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Original Article

Thrombocytopenia is more Frequent in Gram negative Neonatal Septicemia

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Abstract:
Background:
Sepsis is one of the major causes of neonatal thrombocytopenia.
Aim of the work: To identify the frequency, severity, and clinical outcome of thrombocytopenia associated with culture-proven neonatal septicemia in the Neonatal Intensive Care Units (NICUs) of Cairo University Children's Hospitals.
Methods: We conducted a retrospective cohort study that included all neonates with culture-proven sepsis and thrombocytopenia who were admitted to the NICUs over a one-year period (from January 2017 to December 2017). Thrombocytopenia was defined as platelet count less than $150x10^3/\mu L$. The thrombocytopenic neonates were divided into two groups according to the type of cultured bacteria (gram-positive and gram-negative). Both groups were compared regarding maternal and neonatal risk factors, onset and severity of thrombocytopenia, complications, and patient survival.
Results: A total of 316 out of 2172 (total number of NICU admissions) newborns were found to have culture proven-sepsis (14.5%). The frequency of thrombocytopenia in neonates with culture proven-sepsis was 30.3% (n = 96/316). Prematurity is a risk factor for early onset sepsis with thrombocytopenia (p= 0.001). The frequency of severe thrombocytopenia is more in gram-negative sepsis than that in gram-positive sepsis at the onset of sepsis and at the lowest platelet count (p= 0.014, 0.015) respectively. The frequency of hemorrhage in neonates with sepsis and thrombocytopenia was 20.8 % (n = 20/96) and it was mainly pulmonary hemorrhage 10.4 % (n=10). The overall mortality among the study group was 40.6% (n=39/96), with a higher mortality rate (46.3%) in gram-negative sepsis with thrombocytopenia (OR 2.65, p= 0.042).
Conclusion: Neonatal thrombocytopenia is a common finding in neonatal sepsis, and the frequency of severe thrombocytopenia is more in gram negative sepsis. Pulmonary hemorrhage is a common type of bleeding in thrombocytopenic neonates with sepsis. Gram-positive sepsis associated thrombocytopenia has a better prognosis than gram-negative sepsis.

Level of Evidence of Study: IIB (*1*).
Keywords: thrombocytopenia; neonatal sepsis; neonatal hemorrhage.
Abbreviations: AGA: Appropriate for gestational age; ANC: Absolute neutrophil count; CBC: Complete blood count, CONS: Coagulase-negative *Staphylococci*; CPAP: Continuous positive airway pressure; CRP:C-reactive protein; CS: Cesarean section; FT: Full-term; GIT: Gastrointestinal tract; HB: Hemoglobin; HFOV: High-frequency oscillatory ventilation; HTN: Hypertension; IPPV: Intermittent positive pressure ventilation; IT: Immature to total neutrophil ratio; IUGR: Intra-uterine growth retardation; IVH: Intraventricular hemorrhage; LGA: Large for gestational age; MAS: Meconium aspiration syndrome; MDR: Multidrug resistant; MRSA: Methicillin-resistant staphylococcus aureus; MV: Mechanical ventilation; NICUs: Neonatal Intensive Care Units; PEEP: Positive end-expiratory pressure; PROM: Premature rupture of membrane; PT: Pre-term; RDS: Respiratory distress syndrome; SD: Standard deviation; SGA: Small for gestational age; TLC: Total leukocyte count; VD: Vaginal delivery.

Introduction

Thrombocytopenia, defined as a platelet count below $150x10^3/\mu L$, is a frequent problem in neonatal intensive care units. It complicates the clinical course in 22-35% of intensive care

admissions (*2*). Neonatal septicemia is a recognized cause of thrombocytopenia (*3*). Despite a lack of consensus, neonatal septicemia is condition of hemodynamic compromise (e.g., poor peripheral perfusion, pallor, hypotonia, poor responsiveness) caused by blood stream invasion by pathogenic microorganisms. Early onset sepsis is the one acquired during the first 72 hours of life, while late onset us acquired after the first 72 hours. Blood culture remains the gold standard in the diagnosis of neonatal septicemia (*4*). The pathogenesis of thrombocytopenia in neonatal septicemia has been suggested to result from endothelial damage that activates reticuloendothelial damage of platelets. Thrombocytopenia occurs when rate of consumption exceeds the rate of platelet production (*5*). Thrombocytopenia is independently predictive for sepsis-associated mortality in neonates (*6*). The aim of this study was to identify the frequency, severity, and clinical outcome of thrombocytopenia associated with culture-proven neonatal septicemia in the Neonatal Intensive Care Units (NICUs) of Cairo University Children's Hospitals.

Subjects and Methods

This retrospective descriptive cohort study was carried out among the neonates with culture-proven sepsis who developed thrombocytopenia during sepsis who were admitted to the neonatal intensive care units of Cairo University Children's Hospital during the period from January 2017 to December 2017 (Figure 1). The study was approved by the Scientific Research Ethics Committee of the Pediatrics Department, Faculty of Medicine, Cairo University, Egypt in compliance with Revised Helsinki Declaration of Bioethics (2013) (*7*).

Participants

The study included 316 full-term and preterm neonates with gram positive or gram negative bacteria positive blood culture who developed thrombocytopenia. Thrombocytopenia was defined as platelet count < 150,000/mm^3. The thrombocytopenic neonates were divided into two groups according to the type of cultured bacteria. Both groups were compared regarding risk factors (maternal and neonatal), onset and severity of thrombocytopenia, complications, and patient survival. We excluded neonates with positive cultures of both types of bacteria (to compare between both types of bacteria), those who were transferred within the first 24 hours after the clinical sepsis onset and those with other causes of thrombocytopenia, such as early transient causes as intra-uterine growth retardation (IUGR), hypoxia and placental insufficiency (excluded by maternal history), intra-uterine infection (excluded by TORCH screening), neonatal alloimmune thrombocytopenia (normal maternal platelets count) or thrombocytopenic purpura (low maternal platelets count) (*8*).

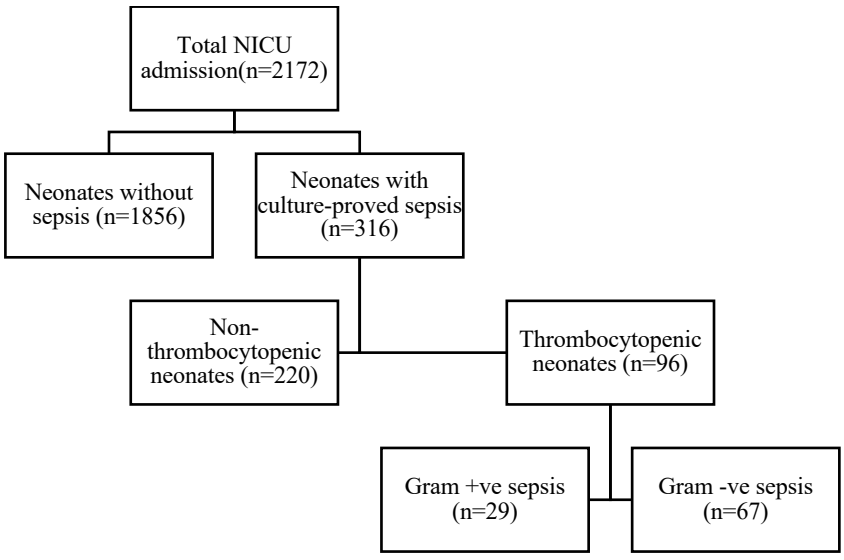

Figure 1. Flow Chart of the study population

Methods

Thrombocytopenia was defined as platelet count < 150,000/mm^3. Mild thrombocytopenia was defined as counts of 100,000 to < 150,000/mm^3, moderate thrombocytopenia as counts between 50,000 and < 100,000/mm^3 and severe thrombocytopenia as counts < 50,000/mm^3 (*2*).

Data collection

The data were collected from the medical records of the neonates who were admitted to the NICUs of Cairo University Children's Hospital.

Maternal data included maternal hypertension (was defined as a diastolic blood pressure of 90 mmHg or more on two occasions more than four hours apart, or a single diastolic blood pressure above 110 mmHg) (*9*), mode of delivery, premature rupture of membranes (defined as rupture of membranes before 37 weeks of gestational age) (*10*).

Neonatal data included the gender, gestational age, birth weight (the body weights were calculated in relation to gestational age. Small for gestational age (SGA) was coined to a birth weight of less than the 10th percentile for gestational age. Large for gestational age (LGA) was coined to a birth weight of more than the 90th percentile for gestational age. Appropriate for gestational age (AGA) was coined to the birth weight being between the 10th and 90th percentiles for gestational age) (*11*). The day of onset and duration of thrombocytopenia, occurrence of hemorrhage and its site, platelets transfusion (platelets transfusion indications either therapeutic in cases of active bleeding or prophylactic in cases of platelet count less than 25 x10^3/µL and the outcome whether survival or mortality were also included.

Laboratory data included initial platelet count at clinical sepsis onset and lowest platelet count during sepsis episode, quantitative C-reactive protein (CRP) and blood cultures. The sepsis screen profile that included total leukocyte count (TLC), absolute neutrophil count (ANC), immature to total (IT) neutrophil ratio, and CRP was also included. If two or more parameters were abnormal (TLC <5000/mm^3, absolute neutrophil count or low counts less than 1800/cmm, immature/total neutrophil ratio >0.2, CRP >10 mg/dl), this was considered positive sepsis screen and blood culture was done to prove the sepsis (*12*). If blood culture was negative the data of the neonate was excluded.

Statistical Analysis

Data were coded and entered using the statistical package SPSS (IBM Statistical Package for the Social Sciences) version 25. Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. P-values less than 0.05 were considered as statistically significant.

Results

This retrospective cohort study was carried out among all neonates with culture-proven sepsis who developed thrombocytopenia during admission to NICUs over a one-year period. Sepsis was diagnosed in 316 of 2172 neonates (14.5%) over the period of the study. Thrombocytopenia developed in 96 of 316 neonates with sepsis (30.3%) with a male predominance 64/96 (66.7%). The mean gestational age (GA) of the neonates who had culture–proven sepsis and developed thrombocytopenia was 34.5±3.36 weeks. The mean percentile of the birth weight among the study group was 32.8 ±32 percentile. The mean day of onset of thrombocytopenia in neonates with sepsis was 9± 6.52 day. The mean duration of thrombocytopenia was 14.3±8.53 days till the platelet count reached (150x10^3/µL). Fifty percent 53% (n=51) of the neonates were preterm (GA: 27-32 weeks), 37 (38.5 %) were full-term (GA≥37 weeks) and 8.3 %(n=8) were near term (GA: 36 weeks). Sixty five (65.6%) of the neonates were SGA and 31 (32.3%) were AGA. (Figure 2).

Frequency, Severity and Clinical Outcome

Early onset sepsis was encountered in 52.1 %(n=50) and 47.9% (n=46) of cases acquired late onset sepsis. At the onset of sepsis the complete blood count (CBC) demonstrated a mean TLC was 12.8 (range 2.9-53.3)10^3/µL. The mean platelet count at onset of sepsis was 66 (range 11-143) x10^3/µL. (Table 2). Gram-negative sepsis was more frequently associated with

thrombocytopenia. Culture revealed gram-negative bacteria in 67 (69.8 %) of neonates with sepsis and thrombocytopenia and gram-positive bacteria in 29 (30.2 %). The most commonly isolated organisms in sepsis with thrombocytopenia was *Klebsiella* 43.7% (n = 42), followed by coagulase-negative *Staphylococci* (CONS) at 15.6% (n = 15), then *Acinetobacter* 12.5% (n =12) and methicillin-resistant *Staphylococcus aureus* (MRSA) at 13.5% (n = 13). (Figure 3).

Table 1. Gestational age, birth weight, day of onset and duration of thrombocytopenia of studied cohort with neonatal sepsis.

	Mean	SD	Median	Minimum	Maximum
GA (weeks)	34.5	3.36	35	27	42
Birth weight percentile	32.8	32	20.35	3.7	100
Day of onset	9.03	6.52	7	2	26
Thrombocytopenia Duration (days)	14.3	8.53	11.5	6	57

GA: gestational Age; SD: standard deviation

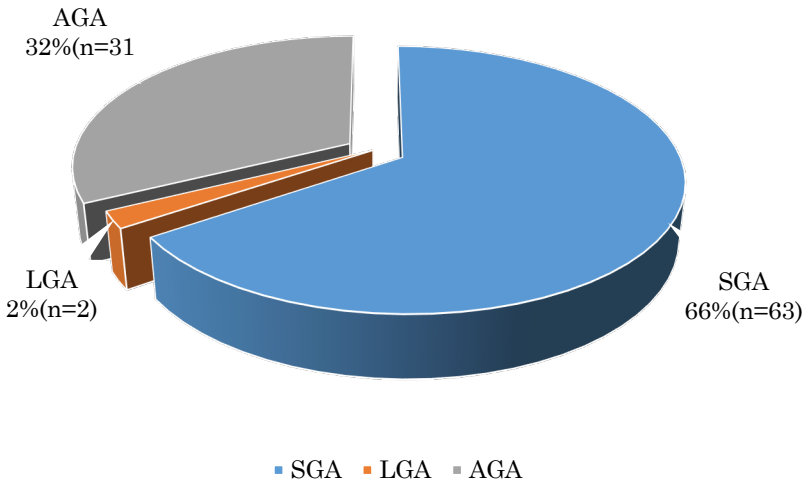

Figure 2. Birthweight of the studied cohort with neonatal sepsis.

Table 2.CBC parameters and CRP at the onset of sepsis.

		Mean	SD	Median	Minimum	Maximum
CBC	HB (g/dl)	14.39	3.24	14.5	6.7	21.3
	WBC (x10³/µL)	12.84	9.13	10.2	2.9	53.3
	Platelet (x10³/µL)	66.09	38.5	101.5	11	143
CRP		58.71	42.3	48	12	221

CBC: complete blood count; CRP: C-reactive protein; HB: Hemoglobin; SD: standard deviation; WBCs: white blood cells.

Among the neonates with sepsis and thrombocytopenia, 51 % (n = 49) developed moderate thrombocytopenia (platelet count from 50-100 x 10³/µL), 39.6 % (n = 38) of the neonates developed severe thrombocytopenia (platelet count less than 50 x 10³/µL), and 9.4 % (n= 9) of neonates had mild thrombocytopenia (platelet count from 100-150 x 10³/µL). (Figure 4). The frequency of severe thrombocytopenia was more in Gram-negative sepsis than that in Gram-positive sepsis at the onset of sepsis and at the lowest platelet count (p= 0.014, 0.015) respectively. Out of 96 neonates with sepsis and thrombocytopenia, 20 neonates developed hemorrhage (20.8%) as a complication of thrombocytopenia. Of them, 10 (10.4%) neonates developed pulmonary hemorrhage (8 were Gram-negative sepsis), 8 (8.3%) neonates had GIT hemorrhage (5 were Gram-negative sepsis), one neonate developed intraventricular hemorrhage (IVH) (was infected with multidrug-resistant *Acinetobacter*), and one neonate developed both intraventricular and GIT hemorrhage (was infected with MRSA) as shown in Figure (5). Seven of the 10 neonates who

developed pulmonary hemorrhage were preterm (gestational age (GA): 27-32 weeks), 2 patients were full term (GA≥37 weeks) and one patient was near-term (GA:36 weeks). All of them were on respiratory support, 8 neonates (6 preterm and 2 full-term) were on assisted mechanical ventilator and two neonates (one preterm and one near term) were on continuous positive airway pressure (CPAP) support. The neonates (8 neonates who were mechanical ventilator and the one preterm on CPAP received surfactant. (Figure 5). Mechanical ventilation was found to be a predictor of pulmonary hemorrhage in neonatal sepsis with thrombocytopenia (OR 17.3, 95% CI 1.97-150.5, p= 0.010), in addition to platelets transfusion (OR 5.32, 95% CI 1.02-27.8, p= 0.047).

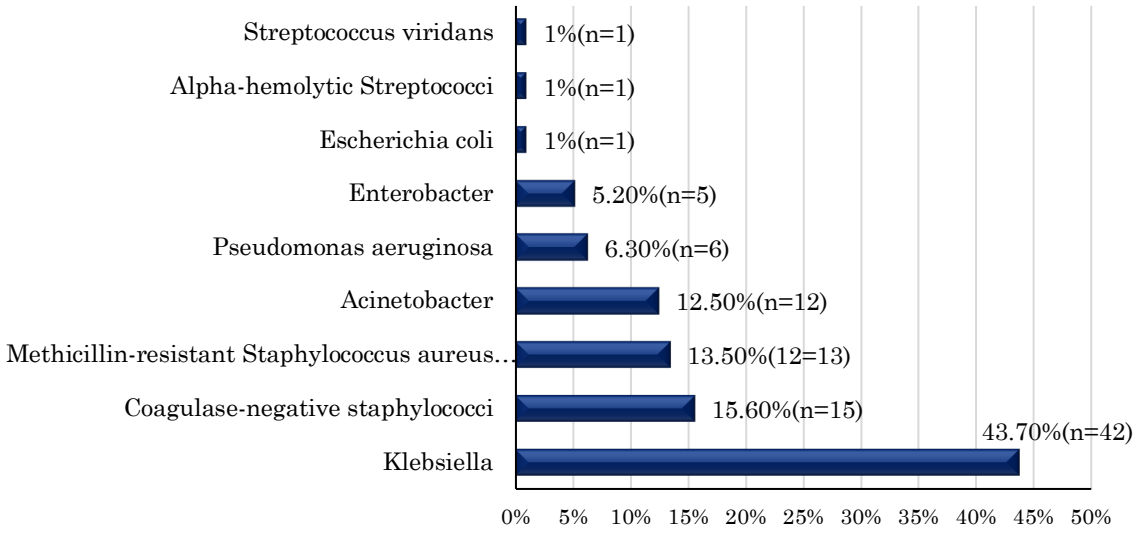

Figure 3. Type of bacteria according to blood culture i the studied cohort with thrombocytopenic neonatal sepsis.

The mean± SD age in early onset sepsis was 33.48±3.35 weeks (range 29-42, median 33), while the mean age in late onset sepsis is 35.61± 3.04 weeks (range 27-40, median 37) indicating that prematurity is a significant risk factor for early onset sepsis with thrombocytopenia (p= 0.001). The mean duration of thrombocytopenia in gram-negative sepsis was 14.6±9.52 days and gram-positive sepsis was 11.28±5 days. The mean initial platelet count in gram-negative sepsis was 98.87 $x10^3$±43.06$x10^3$/µL and in gram-positive sepsis was 112.62$x10^3$/µL ±22.82 $x10^3$ /µL.

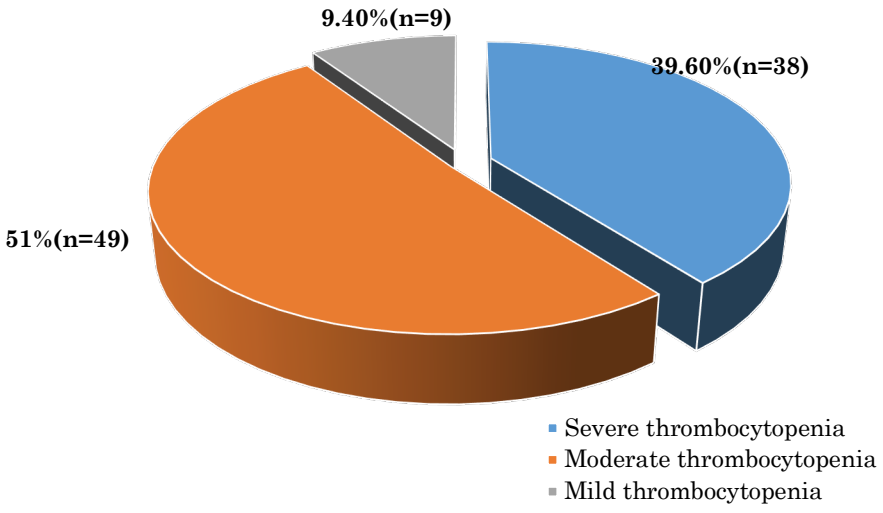

Figure 4. Severity of thrombocytopenia in the studied cohort with thrombocytopenic neonatal sepsis.

Table 3. Severity of thrombocytopenia in sepsis according to culture.

		Thrombocytopenic Gram negative sepsis (n=67)	Thrombocytopenic Gram positive sepsis (n=29)	P value
		Number (%)	Number (%)	
Severity of thrombocytopenia at onset of sepsis	Severe	9 (13.4)	1(3)	0.014
	Moderate	35 (52.2)	9 (31)	
	Mild	23 (34.3)	19(65.5)	
Severity of thrombocytopenia at lowest platelet count	Severe	31 (46.3)	7 (24.1)	0.015
	Moderate	33 (49.3)	16 (55.2)	
	Mild	3 (4.5)	6 (20.7)	
Platelet transfusion	Yes	11 (16.4)	2 (6.9)	0.210
	No	56 (83.6)	27 (93.1)	
Outcome	Survival	36 (53.7)	21 (72.4)	0.087
	Death	31(46.3)	8 (27.6)	

Table 4. Gestational age, birth weight duration of thrombocytopenia and initial platelet count according culture.

	Thrombocytopenic Gram negative sepsis					Thrombocytopenic Gram positive sepsis					P value
	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	
GA (week)	34.79	3.04	35.00	27.00	39.00	33.83	3.98	33.00	27.00	42.00	0.195
Birth weight (Kg)	2.01	0.68	1.92	0.89	4.38	2.06	0.80	1.80	0.75	4.00	0.943
Duration of thrombocytopenia (Days)	14.61	9.52	13.00	3.00	57.00	11.28	5.00	11.00	6.00	23.00	0.135
Initial platelet count ($x10^3$/uL)	98.87	43.06	95	11	138	112.62	22.82	118	70	143	0.068

GA: gestational age; Min: minimum: Max: maximum; SD: standard deviation.

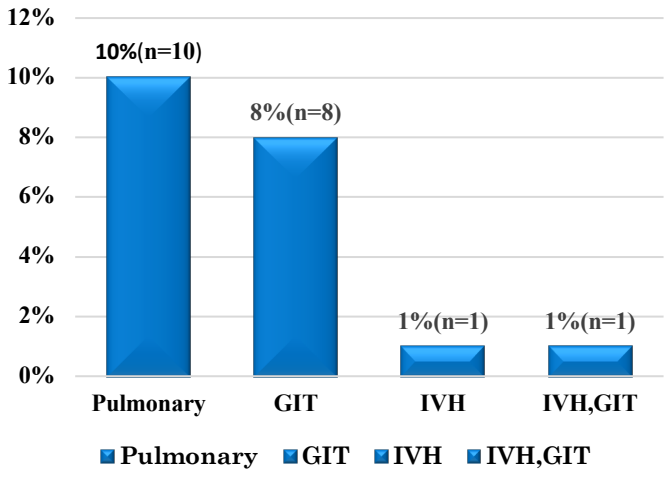

Figure 5. Site of hemorrhage in neonates with sepsis and thrombocytopenia.
GIT: gastrointestinal tract , IVH: intraventricular hemorrhage.

There was no significant difference between gram-positive and gram-negative sepsis with thrombocytopenia regarding gender, gestational age, birth weight, presence of hemorrhage, need for transfusion therapy, mode of delivery, premature rupture of membrane, and maternal

hypertension. The overall mortality among the study group was 39 (40.6%), and gram-positive sepsis associated thrombocytopenia had lesser mortality (27.6% mortality rate) than gram-negative (46.3%) but did not reach statistical significance. *Klebsiella* MDR had the highest mortality rate (100%), followed by MRSA and *Pseudomonas*, each of which had a mortality rate of 66.7 %. *Acinetobacter* came in second with a 50% mortality rate, followed by Klebsiella with a 46.3 % mortality rate. The type of cultured bacteria that causes sepsis and thrombocytopenia has a significant impact on the outcome (p= 0.001). (Table 6 and 7) Gram-negative sepsis was one of the predictors of the mortality among the study group (OR 2.65, 95% CI 1.035-6.768, p= 0.042).

Table 5. Gestational age, birth weight, hemorrhage, risk factors for sepsis according to culture.

		Thrombocytopenic GM negative sepsis		Thrombocytopenic GM positive sepsis		P value
		Count	%	Count	%	
Gender	Male	47	58.6	17	58.6	0.271
	Female	20	41.4	12	41.4	
GA	PT	39	69.0	20	69.0	0.320
	FT	28	31.0	9	31.0	
Birth weight	SGA	46	58.6	17	58.6	0.457
	LGA	1	3.4	1	3.4	
	AGA	20	37.9	11	37.9	
Hemorrhage	Yes	15	17.2	5	17.2	0.596
	No	52	82.8	24	82.8	
Transfusion	Platelets	4	3.4	1	3.4	0.416
	Blood	20	20.7	6	20.7	
	Blood &platelet	7	3.4	1	3.4	
	No	36	72.4	21	72.4	
Mode of delivery	V.D	15	24.1	7	24.1	0.851
	C.S	52	75.9	22	75.9	
PROM	Yes	32	62.06	18	62.06	0.405
	No	35	37.9	11	37.9	
Maternal HTN	Yes	38	55.1	16	55.1	0.824
	No	29	44.8	13	44.8	

AGA: appropriate for gestational age; CS: caesarian section; FT: full-term; GA: gestational age; HTN: hypertension; LGA: large for gestational age; PROM: premature rupture of membrane; PT: pre-term; SGA: small for gestational age; VD: vaginal delivery.

Table 6. Outcome according to gram stain in sepsis with thrombocytopenia

		Thrombocytopenic GM negative sepsis		Thrombocytopenic GM positive sepsis		P value
		Count	%	Count	%	
Outcome	Survival	36	53.7	21	72.4	0.087
	Death	31	46.3	8	27.6	

Table 7. Outcome according to culture in sepsis with thrombocytopenia

Sepsis with thrombocytopenia		The Outcome				P value
		Survival		Death		
		Number	%	Number	%	
Blood culture	*Klebsiella* (MDR)	0	00.0	1	100.0	<0.001
	MRSA	4	33.3	9	66.7	
	Pseudomonas	2	33.3	4	66.7	
	Acinetobacter	6	50.0	6	50.0	
	Klebsiella	22	53.7	19	46.3	
	Enterobacter	5	100.0	0	0.0	
	Alpha-hemolytic *Streptococci*	1	100.0	0	00.0	
	CONS	15	100.0	0	00.0	
	E.coli	1	100.0	0	00.0	
	Streptococcus viridans	1	100.0	0	0.0	

CONS*:* Coagulase-negative *Staphylococci;* MDR: multiple drug resistant.

Table 8. Multivariate analysis of the predictors of the pulmonary hemorrhage in neonatal sepsis with thrombocytopenia

Predictor	Odd ratio (OR)	95% Confidence Interval		P value
		Lower	Upper	
GA≤ 37weeks	0.87610	0.174	4.404	0.872
Gram-negative sepsis	1.8127	0.273	12.056	0.538
PLT	0.99524	0.973	1.018	0.680
MV	17.24923	1.976	150.539	0.010
Blood transfusion	1.52085	0.341	6.775	0.582
Platelets transfusion	5.327	1.020	27.815	0.047

GA: gestational age; MV: mechanical ventilation; PLT: platelets count.

In multivariate analysis, two variables were found to be independently associated with pulmonary hemorrhage in neonates with sepsis and thrombocytopenia during their NICU stay: mechanical ventilation (OR 17.24, 95% CI 1.976–150.539, p = 0.010) and platelets transfusion (OR 5.327, 95% CI 1.020–27.815, p = 0.047). (Table 8).

Discussion

In this study a total of 316 out of 2172 newborns were found to have culture proven-sepsis (14.5%). The frequency of thrombocytopenia in neonates with culture proven -sepsis was 30.3% (n = 96/316) with a male predominance of 66.7% (n = 64/96) which was noted previously (*13*, *14*).

Prematurity and low birth weights are the most important neonatal factors predisposing to infection (14). This might be attributed to immature and often less-effective immune system and often necessitate prolonged support and hospitalization (15).Yet, our findings illustrate that full term and normal weight for age are not protective against neonatal sepsis as only 61.5% were preterm neonates, and 65.6 % were small for gestational age.

There was a predominance of gram negative bacteria among the thrombocytopenic neonates with sepsis. Yet, this finding was noted previously, and was attributed to the ability to secrete endotoxins. We did not study the endotoxemia in our studied group (*15*). But once gram negative bacteria is there in the blood culture, it is prognostic of poor outcome (OR 2.65, p= 0.042).

More than 70% of our studied cohort was born by caesarian section, it is not clear how they acquired the gram negative organisms that was detected by the culture. While, caesarian section is known to increase risk of sepsis generally (*16*), we did not investigate the underlying factors.

The predictive factors for pulmonary hemorrhage in our studied group were mechanical ventilation (OR 17.24, p = 0.010) and platelets transfusion (OR 5.327, p = 0.047), we did not study other hemodynamic factors as blood pressure, or effect of medications apart from surfactant use. It was noted that was not responsive to therapy, hence it is mostly preventable and ominous. Pulmonary hemorrhage in ventilated neonates can occur as a result of ventilation being initiated due to underlying respiratory problems (respiratory distress syndrome (RDS), meconium aspiration syndrome (MAS), and bronchopneumonia), particularly if associated with thrombocytopenia requiring platelet transfusion, and it is recommended to increase positive end-expiratory pressure (PEEP) in intermittent positive pressure ventilation (IPPV) or better to use high-frequency oscillatory ventilation (HFOV) (*17*).

The overall mortality among the study group was 40.6%, and gram-positive sepsis associated thrombocytopenia had a better outcome (27.6% mortality rate) than gram-negative (46.3%) but did not reach statistical significance. The type of cultured bacteria that causes sepsis and thrombocytopenia has a significant impact on the outcome (p= 0.001). Prematurity (gestational age ≤37 weeks) (OR 0.330, p = 0.047), thrombocytopenia (OR 1.023, p = 0.009), hemorrhage (OR 6.259, p = 0.010) and platelets transfusion (OR 4.860, p = 0.037) were predicative factors of death in neonatal sepsis. Infection control, platelet transfusion and controlling causes of prematurity are vital to reduce the morbidity and mortality among preterm and full term neonates. Managing both maternal (frequent prenatal visits, early and appropriate management of maternal HTN and PROM, limiting CS delivery unless indicated, and antenatal steroids when preterm labour is predicted) and neonatal risk factors (proper and early treatment of the primary infections, especially gram negative infections, minimizing invasive procedures such as umbilical catheters and urinary catheters, and avoiding prolonged mechanical ventilation) is recommended to reduce the risk of neonatal sepsis and prematurity (*18*).

In this study, it was found that platelet transfusion is significantly associated with mortality and pulmonary hemorrhage. It can be explained that the need for a platelet transfusion indicates the severity of the underlying disease, and it might reflect the effect of the preservatives present

in the platelet transfusion (*19*). Specific guidelines should be administered in accordance with platelet transfusion. To avoid the risks of unindicated transfusion, keep track of not only the platelet count but also the neonate's general condition, gestational age, the presence of bleeding, and the severity of the bleeding (*20*, *21*).

Conclusions

Neonatal thrombocytopenia is a common finding in neonatal sepsis, and the frequency of severe is more in Gram negative sepsis. Prematurity is a risk factor of neonatal sepsis with thrombocytopenia. Pulmonary hemorrhage a common type of bleeding in thrombocytopenic neonates with sepsis. Both thrombocytopenia and gram-negative sepsis are associated with a higher risk of mortality. Therefore, it is an important consideration in the management of neonates with sepsis.

Author Contributions:
All authors shared in conceptualization, supervising, data curation, data analysis, writing original draft, data interpretation, writing original draft, supervising and revising. All authors reviewed the final manuscript. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the study.

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