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Cranial Ultrasound and Serum Amyloid A as Predictors of Outcome in Term Newborn with Hypoxic-Ischemic Encephalopathy

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ABSTRACT

Background: The use of serum amyloid A as a synergistic predictor of the level and extent of brain injury has been mentioned by many literatures yet no correlation between resistive index -as a reflector of cerebral blood flow velocity- cranial imaging and mortality outcomes have been detected.

Objectives: This study aimed to evaluate serum amyloid A and cranial ultrasound (CUS) in hypoxic ischemic insult and assess its relation to consequences as mortality in neonates.

Subjects and Methods: A prospective cohort study was done on 35 full term (>35 weeks) neonates in Intensive Care Unit-Fayoum Hospital - Egypt. Full neurological examination was done during the first 24 hours and after 7 days.

Results: Severe hypoxic ischemia was found strongly correlated with high mortality. Low resistive index and high serum amyloid A were both indicators of poor prognostic condition in asphyxiated neonates.

Conclusion: The serum amyloid A and ultrasound can be involved to evaluate the extent and level of asphyxia in neonates upon the first days of life.

Keywords: Hypoxic ischemia, Encephalopathy, Resistive index, Serum amyloid A.

INTRODUCTION

Birth asphyxia is also known as intrapartum asphyxia, Neonatal Encephalopathy (NE) and Hypoxic Ischemic Encephalopathy (HIE) [(1)]. The disease is complexed and is characterized by alteration in consciousness level, seizures, and difficulty in maintaining or initiating respiration [(2)]. The disease is detected in infants born at or beyond 35 weeks of gestation [(3)]. Antenatal, perinatal, or a combination of both can cause HIE [(4)]. Antenatal maternal factors, hereditary and familial factors, infections, coagulation defects, placental abnormalities, and metabolic disorders were all involved as causes in HIE [(1)]. Unfortunately, 15%–20% of HIE cases will die post-tnatally and in some reports fatality rate reached 60% [(1)] while about 30% of whom will survive will suffer from neurodevelopmental disorders [(1)].

Brain imaging is crucial in managing and predicting neonatal neurodevelopmental consequences. Magnetic Resonance Imaging (MRI) is the benchmark technique used in HIE. However, in developing countries, MRI is not always available and could present a challenge [(5)].

Cranial Ultrasonography (CUS) has become useful in determining the extent of injury, pattern and timing in HIE. CUS has many other advantages such as portability, no need for sedation, and affordability compared to MRI [(6)].

The echogenicity of deep gray matter structures has been identified when CUS is performed beyond the day 7 of life. In addition, ultrasonography is a procedure of choice in diagnosis and screening of germinal matrix hemorrhage. Nevertheless, CUS was limited in detecting extraaxial hemorrhage i.e. subdural, subarachnoid and extradural hemorrhage [(7)]. Some studies have reported that white matter/gray matter echogenicity ratio could be a benchmark in detecting brain defects and has been associated with a change in resistive index (RI) of the middle cerebral artery (MCA) on Doppler sonography that could be used as helpful tools for assessing HIE severity [(3)]. Knowing that HIE influence normal brain autoregulation, it is recommended to measure relative RI [(8)].

The resistive index is the simplest and most common vascular ultrasound indices used for assessing vascular resistance. RI is influenced by many factors such as flow velocity, blood volume, presence of congenital cardiac anomalies, and peripheral vascular resistance [(9)].

Abnormality of RI in the first 72 hrs of life has been found to be highly predictive of poor prognosis with either death or severe disability [(6)].

Serum amyloid A (SAA) is released when an inflammation occurs. Inflammatory cytokines such as interleukin-6, interleukin-1, transforming growth factor and tumor necrosis factor and interferon-γ are responsible for the release of SAA. The optimum concentration of SAA reaches within 5-6 hours after an injury or inflammation with 1000-fold greater than normal [(10)].

In asphyxiated neonates, an inflammatory response occurs which triggers the release of SAA. It has been suggested that the release and prolonged existence of SAA in serum have been linked to poor prognosis, particularly, in HIE [(11,12)]. Additionally, intense and degree of tissue damage was linked in many literatures to high SAA [(13-15)].

Accordingly, this study aimed to evaluate both SAA and CUS in asphyxiated newborn in the first week of life. As well, as to assess the relation between SAA

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and CUS and the degree of asphyxia morbidity, and mortality at discharges.

METHODOLOGY

This prospective cohort study was done by enrolling 35 clinically diagnosed full term neonates (>35 weeks) with HIE and classified according to Sarnat and Sarnat classification [16] in Neonatal Intensive Care Units (NICUs) at Fayoum University Hospital. Patients fulfilling at least two of the clinical findings in the inclusion criteria were enrolled. Full medical history (maternal and prenatal) was obtained for all sampled cases. Full neurological examination was assessed during the first 24 hours including level of consciousness, muscle tone, reflexes, seizures and autonomic functions.

The inclusion criteria:

(1) Apgar score < 5 at 5 min [17], (2) metabolic acidosis pH below 7.2 in fetal umbilical cord or in neonatal blood samples obtained on the first day of life, (3) fetal distress (such as abnormal fetal heart rate and meconium stained amniotic fluid), (4) delayed onset of respiration, (5) need for assisted ventilation (mask/balloon or intubation), (6) multiple organ dysfunction (encephalopathy along with the involvement of at least one organ), (7) presence of convulsions in the first 24 h of life, (8) encephalopathy (lethargy/ stupor, hypotonia and abnormal reflexes including an absent or weak suck), (9) Agreed written informed consent from caregivers/parents and (10)q1 in accordance with the Declaration of Helsinki.

Exclusion criteria: Infants were excluded from the study if they met any of the following conditions: (a) conditions known to increase SAA such as localized infection or sepsis, (b) congenital anomalies, (c) inborn errors of metabolism and (d) preterm babies before 36 completed weeks.

Cranial Ultrasonography with Doppler

Standard CUS technique

Anterior fontanelle is used as acoustic window for CUS procedure. The brain was scanned from frontal to occipital and from right to left. Six coronal planes and 5 sagittal planes were recorded. Suspected abnormalities images were recorded in two planes.CUS and Doppler were performed after 48 hours and seven days of life.

Doppler ultrasound

RI was measured in middle cerebral artery through the right and left temporal bone on axial planes. Also, peak systolic velocity and diastolic velocity were measured

RI is defined as peak systolic velocity minus end diastolic velocity divided by peak systolic velocity. Normally in term infants, RI in middle cerebral artery is 0.7. Abnormal RI is defined as 0.55 or less measured at least in one artery [18].

Serum amyloid A

Blood samples were collected from cases at 1st day and 7th day postnatal. Serum Amyloid A was measured by ELISA and then was measured spectrophotometrically at 450 nm (Sinogeneclon Co., Ltd Hang Zhou, China kit).

Ethics approval:

Ethical approval was obtained in 25/3/2014 under the number (D3) from Fayoum University Hospital- Ethics Committee. All caregivers/parents had written informed consent . This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Data analysis

Collected data were presented as parameters, tables and graphs. The appropriate statistical methods of association and difference were used after computerization using SPSS V. 22 (SPSS Inc., USA). For quantitative data, the mean, median, and Inter-Quartile Range (IQR) were calculated. Kolmogorov-Smirnov test (KS) test was used as a test of normality. If variables were not normally distributed, either Mann-Whitney-U test or Kruskal-Wallis test was used while comparing between any two or three groups, respectively. Qualitative data were presented as number and percentages. Spearman correlation was run to identify relation between SAA and several parameters among HIE cases. ROC curve was used to determine the cut-off point in which highest sensitivity and specificity of SAA as predictor in differentiating between different classifications. Significance was adopted at $P \leq 0.05$.

RESULTS

According to Sarnat & Sarnat staging [16] stage I involved 8.6% of the total patients while stage II and stage III involved 57.1% and 34.3%, respectively as shown in table (1) and figure (1).

Table (1): Grading of HIE

HIE grading	No	%
Grade I	3	8.6%
Grade II	20	57.1%
Grade III	12	34.3%

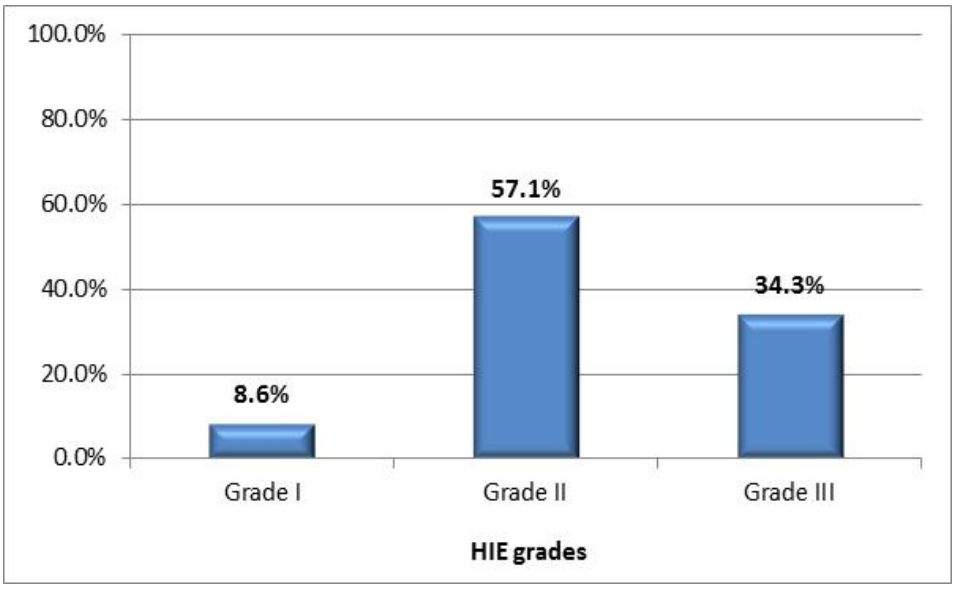

Figure (1): Grading of HIE

Brain edema was found in about one third of the 12 sampled neonates within 48 hours of birth. At 7th day, the proportion of the neonates with brain edema was decreased to less than one-fifth 5/26 (represented 19.2%) as presented in table (2) and figure (2).

Table (2): Cranial Ultrasound finding in HIE neonates at different times

	Within 48 hours (N=35)		**At 7th day (N=26)**	
	No	%	No	%
Edema	12	34.3%	5	19.2%
Increased Parenchymal Echogenicity	4	11.4%	3	11.5%
Increased Basal Ganglion Echogenicity	3	8.6%	1	3.8%
Normal	16	45.7%	17	65.4%

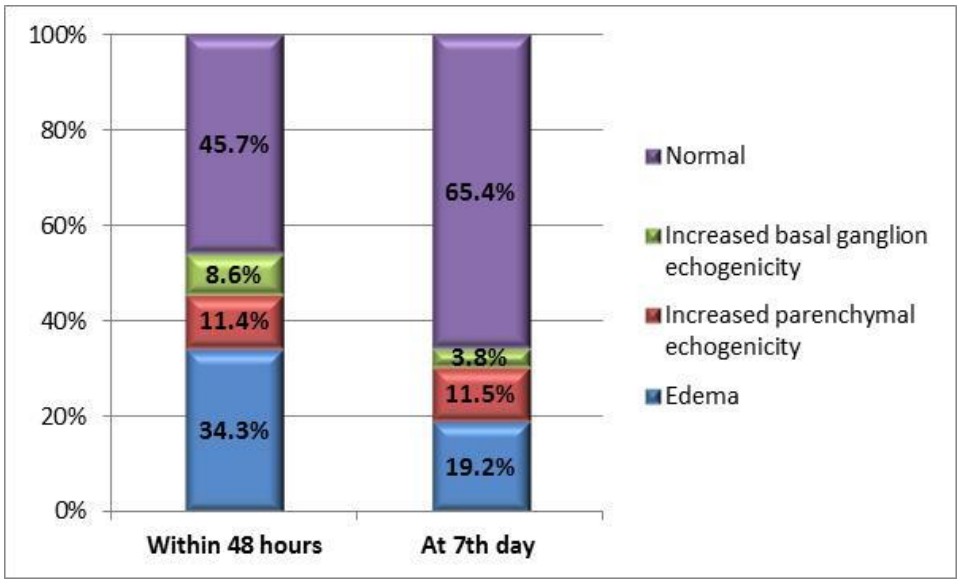

Figure (2): Cranial ultrasonography of HIE neonates

Regarding RI, median RI for dead neonates with HIE showed statistically significant lower value than those who survived (0.53% vs. 0.60%) within 48 hours of birth. At day 7, no statistically significant difference between the two groups was observed as shown in table (3) and figure (3).

Table (3): Comparison in the differences in RI at different times between dead and survived neonates with HIE.

	Died	Survived	*P*-value
	Median (IQR) RI		
Within 48 hours	0.53 (0.38-0.59)	0.60 (0.54-0.66)	0.015*
At 7th day	0.59 (0.51-0.80)	0.60 (0.59-0.66)	0.574

*Significant $P \leq 0.05$

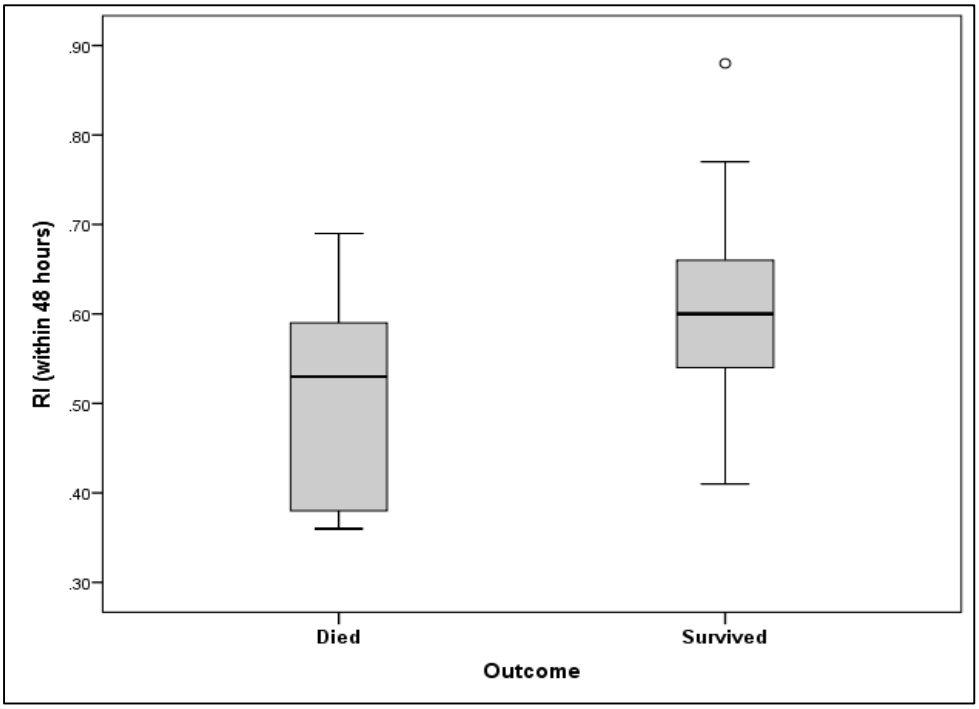

Figure (3): Comparison in the differences in RI at different times between dead and survived neonates with HIE

The SAA was detected significantly higher in neonates who died as compared to those who survived (105.24% vs. 89.24%) within 24 hours of birth. While at day 7, no a statistically significant difference between died and survived groups in SAA was observed as presented in table (4) and figure (4).

Table (4): Differences in SAA at different times between dead and survived HIE neonates

	Died	Survived	P-value
	Median (IQR) SAA		
Within 24 Hours	105.24 (92.71-108.81)	89.24 (60.42-102.62)	0.020*
At 7th Day	98.26 (78.47-173.33)	83.16 (75.35-100.48)	0.178

*Significant: $P \leq 0.05$

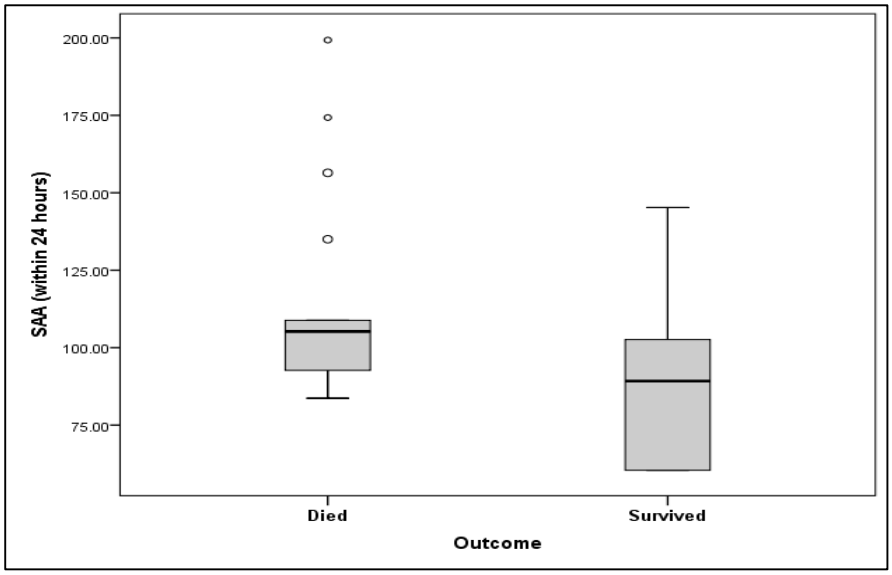

Figure (4): Differences in SAA (within 24 hours) between dead and survived HIE neonates

There was a weak negative correlation between the grades of HIE and RI value (P=0.037) within 48 hours however, RI at 7th day showed no statistically significant correlation with HIE grades as shown in table (5).

Table (5): Correlation between RI at different times and HIE stages

	RI (within 48 hours)		RI (at 7th day)	
	r	P-value	r	P-value
HIE Grades	-0.355	0.037*	0.59	0.499

*Significant P ≤ 0.05

As regards serum amyloid A, a statistically significant positive correlation between the grades of HIE and SAA within 24 hours was observed (r= 0.405%, P=0.016%). While at 7th day, no statistically significant correlation was detected as indicated in table (6).

Table (6): Correlation between SAA at different time and HIE stages

	SAA (within 24 hours)		SAA (at 7th day)	
	r	P-value	r	P-value
HIE Grades	0.405	0.016*	0.021	0.921

*Significant P ≤ 0.05

HIE neonates with brain edema showed a statistically significant lower median RI value within 48 hours of birth compared to other brain symptoms as shown in table (7).

Table (7): RI at different time in relation to brain edema

	RI (within 48 hours)		RI (at 7th day)	
	Median (IQR)	P-value	Median (IQR)	P-value
Edema	0.46 (0.4-0.56)	0.018*	0.59 (0.54-0.67)	0.499
No Edema	0.6 (0.56-0.68)		0.6 (0.6-0.63)	
Increased Parenchymal Echogenicity	0.59 (0.59-0.64)		0.63 (0.63-0.63)	
Increased Basal Ganglion Echogenicity	0.59 (0.47-0.59)		0.71 (0.71-0.71)	

*Significant P ≤ 0.05

As regards SAA change during the first and seven days of life, there was no statistically significant difference between the categories of brain edema within 24 hours or at 7th day as shown in table (8).

Table (8): SAA at different time in relation to brain edema

	SAA (within 24 hours)		SAA (at 7th day)	
	Median (IQR)	P-value	Median (IQR)	P-value
Edema	93.75 (85.59-106.63)	0.383	93.15 (78.47-125.95)	0.341
No edema	91.5 (60.42-116.06)		78.47 (75.35-87.85)	
Increased Parenchymal Echogenicity	102.63 (95.31-131.72)		98.26 (98.26-98.26)	
Increased Basal Ganglion Echogenicity	105.24 (97.22-135)		106.43 (106.43-106.43)	

Mortality was found statistically higher among neonates with grade III than those with grade I and II (83.3% versus 0% and 35% respectively). As well, brain edema was found higher within neonates who died compared to those who survived as shown in table (9) and figures (5) and (6).

Table (9): Mortality within different clinical and radiological features in HIE neonates:

	Died		Survived		P-value
	N	%	N	%	
Sarnat & Sarnat grading					
Grade I	0	0.0%	3	100.0%	**0.006***
Grade II	7	35.0%	13	65.0%	
Grade III	10	83.3%	2	16.7%	
Brain edema within 48 hours					
Edema	8	66.7%	4	33.3%	**0.008***
Increased Parenchymal Echogenicity	3	18.8%	13	81.3%	
Increased Basal Ganglion Echogenicity	4	100.0%	0	0.0%	
Normal	2	66.7%	1	33.3%	

*Significant P ≤ 0.05

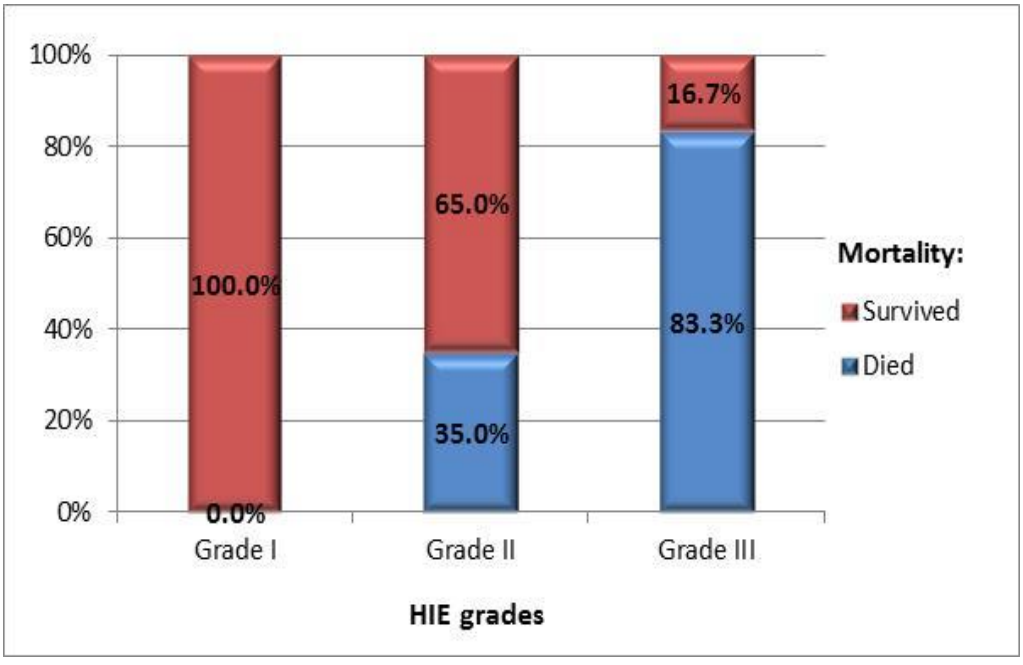

Figure (5): Mortality in HIE grading

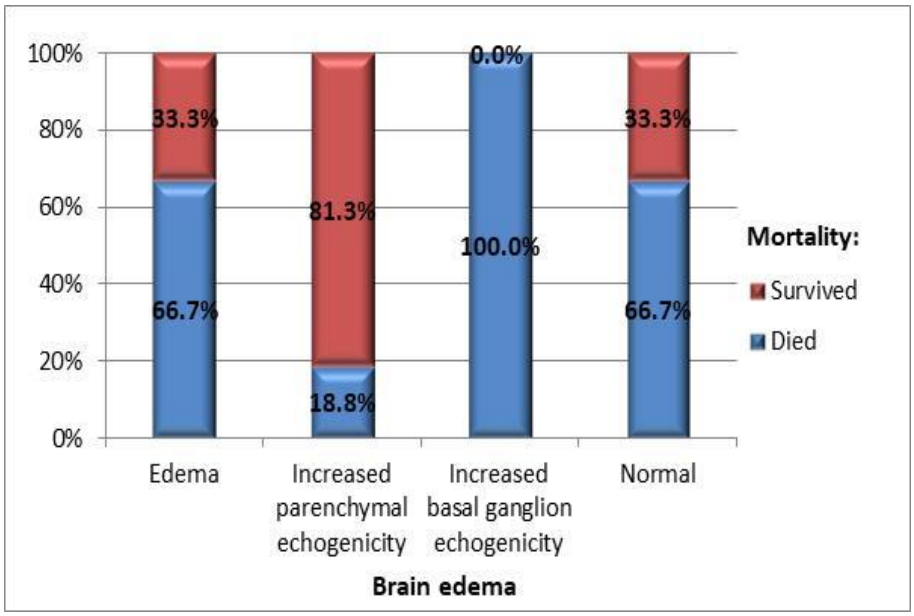

Figure (6): Mortality in brain edema

There was a statistically significant negative correlation between RI within the first 48 hours and SAA r= 0.361% and p= 0.033%, as shown in figure (7).

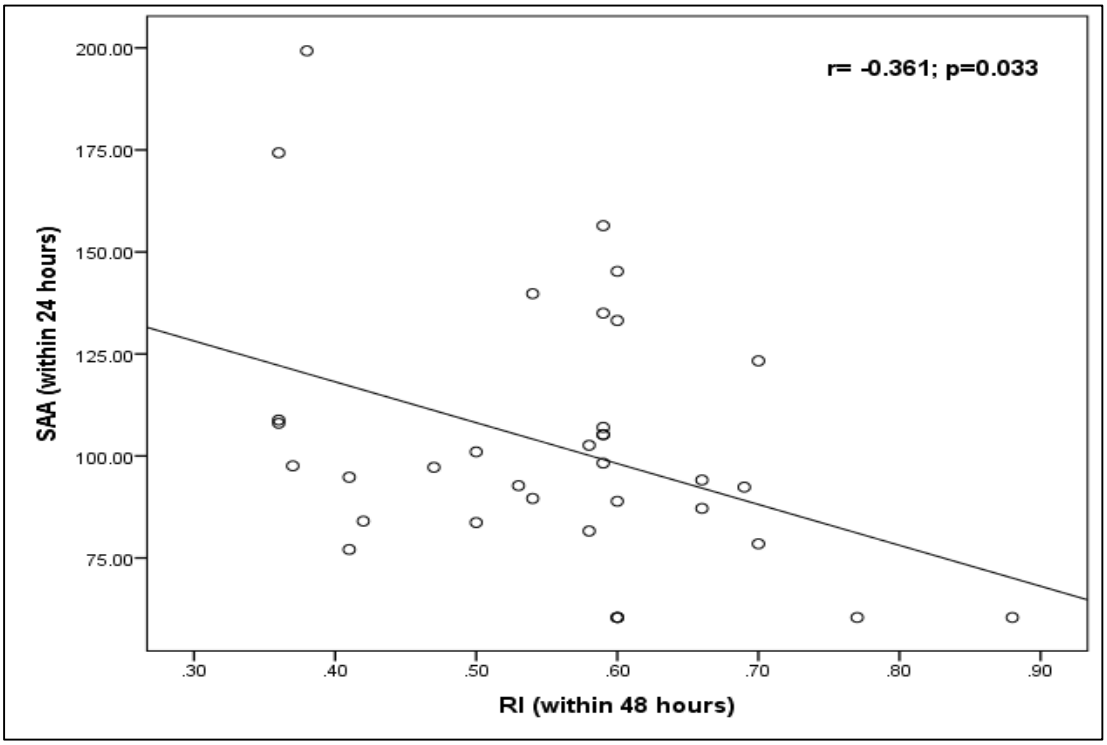

Figure (7): Correlation between RI within 48 hours and SAA within 24 hours

In table (10) and figure (8), the ROC curve showed high sensitivity of 88.2% and specificity of 61.1% in predicting RI while in SAA, the sensitivity was 70.6% and specificity was 72.2% implying significant prediction of mortality among the studied neonates.

Table (10): Sensitivity and specificity of RI and SAA at base line (24 hrs) in predicting mortality

	AUC	P-value	Cut-off point	Sensitivity	Specificity
RI (within 48 hours)	0.737	0.017*	0.59	88.2%	61.1
SAA (within 24 hours)	0.729	0.021*	97.39	70.6%	72.2

* Significant P ≤ 0.05

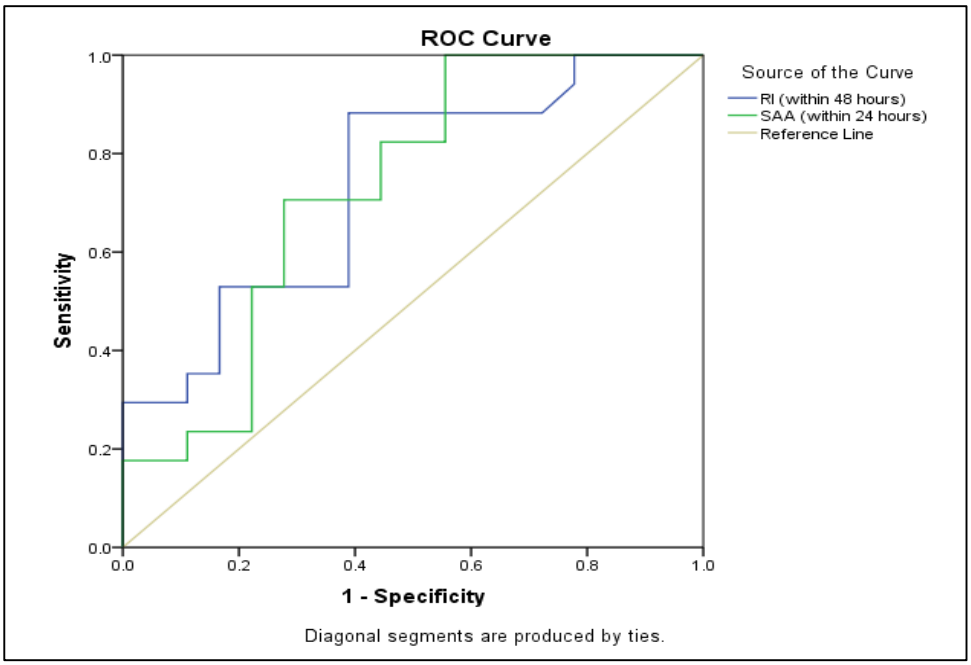

Figure (8): ROC curves of RI and SAA at base line (24hrs)

Incidence of mortality was higher in males than in females (p-value = 0.877%) as shown in Table (11).

Table (11): Distribution of dead cases among both genders

	Died		Survived		P-value
	N	%	N	%	
Male	8	50.0%	8	50.0%	0.877
Female	9	47.4%	10	52.6%	

Among the studied neonates, 48.6% died within 7 days from birth as shown in table (12) and figure (9)**.**

Table (12): Incidence of mortality among the studied neonates

	No	%
Died	17	48.6%
Survived	18	51.4%

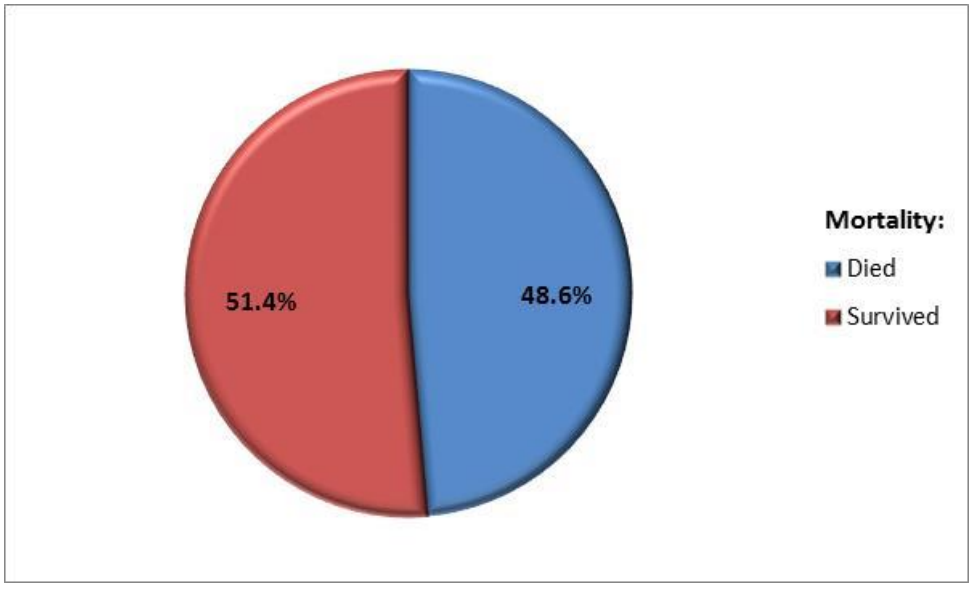

Figure (9): Incidence of mortality among the studied neonates

DISCUSSION

The most common cause of morbidity and mortality among neonates is HIE [1]. During an inflammatory process or an injury, SAA is released in high concentration as an acute-phase protein [19]. Therefore, the presence of SAA during hypoxic- ischemia could predict the extent of brain injury in asphyxia [13]. Our study has detected an increase in SAA within the first 24 hours among neonates who died compared to those who survived. This result matches results concluded by **Aly and colleagues [11]** that reported an increase in SAA at first day of life in those who died compared to those who survived with no significant difference between those who died and survived at day seven. Similarly, **Sezer *et al.*** [15] have reported the association between elevation of SAA and the severity of cerebrovascular stroke.

The level of SAA In present work was correlated with the severity of HIE. This agrees with other studies. **Aly *et al.*** [11], **Wicker *et al.*** [12], **Amin *et al*.** [13]and **Carabias *et al.*** [14], which reported that increased SAA in asphyxia is considered a predictor of brain injury and true marker of tissue damage. Also, evaluation of SAA can help assessing the outcome and mortality in neonates with brain injury [14].

Assessment of our HIE neonates using Grey scale sonography showed edema, increased parenchymal echogenicity and increased basal ganglion echogenicity. Brain edema was a common finding in this study in one third of the patients. This is in agreement with other study findings where brain edema is common in the cases following brain injury [20]. In addition, CUS has revealed an increase in cerebral echogenicity that is presented at 1st week of life and become more apparent after 7 days [21]. In this study, about half of the total cases showed normal ultrasonography (USG) scan despite having features of HIE within 48 hours and at day seven. A study was done to evaluate the recommendations of The Canadian Neonatal Network (CNN) and Canadian Preterm Birth Network (CPTBN) regarding the use of CUS in neonatal brain injury has agreed that applying CUS within 1st day of life will allow the identification of congenital malformations or antenatal injury.

Additionally, the use of CUS during the first seven days of life can detect intracranial hemorrhage and periventricular leukomalacia. Urging the use of ultrasonography in diagnosis and evaluation of neonatal HIE [22]. Resistive index is used globally as a blood flow measure, which may help indicating brain injury. Studies have found that low RI was correlated with severe brain injury in HIE neonates [23]. In one study, the cerebral blood flow velocities changed at 12 ± 2 hours of age implying the severity of HIE and negative outcomes at 18 months of age. The study revealed that RI < 0.56 at the age of 1-3 days had been associated with poor outcomes at 3 years of age [24]. Similarly, severe asphyxia was found associated with RI ≤ 0.57, moderate at RI = 0.58–0.62 while mild was considered as RI = 0.63– 0.67 [25]. It has been proven that impaired cerebral circulation, particularly, the first 12 h plays a critical role in the pathogenesis of hypoxic-ischemic encephalopathy [26]. Cerebral blood flow parameters measured by Doppler sonography in first three days of life can predict outcome in HIE [24]. Severe asphyxia with RI < 0.50 or RI > 0.90 and RI> 1.0 was associated with brain death in neonatal HIE [27]. These studies go in line with our current study where subjects with worse outcome had significantly lower RI ≤ 0.53 compared to survived group (RI ≤ 0.6).

Increased basal ganglion echogenicity was found in about 8.6% within 48 hours of our patients and in 3.8% at 7thday. This is in agreement with the study reported by **Prithviraj *et al.*** **[28]** that was conducted on 100 critically ill neonates. They reported that 23% of neonates with HIE had thalamic hyper-echogenicities, 38% had cerebral edema, 30% had intracranial bleeding and 46% had normal scan. Changes in echogenicity of the deep grey matter (basal ganglia and thalami), suggest a more severe injury and correlate with a poor outcome. **Ilves [9]** investigation pointed to the delayed appearance of the increased echogenicity in the basal ganglia, thalami after 7 days in severe asphyxiated neonates [9].With hypoxia, RI is decreased due to vasodilatation secondary to brain hypoxia [29]. In our study, there was a statistically significant negative correlation between the grades of HIE and RI within 48 hours. This is in agreement with the study conducted by **Ilves *et al.*** [30] who reported that RI was decreased in severely asphyxiated neonates with HIE and was associated with poor outcomes compared to those with respectively mild and moderate HIE. Contrary to present study, **Guan *et al.*** **[31]** found that neonates with severe HIE had elevated RI with a decrease in cerebral artery blood flow. The study has justified the drop in blood pressure through the decreased cerebral blood flow and increased cranial pressure. As well, as a compensatory mechanism, cerebral blood flow changes according to vascular resistance. Regarding the relation between brain edema and RI, the findings of **Zanon and Pasca [32]** showed significantly more frequent brain edema (absent cortico-medullar differentiation) and significantly reduced RI in neonates with HIE, which agrees with our study findings where a statistically significant lower median RI value within 48 hours compared to others was detected.

Regarding mortality, incidence of mortality was statistically higher among neonates with grade III than those with grade I and II (represented 83.3% versus 0% and 35% respectively), which agrees with other study results demonstrating that higher grades of HIE were associated with mortality more often than those with mild or moderate cases [1]. As well, there was a statistically significant relation between mortality and brain edema. This is in agreement with other studies where presence of cerebral edema indicates cell death [6-10], impaired cerebral blood flow and reduced RI [31] which agrees with our finding that a statistically

significant negative correlation between RI within 48 hours and increase in SAA within 24 hours from birth following dilatation of the vessels were detected (r= 0.361 and p= 0.033). Similarly**, Clay *et al.*** [33] has concluded that edema was strongly associated with severe HI insult and with poor prognostic outcome.

Calculating sensitivity and specificity of RI in predicating mortality showed 88.2% and 61.1% respectively. This is in agreement with other studies where sensitivity and specificity values of abnormal RI to detect abnormal neurological outcomes were above 85% [33]. As well, our study results were capable of detecting correlation between SAA and mortality. SAA in this study was proved to be very reliable in predicting severity of injury that led to mortality with a sensitivity of 70.6% and a specificity of 72.2% at cutoff point =97.39. This result comes in line with **Aly *et al.*** **[11]** who revealed that SAA at day one could significantly predict mortality of the sampled cases with a sensitivity of 75% and a specificity of 100%. SAA level could be a useful marker for early HIE diagnosis in the full-term neonates and also in determining the grade of hypoxia and hence predicting the outcome [13, 14, 19].

No gender difference regarding hypoxic insult was found in the present study. This is in accordance with a study conducted by **Kirimi *et al.*** [34] who reported that hypoxic insult was statistically similar in both males and females of HIE cases. Nevertheless, **Aly *et al.*** [11] in their study showed a significant relation between HIE and male gender as a risk factors of HIE. They supposed that male gender is highly vulnerable to any threatening factors such as placenta insufficiency or increased metabolic demands in fetal males.

CONCLUSION

Cranial ultrasound was proved to be a reliable method for assessing neonates with HIE. RI was shown to be with highly specificity and sensitivity in detecting mortality upon discharge and that the presence of edema was a strong indicator of severe hypoxic-ischemic insult and a predicator of poor prognosis. Finally, SAA level was a useful marker for early HIE diagnosis in the full-term neonates and significantly correlated with the severity of encephalopathy.

Limitations and strength points:

This is the first study, which analyzed the relation between (RI) and (SAA). This study is also one of the first to examine the relationship between neonatal RI values following HIE and specific neurobehavioral outcomes in early childhood. Unfortunately, the RI values were obtained via single artery (middle cerebral artery). The study recommends further measurements within the anterior and posterior cerebral artery to be collected as long as follow-up for behavioral and skeletal neurological development in those neonates.

Acknowledgement: Authors would like to commemorate Professor Dr. Nashwa Mamdouh Samra, professor of pediatrics at Faculty of Medicine, Fayoum University who passed away during the preceding of this research.

List of abbreviations:
CBFV: Cerebral Blood Flow Velocity, **CNN:** Canadian Neonatal Network, **CSF:** Cerebrospinal Fluid, **CPTBN:** Canadian Preterm Birth Network, **CUS:** Cranial Ultrasonography **HIE:** Hypoxic Ischemic Encephalopathy **IQR:** Inter-quartile range **IL-6:** Interleukin-6, **GMH-IVH:** Germinal Matrix Hemorrhage-Intraventricular Hemorrhage **MCA:** Middle Cerebral Artery, **MRI:** Magnetic Resonance Imaging, **NE:** Neonatal Encephalopathy, **NICUs:** Neonatal Intensive Care Units, **PHVD:** Post-Hemorrhagic Ventricular Dilatation, **PVHI:** Periventricular Hemorrhagic Infarction, **RI:** Resistive Index, **TGF:** Transforming Growth Factor, **TNF:** Tumor Necrosis Factor
USG: Ultrasonography.

What is Known – What is New"

What is Known:

- Studies have pointed to the ability of cranial ultrasonography to detect brain changes in asphyxiated neonates yet it has many disadvantages.
- Fortunately, the use of serum amyloid A, an acute phase protein, as a synergistic predictor of the level and extent of brain injury has been mentioned by many literatures with no strong evidence found between resistive index, as a reflector of cerebral blood flow velocity, cranial imaging and mortality outcomes.

What is New:

- Low resistive index and high serum amyloid A were proved to act as indicators of poor prognostic condition in asphyxiated neonates.
- Serum amyloid A and ultrasound can be involved to evaluate the extent and level of asphyxia in neonates upon the first days of life.

DECLARATION

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- **Conflicts of interest/Competing interests:** Authors declared no conflict of interests.
- **Availability of data and material:** Materials are available upon request via contacting corresponding author email
- **Code availability:** 'N/A'
- **Authors' contributions:** Ahmed Abdelmoktader has conceived and designed the analysis. Mohamed Saad was responsible for radio-diagnostic evaluation of the patients and data analysis. Tarek Rashad has collected the data**.** All authors had revised and agreed on the final version of the manuscript.
- **Consent for publication:** 'N/A

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