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A Prospective Study on the Incidence and Outcomes of Neonatal Thrombocytopenia at a Tertiary Care Facility in Central Saudi Arabia

Mohamed Eltawel, MBBS, MRCPCH; Talal AlHarbi, MD, MBBS; Khaled AlJamaan, MD, MBBS; Saif Alsaif, MD, MBBS; Yosra Ali, MBA; Mahmoud Salam, RN, MSN

ABSTRACT

Background: The incidence of neonatal thrombocytopenia is low, yet highly dependent on the populations studied.

Purpose: To assess the incidence of neonatal thrombocytopenia and identify factors associated with its outcomes, namely time to disease onset, recovery duration, and platelet count.

Methods: A prospective observational study was conducted between May and October 2013 at a large tertiary care facility in Saudi Arabia. Neonates with a platelet count of fewer than 150,000/μL of blood were followed up until their recovery or death.

Results: The period incidence of neonatal thrombocytopenia was 84/4379 (1.9%). The mortality rate associated with the condition was 68/100,000 births. The male-female ratio of neonates with thrombocytopenia was 2.4:1. The mean (standard deviation) time to disease onset was 1.83 (1.29) days, whereas that of recovery duration was 15.35 (18.46) days. The mean (standard deviation) platelet count at onset was 109,543 (32,826)/μL of blood, whereas that of the increase in platelet count from onset to recovery was 121,876 (78,218)/μL of blood. Treatment comprised monitoring/spontaneous recovery (n = 52, 64.2%) or platelet transfusion (n = 9, 11.1%), immunoglobulins (n = 8, 9.9%), or a combination of both (n = 12, 14.8%). Neonates with a higher gestational age (β = 8061, t = 2.456) and late disease onset (β = 26,178, t = 3.969) were more likely to have a larger increase in platelet count from onset to recovery than those with a lower gestational age (adjusted P = .017) and earlier disease onset (adjusted $P < .001$).

Implications: The high incidence of neonatal thrombocytopenia in this Middle Eastern setting indicates that it may be dependent on the population studied. Special attention should be focused on neonates of lower gestational ages and with an early disease onset, because their platelet count recovery may be slower than that of the countergroup.

Key Words: factors, incidence, neonatal, onset, recovery, thrombocytopenia

Neonatal thrombocytopenia is a rare hematologic abnormality, defined as a platelet count of fewer than 150,000/μL of blood. Throughout pregnancy, fetal platelet numbers gradually increase to reach 150,000/μL of blood at the beginning of the second trimester. A neonate born at 22 or more weeks' gestation usually has platelet numbers within the normal range for adults (150,000–450,000/μL of blood).[1] The rate of thrombocytopenia among neonates varies and is highly dependent on the population studied.[2] The overall incidence of thrombocytopenia among newborns is relatively low (0.7-0.9%).[3] In fact, one national cohort study, based on data sourced from the

Author Affiliations: Pediatric Hematology Oncology Department, King Abdullah International Medical Research Center/King Saud bin Abdulaziz University for Health Sciences—King Abdullah Specialized Children Hospital—Ministry of National Guard-Health Affairs, Riyadh, Saudi Arabia (Dr. Eltawel, Drs AlHarbi, AlJamaan, and Alsaif, and Ms Ali); and Science and Technology Unit, King Abdullah International Medical Research Center/King Saud bin Abdulaziz University for Health Sciences—Ministry of National Guard-Health Affairs, Riyadh, Saudi Arabia (Mr Salam).

M.E.T., T.A.H., K.A.J., and S.A.S. conceptualized and designed the study. Y.A. supervised the conduct of the study and data collection. M.E.T., T.A.H., K.A.J., S.A.S., and Y.A. undertook and supervised the recruitment of patients and managed the data. M.S. was accounted for the quality control, provided statistical advice on study design and data analysis. M.E.T. and M.S. drafted the manuscript, and all authors contributed substantially to its revision as submitted and agree to be accountable for all aspects of the work.

A self-explanatory letter of invitation to participate was handed to each of the parents. Parents signed informed consents. Study was approved by the Institutional Review Board of the Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia (Protocol#RC12/043).

The datasets generated and/or analyzed during the current study are not publicly available as per the policies of the Institutional Review Board of the Ministry of National Guard Health Affairs, but are available from the corresponding author.

The authors declare no conflicts of interest.

Correspondence: Mahmoud Salam, RN, MSN, Science and Technology Unit, King Abdullah International Medical Research Center, King Saud bin Abdulaziz University for Health Sciences (Mail Code 1515), Ministry of National Guard Health Affairs, Riyadh 22490, Saudi Arabia (salamma@ngha.med.sa).

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United Kingdom Obstetric Surveillance System, reported that the incidence of severe autoimmune thrombocytopenia is 0.83/10,000 pregnancies.[4] Another study reported a range between 1% and 5% at birth.[5] Despite its low incidence, newborns with the condition occupy between 22% and 35% of the beds in neonatal intensive care units (NICUs).[6]

The etiology of neonatal thrombocytopenia has been investigated in previous studies by testing the relationships between maternal and fetal characteristics. The relationship elucidated was generally based on association rather than true causation. For instance, neonatal thrombocytopenia that developed in the second or third trimesters can be linked to preeclampsia, prematurity, congenital infections, chronic fetal hypoxia, low maternal platelet count, or a history of thrombocytopenia in prior pregnancies.[7-9] Others were immune related, such as auto- or alloimmune thrombocytopenia, disorders caused by the platelet opsonization with fetal or maternal antibodies that destroy human platelet antigens in fetuses.[10] In fetomaternal alloimmune thrombocytopenia, neonates are the only ones affected but generally endure mild symptoms such as petechial and other skin lesions. However, in autoimmune thrombocytopenia both the mother and the fetus are affected by the action of maternal autoantibodies.[11] A Saudi Arabian study published in 1998 reported that 12/28 (42.8%) infants delivered by mothers with idiopathic thrombocytopenic purpura (an autoimmune hematologic disorder of pregnancy) developed neonatal thrombocytopenia, all of whom lived.[12] Meanwhile, alloimmune thrombocytopenia was reported in 1/1000 live neonates.[9] One study noted that the most common cause of early thrombocytopenia was intrauterine growth restriction, whereas hospital-acquired sepsis was reported to be a leading cause of late thrombocytopenia.[13]

The severity of neonatal thrombocytopenia ranges from mild to moderate, but it is the presence of comorbidities and hemorrhagic complications that lead to a delayed recovery and even death.[14] Mild thrombocytopenia often spontaneously resolves within the first weeks of life without clinical intervention.[5] However, in some neonates severe thrombocytopenia may reflect an inborn platelet disorder or systemic disorder. Therefore, intraventricular bleeding combined with hospital-acquired infections or congenital disorders such as developmental delay often exposes neonates with thrombocytopenia to further clinical risks. As reported in one study, the mortality rates among neonates with and without thrombocytopenia were 39/422 (9%) and 32/1147 (3%) of the total number of neonates investigated within a 3-year study period.[15] Mortality rates vary based on the severity of hemorrhages in neonates with the condition, ranging from 7% to 38%.[14] Because of the low incidence of thrombocytopenia in neonates, this disorder should be investigated and reported by all healthcare settings. Neonatologists and neonatal advanced nurse practitioners continuously attempt to seek rigorous scientific findings derived from few cases identified to add to the body of knowledge. The purpose of this study was to assess the incidence of neonatal thrombocytopenia and identify factors associated with its outcomes at a tertiary care facility, in central Saudi Arabia. This was fulfilled by

- identifying diagnosed cases of neonatal thrombocytopenia;
- describing their characteristics; and
- highlighting factors contributing to their outcomes, such as time to onset of disease, recovery duration, and platelet counts at onset and recovery.

What This Study Adds

- Provided further insights into the etiology of neonatal thrombocytopenia, identified high-risk patients, and described the efficiency of treatment modalities in a community with distinctive characteristics.
- Noted the importance of complete blood profiling in all newborns, as neonatal thrombocytopenia may emerge in less than 72 hours.
- Recommended from hematology and genetics experts to investigate for a possible genetic predisposition associated with neonatal thrombocytopenia.

MATERIALS AND METHODS

Study Design

This was a prospective observational study, based on recruiting emerging cases of neonatal thrombocytopenia postdelivery and prior to discharge and following up on the infants until their recovery or death. The period incidence was measured over 6 months between May and October 2013 at the King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia. The KAMC was established in 1983 and is currently accredited by the Joint Commission International. The nursery (61 beds), intensive care nursery (ICN; 36 beds), and NICU (40 beds) provide services to 6800 to 7500 newborns per year. Eligible patients were newborns (up to 7 days postdelivery) with platelet counts of fewer than 150,000/μL of blood hospitalized at the KAMC within the study period. Written informed consent was sought from their parents prior to study enrollment and follow-up examinations. Data collection was based on both face-to-face interviews and chart reviews. Patients' identifiers and clinical information were preserved and maintained as confidential. Identifiers were utilized to follow up on the outcomes and for validation. This study was approved by the Institutional Review

Board of the Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia (RC 12/043).

Data Collection

Patient enrollment and data collection were conducted by licensed pediatric and assistant consultants. All births within the targeted setting and study period were screened for platelet counts as clinically recommended, because obtaining platelet counts for all newborns and prior to discharge is not a standard practice.[16] Complete blood count profiling is only conducted for symptomatic newborns or those with significant risk factors.[16] Patients with normal platelet counts were excluded from the outcome analysis, because the official clinical diagnosis of neonatal thrombocytopenia was not confirmed. The period incidence of neonatal thrombocytopenia was defined as the number of confirmed cases over the total number of live births within the study period multiplied by 100. The various degrees of thrombocytopenia were subdivided into mild (platelet count 100,000-150,000/μL of blood), moderate (50,000-99,999/μL of blood), and severe (<50,000/μL of blood).[17] Details of newborns with thrombocytopenia were mainly extracted from electronic records and validated using medical charts if information was missing. The data collection forms gathered information on neonatal characteristics, including sex and gestational age measured in weeks and categorized as normal (≥37 weeks), moderate to late preterm (32-36 weeks), very preterm (28-31 weeks), or extremely preterm (≤27 weeks).[18] In addition, birth weight was obtained in grams and categorized as normal (≥2500 g), low (1500-2499 g), very low (1000-1499 g), and extremely low (<1000 g).[19] Developmental delay was also recorded. Hemoglobin level (g/dL) at birth was measured and categorized into <15, 15-20, and >20 g/dL. Maternal characteristics were also gathered such as maternal age, gravidity, parity, previous abortions, complications during pregnancy, conception method, delivery mode, and maternal platelet count. Both fetomaternal and neonatal characteristics were analyzed as potential contributory factors to or causes of neonatal thrombocytopenia.

The time to onset of thrombocytopenia and duration of recovery were measured, as well as the platelet count at onset (baseline measure), and the difference between the platelet counts at onset and recovery. These outcomes were used as measures of the severity of the disease. The mean difference between the platelets counts at onset and recovery was also a reflection of the neonatal response to treatment. The type of thrombocytopenia (auto- vs alloimmune) was recorded. Treatment of thrombocytopenia was achieved by either simple monitoring/spontaneous recovery, platelet transfusion, or intravenous immunoglobulin (IVIG) therapy or a combination of platelet transfusion and IVIG. Complications that occurred throughout the course of hospitalization such as sepsis, or intraventricular bleeding, were also documented. The admission ward to which the patient was referred postdelivery was noted, as was the final status (alive/dead). Neonates who died were excluded from the analyses of outcomes.

Data Analysis and Management

Statistical software (SPSS version 24; IBM Corp, Armonk, New York) was used for data entry and analysis. Categorical variables, such as fetomaternal and neonatal characteristics, were presented as frequencies and percentages, whereas continuous variables, such as onset time, duration of thrombocytopenia, platelet count, and the difference in platelet counts between onset and recovery were presented as means (standard deviation, SD). Bivariate analysis was conducted using the *t* test and 1-way analysis of variance for the onset of disease, recovery duration, and the mean difference in platelet counts between onset and recovery, whereas the Mann-Whitney and Kruskal-Wallis tests were applied for baseline platelet count (which was nonnormally distributed). Linear regression analyses were applied to identify the factors significantly associated with the outcomes of neonatal thrombocytopenia. Statistical significance was set at $P < .05$.

RESULTS

Fetomaternal Characteristics

In total, 84 neonates with thrombocytopenia were identified among 4379 deliveries. The mean maternal age was 30 (5.5) years, with 46 (54.8%) older than 30 years. Mothers with a gravidity of 3 or less numbered 49 (58.3%), whereas those with a parity of 2 or less numbered 51 (60.7%). Mothers with a history of abortion numbered 24 (28.6%), and those with complicated pregnancies (featuring, for example, oligohydramnios, membrane rupture, hypertension, or gestational diabetes) numbered 17 (21.2%). Almost 5% of these births were conceived through assisted reproductive therapies, and 46% were delivered by cesarean method. Five mothers (6%) had subnormal platelet counts. The relationship between maternal characteristics and baseline platelet counts of their neonates with thrombocytopenia showed no statistically significant differences.

Neonatal Characteristics

The duration of the follow-up period ranged from 1 to 89 days. The period incidence of neonatal thrombocytopenia was 1.9%. The incidence of alloimmune neonatal thrombocytopenia was 79/4379 (1.8%), whereas that of autoimmune neonatal thrombocytopenia was 5/4379 (0.1%). The mortality rate among neonatal thrombocytopenia cases in this setting was 3/84 (3.5%) and 68/100,000 births

per study period. Of the live neonates, the incidences of mild, moderate, and severe thrombocytopenia were 56 (1.3%), 19 (0.4%), and 6 (0.1%), respectively. More than two-thirds (57, 70.4%) were males, whereas 24 (29.6%) were females. Almost half of the neonates (n = 42, 51.9%) were full-term, whereas 20 (24.7%) were classed as moderate to late preterm, 14 (17.3%) were very preterm, and 5 (6.1%) were extremely preterm, with a mean (SD) gestational age of 35.2 (4.7) weeks. Neonates with a normal birth weight comprised 39 (48.1%) of the sample, followed by 18 (22.2%) with a low birth weight, 17 (21%) with a very low birth weight, and 7 (8.7%) with an extremely low birth weight, and the mean (SD) birth weight was 2275 (974) g. The neonates with developmental delay numbered 11 (13.5%), of whom 2 were diagnosed with Down syndrome. At the onset of disease, neonates with hemoglobin levels of less than 15 g/dL numbered 19 (23.5%), those with levels of 15 to 20 g/dL numbered 49 (60.5%), and those with levels of more than 20 g/dL numbered 13 (16%), with a mean (SD) hemoglobin level of 16.9 (3.7) g/dL (Table 1). Bone marrow aspirates were performed on 4 patients, and their results showed normal findings.

TABLE 1. Neonatal Characteristics

Characteristics	n (%)
Total	81 (100)[a]
Sex of neonate	
Male	57 (70.4)
Female	24 (29.6)
Gestational age, wk	
Normal (≥37)	42 (51.9)
Moderate to late preterm (32-36)	20 (24.7)
Very preterm (28-31)	14 (17.3)
Extreme preterm (≤27)	5 (6.1)
Mean (SD) = 35.2 (4.7)	
Birth weight, g	
Normal (≥2500)	39 (48.1)
Low (1500-2499)	18 (22.2)
Very low (1000-1499)	17 (21.0)
Extremely low (<1000)	7 (8.7)
Mean (SD) = 2275 (974)	
Development delay	11 (13.5)
Hemoglobin level, g/dL	
<15	19 (23.5)
15-20	49 (60.5)
>20	13 (16.0)
Mean (SD) = 16.9 (3.7)	
Onset of disease, h	
<72	63 (77.8)
≥72	18 (22.2)
Treatment type	
Monitoring	52 (64.2)
Platelet transfusion	9 (11.1)
IVIG	8 (9.9)
IVIG and transfusion	12 (14.8)
Medical complications	
Sepsis	11 (13.6)
Intraventricular bleeding	12 (14.8)
Admission area	
Nursery	21 (25.9)
ICN	19 (23.5)
NICU	41 (50.6)
Mortality	
Alive	81 (96.4)
Dead	3 (3.6)

Abbreviations: ICN, intensive care nursery; IVIG, intravenous immunoglobulin; NICU, neonatal intensive care unit; SD, standard deviation.

[a]*Live cases.*

Disease Outcome Characteristics

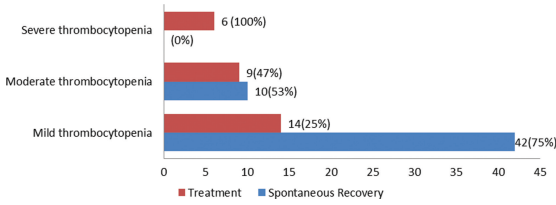
The mean (SD) time to thrombocytopenia onset was 1.83 (1.29) days. Those with an onset of less than 72 hours numbered 63 (77.8%), whereas those with 72 hours or more numbered 18 (22.2%). The mean (SD) duration of recovery prior to discharge was 15.35 (18.46) days. The mean (SD) platelet count upon diagnosis was 109,543 (32,826)/μL of blood, whereas that of the increase in platelet counts from onset to recovery was 121,876 (78,218)/μL of blood. Half of the neonates (n = 41, 50.6%) were admitted to the NICU, followed by 21 (25.9%) to the nursery, and 19 (23.5%) to the ICN. Intraventricular bleeding occurred in 15.5% of the newborns. Those who required no therapeutic intervention, but received monitoring, numbered 52 (64.2%), whereas 9 (11.1%) received platelet transfusions alone, 8 (9.9%) received IVIG treatment alone, and 12 (14.8%) received a combination of platelet transfusions and IVIG treatment. Only one patient required a bone marrow transplant, and this patient died at the age of 3 years. The severity of disease and its distribution between the spontaneous recovery and treatment groups is illustrated in Figure 1.

Factors Associated With Disease Severity and Outcomes

An initial bivariate analysis showed that the mean time to disease onset was significantly higher in neonates with developmental delay (2.55 ± 2.02 days) than in those with no delay (1.71 ± 1.12 days; $P = .047$). Neonates with thrombocytopenia of an extremely low birth weight had significantly higher baseline platelet counts (at disease onset) than neonates in other birth-weight subgroups ($P = .029$). Moreover, newborns who received treatment had significantly lower initial platelet counts than those who manifested spontaneous recovery (118,942 ± 24,535; $P = .01$) (Table 2).

Another bivariate analysis was conducted to test factors associated with the duration of recovery and

FIGURE 1



Severity of thrombocytopenia observed in the spontaneous recovery versus treatment groups.

mean difference in platelet counts between onset and recovery. The duration of recovery from neonatal thrombocytopenia was observed to be higher in neonates in some subcategories, but without statistically significant differences. For example, neonates with a very low birth weight took a longer duration (18.88 ± 20.25 days) to recover than neonates in other birthweight subgroups. Those born with developmental delays took a longer duration to recover compared with healthy neonates (Down syndrome cases recovered without treatments). Other results are listed in Table 3. No linear regression models were fit for the onset of disease, platelet count at baseline, or recovery duration. However, one linear regression model showed that some neonatal characteristics had a certain mediating effect on the increase in platelet count between onset and recovery, which reflects disease prognosis. Neonates with thrombocytopenia of a higher gestational age ($\beta = 8061$, $t = 2.456$), who received treatment ($\beta = 57{,}140$, $t = 3.181$), and with late-onset disease ($\beta = 26{,}178$, $t = 3.969$) were more likely to have a larger increase in platelet count between onset and recovery than those with lower gestational ages (adjusted $P = .017$), who recovered spontaneously (adjusted $P = .002$), and with an earlier disease onset (adjusted $P < .001$), respectively (Table 4).

DISCUSSION

The period incidence of neonatal thrombocytopenia evident in this study was higher than some figures reported in the literature.[9,20] However, a Turkish study reported that their 3-year period incidence of neonatal thrombocytopenia was 208/2218 (9.4%) between 2009 and 2012,[21] which is much higher than the incidence observed in this study. As previously reported, the incidences vary between different study populations, and the Saudi Arabian population in general has distinctive characteristics. A great number of Saudi Arabian couples descend from relatively conservative and tribally bound families, where consanguineous marriages are very common (57.7%).[22] This suggests that there is a certain degree of genetic predisposition to neonatal thrombocytopenia in Saudi Arabia compared with Western communities.

Since neonatal thrombocytopenia is generally diagnosed prior to hospital discharge, the focus for both neonatologists and advanced practice nurses should not be on environmental factors, nutrition, community-acquired infections, trauma, etc, but rather on coexisting fetomaternal characteristics. In 2 regional studies, neonates born to women with idiopathic thrombocytopenic purpura had 16/32 (50%) and 20/30 (67%) incidences of thrombocytopenia.[23,24] Mothers of thrombocytopenic neonates enrolled in this study who had subnormal platelet counts during pregnancy were 5/81 (6.1%), yet the diagnosis of idiopathic thrombocytopenic purpura was not confirmed by study investigators. The incidence of thrombocytopenia is inversely proportional to gestational age and birth weight.[25] A study reported that this disorder was more prevalent among newborns with a sonographic fetal weight less than the fifth percentile at each specific gestational age.[26] This indicated that newborns with lower fetal weight can be a risk predictor for lower platelet counts. Although no differences between the sexes were observed in this study, male sex was also identified as a significant predictor in one study.[27]

The onset of neonatal thrombocytopenia typically falls within a short period, just after birth and prior to discharge home. One study claimed that thrombocytopenia was diagnosed within 3 days of delivery in approximately 74% of newborns.[13] Unfortunately, not all newborns are screened for a platelet count prior to discharge, and the investigation of neonatal thrombocytopenia is often triggered by clinical manifestations such as purpura or poor physical examination scores. In this study, developmentally delayed neonates with thrombocytopenia had a late disease onset. Significant developmental differences associated with platelet production have been reported in neonates.[28] One study noted that thrombocytopenia occurring less than 72 hours postdelivery can be considered secondary to placental insufficiency, and most of these patients were expected to suffer mild or moderate disease with a spontaneous recovery. Neonatal thrombocytopenia occurring 72 hours or more after birth is usually induced by sepsis or metabolic diseases, and is often characterized by a higher severity and prolonged recovery.[5] In this study, neonates with an onset of thrombocytopenia either less than 72 hours or 72 hours or more after birth did not differ in terms of their recovery duration or increase in platelet count. Therefore, both physicians and nurse care coordinators should be aware that regardless of the onset cutoff point of 72 hours introduced by one study,[5] physicians and nurse care coordinators need to be aware that neonates will still have short recovery durations.

Case managers and specifically bed coordinators are cautioned that, once neonatal thrombocytopenia has been diagnosed, it is likely that newborns

TABLE 2. Onset of Thrombocytopenia and Baseline Platelet Count With Neonatal Characteristics and Treatment Modality

	Onset of Thrombocytopenia, d Mean (SD)	Platelet Count,/μL Blood Mean (SD)
Total	1.83 (1.29)	109,543 (32,826)
Sex		
Male	1.82 (1.43)	106,403 (34,743)
Female	1.83 (0.92)	117,000 (26,605)
	$t = -0.028$, $P = .978$	$z = -1.148$, $P = .251$
Gestational age, wk		
Normal (≥37)	1.62 (0.93)	108,927 (30,607)
Moderate to late preterm (32-36)	2.10 (1.92)	95,750 (40,122)
Very preterm (28-31)	1.93 (1.19)	124,571 (22,896)
Extremely preterm (≤27)	2.20 (1.10)	127,800 (20,873)
	$F = 0.822$, $df = 3$, $P = .486$	$\chi^{2KWT} = 6.103$, $P = .107$
Birth weight, g		
Normal (≥2500)	1.73 (1.26)	108,928 (30,607)
Low (1500-2499)	1.56 (1.25)	95,750 (40,122)
Very low (1000-1499)	2.47 (1.46)	124,571 (22,896)
Extremely low (<1000)	1.43 (0.54)	127,80 (15,805)
	$F = 2.333$, $df = 3$, $P = .08$	$\chi^{2KWT} = 9.033$, $P = .029$[a]
Physical examination		
Sepsis	1.64 (0.92)	117,181 (28,798)
Yes	1.86 (1.34)	108,342 (33,442)
No	$t = -0.524$, $P = .502$	$z = -0.765$, $P = .444$
Development delay	2.55 (2.02)	113,818 (27,414)
Yes	1.71 (1.12)	108,871 (33,720)
No	$t = -2.021$, $P = .047$[a]	$z = -0.062$, $P = .951$
Intraventricular bleeding	2.08 (0.99)	116,000 (22,021)
Yes	1.78 (1.34)	108,420 (34,361)
No	$t = -0.912$, $P = .373$	$z = -0.253$, $P = .801$
Treatment type		
Monitoring	2.10 (1.45)	118,942 (24,535)
Platelet transfusion	1.56 (1.01)	112,777 (22,532)
IVIG	1.50 (0.75)	96,750 (40,368)
IVIG and transfusion	1.08 (0.52)	74,916 (42,264)
	$F = 2.515$, $df = 3$, $P = .064$	$\chi^{2KWT} = 11.35$, $df = 3$, $P = .01$[a]
Hemoglobin level, g/dL		
<15	2.26 (1.19)	115,526 (31,394)
15-20	1.73 (1.42)	108,877 (33,159)
>20	1.54 (0.66)	103,307 (34,735)
	$F = 1.553$, $df = 2$, $P = .218$	$\chi^{2KWT} = 1.079$, $df = 2$, $P = .583$

Abbreviations: df, degree of freedom; IVIG, intravenous immunoglobulin; χ^{2KWT}, Kruskal-Wallis test; SD, standard deviation; z, Mann-Whitney test z-score; t, student's t-test; F, one way ANOVA.

[a]*Statistically significant at < .05.*

will be reallocated to advanced care wards such as the ICN or NICU. In the literature, the percentage of neonates with thrombocytopenia admitted to these wards ranges from 18% to 35%.[29] The admission rate evident in this study was higher than figures reported internationally, which reflects both the higher incidence of local disease and increased severity of thrombocytopenia. The medical and nursing management of neonatal thrombocytopenia is highly reliant on the severity of the disease, which is the platelet count and accompanying health status of the neonate. Some neonates with thrombocytopenia require only monitoring, because spontaneous recovery can be expected for most patients. Others require single or multiple platelet transfusions with or without IVIG therapy. In rare cases, a bone marrow transplant is necessary. The duration of spontaneous recovery from neonatal thrombocytopenia reported in the literature is 10 days,[25] which is lower than the mean recovery time of 15 days observed in this study. In addition to these treatment modalities and subsequent complications, neonatologist and advance practice nurses need to be aware that the outcomes

TABLE 3. Duration of Recovery and Mean Difference in Platelet Count Between Baseline and Recovery With Neonatal Characteristics, Treatment Modality, and Onset of Disease

	Duration of Recovery, d Mean (SD)	Difference in Platelet Count Between Recovery and Baseline,/μL Blood Mean (SD)
Total	15.35 (18.46)	121,876 (78,218)
Sex		
Male	15.53 (15.63)	124,614 (80,507)
Female	14.96 (21.30)	115,888 (73,736)
	$t = -0.135$, $P = .893$	$t = -0.483$, $P = .630$
Gestational age, wk		
Normal (≥37)	15.05 (20.21)	124,238 (75,529)
Moderate to late preterm (32-36)	17.80 (18.23)	150,850 (96,127)
Very preterm (28-31)	12.86 (16.25)	82,642 (42,756)
Extremely preterm (≤27)	15.00 (11.59)	96,000 (44,911)
	$F = 0.201$, $df = 3$, $P = .896$	$F = 2.404$, $df = 3$, $P = .074$
Birth weight, g		
Normal (≥2500)	15.35 (20.87)	134,358 (83,083)
Low (1500-2499)	13.56 (13.56)	120,444 (90,807)
Very low (1000-1499)	18.88 (20.25)	109,235 (60,084)
Extremely low (<1000)	12.14 (10.54)	86,714 (42,026)
	$F = 0.327$, $df = 3$, $P = .806$	$F = 0.951$, $df = 3$, $P = .420$
Physical examination		
Sepsis	9.45 (5.26)	135,818 (83,844)
Yes	16.27 (19.61)	119,685 (77,709)
No	$t = -1.141$, $P = .257$	$t = 0.599$, $P = .560$
Development delay	22.00 (22.30)	139,909 (98,886)
Yes	14.30 (17.73)	119,042 (74,942)
No	$t = -1.292$, $P = .200$	$t = 0.670$, $P = .516$
Intraventricular bleeding	16.00 (19.17)	106,916 (41,736)
Yes	15.23 (18.47)	124,478 (82,883)
No	$t = -0.129$, $P = .899$	$t = -1.123$, $P = .271$
Treatment type		
Monitoring	13.67 (19.05)	114,019 (78,325)
Platelet transfusion	20.00 (20.75)	100,777 (47,936)
IVIG	18.63 (16.90)	163,500 (101,030)
IVIG and transfusion	16.92 (16.04)	144,000 (73,725)
	$F = 0.437$, $df = 3$, $P = .727$	$F = 1.496$, $df = 3$, $P = .222$
Hemoglobin level, g/dL		
<15	13.68 (15.95)	114,105 (61,844)
15-20	14.02 (16.08)	124,591 (81,683)
>20	22.77 (27.99)	123,000 (90,743)
	$F = 1.263$, $df = 2$, $P = .288$	$F = 0.122$, $df = 2$, $P = .885$
Onset of disease, h		
<72	15.97 (19.26)	116,619 (69,547)
≥72	13.17 (15.59)	140,277 (10,3392)
	$t = -0.480$, $P = .564$	$t = -1.134$, $P = .260$

Abbreviations: df, degree of freedom; IVIG, intravenous immunoglobulin; SD, standard deviation; t, student's t-test; F, one way ANOVA. Statistically significant at < .05.

of newborns suffering from this disease may also rely on their birth weight, gestational age, platelet count, and the actual etiology of the disease.[13] Both this study and a Turkish study reached similar conclusions that the outcomes of neonates with thrombocytopenia depended on lower gestational age.[20] Neonates with thrombocytopenia are battling a potential threat to life, so prompt diagnosis, early identification of risk predictors, and efficient treatment modalities are required by all healthcare practitioners for their survival and for prevention of neurologic injuries.

Neonates with late-onset thrombocytopenia exhibited a larger increase in platelet count between onset and recovery than neonates with an earlier disease onset. Notably, spontaneous recovery was more prevalent among neonates with late-onset thrombocytopenia in this study. Thus, patients with late-onset thrombocytopenia may require only monitoring and undergo a more rapid

TABLE 4. Factors Significantly Associated with a Larger Increase in Platelet Count in Neonates With Thrombocytopenia

	β	*t*	Adj *P* Value
Constant	−204,397	−2.283	.025[a]
Gestational age, wk	8061	2.456	.017[a]
Birth weight, g	−13.365	−0.909	.366
Onset of thrombocytopenia, d	26,178	3.969	<.001[a]
Hemoglobin level at onset, g/dL	211.72	0.080	.936
Recovered spontaneously[b] Recovered by treatment[c]	57,140	3.181	.002[a]

Abbreviations: Adj, adjusted; β, coefficient of determination.
[a]Statistically significant at P < .05.
[b]Reference group.
[c]Compared group.

recovery of platelet count than patients with early-onset disease. This was comparable with findings of a study reporting that, in rapid onset and progression of thrombocytopenia, a slow recovery over 5 to 7 days is expected.[5] In other words, rapid disease onset indicates rapid platelet consumption followed by impaired platelet production and a slower recovery phase.

The treatment modalities used for neonatal thrombocytopenia vary based on the severity of the disease. The rate of intraventricular hemorrhages in this study was higher than that reported in 2 previous studies (5% and 7.2%).[15,21] These hemorrhagic complications may have been aggravated by low platelet count alone, underlying abnormalities in the vessel walls, or coexisting coagulopathies. Even in the case of recovery, chronic complications such as mental retardation, cerebral palsy, cortical blindness, and seizures affect 14% to 26% of neonates.[11] Some neonates with thrombocytopenia in this study exhibited developmental delay. In the literature, it has been noted that adverse neurodevelopmental outcomes were expected to follow intraventricular hemorrhages, posing potential complications in neonates with subnormal platelet counts.[5]

The mortality rate among patients with neonatal thrombocytopenia in this study was 3.5%, whereas in the literature it ranged from 1% to 10%.[11,15] A Turkish study noted that 134/3515 (3.8%) neonates with signs of thrombocytopenia had a mortality rate of 4.5%.[30] Neonatal thrombocytopenia cannot be directly linked to these mortalities, but they were probably due to other causes such as hemorrhagic complications, hospital-acquired sepsis and underlying metabolic diseases. Some studies reported no statistically significant differences between the mortality rates of subgroups of neonates with thrombocytopenia,[15] but this may be because of a lack of statistical power as a result of small sample sizes or the rarity of the disorder. A drop in platelet count within 7 days of birth is a predictor of a higher mortality rate, length of stay (recovery duration), and the development of severe morbidities among preterm newborns.[31] A striking conclusion of this Saudi Arabian study indicates that an increase or decrease in platelet count, which was used as an outcome measure in this study, should be monitored and its associated factors anticipated.

Limitations

In this study, the main fetal characteristics were described and tested for their potential associations with 4 main outcomes: timing of onset of disease, recovery duration, platelet count at baseline, and at recovery. One drawback of the study was its inability to generate more rigorous outcome analysis from the substandard sample size. The duration of recruitment of eligible study participants was 6 months, but the follow-up required extensive efforts. Considering the rarity of the disease, the data collected were analyzed using suitable and applicable statistical tests, but a larger sample size would have increased its statistical power. The study investigators had to abide by the approved time limit for data collection. In addition, these findings were drawn from a single setting, which may limit their generalizability. However, this is an uncommon disease that should be reported even in low numbers. The high incidence of this disease among Saudi Arabian neonates is alarming, and suggests that Saudi Arabians may be genetically predisposed to neonatal thrombocytopenia because of the high degree of consanguinity in this population. However, this variable was not initially recognized in this study as a potential contributor to this disorder.

Unfortunately, performing a complete blood count on newborns at birth is not a standard

Summary of Recommendations for Practice and Research	
What we know:	• Neonatal thrombocytopenia is a rare hematologic abnormality, classically diagnosed when the platelet level is fewer than 150,000/μL of blood. • The rate of thrombocytopenia among neonates varies and is highly dependent on the population studied. • The etiology of neonatal thrombocytopenia was highlighted in literature, based on testing the relationships between the numerous maternal and fetal characteristics. This is generally based on association rather than true causation. • The severity of neonatal thrombocytopenia ranges from mild to moderate levels, but the presence of comorbidities and hemorrhagic complications may lead to a delayed recovery and even death.
What needs to be studied:	• Due to the low incidence of thrombocytopenia in neonates, this disorder ought to be investigated and reported by both neonatologists and neonatal advanced practice nurses in all healthcare settings. • Scientific findings derived from even few cases can contribute to the medical and nursing body of knowledge in an attempt to address potential fetomaternal factors associated with neonatal thrombocytopenia and to identify high-risk groups.
What can we do today that would guide caregivers in the practice setting considering use of this evidence for guiding practice:	• This study presented the main fetal characteristics and tested them as potential associated factors affecting 4 main neonatal outcomes, which were the timing of onset of disease, duration of recovery, platelet count at baseline, and at recovery. • The high incidence of neonatal thrombocytopenia at a Middle Eastern setting indicates that thrombocytopenia could be dependent on the population studied. • Special attention is required by all health practitioners for neonates with lower gestational age and those with early onset of disease, as their platelet count recovery is expected to be slower compared with their counterparts.

practice in this setting, so the authors fear that the disease onset may have been earlier than reported. Therefore, the authors designated disease onset and measured the baseline platelet count at the time when neonatal thrombocytopenia was officially diagnosed. All neonates underwent at least one platelet count test between the initial diagnosis of thrombocytopenia and discharge. The results of these tests were obtained and all were higher than the baseline platelet counts, but this information was not stated in this article.

Recommendations

Thrombocytopenia among newborns is unfortunate, and every effort should be made by both neonatologists and advance nurse practitioners to anticipate its occurrence, diagnose it promptly, and resolve it efficiently. This starts with maintaining full and complete records of all maternal, fetal, and disease-pertinent data in all healthcare facilities. These archives will pool into local registries that will provide better insights into the etiology of this disease, identify high-risk groups, and focus on enhancing the efficiency of diagnostic/treatment modalities. International collaborations and symposia are of great importance because neonatal thrombocytopenia has been proven to be related to certain population characteristics. Complete blood profiling is highly advised for newborns. Although the majority may present with normal findings, thrombocytopenia may emerge in less than 72 hours, so special consideration should be paid to high-risk births. Because the Saudi Arabian community has a high rate of consanguineous marriages, hematology and genetics experts must be more inquisitive about whether Saudi Arabian individuals have a genetic predisposition to neonatal thrombocytopenia.

CONCLUSION

The high incidence of neonatal thrombocytopenia in this Middle Eastern setting indicates that it may be dependent on the population studied. Special attention should be paid to neonates of lower gestational ages and with an early onset of disease, because their platelet count recovery can be expected to be slower than that of their countergroups.

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