

Cardiac Troponin I and Electrocardiographic Changes as Markers of Myocardial Injury and Mortality in Term Neonates with Birth Asphyxia: A Comparative Study in Uyo, Southern Nigeria

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Research Article

Keywords:

Posted Date: July 29th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10349535/v1>

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Additional Declarations: No competing interests reported.

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Abstract

Background:

Birth asphyxia accounts for more than a million neonatal deaths worldwide. Cardiovascular dysfunction following hypoxic myocardial injury has been reported in up to a third of these asphyxiated neonates and is known to contribute to the high mortality rate associated with birth asphyxia. This study aimed to compare cardiac troponin I levels and electrocardiographic (ECG) changes in asphyxiated and non-asphyxiated neonates and determine the prognostic value of both in asphyxiated neonates at the University of Uyo Teaching Hospital (UUTH).

Method: The study was conducted at the Newborn Unit of the UUTH over seven months from March 2023 to September 2023. Fifty term neonates (25 with birth asphyxia and 25 healthy controls) aged twelve hours or less, were enrolled after informed parental consent. A structured study proforma was completed for each participant before physical examination, electrocardiography, and cardiac troponin I assay. Neonates who had moderate or severe birth asphyxia using the combined criteria of APGAR score at 5th minute and Sarnat and Sarnat staging were recruited as the asphyxiated group while age and sex-matched healthy neonates were recruited as the non-asphyxiated group.

Result:

The median (Interquartile Range) cardiac troponin I value in asphyxiated neonates was 0.29 ng/mL (0.21-0.47), which was significantly higher than the median (Interquartile Range) of 0.023 ng/mL (0.018-0.030) obtained in the non-asphyxiated neonates ($p < 0.001$) and also higher than the 0.1 ng/mL considered as upper limit for normal levels. Also, cardiac troponin I level greater than 0.5 ng/mL was associated with an increased likelihood of mortality from asphyxia ($p = 0.010$). All asphyxiated neonates

had abnormal ECG patterns and 56% had ST-segment abnormalities classified as grade III according to Jedeikin's criteria compared to the non-asphyxiated neonates where only 3(12%) had abnormal ECG findings, most of which were T wave abnormalities.

Conclusion:

Elevated cardiac troponin I concentrations and abnormal ECG findings were significantly more common among neonates with birth asphyxia in this study when compared to non-asphyxiated neonates. Also, cardiac troponin I was demonstrated to be a better predictor of mortality than electrocardiographic abnormalities in asphyxiated neonates

Background:

The World Health Organisation (WHO) defines birth asphyxia as the inability to initiate or sustain respiration at birth.¹ Approximately four million babies are estimated to be asphyxiated at birth annually² and about a quarter of affected babies die, making birth asphyxia responsible for approximately one million deaths annually³ and one of the leading causes of neonatal and under-five mortality.³ Resource-limited countries, especially those in sub-Saharan Africa have higher rates of birth asphyxia⁴ with Nigeria bearing one of the highest burdens of asphyxiated neonates in sub-Saharan Africa.⁵ Several studies have reported that birth asphyxia is responsible for at least a fifth of admissions in neonatal units of tertiary hospitals across the country.^{5,6,7,8} High mortality rates have also been reported in the asphyxiated neonates described in these studies and in the University of Uyo Teaching Hospital it is the third most common cause of death in the neonatal unit.⁹

The widespread hypoxia resulting from birth asphyxia causes a "diving reflex" which is instituted as a protective measure and leads to the redistribution of blood away from non-essential organs (kidneys, liver, gastrointestinal tract) to vital organs, mainly the brain and the heart.¹⁰ Although the resulting hypoxia affects multiple organ systems; the heart and kidneys are the two major extra-cerebral organs affected.¹¹

Although up to a third of asphyxiated neonates have cardiovascular dysfunction,¹² most research and care in asphyxiated neonates is primarily focused on minimising/treating neurological injury and this could be potentially contributing to under-recognition of cardiovascular dysfunction and possible continued high mortality associated with birth asphyxia.

In birth asphyxia, hypoxia and the resulting acidosis lead to a persistently increased pulmonary vascular resistance and persistent pulmonary hypertension.¹³ The sustained elevation of the right ventricular pressure leads to tricuspid regurgitation, ischaemia of the tricuspid papillary muscle and persistent shunting across the foramen ovale.¹⁴ While the initial response of the heart is to increase heart rate, persistent hypoxia will lead to progressive decline in cardiac contractility and heart rate (bradycardia)¹¹ with reduced cardiac output resulting in hypotension, poor perfusion and worsening ischaemia of the muscles of the heart.¹⁵

Common cardiovascular manifestations include tachycardia, cyanosis, reduced oxygen saturation, prolonged capillary refill time, respiratory distress, hypotension, and shock while cardiac murmurs, heart failure and hypertension were not common findings among asphyxiated neonates.^{16,17.}

The variable timeline between myocardial injury and cardiovascular collapse highlights the importance of objective investigations such as electrocardiography (ECG), cardiac biomarkers, and echocardiography for the early detection of myocardial injury.¹⁸

While there are many biomarkers for detecting myocardial injury, cardiac troponins (cardiac troponin I and T) are considered as the gold standard¹⁹ and since Cardiac troponin I has only one specific cardiac isoform with high specificity for myocardial injury,²⁰ it is a very reliable indicator of myocardial injury.

Early detection of myocyte injury in asphyxiated neonates, will lead to early introduction of supportive therapies resulting in a reduction in the mortality rate associated with asphyxiated neonates.²¹

Despite increasing evidence supporting cardiac biomarkers, data comparing the diagnostic and prognostic utility of cardiac troponin I and electrocardiographic abnormalities among asphyxiated neonates in sub-Saharan Africa remain limited. This study therefore compared cardiovascular examination findings, cardiac troponin I concentrations, and electrocardiographic changes in term neonates with birth asphyxia and evaluated their prognostic value for mortality.

Aim/Objectives:

This study aimed to compare cardiovascular system examination findings, cardiac troponin I levels and electrocardiographic (ECG) changes in asphyxiated and non-asphyxiated neonates and determine their prognostic value for mortality among asphyxiated neonates at the University of Uyo Teaching Hospital (UUTH).

Methods:

Study Design:

This was a hospital based comparative cross-sectional study.

Study setting:

The study was conducted at the Newborn Unit of the University of Uyo Teaching Hospital, Uyo, Akwa Ibom State, Nigeria, over seven months, from March to September 2023. It is a tertiary hospital and serves as the referral center for the state serving in-born and out-born neonates.

Study Population:

The study population comprised term neonates delivered at a gestational age of at least 37 completed weeks and assessed within the first 12 hours of life.

Neonates with Apgar scores of six or less, in five minutes and history of poor cry at birth with Hypoxic Ischaemic Encephalopathy stage two or three as classified by the clinical features of Sarnat and Sarnat were recruited as the asphyxiated group. For each asphyxiated neonate, a healthy term neonate without birth asphyxia was recruited into the non-asphyxiated comparison group and matched by sex and postnatal age. Neonates with morphological features suggestive of congenital or chromosomal abnormalities and those whose parents or caregivers declined consent were excluded. Neonates who otherwise met the eligibility criteria but presented to the Newborn Unit more than 12 hours after birth were also excluded.

Sample Size Determination:

The sample size was calculated using the formula used for comparative cross sectional study with a quantitative outcome²² as follows

$$n = \frac{(U + V)^2 (\sigma_1^2 + \sigma_0^2)}{\mu_1 - \mu_2}$$

Where:

n = sample size per group

U was the standard normal deviate corresponding to a statistical power of 90% and was set at 1.28.

V was the standard normal deviate corresponding to a two-sided significance level of 5% and was set at 1.96.

σ = Standard deviation of cardiac troponin levels (σ_0 and σ_1 represent standard deviations for babies without asphyxia and babies with asphyxia respectively)

$\mu_1 - \mu_2$ = difference in means of cardiac troponin levels for the outcome of the two groups that the investigator will not want to miss.

For this study, σ_0 of 0.22; σ_1 of 0.22; and $\mu_1 - \mu_2$ of 0.2ng/mL was assumed based on a previous similar study¹⁶ Hence:

$$n = \frac{(1.28 + 1.96)^2 (0.22^2 + 0.22^2)}{(0.2)^2}$$

The calculated minimum sample size was 21 neonates per group. After allowing for a 10% non-response or attrition rate, the minimum sample size increased to 23 neonates per group. Twenty-five neonates were therefore recruited into each group to account for possible incomplete data or loss of participants before completion of all study procedures. A total of 50 neonates were enrolled.

Sampling Technique:

Eligible neonates were consecutively recruited within the first twelve hours of life. Each recruited neonate underwent a detailed clinical examination to identify any congenital abnormalities and document baseline clinical findings before blood sampling and electrocardiography. Twenty-five eligible neonates with birth asphyxia were consecutively recruited during the study period. For each asphyxiated neonate, one non-asphyxiated neonate matched by sex and postnatal age was recruited. Data were collected using a structured investigator-administered proforma.

Data Collection:

Following written informed consent, eligible neonates were recruited and assessed using a structured proforma. Recruitment and all baseline study assessments were completed within the first 12 hours of life. The study procedures were explained to the parents or caregivers of eligible neonates, and written informed consent was obtained before enrolment. A structured proforma was then completed for each participant.

Biodata and sociodemographic and obstetric history were recorded in the proforma. Anthropometric measurements (weight, length, occipitofrontal circumference) were taken and recorded on the proforma.

A general examination was documented with details of axillary temperature (measured in degree Celsius), oxygen saturation (before oxygen supplementation), pallor, capillary refill time and jaundice. Heart rate, apex beat location, presence/absence of murmur, respiratory rate, presence/absence of dyspnea and breath sounds were documented.

A detailed neurological examination was performed in asphyxiated neonates. The level of consciousness, muscle tone, primitive reflexes, including sucking and Moro reflexes, pupillary responses, autonomic function, and the presence of seizures were assessed and used to classify hypoxic–ischaemic encephalopathy according to the Sarnat and Sarnat staging system.

Blood sampling/ serum preparation method:

Two milliliters (mls) of venous blood was taken from each participant under strict aseptic procedure and put in a properly labeled sterile plain bottle. Sample was promptly taken to the chemical pathology laboratory of the University of Uyo Teaching Hospital for analysis of troponin I levels. Samples were allowed to clot after which serum was separated immediately via centrifugation. Serum was analyzed immediately or at most within 24hrs of collection.

Troponin I assay:

The cardiac troponin I assay was performed in the Chemical Pathology Research Laboratory of the University of Uyo Teaching Hospital. Serum cardiac troponin I was measured using the mini VIDAS® high-sensitivity cardiac troponin I assay manufactured by bioMérieux. The assay is a fully automated immunoassay based on the enzyme-linked fluorescent assay principle.

Electrocardiography (ECG):

A standard 12-lead electrocardiogram was recorded for each participant by the principal investigator using a UNI-EM Cardiomin 12B digital electrocardiograph. The electrocardiograph was calibrated at the standard setting of 10 mm/mV for all leads. The recording speed was set at 25 mm/s. After electrode placement, each neonate was allowed approximately 10 minutes to settle before recording. A caregiver assisted with gentle positioning when necessary to minimize movement artefact.

Once regular tracings were noted without artefacts, ECG results were printed out for each participant. The ECG results were categorized using Jediekin's²³ criteria as follows:-

Grade 1: T wave is flat or inverted in one or two leads except AVR; normal ST, and normal Q.

Grade 2: T wave is flat or inverted in greater than three leads except AVR; normal ST, and normal Q.

Grade 3: Flat or inverted T waves in three or more leads other than aVR, with one or more of the following: ST-segment elevation or depression greater than 2 mm in at least two precordial leads; ST-segment elevation or depression greater than 1 mm in at least two limb leads; or pathological Q waves, defined as a duration greater than 0.02 seconds or an amplitude greater than 25% of the corresponding R-wave amplitude in one anterior lead or three related precordial leads.

Grade 4: Classical segmental infarction with abnormal Q wave and markedly raised ST segments or complete left bundle branch block.

Infants whose ECG results did not show any of these abnormalities listed above were categorized as "No changes". Electrocardiograph results were interpreted by the lead researcher and corroborated by the paediatric cardiologist to enhance validity of results.

Data Management & Analysis:

The data relating to study participants were extracted from the study proforma and entered into Microsoft excel software. The data was then exported from Microsoft excel to Statistical Package for Social Science for Windows (SPSS Inc. Chicago IL, USA) version 27 for further analysis.

The independent variables in the study were presence or absence of asphyxia, while cardiac troponin level and ECG patterns were the dependent variables. Mortality from asphyxia was the secondary outcome variable. Normality of data was assessed using histogram.

Cardiac troponin I levels were summarized using median, range, and inter-quartile range (IQR). The median and mean ranks of cardiac troponin I levels of the asphyxiated and non-asphyxiated groups were compared using a Mann-Whitney U-test because the serum troponin I distribution of the asphyxiated study group was moderately skewed. The same test was carried out to compare the mean ranks of neonates who died and those who survived among the asphyxiated study group. Other numerical variables (number of neonates, gestational age, age at sample collection, and birth weight,) were summarized using mean and standard deviation, and compared using independent T-test. A Kruskal-Wallis H test was done to compare the mean ranks of serum troponin I levels across the different ECG changes seen in asphyxiated neonates.

Categorical variables were summarized using frequencies and percentages and compared using Fisher's exact test.

Binary logistic regression was performed to evaluate factors associated with mortality among asphyxiated neonates. Effect estimates were reported as odds ratios with 95% confidence intervals. Cardiac troponin levels and ECG changes met the criteria of being added to the regression model and significantly contributed to the model [P-value (P) = .002]

The study results were presented using tables and charts, and P-values of less than 0.05 were considered statistically significant.

Result:

Fifty (50) term neonates were recruited into the study: twenty-five asphyxiated and twenty-five non-asphyxiated. The sexes in both groups were equally matched, with each group having thirteen females and twelve males. The oxygen saturation (%) level in non-asphyxiated neonates was significantly higher than that of the asphyxiated neonates ($p < 0.010$), while capillary refill time (sec.) was significantly longer in asphyxiated neonates ($p = .010$).

Table 1a shows the demographics and some clinical features of the participants. The median age (range) of the participants' mothers was 29 (20-45) years, and the median parity (range) was 2 (1-4). There was a significant difference in the place of delivery of mothers ($p < 0.001$), and the duration of labour was significantly longer for mothers of asphyxiated neonates ($p < 0.001$). Figure 1 shows a significant difference between the modes of delivery of the mothers of asphyxiated neonates and non-asphyxiated neonates ($\chi^2 = 12.81$; $p = 0.002$).

Table I: Maternal and obstetric characteristics of asphyxiated and non-asphyxiated neonates

Variable, n (%)	Asphyxiated (n=25)	Non- asphyxiated (n=25)	Total (N=50)	Test statistic	<i>p-value</i>
Age of mother (years)					
<25	5 (20.0%)	3 (12.0%)	8 (16.0%)	FET=2.415	0.539
25-34	16 (64.0%)	16 (64.0%)	32 (64.0%)	d.f=3	
35-44	3 (12.0%)	6 (24.0%)	9 (18.0%)		
≥ 45	1 (4.0%)	0 (0.0%)	1 (2.0%)		
Social Class of parents					
Class 1	4 (16.0%)	11 (44.0%)	15 (30.0%)	FET=7.002	0.123
Class 2	4 (16.0%)	6 (24.0%)	10 (20.0%)	d.f=4	
Class 3	7 (28.0%)	4 (16.0%)	11 (22.0%)		
Class 4	4 (16.0%)	2 (8.0%)	6 (12,0%)		
Class 5	4(16%)	1(4%)	5(10%)		
Class 6	2 (8.0%)	1 (4.0%)	3 (6.0%)		
Number of ANC visits					
None	8 (32.0%)	4 (16.0%)	12 (24.0%)	FET=6.274	0.071
< 3	3 (12.0%)	0 (0.0%)	3 (6.0%)	d.f=3	
3-5	2 (8.0%)	1 (4.0%)	3 (6.0%)		
≥ 5	12 (48.0%)	20 (80.0%)	32 (64.0%)		

Place of Delivery

Home	10 (20.0%)	0 (0.0%)	10 (20.0%)	<i>FET</i> =12.5	<0 .001
Health Facility	15 (37.5%)	25 (62.5%)	40 (80.0%)	d.f=1	

Duration of Labour

Median (Range)	18.0(6.0-80.0)	9.0(6.0-14.0)		<i>U</i> =534.000	<0 .001
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FET: Fishers Exact test; d.f: degree of freedom; U: Mann-Whitney U test

Variable	Asphyxiated (n=25)	Non-asphyxiated (n=25)	Test value	<i>p-value</i>
Mode of delivery, n (%)				
SVD	14 (73.7%)	5 (26.3%)	<i>FET</i> =12.81	0.002
Elective CS	2 (13.3%)	13 (86.7%)	d.f=2	
Emergency CS	9 (56.3%)	7 (43.8%)		
Gestational age at birth (weeks), mean $\pm$ SD	39.12 $\pm$ 1.39	39.60 $\pm$ 1.26	t= -1.278	0.207
Age at sample collection (hours), mean $\pm$ SD	7.28 $\pm$ 3.26	5.80 $\pm$ 3.25	t= -1.607	0.115
Birth weight (kg), mean $\pm$ SD	3.15 $\pm$ 0.43	3.12 $\pm$ 0.58	t=0.153	0.879

Oxygen saturation (%), mean $\pm$ SD	89.04 $\pm$ 10.65	97.52 $\pm$ 1.69	t= 3.933	< 0.001
Heart rate(b/m), mean $\pm$ SD	153.72 $\pm$ 18.02	148.28 $\pm$ 10.19	t= -1.293	0.202
Respiratory rate (c/m), mean $\pm$ SD	69.88 $\pm$ 14.69	60.32 $\pm$ 9.71	t= -2.714	0.009
Capillary refill time (sec.), n (%)				
< 3	18(72.0%)	25(100.0)%	FET=8.140	0.010
$\geq$ 3	7(28.0%)	0(0.0%)	d.f=1	
Appearance of neonate, n (%)				
Pink	9(26.5%)	25(73.5%)	FET=25.002	<0.001
Dusky	12(100.0%)	0(100.0%)	d.f=2	
Cyanosed	4(100.0%)	0(100.0%)		
APGAR score				
1 to 3	4(100.0%)	0(0.0%)	FET=58.211	<0.001
4 to 6	12(100.0%)	0(0.0%)	d.f=3	
7 and above	0(0.0%)	25(100.0%)		
No score	9(100.0%)	0(0.0%)		
BCS category				
Unconscious	2(100.0%)	0(0.0%)	FET=16.492	<0.001
Semi-conscious	10(100.0%)	0(0.0%)	d.f=2	
Fully conscious	13(34.2%)	25(65.8%)		
Sarnat and Sarnat HIE stage				
No/mild HIE	0(0.0%)	25(100.0%)	FET=59.694	<0.001

Moderate HIE	14(100.0%)	0(100.0%)	d.f=2
Severe HIE	11(100.0%)	0(100.0%)	

SD: Standard deviation; t: Independent t test value; FET: Fishers Exact test; BCS: Blantyre Coma Score; HIE:

General Characteristics of Survivors and Non-survivors of Birth Asphyxia

Table IIa shows that demographic and clinical characteristics of asphyxia survivors and non-survivors were comparable. In this study, approximately a third of asphyxiated neonates died giving a case fatality rate (CFR) of twenty-eight percent (28%).

Table IIa Characteristics of non-survivors and survivors of birth asphyxia

Variable	Non-survivors (n=7)	Survivors (n=18)	Total (n=25)	Test value	<i>p-value</i>
Gestational age at birth (weeks), mean $\pm$ SD	39.7 $\pm$ 0.8	39.6 $\pm$ 1.4		t= -0.360	0.722
Age at sample collection (hours), mean $\pm$ SD	7.9 $\pm$ 3.4	9.6 $\pm$ 3.6		t= 1.154	0.260
Birth Weight (kg)					
2.50 - 3.99	6 (26.1%)	17 (73.9%)	23 (100.0%)	FET=0.522	0.490
$\geq$ 4.00	1 (50.0%)	1 (50.0%)			
SD: Standard deviation; t: Independent t test; FET: Fishers Exact test					

Table IIb. Characteristics of non-survivors and survivors of birth asphyxia (continued)

Variable	Died (n=7)	Survived (n=18)	Total (n=25)	Test value	<i>p-value</i>
Oxygen Saturation (%)					

≤ 92	5 (33.3%)	10 (66.7%)	15 (100.0%)	FET=0.529	0.659
> 92	2 (20.0%)	8 (80.0%)	10 (100.0%)	d.f=1	
Capillary Refill (seconds),					
< 3	5 (27.8%)	13(72.2%)	18 (100.0%)	FET=0.002	1.000
≥ 3	2 (28.6%)	5 (71.4%)	7 (100.0%)	d.f=1	
HIE Stage					
Moderate	4 (28.6%)	10 (71.4%)	14 (100.0%)	FET=0.005	1.000
Severe	3 (27.3%)	8 (72.7%)	11 (100.0%)	d.f=1	

FET: Fishers Exact test; d.f: degree of freedom

Cardiac Troponin I Levels in the Study Groups

The median (IQR) cardiac troponin I values for the asphyxiated neonates [0.288 (0.21-0.47) ng/mL] was 13 times higher than that of the non-asphyxiated neonates [0.023 (0.018 - 0.03) ng/mL]. The Mann-Whitney U test showed a significant difference between the distribution of cardiac troponin I of asphyxiated and non-asphyxiated neonates. ($U=624.000$; $p= 0.001$).

No neonate in the non-asphyxiated group had troponin level of up to 0.1ng/mL or more.

Figure 2 is a box and whisker plot showing that the maximum cardiac troponin value among the neonates without asphyxia (0.075ng/mL) was similar to the minimum cardiac troponin value observed among the neonates with asphyxia (0.075ng/mL). In addition, the cardiac troponin I scores for the neonates with asphyxia had a wider spread (IQR=0.21 - 0.47) when compared to those of the neonates without asphyxia (IQR= 0.018 – 0.03).

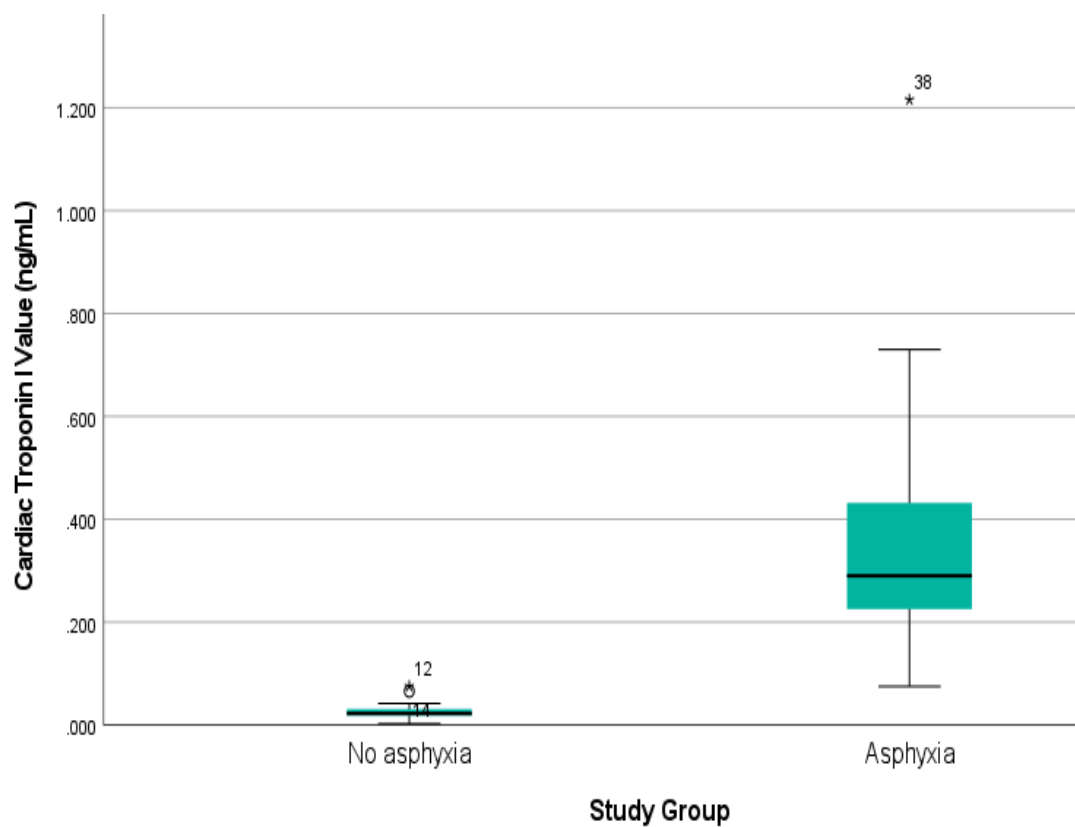


Fig. 11: Distribution of cardiac troponin I levels in asphyxiated and non-asphyxiated neonates

Figure 3 shows the distribution of cardiac troponin I levels across clinical stages of HIE among asphyxiated neonates. Although the median (IQR) level of cardiac troponin I in neonates with HIE Stage 3 [0.28(0.14-0.39) ng/mL] was higher than that of neonates with HIE 2 [0.30(0.25-0.62) ng/mL], the difference was not significant [$U=96.000$, $p=0.298$]. There was no case of HIE stage 1 among the asphyxiated neonates.

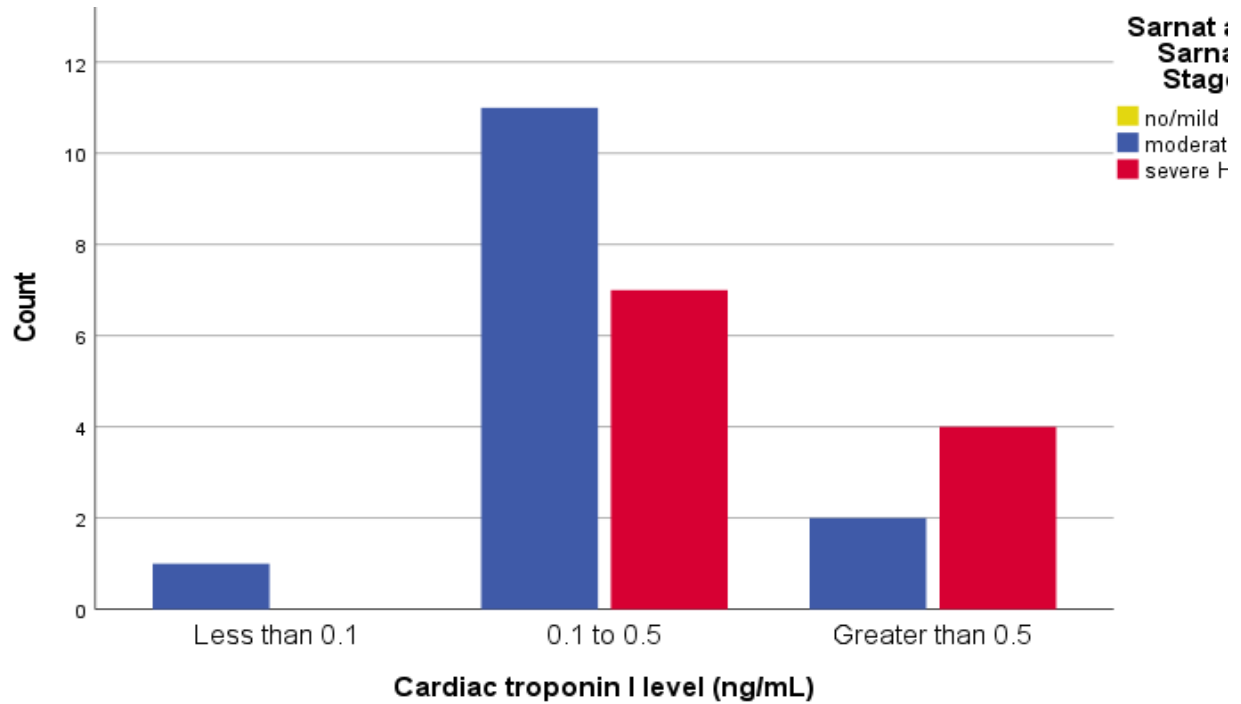


Figure 12: Distribution of cardiac troponin I levels across clinical stages of HIE among asphyxiated neonates.

Electrocardiographic (ECG) patterns in the Study Groups

Figure 4 shows that there was a significantly higher proportions of abnormal ECG changes in asphyxiated neonates than in their non-asphyxiated counterparts ($\chi^2 = 39.567$; $p = < 0.001$). Only three (12%) of the non-asphyxiated neonates had abnormal ECG changes (one Grade I; one Grade II; and one Grade III). Abnormal ECG changes were seen in all the asphyxiated neonates: Fourteen (56%) had Grade III changes; seven (28%) Grade II; and four (16%) Grade I changes. There were no Grade IV changes in either of the study groups.

There was no significant difference in the distribution of ECG patterns across stages of HIE ($U = 79,500$, $p = 0.818$). There was also no significant difference in the distribution of cardiac troponin I levels across ECG changes seen in asphyxiated neonates. A Kruskal-Wallis H test demonstrated a mean rank cardiac troponin I value of 8.75 for Grade I changes; 7.43 for Grade II changes; and 17.00 for Grade III ($H = 9.481$, $p = 0.09$).

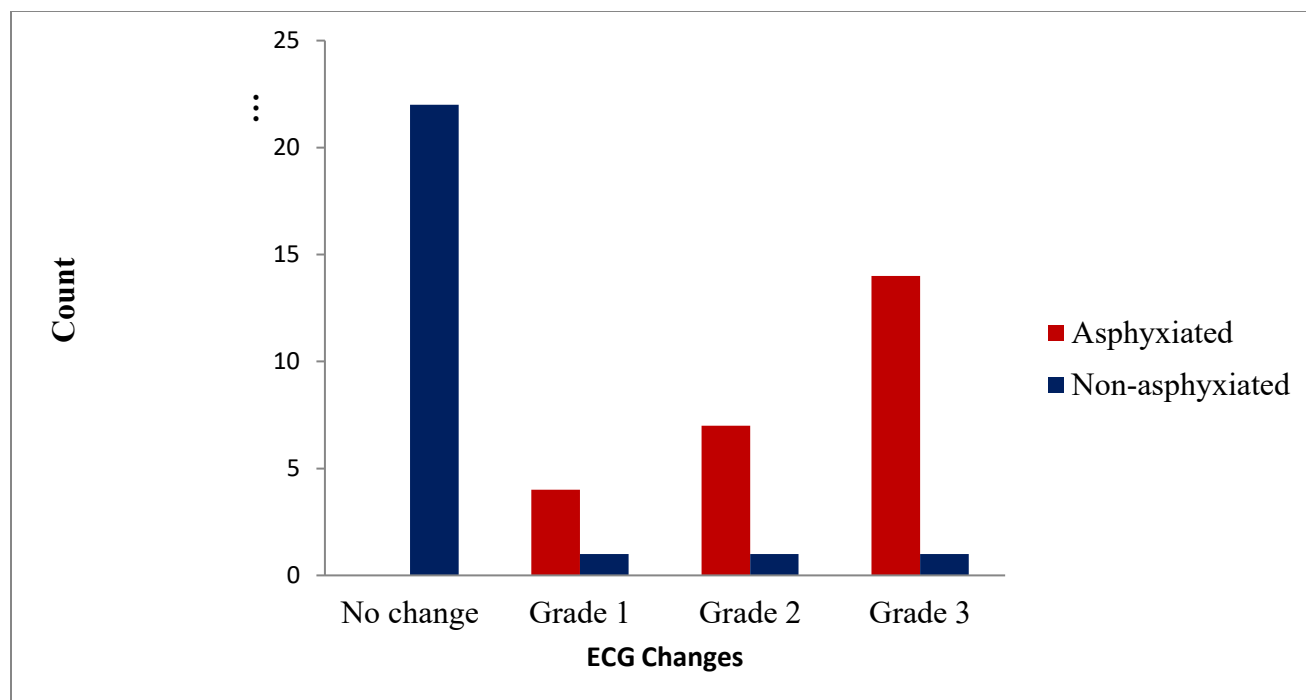


Figure 13: Comparison of ECG patterns in asphyxiated and non-asphyxiated groups of neonates ($\chi^2 = 39.567$; $p = < 0.001$)

Association between cardiac troponin I levels and mortality in Asphyxiated Neonates

While there was no fatality among the non-asphyxiated neonates, the median (range) cardiac troponin I levels in asphyxiated neonates who died was significantly higher [0.52 (0.29-1.22) ng/mL] and almost twice that those who survived [0.25 (0.07-0.62) ng/mL] ($U=117$, $p= <0.001$).

Table III shows a significant association between mortality and cardiac troponin I levels of 0.1 to 0.5ng/mL($p=0.007$) and above 0.5ng/mL. ($p=0.002$). Cardiac troponin I level below 0.1ng/mL showed no significant association with mortality in asphyxiated neonates.

Table III: Association between asphyxia outcome and levels of cardiac troponin I

Cardiac troponin I level	Died (n=7)	Survived (n=18)	Total (n=25)	Test value	<i>p-value</i>
< 0.1ng/mL					
Yes	0 (0.0%)	1 (100.0%)	1(100.0%)	<i>FET</i> =0.405	0.720
No	7 (29.2%)	17 (17.0%)	24 (100.0%)	d.f=1	
0.1 – 0.5ng/mL					
Yes	2 (11.1%)	16(88.9%)	18 (100.0%)	<i>FET</i> =9.095	0.007
No	5 (71.4%)	2 (28.6%)	7 (100.0%)	d.f=1	
>0.5ng/mL					
Yes	5 (83.3%)	1(16.7%)	6 (100.0%)	<i>FET</i> =11.990	0.002
No	2 (10.5%)	17 (89.5%)	19 (100.0%)	d.f=1	

FET: Fishers Exact test; d.f: degree of freedom

Association between ECG changes and mortality in Asphyxiated Neonates

Table IV shows that there was no significant association between mortality and abnormal ECG changes. While newborns with Grade II ECG changes did not die, the proportion of Grade III ECG changes seen in neonates that survived (57.1%) and those who died (42.9%) were comparable ($p=0.076$). A greater proportion (75%) of Grade I ECG changes was seen among newborns that survived ($p=1.000$).

Discussion:

This study demonstrated significant evidence of cardiovascular involvement among term neonates with moderate or severe birth asphyxia. Compared with non-asphyxiated neonates, asphyxiated neonates had lower oxygen saturation, higher respiratory rates, prolonged capillary refill time, markedly elevated cardiac troponin I concentrations, and a higher prevalence of abnormal ECG findings. Cardiac troponin I concentrations were also significantly higher among asphyxiated neonates who died than among those who survived. In contrast, ECG grade was not significantly associated with mortality.

Case fatality for asphyxiated neonates was 28%. This was less than the values obtained from earlier studies^{4,24}, but more than what was earlier obtained by Nyong *et al*²⁵ in the same centre. Differences in case definition, severity of encephalopathy, referral patterns, timing of presentation, availability of neonatal intensive care, and sample size may account for the variation in mortality rates across studies. Nevertheless, this further underscores the fact that indeed, a high mortality rate is associated with birth asphyxia.

Oxygen saturation was significantly less among the asphyxia group of neonates with a mean value of $89\% \pm 10.75$ which was similar to the finding by Issa *et al*¹⁷ which showed oxygen saturation to be the only cardiovascular finding that was consistently low among asphyxiated neonates and worsened across stages of HIE. Prolonged capillary refill time was also significantly noted in neonates suggesting impaired peripheral perfusion as reported by Uzodinma *et al*¹⁶ and Issa *et al*.¹⁷ Dusky appearance of asphyxiated neonates in this study was also in keeping with findings in previously stated studies and is not surprising in the background of increased capillary refill and reduced oxygen saturation.

Mean heart rate did not differ significantly between the groups. One possible explanation is that the participants were assessed within the first 12 hours of life, when compensatory cardiovascular responses may still have been present. Heart rate alone may therefore be insufficient for identifying early myocardial dysfunction, particularly because clinically important cardiac injury may occur before persistent bradycardia or cardiovascular collapse becomes evident.

Cardiac troponin I concentrations were markedly higher among asphyxiated neonates than among non-asphyxiated neonates, consistent with findings from previous studies.^{26,27,28,19,29} This finding supports the occurrence of myocardial injury following hypoxic–ischaemic insult in birth asphyxia. Also, in this study, cardiac troponin I concentrations were also significantly higher among non-survivors than among survivors, supporting its potential prognostic value in asphyxiated neonates. However it is important to note that while these previous studies measured serum troponin I at 72hrs of age when it is said to be at its peak,^{29,30} this study demonstrated that even within few hours of cardiac ischaemia, elevated Troponin I levels can be detected in asphyxiated neonates.

The higher frequency of ECG abnormalities seen in asphyxiated neonates in this study compared to non-asphyxiated neonates collaborates the findings by previous authors.^{31,32,33} Furthermore, the absence of worsening of ECG abnormalities across levels of severity of HIE in this study or higher cardiac troponin I levels were consistent with reports by Aleksandra *et al*³⁴ but was at variance with that from that of Agrawal *et al*³² and this could be because a majority of asphyxiated neonates in the index study had

moderate/ severe asphyxia. In this study and that by Aleksandra *et al*³⁴ while a larger proportion of asphyxiated neonates had grade III changes, a larger proportion of asphyxiated neonates in the study by Agrawal *et al*³² had grade I changes. Although there was an association between severity of abnormal ECG patterns and death in this study, abnormal ECG patterns were not found to be good predictors of mortality. This similar to the finding by Aleksandra *et al*.³⁴

Conclusion:

While reduced oxygen saturation, increased capillary refill time, elevated cardiac troponin I and abnormal ECG patterns were key findings seen in asphyxiated neonates, elevated cardiac troponin I was a more reliable predictor of death.

Recommendation is that this investigation should be included in routine work up for asphyxiated neonates to enable early detection and commencement of resuscitative measures to help reduce mortality.

ETHICAL CONSIDERATIONS

Ethical approval was obtained from the Health Research Ethics Committee of the University of Uyo Teaching Hospital, Uyo, Nigeria, before commencement of the study. The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the parent or legal guardian of each participant before enrolment. Participation was voluntary, and parents or guardians could withdraw their child from the study at any time without affecting the care provided.

FUNDING: This study was self-funded by the authors.

COMPETING INTERESTS: The authors declare that they have no competing interests.

RISK TO PARTICIPANTS: The study posed minimal risk to the participant.

RIGHT TO DECLINE: Participants reserved the right to decline at any point throughout the study

CONSENT FOR PUBLICATION: Not applicable

AVAILABILITY OF DATA AND MATERIALS: The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

AUTHORS' CONTRIBUTIONS:

Conceptualisation : EI. Supervision : OF, NE, AA. Methodology : EI, EE, EA. Lab Analysis: IE,EA. Validation : OF,NE,BK. Original draft preparation EI. Review and editing: OF, NE and BK. Formal analysis and data curation : EE and UM. Resources: IE, UM, AA. All the authours have read and agreed to the submitted version of the manuscript.

ACKNOWLEDGEMENTS: The authors thank the medical and nursing staff of the Labour Ward and Newborn Unit of the University of Uyo Teaching Hospital for their support during participant recruitment and data collection. The authors also appreciate the parents and guardians who consented to their newborns' participation in the study.

ABBREVIATIONS:

CS: Blantyre Coma Score

cTnl: cardiac troponin I

ECG: electrocardiogram

HIE: hypoxic–ischaemic encephalopathy

UUTH: University of Uyo Teaching Hospital

WHO: World Health Organization

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