Original Article

Evaluation of Myocardial Injury Using Serum Cardiac Troponin-I in Asphyxiated Neonates at Enugu State University Teaching Hospital, Enugu, South-East Nigeria

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Received: 26-Feb-2024;
Revision: 02-Apr-2024;
Accepted: 10-May-2024;
Published: 29-Jun-2024

Abstract

Background: The burden of perinatal asphyxia remains high in our environment and when asphyxia is severe, vital organs are affected, with resultant multiorgan hypoxic-iscahemic injury to the heart, the brain, adrenals and other organs. **Study Aim:** To evaluate for myocardial injury in asphyxiated term neonates with hypoxic ischaemic encephalopathy using serum cardiac troponin-I (cTnI). **Methods:** The study was a hospital-based descriptive cross-sectional study involving sixty term asphyxiated neonates and sixty gestational age-and sex-matched controls. The subjects were term neonates with five-minute Apgar score ≤ 6 and HIE while the controls were healthy term neonates with five-minute Apgar score > 6. Five-minute Apgar score was utilized to classify asphyxia into mild, moderate and severe asphyxia. The degree of encephalopathy was determined by modified Sarnat and Sarnat criteria. The serum cTnI was measured in subjects and controls at 12-24 hours of life using Enzyme-linked immunosorbent assay technique. The serum bilirubin levels were also measured in participants to exclude hyperbilirubinemia. **Results:** The median serum cTnI levels was significantly higher in the subjects (0.56ng/mL; 0.25-0.94ng/mL) than in the controls (0.50ng/mL; 0.00-0.67ng/mL), respectively; p=0.001. Similarly, the median serum cTnI level in HIE stage II (0.56ng/mL; 0.38-0.72ng/mL) or III (0.56ng/ml; 0.50-0.94ng/mL) was also significantly higher than the median value in HIE stage I (0.38ng/mL;0.25-0.72ng/mL) or in controls (0.50ng/mL; 0.00-0.67ng/mL); p<0.001. There was significant positive correlation between serum cTnI levels and severity of HIE in asphyxiated neonates (rs = 0.505, p < 0.001). **Conclusion:** serum cTnI levels were elevated in severely asphyxiated neonates with HIE. The concentration of serum cTnI demonstrated significant positive correlation with HIE severity. Hence, the presence of HIE in asphyxiated neonates should prompt an evaluation for myocardial injury using serum cTnI. Any derangement noted should warrant instituting cardiovascular support in order to improve outcome and reduce asphyxia-related mortality.

Keywords: *Serum Cardiac Troponin I; myocardial injury, Perinatal asphyxia; Hypoxic Ischaemic Encephalopathy*

Introduction

In resource-limited settings, birth asphyxia was defined by World Health Organization (WHO) as the failure to initiate and sustain breathing at birth.[1] However, in resource-replete settings, perinatal asphyxia, a broader time-based term, refers to low oxygen or reduced blood

Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_169_24

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How to cite this article: Nwankwo O, Adiele DK, Ekwochi U, Idoko CA, Obidike EK. Evaluation of myocardial injury using serum cardiac troponin-I in asphyxiated neonates at Enugu state University teaching Hospital, Enugu, South-East Nigeria. Niger J Clin Pract 2024;27:792-9.

perfusion insult or injury to the fetus or newborn that is of substantial magnitude and duration as to produce persistent biochemical or functional changes.[2]

The timing of injury leading to perinatal asphyxia may be difficult to establish for an individual fetus or newborn, even though it can occur in the utero, during labor and the postnatal period due to impaired gaseous exchange.[3] Its occurrence at these time periods led to its classification as prepartum, intrapartum, and postpartum asphyxia.[4] The requirement for diagnosis of asphyxia includes a persistently low Apgar score, low blood pH, and an increased base deficit.[2] Despite the fact that Apgar score[5] assesses the condition (Appearance, Pulse rate, Grimace, Activity and Respiratory rate) of a newborn at birth, it is insufficient for diagnosis of perinatal asphyxia.[6] In resource-limited settings where there is scarcity of appropriate facilities for blood gas analysis and pH, the Apgar score has been used as a surrogate assessment for perinatal asphyxia, which is broadly classified as mild, moderate, and severe for Apgar scores of 6–7, 4–5, and 0–3, respectively.[7]

Globally, perinatal asphyxia remains a significant cause of neonatal mortality and morbidity.[8] In Nigeria, the incidence of perinatal asphyxia is 100–180/1000 live births and accounts for 16% to 55% of neonatal deaths,[9] while the prevalence of severe perinatal asphyxia in Enugu State University Teaching Hospital in Southeast Nigeria is 100/1000 live births.[10]

When severe perinatal asphyxia causes hypoxic ischemic encephalopathy (HIE), it is considered significant because although the brain, heart, and adrenals are initially preferentially perfused, the occurrence of encephalopathy would signify that the asphyxia has become prolonged and/or increasingly severe.[11] From a pathophysiologic standpoint, after an asphyxia event, the dive reflex is activated.[12] The reflex consists of redistribution of cardiac output from the skin and splanchnic circulation to the more vital organs (brain, heart, and adrenals).[12] However, with prolonged asphyxia, the more vital organs including the heart become subsequently compromised.[11] Given that the brain and heart are initially preferentially spared, perinatal asphyxia severe enough to cause brain injury most often also leads to cardiac injury.[11] In addition, myocardial injury causes loss of cerebral autoregulation.[13] Hence, when there is HIE, there is often a corresponding myocardial injury.

Generally, regardless of the underlying etiology, cardiac injuries often lead to elevation of serum cardiac proteins. Such proteins are the troponins. Troponin is an inhibitory protein complex located on the actin filament of the cardiac muscle, and its levels rise as a consequence of damage to cardiac myocytes.[14]

HIE is classified into three stages, Stage 1 (mild), stage 2 (moderate), and stage 3 (severe), by the widely used Sarnat and Sarnat classification,[15] which has undergone revision to become the modified Sarnat and Sarnat criteria, which obviate the use of an electroencephalogram, making it beneficial and applicable in resource-restricted settings.[16]

In neonates, biomarkers of myocardial injury include troponin T, troponin I, and creatinine kinase-MB. Among these markers, the serum cardiac troponin I (cTnI) and cardiac troponin T (cTnT) are more useful and reliable markers of myocardial injury.[17] In particular, studies have shown that serum cTnI display higher sensitivity and a better negative predictive value than creatinine kinase-MB fraction (CK-MB) in detecting myocardial injury.[13,18] Despite the high sensitivity and specificity of serum cTnI in detecting myocardial injury, false positive elevation can occur and has been reported in the neonatal period due to some extraneous factors including hyperbilirubinemia.[19]

The presence of myocardial damage and its consequences such as shock increases the degree and severity of other organ damages including the brain, thereby elevating the risk of neurodevelopmental disability and death. As a result of this, the recognition and treatment of myocardial injury resulting from asphyxia become very relevant in order to reduce the morbidity and mortality arising from this condition.

This study was conducted to evaluate the presence or otherwise and degree of myocardial injury as coexisting with HIE in term asphyxiated neonates using serum cTnI assay in Enugu State University Teaching Hospital (ESUTH), Park Lane, a tertiary health care facility in eastern Nigeria in the West African subregion.

Materials and Methods

Study design

This was a hospital-based descriptive cross-sectional study.

Study area

The study was carried out in the Special Care Baby Unit (SCBU) of Enugu State University Teaching Hospital. The hospital is located in the Enugu North local government area of Enugu State in the southeastern part of Nigeria. Enugu state had a population of 3,267,837 people at the last census in 2006 with a projected population increase to 4,411,100 in 2016, giving a population growth rate of 114,326 per annum.[2,12]

The site is a tertiary referral health facility. The SCBU offers 24-hour services to sick babies born within and outside the hospital and is located near the labor ward with an average delivery rate of 144 per month. It has an inborn and outborn section for babies delivered in the hospital and those born outside and referred to the hospital respective a newborn-infant ventilator.

Study population

Study subjects

These were term neonates with a persistently low 5-minute Apgar score ≤6 and HIE who were ≤24 hours of life, admitted in inborn and outborn neonatal units.

The controls

These were normal healthy term neonates with a 5-minute Apgar score >6 who were still in the postnatal wards and aged ≤24 hours of life.

Ethical considerations

Ethical clearance was obtained from the Research and Ethics Committee of the Enugu State University Teaching Hospital, Park Lane, prior to the commencement of the study. Written informed consent was obtained from parents/caregivers of the selected neonates who took part in the study.

Sample size estimation

The sample size was calculated using the formula[20]

$$n = \frac{p\,(1-p)\,(A+B)^2}{d^2}$$

The prevalence of myocardial damage among neonates with HIE using serum cTnI by Trevisanuto *et al*.[21] was 77%, and using an attrition rate of 15%, we arrive at a sample size of 60 subjects and 60 controls.

Sampling method

The sampling method deployed is a multistage sampling method. At first, neonates who met the inclusion criteria were recruited consecutively (for subjects and controls) from the inborn/outborn wards of SCBU and the postnatal ward of the obstetric unit of ESUTH, Park Lane, respectively. The cases and control were recruited concurrently.

The selections continued until the required sample sizes were attained.

The subjects (60) were then assessed and stratified (stratified sampling method) into mild, moderate, and severe HIE and continued to recruit consecutively until we achieve 20 subjects in each of the categories based on modified Sarnat and Sarnat stages 1 to 3.

Patient handling procedure

Inborn neonates with a 5-minute Apgar score of ≤6 were considered for recruitment, and they became eligible when they develop HIE. First, physical examination was done to examine for the presence of any exclusion criteria (like jaundice murmur). Then, the presence of HIE was determined by examining the babies every hour for the first 6 hours and then every 6 hours for the ensuing 18 hours. The HIE scores using the modified Sarnat and Sarnat system were serially documented as HIE stage I, II, or III. For an eligible neonate, a written informed consent was obtained from the parent/caregiver and a study questionnaire was administered.

Outborn babies: Only those referred within the first 12 hours of life with Apgar scores ≤6 at 5 minutes were considered eligible. Undocumented Apgar score outborn were excluded. All other procedures and considerations were as previously described for inborn babies.

The next was blood sampling, which was done at 12–24 hours of life. Three milliliters of venous blood was collected into two plain bottles for serum cTnI (1.5 mls) and total and conjugated bilirubin (1.5 ml).

The New Ballard score and first trimester ultrasound report where available were used to determine the infant's gestational age in cases of unsure dates (last menstrual period). This is then utilized in Sanart and Sanart HIE staging.

Term neonates ≤24 hours of life with a persistently low 5-minuite Apgar score ≤6 in the presence of HIE determined by modified Sarnat and Sarnat criteria, whose parents or caregivers gave written informed consent, were recruited. Infants that are preterm, had cardiac murmur, had persistent central cyanosis with $SpO_2 \leq 92\%$[22] post asphyxia resuscitation, with craniofacial or thoracic congenital malformation, and with neonatal jaundice were excluded from the study. The controls were normal nonasphyxiated (Apgar score > 6) term neonates who are matched for gestational age at birth and sex. With respect to gestational age, controls were matched with cases for ranges such as 37–38 weeks, 39–40 weeks, and 41–42 weeks.

Serum cardiac troponin I assay was determined by the enzyme-linked immunosorbent assay (ELISA) technique modified after Engvall and Periman.[23] The Cell Biolabs' Human Cardiac Troponin I ELISA Kit (Cell Biolabs, Inc., San Diego, California, 2016) with an analytical sensitivity of 0.05 ng/mL and a sample volume of 100 µL/well were used for serum cTnI assay runs.

Data analysis

The data obtained were cleaned and coded for analysis using Statistical Package for Social Sciences (SPSS) version 23.[24] Categorical variables like gender were summarized using frequencies and percentages. Continuous variables such as age and serum cTnI were described using

median and interquartile range as the distribution curve was not symmetric. Serum cTnI levels were compared between subjects, controls, and HIE stages using Mann–Whitney U and Kruskal–Wallis tests. Chi square was used to compare categorical variables, while Spearman's correlation analysis was done between HIE stages and serum cTnI levels. All tests were regarded as significant at *P* values less than 0.05. Results are presented in tables.

Results

A total of 101 neonates were sampled for inclusion as asphyxiated subjects during the period of the study. Thirty-one subjects were initially excluded, of which Apgar score was not documented in 21 and caregivers refused consent in ten subjects. Out of the remaining 70 subjects who developed HIE following assessments, an additional ten were excluded, of which two on closer examination had murmur, three died before 12 hours of life, and serum bilirubin was above the 95 percentile in five neonates. Thus, 60 babies who met the study criteria were recruited as subjects. Similarly, 60 out of the 80 prospective controls were recruited as 20 were excluded (ten babies were discharged before time of sampling, five parents refused consent, and five babies did not match the subjects based on gestational age and gender). Forty-eight (80%) of the subjects were outborn, while 12 (20%) were inborn. All controls were inborn. The mean serum bilirubin levels in subjects and controls were 64 ± 28.95 (μmol/l) and 72 ± 32.51 (μmol/l), respectively, and these were less than 95 percentile using the Bhutani normogram of hour-specific total serum bilirubin concentration.[25]

Demographic characteristics of the study population

Subjects and controls were similar in the distribution of gender, gestational age, and age at sampling and evaluation of serum cTnI assay. For both groups (subjects and controls), each had 24 (40%) males and 36 (60%) females with a male to female ratio of 2:3. The population distribution curve of the study population was skewed, justifying the appropriateness of using median. The median age of the study population at the time of serum cTnI assay was 15 hours, with a range from 12 to 24 hours. The serum cTnI assay evaluation was done in 74 (61.7%) of the study population between 12 and 17 hours of life, while the remaining 46 (38.3%) of the participants had their evaluation between 18 and 24 hours of life. Also, the median gestational age of the study population was 38.5 weeks, ranging between 37 and 42 weeks. The age at sampling, gestational age, and the sex distribution of the study population are shown in Table 1.

Distribution of Apgar scores of the study population

At 5 minutes of life, 16 (26.7%) of the subjects had severe asphyxia, while 44 (73.3%) had moderate asphyxia. All the 60 controls at the 5 minutes were vigorous infants without asphyxia.

Distribution of HIE in the subjects

At 12–24 hours of life, there were 20 asphyxiated neonates with HIE stage 1, 20 asphyxiated neonates with HIE stage 2, and 20 asphyxiated neonates with HIE stage 3.

Distribution of the variables: Serum cTnI, age at evaluation, and gestational age

The normality test for the pattern of distribution of the variables showed a non-Gaussian distribution. The variables were not normally distributed as indicated by the significant values of Kolmogorov–Smirnov and Shapiro–Wilk tests for both subjects and controls.

Table 1: Demographic characteristics of the subjects and controls[a]

Variable	Subject *n*=60	Control *n*=60	Total *n*=120	χ^2	*P*
Sex					
Male	24 (40.0)	24 (40.0)	48 (40.0)	0.000	1.000
Female	36 (60.0)	36 (60.0)	72 (60.0)		
Total	60 (100.0)	60 (100.0)	120 (100.0)		
Age at evaluation (hours)					
12–17	37 (61.7)	37 (61.7)	74 (61.7)	0.000	1.000
18–24	23 (38.3)	23 (38.3)	46 (38.3)		
Total	60 (100.0)	60 (100.0)	120 (100.0)		
Gestational age, (weeks)					
37–38	30 (50.0)	30 (50.0)	60 (50.0)	0.000	1.000
39–40	28 (46.7)	28 (46.7)	56 (46.7)		
41–42	2 (3.3)	2 (3.3)	4 (3.3)		
Total	60 (100.0)	60 (100.0)	120 (100.0)		

Median time of sampling=15.00 h, range of age at evaluation 12–24 h, median GA=38.50 weeks (range 37–42 wks). [a]Values in parenthesis are percentages of *n*

Table 2: Comparison of the serum levels of cTnI between subjects and controls

	Subject (*n*=60)	Control (*n*=60)	Mann–Whitney	*P*
cTnI (ng/mL)				
Median	0.56	0.50	1198.50	0.001*
Minimum–maximum	0.25-0.94	0.00-0.67		
Interquartile range[b]	(0.50-0.66)	(0.25-0.61)		

*Kruskal Wallis test, cTnI, cardiac troponin I. [b](25th-75th percentile)

Table 3: Comparison of serum levels of cTnIin controls with the levels in different stages of HIE

	Asphyxiated group (*n*=60)			Control group (*n*=60)	*P*
	Stage I HIE (*n*=20)	Stage II HIE (*n*=20)	Stage III HIE (*n*=20)		
cTnI (ng/mL)					
Minimum–maximum	0.25-0.72	0.38-0.72	0.50-0.94	0.00-0.67	<0.001*
Median	0.38	0.56	0.56	0.50	
Interquartile range	(0.25-0.56)	(0.50-0.59)	(0.56-0.86)	(0.25-0.61)	

*Kruskal Wallis test

Table 4: Correlation between serum cTnI concentration and the severity of HIE in subjects

Variable	HIE
cTnI (ng/ml)	
Spearman's rho correlation coefficient	0.505
P	<0.001
n	60

cTnI, cardiac Troponin I; HIE, hypoxic-ischemic encephalopathy

The median serum cTnI in asphyxiated term neonates with HIE (subjects) was 0.56 ng/mL with a range of 0.25 ng/ml to 0.94 ng/ml and an interquartile range of 0.5 to 0.66 ng/mL. Similarly, the median serum cTnI in controls was 0.50 ng/mL, ranging from 0.00 ng/ml to 0.67 ng/ml with an interquartile range of 0.25 to 0.61 ng/mL. The median serum cTnI levels were significantly higher in subjects than in controls ($P = 0.001$) as shown in Table 2.

Distribution of serum cTnI based on the stage of HIE

For stage I HIE, the median concentration was 0.38 ng/mL, the interquartile range was 0.25–0.56 ng/mL, and the minimum–maximum range was 0.25–0.72 ng/mL. Similarly, in stage II HIE, the median level was 0.56 ng/mL, the interquartile range was 0.50–0.59 ng/mL, and the minimum–maximum range was 0.38–0.72 ng/mL. Last, the median concentration of serum cTnI in HIE stage III was again 0.56 ng/mL, the interquartile range was 0.56–0.86 ng/mL, and the minimum–maximum range was 0.50–0.94 ng/mL [Table 3].

Pairwise statistical comparison as shown in Table 3 revealed that patients with stages II and III HIE had higher levels of cTnI when compared with stage I and controls. The median value of cTnI in HIE stage II was significantly higher than that of HIE stage I. Also, the median cTnI in HIE stage II was similarly significantly higher than that of controls. Likewise, the median cTnI value in stage III HIE was significantly higher than the median cTnI in stage I and controls. It is however worth noting that the minimum–maximum range of cTnI was particularly higher in HIE stage III than in controls, a pattern that is maintained though at a smaller scale across the other different stages of HIE in comparison to controls. On the contrary, the median value of cTnI in controls was higher than in stage I HIE. However, there was no difference in median value between stages II and III HIE.

Relationship between serum cTnI levels and the severity of HIE in subjects

Using Spearman's rho correlation to determine the relationship between cTnI and HIE severity, there was a significantly positive correlation between serum cTnI levels and severity of HIE in subjects ($r_s = 0.505$, $P < 0.001$), Table 4.

Discussion

Severe perinatal asphyxia causes brain and myocardial ischemic injury as part of multiorgan injury. Brain involvement of varying degrees of severity is often clinically assessed. Although the myocardial injury resulting from asphyxia can also be evaluated clinically, the use of serum cardiac troponins is more beneficial given that the serum cTnI is a sensitive and specific biomarker of myocardial cell death.[13,18]

The serum cTnI concentration among healthy neonates described in the index study falls below 1.8 ng/mL, which has been reported earlier by Bader *et al.*[26] as the upper limit of normal cTnI but lies within that of Turker *et al.*[27] (0.09–1.8 ng/mL) in Turkey and Pal *et al.*[28] in

India, 0.60 ng/mL (0.20–1.00 ng/mL). However, a later study by Gouda *et al*.[13] and Jiang *et al*.[29] recorded lower values of 0.02 ng/mL (0.01–0.03 ng/mL) and 0.016 ng/mL (0.000–0.094 ng/mL), respectively, among healthy neonates. This variation in cTnI level may be due to differences in sensitivities of the assay kits as the kit used by Jiang *et al*.[29] had a lower sensitivity of 1.1 to 1.9 ng/mL as opposed to the index study (0.05 ng/mL), while Gouda *et al*.[13] had a higher sensitivity (0.006 Ng/Ml).

In comparison to the healthy neonates, the asphyxiated term neonates with HIE, in this study, had significantly increased serum cTnI concentrations. This finding could be explained by the fact that when perinatal asphyxia becomes severe and/or prolonged, the initially protective dive reflex subsequently fails to protect the more vital organs including the heart, brain, and adrenal glands, leading to hypoxic-ischemic injury to the myocardium, which results in myocardial cellular death and release of cTnI into the blood stream with subsequent elevation of serum cTnI levels.[21]

Studies have earlier reported that the levels of serum cTnI in asphyxiated neonates were significantly higher than that of controls,[13,21] which is in agreement with the findings of this study. A geographically similar study done by Gouda[13] and colleagues in 2017 appears to be the closest to this study to the best knowledge of the researcher. The median (interquartile range) value of 0.10 ng/mL (0.07–0.30 ng/mL) and a *P* value of 0.000 reported by Gouda *et al*.[13] compare favorably with index study. Apart from kit sensitivity discussed earlier, another methodological difference is the timing of the assay. This study conducted cTnI assay between 12 and 24 hours of life, a time that included the peak levels, while the study by Gouda was done within 12 hours of life before the attainment of peak levels of cTnI; hence, the lower values as they may have sampled before the peak level are reached. It is worthy of note that the two studies used a similar cTnI determination method (quantitative ELISA). In another related study, using a heterogeneous immunoassay module (RxL-HM, Dade Behringer), Trevisanuto *et al*.[21] recorded a slightly lower median cTnI value of 0.36 ng/mL with a much wider range (0.05–11 ng/mL) compared to the index study (0.25–0.94 ng/mL). This variation could be explained by a number of factors. First, the study by Trevisanuto *et al*.[21] recruited preterm/low-birth-weight neonates who are prone to jaundice, a confounding variable that has been shown to cause a false increase in cTnI level.[19] Another possible reason for the difference in range is the frequent occurrence of respiratory distress syndrome in preterm neonates that have been documented to result also in high cTnI levels.[30] Additionally, congenital heart defect was not excluded in the study by Trevisanuto *et al*.,[21] which is also a confounding variable that causes elevation in cTnI levels.

Furthermore, in this study, significantly higher levels of serum cTnI were observed with increasing stages of HIE. This was noted between HIE stages I and II and between stages I and III HIE. The finding of higher levels of serum cTnI in increasing stages of HIE is in agreement with the reports of Simović *et al*.[31] and Shastri *et al*.[32] This finding of a direct relationship between serum cTnI levels and HIE stages could be explained by the fact that the myocardial injury secondary to severe perinatal asphyxia ultimately leads to loss of cerebral autoregulation, resulting in severe encephalopathy and myocardiopathy.[21] Also, Gouda *et al*.[13] corroborated this finding and noted that the higher the degree of myocardial injury, the more the severity of encephalopathy. He even viewed serum cTnl as an HIE-related biomarker.[13] This serum cTnl and HIE severity relationship was also corroborated by Shastri and colleagues.[32]

The index study noted no significant difference between the median value of cTnI in stages II and III HIE, which could be explained by the fact that when the degree of cardiac injury reaches a peak, the worsening of HIE will continue even without further cardiac injury.[13,18] This observation was corroborated by Shastri *et al*.[32]

Furthermore, contrary to expectation, this study also noted that the median (range) values of cTnI in HIE stage 1 were lower than the median (range) values in controls. This unexpected observation is in agreement with the finding by Montaldo *et al*.,[18] who demonstrated that the median value of cTnI in HIE stage 1 (0.09 ng/mL) was lower than the value (0.19 ng/mL) in neonates without encephalopathy. It is noteworthy that in the study by Montaldo *et al*.,[18] the neonates without encephalopathy included both asphyxiated without HIE and healthy neonates which can influence the cTnI levels.[18] Equally important is the fact that arterial blood-gas analysis was not used as a diagnostic criterion for asphyxia in all participants in their study as acidosis in a neonate with an apparently normal Apgar score hightens the odds for adverse outcomes in terms of asphyxia.[13] This can again explain the high value of serum cTnI in controls noted in the index study as relying on Apgar score alone to exclude asphyxia without concomitant arterial blood-gas analysis could lead to potentially missing out some asphyxiated babies and including them as controls.

Finally, the index study noted female preponderance with perinatal asphyxia and HIE, which contradicts the result of previous studies that reported male predominance.[10,33] The observed disparity could be due to differences in sample size and methodology used as these previous studies were incidence studies with larger sample sizes.[10,33] Another possible reason for this finding could be due to a higher birth rate of females during the study period.

Availability of data statement

The data for this study is available on request through the corresponding author.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. WHO (1997) Basic newborn resuscitation: A practical guide. Geneva: World Health Organization. Available from: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/MSM_98_1/en/index.html. [Last accessed on 2018 Aug 27].
2. MacDonald MG, Seshia MMK. Neurological and neuromuscular disorder. In: Avery Textbook of Neonatology, Pathophysiology and Management of Newborn. 7th ed. Philadelphia: Wolters Kluwer; 2015. 46. p. 2125.
3. Adcock LM, Stark AR. Systemic effects of perinatal asphyxia. UpToDate 21_6 Updated 2013. Available from: https://www.uptodate.com/contents/mobipreview.htm?28/59/29623#H3. [Last accessed on 2019 Aug 26].
4. Antonucci R, Porcella A, Pilloni MD. Perinatal asphyxia in the term newborn. J Pediatr Neonat Individual Med 2014;3:1-14.
5. Apgar V. A proposal for a new method of evaluation of the newborn infant. Curr Res Anesth Analg 1953;32:260-7.
6. American Academy of Pediatrics Committee on Foetus and Newborn; American College of Obstetricians and Gynecologists Committee on Obstetric Practice; Watterberg KL, Aucott S, Benitz WE, Cummings JJ, *et al*. The Apgar score. Pediatrics 2015;136:819-22.
7. World Health Organization. Birth Asphyxia – Summary of the previous meeting and protocol overview. 2007 Jun 11. Available from: http://www.curoservice.com/health_professionals/news/pdf/10-09-2007_birth_asphyxia02.pdf. [Last accessed on 2013 Aug 05].
8. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME), 'Levels and Trends in Child Mortality: Report 2020, Estimates developed by the United Nations Inter-agency Group for Child Mortality Estimation', United Nations Children's Fund, New York, 2020. Available from: https://www.unicef.org/reports/levelsand-trends-child-mortality-report-2020. [Last accessed 2020 Oct 10].
9. Njokanma OF, Olarenwaju DM. A study of neonatal deaths at Ogun State University Teaching Hospital, Sagamu Nigeria. J Trop Med Hyg 1995;98:155–60.
10. Ekwochi U, Asinobi NI, Osuorah CDI, Ndu IK, Ifediora C, Amadi FO, *et al*. Incidence and predictors of mortality among newborns with perinatal asphyxia: A 4-year prospective study of newborns delivered in health care facilities in Enugu, South-East Nigeria. Clin Med Insights Pediatr 2017;11:1–10.
11. Shah P, Riphagen S, Beyene J, Perlman M. Multiorgan dysfunction in infants with post-asphyxial encephalopathy. Arch Dis Child Fetal Neonatal Ed 2004;89:152–5.
12. Godek D, Freeman AM. Physiology, Diving Reflex. StatPearls Publishing; 2020. Available from: https://www.ncbi.nlm.nih.gov.books/NBK538245/#_NBK538245_pubdet. Updated 2020 Sep 29. [Last accessed on 2020 Nov 01].
13. Gouda MH, Hammad BS, Amen MA. Short term prognostic value of cardiac troponin I in neonates with perinatal asphyxia. Alex J Pediatr 2017;30:108–19.
14. Kemp M, Donovan J, Higham H, Hooper J. Biochemical marker of myocardial injury. Br J Anaesth 2004;93:63-73.
15. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol 1976;33:696-705.
16. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, *et al*. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005;353:1574–84.
17. Turker G, Babaoglu K, Duman C, Gokalp A, Zengin E, Arisoy AE. The effect of blood gas and Apgar score on cord blood cardiac troponin I. J Matern Fetal Neonatal Med 2004;16:315–9.
18. Montaldo P, Rosso R. Cardiac troponin I concentration as a marker of neurodevelopmental outcome at 18 months in neonates with perinatal asphyxia. J Perinatol 2014;34:292–5.
19. Giacchi V, Mattia C, Betta P, Sciacca P. Should we consider bilirubin when doing troponin in newborns? Case Report. Int J Clin Case Stud 2014;1:101.
20. Hajian-Tilaki K. Sample size estimation in epidemiologic studies. Casp J Intern Med 2011;2:289–98.
21. Trevisanuto D, Picco G, Golin R, Doglioni N, Altinier S, Zaninotto M, *et al*. Cardiac troponin I in asphyxiated neonates. Biol Neonate 2006;89:90-3.
22. American Academy of Pediatrics News. Pulse oximetry screening for congenital heart disease under consideration. May 2011. Available from: www.aapnews.org. [Last accessed on 2020 Mar 09].
23. Engvall E, Periman P. Enzyme linked immuno-sorbent assay, Elisa quantitation of specific antibodies by enzyme –labelled anti -immunoglobulin in antigen-coated tubes. J Immunol 1971;109:29-135.
24. IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.
25. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics 1999;103:6-14.
26. Bader D, Kugelman A, Lanir A, Tamir A, Mula E, Riskin A. Cardiac troponin I serumconcentrations in newborns: A study and reviewof the literature. Clin Chim Acta 2006;371:61–5.
27. Turker G, Sarper N, Babaoglu K, Gokalp AS, Duman C, Arisoy AE. Early prognostic significance of umbilical cord troponin I in critically ill newborns. Prospective study with a control group. J Perinat Med 2005;33:54–9.
28. Pal P, Goel M. ECG changes in birth asphyxia and its correlation with Cardiac troponin-I. Int J Med Res Rev 2015;3:400-3.
29. Jiang L, Li Y, Zhang Z, Lin L, Lui X. Use of high-sensitive cardiac troponin I levels for early diagnosis of myocardial injury after neonatal asphyxia. Int J Med 2019;47:3234–42.

30. Clark SJ, Newland P, Yoxall CW, Subhedar NV. Sequential cardiac troponin T following delivery and its relationship with myocardial performance in neonates with respiratory distress syndrome. Eur J Pediatr 2006;165:87-93.
31. Simović AM, Knezević J, Igrutinović Z, Stojanović N, Kocić S. Cardiac troponin as biochemical marker of perinatal asphyxia and hypoxic myocardial injury. Vojnosanit Pregl 2009;66:881-6.
32. Shastri AT, Samarasekara S, Muniraman H, Clarke P. Cardiac troponin I concentrations in neonates with hypoxic ischemic encephalopathy. Acta Paediatr 2012;10:26-9.
33. Okonkwo IR, Okolo AA. Postnatal magnesium sulfate in asphyxiated newborns in Benin City Nigeria: Effect on mortality. Int J Pediatr Neonat Care 2018;3:136.