The Value of 3D arterial spin labeling in early diagnosis and short-term prognostic grouping of Full-Term neonatal hypoxic-ischemic encephalopathy

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Research Article

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Abstract

Purpose
To investigate the value of 3D arterial spin labeling (ASL) perfusion imaging and DWI for the early diagnosis of hypoxic-ischemic encephalopathy (HIE) in term neonates and the predictive value of 3D ASL for patient prognosis.

Methods
A total of 60 full-term neonates clinically diagnosed with HIE in our hospital from January 2018 to October 2021 and 60 control group was selected. All HIE neonates were divided into favourable outcome and adverse outcome groups according to their prognosis, and all subjects underwent 3D ASL and DWI simultaneously to compare cerebral blood flow (CBF) and apparent diffusion coefficient (ADC) in each region of interest and analyze the agreement. The areas of interest included bilateral basal ganglia, thalamus, and frontal white matter, and the final average was bilaterally taken. To investigate the correlation between CBF value of HIE in neonates and neonatal behavioral neurological assessment (NBNA), the relationship between early changes of CBF value and prognosis of neonates with HIE.

Results
The CBF values of basal ganglia and thalamus in the adverse outcome group were higher than those in the favourable outcome group, and the difference was statistically significant (P < 0.01); the CBF value of frontal white matter in the adverse outcome group and the favourable outcome group were statistically significant (P < 0.01); the CBF values in the basal ganglia and thalamus of neonates in the HIE group were greater than those of normal controls, and the differences were statistically significant (P < 0.01); the CBF values in the frontal white matter area of neonates in the HIE group were smaller than those in the normal control group, and the differences were statistically significant (P < 0.01). The area under the ROC curve for CBF value was 0.973, the specificity and sensitivity of CBF values were 97.5% and 90.2%; the ADC values of area under the ROC curve was 0.881, and the sensitivity and specificity were 82.5% and 92.7%. Respectively CBF values in the basal ganglia region were highly correlated with NBNA scores (r=-0.8196, p < 0.01) and negatively correlated; thalamic CBF values were highly correlated with NBNA scores (r=-0.8504, p < 0.01) and negatively correlated; frontal CBF values were not correlated with NBNA scores (r=-0.0802, p = 0.62).

Conclusion
ASL findings within 1 day after birth in full-term neonates were highly correlated with NBNA scores. It can diagnose HIE early and predict the outcome of functional brain damage with better diagnostic efficacy.
Introduction

Hypoxic-ischemic encephalopathy (HIE) is a clinical condition caused by hypoxia or reduced cerebral blood flow due to perinatal asphyxia in neonates. The alteration of cerebral blood flow (CBF) plays an extremely important role in the occurrence of brain injury, which can manifest clinically as a series of neurological symptoms and signs, and in severe cases, death, and some neonates are left with neurological sequelae of varying degrees (epilepsy, cerebral palsy, cognitive impairment, etc.).

Therefore, early diagnosis, early treatment and prognostic evaluation of HIE are particularly important[1]. MRI is currently the main imaging modality for HIE, but conventional MRI sequences are relatively difficult to observe cerebral blood flow changes in neonates.

3D ASL magnetic resonance perfusion imaging uses magnetically labeled arterial blood water molecules as an endogenous tracer and is a non-invasive perfusion imaging method that allows measurement of CBF without contrast injection and without radiation[2], no cumulative effect, reproducible, longitudinal comparison between multiple scans, and thus for disease follow-up and observation of treatment effects[3]. More importantly, the physiological characteristics of high blood flow and fast blood flow rate in children relative to adults provide conditions to address 2 limitations of ASL (low signal-to-noise ratio and via correlation effects): high CBF under physiological conditions allows elevated SNR on ASL, and fast-flowing labeled blood flows from the labeled area to the cerebral artery, producing the ideal labeling and transport effects for pediatric perfusion images[4]. Therefore, ASL perfusion imaging in children shows a higher signal perfusion signal than in adults, improving the resolution of cortical and subcortical structures and making it the method of choice for studying cerebral perfusion in children[5].

In this study, we used DWI and 3D ASL technology to investigate the clinical value of 3D ASL technology in the early diagnosis and prognostic assessment of HIE in term neonates.

Methods

Study design and participants

This was a prospective study design. Neonates diagnosed with HIE at the First Hospital of the University of Science and Technology of China from January 2018 to October 2021. According to the grading criteria, children with HIE were graded according to the <Diagnostic criteria for neonatal ischemic-hypoxic encephalopathy>[6].

A total of 60 infants diagnosed with neonatal hypoxic-ischemic encephalopathy, aged within 1 day, were diagnosed in the neonatal unit of our hospital. The inclusion criteria were based on the diagnostic criteria of neonatal hypoxic-ischemic encephalopathy, a history of severe fetal intrauterine distress and abnormal obstetric conditions that could explicitly lead to fetal intrauterine distress, or a history of significant
asphyxia during delivery; neurological symptoms appearing shortly after birth and lasting for more than 24 hours, such as altered consciousness, altered muscle tone, abnormal primitive reflexes, convulsions in severe cases, and increased fontanelle tone; exclusion of intracranial convulsions caused by hemorrhage, birth injury, electrolyte disturbance, genetic metabolic diseases, intrauterine infections, and other congenital diseases was excluded. All cases were not treated with hypothermia prior to MRI examination. The child was seen again 1 month after treatment and a prognostic assessment was performed by the associate neonatologist, all newborns were successfully scored on NBNA at follow-up. They were selected and divided into favourable outcome and adverse outcome groups according to the NBNA (neonatal behavioral neurological assessment, NBNA) scores [7].

The control group consisted of 60 full-term normal neonates, 34 males and 26 females (the number of male and female gender was the same as the HIE group), aged within 1 day, they had no neonatal hypoxic-ischemic encephalopathy, asphyxia, epilepsy, congenital heart disease, or other conditions that could potentially affect cerebral blood flow, and no additional medication was given in association with them who underwent routine MR scan and 3D ASL for other diseases, and all neonates had an Apgar 4–10 score and no abnormalities on MR scan.

**Study selection**

All of them underwent cranial MRI examination within 1 day after birth. Parents of the neonates gave informed consent and signed the informed consent form. NBNA scores were completed at 28–30 days after birth to assess the prognosis of the neonates, and the prognosis was grouped according to the score, with 35 or more points being the favourable outcome group and less than 35 points being the adverse outcome group. The NBNA score was performed by two experienced neonatologists and the MRI 3D ASL images were reviewed by two associate radiologists.

**Methods**

A 3.0T MR scanner (GE Discovery MR750, General Electric, USA), ADW4.6 workstation and 16-channel dedicated head coil were used to examine sequences including T1WI, T2WI, DWI and 3D ASL in the transverse position and T2WI in the sagittal position. 3D-ASL sequence parameters: TR = 4376 ms, TE = 11 ms, flip angle = 111°, FOV = 16 cm×16 cm, layer thickness = 4.0 mm, PLD (post labeling delay time, PLD) = 1025 ms [8], 3 NEX (Number of Excitation, NEX). DWI was performed using planar echo imaging (echo-planar imaging, EPI) with TR 4 000 ms, TE 50 ms, layer thickness 4 mm, b-value of 0, 1 000 s/mm2, and 2 NEX.

**Data extraction and assessment of study quality**

The neonate was sedated with 5% chloral hydrate 0.5 ml/Kg orally 30 min before the examination to ensure that the neonate completed the MRI examination in a sleepy state. The neonate’s head was fixed
with a sponge to prevent head movement, and cotton balls were inserted into the neonate's ear to protect hearing. To reduce the risk of transporting the neonate from the ward to the MRI examination room and to monitor the neonate's condition in real time, a neonatologist accompanied the neonate until the examination was completed and the neonate returned to the ward.

All data were uploaded to the GE AW 4.6 workstation. The CBF maps were obtained using Functool software. All measurements and reading were performed by experienced associate radiologists. The CBF value of the area of interest was measured, and the ROI size was $(10 \pm 2)\text{mm}^2$, ROI should be selected to avoid blood vessels, more cerebral sulci, and other locations, and the same site was measured three times each, and the average value was taken as the final result. The level of the area of interest was determined according to the anatomical landmarks.

The area and location were ensured to be the same for all neonates. Mirror drawing method was used to ensure that the contralateral ROI is in a symmetrical position. The area of interest included bilateral basal ganglia, thalamus, and frontal white matter. The ROIs were outlined at the corresponding sites on the apparent diffusion coefficient (ADC) map. The ADC values were measured, and co-alignment of ROI ranges of 3D ASL images with ADC maps.

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**Statistical analysis**

SPSS 20.0 software (IBM SPSS Statistics 20, SPSS Inc., Chicago, IL) was used for statistical analysis. Measures were expressed with chi-squared test; One-way ANOVA was used to observe whether there were
differences between mean values of CBF for Control group, adverse outcome group and favourable outcome groups in the same region of interest. Multiple comparisons were performed using the LSD method (homogeneity of variance) and the Tamhane method (uneven variance) based on the homogeneity of variance test results.

The correlation analysis between CBF values in the area of interest and NBNA score in different prognostic groups was performed by Pearson's method, and r values were listed separately. r > 0 was positive correlation and r < 0 was negative correlation. |r| = 0 for no correlation at all, 0 < |r| < 0.3 for low correlation, 0.3 ≤ |r| < 0.8 for moderate correlation, 0.8 ≤ |r| < 1 for high correlation, and |r| = 1 for complete correlation to assess the correlation between CBF and NBNA scores. All statistical results were considered statistically significant at P < 0.05.

The receiver operating characteristic (ROC) curve was used to analyze the predictive value, the sensitivity and specificity at the recommended cutoff value and the best cutoff value of ROC.

**Results**

Comparison of general clinical data of neonates in the three groups, 30 of 60 neonate had a favourable outcome and 30 had a adverse outcome. Because the gestational age of full-term infants differs in brain maturity, it is necessary to analyze whether there was any difference in the general clinical data of the adverse outcome group, the favourable outcome group, and the control group. The results showed no statistical differences in gender, gestational age, weight, 5 min Apgar score, and maternal age among the three groups of neonates (p > 0.05), as shown in Table 1.
<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD (95% CI)</th>
<th>Median (IQR)</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>favourable outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age</td>
<td>29.78 ± 0.95(27.81–31.73)</td>
<td>30.50(26.00–32.00)</td>
<td>21.00</td>
<td>41.00</td>
</tr>
<tr>
<td>Gestational age*</td>
<td>37.45 ± 0.66(37.32–37.59)</td>
<td>37.40(37.20–37.51)</td>
<td>37.10</td>
<td>38.40</td>
</tr>
<tr>
<td>Birth weight*</td>
<td>3.08 ± 0.41(3.00–3.17)</td>
<td>3.10(2.98–3.20)</td>
<td>2.50</td>
<td>3.40</td>
</tr>
<tr>
<td>5-min Apgar Score*</td>
<td>9.04 ± 0.23(8.56–9.52)</td>
<td>9.50(7.00–10.00)</td>
<td>4.00</td>
<td>10.00</td>
</tr>
<tr>
<td><strong>Adverse outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age</td>
<td>28.57 ± 1.37(25.62–31.52)</td>
<td>28.00(24.75–33.00)</td>
<td>19.00</td>
<td>37.00</td>
</tr>
<tr>
<td>Gestational age</td>
<td>37.45 ± 0.10(37.24–37.67)</td>
<td>37.40(37.18–37.60)</td>
<td>37.00</td>
<td>38.30</td>
</tr>
<tr>
<td>Birth weight</td>
<td>3.05 ± 0.07(2.89–3.21)</td>
<td>3.05(2.88–3.20)</td>
<td>2.50</td>
<td>3.60</td>
</tr>
<tr>
<td>5-min Apgar Score*</td>
<td>7.50 ± 0.45(6.52–8.48)</td>
<td>7.50(5.00–9.00)</td>
<td>3.00</td>
<td>10.00</td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age</td>
<td>29.38 ± 0.85(27.66–31.09)</td>
<td>29.00(25.25–32.00)</td>
<td>19.00</td>
<td>42.00</td>
</tr>
<tr>
<td>Gestational age*</td>
<td>37.46 ± 0.05(37.35–37.56)</td>
<td>37.40(37.20–37.60)</td>
<td>37.00</td>
<td>38.40</td>
</tr>
<tr>
<td>Birth weight</td>
<td>3.07 ± 0.04(2.98–3.15)</td>
<td>3.10(2.90–3.20)</td>
<td>2.30</td>
<td>3.60</td>
</tr>
<tr>
<td>5-min Apgar Score*</td>
<td>9.58 ± 0.13(9.31–9.84)</td>
<td>10.00(9.25–10.00)</td>
<td>7.00</td>
<td>10.00</td>
</tr>
</tbody>
</table>

* Nonnormal distribution

MRI images of ASL in the adverse outcome group, favourable outcome group, and control group, Fig. 1.

A,B,C,and D: MR images of a normal neonate. A. T2-weighted image. B. ADC image. C. DWI image. No significant abnormalities were seen in the structural brain images D. ASL image, no obvious signs of hyperperfusion were observed

E,F,G,and H: MR images of a neonates with hypoxic ischemic encephalopathy (HIE) and adverse outcome E. T2-weighted image. F. ADC image Left lateral paraventricular hyposignal G. DWI image Left lateral paraventricular high signal H. ASL image, pronounced hyperperfusion in the entire brain
I, J, K and L: MR images of neonates with hypoxic ischemic encephalopathy (HIE) and favourable outcome. A. T2-weighted image. B. ADC image. C. DWI image. No significant abnormalities were seen in the structural brain images. D. ASL image. No significant hyperperfusion was seen in the core gray matter and frontal white matter of the brain tissue, and the frontotemporal cortex showed hyperperfusion changes.

The results of statistical analysis among the three groups of adverse outcome group, favourable outcome group, and control group of CBF are shown in Fig. 2, Table 2. Two-by-two comparisons between the three groups revealed that all were statistically significant.

Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>CBF value (ml.100g⁻¹.min⁻¹)</th>
<th>ADC value (x10⁻³ mm⁻².s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>basal ganglia</td>
<td>thalami</td>
</tr>
<tr>
<td>Adverse outcome</td>
<td>43.27 ± 2.80</td>
<td>55.88 ± 4.11</td>
</tr>
<tr>
<td>Favourable outcome</td>
<td>34.53 ± 3.28a</td>
<td>46.34 ± 3.35</td>
</tr>
<tr>
<td>Control</td>
<td>31.75 ± 2.51b</td>
<td>38.33 ± 3.20</td>
</tr>
<tr>
<td>P</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

p = 0.005 between ab; p = 0.014 between cd; p = 0.022 between ef; p = 0.0157 between gh

There were significant differences in frontal lobe, basal ganglia, and thalamus ADC values in the control, favourable, and adverse groups.

There were significant differences in frontal lobe, basal ganglia, and thalamus CBF values in the control, favourable, and adverse groups.

The area under the concentration-time curve (AUC) for the CBF value was 0.973, with a sensitivity and specificity of 97.5% and 90.2%. The AUC for the ADC value was 0.881, with a sensitivity and specificity of 82.5% and 92.7%. Figure 3, Table 3.
Table 3

<table>
<thead>
<tr>
<th>Area under the ROC curve(AUC)</th>
<th>95% Confidence interval</th>
<th>Significance level P(Area = 0.5)</th>
<th>Youden index J</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF 0.9726</td>
<td>0.9438 To 1.001</td>
<td>&lt; 0.01</td>
<td>0.8774</td>
</tr>
<tr>
<td>ADC 0.8811</td>
<td>0.7967 To 0.9655</td>
<td>&lt; 0.01</td>
<td>0.7518</td>
</tr>
</tbody>
</table>

Figure 3

Figure 3 and Table 3 ROC curves of 3D ASL and ADC. 3D ASL had the largest area under the ROC curve, which was 0.9726, Youden index J was 0.8774.

Correlation analysis

CBF values in the basal ganglia were highly correlated with NBNA score, with a negative correlation (r=-0.8196, p < 0.01); CBF values in the thalamus were highly correlated with NBNA score, with a negative correlation (r=-0.8504, p < 0.01). Frontal CBF values were not correlated with NBNA score (r=-0.0802, p = 0.62). Figure 4–6.

Figure 4

Figure 4 Scatter plots demonstrating 3D ASL perfusion values with NBNA scores in the frontal lobe. The threshold values found in this paper are shown as dotted lines. Infants with a favourable outcome are shown in orange; infants with adverse outcome, in blue. Frontal CBF values were not correlated with NBNA score (r=-0.0802, p = 0.6229).

Figure 5

Figure 5 Scatter plots demonstrating 3D ASL perfusion values with NBNA scores in the basal ganglia region. The threshold values found in this paper are shown as dotted lines. Infants with a favourable outcome are shown in orange; infants with adverse outcome, in blue. CBF values in the basal ganglia were highly correlated with NBNA score, with a negative correlation (r=-0.8196, p < 0.01).

Figure 6

Figure 6. Scatter plots demonstrating 3D ASL perfusion values with NBNA scores in the thalamus. The threshold values found in this paper are shown as dotted lines. Infants with a favourable outcome are shown in orange; infants with adverse outcome, in blue. CBF values in the thalamus were highly correlated with NBNA score, with a negative correlation (r=-0.8504, p < 0.01).
Discussion

Neonatal HIE is a brain injury that can result in neurological disorder and has the highest morbidity and mortality rate among neonates. Research[9, 10] reported that the incidence is about 1–3/1,000 of full-term infants, and if left untreated can cause cognitive, motor, and functional impairment, and in severe cases can develop into cerebral palsy[11]. Therefore, in addition to early detection and treatment of this disease, adequate prognostic evaluation is also important. It is helpful to guide clinical management of treatment plans as well as to assess the effectiveness of neuroprotective treatment[12]. The purpose of this study was to explore the value of 3D ASL for the early diagnosis and prognostic assessment of neonates with HIE, with the aim of improving the overall prognostic outcome of neonates with HIE.

In order to ensure blood supply to the brain and other vital organs, the body redistributes blood flow after neonatal hypoxia, causing a significant increase in CBF values. The basal ganglia area, thalamus and other parts of the brain are actively myelinated and have high energy metabolic demand, which are extremely sensitive areas in the neonatal brain to hypoxia[13, 14]. Neonatal hypoxic-ischemic brain injury occurring in the perinatal period is one of the most common causes of severe, long-term neurological deficits in children. Because neonatal hypoxic-ischemic encephalopathy is a heterogeneous disease, predicting long-term neurodevelopment remains challenging. Early prediction of neonatal neurodevelopment is necessary to develop therapeutic interventions and to accurately guide parents based on neurodevelopmental prognosis.

Studies have shown that early (2–4 days) hyperperfusion is always present in the region of neonatal hypoxic-ischemic encephalopathy brain damage[15, 16], so this study selected neonates in the 1–3 days day-old range to ensure that they were all in the period of hyperperfusion, avoiding any effect on the results due to different day ages. Basal ganglia-thalamus pattern (BGT) is a common type of brain injury pattern in HIE, and it is also one of the patterns with a relatively adverse outcome. It mainly affects the bilateral central gray matter nuclei (ventral lateral thalamus and posterior lentiform nuclei) and the surrounding cortex. Children with basal ganglia-thalamic type injury can become severely disabled due to dyskinetic cerebral palsy, and dyskinetic cerebral palsy is also mainly caused by basal ganglia-thalamic type injury[17]. Therefore, our study placed the area of interest for CBF values at these locations, and additionally selected the frontal white matter region as a comparison.

Diffusion weighted imaging (DWI) is a non-invasive functional imaging technique for studying the microscopic motion of water molecules. In early HIE, neonatal neuronal and fibrous tract cell membrane tissue sodium and potassium pumps are dysfunctional, causing changes in the apparent diffusivity and direction of water molecules and inducing cytotoxic edema. Due to the effect of cell membranes and organelles on the ability of water molecules to disperse in the cell, the viscosity is increased and the corresponding reduction of free water in the extracellular space leads to a decrease in ADC values in the ischaemic area, which shows a significant high signal on DWI[18]. As the neonate grows older, the water content of the brain decreases, myelination increases, and as neurons and glial cells continue to grow, the extracellular space shrinks, eventually decreasing ADC values in all parts of the brain[19]. DWI can detect
lesions as early as 24-72h and provides an indication of the time of brain damage within the 2-5d time window[20]. However, DWI is subject to underestimation of damage, false negatives and false normalisation[21]. It is because as the disease progresses, for about 1 week, cytotoxic oedema converts to vasogenic oedema with less restricted diffusion of water molecules, and DWI often appears to be falsely negative. Therefore, newborns with suspected HIE should undergo DWI sequence within 3 days of birth. By comparing DWI examinations of children with HIE, Barkovich[22] et al. found that MRI was negative within 72h of onset, while DWI was seen to be abnormally high signal; in our group of 60 neonates with HIE, there were 35 positive DWI cases, which was basically consistent with the report.

De Vis et al.[23] performed well in predicting the prognosis of ASL after HIE, with a positive predictive value of 100% and a negative predictive value of 96% for ASL perfusion, and higher basal ganglia and thalamic ASL perfusion in the poor outcome group than in the good outcome group, consistent with our findings.

The results of this study showed the presence of intracerebral hyperperfusion in children with HIE within 72h after birth, which is consistent with the results of other related studies[24]. The ADC values for severe HIE were significantly lower than those for mild-moderate HIE in the 3–10 day time window. In the range of 7–14 days or 10–14 days, the statistical significance is much smaller[25, 26]. In neonatal hypoxic-ischemic injury, DWI may behave normally within the first 24 hours of life, with areas of reduced ADC beginning to appear over time[27], and the correlation between low ADC and high CBF suggests the presence of an environment conducive to delayed cell death in a typical reperfusion syndrome with potential therapeutic opportunities[28]. 3D ASL allows early assessment of reperfusion of brain tissue in children after the onset of HIE, and this redistribution of CBF to repair ischemic injury can delay cell death, making 3D ASL important for assessing the prognosis of HIE[29].

We investigated the correlation between CBF values of basal ganglia area, thalamus, and white matter and NBNA scores. The results showed that in our group of HIE neonates, CBF values of the basal ganglia region, CBF values of the thalamus and NBNA score was statistically different between poor and favourable outcome (p < 0.01), and brain perfusion was higher in the adverse outcome group than in the favourable outcome group. This lead to the conclusion that the higher the perfusion in the basal ganglia and thalamus, the lower the NBNA score and the worse the prognosis. The advantage of ASL was that it can assess the reperfusion phenomenon associated with delayed cell death and can therefore be used to predict outcome and assess neuroprotective treatment. Neonatal brain perfusion depends more on the time of gestation, while the subjects of this study were full-term neonates, and there were no statistical differences in clinical data and no significant differences in brain maturation among the three groups; moreover, all MRI examinations were performed within 1 day after birth, avoiding perfusion differences caused by different examination times and effectively avoiding bias.

**Conclusions**
In conclusion, 3D ASL can measure CBF of children with HIE non-invasively and accurately, and is more valuable than DWI for early diagnosis and prognosis assessment of HIE, which can provide an objective and accurate basis for clinical assessment of the prognosis of children with HIE and has high clinical application value.

**Declarations**

**Funding**

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2. Natural Science Foundation of Anhui Province (No. 2008085QH381)

The funding body had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

I confirm that I have read the Editorial Policy pages. This study was approved by the medical ethics committee of affiliated hospital of University of Science and Technology of China (2021-RE-118). This study was conducted in accordance with the declaration of Helsinki. Parents of the neonates gave informed consent and signed the informed consent form.

**Conflicts of interest notification**

The authors declare that they have no competing interests

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**References**


2. ALSOP DC, DETRE JA, GOLAY X, et al. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: a consensus of the ISMRM perfusion study group and the


Figures
Figure 1

A,B,C,and D: MR images of a normal neonate. A. T2-weighted image. B. ADC image. C. DWI image. No significant abnormalities were seen in the structural brain images D. ASL image, no obvious signs of hyperperfusion were observed.


I,J,K and L: MR images of a neonates with hypoxic ischemic encephalopathy (HIE) and favourable outcome. A. T2-weighted image. B. ADC image. C. DWI image. No significant abnormalities were seen in the structural brain images D. ASL image. No significant hyperperfusion was seen in the core gray matter and frontal white matter of the brain tissue, and the frontotemporal cortex showed hyperperfusion changes.
Figure 2

There were significant differences in frontal lobe, basal ganglia, and thalamus ADC values in the control, favourable, and adverse groups.

There were significant differences in frontal lobe, basal ganglia, and thalamus CBF values in the control, favourable, and adverse groups.
Figure 3

ROC curves of 3D ASL and ADC. 3D ASL had the largest area under the ROC curve, which was 0.9726, Youden index J was 0.8774.

Figure 4

Scatter plots demonstrating 3D ASL perfusion values with NBNA scores in the frontal lobe. The threshold values found in this paper are shown as dotted lines. Infants with a favourable outcome are shown in
Frontal CBF values were not correlated with NBNA score ($r = -0.0802, p = 0.6229$).

Figure 5

Scatter plots demonstrating 3D ASL perfusion values with NBNA scores in the basal ganglia region. The threshold values found in this paper are shown as dotted lines. Infants with a favourable outcome are shown in orange; infants with adverse outcome, in blue. CBF values in the basal ganglia were highly correlated with NBNA score, with a negative correlation ($r = -0.8196, p < 0.01$).

Figure 6
Scatter plots demonstrating 3D ASL perfusion values with NBNA scores in the thalamus. The threshold values found in this paper are shown as dotted lines. Infants with a favourable outcome are shown in orange; infants with adverse outcome, in blue. CBF values in the thalamus were highly correlated with NBNA score, with a negative correlation ($r=-0.8504$, $p<0.01$).