HUMAN BIOLOGY
2025, VOL. 95, ISSUE 3
ORIGINAL ARTICLE

OPEN ACCESS

A Nomogram Model for Predicting Early Hyperglycemia in Premature Infants

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ABSTRACT

Background: Hyperglycemia in preterm infants is likely to lead to severe complications and higher mortality. Timely identification of hyperglycemia in preterm infants is vital for the prognosis of patients. We developed and validated predictive models for hyperglycemia in preterm infants < 32 weeks of gestational age to aid in the early detection of these patients.

Methods: A retrospective analysis was performed on 460 premature infants to examine the association of various clinical variables with hyperglycemia. We collected data from June 1, 2021, to May 31, 2023. clinical and demographic parameters were analyzed using univariable and multivariable logistic regression analysis (backward method). We constructed a nomogram to assess the risk of hyperglycemia. The model's accuracy was validated using bootstrap resampling (n=500), and the POC curve was used for discrimination analysis to calibrate function and value. Calibration was evaluated via a calibration curve. The model's clinical utility was evaluated through decision curve analysis

Results: Of the 29 potential predictors analyzed in 460 premature infants, the incidence of hyperglycemia was 24.1%. Multivariable logistic regression analysis identified birth weight, invasive ventilation, and Intraventricular hemorrhage as independent risk factors for premature infants with hyperglycemia. The resulting nomogram accurately predicted hyperglycemia risk with an area under the curve of 0.735(95%CI: 0.685-0.786). The bootstrap-validated area under the curve remained at 0.735(95%CI: 0.687-0.785). This model exhibited excellent calibration and demonstrated greater predictive efficacy and clinical utility for hyperglycemia.

Conclusion: We have developed a prediction nomogram of hyperglycemia that can assist clinical treatment decision-making.

INTRODUCTION

With advancements in perinatal medicine and neonatal intensive care technology, the survival rate of preterm infants has steadily increased Qiao et al. (2021), Hug et al. (2019). However, these infants exhibit a high incidence of complications, including brain injuries, bronchopulmonary dysplasia, retinopathy of prematurity, and necrotizing enterocolitis (NEC). One significant complication is the disruption of glucose metabolism, with hyperglycemia occurring more frequently as gestational age decreases Zamir et al. (2018), Butorac Ahel et al. (2022). This is attributed to inadequate pancreatic β cell function and immature glycogenolytic enzymes, leading to insulin resistance. Additionally, newborns with asphyxia, infections, or hypothermia are at a heightened risk for hyperglycemia Adeniji et al. (2020). Iatrogenic hyperglycemia is particularly when the intravenous glucose infusion rate exceeds 5.1 mg/kg/min Stensvold et al. (2018). Existing literature indicates that hyperglycemia correlates not only with acute complications such as mortality and intracranial hemorrhage but also with long-term sequelae, including visual impairment, hypertension, and neurodevelopmental disabilities Butorac Ahel et al. (2022), Rath et al. (2022), Lei et al. (2021), Almeida et al.

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Keywords : Neonate, premature infants, hyperglycemia, Nomogram, Predictive model.

(2021), Leung et al. (2020), Zamir et al. (2019), Puzone et al. (2023). Thus, investigating risk factors for hyperglycemia in preterm infants and developing a predictive nomogram model is imperative for clinicians to effectively identify and manage this complication. In this study, we retrospectively analyzed data from premature infants with gestational ages under 32 weeks across three tertiary hospitals and one secondary hospital in the Ningxia Hui Autonomous Region, focusing on factors influencing early hyperglycemia. The resulting risk factor diagram model aims to provide valuable insights for clinical practice.

MATERIALS AND METHODS

This study was conducted in accordance with the Helsinki Declaration. The need for informed consent was waived by the Institutional Review Board (IRB) of Yinchuan Maternal and Children's Healthcare Hospital due to its retrospective nature (approval number: 2024-51). All data generated or analyzed during this study are included in this published article and its supplementary information files.

Participants

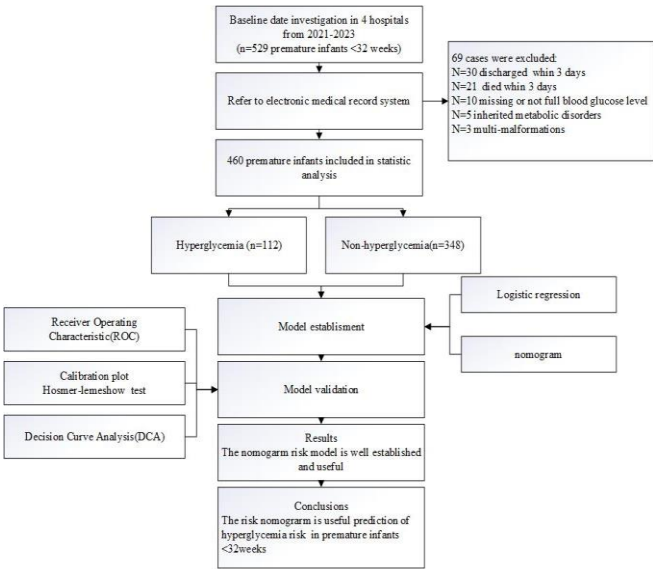
This retrospective, multicenter, case-control study utilized electronic medical records to identify participants. All infants with gestational ages less than 32 weeks who were admitted to the neonatal intensive care unit (NICU) of four hospitals from June 1, 2021, to May 31, 2023, were included. Inclusion criteria were: (1) hospitalization within 24 hours postnatally; (2) length of stay ≥ three days; (3) blood glucose levels monitored at least three times on the first day post-birth and at least twice on each of the second and third days. Exclusion criteria comprised: (1) newborns diagnosed with genetic or metabolic disorders; (2) congenital malformations, including chromosomal abnormalities. Out of 529 preterm infants admitted, 69 were excluded due to death, discharge, missing or integrated blood glucose values, inherited metabolic disorders, or significant malformations, resulting in a 13.0% loss rate. The final cohort consisted of 460 participants. A flow diagram of the study design is presented in (Figure. 1).

Measurements and Definitions

Blood glucose concentrations were measured from capillary blood samples collected after warming the infants' heels prior to feeding, using a Roche micro-blood glucose meter (ACCU-CHEK Active). Hyperglycemia is defined as two consecutive blood glucose measurements exceeding 150 mg/dL when the glucose infusion rate is adjusted to 5 mg/kg.min or lower within the first three days after birth. Paulsen et al. (2021). Respiratory distress syndrome (RDS) was diagnosed based on the necessity for supplemental oxygen to maintain oxygen saturation within the range of 88-94% Sweet et al. (2023).

Intraventricular hemorrhage (IVH) was categorized and graded according to established criteria Papile et al. (1978). Hemodynamically significant patent ductus arteriosus (hs-PDA) was defined through specific echocardiographic parameters as specified in the literature Hamrick et al. (2020). Feeding intolerance (FI) was characterized by an inability to adequately digest enteral feedings, indicated by gastric residual volumes exceeding 50% or abdominal distension Ortigoza et al. (2022). Apnea was defined as a pause in breathing lasting 20 seconds or longer or a shorter duration associated with bradycardia (< 100 bpm), cyanosis, or pallor Eichenwald et al. (2016).

Figure 1: Flow diagram of study design.



Data Collection

Demographic and perinatal data were extracted from medical charts, including maternal information (age, body mass index at delivery, total prenatal glucocorticoid administration, mode of delivery, incidence of multiple pregnancies, maternal hypertension, presence of gestational diabetes, maternal hypothyroidism, and history of assisted reproductive technology) and infant information (sex, gestational age, birth weight, age at admission, Apgar scores, premature rupture of membranes, fasting duration, feeding commencement timing, initiation of parenteral nutrition, breastfeeding status, glucose infusion rate, umbilical vein catheterization, umbilical artery catheterization, use of invasive or noninvasive ventilation, occurrences of RDS, IVH, FI, apnea, and hs-PDA).

Statistical Analysis

Variables with more than 20% missing values were excluded from analysis. Remaining missing values were handled using simple imputation methods; categorical data were filled using mode, while median was utilized for continuous data. Statistical analyses were conducted using

R software (version 4.2.0). Baseline characteristics and univariate analyses were performed using the compare-groups package, while multifactorial logistic regression was executed with the glm package.

The pROC package facilitated discrimination analyses for calibration assessments. Calibration curves were generated utilizing the prob function from the rms package, with the risk regression package employed for the calibration curve and decision curve analysis (DCA) conducted using the rmda package. Nomograms were developed through the rms package. Statistical significance was determined at $P < 0.05$.

RESULTS

A total of 460 premature infants were enrolled to develop and validate our predictive nomogram model. The clinical characteristics of the subjects are summarized in Table 1. Among the 460 patients, 258 (56.1%) were male and 202

Table 1: Clinical characteristics of patients

Variable	(ALL]) n=460	Non-hyperglycemia group (n=349)	Hyperglycemia group (n=111)	*P* value
Sex N (%)	-	-	-	0.713
female	202 (43.9)	155 (44.5)	47 (42.0)	-
male	258 (56.1)	193 (55.5)	65 (58.0)	-
Age, minutes	13.0 [11.0;19.2]	13.0 [11.0;20.0]	13.0 [11.0;19.0]	0.743
Apgar score1min≤7, yes, N (%)	137 (29.8)	93 (26.6)	44 (39.6)	0.016
Apgar score 5min≤7, yes, N (%)	17 (3.70)	9 (2.58)	8 (7.21)	0.04
Cesarean, yes, N (%)	336 (73.0)	250 (71.8)	86 (76.8)	0.366
Multiple pregnancy, yes, N (%)	83 (18.0)	54 (15.5)	29 (26.1)	0.019
Mother's age, year	30.0 [26.0;33.0]	30.0 [26.0;33.0]	30.0 [27.0;33.0]	0.512
MBMI	25.8 [24.2;28.1]	25.8 [24.2;27.9]	26.6 [24.6;28.7]	0.203
GDM, yes, N (%)	51 (11.1)	33 (9.48)	18 (16.1)	0.079
Maternal hypertension, yes, N (%)	145 (31.5)	102 (29.3)	43 (38.4)	0.092
Maternal hypothyroidism, yes, N (%)	24 (5.22)	18 (5.17)	6 (5.36)	1
Assisted reproduction,yes, N (%)	37 (8.04)	24 (6.88)	13 (11.7)	0.163
Fast time≥24h, yes, N (%)	245 (53.3)	177 (50.9)	68 (60.7)	0.087
Start feeding time≥24h, yes, N (%)	202 (43.9)	147 (42.2)	55 (49.1)	0.244
Breastfeeding, yes, N (%)	183 (39.8)	134 (38.5)	49 (43.8)	0.454
PN start time≥24h, yes, N (%)	157 (34.1)	114 (32.8)	43 (38.4)	0.327
UVC, yes, N (%)	343 (74.6)	245 (70.4)	98 (87.5)	< 0.001
UAC, yes, N (%)	54 (11.7)	31 (8.91)	23 (20.5)	0.002
RDS, yes, N (%)	288 (62.6)	201 (57.8)	87 (77.7)	<0.001
IVH, yes, N (%)	119 (25.9)	72 (20.7)	47 (42.0)	<0.001
FI, yes, N (%)	273 (59.3)	192 (55.2)	81 (72.3)	0.002
Apnea, yes, N (%)	188 (40.9)	133 (38.1)	55 (49.5)	0.054
Hs-PDA, yes, N (%)	42 (9.13)	22 (6.32)	20 (17.9)	<0.001
Invasive ventilation, yes, N (%)	239 (52.0)	156 (44.8)	83 (74.1)	<0.001
Noninvasive ventilation, yes, N (%)	425 (92.4)	316 (90.8)	109 (97.3)	0.04
Total prenatal glucocorticoids, yes, N (%)	350 (76.1)	269 (77.3)	81 (72.3)	0.344
GIR, mg/kg.min	5.7 [5.5; 6.0]	5.7 [5.6; 6.0]	5.7 [5.3; 6.1]	0.633
BW	-	-	-	<0.001
≥1500g, yes, N (%)	174 (37.8)	152 (43.7)	22 (19.6)	-
1000g-1499g, yes, N (%)	241 (52.4)	170 (48.9)	71 (63.4)	-
<1000g, yes, N (%)	45 (9.78)	26 (7.47)	19 (17.0)	-
GA	-	-	-	<0.001
≥30w, yes, N (%)	298 (64.8)	244 (70.1)	54 (48.2)	-
<30w, yes, N (%)	162 (35.2)	104 (29.9)	58 (51.8)	-
PROM ≥18h, yes, N (%)	78 (17.0)	62 (17.8%)	16 (14.3%)	0.471

Patients in this region use Dexamethasone, which promotes fetal lung maturation. The total prenatal glucocorticoid means 6mg dexamethasone intramuscular injection, q12h, for two days. MBMI maternal body mass index, GDM gestational diabetes mellitus.PN parenteral nutrition, UVC umbilical vein catheterization, UAC umbilical artery catheterization, RDS respiratory distress syndrome, IVH intraventricular hemorrhage, FI feeding Intolerance, hs-PDA Hemodynamically significant patent ductus arteriosus, GIR glucose infusion rate, BW birth weight, GA gestational age.

(43.9%) were female. The age of the infants ranged from 3 minutes to 2 hours (median: 13 minutes), with a gestational age between 25 and 31+6 weeks (median: 30+6 weeks) and a birth weight from 650 to 2310 g (median: 1400 g). The hyperglycemia group included 111 infants (24.1%).

Selected predictors for the model

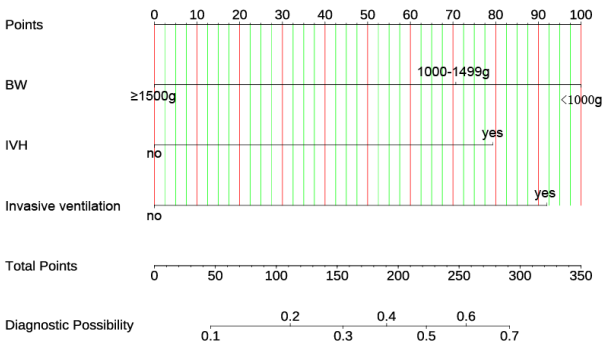
Following univariate logistic analysis (Table2), we identified several predictors for inclusion in the multivariable logistic regression: Apgar score ≤ 7, multiple pregnancies, UVC, UAC, RDS, IVH, FI, hs-PDA, invasive ventilation, non-invasive ventilation, birth weight (BW), and gestational age (GA).

The backward stepwise multivariable logistic analysis revealed that hyperglycemia in premature infants was significantly associated with BW (1000-1499g) (P=0.038), IVH (P<0.001), and invasive ventilation (P=0.001) (Table 2).
Infants with BW (1000-1499g), IVH, and requiring invasive ventilation had an increased risk of hyperglycemia compared to those without these factors.

Predictive nomogram for the risk of hyperglycemia

Using the final multivariable logistic regression outcomes, we developed a nomogram incorporating three significant predictors: BW, IVH, and invasive ventilation Figure. 2. This nomogram provides a quantitative assessment of hyperglycemia risk in premature infants with GA < 32 weeks.

Figure 2: Nomogram developed with BW, IVH and Invasive ventilation incorporated.

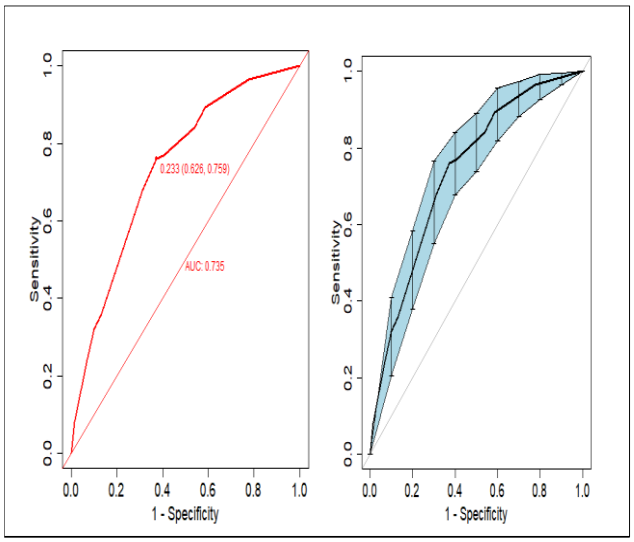


Predictive Model Validation

The receiver operating characteristic (ROC) curve was employed to assess the discriminatory capacity of the predictive model. The area under the ROC curve for the nomogram was 0.735 (95% CI: 0.685-0.786) (DeLong), indicating moderate predictive performance Figure. 3. Internal validation was conducted using the bootstrap method with 500 repetitions, yielding a persistent area under the ROC curve of 0.735 (95% CI: 0.687-0.784) Figure.3,
which confirms moderate discrimination in hyperglycemia risk estimation.

Figure 3: Receiver operating characteristic curve (ROC) validation of the hypweglycemia risk nomogram prediction. The y-axis represents the true positive rate of the risk prediction, the x-axis represents the false positive rate of the risk prediction.

The thick red line represents the performance of the nomogram in the entire set (a) and bootstrap (500 repetitions).



Calibration of the predictive model was performed using a calibration plot and the Hosmer–Lemeshow test.
The calibration curves demonstrated a satisfactory fit for the predictive model and its bootstrap validation. The Hosmer–Lemeshow test indicated high consistency between predicted and bootstrap probabilities ($\chi 2$=1.485, P=0.997) Figure. 4.

The decision curve analysis (DCA) illustrated that for an individual threshold probability between 6% and 52%, the use of this model for predicting hyperglycemia provides greater clinical benefit compared to the treat-all or treat-none strategies Figure. 5.

Table 2: Univariable and multivariable logistic regression analysis of the predictor of hyperglycemia in premature infants.

Variables	Univariable analysis		Multivariable analysis	
	OR (95%CI)	***P***	**OR (95%CI)**	***P***
GA <30weeks	2.520(1.631-3.906)	<0.001	-	-
BW				
≥1500g	-	-	-	-
1000-1499g	2.886(1.73-4.975)	<0.001	1.878(1.047-3.449)	0.038
<1000g	5.049(2.405-10.66)	<0.001	2.184(0.932-5.089)	0.07
Total prenatal glucocorticoids,	0.767(0.476-1.257)	0.284	-	-
Hs-PDA	3.221(1.675-6.171)	<0.001	-	-
Apnea	1.560(1.015-2.397)	0.042	-	-
FI	2.123(1.346-3.417)	0.001	-	-
IVH	2.772(1.754-4.376)	<0.001	2.552(1.536-4.244)	<0.001
RDS	2.545(1.575-4.236)	<0.001	-	-
UAC	2.643(1.456-4.747)	0.001	-	-
UVC	2.943(1.654-5.598)	<0.001	-	-
PN start time≥24h	1.279(0.819-1.984)	0.275	-	-
Breastfeeding	0.856(0.543-1.348)	0.501	-	-
Start feeding time≥24h	1.319(0.860-2.024)	0.204	-	-
Fast time≥24h	1.493(0.971-2.314)	0.07	-	-
Noninvasive ventilation	3.679(1.284-15.520)	0.034	-	-
Invasive ventilation	3.523(2.219-5.725)	<0.001	2.358 (1.398-4.044)	0.001
GIR	0.759(0.488-1.181)	0.222	-	-
Assisted reproduction	1.773(0.848-3.560)	0.115	-	-
Maternal hypothyroidism	1.038(0.368-2.547)	0.939	-	-
Maternal hypertension	1.503(0.959-2.341)	0.073	-	-
GDM	1.828(0.968-3.36)	0.056	-	-
PROM	0.769(0.412-1.366)	0.387	-	-
MBMI	1.027(0.969-1.089)	0.371	-	-
Mother's age, year	1.010(0.972-1.049)	0.608	-	-
multiple	1.902(1.130-3.160)	0.014	-	-
cesarean	1.297(0.798-2.162)	0.306	-	-
Apgar score 5min	2.897(1.063-7.765)	0.033	-	-
Apgar score 1min	1.774(1.130-2.771)	0.012	-	-
Age(minute)	0.996(0.989-1.000)	0.194	-	-
Sex	1.111(0.723-1.715)	0.633	-	-

Patients in this region use Dexamethasone, which promotes fetal lung maturation. The total prenatal glucocorticoids mean 6mg dexamethasone intramuscular injection, q12h, for two days. MBMI maternal body mass index, GDM gestational diabetes mellitus, PN parenteral nutrition, UVC umbilical vein catheterization, UAC umbilical artery catheterization, RDS respiratory distress syndrome, IVH intraventricular hemorrhage, FI feeding Intolerance, hs-PDA Hemodynamically significant patent ductus arteriosus, GIR glucose infusion rate, BW birth weight, GA gestational age.

Figure 4: Calibration curves of the predictive hyperglycemia risk nomogram. The y-axis represents actual diagnosed cases of hyperglycemia, the x-axis represents the predicted risk of hyperglycemia. The dotted line represents a perfect prediction by an ideal model, the blue line represents the performance of the entire cases, and red line the performace of bias-correction by bootstrapping (500 repetitions). The calibration curves show a good fit for the predictive model and the bootstrap.

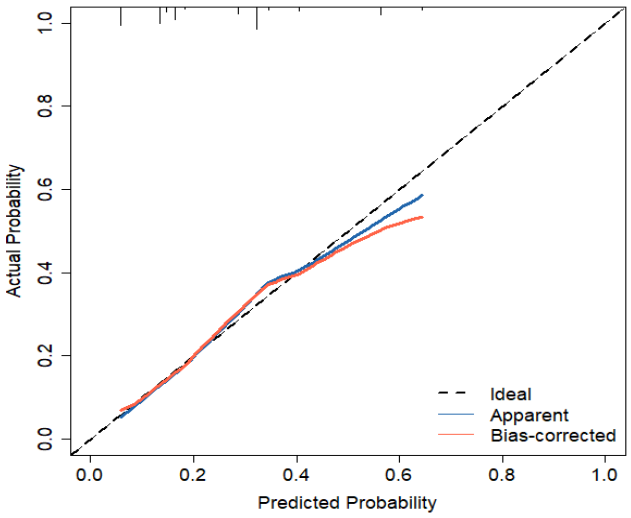
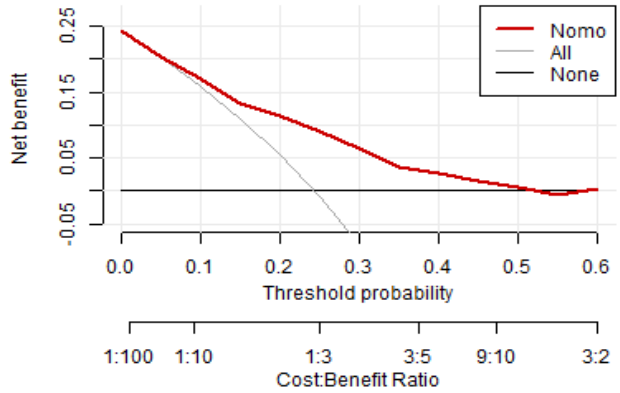


Figure 5: Decision curve analysis for the hyperglycemia risk nomogram. The y-axis represents the net benefit, The x-axis shows the threshold probability. The red line represents the nomogram. The thin grey solid line represents the assumption that all patients have hyperglycemia, the thick black horizontal solid line that all patients have no heyperglycemia.



DISCUSSION

We developed a straightforward statistical predictive model to quantify hyperglycemia in premature infants with gestational age <32 weeks, utilizing readily available demographic and clinical variables. The model identifies birth weight, invasive ventilation, and intraventricular hemorrhage (IVH) as independent risk factors for hyperglycemia in this population. Internal validation using the bootstrap method demonstrated good discrimination and calibration, with a receiver operating characteristic (ROC) curve area of 0.735, consistent across bootstrapping validations. Calibration curves confirmed the model's appropriateness, and the Hosmer–Lemeshow test indicated no significant deviation (P = 0.997). Decision curve analysis (DCA) revealed that when individual threshold probabilities range between 6% and 50%, the model offers additional clinical benefits for predicting hyperglycemia.

Our findings confirm that lower birth weight is an independent risk factor for hyperglycemia in premature infants (GA < 32 weeks), with an increased incidence corresponding to reduced birth weight. Previous studies have similarly identified birth weight as a significant predictor of hyperglycemia in this demographic, with estimates suggesting a 1.6-fold increase in hyperglycemia risk for each standard deviation of weight loss.

Furthermore, hyperglycemia has been implicated in exacerbating intracranial hemorrhage and subsequent neurological damage. Our study demonstrated a strong association between hyperglycemia and any grade IVH, aligning with prior meta-analyses (OR = 2.60). While some prospective studies corroborated this relationship, others found no significant association, indicating potential variability due to subject selection, sample size, timing, and methodologies for IVH assessment.

Mechanical ventilation was found to triple the likelihood of developing hyperglycemia. One study noted a significant correlation between hyperglycemia and reduced duration of mechanical ventilation, possibly reflecting stress-induced hyperglycemia in this vulnerable population.

The presented nomogram serves as a visual statistical tool for calculating risk scores based on selected predictors, aiding clinicians in identifying and managing at-risk infants. It effectively screens relevant variables, pinpointing the most significant risk factors.

However, there are limitations to this nomogram. It was developed through a retrospective analysis of medical records, lacking comprehensive data on other hyperglycaemia risk factors, such as early-onset sepsis and glucose infusion rates, which may introduce selection bias. Additionally, inconsistencies in blood glucose monitoring methods and timing across different centers could contribute to measurement bias. The nomogram includes only three factors (birth weight, invasive ventilation, and IVH), limiting its predictive capacity for hyperglycemia beyond three days. A multicenter prospective trial is warranted to validate the

model's accuracy.

CONCLUSION

In conclusion, our study introduces a nomogram that calculates risk scores for hyperglycemia in premature infants with GA <32 weeks. Utilizing this model could enhance clinical decision-making by providing a targeted and user-friendly tool for identifying at-risk patients.

DECLARATIONS

Author Contribution

Yongming Wang, Fengzhi Xu participated in study concept, design, and drafting of the manuscript; Huijuan Yin participated in the statistical analysis and manuscript revision; Wang Xu Jiangping He Shasha Wu participated in acquisition, analysis and interpretation of data; Jingxia Luo participated in critical revision of the manuscript for important intellectual content.

Data Availability

Data is provided within the manuscript and supplementary information files

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