Original Article

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Significance of platelet parameters in the diagnosis of neonatal sepsis

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ABSTRACT

Background: The gold standard test for diagnosing neonatal sepsis is blood culture; however, no single laboratory test achieves 100% sensitivity and specificity. The diagnosis of sepsis cannot be made with a single test or any specific combination of testing methods. Therefore, it is essential to identify diagnostic indicators that are both practical and affordable for every healthcare facility while also possessing adequate sensitivity and specificity. **Aim**: This study aims to evaluate the role of platelet indices in diagnosing neonatal sepsis. **Methods**: A prospective, case-control study was conducted over 12 months at Al-Kadhymiah Pediatric Hospital in Baghdad. The study involved comparing 82 neonates with sepsis to 82 healthy controls. Basic investigations were performed before commencing antibiotic treatment and compared between both groups. **Results**: The only factor that differed significantly between the two groups was the type of pregnancy, where 18.29% of neonates with sepsis were from multiple pregnancies compared to only 7.32% of normal neonates. Total platelet count was significantly lower ($p = 0.021$), while mean platelet volume and platelet distribution width (PDW) were considerably higher in the case group than in the control group ($p < 0.001$). Blood culture was positive in 45 neonates (54.88%), with *Staphylococcus aureus* being the most commonly isolated bacteria. **Conclusion**: Neonates with sepsis exhibit significantly lower platelet counts and higher levels of mean platelet volume and PDW. Platelet parameters are easily obtained from complete blood counts and could serve as valuable adjuvant indices for diagnosing neonatal sepsis.

Keywords: neonates, sepsis, platelet parameters.

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INTRODUCTION

Neonatal sepsis is a clinical condition that manifests within the first 28 days of life as infection-related signs and symptoms, with or without concomitant bacteremia.[1] It is a significant cause of morbidity and mortality, accounting for 25% of neonatal deaths.[1,2] Although no single laboratory test has 100% sensitivity and specificity, blood culture is the gold standard for diagnosis. However, this test has a low positivity rate, is somewhat expensive, and takes approximately 2–8 days to yield results.[3] The diagnosis of sepsis cannot be made with a single test or any particular combination of testing methods. Therefore, it is necessary to identify diagnostic

indicators that are both practical and affordable for every healthcare facility while also possessing adequate sensitivity and specificity.[4]

Total leukocyte count, absolute neutrophil count (ANC), C-reactive protein (CRP), erythrocyte sedimentation rate, and procalcitonin are components of a septic screen that should be performed on all newborns suspected of having sepsis. The latter three vary in terms of sensitivity, specificity, positive predictive value, and negative predictive value in various studies.[1,5,6]

Mean platelet volume (MPV) refers to the average size of platelets in blood, typically ranging from 8.5 fL to 12.5 fL. It is a coulter-generated parameter that is generally available with complete blood counts (CBCs).[7] MPV has a direct correlation with the rate of platelet production in the bone marrow and an inverse relationship with the level of platelet maturation.[8] Due to platelet breakdown, platelet synthesis increases with the onset of septicemia, resulting in younger and larger platelets being secreted into peripheral circulation. However, bone marrow is subsequently suppressed, leading to thrombocytopenia.[9] Platelet distribution width (PDW; normal range 10%–17%) refers to the variation in platelet size in peripheral circulation, which is increased in sepsis due to destructive thrombocytopenia and platelet activation. Another significant parameter is the ratio of MPV to platelet count (PLT), which is elevated during platelet activation with a typical value of up to 7.2%.[4] Therefore, evaluating platelet parameters is essential to determine their potential as early and sensitive markers of neonatal sepsis.[10] This study aims to evaluate the role of platelet indices in diagnosing neonatal sepsis.

MATERIALS AND METHODS

A prospective, case-control study was conducted at Al-Kadhimiya Pediatric Hospital in Baghdad, Iraq, from July 1, 2023 to June 30, 2024. The study involved comparing 82 randomly selected neonates diagnosed with sepsis to 82 age- and gender-matched healthy newborns examined in outpatient clinics for routine health visits.

All cases with congenital anomalies, dysmorphic features, chromosomal abnormalities, hypoxic-ischemic encephalopathy, congenital heart diseases, respiratory distress syndrome, a history of maternal diabetes during pregnancy, prior antibiotic treatment, and previous surgery were excluded.

Detailed neonatal information was collected according to a standardized questionnaire, which included age at admission, sex, gestational age (term vs. preterm), mode of delivery (vaginal vs. cesarean section), type of pregnancy (single or multiple), and birth weight. Birth weight ≥ 2,500 grams was regarded as normal, while low birth weight was defined as less than 2,500 grams. Basic investigations were performed before commencing antibiotic treatment, including CBC with differential white blood cell counts (WBC), CRP, and blood culture. Platelet parameters, including PLT, MPV, and PDW, were documented from CBC. The MPV/PLT ratio was calculated by dividing MPV by PLT. All neonates in the control group had negative CRP levels and negative blood cultures.

The Pediatric Committee of the European Medicines Agency (EMA) proposed the sepsis criteria in 2010 to standardize the definition of neonatal sepsis (Table 1). The current study considered these criteria when diagnosing neonatal sepsis. Clinical sepsis is defined as positivity in two or more clinical categories plus two or more laboratory categories.[11] Patients with blood culture positivity were considered to have proven sepsis.

Ethical Consideration

This study was approved by Mustansiriyah University's local ethics committee (IRB 2 in April 2023).

Statistical Analysis

All statistical analyses were performed using version 26.0 of Statistical Package for the Social Sciences software (SPSS). The Student's t-test was used for analyzing continuous data presented as mean and standard deviation. A Chi-square test was used to assess categorical variables, presented as numbers and percentages. The predictive value of platelet indices in sepsis prediction was evaluated using the receiver operating characteristic (ROC) curve. A statistically significant difference was defined as a p-value of less than 0.05.

Table 1: EMA sepsis scoring system.

Clinical signs	Laboratory signs
Body temperature: Higher than 38.5°C OR lower than 36°C AND/OR temperature instability Cardiovascular manifestations: • Bradycardia OR Tachycardia AND/OR Unstable rhythm • Decreased urinary output (< 1 mL/kg/hour) • Low blood pressure • Mottling of skin • Impaired peripheral perfusion Skin and subcutaneous manifestations: • Petechial rash • Sclerema Respiratory instability: Apnea OR Tachypnea OR Increased oxygen demand OR Increased need for ventilation support Gastrointestinal: Nutritional intolerance OR Inadequate feeding OR Abdominal distention Non-specific: Irritability OR Lethargy OR Hypotonia	WBC count: < 4000 x109 cells/L OR > 20000 x109 cells/L Immature to total neutrophil ratio (I/T) ≥ 0.2 Platelet count < 100000 x109 cells/L CRP more than 15mg/L OR Procalcitonin ≥ 21 ng/ml. Glucose intolerance confirmed at least 2 times Hyperglycemia (blood glucose > 180 mg/dL or 10 mMol/L) OR Hypoglycemia (glycaemia < 45 mg/dL or 2.5 mMol/L) Metabolic acidosis: Base deficit > 10 mEq/L OR Serum lactate > 2 mMol/L

RESULTS

Association of Demographic Characteristics with Sepsis

The only factor that differed significantly between the two groups was the type of pregnancy, where 18.29% of neonates with sepsis were from multiple pregnancies compared to only 7.32% of normal neonates. Other factors were comparable between the two groups with no significant differences. (Table 2)

Association of Leukocyte and PLT Indices with Sepsis

All included indices significantly differed between neonates with and without sepsis. Except lymphocyte percentage, all leukocyte indices were higher in patients than in controls with significant differences. The mean PLT count in neonates with sepsis was 278.86 ± 122.92 × 10^9/L, which was lower than that of healthy neonates (329.15 ± 153.57 × 10^9/L), with a significant difference. In contrast, neonates with sepsis displayed higher MPV, PDW, and MPV/PLT ratios (11.12 ± 1.84 fL, 13.17 ± 2.39%, and 4.73 ± 2.06, respectively) than those without sepsis (9.79 ± 0.72 fL, 11.67 ± 1.88%, and 3.64 ± 1.74, respectively), with highly significant differences. (Table 3)

Predictive Value of PLT Indices

The predictive value of platelet indices in sepsis prediction was evaluated using the ROC curve. For MPV, the area under the curve (AUC) was 0.755, 95%, Confidence Interval (CI) = 0.682–0.828, $p < 0.001$. The sensitivity and specificity of the test at MPV = 9.95 fL were 78% and 60%, respectively. For PDW, the AUC was 0.686, 95% CI = 0.606–0.768, $p < 0.001$. The sensitivity and specificity of the test at PDW = 11.65% were 70% and 59%, respectively. (Fig. 1)

For the MPV/PLT ratio, the AUC was 0.671, 95% CI = 0.589–0.753, $p < 0.001$. The sensitivity and specificity of the test at MPV/PLT ratio = 3.95 were 63% and 65%, respectively.

For PLT, the AUC was 0.601, 95% CI = 0.514–0.688, p = 0.025. The sensitivity and specificity of the test at PLT = 264 × 109/L were 63% and 53%, respectively. (Fig. 2)

Blood Culture and Bacterial Species

Out of 82 neonates with sepsis, 45 (54.88%) tested positive for blood culture. Staphylococcus aureus was the most commonly isolated bacteria, accounting for 15.85% of the patients, followed by Klebsiella spp. (12.19%), Acinetobacter spp. (10.98%), and Streptococcus viridans (9.76%). Other bacteria, including Listeria monocytogenes, Enterococcus, E. coli, and Burkholderia cepacia, collectively accounted for 6.1% of the patients

Table 2: Association of demographic characteristics with sepsis.

Variables	Cases (n = 82)	Controls (n = 82)	p-value
Age, days			
Mean ± SD	10.42 ± 6.36	8.63 ± 4.61	0.271
Range	1.0–28	1.0–25	
Gender			
Male	50 (60.98%)	49 (59.76%)	0.873
Female	32 (39.02%)	33 (40.24%)	
Birth weight			
Normal	56 (68.29%)	60 (73.17%)	0.558
Low	26 (31.71%)	22 (26.83%)	
Gestational age			
Term	65 (79.27%)	71 (86.59%)	0.213
Preterm	17 (20.73%)	11 (13.41%)	
Mode of delivery	40 (48.78%)	51 (62.2%)	0.084
Vaginal	42 (51.22%)	31 (37.8%)	
Cesarean section			
Type of pregnancy	67 (81.71%)	76 (92.68%)	0.035
Single	15 (18.29%)	6 (7.32%)	
Multiple			

Table 3: Association of leukocyte and PLT indices with sepsis.

Indices	Patients (n = 82)	Controls (n = 82)	p-value
Leukocyte × 10^9/L			
Mean ± SD	17.42 ± 7.19	11.35 ± 3.45	0.0001
Range	5.50–23.10	5–23.10	
Neutrophil, %			
Mean ± SD	49.78 ± 19.90	43.12 ± 14.84	0.016
Range	15.50–86.60	16.90–82	
Lymphocyte, %			
Mean ± SD	37.88 ± 19.22	43.59 ± 14.45	0.033
Range	8.90–76.60	13.30–76.60	
N/L ratio			
Mean ± SD	2.09 ± 18.87	1.24 ± 0.94	0.0004
Range	0.23 - 9.73	0.25–6.17	
ANC × 10^9/L			
Mean ± SD	9.08 ± 6.19	5.01 ± 2.69	0.0002
Range	1.50–40.20	1.10–14.97	
ALC × 10^9/L			
Mean ± SD	6.15 ± 3.29	4.81 ± 1.79	0.001
Range	1.07–19.88	1.14–9.88	
PLT × 10^9/L			
Mean ± SD	278.86 ± 122.92	329.15 ± 153.57	0.021
Range	101–598	103–882	
MPV, fL			
Mean ± SD	11.12 ± 1.84	9.79 ± 0.72	0.0001
Range	9.0–17.0	8.10–12.2	
PDW, %			
Mean ± SD	13.17 ± 2.39	11.67 ± 1.88	0.0003
Range	9.3–20.0	9.10–19.80	
MPV/PLT ratio			
Mean ± SD	4.73 ± 2.06	3.64 ± 1.74	0.0001
Range	1.74–11.0	1.07–9.61	

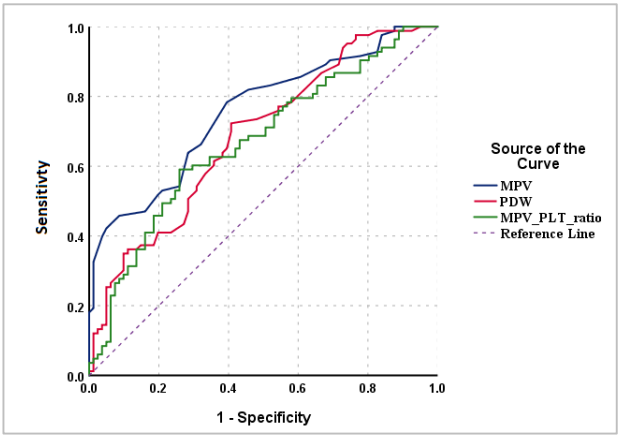

Figure 1: ROC curve for MPV, PDW, and MPV/PLT ratio in predicting neonatal sepsis.

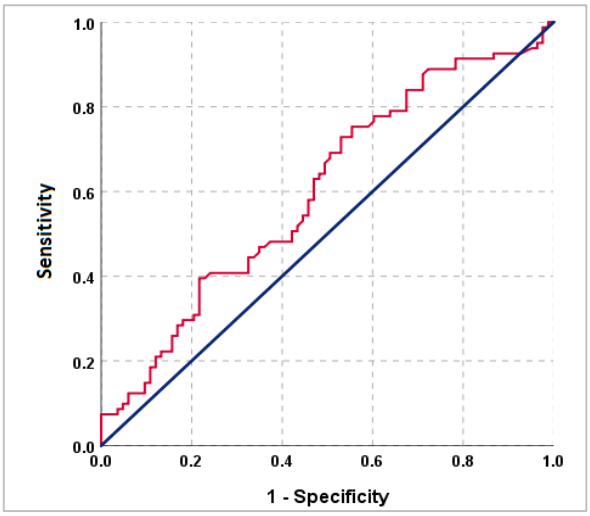

Figure 2: ROC curve for PLT count in predicting neonatal sepsis.

DISCUSSION

Most cases of sepsis were in males with normal birth weight, born of term pregnancy, which may be explained by exclusion of the cases with respiratory distress syndrome, primarily associated with premature delivery and low birth weight. Multiple births (twins or triplets) constituted 18.29% neonates with sepsis, significantly higher than in the control group, which indicates their higher risk for acquiring neonatal sepsis is potentially due to a compromised immune system or prolonged hospital stays.

Inflammation is the pathophysiological basis for neonatal sepsis. Thus, investigating inflammatory biomarkers is a vital component of sepsis research. Recent study had increasingly focused on the impact of inflammation, particularly on blood cells such as neutrophils, lymphocytes, and platelets. When an infection occurs, neutrophils respond immediately and migrate quickly towards the site of inflammation. Consequently, more immature neutrophils are released into circulation due to compensatory increases in bone marrow production.[6] Laboratory investigations in this study revealed significantly higher leukocyte counts and ANCs in newborns with sepsis compared to healthy individuals. These results are similar to those found in an Indian study by Patidar et al.,[1] an Iranian study by Sagheb et al.,[8] and Egyptian studies by El-Mashad et al.[12] and Shalaby et al.[13] Prathyusha et al.'s[3] study in India found that total leucocyte count was higher in newborns with sepsis but did not reach statistical significance, which may be explained by the smaller sample size in that study (53 cases only). Additionally, the current study demonstrated that the absolute lymphocyte count was significantly lower and the neutrophil/lymphocyte ratio was significantly higher in the case group compared to the control group, consistent with findings from a Turkish study by Karabulut et al.[6]

The current study also demonstrated a significantly lower total platelet count in the case group, which is similar to several other studies. similar to several other studies.[1-4,6,12,13] Platelets are essential components of the coagulation system, inflammatory response, and host defense, and may undergo changes similar to neutrophils and lymphocytes. Platelet destruction during sepsis results in reduced platelet counts, which explains these findings.[14,15]

MPV, PDW, and the MPV/PLT ratio were higher in the case group compared to the healthy control group, with statistical significance. These results are consistent with findings from various studies.[4,16–19] During platelet activation, platelets undergo morphological changes from biconcave discs to spheres with prominent pseudopod development, which increases MPV. Conversely, PDW serves as a measure of volume variability in platelet size, which is elevated in platelet anisocytosis and cases of destructive thrombocytopenia, such as neonatal sepsis.[4]

In this study, an MPV of 9.95 fL was determined as a predictive cut-off value for neonatal sepsis (sensitivity 78%, specificity 60%, AUC 0.755, p-value < 0.001). These results approximately align with Shalaby et al.'s [13] study in Egypt and Nguyen et al.'s[19] findings in Vietnam. Slightly lower values were reported in an Indian study by Panda et al.[17] (MPV cut-off value 9 fL, sensitivity 63.4%, specificity 53.8%, AUC 0.641, p-value= 0.020), while Metwally et al.'s[20] study in Egypt found much higher results (sensitivity 96.7%, specificity 93.3%, AUC 0.67, p-value= 0.045). This could be linked to the small sample size in the latter (30 cases, 15 controls), which may not reflect the actual population.

For PDW, the present study determined 11.56% as a predictive cut-off value for neonatal sepsis (sensitivity 70%, specificity 59%, AUC 0.686, p-value < 0.001). Different results were found in studies by Bagchi et al.[4] and Nguyen et al.[19] (cut-off value > 19.1% and 11.2%, sensitivity 80.2% and 63.3%, specificity 35.5% and 87.2%, respectively). Regarding the MPV/PLT ratio, the current study established a predictive cut-off value of 3.95 (sensitivity 63%, specificity 65%, AUC 0.671, p-value < 0.001). Different results were demonstrated by Panda et al.'s[17] study, in which the cut-off value was ≥ 7.2 and

sensitivity and specificity were 48.8% and 96.2%, respectively.

The cut-off value for platelet count in this study was 264 × 10^9/L (sensitivity 63%, specificity 53%, AUC 0.601, p-value= 0.025), while Panda et al.[17] reported different cut-off points (< 150 × 10^9/L) with low sensitivity (41.5%) and high specificity (96.15%). In contrast, Bagchi et al.'s [4] study showed high sensitivity (88.5%) and low specificity (22.8%) for the same cut-off value as Panda et al.[17] These variations make more studies with larger sample sizes mandatory.

Positive blood cultures were found in 54.88% of cases in the current study, which is approximately similar to results found in other studies.[2,16] Additionally, *Staphylococcus aureus* was the most commonly isolated bacterium, consistent with Hussein et al.'s study,[21] while *Klebsiella spp*. was the most commonly encountered in El-Mashad et al.'s [2] study. These differences may be attributed to variations in sample size and the general characteristics of the population as well as the higher percentage of low birth-weight neonates included in El-Mashad et al.'s [2] study.

CONCLUSIONS

Neonates with sepsis exhibit significantly lower platelet counts and higher levels of MPV, PDW, and MPV/PLT ratios compared to healthy neonates. Platelet parameters are easily obtained from the CBCs and could serve as adjuvant indices in the diagnosis of neonatal sepsis.

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