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# Association between cerebral oxygen saturation and neurological injury in asphyxiated neonates in a middle-income country: a retrospective cohort study

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## ABSTRACT

**Background** Neonatal outcomes following perinatal asphyxia vary significantly between low- and middle-income countries (LMICs) and high-income settings. Near-infrared spectroscopy is a non-invasive method for monitoring regional cerebral oxygen saturation ($rScO_2$), providing real-time insights into brain oxygenation. In LMICs, where healthcare resources are limited, early $rScO_2$ monitoring during therapeutic hypothermia (TH) may support neurological risk stratification. This study aimed to evaluate the association between early $rScO_2$ levels and brain MRI abnormalities in asphyxiated neonates during their first week of life.

**Methods** A retrospective longitudinal study was conducted on term neonates with moderate-to-severe perinatal asphyxia undergoing TH at a high-complexity healthcare institution in an LMIC. Continuous $rScO_2$ monitoring was performed for 72 hours during cooling and rewarming. Values were analysed at 6-hour intervals. The primary outcome was abnormal brain MRI findings during the first week, defined as radiological injury to the basal ganglia, thalami, cortical/watershed areas, white matter or vascular territories. Logistic regression was used to assess the association between $rScO_2$ and MRI abnormalities, and receiver operating characteristic analysis was used to evaluate predictive performance.

**Results** 88 neonates were included, of which 29 had abnormal MRI findings. All patients were referred from lower-complexity centres. Elevated $rScO_2$ in the first 6 hours was significantly associated with abnormal MRI findings (adjusted OR, 1.10; 95% CI 1.02 to 1.18). The $rScO_2$ threshold showed limited sensitivity and moderate specificity.

**Conclusions** Higher $rScO_2$ values during the first 6 hours of TH were associated with abnormal brain MRI findings. Although not definitive, early $rScO_2$ monitoring may aid in identifying neonates at risk of neurological injury in LMICs.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cerebral oxygen saturation ($rScO_2$) monitoring using near-infrared spectroscopy during therapeutic hypothermia (TH) has been studied as a complementary neuromonitoring tool to help identify neonates at risk for neurological injury after perinatal asphyxia. However, its predictive value remains limited owing to interindividual variability, device dependency and lack of standardised thresholds, particularly in resource-constrained settings where monitoring infrastructure may be limited.

### WHAT THIS STUDY ADDS

⇒ Elevated $rScO_2$ levels during the first 6 hours of TH were associated with abnormal brain MRI findings in neonates with perinatal asphyxia in a middle-income setting. Although its direct prognostic impact is limited and influenced by systemic factors, early $rScO_2$ monitoring may offer complementary physiological information to support risk stratification and guide clinical decision-making during TH, particularly in settings with restricted access to multimodal neuromonitoring.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results support the integration of early rScO2 monitoring as a complementary tool to TH in neonates with perinatal asphyxia. Although TH remains the primary neuroprotective intervention available for asphyxiated newborns, $rScO_2$ monitoring could assist in optimising the management of these patients by providing additional insight into cerebral oxygenation. This information could help guide treatment strategies during TH and prioritise systemic efforts to reduce delays in TH initiation, particularly in middle-income countries where logistical challenges and limited resources often hinder timely intervention.

## INTRODUCTION

Perinatal asphyxia has an incidence of 26 per 1000 live births in low-income and middle-income countries (LMICs).[1] Despite advancements in the prevention of asphyxia and the widespread implementation of therapeutic hypothermia (TH) as a standard treatment, neonates who survive asphyxia in these regions face up to an eightfold higher risk of developing long-term neurodevelopmental

disorders than those in high-income countries.[2 3] Moreover, outcomes vary significantly within LMICs, influenced by geographical and economic disparities, with evidence suggesting that the effectiveness of TH may decrease or even inadvertently increase the risk of adverse outcomes, depending on these contextual factors.[4 5]

The therapeutic window, known as the latent phase, provides an opportunity for the application of neuroprotective interventions.[6] The availability of neuromonitoring tools capable of early prediction of neonates at risk for neurological alterations could optimise therapeutic strategies associated with TH, ultimately improving neurological outcomes.[6 7] However, the current monitoring approaches for predicting neurological outcomes have significant limitations. Brain MRI abnormalities are often detectable only later in the disease course, when brain damage has already occurred.[8] Although electroencephalography (EEG) is a reliable indicator, its interpretation can be challenging because of physiological changes induced by the cooling process during TH.[9] Biochemical markers, such as neuron-specific enolase, S-100 protein and cytokines, show potential; however, their predictive value remains uncertain, and their use requires blood sampling, time, and laboratory resources, which may not always be readily available.[8–10]

Monitoring regional cerebral oxygen saturation ($rScO_2$) during TH has emerged as a complementary neuromonitoring tool that may provide insight into the early cerebral physiological changes associated with neurological injury.[7] An association has been proposed between alterations in cerebral blood flow, which is indirectly reflected by $rScO_2$ values during TH, and the subsequent development of neurological injury, both in the short and long term.[11 12] However, the findings of these studies remain inconsistent and heterogeneous, highlighting the need for further research to validate the predictive value of $rScO_2$ in neurological outcomes.[13] Additionally, the exact timing at which changes in $rScO_2$ reliably indicate neurological injury remains unclear, particularly given that TH encompasses both a 72-hour cooling phase and a rewarming phase.[13–15]

Moreover, most of these studies were conducted in high-income settings, where healthcare resources and outcomes differ significantly from those in LMICs. Importantly, outcomes in perinatal asphyxia and TH vary based on the economic and healthcare context of each country, particularly in LMICs.[16] These disparities underscore the need to generate context-specific evidence on neuromonitoring tools, such as $rScO_2$, to explore their potential role in broader neonatal care strategies in LMICs. Recent data from LMICs also support this approach. For example, Farag *et al* in Egypt demonstrated that near-infrared spectroscopy (NIRS)-derived cerebral $rScO_2$ and fractional tissue oxygen extraction measurements during TH are associated with both clinical seizures and abnormal MRI findings in asphyxiated neonates.[17]

This study aimed to evaluate the association between $rScO_2$ measured using NIRS during TH and brain MRI abnormalities in neonates with moderate-to-severe asphyxia in the first week of life. In addition, we sought to assess the predictive capacity of $rScO_2$ during TH to identify brain abnormalities detected using MRI. This study was conducted at a high-complexity referral hospital in a middle-income country.

## METHODS

This retrospective, longitudinal study included newborns admitted to the neonatal intensive care unit (NICU) between November 2021 and November 2022. The inclusion criteria were term and late preterm infants (Ballard ≥36 weeks) with postnatal age ≤12 hours, moderate or severe perinatal asphyxia, and moderate or severe hypoxic-ischaemic encephalopathy, as defined by Sarnat II/III, who met the TH criteria.[18] Neonates with evidence of severe intraparenchymal haemorrhage with an extremely poor neurodevelopmental prognosis, major congenital or genetic anomalies incompatible with life, or severe intrauterine growth restriction with a birth weight <1800 g were excluded.

The diagnosis of severe perinatal asphyxia was confirmed by the presence of at least three of the following criteria[18]: an Apgar score of ≤5 at 10 min, cord blood gases or peripheral blood drawn within the first hour of life with a pH <7.0, a base deficit of ≤−16 mmol/L, lactate levels ≥12 mmol/L and moderate or severe encephalopathy as classified by Sarnat stages II/III. Moderate asphyxia was confirmed by the presence of at least two of the following criteria: moderate to severe encephalopathy as determined by Sarnat stages II/III, an Apgar score of ≤7 at 10 min and cord blood gases or peripheral blood drawn within the first hour of life with pH<7.0.

TH was induced using total body cooling with a ThermoWrap cooling blanket. The core temperature was monitored continuously using an oesophageal thermal probe placed in the lower third of the oesophagus. During the induction phase, the core temperature was reduced to 33°C–34°C within 30–40 min. In the maintenance phase, a target temperature of 33.5°C±0.5°C was maintained for 72 hours. Rewarming was performed over 6 hours at a rate of 0.5°C per hour until a final temperature of 36.5°C was reached. Morphine was administered as a sedative to alleviate discomfort and pain associated with TH according to the institutional protocol. All patients received morphine in a standardised manner to reduce variability.

### Data collecting and processing

The $rScO_2$ was continuously monitored using an INVOS neonatal brain oximetry sensor placed in the frontal cranial region. Readings were recorded every 30 s over 72 hours of TH and the subsequent 6 hours of rewarming. Data were exported to an Excel spreadsheet for processing. Data cleaning and preprocessing involved several steps to ensure the accuracy and reliability of the dataset: (1) Missing data points in the time series were

identified and addressed by using linear interpolation to ensure data continuity. (2) Outliers and spurious values were systematically identified and removed during data processing to account for potential aberrations caused by patient movement or artefacts. (3) Detrending: Linear trends that could influence $rScO_2$ measurements were eliminated by detrending within each subgroup, with a focus on underlying physiological phenomena.

$rScO_2$ values were then averaged over 6-hour intervals to align with the timeframes used for assessing brain MRI abnormalities. This 6-hour interval was selected as it provides a balance between capturing significant temporal changes in cerebral oxygenation during TH and minimising variability.

The primary outcome was the presence of brain MRI abnormalities within the first week of life (between 5 and 7 days), assessed using a 1.5T system (MR Systems Achieva dStream, Philips). The severity of the brain injury was evaluated using conventional T1-weighted and T2-weighted spin-echo sequences, diffusion-weighted imaging and apparent diffusion coefficient maps. MRI abnormalities were classified according to their anatomical location following the framework established by the National ASCON consensus (Colombian Association of Neonatology - Asociación Colombiana de Neonatología)[18]: (1) lesions involving the basal ganglia and thalami, (2) cortical and watershed regions, (3) subcortical white matter, (4) periventricular white matter, (5) vascular territories (arterial infarcts) and (6) venous system (sinovenous thrombosis). This approach reflects the typical topographic distribution of hypoxic-ischaemic and vascular lesions in neonates and was chosen because of its applicability in our LMIC setting. The presence of at least one of these criteria can lead to abnormal MRI findings in the brain. Due to the sample size and low frequency of events, it was not feasible to conduct statistical analyses stratified by severity or specific types of brain injury. To facilitate analysis and enhance statistical robustness, MRI findings were dichotomised into two categories: normal and abnormal. The presence of at least one of these criteria was considered abnormal.

### Patient and public involvement

No patients were involved. This retrospective study used anonymised clinical data collected during routine care. Patients or the public were not involved in the development of the research question, study design, recruitment, conduct or dissemination of results.

### Statistical analysis

Qualitative variables are summarised as absolute and relative frequencies, whereas quantitative variables are expressed as measures of central tendency and dispersion. The normality of the distributions was assessed using the Shapiro-Wilk test.

Friedman's test was used to evaluate intragroup changes in $rScO_2$ during TH in neonates with and without brain MRI abnormalities. To determine the predictive capacity of $rScO_2$ for identifying abnormal brain MRI findings at 1 week of life, receiver operating characteristic curves were generated for each time interval, and the area under the curve (AUC) was calculated. The Youden index was used to identify the optimal cut-off point, maximising the combination of sensitivity and specificity. The diagnostic performance of $rScO_2$ at this cut-off was further assessed by calculating the positive likelihood ratio (LH+) and negative likelihood ratio (LH−).

Associations between brain MRI abnormalities and qualitative variables were assessed using the $\chi^2$ test or Fisher's exact test, as appropriate. Associations between brain MRI abnormalities and rScO2 values across intervals were evaluated using either Student's t-test or Mann-Whitney U test, depending on the distribution of the data.

Finally, a multiple logistic regression (MLR) model was constructed to assess the association between brain MRI abnormalities and $rScO_2$, after adjusting for potential confounding variables. The selection of variables for inclusion in the MLR model was based on a combination of statistical, biological and literature-supported criteria. Variables with a $p<0.25$ in univariate analyses were considered for inclusion to ensure that potentially relevant predictors were not excluded prematurely. Additionally, variables with strong biological plausibility or previously reported associations in similar studies were prioritised. Prior to constructing the final model, collinearity between variables was assessed using variance inflation factors and correlation matrices to ensure model stability and interpretability. Variables with evidence of high collinearity were excluded or adjusted to avoid redundancy and preserve the robustness of the analysis. In this context, cord blood pH, despite showing a significant association in the univariate analysis, was excluded because of its high collinearity with the composite variable severity of asphyxia. The confounding variables included in the final model were the severity of asphyxia, encephalopathy (Sarnat II/III), initiation of TH (<6 hours vs ≥6 to ≤12 hours), resuscitation at birth and the presence of electroclinical seizures confirmed via video-EEG (video telemetry) monitoring, performed as part of the institutional neurocritical care protocol and interpreted by a paediatric neurologist. Differences were considered statistically significant at $p<0.05$. Statistical analyses were performed using STATA V.14 software.

## RESULTS

A total of 88 infants were included in this study (figure 1). All patients were referred from lower-complexity healthcare institutions. The median time to initiate TH and, consequently, $rScO_2$ monitoring was 7.1 hours (IQR 3). Abnormal brain MRI findings were observed in 29 neonates. Among neonates with abnormal MRI findings, the most frequent topographic lesion pattern involved the watershed or cortical-subcortical regions (n=14), followed by lesions consistent with perinatal ischaemic

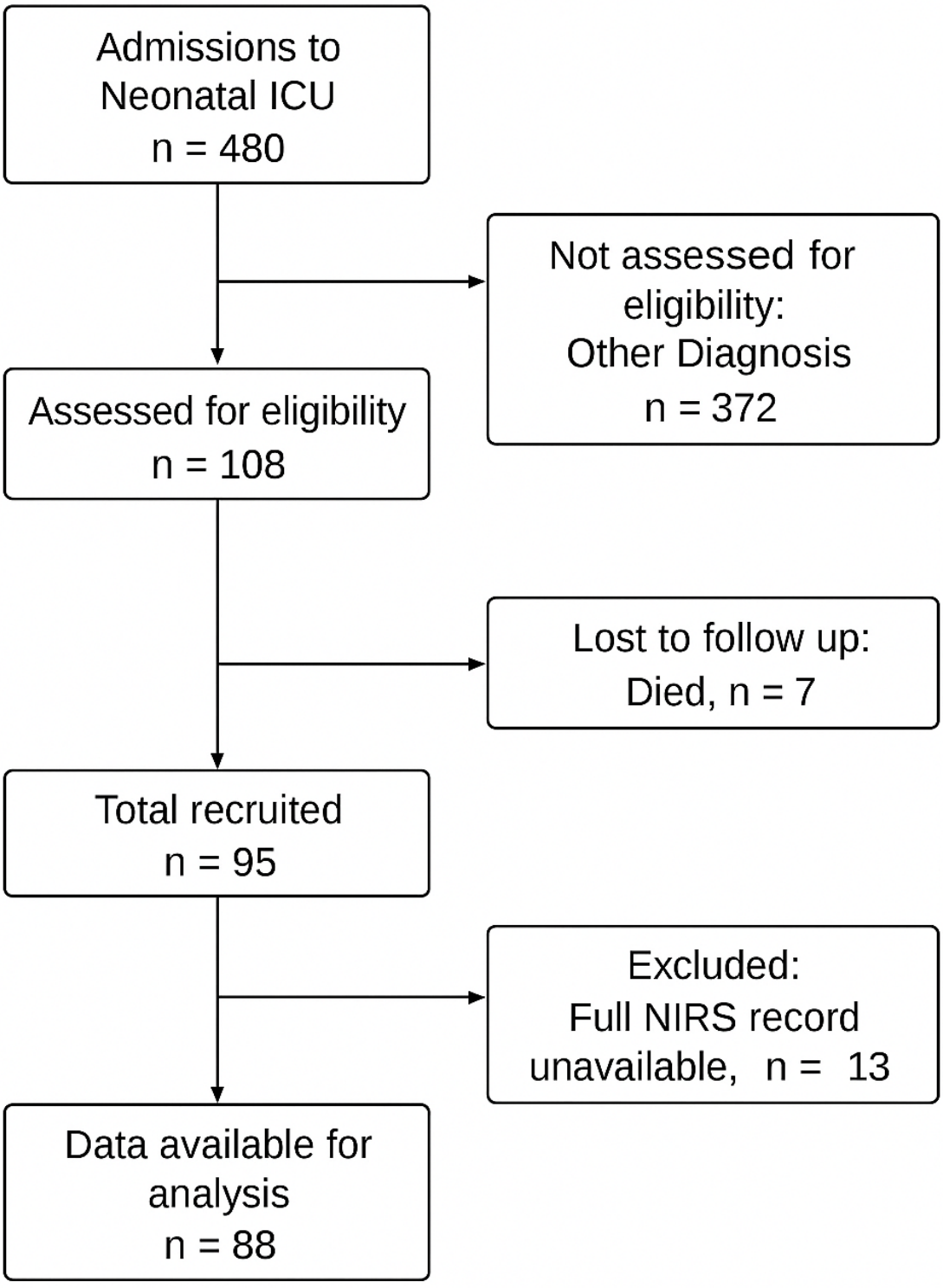


**Figure 1** Study flow chart. ICU, intensive care unit.

or haemorrhagic stroke (n=8). No significant differences were observed in the baseline patient characteristics (table 1). In univariate analysis, neonates with abnormal brain MRI findings had significantly lower cord blood pH values (p=0.02; OR 0.005, 95% CI 0.00007 to 0.40) and a higher frequency of electroclinical seizures confirmed via video-EEG monitoring (p=0.02; OR 3.00, 95% CI 1.16 to 7.70), compared with those with normal MRI findings (table 1).

Intragroup changes in $rScO_2$ were analysed separately for neonates with and without brain MRI abnormalities. Among neonates with abnormal brain MRI findings, no statistically significant changes in $rScO_2$ were observed during the TH or rewarming phases (p=0.55). In contrast, neonates without brain MRI abnormalities exhibited significant differences in $rScO_2$ values across the different measurement intervals (p<0.001). Specifically, this group showed a progressive increase in rScO2 during the first 24 hours of treatment (figure 2).

Furthermore, a significant association was observed between abnormal brain MRI findings and $rScO_2$ values during the first 6 hours of TH (p=0.005) and between 13 and 18 hours (p=0.04), with higher rScO2 values consistently observed in the group with abnormal brain MRI findings (figure 3).

Among all measurement intervals, only the $rScO_2$ value during the first 6 hours of TH demonstrated a moderate ability to predict brain MRI abnormalities within the first week of life, with an area under the curve (AUC) of 0.68 (95% CI 0.55 to 0.88) (table 2). For this period, the optimal cerebral oxygen saturation cut-off value determined using the Youden Index was 83.7%, yielding a sensitivity of 55.2% and a specificity of 83.1%. This threshold was associated with an LR+ of 3.25 and LR− of 0.53.

Finally, when controlling for confounding variables in the multivariate model, brain MRI abnormalities were associated with $rScO_2$ values between 0 and 6 hours (adjusted OR 1.10; 95% CI 1.02 to 1.18) (table 3).

## DISCUSSION

This study suggests that elevated $rScO_2$ levels during the first 6 hours of TH may be associated with abnormal brain MRI findings in neonates with perinatal asphyxia. Importantly, the cohort included infants born extramurally and referred to a specialised centre for TH, a common scenario in middle-income countries (LMICs). These logistical challenges underscore the need for early, accessible neuromonitoring tools that can support timely risk stratification. In this context, $rScO_2$ monitoring may offer supportive physiological information during the initial window of therapeutic intervention.

Our findings indicate that $rScO_2$ during the first 6 hours of TH demonstrated a moderate discriminative ability for identifying brain MRI abnormalities, as reflected by an AUC of 0.68. While the diagnostic performance was optimised with an identified cut-off value of 83.7%, this threshold had limited sensitivity (55.2%), and the results should therefore be interpreted cautiously. This modest sensitivity may be partly explained by the variability in postnatal age at the time of $rScO_2$ measurement due to heterogeneity in referral times among extramural births.

In healthy term neonates during the first 15 min of postnatal transition, $rScO_2$ levels typically range from 45% to 66%, progressively increasing over the first 3 days of life to an average of 76.8%±8.5%.[19 20] In contrast, the $rScO_2$ threshold of 83.7% identified in this study during the first 6 hours of TH was observed in neonates with perinatal asphyxia and abnormal brain MRI. This contrast supports the hypothesis that elevated $rScO_2$ levels may reflect altered cerebral haemodynamics in neonates with perinatal asphyxia.

Our results are consistent with those of previous studies conducted in high-income countries, which also reported an association between increased $rScO_2$ and subsequent neurological injury in neonates undergoing TH.[21] Notably, in our study, this association emerged early, within the first 6 hours of cooling, whereas other investigations have reported significant associations at later stages, particularly during the rewarming phase.[13 19 22] Szakmar *et al* observed increased $rScO_2$ levels between the first and second days in neonates with abnormal MRI findings,[23] and Peng *et al* identified $rScO_2$ as a predictive measure within the first 10 hours.[12] Conversely, Goeral *et al*[24] reported no significant differences in $rScO_2$ within the first 6 hours .[21] These inconsistencies across studies may be explained by variations in the timing of TH initiation, differences in population characteristics or monitoring protocols.

Most existing studies have been conducted in settings in which TH is typically initiated within the first 3–6 hours of life.[25 26] Systematic reviews by Garvey *et al* and Mitra *et al*, which included such early treated cohorts, found that the predictive value of $rScO_2$ was stronger after 24–72 hours of treatment.[13 22] In contrast, our study reflects real-world challenges in LMICs, where the median time to initiate TH was 7 hours due to the need for interfacility transfers.

Interestingly, we did not observe significant differences in brain MRI abnormalities based on whether hypothermia was initiated before or after 6 hours, although the sample size may have limited this analysis. Similarly, Szakmar *et al* found $rScO_2$ elevations in patients who started cooling at a median age of 7.7 hours, suggesting that the timing of therapy and stage of injury may interact to affect outcomes.[23] While TH initiated within 6 hours of birth remains the standard of care, the potential benefit of initiating treatment between 6 and 24 hours is still under investigation.[27 28] Existing evidence suggests a possible neuroprotective effect, although its efficacy is uncertain, particularly in LMIC settings, where delayed referral is common.[4 5]

The observed elevation in $rScO_2$ among neonates with MRI-confirmed brain injury likely reflects the pathophysiological changes associated with impaired cerebral autoregulation, secondary energy failure and reduced

**Table 1** Baseline clinical characteristics of neonates with and without abnormal brain MRI findings

| Variable | Total cohort n=88 | | Normal MRI n=59 | | Abnormal MRI n=29 | | P value |
|---|---|---|---|---|---|---|---|
| Gestational age—Ballard, n (%) | | | | | | | |
| ≥37 weeks | 76 | (86.4) | 52 | (68.4) | 24 | (31.6) | 0.52* |
| <37 weeks | 12 | (13.6) | 7 | (58.3) | 5 | (41.7) | |
| Birth weight—grams, n (%) | | | | | | | |
| ≥2500 g | 71 | (80.7) | 48 | (67.6) | 23 | (32.4) | 0.81 |
| <2500 g | 17 | (19.3) | 11 | (64.7) | 6 | (53.3) | |
| Sex, n (%) | | | | | | | |
| Female | 41 | (46.6) | 28 | (68.3) | 13 | (31.7) | 0.81 |
| Male | 47 | (53.4) | 31 | (66) | 16 | (34) | |
| Method of birth, n (%) | | | | | | | |
| Vaginal | 41 | (46.6) | 26 | (63.4) | 15 | (36.6) | 0.49 |
| Caesarean | 47 | (53.4) | 33 | (70.2) | 14 | (29.8) | |
| Resuscitation at birth, n (%) | | | | | | | |
| None | 4 | (4.6) | 2 | (50) | 2 | (50) | |
| Basic | 38 | (43.2) | 27 | (71) | 11 | (29) | 0.39 |
| Advanced | 46 | (52.3) | 30 | (65) | 16 | (35) | 0.54 |
| Initiation of therapeutic hypothermia (hours), n (%) | | | | | | | |
| < 6 hours | 18 | (20.5) | 13 | (72.2) | 5 | (27.8) | 0.60 |
| ≥6 to ≤12 hours | 70 | (79.5) | 46 | (65.7) | 24 | (34.3) | |
| Encephalopathy—Sarnat, n (%) | | | | | | | |
| Moderate (Sarnat II) | 80 | (90.9) | 55 | (68.7) | 25 | (31.3) | 0.43* |
| Severe (Sarnat III) | 8 | (9.1) | 4 | (50) | 4 | (50) | |
| Apgar at first minute, n (%) | | | | | | | |
| ≥5 | 44 | (50) | 33 | (75) | 11 | (25) | 0.11 |
| <5 | 44 | (50) | 26 | (59.1) | 18 | (40.9) | |
| Apgar at fifth minute, n (%) | | | | | | | |
| ≥5 | 80 | (90.9) | 56 | (63.6) | 24 | (27.3) | 0.11* |
| <5 | 8 | (9.1) | 3 | (3.4) | 5 | (5.7) | |
| Asphyxia severity, n (%) | | | | | | | |
| Moderate | 36 | (40.9) | 26 | (72.2) | 10 | (27.8) | 0.39 |
| Severe | 52 | (59.1) | 33 | (63.5) | 19 | (36.5) | |
| Electroclinical seizures, n (%) | | | | | | | |
| No | 60 | (68.2) | 45 | (75.0) | 15 | (25.0) | **0.02** |
| Yes | 28 | (31.8) | 14 | (50.0) | 14 | (50.0) | |
| Cord blood gas parameters | | | | | | | |
| pH, median (IQR) | 6.95 | (0.15) | 7 | (0.15) | 6.9 | (0.1) | **0.02**† |
| HCO3, mean (± SD) | 13.04 | (4.21) | 12.8 | (3.7) | 13.42 | (5.1) | 0.52 |
| Base excess, mean (± SD) | −17.6 | (5.2) | −17,3 | (5.1) | −18,3 | (5.2) | 0.38 |
| Lactate, median (IQR) | 10.81 | (3.5) | 10.83 | (4) | 10.78 | (5.3) | 0.33† |
| Inotropic use, n (%) | | | | | | | |
| No | 37 | (42) | 23 | (62.2) | 14 | (37.8) | 0.4 |
| Yes | 51 | (58) | 36 | (70.6) | 15 | (29.4) | |
| Haemoglobin, median (IQR) | 17.8 | (2.8) | 17.9 | (2.8) | 17.8 | (3) | 0.62† |

Bold values indicate statistically significant differences ($p < 0.05$).
*Fisher's exact test.
†Mann-Whitney U test.
$HCO_3$, Bicarbonate concentration.; rScO2, regional cerebral oxygen saturation.

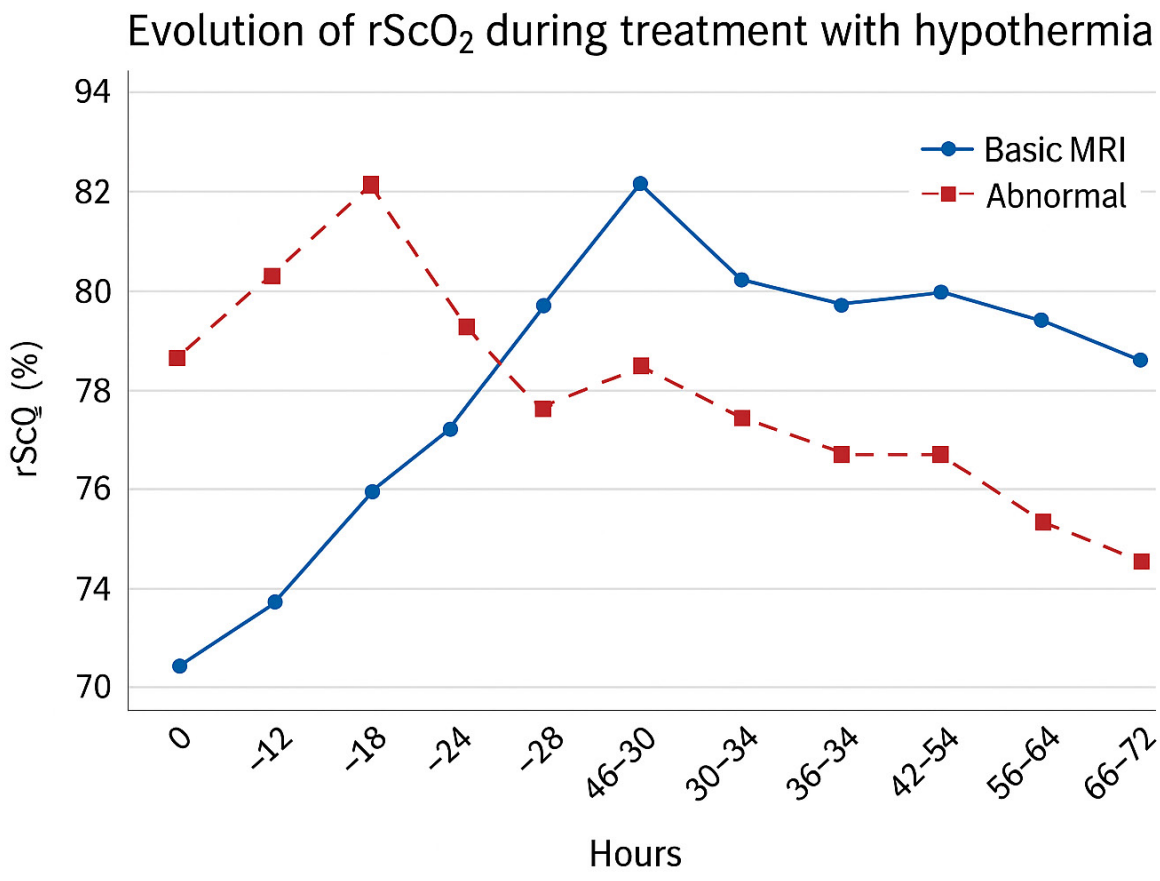


**Figure 2** Evolution of $rScO_2$ during treatment with hypothermia. $rScO_2$, regional brain oxygen saturation.

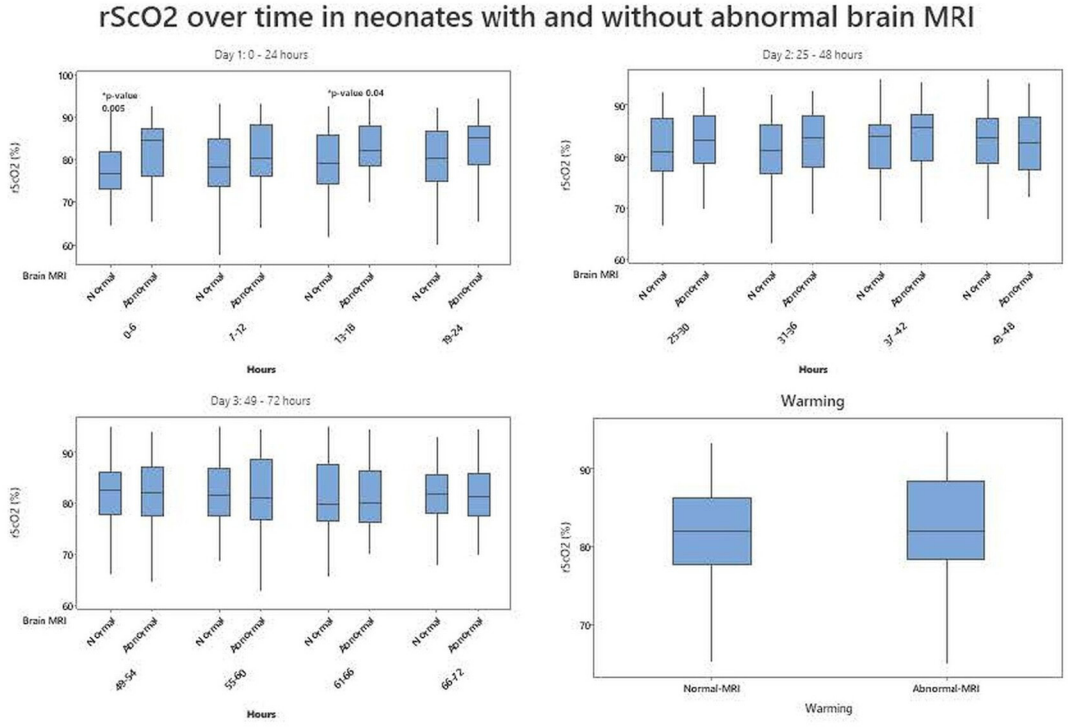


**Figure 3** $rScO_2$ during treatment in neonates with and without abnormal brain MRI. $rScO_2$, regional brain oxygen saturation. *Mann-Whitney U Test.

Table 2 Area under the ROC curve for rScO2 during therapeutic hypothermia and rewarming phases

| rScO2 | Area under the curve | 95% CI | |
|---|---|---|---|
| 0–6 hours | **0.68** | **0.56** | **0.81** |
| 7–12 hours | 0.61 | 0.49 | 0.74 |
| 13–18 hours | 0.63 | 0.51 | 0.76 |
| 19–24 hours | 0.61 | 0.49 | 0.74 |
| 25–30 hours | 0.58 | 0.45 | 0.70 |
| 31–36 hours | 0.60 | 0.46 | 0.72 |
| 37–42 hours | 0.58 | 0.45 | 0.71 |
| 43–48 hours | 0.48 | 0.35 | 0.61 |
| 49–54 hours | 0.50 | 0.37 | 0.64 |
| 55–60 hours | 0.48 | 0.35 | 0.61 |
| 61–66 hours | 0.49 | 0.36 | 0.62 |
| 67–72 hours | 0.47 | 0.34 | 0.61 |
| Rewarming | 0.56 | 0.42 | 0.69 |

Bold values indicate statistically significant differences (p < 0.05).
ROC, receiver operating characteristic; rScO2, regional cerebral oxygen saturation.

oxygen extraction efficiency.[13 29 30] These mechanisms are consistent with the known evolution of hypoxic-ischaemic encephalopathy and may explain the early rise in cerebral saturation observed in our cohort. The stage of injury at the time of TH initiation is highly variable and depends on the timing of the sentinel event, which may occur before, during or after the delivery.[25 26 31–33]

In our study, $rScO_2$ levels increased gradually in neonates without brain lesions during the first few hours of TH, whereas those with MRI abnormalities showed consistently elevated values from the start. These trends contrast with the $rScO_2$ values reported in healthy term neonates, which increased gradually and remained below the abnormal threshold identified in our cohort.[34–36] In contrast, sustained elevations in cerebral perfusion and saturation in asphyxiated neonates are associated with localised neuronal injury and worse outcomes.[37] These patterns suggest that $rScO_2$ monitoring could complement clinical assessments to help differentiate physiological adaptation from pathological cerebral responses in the early postnatal period.

Current guidelines endorse the use of NIRS to better understand cerebral haemodynamics during TH and to improve neuroprotection strategies.[38 39] By offering continuous and non-invasive monitoring, NIRS may support the early detection of impaired cerebral autoregulation and inform goal-directed care.[40 41] However, $rScO_2$ levels should not be interpreted in isolation and must be integrated with clinical, neurophysiological and biochemical data to improve risk stratification.

Although our findings suggest a potential role of NIRS as an adjunctive neuromonitoring tool in the early evaluation of asphyxiated neonates, its clinical application is limited by its moderate predictive performance. Future

Table 3 Logistic regression model of factors associated with abnormal brain MRI in neonates with asphyxia

| | Univariate OR | 95% CI | P value | Adjusted OR (aOR) | 95% CI | P value |
|---|---|---|---|---|---|---|
| Mean $rScO_2$ between 0 and 6 hours | 1.09 | (1.02 to 1.17) | 0.008 | **1.09** | **(1.01 to 1.17)** | **0.02** |
| Initiation of therapeutic hypothermia | | | | | | |
| < 6 hours | Reference | | | Reference | | |
| ≥ 6 to ≤12 hours | 1.35 | (0.43 to 4.25) | 0.6 | 1.05 | (0.28 to 3.82) | 0.94 |
| Resuscitation at birth | | | | | | |
| No | Reference | | | Reference | | |
| Yes | 0.58 | (0.14 to 2.34) | 0.44 | 0.59 | (0.12 to 2.93) | 0.52 |
| Encephalopathy—Sarnat | | | | | | |
| Moderate (Sarnat II) | Reference | | | Reference | | |
| Severe (Sarnat III) | 2.2 | (0.50 to 9.51) | 0.29 | 1.78 | (0.34 to 9.33) | 0.49 |
| Asphyxia severity | | | | | | |
| Moderate | Reference | | | Reference | | |
| Severe | 1.49 | (0.59 to 3.76) | 0.39 | 1.32 | (0.46 to 3.76) | 0.59 |
| Electroclinical seizures | | | | | | |
| No | Reference | | | Reference | | |
| Yes | 3 | (1.16 to 7.70) | 0.02 | 2.45 | (0.88 to 6.84) | 0.08 |

Univariate ORs represent unadjusted associations. aORs account for confounding factors, including initiation of therapeutic hypothermia, resuscitation at birth, severity of encephalopathy (Sarnat scale), severity of asphyxia and electroclinical seizures.
Bold values indicate statistically significant differences (p < 0.05)
aOR, adjusted OR; $rScO_2$, regional cerebral oxygen saturation.

studies should explore the integration of $rScO_2$ with other biomarkers of hypoxia, such as pH, lactate, EEG or inflammatory markers, to improve diagnostic accuracy. Additionally, the cost of disposable NIRS sensors may pose a barrier to routine implementation in LMICs, which warrants evaluation in future cost-effectiveness studies.

A key limitation of this study is its retrospective design, which may have introduced a selection bias. We attempted to mitigate this by applying objective criteria for diagnosing perinatal asphyxia and adhering to standardised guidelines. Furthermore, the severity of MRI abnormalities could not be graded using standardised scoring systems, such as the Barkovich scale, as these are not routinely applied in clinical practice at the time. Instead, we used an anatomical classification based on the ASCON consensus, which has been endorsed in national guidelines and provides a clinically relevant framework in LMIC settings. The limited sample size also precluded subgroup analysis based on the lesion severity or pattern. Despite these limitations, the study's setting in a high-complexity referral centre and its inclusion of extramural neonates enhanced the generalisability of the findings to similar LMIC populations.

In conclusion, this study suggests that elevated $rScO_2$ levels during the first 6 hours of TH may be associated with brain MRI abnormalities in neonates with perinatal asphyxia. These findings underscore the potential utility of $rScO_2$ monitoring as a part of a multimodal neuromonitoring approach for LMICs. Further prospective studies are required to validate these findings, define context-specific thresholds and explore the long-term prognostic value of early cerebral oximetry.

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