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# Dynamic prediction of bleeding risk in thrombocytopenic preterm neonates

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## ABSTRACT

Over 75% of severely thrombocytopenic neonates receive platelet transfusions, though little evidence supports this practice, and only 10% develop major bleeding. In a recent randomized trial, giving platelet transfusions at a threshold platelet count of 50x10$^9$/L compared to a threshold of 25x10$^9$/L was associated with an increased risk of major bleeding or mortality. This finding highlights the need for improved and individualized guidelines on neonatal platelet transfusion, which require accurate prediction of bleeding risk. Therefore, the objective of this study was to develop a dynamic prediction model for major bleeding in thrombocytopenic preterm neonates. This model allows for calculation of bleeding risk at any time-point during the first week after the onset of severe thrombocytopenia. In this multicenter cohort study, we included neonates with a gestational age <34 weeks, admitted to a neonatal intensive care unit, who developed severe thrombocytopenia (platelet count <50x10$^9$/L). The study endpoint was major bleeding. We obtained predictions of bleeding risk using a proportional baselines landmark supermodel. Of 640 included neonates, 71 (11%) had a major bleed. We included the variables gestational age, postnatal age, intrauterine growth retardation, necrotizing enterocolitis, sepsis, platelet count and mechanical ventilation in the model. The median cross-validated c-index was 0.74 (interquartile range, 0.69-0.82). This is a promising dynamic prediction model for bleeding in this population that should be explored further in clinical studies as a potential instrument for supporting clinical decisions. The study was registered at *www.clinicaltrials.gov* (NCT03110887).

## Introduction

Neonatal major bleeding occurs in approximately 5-15% of preterm neonates admitted to a neonatal intensive care unit and can lead to lifelong disabilities and death. The most common type of bleeding is intraventricular hemorrhage.[1,2]

Since platelets are required for primary hemostasis, preterm neonates with severe thrombocytopenia are thought to be particularly at risk of major bleeding. However, the associations between thrombocytopenia, platelet transfusions and bleeding in preterm neonates are not clear. In a recently published systematic review, only six studies could be included. These provided insufficient evidence to

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assess whether platelet counts are causally related to major bleeding, or whether platelet transfusions reduce bleeding risk in thrombocytopenic preterm neonates.[3] Despite this lack of evidence, platelet transfusions are given to approximately 75% of thrombocytopenic preterm neonates.[4,5]

Recently, the results of the first randomized trial assessing currently used platelet count thresholds in preterm infants was published. The trial showed that giving prophylactic transfusions of platelets at a platelet count threshold of $50x10^9$/L was associated with an increased risk of bleeding and mortality compared to a lower threshold of $25x10^9$/L, within 28 days after randomization.[6] These results highlight the need for improved and individualized guidelines on platelet transfusion in neonates.

In addition to lack of evidence regarding transfusion thresholds and identification of platelet transfusion-related harm, indications for platelet transfusions are based primarily on platelet count. However, two neonates with similar platelet counts but different clinical conditions may have very different risks of bleeding, and benefit differently from platelet transfusions.[7] We need to be able to predict which neonates will develop major bleeding and quantify this bleeding risk, using a model that includes not only platelet count but also a set of relevant clinical variables. Such a prediction model could be used to define indications for transfusion in future studies, which is a first step towards individualized platelet transfusion therapy.

Some prediction models for bleeding in neonates have already been developed, but these models were not derived specifically for neonates with thrombocytopenia, and only allow for a risk assessment at baseline.[8–15] The disadvantage of baseline prediction models is that they do not take into account the clinical course of the neonate, which can change substantially over time, and may have a profound impact on bleeding risk. In dynamic predictions, the clinical course can be incorporated into the model. The objective of this study was, therefore, to develop a dynamic prediction model for major bleeding in thrombocytopenic preterm neonates.

## Methods

The study protocol was published online at *www.clinicaltrials.gov* (NCT03110887). The institutional review board of the Academic Medical Center Amsterdam approved the study and waived the need for informed consent. The study was conducted in accordance with the Declaration of Helsinki and reported according to The Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines.[16] An extended methods section is available in the *Online Supplementary Materials*, including the procedure for predictor selection, outcome definitions, a list of participating centers with an overview of their clinical practice, description of the data acquisition process, sample size calculations, details on statistical methods and the role of the funding source.

### Population

We performed a cohort study among consecutive preterm neonates with thrombocytopenia admitted to any one of seven participating neonatal intensive care units in the Netherlands between January 2010 and January 2015. The cohort comprised all neonates with a gestational age at birth <34 weeks and at least one platelet count $<50x10^9$/L. We excluded patients: (i) with severe congenital malformations; (ii) for whom there was a high suspicion of spurious platelet count (e.g. clots in the sample, or spontaneous platelet count recovery within 6 h, or a platelet count labeled as spurious in the medical file); (iii) with thrombocytopenia occurring exclusively in the context of exchange transfusion; (iv) with a prior admission to another neonatal intensive care unit or readmission; and (v) who had major bleeding prior to severe thrombocytopenia. Neonates with major bleeding after the end of the follow-up were not excluded, but registered as not having experienced major bleeding during the study.

### Model development and statistics

The core research team drafted and approved a statistical analysis plan prior to the data analysis. We developed a proportional baseline landmark supermodel, with bleeding within the subsequent 3 days as the outcome.[17] Variables included in the model were gestational age, intrauterine growth retardation (IUGR), mechanical ventilation, platelet count, platelet transfusion, postnatal age at inclusion, and necrotizing enterocolitis (NEC) and/or sepsis (combined).

### Model validation

We validated the model by internal calibration using the heuristic shrinkage factor described by van Houwelingen *et al.*[18] We evaluated the model's accuracy in correctly discriminating between patients with and without major bleeding using the dynamic cross-validated c-index. A c-index of 1.0 indicates perfect discrimination, while a c-index of 0.5 is obtained when the model performs as well as chance. We calculated a c-index at each 2 h timepoint, and reported this series of c-indices as a graph. Analyses were carried out using SPSS (version 24.0), Stata (version 14.1) and R (version 3.4.2).

### Clinical applicability of the model

Our study is a first, basic prediction model for major bleeding in preterm neonates with severe thrombocytopenia. Due to the dynamic nature of the model, it cannot be fully summarized in one table, but once validation studies have been performed, we will develop an online calculator. We have chosen not to publish the calculator along with this paper, in order to prevent inappropriate premature use of the model in clinical practice. The model is available upon request for researchers looking to perform model validation and impact studies.

## Results

### Baseline characteristics

Of 9,333 neonates with a gestational age <34 weeks, 927 had at least one platelet count $<50x10^9$/L. Of these, 67 were excluded due to spurious platelet counts and 29 because thrombocytopenia occurred only during a readmission. Of the remaining 831 neonates, 191 were excluded based on major bleeding prior to thrombocytopenia (n=55), previous admission to another neonatal intensive care unit (n=51), congenital malformations (n=47), missing medical files (n=35) and because thrombocytopenia occurred exclusively during exchange transfusion (n=3). The remaining 640 neonates (7%) were included in the study (Figure 1). The median gestational age at birth was 28.1 weeks, the median birth weight was 900 grams (Table 1 and *Online Supplementary Figures S1* and *S2*) and 73% of the neonates received at least one platelet transfusion. No cases of fetal and neonatal alloimmune thrombocytopenia were identified. The lowest platelet counts dur-

ing study for neonates with and without major bleeding are reported in *Online Supplementary Figure S3*.

## Major bleeds

A total of 71 (11%) major bleeds occurred, of which 55 were intraventricular hemorrhages and other intracerebral hemorrhages, 12 were pulmonary hemorrhages and four were gastrointestinal hemorrhages (Table 2). The major bleeds occurred at a median of 1 day (interquartile range, 1-4) after the onset of severe thrombocytopenia. At the end of the 10-day follow-up period, 73 patients (11%) had died, 63 (10%) had developed major bleeding and 93 (15%) had been discharged or transferred (Figure 2). Of the 93 discharged neonates, 76 (82%) were discharged to a stepdown unit. Ninety-one percent of the neonates underwent at least one ultrasound scan, with a mean of two scans during the 10-day follow-up period. In four neonates, major intracranial hemorrhage was already diagnosed on the first ultrasound scan after birth, on the first day of life.

## Model development

The model contained 12 variables: all seven selected variables, plus the interaction term between platelet count and transfusion, plus interactions between time and IUGR and time and platelet count (both linear and quadratic). Platelet count was converted to a log-scale. The number of major bleeds included in the model was 63, because eight bleeds occurred more than 10 days after $T_0$ (Table 2).

## Final model

The median c-index of the final model was 0.74 (interquartile range, 0.69 - 0.82) (Figure 3). This indicates good predictive performance. An example of a risk-estimation by the model is shown in Figure 4, a plot of bleeding risk of two neonates with distinct risk profiles. During study days 1-3, the predicted risk of major bleeding within the subsequent 3 days in child A is substantially higher than that in child B, indicating that the use of this prediction model during that time-period would have correctly identified child A as being at high risk of bleeding. This image also illustrates that bleeding risk can increase or decrease rapidly. Table 3 shows the details of the model. A hazard ratio >1 indicates that the increase of a risk factor is associated with a higher risk of bleeding, and a hazard ratio <1 indicates that the increase of a risk factor is associated with a lower risk of bleeding. The effects of platelet count and IUGR varied over time, while the effects of all other variables were constant over time. Table 4 shows predicted risks of bleeding for different clinical scenarios.

## Sensitivity analyses

None of the sensitivity analyses resulted in substantial changes in hazard ratios for the individual covariates, indicating that our model is robust (*Online Supplementary Table S3*).

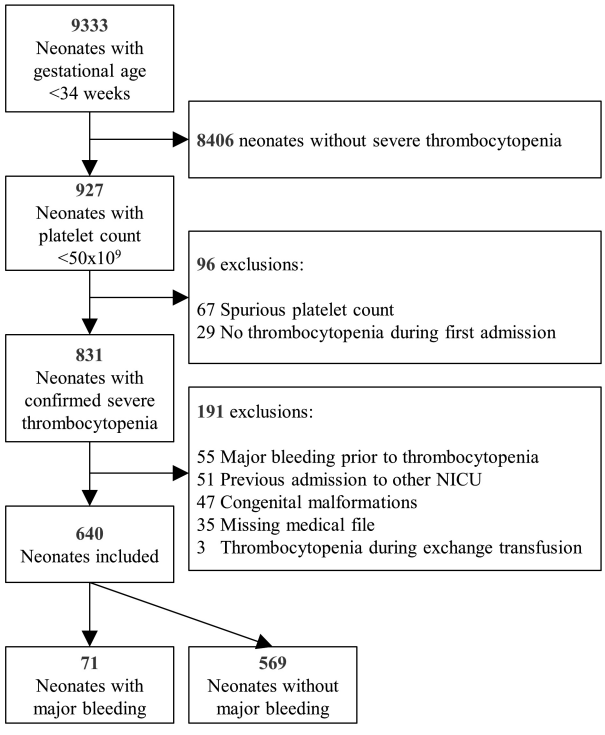


**Figure 1. CONSORT flow chart.** CONSORT: consolidated standards of reporting trials; NICU: neonatal intensive care unit.

**Table 1. Baseline characteristics of the study cohort (n=640).**

| | Total cohort (n=640) | | Major bleed (n=71) | | No major bleed (n=569) | |
|---|---|---|---|---|---|---|
| *At birth* | | | | | | |
| Gestational age in weeks: median (IQR)[1] | 28.1 | (26.4-30.4) | 27.7 | (26.1-29.1) | 28.1 | (26.4-30.6) |
| Birth weight in grams: median (IQR) | 900 | (710-1180) | 945 | (760-1200) | 900 | (705-1178) |
| Intrauterine growth retardation, n (%) | 206 | (32) | 14 | (20) | 192 | (34) |
| *At onset of severe thrombocytopenia* | | | | | | |
| Postnatal age in days: median (IQR) | 3.9 | (1.6-9.25) | 2.6 | (1.0-6.8) | 4.1 | (1.8-9.8) |
| Platelet count x10⁹/L, median (IQR) | 38 | (29-45) | 39 | (31-44) | 38 | (28-45) |
| Mechanical ventilation, n (%) | 329 | (51) | 49 | (69) | 280 | (49) |
| Necrotizing enterocolitis/sepsis, n (%) | 330 | (52) | 39 | (55) | 291 | (51) |
| Sepsis, n (%) | 293 | (46) | 37 | (52) | 256 | (45) |
| Necrotizing enterocolitis, n (%) | 73 | (11) | 5 | (7) | 68 | (12) |

IQR: interquartile range. [1]In five cases the exact gestational age could not be determined due to uncontrolled pregnancies. It was estimated in full weeks.

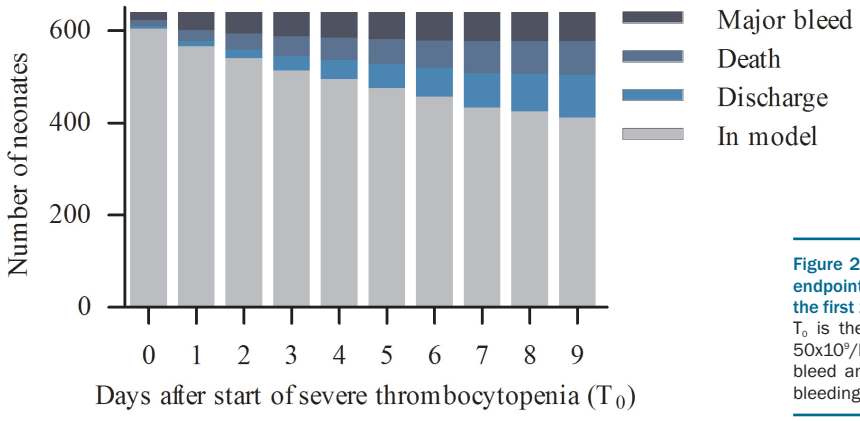


**Figure 2. Number of neonates reaching the different study endpoints (major bleeding, death or discharge/transfer) in the first 10 days after the onset of severe thrombocytopenia.** $T_0$ is the day on which the platelet count dropped below $50x10^9$/L for the first time. Neonates who developed a major bleed and then died were only registered as having major bleeding (no overlap between major bleeding and mortality).

## Discussion

In this study, we developed a dynamic prediction model for major bleeding in thrombocytopenic preterm neonates. The model has a good predictive performance with a median c-index of 0.74. To our knowledge, this is the first dynamic prediction model for bleeding in preterm neonates.

The importance of using a dynamic model is illustrated by a recent survey assessing at which thresholds clinicians would administer a platelet transfusion to a preterm neonate with a gestational age of 27 weeks at birth.[19] The study showed that if this neonate was 2 days old and in a stable condition, most (European) clinicians would transfuse at a threshold platelet count of $30x10^9$/L. However, if the same neonate was septic, mechanically ventilated and receiving vasopressors, most clinicians would transfuse at a threshold of $50x10^9$/L. This illustrates that although neonates may have a comparable clinical status at baseline (gestational age 27 weeks), their clinical course in the following days is perceived as an important determinant of bleeding risk. We have developed a model that allows clinicians to quantify bleeding risk and adjust it as the clinical situation of the neonate changes.

Future validation studies should externally validate and preferably expand the model, to improve its predictive accuracy. Once a larger, externally validated model has been developed, it can be used to study the effect of platelet transfusion indications based on predicted risk of bleeding in an impact study. Ultimately, this is a first step towards individualized platelet transfusion guidelines. Individualized guidelines are important because several studies have shown that there is a large discrepancy between the number of thrombocytopenic neonates receiving platelet transfusions (75%) and the number of neonates who develop major bleeding (9%).[5,20] These numbers are comparable to our results: 70% of neonates received transfusions and 11% developed major bleeding. In addition, results of a recent randomized trial indicate platelet transfusion-related harm when using a platelet count threshold of $50x10^9$/L compared to $25x10^9$/L. Although the overall results of this study showed benefit associated with the low threshold, not all neonates in the high threshold group developed major bleeding or died. Moreover, 19% of neonates in the low threshold group died or developed major bleeding. This indicates that a platelet count-based transfusion threshold does not accurately separate neonates whose bleeding or death will be prevented by a platelet transfusion. A threshold that includes clinical variables, such as one based on our dynamic prediction model, might perform better and thereby improve outcomes.

**Table 2. Types of bleeding.**

| | | |
|---|---|---|
| Major bleeds, n (%) | 71 | (11) |
| Type of major bleeding, n (%) | 32 | (45) |
| Uni-/bilateral IVH grade 3 with or without parenchymal involvement | | |
| IVH grade 1 or 2 (uni- or bilateral) with parenchymal involvement | 4 | (6) |
| Solitary (non-cerebellar) parenchymal hemorrhage | 4 | (6) |
| Cerebellar parenchymal hemorrhage | 11 | (15) |
| Subdural hemorrhage | 4 | (6) |
| Pulmonary hemorrhage | 12 | (17) |
| Gastrointestinal hemorrhage | 4 | (6) |

Eight bleeds (of 71) were excluded from the model because they occurred more than 10 days after $T_0$.: one cerebellar, one IVH grade 1 plus basal ganglia infarction, one IVH grade 1 and grade 2 plus basal ganglia infarction, one gastrointestinal bleed, one pulmonary bleed, one bilateral IVH grade 3, one frontal-parietal bleed and one subdural hemorrhage. IVH: intraventricular hemorrhage.

It is important to note that individual covariates in the model should not be interpreted as causal associations, because the associations may be confounded in multiple ways. For example, IUGR was associated with lower predicted bleeding risk in our model, but we cannot conclude that IUGR protects against bleeding. Firstly, because IUGR is also a risk factor for thrombocytopenia, and we restricted our population to neonates with thrombocytopenia. It is possible that other causes of thrombocytopenia, for example viral infections, are associated with a higher risk of bleeding than that of IUGR. A neonate with thrombocytopenia as a result of IUGR is therefore not protected by IUGR, but has a lower bleeding risk because the thrombocytopenia was not caused by a viral infection. This is an epidemiological concept called collider stratification bias.[21] Secondly, perhaps neonates with IUGR received more treatments intended to decrease the risk of bleeding as compared to neonates without IUGR, as neonatologists perceived them to be at higher risk of bleeding (confounding by indication). And lastly, because the number of events in our study was limited, we were not able to cor-

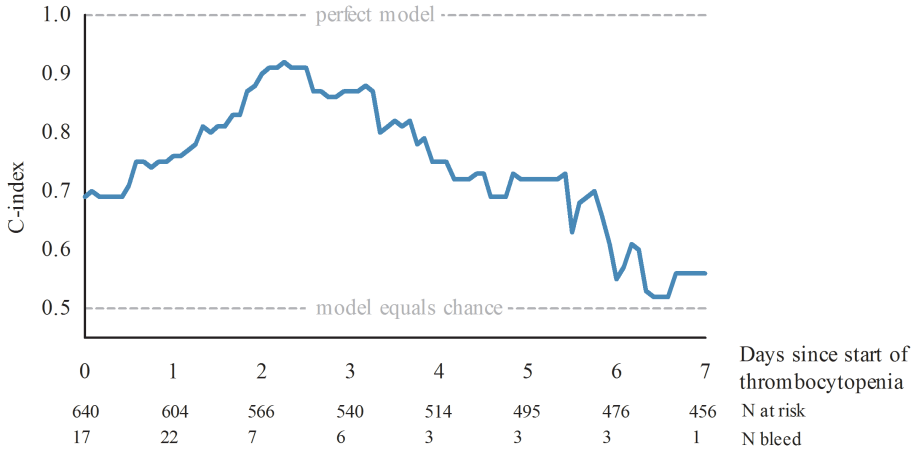


**Figure 3. Dynamic, cross-validated c-index.** This graph represents the dynamic, cross-validated c-index of the main model. A c-index of 1 resembles a model that discriminates perfectly between patients with and without major bleeding, while a c-index of 0.5 indicates that the prediction is as good as chance. For each time-point, the number at risk at the beginning of that day has been reported, as well as the total number of major bleeds that occurred during those 24 hours. For example, at the start of day 1, the number of patients still at risk was 604, and during this day 22 neonates developed a major bleed.

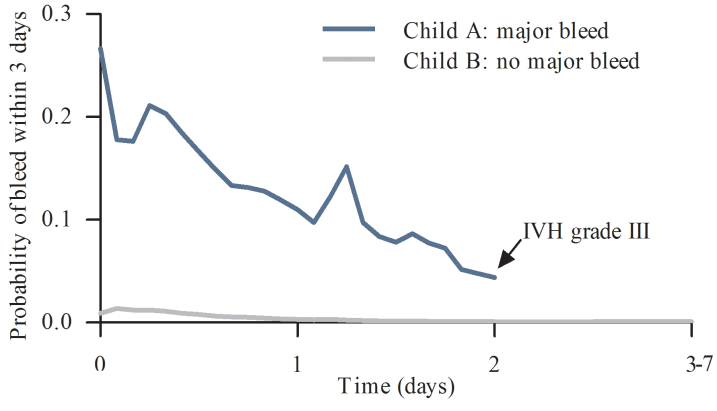


**Figure 4. Change in probability of having a major bleed within 3 days for two example patients.** Day 0 is the day of onset of severe thrombocytopenia ($T_0$). Characteristics of child A: gestational age (weeks+days) 27+2, birthweight 1100 grams, 2 days old at $T_0$, sepsis, mechanical ventilation, two platelet transfusions, platelet counts (x$10^9$/L): 41, 104, 47, and 88. Bilateral grade III intraventricular hemorrhage on day 2. Characteristics of child B: gestational age (weeks+days) 32+3, birth weight 1175 grams, 5 days old at $T_0$, sepsis, no mechanical ventilation, no platelet transfusions, platelet counts (x$10^9$/L) 4, 53, 49, 63, 195 and 376. No major bleed. Days 3-7 not shown because no substantial change in bleeding risk occurred. During study days 1-3, the predicted risk of major bleeding within the subsequent 3 days is substantially higher in child A than in child B, indicating that the use of this prediction model during that time-period would have correctly identified child A as being at a high risk of bleeding.

rect for all possible confounders. In short, the association between IUGR and bleeding is complex, our model only indicates that it is a good predictor for bleeding, but we cannot draw any causal conclusion based on this information. This applies to all individual covariates in the model.

Various possible limitations of our study need to be discussed. Firstly, we could not externally validate our model because a similar database is currently not available. Secondly, identification of prognostic variables could possibly have been improved with a prior systematic review assessing all potential predictors. However, despite this limitation, our model contains variables generally considered best candidates for predicting major bleeding, as many of them were included in various existing baseline models. Some variables, such as mean platelet volume and immature platelet count, could not be included in our model because they were not routinely measured. Thirdly, the time a major bleed occurs is not similar to the time it is diagnosed on an ultrasound scan, because major intracranial bleeds in neonates are often asymptomatic, and detected during routine screening. To address this issue, we performed two additional sensitivity analyses, one in which we corrected time of bleeding based on whether or not minor bleeding was visible on prior ultrasound scans, and one in which we removed events for which we could not determine whether they occurred prior to or after the bleeding. Results of these analyses showed only minor changes in hazard ratios of individual coefficients, suggesting that this problem does not substantially affect the predictive power of our model (*Online Supplementary Table S3*). Fourthly, after day 6, the c-index drops below 0.60, possibly due to a lower event rate, therefore the model should be applied with caution after day 6. We hypothesize that the variation in predictive accuracy over time, depicted in Figure 2, may be caused by a balance between having enough clinical information to predict (difficult on days 1 and 2), and enough events to fit a good model (difficult after day 4). Fifthly, the risk of bleeding in neonates in our population may have been affected by treatment with platelet transfusions. Therefore, the risks calculated using our model may be an underestimation of the 'true' risk (without transfusion). However, there are no cohorts available in which platelet transfusions were not administered and various studies, including the previously described randomized controlled trial, suggest that the effect of platelet transfusions on bleeding risk may be limited.[6,22–24] We therefore estimate that our model's predictions are accurate. Finally, four neonates had a gestational age at birth of less than 24 weeks. In addition, local policies differed with respect to active support for neonates born at a gestational age between 24+0 and 25+6 weeks. Therefore, the neonates with a gestational age less than 26 weeks in our population might be a selection of neonates for whom good out-

**Table 3.** The dynamic prediction model.

| | Hazard ratio | 95% CI |
|---|---|---|
| *Covariates with time-constant effects* | | |
| Gestational age (days) | 1.00 | 0.98 – 1.02 |
| Postnatal age (days) | 0.88 | 0.83 – 0.94* |
| Mechanical ventilation | 5.08 | 2.03 – 10.65* |
| NEC/sepsis | 0.85 | 0.43 – 1.58 |
| Platelet transfusion | 1.06 | 0.38 – 2.95 |
| Interaction term $log_{10}$ platelet count and platelet transfusion | 1.23 | 0.63 – 2.38 |
| *Covariates with time-varying effects* | | |
| LM (2-hour intervals) | 2.30 | 0.89 – 5.94 |
| LM2 (2-hour intervals) | 0.85 | 0.74 – 0.98* |
| IUGR constant | 0.51 | 0.17 – 1.59 |
| IUGR time-varying: LM | 0.31 | 0.09 – 1.14 |
| IUGR time-varying: $LM^2$ | 1.22 | 1.04 – 1.44* |
| $Log_{10}$ platelet count constant | 1.74 | 0.72 – 4.24 |
| $Log_{10}$ platelet count time-varying LM | 0.35 | 0.19 – 0.63* |
| $Log_{10}$ platelet count time-varying: $LM^2$ | 1.12 | 1.03 – 1.21* |

A hazard ratio >1 indicates that an increase of the risk factor is associated with a higher risk of bleeding. For example, a mechanically ventilated neonate has a 5.08 times higher risk of bleeding than a neonate who is not mechanically ventilated. If both boundaries of the confidence interval are either higher than 1 or lower than 1, the variable is a statistically significant predictor, indicated by *. LM: landmark time, linear interaction. LM2: landmark time, quadratic interaction. LM or landmark time refers to time since onset of severe thrombocytopenia (time-dependent variable), in 2-hour time intervals. Postnatal age refers to the postnatal age at the onset of severe thrombocytopenia (baseline variables). Time-varying covariates should not be confused with time-dependent covariates, such as platelet count or platelet transfusion, for which the value of the variable is not fixed (it is not a baseline variable) but can change over time. In time-varying covariates, the effect of the covariate can change over time, for example, the strength and direction of a potential association of intrauterine growth retardation with bleeding could be different immediately after the onset of thrombocytopenia compared to a few days after the onset of thrombocytopenia, due to interactions with other risk factors and changes in the clinical situation of the neonate. NEC: necrotizing enterocolitis; IUGR: intrauterine growth retardation. 95% CI:. 95% confidence interval.

**Table 4.** Risk predictions for different clinical scenarios.

Patient's characteristics: GA 28 weeks, platelet count $10x10^9$/L at day 3 of life (first time <$50x10^9$/L), no transfusion.

| | Ventilation | No ventilation |
|---|---|---|
| NEC/sepsis; IUGR | 8% | 2% |
| No NEC/sepsis No; IUGR | 17% | 3% |
| NEC/sepsis No; IUGR | 14% | 3% |
| No NEC/sepsis; IUGR | 9% | 2% |

Patient's characteristics: GA 28 weeks, platelet count $50x10^9$/L at day 3 of life (first time <$50x10^9$/L) , no transfusion.

| | Ventilation | No ventilation |
|---|---|---|
| NEC/sepsis; IUGR | 11% | 2% |
| No NEC/sepsis No; IUGR | 24% | 5% |
| NEC/sepsis No; IUGR | 20% | 4% |
| No NEC/sepsis; IUGR | 13% | 3% |

GA: gestational age; NEC: necrotizing enterocolitis. IUGR: intrauterine growth retardation.

comes were expected. The model should thus be applied with caution in neonates with a gestational age of less than 26 weeks.

Strengths of our study are the size of the cohort and the fact that we selected the predictors prior to data analysis rather than performing a stepwise selection. In addition, our data collection was meticulous and we performed multiple additional sensitivity analyses to confirm the robustness of our model. Our model is easy to apply, because we have used clear and simple definitions of the covariates. Once the model has been externally validated, we will develop an online calculator, with which it should only take a few minutes to enter the variables and calculate absolute risk of bleeding.

In short, this dynamic prediction model allows clinicians to quantify bleeding risk and adjust it as the clinical situation of the neonate changes. Risk can be predicted at any time-point during the first week after the onset of severe thrombocytopenia. This is a promising model that should be explored in future studies, as it is a first step towards individualized platelet transfusion guidelines.

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