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ORIGINAL ARTICLE

Platelet count and indices as postpartum hemorrhage risk factors: a retrospective cohort study

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Abstract

Background: Severe postpartum hemorrhage (SPPH) is the leading cause of maternal mortality and morbidity worldwide. Platelet anomalies frequently occur during pregnancy. However, their role in the etiology of SPPH is largely unknown.

Objective: To study the relation between platelet parameters and SPPH.

Methods: This retrospective single-center cohort included deliveries between 2009 and 2017. SPPH was defined as ≥1000 ml blood loss within 24 h after delivery. Platelet parameters were measured within 72 h before delivery. Multiple imputation was performed for missing data. Odds ratios were adjusted (aORs) for maternal age, multiple gestation, macrosomia, induction of labor, preeclampsia, and hemolysis, elevated liver enzymes, and low platelets syndrome.

Results: A total of 23 205 deliveries were included. Of the 2402 (10.4%) women with thrombocytopenia (<150 × 10^9/L), 10.3% developed SPPH, compared with 7.6% of women with a normal platelet count (aOR: 1.34, 95% CI: 1.14–1.59). Women with a platelet count of <50 × 10^9/L were most at risk (aOR of 2.24 [1.01–4.94]) compared with the reference group with normal platelet counts; the aOR was 1.22 (0.77–1.93) for the 50–99 × 10^9/L platelet count group and 1.31 (1.10–1.56) for the 100–149 × 10^9/L platelet count group. Plateletcrit was associated with SPPH (aOR 1.15 [1.08–1.21] per 0.05% decrease), and, although rarely present, a platelet distribution width (PDW) ≥23% (n = 22) also increased the odds of SPPH (aOR 6.05 [2.29–16.20]).

Conclusion: Different degrees of thrombocytopenia were independently associated with the occurrence of SPPH. Despite their relation to SPPH, plateletcrit and a PDW of ≥23% have limited additional value in addition to platelet count.

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KEYWORDS
mean platelet volume, platelet count, postpartum hemorrhage, pregnancy complications, thrombocytopenia

1 | INTRODUCTION

Postpartum hemorrhage (PPH) is the leading cause of maternal mortality and morbidity worldwide.[1,2] The World Health Organization defines PPH as >500 ml of blood loss and severe PPH (SPPH) as >1000 ml. In the Netherlands, 4%–6% of pregnancies are complicated by SPPH, and this percentage has increased in high income countries over the past decade.[3-5]

Thrombocytopenia is defined as a platelet count of <150 × 10^9/L. In nonpregnant populations, thrombocytopenia is a well-known risk factor for bleeding, particularly in the lower ranges of the platelet count (<10–50 × 10^9/L).[6] It is the second most common hematologic anomaly in pregnant women, occurring in 7%–12% of pregnancies.[7,8] Thrombocytopenia in pregnancy can have multiple causes. Approximately 75% is due to gestational thrombocytopenia, 20% to preeclampsia and hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, and 3%–5% to other causes.[9] Preeclampsia and HELLP syndrome, and HELLP syndrome severity, are established risk factors for PPH.[10-13]

Moreover, the relation between thrombocytopenia in pregnancy and PPH has been studied several times, yet these studies showed mixed results,[14-17] lacked statistical power,[18-22] or only studied subgroups.[23,24] Furthermore, these studies mostly focused on PPH or PPH surrogates rather than the more clinically relevant outcome parameter SPPH. In current guidelines, women with a platelet count of <50 × 10^9/L are considered to have an increased (S)PPH risk, and platelet transfusion is recommended if the platelet count falls below 20–30 × 10^9/L for vaginal delivery and 50 × 10^9/L for surgical delivery. However, these recommendations are based mainly on expert opinion and more empirical evidence is needed to support them.[9,25,26]

In addition to the platelet count, most hematology analyzers also routinely measure or calculate several other platelet indices. These parameters include the mean platelet volume (MPV) and the platelet distribution width (PDW), which are regarded as surrogate markers of platelet activation.[27-29] They also include the plateletcrit, which is the product of the MPV and the platelet count, and indicates the fraction of blood volume occupied by platelets, and the immature platelet fraction (IPF), which indicates the fraction of newly released platelets, that may be more hemostatically active than mature platelets. These parameters have been linked to both thrombotic and hemorrhagic events, although the evidence is nonunanimous.[30-53] To date, no studies have investigated the relation between platelet indices and (S)PPH.

In this study, therefore, we aimed to investigate the association between SPPH, and the platelet count and platelet indices in a population-based cohort including both vaginal and cesarean deliveries. We hypothesized that women with a lower platelet count, lower MPV, lower PDW, and a lower IPF are at an increased risk of SPPH.

Essentials

- The relation between platelet count and -indices, and severe postpartum hemorrhage (SPPH) was unclear.
- This retrospective study was conducted in a cohort of 23 205 deliveries at a tertiary hospital.
- Platelet count is related to SPPH (≥1L).
- Plateletcrit and a high platelet distribution width (≥23%) have limited additional value despite their relation to SPPH.
- Platelet volume and immature platelet fraction are not related to SPPH (≥1L).

2 | METHODS

2.1 | Study population

This retrospective cohort study was conducted in a cohort of 23 493 deliveries between 2009 and 2017 at the birth center of the University Medical Centre Utrecht (UMCU), Utrecht, the Netherlands, including primary, secondary, and tertiary obstetric care. We included all deliveries at a gestational age of ≥20 weeks. Patients were not involved in the realization of this article. This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008,[54] and does not fall under the scope of the Medical Research Involving Human Subjects Act, as judged by the Medical Research and Ethics Committee of the UMCU.

2.2 | Definitions

SPPH was defined as ≥1000 ml blood loss within 24 h after delivery, in accordance with the World Health Organization,[55] the American College of Obstetricians and Gynecologists,[2] and the Dutch Association for Obstetrics and Gynaecology.[56] Thrombocytopenia was defined as a platelet count of <150 × 10^9/L.[9] The cause of the thrombocytopenia was categorized into gestational thrombocytopenia, HELLP syndrome, ITP, thrombopathy, and other, based on the clinical diagnosis. The thrombopathy category included patients with functional platelet defects in addition to the thrombocytopenia (eg, storage pool disease, uremic

thrombopathy), and the other category included patients with, for example, von Willebrand disease, leukemia, or antiphospholipid syndrome. Because gestational thrombocytopenia is a diagnosis of exclusion, this category included patients with thrombocytopenia of unknown origin.

Primary cesarean section was defined as a cesarean section that was planned before labor. Emergency cesarean section was defined as an unplanned cesarean section where the need for a section arose during labor.

Pregnancies with a low or high risk of complications were defined using the Dutch midwife indication list (verloskundige indicatielijst),[57] which is a guideline used to assess if primary or secondary obstetric care is indicated. If one of the following indications for secondary care was present, the pregnancy was regarded as a high-risk pregnancy: platelet or coagulation disorders, prior SPPH, prior cesarean delivery, prior manual placenta removal, gestational age ≤37 or ≥42 weeks, HELLP or preeclampsia, multiple gestation, vasa previa, placental abruption, retained placenta, and breech presentation. Platelet transfusion was defined as a platelet transfusion between the last measurement of the platelet count, and 24 h after delivery, as a transfusion within this interval could have influenced the relationship between the platelet count and postpartum blood loss.

Aspirin use during pregnancy was defined as the presence of an electronic prescription of aspirin or carbasalate calcium at any time during the pregnancy.

2.3 | Data source and collection

For this study, demographic, obstetric, labor, postpartum and laboratory characteristics were collected from the Utrecht Patient Oriented Database, which is an infrastructure of relational databases comprising data on patient characteristics, hospital discharge diagnoses, medical procedures, medication orders, and laboratory tests for all patients treated at the UMCU.[58] As determinants, the last known platelet count and platelet indices within 72 h before delivery were used, which were available if any variable of the complete blood count was measured by clinical indication. Platelet count and platelet indices were measured using an Abbott Diagnostics CELL-DYN Sapphire (Santa Clara, CA, USA). Blood loss was preferably measured by weighing gauzes and catching blood in a measuring cylinder, and otherwise estimated by the attending physician or midwife. There was no information available on how often blood loss was measured or estimated. To identify the presence of HELLP syndrome, preeclampsia, or other platelet disorders, the diagnosis of the attending physician was used, as noted in the medical files and correspondence. If a condition (eg, preeclampsia, induction of labor) was not reported in medical files, we presumed women were not exposed to this condition. Data on manual placenta removal and perineal or birth tract injuries were extracted from medical files and surgical records.

2.4 | Statistical analysis

To reduce bias because of missing data, we performed multiple imputation. Most data were missing in the platelet variables body mass index (BMI), blood loss, and mode of delivery (Supporting information 1). We assumed platelet count and indices, blood loss, and mode of delivery were missing at random (ie, missingness is random conditional on other observed patient characteristics), and BMI was missing completely at random.[59] We ran 30 multiple imputations with 100 iterations each.[60] The used imputation methods were predictive mean matching for numeric data, logistic regression imputation for binary data, and polytomous regression imputation for unordered categorical data. A list of variables used in the imputation is found in Supporting information 2. The estimates from the imputed data were pooled using Rubin's rules.[61] Separate imputations were performed for each stratified cohort. Complete case analysis was also performed, which is found in Supporting information 3.

For the summary statistics of continuous variables, we reported means with standard deviation if data were normally distributed, and medians with interquartile range if data were not normally distributed. We calculated *p* values for differences in baseline characteristics using Student's *t* test for means, Wilcoxon rank-sum test for medians, and chi-squared test for discrete variables. The Benjamini-Hochberg method was used to account for multiple testing.

Odds ratios (ORs) for SPPH were calculated using multivariate logistic regression. A separate model was made for each platelet variable of interest: platelet count, MPV, plateletcrit, PDW, and IPF. The platelet count was categorized in $<50 \times 10^9$/L, $50–99 \times 10^9$/L, $100–149 \times 10^9$/L, $150–350 \times 10^9$/L (reference category), and $\geq 350 \times 10^9$/L based on previous literature. For the stratified analysis, we combined the $50–99 \times 10^9$/L and the $100–149 \times 10^9$/L categories into one group, to retain statistical power. For the other platelet indices, literature was sparse, thus categorization of data, if necessary, was based on the distribution of data in our cohort (Figure 2): we analyzed the MPV and the plateletcrit as continuous measures, as they had a linear relationship with SPPH, and the PDW and IPF with cutoff values of 23% and 6% respectively. To adjust for confounding, we included maternal age, multiple gestation, macrosomia, defined as a birth weight ≥4000 g, induction of labor, preeclampsia, and HELLP syndrome in the logistic regression models. The analyses were stratified by mode of delivery, because this might influence bleeding risk, and because previous research focused on these subgroups. Several sensitivity analyses were performed. First, we assessed whether the relationship between platelet indices and SPPH differed between high- and low-risk pregnancies (Supporting information 4). Second, we repeated the analyses with aspirin use added to the original models. Last, we combined PDW and platelet count in one adjusted model to assess the interrelation between these two parameters in the effect on SPPH. For the complete case analysis IBM SPSS (release 25.0.0.2) was used. For the imputation and the analysis of the imputed dataset, RStudio (Version 1.1.456) was used. Imputation was performed using the MICE (Multivariate Imputation by Chained Equations, version 3.8.0) package.

3 | RESULTS

Of the 23 493 eligible deliveries, 23 205 met the inclusion criterion (Figure 1). The imputed cases (with ≥1 variable used in the analysis missing, $n = 11\ 430$, 49.3%) overall comprised lower risk pregnancies, with a lower rate of nulliparity, multiple gestation, cesarean delivery, induction of labor, SPPH, pregnancy complications, prior SPPH, and prior cesarean delivery (Supporting information 1).

The baseline characteristics of deliveries with and without thrombocytopenia are depicted in Table 1. The groups differed significantly regarding multiple gestation (adjusted $p < 0.001$), mode of delivery (adjusted $p < 0.001$), HELLP syndrome (adjusted $p < 0.001$), maternal age (adjusted $p < 0.001$), preeclampsia (adjusted $p < 0.001$), BMI (adjusted $p < 0.001$), macrosomia ($p = 0.013$), and induction of labor ($p = 0.047$). In total, 2402 (10.4%) deliveries were complicated by thrombocytopenia, of which 2109 (9.1%) had a platelet count of 100–149 × 10^9/L, 241 (1.0%) a platelet count of 50–99 × 10^9/L, and 52 (0.2%) a platelet count of <50 × 10^9/L. The baseline characteristics per platelet count group are depicted in Supporting information 5.

In total, 1819 (7.8%) deliveries were complicated by SPPH. SPPH occurred more frequently in patients with thrombocytopenia (10.3% versus 7.6% in patients without thrombocytopenia; OR: 1.46, 95% CI: 1.24–1.71; aOR: 1.34, 95% CI: 1.14–1.59). Generally, the risk of SPPH increased as the platelet count decreased (Figure 2). The proportion SPPH was highest in the group with <50 × 10^9 platelets/L (15.4%).

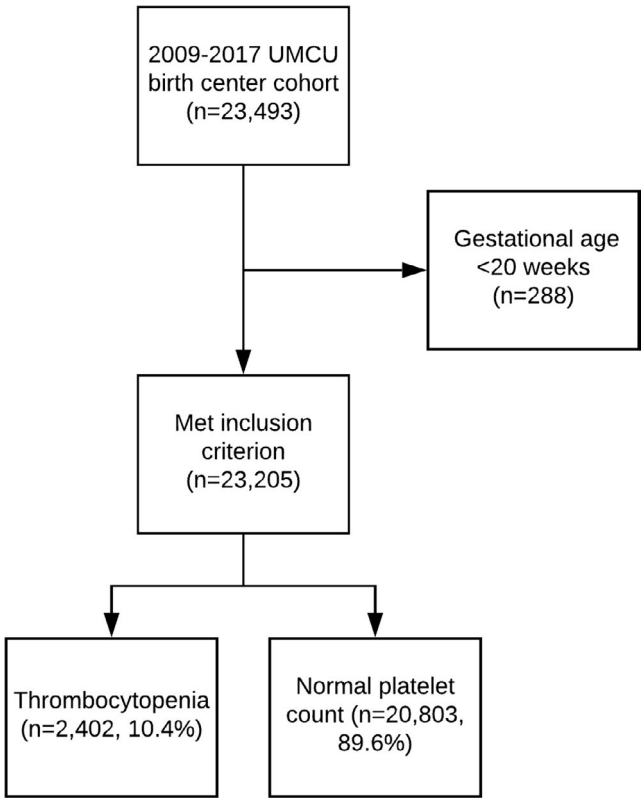

FIGURE 1 Flowchart describing study population

Both unadjusted and adjusted ORs (aORs) of SPPH for platelet count and platelet indices are shown in Table 2. A platelet count of <150 × 10^9/L, a low plateletcrit, and a PDW of ≥23% were associated with an increased SPPH risk after adjusting for known PPH risk factors. The adjustment for confounders (maternal age, multiple gestation, macrosomia, induction of labor, preeclampsia, and HELLP syndrome) did not considerably influence the relationships between platelet count and indices, and SPPH.

Figure 3 shows the aORs for platelet count stratified by mode of delivery. The aORs for the other platelet indices are shown in Table 3. In vaginal deliveries, women with a platelet count of <50 × 10^9/L did not have an increased SPPH risk, whereas women with a platelet count of 50–149 × 10^9/L had a higher SPPH risk compared with women with a normal platelet count (aORs for <50 × 10^9/L: 2.06 [0.67–6.27]; for 50–149 × 10^9/L: 1.34 [1.09–1.64]). Women with a platelet count of ≥350 × 10^9/L had a lower SPPH risk (OR: 0.56 [0.39–0.80]). In primary cesarean deliveries, the platelet count was not related to SPPH. In emergency cesarean deliveries, women with a platelet count of 50–149 × 10^9/L had a higher SPPH risk, and women with a platelet count of <50 × 10^9/L or ≥350 × 10^9/L had no significantly different SPPH risk compared with women with a normal platelet count (aORs for <50 × 10^9/L: 3.49 [0.66–18.5]; for 50–149 × 10^9/L: 1.63 [1.10–2.43]; for ≥350 × 10^9/L 0.89 [0.44–1.80]). In vaginal and emergency cesarean deliveries, a low plateletcrit was related to an increased SPPH risk. A decreased MPV and an IPF of ≥6% conferred a higher SPPH risk in primary cesarean deliveries (Table 3). There were not enough subjects to calculate aORs for PDW ≥23% stratified by mode of delivery. Of the women delivering vaginally, 25 (0.15%) received a platelet transfusion. In the primary cesarean group, 30 (1.01%) women received a platelet transfusion, and in the emergency cesarean group, 8 (0.30%) women received a platelet transfusion.

3.1 | Sensitivity analysis

Sensitivity analysis for high- and low-risk pregnancies showed that the relation between SPPH and platelet parameters was similar in these groups (Supporting information 4).

Second, we repeated all analyses with additional correction for aspirin. Aspirin was used by 385/23 205 (1.7%) of the patients, primarily by patients with platelet counts <50 × 10^9/L and between 50 and 99 × 10^9/L (5.8% and 5.4%, respectively). The aORs for all platelet count groups were similar to the adjusted models without aspirin (aORs: 2.21 [1.02–4.80] for <50 × 10^9/L platelets, 1.20 [0.76–1.87] for 50–99 × 10^9/L platelets, 1.30 [1.09–1.54] for 100–149 × 10^9/L platelets, 0.67 [0.50–0.88] for >350 × 10^9/L platelets, and 0.99 [0.68–1.45] for aspirin). Additionally, the aORs for the platelet indices were similar to the adjusted models without aspirin (data not shown).

To assess the interrelation between a high PDW and the platelet count, we combined these parameters in one model. The effect of a PDW ≥23% on the risk of PPH remained significant (aOR 5.59, 95%

TABLE 1 Baseline characteristics

Variable	Thrombocytopenia ($n = 2402$, 10.4%)	Normal Platelet Count ($n = 20\,803$, 89.6%)	All Patients ($n = 23\,205$)
Maternal age (± SD)	32.8 (4.8)	32.1 (5.0)	32.2 (5.0)
Prepregnancy BMI (IQR)	23.0 (20.9–25.8)	23.5 (21.2–26.9)	23.4 (21.2–26.8)
Gestational age at delivery (IQR)	39.6 (37.7–40.8)	39.7 (38.1–40.7)	39.7 (38.0–40.7)
Gravidity (± SD)	2.3 (1.5)	2.3 (1.5)	2.3 (1.5)
Nulliparous, *n* (%)	1137 (47.3)	9726 (46.8)	10 863 (46.8)
Multiple gestation, *n* (%)	209 (8.7)	723 (3.5)	932 (4.0)
Birth weight, g (IQR)	3339 (2783–3756)	3348 (2866–3720)	3346 (2857–3725)
Macrosomia, *n* (%)	332 (13.8)	2070 (10.0)	2402 (10.4)
Mode of delivery, *n* (%)			
Normal vaginal	1473 (61.3)	14 215 (68.3)	15 688 (67.6)
Instrumental	179 (7.5)	1538 (7.4)	1717 (7.4)
Primary cesarean	449 (18.7)	2609 (12.5)	3058 (13.2)
Emergency cesarean	301 (12.5)	2441 (11.7)	2742 (11.8)
Induction of labor, *n* (%)	608 (25.3)	4832 (23.2)	5440 (23.4)
Pregnancy complications, *n* (%)			
Manual placenta removal	141 (5.9)	1121 (5.4)	1262 (5.4)
Perineal or birth tract injuries	83 (3.5)	631 (3.0)	714 (3.1)
Preeclampsia	114 (4.7)	542 (2.6)	656 (2.8)
Prior SPPH, *n* (%)	102 (4.2)	895 (4.3)	997 (4.3)
Prior cesarean delivery, *n* (%)	275 (11.4)	2319 (11.1)	2594 (11.2)
Platelet count (IQR)	134 (116–143)	223 (186–274)	
Platelet disorders, *n* (%)			
Gestational thrombocytopenia	2206 (91.8)	–	2206 (9.5)
HELLP syndrome	171 (7.1)[a]	84 (0.4)	255 (1.1)
ITP	20 (0.8)[a]	10 (<0.1)	30 (0.1)
Thrombopathy	4 (0.2)	16 (0.1)	20 (0.1)
Other	2 (0.1)	3 (<0.1)	5 (<0.1)
Platelet transfusion between last platelet count before delivery, and 24 h after delivery, *n* (%)	35 (1.5)	28 (0.1)	63 (0.3)

Abbreviations: BMI, body mass index; HELLP, hemolysis, elevated liver enzymes, and low platelets; IQR, interquartile range; ITP, immune thrombocytopenic purpura; SD, standard deviation; SPPH, severe postpartum hemorrhage.

[a]One case had both ITP and HELLP syndrome.

CI 1.93–16.26). However, the effect of a platelet count $<50 \times 10^9$/L compared with a normal platelet count was no longer significant (aOR 1.80, 95% CI 0.80–4.05). Of note, only 3/52 patients had a PDW of ≥23% in this group (Supporting information 4). The effect of the other platelet count categories remained largely unaltered (data not shown).

4 | DISCUSSION

4.1 | Main findings

In this retrospective cohort study, we investigated the relationship between platelet count and platelet indices, and SPPH. We found that a low platelet count, a low plateletcrit, and a PDW of ≥23% were independently related to an increased risk of SPPH. Stratification revealed similar relations between platelet parameters and severe postpartum hemorrhage for vaginal and emergency cesarean deliveries, but not for primary cesarean deliveries.

4.2 | Strengths and limitations

A strength of this study is the size of the cohort, which allowed for high statistical precision. Overall, the documentation of patient characteristics was good (Supporting information 1). Our cohort included women with both vaginal and cesarean deliveries in both primary and secondary/tertiary care, making our results broadly applicable.

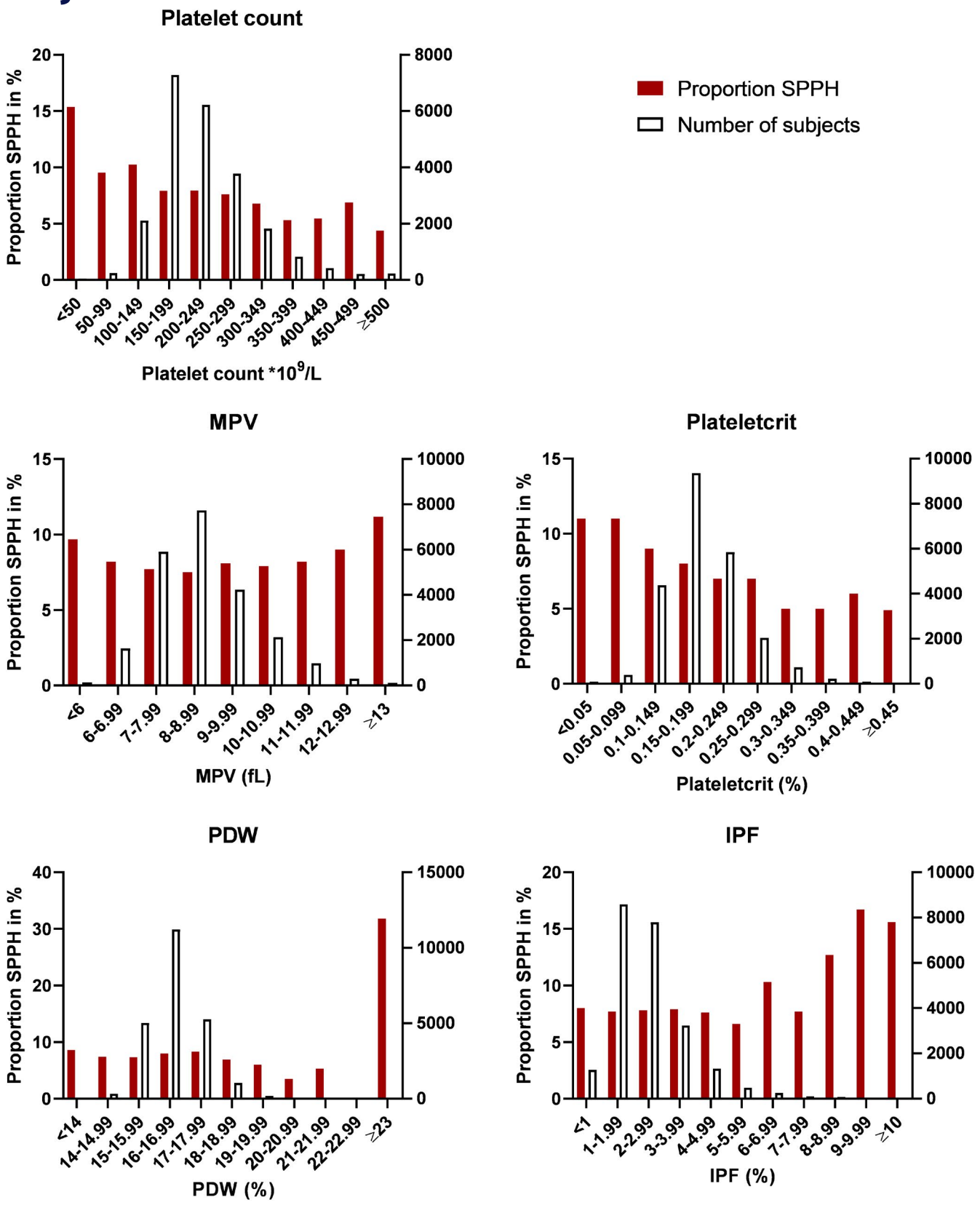

FIGURE 2 Proportion SPPH and number of subjects in each group, per platelet characteristic. Abbreviations: IPF, immature platelet fraction; MPV, mean platelet volume; PDW, platelet distribution width; SPPH, severe postpartum hemorrhage

TABLE 2 Odds ratios of SPPH for platelet characteristics

	Platelet Count *10^9/L					MPV	Plateletcrit	PDW	IPF
Platelet Characteristic	**<50**	**50–99**	**100–149**	**150–349**	**≥350**	**1 fL decrease**	**0.05% decrease**	**≥23%**	**≥6%**
All women (n = 23 205)									
N	52	241	2109	19 106	1697	NA	NA	22	492
Unadjusted OR (95% CI)	**2.21** (1.03–4.73)	1.33 (0.86–2.08)	**1.41** (1.18–1.67)	1 (ref.)	**0.63** (0.47–0.83)	0.98 (0.94–1.02)	**1.17** (1.11–1.23)	**6.23** (2.34–16.6)	1.35 (0.96–1.90)
Adjusted OR* (95% CI)	**2.24** (1.02–4.94)	1.22 (0.77–1.93)	**1.31** (1.10–1.56)	1 (ref.)	**0.67** (0.51–0.89)	1.01 (0.97–1.05)	**1.15** (1.08–1.21)	**6.05** (2.25–16.2)	1.38 (0.97–1.96)

Odds ratios were calculated using multivariate logistic regression. Statistically significant results are displayed in bold.

Abbreviations: CI, confidence interval; HELLP, hemolysis, elevated liver enzymes, and low platelets; IPF, immature platelet fraction; MPV, mean platelet volume; NA, not applicable; OR, odds ratio; PDW, platelet distribution width; ref., reference category; SPPH, severe postpartum hemorrhage.

*Adjusted for: maternal age, multiple gestation, macrosomia, induction of labor, preeclampsia, and HELLP syndrome.

The main limitation of this study lies in the retrospective nature of the data collection. Although we aimed to correct for all relevant confounders, residual confounding might be present. Furthermore, there could be bias because blood tests were ordered by medical indication; thus, complete cases might comprise more "high-risk" pregnancies. We aimed to reduce this possible bias by using multiple imputation. Furthermore, our sensitivity analysis showed that the relationship between platelet characteristics and SPPH did not differ importantly between high- and low-risk populations (Supporting information 4). Furthermore, estimating rather than measuring the amount of blood loss is known to have poor accuracy, and this method was used in an unknown proportion of the cases.[62,63] Also, estimation of blood loss might have biased the results towards a higher estimated blood loss in women at risk of SPPH (for example, women with thrombocytopenia). However, guidelines state that women with thrombocytopenia are mostly not at an increased risk of SPPH, and the role of platelet indices in SPPH is unknown. Because of this, and because we used SPPH as a dichotomous outcome, we expect this to have a limited effect on our results. Another limitation was the limited number of subjects in the <50 × 10^9/L platelet count group, impairing statistical precision.

4.3 | Interpretation

4.3.1 | Platelet count and SPPH

We found a relation between a lower platelet count and an increased risk of SPPH. The results of our study are consistent with the study conducted by Biguzzi et al. in a prospective cohort of 6011 singleton vaginal deliveries, where an increased PPH risk was seen with lower platelet counts.[23] Carlson et al. also found a relation between thrombocytopenia and PPH, in a prospective cohort of 54 597 women delivering by cesarean section, or vaginally after a prior cesarean section.[24]

The difference in outcomes between vaginal and emergency cesarean deliveries on one hand and primary cesarean deliveries on the other hand is remarkable. Blood loss is generally higher in cesarean deliveries than in vaginal deliveries, and it seems that platelet count plays a more important role in the amount of blood loss after emergency cesarean deliveries and vaginal deliveries than in primary cesarean deliveries. A possible explanation for this is that cesarean deliveries offer the opportunity to control the bleeding locally, and because primary cesarean deliveries are generally more controlled procedures than emergency cesarean deliveries, there is more time for local hemostasis.

Another finding is that women in the 50–99 × 10^9/L platelet count group seemed to have a lower risk of SPPH than women in the 100–149 × 10^9/L platelet count group. However, the first group was relatively small, and thus possibly underpowered. Furthermore, because of the retrospective nature of the study, the results in this group might be biased by treatment effects.

Correction for aspirin did not influence our results, despite a recent study showing that aspirin use increases the risk of SPPH.[64]

Most likely, this difference is due to the fact that our study already included preeclampsia in the model, unlike the other study. Because preeclampsia is closely related to aspirin use during pregnancy, correction for aspirin is unlikely to have any additional value. There were no other obvious differences between our study and Hastie et al.'s to account for the difference in results: the proportion of patients using aspirin (1.7% and 1.3%[64]) and the use of higher (>75 mg) rather than lower doses were similar. Furthermore, both our countries' guidelines advise to stop aspirin treatment at a gestational age of 36 weeks, although both studies lack data about the stop date of aspirin.[64,65]

4.3.2 | Platelet indices and SPPH

The relation between other platelet indices and SPPH has not been studied before. We found that a low plateletcrit and a PDW of ≥23% were related to SPPH in the whole study population.

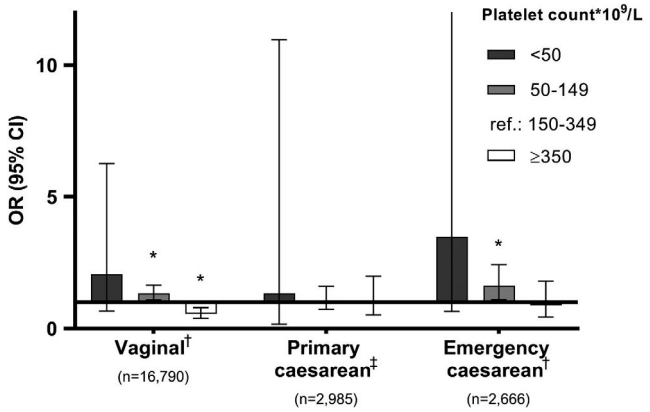

FIGURE 3 Odds ratios were calculated using multivariate logistic regression and stratified by mode of delivery. *$p < 0.05$. †Adjusted for: maternal age, multiple gestation, macrosomia, induction of labor, preeclampsia, and HELLP syndrome. ‡Adjusted for: maternal age, multiple gestation, macrosomia, preeclampsia, and HELLP syndrome. Upper limits confidence intervals: a, 6.27; b, 11.0; c, 18.5. Abbreviations: CI, confidence interval; HELLP, hemolysis, elevated liver enzymes and low platelets; OR, odds ratio; SPPH, severe postpartum hemorrhage

Plateletcrit is the product of MPV and platelet count, was related to an increased SPPH risk. Plateletcrit did not seem to be more strongly related to SPPH than the platelet count. This corresponds with our finding that the MPV is not significantly related to SPPH, and thus the platelet count component of the plateletcrit mainly seems to dictate its relation to SPPH risk. Because most physicians are used to working with the platelet count, and not the plateletcrit, we consider plateletcrit to be of no added value in clinical practice.

Another finding of our study is that a PDW of ≥23% was strongly related to SPPH. Only a small subset of patients met this criterion, possibly because PDW is known to have low reproducibility and thus large variability in patients. This finding is remarkable as previous studies have shown that a high PDW was associated with thrombotic rather than bleeding events.[34,36] However, a high PDW has also been associated with mortality and morbidity in several non-thrombotic conditions.[66-70] Although we suspected that the PDW could be surrogate for more ill patients with severe thrombocytopenia, the finding remained significant after adjustment for platelet count. Our analysis suggests that in fact the PDW might be a better explanatory variable for SPPH than a platelet count $<50 \times 10^9$. A high PDW could be of additional value in patients with a low platelet count, possibly because of an association with a poor general condition or (subclinical) underlying conditions.[71] However, our results for PDW could be partly data-driven because no a priori cutoff could be selected, and the number of subjects in particularly the group with very low platelet counts are very small. Therefore, we suggest to not take this finding too seriously; more research is needed to confirm a possible additional value in clinical practice.

A low MPV and an IPF of ≥6% were only related to SPPH in primary caesarean deliveries. Given the mixed results of other studies regarding MPV and bleeding risk,[47-53] and that we have no clear explanation for this finding, we consider the MPV of limited value in clinical practice. A low IPF is known to be related to bone marrow failure and increased bleeding risk in subjects with Immune thrombocytopenic purpura,[45] and a high IPF has been shown to correlate with acute coronary syndromes. This is in contrast to our finding that a high IPF is related to an increased bleeding risk. However, the IPF is generally higher in smokers and diabetics, and thus could have been subject to confounding in our study.[43]

TABLE 3 aORs of SPPH for platelet indices, stratified by mode of delivery

Platelet Index	MPV, 1 fL Decrease, aOR (95% CI)	Plateletcrit, 0.05% Decrease, aOR (95% CI)	IPF, ≥6%, aOR (95% CI)
Vaginal delivery[a] (n = 16 790)	0.97 (0.92–1.02)	**1.15** (1.08–1.23)	1.10 (0.69–1.77)
Primary cesarean[b] (n = 2985)	**1.17** (1.04–1.31)	1.09 (0.94–1.26)	**2.27** (1.20–4.28)
Emergency cesarean[a] (n = 2666)	1.04 (0.93–1.17)	**1.25** (1.07–1.45)	1.54 (0.61–3.88)

Odds ratios were calculated using multivariate logistic regression. Statistically significant results are displayed in bold.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HELLP, hemolysis, elevated liver enzymes, and low platelets; IPF, immature platelet fraction; MPV, mean platelet volume; SPPH, severe postpartum hemorrhage.

[a]Adjusted for: maternal age, multiple gestation, macrosomia, induction of labor, preeclampsia, and HELLP syndrome.

[b]Adjusted for: maternal age, multiple gestation, macrosomia, preeclampsia, and HELLP syndrome.

5 | CONCLUSION

5.1 | Practical recommendations

We found that a low platelet count was related to an increased risk of SPPH. Most platelet indices do not seem of additional value in the occurrence of SPPH, although extra research is warranted to address the relevance of a PDW of ≥23%. Because the aORs for different degrees of thrombocytopenia were relatively small, the clinical significance of these findings might be limited. Our results, however, underline the cutoff of $>50 \times 10^9$/L platelets for safe delivery. We also recommend increased vigilance when patients have mild thrombocytopenia in the days before delivery.

5.2 | Research recommendations

Further research on this topic should focus on women with thrombocytopenia, as we had limited statistical precision in the lowest platelet count group. Furthermore, the value of platelet count and platelet indices in SPPH prediction models should be investigated because they are related to SPPH with little dependence on other SPPH risk factors. Our dataset is available on request for the development and validation of such prediction models.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Wobke E.M. van Dijk, Roger E.G. Schutgens, A.T. Lely, Karin P.M. van Galen. Methodology: Wobke E.M. van Dijk, Jelle S. Nijdam, Saskia Haitjema, Mark C.H. de Groot, Roger E.G. Schutgens, A.T. Lely, Karin P.M. van Galen. Formal analysis: Wobke E.M. van Dijk, Jelle S. Nijdam. Investigation: Wobke E.M. van Dijk, Jelle S. Nijdam, A.T. Lely, Karin P.M. van Galen. Data curation: Wobke E.M. van Dijk, Jelle S. Nijdam, Saskia Haitjema, Mark C.H. de Groot. Writing – original draft: Wobke E.M. van Dijk, Jelle S. Nijdam. Writing – review & editing: Wobke E.M. van Dijk, Jelle S. Nijdam, Saskia Haitjema, Mark C.H. de Groot, Albert Huisman, Marieke C. Punt, Annemiek C.C. Evers, Roger E.G. Schutgens, A.T. Lely, Karin P.M. van Galen. Visualization: Wobke E.M. van Dijk, Jelle S. Nijdam, A.T. Lely, Karin P.M. van Galen. Supervision: Roger E.G. Schutgens, A.T. Lely, Karin P.M. van Galen. Project administration: Wobke E.M. van Dijk, Jelle S. Nijdam. Funding acquisition: Roger E.G. Schutgens, A.T. Lely, Karin P.M. van Galen.

ETHICS APPROVAL

This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008,[54] and does not fall under the scope of the WMO (Medical Research Involving Human Subjects Act), as judged by the Medical Research and Ethics Committee of the UMCU on the 19th of September 2018 (reference number WAG/mb/18/033284).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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