International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 20s, 2025
https://www.theaspd.com/ijes.php

Assessment of Myocardial Functions and Biological Markers in Newborns with Hypoxic-Ischemic Encephalopathy.

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Abstract

Introduction: *Hypoxic-ischemic encephalopathy (HIE) is a neonatal neurological disorder caused by reduced cerebral blood flow and oxygen supply, often affecting myocardial function.*

Objective: *To evaluate cardiac troponin, I (cTnI) levels in newborns with HIE, correlate them with myocardial function, and analyze HIE association with nitric oxide synthase (NOS3) gene polymorphism.*

Methods: *This study included 30 newborns with perinatal asphyxia and 20 healthy controls matched for gestational age and birth weight. All underwent history taking, clinical assessment, and cardiac evaluation. Serum cTnI was measured as a biomarker for myocardial injury. NOS3 (rs1808593) polymorphism was detected using real-time PCR (RT-qPCR). Echocardiography assessed systolic function via Shortening Fraction (SF%), Ejection Fraction (EF%), Mitral Annular Plane Systolic Excursion (MAPSE), and Tricuspid Annular Plane Systolic Excursion (TAPSE) using M-mode. Pulsed-wave Doppler of mitral valve inflow was performed to evaluate diastolic function (E/A ratio, Deceleration Time).*

Results: *Serum cTnI was significantly higher in HIE cases (2.97 ± 1.74 ng/ml) than controls (1.01 ± 0.57 ng/ml, P<0.05). Levels were significantly elevated in Sarnat stage III (3.96 ± 1.95 ng/ml) compared to stage II (2.11 ± 0.91 ng/ml, P<0.05). The TT genotype of NOS3 rs1808593 occurred in 66.7% of HIE cases, showing a significant correlation with cTnI (P=0.024). Both systolic and diastolic functions were significantly impaired in HIE compared to controls (P<0.001). Stage III HIE showed significant cardiac impairment in SF%, EF%, TAPSE, MAPSE, and mitral valve deceleration time versus stage II (P<0.001, <0.001, 0.007, 0.003, respectively).*

Conclusion: *Elevated cTnI levels, NOS3 rs1808593 polymorphism, and impaired myocardial function are strongly associated with HIE severity. Combined biomarker and echocardiographic assessment may provide valuable diagnostic and prognostic information for affected newborns.*

Keywords: *Newborns; Hypoxic-Ischemic Encephalopathy; Cardiac Troponin I; Myocardial Function; Nitric Oxide Synthase*

INTRODUCTION

Hypoxic-Ischemic Encephalopathy (HIE) is a severe neonatal condition affecting 0.5–2% of live births, resulting from reduced cerebral blood flow and oxygen deprivation during the perinatal period. This leads to neuronal injury and systemic complications, including significant effects on myocardial function (1,2).

Cardiac involvement in HIE may manifest as myocardial ischemia, reduced ventricular function, or hemodynamic instability (3,4). Echocardiography and cardiac biomarkers are valuable for detecting myocardial injury in up to two-thirds of affected infants, aiding in early diagnosis and management (5,6).

Cardiac troponin I (cTnI) is a highly specific biomarker for myocardial injury, regulating cardiac muscle contraction by inhibiting actin-myosin interaction in the absence of calcium. Damage to cardiac myocytes causes cTnI release into the bloodstream. Its N-terminal region binds cardiac troponin C

(cTnC), enhancing calcium sensitivity of the sarcomere, the basic functional unit of striated muscle (7-9).

Several studies have demonstrated cTnI as a reliable indicator of myocardial damage, correlating with HIE severity and neonatal mortality rates. Echocardiographic measures, including left ventricular output and myocardial performance index, further assess the hemodynamic impact of hypoxic-ischemic events (10).

Nitric oxide synthase 3 (NOS3), also known as endothelial nitric oxide synthase (eNOS), produces nitric oxide (NO), a critical molecule for vascular tone regulation, blood flow maintenance, and endothelial function. NO promotes vasodilation, inhibits platelet aggregation, and reduces inflammation, contributing to cardiovascular homeostasis (11).

During hypoxic events, NO from NOS3 helps preserve cerebral blood flow, offering neuroprotection. Genetic variations in the NOS3 gene, particularly single nucleotide polymorphisms (SNPs), have been linked to differences in HIE severity, suggesting NOS3 activity may influence individual susceptibility (12,13).

Understanding the interplay between HIE, myocardial injury, cTnI levels, and NOS3 genetic polymorphisms is essential for optimizing diagnostic strategies, guiding treatment, and improving long-term outcomes for affected infants (14,15).

PATIENTS AND METHODS

Study Population

This cross-sectional case-control study included 50 newborns: 30 term infants diagnosed with HIE admitted to the Neonatal Intensive Care Unit (NICU) of Cairo University Specialized Children's Hospital and 20 healthy newborns matched for gender, gestational age, and birth weight as controls. Written informed consent was obtained from parents or guardians before participation.

Infants with cardiac arrhythmia or congenital anomalies were excluded. HIE severity was classified using the Sarnat Staging Scale into Stage II and Stage III groups.

All subjects underwent full maternal and neonatal history taking, including perinatal complications, demographic data (gestational age, sex, weight, mode of delivery), and NICU course (need for respiratory or inotropic support). Clinical examination was performed for all participants.

Assessment of Cardiac Troponin I

A 5-ml blood sample was collected from each newborn within the first 6 days of life. Serum cardiac troponin I (cTnI) levels were measured using the enzyme-linked immunosorbent assay (ELISA) technique.

Genetic Analysis of NOS3 Polymorphism

Whole blood samples were used for DNA extraction with a QIAamp DNA kit (Qiagen, USA). DNA quantitation and purity were assessed using a NanoDrop® ND-1000 spectrophotometer (NanoDrop Technologies, USA). Genotyping for the NOS3 rs1808593 (G/T) single nucleotide polymorphism (SNP) was performed using real-time polymerase chain reaction (RT-PCR) with a TaqMan allelic discrimination assay.

Echocardiographic Assessment

Echocardiography was performed within the first 6 days of life for both HIE and control groups using a Sonosite ultrasound system with an age-appropriate transducer. All scans were recorded while patients were in sinus rhythm.

M-mode imaging was performed at the tips of the mitral valve leaflets in the parasternal long-axis view. Left ventricular dimensions were measured in systole and diastole, and shortening fraction (SF%) and ejection fraction (EF%) were automatically calculated.

Mitral annular plane systolic excursion (MAPSE) and tricuspid annular plane systolic excursion (TAPSE) were measured in the apical 4-chamber view as indicators of left and right ventricular systolic function.

Pulsed-wave Doppler assessed mitral valve inflow velocities, including peak E and A waves, E/A ratio, and E-wave deceleration time for evaluation of left ventricular diastolic function. To reduce respiratory variability, three consecutive cycles were averaged.

Statistical Analysis

Data were analyzed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). The Kruskal-Wallis test assessed normality. Parametric data were analyzed with independent t-tests and expressed as mean ± SD. Chi-square tests (χ^2) compared categorical variables. Pearson correlation (r) assessed relationships between quantitative variables. Receiver Operating Characteristic (ROC) curves were used to determine diagnostic accuracy, with significance set at $p \leq 0.05$.

RESULTS

Demographic data

Patients included in the study were 16 males (53.3%) and 14 females (46.7%). Healthy controls were 12 males (60.0%) and 8 females (40.0%), with no statistically significant difference (P=0.642). On comparing gender, gestational age and body weight, between patients and healthy controls there was no statistical significance (P value>0.05) (Table 1)

Maternal, Neurological and laboratory data

Maternal parity and the Number of Pregnancy have been reported showing that the majority of the cases with HIE were single pregnancy with a ratio of 28(93.3%): 2(6.7%) multiple pregnancy. On comparing Primigravida: Multigravida, results revealed that most of HIE cases were born to multigravida mothers 11(36.7%): 19(63.3%) respectively.

Regarding the neurological findings among the studied HIE cases. Lethargy was found in16 cases (53%) and coma was found in 14 cases (46.7%). Hypotonia and hyporeflexia were detected in 23 cases (76.6%) and hypertonia and hypereflexia were detected in 7 cases (23.3%). Seizures were detected in 25 cases (83.3%). Other NICU and laboratory data, blood gases and APGAR score presented in Table 2

According to Sarnat staging Scale of HIE, 16 cases belonged to stage II (53.3%) and 14 cases belonged to stage III (46.7%). As regards the need of mechanical ventilation and inotropic support we found that 31.2% of HIE Sarnat Stage II and about 100% of HIE Stage III required mechanical ventilation and inotropic support with statistically significant difference (P<0.001)

Cardiac troponin I

There was a significantly increase in serum level of cTnI in HIE cases (2.97ng/ml ±1.74) in comparison with controls (1.01 ng/ml ±0.57) (P<0.001). There was also a significant increase in serum level in HIE cases with Sarnat stage III (3.96 ng/ml ± 1.95) in comparison with stage II (2.11 ng/ml ±0.91) (P=0.013) supporting the correlation between cTnI and HIE severity. (Figure 1)

Sensitivity and specificity of Cardiac Troponin I in serum among the studied HIE cases

According to the calculation of the results of the concentration level of cTnI in serum samples of HIE patients, the applied values of the biomarker were determined as indicators for the diagnosis of patients. Receiver Operating Characteristics (ROC) curves were carried out for analysis showing the area under curve (AUC) was 0.808 a with sensitivity and specificity of 96.7%; 60.0% respectively at cut-off value >1.117ng/mL (Figure 2)

Echocardiography data

Both systolic (SF%, EF%, MAPSE and TAPSE) and diastolic (Mitral E/A ratio and DT) cardiac functions showed significant impairment in HIE cases in comparison with healthy controls (P value<0.05). (Table 3)

On comparing HIE cases with Sarant stage II and stage III, there was significant impairment in systolic functions in stage III HIE cases as regards SF%, EF%, TAPSE and MAPSE. Also, there was significant impairment in diastolic function in stage III HIE cases as regard deceleration time (P <0.05) which indicates that cardiac function impairment correlates with the HIE severity (Table 4).

There was also statistically significant negative correlation between cTnI levels and cardiac systolic function parameters (SF%, EF %, MAPSE and TAPSE). The higher levels of cTnI associated with more impairment of systolic function (Figure 3 & 4). On other side, there was no significant correlation between cTnI levels and Diastolic function parameters.

Assessment of genetic polymorphisms of NOS3 related SNPs rs1808593 (G/T)

The genotype analysis of NOS3 single nucleotide polymorphism (SNP) (rs1808593) in cases with hypoxic-ischemic encephalopathy (HIE) showed that TT genotype of rs1808593 polymorphism was twice (20 cases, 67.7 %) as common as TG and GG in the HIE group (Figure 5). Also, the incidence of the TT genotype was significantly higher is HIE cases (67.7 %) in comparison to controls (35 %) (P value 0.039)

There was no statistically significant relation the TT genotype Of SNP of NOS gene in newborns with HIE and Echocardiography parameters. Regarding serum level of cTnI, it was significantly elevated among TT genotype individuals (P value 0.024).

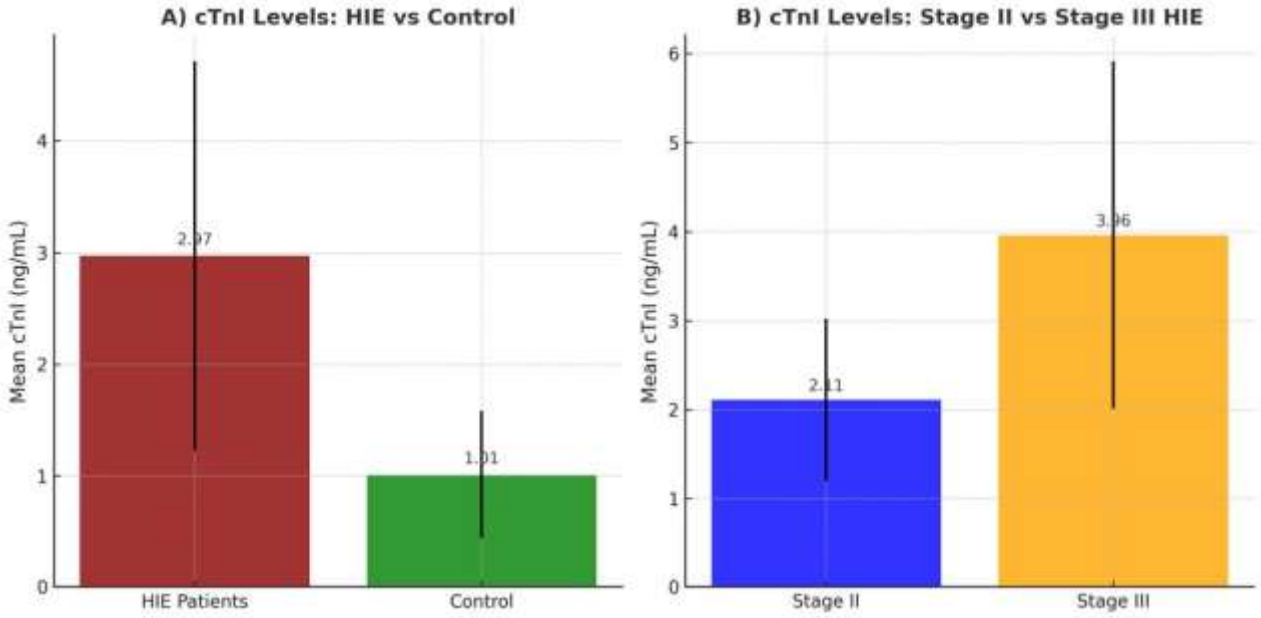
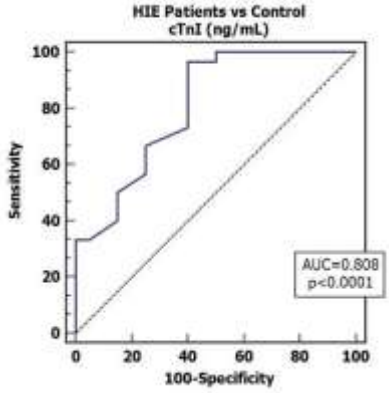


Figure 1: (A) Cardiac Troponin I level between HIE cases and Controls, (B) Cardiac troponin I level in Cases with Sarnat Stage II and Stage III



Diagnostic and prognostic performances of cTnI serum biomarkers of HIE patients

Biomarker	cTnI (ng/mL)
AUC	0.808
Cut-off value	>1.117
Sensitivity	96.7%
Specificity	60.0%
95% C.I	0.672 to 0.906
Accuracy	78.35%
p-value	<0.0001

AUC: area under curve. Bold values are significant (P≤0.05).

Figure 2: ROC curve analysis for serum level of Cardiac Troponin I among the studied groups

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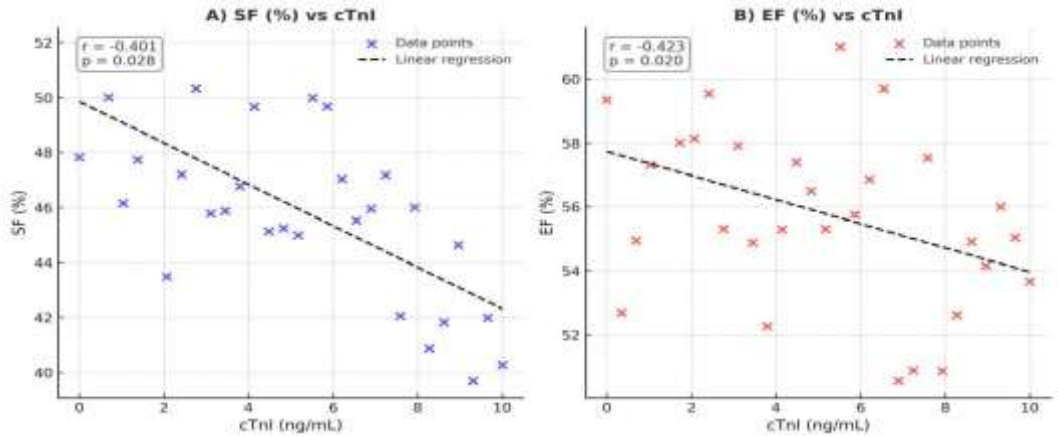

Figure 3: (A) Correlation between Shortening Fraction % and Cardiac troponin I level in HIE cases (B) Correlation between Ejection fraction% and Cardiac Troponin level in HIE cases

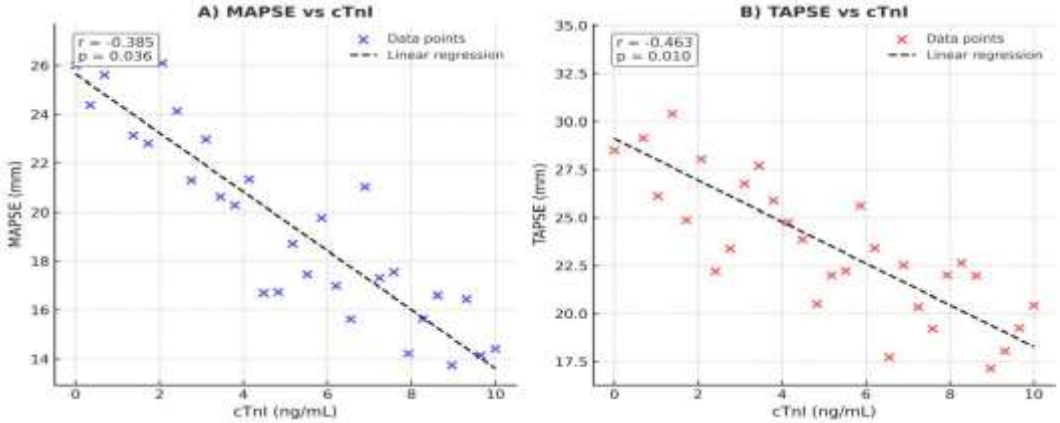

Figure 4: (A) Correlation between MAPSE and cardiac troponin I level in HIE cases (B) Correlation between TAPSE and cardiac troponin I level in HIE cases

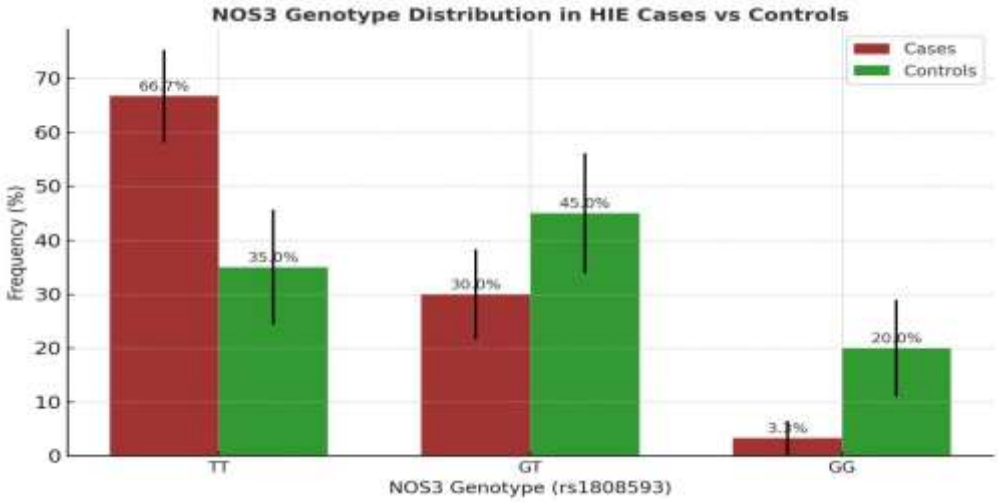

Figure 5: Genetic polymorphisms of NOS3 related SNPs rs1808593 in serum for HIE and healthy control groups

Table (1) Mean gestational age, post-natal age & body weight among cases and controls

Variable	Cases (n= 30) Mean±SD	Controls (n=20) Mean±SD	P value
Gestational age	37.73±1.62 wks	37.35±1.18 wks	0.534
Postnatal age	5.13±2.11dys	4.35±1.66 dys	0.170
Birth weight	2.53±0.54 kg	2.73±0.33kg	0.079

Values are expressed as mean ± standard deviation. P value<0.05 is considered significant)

Table 2: Medical, Neurological and laboratory data of HIE patients' group (N=30)

Variable	HIE Patients (N=30)
Medical data and obstetric problems	
Meconium aspiration	7(23.3%)
Premature ruptur of membrane	3(10.0%)
Accidental delivery	2(6.7%)
Cephalhematoma	5(16.7%)
Preeclampsia	1(3.3%)
IDM	1(3.3%)
IUGR	2(6.7%)
Seizures	25(83.3)
Mortality	4 (13.3 %)
Number of Pregnancy	
Single	28(93.3)
Multiple	2(6.7%)
Gravida	
Primigravida	11(36.7%)
Multigravida	19(63.3%)
Neurological manifestations	
Conscious level	
Lethergy	16(53.3%)
Coma	14(46.7%)
Tone & reflexes	
Hypotonia and Hyporeflexia	23(76.7%)
Hypertonia and hyperreflexia	7(23.3%)
Respiratory support	
Nasal_O2	7(23.3%)
CPAP	4(13.3%)
SIMV	19(63.3%)
Inotropic support	19(63.3%)
Laboratory data	(Mean±STD)
pH	6.7083±1.82
pCo2(mmHg)	41.58±17.74
HCo3(meq/l)	14.730±6.27
Serum_creatinine	1.07367±0.747
Base excess Median (IQR)	-10.10 (5.50)

APGAR score (min)	(Median (IQR)
APGAR1	0 (1.0)
APGAR5	3.0 (1.0)
APGAR10	5.0 (2.0)

IDM: Infant of diabetic mother, IUGR: Intrauterine growth restriction, nasal O2: nasal Oxygen, CPAP: Contanous positive airway pressure, SIMV: Synchronized intermittent mandatory ventilation, pH: Potential of Hydrogen, PCO2 Partial Pressure of Carbon Dioxide, HCO3: Hydrogen Carbonate, APGAR1/5/10 APGAR scoure at 1/5/10 minutes. Data shown as N (%) Chi-squared Test is used. pH, pCo2, HCo3, Serum_creatinine data shown as mean±SD. Independent Student t-test was used for parametric data. Base excess, APGAR1, APGAR5, APGAR10 data shown as median (IQR) are shown as Median (Range). Mann-Whitney U Test is used. *Significant at p≤0.05.

Table (3): Echocardiography parameters of systolic and diastolic cardiac function in HIE cases and healthy controls

Parameter	Cases (Mean ± SD)	Controls (Mean ± SD)	P value
Systolic Function			
LVEDD (mm)	18 ± 1.61	18.83 ± 1.81	0.181
LVESD (mm)	13.4 ± 1.31	13.08 ± 1.31	0.258
SF %	25.07 ± 4.69	30.15 ± 2.30	<0.001
EF %	58.0 ± 7.91	65.76 ±3.63	<0.001
MAPSE (mm)	8.30 ± 0.69	9.08 ± 0.51	<0.001
TAPSE (mm)	13.37 ± 1.47	16.15± 0.93	<0.001
Diastolic Functions			
E/A ratio	1.02 ± 0.16	1.18 ± 0.06	<0.001
DT (ms)	112.03 ±7.88	122.6 ± 4.86	<0.001

Data shown as mean±SD. Independent Student t-test was used for parametric data. LVEDD: Lift ventricle end diastolic diameter, LVESD: Lift ventricle end systolic diameter, SF%: Fraction shortening, EF%: Ejection fraction, TAPSE: Tricuspid annular plane systolic excursion, MAPSE: Mitral annular plane systolic excursion. Categorical data shown as N (%) Chi-squared Test is used. Mann-Whitney U Test is used. *Significant at p≤0.05.

Table (4): Echocardiography parameters of systolic and diastolic function in HIE cases Sarnat Stage II and Sarnat Stage III.

Parameter	Stage II (Mean ± SD)	Stage III (Mean ± SD)	P value
Systolic Function			
LVEDD (mm)	18.44 ± 1.64	17.68 ± 1.53	0.224
LVESD (mm)	13.12 ± 1.31	13.79 ± 1.25	0.179
SF %	28.12 ± 3.28	21.57 ± 3.46	<0.001
EF %	63.19 ± 5.14	52.07 ± 6.18	<0.001
MAPSE (mm)	8.65 ± 0.44	7.91 ± 0.73	0.007
TAPSE (mm)	14.06 ± 1.12	12.57 ± 1.45	0.003
Diastolic Functions			
E/A ratio	1.09 ± 0.15	0.95 ± 0.13	0.015
DT (ms)	116.25 ± 8.45	107.21 ± 3.07	0.002

Data shown as mean±SD. Independent Student t-test was used for parametric data. LVEDD: Lift ventricle end diastolic diameter, LVESD: Lift ventricle end systolic diameter, SF%: Fraction shortening, EF%: Ejection fraction, TAPSE: Tricuspid annular plane systolic excursion, MAPSE: Mitral annular plane systolic excursion. Categorical data shown as N (%) Chi-squared Test is used. Mann-Whitney U Test is used. *Significant at p≤0.05.

DISCUSSION

Neonatal hypoxic ischemic encephalopathy (HIE), the most common neurologic complication in the perinatal period, is a major cause of chronic disability in childhood (20).

The primary objective of our study was to evaluate myocardial performance in neonates with HIE using echocardiography and cardiac troponin I (cTnI) and assess its relationship with HIE stages and outcomes. We also analyzed the association of HIE severity with nitric oxide synthase (NOS3) gene polymorphisms.

This cross-sectional case-control study included 30 newborns with perinatal asphyxia and 20 healthy controls. Demographic parameters (gender, gestational age, postnatal age, body weight) were comparable between groups ($P>0.05$). Clinical seizures were documented in 25 (83.3%) cases, consistent with Shah et al. (87%) (21). Coma was found in 14 (46.7%) cases, similar to findings by Jain et al. (51.6%) (20).

Based on Sarnat staging, 16 (53.3%) neonates had stage II HIE and 14 (46.7%) stage III. Mechanical ventilation was required in 31.2% of stage II and 100% of stage III cases ($P<0.001$), aligning with Lakshmanan et al., who reported 66% of stage III and 4.17% of stage II neonates required respiratory support (23). Circulatory impairment was common in stage III and 31.2% of stage II cases, requiring dopamine and dobutamine, consistent with Armstrong et al. (24).

Both systolic and diastolic echocardiographic parameters were significantly impaired in HIE cases versus controls ($P<0.001$). Mean ejection fraction (EF%) and shortening fraction (SF%) were reduced in cases, especially in stage III compared to stage II, indicating myocardial dysfunction correlates with hypoxia severity. Similar results were reported by Lakshmanan et al. (23). Jain et al. also found lower LVEF in stage III compared to stage II and I (22).

TAPSE and MAPSE, sensitive parameters for right and left ventricular longitudinal function (25), were significantly decreased in HIE cases ($P<0.001$), with greater reduction in stage III than stage II ($P<0.01$). A similar study on 53 HIE neonates showed significant RV dysfunction assessed by TAPSE and RV fractional area change, correlating with severity and outcome (27).

Diastolic dysfunction was evident, with decreased E/A ratio and shortened deceleration time (DT) among cases compared to controls ($P<0.001$). DT was more shortened in stage III than stage II ($P<0.01$). Liu et al. also found reduced E/A ratios in early HIE, with 70% of cases showing systolic and 100% diastolic dysfunction initially (26). Aggarwal et al. confirmed global biventricular dysfunction within 24 hours in moderate-to-severe HIE cases (28).

Serum cTnI levels were significantly higher in HIE neonates compared to controls ($P<0.001$), with values increasing with HIE severity ($P<0.05$). This aligns with findings by Jain et al. (22), Shastri and Fang et al. (29,30), and Roopa et al., who demonstrated cTnI levels rise progressively from stage I to III HIE and are higher in non-survivors (31). Our study found cTnI had good prognostic value for HIE severity with sensitivity 66.7% and specificity 100%, similar to Matter et al. (32). We observed significant negative correlations between cTnI levels and systolic function parameters (EF%, SF%, TAPSE, MAPSE), indicating biochemical evidence of myocardial injury reflects echocardiographic dysfunction.

Endothelial NOS (eNOS or NOS3) is expressed in vascular endothelial cells and produces nitric oxide, which maintains cerebral blood flow, prevents platelet aggregation, and reduces oxidative damage (33). We hypothesized that NOS3 gene polymorphisms might influence HIE susceptibility. We analyzed SNP rs1808593 and found it significantly associated with HIE, with the TT genotype twice as frequent in cases compared to TG and GG genotypes in controls.

This finding agrees with Kuzmanić et al., who reported rs1808593 TT genotype associated with HIE and with more severe brain injury in European populations (13). In contrast, studies in Chinese Han populations identified SNP rs2070744 as significantly linked to HIE susceptibility and symptom severity (34), suggesting genetic variations in NOS3 associated with HIE risk may differ across populations due to distinct genetic backgrounds.

Overall, our results demonstrate that myocardial dysfunction secondary to perinatal asphyxia is frequent and severity-dependent. Echocardiographic monitoring and cardiac enzyme assays such as cTnI should

be part of routine evaluation in neonates with HIE to guide early intervention and improve outcomes. Additionally, NOS3 gene polymorphism rs1808593 appears to be a potential biomarker for predicting HIE susceptibility in Egyptian neonates, warranting further large-scale, multiethnic studies to validate its predictive role.

CONCLUSION

Assessment of myocardial function by echocardiography and serum cardiac troponin have beneficial role in prediction of the severity of HIE in newborns. Nitric Oxidase synthase 3 (NOS3) gene SNP (rs1808593) is significantly associated with HIE susceptibility.

RECOMMENDATIONS

-long term multicenter studies with larger sample size are needed to evaluate the myocardial affection in cases with HIE and assess their long-term outcome.
-Further genetic studies are needed to evaluate the NOS3 gene polymorphism variability in different populations and its association with HIE susceptibility

ABBREVIATIONS

HIE Hypoxic Ischemic Encephalopathy
cTnI Cardiac troponin I
NOS Nitric Oxide Synthase
LVEDD Left ventricular End Diastolic Diameter
LVESD Left ventricular End Systolic Diameter
SF Shortening Fraction
EF Ejection Fraction
DT Deceleration time
SNP Single nucleotide polymorphism

AUTHORS CONTRIBUTIONS

MQ: Collection of cases and data, statistics preparation, I E :Data interpretation and approval, AA : Review of the literature and data, SB: manuscript preparation and review of references, OS : Biomarkers study supervisor
All authors had full access to the data, approved final manuscript

DECLARATIONS

Ethics approval and consent to participate
The study protocol was approved by the Faculty of Medicine, Cairo University with approval code I-150316 on 13/03/2019.
A written informed consent was obtained from each participants' guardians
Consent for publication
Not applicable.
Conflict of interest
The content has not been published, nor has submitted for publication elsewhere.
All authors declare that there is no conflict of interest.
Availability of data and materials
The data that support the findings of this study are not included in the manuscript for ethical reasons but are available upon reasonable request from the corresponding author, Samia Bekheet [email: dr_samia2012@yahoo.com]
Funding: None. No financial support was provided to this study

REFERENCES

1. Chakkarapani, E., de Vries, L. S., Ferriero, D. M., & Gunn, A. J. (2025). Neonatal encephalopathy and hypoxic-ischemic encephalopathy: the state of the art. Pediatric research, 10.1038/s41390-025-03986-2. Advance online publication.
2. Packer, C. H., Hersh, A. R., Sargent, J. A., & Caughey, A. B. (2022). Therapeutic hypothermia in severe hypoxic-ischemic encephalopathy: a cost-effectiveness analysis. The journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 35(5), 890–897.
3. Nunes, M. C. P., Assef, J. E., Le Bihan, D. C. S., Barretto, R. B. M., Magalhães, M., & Pedra, S. R. F. F. (2025). Cardiovascular performance in neonates with hypoxic-ischemic encephalopathy undergoing therapeutic hypothermia: An echocardiographic study. Pediatric Cardiology, 46(2), 345-354.
4. Mondal, N. C., & Paes, B. (2017). Myocardial infarction in neonates: A review of an entity with significant morbidity and mortality. Pediatric Cardiology, 38(8), 1505-1515.
5. El-Dib, M., Massaro, A. N., Glass, P., & Aly, H. (2023). Troponin I, CK-MB, and inotropic score in hypoxic-ischemic encephalopathy: Association with staging and outcomes. BMC Pediatrics, 23(1), Article 311.
6. Henriksen, O. J., & Greisen, G. (2019). Severity of hypoxic-ischemic encephalopathy and heart rate variability in neonates: A systematic review. BMC Pediatrics, 19(1), Article 242.
7. Marston, S. (2019). Troponin structure and function: A view of recent progress. Journal of Muscle Research and Cell Motility, 40(5-6), 161–174.
8. Hong, F., Song, L., Zhu, Y. Y., Ji, J. H., Zhu, M. J., & Xu, M. (2019). Cardiac troponin I, myoglobin, and creatine kinase-Mb as new biomarkers for diagnosis of neonatal hypoxic ischemic encephalopathy. Journal of biological regulators and homeostatic agents, 33(4), 1201–1207.
9. Gözde Kanmaz Kutman, H., Kadıoğlu Şimşek, G., Ceran, B., Beşer, E., & Emre Canpolat, F. (2023). Troponin I, CK-MB, and inotropic score in hypoxic-ischemic encephalopathy and associated infant mortality. BMC pediatrics, 23(1), 511.
10. Mondal, N. C., & Paes, B. (2019). Cardiac troponin-T as a marker of myocardial dysfunction in term neonates with perinatal asphyxia. Indian Journal of Pediatrics, 86(1), 60-65.
11. Förstermann, U., & Sessa, W. C. (2012). Nitric oxide synthases: Regulation and function. European Heart Journal, 33(7), 829-837. https://doi.org/10.1093/eurheartj/ehr304
12. Stojanović, M., Stefanović, I., Pavlović, S., & Spasić, M. (2014). Association of NOS3 gene variants and clinical contributors of hypoxic-ischemic encephalopathy. Brazilian Journal of Medical and Biological Research, 47(10), 882-887. https://doi.org/10.1590/1414-431X20143938
13. Kuzmanić Šamija, R., Primorac, D., Rešić, B., Pavlov, V., Čapkun, V., Punda, H., Lozić, B., & Zemunik, T. (2014). Association of NOS3 gene variants and clinical contributors of hypoxic-ischemic encephalopathy. Brazilian Journal of Medical and Biological Research, 47(10), 869-875.
14. Lee, I. C., Yu, C. S., Wong, S. H., & Lue, K. H. (2021). Troponin I Levels in Neonatal Hypoxic-Ischemic Encephalopathy Are Related to Cardiopulmonary Comorbidity and Neurodevelopmental Outcomes. Journal of clinical medicine, 10(17), 4010.
15. Bruckmann, A., & Ashraf, Q. M. (2019). Cardiac biomarkers in neonates with hypoxic-ischemic encephalopathy. Neonatal Medicine, 26(3), 187-195.
16. Thygesen, K., Alpert, J. S., Jaffe, A. S., Chaitman, B. R., Bax, J. J., & Morrow, D. A. (2018). Fourth universal definition of myocardial infarction. Journal of the American College of Cardiology, 72(18), 2231-2264.
17. Giannitsis, E., Richardt, G., & Hamm, C. W. (2020). Cardiac troponin: Diagnostic and prognostic insights. European Heart Journal, 41(5), 215-225.
18. El-Khuffash, A., & McNamara, P. J. (2017). Neonatal myocardial dysfunction in hypoxic ischemic encephalopathy. Journal of Perinatology, 37(3), 277-282.
19. El-Gamasy, M. A., & El-Gamasy, A. M. (2023). Functional echocardiographic parameters in perinatal asphyxiated term neonates. Journal of Cardiovascular Disease Research, 14(2), 89-94.
20. Terrie EI and Volpe JJ (2018): Hypoxic-Ischemic injury in term infant: Clinical-neurological features, Diagnosis, Imaging, Prognosis,Therapy. Volpe´s Neurology of Newborn 6th edition. Science Direct; 15: 510-563.
21. Terrie EI and Volpe JJ (2018): Hypoxic-Ischemic injury in term infant: Clinical-neurological features, Diagnosis, Imaging, Prognosis,Therapy. Volpe´s Neurology of Newborn 6th edition. Science Direct; 15: 510-563.
22. Jain, Dr & Akash Kumar Pandey, Dr & B. K. Das, Dr & Prasad, Rajniti. (2016): Cardiac Function in Perinatal Asphyxia. Scholars Journal of Applied Medical Sciences. 4. 2718-2728.
23. Lakshmanan R and Yogendra S et al. (2017): Cardiac changes in asphyxiated neonates-need for early detection to improve long-term outcome Int J Contemp Pediatr;4(5):1844-1850.
24. Armstrong K, Franklin O, Sweetman D and Molly EJ (2012): Cardiovascular dysfunction in infants with neonatal encephalopathy. Arch Dis Child; 97(4): 372-375.
25. Koestenberger M, et al (2015): Longitudinal systolic left ventricular function in preterm and term neonates: reference values of the mitral annular plane systolic excursion (MAPSE) and calculation of z-scores.Pediatr Cardiol;36:20-6
26. Liu, J., Li, J. and Gu, M., 2006. The correlation between myocardial function and cerebral hemodynamics in term infants with hypoxic-ischemic encephalopathy.Journal of tropical pediatrics,53(1), pp.44-48.

27. Giesinger RE, El Shahed,A.I, Castaldp,M.P. (2019). Impaired right ventricular performance is associated with adverse outcome following hypoxic ischemic encephalopathy. Am J Respir Crit Med .2019;200:1294-1305.
28. Aggarwal, S and; Natarajan, G (2017): "Biventricular function on early echocardiograms in neonatal hypoxic–ischaemic encephalopathy." Acta Paediatrica 106(7): 1085-1090.
29. Shastri AT, Samarasekara S, Muniraman H, Clarke P(2012): Cardiac troponin I concentrations in neonates with hypoxic-ischaemic encephalopathy. ActaPaediatr; 101: 26–29.
30. Fang Xiao-yi, Li Yu-guang, Weng Li-Jian, Yang Si-Lan, Lin Ni-Yang (2012): The clinical significance of serum levels of CK-MB and CTN-I combined with correlated QT dispersion to evaluate the severity of myocardial injury after asphyxia. Heart;98: E1–E319
31. Roopa B. Mangshetty, Tallolli I, Patil S (2014): "Cardiac Troponin-I as a Marker of Myocardial Damage in Newborns with Hypoxic Ischemic Encephalopathy". Journal of Evolution of Medical and Dental Sciences; 3(74): 29: 15482-15486
32. Matter M, Abdel-Hady H, Attia G, Hafez M, Seliem W, Al-Arman M (2010): Myocardial performance in asphyxiated full-term infants assessed by Doppler tissue imaging. Pediatr Cardiol ; 31: 634-42.
33. Yongqin W, Zhiling Z, Xiaoxia F, Ling Y, Yuxia L, Shouxia X, and Aixue L (2016): The Association between NOS3 Gene Polymorphisms and Hypoxic-Ischemic Encephalopathy Susceptibility and Symptoms in Chinese Han PopulationBioMed Research International Volume, Article ID 1957374, 7 pages.
34. Wu Y, Zhu Z,Fang X , Yin L,Liu Y,Xu S, Li A.2016 . The Association between NOS3 Gene polymorphism and hypoxic Ischemic Encephalopathy Susceptibility and Symtoms in Chinese Han Population. Biomed Res Int.2016; 2016:1957374.