A Risk Score for Predicting the Incidence of Hemorrhage in Critically Ill Neonates: Development and Validation Study

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Abstract

The aim of the study was to develop and validate a prediction model for hemorrhage in critically ill neonates which combines rotational thromboelastometry (ROTEM) parameters and clinical variables. This cohort study included 332 consecutive full-term and preterm critically ill neonates. We performed ROTEM and used the neonatal bleeding assessment tool (NeoBAT) to record bleeding events. We fitted double selection least absolute shrinkage and selection operator logit regression to build our prediction model. Bleeding within 24 hours of the ROTEM testing was the outcome variable, while patient characteristics, biochemical, hematological, and thromboelastometry parameters were the candidate predictors of bleeding. We used both cross-validation and bootstrap as internal validation techniques. Then, we built a prognostic index of bleeding by converting the coefficients from the final multivariable model of relevant prognostic variables into a risk score. A receiver operating characteristic analysis was used to calculate the area under curve (AUC) of our prediction index. EXTEM A10 and LI60, platelet counts, and creatinine levels were identified as the most robust predictors of bleeding and included them into a Neonatal Bleeding Risk (NeoBRis) index. The NeoBRis index demonstrated excellent model performance with an AUC of 0.908 (95%

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confidence interval [CI]: 0.870–0.946). Calibration plot displayed optimal calibration and discrimination of the index, while bootstrap resampling ensured internal validity by showing an AUC of 0.907 (95% CI: 0.868–0.947). We developed and internally validated an easy-to-apply prediction model of hemorrhage in critically ill neonates. After external validation, this model will enable clinicians to quantify the 24-hour bleeding risk.

Introduction

Neonatologists handle a multitude of pathological conditions in critically ill neonates; hemostatic imbalance represents one of the most serious. Testing for defects of hemostasis is imperative in predicting the bleeding risk of sick neonates, including all admissions to the neonatal intensive care unit (NICU). However, the standard practice of neonatal coagulation screening with conventional tests is inadequate,[1] while further complexity results from the issue of developmental hemostasis, which requires both appropriate age-related and specific reference ranges for the testing system used.[2]

Neonatologists are understandably interested in performing real-time monitoring of the coagulation pathways by means of a bedside analysis tool, such as the viscoelastic whole blood methods (VMs) of rotational thromboelastography (TEG) and thromboelastometry (ROTEM), which estimate the dynamics of blood coagulation.[3] Their use in diagnosing neonatal coagulation disorders becomes gradually widespread.[4]

Our research group has recently established local reference ranges for standard extrinsically activated ROTEM assay (EXTEM) in healthy full-term and preterm neonates.[5] Using these baseline values, we detected hypocoagulation on septic neonates.[6] Similarly, hypoxic neonates demonstrated a hypocoagulable EXTEM profile compared with healthy neonates, indicating a potential role of ROTEM in the early detection of coagulation derangement in perinatal hypoxia.[7] This was also in keeping with hemostatic dysfunction detected among neonates with moderate to severe hypoxic-ischemic encephalopathy, which was associated with an increased risk of bleeding.[8] Thus, septic and hypoxic newborns admitted to NICUs have high risk of hemorrhage due to coagulopathy and commonly receive transfusion.[9] Despite low-grade evidence to support it, a national audit of transfusion practice in the United Kingdom indicated that almost 50% of plasma transfusions are given prophylactically to neonates with "abnormal coagulation values" but without evidence of active bleeding, to prevent intraventricular hemorrhage (IVH).[10]

Therefore, clinically important issues emerge in neonatal platelet and plasma transfusions, like the need of validated tools to characterize the global hemostatic profile of neonates, estimate bleeding risk, and guide plasma and platelet transfusion therapy. As relevant data in high-risk newborns are missing, further research on the potential of VMs to evaluate the global hemostatic profile of these neonates and predict their bleeding risk, is warranted.[11]

Our aim was to develop and validate a prediction model for hemorrhage in critically ill neonates, which combines ROTEM parameters of global hemostatic profile with relevant clinical and laboratory variables. This model will effectively and promptly guide clinical decision making related to plasma and platelet transfusion in high-risk neonates.

Methods

We conducted this cohort study, and reported its results, in agreement with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[12] The study population consisted of consecutive full-term and preterm neonates with sepsis, suspected sepsis, and/or perinatal hypoxia, hospitalized in the NICU of General Hospital of Nikaia, Piraeus, Greece, over a period of 54 months (July 2014–January 2019). The Institutional Review Board of Nikaia General Hospital approved the study protocol (15/07/2014, 32/3). Data for recruitment procedure are presented in flowchart (►**Fig. 1**). The neonates were categorized in three groups: confirmed sepsis (group A), suspected sepsis (group B), and perinatal hypoxia (group C). Inclusion criteria for all three groups have been previously described[6,7] and are presented within the supplementary material (►**Supplementary Methods**, available in the online version). Neonates with congenital malformations, those previously transfused with fresh frozen plasma or platelets, and those with major IVH diagnosed by cranial ultrasounds at least 1 day before ROTEM analysis, were excluded from the study.

Data on demographics, maternal and pregnancy history, maternal medications during pregnancy, neonatal physiological parameters, and clinical findings were recorded. On the first day of sepsis or suspected sepsis and/or hypoxia arterial blood, anticoagulated with 0.109 mol/L trisodium citrate (9:1, v/v blood anticoagulant), was analyzed on the ROTEM analyzer (Tem Innovations GmbH, Munich, Germany) using the EXTEM, the intrinsically activated (INTEM), and fibrin-based extrinsically activated (FIBTEM) thromboelastometry assays, as formerly described.[6,7] ROTEM tests performance is reported in the supplementary material (►**Supplementary Methods**, available in the online version). The intra-assay coefficient of variation for EXTEM analysis has been previously assessed[7] and was 5.3% (95% confidence interval [CI]: 4.6–6.3) for clotting time (CT), 4.8% (95% CI: 4.6–6.5) for clot formation time (CFT), 1.9% (95% CI: 1.3–2.1) for maximum clot firmness (MCF), 0.8% (95% CI: 0.7–1.0) for α angle(^{0}), and 0.8% (95% CI: 0.7–0.9) for lysis index at 60 minutes (LI60).

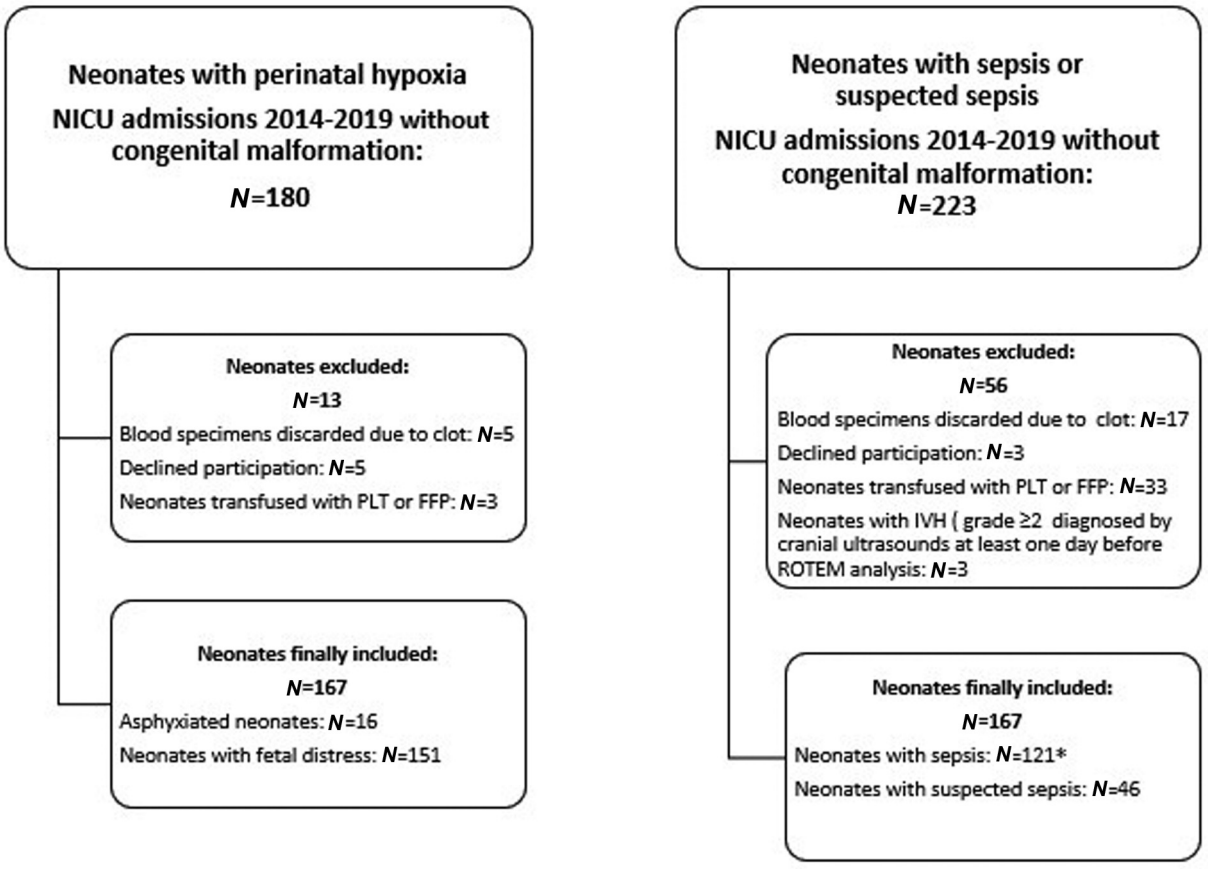

Fig. 1 Flowchart of study population. *2 neonates with perinatal hypoxia were also included in this subgroup, as they suffered from sepsis on days 15 and 17. FFP, fresh frozen plasma; IVH, intraventricular hemorrhage; NICU, neonatal intensive care unit; PLT, platelets.

On the same day with ROTEM testing and prior to initiating antibiotic therapy, blood specimens for culture, routine biochemical tests, complete blood count, and C-reactive protein (CRP) were obtained. Chest radiograph, cerebrospinal fluid culture, and urine culture were performed whenever clinically indicated, as per our NICU protocol. In all neonates, we performed brain and abdomen ultrasound scans, we calculated the Score for Neonatal Acute Physiology Perinatal Extension[13] and we used the neonatal bleeding assessment tool (NeoBAT)[14] to assess and record the clinical bleeding events on the same day with the ROTEM analysis.

The primary study endpoint was hemorrhage of any grade according to NeoBAT, within 24 hours of ROTEM testing. Secondary outcome was severe bleeding with NeoBAT score equal or higher than 3.

Statistical Analysis

We presented descriptive statistics of the baseline characteristics and ROTEM parameters as means ± standard deviations (SDs), medians and interquartile ranges (IQRs), or percentages when appropriate. Preliminary investigations consisted of univariable logistic regression analyses of the association between bleeding within 24 hours of ROTEM testing and each individual potential ROTEM prognostic variable. To investigate multicollinearity, we assessed pairwise correlations among these 27 potential predictor variables (correlation matrix: ►**Supplementary Table S1**, available in the online version). As expected, we noted clusters of highly correlated variables. By using clinical and statistical criteria, we decided to include in the model development phase only EXTEM among the ROTEM variables. Given the high similarity in terms of clinical meaning between A10, A20, and A30, very similar association with the outcome variable, and very high collinearity, we decided to consider only A10 for entering the multivariable selection process.

Model Development

We fitted double selection least absolute shrinkage and selection operator (LASSO) logit regression to build our prediction model.[15,16] Variable selection through this penalization procedure is less prone to multicollinearity, misclassification, overfitting, and optimism in the predictive performance.[16–18] As internal validation techniques, we used both cross-validation and bootstrap (1,000 replications). Our outcome variable was bleeding within 24 hours of the ROTEM testing. We developed the model on a subset of 272 patients with no missing information. The candidate predictor variables were EXTEM variables (CT, amplitude recorded at 10 minutes [A10], CFT, MCF, α angle, LI60, maximum lysis) and patient characteristics, as well as biochemical and hematological measurements treated either as continuous (gestational age, birth weight, hematocrit, white blood cell count, neutrophils, platelets, CRP, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, total bilirubin, direct bilirubin, blood

urea nitrogen, and creatinine) or binomial (gender, cesarean section, respiratory distress syndrome, suspected sepsis, sepsis, intrauterine growth retardation, perinatal hypoxia, acute renal failure, and necrotizing enterocolitis).

Internal Validation

We verified the calibration of our final model through a predicted versus observed probability plot. We plotted the calibration in decile groups across the risk spectrum as recommended by the TRIPOD guideline, and displayed the 95% CIs for the groupings. Further, we displayed the lowest smoother allowing assessment of the calibration at the individual patient level. Finally, we developed a prognostic Neonatal Bleeding Risk (NeoBRis) index by converting the β coefficient from the final model of each relevant prognostic variable into a weighted score while preserving monotonicity.[19] We performed receiver operating characteristic (ROC) analyses to calculate the area under curve (AUC) of our prediction index. To allow for an easy interpretation, we divided our score into four groups corresponding to "very low," "low," "moderate," and "high risk" of bleeding and reported in a table the corresponding observed risk of the outcome. All tests were two-sided. Stata software was used for statistical modeling and analysis (Stata Corp., College Station, Texas, United States).

Results

This cohort study included 332 consecutive, critically ill, full-term and preterm neonates. The population consisted predominantly of males (67%) with a median gestational age of 37 weeks (IQR: 32–39) and median birth weight of 2,585 g (IQR: 1,480–3,290). About half ($n = 156$; 47.0%) of the included newborns were preterm (< 37 weeks of gestation) and 53.0% ($n = 176$) were full-term (≥ 37 weeks). The mean age was 9.3 days (SD = 13.5), while the median was 4 days (IQR: 2–11).

We report the baseline characteristics, and biochemical and hematological measurements in ►**Table 1**. Out of the 332 neonates, 114 (34.3%) experienced bleeding within 24 hours of ROTEM testing (29 neonates experienced severe bleeding as defined by a NeoBAT score of ≥ 3).

Model Development

We fitted a LASSO logit regression considering bleeding as outcome variable and EXTEM parameters as prognostic variables. A10 (329 observations) and LI60 (272 observations) were identified as the most robust predictors ($p < 0.001$). We fitted a double selection LASSO logit regression forcing the two EXTEM variables in the model and considering baseline characteristics and biochemical and hematological measurements as additional potential predictors (control variables). The LASSO procedure identified platelet count (332 observations) and creatinine levels (331 observations) as additional significant predictors of bleeding. To develop an easy-to-use prediction index, we converted these variables into dichotomous/categorical. We divided platelet count into three strata: over 150,000,[20] between 50,000 and 150,000, and less than 50,000 cells/μL, according to clinical criteria. We divided creatinine level into two strata based on the threshold of 1.5 mg/dL. This threshold was identified by a ROC curve as the one with best discrimination between patients with and without the bleeding event. We reported the β coefficients of our final model in ►**Table 2**. We derived the NeoBRis index by converting the β coefficients into a weighted score. We provided detailed and easy-to-apply instructions to derive the NeoBRis index score for each patient given his/her A10, LI60, platelet count, and creatinine level (►**Fig. 2**).

Model Performance and Internal Validation

We plotted the area under the ROC curve of the NeoBRis index (►**Fig. 3**). We obtained an AUC of 0.908 (95% CI, 0.870–0.946), which indicates an excellent model performance. We plotted a calibration plot (predicted vs. observed probability plot) to check internal validity (►**Fig. 4**). The 95% CI around the observed rate of outcome in each decile group of predicted probability crossed the perfect fit line, demonstrating optimal calibration and discrimination. We conducted bootstrap resampling (1,000 repetitions) to further verify the internal validity of the prognostic model. We obtained an AUC of 0.907 (95% CI, 0.868–0.947) ensuring internal validity. Additionally, we verified the performance of the NeoBRis index in the three subpopulations of included neonates. The AUC calculated in newborns with sepsis was 0.924 (95% CI, 0.872–0.976), it was 0.896 (95% CI, 0.782–0.999) in those with suspected sepsis and 0.885 (95% CI, 0.821–0.950) in those with perinatal hypoxia.

We plotted the predicted probability of bleeding according to the prediction score (►**Fig. 5**). Then, we categorized our final NeoBRis index into four risk categories: "*very low risk*" (score ≤ 0), "*low risk*" (0 < score ≤ 150), "*medium risk*" (150 < score ≤ 300), and "*high risk*" (300 < score). To allow for an easy interpretation of the NeoBRis index, we displayed the observed risk of bleeding and the observed risk of severe bleeding (as defined by a NeoBAT score ≥ 3) for each risk category (►**Table 3**). In our study cohort, the "*very low*" and the "*low*" risk categories indicate small-to-modest risk of bleeding and virtually no risk of severe bleeding. The "*medium*" risk category is associated with a moderate risk of bleeding and a very small risk of severe bleeding, whereas the "*high-risk*" category is associated with a very high risk of bleeding and a moderate risk of severe bleeding (►**Table 3**).

Discussion

We developed a multivariable prediction model for 24 hours bleeding risk in critically ill neonates. EXTEM A10 and LI60 parameters, platelet count, and creatinine levels were identified as the most robust predictors of hemorrhage. Based on these variables, we built and internally validated an easy-to-apply index of bleeding risk, which showed excellent performance.

One-tenth of neonates admitted to NICUs develop major hemorrhage.[14] The extent to which different clinical and laboratory factors contribute to this bleeding risk is unclear and difficult to assess.[21] The estimation of the hemostatic

Table 1 Characteristics of the study population ($n = 332$)

	Mean ± SD; median (IQR) or *n* (%)
Gender (males)	213 (64.2%)
Gestational age (wk)	35.2 ± 4.40; 37 (32–39)
Birth weight (g)	2,437 ± 1,015; 2,585 (1,480–3,290)
Cesarean section	216 (65.1%)
Perinatal conditions	
Suspected sepsis	46 (13.9%)
Sepsis	121 (36.5%)
Respiratory distress syndrome	169 (50.9%)
Intrauterine growth retardation	41 (12.4%)
Perinatal hypoxia	167 (50.3%)
Acute renal failure	65 (19.6%)
Disseminated intravascular coagulopathy	65 (19.6%)
Necrotizing enterocolitis	12 (3.6%)
Laboratory parameters	
WBC ($\times 10^3$), cells/μL	14.9 ± 8.22; 13.6 (9.56–18.5)
Neutrophils (%)	60.0 ± 17.4; 64 (48.0–73.0)
Platelets ($\times 10^3$), cells/μL	197 ± 129; 208 (81.5–280)
C-reactive protein, mg/L	36.0 ± 46.8; 15.6 (3.40–52.5)
SGOT, IU/L	116 ± 256; 60.0 (38.0–100)
SGPT, IU/L	47.9 ± 113; 19.0 (13.0–36.0)
Total bilirubin, mg/dL	8.21 ± 7.34; 6.35 (4.40–9.90)
Direct bilirubin, mg/dL	1.81 ± 5.17; 0.30 (0.20–0.50)
Blood urea nitrogen, mg/dL	44.5 ± 39.5; 33.0 (20.0–55.0)
Creatinine, mg/dL	0.69 ± 0.47; 0.60 (0.40–0.90)
EXTEM parameters	
CT	100 ± 451; 54.0 (46.0–67.0)
A10	47.6 ± 15.1; 52.0 (37.0–59.0)
A20	53.0 ± 15.0; 57.0 (44.0–63.5)
A30	54.1 ± 14.8; 57.0 (45.0–64.0)
CFT	208 ± 585; 93.5 (67.5–157)
MCF, mm	55.6 ± 15.1; 58.0 (47.0–65.0)
α-angle	71.1 ± 11.5; 74.0 (68.0–78.0)
LI60, %	94.2 ± 6.48; 95.0 (92.0–98.0)
ML, %	9.84 ± 12.0; 8.00 (2.00–12.00)
Type of hemorrhage (clinical outcome)	
Intraventricular hemorrhage	96 (28.9%)
Gastrointestinal hemorrhage	39 (11.8%)
Pulmonary hemorrhage	15 (4.5%)
Venipuncture site hemorrhage	82 (24.7%)
Urinary tract hemorrhage	13 (3.9%)

Abbreviations: A10, clot amplitude at 10 minutes; A20, clot amplitude at 20 minutes; A30, clot amplitude at 30 minutes; CFT, clot formation time; CT, clotting time; IQR, interquartile range; LI60, lysis index at 60 minutes; MCF, maximum clot firmness; ML, maximal lysis; SD, standard deviation; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; WBC, white blood cell.

dysfunction could be useful in predicting the bleeding risk of critically ill neonates.[22] Given that overall hemostasis depends on a complex relationship among endothelium, platelets, fibrinolysis, pro-, and anticoagulant factors, it is expected that an

Table 2 Risk of bleeding within 24 hours of ROTEM testing: multivariable model selected and fitted by double selection least absolute shrinkage and selection operator (LASSO) logit regression

Predicting variable	β coefficient (95% CI)[a]	*p*-Value
A10	−0.103 (−0.143, −0.061)	< 0.001
LI60	+0.064 (+0.020, +0.108)	0.005
Creatinine ≥1.5 mg/dL	+2.501 (+0.448, +4.554)	0.017
Platelet count, cells/μL		
$> 150 \times 10^3$	0.000	–
$50–150 \times 10^3$	+0.902 (−0.002, +1.807)	0.051
$< 50 \times 10^3$	+3.020 (+0.808, +5.233)	0.007

Abbreviations: A10, clot amplitude at 10 minutes; CI, confidence interval; LI60, lysis index at 60 minutes.
[a]The β coefficients correspond to the logarithm of the odds ratio from logit regression.

1. A10
   a. Obtain the A10 value of the EXTEM test of the patient
   b. Calculate: –10.3×A10
2. LI60
   a. Obtain the LI60 value of the EXTEM test of the patient
   b. Calculate: +6.4×LI60
3. Creatinine
   a. Obtain the score associated with the patient creatinine (mg/dL) from the look up table

Creatinine look up table		
Creatinine, mg/dL	Score	
<1.5	0	
≥1.5	250	

4. Platelet count
   a. Obtain the score associated with the patient platelet count (cells/μL) from the look up table.

Platelet count look up table		
Platelet ($\times 10^3$), cells/μL	Score	
>150	0	
50–150	90	
<50	300	

5. Overall Score
   a. Calculate: 1b + 2b + 3a + 4a = ☐
   b. Categorize the patient into "very low", "low", "medium" or "high risk" of bleeding within 24 hours of ROTEM testing by using the score obtained in 5a and the categorization table.

Categorization table		
Category	Cut-offs	
Very low risk	score ≤0	
Low risk	0< score ≤150	
Medium risk	150< score ≤300	
High risk	300< score	

Fig. 2 Clinical prediction index scoring algorithm.

abnormality in just one component does not accurately and reliably represent the status of clinical hemostasis. A composite approach to individual hemorrhagic risk would be more appropriate to identify the neonates who really are at significant bleeding risk. Therefore, VMs that have the advantage of measuring the total clotting capacity could provide immediate information about the coagulation profile of neonates, and be more useful in predicting the probability of a bleeding event.

Until now, several prediction models for hemorrhage in neonates have been developed, but most of them allow only a risk assessment at baseline and use mainly clinical variables without taking into account the clinical course and the hemostatic profile of the neonate.[23–26] Fustolo-Gunnink et al recently presented a dynamic prediction model for major bleeding in thrombocytopenic preterm neonates including platelet count, in addition to well-known clinical variables.[27] However, there is insufficient evidence about the association of platelet counts with major bleeding, especially in preterm neonates.[21] A reasonable assumption is that assessment of the overall platelet function and the global hemostatic profile of neonates using VMs can better predict the bleeding risk.[11] That is why, in addition to the most evident clinical variables and platelet counts assessed in former prediction models, we selected ROTEM parameters for inclusion in our model. Eventually, four variables (A10, LI60, platelet counts, and creatinine levels) proved to be the most robust predictors of 24 hours bleeding risk in critically ill neonates, when entered simultaneously into the multivariable prediction model.

Platelets have central role in primary hemostasis, therefore, thrombocytopenia, present in 20 to 35% of neonates in the NICU, is a risk factor for major hemorrhage.[21] Although a

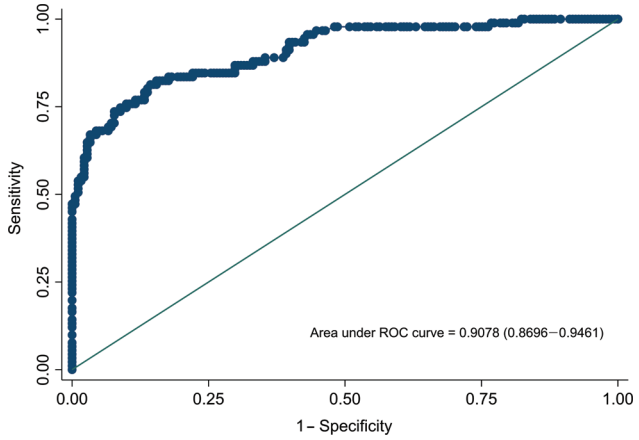

Fig. 3 Area under receiver-operating characteristic (ROC) curve of the Neonatal Bleeding Risk (NeoBRis) index.

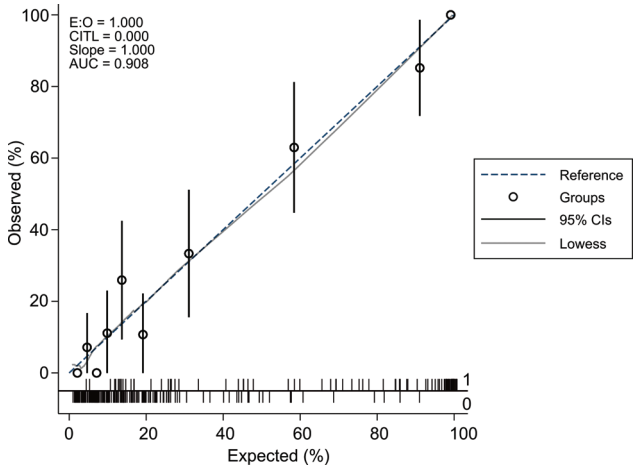

Fig. 4 Calibration plot (predicted vs. observed probability plot). AUC, area under curve.

clear relationship between low platelet counts and clinical bleeding has not been firmly established in neonates,[28] we identified thrombocytopenia, especially at a count less than 50,000/μL as a significant predictor of hemorrhagic risk.

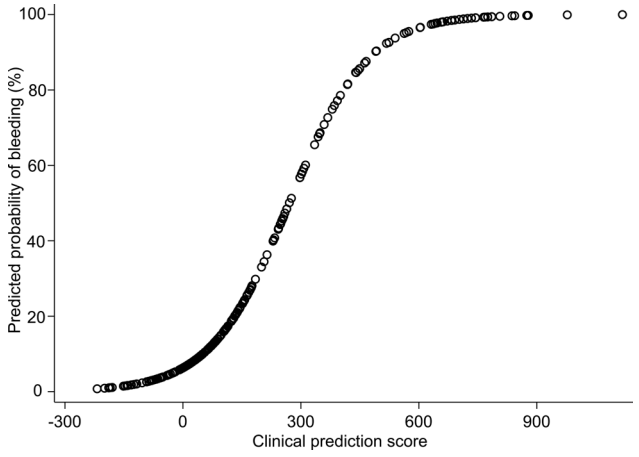

Fig. 5 Predicted probability of bleeding according to the Neonatal Bleeding Risk (NeoBRis) index.

Table 3 NeoBRis clinical prediction score: observed risk of bleeding and observed risk of severe bleeding for each risk category

Risk category	Score range	Observed risk of bleeding	Observed risk of severe bleeding[a]
Very low risk	score ≤ 0	3% (2/58)	0% (0/58)
Low risk	$0 <$ score ≤ 150	12% (13/106)	0% (0/106)
Medium risk	$150 <$ score ≤ 300	38% (15/40)	3% (1/40)
High risk	$300 <$ score	90% (61/68)	32% (22/68)

Abbreviation: NeoBRis, Neonatal Bleeding Risk.
[a]As defined by a neonatal bleeding assessment tool (NeoBAT) score ≥ 3.

We also found that an elevated value of serum creatinine (≥ 1.5 mg/dL) affected the bleeding risk of our study population. In adult patients with acute kidney injury (AKI), uremia has been reported to contribute to platelet dysfunction and coagulopathy. Acute uremia per se provokes disturbances of the hemostatic system, with concomitant bleeding and a hypercoagulable tendency.[29] In keeping with this, TEG pattern was either normal or hypocoagulable compared with normal controls in the presence of AKI secondary to acute liver failure.[30] Although an elevated serum creatinine level is a predictor of bleeding in critically ill neonates, it is unclear if this finding represents a causal relationship or a confounded association due to disease severity.

Among ROTEM parameters used to evaluate the global hemostatic profile, two of them were kept in our model as the most robust predictors: EXTEM A10 and LI60. The amplitude recorded at 10 minutes was the EXTEM variable earlier and strongly reflecting the relation between the hypocoagulable status and clinical bleeding events. This is in line with the more intense hypocoagulable profile recently detected by our group, in septic neonates with hemorrhagic diathesis as compared with those without.[6] Since a higher A10 value represents a stronger ability to make a sufficient blood clot, this relationship is interpreted as a causal one.

An intriguing study finding was that decreased fibrinolysis, as reflected by an increased LI60, was a predictor of clinical bleeding in critically ill neonates. In septic adult patients, fibrinolysis is often significantly reduced[31] and LI60 has been reported as an early and reliable biomarker of severe sepsis in critically ill adults.[32] Similarly, fibrinolysis shutdown in neonates admitted to NICUs might be an index of disease severity and/or a marker of acute hemostatic derangement and consequently might act as a significant predictor of bleeding risk.

Our prediction model combined multiple variables by assigning relative weights to each predictor to obtain a probability of bleeding events.[33] It is noteworthy that none of the clinical variables was retained as significant in the prediction model, as opposed to laboratory measurements evaluating or relating with coagulation status. Possibly, the impact of all the clinical variables on bleeding risk is indirectly assessed through ROTEM test values, which estimate

the dynamics of blood coagulation, in association with platelet count and serum creatinine levels.

Several limitations of our study have to be acknowledged. This was a single-center study, and the sample size was relatively small for the development of the predictive model. Bleeding risk was assessed only for the first 24 hours after laboratory analysis and long-term risk estimation for bleeding events was not addressed. Finally, to evaluate our model performance, only internal validation was undertaken: the model has to be externally validated before broader clinical application. On the other hand, the strength of our study is that the current model included, besides well-known clinical risk factors, laboratory parameters related to hemostatic status of neonates. This resulted in a dynamic prediction model taking into account the hemostatic profile of the neonate, which can alter substantially over time and has a strong effect on the probability of hemorrhagic event. Moreover, in our study population, the risk of bleeding was not affected by treatment with platelet and plasma transfusions, since we excluded previously transfused neonates. The excellent model performance and the fact that all four significant variables retained in the prognostic index are easily obtained and used, render our model attractive, practical, and convenient to apply in all critically ill neonates, both full-term and preterm, thrombocytopenic or not. Although the outcome variable used in our model was clinical bleeding, we could also draw conclusions on the risk of severe bleeding (as defined by a NeoBAT score ≥ 3) for each risk category. It is considerable that the probability of severe bleeding was substantially limited only to the high-risk category neonates.

We believe that our ROTEM-based prediction model of bleeding risk among critically ill neonates has excellent performance and usability. After this model has been externally validated, it will enable clinicians to easily quantify the 24-hour bleeding risk and timely address it by individualized therapeutic decisions.

What is known about this topic?

- Critically ill neonates have a high risk of hemorrhage due to coagulopathy and commonly receive transfusion. However, there is lack of a clear association between conventional coagulation parameters and clinical bleeding risk.
- There is a need for validated tools to characterize the global hemostatic profile of neonates, to estimate bleeding risk, and to guide plasma and platelet transfusion therapy.

What does this paper add?

- We developed and internally validated an easy-to-apply, rotational thromboelastometry-based, prediction model of hemorrhage in critically ill neonates.
- After external validation, this model will enable clinicians to quantify the 24-hour bleeding risk.

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Conflict of Interest
None declared.

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