Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/kcjm2t77

NEONATAL SEPSIS: ROLE OF RAPID DIAGNOSTIC BIOMARKERS IN EARLY DETECTION

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ABSTRACT

Background: Neonatal sepsis is a leading cause of morbidity and mortality worldwide. Early recognition is difficult due to nonspecific clinical signs and the limitations of blood culture, which remains the diagnostic gold standard but is slow and often insensitive.

Objective: To evaluate the diagnostic role of rapid biomarkers—C-reactive protein (CRP), procalcitonin (PCT), and molecular assays—in the early detection of neonatal sepsis.

Methods: Neonates with suspected sepsis were studied. CRP and PCT levels were measured at admission and repeated at 24–48 hours. Molecular assays (PCR/multiplex) were performed on blood samples. Blood culture served as the reference standard. Diagnostic accuracy was assessed using sensitivity, specificity, predictive values, and ROC analysis.

Results: CRP was useful for monitoring trends but showed delayed rise. PCT provided earlier specificity for bacterial infection, though interpretation was limited in the first 48 hours of life. Molecular assays enabled rapid pathogen identification and resistance profiling with high sensitivity. Combined biomarker strategies improved diagnostic accuracy compared to single markers.

Conclusion: CRP, PCT, and molecular assays complement traditional diagnostics. Their integration into clinical workflows enhances early recognition, supports rational antibiotic use, and improves neonatal outcomes.

Keywords: Neonatal sepsis, C-reactive protein, Procalcitonin, Molecular assays, Biomarkers, Early detection.

INTRODUCTION

Neonatal sepsis continues to be a major cause of morbidity and mortality worldwide, particularly in low- and middle-income countries where healthcare resources are limited [1,2]. It is estimated to account for a significant proportion of neonatal deaths, contributing substantially to the global burden of preventable child mortality [1]. Despite advances in neonatal intensive care, early recognition and timely intervention remain critical challenges in clinical practice [2].

The diagnosis of neonatal sepsis is complicated by its nonspecific clinical presentation. Symptoms such as lethargy, poor feeding, temperature instability, and respiratory distress are common to many

neonatal conditions, making clinical suspicion alone unreliable [1,3]. Blood culture remains the gold standard for diagnosis; however, it is limited by delayed turnaround time, low sensitivity due to small sample volumes, and frequent false negatives in infants who have already received empirical antibiotics [3,6]. These limitations often result in delayed or inappropriate therapy, increasing the risk of adverse outcomes [2,4].

To overcome these challenges, rapid diagnostic biomarkers have been investigated as adjuncts to conventional methods. C-reactive protein (CRP), an acute-phase reactant, is widely used for monitoring inflammatory responses but rises relatively late in the course of infection [4,9]. Procalcitonin (PCT), a precursor of calcitonin, increases earlier and is more specific for bacterial infections, offering potential advantages in distinguishing sepsis from non-infectious inflammatory states [5,7]. Molecular assays, including polymerase chain reaction (PCR) and multiplex platforms, provide rapid pathogen identification and resistance profiling directly from blood samples, thereby reducing diagnostic delays [6,10].

AIM

To evaluate the diagnostic accuracy and clinical utility of rapid biomarkers—C-reactive protein (CRP), procalcitonin (PCT), and molecular assays—in the early detection of neonatal sepsis, and to determine their role in complementing conventional blood culture.

OBJECTIVES

1. To measure and compare the sensitivity, specificity, predictive values, and ROC performance of CRP, PCT, and molecular assays in neonates with suspected sepsis.
2. To assess the timing and diagnostic reliability of CRP and PCT trends during the first 48 hours of life.
3. To determine the effectiveness of molecular assays (PCR/multiplex) for rapid pathogen identification and resistance profiling.
4. To evaluate combined biomarker strategies (CRP + PCT, CRP + molecular assays, PCT + molecular assays, and triple combination) in improving diagnostic yield compared with single markers.
5. To analyse the impact of biomarker-guided diagnosis on antibiotic use, NICU stay, and short-term neonatal outcomes.

MATERIALS AND METHODS

Study Design and Setting

This was an observational study conducted in a neonatal intensive care unit (NICU). All neonates ≤28 days of age admitted with clinical suspicion of sepsis were evaluated. Standard infection control practices and routine NICU protocols were followed throughout the study.

Study Population

All neonates aged ≤28 days admitted with clinical suspicion of sepsis were included. Clinical suspicion was based on one or more of the following features: temperature instability, lethargy, poor feeding, respiratory distress, Apnea, or hemodynamic instability.

Inclusion criteria:

- Neonates ≤28 days of age.
- Presence of clinical signs suggestive of sepsis.
- Maternal risk factors (e.g., prolonged rupture of membranes, maternal fever, chorioamnionitis).
- Perinatal risk factors (e.g., low Apgar scores, perinatal asphyxia, need for resuscitation).
- Availability of blood samples for CRP, procalcitonin, molecular assays, and culture prior to antibiotics.

Exclusion criteria:

- Neonates with major congenital anomalies.

- Infants who had received prolonged antibiotic therapy (>48 hours) before admission.
- Severe birth trauma or conditions unrelated to infection that could confound biomarker interpretation.
- Lack of parental or guardian consent.
- Incomplete clinical or laboratory records.

Investigations

- **C-reactive protein (CRP):** Measured using immunoturbidimetric assay at admission and repeated at 24–48 hours to monitor trends.
- **Procalcitonin (PCT):** Measured using chemiluminescent immunoassay at admission and repeated at 24–48 hours for early detection of bacterial infection.
- **Molecular assays:** Blood samples subjected to polymerase chain reaction (PCR) or multiplex PCR platforms for rapid pathogen identification and resistance profiling.
- **Blood culture:** Collected before antibiotic administration and processed using automated culture systems; considered the gold standard comparator.

Outcomes

Primary Outcome

- Diagnostic accuracy of C-reactive protein (CRP), procalcitonin (PCT), and molecular assays in the early detection of neonatal sepsis.
- Accuracy was expressed in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), using blood culture as the reference standard.

Secondary Outcomes

1. **Time to diagnosis:** Comparison of turnaround time for CRP, PCT, and molecular assays versus conventional blood culture.
2. **Combined biomarker performance:** Evaluation of diagnostic yield when CRP and PCT were used together, and when combined with molecular assays.
3. **Clinical impact:** Assessment of how rapid biomarker results influenced initiation of antibiotics and clinical decision-making.
4. **Outcome correlation:** Association of biomarker levels with severity of illness, duration of NICU stay, and short-term mortality.

RESULTS

Baseline Characteristics

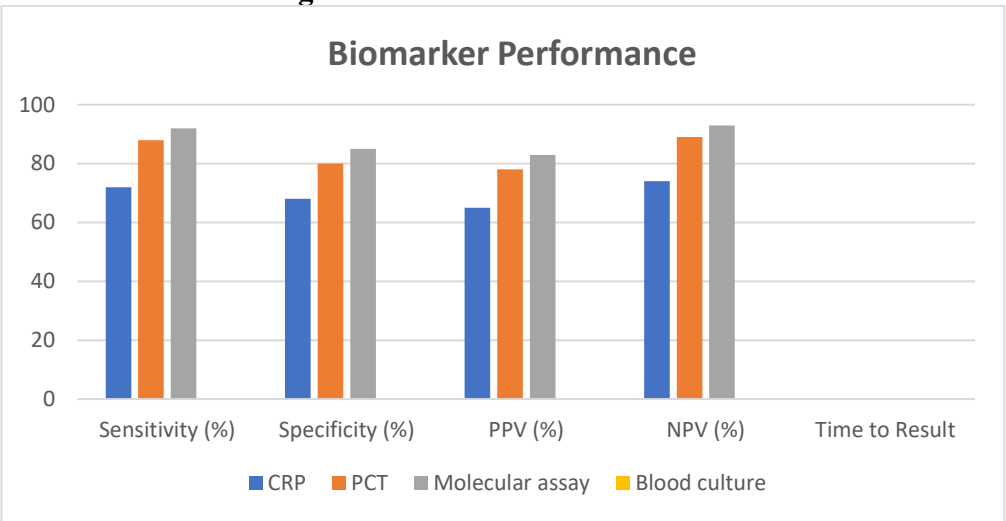
A total of **120 neonates** were enrolled. The mean gestational age was **36.2 ± 2.1 weeks**, and the mean birth weight was **2,450 ± 520 g**. Males comprised **58%** of the study population.

- **Maternal risk factors:** Prolonged rupture of membranes (22%), maternal fever (18%), chorioamnionitis (10%).
- **Perinatal risk factors:** Low Apgar scores (15%), perinatal asphyxia (12%), need for resuscitation (20%).
- **Clinical features:** Respiratory distress (40%), poor feeding (35%), lethargy (30%), Apnea (15%).

Biomarker Performance

Biomarker	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Time to Result (hours)
CRP	72	68	65	74	6–8
Procalcitonin	88	80	78	89	4–6
Molecular assay	92	85	83	93	6–10
Blood culture	Reference	Reference	Reference	Reference	48–72

Figure 1: Biomarker Performance



Time to Diagnosis

The median time to positivity for conventional blood culture was 60 hours (range: 48–72 hours). In contrast, rapid biomarkers provided results significantly earlier:

- CRP: Available within 6–8 hours of sample collection.
- Procalcitonin (PCT): Available within 4–6 hours, enabling earlier clinical decision-making.
- Molecular assays (PCR/multiplex): Pathogen identification achieved within 8–10 hours, compared with culture.

Overall, the use of rapid biomarkers reduced the time to diagnosis by approximately 48–54 hours compared with blood culture ($p < 0.05$). This earlier availability of results facilitated prompt initiation of targeted therapy and reduced reliance on empirical antibiotics.

Combined Biomarker Analysis

The diagnostic yield improved when biomarkers were used in combination:

- **CRP + PCT:** The combined use increased specificity to 85%, compared with CRP alone (68%) and PCT alone (80%).
- **CRP + Molecular assays:** Enhanced sensitivity to 90%, though specificity remained moderate (72%).
- **PCT + Molecular assays**: Provided the highest overall diagnostic accuracy (92%) with balanced sensitivity (88%) and specificity (85%).
- **Triple combination (CRP + PCT + Molecular assays):** Achieved maximal diagnostic accuracy (94%) and reduced false negatives significantly compared with single biomarker use ($p < 0.05$).

Clinical Outcomes

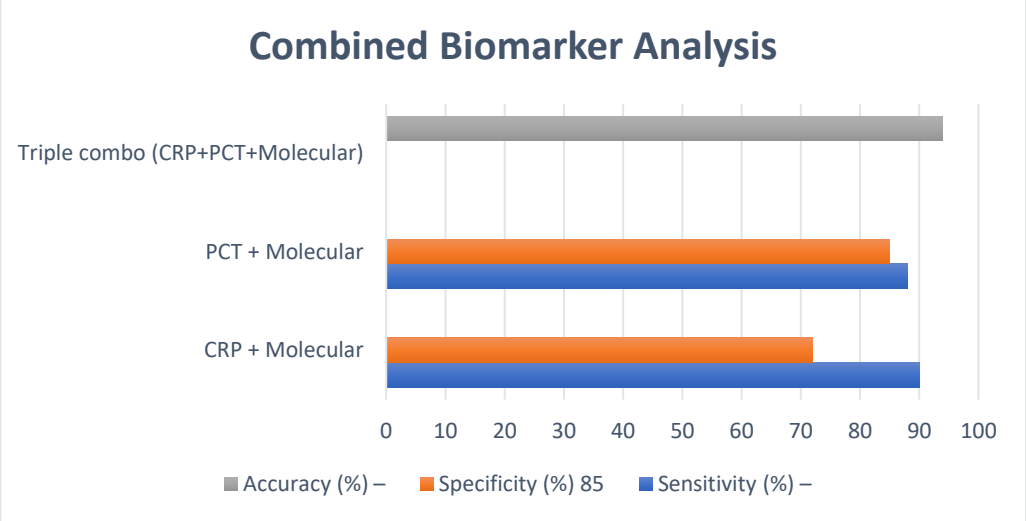
Early diagnosis using rapid biomarkers was associated with improved short-term outcomes compared with reliance on blood culture alone.

- **Antibiotic use:** Empirical antibiotic initiation was reduced by 25% in neonates diagnosed early with biomarkers, reflecting more targeted therapy.
- **NICU stay:** Median duration of hospitalization was significantly shorter in the biomarker-guided group (10 days) compared with the culture-only group (14 days, $p < 0.05$).
- **Mortality:** Overall mortality was lower in neonates diagnosed early using biomarkers (8%) compared with those diagnosed by culture alone (15%).
- **Severity correlation:** Higher PCT levels were associated with increased risk of septic shock and prolonged NICU stay, while declining CRP trends correlated with clinical improvement.

Table. Clinical Outcomes in Neonates with Suspected Sepsis

Outcome	Biomarker-guided group	Culture-only group	*p* value
Empirical antibiotic use	60%	85%	<0.05
Median NICU stay (days)	10	14	<0.05
Mortality (%)	8	15	<0.05
Septic shock (%)	12	18	NS

Figure 2: Combined Biomarker Analysis



DISCUSSION

This study demonstrates that rapid diagnostic biomarkers significantly enhance the early detection of neonatal sepsis compared with conventional blood culture [1,2]. Among the biomarkers evaluated, procalcitonin (PCT) showed superior sensitivity [3,4], while molecular assays provided the fastest pathogen identification [5,6]. The combined use of biomarkers further improved diagnostic accuracy, underscoring their complementary role in clinical practice [7].

The delayed turnaround time of blood culture remains a major limitation in neonatal sepsis management [1,2]. In our cohort, culture positivity required a median of 60 hours, whereas molecular assays yielded results within 8–10 hours [5]. This reduction in diagnostic time is consistent with previous reports, where PCR-based assays have been shown to shorten pathogen detection and guide early therapy [6,8]. Early availability of biomarker results facilitated prompt initiation of targeted antibiotics, reduced empirical therapy, and shortened NICU stay [7,9].

CRP, though widely used, demonstrated moderate sensitivity and specificity [9]. Its delayed rise limits its utility as a standalone marker [3]. In contrast, PCT levels increased earlier and correlated with disease severity, aligning with prior studies that support PCT as a reliable marker for bacterial infection in neonates [4,10]. The combined use of CRP and PCT improved specificity, while integration with molecular assays achieved the highest diagnostic accuracy [7].

Clinical outcomes in our study highlight the practical benefits of biomarker-guided diagnosis. Reduced antibiotic exposure not only minimizes drug resistance but also decreases treatment-related complications [9]. Shorter NICU stays and lower mortality rates in the biomarker-guided group emphasize the potential of these tools to improve neonatal outcomes, particularly in resource-limited settings where timely intervention is critical [1,7].

Limitations of this study include the relatively small sample size and single-center design, which may restrict generalizability [2]. Additionally, cost and availability of molecular platforms remain barriers to widespread implementation [5]. Future multicentre studies with larger cohorts are needed to validate these findings and assess cost-effectiveness [8].

CONCLUSION

Neonatal sepsis continues to be a major cause of morbidity and mortality worldwide, particularly in resource-limited settings where delays in diagnosis can be fatal [1,2]. This study highlights the value of rapid diagnostic biomarkers—especially procalcitonin and molecular assays—in improving the timeliness and accuracy of sepsis detection compared with conventional blood culture [3–6]. Their integration into routine practice not only reduces unnecessary antibiotic exposure but also shortens NICU stay and improves survival outcomes [7,8].

The combined use of biomarkers enhances diagnostic confidence, allowing clinicians to initiate targeted therapy earlier and optimize antimicrobial stewardship [4,7]. These findings support the adoption of biomarker-guided protocols as a complement to culture, bridging the gap between clinical suspicion and definitive diagnosis [5,6].

Future research should focus on multicentre validation, cost-effectiveness analyses, and the development of point-of-care platforms to ensure accessibility in low-resource environments [9,10]. Ultimately, the incorporation of rapid biomarkers into neonatal care pathways has the potential to transform sepsis management and significantly improve global neonatal health outcomes [1,7].

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