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ORIGINAL RESEARCH

Predictive Value of Cord Blood Concentrations of Selected Hepatic Enzymes in Hypoxic-Ischaemic Encephalopathy and Related Mortality

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Abstract

Background: Hypoxic-ischaemic encephalopathy remains a major threat to newborn survival, especially in developing countries.
Objectives: To evaluate the predictability of some hepatic biomarkers for hypoxic-ischaemic encephalopathy (HIE) and mortality post-asphyxia event.
Methods: This case-control cross-sectional study was carried out among 70 asphyxiated newborns and 70 healthy newborns. A cord blood sample was obtained at delivery for analysis of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH). The enzyme assay was done using spectrophotometric methods. The Receiver Operating Characteristics (ROC) curve was used to determine the sensitivity and specificity of the enzymes, and the positive and negative predictive values were extrapolated from these.
Results: Out of the 70 asphyxiated babies, 48 (68.6%) had HIE, and five (7.1%) died. The area under curve (AUC) values for AST, ALT, and LDH levels in the ROC curve were all statistically significant as predictors of HIE, best for AST (AUC = 0.873, $p < 0.001$). A cut-off level of ≥71.5U/L for cord blood AST was the best predictor of HIE with sensitivity, specificity and positive predictive values of 64.6%, 95.5% and 96.9%, respectively. Meanwhile, the AUC value for predicting mortality was only significant for AST (AUC = 0.783, $p = 0.036$).
Conclusion: Hepatic enzymes, especially AST, can be used as early diagnostic biomarkers of perinatal asphyxia and can predict HIE. However, they are less reliable as predictors of mortality.

Keywords: Asphyxia, Hypoxic-Ischaemic Encephalopathy, Alanine transaminase, Aspartate Transaminase, Lactate Dehydrogenase, Neonate.

Introduction

Perinatal asphyxia accounts for a significant proportion of neonatal morbidity and mortality, especially in developing countries like Nigeria, where unskilled health attendants are still undertaking a huge fraction of deliveries. It is estimated to account for about 23% of neonatal deaths globally.[1] There is the diversion of blood to the brain, adrenals and heart in response to a persistent asphyxia event in the newborn, a mechanism called the diving reflex.[2] This process leaves the less vital organs, including the liver, less nourished with oxygen-rich blood, resulting in multi-organ dysfunction.[3,4] The hypoxic injury to the liver manifests as an early but temporary increase in the hepatic enzymes, which often return to normal within 6-10 days.[5,6] Elevated Aspartate transaminase (AST), Alanine transaminase (ALT) and Lactate dehydrogenase (LDH) can signal hepatic injury (including hypoxic hepatitis). The normal ranges of AST and ALT in plasma in the first five days of life are 35-140U/L and 6-50U/L respectively, whereas LDH from birth through the first year of life ranges from 170 to 580U/L. [7-9]

Hypoxic ischaemic encephalopathy is an attendant neurologic complication of prolonged asphyxia and often precedes the ultimate untoward outcome of death in the newborn. Apgar score is still the most available tool for the assessment of newborns; its use alone is, however, limited in predicting both immediate and long-term outcomes in asphyxiated neonates.[10-12] It, therefore, becomes imperative to identify biomarkers that can predict the presence of HIE as well as mortality right from the cord blood assay, especially in settings where delivery is conducted by auxiliary nurses or unskilled midwives, as seen in some private hospitals, mission houses and nursing homes. Early biochemical signals of poor outcomes would allow for the prompt institution of the available neuroprotective management to reverse or limit attendant morbidity and mortality.

There is a paucity of published work on this subject matter in Nigeria and many developing countries where perinatal asphyxia still constitutes a high burden on newborn care. The present study determined the use of selected hepatic enzymes (AST, ALT, and LDH) in the cord blood in evaluating asphyxiated babies and presented their predictive values for HIE and immediate postnatal outcome.

Methods

This case-control cross-sectional study was carried out at the labour ward and neonatal intensive care unit of a tertiary hospital in Northcentral Nigeria, from August 2020 to October 2021.

The sample size was calculated using the formula for comparing two means.[10] The mean values of ALT for asphyxiated and apparently healthy babies in a study by Choudhary *et al.* [6] were inputted into the formula. A minimum sample size of 57 was obtained. Using a non-response rate of 10%, the sample size became 63, and this was thereafter rounded up to 70. Thus, a total of 70 asphyxiated babies and 70 apparently healthy gestational age- and sex-matched babies who fulfilled the inclusion criteria were recruited consecutively for the study.

Cord blood pH and Apgar score were determined for the subjects at delivery. Babies with cord blood pH < 7.2 and Apgar score < 7 at the fifth minute of life were diagnosed with perinatal asphyxia and were regarded as the cases, while babies with cord blood pH ≥ 7.2 with fifth minute Apgar score ≥ 7 were recruited as controls.[12,14] Babies with gross congenital malformation or neuromuscular disorders, those whose mothers had features suggestive of chorioamnionitis, and those who had active hepatitis or were on medications that affect hepatic enzymes (such as phenytoin and cimetidine) were excluded from the study.

Detailed clinical and neurological assessments were conducted for each baby at delivery. HIE was diagnosed and staged according to the Sarnat and Sarnat criteria. [15] A cord blood sample was obtained to assay selected liver enzymes (AST, ALT and LDH). These enzymes were assayed using an ultraviolet spectrophotometer at the Chemical Pathology laboratory of the teaching hospital. The data on the correlation of cord blood hepatic enzyme levels with HIE staging and mortality have been published earlier.[16]

Ethical approval

Ethical clearance was obtained from the University of Ilorin Teaching Hospital Ethics and Research Committee with the approval number ERC PAN/2021/03/122. Informed consent was obtained from the parents/caregivers after explaining the details and modes of execution of the study to them. The benefits and potential risks of participation were also explained to the parents.

Data analysis

All the data obtained were entered into a Statistical Package for Social Sciences software version 23 (SPSS Inc., USA) for analysis. The means and standard deviation (SD) of continuous variables (AST, ALT and LDH) and the proportion of categorical variables (e.g., babies that survived or died, babies with HIE and those without HIE) were determined. Student's t-test was used to compare the means of continuous variables between the cases and controls. The receiver operating characteristics curve (ROC) and the area under the curve (AUC) were obtained for the hepatic enzymes to determine the sensitivity and specificity using optimum criterion values of the serum enzymes that maximized the sensitivity and specificity results at different coordinates of the ROC curve. The positive predictive values (PPV) and negative predictive values (NPV) were calculated using the sensitivity, specificity and prevalence of HIE and mortality obtained in this study. A sensitivity rate, specificity rate, PPV or NPV <50% is classified as low/poor, >50-<60% is fair, 60-<80% as moderate/good, 80-<90% as very good/high and ≥90% as excellent. AUC of 0.9 – 1 represented outstanding diagnostic ability, 0.8 – 0.9 excellent, 0.7 – 0.8 good, 0.6 – 0.7 fair, 0.5 – 0.6 poor, while ≤ 0.5 indicates failed diagnostic capability of the modality. [17] For all tests, a p-value less than 0.05 was considered statistically significant.

Results

Of the 70 asphyxiated babies, 48 (68.6%) had HIE, while 5 (7.1%) died. The mean levels for all the enzymes were significantly higher in the cases than in the control group ($p < 0.001$), as shown in Table I. The levels of the three enzymes were significantly higher in asphyxiated neonates with HIE compared to those without HIE (p <0.03). Table II shows 48 neonates had HIE out of the 70 asphyxiated neonates studied, of which five died, with a case fatality of 10.4% for HIE and 7.1% for the entire asphyxia cases. The mean AST, ALT and LDH levels were significantly elevated in the neonates that died when compared to those who survived (p = 0.006, 0.003 and 0.004 respectively).

Predictive value of hepatic enzymes for the presence of HIE and mortality

A ROC curve was obtained to determine the predictive value of the hepatic enzymes for the presence of HIE, as shown in Figure 1. The AUC values for cord blood AST, ALT and LDH levels in the ROC curve were all statistically significant as predictors of HIE, as shown in Table III.

Table I: Cord blood AST, ALT and LDH in cases and control group; no HIE versus HIE cases [16]

Enzymes	*Mean ± SD (U/L)*		*t*	*p-value*
	Cases (n = 70)	**Controls (n = 70)**		
AST	85.47 ± 37.83	20.05 ± 9.58	8.46	< 0.001
ALT	25.73 ± 9.56	5.22 ± 1.74	5.75	< 0.001
LDH	483.51 ± 144.16	219.29 ± 77.81	7.21	< 0.001
	Cases			
	No HIE (n = 22)	**HIE (n = 48)**		
AST	107.98 ± 21.48	36.36 ± 14.42	5.15	<0.001
ALT	32.69 ± 9.26	10.55 ± 4.87	3.10	0.030
LDH	561.31 ± 140.59	313.77 ± 92.69	3.66	0.001

Table II: Immediate outcome in the asphyxiated neonates and the mean hepatic enzyme levels [16]

Enzymes	*Survived (n = 65)*	*Died (n = 5)*	*t*	*p-value*
AST (U/L)	79.82 ± 25.54	159.00 ± 69.44	-2.833	0.006
ALT (U/L)	22.86 ± 6.26	63.00 ± 20.57	-3.119	0.003
LDH (U/L)	456.74 ± 122.26	831.60 ± 466.95	-2.986	0.004

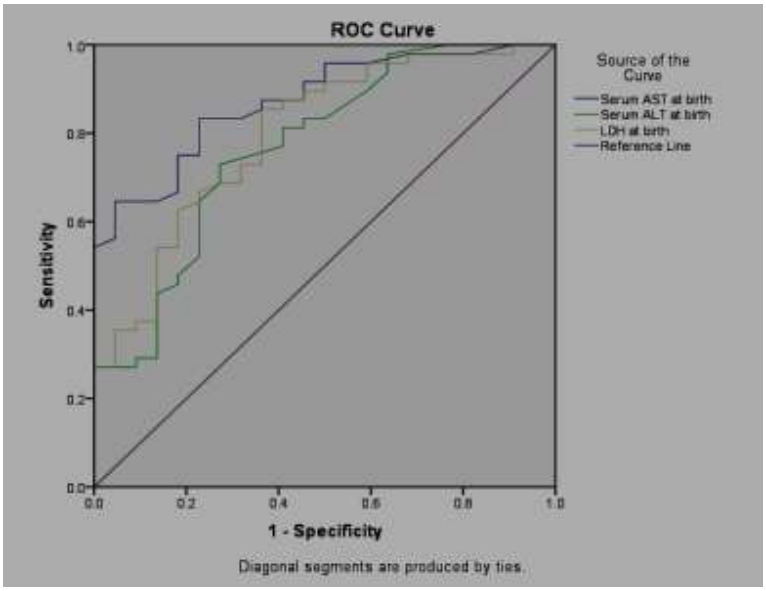

Figure 1: ROC curve for AST, ALT, and LDH predicting HIE

The value was excellent for AST (AUC = 0.873, p < 0.001). Also, a ROC curve was generated to determine the ability of the enzymes to predict mortality (Figure 2), and the AUC values were obtained as depicted in Table III. The AUC value was good and statistically significant for only AST (AUC = 0.783, p = 0.036). Table IV represents the sensitivity and specificity rates of serum AST, ALT, and LDH levels at birth for HIE at different criterion values and coordinates of the ROC curve.

Table III: Area under the curve for the hepatic enzymes predicting HIE and mortality

Enzymes Level	*Area Under Curve*	*95%CI*	*p-value*
	Hypoxic-Ischaemic Encephalopathy		
AST	0.873	0.792 – 0.954	< 0.001
ALT	0.771	0.650 – 0.892	< 0.001
LDH	0.797	0.685 – 0.910	< 0.001
	Mortality		
AST	0.783	0.594-0.972	0.036
ALT	0.765	0.495-1.000	0.05
LDH	0.718	0.466-0.971	0.105

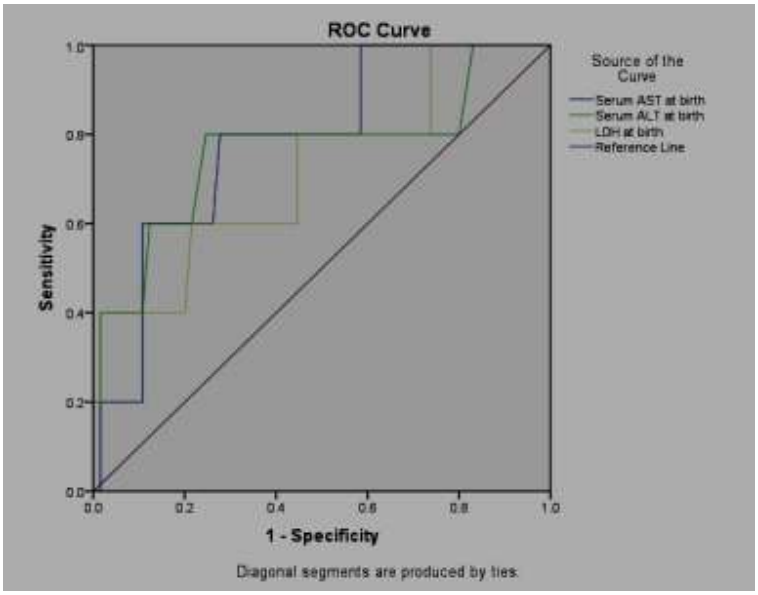

Figure .2: ROC curve for hepatic enzymes (AST, ALT and LDH) predicting mortality

Comparing the sensitivity and specificity rates, and the calculated PPV and NPV of the cord blood hepatic enzymes studied, serum AST had the best predictive ability, with 64.6% sensitivity, 95.5% specificity, 96.9% PPV and 55.3% NPV for HIE, at an optimum cut-off value of ≥ 71.5U/L as shown in Table V.

The sensitivity and specificity rates of serum AST, ALT and LDH levels at birth for mortality at different criterion values and coordinates of the ROC curve were also represented in Table V. Comparing the sensitivity and specificity rates, PPV and NPV of the three hepatic enzymes studied, serum AST also had the best predictive value, with 80.0% sensitivity, 72.3% specificity, 18.1% PPV and 97.9% NPV for mortality, at an optimum cut-off value of ≥ 113U/L as shown in Table VI.

Discussion

There were significantly elevated mean cord blood serum aminotransferases (AST and ALT) and LDH in the setting of perinatal asphyxia and its severity in affected newborns when compared with the apparently healthy newborns earlier published [16], and these findings corroborated that of other authors.[18-22] Elevated levels of AST, ALT and LDH often signal hepatic dysfunction, which can be consequent upon prolonged asphyxia.

Table IV: Sensitivity and specificity of serum AST, ALT and LDH at birth for HIE at different cut-off values of the enzymes (criterion values and coordinates of ROC curve)

Serum AST at birth			*Serum ALT at birth*			*Serum LDH at birth*		
Criterion	**Sensitivity**	**Specificity**	**Criterion**	**Sensitivity**	**Specificity**	**Criterion**	**Sensitivity**	**Specificity**
≥5.0	100.0	0.0	≥1.0	100.0	0.0	≥123.0	100.0	0.0
≥16.5	97.9	18.2	≥4.5	93.8	36.4	≥151.5	97.9	9.1
≥25.0	95.8	50.0	≥7.0	83.3	50.0	≥224.0	95.8	31.8
≥42.5	87.5	63.6	≥10.5	81.3	59.1	≥257.5	91.7	40.9
≥49.5	83.3	68.2	≥12.5	77.1	59.1	≥285.5	89.6	50.0
≥54.0	81.3	77.3	≥14.5	68.8	72.7	≥300.0	87.5	54.5
≥58.5	75.0	81.8	≥16.0	64.5	77.3	≥353.5	79.2	63.6
≥68.5	64.6	86.4	≥19.5	47.9	81.8	≥403.0	66.7	77.3
≥71.5	64.6	95.5	≥22.5	41.7	86.4	≥444.0	54.2	86.4
≥96.0	54.2	100.0	≥29.0	29.2	90.9	≥503.5	45.8	86.4
≥102.0	50.0	100.0	≥33.0	27.1	100.0	≥569.5	35.4	95.5
≥152.0	20.8	100.0	≥52.0	22.9	100.0	≥631.0	27.1	100.0

Table V: Sensitivity and specificity rates of serum AST, ALT and LDH at birth for mortality at different cut-off values of the enzymes (criterion values and coordinates of ROC curve)

Serum AST level at birth			*Serum ALT level at birth*			*Serum LDH level at birth*		
Criterion	*Sensitivity*	*Specificity*	*Criterion*	*Sensitivity*	*Specificity*	*Criterion*	*Sensitivity*	*Specificity*
≥5.0	100.0	0.0	1.5	100.0	7.7	123.0	100.0	0.0
≥25.0	100.0	20.0	9.5	80.0	30.8	253.0	100.0	18.5
≥31.5	100.0	23.1	14.5	80.0	46.2	295.5	80.0	26.2
≥56.5	80.0	41.5	20.5	80.0	66.2	397.5	80.0	46.2
≥71.5	80.0	56.9	22.5	80.0	70.8	432.5	60.0	55.4
≥113.0	80.0	72.3	31.0	60.0	81.5	578.5	60.0	78.5
≥126.0	60.0	83.1	59.0	40.0	89.2	698.5	40.0	87.7
≥171.0	40.0	89.2	106.0	20.0	98.5	732.5	40.0	90.8
≥213.0	20.0	96.9	122.5	20.0	100.0	1236.0	40.0	98.5
≥281.0	0.0	100.0	133.0	0.0	100.0	1551.0	0.0	100.0

Table VI: Sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) of the cord blood hepatic enzymes for HIE at optimum cut-off values

Enzyme levels	*Cut-off value (u/l)*	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
		Hypoxic-Ischaemic Encephalopathy			
AST	≥ 71.5	64.6	95.5	96.9	55.3
ALT	≥ 16.0	64.5	77.3	86.1	50.0
LDH	≥ 403	66.7	77.3	86.5	51.5
		Mortality			
AST	≥ 113.0	80.0	72.3	18.1	97.9
ALT	≥ 22.5	80.0	70.8	17.3	97.9
LDH	≥ 578.5	60.0	78.5	17.6	96.3

There is, therefore, a possibility of spillage of these enzymes into circulation following hypoxic injury, even before the delivery of the baby. Elevated cord blood AST, ALT, and LDH levels predicted HIE in the present study, all having high PPV values. This implies that elevations beyond the optimum cut-off values indicate a high likelihood of HIE occurrence. The best predictive values were observed for AST, with a PPV of 96.9%, NPV of 55.3%, sensitivity of 64.6% and specificity of 95.5% at a cut-off value of 71.5U/L. This finding is contrary to an Indian

report [22] where AST reportedly showed the lowest predictive value among the three enzymes. In the authors' report, the sensitivity and specificity of AST in predicting HIE were 75% and 63%, respectively, at a cut-off value of > 54U/l. The authors used venous blood taken on the third day of life to estimate serum AST, ALT and LDH levels, unlike cord blood used in the present study. In the study at Ile Ife, Nigeria, [23] where the enzymes were assayed from venous blood at the 12th hour of life, they reported the highest predictive values for LDH at a cut-off value of 1006.8U/l, with 100% sensitivity, specificity, positive and negative predictive values. In the present study, LDH had good sensitivity and specificity of 66.7% and 77.3% at a cut-off value of 403U/L but a lesser performance when compared with AST. The variation in the findings in different studies may be due to the timing of sample collection, the differences in the methods used for estimating the enzymes in various laboratories and the cut-offs used. In their work, hepatic enzymes were estimated in the blood within the 12th to 72nd hour of life as opposed to the cord blood sample at delivery used in the present work.

Five out of the 70 asphyxiated babies died, giving a case fatality rate of 7.1 per cent. We have earlier reported higher mean AST, ALT and LDH levels for dead asphyxiated babies when compared to the survivors. [16] The predictive values of the cord blood levels of these hepatic enzymes for mortality were best for AST at an optimum cut-off value of ≥113U/l. The three enzymes had moderate sensitivity (60-80%) and specificity rates (70.8-78.5%) for mortality above their critical cut-offs. They, however, showed excellent negative predictive values (96.3-97.9%), with low positive predictive values for mortality. This implies that death is an improbable outcome in a baby with normal cord blood serum hepatic enzyme levels while looking at the degree of hepatic dysfunction from asphyxia only. A low positive predictive value for mortality, as seen in this study, means the enzymes cannot strongly predict the likelihood of death in the asphyxiated babies, even above the optimum cut-off values. Most of the published studies did not measure these enzymes' predictive values for mortality, so it is difficult to compare results. The findings in this study, therefore, suggest that even though babies with severely elevated hepatic enzyme levels may have HIE, other variables may also account for mortality in them beyond just hepatic dysfunction.

The strength of this study was in the use of cord blood pH in combination with Apgar scores for the diagnosis of perinatal asphyxia in a resource-poor setting. More so, the predictive value of the hepatic enzymes for mortality was determined in this study, an improvement over most of the previous studies.
A limitation of this study is the small sample size, which may make the findings non-generalizable. Therefore, a large sample size in a multi-centre study is recommended subsequently. Also, the blood pressure of the asphyxiated babies was not measured to establish the presence of circulatory shock, which may also negatively impact the liver functions and worsen the babies' outcomes.

Conclusion

Hepatic biomarkers may be useful as supportive tools for the objective assessment of neonates with asphyxia rather than relying on physical parameters (Apgar score) alone. In this study, aspartate aminotransferase appears to be a reliable surrogate biomarker for predicting the presence of HIE. All the enzymes had excellent negative predictive values for mortality.

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Authors' Contributions: ASO conceptualized and designed the study, was involved in data analysis and interpretation, and drafted the manuscript. OAI, AOO and AOV contributed to the concept and design of the study and were involved in data analysis, data interpretation, and revision of the draft manuscript. OAO, REO and SIA contributed to the revision of the draft manuscript. OKA contributed immensely to the laboratory analysis. All the authors approved the final version of the manuscript.
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