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Original Article

Risk Factors of Thrombocytopenia in Newborns Admitted to the Neonatal Care Unit

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Abstract *- Background: Thrombocytopenia remains a common complication in neonates admitted to the neonatal intensive care unit(NICU) with poor outcomes, especially in severe cases. Objective: This study aimed to evaluate the risk factors associated with the occurrence of thrombocytopenia in neonates. Materials and Methods: An analytic prospective cohort study was conducted for the period of one year (2021 – 2022) at Tishreen University Hospital in Lattakia-Syria. The study included two groups of neonates that were compared: group I consisted of 153 neonates with thrombocytopenia, whereas group II consisted of 258 neonates without thrombocytopenia. Results: The results showed that 37.2% of the study population had thrombocytopenia, including 39.8% of mild grade,34.6% of moderate grade, and 25.5% of severe grade. The prevalence of thrombocytopenia was increased significantly with decreasing gestational age (p:0.0001), low birth weight (p:0.005), presence of gestational hypertension(p:0.001), premature rupture of membranes(p:0.002), perinatal asphyxia(p:0.0001), respiratory distress syndrome(p:0.0001) and sepsis (p:0.0001). Gestational age <37 weeks (RR 4.2), pregnancy hypertension (RR 2.9), perinatal asphyxia (RR 2.7), sepsis (RR 6.3), and respiratory distress syndrome(RR 4.1) were independent factors associated with the risk of progression thrombocytopenia. Conclusion: There is an important prevalence of thrombocytopenia in our health center, and the presence of prematurity, pregnancy hypertension, perinatal hypoxia, sepsis, and respiratory distress syndrome are all warning flags that may predispose to thrombocytopenia.*

Keywords *- Neonates, Prematurity, Risk factors, Thrombocytopenia.*

1. Introduction

Thrombocytopenia (platelet count < 1,50,000/µL) is one of the most common hematological problems in neonatal intensive care units (NICUs) [1]. It is classified according to the initiation time into early thrombocytopenia that occurs in the first 72 hours of life and late form that presents after 72 hours of life[2]. Early thrombocytopenia is associated with placental insufficiency and perinatal hypoxia whereas late form results from sepsis and necrotizing enterocolitis (NEC) [3,4]. Thrombocytopenia can be classified into three groups depending on platelet count: mild (100-149*103/mm3), moderate (50-99*103/mm3), and severe (lower than 50*103/mm3) [5,6]. Several neonatal and maternal factors contribute to thrombocytopenia development.

Thrombocytopenia is considered a common clinical problem in the neonatal period. The overall prevalence of thrombocytopenia in neonates ranges from 1 to 5% and is reported to be much higher in neonates admitted to neonatal intensive care units, ranging from 22 to 35%, and up to 50% of those admitted to NICU who require intensive care[7,8]. Clinical manifestations of thrombocytopenia are variables according to the severity of reduction and usually is insidious which include lethargy, poor feeding, spasms, petechiae, hemorrhage in severe cases(intracranial, pulmonary, umbilical cord and circumcision sites bleeding), and death[9,10]. Various risk factors are known for thrombocytopenia in neonates including maternal factors such as pregnancy-induced hypertension, premature rupture of membranes, TORCH infections, drugs(thiazide diuretics, chloramphenicol), and neonatal factors such as perinatal hypoxia, low birth weight, intrauterine growth restriction IUGR, and meconium aspiration syndrome[11,12]. There are two main underlying Pathological mechanisms of thrombocytopenia: decreased platelet production, increased platelet consumption, or both. Thrombocytopenia remains a significant cause of both mortality and morbidity represented by life-threatening hemorrhage especially in NICU due to exposure to multiple risk factors [13]. It is essential to identify risk factors for thrombocytopenia in neonates and develop effective prevention strategies. Therefore, this study aimed to investigate the risk factors for thrombocytopenia in infants admitted to neonatal ICU.

2. Patients and Methods

2.1. Study Population

After approval by the local research ethics committee, an analytic-prospective cohort Study was conducted on neonates admitted to the neonate intensive care unit (NICU) of Tishreen University Hospital over one year (2021 - 2022).

Inclusion Criteria were as follows: neonates of both sexes, all gestational ages, and birth weight with proven diagnosis of thrombocytopenia. Exclusion Criteria: neonates with the presence of one of the following: hemangioma, congenital leukemia, hereditary and genetic diseases (Down syndrome, Turner syndrome, Chediak-Higashi, and Wiskott Aldrich).

A complete history, review of systems, physical examination including measurements of weight, length, and head circumference, and laboratory investigations including complete blood count, C-reactive protein(CRP), and blood culture were performed. Patients were assigned to group I(153 neonates) with a diagnosis of thrombocytopenia and group II(258 neonates), which included neonates with normal platelet levels. Thrombocytopenia was graded based on platelet count: mild(61 neonates), moderate(53 neonates), and severe thrombocytopenia(39 neonates). Characteristics of the study population were compared according to the presence of thrombocytopenia.

2.2. Statistical Analysis

IBM SPSS version20 was used to perform statistical analysis. Basic descriptive statistics included means, median, frequency, percentages, and standard deviations(SD). Chi-square test or Fisher's test was used to examine the relationships and comparisons between the two groups. An Independent t-student test was used to compare two independent groups. Multivariate logistic regression analysis was performed to estimate independent risk factors. This included risk factors first identified through univariate analysis. Tests were considered significant at 5% type I error ($p<0.05$), β:20%, and power of the study:80%.

3. Results

The study included 411 neonates who fulfilled the criteria of the study. Gestational age ranged from 26 to 40 weeks, with a mean age of 37.06±3.2 weeks. Birth weight ranged from 900 to 4500 g, the average was 2445.92±662.7 g, and males represented 59.4% of the study sample.

Table 1. The relationship between thrombocytopenia and neonatal variables of the study population

Variable	Group I Thrombocytopenia (153)	Group II Non-Thrombocytopenia (258)	p-value
Gender			
Male	95(62.1%)	149(57.8%)	0.3
Female	58(37.9%)	109(42.2%)	
Gestational age(week)			
Prematurity	67(43.8%)	35(13.6%)	0.0001
Full term	86(56.2%)	223(86.4%)	
Low birth weight(g)			
Present	42(27.5%)	42(16.3%)	0.005
Absent	111(72.5%)	216(83.7%)	
Perinatal hypoxia			
Present	23(15%)	12(4.7%)	0.0001
Absent	130(85%)	246(95.3%)	
Respiratory distress syndrome			
Present	37(24.2%)	13(5%)	0.0001
Absent	116(75.8%)	245(95%)	
Sepsis			
• Present	138(90.2%)	149(57.8%)	
Early	107	114	
Late	31	35	0.0001
• Absent	15(9.8%)	109(42.2%)	

During the study period, 153(37.2%) neonates had thrombocytopenia, which classified to mild (61:39.8%), moderate(53:34.6%), and severe (39:25.5%) . The baseline characteristics of neonates according to the presence of thrombocytopenia are shown in Table (1). The percentage of Males and Females among neonates with thrombocytopenia was 62.1% and 37.9%, and among neonates with non-thrombocytopenia 57.8% and 42.2%, respectively, with no statistically significant difference between the two groups (P=0.3). Regarding the gestational age, the majority of cases among neonates with thrombocytopenia and with non-thrombocytopenia were preterm infants (43.8% versus 13.6%, P <0.001) cases, while full-term babies were (56.2% versus 86.4%, P <0.001), with significant variations between neonates in thrombocytopenic and nonthrombocytopenic groups (P =0.0001). Low birth weight was significantly higher in group I versus group II (27.5% versus 16.3%, P=0.005). Gestational hypertension and premature rupture of membranes were detected significantly in group I than in group II (12.4% versus 3.5%, P: 0.001) and (34% versus 20.2%,p:0.002), respectively. A history of perinatal

asphyxia was significantly elevated in group I versus group II (15% versus 4.7%, P=0.0001). The respiratory distress syndrome was detected significantly in group I versus group II (24.2% versus 5%, p=0.0001). Among multiple neonatal risk factors, sepsis was the most common cause of neonatal thrombocytopenia. It was found in 138(90.2%) babies, and it was classified as either early or late (107 versus 114) and (31 versus 35), respectively, p:0.0001.

In the multivariate logistic regression analysis, gestational age <37 weeks (RR 4.2,95% CI 2.9-7.3, p=0.0001), presence of gestational hypertension (RR 2.9,95% CI 1.8-9.3, p=0.0001), asphyxia (RR 2.7,95% CI 1.7-8.2, p=0.003), sepsis (RR 6.3,95% CI 2.9-10.9, p=0.0001), and respiratory distress syndrome (RR 4.1,95% CI 2.3-9.9, p=0.001 were factors that associated with the risk of progression thrombocytopenia, Table (2).

Table 2. The relationship between thrombocytopenia and maternal variables of the study population

Variable	Group I Thrombocytopenia (153)	Group II Non-Thrombocytopenia (258)	p-value
Gestational hypertension			
Present	19(12.4%)	9(3.5%)	0.001
Absent	134(87.6%)	249(96.5%)	
Premature rupture of membranes			
Present	52(34%)	52(20.2%)	0.002
Absent	101(66%)	206(79.8%)	

In the multivariate logistic regression analysis, gestational age <37 weeks (RR 4.2,95% CI 2.9-7.3, p=0.0001), presence of gestational hypertension (RR 2.9,95% CI 1.8-9.3, p=0.0001), asphyxia (RR 2.7,95% CI 1.7-8.2, p=0.003), sepsis (RR 6.3,95% CI 2.9-10.9, p=0.0001), and respiratory distress syndrome (RR 4.1,95% CI 2.3-9.9, p=0.001 were factors that were associated with the risk of progression thrombocytopenia, Table (2).

Table 3. Risk factors for thrombocytopenia of the study population

Variable	RR b [CI 95%]	RR a [CI 95%]	p-value
Prematurity	4.09[3.04-7.9]	4.2[2.9-7.3]	0.0001
Gestational hypertension	3.8[1.7-8.8]	2.9[1.8-9.3]	0.0001
Perinatal asphyxia	3.6[1.7-7.4]	2.7[1.7-8.2]	0.003
Sepsis	6.6[3.6-11.8]	6.3[2.9-10.9]	0.0001
Respiratory distress syndrome	5.9[3.04-11.5]	4.1[2.3-9.9]	0.001

4. Discussion

Thrombocytopenia remains a serious condition among neonates admitted to NICU, especially in critical cases with increasing evidence of worsening outcomes. Prevention of thrombocytopenia, halting its progression, and reducing its complications represent the main goal of identifying risk factors for thrombocytopenia.

Thrombocytopenia was present in 37.2% of neonates admitted to the NICU, and most cases ranged in severity from mild to moderate. The result of the current study revealed that, compared with the control group, thrombocytopenia was associated with a significant relationship with gestational age <37 weeks and low birth weight, which might be related to an inability to prevent platelet consumption and transfer of IgG across the placenta in low birth weight newborns is not optimal leading to predisposing to infection and thrombocytopenia. In addition, prematurity is considered an important risk factor for thrombocytopenia due to decreased platelet and neutrophil production as a consequence of a reduced number of megakaryocytes and CFU/granulocyte/monocyte progenitors. This finding is in agreement with Meena et al. (14), Zekry et al. (15), Gebreselassie et al. (16), and Tirupathi et al. (17). thrombocytopenia was observed more frequently in males than females without significant difference, which a high frequency of sepsis might explain in males because the factors regulating the synthesis of gamma Respiratory distress syndrome represented a significant factor for thrombocytopenia, which might be related to hypoxia that leads to dysfunction of megakaryocyte production in the bone marrow and development of disseminated intravascular coagulation(DIC) in this situation. This finding is in agreement with Basil et al. (18)and Jack et al. (25). In contrast to the current study, Tirupathi et al. (17) did not find a significant correlation between sepsis and thrombocytopenia.

In summary, Neonatal thrombocytopenia is a treatable and reversible condition; clinical circumstances around birth and during the first days of life are critical for developing thrombocytopenia. Hence, it is important to identify neonates at risk and initiate appropriate therapy to prevent severe bleeding and potentially significant morbidity.

5. Conclusion

The incidence of thrombocytopenia in newborns admitted to the intensive care unit at Tishreen University

Hospital was 37.2%, and in most cases, it was of mild to moderate severity. A significant association has been recorded between A significant association has been recorded between thrombocytopenia and gestational hypertension.

Thrombocytopenia and neonatal risk factors (sepsis, severe prematurity, perinatal hypoxia, respiratory distress syndrome). globulin are situated on the X-chromosome, and the male has only one X-chromosome. This finding agrees with Tirupathi et al. (17), Basil et al. (18), Chandra et al. (19), and Antoniette et al. (20).

Pregnancy-induced hypertension is associated significantly with the development of thrombocytopenia, which might be explained by decreased platelet production as the main mechanism and low levels of megakaryocyte precursors in blood. This finding is in agreement with Tirupathi et al. (17), Zekry et al. (15), and Eslami et al. (21). In addition, there was a significant association between premature rupture of membranes and thrombocytopenia, in which membrane rupture leads to early neonatal sepsis predisposing to thrombocytopenia. This finding was in agreement with Tirupathi et al. (17), Zekry et al. (15), Oren et al. (22), and Meena et al. (14). In contrast to the current study, Biener et al. (23) did not find any correlation between premature rupture of membranes and the occurrence of thrombocytopenia which differences in the study sample might explain. Perinatal asphyxia was associated significantly with thrombocytopenia, which might be related to dysfunction of megakaryocyte production in bone marrow. This finding is in agreement with Zekry et al. (15), Basil et al. (18), and Nandyal et al. (24). There was a significant correlation between sepsis and thrombocytopenia, representing the most important factor for developing thrombocytopenia in the current study. It might be related to decreased platelet production, increased platelet consumption, and the development of severe thrombocytopenia. This finding is in agreement with Zekry et al. (15), Meena et al. (14), and Tirupathi et al. (17). Sepsis was the most important risk factor for developing thrombocytopenia in the study sample

6. Recommendations

Considering that sepsis was the most important risk factor for thrombocytopenia, we recommend taking all necessary measures to limit its spread in neonatal intensive care units.

Recommending that all measures be taken to care for the health of pregnant women to reduce the high frequency of premature births and the resulting complications.

Ethical Consideration

After discussing the study with the parents, all of them gave complete and clear informed consent to participate in the study.

Availability of Data and Materials

Most of the data was in the article, and other data can be asked from the corresponding author.

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References

[1] Irene Roberts, Simon Stanworth, and Neil A Murray, "Thrombocytopenia in the Neonate," *Blood Reviews*, vol. 22, no. 4, pp. 173-186, 2008. [CrossRef] [Google Scholar] [Publisher Link]

[2] Hugo Donato, "Neonatal Thrombocytopenia: A Review: Definitions, Differential Diagnosis, Causes, Immune Thrombocytopenia, *Arch Argent Pediatr*, vol. 119, no. 3, pp. 1-13, 2021. [CrossRef] [Google Scholar] [Publisher Link]

[3] Robert Carr, Anne M. Kelly, and Lorna M. Williamson, "Neonatal Thrombocytopenia and Platelet Transfusion- A UK Perspective," *Neonatology*, vol. 107, no. 1, pp. 1-7, 2015. [CrossRef] [Google Scholar] [Publisher Link]

[4] Suzanne F. Gunnink et al., "Neonatal Thrombocytopenia: Etiology, Management and Outcome," *Expert Review of Hematology*, vol. 7, no. 3, pp. 387-395, 2014. [CrossRef] [Google Scholar] [Publisher Link]

[5] S.E Wiedmeier et al., "Platelets Reference Ranges for Neonates, Defined using Data from Over 47.000 Patients in Multihospital Healthcare System, *Journal of Perinatology*, vol. 29, no. 2, pp. 130-136, 2009. [CrossRef] [Google Scholar] [Publisher Link]

[6] Vickie L. Baer et al., "Severe Thrombocytopenia in the NICU," *Pediatrics*, vol. 124, no. 6, pp. 1095-1100, 2009. [CrossRef] [Google Scholar] [Publisher Link]

[7] Aparajita Gupta, Sheila Samanta Mathai, and Madhuri Kanitkar, "Incidence of Thrombocytopenia in the Neonatal Intensive Care Unit," *Medical Journal Armed Forces India*, vol. 67, no. 3, pp. 234-236, 2011. [CrossRef] [Google Scholar] [Publisher Link]

[8] Fatih Bolat et al., "The Prevalence and Outcomes of Thrombocytopenia in a Neonatal Intensive Care Unit: A Three-Year Report," *Pediatric Hematology and Oncology*, vol. 29, no. 8, pp. 710-720, 2012. [CrossRef] [Google Scholar] [Publisher Link]

[9] Susanne Holzhauer, and Barbara Zieger, "Diagnosis and Management of Neonatal Thrombocytopenia," *Seminars in Fetal and Neonatal Medicine*, vol. 16, no. 6, pp. 305-310, 2011. [CrossRef] [Google Scholar] [Publisher Link]

[10] Subarna Chakravorty, and Irene Roberts, "How I Manage Neonatal Thrombocytopenia," *British Journal of Hematology*, vol. 156, no. 2, pp. 155-162, 2012. [CrossRef] [Google Scholar] [Publisher Link]

[11] Robert D. Christensen et al., "Thrombocytopenia in Small for Gestational-Age Infants, *Peditrics*, vol. 136, no. 2, pp. 361-370, 2015. [CrossRef] [Google Scholar] [Publisher Link]

[12] M. Sola, H. Sallomon, and R. Brown, "Thrombocytopenia in Small-for Gestational Age Infants," *Semin Perinatol*, vol. 33, no. 1, 2009.

[13] Elisabeth Resch et al., "Neonatal Thrombocytopenia – Causes and Outcomes Following Platelet Transfusions," *European Journal of Pediatrics*, vol. 177, no. 7, pp. 1045-1052, 2018. [CrossRef] [Google Scholar] [Publisher Link]

[14] Sumarth Lal Meena et al., "Clinical Profile and Outcome of Neonatal Thrombocytopenia in a Tertiary Care Hospital," *International Journal of Contemporary Pediatrics*, vol. 6, no. 3, pp. 1344-1348, 2019. [CrossRef] [Google Scholar] [Publisher Link]

[15] Sylvia R. Zekry et al., "Incidence and Risk Factors for Neonatal Thrombocytopenia among Newborns Admitted to NICU of Assiut University Children's Hospital-A Prospective Observational Study," *Annals of Neonatology*, vol. 4, no. 1, pp. 7-26, 2022. [CrossRef] [Google Scholar] [Publisher Link]

[16] Hana Abebe Gebreselassie et al., "Incidence and Risk Factors of Thrombocytopenia in Neonates Admitted with Surgical Disorders to Neonatal Intensive Care Unit of Tikur Anbessa Specialized Hospital: A One-Year Observational Prospective Cohort Study from a Low-Income Country," *Journal of Blood Medicine*, vol. 12, pp. 691-697, 2021. [CrossRef] [Google Scholar] [Publisher Link]

[17] Keerthi Tirupathi, Keerti Swarnkar, and Jayant Vagha, "Study of Risk Factors of Thrombocytopenia," *International Journal of Contemporary Pediatrics*, vol. 4, no. 1, pp. 191-196, 2017. [CrossRef] [Google Scholar] [Publisher Link]

[18] Basil M. Hanoudi, "Study of Risk Factors for Neonatal Thrombocytopenia in Preterm Infants," *Mustansiriya Medical Journal*, vol. 14, no. 1, pp. 64-69, 2015. [Google Scholar] [Publisher Link]

[19] Anita Chandna et al., "Rapid Diagnostic Test in Neonatal Septicemia," *The Indian Journal of Pediatrics*, vol. 55, no. 6, pp. 947-953, 1988. [CrossRef] [Google Scholar] [Publisher Link]

[20] Willa Antoniette B. Mayuga, and Pura Flor D. Isleta, "Clinical Correlation of Neonatal and Maternal Haematological Parameters as Predictors of Neonatal Sepsis," *Pediatric Infectious Disease Society of the Philippines*, vol. 9, no. 2, pp. 36-43, 2005. [Google Scholar] [Publisher Link]

[21] Z. Eslami et al., "Thrombocytopenia and Associated Factors in Neonates Admitted to NICU during Years 2010–2011," *Iranian Journal of Pediatric Hematology and Oncology*, vol. 3, no. 1, pp. 205-215, 2013. [Google Scholar] [Publisher Link]

[22] Hale Ören et al., "Assessment of Clinical Impact and Predisposing Factors for Neonatal Thrombocytopenia," *The Indian Journal of Pediatrics*, vol. 61, no. 5, pp. 551-558, 1994. [CrossRef] [Google Scholar] [Publisher Link]

[23] Mario E. Beiner et al., "Risk Factors for Neonatal Thrombocytopenia in Preterm Infants," *American Journal of Perinatology*, vol. 20, no. 1, pp. 49-54, 2003. [Google Scholar] [Publisher Link]

[24] Sonam S. Nandyal, P. Shashikala, and Vidhushi Sahgal, "Study of Thrombocytopenia in Neonatal Intensive Care Unit," *Indian Journal of Pathology and Oncology*, vol. 3, no. 1, pp. 55-59, 2016. [Google Scholar] [Publisher Link]

[25] P. Jack, "Analysis of Neonatal Thrombocytopenia in 356 Infant in First Hospital of Jilin University," *Pediatr Res*, vol. 28, no. 148, 2013.