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Original Article

Platelet indices as predictors of late-onset sepsis and mortality in thrombocytopenic neonates: A retrospective cohort study

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ABSTRACT

Objective: Late-onset neonatal sepsis (LOS) is frequently complicated with thrombocytopenia. The aim of this study was determine the prevalence of LOS, and whether platelet indices affect LOS and mortality in neonates with thrombocytopenia in the neonatal intensive care unit (NICU) population.

Materials and Methods: This retrospective observational cohort study included neonates admitted to a level 4 NICU between 2018 and 2022 who developed thrombocytopenia (platelet count <150×10^9/L). Platelet indices were recorded during thrombocytopenic episodes preceding or coinciding with late-onset sepsis (LOS). Multivariable logistic regression and Cox proportional hazards models were used.

Results: A total of 223 (13.3%) thrombocytopenic neonates were included in the study. According to multivariable logistic regression analysis, multiparity (OR: 3.32 95% CI 1.40-7.89, p=0.006), caesarean section (OR: 5.81, 95% CI 1.99-16.89, p<0.001), invasive ventilation (OR: 8.43 95% CI 3.60-19.75, p<0.001, high MPV levels (OR: 1.62 95% CI 1.24-2.12, p<0.001) and duration of thrombocytopenia (OR: 1.13 95% CI 1.06-1.20, p=0.001), duration of hospitalization (OR: 1.03 95% CI 1.01-1.05, p=0.004) were independently associated with the development of LOS. Multivariable Cox hazard modelling demonstrated that invasive ventilation (HR: 9.459, 95% CI 3.38-26.45, p<0.001), platelet transfusion (HR: 2.833 95% CI 1.54-5.20, p=0.001), lymphopenia (HR: 0.766, 95% CI 0.64-0.92, p=0.003), grade 2≥ of NEC (HR: 7.274, 95% CI 1.68-31.52, p=0.008), any type of haemorrhage (HR: 2.728, 95% CI 1.69-9.10, p=0.001), platelet nadir (HR: 0.972, 95% CI 0.96-0.98, p<0.001), MPV (HR: 0.805, 95% CI 0.66-0.98, p=0.032), and lymphopenia (HR: 0.745, 95% CI 0.63-0.89, p=0.001) independently predicted overall mortality.

Conclusion: Key findings indicate that larger platelet sizes, prolonged thrombocytopenia, and extended hospitalization are linked to late neonatal sepsis. Furthermore, lower platelet levels characterized by smaller platelet sizes and the necessity for platelet transfusions may also contribute to these adverse outcomes.

Keywords: Mean platelet volume, newborn, late neonatal sepsis, thrombocytopenia

Introduction

Platelets are central players in hemostasis and thrombosis. Thrombocytopenia is a common hematological issue in neonates, with varying incidence across different populations. Thrombocytopenia affects an estimated 22-35% of neonates in the NICU, particularly in younger and more vulnerable infants (1,2).

Platelets play a vital role in innate immunity by directly binding to pathogens, aiding in their neutralization and destruction. They are crucial for containing infections, eliminating pathogens, and facilitating immune responses (3-4). Current clinical research on platelet function now emphasizes its role beyond hemostasis.

Neonatal sepsis is categorized as early or late onset, with late-onset sepsis (LOS) occurring after 72 hours postnatally. It is often associated with nosocomial or community settings and significantly impacts morbidity and mortality in the NICU (5). Early identification, thorough evaluation, and prompt treatment are crucial to prevent serious complications. Late neonatal sepsis is often associated with thrombocytopenia (6). Research has mostly focused on the link between platelet indices and transfusion practices concerning intraventricular hemorrhage (IVH) and mortality. Growing interest in platelets

as mediators of inflammation enhances our understanding of neonatal and pediatric sepsis (7-9). To understand the role of platelets in infections in newborns, we need to study conditions with low platelet counts. Our focus should be on two main areas: how platelets affect the prevalence of infections and how they influence clinical outcomes once an infection is established.

Despite increasing interest in platelet indices as biomarkers in neonatal sepsis, evidence specifically addressing thrombocytopenic neonates remains limited. In this population, platelet dynamics may differ significantly due to both consumption and production abnormalities. Furthermore, the temporal relationship between thrombocytopenia and LOS remains unclear, making causal interpretation challenging. The study aimed to assess the prevalence of LOS among thrombocytopenic neonates and evaluate the impact of platelet indices on LOS and mortality in this NICU population. We hypothesized that platelet indices measured during thrombocytopenic episodes are independently associated with the development of LOS and mortality in NICU patients.

Materials and Methods

This study was performed between January 2018 and December 2022 at Gülhane Training and Research Hospital. A total of 372 neonates who developed at least one episode of thrombocytopenia (platelet count <150×10^9/L) were identified. Neonates with only a single transient thrombocytopenic episode without adequate follow-up (n=129), lack of informed consent (n=11), missing hematological data (n=6), and those transferred within 24 hours (n=3) were excluded. The final cohort consisted of 223 neonates. Due to the retrospective design, a formal sample size calculation was not performed; however, all eligible neonates within the study period were included to maximize statistical power (Figure 1).

The main objective was to assess the prevalence of LOS in thrombocytopenic neonates. Secondary outcomes included

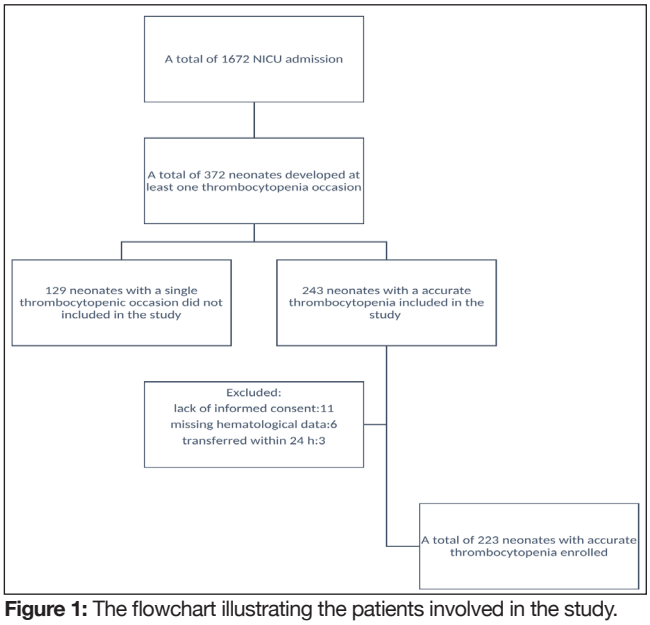

Figure 1: The flowchart illustrating the patients involved in the study.

the relationship between platelet count, plateletcrit, mean platelet volume (MPV), LOS, and mortality. Sepsis was identified by positive blood cultures in infants with clinical signs, with LOS occurring after 48 hours of life, typically acquired from the environment (10-11). To reduce confounding factors, the study focused solely on hematologic parameters associated with the thrombocytopenic episode linked to LOS, excluding earlier sepsis instances that might have affected platelet levels.

Data were extracted from the hospital's patient database, which includes medical histories, diagnoses, treatment plans, and lab results.

The recorded maternal data included pregnancy-induced hypertension, preeclampsia, eclampsia, diabetes, intrauterine growth failure, premature rupture of membranes, placental abruption, TORCHes infection, chorioamnionitis, opioid abuse, and mode of delivery. The neonatal data included gestational age, birth weight, small for gestational age (SGA), day of NICU admission, asphyxia, early and late-onset sepsis, duration of thrombocytopenia, hemorrhage occurrences, platelet transfusions, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), neonatal alloimmune thrombocytopenia (NAIT), hemolytic disease of the newborn (HDN), length of hospital stay, and in-hospital mortality.

Thrombocytopenia is categorized into four groups based on platelet levels: mild (101-149x10^9/L), moderate (51-100x10^9/L), severe (21-50x10^9/L), and very severe (≤20x10^9/L). The onset is noted on the day of initial presentation, while duration refers to the time from diagnosis until platelet counts exceed 150x10^9/L, confirmed by two measurements 24 hours apart. Hematologic parameters for each neonate include initial platelet count, nadir count, mean platelet volume (MPV), and plateletcrit. For cases associated with late-onset sepsis (LOS), these parameters were closely monitored. This study focused on a specific instance of thrombocytopenia, analyzing selected platelet parameters related to the lowest recorded count.

Platelet transfusions followed department protocols. The observed bleeding disorders included intraventricular hemorrhage (IVH), pulmonary hemorrhage, gastrointestinal bleeding, hematuria, and cutaneous bleeding such as petechiae, ecchymoses, and hematomas. IVH was classified per Papile et al. (12), and necrotizing enterocolitis was determined to be stage 2A or greater per modified Bell criteria. Patent ductus arteriosus (PDA) was identified as an open ductus requiring intervention.

Statistical analysis:

Descriptive statistics were reported as mean and standard deviation for normally distributed variables, median with interquartile range (IQR) for non-normally distributed variables, and as counts and percentages for nominal and ordinal data. Bivariate associations between the primary outcome and independent variables were analyzed using Student's t-test, Mann-Whitney U test, Pearson's chi-square test, or Fisher's exact tests. Multivariable logistic regression controlled for associations among independent variables based on theoretical rationale, timing of occurrences, and minimizing reverse causation. The analysis included the most clinically significant correlated risk factor to avoid multicollinearity. Final models featured main effects significant at p<0.050 and

interactions significant at p<0.200, employing the backward method. Adjusted odds ratios (OR) and 95% confidence intervals were calculated. Univariable and multivariable Cox regression identified independent predictors of exitus development, with adjusted hazard ratios (HR) calculated as well. Gestational age and birth weight were evaluated as potential confounders. These variables were initially included in multivariable models; however, due to collinearity with clinical severity indicators, the most clinically relevant variables were retained in the final models. Overall survival was measured from hospital admission to death and analyzed via the Kaplan-Meier method and Log-rank test. A p-value <0.050 indicated statistical significance, with analyses conducted using IBM Statistical Package for the Social Sciences, version 21.0 (SPSS Inc., Armonk, NY, IBM Corp., USA).

Results

Among the enrolled neonates, there were 263 instances of thrombocytopenia, with 26 cases (11.7%) being recurrent. The distribution of platelet counts showed: 44 neonates

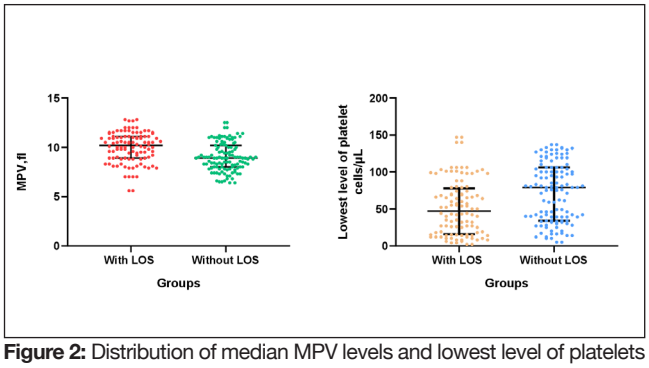

Figure 2: Distribution of median MPV levels and lowest level of platelets between subgroups.

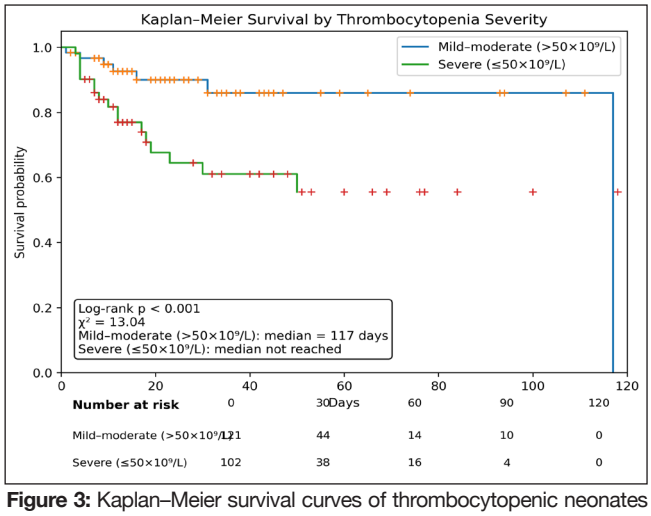

Figure 3: Kaplan–Meier survival curves of thrombocytopenic neonates stratified by severity of thrombocytopenia. Survival probability was significantly lower in neonates with severe thrombocytopenia (platelet count ≤50×10^9/L) compared to those with higher platelet counts (>50×10^9/L). Survival distributions were compared using the log-rank test. Hazard ratios were estimated using Cox proportional hazards models adjusted for clinically relevant covariates. Kaplan–Meier survival analysis demonstrated significantly lower survival in neonates with severe thrombocytopenia (log-rank p<0.001).

Table I: Neonatal thrombocytopenia related maternal and infantile conditions in the study

Identifiable cause	No (%)
Late onset neonatal sepsis	99 (44.4)
Intrauterine growth failure	36 (16.1)
Maternal preeclampsia	24 (10.8)
Early onset neonatal sepsis	20 (8.9)
Hypoxic ischemic encepahalopathy	14 (6.3)
Placental abruption	10 (4.5)
TORCHes infection	6 (2.7)
Maternal pregnancy-induced hypertension	4 (1.8)
Thrombosis	4 (1.8)
Neonatal alloimmune thrombocytopenia	3 (1.3)
Hemolytic disease of the newborn	2 (0.9)

(19.7%) with very severe thrombocytopenia, 58 (26%) with severe, 75 (33.6%) with moderate, and 46 (20.6%) with mild. Overall, 70 neonates (31.4%) received at least one platelet transfusion, 44 (19.7%) had hemorrhages, and 48 (21.5%) experienced neonatal mortality. Maternal and neonatal factors linked to thrombocytopenia are detailed in Table I.

Late-onset sepsis was identified in 99 of 223 neonates with thrombocytopenia, a 44.4% incidence. Among these, gram-positive pathogens dominated with 70 cases (70.7%), while gram-negative pathogens accounted for 34 cases (34.3%). The most common organism was coagulase-negative *Staphylococcus* in 57 cultures, followed by *Klebsiella pneumoniae* in 28, *Staphylococcus aureus* in 7, vancomycin-resistant *Enterococcus* in 6, and *Enterobacter* in 4. No fungal growth was seen. Infants who developed LOS exhibited significantly lower gestational ages and birth weights than those without LOS (p<0.001). Infants diagnosed with thrombocytopenia who subsequently developed LOS exhibited a higher incidence of multiparity, twin gestations, and cesarean section deliveries. Detailed baseline characteristics of the cohort are outlined in Table II.

The clinical and hematologic parameters distinguishing infants with LOS from those without are detailed in Table III. The median day of presentation for thrombocytopenia was 9 (IQR 11) in the LOS group, compared to 1 (IQR 1) in the non-LOS group (p<0.001). Initial platelet count before decline was 100x10^9/L (IQR 56) in LOS versus 116 x10^9/L (IQR 57) in non-LOS (p=0.352). Platelet counts were significantly lower in LOS: median 44x10^9/µL (IQR 59) vs. 77.5x10^9/L (IQR 72) (p<0.001). Median plateletcrit was 74.75 (IQR 79.90) in LOS and 120 in non-LOS (p=0.006). No link between gestational age or birth weight and lowest platelet levels (p=0.149 and p=0.738). Platelet sizes were larger in LOS, with MPV of 10.4 fl vs. 8.9 fl in non-LOS (p<0.001). Figure 2 illustrates the distribution of median MPV levels alongside the minimum platelet counts across the different study groups. The duration of thrombocytopenia was significantly longer in the LOS group, with a median of 9 days (IQR 10) versus 6 days (IQR 6) in the non-LOS group (p<0.001). A higher proportion of neonates with LOS received platelet transfusions, at 48.5% (48 out of 99), versus 17.7% (22 out of 124) for those without LOS (p<0.001). Among transfusion recipients, the median number of transfusions was similar: 1.5 (IQR 3) for the LOS group and 2 (IQR 2) for the non-LOS group (p=0.914), as shown in Table III. In neonates with late-onset sepsis, the median platelet

Table II: Demographic variables of thrombocytopenic neonates, divided into subgroups by late onset septicemia (LOS)

	Overall	With	Without	p
Total number of patients	223	99	124	-
Maternal age, y	29 (25-34)* 29.34±6.10†	29 (25-34)* 29.62±5.96†	29 (25-34.5)* 29.09±6.24†	0.530 0.523
Primiparous‡	87 (39)	25 (25.3)	62 (50)	0.001
IVF‡	6 (2.6)	2 (2.02)	4 (3.25)	0.428
Infant gender‡ female male	 84 (37.7) 139 (62.3)	 38 (38.4) 61 (61.6)	 46 (37.1) 78 (62.9)	0.844
Vaginal delivery‡	67 (30)	16 (16.2)	51 (41.1)	<0.001
Birth place‡ outborn inborn	 98 (43.9) 125 (56.1)	 45 (45.5) 55 (55.5)	 53 (42.7) 70 (56.5)	0.775
Gestational age, w*	34 (7)	32 (7)	35 (6)	<0.001
Birth weight, g*	2010 (1590)	1460 (1508)	2200 (1135)	<0.001
Twin pregnancy	28 (12.6)	20 (20.2)	8 (6.5)	0.002
Proportion‡ SGA AGA LGA	 54 (24.2) 155 (69.5) 14 (6.3)	 15 (15.2) 74 (74.7) 10 (10.1)	 39 (31.5) 81 (65.5) 4 (3.2)	0.004
PROM‡	8 (3.6)	4 (4)	4 (3.2)	0.745
Chorioamnionitis‡	6 (2.7)	2 (2)	4 (3.2)	0.566
Maternal UTI‡	4 (1.8)	2 (2)	2 (1.6)	0.820
Preeclampsia‡	24 (10.8)	11 (11.1)	13 (10.5)	0.881
IUGR‡	36 (16.1)	10 (10.11)	26 (21)	0.028
Gestational diabetes‡	6 (2.7)	0 (0)	6 (4.8)	0.035
Congenital disorder	35 (15.7)	14 (14.1)	21 (16.9)	0.569
HIE‡	14 (6.3)	2 (2)	12 (9.7)	0.019
Invasive ventilation‡	100 (44.8)	67 (67.7)	33 (26.6)	<0.001
Surfactant administration‡	66 (29.6)	43 (43.4)	23 (18.5)	<0.001
PDA‡	18 (8.1)	14 (14.1)	4 (3.2)	0.005
NEC‡	22 (9.9)	20 (21)	2 (0.8)	<0.001
Severe thrombocytopenia‡	102 (45.7)	51 (51.5)	51 (41.1)	0.003
Length of hospital stay, days˙	18 (32)	35.5 (49)	12 (15)	<0.001
Mortality‡	48 (21.5)	27 (27.3)	21 (16.9)	0.062

:** *median (IQR) (Mann-Whitney U Test),* **†:** *mean±SD (Independent Samples t Test),* **‡:** *n (%)(Pearson Chi-Square Test) (Fisher's Exact Test).* ***SGA: *Small for gestational age (birthweight <10th percentile for gestational age),* ***AGA:*** *Appropriate for gestational age (birth weight between 10–89th percentile for gestational age),* ***LGA:*** *Large for gestational age (birthweight >90 th percentile for gestational age),* ***PROM:*** *Premature rupture of membranes,* ***UTI:*** *Urinary Tract Infection,* ***IUGR:*** *Intrauterine Growth Retardation,* ***HIE:*** *Hypoxic Ischemic Encephalopaty (Grade ≥2),* ***PDA :*** *Patent ductus arteriosus,* ***NEC:*** *Necrotising Enterocolitis (Grade ≥2)*

transfusions were 1 (IQR 1-2.25) for the gram-positive subgroup and 1.5 (IQR 1-5.5) for the gram-negative subgroup (p=0.424). A higher percentage of neonates with gram-negative sepsis received platelet transfusions (70.6%, 24 out of 34) compared to those with gram-positive sepsis (37.1% - 26 of 70) (p=0.001).

In the multivariable logistic regression analysis, factors including multiparity (OR: 3.32, 95% CI 1.40-7.89, p=0.006), cesarean delivery (OR: 5.81, 95% CI 1.99-16.89, p<0.001), invasive mechanical ventilation (OR: 8.43, 95% CI 3.60-19.75, p<0.001), elevated MPV levels (OR: 1.62, 95% CI 1.24-2.12, p<0.001), prolonged thrombocytopenia (OR: 1.13, 95% CI 1.06-1.20, p=0.001), and extended hospital stay (OR: 1.03, 95% CI 1.01-1.05, p=0.004) were found to be independently linked to the occurrence of LOS in neonates with thrombocytopenia during their NICU stay. Table IV illustrates the various risk factors that are associated with LOS, providing a comprehensive overview of the elements that may influence this metric.

The overall mortality rate in our group was 21.5% (48 out of 223) and was greater among neonates with platelet counts of ≤ 50x10^9/L (33.3%, 34 out of 102) when compared to those with platelet counts > 50 x 10^9/L (11.6%, 14 out of 121) (p<0.001). The mortality rates were comparable in neonates with late-onset sepsis (27.3%, 27 out of 99) when compared to those without late-onset sepsis (16.9%, 21 out of 124) (p=0.062). In the Cox proportional multivariable analysis, model b showed that invasive ventilation (HR: 9.459, 95% CI 3.38-26.45, p<0.001), platelet transfusion (HR: 2.833, 95% CI 1.54-5.20, p=0.001), and lymphopenia (HR: 0.766, 95% CI 0.64-0.92, p=0.003) were significantly associated with mortality. In model c, invasive ventilation (HR: 12.593, 95% CI 4.48-35.41, p<0.001), grade 2 or higher of NEC (HR: 7.274, 95% CI 1.68-31.52, p=0.008), any hemorrhage (HR: 2.728, 95% CI 1.69-9.10, p=0.001), platelet nadir (HR: 0.972, 95% CI 0.96-0.98, p<0.001), MPV (HR: 0.805, 95% CI 0.66-0.98, p=0.032), and lymphopenia (HR: 0.745, 95% CI 0.63-0.89, p=0.001) were independently linked to increased mortality in neonates experiencing thrombocytopenic events during their NICU stay (Table V). The Kaplan-Meier analysis of survival outcomes for patients with thrombocytopenia is presented in Figure 3. The findings indicate that survival rates are significantly lower in cases of severe thrombocytopenia.

Discussion

This retrospective observational cohort study aimed to assess the prevalence of LOS in thrombocytopenic neonates at a single center. Our findings revealed that approximately half of the thrombocytopenia cases within our cohort were linked to LOS. Over a five-year period, the overall prevalence of thrombocytopenia among neonates admitted to the NICU was recorded at 13.3%. Notably, the proportions of neonates with severe and very severe thrombocytopenia were higher than those reported in prior studies (13,14). Von Lindern et al. (15) indicated that the rate of mild to moderate thrombocytopenia was 68%, while Resch et al. (16) reported a slightly higher rate of 71%. Our study observed that the proportion of mild and moderate cases was 54.2%, highlighting some variability in findings across different studies.

Gestational age is a well-established determinant of thrombocytopenia, sepsis, and mortality. Previous studies, including those by Christensen et al.(17), have shown that both the incidence and severity of thrombocytopenia are strongly influenced by prematurity. In our study, although gestational age differed between LOS and non-LOS groups, it did not remain an independent predictor after adjustment, possibly due to its interaction with clinical severity factors. The main factors increasing the risk of LOS in neonates are decreased gestational age and low birth weight, with our study showing

Table III: Clinical characteristics and complete blood count parameters (CBC) of thrombocytopenic neonates, divided into subgroups by late onset septicemia (LOS)

	Overall	With	Without	p
Total number of patients	223	99	124	-
Presentation day of thrombocytopenia, d*	2 (8)	9 (11)	1(1)	<0.001
Initial platelet count just before declining, cells/μL*	103 (61)	100 (56)	116 (57)	0.186
Lowest level of platelet, cells/μL*	59 (71)	44 (59)	77.5 (72)	<0.001
Duration of thrombocytopenia, d*	6 (9)	9 (10)	6 (6)	<0.001
PDW,%*	15.35 (4.03)	15.3 (2.88)	17.5 (4.90)	0.512
MPV, fl*	9.4 (2.60)	10.4 (2.10)	8.9 (2.25)	<0.001
Plateletcrit*	79.62 (84.75)	74.75 (79.90)	120 (101.66)	0.006
WBC cells/mm^{3*}	8.30 (6.60)	8.30 (8.1)	8.25 (5)	0.537
Neutrophil cells/mm^{3*}	3.60 (4.73)	3.70 (6.50)	3.50 (3.65)	0.689
Neutrophil/Lymphocyte*	1.24 (1.80)	1.50 (2.08)	1.10 (1.60)	0.257
Lymphocyte cells/mm^{3*}	3.00 (2.10)	2.60 (2.70)	3.1 (2)	0.112
Platelet transfusion†	70 (31.4)	48 (48.5)	22 (17.7)	<0.001
Platelet transfusion counts, n*	2 (2)	1.5 (3)	2 (2)	0.914
Any type of hemorrhage†	44 (11.7)	22 (22.2)	22 (17.7)	0.404
Pulmonary hemorrhage†	10 (4.5%)	8 (8.1)	4 (3.2)	0.110
Gastrointestinal hemorrhage†	12 (5.4)	6 (6)	6 (4.9)	0.712
Skin hemorrhage†	2 (0.9)	2 (2)	0 (0)	0.196
IVH†	22 (10.7)	10 (11.9)	12 (9.9)	0.651
Severe IVH†	2 (1)	0(0)	2 (1.7)	0.514

:** *median (IQR) (Mann-Whitney U Test),* **†:** *n(%) (Pearson Chi-Square/ Fisher's Exact Test).* ***MPV: *Mean platelet volume,* ***WBC:*** *White blood cell,* ***IVH:*** *Intraventricular hemorrhage*

Table IV: Risk factors for late onset septicemia: Univariable and multivariable Logistic Regression results

	Univariable*			Multivariable (Adjusted Model)†		
	OR	95% CI	p	OR	95% CI	p
Multiparity	3.05	1.72-5.41	<0.001	3.32	1.40-7.89	0.006
Twin-pregnancy	3.59	1.51-8.56	0.004	-	-	-
Cesarean delivery	3.34	1.78-6.30	<0.001	5.81	1.99-16.89	0.001
Gestational age	0.85	0.79-0.91	<0.001	-	-	-
Strata <34 GA	5.147	2.90-9.11	<0.001	-	-	-
Birth weight	1.00	0.99-1.00	0.002	-	-	-
Invasive ventilation	6.04	3.38-10.82	<0.001	8.43	3.60-19.75	<0.001
Surfactant administration	3.61	1.97-6.62	<0.001	-	-	-
Platelet transfusion	4.583	2.47-8.48	<0.001	-	-	-
Lowest level of platelet	0.985	0.98-0.99	<0.001	-	-	-
MPV	1.69	1.38-2.06	<0.001	1.62	1.24-2.12	<0.001
Plateletcrit	0.989	0.982-0.997	0.004	-	-	-
Platelet transfusion counts	1.52	1.19-1.95	0.001	-	-	-
Duration of thrombocytopenia	1.18	1.1-1.26	<0.001	1.13	1.06-1.20	0.001
Length of hospital stay	1.05	1.03-1.06	<0.001	1.03	1.01-1.05	0.004

GA: *Gestational age,* ***PDA:*** *Patent ductus arteriosus requiring treatment,* ***MPV:*** *Mean platelet volume.* ****:*** *Variables were separately included in the model if they if they were considered potential factors in preliminary analyses.* ***†:*** *In adjusted model, platelet nadir and MPV were simultaneously included as variables. Additionally, parity, twin pregnancy, mode of delivery, gestational age, invasive ventilation, surfactant administration, platelet transfusion and counts, duration of thrombocytopenia, length of hospital stay were included, which a backward elimination method was utilized for logistic regression*

that 70% of cases were born before 37 weeks (18). However, we found no significant link between prematurity or low birth weight and the lowest observed platelet levels, consistent with a recent study by Ree et al.(19) We noted significant differences in factors like twin births, cesarean deliveries, invasive ventilation needs, surfactant administration, and PDA of grade 2 or higher among infants with and without LOS. The rise in cesarean deliveries may be connected to a higher prevalence of twin births and maternal preeclampsia, which can increase the likelihood of surgery. Higher rates of invasive procedures and conditions like NEC were observed in infants with LOS and thrombocytopenia, likely due to younger gestational ages, making them not significant risk factors in our logistic regression analysis. Our research also indicates that elevated MPV levels are independently linked to a higher incidence of LOS in thrombocytopenic neonates, with each increase in MPV correlating to a 62% increased risk of this condition. In sepsis, the clotting cascade is disrupted, leading to the release of pro-inflammatory and anti-inflammatory cytokines. This results in thrombi formation, depletion of fibrinolytic

Table V: Univariable and multivariable Cox proportional hazards regression analyses of factors associated with mortality

	Univariable*			Multivariable (Adjusted Model)†			Multivariable (Adjusted Model)‡		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Gestational age	0.935	0.87-1.00	0.062	-	-	-	-	-	-
Congenital disorder	1.845	0.96-3.56	0.068	-	-	-	-	-	-
Invasive ventilation	10.562	3.77-29.57	<0.001	9.459	3.38-26.45	<0.001	12.593	4.48-35.41	<0.001
Surfactant administration	2.606	1.45-4.70	0.001	-	-	-	-	-	-
PDA requiring treatment	3.569	1.98-6.45	<0.001	-	-	-	-	-	-
NEC	3.840	1.06-6.98	0.038	-	-	-	7.274	1.68-31.52	0.008
Any type of hemorrhage	2.192	1.12-4.28	0.022	-	-	-	2.728	1.69-9.10	0.001
Pulmonary hemorrhage	2.318	0.93-5.81	0.073	-	-	-	-	-	-
Platelet transfusion	2.892	1.60-5.24	<0.001	2.833	1.54-5.20	0.001	-	-	-
Platelet nadir	0.983	0.97-0.99	<0.001	-	-	-	0.972	0.96-0.98	<0.001
Plateletcrit	0.983	0.97-0.99	<0.001	-	-	-	-	-	-
MPV	0.983	0.82-1.18	0.853	-	-	-	0.805	0.66-0.98	0.032
Hemoglobin	0.898	0.83-0.97	0.009	-	-	-	-	-	-
Hematocrit	0.972	0.95-1.00	0.033	-	-	-	-	-	-
Lymphocyte	0.812	0.68-0.96	0.018	0.766	0.64-0.92	0.003	0.745	0.63-0.89	0.001

HR: *Hazard Ratio,* ***PDA:*** *Patent ductus arteriosus requiring treatment,* ***NEC:*** *Necrotising Enterocolitis (Grade ≥2),* ***MPV:*** *Mean platelet volume,* ****:*** *Variables were separately included in the model if they if they were considered potential factors in preliminary analyses.* ***†:*** *In adjusted model, MPV was simultaneously included as variable. Additionally, gestational age in weeks, congenital disorder, invasive ventilation, surfactant administration, any type of haemorrhage, pulmonary haemorrhage, platelet transfusion, platelet transfusion counts, Hb and lymphocyte levels were included, which a backward elimination method was utilized for cox regression.* ***‡:*** *In adjusted model, platelet nadir and MPV were simultaneously included as variables. Additionally, gestational age in weeks, congenital disorder, invasive ventilation, surfactant administration, PDA requiring treatment, Grade ≥2 of NEC, any type of haemorrhage, pulmonary haemorrhage, platelet transfusion, platelet transfusion counts, Hb and lymphocyte levels were included, which a backward elimination method was utilized for cox regression.*

substances, and potential disseminated intravascular coagulation (DIC). Sepsis can also cause thrombocytopenia due to non-immune peripheral destruction, histiocytosis, and bone marrow suppression, stimulating the production of larger, more active young platelets that enhance overall platelet function (9,20-22). Research indicates that MPV may be a predictive marker for neonatal sepsis. A recent meta-analysis by Wang et al. (23) found elevated MPV levels in neonatal sepsis cases, suggesting it could aid in the timely diagnosis of late-onset sepsis. Since the nonspecific symptoms of sepsis complicate prompt diagnosis, it's vital to avoid unnecessary antibiotic treatment for non-septic infants and to start antibiotics quickly when needed. Thus, accessible and affordable laboratory tests like MPV are essential. Omran et al. (24) found serum MPV had 100% sensitivity and 94.4% specificity (cutoff ≥ 9.2 fL) for LOS in full-term neonates. Milas et al. (25) indicated MPV shows good diagnostic accuracy for sepsis, which our study supports for thrombocytopenic infants with LOS. Our findings suggest that longer thrombocytopenia duration and extended hospital stays are independently associated with length of stay, consistent with previous research (11,18-19).

The overall mortality rate was 21.5%, with the LOS group at 27.3%, higher than previous studies (14-15). In thrombocytopenic neonates, mortality correlated significantly with invasive ventilation, NEC, platelet nadir severity, and any hemorrhage. Platelet transfusion was associated with increased mortality, consistent with previous research although the number of transfusions did not show a similar link (26,27). We assessed platelet nadir and mean platelet volume (MPV) as covariates, independent mortality risk factors. Each decrease in platelet count increased mortality by 2.8%, while decreased MPV raised it by nearly 20%. Without considering platelet nadir, transfusion raised mortality risk by 2.8 times.

The study primarily focused on objectives other than bleeding outcomes in thrombocytopenic infants. It found that infants with LOS showed no preference for specific types of hemorrhage, but any bleeding event was identified as an independent risk factor for death. Major bleeding occurs in 5% to 15% of neonates with severe thrombocytopenia, with intraventricular hemorrhage (IVH) being the most severe type (27). This prevalence of severe IVH is lower than reported by Ree et al.(19) Severe bleeding often happens early in a newborn's life during the peak of neonatal thrombocytopenia, but this correlation does not imply a direct cause-and-effect relationship, as factors like cardiovascular stability and capillary fragility also contribute. Other clinically important bleeding, such as pulmonary hemorrhage, complicates the care of critically ill neonates (28). A study by Stanworth et al. (20) found that 9% of 169 patients with severe thrombocytopenia experienced significant hemorrhagic events, excluding IVH, such as pulmonary hemorrhage, gastrointestinal bleeding, and hematuria. Our analysis indicated a higher incidence of gastrointestinal and pulmonary hemorrhages in neonates compared to this study.

The most important finding of this study is the divergent association of MPV with outcomes. While elevated MPV was independently associated with LOS, lower MPV was associated with increased mortality. This may reflect different stages of disease progression. Increased MPV likely represents heightened platelet activation during early inflammatory responses, whereas decreased MPV in critically ill patients may indicate bone marrow suppression and exhaustion in advanced disease.

Limitations

This study has limitations due to retrospective observational cohort data collection, which restricts detailed information on nutrition and antibiotic exposure. Additionally, residual confounding by prematurity and illness severity cannot be completely excluded. Although retrospective, the cohort design of this study allows temporal assessment of outcomes such as LOS and mortality, strengthening causal inference compared to purely cross-sectional analyses. Furthermore, prior research has already demonstrated correlations among gestational age, line utilization, and duration of hospitalization. Our findings highlight factors associated with late neonatal sepsis in thrombocytopenic NICU patients, such as multiparity, cesarean sections, and invasive ventilation. Mortality risk factors include invasive ventilation, NEC, hemorrhage, and lymphopenia. These insights underscore the importance of platelet indices for enhancing NICU care. This study has several strengths. First, it focuses on a specific high-risk population of thrombocytopenic neonates. Second, it integrates both logistic and survival analyses, providing comprehensive outcome assessment. Third, it evaluates widely available platelet indices, enhancing clinical applicability. We propose an intervention to help integrate these indices into clinical protocols, improving care quality for neonates.

Conclusion

Platelet indices, particularly MPV and thrombocytopenia duration, are independently associated with late-onset sepsis in thrombocytopenic neonates. Their relationship with mortality suggests a potential role in risk stratification; however, prospective studies are required to confirm these findings.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Gülhane Training and Research Hospital (01.04.2024, reference number: 2024-197).

Contribution of the authors

DY and BSK conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. **DY and MM** designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. All the tables and figures were prepared by **ED. DY, MM** and **BSK** coordinated and supervised data collection and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Conflict of interest

The authors declare that there is no conflict of interest.

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