Advanced Medical Journal, Vol.10, No.3, P.151-159,2025 https://doi.org/10.56056/amj.2025.380

Thrombocytopenia as predictor of neonatal sepsis in NICU of Erbil Pediatric hospitals

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Abstract

Background and objective: Neonatal thrombocytopenia is a common condition in neonatal intensive care unit newborns. The aim of this study was to explore the prognostic value of thrombocytopenia as a screening and monitoring tool in neonatal sepsis.

Methods: This cross-sectional study was conducted on neonates hospitalized in neonatal intensive care unit of two centers in Erbil, Iraq, during a period of 6 months with probable or proven sepsis. Thrombocytopenia cases are divided into mild (101-149×109/L), moderate (51-100×109/L), severe (21-50×109/L), and very severe (≤20×109/L) based on platelet count. Prenatal (maternal fever and membrane rupture duration) and post-natal (clinical examination results, laboratory parameters, blood culture and mortality rate) finding were recorded.

Results: In this study, a total of 82 neonates admitted with proven (63.41%) or possible (36.59%) diagnoses of sepsis with an average age of 12.31±7.87 days were investigated (63.4% male). the most common symptoms were poor feeding (75.6%), and lethargy (57.3%). Among all neonates, 14.6% died. Thrombocytopenia was reported in 90.2% of neonates. The frequency of severe thrombocytopenia in the deceased (83.3%) was significantly higher than that of the discharged (34.3%) ($P<0.05$).

Conclusion: Thrombocytopenia has a definite association with neonatal sepsis. The presence and severity of thrombocytopenia can serve as an important indicator of prognosis of infants with sepsis admitted to the neonatal intensive care unit.

Keywords: Neonatal intensive care unit, Neonatal sepsis, Prognosis, Thrombocytopenia

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Introduction

Neonatal thrombocytopenia is defined as a platelet count of less than 150×10^9/L. It is a common condition in Neonatal intensive care unit (NICU) newborns. However, its prevalence is less than 5% in all neonates.[1] A study of 191 infants brought to the NICU found that 47.1% of them had this condition.[2] It has been shown that thrombocytopenia is linked to prematurity and a low birth weight.[3] Because there are fewer platelets, thrombocytopenia can lead to bleeding problems in infants, including potential life-threatening intracranial hemorrhage.[4] It has been found in studies that sepsis is one of the primary causes of thrombocytopenia in newborns. Nevertheless, its cause is not well understood. One idea comes from the fact that sepsis damages endothelial cells. Therefore, they move platelets out of the body by activating the reticuloendothelial system.[5, 6] Neonatal sepsis is a systemic infection in newborns less than one-month-old. It is a common and dangerous condition in infants, especially those who are preterm.[7] Some studies have found that up to 52.7% of sick infants in the NICU are affected by sepsis.[8] There are many types of Gram-positive and Gram-negative bacteria that can cause sepsis. Group B streptococcus is the most common, and Escherichia coli is the most dangerous.[9] In the past, various studies have investigated the relationship between neonatal thrombocytopenia and sepsis. A cross-sectional study on 119 infants with neonatal sepsis reported the prevalence of thrombocytopenia to be 68.9%.[10] Another cohort study showed that severe thrombocytopenia was observed in 20% of cases of neonatal sepsis. The authors also reported that thrombocytopenia increases the mortality rate of infants with sepsis up to 4 times, and if the cause is gram-negative, the mortality rate increases 6 times.[11] However, another study found no difference between gram-negative and gram-positive sepsis as a factor associated with sepsis severity and mortality.[12] However, there is no consensus on whether thrombocytopenia can be considered as a predictor of sepsis in infants. In addition, the relationship between the severity of neonatal thrombocytopenia and the prognosis of newborns is not well known. The aim of this study was to explore the prognostic value of thrombocytopenia as a screening and monitoring tool in neonatal sepsis.

Patients and methods

This cross-sectional study was conducted after approval by the local ethics committee and Kurdistan Higher Council of Medical Specialties (KHCMS) in the setting of NICU of Raparin Pediatric Teaching Hospital and NICU of Maternity and Obstetric Teaching Hospital in Erbil city during a period of 6 months. Neonates with proven or probable sepsis hospitalized in the NICU of the above two centers were included in the study. Proven sepsis was identified by clinical manifestations of sepsis with pathogen isolation from blood. Probable sepsis was diagnosed when clinical signs of sepsis were evident without an isolated pathogen, with one or more of the following criteria: Predisposing factors such as maternal fever, foul-smelling liquor, or prolonged rupture of membrane more than 18 hrs., Positive sepsis screen with two of the following parameters: total leukocyte counts less than 5000/mm3, or more than 20,000/mm3 according to age, ANC, C-reactive protein (CRP) more than or equal to 6 mg/dl, platelet count using hematological scoring system (HSS), and radiological evidence of pneumonia. Exclusion criteria of the study include infants less than 32 weeks gestational age (to eliminate biases caused by the specific conditions of very preterm neonates), infants with congenital heart diseases, congenital anomalies (TAR syndrome, large hemangioma...), hypoxic-ischemic encephalopathy, and infants whose mothers

https://doi.org/10.56056/amj.2025.380


have a history of Systemic lupus erythematosus (SLE), Immune thrombocytopenic purpura (ITP), or under medications (such as Thiazide, Heparin) during pregnancy. After identifying the neonates who met the mentioned criteria, 82 neonates were randomly selected. The required information was extracted from each child's hospital records. The investigated variables included prenatal findings including maternal temperature and membrane rupture duration; natal findings including age, sex, gestational age, and mode of delivery (MOD).

In addition, postnatal findings, including the newborn's clinical examinations and physical examination results, along with laboratory and paraclinical findings (blood culture results) were also recorded. The mortality rate of neonates was determined until the time of discharge. Thrombocytopenia cases are divided into mild (101-149×10^9/L), moderate (100-51×10^9/L), severe (21-50×10^9/L), and very severe (≤20×10^9/L) based on platelet count. At the end, the data was entered into the statistical software SPSS version 26 and analyzed using chi-square statistical tests, one-way ANOVA, independent T, and univariate and multivariate regression at a significance level of 0.05.

Results

In this study, a total of 82 neonates admitted to the NICU with proven (63.41%) or possible (36.59%) diagnoses of sepsis with an average age of 12.31±7.87 days were investigated. 63.4% of the neonates were male, and only 52.4% were born by natural vaginal delivery. 67.15% of the neonates were near-term (gestational age between 34 and 37). The average age of infants with mild to moderate thrombocytopenia (10.35±6.67) was significantly lower than that of neonates with normal platelets (18.78±10.43) (Table 1). Prenatal findings show that 26.8% of mothers had a fever before delivery, and 7.35% of cases also reported prolonged rupture of membranes (more than 24 hours). Neonate symptoms from the most common to the rarest were Poor feeding (75.6%), Lethargy (57.3%), Grunting (40.2%), Shortness of breath (34.1%), Vomiting (29.3%), Seizure (24.4%), Irritability (23.2%) and Cough (11%). The findings of the physical examination showed that 19.5% of the neonates had hypothermia and the same percentage had hyperthermia. Hypotonia, hyporeflexia, and tachypnea were the most common signs, which were reported in 70.7%, 52.4%, and 36.6% of neonates, respectively. Blood culture was not done for 16 neonates (19.5%). The most common microorganisms identified were Klebsiella, Escherichia coli, and Pseudomonas, which accounted for 38.5%, 26.9%, and 15.4% of positive blood cultures (n=52), respectively. Among all neonates, 14.6% passed and the rest were discharged (Table 1). Thrombocytopenia was reported in 90.2% of neonates (7.3% mild, 41.5% moderate, 29.3% severe, and 12.2% very severe). Due to the limited sample size and to obtain more reliable results, we changed thrombocytopenia from four categories to two categories: mild to moderate and severe to very severe. The results of the chi-square test showed that the prevalence and severity of thrombocytopenia in cases where the duration of rupture of membranes (ROM) is 18-24hrs is significantly low (P=0.001). The severity of thrombocytopenia was significantly higher in males than in females (P=0.048). Severe thrombocytopenia in near-term neonates (52.7%) was significantly higher than in term neonates (18.5%) (P=0.001). Thrombocytopenia and its severity were not correlated with MOD (P=0.363) and maternal fever (P=0.906). Among the symptoms, lethargy (P=0.001), irritability (P=0.005), and vomiting (P=0.041) were associated with greater severity of thrombocytopenia. The

https://doi.org/10.56056/amj.2025.380

respiratory rate in neonates with mild to moderate thrombocytopenia was significantly higher than others (P=0.006). Among the findings of the physical examination, only Hyporeflexia (P=0.002) and Hypotonia (P=0.006) were associated with greater severity of thrombocytopenia. The severe type of thrombocytopenia in cases of positive blood culture (57.7%) was significantly more than negative blood culture (28.6%) (P=0.001). Severe thrombocytopenia was significantly less common in subjects with evidence of pneumonia on CXR (16.7%) than in others (51.7%) (P=0.007). The frequency of severe thrombocytopenia in the deceased (83.3%) was significantly higher than that of the discharged (34.3%) (P=0.006). Other laboratory findings and the type of pathogens were not related to thrombocytopenia and its severity (P>0.05), as shown in Table (1).

Table (1): Correlation of thrombocytopenia with demographic, clinical and laboratory characteristics of neonates with sepsis

		Total	Normal platelet (n=8; 9.8%)	Thrombocytopenia		P
				Mild to moderate (n=40; 48.8%)	Severe to very severe (n=34; 41.4%)	
Prenatal findings						
Maternal fever	yes	22 (26.8%)	2 (9.1%)	10 (45.5%)	10 (45.5%)	0.906
	no	60 (73.2%)	6 (10%)	30 (50%)	24 (40%)	
duration o f ROM	<18hrs	74 (90.2%)	6 (8.1%)	38 (51.4%)	30 (40.5%)	0.001
	18-24hrs	2 (2.4%)	2 (100%)	0 (0%)	0 (0%)	
	>24hrs	6 (7.3%)	0 (0%)	2 (33.3%)	4 (66.7%)	
Natal findings						
gender	Male	52 (63.4%)	6 (11.5%)	20 (38.5%)	26 (50%)	0.048
	female	30 (36.6%)	2 (6.7%)	20 (66.7%)	8 (26.7%)	
Age (days)		12.31 ±7.87	18.87 ±10.43	10.35 ±6.67	13.08 ±7.87	0.013
Gestation al age	term	27 (32.9%)	0 (0%)	22 (81.5%)	5 (18.5%)	0.001
	Near-term	55 (67.1%)	8 (14.5%)	18 (32.7%)	29 (52.7%)	
MOD	NVD	43 (52.4%)	6 (14%)	21 (48.8%)	16 (37.2%)	0.363
	C/S	39 (47.6%)	2 (5.1%)	19 (48.7%)	18 (46.2%)	
Postnatal findings						
Poor feeding		62 (75.6%)	8 (12.9%)	29 (46.8%)	25 (40.3%)	0.238
Lethargy		47 (57.3%)	5 (10.6%)	15 (31.9%)	27 (57.4%)	0.001
Irritability		19 (23.2%)	3 (15.8%)	3 (15.8%)	13 (68.4%)	0.005
Vomiting		24 (29.3%)	2 (8.3%)	7 (29.2%)	15 (62.5%)	0.041
Cough		9 (11%)	2 (22.2%)	4 (44.4%)	3 (33.3%)	0.404
SOB		28 (34.1%)	2 (7.1%)	18 (64.3%)	8 (28.6%)	0.129
Grunting		33 (40.2%)	2 (6.1%)	21 (63.6%)	10 (30.3%)	0.085
Seizure		20 (24.4%)	2 (10%)	6 (30%)	12 (60%)	0.128
Temperat ure	Hypothermia	16 (19.5%)	3 (18.8%)	6 (37.5%)	7 (43.8%)	0.404
	Normothermia	50 (61%)	5 (10%)	24 (48%)	21 (42%)	
	Hyperthermia	16 (19.5%)	0 (0%)	10 (62.5%)	6 (37.5%)	
Abdominal distension		5 (6.1%)	0 (0%)	2 (40%)	3 (60%)	0.593
Jaundice		10 (12.2%)	0 (0%)	8 (80%)	2 (20%)	0.098

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Respiratory rate		47.6 ±13.50	39.1 ±7.37	52.2 ±14.43	44.1±11.60	0.006
Pulse rate		122.8±17.54	126.3± 4.27	126.7±16.58	117.4±19.35	0.062
Apnea		9 (11%)	0 (0%)	4 (44.4%)	5 (55.6%)	0.470
Tachypnea		30 (36.6%)	2 (6.7%)	18 (60%)	10 (33.3%)	0.296
Flaring		19 (23.2%)	2 (10.5%)	11 (57.9%)	6 (31.6%)	0.601
Hyporeflexia		43 (52.4%)	6 (14%)	13 (30.2%)	24 (55.8%)	0.002
Hypotonia		58 (70.7%)	8 (13.8%)	22 (37.9%)	28 (48.3%)	0.006
Bulging fontanel		10 (12.2%)	2 (20%)	4 (40%)	4 (40%)	0.494
WBC		18233.05 ±9232.84	20037.50 ±9686.06	16622.75 ±9785.67	19702.94 ±8367.13	0.307
CRP		120.56 ±238.80	176 ±108.30	136.12 ±336.35	89.20 ±41.57	0.558
ANC	Increased	72 (87.8%)	6 (8.3%)	34 (47.2%)	32 (44.4%)	0.249
	Normal	10 (12.2%)	34 (47.2%)	6 (60%)	2 (20%)	
Blood culture	Positive	52 (78.8%)	6 (11.5%)	16 (30.8%)	30 (57.7%)	0.001
	Negative	14 (21.2%)	0 (0%)	10 (71.4%)	4 (28.6%)	
CXR	Pneumonia	24 (29.33%)	2 (8.3%)	18 (75%)	4 (16.7%)	0.007
	None	58 (70.7%)	6 (10.3%)	22 (37.9%)	30 (51.7%)	
outcome	Expired	12 (14.6%)	0 (0%)	2 (16.7%)	10 (83.3%)	0.006
	Discharged	70 (85.4%)	8 (11.4%)	38 (54.3%)	24 (34.3%)	
Isolated bacteria	Klebsiella spp	20 (38.5%)	4 (20%)	4 (20%)	12 (60%)	0.113
	coagulase-negative staphylococci	6 (11.5%)	0 (0%)	4 (66.7%)	2 (33.3%)	
	Pseudomonas spp	8 (15.4%)	0 (0%)	4 (50%)	4 (50%)	
	Enterobacter spp	2 (3.8%)	0 (0%)	2 (100%)	0 (0%)	
	E.Coli	14 (26.9%)	2 (14.3%)	2 (14.3%)	10 (71.4%)	
	Streptococcus viridans	2 (3.8%)	0 (0%)	0 (0%)	2 (100%)	

MOD: mode of delivery; SOB: Shortness of breath; ANC: absolute neutrophil count; WBC: White blood cells; CRP: C-reactive protein; CXR: chest X-ray; ROM: rupture of membranes
n (%) or mean ±SD

Prenatal and natal findings had no significant relationship with the type of bacteria isolated (in terms of gram staining) (P>0.05). The symptoms of shortness of breath and grunting were significantly more common in patients with isolated gram-positive bacteria than those whose sepsis was caused by gram-negative bacteria. (P<0.05). Jaundice and tachypnea were associated with Gram-positive infection and Hyporeflexia (P=0.014) and Hypotonia (P=0.001) were associated with Gram-negative infection. The average WBC in Gram-negative infected cases (21132.95±8744.52) was significantly higher than Gram-positive infected patients (6255.61±10012.50) (P=0.001). The prevalence of pneumonia in cases of sepsis caused by gram-positive bacteria (75%) was higher than that of gram-negative bacteria (9.1%) (P=0.001), as shown in Table (2).

https://doi.org/10.56056/amj.2025.380

Table (2): Correlation of the type of organism isolated with demographic, clinical and laboratory characteristics of neonates with sepsis

		Isolated organism		p-value
		Gram positive	Gram negative	
Prenatal findings				
Maternal-fever	yes	2 (25%)	10 (22.7%)	0.888
	no	6 (75%)	34 (77.3%)	
duration of ROM	<18hrs	8 (100%)	40 (90.9%)	0.674
	18-24hrs	0 (0%)	2 (4.5%)	
	>24hrs	0 (0%)	2 (4.5%)	
Natal findings				
gender	Male	4 (50%)	32 (72.7%)	0.200
	female	4 (50%)	12 (27.3%)	
Age (days)		15.37 ±9.21	13.38 ±8.08	0.533
Gestational age	term	2 (25%)	9 (20.5%)	0.772
	Near term	6 (75%)	35 (79.5%)	
MOD	NVD	2 (25%)	27 (61.4%)	0.057
	C/S	6 (75%)	17 (38.6%)	
Postnatal findings				
Poor feeding		7 (87.5%)	34 (77.3%)	0.515
Lethargy		6 (75%)	34 (77.3%)	0.888
Irritability		2 (25%)	15 (34.1%)	0.614
Vomiting		1 (12.5%)	17 (38.6%)	0.153
Cough		1 (12.5%)	2 (4.5%)	0.375
SOB		6 (75%)	6 (13.6%)	0.001
Grunting		8 (100%)	8 (18.2%)	0.001
Seizure		1 (12.5%)	17 (38.6%)	0.153
temperature	hypothermia	0 (0%)	13 (29.5%)	0.207
	normothermia	6 (75%)	23 (52.3%)	
	hyperthermia	2 (25%)	8 (18.2%)	
Abdominal distension		0 (0%)	3 (6.8%)	0.447
Jaundice		4 (50%)	2 (4.5%)	0.001
Apnea		0 (0%)	7 (15.9%)	0.225
tachypnea		8 (100%)	8 (18.2%)	0.001
Flaring		2 (25%)	8 (18.2%)	0.653
Hyporeflexia		2 (25%)	31 (70.5%)	0.014
Hypotonia		2 (25%)	42 (95.5%)	0.001
Bulging fontanel		0 (0%)	8 (18.20%)	0.190
WBC		10012.50 ±6255.61	21132.95 ±8744.52	0.001
CRP		353.35 ±744.58	103.52 ±53.05	0.374
ANC	increased	8 (100%)	38 (86.4%)	0.267
	normal	0 (0%)	6 (13.6%)	
CXR	pneumonia	6 (75%)	4 (9.1%)	0.001
	none	2 (25%)	40 (90.9%)	
outcome	expired	0 (0%)	8 (18.2%)	0.190
	discharged	8 (100%)	36 (81.8%)	
thrombocytopenia	Normal platelet	0 (0%)	6 (13.6%)	0.313
	Mild to moderate	4 (50%)	12 (27.3%)	
	Severe to very severe	4 (50%)	26 (59.1%)	

MOD: mode of delivery; SOB: Shortness of breath; ANC: absolute neutrophil count; WBC: White blood cells; CRP: C-reactive protein; CXR: chest X-ray; ROM: rupture of membranes
n (%) or mean ±SD

https://doi.org/10.56056/amj.2025.380


The results of univariate and multivariate regression analysis showed that severe thrombocytopenia can considered as independently (P: 0.006; OR: 9.58 (1.94-47.29)) and by adjusting the effect of other variables (P: 0.007; OR: 26.67 (2.48-286.30)) predictor of the mortality of neonates with sepsis, as shown in Table (3).

Table (3): Univariate and multivariate analysis of mortality predictors in neonatal sepsis

	Discharged neonates (n=70)	Expired neonates (n=12)	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Severe to very severe Thrombocytopenia	24 (34.3%)	10 (83.3%)	9.58 (1.94-47.29)	0.006	26.67 (2.48-286.3)	0.007
Prolonged ROM	4 (5.7%)	2 (16.7%)	3.30 (0.53-20.43)	0.199	1.41 (0.09-21.26)	0.804
Maternal fever	18 (25.7%)	4 (33.3%)	1.44 (0.39-5.37)	0.583	1.47 (0.22-9.98)	0.693
Male gender	42 (60.0%)	10 (83.3%)	3.33 (0.67-16.37)	0.138	2.82 (0.42-18.68)	0.282
Near term GA	47 (67.1%)	8 (66.7%)	0.97 (0.26-3.59)	0.974	0.49 (0.06-3.87)	0.503
C/S	35 (50.0%)	4 (33.3%)	0.50 (0.14-1.81)	0.292	0.41 (0.09-1.86)	0.248
Positive blood culture	44 (62.9%)	8 (66.7%)	1.18 (0.32-4.31)	0.800	0.25 (0.02-2.77)	0.257

Discussion

The present study was conducted to investigate the prognostic value of thrombocytopenia in neonatal sepsis. Among 82 newborns admitted to the NICU with proven or probable diagnosis of sepsis in two centers in Erbil, Iraq, thrombocytopenia was reported in 74 (90.2%). This shows that thrombocytopenia is indeed a very common condition in neonates with sepsis. A recent study by Ahmad et al. (2023) in Pakistan, evaluating 190 neonates referred to the NICU with a diagnosis of sepsis, reported a prevalence of thrombocytopenia of 67.9%, with 18.4% for its severe type.[13] The prevalence of thrombocytopenia in neonates with sepsis was reported as 81.7% and 83.5% in two other studies.[14, 15] Although these values are closer to what was reported in the present study, the present study shows the highest prevalence of thrombocytopenia in neonates with sepsis. In a recent study, the prevalence of severe thrombocytopenia in neonatal sepsis was reported as 16.9%.[1] In the current study, the severe type of thrombocytopenia was seen in 41.4% of infants, which is much more than previous reports. However, Kausar et al.'s study reported the prevalence of severe and very severe thrombocytopenia in 85 neonates with sepsis to be 53.45%.[16] These findings are consistent with the results of the present study. It seems that the prevalence and severity of thrombocytopenia are higher in the studied centers than in other regions. In this study, there were more males than females, which is consistent with the findings of previous studies in terms of the higher prevalence of neonatal sepsis in males.[13, 17] The most common symptoms were Poor feeding (75.6%), Lethargy (57.3%), respectively. In the study of Talat et al. (2023), poor feeding and lethargy were seen in 67.6% and 61.0% of infants with neonatal sepsis, respectively.[1] Another study by Lim et al. reported similar results.[18] These findings were consistent with the results of the present

https://doi.org/10.56056/amj.2025.380

study. The most common microorganisms identified in the present study were Klebsiella (38.5%), Escherichia coli (26.9%) and Pseudomonas (15.4%). Talat et al.'s study, consistent with our findings, reported the most common organisms isolated as Klebsiella pneumoniae (32.8%), Coagulase negative staphylococcus (18.9%) and Pseudomonas (17.72%) respectively.[1]A study by Ahmad et al. in 2023 showed that age and severity of thrombocytopenia are two factors related to the outcome of neonatal sepsis.[13] In the present study, only the severity of thrombocytopenia was recognized as a predictor of outcome in neonatal sepsis. In the study of Kausar et al., the mortality rate among neonatal sepsis cases with thrombocytopenia and without thrombocytopenia was reported as 21.18% and 3.53%, respectively, which indicates a worse prognosis in the presence of thrombocytopenia.[16] In the present study, the prevalence of severe thrombocytopenia was 34.3% in survivors and 83.35% in dead neonates. In previous studies, it has been reported that the isolation of Gram-negative bacteria from neonates with sepsis is associated with poorer prognosis and higher mortality.[11, 13] In the present study, because some patients had not done any blood culture, it was not possible to analyze in this regard, but all cases of expiration in individuals with positive blood culture had sepsis with Gram-negative pathogen. Gram-negative sepsis is more severe than gram-positive cases, and since sepsis can cause disseminated intravascular coagulation, it may cause thrombocytopenia. Endotoxins produced by Gram-negative bacteria can also be one of the poor prognostic factors in neonatal sepsis caused by these pathogens.

Conclusion

Thrombocytopenia has a definite association with neonatal sepsis. The presence and severity of thrombocytopenia can serve as important factors in determining the prognosis of infants with sepsis admitted to the NICU.

Acknowledgment

We would also like to extend our gratitude to the staff of Raparin Pediatric Teaching Hospital for their cooperation in data collection.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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https://doi.org/10.56056/amj.2025.380