Original Article

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Accuracy of C-reactive protein (CRP) and hematological indices as a screening tool in neonatal bacterial sepsis

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ABSTRACT

Background: Early recognition of neonatal sepsis is challenging due to its subtle and nonspecific symptoms. Failure to recognize or delays in diagnosis can result in significant mortality and morbidity. Laboratory sepsis markers complement clinical signs and risk factors in diagnosing sepsis. The current approach for early recognition of sepsis combines clinical presentation, biomarkers, and blood culture. **Aims**: This study aims to assess the effectiveness of C-reactive protein and basic hematological indices, such as neutropenia, leukopenia, and thrombocytopenia, in diagnosing sepsis, measuring the sensitivity of each test, and evaluating the outcomes of the studied sample. **Methods**: This study consisted of 90 patients with clinical suspicion of sepsis who were admitted to the neonatal care unit at Central Child Teaching Hospital in Baghdad. Patients were classified according to the age at which symptoms began into early onset and late onset sepsis. All patients underwent blood culture and sensitivity testing, complete blood count, and serial C-reactive protein measurements. **Results**: late onset sepsis was more common than early onset sepsis, and males outnumbered females. The sensitivity of C-reactive protein was 84%, with a specificity of 13%. The positive predictive value (PPV) and negative predictive value (NPV) were 21% and 75%, respectively. Total leukocyte count (TLC) demonstrated a sensitivity of 42%, specificity of 77%, PPV of 33%, and NPV of 83%. Absolute neutrophil count (ANC) showed a sensitivity of 5%, specificity of 97%, PPV of 33%, and NPV of 79%. Thrombocytopenia exhibited a sensitivity of 32%, specificity of 85%, PPV of 35%, and NPV of 82%. **Conclusion**: C-reactive protein had the highest sensitivity, while ANC had the highest specificity. Complete blood count showed little correlation with sepsis, and thrombocytopenia was a late finding associated with increased mortality. All tests utilizing the hematological profile can be employed using hematological profile can be used on primary health center level, with results obtainable within hours.

Keywords: C-reactive protein, neonatal sepsis, blood culture, hematological parameters

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INTRODUCTION

Neonatal sepsis is a systemic inflammatory response syndrome (SIRS) secondary to infection and is a leading cause of morbidity and mortality among newborns worldwide. It is estimated that nearly 430,000 neonatal deaths occurred in 2013 due to neonatal sepsis.[1,2] The incidence of sepsis is approximately 1:1,500 in full-term infants and 1:250 in preterm infants.[3] Neonatal infections in the first few weeks of life are classified into early-onset (EOS), occurring within the first six days of life and acquired during the antepartum or intrapartum period from the maternal genital tract, and late-onset sepsis (LOS), occurring after seven days of life and caused by postnatal acquisition (nosocomial or community sources).[4,5]

Although blood culture is the gold standard for diagnosing sepsis, various serum biomarkers have been investigated for their ability to identify infants with serious bacterial infections.[2,6] The White Blood Cells (WBC) and absolute neutrophil count (ANC) are most predictive of infection when these values are low. The immature/total neutrophil count (I/T) ratio is most informative if measured four hours after birth.[7] Thrombocytopenia is observed in systemic bacterial or viral infections.[6]

Inflammatory biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) have been studied for their utility in determining the risk of sepsis, both as single screening values and as serial assessments.[8] Any elevation of CRP indicates endogenous synthesis, as it passes the placenta in exceedingly low quantities.[9]

We aim to evaluate the effectiveness of laboratory markers and complete blood count (CBC) as screening tools for diagnosing neonatal sepsis and assessing the sensitivity of each test, whether single or combined, and their outcomes.

PATIENTS AND METHODS

This prospective, single-center study was conducted over six months, from June 1 to November 30, 2023, in the neonatal care unit of Central Child Teaching Hospital in Baghdad, Iraq. After obtaining informed consent from parents, neonates with a gestational age of 28 weeks or more and a birth weight of > 750 grams, with or without maternal risk factors, exhibiting any of the following features, were selected for evaluation:

Respiratory symptoms: tachypnea, apnea, dyspnea, grunting, and cyanoses. Cardiovascular: bradycardia, tachycardia, and cold clammy skin. General: fever and poor feeding. Neurologic: lethargy, poor reflexes, decreased activity, seizures, bulging fontanel, and irritability. Gastrointestinal: feeding intolerance, jaundice, abdominal distention, and vomiting. Genitourinary: decreased urine output and poor urine stream.

Neonates with congenital anomalies, metabolic disorders, maternal diabetes or hypertension, hemolytic jaundice, respiratory distress syndrome, meconium-stained amniotic fluid, and those who underwent surgery or received antibiotics before culture were excluded from the study. Initially, 93 patients met the inclusion and exclusion criteria; after evaluation, three patients were found to have illnesses other than sepsis (hypothyroidism, hypoglycemia) and were excluded, leaving 90 patients. A standardized questionnaire was used to a standardized questionnaire, full maternal history was taken including perinatal risk factors, maternal diseases, or antibiotic prophylactic before delivery, demographical data including gestational (term vs. preterm) and postnatal age, gender, mode of delivery (vaginal vs. cesarean), and weight (normal vs. low birth weight). A complete history was recorded, and each neonate was examined and classified according to the age at which presumed signs and symptoms began into early and late-onset sepsis. Blood samples were sent for blood culture and sensitivity, CRP, and CBC. BHI broth was used as culture media. Two CRP values were measured: one on admission and the second within 24 to 48 hours after admission. CRP levels > 6 mg/dl were considered positive according to the laboratory kit reference. Total Leukocytes Count (TLC), platelet count, and ANC were calculated for all patients. Thrombocytopenia was defined as a platelet count < 150,000/µl, leukopenia as WBC count < 5000/µl, and Leukocytosis as TLC > 30000/ul.[10,11] ANC was calculated as follows: ANC = WBC x neutrophil percentage.

Neutropenia was defined as less than 2,000/µl in the first 24 hours of life and less than 1,000/µl after 48 hours of life.[12] All hematological investigations were carried out by the hospital laboratory simultaneously with the CRP test. All neonates received antibiotics after the septic screen. This study was approved by Mustansiriyah University's local ethics committee (IRB 5 on May 2023).

Statistical Analysis

Data were first input into an Excel file and then analyzed using a statistical package for social sciences (SPSS) version 24. Discrete variables were presented as numbers with their percentages. The chi-square test for independence was used to test the significance of

associations between discrete variables. The Epicalc program was used to estimate the performance of screening tests (sensitivity, specificity, accuracy, as well as predictive values). The level of significance was set at a P value of ≤ 0.05.

RESULTS

A total of 90 neonates suspected of having sepsis were included in this study (Fig. 1). This study found no significant association between sex, age of onset, or gestational age with blood culture results (P > 0.05) (Table 1)

Table 2 show the distribution of blood culture according to weight and mode of delivery.

Out of 19 positive culture cases, eight (42.1%) had abnormal TLC; five had TLC > 20,000 with sensitivity, specificity, and accuracy of 21%, 85%, and 72%, respectively, and three had TLC < 5,000 with SS, SP, ACC 16%, 93%, and 77% respectively. Out of 71 negative culture cases, 16 (22.5%) had abnormal TLC; 11 of them had TLC > 21,000, and five had TLC < 5,000. Out of 19 positive cultures, only one (5.3%) had abnormal ANC, six (31.6%) had abnormal platelet counts, and 16 (84.2%) had positive CRP on admission day. Out of 71 negative culture cases, two (2.8%) had abnormal ANC and 11 (15.5%) had abnormal platelet counts, while 62 (87.3%) had positive CRP on admission. All 19 positive cultures had positive CRP 2 measured two days after admission and out of 71 negative culture cases, 68 (95.8%) had positive CRP 2 measured two days after admission (Table 3).

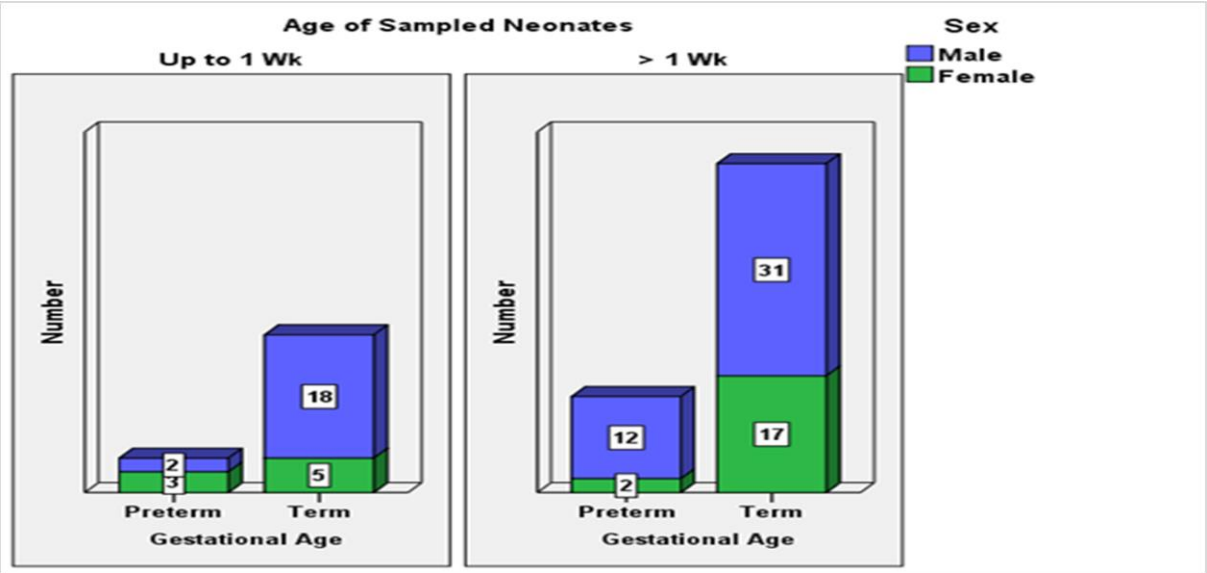

Figure 1: Distribution of sampled neonates according to age of onset, gestational age, and sex.

Table 1: Characteristics of sampled patients.

	Total	Blood culture				P value
Variables	N = 90	Positive		Negative		
Sex						0.866
Male	63	13	20.6%	50	79.4%	
Female	27	6	22.2%	21	77.8%	
Age of onset						0.104
Up to 1 week	28	3	10.7%	25	89.3%	
More than 1 week	62	16	25.8%	46	74.2%	
Gestational age						0.059
Preterm	19	7	36.8%	12	63.2%	
Term	71	12	16.9%	59	83.1%	
Total	**90**	**19**	**21.1%**	**n=71**	**78.9%**	

Table 2: Distribution of blood culture according to weight and mode of delivery.

	Total	Blood culture			
Variables	N = 90	Positive		Negative	
Weight					
Normal	74	12	16.22%	62	83.78%
Low	16	5	31.25%	11	68.75%
Mode of Delivery					
Vaginal delivery	23	8	34.78%	15	65.22%
Cesarean section	67	11	16.42%	56	83.58%

Table 3: Distribution of gestational age and gender according to age of onset.

Age of onset	Gestational age	Gender
Up to 1 week: (n = 3)	Term: (n = 2)	Male: 1
		Female: 1
	Preterm: (n = 1)	Male: 1
		Female: 0
More than 1 week: (n = 16)	Term: (n = 10)	Male: 7
		Female: 3
	Preterm: (n = 6)	Male: 4
		Female: 2

Table 4: Summary performance of proposed screening tests for neonatal sepsis.

		Screening Performance			
Proposed screening test	SN	SP	ACC	PPV	NPV
A - Positive CRP 1	0.84	0.13	0.28	0.21	0.75
B - Abnormal Platelet Count	0.32	0.85	0.73	0.35	0.82
C - Abnormal TLC	0.42	0.77	0.70	0.33	0.83
D - Abnormal ANC	0.05	0.97	0.78	0.33	0.79
E - Positive if positive for A & B	0.32	0.85	0.73	0.53	0.82
F - Positive if positive for A & C	0.42	0.77	0.70	0.33	0.83
G - Positive if positive for A, B & C	0.26	0.93	0.79	0.50	0.82
H - CRP 2	1.00	0.04	0.24	0.22	1.00

SN: sensitivity, SP: specificity, ACC: accuracy, PPV: positive predictive value, NPV: negative predictive value, CRP: C-reactive protein, TLC: total leukocyte count, ANC: absolute neutrophil count, CRP 2: C-reactive protein test after two days of admission.

DISCUSSION

Diagnosing neonatal sepsis remains challenging due to various factors, including nonspecific symptoms and the absence of specific markers for diagnosis. The objective of this study was to establish screening tests that assist in the time management of neonatal sepsis and prevent complications, considering their simplicity, rapid availability of results, and cost-effectiveness. The hematological response to infection includes changes in total WBC, total neutrophil count, and platelet numbers. The CBC with various neutrophil parameters (ANC) and CRP are the most frequently used. Sepsis was confirmed in 21% of patients (19 cases) based on positive blood cultures. Many national and international studies have reported a sepsis rate of 20–30%. Godbole et al.[13] reported a culture-positive sepsis rate of 25%, while Makadia et al.[14] reported a culture positivity rate of 50.5%. This variation may result from differences in the criteria of the studied group, sample size, or technical limitations in obtaining blood cultures.

Sepsis was reported to be more common in males, with 63.5% of confirmed sepsis cases and 31.5% were found in females. This finding is consistent with that observed by Adane et al.,[15] who reported that 63.6% of culture-positive cases were found in males and 36.4% were found in females. This may be because factors regulating gamma-globulin synthesis are located on the X chromosome, and males have only one X chromosome.[16] TLC sensitivity was 42%, and specificity was 77%. Bharathi et al.[17] found a sensitivity of 21.43% and specificity of 78.79%, while Khanum et al.[18] found a sensitivity of 71% and specificity of 66%. The PPV and NPV of TLC were 33% and 83%, respectively. Bharathi et al.[17] reported a PPV and NPV of 22.22% and 78.5% respectively, while Buch et al. (16) found a PPV of 62% and NPV of 52%.

This study observed ANC sensitivity to be 5%, with a specificity of 97%, a PPV of 33%, and an NPV of 87%. Ahmed I et al.[19] also found an ANC sensitivity of 16%; in contrast, other studies showed different results. Joshi et al.[20] reported an ANC sensitivity of 41.2%, specificity of 59%, PPV of 17.1%, and NPV of 83.1%. Thrombocytopenia was infrequently associated with sepsis. The present study found a sensitivity of 32% and specificity of 85%, with a PPV of 35% and NPV of 82%. This is comparable to results observed by Sarma MR et al.,[21] who reported a specificity of 80%, PPV of 54%, and NPV of 83.3%. Joshi et al.[20] found a sensitivity of 29.4%. Regarding CRP, sensitivity was 84%, comparable to results observed by Chaudhari S et al.[22] at 84.21% and Kuar S et al.[23] at 87.5%. Specificity was 13%, similar to results observed by Chaudhari S et al.,[22] who reported a specificity of 4.16%, and Kuar S et al.,[23] who observed a specificity of 43%, while Bunduki GK et al.[24] observed a specificity of 82.4%. The PPV was 21%, and the NPV was 75%; Soltani B et al.[25] reported an NPV of 90%. This discrepancy in observed results may be attributed to different methods of CRP estimation, differences in criteria for positivity (cut-off values), or variations in the number and timing of sample collection.

Regarding combined test results, the sensitivity of tests decreased while specificity increased. CRP was positive in 78 out of 90 cases; it became positive in 87 out of 90 patients 48 to 72 hours after admission. This means that a single CRP test does not exclude sepsis, which is similar to the suggestion by Gerland et al.[26]

CONCLUSIONS

CRP appears to be a good screening tool that complements clinical decision-making and has practical advantages over other tests, as it is not affected by prior antimicrobial therapy. The combination of the triplet (CRP, thrombocytopenia, and low ANC) was found to be the most accurate. Negative results of CRP after two days of admission were solid and excluded sepsis in 100% of cases in this study, as any sepsis marker (TLC, ANC, and platelet count) alone was neither helpful for confirming sepsis nor beneficial for excluding it. Platelets poorly correlate with sepsis but have prognostic value. Thrombocytopenia is more sensitive than blood culture in predicting mortality.

Recommendations

1. CRP titer is recommended to monitor response to treatment; accuracy dramatically improves with serial determinations.
2. To maximize the diagnostic yield of blood cultures, multiple sets of cultures consisting of aerobic and anaerobic vials, along with increasing the sample

size, if possible, can enhance the probability of discovering a pathogenic organism.

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