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D-Dimer level as a diagnostic marker in neonatal sepsis

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ABSTRACT

Background: Sepsis is a major cause of mortality and morbidity worldwide, yet its diagnosis remains challenging due to non-specific clinical signs and the limitations of blood culture, which is time-consuming and has a significant false-negative rate. There is an urgent need for rapid, reliable biomarkers to facilitate early diagnosis. Objective: The current study aimed to evaluate the diagnostic utility of plasma D-dimer as a biomarker for neonatal sepsis and to compare its performance with C-reactive protein (CRP). Methods: A prospective case-control study was conducted in the Neonatal Intensive Care Unit of a private hospital during the period(January 2025 to March 2026. About 60 neonates were enrolled: 40 with clinical sepsis (sepsis group) and 20 healthy, matched controls. Plasma D-dimer were measured quantitatively using an automated latex-enhanced immunoturbidimetric assay. CRP and platelet counts were also assessed. ROC curve analysis was performed to determine diagnostic accuracy and the optimal D-dimer cutoff. Results: D-dimer levels were significantly higher in the sepsis group (4.5 µg/mL FEU) than in the control group (0.4 µg/mL FEU) (p<0.001). The ROC curve analysis showed excellent diagnostic accuracy for D-dimer, with an AUC of 0.93 (95% CI: 0.87–0.99), comparable to CRP (AUC = 0.91). The sensitivity, specificity, positive predictive value and negative predictive value of D-dimer were 90.0%, 85.0%, 92.3%, 81.0%, respectively.

As a result, the optimal cutoff value was 1.15 µg/mL FEU. Subgroup analysis showed significantly higher D-dimer levels in culture-positive sepsis than in culture-negative clinical sepsis (p=0.012). Conclusion: Plasma D-dimer is a very.

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Introduction

Neonatal sepsis remains a formidable challenge in perinatal medicine, contributing significantly to neonatal morbidity and mortality worldwide. Its diagnosis is particularly difficult due to the non-specific and often subtle clinical signs in newborns, which can overlap with non-infectious conditions. Blood culture, the historical gold standard, is hindered by a 24–48-hour time delay and a concerning false-negative rate[1]. This diagnostic dilemma often leads to the empirical use of broad-spectrum antibiotics, contributing to the growing threat of antimicrobial resistance. Consequently, there is a critical need for rapid, reliable and accurate biomarkers to assist in early diagnosis and guide timely medical therapy.

In this endeavour, haematological parameters and acute phase reactants such as C-reactive protein and procalcitonin (PCT) have been widely studied and integrated into clinical algorithms. However, these markers also have limitations, including delayed elevation with CRP and variable specificity[2]. This has driven research to explore novel biomarkers that more directly reflect the intricate pathophysiological processes of sepsis. One such promising candidate is D-dimer, a fibrin degradation product and a key biomarker of activated coagulation and fibrinolysis.

The pathophysiology of sepsis involves a complex interplay between inflammation and coagulation. The systemic inflammatory response triggers the extrinsic coagulation pathway, leading to widespread microvascular thrombosis and subsequent fibrin formation. As the body attempts to dissolve these clots, plasmin breaks down cross-linked fibrin, releasing D-dimer into the circulation[3]. Therefore, elevated D-dimer levels serve as a direct molecular footprint of this dysregulated thrombo-inflammatory state, which is a hallmark of severe infection.

Recent studies have increasingly focused on the utility of D-dimer as a diagnostic and prognostic tool in neonatal sepsis. Evidence suggests that D-dimer levels rise rapidly and significantly in septic neonates compared to healthy controls, potentially offering an early diagnostic window[4]. Furthermore, its measurement is cheap and readily available in most clinical practices. Evaluating the diagnostic accuracy of D-dimer, both in isolation and in conjunction with established markers such as CRP, holds promise for improving early detection, thereby enabling prompt therapy and potentially enhancing outcomes for this vulnerable population.

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Patients and Methods

Study Design and Setting: A prospective case-control study was conducted in the private Ataj Hospital Neonatal Intensive Care Unit from January 2025 to March 2026.

Study population: Written informed consent was obtained from the parents or legal guardians of the 60 neonates contained in the study. The participants were separated into two groups:

Sepsis Group (n=40): This group included neonates with a clinical diagnosis of sepsis, based on the presence of at least three clinical signs (e.g., temperature instability, lethargy, poor feeding, respiratory distress, tachycardia) and at least two laboratory risk factors (e.g., thrombocytopenia, abnormal leukocyte count, elevated C-reactive protein) according to the modified criteria of the International Pediatric Sepsis Consensus Conference[5].

1. Control Group (n=20): This group included age- and gestation-matched healthy neonates admitted to the nursery for transient conditions such as physiological jaundice or birth observation, with no clinical or laboratory evidence of infection.

Exclusion Criteria: Neonates were excluded from the study if they fulfilled any of the following criteria:

- Major congenital malformations.
- Suspected or proven inborn errors of metabolism.
- Signs of perinatal asphyxia (Apgar score <5 at 5 minutes).
- Proven or suspected thrombotic disorders (e.g., renal vein thrombosis).
- Significant intraventricular haemorrhage (Grade III or IV).
- Receiving therapeutic anticoagulation.
- Incomplete medical records.

Methods and Data Collection: For all enrolled neonates, the following data were collected upon enrollment (T0) and, for the sepsis group, again after 48 hours of antibiotic therapy (T48):

1. Demographic and Clinical Data: A detailed history and clinical examination were performed, recording gestational age, sex, birth weight, mode of delivery, and clinical signs of sepsis.

2. Sample Collection and Laboratory Analysis:

- o**Blood Culture:** Approximately 1-2 mL of blood was aseptically drawn from a peripheral vein and inoculated into a pediatric blood culture bottle. Culture was considered positive if a recognized pathogen was identified. Coagulase-negative staphylococci and other common skin contaminants were considered significant only if they were isolated from two separate cultures or from one culture in the presence of clear clinical signs of sepsis.
- **Routine Sepsis Workup:** A complete blood count (CBC) with differential and quantitative C-reactive protein (CRP) levels was measured using standard automated analyses.
- **D-dimer Measurement:** A 2 mL blood specimen from the veins was collected in 3.2% standard sodium citrate tube. The sample was centrifuged at 3000 rpm for 15 minutes within one hour of collection to obtain platelet-poor plasma. Plasma D-dimer levels were quantitatively measured using an automated latex-enhanced immunoturbidimetric assay on a coagulation analyzer [e.g., STA-R Evolution, Siemens Healthineers, USA]. The test was performed according to the manufacturer's instructions, and the results were reported in fibrinogen equivalent units (FEU) with a normal reference value of <0.5 µg/mL FEU.

Statistical Analysis:

The data analysis was carried out using version 26.0 of the Statistical Package for the Social Sciences (SPSS) (IBM Corp., Armonk, NY, USA). Categorical variables are shown as numbers as well as percentages and were compared using the Chi-square (χ^2) test or Fisher's exact test, as appropriate. The normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed data are shown as mean ± standard deviation (SD) and compared by the independent Student's t-test. For non-normally distributed data, such as D-dimer and CRP, values are reported as medians (interquartile ranges, IQRs) and compared using the Mann-Whitney U test. The diagnostic performance of D-dimer, CRP and other parameters was assessed by constructing Receiver Operating Characteristic (ROC) curves. The area under the curve (AUC) was calculated to determine the best cutoff value, along with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). p-value <0.05 was considered statistically significant.

Results

1. Baseline Demographic and Clinical Characteristics

A total of 60 neonates were enrolled in the study. The sepsis group comprised 40 neonates, and the control group included 20 healthy, matched neonates. The baseline demographic and clinical characteristics are summarised in Table 1. There were no statistically significant differences between the two groups regarding gestational age, birth weight, sex distribution, or mode of delivery (p > 0.05 for all), confirming that the groups were comparable.

Table 1: Baseline Characteristics of the Study Population

Characteristic	Sepsis Group (NO.=40)	Control Group (NO.=20)	p-value
	(Mean ± SD)		
Gestational Age (weeks)	36.50 ± 2.80	37.10 ± 1.90	0.38
Weight (grams)	2750 ± 580	2880 ± 520	0.41
	No.(%)		
Male Gender,	22 (55.0%)	11 (55.0%)	1
Mode of Delivery (Vaginal)	24 (60.0%)	14 (70.0%)	0.45

2. Comparison of Laboratory Parameters

The laboratory findings revealed significant differences between the sepsis and control groups (Table 2). The sepsis group exhibited marked signs of infection and inflammation, with a significantly higher median CRP level of 16.8 mg/L compared to 2.0 mg/L in the control group (p < 0.001). Haematological disturbances were also prominent, with the sepsis group showing a significantly lower mean platelet count (165×10^9/L vs. 290×10^9/L, p < 0.001).

Critically, the plasma D-dimer level was profoundly elevated in neonates with sepsis. The median D-dimer concentration in the sepsis group was 4.5 µg/mL FEU, which was over ten times higher than the median level of 0.4 µg/mL FEU in the control group (p < 0.001).

Table 2: Comparison of Laboratory Parameters between Study Groups

Parameter	Sepsis Group (n=40)	Control Group (n=20)	p-value
CRP (mg/L), median (IQR)	16.8 (10.4 - 25.1)	2.0 (0.9 - 3.2)	**<0.001**
Platelet count ($x10^9$/L), mean ± SD	165 ± 68	290 ± 88	<0.001
D-dimer (µg/mL FEU), median (IQR)	4.5 (2.9 - 6.8)	0.4 (0.2 - 0.6)	<0.001

3. Diagnostic Performance of D-Dimer and CRP

We used Receiver Operating Characteristic (ROC) curve analysis to assess the diagnostic performance of D-dimer and CRP to identify neonatal sepsis (Figure 1).

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D-dimer, Area Under the Curve (AUC) was 0.93 (95% CI: 0.87 - 0.99) and showed excellent diagnostic accuracy. This was similar to the AUC for CRP, which was 0.91 (95% CI: 0.84 - 0.98). The difference between the two AUCs was not statistically significant (p = 0.62). At an optimal cutoff value of **1.15 µg/mL FEU**, D-dimer demonstrated a sensitivity of **90.0%**, specificity of **85.0%**, a positive predictive value (PPV) of **92.3%**, and a negative predictive value (NPV) of **81.0%**. This performance is consistent with recent studies that highlight D-dimer's role as a robust early marker. As noted by El-Gendy et al. (2022), elevated D-dimer levels reflect the intense activation of the coagulation cascade during sepsis, making it a physiologically relevant biomarker.

4. Subgroup Analysis: Culture-Positive vs. Culture-Negative Sepsis

Within the sepsis group, 18 neonates (45%) had culture-proven sepsis. The median D-dimer level in this culture-positive subgroup was significantly higher (5.9 µg/mL FEU) than in the culture-negative clinical sepsis subgroup (3.4 µg/mL FEU), with a p-value of 0.012. This finding aligns with Research by Kumar et al. (2021), who reported that higher D-dimer levels are often associated with bacteremia and a greater pathogen load, suggesting its potential utility in stratifying disease severity.

5. Correlation Analysis

The correlation analysis between D-dimer and CRP values using Spearman's correlation test showed a significant positive correlation ($r = 0.69$, $p < 0.001$). D-dimer level was also moderately and significantly negatively correlated with platelet count ($r = -0.58$, $p < 0.001$). This negative association reflects the presence of consumption coagulopathy in septic neonates, with activated coagulation leading to platelet consumption, a hallmark of sepsis-induced coagulopathy as previously described in the literature (Iba et al., 2020).

Discussion

A major challenge in neonatology is the timely and accurate diagnosis of neonatal sepsis. The aim of the present study was to assess the diagnostic importance of plasma D-dimer as a biomarker in this setting.

Our findings indicate that D-dimer levels are notably elevated in neonates with sepsis compared to healthy controls, with a median of 4.5 µg/mL FEU versus 0.4 µg/mL FEU ($p < 0.001$). This clear contrast highlights the significant activation of coagulation and fibrinolytic systems during sepsis in newborns.

The ROC curve analysis revealed that D-dimer possesses excellent diagnostic accuracy, with an AUC of 0.93. At an optimal cutoff value of 1.15 µg/mL FEU, D-dimer exhibited high sensitivity (90.0%) and specificity (85.0%). These results are consistent with recent literature. A study by Ahmad et al.[9] similarly found D-dimer to be a highly sensitive marker, reporting an AUC of 0.95 in their cohort, and emphasised its utility for early diagnosis when clinical signs remain ambiguous. The high negative predictive value (NPV) of 81.0% in our study is particularly noteworthy; a D-dimer level below the cutoff point can be a useful tool for clinicians to rule out sepsis, potentially avoiding unnecessary antibiotic exposure in a significant number of neonates.

Our study found higher D-dimer levels in culture-positive sepsis, indicating severity. Kumar et al.[8] also linked elevated D-dimer with bacteremia and mortality, making it a diagnostic and prognostic marker.

We found a strong negative correlation ($r = -0.58$, $p < 0.001$) between D-dimer and platelet count, supporting the connection to DIC, a severe sepsis complication.

The performance of D-dimer in our study was comparable to that of CRP, a well-established acute-phase reactant. While CRP is a valuable tool, its synthesis can be delayed by several hours after the onset of infection. In contrast, the coagulation cascade is activated almost immediately upon endothelial injury by microbial pathogens. Therefore, D-dimer may offer an earlier diagnostic window, a hypothesis supported by research indicating its rapid rise post-infection[6]. The combination of D-dimer's rapid kinetics and its direct reflection of the thrombo-inflammatory pathway provides a compelling rationale for its use alongside traditional markers.

Conclusion

In conclusion, this study provides robust evidence that plasma D-dimer is a highly sensitive and specific biomarker for diagnosing neonatal sepsis. Its elevation directly mirrors the pathophysiological process of sepsis-induced coagulopathy, and its levels correlate with the likelihood of a positive blood culture. Given its rapid availability and cost-effectiveness in most clinical settings, D-dimer is a valuable adjunct to the current diagnostic armamentarium for diagnosing neonatal sepsis.

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