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Original Article

Predictive value of transcranial Doppler ultrasound for brain development and craniocerebral injury in premature infants

Qin Lu[1], Ya-Juan Lu[1], Zhen-Hua Chen[2], Chao-Ye Cao[1], Wei Wu[1]

[1]*Department of Neonatology, Affiliated Changzhou Children's Hospital of Nantong University, Changzhou 213000, Jiangsu, China;* [2]*Department of Medical Imaging, Affiliated Changzhou Children's Hospital of Nantong University, Changzhou 213000, Jiangsu, China*

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Abstract: Objective: To investigate the diagnostic value of early transcranial Doppler (TCD) ultrasound in assessing brain function development and intracranial diseases in preterm infants. Methods: A retrospective analysis was conducted on the data of 100 preterm infants admitted to the neonatal intensive care unit (NICU) of Affiliated Changzhou Children's Hospital of Nantong University from June 2022 to December 2023. Based on clinical diagnosis, the infants were divided into two groups: brain injury group (47 cases) and non-brain injury group (53 cases). All infants underwent bedside transcranial ultrasound examination using a color Doppler ultrasound diagnostic instrument. Ultrasound imaging and hemodynamic indices were compared between the two groups. The diagnostic value of color Doppler ultrasound for brain injury in premature infants and the correlation between cerebral hemodynamic indices and brain injury severity were analyzed. Results: The sensitivity and accuracy of TCD ultrasound for diagnosing brain injury in preterm infants were 82.98% and 85.00%, respectively. Hemodynamic findings showed that the mean velocity (Vm) in the brain injury group was higher than in the non-brain injury group within 12-24 hours after birth, while the pulsatility index (PI) and resistance index (RI) were lower (both $P<0.001$). In the moderate to severe brain injury group, Vm was markedly higher, while PI and RI were significantly lower than those of the mild brain injury group within 12-24 hours after birth ($P<0.001$). The area under the ROC curve for Vm, PI, and RI in predicting brain injury in preterm infants was 0.898, 0.940, and 0.794, respectively, with PI showing the highest diagnostic value. Vm was positively correlated with the degree of brain injury with a coefficient of 0.713; However, PI and RI were negatively correlated with the degree of brain injury ($r=-0.706$ and -0.645, respectively). Conclusion: Bedside transcranial ultrasound can effectively reflect the brain parenchymal development of preterm infants. Its hemodynamic indicators can accurately assess intracranial blood flow, making it valuable for detecting brain hemorrhage. Additionally, this method is convenient, non-invasive, and well-accepted by patients, making it a promising tool for clinical practice.

Keywords: Transcranial Doppler ultrasound, preterm infants, brain function development, brain injury

Introduction

Preterm infants, defined as those born alive at a gestational age of less than 37 weeks, have seen increased birth and survival rates in China due to advancements in medical technology and the widespread establishment of Neonatal Intensive Care Units (NICUs) [1, 2]. However, the underdevelopment of vital organs, such as the heart, lungs, and brain, places preterm infants at heightened risk for complications like passive pressure perfusion, fluctuating blood oxygen levels, and unstable blood pressure. As a result, these infants exhibit a higher incidence of brain injury compared to full-term neonates [3]. Early clinical signs of brain injury in preterm infants are often subtle or absent, complicating early diagnosis and possibly delaying reversible interventions. This can lead to significant long-term neurological impairments, severe sequelae, and, in some cases, life-threatening conditions [4, 5]. Therefore, timely and accurate assessment of brain development and early detection of brain injury are essential for guiding appropriate clinical management.

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Imaging modalities are crucial for diagnosing brain injury in preterm infants. However, techniques such as CT and MRI are not suitable for preterm neonates with unstable vital signs due to challenges with transportation and the risks associated with radiation exposure, limiting their use for early brain injury screening [6]. In contrast, advanced ultrasound technologies offer several advantages, including ease of use, absence of radiation, cost-effectiveness, and the ability to provide real-time dynamic monitoring of brain conditions [7]. Transcranial Doppler (TCD) ultrasound, a non-invasive and radiation-free technique, can be repeatedly performed at the bedside, making it a widely used monitoring and diagnostic tool in NICUs worldwide [8]. Previous studies have demonstrated that cranial ultrasound possesses moderate sensitivity for detecting intracranial hemorrhage, cerebral edema, and focal white matter injury, and it can serve as a predictive tool for the development of cerebral palsy. However, it has limitations for providing a comprehensive evaluation of the entire brain, particularly in diagnosing diffuse white matter injury and other forms of brain damage [9].

To further confirm the value of early TCD ultrasound in the assessment of brain function in preterm infants, we conducted a retrospective analysis of 100 preterm infants born at our hospital, aiming to provide further insight.

Materials and methods

Case selection

A retrospective analysis was conducted on 100 preterm infants admitted to the NICU of Affiliated Changzhou Children's Hospital of Nantong University from June 2022 to December 2023. Based on clinical diagnosis, infants were divided into two groups: the brain injury group (47 cases) and the non-brain injury group (53 cases).

Inclusion criteria for brain injury group: (1) Imaging examination showed obvious brain structural damage; (2) A history of obstetric conditions leading to intrauterine fetal distress, visible fetal distress, and asphyxia during delivery; (3) A 1-minute Apgar score ≤3 and a 5-minute Apgar score ≤7 [10]; (4) Gestational age <34 weeks; (5) Noticeable neurological symptoms, such as altered consciousness, seizures, and brainstem symptoms, occurring shortly after birth and persisting for over 24 hours; (6) Complete medical records.

Inclusion criteria for non-brain injury group: (1) Patients with a clear history of obstetric conditions leading to fetal distress, visible signs of fetal distress, and asphyxia during delivery; (2) No brain damage confirmed by comprehensive assessments, including imaging; and (3) Complete medical records.

Exclusion criteria: (1) Congenital malformations; (2) Genetic metabolic diseases or other severe complications; (3) Severe intrauterine infection; (4) Full-term birth. This study was approved by the hospital's medical ethics committee and complied with the Declaration of Helsinki.

Early transcranial Doppler ultrasound detection methods

Bedside transcranial ultrasound examinations were performed using a color Doppler ultrasound diagnostic instrument (Mindray, China) with a V11-3Ws probe, operating at a frequency 2-6 MHz. The infant was positioned supine, and an ultrasound probe was placed at the anterior fontanel for coronal plane scanning. This examination focused on the frontal horn of the lateral ventricle, the frontal lobe, the occipital lobe, and the third ventricle. The probe was then rotated 90° to obtain mid-sagittal and lateral sagittal planes, enabling the scanning of the frontal horn, central part, and posterior horn of the lateral ventricles. This procedure enabled the identification of neonatal cranial ultrasound images, brain injury images, and the recording of the shape of the cavum septi pellucidi and the structures of both cerebral hemispheres and the entire brain parenchyma. Measurements were taken at the frontal horn of the lateral ventricle, and the shape of the third ventricle was observed. Examinations were conducted within 12 hours of birth, with weekly follow-ups for three weeks. Imaging results were analyzed by a review panel of clinicians with over five years of experience in ultrasound and pediatrics.

Main outcome measures

Assessment of TCD ultrasound monitoring results: abnormal ultrasound findings included ventricular wall thickening, cavity enlargement,

Table 1. Comparison of general information between the two groups of preterm infants

Variable	Brain Injury Group n=47	Non-Brain Injury Group N=53	X^2	P
Gender			0.007	0.932
Male	27 (57.45)	30 (56.60)		
Female	20 (42.55)	23 (43.40)		
Gestational age (weeks)			0.001	0.971
≤30	25 (53.19)	28 (52.83)		
>30	22 (46.81)	25 (47.17)		
Birth weight (g)			0.126	0.723
≤2000	30 (63.83)	32 (60.38)		
>2000	17 (36.17)	21 (39.62)		
Suffocation situation				
Mild	31 (65.96)	-		
Moderate to severe	16 (34.04)	-		

widening of the lateral ventricles, presence of strong echoes, and flocculent echoes in some infants. Positive lesions were observed on cranial ultrasound.

Secondary outcome measures

(1) Hemodynamic indicators, including mean blood flow velocity (Vm), pulsatility index (PI), and resistance index (RI). were recorded (2) Receiver operating characteristic (ROC) curves were plotted to analyze the diagnostic value of cranial ultrasound for brain injury.

Statistical methods

Statistical analysis was performed using SPSS 20.0 software. Measured data were expressed as mean ± standard deviation (x ± s) and compared using t-tests. Counted data were expressed as percentages and compared using chi-square tests. Pearson correlation analysis was used to analyze the correlation between Vm, PI, RI and the severity of brain injury. Receiver operating characteristic (ROC) curve analysis was applied to evaluate the diagnostic values of Vm, PI, and RI for early brain injury in preterm infants. A *P*-value of <0.05 was considered significant.

Result

Comparison of general data between the two groups of preterm infants

There were no significant differences in gender, age, or average gestational age between the two groups of premature infants (P>0.05, **Table 1**).

Ultrasound images of brain injury in preterm infants

We used transcranial Doppler ultrasound to evaluate brain injury in the infants. The primary types of injury included hemorrhage in the posterior horn of the lateral ventricle, intraventricular hemorrhage, ventricular enlargement, and brain edema (**Figure 1**). Based on the comprehensive final diagnosis, the sensitivity and accuracy of transcranial Doppler ultrasound in diagnosing brain injury in preterm infants were 82.98% and 85.00%, respectively, indicating high diagnostic value (**Table 2**).

Comparison of hemodynamic results between the two groups of preterm infants

Cerebral hemodynamics were monitored in both groups. The results showed that within 12-24 hours after birth, the Vm in the brain injury group was evidently higher than in the non-brain injury group, while PI and RI were significantly lower. This indicates that preterm infants with brain injury exhibited low resistance and high perfusion early after birth (**Table 3**).

Predictive value of ultrasound cerebral hemodynamic data for early detection of brain injury in preterm infants

To determine the predictive value of cerebral hemodynamic parameters for early brain injury in preterm infants, we plotted ROC curves (**Figure 2**). The area under the curve (AUC) for Vm, PI, and RI for predicting early brain injury were 0.898, 0.940, and 0.794, respectively. All measures demonstrated diagnostic value, with PI having an AUC greater than 0.9, indicating a high diagnostic value (**Table 4**; **Figure 2**).

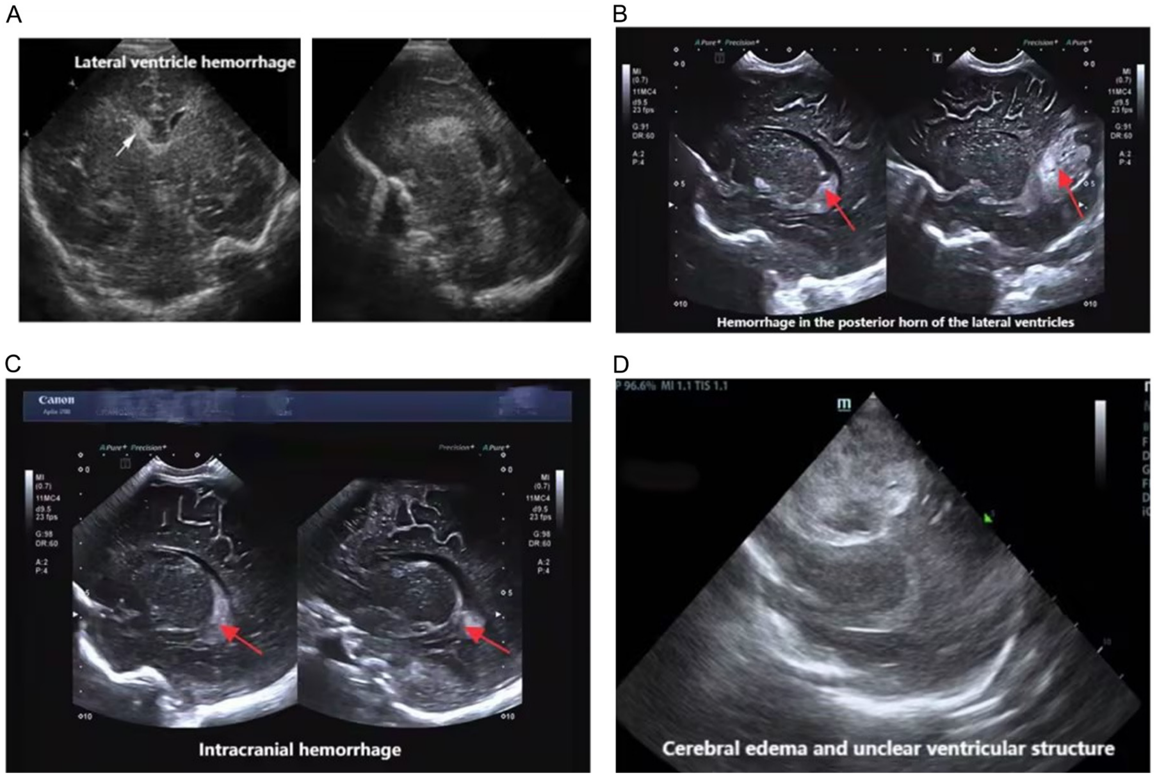

Figure 1. Ultrasound images of brain injury in preterm infants (partial). A: Lateral ventricular hemorrhage. B: Lateral ventricular posterior horn hemorrhage. C: Intraventricular hemorrhage. D: Cerebral edema.

Table 2. Ultrasound diagnosis of brain injury in preterm infants

Examination Methods	Final Diagnosis		
	Brain Injury	Non-Brain Injury	Total
Ultrasound Diagnosis			
Brain Injury	39	7	46
Non-Brain Injury	8	46	54
Total	47	53	100

Table 3. Comparison of hemodynamic data between the two group of preterm infants

Indicator	Brain Injury Group n=47	Non-Brain Injury Group N=53	t	P
Vm (cm/s)	22.1±1.09	19.41±1.91	8.502	<0.001
PI	1.48±0.14	1.9±0.22	11.22	<0.001
RI	0.73±0.09	0.86±0.12	6.07	<0.001

Notes: Vm, mean blood flow velocity; PI, pulsatility index; RI, resistance index.

Hemodynamic results in infants with different degrees of brain injury

We analyzed hemodynamic data in 29 infants with mild brain injury and 18 infants with moderate to severe brain injury. Notable differences in early postnatal cerebral blood flow values were observed between the two groups. The moderate to severe brain injury group exhibited significantly higher Vm, and significantly lower PI and RI compared to the mild brain injury group (**Table 5**).

Correlation analysis between cerebral hemodynamic data and the degree of brain injury in children

Pearson correlation analysis revealed a positive correlation between Vm and the degree of brain injury with a coefficient (r) of 0.713. This suggests that Vm could predict the severity of brain injury in preterm infants; the higher the cerebral blood flow rate, the greater the likelihood of severe brain injury. Additionally, Pearson correlation analysis revealed a negative relationship between PI, RI and the degree of brain

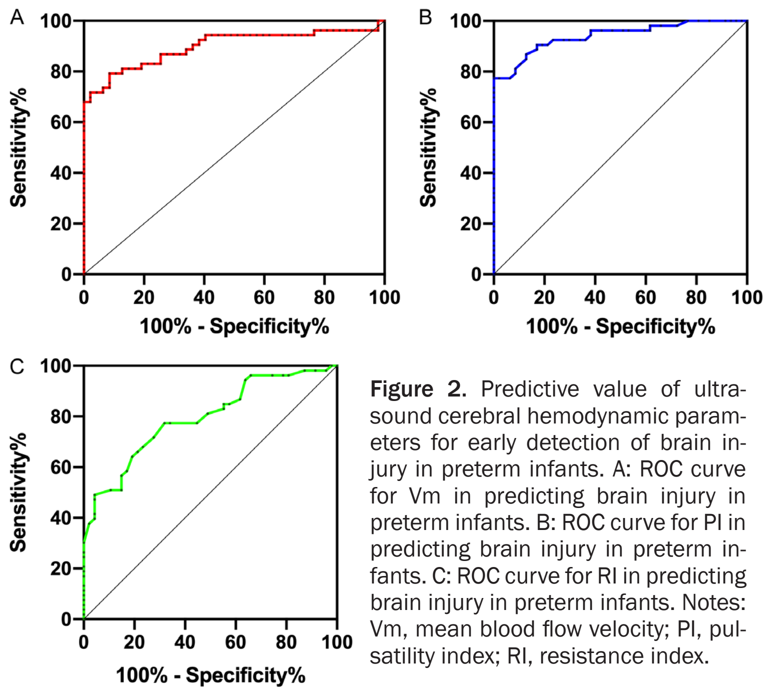

Figure 2. Predictive value of ultrasound cerebral hemodynamic parameters for early detection of brain injury in preterm infants. A: ROC curve for Vm in predicting brain injury in preterm infants. B: ROC curve for PI in predicting brain injury in preterm infants. C: ROC curve for RI in predicting brain injury in preterm infants. Notes: Vm, mean blood flow velocity; PI, pulsatility index; RI, resistance index.

injury, with r values of -0.706 and -0.645, respectively (both P<0.001). Therefore, PI and RI can also predict the severity of brain injury in premature infants, with lower PI and RI values associated with a higher likelihood of severe brain injury (**Table 6**).

Discussion

Brain injury in preterm infants refers to ischemic and/or hemorrhagic damage of varying severity, resulting from prenatal, perinatal, and/or postnatal pathologic factors. This injury can manifest as clinical symptoms and signs of neurological impairment, and, in severe cases, may lead to long-term neurological sequelae or even mortality [11]. The immature brain of preterm infants exhibits considerable plasticity, allowing for partial recovery from damage, which presents opportunities for therapeutic intervention [12]. Research has indicated that early neuroprotective strategies can reduce neuronal apoptosis, thereby attenuating the extent of brain injury [13]. Consequently, prompt and accurate assessment of brain function and identification of brain injury are critical for guiding timely clinical interventions, minimizing both short-term and long-term neurological damage.

Cranial ultrasound is a non-invasive technique for evaluating brain function and development in preterm infants. It enables monitoring of areas such as the subcortical white matter and cerebellum, providing precise assessment of brain development, particularly in regions near the midline of the brain [14]. Spectral Doppler ultrasound can capture the blood flow spectrum of these arteries, measuring hemodynamic data such as Vm, PI, and RI. Given the variability in vascular maturity and hemodynamic characteristics across preterm infants of different gestational ages, this method is effective in evaluating brain development [15, 16]. Compared to full-term infants, preterm infants exhibit less mature brain development. In our study, Doppler ultrasound images of infants with brain injury demonstrated fine, homogeneous hypoechoic brain parenchyma, sparse and broad gyri, shallow sulci, and poorly differentiated insular regions, with few or no visible gyri on two-dimensional images. Additionally, the brain structure exhibited smaller diameters and a reduced overall brain volume. The analysis demonstrated that Doppler ultrasound offers high sensitivity and specificity for diagnosing brain injury, highlighting its considerable diagnostic value for detecting brain injury in preterm infants.

Previous studies [17, 18] have indicated that hemodynamic changes in brain injury precede morphologic alterations. In this study, we compared the arterial blood flow in infants across different groups, revealing that the Vm in the brain injury group was significantly higher than that of the non-brain injury group within 12-24 hours after birth, while the PI and RI were significantly lower, suggesting lower resistance and higher perfusion in preterm infants with brain injury. Additionally, within this time frame, the moderate to severe brain injury group also exhibited significantly higher Vm and significantly lower PI and RI compared to the mild brain injury group. These findings suggest a close correlation between the severity of brain injury in preterm infants and the arterial blood flow patterns.

Table 4. Predictive value of hemodynamic data for brain injury in preterm infants

Predictive Indicator	AUC	95 CI%	Specificity	Sensitivity	Cut-off
Vm (cm/s)	0.898	0.833-0.963	63.83%	90.57%	21.72
PI	0.940	0.895-0.985	61.70%	96.23%	1.50
RI	0.794	0.708-0.880	68.09%	77.36%	0.78

Notes: Vm, mean blood flow velocity; PI, pulsatility index, RI, resistance index.

Table 5. Comparison of hemodynamic data between preterm infants with different brain injury severity

Indicator	Mild Brain Injury Group (n=29)	Moderate to Severe Brain Injury Group (n=18)	t	P
Vm (cm/s)	21.55±0.79	23.17±0.76	6.932	<0.001
PI	1.55±0.11	1.35±0.05	7.241	<0.001
RI	0.77±0.08	0.66±0.06	5.016	<0.0001

Notes: Vm, mean blood flow velocity; PI, pulsatility index; RI, resistance index.

Table 6. Correlation between cerebral hemodynamic data and the severity of brain injury in preterm infants

		Vm	PI	RI
Severity of brain injury	r	0.713	-0.706	-0.645
	P	<0.001	<0.001	<0.001

Notes: Vm, mean blood flow velocity; PI, pulsatility index; RI, resistance index.

In the germinal matrix of the preterm brain, angiogenesis is notably active. Located at the junction of the caudate nucleus and thalamus, the germinal matrix is characterized by capillaries with large diameters, thin walls, and minimal connective tissue support, making it highly vulnerable to fluctuations in blood pressure and blood flow alterations. The lower the gestational age, the greater the likelihood of capillary rupture and periventricular-intraventricular hemorrhage [19, 20]. Previous research [21] has demonstrated that dysregulation of cerebral blood flow occurs prior to intracranial hemorrhage in preterm infants. Another study [22] reported that preterm infants who developed brain injury had higher cerebral blood volume on the second day after birth compared to those who did not, which is consistent with our observations. Finally, we analyzed the diagnostic value of hemodynamic measurements for detecting brain injury in preterm infants. The AUCs for Vm, PI, and RI were 0.898, 0.940, and 0.794, respectively, with PI showing an AUC greater than 0.9, indicating high diagnostic value.

In conclusion, bedside cranial ultrasound examination provides valuable insight into the brain parenchymal development of preterm infants. The hemodynamic indicators derived from this technique effectively reflect intracranial blood flow conditions, making it an essential tool for assessing brain hemorrhage. This method is convenient, non-invasive, and well-accepted by patients.

However, there are some limitations to this study. First, the sample size was relatively small, and the results would benefit from further analysis and verification with larger sample sizes. Second, this study focused solely on the diagnostic value of ultrasound. It is worth exploring whether there are more convenient, accurate and non-invasive diagnostic options for brain injury. In the future, we will conduct more comprehensive diagnostic analysis to provide a more accurate and practical solution for the diagnosis of brain injury in preterm infants.

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Disclosure of conflict of interest

None.

Address correspondence to: Wei Wu, Department of Neonatology, Affiliated Changzhou Children's Hospital of Nantong University, No. 958, Zhongwu Avenue, Tianning District, Changzhou 213000, Jiangsu, China. Tel: +86-0519-69808108; E-mail: ilove_236957@163.com

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