IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

Open Access
Original Article

Can a Single Value of Cardiac Troponin I Predict Short-term Adverse Outcomes in Premature Newborns?

Kamyar Kamrani[1], MinaSadat Khazraee[1], MohammadReza Zarkesh[2,*], Roksana Moeini[3], Mamak Shariat[4]

1. Department of Pediatrics, Bahrami Hospital, Tehran University of Medical Sciences, Tehran, Iran
2. Maternal, Fetal, and Neonatal Research Center, Family Health Research Institute, Tehran University of Medical Sciences, Tehran, Iran
3. Department of neonatology, Yas Women Hospital, Tehran University of Medical Sciences, Tehran, Iran
4. Breastfeeding Research Center, Family Health Institute, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Background: Cardiac troponin I (cTn I) has been demonstrated as a possible useful biomarker for myocardial injuries. The present study aimed to evaluate potential relationships between this biomarker and neonatal morbidities among preterm neonates.

Methods: This cohort study was carried out at an Iranian Hospital (Tehran-Iran; 2021). Newly-born preterm neonates entered the study. Blood sampling was performed immediately after neonatal intensive care unit (NICU) admission and sent to the laboratory to detect levels of plasma cTnI. The correlations between the levels of plasma Tn I and each neonatal outcome were evaluated as the primary outcome.

Results: A total of 101 NICU hospitalized neonates with the mean gestational age, 1st, and 5th minutes Apgar scores of 33.750±2.125 (Range: 29-37) weeks, 7.6471±1.766, and 9.188±1.205 entered the study. The mean and median of Troponin I levels were 0.131±0.126 and 0.0920 ng/ml. The results pointed out that neonates who died during hospitalization or required CPR (cardiopulmonary resuscitation) had lower troponin I in comparison with their controls; nonetheless, the differences were not significant (P=0.950 & P=0.557). The mean±SD of troponin I was not significantly different between neonates with and without PDA (p=0.741), asphyxia (P=0.298), and intubation (P=0.212). The occurrences of necrotizing enterocolitis, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, and sepsis were not also significant factors for the alteration of troponin I (P>0.05).

Conclusion: Since there were no relationships between cTn I and neonatal outcomes, great caution should be implemented regarding the use of single cTn I value as a diagnostic marker for short-term neonatal adverse outcomes. Further investigations with larger sample sizes are strongly suggested.

Keywords: Cardiac troponin I, Morbidity, Newborn, Premature birth

Introduction

Preterm newborns are at great risk of neonatal mortality and morbidity. Among the life-threatening complications related to preterm birth, we can refer to cerebral palsy, respiratory distress syndrome, patent ductus arteriosus (PDA), sepsis, necrotizing enterocolitis (NEC), severe intraventricular hemorrhage, hospitalization, and hospital readmissions (1-3). Numerous studies have been conducted to find distinctive biomarkers to predict mortality, the development of morbidity, and treatment requirement in preterm neonates. The diagnostic values of neutrophil gelatinase-associated lipocalin (NGAL) and epidermal growth factor (EGF) levels have been demonstrated in the development of acute kidney injury among preterm neonates (4). Other biochemical biomarkers, such as procalcitonin, neutrophil CD64, and presepsin, have been used to predict neonatal sepsis (5). β-glucosidase, C reactive protein, serum amyloid A, IL-6, IL-8, IL-10, and neutrophil CD64 have also been

* *Corresponding author*: Mohammad Reza Zarkesh, Sarv Ave., North Nejatolahi Street, Tehran-Iran. Tel: +989121797758, Email; zarkesh@tums.ac.ir

Please cite this paper as:
Kamrani K, Khazraee MS, Zarkesh MR, Moeini R, Shariat M. Can a Single Value of Cardiac Troponin I Predict Short-term Adverse Outcomes in Premature Newborns?. Iranian Journal of Neonatology. 2023 Feb: 14(1). DOI: 10.22038/IJN.2023.65396.2267

reported as diagnostic biomarkers of NEC (6).

Cardiac troponin I (cTn I) has also been proposed as another useful biomarker for myocardial and coronary injuries (7). An investigation pointed to a significant increase in high-sensitivity cTnI in asphyxiated newborns with myocardial injuries (8). Elevated serum troponin I levels have been shown in neonates with respiratory distress, pulmonary hypertension, and mechanical ventilation (9). A significant correlation was also observed between increased cTn I and severe hypoxic-ischaemic encephalopathy (10). The relationship of elevated serum cTnI with neonatal mortality and perinatal asphyxia suggested that cTn I could be a valuable predicting factor for neonatal morbidity and mortality (11, 12). In contrast to these findings, other investigations demonstrated that cTn I could not be a precise biomarker of neonatal outcomes (13, 14).

The introduction of a biomarker helps in the diagnosis of early stages of morbidities; nonetheless, diversities in the existent results related to cTn I demonstrated a potential capacity for more investigation. In light of the aforementioned issues, the present cohort study aimed to evaluate the possible relationship of this biomarker with several neonatal morbidities, as well as mortality among preterm neonates.

Methods

This cohort study was carried out at the neonatal intensive care unit (NICU) of an Iranian Hospital (Yas Hospital, affiliated with Tehran University of Medical Sciences, Tehran-Iran) in 2021. Newly-born preterm neonates who were admitted to NICU entered the study. The inclusion criteria were preterm birth (gestational age<37 weeks), singleton pregnancy, and NICU hospitalization. Newborns with chromosomal anomalies and congenital heart diseases were excluded from the study. Before the admission of the participants, their parents were informed about the study and asked to sign written informed consent. Blood sampling was performed immediately after admission. The heparinized blood tube was centrifuged, labeled, stored at -20^{o} C, and sent to the laboratory. The levels of plasma cTn I were detected using the Elisa Kit (100887-097F; cTnI 3rd-Gen; Immuno Enzymometric Assay; AIA-360; TOSOH; Assay range: 0.03 - 50 ng/mL, India).

Demographic characteristics, such as the mother's age, the numbers of gravidity and parity, type of delivery, neonate's birth weight, height, head circumference, as well as 1st and 5th minutes Apgar scores, were recorded. During NICU hospitalization, data related to early neonatal outcomes, including neonatal intraventricular hemorrhage, respiratory distress syndrome, sepsis, hospitalization duration, intubation duration, death, age at death, and resuscitation requirements, were gathered and recorded. Finally, the correlations between the levels of plasma Tn I (ng/ml) and each neonatal outcome were evaluated as the primary outcome. Moreover, the relationships between the variables and the levels of cTn I were assessed as the secondary outcome.

Data Analysis

All statistical analyses were conducted in SPSS software (version 22). Quantitative and qualitative variables were presented as mean±standard deviation and number (%), respectively. Independent samples t and Chi-square tests (or Fisher Exact) were used for analyzing the relationships among variables with a normal distribution. Since the Kolmogorov-Smirnov Test displayed non-normal distribution in quantitative variables, Mann-Whitney analysis was also used. The Correlation Coefficient was also determined using Spearman's Correlation test to show the levels of significance between variables. A p-value less than 0.05 was considered statistically significant.

Results

A total of 101 NICU hospitalized neonates (59 males and 42 females) with the mean gestational age, 1st, and 5thminutes Apgar scores of 33.750±2.125 (Range: 29-37) weeks, 7.6471±1.766, and 9.188±1.205 entered the study. The majority of neonates (90.2%)were born via cesarean section. The mean and median of Troponin I levels were 0.131±0.126 and 0.0920 ng/ml. Five cases died after birth with a mean age of 1.148±10.072 days. The mean maternal age was 30.549±5.755 years, and thyroid disorder was the most frequent complication among mothers. Detailed maternal and neonatal demographic characteristics are displayed in Table 1.

As illustrated in Table 2, the relationships between Troponin I levels and neonatal outcomes were assessed. The results pointed out that neonates who died during the hospitalization period or required resuscitation had lower troponin I in comparison with controls; nonetheless, the differences were not significant (P=0.950 and

Table 1. Demographic and clinical characteristics of neonates and their mothers

Variables	Case group n=101
Maternal age (year; Mean±SD)	30.549±5.755
Gestational age (weeks; Mean±SD)	33.750±2.125
Gravidity (Mean±SD)	2.019±1.043
Parity (Mean±SD)	0.588±0.708
Maternal disease (n%)	
Diabetes	13(12.7)
Hypertensive disorders	16(15.7)
Thyroid disorders	23(22.5)
Other	2 (2.9)
None	47(46.1)
Type of delivery (n%)	
Cesarean Section	92 (90.2)
Vaginal delivery	8 (7.8)
Missing	1 (2)
Gender (n%)	
Male	59(57.8)
Female	42(42.2)
Birth Weight (Mean±SD)	2040.480±639.406
Birth height (Mean±SD)	45.348±4.78228
Birth Head Circumference (Mean±SD)	31.113±2.446
1st minute Apgar Score(Mean±SD)	7.6471±1.766
5th minute ApgarScore (Mean±SD)	9.188±1.205
NICU* duration (Day; Mean±SD)	25.176±19.000
Troponin I levels (Mean± SD)	0.131±0.126

* Neonatal intensive care unit

Table 2. Assessing the relationships between neonatal morbidities and Troponin I levels

Neonatal outcomes	Frequency (number and percent)	Troponin I levels (Mean± SD)	P Value
Patent ductus arteriosus			
Yes	36 (35.3)	0.133±0.128	0.741
No	65 (64.7)	0.130±0.126	
Intubation			
Yes	42 (42.2)	0.154±0.145	0.212
No	57(55.9)	0.116±0.111	
Missing	2(2.0)		
Sepsis			
Yes	12(11.8)	0.107±0.069	0.925
No	89(88.2)	0.134±0.132	
Asphyxia			
Yes	3 (2.9)	0.234±0.225	0.298
No	98 (97.1)	0.128±0.122	
Resuscitation requirement			
Yes	5(4.9)	0.110±0.040	0.557
No	96(95.1)	0.132±0.129	
Necrotizing enterocolitis			
Yes	3(2.9)	0.110±0.020	0.471
No	98 (97.1)	0.132±0.128	
Respiratory distress syndrome			
Yes	81 (80.4)	.1316±.12407	0.653
No	20 (19.6)	0.130±0.139	
Bronchopulmonary dysplasia			
Yes	1(1.0)	0.033±1.287	0.135
No	100(99.0)	0.132±0.126	
Death			
Yes	5 (4.9)	0.099±0.048	0.950
No	96(95.1)	0.133±0.129	
Intraventricular hemorrage			
Yes	2 (2.0)	0.071±0.030	0.495
No	99(98.0)	0. 132±0.127	

P=0.557, respectively). The mean±SD of troponin I was not significantly different between neonates with and without PDA (P==0.741). Although the asphyxiated neonates had higher troponin I level in comparison with the controls, the difference was not significant (0.234±0.225 vs. 0.128±0.122,

Table 3. Assessing the correlations betweenmaternal/neonatal variables and TroponinI levels

Variables	Correlation Coefficient	P-value
Mother age	0.144	0.148
Gestational age	-0.053	0.595
First-minute Apgar score	0.056	0.574
Fifth-minute Apgar score	0.021	0.834
Gravidity	-0.010	0.918
Birth weight	-0.065	0.514

P=0.298). No significant difference was also observed between 42 intubated newborns and the others without intubation (P=0.212). The occurrences of NEC, RDS, bronchopulmonary dysplasia, intraventricular hemorrhage, and sepsis were not significant factors for the alteration of troponin I (p>0.05). The mean of troponin I level was not significantly different between male and female subjects (0.132±.132 and 0.1302±.119; P=.785).

Further analysis was also performed to show the possible impact of each variable on Troponin I concentrations. The results demonstrated that Tn I levels were inversely correlated with neonate's gestational age and birth weight; however, these relationships were not significant (Correlation Coefficient= -0.053; P=0.595 & Correlation Coefficient=-0.065; P=0.514). Mothers with higher numbers of pregnancies had lower Troponin I levels; nonetheless, gravida was not a significant factor in the alteration of Troponin I. The 1st and 5th minutes Apgar scores, as well as the mother's age, were not also significant influencing factors to change Troponin I (Table 3).

Discussion

Cardiac Troponin I is a specific intracellular protein and is not detectable in normal conditions. Serum CTn I rises about 2-4 hours post-myocardial damage and remains high for 7-10 days. This significant characteristic suggested that cTn I may be considered a diagnostic marker for cardiac complications, such as myocarditis, arrhythmias, cardiotoxicity, asphyxia, and ischemia (15). Although a few investigations have assessed the alterations of Troponin I level in term and preterm neonates, their results were diverse. In the present study, we assessed any relationships between this marker and neonatal outcomes. The results of such studies may provide a clarifying light on the existing challenges. According to the results of tis study, the Troponin I level in 101 preterm neonates with the mean gestational age of 33.750±2.125 weeks was 0.131±0.126 ng/ml. The other study by Bader et al. (12) pointed out that the mean of cTn I in 22 preterm neonates (with gestational age 32.6±2.9 weeks) was 1.34±1.63 ng/ml. This diversity between detected values can be ascribed to differences in the number of infants, gestational age, perinatal/neonatal outcome, degrees of complication, the immunoassay kit, or the neonate's age at measuring cTn I.

The results demonstrated no significant difference in the means of cTnI between male and female subjects. Moreover, cTn I level was not significantly correlated with neonates' gestational age, birth weight, or Apgar scores. In accordance with our findings, Bader et al. (12) indicated no remarkable difference between the means of cTnI level in male and female preterm neonates. Several previous studies also denoted that associations between cTn I concentration and gestational age or birth weight were not significant (12, 13, 16). Conversely, Quivers et al. (17) demonstrated a significant and inverse relationship between birth weight and cTn I concentration. Shu-Chi et al. (13) also indicated that first and 5th minutes Apgar scores were negatively correlated with cTn I levels.

As evidenced by the results of the present study, the mean of troponin I in the neonates who died was not significantly different from this value in the controls who survived. Furthermore, the results displayed no significant relationships between the mean of troponin I and different neonatal complications, such as PDA, asphyxia, intubation requirement, NEC, RDS, bronchopulmonary dysplasia, intraventricular hemorrhage, and sepsis. Accordingly, it seems a caution should be considered regarding the use of single cTn I value as a diagnostic marker for adverse outcomes in preterm neonates. Consistent with these findings, Mayasari et al. (16) demonstrated no significant difference in troponin I level among the living and dead neonates. Shu-Chi et al. (13) indicated that cTnI could not be a precise predictive biomarker showing neonatal outcomes.

Based on Bader et al. (12), cTnI concentration showed no significant associations with neonatal respiratory distress syndrome, resuscitation, jaundice, sepsis, and necrotizing enterocolitis. König et al. (18) illustrated that the cTn I level was not significantly different among bronchopulmonary dysplasia cases with and without pulmonary hypertension. In contrast to our findings, Distefano et al. (19) indicated a significant increase in serum cTn I in preterm neonates with idiopathic respiratory distress. Simovic et al. (20) demonstrated a significant correlation between cTnIand adverse outcome/mortality in preterm neonates. EL-Khuffash et al. (21) revealed that plasma cTnT in preterm cases with severe disability or death was significantly higher in comparison with the normal controls or the group with mild disability. Mayasari et al. (16) also reported that CTnI had a weak relationship with the values related to cardiac output and stroke volume in newborns with RDS.

It is supposed that several reasons may be involved in such different results. In the present study, cTn I was assessed immediately after NICU admission, and we did not reexamine its level following the advancement of neonatal complications. It was demonstrated that an increase in the newborn's age or deterioration of neonatal complications, such as respiratory distress, could increase cTn I level (16). Moreover, electrocardiography or echocardiography examinations were not performed for our participants to indicate the degrees of myocardial infarction or alterations of cardiac function that may affect cTn I levels.

The current study had several limitations. CTn I level was not assessed in the term controls or the cases with congenital anomalies that could have provided much more comparable and informative data. The values related to cardiac function were not evaluated to show the degrees of cardiac damage in every neonatal outcome. CTn I level was not rechecked after a few days to illustrate the relationship between the neonate's age or advanced neonatal adverse outcomes and cTn I alterations. Finally, our sample size was too small to generalize our findings.

Conclusion

Since there were no relationships between cTn I and neonatal outcomes, caution should be implemented regarding the use of single cTn I value as a diagnostic marker for neonatal adverse outcomes. Further investigations with larger sample sizes are strongly suggested.

Declarations

Ethics and consent to participate

Our study was approved by the Institutional Review Board of Tehran University of Medical Sciences according to the Helsinki declaration (IR.TUMS.IKHC.REC.1399.182). The participant's parents of the minors included in this study signed written consent before enrollment. Participants' data were considered confidential, and no extra cost was imposed on our participants.

Consent for Publication

Written informed consent was obtained from the patient's legal guardian for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

The datasets related to our study are available from the corresponding author on reasonable request.

Acknowledgments

This study was supported by the Tehran University of Medical Sciences (TUMS) and the Maternal, Fetal, and Neonatal Research Center. Our most profound appreciation goes to them.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Crilly CJ, Haneuse S, Litt JS. Predicting the outcomes of preterm neonates beyond the neonatal intensive care unit: What are we missing? Pediatric Research. 2021;89(3):426-45.
2. Wang L-W, Lin Y-C, Wang S-T, Huang C-C, Tsou K-I, Tsao P-N, et al. Trendsin survival, neonatal morbidity and neurodevelopmental outcome of very preterm infants in Tainan, Southern Taiwan, 1995–2016. Journal of the Formosan Medical Association. 2021;120(6):1314-23.
3. Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, Barfield W ,Weiss J, Evans S, editors. Risk factors for neonatal morbidity and mortality among "healthy," late preterm newborns. Seminars in perinatology; 2006: Elsevier.
4. Hanna M, Brophy PD, Giannone PJ, Joshi MS, Bauer JA, RamachandraRao S. Early urinary biomarkers of acute kidney injury in preterm infants. Pediatric research. 2016;80(2):218-23.
5. Gilfillan M, Bhandari V. Neonatal sepsis biomarkers: where are we now? Research and Reports in Neonatology. 2019;9:9-20.
6. Ng PC, editor An update on biomarkers of

necrotizing enterocolitis. Seminars in Fetal and Neonatal Medicine; 2018: Elsevier.
7. Usluer H, Turker G, Gokalp AS. Value of homocysteine levels, troponin I, and score for neonatal acute physiology and perinatal extension II as early predictors of morbidity. Pediatrics International. 2012;54(1):104-10.
8. Jiang L, Li Y, Zhang Z, Lin L, Liu X. Use of high-sensitivity cardiac troponin I levels for early diagnosis of myocardial injury after neonatal asphyxia. Journal of International Medical Research. 2019;4. 3234-42:(7)7
9. Tanasan A, Eghbalian F, Sabzehei MK, Rastgoo Haghi A. The relationship between serum levels of troponin I and myocardial function in neonates under mechanical ventilation. Iranian Journal of Pediatrics. 2020;30(1.(
10. Shastri AT, Samarasekara S, Muniraman H, Clarke P. Cardiac troponin I concentrations in neonates with hypoxic-ischaemic encephalopathy. Acta Paediatrica. 2012;101(1):26-9.
11. Mahmoud AT, El-Bassuny M, Shebl A. Cardiac troponin I as an early predictor of perinatal asphyxia . Menoufia Medical Journal. 2013;26(2):145.
12. Bader D, Kugelman A, Lanir A, Tamir A, Mula E, Riskin A. Cardiac troponin I serum concentrations in newborns: A study and review of the literature. Clinica Chimica Acta. 2006;371(1):61-5.
13. Mu SC, Wang LJ ,Chen YL, Lin MI, Sung TC. Correlation of troponin I with perinatal and neonatal outcomes in neonates with respiratory distress. Pediatrics International. 2009;51(4):548-51.
14. McAuliffe F, Mears K, Fleming S, Grimes H, Morrison JJ. Fetal cardiac troponinI in relation to intrapartum events and umbilical artery pH. American journal of perinatology. 2004;21(03):147-52.
15. Tarkowska A, Furmaga-Jabłońska W. The Evaluation of Cardiac Troponin T in Newborns. Biomedicine hub. 2017;2(3):1-7.
16. Mayasari NMC. Correlation between Troponin-I and Lowering Cardiac Function in Newborn with Respiratory Distress. EC Paediatrics. 2019;8:192-201.
17. Quivers ES, Murthy JN, Soldin SJ. The effect of gestational age, birth weight, and disease on troponin I and creatine kinase MB in the first year of life. Clinical biochemistry. 1999;32(6):419-21.
18. König K, Guy KJ, Nold-Petry CA, Barfield CP, Walsh G, Drew SM, et al. BNP, troponin I, and YKL-40 as screening markers in extremely preterm infants at risk for pulmonary hypertension associated with bronchopulmonary dysplasia. American Journal of Physiology-Lung Cellular and Molecular Physiology. 2016;311(6):L1076-L81.
19. Distefano G, Sciacca P, Mattia C, Betta P, Falsaperla R, Romeo M, et al. Troponin I as a biomarker of cardiac injury in neonates with idiopathic respiratory distress. American journal of perinatology. 2006;23(04):229-32.
20. Simovic AM, Stojkovic AK, Dejan JM, Savic D. Is it Possible to Predict Mortality in Preterm Neonates, Based on a Single Troponin I Value at 24 h? Indian journal of pediatrics. 2016;83(5):466-7.
21. El-Khuffash AF, Slevin M, McNamara PJ, Molloy EJ. Troponin T, N-terminal pro natriuretic peptide and a patent ductus arteriosus scoring system predict death before discharge or neurodevelopmental outcome at 2 years in preterm infants. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2011;96(2):F133-F7.