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Most major bleeds in preterm infants occur in the absence of severe thrombocytopenia: an observational cohort study

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ABSTRACT

Objective To describe the incidence of major bleeds according to different platelet counts in very preterm infants, and to explore whether this association is influenced by other risk factors for bleeding.

Design Observational cohort study.

Setting A Dutch tertiary care neonatal intensive care unit.

Patients All consecutive infants with a gestational age at birth <32 weeks admitted between January 2004 and July 2022.

Exposure Infants were stratified into nine groups based on their nadir platelet count ($\times 10^9/L$) during admission (<10, 10–24, 25–49, 50–99, 100–149, 150–199, 200–249, 250–299 and ≥ 300), measured before the diagnosis of a major bleed and before any platelet transfusion was administered.

Main outcome measure Incidence of major bleeds during admission. Logistic regression analysis was used to quantify the relationship between nadir platelet count and incidence of major bleeds.

Results Among 2772 included infants, 224 (8%) developed a major bleed. Of the infants with a major bleed, 92% (206/224) had a nadir platelet count $\geq 50 \times 10^9/L$. The incidence of major bleeds was 8% among infants with and without severe thrombocytopenia (platelet count $< 50 \times 10^9/L$), 18/231 (95% CI 5 to 12) and 206/2541 (95% CI 7 to 9), respectively. Similarly, after adjustment for measured confounders, there was no notable association between nadir platelet counts below versus above $50 \times 10^9/L$ and the occurrence of major bleeds (OR 1.09, 95% CI 0.61 to 1.94).

Conclusion In very preterm infants, the vast majority of major bleeds occur in infants without severe thrombocytopenia.

INTRODUCTION

Major bleeds, particularly severe intraventricular haemorrhage (IVH), are a serious complication in preterm infants and are associated with adverse neurodevelopmental outcomes.¹ Because platelets play a crucial role in primary haemostasis, thrombocytopenia is widely considered a risk factor for IVH and other types of bleeds, such as pulmonary and gastrointestinal bleeds.² However, multiple studies found no clear linear relationship between the degree of thrombocytopenia and the incidence

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Major bleeds, particularly severe intraventricular haemorrhage, are a serious complication in preterm infants, associated with adverse neurodevelopmental outcomes.
- ⇒ Multiple studies found a poor association between the severity of thrombocytopenia and major bleeds, but they often excluded normal platelet counts or lacked detailed information.

WHAT THIS STUDY ADDS

- ⇒ Most major bleeds (92%) occurred in infants with normal platelet counts.
- ⇒ In this large cohort, the incidence of major bleeds among infants with normal platelet counts was the same as among those with severe thrombocytopenia.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This study confirms no linear association between platelet counts and major bleeds, emphasizing the need for improved bleeding prediction, including infants with normal platelet counts.

of severe bleeds in thrombocytopenic infants.^{3–8} Similarly, in paediatric and adult patients with chemotherapy-induced thrombocytopenia, the risk of bleeding did not increase in direct correlation with the severity of thrombocytopenia.^{9,10} Increasing evidence suggests that the pathogenesis of bleeding is multifactorial, including vascular fragility and susceptibility to haemodynamic instability,^{11,12} and that other risk factors such as gestational age (GA), postnatal age within 10 days of birth and necrotising enterocolitis (NEC) are important predictors of bleeding.^{3,5,13} When examining the association between thrombocytopenia and bleeding risk, it is essential to consider that IVH is usually asymptomatic and most frequently detected during routine cranial ultrasound screening. In addition, thrombocytopenia is often asymptomatic and only detected during routine full blood count measurements, which are not performed on a daily basis. Furthermore, studies assessing the relation between platelet counts and bleeding incidence are often limited by temporal ambiguity, which means that it is unclear

whether thrombocytopenia occurred before or after a major bleed, making it difficult to interpret whether thrombocytopenia was a cause or effect of the bleed.¹⁴ Some studies have attempted to avoid temporal ambiguity, but they often restricted their study population to infants with severe thrombocytopenia as a target for intervention by platelet transfusions,^{3 5 6 15} while it is unclear how many infants with normal platelet counts develop a major bleed. If the majority of major bleeds occur in infants without thrombocytopenia, more research attention may be warranted to prevent bleeding in this population.

The aim of this study was to describe the incidence of major bleeds at varying platelet counts and to explore if the association with major bleeds is influenced by other known and measured risk factors, while taking chronological order of events into account, thus avoiding temporal ambiguity as best as possible.

METHODS

Study design, setting and population

We performed an observational cohort study of infants with a GA <32 weeks, who were admitted immediately after birth to the neonatal intensive care unit (NICU) of the Leiden University Medical Centre, one of nine tertiary NICUs in the Netherlands, between January 2004 and July 2022. We included all consecutive infants who met our inclusion criteria during this period to prevent selection bias. Follow-up started at the moment of birth and ended at NICU discharge, transfer to another hospital or death, whichever occurred first. We excluded all infants with (1) no or only spurious platelet counts available during admission; (2) date of diagnosis of major bleed not available; (3) only platelet counts measured after a major bleed or platelet transfusion and (4) absence of cranial ultrasound(s) due to transfer within 24 hours after birth. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guideline.¹⁶

Exposure

Temporal ambiguity is present when it is unclear whether an exposure occurred before or after the outcome. If thrombocytopenia is present after a major bleed, it may be a result—and not a cause—of the bleed, making a causal interpretation of the study results impossible.¹⁴ To avoid temporal ambiguity as much as possible, we defined the nadir as the lowest platelet count measured before the diagnosis of a major bleed. For infants who received platelet transfusions, we selected the nadir before the first transfusion, because the direction of the effect of platelet transfusions on bleeding risk is not known; platelet transfusions may have prevented bleeds, but there is also evidence of increased bleeding risk following transfusions at platelet count thresholds $>25 \times 10^9/L$.^{17 18} For infants without major bleed and transfusions, we selected the nadir during the whole NICU period (figure 1).

Prior to statistical analyses, infants were stratified into nine groups based on their nadir platelet count using the following cut-off points ($\times 10^9/L$): 10, 25, 50, 100, 150, 200, 250 and 300. For thrombocytopenic infants (nadir $<150 \times 10^9/L$), we chose these cut-off points based on randomised controlled trials (RCTs) comparing different platelet transfusion strategies in preterm infants,^{19–21} except for the threshold of $10 \times 10^9/L$, which has only been used in trials among adults.^{10 22–27} We categorised infants with nadirs $\geq 150 \times 10^9/L$ in groups per $50 \times 10^9/L$, because of the relatively large number in this group (n=1627) and to explore whether each $50 \times 10^9/L$ decrease in

Non-bleeders

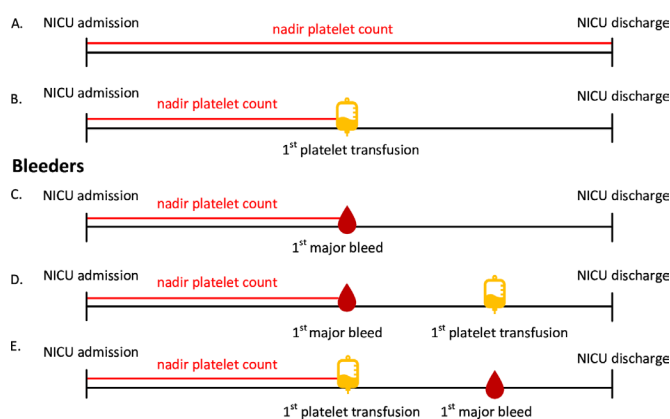


Figure 1 Selection of the nadir platelet count. This figure shows how we selected the nadir (ie, lowest) platelet count, with the red line indicating the period in which the nadir was determined, in the following situations. (A, B) In infants without a major bleed during NICU admission ('non-bleeders') without any platelet transfusions and with at least one prophylactic platelet transfusion before NICU discharge. (C–E) In infants with a major bleed during NICU admission ('bleeders') without any platelet transfusions, with only therapeutic platelet transfusion(s) after a major bleed, and with at least one prophylactic platelet transfusion before the diagnosis of a major bleed. NICU, neonatal intensive care unit.

platelet count significantly increased bleeding risk, as reported in a recent cohort study.²⁸

Outcomes

The primary outcome was a diagnosis of a major bleed during NICU admission. This included major intracranial, pulmonary and gastrointestinal bleeds. According to our cranial ultrasound screening protocol, infants born at a GA <30 weeks underwent routine cranial ultrasound scans on days 1, 3 and 7 after birth, followed by biweekly scans until NICU discharge. For infants of 30–32 weeks gestation, scans were conducted on days 1 and 7 after birth and prior to NICU discharge. Additional ultrasounds were performed at the neonatologists' discretion, for example if an ultrasound showed abnormalities, in case of clinical deterioration, a sudden drop in haemoglobin or if surgery was required. Definitions of major bleeds were based on the modified neonatal WHO bleeding score.^{19 29} Major IVH was defined as IVH filling $\geq 50\%$ of the cerebral ventricle (grade 3) and IVH of any grade complicated by parenchymal periventricular haemorrhagic infarction (PVHI) according to the Volpe classification.³⁰ Other types of intracranial bleeds, including isolated parenchymal, subdural and cerebellar bleeds, were considered major if they showed a midline shift on radiological imaging, required neuro-surgical intervention or were associated with haemodynamic instability necessitating volume boluses, inotropes or blood products within 24 hours. Major pulmonary bleeds were characterised by acute respiratory deterioration combined with a fresh bleed from the trachea requiring mechanical ventilation, or a fresh bleed from the endotracheal tube requiring increased ventilatory settings. Gastrointestinal bleeds were defined as fresh visible rectal bleeds, except for mild bleeding caused by NEC.

Secondary outcomes were mortality before NICU discharge to a stepdown unit, and a composite of a major bleed or death, where infants who developed a major bleed and then died were only recorded as having a major bleed.

Original research

Covariates

Baseline characteristics included GA at birth, sex, birth weight, small-for-gestational age (birth weight $< p10$),³¹ multifetal pregnancy, mode of delivery, perinatal asphyxia, major congenital malformation, postnatal age at nadir and length of NICU stay. In addition, we gathered medical record data on conditions associated with a higher bleeding risk: NEC with Bell's stage $\geq$ IIA,³² culture-positive sepsis, inotrope use and mechanical ventilation. Laboratory data on platelet counts and platelet transfusions were extracted from the laboratory system.

Statistical analyses

For each nadir platelet count, we calculated the incidence of subsequent major bleed and mortality, including their corresponding 95% CIs (for binomial proportions). Together with neonatology, haematology and epidemiology experts, we made a directed acyclic graph to identify potential confounders for the association between nadir platelet count and major bleeds (online supplemental figure S1). After univariable logistic regression, we performed multivariable regression analyses to adjust for confounders (reference group: $200\text{--}249 \times 10^9/\text{L}$).³³ Since mortality is a competing risk for the occurrence of a major bleed, we also analysed the composite outcome of major bleed or death. In addition, we conducted sensitivity analyses excluding infants with major congenital malformations and using the year 2012 as a stratification cut-off to account for changes in neonatal practice over time, as findings from the second decade may be more relevant to current practice.

RESULTS

Patient characteristics

Of 3138 infants admitted to the NICU during the study period, 2772 infants were included (figure 2). The median GA was 29 weeks (IQR 27–30) and the mean birth weight was 1236 g (SD 367) (table 1). The incidence of thrombocytopenia ($< 150 \times 10^9/\text{L}$) and severe thrombocytopenia ($< 50 \times 10^9/\text{L}$) was 41% (1145/2772) and 8% (231/2772), respectively.

Major bleeds and mortality

A total of 224 (8%, 95%CI 7 to 9) major bleeds occurred (figure 3), of which 178 (79%) were major IVH, 5 (2%) were other major intracranial bleeds, 35 (16%) were pulmonary bleeds and 6 (3%) were gastrointestinal bleeds (online supplemental table S1). The median age at which a major bleed was diagnosed was 2 days after birth (IQR, 2–4 days), and 74% of all bleeds occurred during the first 3 days of life, with only 18 (8%) bleeds after the first week (online supplemental figure S2). Most pre-bleeding nadirs were measured on the same day as the diagnosis of a major bleed, except for nadirs $10\text{--}24 \times 10^9/\text{L}$ and $25\text{--}49 \times 10^9/\text{L}$, with a median time from nadir to diagnosis of 1 and 2 days (both IQR 0–3), respectively (online supplemental table S1). The incidence of major bleeds did not differ between infants with severe thrombocytopenia (18/231, 8%, 95%CI 5 to 12) and those with a nadir $\geq 50 \times 10^9/\text{L}$ (206/2541, 8%, 95%CI 7 to 9) (p value=0.9, figure 4). Among infants with a major bleed, 8% (18/224) had a pre-bleeding nadir $< 50 \times 10^9/\text{L}$ and 92% (206/224) had a pre-bleeding nadir $\geq 50 \times 10^9/\text{L}$. The major bleeds in five infants with nadirs below $25 \times 10^9/\text{L}$ were all bleeds other than IVH: two pulmonary bleeds, one subdural

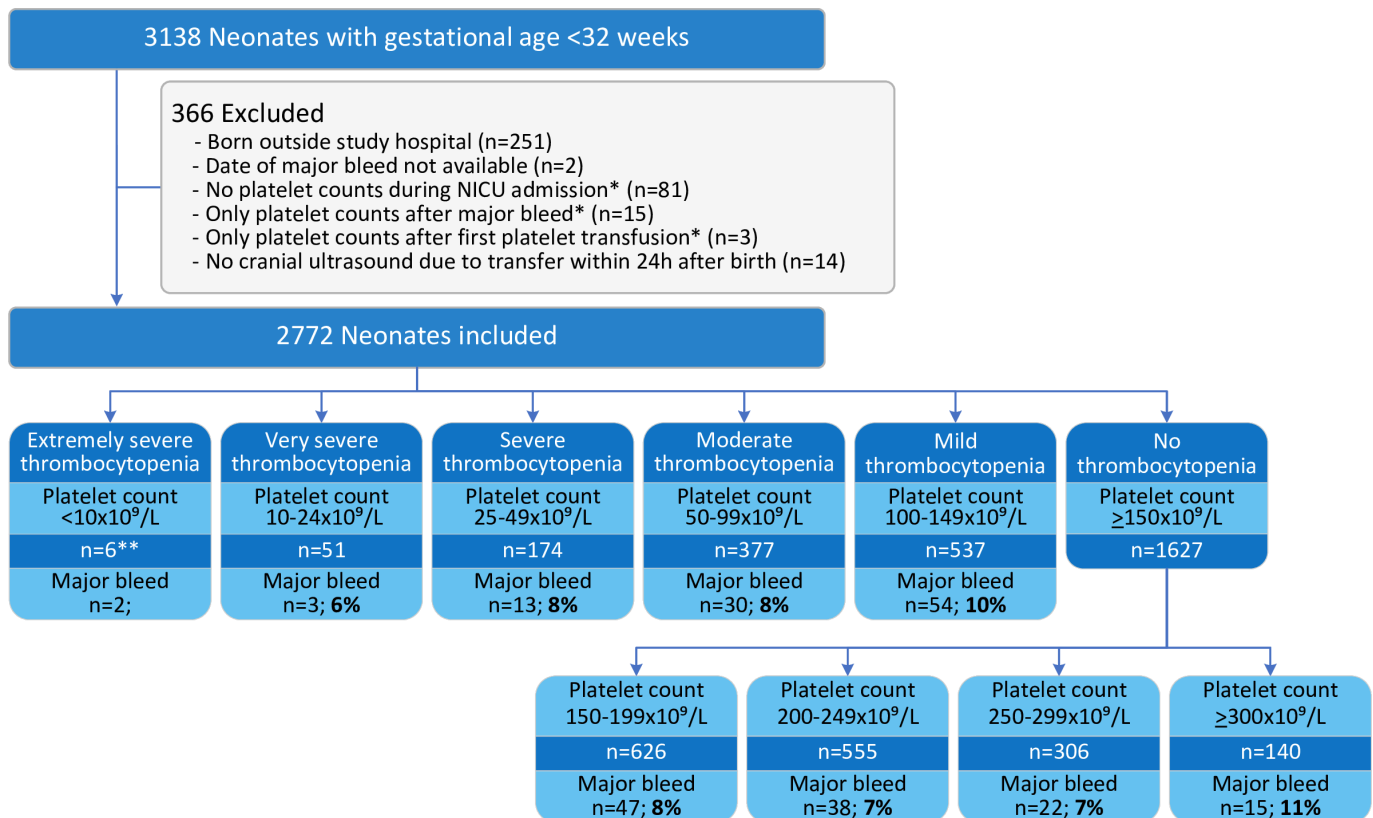


Figure 2 Study flow chart showing the selection of study participants and the number of major bleeds, stratified by nadir platelet count. *Or only spurious platelet counts. **This group of six is too small to provide robust estimates. NICU, neonatal intensive care unit.

Table 1 Baseline characteristics

Characteristic	Nadir platelet count ($\times 10^9/L$)									
	Overall (n=2772)	<10 (n=6)	10–24 (n=51)	25–49 (n=174)	50–99 (n=377)	100–149 (n=537)	150–199 (n=626)	200–249 (n=555)	250–299 (n=306)	≥ 300 (n=140)
GA at birth, median (IQR), weeks	29 (27–30)	29 (27–30)	28 (27–30)	28 (27–30)	28 (27–30)	29 (27–30)	29 (27–31)	30 (28–31)	30 (28–31)	30 (28–31)
Male sex, n (%)	1478 (53)	4 (67)	25 (49)	103 (59)	208 (55)	287 (54)	356 (57)	293 (53)	139 (45)	63 (45)
Birth weight, mean $\pm$ SD, g	1236 $\pm$ 367	1627 $\pm$ 834	962 $\pm$ 355	977 $\pm$ 318	1048 $\pm$ 314	1166 $\pm$ 343	1261 $\pm$ 346	1366 $\pm$ 338	1390 $\pm$ 334	1454 $\pm$ 354
SGA, n (%)	926 (33)	2 (33)	34 (67)	116 (67)	192 (51)	204 (38)	188 (30)	109 (20)	65 (21)	16 (11)
Caesarean section, n (%)	1399 (51)	6 (100)	37 (73)	139 (80)	228 (61)	301 (56)	298 (48)	234 (42)	111 (36)	45 (32)
Twin pregnancy, n (%)	1127 (41)	0 (0)	11 (22)	61 (35)	135 (36)	240 (45)	274 (44)	239 (43)	121 (40)	46 (33)
Birth asphyxia, n (%)	55 (2)	1 (17)	1 (2)	8 (5)	11 (3)	16 (3)	9 (1)	5 (1)	4 (1)	0 (0)
Mechanical ventilation, n (%)	1241 (45)	6 (100)	43 (84)	123 (71)	238 (63)	305 (57)	247 (40)	182 (33)	68 (22)	29 (21)
Sepsis,* n (%)	715 (26)	4 (67)	28 (55)	81 (47)	146 (39)	178 (33)	133 (21)	80 (14)	50 (16)	15 (11)
NEC,† n (%)	117 (4)	0 (0)	7 (14)	13 (8)	22 (6)	24 (5)	24 (4)	20 (4)	6 (2)	1 (1)
Inotropes, n (%)	382 (14)	3 (50)	14 (28)	59 (34)	92 (24)	95 (18)	68 (11)	38 (7)	8 (3)	5 (4)
Major congenital malformation,‡ n (%)	90 (3)	2 (33)	4 (8)	5 (3)	19 (5)	23 (4)	11 (2)	14 (3)	11 (4)	1 (1)
Number of PLT transfusions per infant,§ median (IQR), n	1 (1–2) (n=181)	3 (3–5) (n=4)	2 (1–3) (n=50)	1 (1–2) (n=104)	1 (1–2) (n=20)	1 (1–1) (n=1)	0 (n=0)	1 (1–1) (n=2)	0 (n=0)	0 (n=0)
Postnatal age at nadir,¶ median (IQR), days	2 (1–3)	6 (1–13)	5 (3–10)	4 (2–6)	3 (2–5)	2 (1–4)	1 (1–3)	1 (1–2)	1 (1–2)	1 (1–1)
Length of NICU stay, median (IQR), days	13 (6–29)	11 (6–42)	19 (11–43)	23 (11–43)	21 (10–39)	18 (8–35)	12 (6–26)	10 (5–23)	8 (4–16)	8 (4–17)

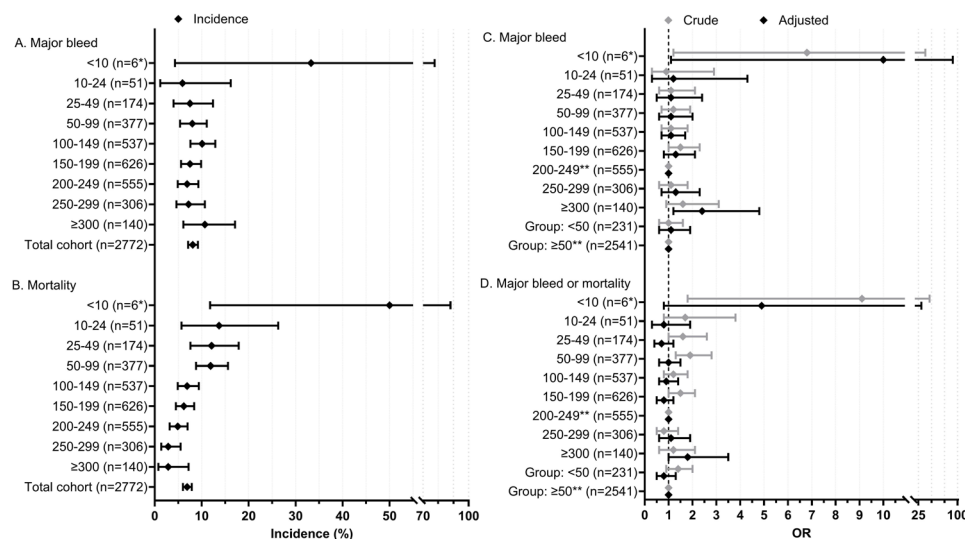
*Culture-positive sepsis.

†NEC $\geq$ grade IIA as per Bell's criteria.

‡Congenital malformation associated with a poor prognosis or life-threatening condition.

§Number of prophylactic platelet transfusions (after the nadir) per transfused infant. The transfusion indications in the group of $100\text{--}149 \times 10^9/L$ (n=1) and $200\text{--}249 \times 10^9/L$ (n=2) were resuscitation setting and cardiac surgery, respectively.

¶The first 24 hours after birth are counted as day 1.

GA, gestational age; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; PLT, platelet; SGA, small-for-gestational age (birth weight $< p10$).**Figure 3** Incidence of major bleeds and mortality and logistic regression models. *This group of six is too small to provide robust estimates.

**Reference category. (A, B) Incidence of major bleeds and mortality during admission to the neonatal intensive care unit with 95% CIs, stratified by nadir platelet count. (C, D) ORs of the crude (grey) and adjusted (black) logistic regression analyses for the association between nadir platelet count and major bleeds and the composite of major bleed or mortality with 95% CI. In the crude analysis, only nadir platelet count categories were included. In the adjusted analyses, also gestational age, postnatal age at nadir platelet count, small-for-gestational age (birth weight $< p10$), perinatal asphyxia, proven sepsis, necrotising enterocolitis $\geq$ grade IIA, mechanical ventilation and inotropes were included.

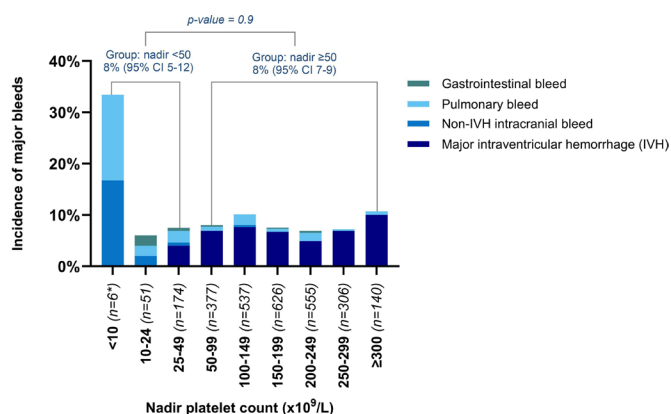


Figure 4 Incidence of the first major bleed per bleeding type, stratified by nadir platelet count. *This group of six is too small to provide robust estimates. Incidence of major bleeds for infants with a nadir $<50 \times 10^9/L$ was 8% (18/231, 95% CI 5 to 12) and for those with a nadir $\geq 50 \times 10^9/L$ also 8% (206/2541, 95% CI 7 to 9). The p value refers to a two-sample test for equality of proportions.

bleed, one frank rectal bleed requiring transfusion and one severe cerebellar bleed (figure 4). Major bleeding incidence decreased with increasing GA (online supplemental figure S2). The overall mortality rate was 7% (95% CI 6 to 8) and was higher for infants with lower nadirs (figure 3). Of the total of 192 deaths, 6 infants (3%) died in the first 24 hours before a cranial ultrasound was made, including 1 with a major pulmonary bleed and the other 5 with no clinical signs of bleeding. Neither univariable nor multivariable logistic regression analysis demonstrated noteworthy associations between the nadir and major bleeds, OR 0.96 (95% CI 0.58 to 1.58, p value=0.9) and OR 1.09 (95% CI 0.61 to 1.94, p value=0.8) for the crude and adjusted analysis of nadir $<50 \times 10^9/L$ versus $\geq 50 \times 10^9/L$, respectively (figure 3, online supplemental table S2). Sensitivity analyses excluding major congenital malformations and stratified by the year 2012 showed comparable results (online supplemental figure S3 and online supplemental table S3).

DISCUSSION

This study shows that most major bleeds (92%) occurred among very preterm infants without severe thrombocytopenia. We saw no substantial differences in the incidence of major bleeds between infants with and without (severe) thrombocytopenia, except for a higher incidence among those with nadirs $<10 \times 10^9/L$. However, more data are needed to assess the risk of bleeding among these infants, as this group of six is too small to provide robust estimates.

We are not the first to report no clear linear association between platelet count and bleeding incidence in preterm infants.^{3-6 8 34} However, others found an association between lower platelet counts and an increased bleeding risk,^{15 28 35 36} although some did not take into account temporal ambiguity.^{35 36} In general, the problem with all these studies—which may also explain the different findings—is that most infants with low platelet counts received one or more prophylactic platelet transfusions with the aim to reduce the risk of bleeding, but it is unclear to what extent these transfusions benefit patients with severe thrombocytopenia.¹⁴ On the one hand, they may have prevented bleeds, that is, the risk of bleeding in severely thrombocytopenic infants may be lowered by prophylactic transfusions to the same risk as among those with normal counts. On the other hand, they may also have increased the risk of bleeding, as a large RCT

suggested harm with higher transfusion thresholds.¹⁹ To mitigate the potentially distorting effect of platelet transfusions, we selected the nadir before any platelet transfusions rather than the last platelet count before a major bleed. However, fully disentangling the effect of nadir platelet count from the effect of platelet transfusion on bleeding risk is also not possible in this study and would require RCTs comparing a prophylactic platelet transfusion strategy with a no-prophylaxis strategy (ie, therapeutic platelet transfusions only), which has not yet been studied in infants.

Strengths are that we described the incidence of major bleeds in an unselected and representative large study population, including preterm infants with all platelet counts, which are often not reported in studies investigating risk factors for bleeding. In addition, we minimised temporal ambiguity as much as possible by analysing nadir platelet counts prior to bleeding. Furthermore, there was a strict adherence to the cranial ultrasound screening protocol.

The study has limitations that may have influenced the results. First, this is a single-centre study over an 18-year period. This has implications for the generalisability of our results, as patient characteristics and local guidelines may differ in other centres and changes in neonatal practice have occurred over time, such as the introduction of delayed cord clamping and more non-invasive ventilation. We did not have detailed enough information to account for these time-dependent changes, but as the total incidence of major bleeds and mortality per nadir platelet count was comparable with the subgroup of infants admitted after 2012, this provides some reassurance that our findings are still relevant to current NICU practice.

Second, selection bias may have been introduced by excluding infants without cranial ultrasound because they were transferred within 24 hours after birth due to limited NICU bed availability. However, this was the case for only 14 infants. Infants excluded because of missing platelet counts were mainly those born before 2006, for whom not all laboratory data could be retrieved, and some clinically stable infants $>GA$ 30 weeks in whom no blood count screening was performed.

Third, our definition of non-IVH intracranial bleeds may have under-reported lobar parenchymal haemorrhage, which often does not involve a midline shift, surgical intervention or haemodynamic instability, but may still have long-term neurocognitive consequences.

Fourth, although we assumed that the nadir served as an acceptable surrogate for ‘being at risk for bleeding due to a low platelet count’, platelet counts can decline rapidly without being measured. In addition, despite routine serial cranial ultrasounds, the exact timing of intracranial bleeds is difficult to determine as these bleeds are usually asymptomatic, so the nadir may not necessarily reflect the infant’s actual platelet count status before bleeding.

This study emphasises the importance of ongoing research initiatives to find better approaches to identify infants who are at significant risk of bleeding. Other indications than platelet count thresholds alone should be investigated for prophylactic platelet transfusion decisions, and more research is needed into interventions that are also applicable to infants with normal platelet counts to prevent bleeds. Attention for both antenatal and postnatal neuroprotective strategies is important, such as the administration of antenatal corticosteroids and measures to prevent rapid changes in cerebral blood volume,^{11 37 38} which may also be implemented in neonatal care bundles of multiple interventions aimed at reducing IVH.^{39 40}

CONCLUSION

Ninety-two percent of the major bleeds occurred in preterm infants without severe thrombocytopenia. Importantly, the vast majority of infants had nadirs above $50 \times 10^9/L$ and there was no meaningful association between platelet counts above $10 \times 10^9/L$ and major bleeds. This underscores the importance of finding better approaches to predict severe bleeds in both thrombocytopenic and non-thrombocytopenic infants.

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Contributors HvdS, CC-D, JGvB and EL contributed substantially to the planning, conceptualisation and methodological design of the study. NMAH, HvdS and CC-D contributed substantially to the data collection, data cleaning and data analysis. HvdS and NMAH wrote the first draft of the manuscript. EL, JGvB, CC-D, SG, KF, SJS and LsDv gave significant input on the interpretation of the data and critically reviewed and edited the work. HvdS is the guarantor.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by 'nWMO-commissie divisie 3' of the Leiden University Medical Centre, reference number 23-3021, email: nWMO-div3@lumc.nl (website: <https://www.mtc-ldd.nl/indienen-niet-wmo-en-mdr>). Participants gave informed consent to participate in the study before taking part (opt-out consent procedure).

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