

RESEARCH ARTICLE

Perinatal factors affecting platelet parameters in late preterm and term neonates

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Abstract

Platelets parameters including platelet count (PLT), plateletcrit (PCT), mean platelet volume (MPV) and platelet distribution width (PDW) are associated with various physiological and pathological functions in various disease. However, few studies have addressed whether perinatal factors may be associated with platelet parameters at birth in a large cohort of late preterm and term neonates. The aim of this study to investigate perinatal factors affecting platelet parameters in late preterm and term neonates. We retrospectively investigated platelet parameters including PLT, PCT, MPV, and PDW on the first day of life in 142 late preterm and 258 term neonates admitted to our NICU from 2006 through 2020. PLT, MPV, PCT, PDW on Day 0 did not significantly differ between the two groups. In term neonates, multivariate analysis revealed that PCT correlated with being small for gestational age (SGA) ($\beta = -0.168$, $P = 0.006$), pregnancy induced hypertension (PIH) ($\beta = -0.135$, $P = 0.026$) and male sex ($\beta = -0.185$, $P = 0.002$). PLT was associated with SGA ($\beta = -0.186$, $P = 0.002$), PIH ($\beta = -0.137$, $P = 0.024$) and male sex ($\beta = -0.166$, $P = 0.006$). In late preterm neonates, multivariate analysis revealed that PLT were associated with PIH, whereas no factors associated with PDW and MPV were found. In all patients studied, chorioamnionitis (CAM) was significantly associated with MPV (CAM = 10.3 fL vs. no CAM = 9.7 fL, $P < 0.001$). Multivariate analysis showed that SGA, male sex and PIH were associated with PCT and PLT. This study demonstrates that different maternal and neonatal complications affect platelet parameters in late preterm and term neonates.

Introduction

Platelets parameters including platelet count (PLT), plateletcrit (PCT), mean platelet volume (MPV) and platelet distribution width (PDW) are associated with various physiological and pathological functions in various disease [1–3]. Platelet production is a complex process arising from the proliferation and differentiation of megakaryocytes under the stimulating

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influence of thrombopoietin. Platelet function in premature neonates is immature. Previous research indicated that low birth weight infants were at almost 2.5-fold increased risk for thrombocytopenia [4]. On the other hand, MPV, PDW, PCT are associated with neonatal disease such as sepsis, fungal infection and intraventricular hemorrhage [5–8]. Among extremely low birth weight neonates born to mothers with preeclampsia, the MPV/platelet count (PLT) ratio at birth significantly correlated with mortality [9]. Also, changes of PDW during the neonatal period were associated with thrombocytopenia and with neonatal sepsis in very low birth weight infants [10]. We previously reported that higher MPV correlates with mortality among those born at < 32weeks' gestation [11].

On the other hand, Alicja et al reported decreased PCT and PLT in late preterm neonates compared with term neonates [12]. However, few studies have addressed whether perinatal factors may be associated with platelet parameters (PCT, PLT, MPV and PDW) at birth in a large cohort of late preterm and term neonates. Recently, some studies have been associated maternal complication such as premature rupture of membranes (PROM), chorioamnionitis (CAM), and pregnancy induced hypertension (PIH) were associated with platelet parameters [13–15]. Therefore, we hypothesized that platelet parameters such as MPV, PCT and PDW could be affected by perinatal factors. The objective of this study was to investigate the factors affecting platelet parameters at birth in late preterm and term neonates.

Materials and methods

Study design and population

This retrospective, single center, cohort study examined records from 2006 through 2020 at the neonatal intensive care unit (NICU) of Fukushima Medical University Hospital. The study protocol was approved by our institutional review board, The Ethics Committee of Fukushima Medical University, Fukushima, Japan. After deliberation, the board decided that no written consent was needed. Of 1789 neonates admitted to our NICU between January 2006 and Mar 2020, there were 400 born at term or late preterm (weeks 35–36). Late preterm neonates and full term neonates numbered 142 and 258, respectively (Fig 1). Exclusion criteria were congenital anomalies, neonatal alloimmune thrombocytopenia, and neonates not tested within 12 hours of birth.

Platelet parameter measurements

Blood samples were collected through peripheral venipuncture to measure PLT, PCT, MPV and PDW of each newborn. Complete blood counts were measured using a Sysmex CS-5100 coagulation analyzer (Sysmex, Kobe, Japan) on admission.

Prenatal and postnatal risk factors

Platelet parameters were compared with demographic variables including gender, birth weight (BW), and gestational age (GA). Furthermore, we considered pregnancy-induced hypertension (PIH), chorioamnionitis (CAM, defined clinically, with histopathological confirmation in pre-term placentas) [16], premature rupture of membranes (PROM), and placental abruption (PA) as possible prenatal risk factors, and small for gestational age (SGA), respiratory distress syndrome (RDS), and Apgar scores as possibly associated with platelet parameters. Infants whose birth weight and height were below the 10th percentile of the normal curve at each GA were classified as SGA.

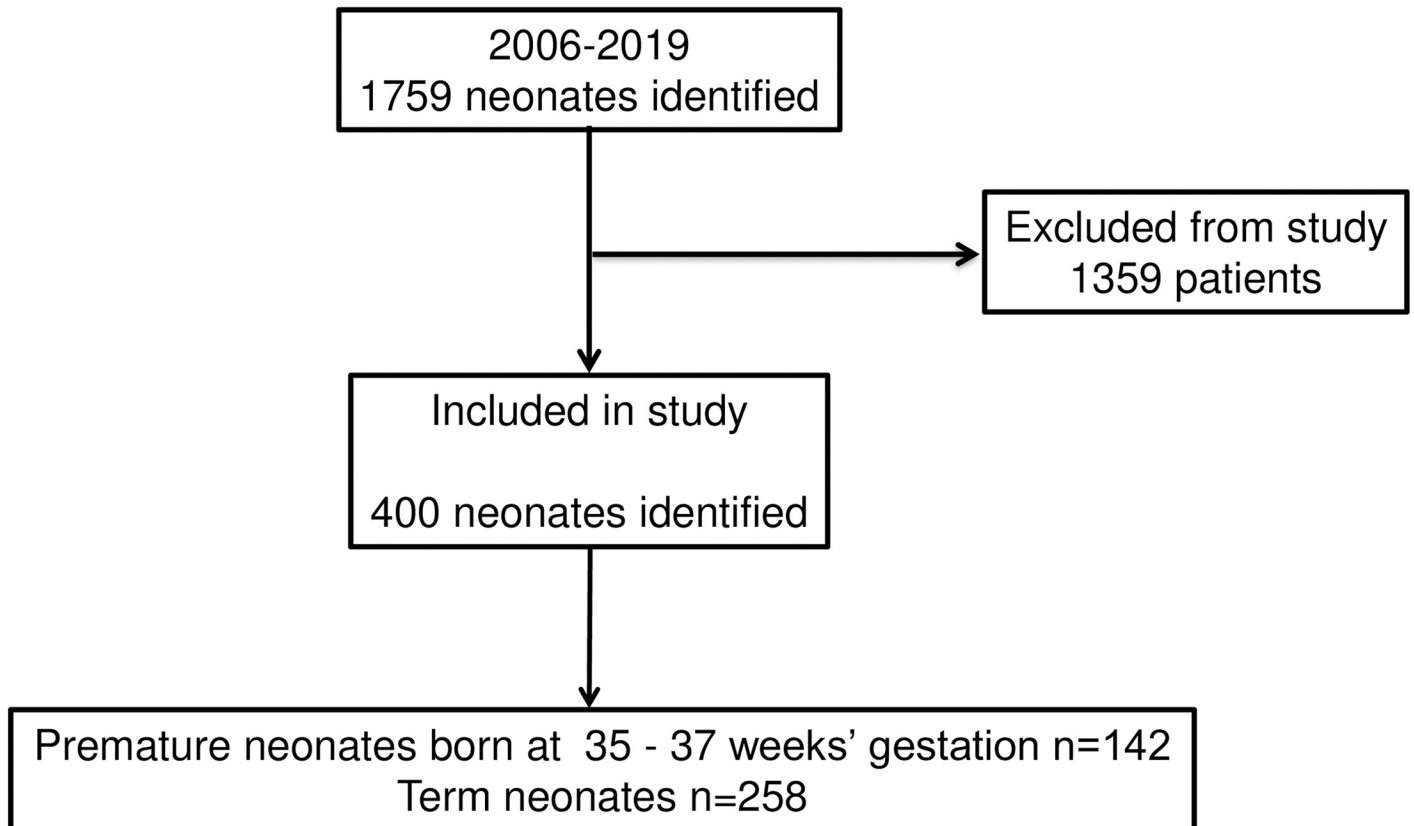


Fig 1. Flowchart showing enrollment of study subjects.

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Statistical analysis

Platelet parameters from medical records were rendered into median and interquartile range (IQR) as non-normally distributed continuous variables. Differences in categorical variables and continuous variables were assessed for significance using Chi-square and Mann–Whitney U test. Likewise, correlations between BW, GA, and Apgar scores versus platelet parameters were also investigated using Spearman's rank correlation (r) with $P < 0.05$ considered to be statistically significant. Moreover, the variables at $P < 0.05$ in univariate analysis were entered into a multiple regression analysis to identify independent prognostic factors.

Data analysis was performed with SPSS for Mac, release 25.0 (SPSS, Chicago, IL) and Prism 8 (GraphPad Software, San Diego, CA).

Results

Table 1 shows platelet parameters in late preterm and term neonates. There are no significant differences in platelet parameters between late preterm and term neonates. The median of sampling time was 82 min as shown in **Fig 2**. **Fig 3A and 3B** show no significant correlation between BW, GA and PLT. Likewise, **Fig 3C and 3D** show no significant correlation between BW, GA and PCT in late preterm and term neonates.

Tables 2 and 3 outline the results of univariate and multivariate analyses for the correlation between perinatal factors and platelet parameters in preterm and term neonates, respectively.

Table 1. Platelet parameters in late preterm and term neonates.

	Late preterm (n = 142) Median [IQR]	Term (n = 258) Median [IQR]	p-value
GA (weeks)	36.0 [35.4–36.4]	38.2 [37.5–39.3]	<0.001
BW (grams)	2180 [1802–2602]	2758 [2463–3106]	<0.001
SGA n (%)	57 (39.8%)	52 (20.2%)	<0.001
PCT (%)	0.25 [0.21–0.31]	0.26 [0.21–0.30]	0.661
PDW	10.9 [10.0–12.7]	10.9 [10.2–12.2]	0.810
MPV (fL)	9.9 [9.2–10.3]	9.7 [9.3–10.3]	0.792
PLT ($\times 10^3/\mu\text{L}$)	26.6 [22.2–32.3]	26.4 [21.5–31.4]	0.807

GA, gestational age; BW, birth weight; PCT, plateletcrit; PDW, platelet distribution width; MPV, mean platelet volume; PLT, platelet count; IQR, median interquartile range.

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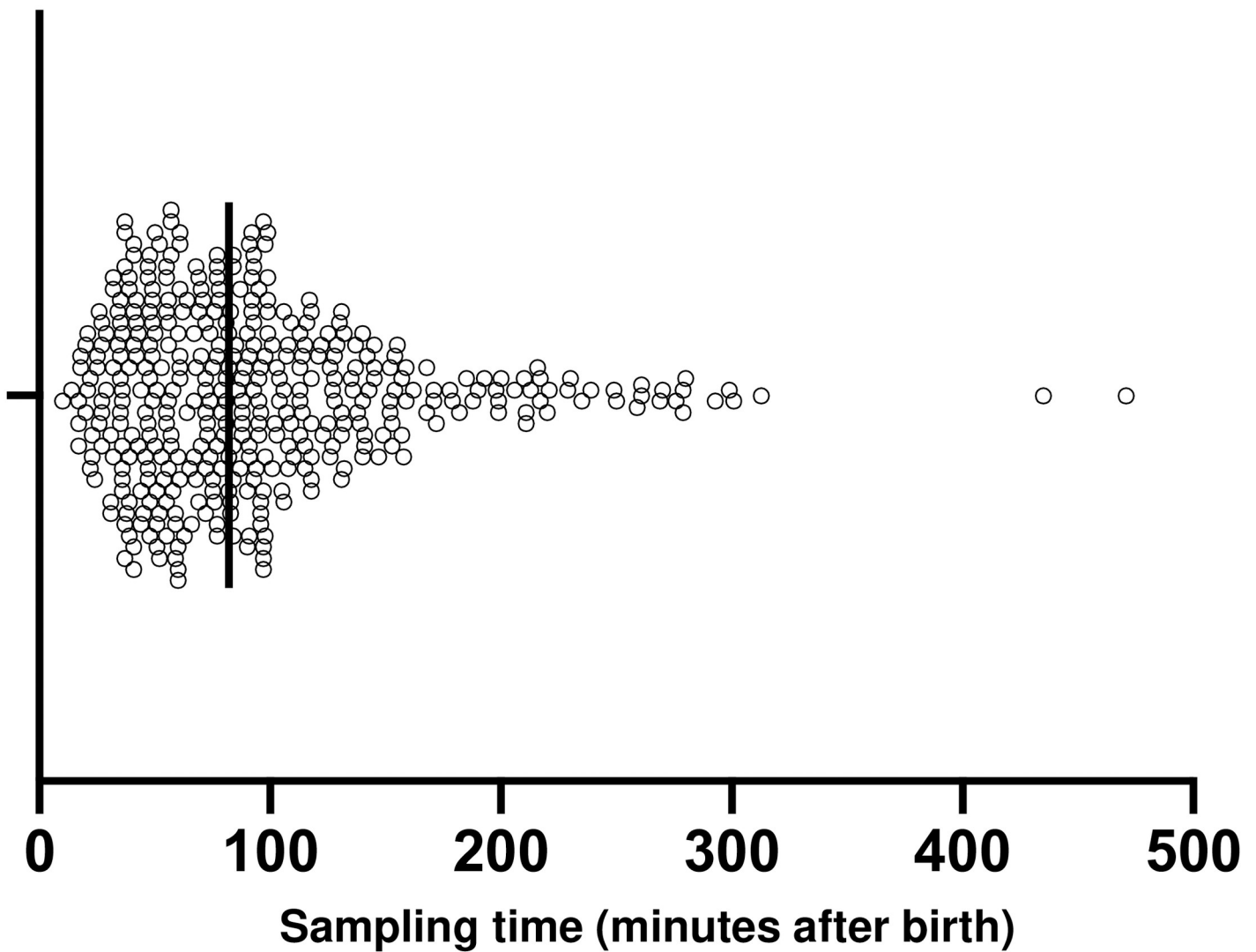


Fig 2. Peripheral blood sampling time distribution.

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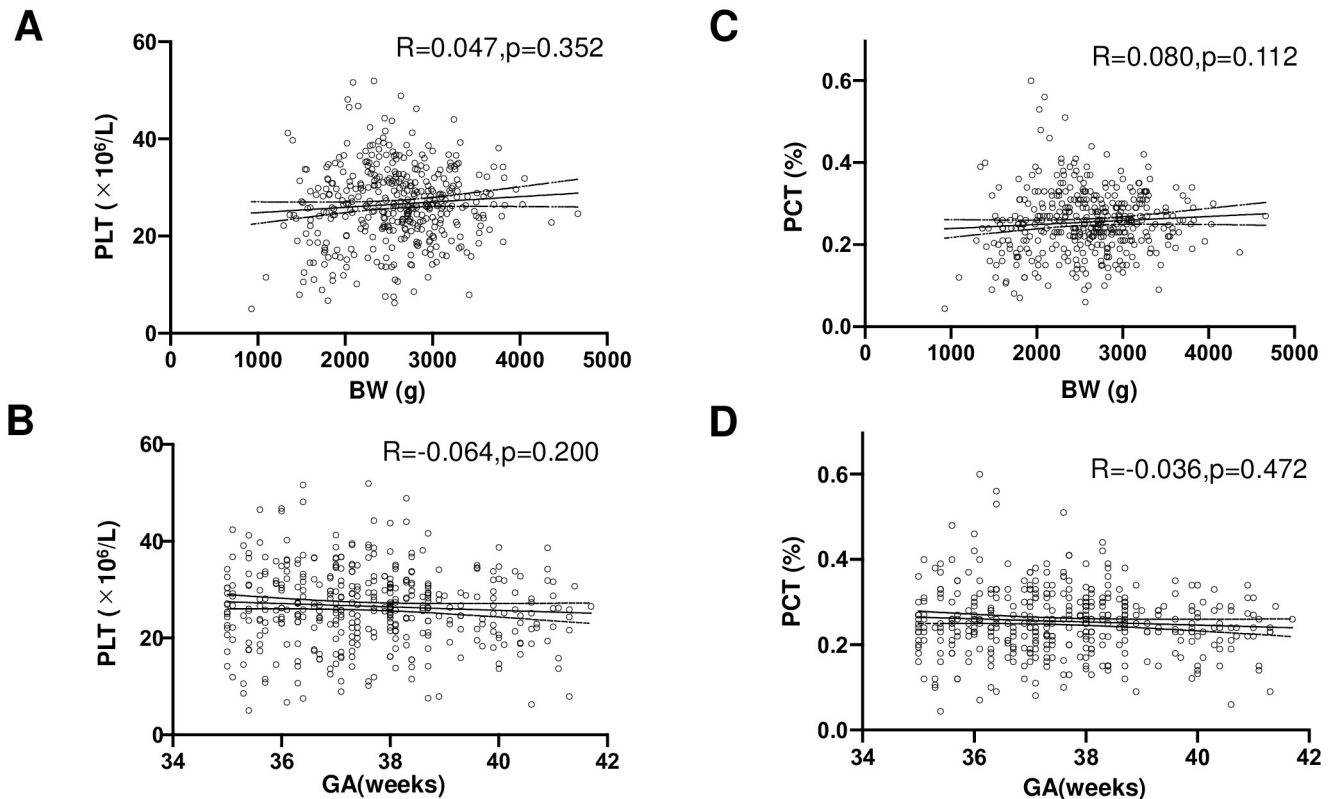


Fig 3. Correlation between platelet count, plateletcrit, GA, and BW. R is Spearman's correlation coefficient.

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As shown in [Table 2](#), in term neonates, MPV was associated with CAM (CAM = 10.4 fL vs. no CAM = 9.7 fL, $P = 0.005$). Furthermore, PCT was associated with male sex (male = 0.24% vs. female = 0.27%, $P = 0.005$), SGA (SGA = 0.23% vs. no SGA = 0.26%, $P = 0.024$) and PIH (PIH = 0.19% vs. no PIH = 0.50%, $P = 0.009$), respectively. PLT was also associated with male sex (male = $25.9 \times 10^3/\mu L$ vs. female = $28.8 \times 10^3/\mu L$, $P = 0.009$), SGA (SGA = $24.8 \times 10^3/\mu L$ vs. no SGA = $26.7 \times 10^3/\mu L$, $P = 0.023$) and PIH (PIH = $17.4 \times 10^3/\mu L$ vs. no PIH = $26.5 \times 10^3/\mu L$, $P = 0.007$), respectively. Multivariate analysis revealed that PCT correlated with male sex ($\beta = -0.185$, $P = 0.002$), SGA ($\beta = -0.168$, $P = 0.006$) and PIH ($\beta = -0.135$, $P = 0.026$). PLT was associated with male sex ($\beta = -0.166$, $P = 0.006$), SGA ($\beta = -0.186$, $P = 0.002$) and PIH ($\beta = -0.137$, $P = 0.024$).

As shown in [Table 3](#), univariate analysis revealed that MPV was correlated with PROM in late preterm neonates (PROM = 10.1 fL vs. no PROM = 9.8 fL, $P = 0.044$). Multivariate analysis associated PLT with PIH ($\beta = -0.194$, $P = 0.023$), whereas no associations with PCT were found in late preterm neonates.

When all patients were studied, multivariate analysis showed that SGA, male sex and PIH were associated with PCT and PLT ([S1 Table](#)). Furthermore, MPV was significantly associated with CAM (CAM = 10.3 fL vs. no CAM = 9.7 fL, $P = 0.001$) and male sex (male = 9.7 fL vs. female = 9.9 fL, $P = 0.011$).

Next, we compared the differences of platelet parameters, sex and PIH between SGA and not SGA ([S2 Table](#)). [S2 Table](#) showed that SGA was significantly associated with PIH in preterm neonates. Furthermore, PCT and PLT were significantly decreased in SGA neonates

Table 2. Factors affecting platelet parameters in term neonates.

(n)	PCT (%)		PDW (%)	MPV (fL)	PLT ($\times 10^3/\mu\text{L}$)	
	univariate analysis	multivariate analysis	univariate analysis	univariate analysis	univariate analysis	multivariate analysis
	Median [IQR]	p-value (β)	Median [IQR]	Median [IQR]	Median [IQR]	p-value (β)
Male (131)	0.24 [0.20–0.29]		10.8 [10.1–12.0]	9.7 [9.3–10.2]	25.9 [20.6–29.3]	
Female (127)	0.27 [0.22–0.32]		11.1 [10.3–12.5]	9.8 [9.4–10.4]	28.8 [22.6–32.8]	
	P = 0.005	P = 0.002 (-0.185)	P = 0.053	P = 0.139	P = 0.009	P = 0.006 (-0.166)
RDS (18)	0.26 [0.22–0.29]		10.9 [10.0–13.2]	9.4 [8.9–10.4]	26.3 [22.9–34.9]	
non-RDS (240)	0.24 [0.21–0.30]		10.9 [10.0–12.3]	9.8 [9.3–10.3]	26.6 [21.4–31.3]	
	P = 0.720		P = 0.842	P = 0.193	P = 0.580	
SGA (52)	0.23 [0.16–0.29]		11.0 [10.4–12.5]	10.0 [9.4–10.4]	24.8 [17.4–30.5]	
non-SGA (206)	0.26 [0.22–0.30]		10.9 [10.9–12.1]	9.7 [9.3–10.3]	26.7 [22.3–31.8]	
	P = 0.024	P = 0.006 (-0.168)	P = 0.299	P = 0.193	P = 0.023	P = 0.002 (-0.186)
PROM (8)	0.22 [0.21–0.25]		10.3 [9.8–10.9]	9.4 [9.3–9.8]	23.8 [20.5–28.1]	
non-PROM (250)	0.26 [0.21–0.30]		10.9 [10.2–12.3]	9.7 [9.3–10.3]	26.5 [21.5–31.5]	
	P = 0.186		P = 0.194	P = 0.286	P = 0.230	
CAM (9)	0.21 [0.19–0.29]		11.3 [11.0–12.1]	10.4 [10.1–10.9]	22.5 [20.1–28.2]	
non-CAM (249)	0.26 [0.21–0.30]		10.9 [10.2–12.3]	9.7 [9.3–10.2]	26.5 [21.7–31.5]	
	P = 0.553		P = 0.144	P = 0.005	P = 0.199	
PA (5)	0.21 [0.19–0.24]		11.1 [9.8–14.9]	10.2 [8.1–10.3]	23.1 [20.5–27.8]	
non-PA (243)	0.26 [0.21–0.30]		10.9 [10.2–12.3]	9.7 [9.3–10.3]	26.5 [21.7–31.4]	
	P = 0.086		P = 0.725	P = 0.913	P = 0.319	
PIH (4)	0.19 [0.12–0.30]		11.1 [10.9–12.2]	9.9 [9.3–10.3]	17.4 [12.3–19.8]	
non-PIH (244)	0.50 [0.12–0.19]		10.9 [10.2–12.3]	9.7 [9.5–10.2]	26.5 [21.9–31.4]	
	P = 0.009	P = 0.026 (-0.135)	P = 0.447	P = 0.683	P = 0.007	P = 0.024 (-0.137)
GA	r = -0.121		r = -0.003	r = 0.048	r = -0.072	
	P = 0.052		P = 0.958	P = 0.446	P = 0.149	
BW	r = 0.070		r = -0.053	r = 0.027	r = 0.020	
	P = 0.260		P = 0.400	P = 0.666	P = 0.753	
AP 1	r = 0.026		r = -0.039	r = -0.052	r = 0.022	
	P = 0.677		P = 0.530	P = 0.409	P = 0.730	
AP5	r = 0.072		r = -0.074	r = -0.048	r = 0.087	
	P = 0.251		P = 0.235	P = 0.445	P = 0.165	

PCT, platelet count; PDW, platelet distribution width; MPV, mean platelet volume; PLT, platelet count; GA, gestational age; BW, birth weight; RDS, respiratory distress syndrome; SGA, small for gestational age; AP1, Apgar score at 1 min.; AP5, Apgar score at 5 min.; PROM, premature rupture of membranes; CAM, chorioamnionitis; PA, placental abruption; PIH, pregnancy-induced hypertension; IQR, median interquartile range. Significant correlation between GA, BW, Apgar score and platelet parameters were analyzed using Spearman's rank correlation (r). β means standardized regression coefficient.

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compared with not SGA neonates. All data pertaining to our analyses are contained within the [S1 Text](#).

Discussion

This large cohort showed no differences in platelet parameters at birth between late preterm and term neonates. Previous reports indicated that PLT and PCT were lower in late preterm neonates compared with term neonates [12, 17]. Furthermore, they suggested that GA was significantly correlated with PLT, however, in our study, GA did not correlate with PLT [12]. Instead, there was positive correlation between BW and PLT in late preterm neonates by univariate analysis. These differences may be due to differences in sample size and time of

Table 3. Factors affecting platelet parameters in late preterm neonates.

(n)	PCT (%)		PDW (%)	MPV (fL)	PLT ($\times 10^3/\mu\text{L}$)	
	univariate analysis Median [IQR]	multivariate analysis p-value (β)	univariate analysis Median [IQR]	univariate analysis Median [IQR]	univariate analysis Median [IQR]	multivariate analysis p-value (β)
Male (76)	0.25 [0.19–0.30]		10.9 [9.9–13.5]	9.8 [9.0–10.2]	26.9 [22.0–31.7]	
Female (66)	0.25 [0.21–0.31]		10.9 [0.3–12.6]	9.9 [9.5–10.4]	25.8 [22.6–32.7]	
	P = 0.568		P = 0.373	P = 0.167	P = 0.995	
RDS (13)	0.22 [0.16–0.26]		11.2 [10.0–13.3]	9.6 [9.0–10.1]	23.9 [18.6–28.9]	
non-RDS (129)	0.25 [0.21–0.31]		10.9 [10.0–12.5]	9.9 [9.2–10.3]	27.0 [22.1–32.6]	
	P = 0.050		P = 0.883	P = 0.374	P = 0.138	
SGA (57)	0.24 [0.17–0.28]		10.9 [10.1–13.5]	9.9 [9.2–10.4]	24.4 [16.9–29.8]	
non-SGA (85)	0.26 [0.22–0.31]		11.0 [10.0–12.5]	9.8 [9.1–10.2]	28.0 [23.8–32.8]	
	P = 0.020	P = 0.357 ($\beta = -0.116$)	P = 0.533	P = 0.454	P = 0.010	P = 0.165 ($\beta = -0.172$)
PROM (33)	0.25 [0.20–0.32]		11.3 [10.5–12.0]	10.1 [9.8–10.4]	25.9 [20.1–32.5]	
non-PROM (109)	0.25 [0.20–0.30]		10.9 [10.0–13.1]	9.8 [9.2–10.4]	26.7 [22.9–32.2]	
	P = 0.847		P = 0.496	P = 0.044	P = 0.673	
CAM (7)	0.26 [0.21–0.31]		11.2 [10.0–12.0]	10.3 [9.8–10.6]	28.0 [24.1–32.4]	
non-CAM (135)	0.25 [0.20–0.31]		10.9 [10.0–13.1]	9.9 [9.0–10.2]	26.6 [22.1–32.4]	
	P = 0.752		P = 0.936	P = 0.087	P = 0.588	
PA (9)	0.25 [0.12–0.36]		10.1 [10.0–13.5]	9.8 [9.5–10.6]	26.6 [11.3–37.2]	
non-PA (133)	0.25 [0.21–0.30]		10.9 [10.2–12.5]	9.9 [9.1–10.3]	26.7 [22.7–32.0]	
	P = 0.937		P = 0.566	P = 0.586	P = 0.834	
PIH (24)	0.23 [0.21–0.32]		10.9 [9.9–12.2]	9.9 [9.1–10.3]	23.7 [15.6–29.1]	
non-PIH (118)	0.25 [0.16–0.27]		10.9 [10.0–13.1]	9.8 [9.4–10.4]	27.1 [23.1–32.9]	
	P = 0.036	P = 0.051 ($\beta = -0.170$)	P = 0.685	P = 0.564	P = 0.007	P = 0.023 ($\beta = -0.194$)
GA	r = 0.011		r = 0.030	r = 0.053	r = 0.026	
	P = 0.895		P = 0.722	P = 0.533	P = 0.757	
BW	r = 0.180		r = -0.040	r = -0.046	r = 0.173	
	P = 0.032	P = 0.929 ($\beta = -0.011$)	P = 0.637	P = 0.590	P = 0.039	P = 0.960 ($\beta = -0.006$)
AP 1	r = 0.028		r = 0.115	r = 0.046	r = 0.049	
	P = 0.744		P = 0.172	P = 0.583	P = 0.565	
AP5	r = -0.002		r = 0.117	r = 0.122	r = -0.006	
	P = 0.978		P = 0.164	P = 0.149	P = 0.941	

PCT, platelet count; PDW, platelet distribution width; MPV, mean platelet volume; PLT, platelet count; GA, gestational age; BW, birth weight; RDS, respiratory distress syndrome; SGA, small for gestational age; AP1, Apgar score at 1 min.; AP5, Apgar score at 5 min.; PROM, premature rupture of membranes; CAM, chorioamnionitis; PA, placental abruption; PIH, pregnancy-induced hypertension; IQR, median interquartile range. Significant correlation between GA, BW, Apgar score and platelet parameters were analyzed using Spearman’s rank correlation (r). β means standardized regression coefficient.

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sampling. Other research included 129 neonates: 58 late preterm and 71 full term. Moreover, they found that PLT measured using cord blood was associated with GA and BW in late preterm and term neonates. In our study, we used venous blood at admission to NICU. The mean time of sampling in this study was just under 2 hours after birth.

This study also demonstrates that various maternal and neonatal factors affect platelet parameters in late preterm and term neonates. Especially, late preterm and term SGA neonates

had lower PLT and PCT compared with not SGA neonates as previously described [18, 19]. Lower PLT in SGA indicates the immaturity of thrombopoiesis [20, 21]. Roberts suggested that reduced platelet production was characteristic of preterm neonates and they had fewer circulating megakaryocytes [22]. Another study reported that plasma thrombopoietin concentrations were low in thrombocytopenic newborns, indicative of inadequate up-regulation of TPO production [23]. Platelets are produced in the fetal liver, with production transferred to bone marrow in the third trimester [24]. The liver is one of the first organs to be affected by growth restriction. Furthermore, in this study, PIH was associated with lower PLT and PCT. Moreover, PIH is also a significant risk factor for SGA in this study as previously reported. Maternal PIH can result in neonatal thrombocytopenia [13, 25]. However, the pathogenesis of thrombocytopenia among infants born to mothers with PIH remain unknown. One potential mechanism is that maternal hypertension and resultant fetal hypoxia affects megakaryocyte proliferation [13, 26].

The present study suggested that CAM was associated with MPV in term neonates. However, PROM is not associated with MPV as in a previous study [27]. Recently, a retrospective study has reported significant correlation between MPV and intrauterine infection in neonates with thrombocytopenia and leukopenia at birth [23, 28]. Since CAM was indicative of intrauterine infection, our results are consonant with previous studies. Furthermore, PDW in SGA neonates did not differ from those of not SGA neonates. This result agrees with a previous study [29]. Recently, elevated PDW was associated with poor prognosis of various conditions such as carcinoma and cardiovascular disease [1, 30, 31]. Although, Patrick et al reported that high MPV and PDW showed high specificity in neonates with late sepsis [32], there are no late sepsis cases in this study.

Another important finding of the present study concerns PLT differences by sex. Although there are few reports about the relationships between PLT and sex in neonates, a previous study reported that school-age females had higher PLT than their male counterparts [33]. However, the mechanisms responsible for PLT differences by sex are unknown.

Our study has several limitations. First, we used samples of venous blood on admission. The timing of samples might affect platelet parameters. Second, we could not investigate the relationship between platelet parameters and sepsis because few of our preterm infants had sepsis at birth and we did not investigate changes of platelet parameters during the postnatal period. Some studies associated sepsis with elevated MPV in neonates during the postnatal period [32, 34]. Third, Apgar score was not associated with lower PLT in late preterm and term neonates in this study. Some studies previously showed that low Apgar score at 5 minutes was related to thrombocytopenia [35, 36]. Mario et al showed that SGA, low Apgar score at 5 minutes, cesarean delivery and lower gestational age were risk factors for thrombocytopenia in preterm deliveries between 27 and 35 weeks of gestation [35]. In murine models, it is known that hypoxia affects megakaryocyte progenitors and induces thrombocytopenia [37, 38]. Castle et al reported that severe hypoxia significantly shortened the survival of platelets in a murine model [39]. In this study, there were too few subjects with severe birth asphyxia to make any inferences. Since very low birth weight neonatal platelets were markedly less reactive than adult platelets to ADP/epinephrine, further study to investigate the relationship between severe birth asphyxia requiring epinephrine and PLT reactivity is needed [40]. Finally, the subjects of term neonates admitted to our NICU in this study have various diseases such as transient tachypnea of newborn, pneumothorax and RDS or hypoglycemia or birth asphyxia. Although RDS is not associated with platelet indices in this study, these term neonates strictly differ from healthy term neonates.

In summary, this study demonstrates that various maternal and neonatal factors affect platelet parameters in late preterm and term neonates. In particular, SGA male sex, and PIH

were associated with lower PLT and PCT in late preterm and term neonates. Furthermore, CAM was significantly associated with MPV. Thus, this study demonstrates that different maternal and neonatal complications affect platelet parameters in late preterm and term neonates.

Supporting information

S1 Table. Factors affecting platelet parameters in late preterm and term neonates.
(DOCX)

S2 Table. Platelet parameters in SGA and not neonates.
(DOCX)

S1 Text. This study's data set.
(XLSX)

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Author Contributions

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References

1. Martin JF, Kristensen SD, Mathur A, Grove EL, Choudry FA. The causal role of megakaryocyte-platelet hyperactivity in acute coronary syndromes. *Nat Rev Cardiol.* 2012; 9(11):658–70. <https://doi.org/10.1038/nrcardio.2012.131>
2. Han L, Liu X, Li H, Zou J, Yang Z, Han J, et al. Blood coagulation parameters and platelet indices: changes in normal and preeclamptic pregnancies and predictive values for preeclampsia. *PLoS One.* 2014; 9(2): e114488. <https://doi.org/10.1371/journal.pone.0114488> PMID: 25464515
3. Coban E, Adanir H, Bilgin D. The association of mean platelet volume levels with hypertensive retinopathy. *Platelets.* 2008; 19(2):115–8. <https://doi.org/10.1080/09537100701230451> PMID: 17852776
4. Roberts I, Murray NA. Neonatal thrombocytopenia: causes and management. *Arch Dis Child Neonatal Ed.* 2003; 88: F359–364. <https://doi.org/10.1136/fn.88.5.f359> PMID: 12937037
5. Catal F, Tayman C, Tonbul A, Akca H, Kara S, Tatli MM, et al. Mean platelet volume (MPV) may simply predict the severity of sepsis in preterm infants. *Clin Lab.* 2014; 60(7):1193–200. <https://doi.org/10.7754/clin.lab.2013.130501> PMID: 25134389
6. ZhaO D, Qiu G, Luo Z, Zhang Y. Platelet parameters and (1,3)- β -D-gulcan as a diagnostic and prognostic marker of invasive fungal disease in preterm infants. *PLoS One.* 2015; 10(4):e0123907. <https://doi.org/10.1371/journal.pone.0123907> PMID: 25874376
7. Aydemir C, Aydemir H, Kokturk F, Kulah C, Mungan AG. The cut-off levels of procalcitonin and C-reactive protein and the kinetics of mean platelet volume in preterm neonates with sepsis. *BMC Pediatr.* 2018; 18(1):253. <https://doi.org/10.1186/s12887-018-1236-2> PMID: 30068303

8. Mitsiakos G, Papathanasiou AE, Kyriakidis I, Karagianni P, Tsepis K, Tzimou I, et al. Intraventricular Hemorrhage and Platelet indices in Extremely Premature Neonates. *J Pediatr Hematol Oncol*. 2016; 38(7):533–538. <https://doi.org/10.1097/MPH.0000000000000631> PMID: 27849673
9. Aksoy HT, Güzoğlu N, Eras Z, Canpolat FE, Uraş N. Mean platelet volume/count and mortality in extremely low birth weight infants of preeclamptic mothers. *Clin Invest Med*. 2018; 41(3):E130–135. <https://doi.org/10.25011/cim.v41i3.30789> PMID: 30315748
10. Kim JY, Yoon J, Lim CS, Choi BM, Yoon SY. Clinical significance of platelet-associated hematological parameters as an early supplementary diagnostic tool for sepsis in thrombocytopenic very-low-birth-weight infants. *Platelets*. 2015; 26(7):620–6. <https://doi.org/10.3109/09537104.2014.963542> PMID: 25275826
11. Go H, Ohto H, Kenneth N, Takano S, Kashiwabara N, Chisiki M, et al. Using Platelet Parameters to Anticipate Morbidity and Mortality Among Preterm Neonates: A Retrospective Study. *Front Pediatr*. 2020; 8:90. <https://doi.org/10.3389/fped.2020.00090> PMID: 32232019
12. Alicja W, Agnieszka P, Piotr L, Slawomir R, Barbara KW, Milena D, et al. Platelet indices in late preterm newborns. *J Matern Fetal Neonatal Med*. 2017; 30(14):1699–1703. <https://doi.org/10.1080/14767058.2016.1222519> PMID: 27628188
13. Backes CH, Markham K, Moorehead P, Cordero L, Nankervis CA, Giannone PJ. Maternal preeclampsia and neonatal outcomes. *J Pregnancy* 2011; 214365. <https://doi.org/10.1155/2011/214365> PMID: 21547086
14. Thalor N, Singh K, Pujani M, Chauhan V, Agarwal C, Ahuja R. A correlation between platelet indices and preeclampsia. *Hematol Transfus Cell Ther*. 2019; 41(2)129–133. <https://doi.org/10.1016/j.htct.2018.08.008> PMID: 31084762
15. Ekin A, Gezer C, Kulhan G, Avci ME, Taner CE. Can platelet count and mean platelet volume during the first trimester of pregnancy predict preterm premature rupture of membranes? *J Obstet Gynaecol Res*. 2015; 41(1):23–28. PMID: 25130327
16. Tita AT, Andrew WW. Diagnosis and management of clinical chorioamnionitis. *Clinics in Perinatology*. 2010; 37(2):339–354. <https://doi.org/10.1016/j.clp.2010.02.003> PMID: 20569811
17. Wasiluk A, Osada J, Dabrowska M, Szczepański M, Jasinska E. Does prematurity affect platelet indices? *Adv Med Sci*. 2009; 54(2):253–5. PMID: 19808160
18. Christensen RD, Baer VL, Henry E, Snow GL, Butler A, Sola-Visner MC. Thrombocytopenia in Small-for-Gestational-Age Infants. *Pediatrics*. 2015; 135(2):e361–70.
19. Wasiluk A, Mantur M, Kemona H, Szczepański M, Jasińska E, Milewski R. Thrombopoiesis in small for gestational age newborns. *Platelets*. 2009; 20(7):520–524. <https://doi.org/10.3109/09537100903207505> PMID: 19852692
20. Fustolo-Gunnink SF, Vlug RD, Smits-Wintjens VE, Heckman EJ, Te Pas AB, Fijnvandraat K, et al. Early-Onset Thrombocytopenia in Small-For-Gestational-Age Neonates: A retrospective Cohort Study. *PLoS One*. 2016; 11(5):e0154853. <https://doi.org/10.1371/journal.pone.0154853> PMID: 27177157
21. Lee E, Lim Z, Malhotra A. Thrombocytopenia in well small for gestational age neonates. *Blood Coagul Fibrinolysis*. 2019. 30(3):104–110. <https://doi.org/10.1097/MBC.0000000000000802> PMID: 30864963
22. Murray NA, Watts TL, Roberts IA. Endogenous thrombopoietin levels and effect of recombinant human thrombopoietin on megakaryocyte precursors in term and preterm babies. *Pediatr Res*. 1998; 43:148–151. <https://doi.org/10.1203/00006450-199801000-00023> PMID: 9432127
23. Watts TL, Murray NA, Roberts IA. Thrombopoietin has a primary role in the regulation of platelet production in preterm babies. *Pediatr Res*. 1999; 46(1):28–32. <https://doi.org/10.1203/00006450-199907000-00005> PMID: 10400130
24. Maruyama H, Shinozuka M, Kondoh Y, Akahori Y, Matsuda M, Inoue S, et al. Thrombocytopenia in Preterm Infants with Intrauterine Growth Restriction. *Acta Med. Okayama*, 2008; 62(5):313–317. <https://doi.org/10.18926/AMO/30973> PMID: 18985091
25. Brazy J. E., Grimm J. K., and Little V. A. Neonatal manifestations of severe maternal hypertension occurring before the thirty-sixth week of pregnancy. *J Pediatr*. 1982; 100(2):265–271. [https://doi.org/10.1016/s0022-3476\(82\)80653-7](https://doi.org/10.1016/s0022-3476(82)80653-7) PMID: 7057337
26. Weiner C. P. and Williamson R. A. Evaluation of severe growth retardation using cordocentesis—hematologic and metabolic alterations by etiology. *Obstet Gynecol*. 1989; 73(2): 225–229. PMID: 2536145
27. Ekin A, Gezer C, Kulhan G, Avci ME, Taner CE. Can platelet count and mean platelet volume during the first trimester of pregnancy predict preterm premature rupture of membranes? *J Obstet Gynaecol Res*. 2015; 41(1):23–28. <https://doi.org/10.1111/jog.12484> PMID: 25130327
28. Chen CY, Essien MD, Johnson AJ, Lee GT, Chou FS. Use of mean platelet volume in the assessment of intrauterine infection in newborns with thrombocytopenia and leukopenia at birth. *J Matern Fetal Neonatal Med*. 2019; 1–7. <https://doi.org/10.1080/14767058.2019.1608174> PMID: 30983434

29. Wasiluk A, Mantur M, Kenoma H, Szczepański M, Jasińska E, Milewski R. Platelet indices in SGA newborns. *Adv Med Sci*. 2011. 20(7):520–524. <https://doi.org/10.2478/v10039-011-0030-2> PMID: [21940264](https://pubmed.ncbi.nlm.nih.gov/21940264/)
30. Zuo X, Kong W, Feng L, Zhang H, Meng X, Chen W. Elevated platelet distribution width predicts poor prognosis in hepatocellular carcinoma. *Cancer Biomark*. 2019; 24(3):307–313. <https://doi.org/10.3233/CBM-182076> PMID: [30829614](https://pubmed.ncbi.nlm.nih.gov/30829614/)
31. Xie X, Zeng X, Cao S, Hu X, Shi Q, Li D, et al. Elevated pretreatment platelet distribution width and platelet count predict poor prognosis in nasopharyngeal carcinoma. *Oncotarget*. 2017; 8(62):106089–106097. <https://doi.org/10.18632/oncotarget.22528> PMID: [29285316](https://pubmed.ncbi.nlm.nih.gov/29285316/)
32. Patrick CH, Lazarchick J. The effect of bacteremia on automated platelet measurements in neonates. 1990; 93(3):391–4.
33. Taylor ME, Holland CV, Spencer R, Jackson JF, O'Connor GI, O'Donnell JR. Haematological reference ranges for schoolchildren. *Clin Lab Haematol*. 1997; 19(1):1–15. <https://doi.org/10.1046/j.1365-2257.1997.00204.x> PMID: [9146941](https://pubmed.ncbi.nlm.nih.gov/9146941/)
34. Hanaganahalli SB, Sreeram S, Bompada M, Kuppannagari SK, Suresh PK, Philipose CS. Is MPV a Predictive Marker for Neonatal Sepsis? A Pilot Study. *J Pediatr Hematol Oncol*. 2018; 40(7):548–552. <https://doi.org/10.1097/MPH.0000000000001272> PMID: [30080755](https://pubmed.ncbi.nlm.nih.gov/30080755/)
35. Beiner ME, Simchen MJ, Sivan E, Chetrit A, Kuint J, Schiff E. Risk factors for neonatal thrombocytopenia in preterm infants. *Am J Perinatol*. 2003; 20(1):49–54. <https://doi.org/10.1055/s-2003-37948> PMID: [12638081](https://pubmed.ncbi.nlm.nih.gov/12638081/)
36. Nadkarni J, Patne SK, Kispotta R. Hypoxia as a predisposing factor for the development of early onset neonatal thrombocytopenia. *J Clin Neonatol*. 2012; 1(3):131–134. <https://doi.org/10.4103/2249-4847.101693> PMID: [24027708](https://pubmed.ncbi.nlm.nih.gov/24027708/)
37. Cremer M, Weimann A, Schmalisch G, Hammer H, Bühner C, Dame C. Immature platelet values indicate impaired megakaryopoietic activity in neonatal early-onset thrombocytopenia. *Thromb Haemost*. 2010; 103:1016–1021. <https://doi.org/10.1160/TH09-03-0148> PMID: [20216981](https://pubmed.ncbi.nlm.nih.gov/20216981/)
38. Saxonhouse MA, Rimsza LM, Stevens G, Jouei N, Christensen RD, Sola MC. Effects of hypoxia on megakaryocyte progenitors obtained from the umbilical cord blood of term and preterm neonates. *Biol Neonate*. 2006; 89:104–108. <https://doi.org/10.1159/000088561> PMID: [16192692](https://pubmed.ncbi.nlm.nih.gov/16192692/)
39. Castle V, Coates G, Mitchell LG, O'Brodovich H, Andrew M. The effect of hypoxia on platelet survival and site of sequestration in the newborn rabbits. *Thromb Haemost*. 1988; 59(1):45–48.
40. Rajasekhar D, Barnard MR, Bednarek FJ, Michelson AD. Platelet hyporeactivity in very low birth weight neonates. *Thromb Haemost*. 1997; 77(5):1002–1007. PMID: [9184418](https://pubmed.ncbi.nlm.nih.gov/9184418/)