Article

Discovery Medicine 2025; 37(198): 1324–1330
https://doi.org/10.24976/Discov.Med.202537198.115

Combining MRI With Color Doppler Ultrasound Enhances Early Diagnosis of Neonatal Hypoxic-Ischemic Encephalopathy

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Published: 20 July 2025

Background: Early neonatal hypoxic-ischemic encephalopathy (HIE) diagnosis is crucial for prompt neuroprotective intervention. However, current diagnostic methods are restricted by suboptimal sensitivity and delays in prompt identification. Therefore, this study evaluates the impact of combining magnetic resonance imaging (MRI) with color Doppler ultrasound (CDU) on the diagnostic accuracy of early-stage neonatal HIE.

Methods: This retrospective cohort study included 56 neonates with HIE and 47 healthy controls. All study participants underwent both MRI and CDU examinations. MRI provided diffusion-weighted imaging sequences and apparent diffusion coefficient (ADC) values, while CDU assessed cerebral hemodynamics in the middle cerebral artery (MCA) and anterior cerebral artery (ACA). Furthermore, the diagnostic performance of this multimodal approach was evaluated using receiver operating characteristic (ROC) analysis.

Results: MRI showed significantly higher ADC values in the HIE group (14.44 $\pm$ 4.43) compared to controls (9.43 $\pm$ 3.42, $p <$ 0.001). However, CDU findings revealed significantly lower peak systolic velocity (Vs) and end-diastolic velocity (Vd) values, along with higher resistance index in both MCA and ACA among the HIE group ($p <$ 0.001). The combined MRI and CDU approach demonstrated significantly higher diagnostic accuracy for HIE (area under the curve (AUC): 0.918) compared to MRI alone (AUC: 0.797).

Conclusion: Integrating MRI and CDU significantly enhances early detection of neonatal HIE, enabling the prompt initiation of neuroprotective therapies and improving prognostic assessment. This multimodal strategy may bridge critical gaps in early HIE diagnosis.

Keywords: hypoxic-ischemic encephalopathy; magnetic resonance imaging; color Doppler ultrasound; neonatal brain injury; diagnosis

Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE) is a leading cause of brain injury, morbidity, and mortality in newborns [1]. It occurs when cerebral blood flow is impaired and oxygen supply to the brain is inadequate during the perinatal period [2]. In infants, HIE typically manifests as altered consciousness, seizures, and abnormalities in muscle tone and reflexes [3,4]. Despite advances in obstetric management and neonatal supportive care, HIE remains a significant health issue, often resulting in severe long-term consequences, including cerebral palsy, epilepsy, and cognitive impairments [5]. Early diagnosis and prompt intervention are critical to preventing irreversible brain injury. Initiating therapeutic hypothermia within six hours of birth has been shown to improve neurological outcomes [6]; however, its effectiveness relies on the prompt and accurate identification of affected neonates [7].

Magnetic resonance imaging (MRI), particularly diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping [8], is widely recognized as the gold standard for detecting and characterizing brain injuries associated with HIE [9,10]. It provides high-resolution visualization and detailed evaluation of tissue injury, especially within deep gray matter structures and white matter tracts. However, its clinical utility in acute situations is constrained by logistical challenges, including limited equipment availability, the need for neonatal sedation, and the urgency of early HIE assessment [11,12].

Color Doppler ultrasound (CDU) is a widely accessible, non-invasive imaging modality that enables the real-time evaluation of cerebral hemodynamics [13]. It provides insights into key blood flow metrics, such as peak systolic velocity (Vs), end-diastolic velocity (Vd), and resistance index (RI), particularly in vessels like the middle cerebral artery (MCA) and anterior cerebral artery (ACA)

[14]. However, its limited sensitivity in detecting parenchymal brain injuries restricts its diagnostic accuracy when used alone. Given the complementary strengths and limitations of MRI and CDU, combining these imaging approaches may enhance early HIE diagnosis. MRI provides high-resolution anatomical detail and specific identification of brain injuries [15], while CDU offers rapid assessment of cerebral hemodynamics and vascular abnormalities [16]. Despite this potential, few studies have systematically evaluated their combined diagnostic performance. Therefore, this study aims to assess the integrated performance of MRI and CDU in the early diagnosis of neonatal HIE, hypothesizing that this multimodal imaging approach will improve diagnostic accuracy, inform prompt therapeutic interventions, and ultimately enhance clinical outcomes.

Materials and Methods

Study Participants

This retrospective cohort study was conducted between October 2021 and October 2023, including 56 neonates diagnosed with HIE and 47 healthy full-term neonates as controls, all born and treated at the Neonatal Intensive Care Unit of Taihe Hospital, Hubei University of Medicine, China. Ethical approval was obtained from the clinical research and ethics committee of Taihe Hospital (Approval No. 20240223), and informed consent was obtained from all parents following the Declaration of Helsinki.

Inclusion criteria for patient selection were as follows: neonates with gestational age between 37 and 42 weeks; neonates with birth weight ranging from 2500 to 4000 grams; neonates with clinical diagnosis of HIE based on neurological assessment [17], including consciousness level, neuromuscular control, complex reflexes, autonomic function, and seizure activity; and those underwent both MRI and CDUs examinations. However, patients meeting the following criteria were excluded: the presence of congenital diseases such as congenital heart disease, pulmonary disorders, or brain tumors; maternal conditions like diabetes or hypertension, or a history of significant intrauterine infection; and the presence of trauma-related intracranial hemorrhage.

Data Collection

Neonatal demographic and clinical data were acquired through chart review. A neonatal neurologist established a neurological diagnosis by reviewing their medical records and imaging findings. Collected data included neonate gender, gestational age, birth weight, Apgar scores, and delivery method.

CDU Protocol

CDU examinations were conducted with each neonate lying supine in a calm state, using GE Vivid i and Vivid q systems (GE Healthcare, Chicago, IL, USA). High-frequency linear (5–13 MHz) and micro-convex array probes (4.7–11 MHz) were utilized, employing the temporal suture and anterior fontanelle as acoustic windows to assess the hemodynamic parameters of the MCA and ACA, specifically Vs, Vd, and RI. Measurements were recorded within 24 hours and compared between the HIE and control groups. To minimize operator-related bias during CDU examinations and parameter acquisition, all ultrasound assessments were performed by the same experienced sonographer who was blinded to the neonates' clinical classification. Standardized protocols were strictly followed, and each parameter was measured in triplicate, with the mean value used for subsequent analysis to ensure reliability and consistency.

MRI Protocol

MRI was conducted within 24 hours after birth using a GE Signa HDx 3.0T superconducting scanner and the SDC-ADW4.4 MR imaging workstation (GE Healthcare, Chicago, IL, USA). Diffusion-weighted imaging (DWI) utilized Spin Echo and Echo Planar Imaging techniques through a 2D Propeller DWI sequence, with parameters set to Repetition Time/Echo Time equal to 3300/97 ms, b-values of 0, 500, and 1000 s/mm^2, a slice thickness of 5.0 mm, and an inter-slice gap of 1.5 mm. The matrix size was 128 $\times$ 128 with a field of view of 230 $\times$ 230 mm. ADC maps were examined for injury-related signs such as edema, hemorrhage, and infarction, with Regions of Interest (ROI) drawn around areas of damage to measure ADC values. Then, ADC values were compared between the HIE and control groups.

Statistical Analysis

Statistical analysis was performed using SPSS version 19.0 software (IBM Corp., Armonk, NY, USA). Continuous data were expressed as mean $\pm$ standard deviation (SD). The Shapiro-Wilk test was used to assess normality within the data. Normally distributed data were analyzed using independent *t*-tests. Categorical data were presented as frequencies and analyzed using the Chi-square test.

Furthermore, receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic performance of MRI and its combination in identifying neonatal HIE. Diagnostic accuracy metrics, such as the area under the curve (AUC), sensitivity, specificity, and optimal cut-off values, were determined to evaluate diagnostic accuracy. For the combined model, features from both MRI and CDU were integrated using a weighted average method, with weights determined based on the individual performance of each approach. The resulting combined model's diagnostic accuracy was then assessed using its AUC, sensitivity, specificity, and corresponding cut-off values.

Table 1. Comparison of baseline characteristics between the two groups.

Variable	HIE group (n = 56)	Control group (n = 47)	χ^2/t	p-value
Sex (male/female)	36/20	31/16	0.031	0.859
Gestational age (week)	38.07 ± 0.83	37.91 ± 0.76	0.984	0.328
Birth weight (g)	3170.99 ± 77.26	3183.82 ± 75.26	–0.850	0.398
Apgar score (5 minutes)	4.71 ± 1.53	8.92 ± 1.19	–15.279	0.000
Delivery method			1.012	0.314
Cesarean section	42 (75.0)	31 (66.0)		
Vaginal delivery	14 (25.0)	16 (34.0)		

$p < 0.05$ represents statistical significance. HIE, hypoxic-ischemic encephalopathy.

Results

Comparison of Baseline Characteristics Between the HIE and Control Groups

This study included 56 neonates diagnosed with the HIE group (36 males, 20 females) and 47 healthy full-term neonates (31 males, 16 females). The two groups showed no significant differences in gender distribution, gestational age, birth weight, and delivery method ($p > 0.05$) (Table 1). However, the Apgar scores at 5 minutes were significantly lower in the HIE group (4.71 ± 1.53) compared to the control group (8.92 ± 1.19, $p < 0.001$). These results indicate that the two groups were comparable in demographic factors but differed significantly in neonatal health status at birth.

MRI Findings

The ADC values obtained from diffusion-weighted imaging were significantly higher in the HIE group (14.44 ± 4.43) compared to the control group (9.43 ± 3.42) ($p < 0.001$). In addition to these quantitative differences, qualitative assessment revealed characteristic imaging changes in the HIE group. For instance, in Case 2, cranial ultrasound findings suggested brain edema and HIE; however, the cranial MRI showed no abnormal parenchymal signal, and this case was categorized as a control. In contrast, Case 1 (with a history of neonatal asphyxia and resuscitation) and Case 3 (with a history of shortness of breath after premature birth) showed patchy T2FSE hyperintensity and corresponding T1Flair and T2Flair hypointensity in the bilateral corona radiata, consistent with hypoxic-ischemic encephalopathy. Representative MRI images are shown in Fig. 1.

CDU Findings

CDU revealed significant cerebral hemodynamic differences between the HIE and control groups (Table 2). In the MCA, the Vs and Vd were significantly lower in the HIE group (9.38 ± 2.34 cm/s and 4.76 ± 0.53 cm/s, respectively) than in the control group (11.79 ± 2.41 cm/s and 6.46 ± 0.55 cm/s) ($p < 0.001$). Furthermore, the MCA resistance index (RI) was substantially higher in the HIE group compared to controls (0.75 ± 0.06 vs. 0.58 ± 0.07, $p < 0.001$).

Similarly, in the ACA, Vs (31.46 ± 1.91 vs. 40.69 ± 2.21, $p < 0.001$) and Vd (6.54 ± 0.85 vs. 12.35 ± 1.50, $p < 0.001$) were significantly lower in HIE neonates, whereas RI (0.82 ± 0.05 vs. 0.60 ± 0.08, $p < 0.001$) and Vs/Vd Ratio (4.89 ± 0.71 vs. 3.35 ± 0.51, $p < 0.001$) were significantly higher compared to controls. These findings indicate impaired cerebral perfusion and increased vascular resistance in the HIE group.

In addition to quantitative differences, qualitative evaluation of representative CDU images further supported these observations. The control group showed normal cerebral blood flow velocity, uniform color Doppler filling, and regular spectral waveforms. In contrast, the HIE group exhibited reduced flow velocity and increased vascular resistance, as evidenced by diminished color flow signals and abnormal spectral patterns (Fig. 2).

Diagnostic Accuracy Comparison

ROC curve analysis showed that combining MRI with CDU significantly improved diagnostic accuracy for neonatal HIE compared to MRI alone (Table 3, Fig. 3). The combined MRI+CDU model achieved an area under the curve (AUC) of 0.918, with a sensitivity of 90.91% and specificity of 87.50% at an optimal cut-off value of 0.264. In comparison, MRI alone yielded an AUC of 0.797, with a sensitivity of 76.79% and specificity of 72.34%, based on a cut-off value of 13.385. These results suggest that integrating CDU with MRI enhances early detection and overall diagnostic performance for neonatal HIE.

Discussion

HIE results from impaired cerebral blood flow and inadequate oxygen supply during the perinatal period, leading to cellular energy failure, excitotoxicity, and oxidative stress that can cause irreversible neuronal damage [17]. Our findings align with previous studies, demonstrating significant abnormalities in cerebral hemodynamics and brain tissue diffusion in neonates with HIE. The observed decrease in Vs and Vd in both the MCA and ACA via CDU suggests increased cerebral vascular resistance due to impaired autoregulation and ischemic injury [18,19]. Additionally, the elevated RI reflects a compromised cerebrovascular re-

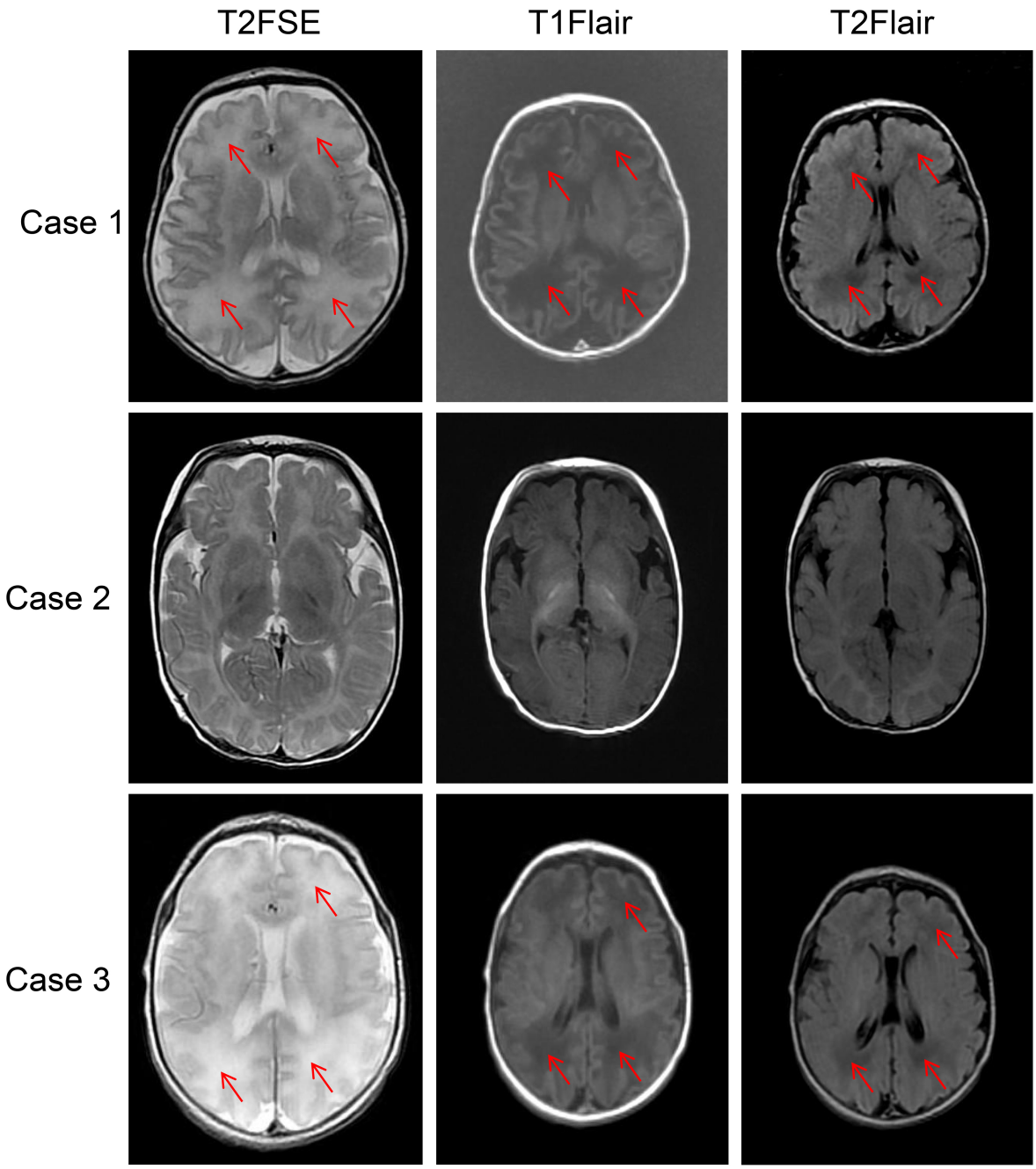

Fig. 1. Representative magnetic resonance imaging (MRI) images of neonatal hypoxic-ischemic encephalopathy (HIE) cases. MRI images of three neonates diagnosed with HIE, illustrating characteristic abnormalities on different sequences. The T2FSE images (left column) demonstrate hyperintense signals in the periventricular white matter and basal ganglia, consistent with edema. The T1Flair images (middle column) show corresponding hypointense areas, indicating tissue injury. The T2Flair images (right column) highlight diffuse hyperintensity in cortical and subcortical regions, suggestive of gliosis and chronic ischemic changes. Case 1 (Male, 37 weeks gestation); Case 2 (Male, 39 weeks gestation); Case 3 (Male, 38 weeks gestation). The red arrows indicate regions of T2 hyperintensity, T1 hypointensity, and T2Flair hypointensity.

sponse to hypoxia-ischemia [19]. MRI, particularly DWI, provides crucial insights into the extent and severity of cerebral ischemia, as evidenced by higher ADC values in the HIE group compared to controls [20]. This elevation is indicative of cytotoxic edema and neuronal injury, consistent with the pathophysiological changes of HIE [21].

The significant decrease in Vs and Vd and the corresponding increase in RI in neonates with HIE suggest that

Table 2. The outcomes of the CDU examination.

	HIE group (n = 56)	Control group (n = 47)	*t*	*p*-value
MCA				
Vs	9.38 ± 2.34	11.79 ± 2.41	–5.150	<0.001
Vd	4.76 ± 0.53	6.46 ± 0.55	–15.968	<0.001
RI	0.75 ± 0.06	0.58 ± 0.07	12.837	<0.001
Vs/Vd	1.79 ± 0.24	1.96 ± 0.26	–3.386	0.001
ACA				
Vs	31.46 ± 1.91	40.69 ± 2.21	–22.740	<0.001
Vd	6.54 ± 0.85	12.35 ± 1.50	–23.532	<0.001
RI	0.82 ± 0.05	0.60 ± 0.08	16.920	<0.001
Vs/Vd	4.89 ± 0.71	3.35 ± 0.51	12.443	<0.001

$p < 0.05$ represents statistical significance. HIE, hypoxic-ischemic encephalopathy; CDU, color Doppler ultrasound; ACA, anterior cerebral artery; MCA, middle cerebral artery; Vs, peak systolic velocity; Vd, end-diastolic velocity; RI, resistance index.

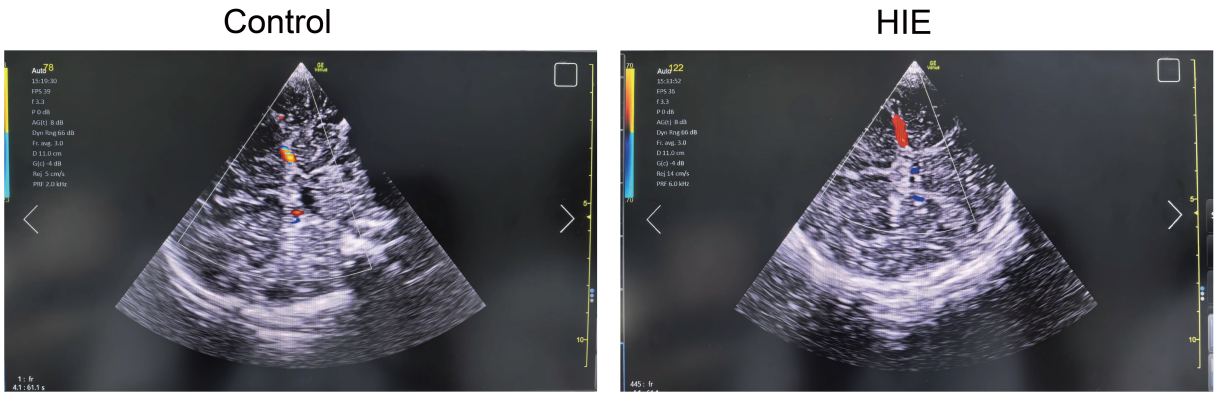

Fig. 2. Representative color Doppler ultrasound images of the middle cerebral artery in the control and HIE groups. Color Doppler ultrasound (CDU) images show cerebral blood flow in the middle cerebral artery (MCA). (Left) The control group demonstrates normal flow velocity and uniform color filling, indicative of normal cerebral perfusion. (Right) Neonate with hypoxic-ischemic encephalopathy (HIE) exhibits reduced flow velocity, decreased color signal intensity, and abnormal flow distribution, consistent with impaired cerebral perfusion and increased vascular resistance.

Table 3. Diagnostic performance of MRI and CDU for patients with HIE.

	AUC	Cut-off	95% CI	Specificity	Sensitivity	*p*-value
MRI	0.797	13.385	0.708–0.886	72.34%	76.79%	<0.001
CDU	-	-	-	73.91%	77.19%	-
MRI+CDU	0.918	0.264	0.867–0.968	87.50%	90.91%	<0.001

AUC, area under the curve; HIE, hypoxic-ischemic encephalopathy; CDU, color Doppler ultrasound; MRI, magnetic resonance imaging. *p*, Significance level for the diagnostic performance of each model.

CDU effectively identifies hemodynamic changes associated with HIE. These observations support the use of CDU as a rapid, non-invasive screening approach for early detection of cerebral vascular abnormalities in neonates at risk of HIE [16]. Conversely, MRI provides a more detailed assessment of brain injury, particularly in deep gray matter structures and periventricular white matter that are most vulnerable to ischemic damage [22]. In our findings, the AUC was 0.797 for MRI individually; however, when combined, the AUC improved to 0.918, highlighting the complementary significance of these imaging techniques in the early diagnosis of HIE.

Previously, Charon *et al.* [23] demonstrated the utility of MRI and DWI in diagnosing and grading the severity of neonatal HIE, particularly in identifying deep gray matter injury. Our study corroborates these findings and further underscores the role of ADC measurements in differentiating HIE from normal neonates. Similarly, our CDU

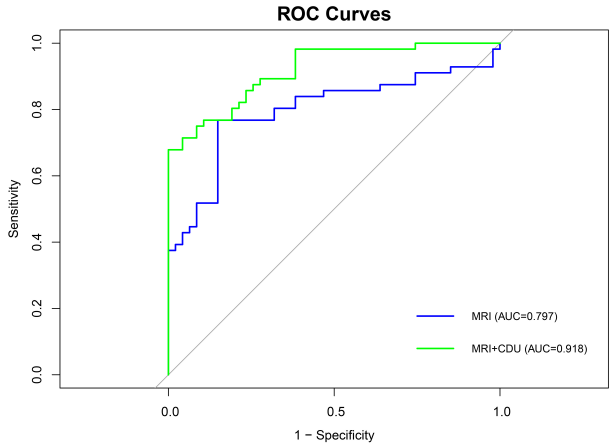

Fig. 3. Receiver operating characteristic (ROC) curve analysis of MRI and the combined MRI+CDU model for patients with HIE. The diagonal gray line represents the line of no discrimination. HIE, hypoxic-ischemic encephalopathy; MRI, magnetic resonance imaging; AUC, area under the curve.

findings align with those reported by Aly and AL-Ghannam [24], who found decreased Vs and Vd values in the MCA and ACA of neonates with HIE. Importantly, previous studies have focused solely on MRI or CDU, whereas our study demonstrates the added diagnostic benefit of their combination. This combination offers improved diagnostic accuracy, enabling a more comprehensive assessment of cerebral perfusion and structural injury, thereby providing a more holistic understanding of the disease process.

Despite several promising outcomes, we acknowledge some limitations in our study. First, the retrospective study design may introduce selection bias. Second, although the sample size was sufficient to demonstrate statistical significance, it limits the generalizability of our findings. Third, variability in imaging timing among participants may have affected the detection of certain injury patterns. Furthermore, this study did not consider the potential effects of therapeutic interventions, such as therapeutic hypothermia, on the imaging findings.

Future research should prioritize larger, prospective cohort studies to validate our findings and optimize the combined imaging protocol. Standardizing and stratifying scan timing is crucial, as the interval between injury onset and imaging can impact the identification of specific impairments. Investigating how imaging findings evolve over time, especially in relation to the initiation and duration of therapeutic hypothermia, may provide valuable insights into optimizing treatment strategies. Given the dynamic progression of neonatal HIE, accounting for imaging timing is crucial in enhancing diagnostic accuracy and elucidating its effects on outcome prediction. Furthermore, incorporating advanced MRI techniques, such as magnetic resonance spectroscopy and arterial spin labeling, to examine cerebral perfusion, could further enhance the understanding of pathophysiological processes in neonatal HIE [25].

Our study further highlights the importance of combining MRI and CDU for early diagnosis of neonatal HIE, particularly in assessing cerebral perfusion and tissue injury. Integrating these two imaging techniques rather than relying on either alone provides a more comprehensive evaluation, improves diagnostic accuracy, and aids in the early identification of infants for neuroprotective therapy. This multimodal approach is especially valuable in settings with limited MRI availability.

Conclusion

This study underscores the significance of combining MRI and CDU for the early diagnosis of neonatal HIE. This multimodal imaging strategy enables a more comprehensive assessment of cerebral perfusion and brain injury, facilitating more effective identification of candidates for neuroprotective therapy and ultimately improving patient management and prognosis.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

KZ and RBZ contributed to the conception and design of the study, and were involved in drafting the manuscript and revising it critically for important intellectual content; LR and JP made substantial contributions to the acquisition of data, and were involved in revising it critically; HL and XLF made analysis and interpretation of data and were involved in revising it critically; and all authors gave final approval of the version to be published. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study included a total of 56 neonates with HIE and 47 healthy neonates in the control group. This study was conducted in accordance with the Declaration of Helsinki, and ethical approval was obtained from the clinical research and ethics committee of Taihe Hospital, Hubei University of Medicine (Approval No. 20240223). Informed consent was obtained from all parents or legal guardians of the neonates involved in the study.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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