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Original Research Article

Evaluation of Neonatal Hypoxic and Ischemic Injuries with Transcranial Ultrasonography

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Abstract:

Introduction: Neonatal hypoxic-ischemic injuries (NHII) are a major cause of long-term neurological deficits and developmental disabilities, often resulting from perinatal oxygen deprivation. Hypoxic-ischemic encephalopathy (HIE) is the most severe form, contributing to significant neonatal morbidity and mortality. Transcranial ultrasonography (TUS) offers a non-invasive, radiation-free imaging modality for evaluating NHII, providing real-time insights into cerebral structures and blood flow dynamics, making it valuable for bedside assessment and monitoring in critically ill neonates.

Material and Methods: This prospective observational study evaluated neonatal hypoxic and ischemic brain injuries using transcranial ultrasound and color Doppler over 15 months, involving 116 neonates with birth asphyxia or suspected hypoxic-ischemic injury. The study included bedside ultrasound assessments on day 3, followed by scans on day 7, and at 1st, 2nd, and 3rd months, to detect brain abnormalities like hemorrhages, periventricular leukomalacia, and blood flow irregularities. The data were analyzed using SPSS, with statistical significance set at $p < 0.05$.

Results: The study found that 67.52% of neonates were male and 32.48% were female. The most common antenatal finding was a normal USG (52.99%), followed by fetal growth restriction (17.09%) and other conditions like abruptio placenta (10.26%). Preterm births comprised 50.43%, and vaginal deliveries accounted for 65.81% of cases. Color Doppler showed normal resistive index (RI) in 82.76% and normal peak systolic velocity (PSV) in 81.90% of cases. MRI findings revealed Grade I Periventricular Leukomalacia (PVL) in 76.47%, while USG findings correlated significantly with lower APGAR scores, particularly for PVL. The sensitivity and specificity of USG in detecting PVL were notable, with USG showing high sensitivity for early detection of PVL and moderate specificity when compared to MRI findings.

Conclusion: In conclusion, our study emphasizes the importance of early detection and monitoring for managing neonatal hypoxic-ischemic injuries. Preterm and low birth weight infants are particularly vulnerable to brain injuries like PVL and GMH. Maternal comorbidities and mode of delivery also significantly influence risk. While MRI is superior for detailed imaging, USG proves valuable for early bedside diagnosis, especially in urgent settings.

Keywords: Hypoxic-Ischemic Injuries, Periventricular Leukomalacia (PVL), Transcranial Ultrasonography (USG).

Introduction

Neonatal hypoxic-ischemic injuries (NHII) present a significant challenge in neonatal medicine, often leading to long-term neurological deficits and developmental disabilities. [1] These injuries occur due to a deprivation of oxygen and blood flow to the infant's brain during the perinatal period, resulting in cellular damage and potential neurodevelopmental impairment. [2] NHII remains a leading cause of mortality and morbidity among newborns globally, necessitating accurate and timely diagnosis to mitigate adverse outcomes. [3,4] Transcranial ultrasonography (TUS) has emerged as a promising non-invasive imaging modality for evaluating neonates with suspected NHII, offering real-time visualization of cerebral structures and blood flow dynamics. [5]

The perinatal period represents a critical window of vulnerability for the developing brain, during which any insult to cerebral oxygenation and perfusion can have profound and lasting consequences.[6] Hypoxic-ischemic encephalopathy (HIE) is the most severe form of NHII, characterized by global cerebral hypoxia and ischemia, often resulting from events such as birth asphyxia or placental insufficiency. [7] Conventional neuroimaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) scans are valuable but may not always be feasible in the neonatal setting due to factors such as the need for sedation, transport risks, and limited availability. [8] TUS offers a radiation-free, bedside alternative with the potential for rapid assessment and serial monitoring of neonatal brain injury. [5]

Neonatal encephalopathy presents with a spectrum of neurological disturbances in the early days of life, encompassing feeding difficulties, irritability, abnormal tone, seizures, and altered consciousness, often compounded by respiratory challenges. [9] When attributed to diffuse hypoxic-ischemic brain injury, it is termed hypoxic-ischemic encephalopathy (HIE), a significant contributor to cerebral palsy and severe neurological impairments in children, with an incidence ranging from 2 to 9 per 1000 live births, and a particularly high rate of occurrence in premature infants, constituting 60% of all live births. [10,11] The TUS is readily accessible, cost-effective, and does not require sedation or contrast agents, making it particularly suitable for use in critically ill neonates. However, the utility of TUS in diagnosing NHII remains an area of ongoing research, with variable sensitivity and specificity reported across studies. [5] Our study aims to assess the effectiveness of TUS in diagnosing and monitoring neonatal hypoxic and ischemic injuries, thereby improving clinical decision-making and patient outcomes.

Material and Methods

This was a prospective observational study conducted in the Department of Radiodiagnosis to evaluate neonatal hypoxic and ischemic brain injuries using transcranial ultrasound and color Doppler. The study was carried out over 15 months following ethical approval, with an additional 3 months for data compilation, analysis, and result finalization. The study included all preterm and term neonates admitted to the Neonatal Intensive Care Unit (NICU) with a history of birth asphyxia or clinical suspicion of hypoxic and ischemic brain injury. The calculated sample size was 107 neonates, with a 10% additional allowance for potential loss to follow-up. Total 116 subjects were taken.

Inclusion Criteria: Preterm and term neonates with a documented history of birth asphyxia. Neonates clinically suspected of hypoxic and ischemic brain injury without a definite history of birth asphyxia. **Exclusion Criteria:** Neonates older than 28 days, Neonates with a normal cry, Neonates whose parents did not consent to participate in the study. All neonates meeting the inclusion criteria were evaluated using bedside transcranial ultrasound and color Doppler. The initial ultrasound examination was performed on the 3rd day of life, with follow-up scans scheduled on the 7th day and subsequently at the 1st, 2nd, and 3rd months, depending on the initial findings.

Bedside transcranial ultrasound was performed using a high-frequency transducer (3.5–12 MHz) to obtain high-quality images of the neonatal brain. This modality allowed comprehensive visualization of the entire brain, detecting intracranial and intraventricular hemorrhages, periventricular leukomalacia (PVL), and other hypoxic-ischemic injuries. The use of color Doppler facilitated the assessment of blood flow abnormalities, including resistive index (RI), peak systolic velocity (PSV), and end-diastolic velocity (EDV) of the middle cerebral artery (MCA).

All eligible neonates were evaluated in the radiology outpatient department or bedside in the NICU, based on their clinical condition. A detailed clinical evaluation was conducted, including. Details of maternal comorbidities, antenatal ultrasound findings, history of any similar insults in previous pregnancies, and any antenatal drugs or treatments taken. Mode of delivery (LSCS/vaginal), presence of complications (e.g., cyanosis, jaundice, seizures), and general examination parameters (e.g., heart rate, respiratory rate, oxygen saturation). Included muscle tone, posture, Moro's reflex, and autonomic features such as heart rate and bronchial secretions.

Each neonate was graded according to the extent of brain involvement based on ultrasound findings. Key findings recorded included echogenicity, ventricular dilation, periventricular echogenicity, periventricular cysts, and subcortical cysts. Color Doppler findings included measurements of RI, PSV, and EDV of the MCA. Follow-up scans were conducted at 1st, 2nd, and 3rd months to detect both early and late changes associated with hypoxic-ischemic encephalopathy (HIE), particularly in neonates with abnormalities detected on earlier scans.

The study was approved by the institutional ethics committee. Written informed consent was obtained from the parents or guardians of all participating neonates. No blood samples were taken, and there was no risk of radiation exposure as ultrasound is a non-invasive and safe imaging modality. Data were compiled and analyzed using SPSS version 24. Statistical significance was set at a p-value of less than 0.05.

Results

The majority of the neonates in the study were male, accounting for 67.52% of the sample, while female neonates comprised 32.48%. The most common finding was a normal antenatal USG, observed in 52.99% of the cases. FGR was the second most frequent finding, appearing in 17.09% of the cases.

Other notable conditions include Abruptio Placenta (10.26%), high resistance flow (5.98%), and Breech presentation (4.27%). Each of the remaining conditions, including Placenta Previa, Short Cervix, VSD, and others, had lower frequencies. The majority, 42.74%, had no comorbidities. The most common comorbidity was preeclampsia, affecting 17.09% of the mothers. Other notable conditions included gestational hypertension (8.55%), advanced maternal age (7.69%), and gestational diabetes mellitus (6.84%). A significant majority, 79.49%, reported no previous incidents of similar insults. Meanwhile, 20.51% had a history of similar insults in previous pregnancies.

In our study, the majority of the neonates were preterm, accounting for 50.43% of the cases, while 44.44% were term. Post term births comprised 5.13% of the cases. Oligohydroamnios was present in 49.57% of cases, followed by normal liquor in 43.59%. Polyhydroamnios was observed in 5.98%, while adequate liquor was noted in 0.85% of the cases. The majority of deliveries were vaginal, accounting for 65.81% of the cases. LSCS (Lower Segment Cesarean Section) deliveries comprised 34.19%.

Table 1

Parameter	Mean ± SD / Frequency (%)	Test Name	p-value
APGAR Score (1st minute)	4.91 ± 1.55	t-test	0.001
APGAR Score (5th minute)	7.29 ± 1.42	t-test	
Below 6 (1st minute)	76 (64.96%)	Chi-square	0.001
Below 6 (5th minute)	11 (9.40%)	Chi-square	
6 or more (1st minute)	41 (35.04%)	Chi-square	0.001
6 or more (5th minute)	106 (90.60%)	Chi-square	

In our study, 89.74% of neonates did not exhibit cyanosis, while 10.26% did. Seizures were absent in 69.23% of neonates, with 30.77% experiencing them. Most neonates (72.65%) had normal vitals, while 27.35% had abnormal vitals. Normal heart rates were observed in 58.12% of cases, with the remaining 41.88% exhibiting abnormal rates. Bilateral air entry was normal in all neonates (100%). Muscle tone was normal in 59.83% of cases and abnormal in 40.17%. The Moro's reflex was normal in 59.83% of neonates, and abnormal in 40.17%.

Table 2: Neonatal USG Findings

Parameter	Category	Frequency	Percentage (%)
Germinal Matrix Hemorrhage	Absent	91	77.78
	Present	26	22.22
GMH Grade	None	93	79.49
	Grade 1	14	11.97
	Grade 2	6	5.13
	Grade 3	2	1.71
	Grade 4	1	0.85
	Not done	1	0.85
Periventricular Leucomalacia	Absent	92	78.63
	Present	21	17.95
	Not done	1	0.85
Periventricular Leukomalacia Grade	None	95	81.20
	Grade 1	13	11.11
	Grade 2	3	2.56
	Grade 3	2	1.71
	Grade 4	3	2.56
	Not done	1	0.85
Periventricular cyst	Absent	106	90.60
	Present	9	7.69
	Not done	1	0.85
Total	**-**	**117**	**100.00**

The study's Color Doppler findings revealed that the majority of participants had normal Resistive Index (RI) and Peak Systolic Velocity (PSV) values in the Middle Cerebral Artery (MCA). Specifically, 82.76% of participants exhibited a normal RI, while 17.24% had a decreased RI. Similarly, 81.90% showed normal PSV, with 18.1% demonstrating an increased PSV.

Table 3: Color doppler findings

Color doppler findings	Category	Frequency (n)	Percentage (%)
RI (Resistive Index) of MCA (Middle Cerebral Artery)	Normal	96	82.76
	Decreased	20	17.24
PSV (Peak Systolic Velocity) of MCA (Middle Cerebral Artery) cm/s	Normal	95	81.90
	Increased	21	18.1
	Total	116	100%

The MRI findings in the study predominantly indicated Grade I Periventricular Leukomalacia (PVL), observed in 76.47% of the cases. Less frequent findings included Grade IV PVL in 11.76%, Grade II PVL in 5.88%, and a combination of Grade I Germinal Matrix Hemorrhage (GMH) with Grade I PVL in 5.88% of the cases.

USG Efficacy for Identifying Hypoxic Ischemic Injury Findings

Metric	GMH	PVL	Periventricular cyst
Sensitivity	78.95%	69.75%	65.56%
Specificity	59.18%	62.48%	63.70%
PPV	27.27%	12.73%	9.09%
NPV	93.55%	85.48%	93.55%

The study's analysis of USG findings in relation to APGAR scores revealed significant correlations. For periventricular cysts, a positive finding was more frequent with lower APGAR scores (<7), observed in 18.92% of cases, and less common with higher APGAR scores (>7), at 2.56%. The correlation coefficients were 0.272166 for scores <7 and -0.272166 for scores >7, both with a P-value of 0.002992, indicating a modest but significant correlation. Germinal Matrix Hemorrhage (GMH) showed no significant correlation with APGAR scores, with similar frequencies in both groups and correlation coefficients close to zero. Periventricular Leucomalacia (PVL) was significantly more common with lower APGAR scores (47.22%), strongly correlated with a coefficient of 0.472456 and a highly significant P-value. PVL findings were rare in higher APGAR scores (>7), occurring in only 5.19% of cases.

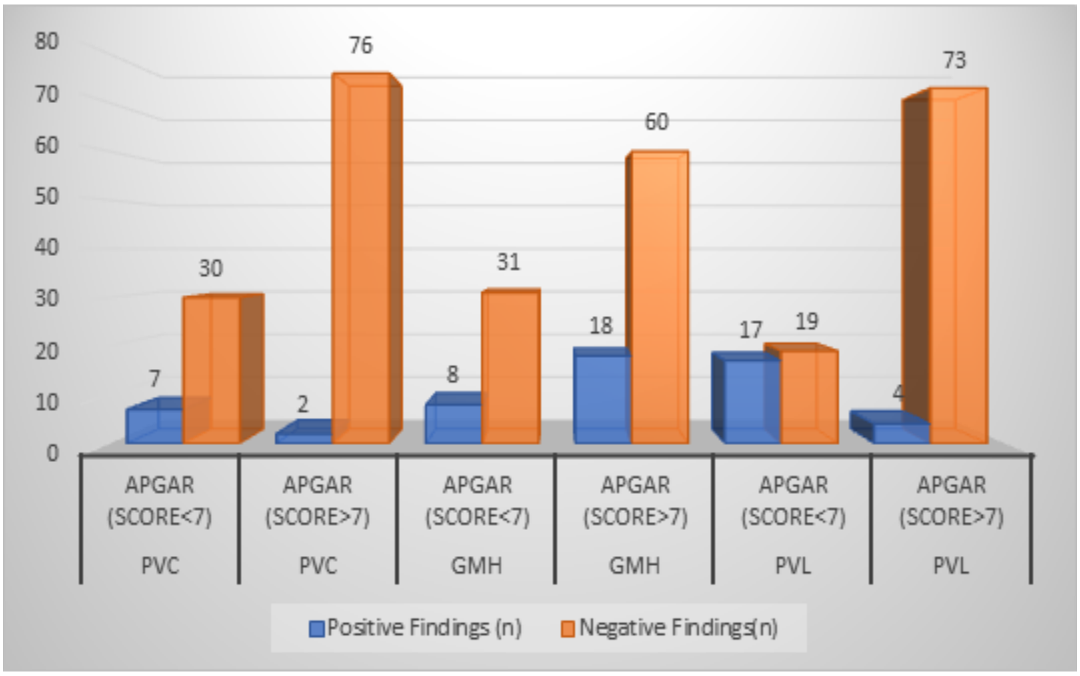

Fig 1: USG Findings with Correlation to APGAR Scores (n)

The follow-up of study subjects over three months revealed varying outcomes. In the first month, the most common findings were "Normal" (55.56%) and "Not done" (23.93%), with 6.84% of subjects passing away. By the second month, "Not done" rose significantly to 56.41%, while "Normal" decreased to 31.62%. Grade I PVL was observed in 7.69% during the first month, dropping to 3.42% in the second and 0.87% in the third month. Mild ventriculomegaly increased over time, from 1.71% in the first month to 6.09% by the third month.

Discussion

In our study, male neonates represented a significant majority, comprising 67.52% of the sample, compared to 32.48% for female neonates. This male predominance is consistent with the general understanding that male neonates are often at a higher risk for various neonatal complications, including hypoxic-ischemic injuries, due to factors like developmental differences and hormonal influences. In contrast, Hossain et al. [12] (2020) reported a more balanced gender distribution, with 48% male and 52% female neonates. This balanced gender ratio suggests that, in their population, the risk factors for perinatal complications might be more evenly distributed between the sexes, or other underlying factors might influence the outcomes differently. Herma et al. [13] (2018) did not specifically report on the sex distribution, which could indicate a focus on other demographic factors or perhaps a more balanced or less relevant gender distribution in their sample. Additionally, Anany et al. [14] (2023) found a slightly different distribution in their study, with male neonates constituting 55% of their sample, reflecting a mild male predominance, which aligns more closely with our findings. This consistency further supports the notion that male neonates are more susceptible to conditions leading to hypoxic-ischemic injuries.

In our study, the most common conditions included preeclampsia (17.09%), gestational hypertension (8.55%), and gestational diabetes mellitus (6.84%). These findings underscore the critical role that maternal health plays in the development of neonatal hypoxic-ischemic injuries. A study by Hossain et al. [12] (2020) reported similar maternal comorbidities, with 8% of mothers experiencing pre-eclamptic toxemia and hypertension, and 6% with diabetes mellitus. This aligns closely with our findings, emphasizing the consistent impact of maternal hypertensive disorders and diabetes on neonatal outcomes.

Our study showed that 35.9% of the neonates were preterm, while 64.1% were term. This distribution is crucial as preterm neonates are generally more susceptible to hypoxic-ischemic injuries due to their immature organs, particularly the brain, which is more vulnerable to damage from insufficient oxygenation. Similarly, Hossain et al. [12] (2020) reported that 44% of the neonates in their study were preterm, with the remaining 56% being term. This slightly higher percentage of preterm neonates reflects the heightened vulnerability of this group to perinatal asphyxia and subsequent brain injuries.

In both our study and those by Hossain et al. [12] and Yasmin et al. [15], preterm neonates exhibited a higher incidence of conditions like periventricular leukomalacia (PVL) and intraventricular hemorrhage (IVH), which are common outcomes of hypoxic-ischemic events in this vulnerable population. These observations reinforce the need for targeted interventions to address the specific vulnerabilities of preterm infants to improve outcomes and reduce the incidence of severe neonatal brain injuries. Overall, the consistent findings across these studies emphasize the critical need for early and continuous monitoring of maternal and fetal health indicators such as liquor volume, infection status, and gestational age to effectively manage and reduce the risk of hypoxic-ischemic injuries in neonates.

In our study, 64.1% of neonates were term (≥37 weeks of gestation), while 35.9% were preterm (<37 weeks). This distribution is important as preterm neonates are generally more vulnerable to hypoxic-ischemic injuries due to their immature organs. Comparatively, Hossain et al. [12] (2020) reported a similar distribution with 56% term and 44% preterm neonates, highlighting the higher risk associated with preterm births. Yasmin et al. [15] (2016) also found a comparable distribution, with 56% term and 44% preterm neonates. The consistent observation across these studies emphasizes the significant risk that preterm birth poses for neonatal hypoxic-ischemic injuries.

In our study, the overall incidence of Germinal Matrix Hemorrhage (GMH) was 22.22%, with most cases being Grade I (11.97%), followed by Grade II (5.13%), Grade III (1.71%), and Grade IV (0.85%). This pattern suggests that while GMH was present in a significant portion of neonates, the majority were mild cases. Compared to other studies, such as Hossain et al. [12] (2020), which reported a 14% incidence of GMH among preterm neonates, our study shows a higher prevalence, likely due to the inclusion of both term and preterm neonates. Sharma et al. [16] (2022) found a 17% overall incidence of GMH, with most cases being Grade I (41%) hemorrhages, followed by Grade II and III (23.5% each) and Grade IV (11.7%). This grading distribution mirrors the trend in our study, where less severe grades were more common. These similarities and differences across studies may result from variations in neonatal care practices, demographic factors, and criteria for grading hemorrhages.

The importance of early detection and grading of GMH in neonates is emphasized by these studies, as the presence and severity of hemorrhage can significantly affect neurodevelopmental outcomes. Sharma et al. [16] (2022) highlights the sensitivity of neurosonography in detecting GMH, particularly in preterm infants, aligning with our findings where a substantial proportion of mild cases (Grades I and II) were identified. Collectively, these studies underscore that GMH is a common finding in neonatal brain injury assessments, and its incidence may vary depending on the population studied and the diagnostic criteria employed. The higher prevalence of GMH in our study may also reflect the inclusion of a broader neonatal population, encompassing both preterm and term neonates, compared to other studies that focus primarily on high-risk or preterm infants.

In terms of Periventricular Leukomalacia (PVL), our study reported an overall incidence of 17.95%, with the majority of neonates (81.20%) showing no signs of PVL. Among those affected, 11.11% had Grade I PVL, while Grades II, III, and IV were less common (2.56% each for Grades II and IV, and 1.71% for Grade III). This distribution indicates that while PVL is relatively uncommon, it is predominantly mild when it does occur. In contrast, Hossain et al. [12] (2020) reported a notably higher incidence of PVL at 29%, but this was specifically among preterm neonates, reflecting their greater susceptibility to hypoxic-ischemic brain injuries and immature cerebral vascular structures, which are more prone to ischemic damage. Sharma et al. [16] Study (2022) observed a lower overall incidence of PVL at 14%, which is closer to our study's findings, highlighting that the prevalence can vary depending on the specific neonatal population studied, the clinical settings, and the criteria for PVL diagnosis.

In our study, abnormal Color Doppler findings, particularly high resistance flow in the umbilical artery, were associated with worse neonatal outcomes, indicating significant compromise in fetal blood flow. Herma et al. [13] (2018) supported these findings, showing that transcranial Doppler studies effectively detected early hypoperfusion, which correlated with poor outcomes in neonates with hypoxic-ischemic encephalopathy (HIE). Sultana et al. [17] (2020) also emphasized the role of Doppler studies in predicting the extent of neonatal brain injury and guiding timely interventions. Okasha et al. [18] (2024) further highlighted that while MRI remains the gold standard for diagnosing brain injuries, Doppler ultrasound is invaluable for real-time monitoring and early detection of at-risk neonates.

The comparison reveals variations in the diagnostic performance of USG across different studies. For GMH, our study reported a sensitivity of 78.95%, which is lower than the 85.00% reported by Hossain et al. (2020) but close to the 80.00% reported by Sharma et al. [16] (2022). This suggests that while USG is generally effective in detecting GMH, the sensitivity may vary depending on the study population, setting, and operator expertise. Specificity for GMH in our study was 59.18%, while Sharma et al. [16] (2022) reported a slightly higher specificity of 65.00%, indicating moderate effectiveness in correctly identifying patients without GMH. PPV and NPV values also differ across studies, with Sharma et al. [16] (2022) showing a higher PPV (30.00%) and NPV (95.00%) compared to our study, suggesting greater reliability in both confirming and ruling out GMH when present.

For PVL, our study demonstrated a sensitivity of 69.75%, which is somewhat lower than the 72.00% reported by Hossain et al. [12] (2020). The specificity was similar, with our study at 62.48% and Hossain et al. (2020) at 60.00%, indicating comparable accuracy in detecting true negatives. The PPV for PVL was low across both studies, with our study at 12.73% and Hossain et al. [12] (2020) at 15.00%, reflecting challenges in accurately diagnosing PVL given its lower prevalence and potentially subtle sonographic findings. The NPV values were relatively high in both studies (85.48% in our study and 88.00% in Hossain et al. (2020)), suggesting that USG is effective in ruling out PVL when findings are negative. These variations highlight the importance of considering multiple factors, such as patient demographics, clinical context, and technological differences, when interpreting USG findings in neonatal brain injury assessments. In our study, we found a significant correlation between USG findings and APGAR scores, where lower APGAR scores at 1 and 5 minutes were strongly associated with more severe hypoxic-ischemic injuries detected on ultrasound. Neonates with APGAR scores below 5 at 1 minute frequently showed abnormalities such as periventricular leukomalacia (PVL) and cerebral edema on USG, indicating that these lower scores were predictive of more severe brain injuries. This correlation suggests that APGAR scores, which are quick and easily accessible indicators of neonatal well-being immediately after birth, can be a useful predictor of the severity of hypoxic-ischemic injuries.

One limitation of our study is that it primarily relied on transcranial ultrasound and colour Doppler for the detection of hypoxic-ischemic injuries, which, while effective, may not be as comprehensive as MRI in detecting subtle or deep brain injuries. Additionally, the study's follow-up period, though sufficient to observe early changes, may not capture long-term outcomes of neonatal brain injuries, limiting our ability to assess the full spectrum of neurodevelopmental impacts. Furthermore, the study was conducted at a single center, which may limit the generalizability of the findings to broader populations.

Conclusion

In conclusion, our study highlights the indispensable role of early detection and monitoring in managing hypoxic-ischemic injuries in neonates. The significant correlations observed between gestational age, birth weight, and the incidence of brain injuries such as PVL and GMH underscore the vulnerability of preterm and low birth weight infants to severe neurological outcomes. Additionally, the mode of delivery and maternal comorbidities were found to significantly influence the risk of these injuries, emphasizing the need for careful management of high-risk pregnancies and timely interventions during delivery to improve neonatal outcomes. While MRI provides superior detail and comprehensive imaging, which is critical for a thorough diagnosis, the strong alignment between USG and MRI findings demonstrates that USG is also a valuable tool, particularly for early diagnosis in settings where rapid bedside evaluation is essential.

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