Medicine Updates Faculty of medicine
July 2023,volume 14, issue 14
https://muj.journals.ekb.egdean@med.psu.edu.eg
vice_dean_postgraduate@med.psu.edu.eg
DOI: 10.21608/MUJ.2023.219149.1142

ISSN : 2682-2741

Submitted: 21 /06/2023
Accepted : 23/06/2023
Pages: 95 - 111

"Role of Trans-cranial Ultrasonography and Color Doppler in Diagnosis and Grading of Neonatal Hypoxic-Ischemic Encephalopathy"

Authors

Aliaa Anany [1], Mohamed Elrakhawy [2], Carmen Ali Zarad [3],

Waleed Said Abo Shanab [3]

[1] Elnasr Hospital Port Said

[2] Faculty of medicine Mansoura University

[3] Diagnostic radiology faculty of medicine Port Said University

ABSTRACT:

Objective: To evaluate the role of trans-cranial ultrasound and trans-cranial Doppler of the anterior and middle cerebral arteries in diagnosis and grading of hypoxic ischemic encephalopathy (HIE).

Methods: The study was conducted on 26 cases and 26 controls in the neonatal intensive care unit incubator of Al-Salam Hospital and at Al-Nasr hospital in Port Said governorate in Egypt. Each patient was subjected to full history taking, clinical examination, and transcranial ultrasound examination e.g., anterior cerebral artery and middle cerebral artery blood flow parameters using color Doppler flow image (CDFI), color Doppler energy (CDE), pulsed wave Doppler and measuring RI of both arteries.

Results: In 26 cases and 26 controls, there was statistically significant negative correlation between MCA RI and presence of HIE, and Apgar score. There was statistically significant positive correlation between MCA RI and both periventricular leukomalacia, and Periventricular leukomalacia grade.

There was statistically significant negative correlation between ACA RI and presence of HIE, and Apgar score, and statistically significant positive correlation between ACA RI and both of periventricular leukomalacia, periventricular leukomalacia grade, and Sarnat stages of HIE.

The mean right-side MCA, left-side MCA, and mean average MCA in control group were statistically significantly higher than the study group.

Conclusion: The newborn brain can be evaluated with trans-cranial ultrasonography and trans-cranial Doppler. For displaying the most typical types of cerebral damage in preterm neonates, gauging the lesion's progression, and monitoring brain growth, they are safe and reliable approaches. Early transcranial Doppler ultrasonography should be performed on neonates with HIE to predict the course of their clinical treatment.

Keywords: Encephalopathy, Ultrasonography, Doppler, Trans-cranial.

1. Introduction:

One of the main factors contributing to childhood neurological disorders is neonatal hypoxic-ischemic (HI) brain damage. It accounts for over half of all occurrences of cerebral palsy [(1)]. The most frequent cause of mortality and impairment in newborn humans is neonatal hypoxia-ischemia [(2)]. In addition, HIE is one of the leading causes of cerebral palsy and numerous severe neurological impairments, which affect 2 to 9 infants born alive every 1000 [(3)].

A reduction in mortality or severe impairment at the age of 18 months was shown in various randomised control studies using therapeutic hypothermia (TH) for HIE. However, regardless of the cooling therapy, 30% to 70% of newborns with moderate-to-severe encephalopathy may die or become disabled [(4,5)]. The progression of brain damage during hypoxia-ischemia begins with the hypoxic-ischemic insult and extends to the reperfusion phase during recovery [(6)].

Brain damage develops after a delay following hypoxic-ischemic insults, which is preceded by a time in which there are no symptoms or a brief improvement in the clinical picture immediately

following the insult. Before brain injury has fully developed, there is a window of opportunity for therapeutic intervention [7]. Therefore, it is essential to assess the newborn infant's hypoxia severity as soon as possible so that the appropriate care and treatment may be given before the ultimate harm occurs. Given that it is challenging to predict the duration and degree of asphyxia, it may be difficult to predict the level of organ damage that occurs soon after delivery based only on clinical signs [8].

A simple radiological technique with applicability for children who are severely unwell is ultrasound. The early diagnosis of developmental anomalies and the elimination of causes of encephalopathy other than hypoxia-ischemia are both aided by two-dimensional transcranial doppler ultrasonography (TCD) [9].

TCD is a non-invasive technology that enables frequent, safe evaluation of hemodynamics in newborn units. Numerous studies have demonstrated the high repeatability of the pulsed Doppler technique for the assessment of the pattern of blood flow velocity (BFV) in major brain arteries in newborns. Additionally, BFV results have therapeutic significance in interpreting the cardiovascular adaptation of disturbed newborn infants who have decompensated circulatory responses and the possibility for multi-organ failure, including brain injury [10].

The aim of the work is to evaluate the role of trans-cranial ultrasound and trans-cranial Doppler of the anterior and middle cerebral arteries in diagnosis and grading of hypoxic ischemic encephalopathy (HIE).

2. Materials and methods:

The study was conducted on 26 cases and 26 controls. In the neonatal intensive care unit incubator of Al-Salam Hospital and at Al-Nasr hospital in Port Said governorate in Egypt.

- **Data collection**

All neonates subjected to the study were undergoing the following:

- **History taken on (**Sex ,date of birth, Time between delivery and imaging: days /hours, Birth weight ,Gestational age at delivery (baby is preterm/full-term), Type of delivery: Normal or Caesarean Section, Is there is birth injury?, Mothers' problem during pregnancy or delivery: hypertensive/diabetic or others , Maternal age , Maternal body mass index (BMI), Hypoxic ischemic encephalopathy risk factor (resuscitation ,perinatal hypoxia and fetal acidosis)

- **Clinical examination**
    - Apgar Score: a method for standardized assessment for infants after delivery, usually recorded at minute, minute of age and after if needed). It is comprised of five components:(Color, Heart rate , Reflexes, Muscle tone, Respiration)
    - Neonate were be assessed clinically and classified according to the clinical spectrum of HIE as mild, moderate and severe according to Sarnat stages of HIE comprise of these components: alertness, muscle tone, seizure, pupils, respiration, duration, outcome.
- **Transcranial Ultrasound Examination**
    - The procedure was performed neonatal intensive care unit incubator using a linear 7-14 MHz transducer.
        - Transcranial ultrasound technique done in different views through the anterior fontanelle : Sagittal views (Midline Sagittal , parasagittal), Coronal views at level of (Anterior Horns of the Lateral Ventricles, The Third Ventricle, Level of Trigone)
    - Location of ultrasound abnormalities finding in hypoxic ischemic encephalopathy (periventricular leukomalacia PVL)
    - Detection of (ACA) and (MCA) blood flow parameters using color Doppler flow image (CDFI), color Doppler energy (CDE), pulsed wave Doppler (PWD) and measuring RI of both arteries

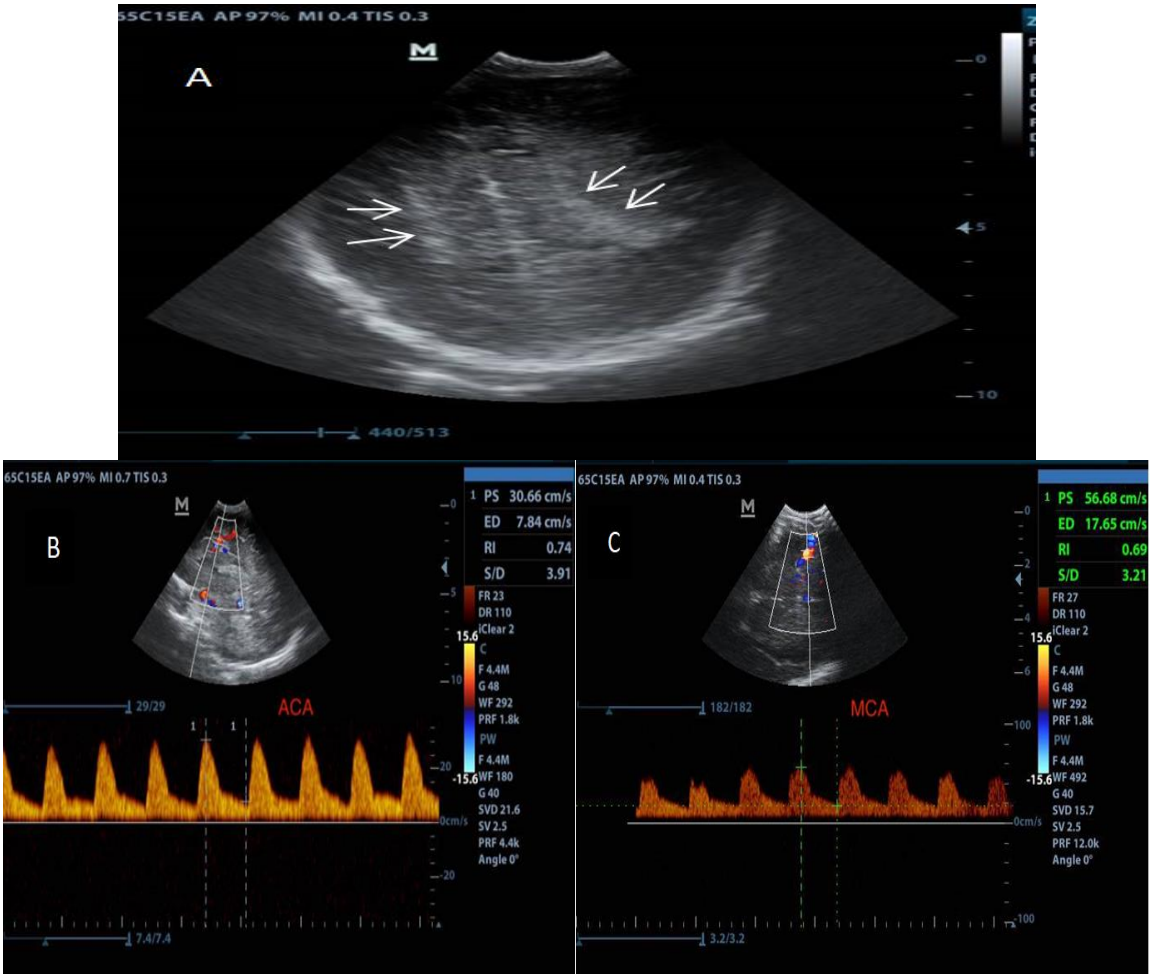

Figure 1: 10 days age (on the day scanning) , with mild degree of clinical severity ‘ Sarnat Staging ‘ (stage 1), and 6 (moderately abnormal) Apgar score (Recorded at 5 min). (A) Trans-cranial ultrasound (coronal view) through the anterior fontanelle showing increase periventricular echodensities (arrows) at 10th day denoting PVL grade I. (B) Trans-cranial Doppler ultrasound (TCD) showing pulsed Doppler of the middle cerebral artery (ACA) with RI 0.74. (C) Trans-cranial Doppler ultrasound (TCD) showing pulsed Doppler of the middle cerebral artery (MCA) with RI 0.69.

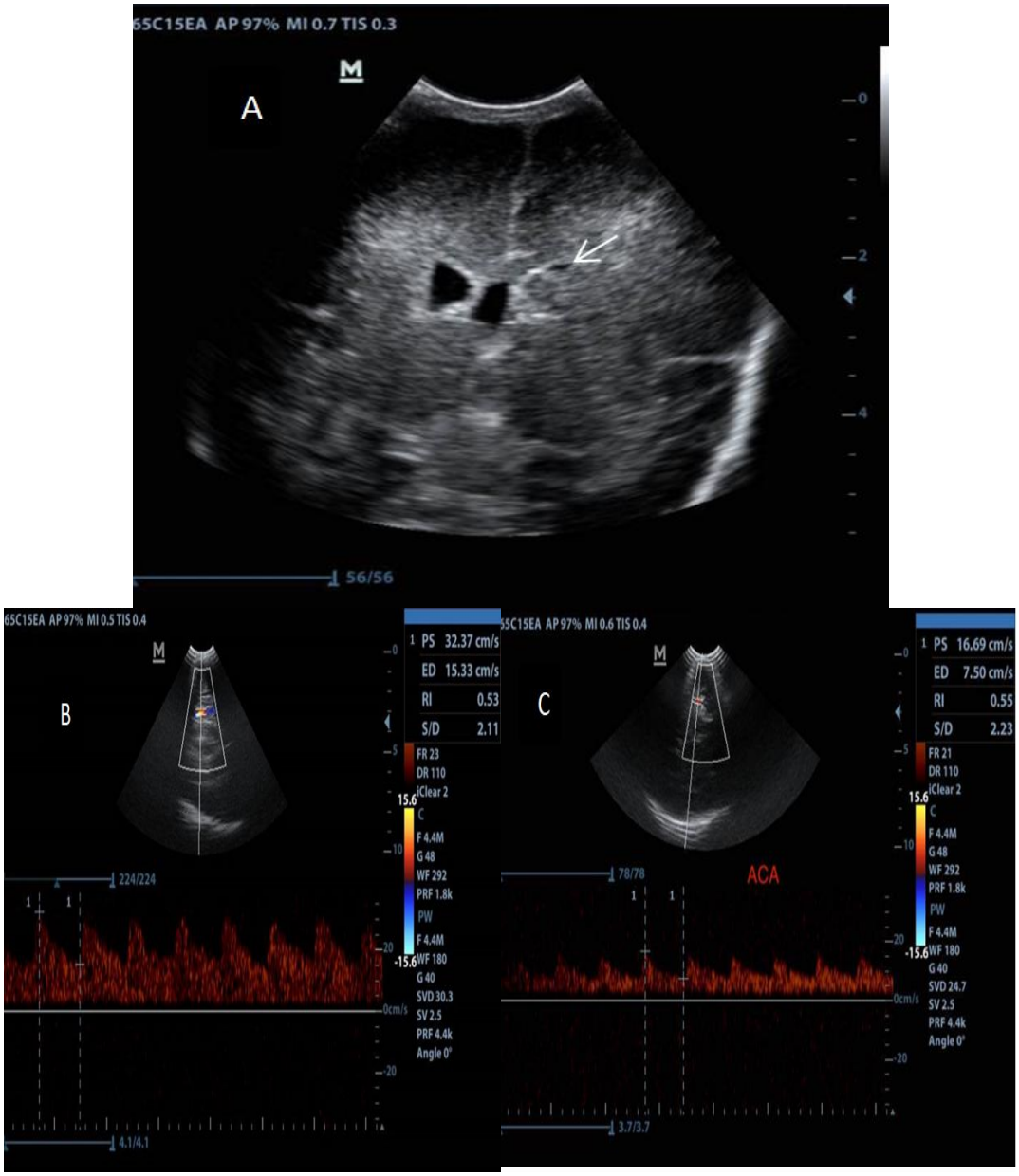

Figure 2: 11 days age (on the day scanning), with mild degree of clinical severity ‘ Sarnat Staging ‘ (stage 1), and 4 (moderately abnormal) Apgar score (Recorded at 5 min). (A) Trans-cranial ultrasound (sagittal view) through the anterior fontanelle showing increase periventricular echogencities with developing small periventricular cysts (white arrow) at 11th day denoting PVL grade II. (B) TCD showing color and pulsed Doppler of the ACA with RI 0.53. (C) TCD showing color and pulsed Doppler of the MCA with RI 0.55.

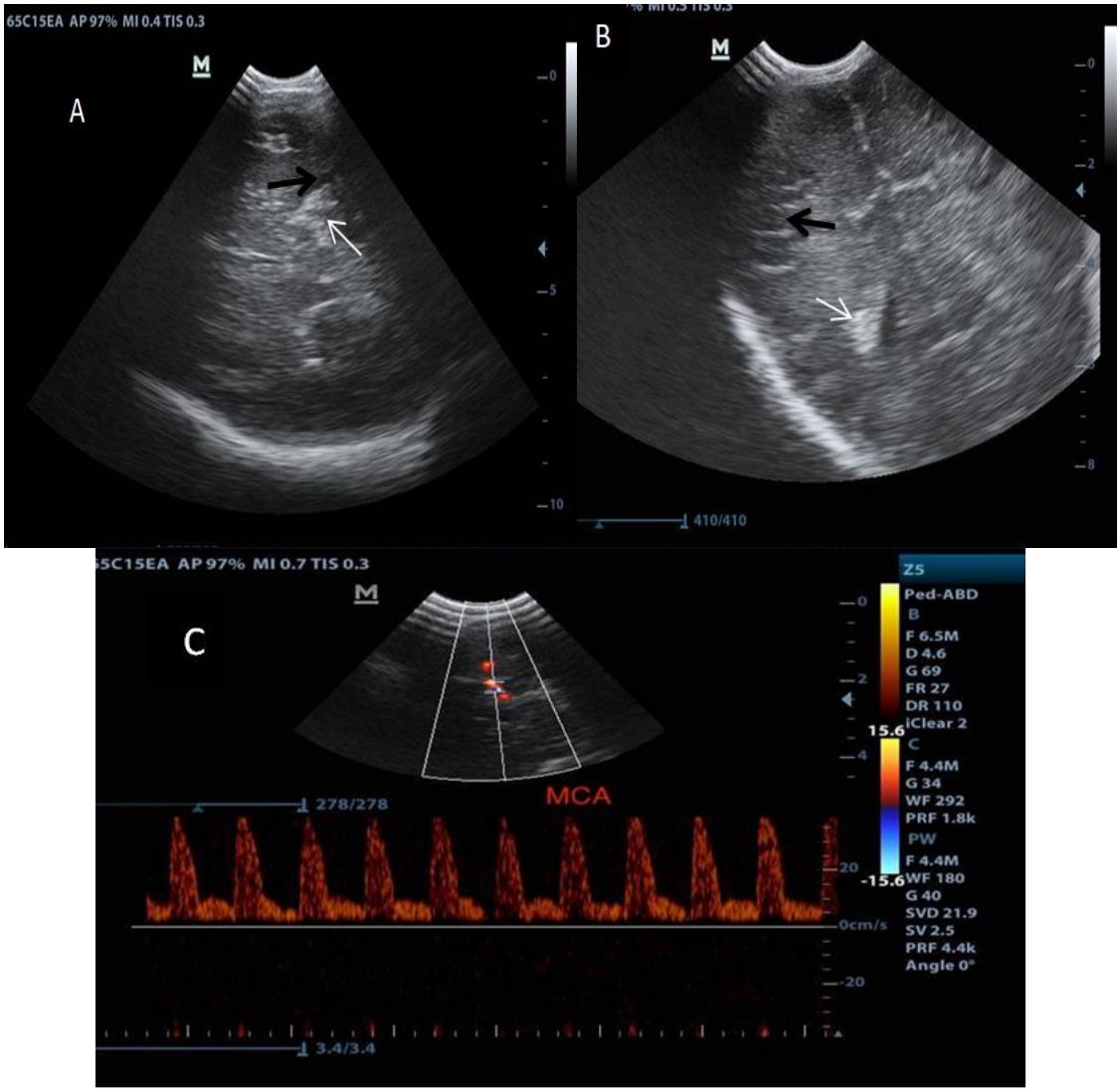

Figure 3: 15 days age (on the day scanning), with severe degree of clinical severity ‘ Sarnat Staging ‘ (stage 3), and 4 (moderately abnormal) Apgar score (Recorded at 5 min). (A,B)Transcranial ultrasound showing extensive increase in echogenicities (white arrows) and developing small cystic lesions (black arrows) involving fronto-parietal region , denoting PVL grade III. (C) TCD showing color and pulsed Doppler of the MCA with RI 0.85.

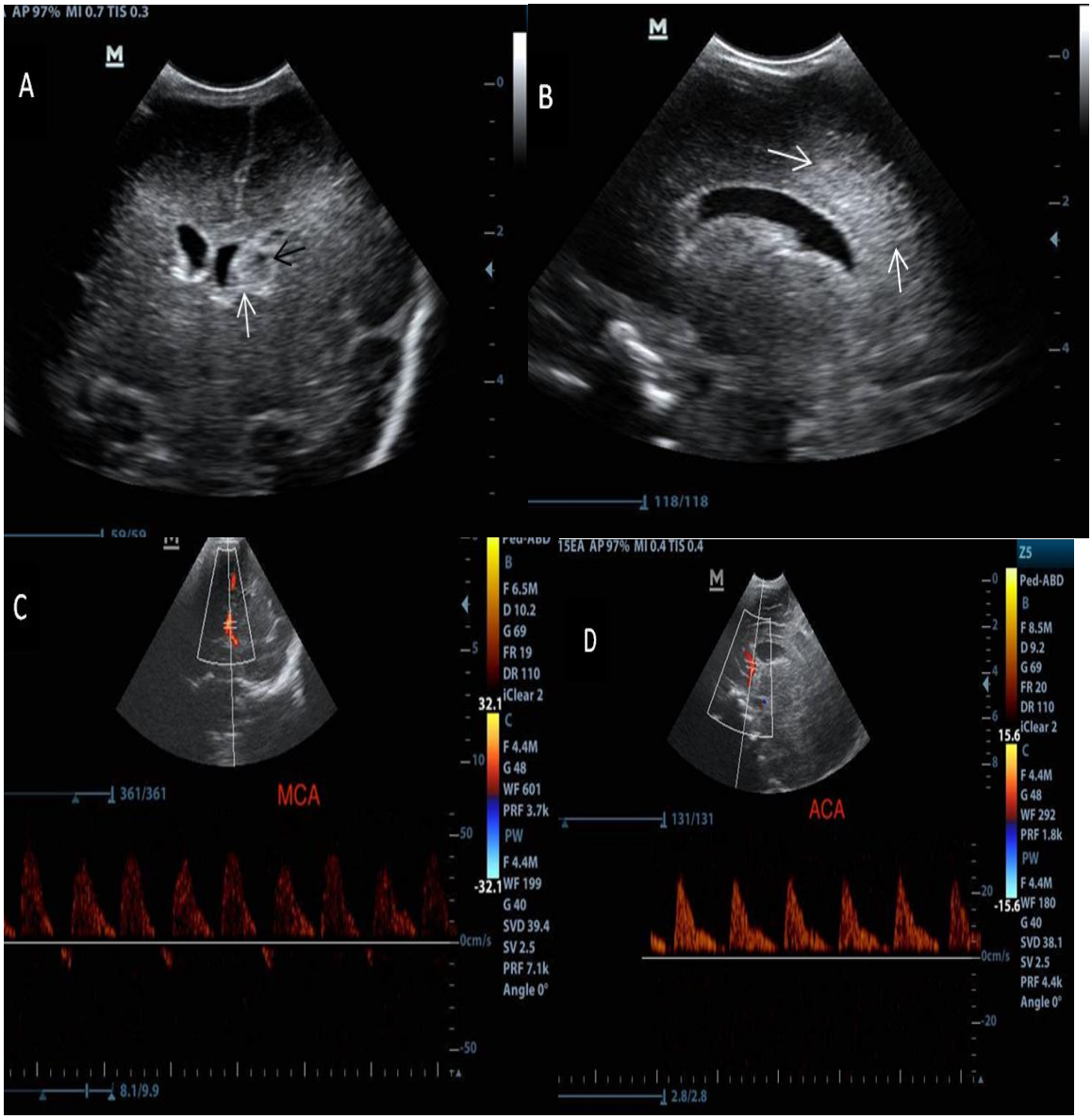

Figure 4: 20 days age (on the day scanning), with severe degree of clinical severity ‘ Sarnat Staging ‘ (stage 3), and 4 (moderately abnormal) Apgar score (Recorded at 5 min). (A,B) Transcranial ultrasound showing extensive increase in echogenicities (white arrows) and developing small cystic lesions (black arrow) involving fronto-parietal region , denoting PVL grade III. (C) TCD showing color and pulsed Doppler of the MCA with RI more than 1 (absent and reversed diastole). (D) TCD showing color and pulsed Doppler of the ACA with RI 0.9.

3**. Results:**

Incidence of periventricular leukomalacia

26 (100%) in the study group had periventricular leukomalacia and no one in the control group had periventricular leukomalacia ($p < 0.001$) (Table 1).

Table (1): Incidence of periventricular leukomalacia

Table (1)	Study group (n= 26)	Control group (n= 26)	P
Periventricular leukomalacia	26 (100.0%)	0 (0.0%)	**< 0.001**
Data is expressed as frequency and percentage. P is significant when < 0.05.			

Grade of periventricular leukomalacia

Periventricular leukomalacia was grade I in 11 (42.3%), grade II in 10 (38.4%), and grade III in 5(19.2%) (figures 1,2,3,4).

MCA RI and other studied variables

There was statistically significant positive correlation between MCA RI and Apgar score (r= 0.387; p= 0.005). There was statistically significant positive correlation between MCA RI and both of periventricular leukomalacia (r= 0.613; p< 0.001), and Periventricular leukomalacia grade (r= 0.788; p< 0.001) (Table 2).

Table (2). Correlation between MCA RI and other studied variables.

MCA RI	Correlation coefficient	P
Apgar score	0.387	**0.005**
Periventricular leukomalacia	0.613	**< 0.001**
Periventricular leukomalacia grade	0.788	**< 0.001**
Sarnat stages of HIE	0.470	0.015
P is significant when < 0.05.		

ACA RI and other studied variables

There was statistically significant positive correlation between ACA RI and Apgar score (r= 0.382; p= 0.005). There was statistically significant positive correlation between ACA RI and both of periventricular leukomalacia (r= 0.598; p< 0.001), Periventricular leukomalacia grade (r= 0.799; p< 0.001), and Sarnat stages of HIE (r= 0.466; p=0.016) (Table 3)

Table (3). Correlation between ACA RI and other studied variables.

ACA RI	Correlation coefficient	P
Apgar score	0.382	**0.005**
Periventricular leukomalacia	0.598	**< 0.001**
Periventricular leukomalacia grade	0.799	**< 0.001**
Sarnat stages of HIE	0.466	**0.016**
P is significant when < 0.05.		

Doppler assessment of MCA

The mean right-side MCA of control group was (0.78 ± 0.226) statistically significantly higher than (0.71 ± 0.076) the study group (p< 0.001). The mean left-side MCA of control group was (0.79 ± 0.220) statistically significantly higher than (0.68 ± 0.076) the study group (p< 0.001). The mean average MCA of control group was (0.78 ± 0.222) statistically significantly higher than (0.70 ± 0.075) the study group (p< 0.001) (Table 4)

Table (4). Doppler assessment of MCA in the studied groups.

MCA	Study group (n= 26)	Control group (n= 26)	95% CI	P
Right side	0.78 ± 0.226	0.71 ± 0.076	0.15, 0.34	**< 0.001**
Left side	0.79 ± 0.220	0.68 ± 0.076	0.17, 0.35	**< 0.001**
Average	0.78 ± 0.222	0.70 ± 0.075	0.16, 0.34	**< 0.001**
Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05.				

Doppler assessment of ACA

Table 4 demonstrated that the mean right-side ACA on the control group was (0.8 ± 0.225) statistically significantly higher than (0.72 ± 0.073) the study group (p< 0.001). The mean left-side ACA of the control group was (0.79 ± 0.222) statistically significantly higher than (0.72 ± 0.070) the study group (p< 0.001). The mean average ACA was (0.79 ± 0.224) statistically significantly higher than (0.72 ± 0.071) the study group (p< 0.001). (table 5)

Table (5). Doppler assessment of ACA in the studied groups.

ACA	Control group (n= 26)	Study group (n= 26)	95% CI	P
Right side	0.8 ± 0.225	0.72 ± 0.073	0.16, 0.34	**< 0.001**
Left side	0.79 ± 0.222	0.72 ± 0.070	0.15, 0.33	**< 0.001**
Average	0.79 ± 0.224	0.72 ± 0.071	0.15, 0.34	**< 0.001**

Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05.

Diagnostic profile of MCA RI and ACA RI in detecting HIE

Figure 1 and table 5 showed ROC curves that were used to estimate the sensitivity and specificity of MCA RI and ACA RI in detecting HIE. The MCA RI is acceptable with significant area under curve of 0.788 for detecting HIE; At MCA RI 0.79, maximum sensitivity is 73.1% and specificity is 96.2%, PPV is 95%, NPV is 78.1 %, with accuracy 84.6%. The ACA RI is acceptable with significant area under curve of 0.768 for detecting HIE; At ACA RI 0.81, maximum sensitivity is 69.2% and specificity is 100%, PPV is 100%, NPV is 76.5%, with accuracy 84.6%. (figure 1). (table 6)

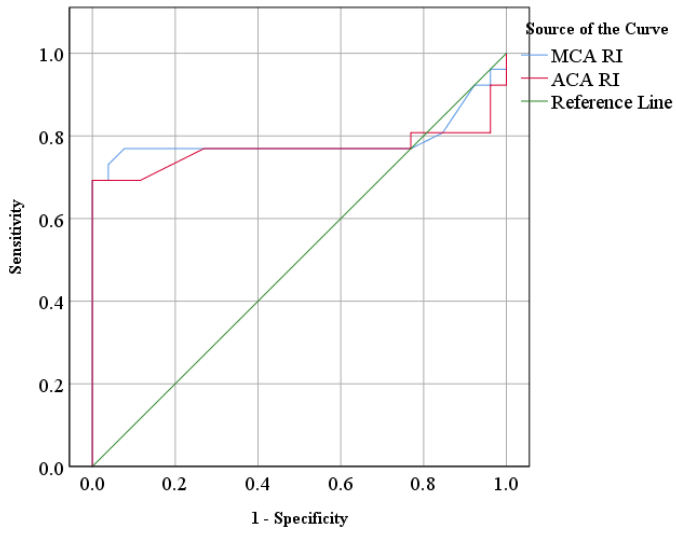

Figure (1). ROC curve of Diagnostic profile of MCA RI and ACA RIin detecting HIE.

Table (6). Diagnostic profile of MCA RI and ACA RI in detecting HIE.

HIE	**MCA RI**	**ACA RI**
AUC	0.788	0.768
95% CI of ACU	0.640, 0.936	0.615, 0.921
P	**< 0.001**	**0.001**
Cutoff point	0.79	0.81
Youden's index	0.69	0.69
Sensitivity	73.1%	69.2%
Specificity	96.2%	100.0%
PPV	95.0%	100.0%
NPV	78.1%	76.5%
Accuracy	84.6%	84.6%
P is significant when < 0.05.		

4. Discussion:

Neonates suffer from hypoxic ischemic encephalopathy, which is common and causes serious brain damage [(11)].

Term neonates and pregnancies with obstetric problems, including placental abruption, prior section, ruptured uterus, and shoulder dystocia, are also at risk for HIE [(12)].

Brain damage can result from perinatal hypoxia, cerebral ischemia, and reperfusion, which are frequently linked to eventual neurological abnormalities such cerebral palsy or mental retardation [(13)].

Transcranial ultrasonography and transcranial doppler enable for both imaging of parenchymal structures and Doppler evaluation of intracranial arteries, providing a real-time physiological monitor that can identify changed cerebral hemodynamics following catastrophic brain damage. They are often non-invasive, safe, reproducible, and have a significant potential in neurocritical care patients in many clinical settings. They are also relevant to paediatric patients, enabling improved care for kids who have suffered neurologic insults [(14,15,16)].

The objective of this study was to assess the diagnostic and grading use of transcranial ultrasonography and transcranial Doppler of the anterior and middle cerebral arteries in diagnosis of HIE.

The current study compares clinical data, evaluates the use of trans-cranial ultrasonography in preterm newborns with hypoxic ischemic brain damage, and aims to identify risk factors for prenatal asphyxia early in order to limit the sequelae.

The current study revealed that 26 cases (100%) in the study group had periventricular leukomalacia and no one in the control group had periventricular leukomalacia (PVL) by trans-cranial ultrasound. As regard the severity of hypoxic ischemic encephalopathy the PVL cases classified as follow; grade I PVL diagnosed in 11 cases (42.3%), grade II PVL diagnosed in 10 cases (38.4%) and grade III PVL diagnosed in 5 cases (19.2%).

Similarly, **Guan et al.** [17] in their study showed differences between color Doppler US results and clinical classifications in neonates with mild HIE. Only 42.6% of newborns with mild HIE had aberrant ultrasonography findings, 93.3% of neonates with intermediate HIE, and 100% of neonates with severe HIE .

Also, **Sharma et al.** [18] study revealed how periventricular echogenicity varied across different gestational age groups. They came to the conclusion that periventricular echogenicity was present in 4 cases (18.18%) out of 22 cases with gestational ages under 32 weeks, 7 cases (13.7%) out of 51 cases with ages between 32 and 37 weeks, and 3 cases (11%) out of 27 cases with ages over 37 weeks. Out of 100 patients, 14 (or 14%) in each group had periventricular echogenicity.

Therefore, the current study was matching with the study of **Guan, et al.** [17] they suggested that US follow-up is helpful for determining the degree of brain injury and forecasting the prognosis, and that US results were well connected to the severity of HIE.

The current study results showed that both MCA RI & ACA RI were statistically significant negative correlated with both presence of HIE and Apgar score. By color Doppler abnormal RI was observed in 11 cases (42.3%) with grade I HIE, 10 cases (38.4%) with grade II HIE and 5 cases (19.2%) with grade III HIE.

In this study the mean average of MCA RI of control group was (0.95 ± 0.222) and it was statistically significantly higher than the study group MCA RI (0.70 ± 0.075). Also, the mean average ACA RI of control group in this study was (0.96 ± 0.224) and it was statistically significantly higher than the study group ACA RI (0.72 ± 0.071).

Compared to **Jain et. al.** [19] study in their study They came to the conclusion that grade II HIE accounted for the majority of study cases, and that 87.5% of subjects with average RI (0.53-0.55 in both MCA and ACA) had abnormal RI.

The fact that the majority of patients in the current research were grade III HIE and the majority of cases in the study by **Jain et al.** [19] were grade II HIE may be the cause of the discrepancy in RI values between the two investigations.

In the current study in HIE groups, the blood flow velocities decreased or increased markedly according to the degree of cerebral hemodynamic disturbance, RI increased or decreased accordingly. In HIE grade 1 (11 cases) showed RI between (0.69 -0.79), HIE grade II (10 cases) showed RI < 0.6 and most of cases were grade III HIE (5 cases) that showed RI between (0.89-1.)

Similarly, to Liu et al [20], in their study indicated that RI was often less than 0.50 (4 instances) or more than 0.90 (8 cases) in patients with severe HIE, but RI more than 1.0 and inverse-perfusion during the diastolic phase was related with subsequent brain death.

Also, this study matched with study of **Guan et al** [17], their results indicated that neonates with HIE have greater RI of ACA and MCA than those in the control group. Except for one newborn, all of the neonates with severe HIE showed high RI, which is a sign of decreased blood flow to the brain tissue in HIE. All of these individuals were clinically classified as having severe HIE because the cerebral blood flow velocity is lowered and RI is raised in babies with clinical HIE, which results in a corresponding drop in blood flow velocity, notably the diastolic velocity.

In the current study there was statistically significant positive correlation between MCA RI & ACA RI and both of periventricular leukomalacia, Periventricular leukomalacia grades and Sarnat stages of HIE.

Similiarly to study **Kumar et al.** [21] they compared the results of the newborn HIE using ultrasonography and doppler to Sarnat's clinical rating. They discovered that early cerebral Doppler values, particularly RI, were considerably greater in individuals with neonatal encephalopathy-related clinical characteristics than in healthy newborns. According to Sarnat's categorization, Doppler parameters were correlated with an increase in newborn encephalopathy severity, particularly RI values between 0.6 and 0.82, which were linked to an increase in severity according to Sarnat's score.

For diagnosis of HIE in the current study, showed that by using MCA RI cut off value equal 0.79; the maximum sensitivity was 73.1%, specificity was 96.2%, PPV was 95%, NPV was 78.1 % and accuracy was 84.6% for diagnosis of HIE. In current study by using ACA RI cut off value equal 0.81, the maximum sensitivity was 69.2%, specificity was 100%, PPV is 100%, NPV was 76.5%, and accuracy was 84.6% for diagnosis of HIE.

These findings were consistent with a study by **Giri et al.** [22], in which the overall sensitivity and specificity of TCUS in detecting imaging findings in 50 neonates with HIE were 78.57% and 62.50%, respectively. This study's findings also showed that TCUS had a diagnostic accuracy of 76%, a positive predictive value of 91.60%, and a negative predictive value of 35.70%.

The total sensitivity and specificity of TCUS in identifying imaging abnormalities in 36 newborns with HIE were shown to be 80% and 66.6%, respectively, by **Aun et al.** [23]; this resulted in a diagnosis accuracy of 78.9%. In comparison to the negative predictive value, which was 40%, the positive predictive value was 92.31%.

In a similar vein, **Giri et al.** [22] discovered that the overall sensitivity and specificity of TCUS were 81.8% and 60%, respectively, with an overall diagnostic accuracy of 78.9% in identifying brain abnormalities. 93.1 was the positive predictive value, while 33.3 was the negative predictive value (95% confidence interval).

Furthermore, **Herma et al.'s** study [24] which demonstrated that TCUS had an 82% sensitivity for HIE diagnosis mirrored our results.

According to **Nath et al.** [25], the TCUS has a sensitivity and specificity of 89.4% and 100%, respectively. Diagnostic accuracy, PPV, and NPV were all 100%, 28.6%, and 89.8%, respectively.

In the examination of 36 patients by **Aun et al.** [23], the sensitivity, specificity, PPV, NPV, and diagnostic accuracy were, respectively, 81.3%, 100%, 100%, 40%, and 83.33%.

According to **Thakkar et al.** [26], the sensitivity and specificity of ultrasonography results for detecting HIE in preterm infants were 83.33% and 92.59%, respectively.

The sensitivity and specificity for diagnosing HIE by USG were 90% and 75%, respectively, in the study done by **Shen et al.** [27].

Conclusion: In the context of acute and critical care, TCUS and color Doppler of MCA and ACA are valuable screening modalities that can also provide a much more practical technique for patient follow-up. But unlike MRI, TCUS might not pick up as many lesions. Consequently, TCUS can significantly underestimate the severity of the injury.

The limitation of this study was ,The relatively small number of patients in the study, We didn't compare our findings with MRI to evaluate if TCUS alone can detect precisely the extent of brain injury compared with MRI ,No follow up done to the most of cases and Finally , As our hospital was a tertiary care centre ,so more severe cases of HIE might be selected in the study compare to general population so finding cannot be generalized to all HIE population.

5. Conclusion:

The newborn brain can be evaluated with trans-cranial ultrasonography and trans-cranial Doppler. For displaying the most typical types of cerebral damage in preterm neonates, gauging the lesion's progression, and monitoring brain growth, they are safe and reliable approaches. Early transcranial Doppler ultrasonography should be performed on neonates with HIE to predict the course of their clinical treatment.

6. References:

1. Aslam S, Strickland T, Molloy EJ. Neonatal encephalopathy: need for recognition of multiple etiologies for optimal management. Frontiers in pediatrics. 2019 Apr 16;7:142.
2. Bornavard M, Fanaei H, Mirshekar MA, Farajian Mashhadi F, Atashpanjeh A. Morphine consumption during pregnancy exacerbates neonatal hypoxia-ischemia injury in rats. International Journal of Developmental Neuroscience. 2020 Apr;80(2):96-105.
3. Kurinczuk JJ, White-Koning M, Badawi N. Epidemiology of neonatal encephalopathy and hypoxic–ischaemic encephalopathy. Early human development. 2010 Jun 1;86(6):329-38.
4. Chevallier M, Ego A, Cans C, Debillon T, French Society of Neonatology. Adherence to hypothermia guidelines: a French multicenter study of fullterm neonates. PLoS One. 2013 Dec 31;8(12):e83742.
5. Groenendaal F, Casaer A, Dijkman KP, Gavilanes AW, De Haan TR, Ter Horst HJ, Laroche S, Naulaers G, Rijken M, Van Straaten HL, Steiner K. Introduction of hypothermia for neonates with perinatal asphyxia in the Netherlands and Flanders. Neonatology. 2013 Apr 23;104(1):15-21.
6. Rodríguez M, Valez V, Cimarra C, Blasina F, Radi R. Hypoxic-ischemic encephalopathy and mitochondrial dysfunction: facts, unknowns, and challenges. Antioxidants & redox signaling. 2020 Aug 1;33(4):247-62.
7. Barseem NF, Badr HS, Abdullah MS. Color Doppler ultrasonography in full term neonates with hypoxic ischemic encephalopathy and prediction of outcome. Egyptian Pediatric Association Gazette. 2016 Mar 1;64(1):38-43.
8. Tanasescu R, editor. Miscellanea on Encephalopathies: a Second Look. BoD–Books on Demand; 2012 Apr 25.
9. Barlinn K, Alexandrov AV. Transcranial Doppler sonography. InNoninvasive Vascular Diagnosis: A Practical Textbook for Clinicians 2021 Aug 24 (pp. 1-34). Cham: Springer International Publishing.
10. Verlhac S. Transcranial Doppler in children. Pediatric radiology. 2011 May;41:153-65.
11. Cao, Y., Liu, H., Zhang, J. et al 2020. Circular RNA cZNF292 silence alleviates OGD/R-induced injury through up-regulation of miR-22 in rat neural stem cells (NSCs). Artificial cells, nanomedicine, and biotechnology, 48(1), pp.594-601.
12. Liljestrom, L., Wikstrom, Jonsson, et al 2018. Obstetric emergencies as antecedents to neonatal hypoxic ischemic encephalopathy, does parity matter?. Acta obstetricia et gynecologica Scandinavica, 97(11), pp.1396-1404.
13. Rodriguez, J., Li, T., Xu, et al., 2021. Role of apoptosis-inducing factor in perinatal hypoxic-ischemic brain injury. Neural regeneration research, 16(2), p.205.
14. Robba, C. and Taccone, F.S., 2019. How I use transcranial Doppler. Critical Care, 23, pp.1-4.
15. Annink, K.V., Meerts, L., van der Aa, et al 2021. Cerebellar injury in term neonates with hypoxic–ischemic encephalopathy is underestimated. Pediatric Research, 89(5), pp.1171-1178.
16. Upadhyay P, Patil KU, Kuber R, Kulkarni V, Singh A. Evaluation of hypoxic-ischaemic events in preterm neonates using trans cranial ultrasound. International J. Healthcare Biomed Res. 2014 Oct;3:67-72.
17. Guan B, Dai C, Zhang Y, Zhu L, He X, Wang N, Liu H. Early diagnosis and outcome prediction of neonatal hypoxic-ischemic encephalopathy with color Doppler ultrasound. Diagnostic and interventional imaging. 2017 Jun 1;98(6):469-75.

18. Sharma M, Kardam NK, and Gupta S.et al. The role of transcranial ultrasound in the evaluation of hypoxic ischemic encephalopathy Int. J. of Adv. Res. 10 (Jun). 2022. 239-246] (ISSN 2320-5407).
19. Jain H1, Arya S2, Thakur K3et al 2016. Study of transcranial colour Doppler in the measurement of cerebral edema in birth asphyxia . Vol 3/ Issue 4 ISSN 2349-5499 .
20. Liu J, Cao HY, Huang XH, et al . 2007. The pattern and early diagnostic value of Doppler ultrasound for neonatal hypoxic-ischemic encephalopathy. J Trop Pediatr. ;53(5):351-4
21. Kumar I, Singh S, Kumar A, Aggarwal P, Shukla RC, Verma A. Early postnatal color Doppler changes in neonates receiving delivery room resuscitation with low 5 min Apgar score—a pilot study. Journal of Perinatology. 2021 Mar;41(3):486-93.
22. Giri S, Sau R, Das S, Das R, Sur P, Mondal A, Haldar R, Hazra S. Correlation of Transcranial Ultrasound and Magnetic Resonance Imaging in Evaluation of Imaging Patterns of Clinically Diagnosed Hypoxic Ischaemic Encephalopathy in Neonates.
23. Aun AE, Hassan HA, Ali WI, Ataky MM. Transcranial ultrasound in comparison to MRI in evaluation of hypoxic ischemic injury in neonates. The Egyptian Journal of Hospital Medicine. 2019 Jan 1;74(4):842-52.
24. Herma P, Kalola J, Sood M, Trivedi A. Transcranial ultrasound: efficient screening tool for detection of hypoxic brain injury in neonates–study of 50 patients. Int. J. Contemporary Med. Surg. Radiol. 2018;3(3):93-5.
25. Nath D, Mili R, Thapa P, Das A. Comparison Between Transcranial Ultrasound And Magnetic Resonance Imaging In The Evaluation Of Neonatal Hypoxic-Ischemic Encephalopathy.
26. Thakkar H, Sonone S, Khodke R. Transcranial Ultrasound in Evaluation of Hypoxic-Ischemic Encephalopathy and Bleed in Preterm Neonates. INTERNATIONAL JOURNAL OF SCIENTIFIC STUDY. 2019;7(4):27-38.
27. Shen W, Pan JH, Chen WD. Comparison of transcranial ultrasound and cranial MRI in evaluations of brain injuries from neonatal asphyxia. International journal of clinical and experimental medicine. 2015;8(10):18319.