scientific reports

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The effect of hemoglobin level in early life on periventricular leukomalacia: a case control study

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Periventricular leukomalacia (PVL) is a distinct form of brain injury that occurs in preterm infants. The aim of this study is to find suitable and easily accessible laboratory indicators for early prediction of PVL occurrence. A retrospective, case control study was conducted. Infants diagnosed with PVL were included and matched 1:3 with infants without PVL by sex and birth weight. A total of 364 infants were included in this study, including 91 in PVL group and 273 in control group. The hemoglobin (Hb) level (t = -2.961, $p = 0.003$) and red blood cell (RBC) count (t = -3.593, $p < 0.001$) in PVL group were lower than those in control group on the 7th day after birth. Logistic regression showed that the Hb level (OR = 0.984, 95%CI 0.972–0.996, $p = 0.010$) and the RBC count (OR = 0.120, 95%CI 0.034–0.424, $p = 0.001$) on the 7th day after birth were significantly correlated with the occurrence PVL disease. The receiver operating characteristic curve analysis showed that the cut-off value of Hb level on the 7th day after birth was 117.5 g/L (sensitivity = 0.553, specificity = 0.637) and the cut-off value of RBC count on the 7th day after birth was 3.025×10^{12}/L (sensitivity = 0.762, specificity = 0.451). The specificities of the combined indicator on the 7th day after birth was 0.821. The Hb level and RBC count in early life can be used to predict the occurrence of PVL, which are suitable and easy to obtain.

Keywords Hemoglobin, Red blood cell, Periventricular leukomalacia, Preterm, Early life

Abbreviations

PVL	Periventricular leukomalacia
NICU	Neonatal intensive care unit
GA	Gestational age
MRI	Magnetic Resonance Imaging
BW	Birth weight
IMV	Invasive mechanical ventilation
CPAP	Continuous positive airway pressure
PROM	Preterm rupture of membrane
PIH	Pregnancy-induced hypertension syndrome
BPD	Bronchopulmonary dysplasia
ROP	Retinopathy of prematurity
IVH	Intracranial hemorrhage
NEC	Necrotizing enterocolitis
Hb	Hemoglobin
RBC	Red blood cell
PLT	Platelet
ROC	Receiver operating characteristic
OL	Oligodendrocytes
EPO	Erythropoietin

Preterm and low birth weight (BW) infants have a high risk of injury to the immature and developing brain. Hemorrhage and periventricular leukomalacia (PVL) are the main types of brain injury affecting preterm infants[1]. PVL often occurs in preterm infants with gestational age (GA) of 24–32 weeks or very low birth weight[2], potentially leading to sequelae in the nervous system, such as cerebral palsy[3,4], visual disorders[4,5] and

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dyskinesia[6,7]. With the development of neonatal intensive care units (NICUs) in recent years, the survival rate of preterm infants has increased, resulting in a significant increase in the incidence of nervous system sequelae associated with PVL[8]. PVL is usually asymptomatic until the obvious neurological sequelae manifest in the later period of infants. And once PVL occurs, there is no specific treatment. At present, researches on PVL mainly focus on the pathogenesis, clinical manifestations and imaging characteristics. Therefore, it is necessary to find suitable and easily accessible indicators for the early prediction of PVL occurrence.

Hypoxia-ischemia has long been considered one of the main mechanisms of perinatal brain injuries[1,9]. As a key protein for transporting oxygen in blood, hemoglobin (Hb) plays a significant role in regulating oxygen transport and maintaining cerebral perfusion[10,11]. In the rat model of hypoxia-ischemia-induced PVL, oligodendrocyte injury and myelinization disorders were observed[12,13]. Low Hb level may lead to insufficient oxygen supply in brain tissue, and then damage unmyelinated periventricular white matter sensitive to hypoxia[14,15]. At present, the clinical evidence about the relationship between Hb level and PVL is still limited, and the related mechanism is not completely clear. Thus, we conducted a retrospective case control study to analyze the relationship between Hb level in early life and PVL. This analysis aims to evaluate if Hb level can be used to predict the occurrence of PVL.

Methods

Study design

A retrospective, case control study was conducted in Children's Hospital Affiliated to Zhengzhou University from January 2021 to December 2023. Infants with GA ≤ 32 weeks were included in the study. The exclusion criteria were as follows: (1) Congenital developmental malformation. (2) Congenital inherited metabolic diseases. (3) Congenital immune deficiency. (4) Lack of clinical data. Infants diagnosed with PVL were included in the PVL group and matched in a 1:3 ratio with infants without PVL by sex and BW. Infants without PVL were included in the control group. This study was approved by the ethics committee of Children' s Hospital Affiliated to Zhengzhou University.

Data collection

Clinical data for each child, including baseline characteristics, neonatal comorbidities, maternal characteristics and blood routine test results in early life, were collected and analyzed. Baseline characteristics included gender, GA, BW, hospital stays, transfusion history, invasive mechanical ventilation (IMV) time and continuous positive airway pressure (CPAP) time. Maternal characteristics included maternal age, mode of delivery, multiple or singleton pregnancy, preterm rupture of membrane (PROM), pregnancy-induced hypertension syndrome (PIH), and placenta previa. Neonatal comorbidities included bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), intracranial hemorrhage (IVH), necrotizing enterocolitis (NEC), and sepsis. Blood routine test results included Hb level, red blood cell (RBC) count and platelet (PLT) count of infants on the 3rd, 7th and 14th day after birth. All preterm infants underwent routine blood tests on the 3rd, 7th and 14th day after birth. Blood samples were collected by experienced nurses in the early morning, and were examined by an automatic routine blood test instrument xe5000 (Shanghai, China, Sysmex company).

Definitions

PVL is defined as the presence of periventricular cysts identified on cranial ultrasound or cranial magnetic resonance imaging (MRI) scans[16]. PROM is defined as rupture of membranes before the onset of labor[17]. PIH is defined as new systolic and/or diastolic blood pressure ≥ 140/90 mmHg after 20 weeks of pregnancy, and postpartum blood pressure can return to normal[18].

Placenta previa is defined as implantation of the placenta in the lower uterine segment partially or completely covering the internal cervical os after 20 weeks of gestation[19]. BPD is defined as the need for supplemental oxygen ($FiO_2 > 21\%$) for at least 28 days after birth[20]. ROP is defined as a developmental disorder of retinal vascular formation, and the stages are based on International Classification of Retinopathy of Prematurity[21]. IVH is a type of intracranial hemorrhage in premature infants, graded according to the Volpe classification based on cranial ultrasound findings[14]. NEC is an acute gastrointestinal disease characterized by variable degrees of intestinal wall inflammation and necrosis, and the staging is based on Bell staging standard[22]. Sepsis is defined as the disorder of host response caused by infection, which in turn leads to life-threatening organ dysfunction[23]. Blood transfusion standards are based on the Guideline for pediatric transfusion[24].

Head imaging

Head ultrasound screening was performed 3–7 days after birth, at 40 weeks of corrected GA and before discharge[25]. The operation standard of brain ultrasound and the diagnosis of abnormal brain ultrasound results refer to the consensus of neonatal and infant brain ultrasound experts and Vries et al.[26,27]. For all hospitalized preterm infants, head MRI is recommended at 40 weeks of corrected GA[25]. All the preterm infants included in this study underwent head MRI examination at 40 weeks of corrected GA. A conventional MRI sequence protocol was applied in all of the infants: AX: T_1WI (TR 400 ms, TE 8.1 ms), T_2WI (TR 4500 ms, TE 99 ms), T_2 Flair (TR 8000 ms, TE 105 ms). Sag: T_1WI (TR200 ms, TE2.6 ms). Doctors who conducted the examination were unaware of the clinical condition of infants. We considered the classifications proposed by Vries et al., Choi et al. and Song et al. and classified PVL into three grades[27–29]. Grade I included local changes in the small capsule cavity around the ventricle. Grade II included extensive cystic changes around the ventricle, which could be fused into pieces. Grade III included cystic changes in the periventricular and subcortical white matter. As shown in Fig. 1.

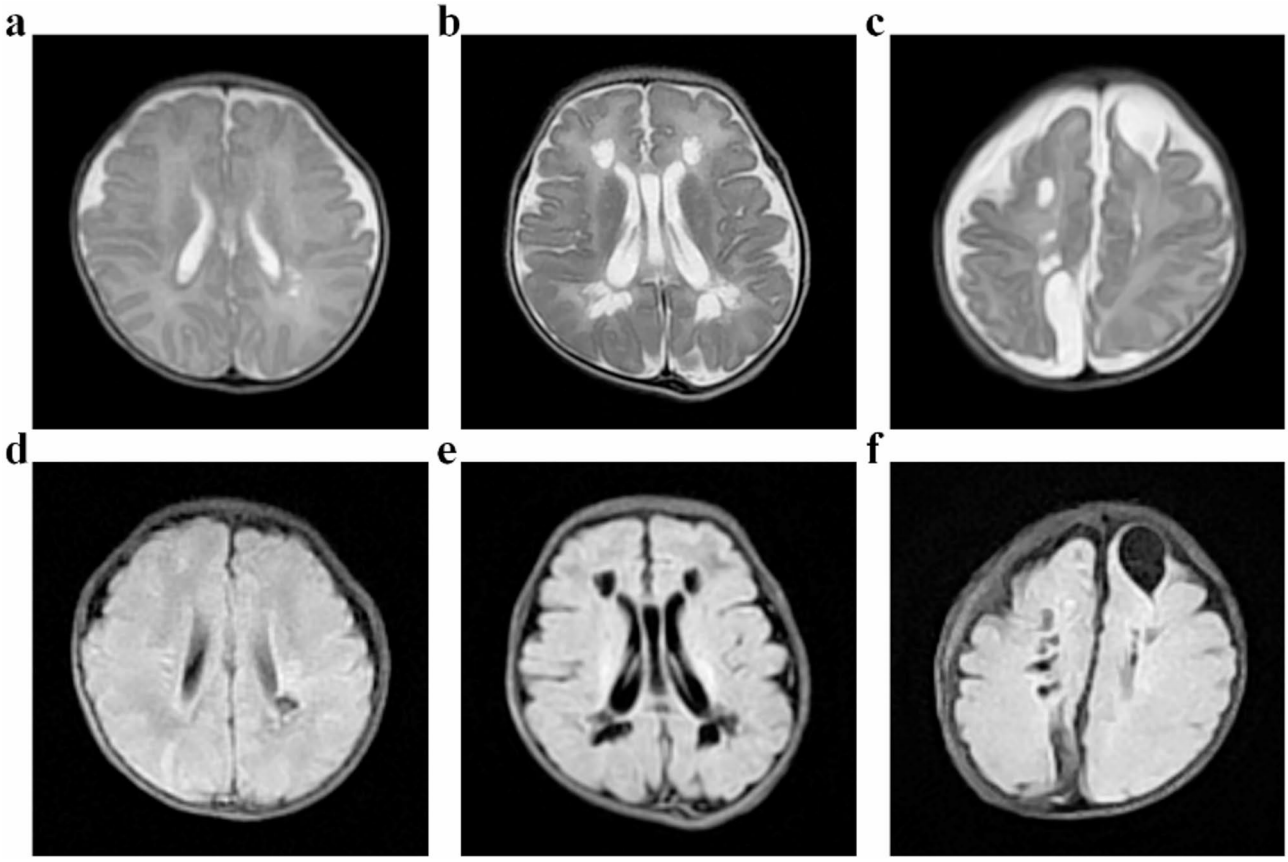

Fig. 1. Three grades of PVL on head MRI. (**a**). Grade I: local changes in the small capsule cavity around the ventricle (T_2WI). (**b**). Grade II: extensive cystic changes around the ventricle, which could be fused into pieces (T_2WI). (**c**). Grade III: cystic changes in the periventricular and subcortical white matter (T_2WI). (**d**). Grade I: local changes in the small capsule cavity around the ventricle (T_2 Flair). (**e**). Grade II: extensive cystic changes around the ventricle, which could be fused into pieces (T_2 Flair). (**f**). Grade III: cystic changes in the periventricular and subcortical white matter (T_2 Flair).

Statistical analysis

Statistical analysis was conducted using SPSS Version 26.0. Quantitative data (normal distribution) were presented as the mean ± standard deviation (mean ± SD), and the Student's t test was used for group comparisons. Measurement data (nonnormally distributed) were expressed as medians, 25th percentiles and 75th percentiles (median [IQR]), and comparisons between groups were made using the Mann-Whitney U test. Count data were expressed as example (n, %), and comparisons between groups were performed using the Chi-square test. Logistic regression model was used to analyze the risk factors of PVL. Important confounding variables were identified from the literature and statistical results. Receiver operating characteristic (ROC) curve was used to analyze the correlation between the observed indicators and PVL occurrence. Binary logistic regression analysis was used to calculate the predicted value of combined indicators. Calculate odds ratios and 95% confidence intervals. Differences were considered statistically significant at $p < 0.05$. The raincloud plots were generated by the online platform named Weishengxin (https://www.bioinformatics.com.cn) to describe the distribution of hemoglobin level data. The heat map was generated by Origin Version 2021 to visualize the difference of baseline characteristics and neonatal complications between the two groups.

Results

Participants

A total of 364 infants were included in this study, including 91 in the PVL group and 273 in the control group. In the PVL group, 78.02% of the infants were male, with an average GA of 29.92 ± 1.63 weeks and an average BW of 1306.26 ± 221.86 g. In the control group, 78.02% of the infants were male, with an average GA of 30.49 ± 1.68 weeks and an average BW of 1341.94 ± 166.59 g. Compared with the control group, preterm infants in the PVL group had lower GA (t = −2.802, $p = 0.005$), longer hospital stays (t = 3.311, $p = 0.001$), more times of blood transfusion (u = 4.780, $p < 0.001$), longer IMV time (u = 2.399, $p = 0.016$) and longer CPAP time (u = 4.717, $p < 0.001$). Moreover, preterm infants in the PVL group were at higher risk of BPD ($\chi^2 = 6.663$, $p = 0.010$), ROP ($\chi^2 = 8.051$, $p = 0.005$), IVH III-IV ($\chi^2 = 33.499$, $p < 0.001$) and sepsis ($\chi^2 = 5.801$, $p = 0.016$) than those in the control group. In addition, there was no significant difference in sex, BW, multiple pregnancy, maternal age,

	PVL group ($n=91$)	Control group ($n=273$)	Statistical values	P value
Baseline characteristics				
Male, n (%)	71.00 (78.02%)	213.00 (78.02%)	0.000	1.000
GA (weeks), (mean ± SD)	29.92 ± 1.63	30.49 ± 1.68	−2.802	0.005**
BW (grams), (mean ± SD)	1306.26 ± 221.86	1341.94 ± 166.59	−1.407	0.162
Hospital stays (days), (mean ± SD)	40.43 ± 21.28	32.29 ± 16.63	3.311	0.001***
Transfusion (times), median (IQR)	2.00 (1.00, 3.00)	1.00 (0.00, 2.00)	4.780	< 0.001***
IMV time (days), median (IQR)	33.00 (23.00, 43.00)	28.00 (20.00, 36.00)	2.399	0.016*
CPAP time (days), median (IQR)	4.00 (2.00, 7.00)	2.00 (0.00, 3.00)	4.717	< 0.001***
Neonatal comorbidities				
BPD, n (%)	22.00 (24.18%)	35.00 (12.82%)	6.663	0.010**
ROP, n (%)	30.00 (32.97%)	51.00 (18.68%)	8.051	0.005**
II-III NEC, n (%)	18.00 (19.78%)	35.00 (12.82%)	2.657	0.103
III-IV IVH, n (%)	32.00 (35.16%)	26.00 (9.52%)	33.499	< 0.001***
Sepsis, n (%)	38.00 (41.76%)	77.00 (28.21%)	5.801	0.016*

Table 1. Comparison of baseline characteristics and neonatal comorbidities in the PVL group and the control group. *PVL* periventricular leukomalacia, *GA* gestational age, *BW* birth weight, *IMV* invasive mechanical ventilation, *CPAP* continuous positive airway pressure, *BPD* bronchopulmonary dysplasia, *ROP* retinopathy of prematurity, *NEC* necrotizing enterocolitis, *IVH* intracranial hemorrhage. ***$P \leq 0.001$; **$P \leq 0.01$; *$P<0.05$.

	PVL group ($n=91$)	Control group ($n=273$)	Statistical values	P value
Maternal age (years), (mean ± SD)	29.90 ± 6.07	28.92 ± 5.99	1.347	0.179
Cesarean, n (%)	52.00 (57.14%)	132.00 (48.35%)	2.110	0.146
Singleton pregnancy, n (%)	84.00 (92.31%)	256.00 (93.77%)	0.238	0.626
PROM, n (%)	10.00 (10.99%)	34.00 (12.45%)	0.138	0.710
PIH, n (%)	9.00 (9.89%)	42.00 (15.38%)	1.710	0.191
Placenta previa, n (%)	4.00 (4.40%)	10.00 (3.66%)	0.099	0.753

Table 2. Comparison of maternal characteristics in the PVL group and the control group. *PVL* periventricular leukomalacia, *PROM* premature rupture of membrane, *PIH* pregnancy-induced hypertension syndrome.

pregnancy mode, PROM, PIH, placenta previa and II-III NEC between the two groups. As shown in Tables 1 and 2; Fig. 2.

Comparisons of blood routine test results

The Hb level of the two groups of preterm infants showed a downward trend early after birth. The Hb level of preterm infants in the PVL group was lower than that in the control group on the 3rd day (t = −3.210, $p=0.001$) and the 7th day after birth (t = −2.961, $p=0.003$). Similarly, the RBC count in the PVL group was lower than that in the control group on the 3rd day (t = −3.226, $p=0.001$) and the 7th day after birth (t = −3.593, $p<0.001$). However, the results were not statistically significant when comparing PLT count in early life between the two groups. The rain cloud map and the heat map showed the differences intuitively. As shown in Table 3; Figs. 2 and 3.

Risk factors and prediction of the occurrence of PVL

Multivariate logistic regression was used to analyze the risk factors of PVL. The results showed that the Hb level on the 7th day after birth (OR = 0.984, 95%CI 0.972–0.996, $p=0.010$) and the RBC count on the 7th day after birth (OR = 0.120, 95%CI 0.034–0.424, $p=0.001$) were significantly correlated with the occurrence PVL disease. In addition, IMV time (OR = 1.028, 95%CI 1.009–1.048, $p=0.004$) and III-IV IVH (OR = 5.888, 95% CI 2.997–11.643, $p<0.001$) were independent risk factors for PVL. As shown in Table 4.

The occurrence of PVL was predicted by the combined indicators of Hb level and RBC count. The ROC curve analysis showed that the cut-off value of Hb level on the 3rd day after birth was 140.5 g/L (sensitivity = 0.604, specificity = 0.582). The cut-off value of Hb level on the 7th day after birth was 117.5 g/L (sensitivity = 0.553, specificity = 0.637). The cut-off value of RBC count on the 3rd day after birth was 3.865×10^{12}/L (sensitivity = 0.619, specificity = 0.615). The cut-off value of RBC count on the 7th day after birth was 3.025×10^{12}/L (sensitivity = 0.762, specificity = 0.451). The sensitivities of combined indicators (Hb level and RBC count) on the 3rd day and 7th day after birth were 0.571 and 0.385, respectively. The specificities of combined index (Hb level and RBC count) on the 3rd day and 7th day after birth were 0.623 and 0.821, respectively. As shown in Table 5; Fig. 4.

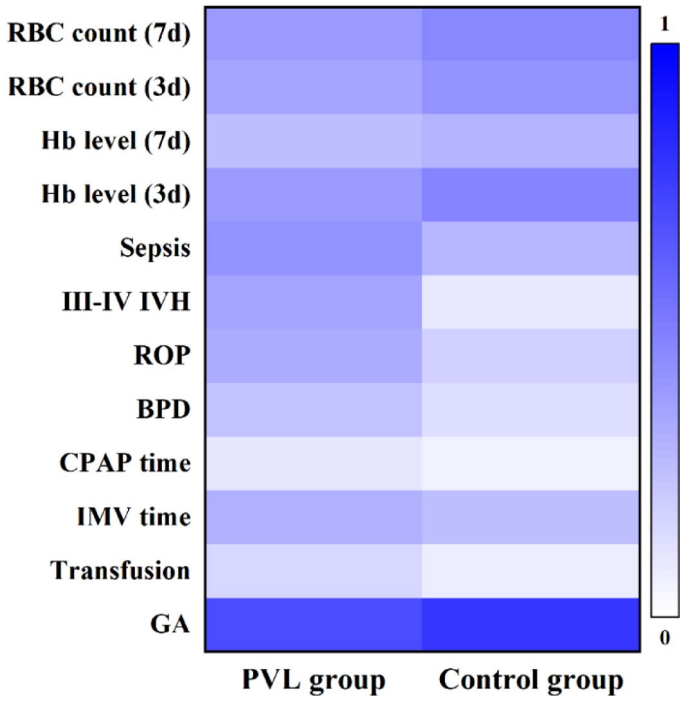

Fig. 2. Heat maps of clinical data and blood routine test results of preterm infants.

	PVL group ($n=91$)	Control group ($n=273$)	Statistical values	*P* value
Hemoglobin level (g/L), (mean ± SD)				
3rd d	134.04 ± 29.64	144.66 ± 26.51	−3.210	0.001***
7th d	111.55 ± 23.95	120.08 ± 23.77	−2.961	0.003**
14th d	103.78 ± 18.59	105.40 ± 17.63	−0.747	0.456
Red blood cell count ($\times10^{12}$/L), (mean ± SD)				
3rd d	3.78 ± 0.65	4.04 ± 0.68	−3.226	0.001***
7th d	3.17 ± 0.53	3.41 ± 0.57	−3.593	< 0.001***
14th d	3.16 ± 0.57	3.13 ± 0.50	0.456	0.649
Platelet count ($\times10^{9}$/L), (mean ± SD)				
3rd d	220.87 ± 110.44	231.13 ± 98.34	−0.835	0.404
7th d	238.40 ± 100.21	253.16 ± 102.90	−1.193	0.234
14th d	249.07 ± 120.34	265.74 ± 113.82	−1.193	0.234

Table 3. Comparison of blood routine test results in the PVL group and the control group. *PVL* periventricular leukomalacia, *3rd d* the 3rd day after birth, *7th d* the 7th day after birth, *14th d* the 14th day after birth. $^{***}P \le 0.001$; $^{**}P \le 0.01$.

Discussion

A retrospective, case control study was conducted on preterm infants with PVL. We found that the Hb level and RBC count on the 7th day after birth were significantly correlated with the occurrence PVL disease, and the Hb level combined with RBC count in the early life can be used to predict the occurrence of PVL. Therefore, our research provided two suitable and easily available laboratory indicators for clinicians to monitor and warn the occurrence of PVL at an early stage.

By analyzing the clinical data of the two groups, we found that preterm infants in the PVL group had smaller GA, more blood transfusion times, longer IMV and CPAP time, and higher incidence of BPD, III-IV IVH and sepsis, which was consistent with the findings of previous studies[30–33]. After eliminating confounding factors by logistic regression analysis, we found that long IMV time and III-IV IVH were independent risk factors for PVL. It has been confirmed in previous studies[34–37]. These factors are associated with hypoxia-ischemia and inflammatory mediators, which are the main pathogenesis of PVL[38]. The occurrence of PVL is mainly related to oligodendrocytes (OLs) of myelin sheath on nerve fiber axons. During brain development of preterm infants, immature OLs are in the stage of premyelinating oligodendrocytes, which have been confirmed to be

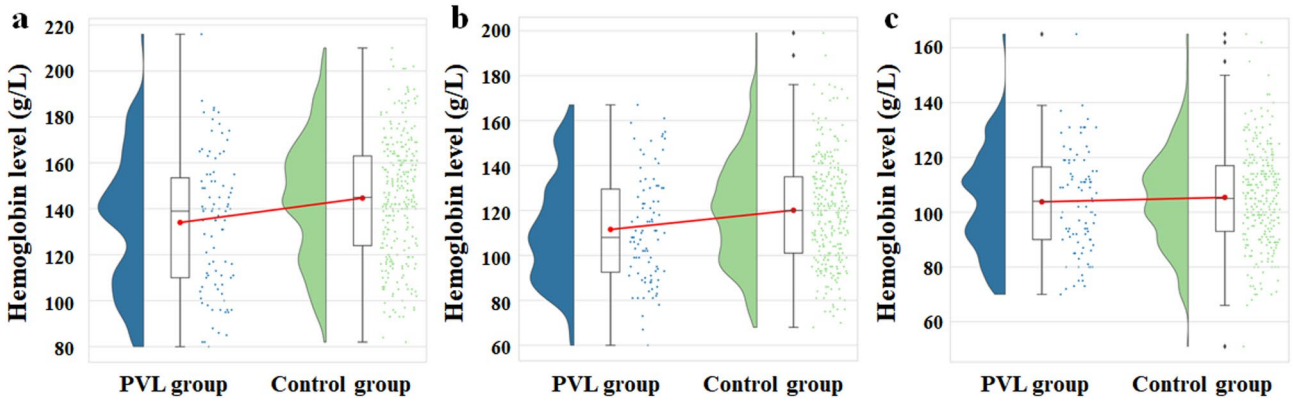

Fig. 3. Raincloud plots of hemoglobin level in early life of preterm infants. (**a**). Hemoglobin level of preterm infants on the 3rd day after birth. (**b**). Hemoglobin level of preterm infants on the 7th day after birth. (**c**). Hemoglobin level of preterm infants on the 14th day after birth.

	B	Wald	*P* value	Exp(B)	95%CI for Exp(B)
GA	−0.108	1.336	0.248	0.898	0.748–1.078
Transfusion	0.107	2.476	0.116	1.113	0.974–1.272
IMV time	0.028	8.278	0.004**	1.028	1.009–1.048
CPAP time	0.013	0.576	0.448	1.013	0.980–1.048
BPD	0.031	0.006	0.938	1.032	0.467–2.278
ROP	0.335	1.099	0.295	1.399	0.747–2.618
III-IV IVH	1.773	25.972	< 0.001***	5.888	2.977–11.643
Sepsis	0.348	1.280	0.258	1.416	0.775–2.588
Hb level (3rd d)	−0.018	1.933	0.164	0.983	0.958–1.007
Hb level (7th d)	−0.016	6.574	0.010**	0.984	0.972–0.996
RBC count (3rd d)	0.128	0.077	0.782	1.137	0.458–2.820
RBC count (7th d)	−2.121	10.831	0.001***	0.120	0.034–0.424

Table 4. Logistic regression analysis of confounding factors for the development of periventricular leukomalacia. *GA* gestational age, *IMV* invasive mechanical ventilation, *CPAP* continuous positive airway pressure, *BPD* bronchopulmonary dysplasia, *ROP* retinopathy of prematurity, *IVH* intracranial hemorrhage, *Hb* hemoglobin, *RBC* red blood cell, *3rd d* the 3rd day after birth, *7th d* the 7th day after birth. $^{***}P \leq 0.001$; $^{**}P \leq 0.01$.

	Area under curve	Standard error	Sensitivity	Specificity	*P* value	95% CI
Hb (3rd d)	0.609	0.035	0.604	0.582	0.002**	0.540–0.678
Hb (7th d)	0.603	0.035	0.553	0.637	0.003**	0.534–0.672
RBC (3rd d)	0.612	0.034	0.619	0.615	0.001***	0.545–0.679
RBC (7th d)	0.619	0.034	0.762	0.451	0.001***	0.552–0.685
Combined indicators (3rd d)	0.610	0.035	0.571	0.623	0.002**	0.543–0.678
Combined indicators (7th d)	0.619	0.034	0.385	0.821	0.001***	0.553–0.685

Table 5. Receiver operating characteristic curves of hemoglobin combined with hematocrit and subject with periventricular leukomalacia. *Hb* hemoglobin, *RBC* red blood cell, *Combined indicators* Hb level combined with RBC count, *3rd d* the 3rd day after birth, *7th d* the 7th day after birth. $^{***}P \leq 0.001$; $^{**}P \leq 0.01$.

susceptible to hypoxia-ischemia and inflammatory mediators[39–42]. Free radicals, excitatory amino acids and cytokines produced by ischemia-reperfusion, oxidative stress and inflammatory reaction can induce cell death through apoptotic mechanisms, thereby contributing to nerve axon injury[43–45]. However, our study did not find significant differences in pregnancy risk factors between the two groups, possibly due to the limited sample size.

Hb levels of the two groups of preterm infants showed a downward trend early after birth, which may be associated with the increase of oxygen saturation and the decrease of erythropoietin (EPO) level[46]. The hematopoietic function of preterm infants is not yet mature. The oxygen-enriched environment after birth

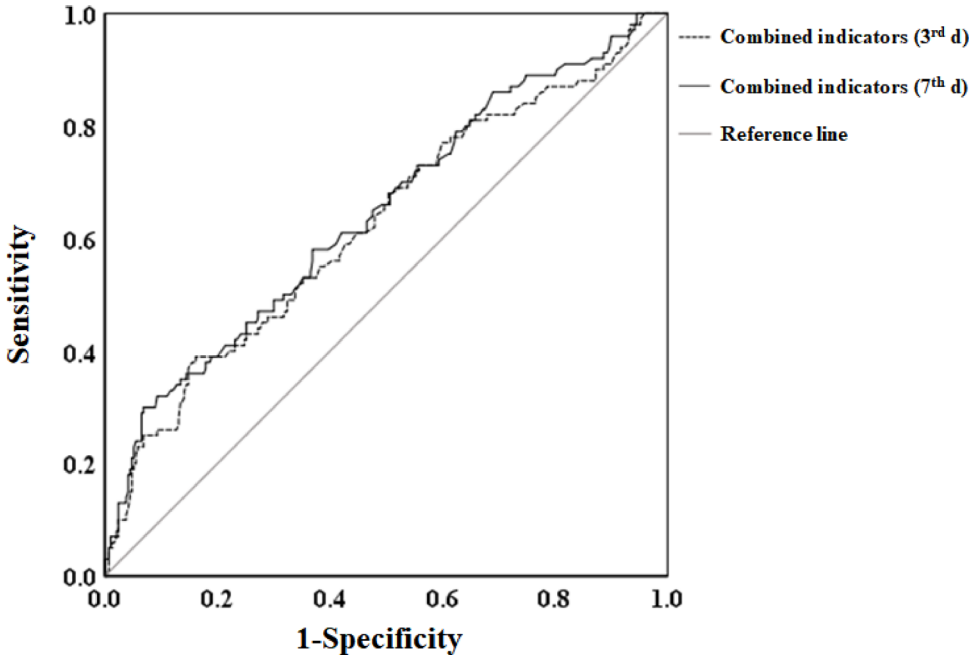

Fig. 4. Receiver Operating Characteristic curves of combined indicators and subject with periventricular leukomalacia.

reduces the production of EPO and accelerates its catabolism. These factors lead to insufficient erythropoiesis, and preterm infants are prone to physiological anemia early after birth[47,48]. In addition, the life span of red blood cells in preterm infants is short (about 60–70 days), and they are more likely to be destroyed under the conditions of hyperoxia exposure and oxidative stress, which aggravates anemia[49]. What's more, the blood routine test of preterm infants in NICU after birth may have a significant impact on very low birth weight infants, which is also one of the main ways of iatrogenic anemia[50].

We found that the Hb level and RBC count on the 3rd and 7th day after birth in the PVL group were lower than those in the control group. However, there were no significant differences in the Hb level and RBC count between the two groups on the 14th day after birth, with all measurements remaining at low levels. After eliminating confounding factors by logistic regression analysis, our study found that high Hb level and RBC count on the 7th day after birth can reduce the risk of the occurrence of PVL. Although this has rarely been analyzed in previous studies and there is a lack of relevant clinical literature reports, the correlation between Hb level and hypoxia-ischemia has drawn our attention to this aspect. Hb is the main carrier of oxygen in the human body, which can reversibly combine with oxygen molecules to generate oxygenated Hb and then transport oxygen to tissues[10]. The decrease of Hb level leads to anemia. As an important inducement of cerebral hypoperfusion, anemia may lead to chronic hypoxia of white matter by reducing the oxygen transport efficiency of brain tissue. At the same time, cerebral blood flow is more likely to fluctuate under anemia, which increases the risk of ischemia-reperfusion injury and then causes PVL[1,39,51]. This difference was not significant on the 14th day after birth. We inferred that continuous clinical treatment and intervention measures were helpful to improve the general condition of preterm infants and promote the recovery of their hematopoietic function. PVL usually occurs after birth. The early ultrasound manifestations of PVL were strong brain echo (on the 3rd to the 10th day after birth)[16]. This is consistent with our findings. Previous studies have shown that Hb is associated with HIE in term infants[52,53]. PVL is one of the manifestations of hypoxic-ischemic brain injury in preterm infants. Our findings suggested that Hb also played a significant role in hypoxic-ischemic brain injury in preterm infants.

Our study found that the Hb level and RBC count in early life can be used to predict the occurrence of PVL. The sensitivity and specificity of the Hb level on the 7th day after birth for predicting the occurrence of PVL were 0.553 and 0.637, respectively. The cut-off value was 117.5 g/L. The sensitivity and specificity of the RBC count on the 7th day after birth for predicting the occurrence of PVL were 0.762 and 0.451, respectively. The cut-off value was 3.025×10^{12}/L. Additionally, the use of combined indicators (Hb level combined with RBC count) enhanced the specificity of the prediction. We found that the specificity of combined indicators on the 7th day after birth was 0.821. Although hematologic measurements within 14 days after birth are influenced by numerous factors, such as iatrogenic losses and blood transfusions, we believe that these hematological measurements still have potential predictive value. On one hand, we incorporated several confounding factors into the regression model to reduce the influence. On the other hand, the alteration of these parameters also reflected the overall oxygen transport status of preterm infants early after birth and the comprehensive influence of early clinical treatment. We suggest that the Hb level and the RBC count should be used as practical auxiliary indicators, especially when neuroimaging and clinical risk factors are considered, to predict the occurrence of PVL at an early stage.

Our study had limitations. First, we did not conduct long-term follow-up of preterm infants in both the PVL group and the control group, and lacked the comparison of neurodevelopmental outcomes between the two groups. Second, the data were obtained from a single tertiary hospital, which potentially limits the generalizability of our results to lower-level medical centers. Finally, we lacked joint analysis of multi-center data. Further comprehensive researches are needed to verify our findings.

Conclusions

We found that the Hb level and RBC count on the 7th day after birth were significantly correlated with the occurrence PVL disease. And low Hb level and low RBC count on the 7th day after birth can jointly predict the occurrence of PVL. Our study provides clinicians with two suitable, easily accessible laboratory indicators for early warning of the occurrence of PVL. Clinicians should strengthen the monitoring of Hb level and RBC count of preterm infants in early life, and select screening time for PVL reasonably and timely. Taking effective prevention and treatment measures as early as possible may contribute to improving brain development outcomes in preterm infants.

Data availability

The datasets used and analyzed during the study are included in this published article.

Received: 8 March 2025; Accepted: 25 July 2025
Published online: 28 August 2025

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Acknowledgements
The participation of all the infants and their parents or legal guardians in this study is greatly appreciated.

Author contributions
Concept and study design: HS and MY. Data acquisition and analysis: ZS, LH and CZ. Drafting of the manuscript and figures: MY. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Funding
This work was provided by Henan Provincial Health Commission (YXKC2021022).

Consent statement

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
All methods were performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments or comparable ethical standards. This study was approved by the National Children's Regional Medical Center, Henan Children's Medical Center, and Henan Pediatric Disease Clinical Medical Research Center.

Informed consent
has obtained from a parent and/or legal guardian.

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