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Original Article

Incidence and Risk Factors for Neonatal Thrombocytopenia among Newborns admitted to Neonatal Intensive Care Unit of Assiut University Children's Hospital-A Prospective Observational Study

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Abstract

Background: Thrombocytopenia is frequent hematological diseases affecting neonates hospitalized to neonatal intensive care unit (NICU). Several maternal and neonatal factors contribute to thrombocytopenia development. **Aim of work:** To identify the incidence and possible risk factors for neonatal thrombocytopenia. **Patients and methods:** This prospective observational study included all newborns aged from 1- 28 days with thrombocytopenia (platelet count <150,000 /L) either full term or preterm, inborn or outborn cases admitted to NICU in Assiut University Children's Hospital from 1st of February 2019 to 31st of January 2020. Thrombocytopenia frequency, as well as associated maternal risk factors as pregnancy-induced hypertension (PIH), diabetes mellitus, premature rupture of membranes (PROM), eclampsia, immunological diseases, and neonatal risk factors as sepsis, birth hypoxia, intrauterine growth retardation (IUGR), and prematurity were evaluated. **Results:** A total of 1590 neonates were enrolled, of them, 420 cases developed thrombocytopenia. Thrombocytopenia incidence was 26.4%. Maternal risk factors linked with neonatal thrombocytopenia were pregnancy-induced hypertensive disorders (PIH), PROM, and immune thrombocytopenia; neonatal risk factors were sepsis, prematurity, necrotizing enterocolitis (NEC), intrauterine growth retardation (IUGR), asphyxia, Toxoplasmosis, Rubella, Cytomegalovirus, and Herpes viruses infection (TORCH), and prolonged hospital stays. Among newborns with thrombocytopenia, 84.5% had late onset thrombocytopenia (> 72 hours of life). Thrombocytopenia was mild in 41.9%, moderate in 37.9%, and severe in 20.2%. Mortality rate was 20.2%. **Conclusions:** Thrombocytopenia frequency was 26.4% of neonates hospitalized in our NICU. The most common etiology associated with thrombocytopenia was PIH, PROM, and immune disorders, followed by neonatal sepsis, prematurity, NEC, and IUGR.

Key words: Incidence, neonates; NICU, risk factors, thrombocytopenia.

Introduction

Thrombocytopenia defined as (platelets count <150 X 10^9/L), it is one of commonest hematological problems in neonates [1]. Thrombocytopenia occurs in 22%–35% of all admissions to neonatal intensive care units (NICUs) [2, 3]. Neonatal thrombocytopenia has a wide range of causes. Increased platelet destruction, decreased platelet production, and mixed mechanisms are the main causes of thrombocytopenia [4]. Neonatal thrombocytopenia due to platelet destruction can be divided into two major disorders, immune and non-immune. The maternal alloantibodies transplacental transfer directed versus paternally inherited antigens found on fetal platelets but missing on maternal platelets causes neonatal alloimmune thrombocytopenia (NAIT), also known as feto-maternal thrombocytopenia **[5]**. Autoimmune thrombocytopenia happens in newborns of mothers with autoimmune diseases caused by placental transfer of maternal platelet autoantibodies [6]. Non-immune neonatal thrombocytopenia due to increased platelet consumption and/or sequestration is present in many disorders including sepsis, NEC, viral infections (rubella, herpes simplex, cytomegalovirus, echovirus, and human immunodeficiency virus), disseminated intravascular coagulation, exchange transfusion, and vascular malformations. In premature infants, thrombocytopenia often complicates persistent pulmonary hypertension, NEC, respiratory distress syndrome, and hyperbilirubinemia treated by phototherapy [7]. Neonatal thrombocytopenia caused by decreased platelet production results from many causes that including hereditary disorders and diseases related to bone marrow infiltration [8].

According to thrombocytopenia onset, there are early onset (less than 72 hours after birth) and late onset (>72 hours after birth). Early-onset thrombocytopenia is frequently attributable to prenatal and maternal

factors, whereas late-onset thrombocytopenia is most often associated with postnatally acquired infections. This classification helps predict the duration and severity of thrombocytopenia since early-onset thrombocytopenia is usually mild to moderate in intensity and heals on its own, but late-onset thrombocytopenia is usually more complicated and lasts longer [9].

The majority of cases of thrombocytopenia in premature infants are caused by pregnancy-induced hypertension (PIH), as preeclampsia and HELLP syndrome (hemolytic anemia, raised liver enzymes and low platelet count), and/or intrauterine growth restriction (IUGR) [10]. NAIT is still the commonest thrombocytopenia reason in term infants, contrary to preterm neonates [4, 11].

Many maternal and neonatal risk factors for neonatal thrombocytopenia have been detected. Age, number of pregnancies, maternal autoimmune diseases, maternal drugs, as non-steroidal anti-inflammatory agents and heparin, and pregnancy-induced hypertension (PIH) are all maternal risk factors that affect the health of newborn babies. Multiple births, prematurity, small for gestational age, and IUGR are all perinatal factors. Sex, sepsis, NEC, toxoplasmosis, rubella, cytomegalovirus, and herpes virus (TORCH) infection, birth asphyxia, neonatal immunological disorders, genetic abnormalities, and metabolic diseases are all neonatal risk factors [12].

For infants with severe thrombocytopenia, significant bleeding, particularly brain haemorrhage, is a critical clinical issue. Premature newborns are at a higher risk of significant intraventricular hemorrhage (IVH), with a reported incidence of more than 25% [6].

The goal of this study was to evaluate incidence of thrombocytopenia in newborns admitted to our institution's NICU in Upper Egypt, as well as maternal and neonatal risk factors

associated with it. There has never been a study done on this subject topic before in our NICU. As a result, our goal is to provide preventive and management approaches for this illness before complications arise, to improve the neonates' outcomes.

Methods

This prospective observational study, included all newborns aged from 1- 28 days with thrombocytopenia (platelet count <150,000 U/L) either full term or preterm, inborn or outborn cases admitted to NICU of Assiut University Children's Hospital through one year from 1st of February 2019 to 31st of January 2020.

Each patient was subjected to complete history including; maternal history (age, previous pregnancies and outcomes, history of hypertensive disorders, diabetes mellitus, autoimmune diseases and therapeutic history during pregnancy), neonatal history (gestational age, mode of delivery, place of delivery, resuscitation data and birth weight), cause of admission and presentation of thrombocytopenia were collected.

Routine investigations as; complete blood picture, prothrombin time and concentration, C- reactive protein (CRP), and blood culture if needed, were made on all patients.

Complete blood picture was estimated with an automated hematology analyzer, Cellenium junior, manufactured by Trivitron with a software version of 1.3 for hematological analysis, New Delhi, India. Platelet numbers were confirmed by counting them manually. Also, a blood film was made and stained by routine Giemsa stain for confirmation of differential leucocytic count and detection of any morphological abnormality of red and white blood cells. Prothrombin time and concentration were analyzed by a laboratory technologist on an automated instrument at 37 °C, as a nominal approximation of normal human body temperature using CoaguChek System for Prothrombin Time (Roche Diagnostics, Indianapolis). CRP was

estimated routinely by immune-turbidimetric assay; measurement at 546 nm or 700 nm of antigen- antibody reaction between antibodies to human CRP bound to polystyrene particles and CRP present in the sample.

The severity of thrombocytopenia was divided into three categories: A platelet count of 100,000 to 150,000/L is considered mild; a platelet count of 50,000 to less than 100,000/L is considered moderate; and a platelet count of 30,000 to less than 50,000/L is considered severe [13].

The timing of the development of neonatal thrombocytopenia has been divided into two categories: early-onset (EOT), which occurs within 72 hours of birth, and late-onset (LOT), which occurs beyond 72 hours of birth [14].

Participating neonates were followed prospectively, and platelet counts were performed at presentation and as needed after that. The Expert Hematologist double-checked all findings, and risk factors for thrombocytopenia were evaluated.

The incidence and degree of thrombocytopenia, reasons and risk factors of thrombocytopenia, nadir platelet counts, presence of pathological hemorrhage, administered treatments, and clinical outcomes were all recorded.

Ethical considerations

The research was approved by Local Ethical Committee Institutional Review Board (IRB) of Assiut University Hospital, Assiut, Egypt (IRB: 17200415, 5/3/2018) that was according to Declaration of Helsinki. Informed written consent was got from mothers or guaranteed of every participant before inclusion and after explaining the research aim to them at admission time.

Statistical analysis

Data analysis was performed utilizing the IBM SPSS program version 25.0 was used to analyze the data. The mean and standard deviations for birth weight and length of hospital stays were computed. The $\chi 2$ test was used to compare

categorical variables. The frequency of risk factors related to the condition was estimated. A P-value of <0.05 was considered significant.

Results

A total of 1590 neonates admitted to NICU at Assiut University Pediatric Hospital, Assiut, Egypt were enrolled during the study period. Out of them, 420 (26.4%) cases developed thrombocytopenia (Figure 1). Females and males among neonates with thrombocytopenia were 54.8% and 45.2% and among neonates with non-thrombocytopenia were 52.1% and 47.9%, with no statistically significant difference between the two groups (P =0.386). Regarding the gestational age, the majority of cases among neonates with thrombocytopenia and with non-thrombocytopenia were preterm infants (61.2% versus 50.4%, P <0.001) cases, while full term babies were (38.8% versus 49.6%, P <0.001), with significant variations between neonates in thrombocytopenic and non-thrombocytopenic groups (P <0.001). Birth weight was significantly higher in non-thrombocytopenic versus thrombocytopenic groups (1975.19 ± 724.17 versus 1773.82 ± 746.94 gram, P = 0.023).

Furthermore, there was non-significant variation between two groups as regards the mode and site of delivery (P= 0.994, P= 0.073 respectively). The number of patients with positive family history was significantly elevated in a thrombocytopenic versus non-thrombocytopenic group (47.6% versus 14.1%, P=0.033). The mean hospital stay duration (days) was significantly elevated in thrombocytopenic group versus non-thrombocytopenic group (13.28±4.68 versus 8.22±4.93 days, P < 0.001) (Table 1).

Thrombocytopenia was mild in 41.9%, moderate in 37.86% and severe in 20.24% of cases (Figure 2).

Regarding maternal risk factors, table (2) showed that pregnancy-induced hypertension (PIH), premature ruptures

of membranes (PROM), systemic lupus erythematosus (SLE), and immune thrombocytopenia, were risk factors for the development of thrombocytopenia (P < 0.001, P < 0.001, P < 0.001, P < 0.004, respectively). While, sepsis, prematurity, NEC, IUGR, asphyxia, and TORCH (Toxoplasmosis, Rubella, cytomegalo-virus, and Herpes viruses) infection were neonatal risk factors for the development of thrombocytopenia (P < 0.001, P = 0.018, P < 0.001, P =0.026, P < 0.001 and P < 0.001 respectively).

Table (3) showed that among the studied cases 15.48% of cases developed thrombocytopenia at age <3 days, 23.81% of cases at 3-7 days, and majority of cases (60.7%) were at age above 7 days.

Table (4) showed that in mild and moderate thrombocytopenia; most of the patients were asymptomatic 76.14% and 37.11% respectively. The most common symptom in mild, moderate, and severe cases was purpura (17.05%, 30.19%, and 47.06% respectively) then ecchymosis (6.82%, 27.67%, and 35.29% respectively). Internal bleedings in moderate and severe cases were intracranial hemorrhage (ICH) (2.52% and 28.29%), GIT bleeding (1.26% and 14.12%), and pulmonary hemorrhage (1.26% and 4.71%).

Table (5) showed different lines of management of thrombocytopenia. In 306 (72.9%) thrombocytopenic neonates, no specific treatment was given. However, 47 neonates (41.2%) were treated by platelet rich plasma (PRP), 40 neonates (35.1%) were treated by fresh blood transfusion, 21 neonates (18.4%) were treated by platelet concentrate, and 6 neonates (5.3%) were treated by IV Gamma globulin. The mortality rate was 20.24% (Figure 3).

Discussion

Thrombocytopenia complicates the clinical course in 22–35% of neonatal admissions in intensive care units. There is wide research on thrombocytopenia and correlation between platelets count and clinically significant bleeding [15].

In the present study, among 1590 neonates admitted to NICU of Assiut University Children's Hospital during one year period. Out of them, 26.4% (420/1590) cases developed thrombocytopenia. Thrombocytopenia severity in this study was mild in 41.9%, moderate in 37.86% and severe in 20.24% of cases. These results were midway between the results recorded in different countries and studies such as in Germany, incidence was 10-24% [1], in Nigeria the overall prevalence of NICU admitted newborn with thrombocytopenia was 53% [16].

In a study conducted by Baer and coworkers [17] on 807 neonates, 22% of neonates were thrombocytopenic with 42% of them had mild, 38% moderate thrombocytopenia, and 20% severe thrombocytopenia. Bolat et al. [18] found that the prevalence of thrombocytopenia among neonates was only 9.4% (208/2218); 57% of the cases occurred in the first 7 days. Eslami et al. [19] found that 100 among 350 neonates (28.5%) had thrombocytopenia and most of them (96.5%) had mild and moderate thrombocytopenia and just 3.5% had severe thrombocytopenia. Inconsistent with the present study, Gupta et al. [20] revealed that (182/258) 70% had thrombocytopenia.

Regarding hospital stay, there was a significant increase in duration of hospital stay in thrombocytopenic versus non-thrombocytopenic group in the present study (13.28 versus 8.22 days). In agreement with our results, Gebreselassie et al. [21] found that the mean length of hospital stay was 10.29 days in neonates with thrombocytopenia. Patients who stayed in NICU for a longer period had a higher rate of thrombocytopenia, which reflected severity of the condition, requiring a longer stay and a higher risk of intensive care acquired sepsis.

Bolat et al. [18] reported that prenatal factors such as preeclampsia, eclampsia, perinatal infection, and fetal distress, as well as premature birth (34 weeks) and low birth weight, were related to the

development of thrombocytopenia, which supported our results. Eslami et al. [19] reported that, sepsis, IUGR, asphyxia, GDM, maternal hypertension and prematurity were risk factors associated with the occurance of neonatal thrombocytopenia. Gupta et al. [20] revealed that sepsis, premature with low birth weight, IUGR, birth asphyxia, and maternal pre-eclampsia were possible risk factors for neonatal thrombocytopenia. Pregnancy-induced hypertension was the most common maternal risk factor in this study, with 76 (18.1%) infants suffering from it. Sanii et al. [22] and Patil et al. [23] found that 17.7% and 72.17 % of neonates had PIH, respectively, in their research. The thrombocytopenia related to PIH is nearly often mild to moderate, and is caused by a combination of reduced platelet production and circulating megakaryocyte progenitors. PROM was found in 72 (17.1%) of the babies in our study, as were mothers with systemic lupus erythromatosis in 8 (1.9%) of the babies, and immune thrombocytopenia in 4 (1%) of the babies. Oren et al. [24] found a link between PROM and thrombocytopenia in a research that was similar to our findings. In addition, Tirupathi [25] found that PROM and PIH in mothers were linked to early onset sepsis and neonatal thrombocytopenia.

Regarding neonatal factors in our study, the most common causes of neonatal thrombocytopenia were sepsis (64.1%) and prematurity (54.1%) followed by NEC (21.4%), IUGR (11.9%), asphyxia (11.2%), and TORCH infection (2.9%). Eslami et al. [19] reported that neonatal sepsis and intrauterine growth restriction were important causes of neonatal thrombocytopenia. Nandyal et al. [25] found that prematurity, sepsis, respiratory distress syndrome, asphyxia, meconium aspiration syndrome, and intrauterine growth retardation, were leading causes of neonatal thrombocytopenia.

In the Nandyal et al. [25], 22.2% of thrombocytopenic neonates developed

sepsis, 42% in the Gupta et al. [20] study, and 24.1% in Khalessi et al. study [22]. Septicemia causes thrombocytopenia, which is caused by a decrease in platelet synthesis and an increase in platelet consumption, resulting in severe thrombocytopenia. Due to decreased platelet production, prematurity is thought to be a risk factor for thrombocytopenia. Furthermore, placental transfer of IgG from maternal to developing fetus improves with age, but it is impeded in premature babies, making them more susceptible to sepsis [26].

Regarding the onset of thrombocytopenia, 15.48% showed early onset thrombocytopenia (<72 hours of life) versus 84.52% who showed late onset thrombocytopenia (>72 hours of life). Possible causes of early thrombocytopenia are Neonatal alloimmune thrombocytopenia, autoimmune thrombocytopenia, perinatal asphyxia, infections like toxoplasmosis, candida, herpes simplex virus, HIV, enteroviruses, and cytomegalovirus. However, sepsis and necrotizing enterocolitis are possible causes of late onset thrombocytopenia [27]. Our results were in line with Gupta et al. **[20]** who found that early onset thrombocytopenia in 28% of patients and late onset thrombocytopenia in 72% of patients. Inconsistent with our results, Eslami et al. [19] found that early onset thrombocytopenia in 75.3% of patients versus late onset thrombocytopenia in 24.7% of patients.

As regards the treatment of thrombocytopenic neonates, our results were consistent with a study performed by Roganović et al. [7] stated that the majority of affected newborns with thrombocytopenia resolved spontaneously within a week and requires no intervention. Specific therapy should be given to patients with identified etiology. Otherwise, treatment of thrombocytopenia is the treatment of the underlying cause or prophylactic to the hemorrhage. According to the

outcomes of neonates with thrombocytopenia, our mortality rate was 20.24%, while Resch et al. [28] reported that the mortality rate was 10.8%. The increased rate of mortality in our study is related to the underlying cause more than the thrombocytopenia itself, and our NICU is considered a referral center for the most critical cases.

Conclusions

Neonatal thrombocytopenia is a prevalent clinical condition in NICU and a prognostic sign for a variety of neonatal diseases. In our NICU, the frequency of neonatal thrombocytopenia was 26.4% with mortality rate 20.2%. The majority of newborn thrombocytopenia degree was mild to moderate and with late onset. The most prevalent maternal risk factors were pregnancy-induced hypertension, PROM, SLE, and immunological diseases While, commonest neonatal risk factors were sepsis and prematurity. Sepsis was associated with late onset thrombocytopenia. Infants born to women with PIH and PROM, as well as those with sepsis and premature should be thoroughly monitored for thrombocytopenia and treated early if necessary.

Author's contributions

All of authors shared equally in this work and have seen and approved the submitted version of the manuscript.

Conflict of interest

The authors have no conflict of interests to declare.

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Table (1): Demographic features of the studied patients.

Variables	Thrombocytopenic babies (n=420)	Non-Thrombocytopenic babies (n=1170)	P. value
Sex			
Male	190 (45.2%)	560 (47.9%)	0.386
Female	230 (54.8%)	610 (52.1%)	
Gestational Age (weeks)			
Preterm (<37 weeks)	257(61.2%)	590 (50.4%)	0.001**
Full term (≥37 weeks)	163(38.8%)	580(49.6%)	
Birth weight (gm) Mean±SD	1773.82±746.94	1975.19±724.17	0.023*
Mode of delivery			
C.S	290 (69.1%)	810 (69.2%)	0.994
NVD	130 (30.9%)	360 (30.8%)	
Site of delivery			
In hospital	252 (60%)	690 (59%)	0.073
Other hospitals	135 (32.1%)	420 (35.9%)	
At home	33 (7.9%)	60 (5.1%)	
Family history			
No	220 (52.4%)	1005 (85.89%)	0.033*
Yes	200 (47.6%)	165 (14.1%)	
Hospital stay (days) Mean±SD	13.28±4.68	8.22±4.93	0.001**

*P value <0.05: significant, **P. value <0.001: highly significant. CS; Cesarean Section, NVD; Normal Vaginal Delivery

Table (2): Univariate analysis of maternal and neonatal risk factors for thrombocytopenic patients

Risk factor	Thrombocytopenic (n=420)	Non-Thrombocytopenic (n=1170)	P. value
Maternal risk factor			
PIH	76 (18.1%)	130 (11.1%)	0.001**
PROM	72 (17.1%)	120 (10.3%)	0.001**
SLE	8 (1.9%)	1 (0.1%)	0.001**
Immune thrombocytopenia	4 (1%)	0 (0.0%)	0.004**
Neonatal risk factor			
Sepsis	269 (64.1%)	360 (30.8%)	0.001**
Prematurity	227 (54.1%)	710 (60.9%)	0.018*
NEC	90 (21.4%)	25 (2.1%)	0.001**
IUGR	50 (11.9%)	95 (8.1%)	0.026*
Asphyxia	47 (11.2%)	35 (2.99%)	0.001**
TORCH	12 (2.9%)	0 (0.0%)	0.001**

PIH; Pregnancy-induced hypertension, PROM; premature ruptures of membranes, SLE; systemic lupus erythematosus. NEC; Necrotizing Enterocolitis, IUGR; Intrauterine Growth Retardation, TORCH; Toxoplasmosis, Rubella, cytomegalovirus, and Herpes viruses.
P. value <0.05*, P. value <0.001**.

Table (3): Age of onset of thrombocytopenia (n=420)

Age at onset (days)	No.	Percentage (%)
<3 days	65	15.48
3-7 days	100	23.81
>7 days	255	60.71

Table (4): Clinical presentation of thrombocytopenia among the studied cases

Clinical presentation	Thrombocytopenia		
	Mild	**Moderate**	**Severe**
	No (%)	**No (%)**	**No (%)**
Asymptomatic	134 (76.14)	59 (37.11)	0
Purpura	30 (17.05)	48 (30.19)	40 (47.06)
Ecchymosis	12 (6.82)	44 (27.67)	30 (35.29)
ICH	0	4 (2.52)	24 (28.24)
GIT Hemorrhage	0	2 (1.26)	12 (14.12)
Pulmonary hemorrhage	0	2 (1.26)	4 (4.71)
P- value	<0.001**	<0.001**	<0.001**

*P value <0.05: significant, **P. value <0.001: highly significant
ICH; Intracranial Hemorrhage, GIT; Gastrointestinal tract.

Table (5): Management of thrombocytopenia in the study groups.

Treatment	No.	%
No	306	72.9
Yes	114	27.1
Platelet Rich Plasma (PRP)	47	41.2
Fresh blood transfusion	40	35.1
Platelet concentrate	21	18.4
IV Gamma globulin	6	5.3

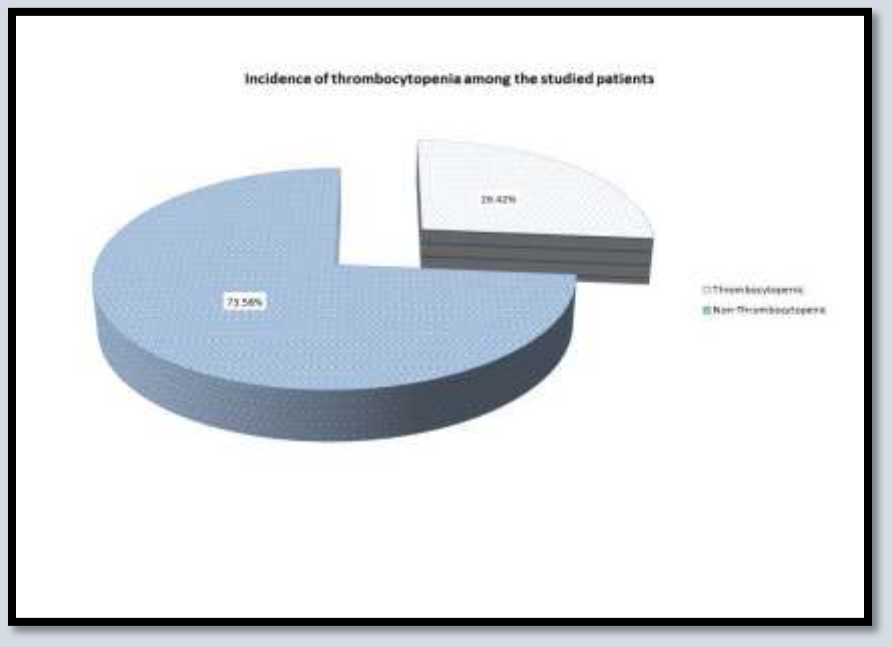

Figure (1): Incidence of thrombocytopenia among the studied patients (n=1590).

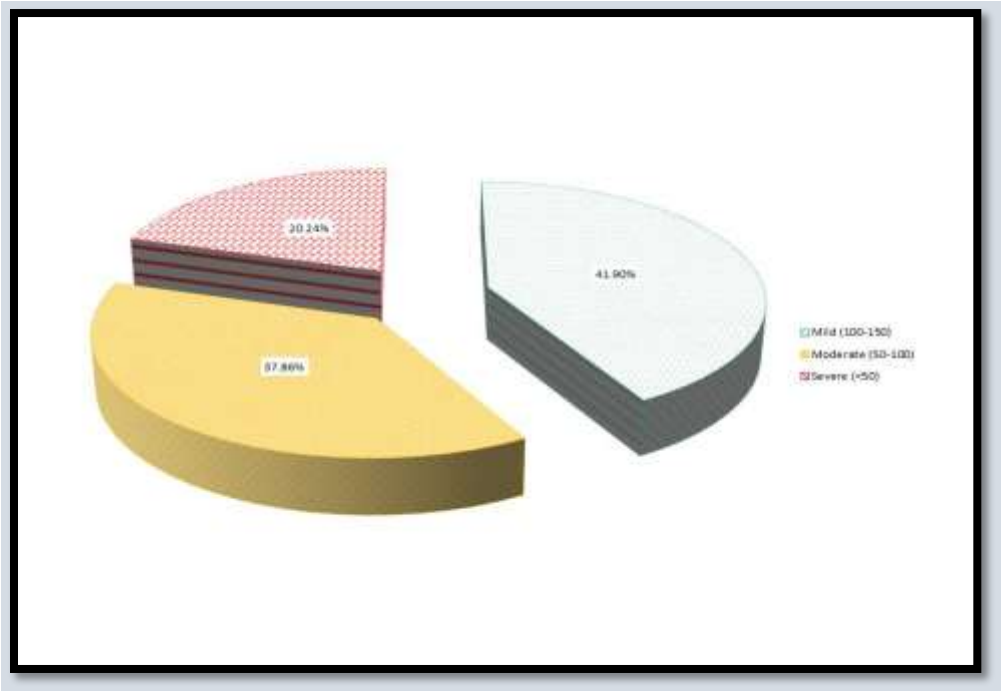

Figure (2): Degree of thrombocytopenia severity (mild, moderate, and severe).

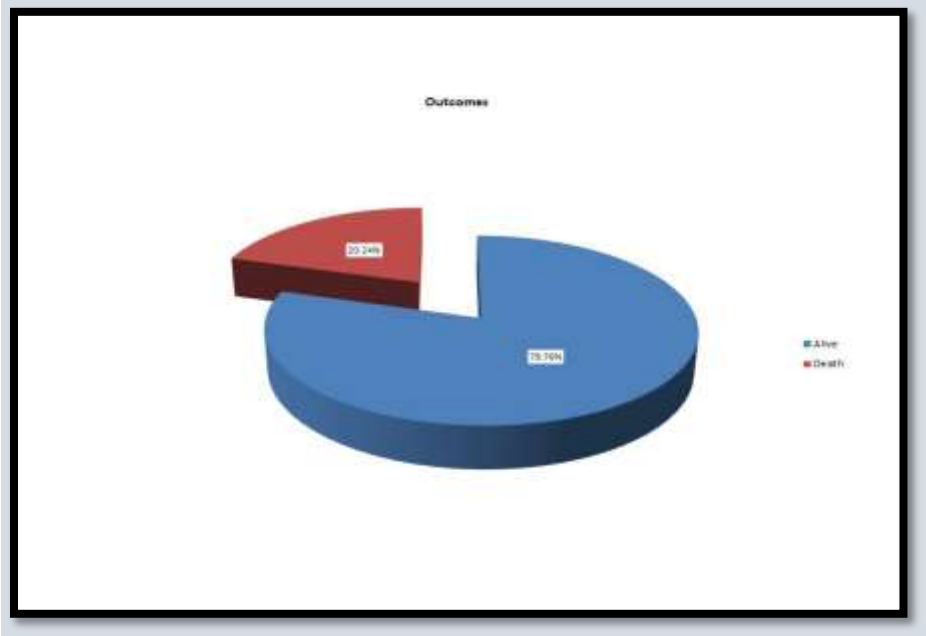

Figure (3): Mortality among thrombocytopenic patients.

Citation: Sylvia R. Zekry; Enas A. Hamed; Farouk E. Hassanen; Safwat M. Abdel-Aziz. "Incidence and Risk Factors for Neonatal Thrombocytopenia among Newborns admitted to Neonatal Intensive Care Unit of Assiut University Children's Hospital-A Prospective Observational Study". *Annals of Neonatology Journal*, 2022: 7-26. doi: 10.21608/anj.2021.89757.1035