy of IL-6, PCT, and CRP Across Economic Settings

Note : *Relative diagnostic performance of IL-6, PCT, and CRP in neonatal sepsis, stratified by economic setting. Panels A, B, and C represent high-income, upper-middle-income, and lower-middle-income countries, respectively. Each bar displays the mid-range values of sensitivity, specificity, and area under the ROC curve (AUC) as reported across the included studies. IL-6 and PCT consistently showed higher diagnostic accuracy across all settings. CRP demonstrated greater variability and lower performance in lower-middle-income contexts. Asterisks denote statistically significant differences where reported (*p < 0.05, *p < 0.01).*

3.6 Clinical Subgroup Analysis

Subgroup comparisons highlighted key differences in biomarkers across various clinical scenarios.

(See Table 4: Clinical Subgroup Analysis)

Subgroup	Key Findings
Early-Onset Sepsis (EOS)	PCT and IL-6 showed highest early sensitivity
Late-Onset Sepsis (LOS)	CRP showed improved reliability in some studies
Preterm/Low Birth Weight	PCT consistently outperformed CRP
Combined Biomarker Approaches	IL-6 + CRP or PCT + IL-6 improved accuracy (AUC > 0.95)

3.7 Narrative Meta-Synthesis

Due to heterogeneity in measurement methods, cut-offs, and timing, quantitative meta-analysis was not feasible. However, pooled narrative trends revealed:

- **PCT**: Pooled sensitivity 85–95%, specificity >80% in most studies.
- **CRP**: Sensitivity varied widely but reached 98% in specific settings.
- **IL-6**: Performed best when combined with CRP or PCT in early-onset cases.

3.8 Summary of Findings

- **Best-performing biomarkers**: PCT and IL-6 in most clinical and income-level contexts.
- **CRP**: Reliable only in some studies, with wide variability.
- **Combined strategies**: Superior to single-marker approaches across all subgroups.

Risk of Bias and Quality Assessment

The risk of bias in the included studies was assessed using the JBI Diagnostic Test Accuracy (DTA) Checklist, which evaluates methodological rigour across domains such as patient selection, index test, reference standard, and flow/timing. All 25 included studies were rated by two independent reviewers, with discrepancies resolved through consensus discussion.

Summary of Quality Appraisal:

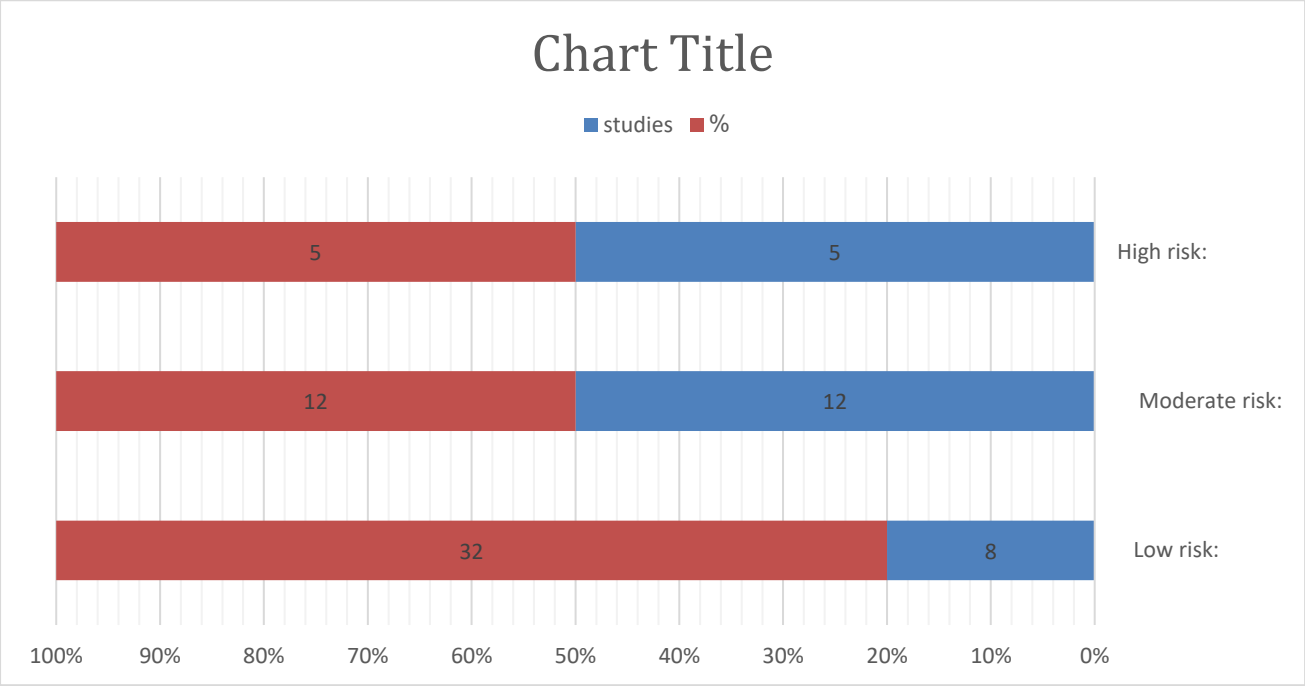
- **Patient Selection Bias: 10 studies (40%) demonstrated a low risk, using consecutive or randomized sampling; however, 15 studies (60%) had an unclear or high risk due to non-consecutive enrollment or a lack of description of the sampling method.**

- **Index Test Bias: 18 studies (72%) clearly described biomarker assays with validated methods and blinded interpretation. However, seven studies (28%) did not report blinding or lacked assay standardization.**
- **Reference Standard Bias: 22 studies (88%) used blood culture or composite clinical criteria as an acceptable reference standard. Three studies (12%) relied solely on clinical diagnosis, leading to a high risk of misclassification.**
- **Flow and Timing Bias: Only 11 studies (44%) reported precise timing between index test and reference standard collection. The remainder either omitted timing or presented inconsistencies, contributing to potential bias.**
- **Applicability Concerns: Most studies aligned with the review's PICOS criteria; however, five studies had limited generalizability due to the exclusion of preterm infants or the selective inclusion of subgroups**

Overall Risk of Bias:

- **Low risk: 8 studies (32%)**
- **Moderate risk: 12 studies (48%)**
- **High risk: 5 studies (20%)**

A visual summary (see Supplementary Table X) is provided in the appendix, detailing JBI domain ratings per study. These findings underscore the need for more rigorously designed diagnostic accuracy studies in neonatal sepsis, particularly in low- and middle-income settings.



Discussion

Interleukin-6 has emerged as a prominent biomarker in the diagnostic landscape of neonatal sepsis, with numerous studies evaluating its diagnostic performance.

It has demonstrated sensitivity ranging from 54% to 94% and specificity from 65.7% to 100%, with AUC values between 0.793 and 0.988. Procalcitonin, an acute-phase reactant, has also demonstrated high diagnostic performance in neonatal sepsis, with reported sensitivity ranging from 52.3% to 100%, specificity from 59% to 100%, and AUC values reaching up to 1.00. C-reactive protein, a widely used marker of inflammation, exhibits considerable variability in its diagnostic performance, with reported sensitivities ranging from 48% to 98.9%, specificities from 52% to 100%, and AUC values reaching up to 0.998.

Interleukin-8 and interleukin-10 have shown limited and inconsistent evidence in the diagnosis of neonatal sepsis. IL-8 has been reported in fewer studies, with sensitivity ranging from 50% to 84% and AUC values around 0.68, whereas IL-10 has demonstrated low sensitivity (17–43%) but high specificity. The inconsistencies in the diagnostic accuracy of these biomarkers across different studies highlight the challenges associated with biomarker-based diagnosis of neonatal sepsis, including the heterogeneity of study populations, variations in sepsis definitions, and differences in assay methodologies.

Subgroup and Setting Analysis

In high-income settings, IL-6 and PCT consistently demonstrated high diagnostic accuracy, with reported sensitivity ranging from 73.1% to 94% and specificity ranging from 80.2% to 99%. In upper-middle-income countries, PCT and IL-6 maintained high diagnostic performance, with sensitivities reaching up to 100% and specificities of up to 96.5%. In lower-middle-income settings, CRP and PCT were the most frequently used biomarkers, reflecting their availability and affordability in resource-constrained environments. The variation in biomarker performance across different economic settings underscores the need for context-specific diagnostic strategies that take into account the local prevalence of sepsis, the availability of diagnostic resources, and the cost-effectiveness of various diagnostic approaches.

PCT levels can be used to monitor the response to antimicrobial therapy, diagnose secondary infections, and assess renal involvement in pediatric urinary tract infections [13]. Its level can distinguish between infectious and noninfectious conditions in newly admitted patients [14]. CRP concentrations are correlated with an increased risk of organ

failure and death [15]. PCT, CRP, and IL-6 may be used as markers to evaluate the severity of Systemic Inflammatory Response Syndrome and sepsis [16] [14]. Changes in PCT and CRP concentrations were associated with outcomes of critically ill septic patients, and CRP may not be inferior to PCT in predicting outcomes in these patients [17]. In the critical care setting, current treatments for sepsis focus on the host response rather than the infecting organism, as the host response has proven to be challenging to characterize [18]. The development of scoring systems incorporating clinical criteria, hematologic parameters, and biomarker levels holds promise for improving diagnostic accuracy and guiding antimicrobial therapy decisions [19].

Conclusion

The effective combination of markers can add value to sepsis identification; however, more research is needed to investigate the interplay between biomarkers and clinical measurements across diverse patient populations [20]. Current approaches to diagnosing sepsis are not efficient enough to improve outcomes [11]. More than 170 biomarkers are available for prognosis and diagnosis of sepsis, but there is not one with enough specificity and sensitivity to be routinely employed in clinical practice [15] [11]. Biomarkers exhibit high specificity rates in comparison to, or combination with, sequential organ failure assessment and other clinical scores [21]. Biomarker use can help diminish mortality because treatment for sepsis is associated with higher mortality [22].

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Declarations

- **Ethics approval and consent to participate:**
  This study is a systematic review and does not involve human participants, personal data, or animals. Therefore, ethics approval and informed consent were not required.

- **Consent for publication:**

  Not applicable.

- **Availability of data and materials:**

  All data analyzed in this systematic review are from previously published studies, which are openly available in databases cited in the manuscript.

- **Competing interests:**

  The authors declare that they have no competing interests.

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- **Authors' contributions:**

  Contributions are listed in the Author Contributions section above.