The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 6, 2025

DIAGNOSTIC ACCURACY OF CRANIAL SONOGRAPHY IN DETECTION OF HYPOXIC-ISCHEMIC ENCEPHALOPATHY IN CLINICALLY SUSPECTED PREMATURE INFANTS KEEPING MRI AS GOLD STANDARD

CRANIAL SONOGRAPHY VERSUS MRI IN NEONATAL HIE

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DOI: https://doi.org/10.5281/zenodo.20064871

Keywords
Hypoxic ischemic encephalopathy, cranial sonography, neonatal imaging, MRI, premature infants, diagnostic accuracy

Article History
Received: 01 May 2025
Accepted: 3rd June 2025
Published: 10 June 2025

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Abstract

Background: *Neonatal hypoxic ischemic encephalopathy (HIE) is one of the leading issues in neonatal morbidity and mortality, specifically for preterm infants. MRI has established itself as the gold standard in diagnosing HIE; however, it may not always be available in low-resource countries. In such scenarios, cranial sonography may provide a portable and cost-effective alternative for diagnosis; however, diagnostic accuracy varies in the literature. To assess the diagnostic accuracy of cranial sonography for the diagnosis of HIE in clinically suspected preterm neonates, with MRI established as a gold standard.*

Methods: *This was a cross-sectional validation study conducted for six months at the Radiology department of Bacha Khan Medical College and Mardan Medical Complex. All preterm neonates clinically suspected of having HIE, of which there were 179 in total, were included in the study. Every patient received both cranial ultrasonography and MRI. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy of cranial ultrasound as compared to the findings of MRI were calculated.*

Results: *Of the 179 neonates, cranial sonography identified 119 of them as having HIE, while MRI noted 126. Cranial ultrasound identified HIE with a sensitivity of 85.7%, specificity of 79.2%, PPV of 90.8%, NPV of 70.0%, and overall diagnostic accuracy of 83.8%. This indicates good overall diagnostic agreement between cranial ultrasound and MRI in terms of HIE.*

Conclusion: *Cranial Sonography showed good diagnostic performance in the detection of HIE among premature neonates, making it a suitable diagnostic tool when MRI is not available. However, due to its limitations with subtle brain lesions, additional studies that include long-term outcomes will help validate these findings, and would like to be demonstrated with the MRI when feasible.*

Introduction

Over the past several decades, sustained community-level awareness and educational efforts have improved the practices of perinatal care (1). However, HIE is still considered the most common cause of cerebral palsy and a significant factor contributing to the development of disabilities in children (2). Timely identification, quick referral, and specialized neonatal care are mandatory in reducing the risk of complications and mortality associated with this condition (3, 4). According to available reports, the incidence of HIE is around 1 to 8 per 1000 live births around the world (5). The rates are higher in low-income countries like Pakistan, due to poor access to perinatal care (6)

MRI, especially when combined with diffusion-weighted imaging and proton MR spectroscopy, is a very sensitive and specific method for delineating the extent and severity of injury in HIE (7). MRI helps in diagnosing acute injury but also aids in prognosis (8, 9). MRI is limited because of restricted availability as an imaging modality at the bedside, high cost, and frequent need for sedation in neonates (10).

In the neonatal intensive care setting, an alternative to MRI is Cranial ultrasonography (CUS) (11). It is noninvasive, portable, and cheap, can be performed at the bedside, and does not require sedation (12). CUS is useful, particularly in the early neonatal period when fontanelles are open and serve as acoustic windows for the brain (13). Previous reports show variable sensitivity and specificity of CUS in detecting HIE, with some studies demonstrating high diagnostic performance comparable to MRI, while others show substantial under-detection, especially in the posterior fossa and deep brain structures (14, 15).

These inconsistencies in the diagnostic performance of cranial sonography across different studies may be related to operator expertise, equipment quality, and variations in inclusion criteria. Given the clinical and logistical importance of having a reliable bedside tool in low-resource settings, there is a need to validate the accuracy of CUS in diagnosing HIE using MRI as a reference standard in the Pakistani context.

Therefore, the present study proposes to assess the diagnostic value of cranial ultrasonography regarding the detection of hypoxic ischemic encephalopathy in clinically suspected premature neonates, with MRI serving as the gold standard. Demonstrating the utility of CUS would bolster its more general use in neonatal practice when MRI is unavailable, allowing earlier diagnosis and possibly better outcomes.

Materials and Methods

Study Design and Setting

This cross-sectional validation study was conducted at the Radiology Department, Bacha Khan Medical College, and Mardan Medical Complex, Mardan. It is a tertiary care teaching hospital that provides all facilities for neonatal care, including imaging. The duration of our study was six months. After approval from the IRB and registration with the RTMC of the CPSP, the study was initiated.

Study Population

This included premature neonates born before 37 completed weeks of gestation, confirmed by pre-delivery obstetric ultrasound or the mother's last menstrual period. Only neonates who were clinically suspected to have HIE were included. The suspicion of HIE was based on an APGAR score of less than 3 at 1 minute and less than 7 at 5 minutes, with the need for neonatal resuscitation. Neonates of both genders were eligible. The exclusion criteria included congenital malformations like hydrocephalus, microcephaly, or anencephaly; any contraindications to MRI, such as active seizures or hypersensitivity reactions; and refusal of informed consent by the parents.

Ethical Considerations

This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval for this study was granted by the Ethical Review Committee of Bacha Khan Medical College, Mardan (426/BKMC). Written informed consent was obtained from parents or guardians of all participants. All data were anonymized and treated with strict confidentiality to protect patient privacy.

Sample Size and Sampling Technique
Sample size calculation was done using the formula for diagnostic test evaluation. Assuming an expected sensitivity of 80%, specificity of 66.67%, a disease prevalence of 66.7%, precision of 12%, and a 95% confidence level, the minimum sample size required was 179 neonates 1. A non-probability consecutive sampling technique was thus used to enroll participants who met the inclusion criteria during the study period.

Data Collection Procedure
Written informed consent was taken from the infant's guardian at enrolment. The demographic and clinical data of the infant, namely gestational age at birth, sex, birth weight, mode of delivery, APGAR scores at 1 and 5 minutes, maternal education status, maternal booking status, and maternal area of residence, were noted on a structured proforma. All neonates underwent both CUS and brain MRI to identify evidence of HIE.

Cranial Sonography Protocol
The examination of the cranial ultrasonography was carried out with the aid of doppler high-resolution linear-array transducer (5-8 MHz) with a small surface area suitable for neonatal skull shape. Sonographic assessment was carried out through the anterior fontanelle in coronal and sagittal planes, and as much as possible through occipital, temporal, and posterior windows. HIE features (diffuse cerebral edema evidenced by loss of sulci and fissure, hemispheric asymmetry, subcortical white matter echogenicity) were found. All US findings were analysed by experienced radiologists unaware of MRI results.

MRI Protocol
MRI was performed using a 1.5 Tesla superconducting scanner and neonatal head coil. When necessary, a sedative (10% chloral hydrate) was used according to neonatal weight under paediatric supervision. MR sequences were T1 and T2-weighted images. MRI diagnostic features of HIE consisted of increased signal intensity in both basal ganglia and thalamus, with loss of the normal hyperintensity found in the posterior limb of the internal capsule on T1-weighted images. All MRI examinations were independently reviewed, in a blinded fashion with respect to the US results, by 2 experienced radiologists.

Statistical Analysis
All data were analyzed using IBM SPSS Statistics version 20. Continuous variables such as gestational age, birth weight, and APGAR scores were summarized using means and standard deviations. Categorical variables including gender, mode of delivery, maternal education, and imaging results were presented as frequencies and percentages. Diagnostic accuracy of cranial sonography was evaluated using a 2×2 contingency table with MRI findings as the reference standard. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy were calculated. Stratified analysis was performed for variables such as gender and age to assess potential effect modifiers, and statistical significance was assessed using the Chi-square or Fisher's exact test where appropriate. A p-value less than 0.05 was considered statistically significant.

Results
There were 179 premature neonates who had clinically suspected hypoxic ischemic encephalopathy (HIE) enrolled in the study. The mean gestational age at birth was 33.2 ± 2.1 weeks and birth weight was 1850 ± 410 grams. Of these, 104 (58.1%) were males and 75 (41.9%) were females. Most of the neonates were delivered through caesarean section (57.5%) and resided in rural areas (62.6%).
CUS detected findings suggestive of HIE in 119 (66.5%) neonates, while MRI confirmed HIE in 126 (70.4%) cases. A 2×2 diagnostic table was constructed to determine the sensitivity, specificity, predictive values, and overall diagnostic accuracy of CUS in detecting HIE using MRI as the gold standard.
Among 126 MRI-confirmed cases of HIE, 108 were also positive on cranial sonography, with 18 false negatives. Of the 53 neonates without HIE on MRI, 11 were wrongly labelled as having HIE by sonography, leaving 42 true negatives.

Table 1: Baseline Demographic and Clinical Characteristics of Neonates (N = 179)

Characteristic	Value (n or Mean ± SD)
Gestational Age (weeks)	33.2 ± 2.1
Birth Weight (grams)	1850 ± 410
Gender	Male: 104 (58.1%)Female: 75 (41.9%)
Mode of Delivery	Caesarean: 103 (57.5%)Vaginal: 76 (42.5%)
Maternal Education	Illiterate: 92 (51.4%)Literate: 87 (48.6%)
Maternal Booking Status	Booked: 70 (39.1%)Unbooked: 109 (60.9%)
Residence	Urban: 67 (37.4%)Rural: 112 (62.6%)

Table 2: Diagnostic Accuracy of Cranial Sonography for HIE

Cranial Sonography	HIE on MRI (Yes)	HIE on MRI (No)	Total
HIE Detected	108 (True Positives)	11 (False Positives)	119
HIE Not Detected	18 (False Negatives)	42 (True Negatives)	60
Total	126	53	179

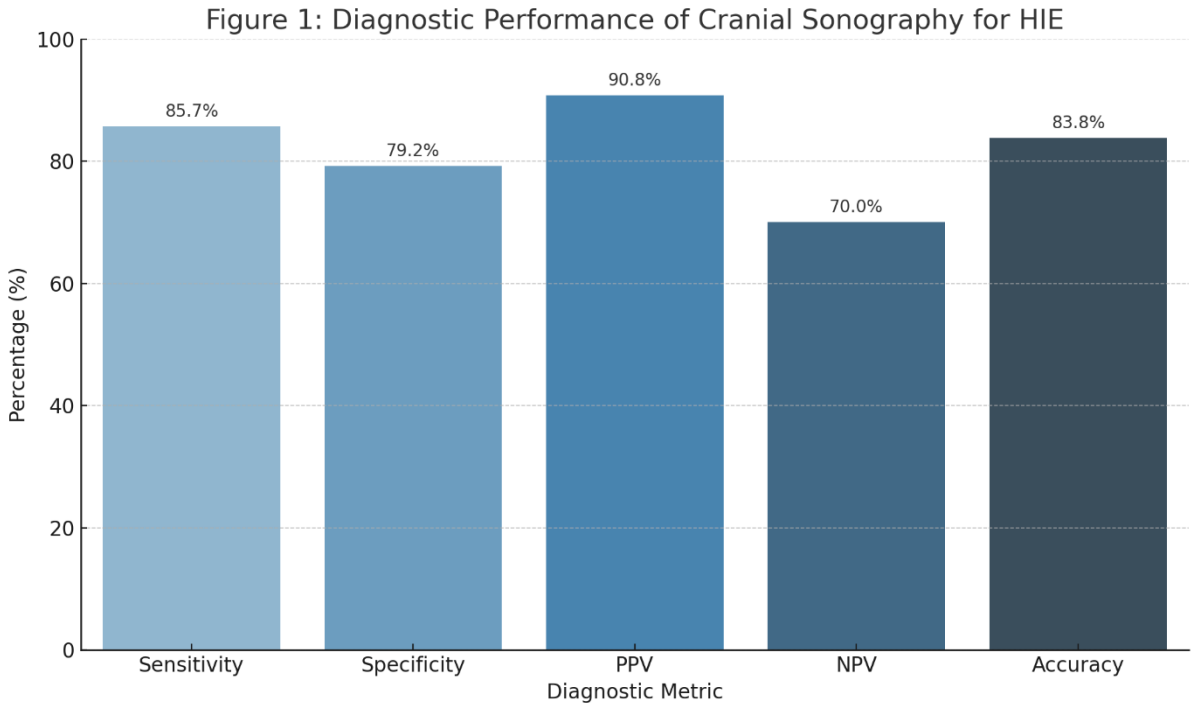

Figure 1: Diagnostic performance metrics of cranial sonography for the detection of hypoxic ischemic encephalopathy (HIE) in premature neonates

Figure 1 is a bar graph showing some of the important diagnostic parameters of sensitivity (85.7%), specificity (79.2%), PPV (90.8%), NPV (70.0%), and overall accuracy (83.8%) of cranial sonography for diagnosing HIE among clinically suspected premature infants. The results confirm that cranial ultrasound has a high predictive value and an acceptable overall accuracy for use as a screening modality in settings where there is limited availability of MRI.

Table 3: Diagnostic accuracy measures of cranial sonography for the detection of hypoxic ischemic encephalopathy using MRI as the gold standard

Metric	Formula	Value (%)
Sensitivity	108 / (108 + 18)	85.7
Specificity	42 / (42 + 11)	79.2
PPV	108 / (108 + 11)	90.8
NPV	42 / (42 + 18)	70
Accuracy	(108 + 42) / 179	83.8

The diagnostic performance for cranial sonography in the diagnosis of HIE in premature neonates is summarised in Table 3, showing each of the metrics, the formula for its calculation, and the percentage value of the metric. Sensitivity, specificity, PPV, NPV, and overall accuracy were calculated from the data in the 2×2 contingency table using MRI as the reference modality.

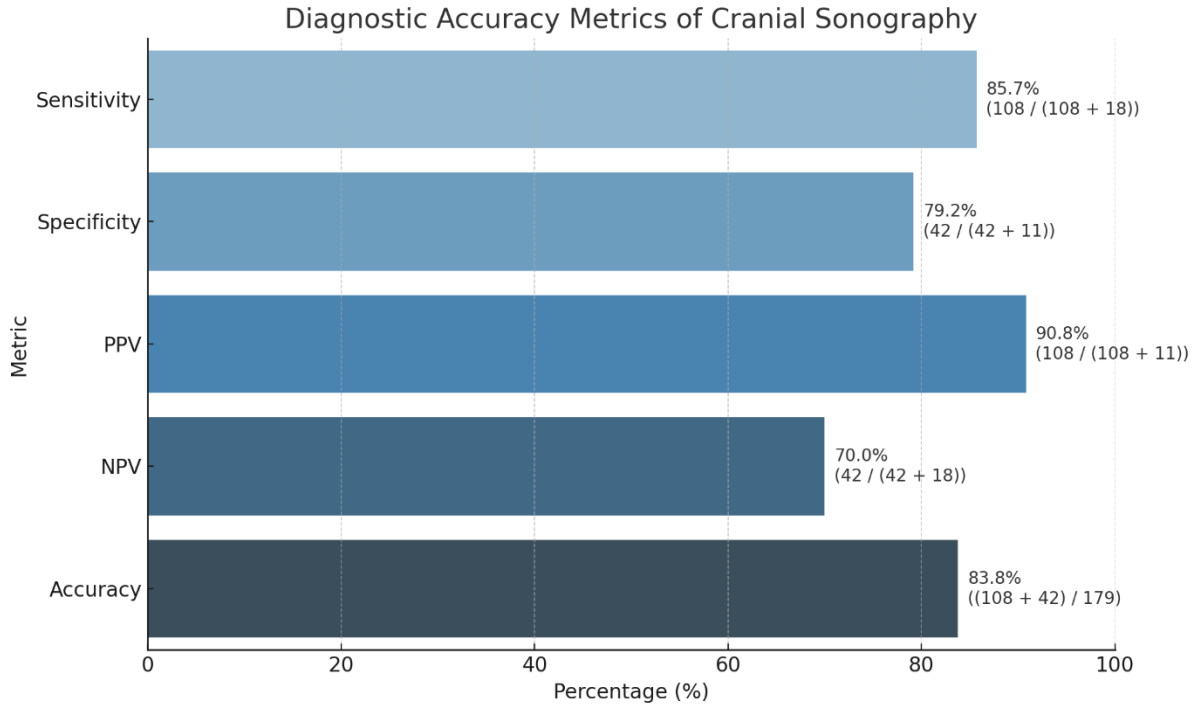

Figure 2: Bar graph representing diagnostic metrics of cranial sonography for hypoxic ischemic encephalopathy (HIE) in premature neonates.

Figure 2 represents the key diagnostic parameters, of sensitivity (85.7%), specificity (79.2%), PPV (90.8%), NPV (70.0%), and accuracy (83.8%). It also represents how they were calculated. The figure reflects the performance of cranial sonography compared to MRI, highlighting its potential as an initial screening tool in a neonatal care setting which have scarce resources.

Discussion

The present study attempts to assess the diagnostic validity of CUS against MRI for diagnosing HIE in premature neonates. The results indicate that CUS has a sensitivity of 85.7% and specificity of 79.2%, with an overall diagnostic accuracy of 83.8%. These findings suggest that CUS is a reliable, available, and inexpensive imaging tool in the early diagnosis of HIE, particularly in resource-poor settings where MRI may not be available.

These results indicate high sensitivity and PPV, at 90.8%, and agree with the findings by Yasin et al., where a sensitivity of 91.7% and specificity of 96.0% were observed in the diagnosis of HIE in premature neonates using cranial ultrasound,

compared to MRI as the standard reference (1). In line with this, Thakkar et al. found CUS to have a sensitivity of 93.3% and specificity of 92.6%, further advocating for its role in routine neonatal screening (2). This extends previous data that cranial ultrasonography is able to reveal early structural abnormalities related to ischemic injury in neonates, particularly in the periventricular white matter and basal ganglia.

Besides, the findings of Mahantesh et al., (3) are supportive of our observations. The authors assessed 40 term neonates and concluded that although duplex sonography had a limited sensitivity in mild HIE, it showed a predictive accuracy of 77% in moderate HIE and 100% in severe HIE cases. The study also put forth the use of cerebral resistive index (RI), as measured by Doppler ultrasound, which correlated significantly with the severity of the disease, as an RI > 0.9 was uniformly associated with severe hypoxic injury. This is in concordance with our observation that CUS tends to be more sensitive for moderate to severe grades of the condition. Fox et al. (4) demonstrated the diagnostic precision of 84% for CUS and described diffuse echogenicity, loss of sulcal markings, and ventriculomegaly among major sonographic features. Epelman et al. (5) have further documented that, when performed by an experienced radiologist, CUS is capable of diagnosing early changes of HIE within the first 24-48 hours of life, much before MRI is possible. All these studies put together reinforce the role of CUS, augmented by the use of Doppler, in the early diagnosis and grading of the disease, thus facilitating timely clinical intervention in the neonate.

However, not all studies have demonstrated such high diagnostic reliability for CUS. For example, Kamal Aun et al., found lower specificity (66.7%) and NPV (40%) for cranial ultrasound compared with MRI, suggesting that subtle or deep injuries to the brain, including the posterior fossa and internal capsule, may be poorly detected by CUS (6). Similarly, Krishan et al. found limitations of CUS in depicting cortical and subcortical white matter regions, and its diagnostic accuracy was only 72% (7). These differences might be due to variations in operator expertise, the resolution of the sonographic equipment used, the gestational age of patients, and the timing of imaging with regard to the hypoxic insult.

The main limitation of cranial sonography is its lower sensitivity for the detection of late subacute or chronic stages of injury to the brain. MRI, particularly DWI studies, provides better characterization of delayed or evolving ischemic changes and helps in prognostication, which sonography cannot reliably provide (8, 9). However, MRI utility is often limited by availability, the need for sedation, cost, and the complexity of logistics in critically ill neonates, especially in developing countries.

In our study, 11 neonates were classified as falsely HIE positive on CUS but did not demonstrate any evidence of injury on MRI. These false positives may be related to transient cerebral edema or increased echogenicity due to other causes such as metabolic encephalopathy or infection. In contrast, the 18 false negatives illustrated the limitations of CUS in detecting focal or subtle lesions. Although CUS is an excellent screening tool, it should not be substituted for MRI; rather, it should serve as the initial modality awaiting conclusive imaging. These findings have clinical significance. Where MRI is not readily available, or the acquisition of MRI will take time, cranial sonography can offer a pragmatic option for early diagnosis and management of neonates with suspected HIE in a given practice scenario. It also facilitates timely application of neuroprotective strategies, including therapeutic hypothermia, monitoring for seizures, and other supportive measures. At the same time, appropriate emphasis needs to be placed on training and standardization of ultrasound protocols to reduce operator dependence and variability.

The present study has a number of limitations. First, it was performed in a single tertiary care center, which may limit its generalizability to other healthcare environments with different levels of radiologic expertise and equipment quality. Second, although the MRI was used as a gold standard, it was performed only once per neonate, without follow-up imaging in order to detect evolving or late-onset lesions, thus not detecting some delayed manifestations of HIE. Third, inter-observer variability in interpreting cranial sonography findings was not analyzed, which could affect reproducibility in various

clinical environments. Moreover, the current study did not stratify results according to the timing of imaging in relation to the hypoxic insult, which may affect sensitivity, especially in the early postnatal period. Lastly, the inability to correlate these findings with long-term neurodevelopmental outcomes limits the assessment of the prognostic utility of cranial ultrasound findings.

Conclusion

For the detection of hypoxic ischemic encephalopathy in premature neonates, Cranial sonography demonstrates good sensitivity and specificity. It serves as an important initial imaging modality in resource-constrained settings. With 83.8% of overall diagnostic accuracy, it can be effectively used for early screening of HIE. Its limitations, however, in the identification of subtle or deep brain lesions emphasize the complementary role of MRI when available. Future multicenter studies with larger sample sizes, including blinded image interpretation and correlation with neurodevelopmental follow-up studies, are recommended to confirm and further delineate the role of cranial ultrasound in the neonatal HIE diagnostic pathway.

Declarations

Ethical Approval:

This study was approved by the Ethical Review Board of Bacha Khan Medical College, Mardan (Approval No. 426/BKMC).

Informed Consent:

Written informed consent was obtained from all study participants prior to inclusion in the study.

Conflict of Interest:

The authors declare no conflict of interest related to this study.

Funding:

No external funding was received for this research.

Authors' Contribution:

All authors contributed substantially to the conception and design of the study, data acquisition, analysis, and interpretation. All authors participated in drafting or critically revising the manuscript for important intellectual content, approved the final version for publication, and agree to be accountable for all aspects of the work.

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