Original article

Development and validation of a novel scoring system to predict severe intraventricular hemorrhage in very low birth weight infants

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Abstract

Objective: We sought to develop and validate a novel scoring system for the prediction of severe intraventricular hemorrhage (SIVH) in very low birth weight infants (VLBWI).

Methods: This retrospective cohort multicenter study included 615 VLBWI born between 24 and 32 weeks gestational age (GA). Multivariable logistic regression analyses were used to determine which factors evaluated within the first 5 days of life were associated with SIVH and the weights of these variables. The accuracy of the predictive scoring system was prospectively tested in the same units.

Results: The final SIVH scoring system included the following variables: antenatal steroid therapy, GA, birth weight (BW), 1-min Apgar score, mechanical ventilation and hypotension. The SIVH scores used to divide the subjects into three tiers (low-risk (<5), moderate-risk (5–8) and high-risk (>8)) were developed based on these variables. Of infants with a score below 5, 1.2% (4/339) developed SIVH. Of those with a score above 8, 42.5% (17/40) developed SIVH. The scores were successfully verified in 99 VLBWI.

Conclusions: These findings suggest that among infants with a score >8, the incidence of SIVH is significantly higher. This scoring system can be used to predict the incidence of SIVH during the first 5 days after birth and may contribute to the early intervention in and prevention of SIVH.

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Keywords: Intraventricular hemorrhage; Prediction; Preterm infant; Scoring system

1. Introduction

Severe intraventricular hemorrhage (SIVH), when classified using the Papile grading system [1] as grade 3 and 4, can be a serious threat to the survival of very low birth weight infants (VLBWI) and their neurodevelopmental outcomes [2]. Despite the development of modern neonatal care, the incidence of SIVH remains very high [3], at approximately 13% among VLBWI

[4,5]. Han et al. [6] reported that the mortality rate of SIVH in preterm infants was 28.2%.

In the first 72 h after birth, 90% of instances of intraventricular hemorrhage (IVH) are fully detected [7]. Therefore, the early diagnosis, prevention and intervention of SIVH is particularly important. Prevention methods should involve prenatal, intrapartum and early postpartum treatment. The potential to identify VLBWI at high-risk of developing SIVH is particularly important.

Our primary goal was to create and validate an easy-to-use and reliable scoring system based on available clinical parameters to predict the risk of SIVH within the first 5 days after birth while minimizing exposure to VLBWI at lower risk.

2. Methods

2.1. Patients

This retrospective cohort study was performed in three large tertiary neonatal intensive care units (NICUs) that belong to Guangzhou Women and Children's Medical Center. The three NICUs are located in different districts of Guangzhou city. Preterm infants born between 24 and 32 weeks GA with a BW from 600 to 1500 g were enrolled. The derivation cohort was abstracted from January 2015 to October 2017, and the validation cohort was abstracted from November 2017 to June 2018. Patient identity was kept confidential.

2.2. Clinical variables

The infants had a cranial ultrasonogram (USG) on days 2 and 5 or underwent additional cranial USG when there were clinical manifestations of IVH. Regarding early deaths, infants who acquired a cranial USG and had clinical data indicating predictor variables were included in this study. Any infant who died before or without a cranial USG was excluded from the study. Furthermore, infants with chromosomal anomalies or congenital malformations were excluded from the study.

2.3. Data collection

Data were collected from three NICUs and included antenatal, natal and postnatal features. All selected clinical variables were obtained during the first 5 days after birth. Furthermore, we checked the time consequence between variables and SIVH, and only those factors that showed up before SIVH were included in this study. GA was documented by the mother's last menstrual history and early fetal USG. IVH was classified as Grade 1–4 according to the Papile grading system [1] and deter-

mined by cranial USG, with grades 3 to 4 considered severe. A chorioamnionitis for clinical diagnosis included the presence of maternal fever (≥38.0 °C) and at least 1 of the following: uterine fundal tenderness, maternal tachycardia (>100 beats/min), fetal tachycardia (>160 beats/min), and purulent or foul amniotic fluid. Patent ductus arteriosus (PDA) was defined by echocardiography. Antenatal steroid therapy was defined when the mother received any dose. Hypoglycemia was defined if two numerical plasma glucose values were lower than 2.2 mmol/L when obtained at least three hours apart. Hyperglycemia was defined when two consecutive numerical plasma glucose values were higher than 7 mmol/L and obtained at least three hours apart. Respiratory distress syndrome (RDS) was defined based on clinical manifestations of the respiratory system and chest X-ray findings. Hypotension was defined when the mean arterial pressure (MAP) was lower than the numerical gestational age and required dopamine or dobutamine treatment [8].

2.4. Statistical analysis

Student's *t*-test and Mann-Whitney *U* test were used to compare continuous variables. Fisher's exact test and the chi-square were used to compare nominal variables. Statistical significance was defined as a *p*-value <0.05. All statistical analyses were performed using SPSS 20.0 program (IBM, Armonk, NY, USA).

For predicting outcomes, candidate variables were selected from univariate analysis, and those variables with $p < 0.05$ were entered into multivariate logistic regression analysis. The Hosmer–Lemeshow method of calibration was investigated to assess model fit. The risk ratio (RR) values of the associated variables were used to build the scoring system. The area under the ROC curve (AUC) was calculated and compared with the predictive characteristics of the scores. After the scoring system was determined, it was applied to the validation cohort.

3. Results

3.1. Clinical and demographic characteristics

Table 1 shows the 516 neonates enrolled in the derivation cohort, including the 32 (6.2%) infants who developed SIVH. Antenatal features were not different between the no-SIVH group and the SIVH group except that the incidence of antenatal steroid therapy was significantly lower in the SIVH group, while that of in vitro fertilization was significantly higher in the SIVH group. BW and GA were lower in the SIVH group. The incidence of 1-min Apgar scores <8, 5-min Apgar scores <8, male gender, mechanical ventilation, RDS, hypoten-

Table 1
Comparison of characteristics between the SIVH and no SIVH groups.

Characteristic	no SIVH n = 484	SIVH n = 32	P-value
Mother's age (y)	31.1 ± 5.4	31.1 ± 6.0	0.968
Preeclampsia, n (%)	78 (16.1)	1 (3.1%)	0.085
Diabetes, n (%)	94 (19.4)	5 (15.6)	0.597
PROM >24 h, n (%)	106 (21.9%)	2 (6.2%)	0.060
Multiple pregnancies, n (%)	132 (27.3%)	12 (37.5%)	0.212
In vitro fertilization, n (%)	37 (7.6)	6 (18.8)	0.028
Antenatal steroid therapy, n (%)	414 (85.5%)	20 (62.5%)	<0.001
Chorioamnionitis, n (%)	88 (18.2%)	1 (3.1%)	0.361
Cesarean section (%)	230 (47.5%)	12 (37.5%)	0.271
1-min Apgar <8, n (%)	139 (28.7%)	18 (56.2%)	<0.001
5-min Apgar <8, n (%)	49 (10.1%)	10 (31.2%)	0.001
Gender (male), n (%)	313 (64.7%)	27 (84.4%)	0.023
Gestational age (wk)	29.2 ± 1.7	27.7 ± 1.6	<0.001
Birth weight (g)	1194.0 ± 196.3	1089.5 ± 240.6	0.004
Hypotension, n (%)	73 (15.1)	15 (46.9)	<0.001
Heart rate (time/min)	141.8 ± 14.0	143.9 ± 16.2	0.565
Admission temperature (°C)	35.9 ± 2.3	36.0 ± 0.6	0.890
Mechanical ventilation, n (%)	285 (58.9)	30 (93.8)	<0.001
RDS, n (%)	430 (88.8)	32 (1 0 0)	0.089
PDA, n (%)	132 (27.3)	10 (31.2)	0.626
Surfactant treatment, n (%)	377 (77.9)	29 (90.6)	0.089
Out-born, n (%)	13 (2.8)	3 (9.4)	0.131
Hyperglycemia, n (%)	7 (1.5)	1 (3.1)	1.000
Hypoglycemia, n (%)	19 (3.9)	4 (12.5)	0.023

SIVH, severe intraventricular hemorrhage; PROM, premature rupture of membrane; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus.

sion and hypoglycemia were higher in the SIVH group than in the no-SIVH group.

3.2. SIVH scoring system and associated risks of SIVH with each category

All risk categories showing values of $p < 0.05$ in the univariate analyses were entered into multivariable logistic regression analyses. Although 10 factors in the univariate analyses were statistically significant, only 6 of these remained significant predictors after the multivariable logistic regression analyses. These data showed that antenatal steroid therapy, GA <28 wk, BW <1000 g, 1-min Apgar score <8, mechanical ventilation and hypotension were associated with the incidence of SIVH (RR = 2.80 for the absence of antenatal steroid therapy, RR = 3.30 for GA <28 wk, RR = 4.19 for BW <1000 g, RR = 2.95 for 1-min Apgar score <8, RR = 4.65 for the presence of mechanical ventilation, and RR = 4.47 for the presence of hypotension). The results of the logistic regression analyses are shown in Table 2.

The SIVH score was considered the RR from the multivariable logistic regression model. According to RR, we gave 1 point for the absence of antenatal steroid therapy and a 1-min Apgar score <8, 2 points for GA

<28 weeks, and 3 points for BW <1000 g or the presence of hypotension or mechanical ventilation. The final SIVH scores ranged from 0 to 13. The scoring system is presented in Table 3.

3.3. The predictive ability of SIVH scores

The scoring system was further tested in a validation cohort. The characteristics of the derivation and validation cohorts according to the scoring characteristics are shown in Table 4. The parameters of the neonates in the validation cohort were not different from those in the derivation cohort except that the incidence of 1-min Apgar score <8 was higher in the derivation cohort ($p < 0.05$). The ROC curves of two cohorts are presented in Fig. 1. The AUC values were 0.830 and 0.853 for the derivation and validation cohorts, respectively.

The scores were further subdivided to obtain three risk categories: low-risk (<5), moderate-risk (5–8) and high-risk (>8). Among infants with a score <5, only 1.2% (4/339) in the derivation cohort and 0% (0/55) in the validation cohort developed SIVH. When the score was between 5 and 8, the percentages of infants who developed SIVH in the derivation and validation cohort were 8.0% (11/137) and 8.0% (2/25), respectively. Among infants with a score above 8, the percentages

Table 2
Multivariable logistic regression models for SIVH.

Factor	Value	Final Model, β Coefficient (95% CI)	p-Value
Birth weight (g)	≥1000	Reference	NA
	<1000	4.19 (1.66–10.57)	0.002
Gestational age (wk)	≥28	Reference	NA
	<28	3.30 (1.29–8.40)	0.012
1-min Apgar	≥8	Reference	NA
	<8	2.94 (1.27–6.77)	0.011
Antenatal steroid therapy		2.80 (1.14–6.84)	0.024
Mechanical ventilation		4.65 (1.03–21.14)	0.046
Hypotension		4.47 (1.92–10.43)	0.001

SIVH, severe intraventricular hemorrhage; CI, confidence interval.

Table 3
SIVH scoring system.

Score	0	1	2	3
Birth weight (g)	≥1000			<1000
Gestational age (wk)	≥28		<28	
1-min Apgar	≥8	<8		
Antenatal steroid therapy	Present	Absent		
Mechanical ventilation	Absent			Present
Hypotension	Absent			Present

SIVH, severe intraventricular hemorrhage.

of infants who developed SIVH in the derivation and validation cohorts were 42.5% (17/40) and 36.8% (7/19) (see Fig. 2).

4. Discussion

Our study provides important early clinical information about risk variables and predictive assessment for SIVH. SIVH has been associated with mortality and poor neurodevelopmental outcomes in preterm neonates [2]. Approximately 35–40% of infants with SIVH will suffer from cognitive delay, severe motor defects, or even cerebral palsy [9]. It is important to institute early prevention or early treatment before any irreversible lesions occur.

The etiology of IVH is unclear and thought to be related to numerous perinatal and neonatal risk factors [10,11]. These factors include those identified in our study in addition to other variables that we did not detect: bleeding diathesis, neonatal transport, indomethacin treatment, electrolyte level, CO_2 level and specific gene mutations [12–14]. The reason we did not include these variables in our study is that there were many missing data points for these variables.

Previous studies have shown that the use of steroids before delivery in pregnant women can reduce the risk of poor health outcomes, including IVH [15,16]. A meta-analysis of randomized trials evaluated by Cochrane in 2006 showed that the risk of IVH was lower when the mother was treated with antenatal steroids (relative risk = 0.54, $p < 0.05$) [17]. Antenatal steroid therapy may promote the maturity of the germinal matrix, thereby reducing the risk of SIVH [17].

Several studies have shown that SIVH increases as GA and BW decrease [14,18,19], consistent with our

Table 4
Comparison of the cohorts according to the scoring categories.

| Characteristic	Derivation cohort n = 529	Validation cohort n = 102	p-Value
Gestational age (wk)	29.1 ± 1.7	29.3 ± 2.1	0.528
<28, n (%)	118 (22.9%)	21 (21.2%)	0.718
Birth weight (g)	1187.5 ± 200.7	1201.8 ± 235.3	0.529
<1000, n (%)	93 (18.0%)	16 (16.2%)	0.657
1-min Apgar	7.6 ± 1.9	7.8 ± 1.6	0.342
<8, n (%)	157 (30.4%)	15 (15.2%)	0.002
Antenatal steroid therapy, n (%)	434 (84.1%)	78 (78.8%)	0.194
Hypotension, n (%)	89 (17.2%)	20 (20.2%)	0.291
Mechanical ventilation, n (%)	315 (61.0%)	53 (53.5%)	0.163
No IVH, n (%)	312 (60.5%)	53 (53.5%)	0.199
Grade 1, 2	172 (33.3%)	37 (37.4%)	0.437
Grade 3, 4	32 (6.2%)	9 (9.1%)	0.291

IVH, intraventricular hemorrhage.
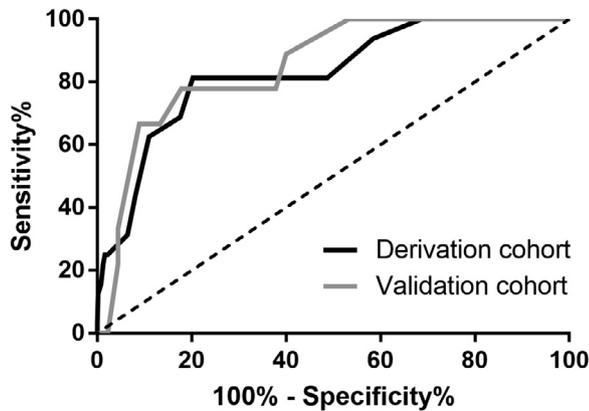
Fig. 1. ROC curves of the derivation and the validation cohorts for the prediction of SIVH.
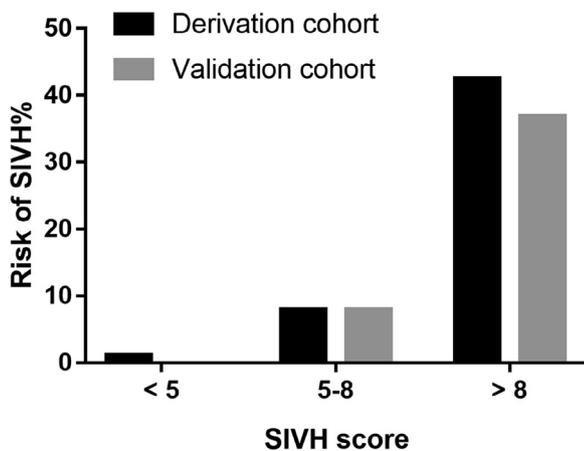

Fig. 2. SIVH scores according to the risk of SIVH in both the derivation and validation cohorts.

research results. Previous results showed that in preterm neonates, GA <28 wk or BW <1000 g may result in fragility of the germinal matrix vasculature, leading to SIVH [20].

The incidence of SIVH in preterm infants has been shown to increase with the presence of mechanical ventilation and a 1-min Apgar <8. The results of our study are consistent with those presented in other studies [21,22]. Poor ventilation has been associated with low blood pressure and low cerebral blood flow fluctuation, and insufficient cerebral perfusion damages the germinal matrix of the brain, leading to SIVH [23]. This may indicate that instability in the respiratory system is closely related to the incidence of SIVH.

Cardiovascular instability in preterm neonates during the early postnatal period has been associated with the development of SIVH [24,25]. Faust et al. [26] and Waitz et al. [27] found that hypotensive infants had a higher rate of IVH, similar to our findings. O'Leary et al. [28] reported that the brain is more resilient to high blood pressure than low blood pressure, and changes in blood pressure correspond to changes in cerebral blood flow, with unstable cerebral blood flow causing damage to the germinal matrix, resulting in SIVH. These findings suggests that hypotension may be a potential predictor of SIVH.

An ideal SIVH scoring system should be repeatable, applicable and easy to use during hospitalization. This predictive scoring system should provide an objective and accurate assessment of SIVH, as well as high negative and positive predictive values that are viable in early life and can guide clinical treatment. To the best of our knowledge, only two predictive models have previously predicted the incidence of SIVH in preterm infants [15,16]. However, those two predictive models are not used for the early prevention of SIVH. Moreover, in a clinical setting, a scoring system is more practical and convenient to use than a predictive model. Coskun et al. [29] developed a scoring system consisting of three clinical parameters (GA, bleeding diathesis and 5-min Apgar score) to calculate the risk of developing IVH in the first 7 days of life. However, that study did not focus on SIVH, and bleeding diathesis is not a routine test in our country.

According to our scoring system, we considered the following measures to reduce the prevalence and prevent the development of SIVH. 1. We suggest more frequently obtaining Doppler measurements of fetal monitoring during preterm delivery. We observed that 1-min Apgar scores at birth were lower in the SIVH group, and this might indicate that more active fetal monitoring can reduce the prevalence of fetal distress. 2. The lack of or uncompleted antenatal steroid treatment should be avoided. Multiple studies have shown that antenatal steroid treatment is a preventive intervention for low Apgar scores, mechanical ventilation, RDS, IVH, neurodevelopmental impairment and neonatal death [30,31]. 3. Blood pressure-related interventions should be considered. Proper blood pressure management can help improve cerebral blood flow perfusion while also providing beneficial effects reducing the IVH incidence or mortality rates in preterm infants [32,33].

The main purpose of our study was to develop a novel and easy-to-use scoring system to predict the incidence of SIVH in VLBWI. AUC values of 0.830 and 0.853 were obtained for the derivation and validation cohorts, respectively, confirming the temporal stability of our scoring system. It must be remembered that even the best scoring system is not perfectly precise and has limitations when used under complex clinical conditions that require verification.

5. Limitations

This study has several limitations. This scoring system may be applicable to our population, but our results must be validated in other populations before wide-

spread dissemination. Previous reports showed that high CO_2 level, hypercapnia and hypernatremia increased the risk of IVH in preterm infants [27,34]. However, in this study, we were unable to collect these data in full, and this may have affected the sensitivity and specificity of the scoring system. Finally, the number of SIVH infants was not large enough. There is still a need to prospectively collect more eligible neonates to assess the predictive capacity of this scoring system.

6. Conclusion

In summary, we have generated a novel, easy-to-use predictive scoring system that replaces six clinical parameters for the early calculation of the risk of SIVH in VLBWI. This scoring system can be used for obstetric counseling and as an adjunct to SIVH preventive clinical decision making.

Funding

Ethical approval

The ethics committee of Guangzhou Women and Children's Medical Center approved this study (number 2017062403).

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