SUPPLEMENTAL MATERIALS

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

H. van der Staaij [1- 4*], N.M.A. Hooiveld [1], C. Caram-Deelder [2], S.F. Fustolo-Gunnink [1,3, 4], K. Fijnvandraat [3,4], S.J. Steggerda [1], L.S. de Vries [1], J.G. van der Bom [2], E. Lopriore [1]

[1] *Department of Pediatrics, Division of Neonatology, Willem-Alexander Children's Hospital, Leiden University Medical Center, the Netherlands*
[2] *Department of Clinical Epidemiology, Leiden University Medical Center, the Netherlands*
[3] *Sanquin Research & Lab Services, Sanquin Blood Supply Foundation, Amsterdam, the Netherlands*
[4] *Department of Pediatric Hematology, Emma Children's Hospital, Amsterdam University Medical Center, Amsterdam, the Netherlands*

CONTENT

Supplemental figures

Supplemental tables

van der Staaij H, *et al. Arch Dis Child Fetal Neonatal Ed* 2025; 110:122–127. doi: 10.1136/archdischild-2024-326959

SUPPLEMENTAL FIGURES

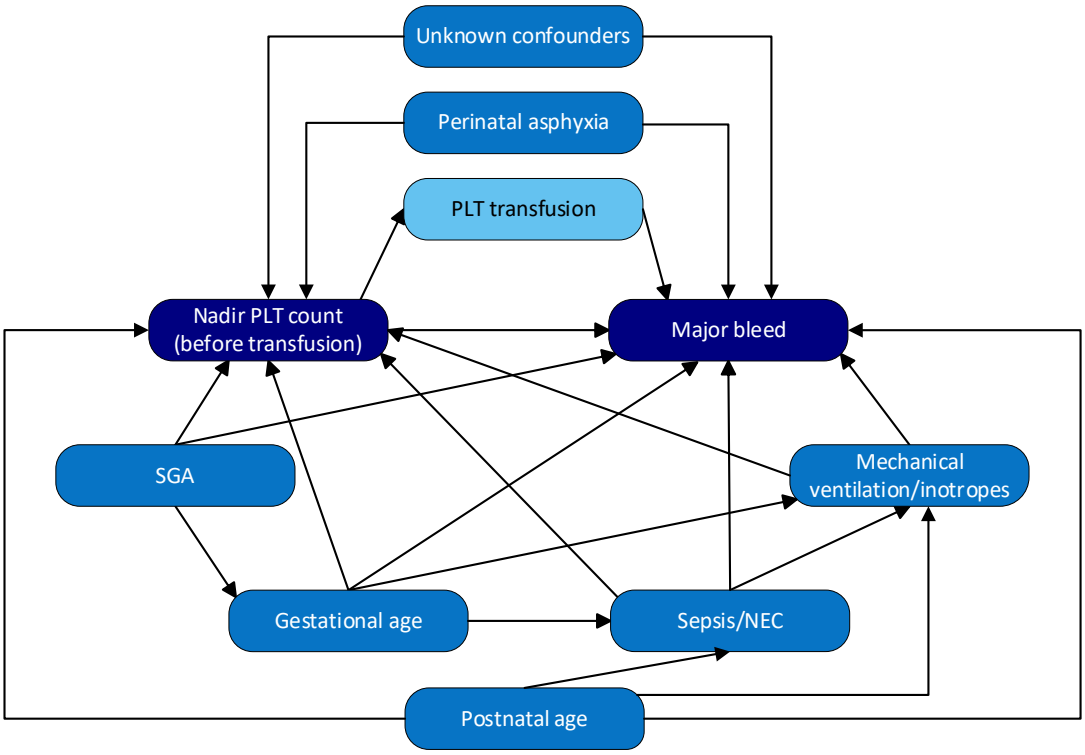

Figure S1. Directed acyclic graph for the association between nadir platelet count and major bleeds. In this directed acyclic graph (DAG), the dark blue boxes show the exposure (nadir platelet count) and the primary outcome (major bleed). The sky blue box represents prophylactic platelet transfusions, shown here as a mediator, since we did not take into account post-transfusion platelet counts, because we selected nadir platelet counts prior to transfusion. The cobalt blue boxes (all other variables) show potential confounders. Abbreviations: NEC, necrotizing enterocolitis; PLT, platelet; SGA, small-for-gestational age.

van der Staaij H, *et al. Arch Dis Child Fetal Neonatal Ed* 2025; 110:122–127. doi: 10.1136/archdischild-2024-326959

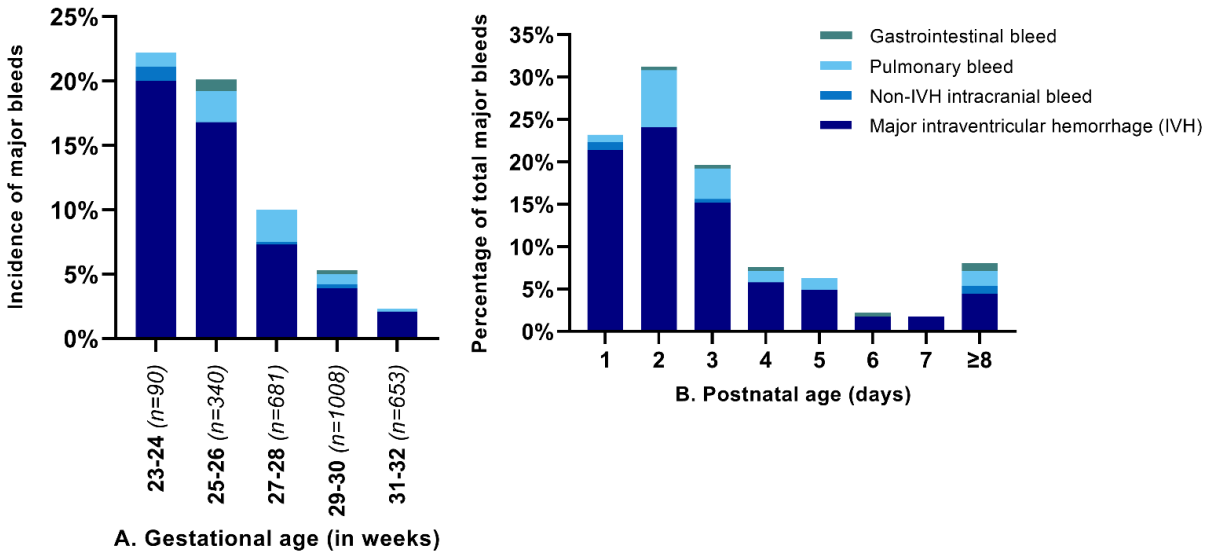

Figure S2. Bleeding profiles.

A. Incidence of the first major bleed per bleeding type, stratified by gestational age at birth in completed weeks.

B. Percentage of the total number of major bleeds (n=224) per bleeding type, stratified by postnatal age in days.

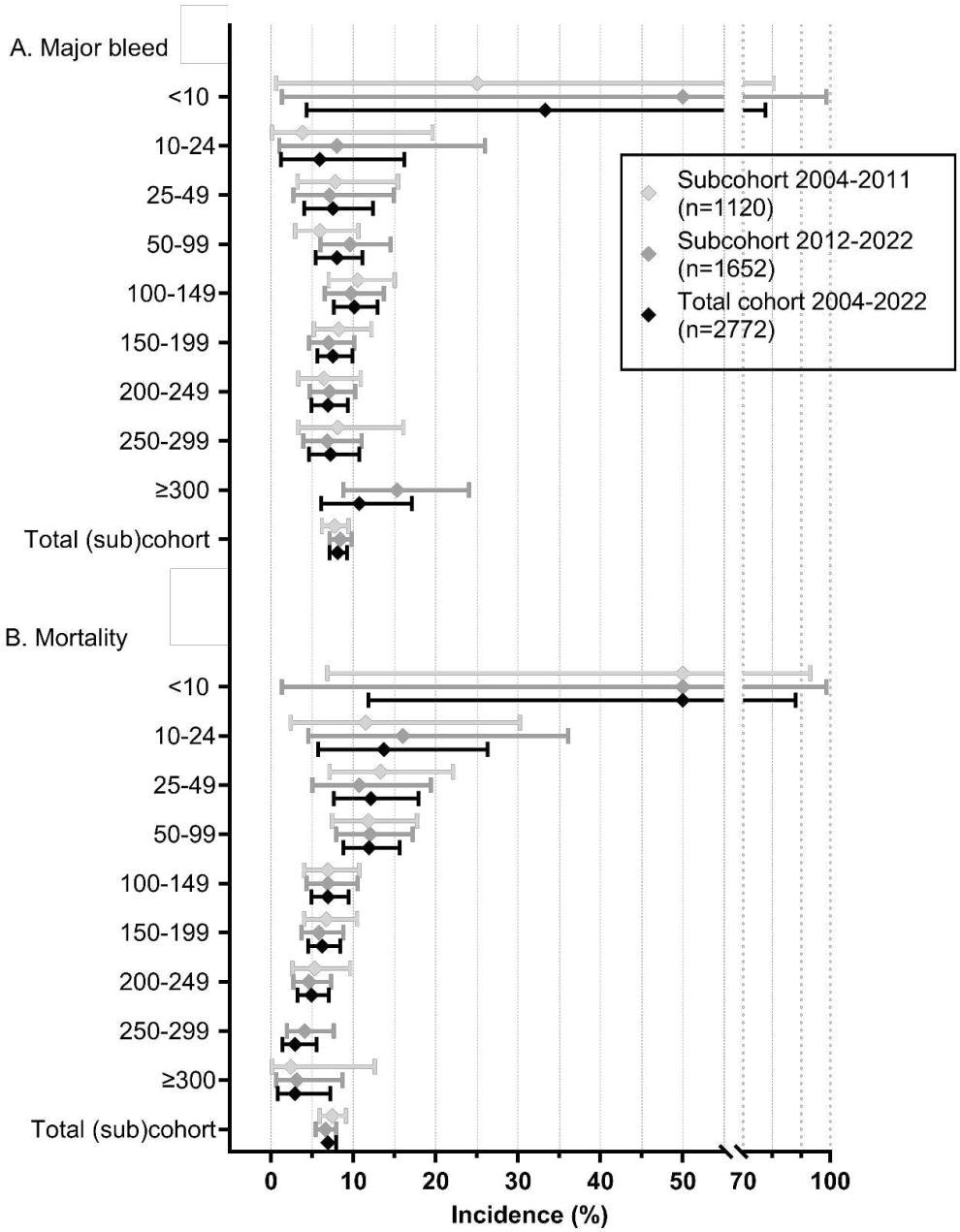

Figure S3. Incidence of major bleeds and mortality in subcohorts of infants admitted to the NICU before and after the year 2012 compared to the total study cohort.

Incidence of major bleeds (A) and mortality (B) with 95% confidence intervals, stratified by nadir platelet count, for subcohorts of infants with NICU admission dates between January 2004 up to December 2011 (light grey) and between January 2012 up to July 2022 (dark grey), compared to the whole study cohort (2004-2022, black*).*

SUPPLEMENTAL TABLES

Table S1. Incidence of major bleeds and mortality according to different platelet count levels.

	Primary and secondary outcomes			Different types of major bleeding			
Nadir platelet count (x10^9/L)	**Time (days) between nadir and major bleed, median (IQR)**	**Major bleed [a], n(%)**	**Mortality [b], n(%)**	**Major IVH [c], n(%)**	**Non-IVH intracranial bleed [d], n(%)**	**Pulmonary bleed [e], n(%)**	**Gastrointestinal bleed [f], n(%)**
<10 (n=6)*	0 (0-0)	2 (33)	3 (50)	0 (0)	1 (17)	1 (17)	0 (0)
10-24 (n=51)	1 (0-3)	3 (6)	7 (14)	0 (0)	1 (2)	1 (2)	1 (2)
25-49 (n=174)	2 (0-3)	13 (8)	21 (12)	7 (4)	1 (0.6)	4 (2)	1 (0.6)
50-99 (n=377)	0 (0-1)	30 (8)	45 (12)	26 (7)	0 (0)	3 (0.8)	1 (0.3)
100-149 (n=537)	0 (0-2)	54 (10)	37 (7)	41 (8)	2 (0.4)	11 (2)	0 (0)
150-199 (n=626)	0 (0-1)	47 (8)	39 (6)	42 (7)	0 (0)	4 (0.6)	1 (0.2)
200-249 (n=555)	0 (0-1)	38 (7)	27 (5)	27 (5)	0 (0)	9 (2)	2 (0.4)
250-299 (n=306)	0 (0-1)	22 (7)	9 (3)	21 (7)	0 (0)	1 (0.3)	0 (0)
≥300 (n=140)	0 (0-2)	15 (10)	4 (3)	14 (10)	0 (0)	1 (0.7)	0 (0)
Total cohort (n=2772)	0 (0-1)	224 (8)	192 (7)	178 (6)	5 (0.2)	35 (1)	6 (0.2)

*[a] Major bleed: only the first major bleed is counted. [b] Mortality before NICU discharge to a stepdown unit. [c] Major IVH: intraventricular hemorrhage ≥grade 3 or IVH of any grade complicated by parenchymal hemorrhagic infarction (PHI). [d] Non-IVH intracranial bleed: other types of intracranial bleeds than IVH showing a midline shift on radiological imaging, requiring neurosurgical intervention, or associated with hemodynamic instability. [e] Pulmonary bleed: an acute fresh bleed through the endotracheal tube associated with the need for intubation or ventilation or increased ventilatory requirements. [f] Gastrointestinal bleed: fresh visible rectal bleed except for mild bleeds caused by necrotizing enterocolitis. *This group of six is too small to provide robust estimates.*

van der Staaij H, *et al. Arch Dis Child Fetal Neonatal Ed* 2025; 110:122–127. doi: 10.1136/archdischild-2024-326959

Table S2. Logistic regression models for the association between nadir platelet counts and major bleeds, and the composite of major bleeds or mortality.

	A. Major bleed				B. Major bleed or mortality			
	Crude analysis[a]		Adjusted analysis[b]		Crude analysis[a]		Adjusted analysis[b]	
Nadir platelet count (x10^9/L)	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
<10 (n=6)*	6.80 (1.21-38.33)	0.03	10.01 (1.10-90.93)	0.04	9.09 (1.79-46.14)	0.01	4.90 (0.79-30.61)	0.09
10-24 (n=51)	0.85 (0.25-2.86)	0.8	1.18 (0.32-4.34)	0.8	1.69 (0.79-3.78)	0.2	0.78 (0.32-1.89)	0.6
25-49 (n=174)	1.10 (0.57-2.11)	0.8	1.14 (0.53-2.44)	0.8	1.60 (0.97-2.64)	0.07	0.68 (0.37-1.23)	0.2
50-99 (n=377)	1.17 (0.72-1.93)	0.5	1.14 (0.65-2.00)	0.8	1.93 (1.31-2.83)	0.001	0.97 (0.61-1.53)	0.9
100-149 (n=537)	1.52 (0.99-2.35)	0.06	1.33 (0.82-2.15)	0.2	1.48 (1.02-2.13)	0.04	0.81 (0.53-1.24)	0.3
150-199 (n=626)	1.10 (0.71-1.72)	0.7	1.06 (0.65-1.70)	0.8	1.22 (0.84-1.76)	0.3	0.92 (0.61-1.39)	0.7
200-249 (n=555)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
250-299 (n=306)	1.05 (0.61-1.82)	0.9	1.29 (0.71-2.32)	0.4	0.84 (0.52-1.38)	0.5	1.08 (0.62-1.87)	0.8
≥300 (n=140)	1.63 (0.87-3.06)	0.1	2.44 (1.24-4.8)	0.01	1.17 (0.65-2.12)	0.6	1.84 (0.96-3.53)	0.07
<50 (n=231)	0.96 (0.58-1.58)	0.9	1.09 (0.61-1.94)	0.8	1.36 (0.94-1.97)	0.1	0.82 (0.53-1.28)	0.4
≥50 (n=2541)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	

OR, odds ratio; 95% CI, 95% confidence intervals. [a] Only nadir platelet count categories included. [b] Also gestational age, postnatal age at nadir platelet count, SGA (birthweight <p10), perinatal asphyxia, proven sepsis, necrotizing enterocolitis ≥grade IIA, mechanical ventilation, and inotropes included.
**This group of six is too small to provide robust estimates.*

van der Staaij H, *et al. Arch Dis Child Fetal Neonatal Ed* 2025; 110:122–127. doi: 10.1136/archdischild-2024-326959

Table S3. Logistic regression models in a cohort of infants without major congenital malformations for the association between nadir platelet counts and major bleeds, and the composite of major bleed or mortality.

	A. Major bleed				B. Major bleed or mortality			
	Crude analysis[a]		Adjusted analysis[b]		Crude analysis[a]		Adjusted analysis[b]	
Nadir platelet count (x10^9/L)	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*- value**	**OR (95% CI)**	***p*-value**
<10 (n=4)*	4.81 (0.49-47.54)	0.2	27.13 (1.06-694.46)	0.05	3.27 (0.33-32.06)	0.3	2.43 (0.19-31.62)	0.5
10-24 (n=47)	0.64 (0.15-2.76)	0.6	1.22 (0.26-5.75)	0.8	1.17 (0.44-3.09)	0.8	0.67 (0.23-1.92)	0.5
25-49 (n=169)	1.20 (0.62-2.33)	0.6	1.44 (0.66-3.15)	0.4	1.63 (0.97-2.74)	0.07	0.78 (0.41-1.46)	0.4
50-99 (n=358)	1.27 (0.76-2.13)	0.4	1.36 (0.76-2.43)	0.3	1.82 (1.21-2.74)	0.004	0.97 (0.59-1.57)	0.9
100-149 (n=514)	1.63 (1.04-2.54)	0.03	1.52 (0.92-2.49)	0.1	1.52 (1.04-2.24)	0.03	0.87 (0.56-1.36)	0.6
150-199 (n=615)	1.11 (0.70-1.76)	0.6	1.10 (0.67-1.80)	0.7	1.22 (0.83-1.79)	0.3	0.94 (0.61-1.45)	0.8
200-249 (n=541)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
250-299 (n=295)	1.05 (0.59-1.86)	0.9	1.30 (0.70-2.42)	0.4	0.83 (0.50-1.39)	0.5	1.04 (0.58-1.86)	0.9
≥300 (n=139)	1.75 (0.93-3.30)	0.09	2.63 (1.32-5.22)	0.01	1.19 (0.65-2.19)	0.6	1.87 (0.95-3.67)	0.07
<50 (n=211) **≥50 (n=2471)**	0.91 (0.54-1.55) 1 (reference)	0.7	1.14 (0.61-2.11) 1 (reference)	0.7	1.23 (0.82-1.84) 1 (reference)	0.3	0.82 (0.50-1.32) 1 (reference)	0.4

OR, odds ratio; 95% CI, 95% confidence intervals. [a] Only nadir platelet count categories included. [b] Also gestational age, postnatal age at nadir platelet count, SGA (birthweight <p10), perinatal asphyxia, proven sepsis, necrotizing enterocolitis ≥grade IIA, mechanical ventilation, and inotropes included.
**This group of four is too small to provide robust estimates.*

van der Staaij H, *et al. Arch Dis Child Fetal Neonatal Ed* 2025; 110:122–127. doi: 10.1136/archdischild-2024-326959