

# Use of high-sensitivity cardiac troponin I levels for early diagnosis of myocardial injury after neonatal asphyxia

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## Abstract

**Objective:** Low-cost diagnostic and prognostic biomarkers could help guide clinical management of neonates with myocardial injury after asphyxia. This study aimed to assess the utility of creatine kinase (CK)-MB, high-sensitivity cardiac troponin I (hs-cTnI), brain natriuretic peptide (BNP), and myoglobin in the early diagnosis of myocardial injury following neonatal asphyxia.

**Methods:** Eighteen neonates with asphyxia and myocardial injury, 22 neonates with asphyxia and no myocardial injury, and 19 neonates without asphyxia (controls) were enrolled consecutively at the Neonatology Department, First Hospital of Lanzhou University (August 2013 to December 2014). Serum CK-MB, hs-cTnI, BNP, and myoglobin levels were evaluated at 12 hours and 7 days after birth. Their diagnostic value for myocardial injury was assessed by receiver operating characteristic (ROC) curve analysis.

**Results:** Levels of all four markers were higher in neonates with asphyxia and myocardial injury than in neonates with asphyxia and no myocardial injury or controls 12 hours after birth. The marker hs-cTnI had the highest diagnostic value. Using a cutoff value of 0.087 µg/L for hs-cTnI, the sensitivity, specificity, and diagnostic accuracy for asphyxia-induced myocardial injury were 55.6%, 95.5%, and 77.5%, respectively.

**Conclusions:** Serum hs-cTnI levels can predict myocardial injury caused by neonatal asphyxia at an early stage.

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## Keywords

Myocardial injury, hypoxia, asphyxia, neonate, troponin I, diagnostic value

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## Introduction

In China, the incidence of neonatal asphyxia is estimated to be 2% to 7%.<sup>1</sup> Neonatal asphyxia results in low fetal tissue perfusion, hypoxic ischemic injury, hypercapnia, and acidosis, and is potentially fatal.<sup>2,3</sup> Survivors from neonatal asphyxia can suffer from morbidities, such as motor and cognitive deficits that originate from cerebral hypoxia–ischemia.<sup>4</sup>

Myocardial damage is the main cause of neonatal mortality associated with hypoxia–ischemia and survivors can show significant myocardial morbidity.<sup>5</sup> Myocardial damage occurs in 28% to 73% of neonatal asphyxia cases.<sup>6</sup> Troponin is considered as the gold standard biomarker and is usually used in conjunction with creatine kinase-MB (CK-MB) and myoglobin.<sup>7</sup> Cardiac troponin I and T are reliable markers for use in adult patients, but the expression of four alternatively spliced transcripts slightly complicates the use of troponin T.<sup>8</sup> Serum cardiac troponin T levels are elevated in infants that have experienced neonatal asphyxia, suggesting that they may be a good indicator for myocardial injury.<sup>5,9</sup> However, there is some concern that cardiac troponin T levels may be influenced by administration of adrenalin during resuscitation<sup>10</sup> and may not be as clinically useful in preterm neonates.<sup>11</sup> Cardiac troponin I and CK-MB have also been used as biomarkers for myocardial ischemia/infarction in infants with neonatal asphyxia.<sup>5,12</sup> Troponin I is considered to be more sensitive than CK-MB for myocardial injury. CK-MB is affected by gestational age and

other factors.<sup>13</sup> Nonetheless, CK-MB has shown great potential as a biomarker for congenital heart disease in newborns.<sup>14</sup> Another potentially useful biomarker for myocardial injury is brain natriuretic peptide (BNP).<sup>15</sup>

There is only limited information regarding the potential diagnostic utility of high-sensitivity cardiac troponin I (hs-cTnI), particularly in the Chinese neonatal population. Therefore, the primary objective of the present study was to measure serum CK-MB, hs-cTnI, BNP, and myoglobin levels in neonates with myocardial injury due to neonatal asphyxia. We compared these neonates with neonates with neonatal asphyxia without myocardial injury and a control group of neonates without any history of asphyxia. The secondary objective of the present pilot study was to assess the feasibility of using these cardiac biomarkers for early diagnosis of asphyxia-induced myocardial injury in neonates in China, with a view to further assessment in a larger scale study.

## Material and methods

### *Study participants and classification of clinical status*

In the present study, 40 neonates with asphyxia were consecutively enrolled between August 2013 and December 2014 following admission to the Department of Neonatology, First Hospital of Lanzhou University, China. A further 19 neonates

without asphyxia were enrolled during the same time period as a control group.

Asphyxia was determined in accordance with the guidance of the American College of Obstetrics and Gynecology<sup>16</sup> using the following criteria: 1) an umbilical arterial blood sample (if obtained) indicated profound metabolic or mixed acidemia ( $\text{pH} < 7.00$ ); 2) persistence of an Apgar score of 0 to 3 for longer than 5 minutes;<sup>17</sup> 3) indications of neonatal neurological symptoms, such as seizures, coma, or hypotonia; and 4) multiple organ involvement. In this study, Apgar scores of  $\leq 3$  in the first minute and/or  $< 5$  in the fifth minute were considered as severe birth asphyxia, while scores of 4 or 5 in the first minute were considered as moderate birth asphyxia.<sup>18</sup> Newborns without any history of asphyxia or cardiovascular diseases and those with Apgar scores  $\geq 7$  were selected during the recruitment period as a non-asphyxia control group. The exclusion criteria for all subjects were as follows: 1) neonates with intrauterine infection, central nervous system abnormalities, respiratory diseases, congenital heart disease, or persistent pulmonary hypertension; and 2) patients whose mothers had infectious or metabolic diseases. The study was approved by the Ethics Committee of the First Hospital of Lanzhou University. The guardians of all the included neonates signed informed consent forms for their participation in the study.

The diagnosis of myocardial injury caused by neonatal asphyxia was made according to the current Chinese diagnostic criteria, which are summarized as follows: 1) a history of perinatal hypoxia; 2) clinical manifestations suggesting myocardial injury, including bradycardia, low blunt heart sounds, or signs of a poor circulation (e.g., a pale face, fingertip cyanosis, or capillary nail refill test  $> 3$  seconds); and 3) ST-T wave abnormalities in an electrocardiogram that lasted 2 to 3 days. Although

the Chinese diagnostic criteria for myocardial injury caused by neonatal asphyxia also include an elevation in CK-MB or troponin T levels, this was not used as an inclusion criterion because the purpose of this study was to evaluate the utility of these (and other) biomarkers. These diagnostic guidelines are similar to those reported previously.<sup>18</sup>

The neonates with asphyxia were divided into two groups according to whether they suffered from myocardial injury: a myocardial injury group (18 cases) and a non-myocardial injury group (22 cases). A total of 19 cases without asphyxia or cardiovascular diseases were included as the non-asphyxia control group. Full-term delivery was defined as parturition at 37 to 40 weeks, preterm delivery as parturition before 37 completed weeks of gestation, and late/post-term delivery as parturition at  $> 40$  completed weeks.

### *Baseline demographic and clinical characteristics*

The following demographic data were recorded for each neonate: sex, birth weight, gestational age at birth, mode of delivery (natural delivery or cesarean section), presence/absence of a nuchal cord (i.e., cord around the neck), and presence/absence of meconium staining of the amniotic fluid.

### *Measurement of primary variables*

The following primary variables were recorded: serum levels of hs-cTnI, myoglobin, BNP, and CK-MB. A total of 2 mL of blood was obtained from each neonate at 12 hours after birth. The blood sample was collected in an EDTA anticoagulation tube and centrifuged (2500 rpm/minute) at room temperature for 15 minutes. The supernatant in the centrifuge tube was used within 24 hours for detection of the cardiac

markers. Serum hs-cTnI, myoglobin, and BNP levels were measured using a chemiluminescence immunoassay (i2000 detection kit; Abbott Laboratories, Chicago, IL, USA). Serum CK-MB levels were measured using an AU5831 Clinical Chemistry Analyzer (Beckman Coulter, Brea, CA, USA). According to the manufacturer, the detection limit for hs-cTnI was 1.1 to 1.9 ng/L and the coefficient of variation was 10% at a concentration of 4.7 ng/L. The biomarker levels were re-measured 7 days after birth (only CK-MB was detected in the non-asphyxia control group at this time point).

### *Statistical analysis*

Because this was a pilot cohort study, no sample size was determined and we recruited all eligible patients during the study period. SPSS 17 software (SPSS Inc., Chicago, IL, USA) was used to perform statistical analyses. Continuous data are presented as the mean  $\pm$  standard deviation (normally distributed data) or median (range) (non-normal distribution), and categorical data are presented as the number of cases (percentage). Comparisons of frequencies among the three groups were performed using the chi-square test or Fisher's exact test. The Apgar score and biomarker levels were compared among groups using the Kruskal–Wallis test. The Mann–Whitney U-test was used for post-hoc analysis. Bonferroni correction was applied for all post-hoc comparisons. Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic utilities of serum CK-MB, hs-cTnI, BNP, and myoglobin levels, which were measured at 12 hours and 7 days, for the diagnosis of myocardial injury after neonatal asphyxia. ROC curves were plotted and the areas under the ROC curves (AUC values) were calculated. The optimal cutoff value for each biomarker was determined by

calculation of the Youden index, which provides the maximal values for sensitivity+specificity–1. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for each biomarker using the optimal cutoff value. A P value of less than 0.05 was considered as statistically significant.

## **Results**

### *Analysis of baseline demographic and clinical data*

There were no significant differences in the main demographic parameters, such as sex, gestational age, and birth weight, between the 40 subjects with neonatal asphyxia and 19 non-asphyxia control subjects (Table 1). The Apgar scores at 1 and 5 minutes were not significantly different between the myocardial injury group and the non-myocardial injury group, whereas the Apgar scores at both time points were significantly lower in both of these groups than in the non-asphyxia control group (both  $P < 0.001$ ). The severity of asphyxia was predominantly mild in the non-myocardial injury group, but severe in the myocardial injury group ( $P = 0.040$ , Table 1). There was no significant difference in the proportion of neonates with a nuchal cord among the three groups. However, the proportion of newborns with meconium-stained amniotic fluid was highest in the non-myocardial injury group and lowest in the non-asphyxia control group ( $P = 0.046$ , Table 1).

### *Analysis of biomarker levels*

The highest levels of all biomarkers were found in the myocardial injury group and the lowest were observed in the non-asphyxia control group, with the exception of myoglobin and hs-cTnI at 7 days (Table 1). At 12 hours after delivery,

**Table 1.** Baseline perinatal data.

	Myocardial injury group (n = 18)	Non-myocardial injury group (n = 22)	Non-asphyxia control group (n = 19)	P value
Sex (male/female)	12/6	11/11	11/8	0.569
Gestational age (weeks)	36 (30, 42)	36.5 (29, 40)	37 (32, 42)	0.865
Delivery				0.553
Full-term	6 (33.3%)	11 (50%)	9 (47.4%)	
Preterm	10 (55.6%)	11 (50%)	9 (47.4%)	
Post-term	2 (11.1%)	0 (0%)	1 (5.2%)	
Birth weight (g)	2565 (1300, 4030)	1930 (1340, 4100)	2240 (1200, 3880)	0.348
Apgar score at 1 minute	3 <sup>a</sup> (2, 7)	5 <sup>a</sup> (0, 8)	8 <sup>b</sup> (8, 9)	<0.001
Apgar score at 5 minutes	7 <sup>a</sup> (5, 9)	8 <sup>a</sup> (0, 10)	9 <sup>b</sup> (8, 10)	<0.001
Severity of asphyxia <sup>†</sup>				0.040
Mild	8 (44.4%)	18 (77.8%)	0	
Severe	10 (55.6%)	4 (22.2%)	0	
Nuchal cord	2 (11.1%)	2 (9.1%)	3 (15.8%)	0.797
MSAF	7 (38.9%)	13 (59.1%)	4 (21.1%)	0.046
Natural delivery/ cesarean section	5/13	9/13	5/14	0.542
CK-MB (IU/L), 12 hours	288 <sup>a</sup> (39, 3336)	192 <sup>a,b</sup> (49, 1126)	111 <sup>b</sup> (46, 1440)	0.001
CK-MB (IU/L), 7 days	33 (10, 980)	26 (14, 227)	25 (13, 60)	0.547
hs-cTnI (μg/L), 12 hours	0.1325 <sup>a</sup> (0, 0.567)	0.0425 <sup>b</sup> (0, 0.221)	0.016 <sup>c</sup> (0, 0.094)	<0.001
hs-cTnI (μg/L), 7 days <sup>†</sup>	0.018 (0, 0.201)	0.023 (0.004, 0.267)	–	0.563
BNP (ng/L), 12 hours	543.0 <sup>a</sup> (72.9, 5000.0)	420.8 <sup>a,b</sup> (20.5, 11044.5)	128.2 <sup>b</sup> (8.0, 2479.6)	0.003
BNP (ng/L), 7 days <sup>†</sup>	79.4 (10.4, 432.4)	67.9 (14.0, 679.0)	–	0.510
Myoglobin (U/L), 12 hours	296.3 <sup>a</sup> (34.6, 3059.0)	114.2 <sup>a,b</sup> (26.0, 547.8)	104.2 <sup>b</sup> (25.0, 601.0)	0.049
Myoglobin (U/L), 7 days <sup>†</sup>	21.5 (11.3, 351.0)	26.5 (13.0, 74.0)	–	0.366

BNP: brain natriuretic peptide; CK-MB: creatine kinase-MB; hs-cTnI: high-sensitivity cardiac troponin I; MSAF: meconium staining of the amniotic fluid. Frequencies were compared among the three groups using the chi-square test or Fisher's exact test. Discrete and continuous variables were compared among groups using the Kruskal–Wallis test. Values with different superscript letters in the same row were significantly different pairwise ( $P < 0.05/3$ ). Bonferroni correction was applied for post-hoc analyses. <sup>†</sup>Values were compared between the myocardial injury and non-myocardial injury groups.

CK-MB ( $P = 0.001$ ), hs-cTnI ( $P < 0.001$ ), BNP ( $P = 0.003$ ), and myoglobin ( $P = 0.016$ ) levels were significantly higher in the myocardial injury group than in the non-asphyxia control group. However, only hs-cTnI levels ( $P = 0.016$ ) were significantly higher in the myocardial injury group than in the non-myocardial injury group. At 7 days after birth, the serum levels of all four biomarkers had decreased, and there were no significant differences among the three groups (Table 1).

### ROC analysis

ROC curve analyses were performed to examine the utility of each biomarker for diagnosing myocardial injury in neonates with asphyxia (i.e., differentiating between the myocardial injury group and non-myocardial injury group) (Table 2). Calculation of AUC values indicated that only hs-cTnI levels at 12 hours had significant discriminatory ability ( $P = 0.013$ ), although CK-MB levels at 12 hours were borderline significant ( $P = 0.055$ ).

**Table 2.** Receiver operating characteristic curve analysis of the utility of each biomarker for differentiating the myocardial injury group from the non-myocardial injury group.

	AUC	P	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
CK-MB (12 hours)	0.672	0.055	>274	61.1	77.3	68.7	70.8	70.0
CK-MB (7 days)	0.587	0.386	>40	44.4	90.9	80.0	66.7	70.0
hs-cTnI (12 h)	0.721	0.013	>0.087	55.6	95.5	90.9	72.4	77.5
hs-cTnI (7 days)	0.554	0.567	≤0.017	50.0	68.2	56.2	62.5	60.0
BNP (12 hours)	0.578	0.398	>455.5	72.2	54.6	56.5	70.6	62.5
BNP (7 days)	0.562	0.508	>37	88.9	36.4	53.3	80.0	60.0
Myoglobin (12 hours)	0.653	0.103	>289	50.0	86.4	75.0	67.9	70.0
Myoglobin (7 days)	0.586	0.405	≤20	50.0	86.4	75.0	67.9	70.0

AUC: area under the receiver operating characteristic curve; BNP: brain natriuretic peptide; CK-MB: creatine kinase-MB; hs-cTnI: high-sensitivity cardiac troponin I; NPV: negative predictive value; PPV: positive predictive value.

The greatest AUC value among the biomarkers was observed for hs-cTnI at 12 hours. Using an optimal cutoff value of >0.087 µg/L, hs-cTnI levels at 12 hours differentiated between the myocardial injury and non-myocardial injury groups, with a sensitivity of 55.6%, specificity of 95.5%, PPV of 90.9%, NPV of 72.4%, and accuracy of 77.5% (Table 2). Hs-cTnI levels at 12 hours would have correctly predicted myocardial injury in 10 of the 18 cases in the myocardial injury group and correctly excluded myocardial injury in 22 of the 22 cases in the non-myocardial injury group.

The ROC analysis was expanded to examine the utility of each biomarker for differentiating neonates in the myocardial injury group from those in the non-myocardial injury and non-asphyxia control groups. The AUC value was highest for hs-cTnI levels at 12 hours (0.78,  $P < 0.001$ ). Using an optimal cutoff value of 0.094 µg/L, hs-cTnI levels at 12 hours differentiated the myocardial injury group from the non-myocardial injury and non-asphyxia control groups, with a sensitivity of 55.6%, specificity of 97.6%, PPV of 90.9%, NPV of 83.3%, and accuracy of 84.7%. Although the specificity, PPV, and accuracy were higher for hs-cTnI levels at

12 hours than for the other biomarkers, sensitivity was higher for CK-MB levels at 12 hours (72.2%) and BNP levels at 12 hours (72.2%).

## Discussion

An important finding of the present study was that serum CK-MB, hs-cTnI, BNP, and myoglobin levels at 12 hours were significantly higher in neonates with asphyxia-induced myocardial injury than in a control group of neonates without asphyxia. However, only hs-cTnI levels were significantly higher in the myocardial injury group than in the non-myocardial injury group.

CK-MB is widely used as a biomarker for myocardial injury because its primary source is the myocardium.<sup>11</sup> The main disadvantage of CK-MB is the extended duration of time that is required for concentration of the protein in serum to increase. In contrast to CK-MB, serum myoglobin and troponin I levels are rapidly elevated following myocardial injury, usually within 2 to 3 hours. Troponin I is specific for the myocardium, whereas myoglobin lacks specificity. BNP is an endogenous hormone that is synthesized by cardiac cells and mainly expressed in the

ventricles.<sup>12,13</sup> Despite the good sensitivity of BNP, it has certain limitations and thus cannot be used as an independent prognostic indicator of myocardial injury.<sup>14,15</sup> The hypoxic nature of asphyxiated neonates affects ventricular BNP gene expression and consequently increases plasma BNP and N-terminal-proBNP levels during the acute phase of myocardial injury.<sup>19</sup>

Several studies have indicated that cardiac troponin T may be a useful indicator of myocardial injury.<sup>5,9</sup> A study of 25 asphyxiated neonates showed that higher cardiac troponin T levels, rather than fractional shortening and Doppler tissue imaging measurements, were a significant predictor of mortality.<sup>20</sup> However, confounding factors, such as preterm delivery or administration of adrenalin, can affect cardiac troponin T levels,<sup>10</sup> potentially limiting its value in the setting of neonatal asphyxia and myocardial damage. A previous investigation of 55 full-term newborns with perinatal asphyxia showed that cardiac troponin I levels increased during the first 12 hours after birth and predicted the risk of death, whereas CK-MB and BNP did not have predictive value for mortality.<sup>21</sup> A retrospective study of 60 neonates with hypoxic-ischemic encephalopathy showed that cardiac troponin I levels were correlated with the severity of hypoxic-ischemic encephalopathy and the duration of inotropic support required.<sup>22</sup> This finding suggested that serum cardiac troponin I levels could be a useful marker for the severity of myocardial dysfunction. Another report showed that cardiac troponin I levels were higher in severely asphyxiated newborns than in newborns who experienced mild asphyxia or neonates with no history of asphyxia.<sup>23</sup> A relatively large study by Zhou et al.<sup>24</sup> showed that troponin I levels at 24 hours had a significant value for mortality in neonates with asphyxia. The present study not only corroborates the above-mentioned findings, but also

advances them by using hs-cTnI, a biomarker with improved detection sensitivity. We also calculated an optimal cutoff value for use in the diagnosis of myocardial injury after neonatal asphyxia. The increased sensitivity and precision of the new high-sensitivity assays over conventional assays provides the potential for earlier diagnosis of myocardial injury.<sup>8</sup>

The indicators examined in the current study showed low sensitivity, except for BNP, which had a sensitivity of 72.2% at 12 hours and 88.9% at 7 days. However, the specificity, PPV, and accuracy of BNP were low. Despite the low sensitivity of hs-cTnI, it showed a considerably higher specificity than BNP. Kanik et al.<sup>25</sup> reported that troponin I had a low sensitivity (33%) and high specificity (80%) in predicting mortality in 34 term newborns with hypoxic-ischemic encephalopathy. Simovic et al.<sup>21</sup> found slightly higher values for sensitivity (84.6%) and specificity (85.9%) of cardiac troponin I in prediction of mortality after perinatal asphyxia. Because troponin I is considered the most specific cardiac biomarker, several studies have concluded that it is superior to CK-MB or BNP for predicting mortality or other outcomes in neonates.<sup>26</sup>

In agreement with previously published reports, our data strongly suggested that among the four biomarkers that were assessed, hs-cTnI had the highest diagnostic value for detecting myocardial injury.<sup>25,26</sup> Notably, the diagnostic performance of hs-cTnI increased when the non-asphyxia control group was included in the analysis. Importantly, all neonates in the healthy non-asphyxia control group were diagnosed as negative for myocardial injury on the basis of hs-cTnI levels. This finding indicated that false positive results in newborns without asphyxia would be unlikely.

Myoglobin is considered a non-specific marker of myocardial injury because of diverse localization of this protein in

various muscle tissues. Myoglobin levels rapidly rise following myocardial injury. In the present study, serum myoglobin levels were mostly similar among the three groups. This finding suggests that myoglobin may not be useful as a potential marker for myocardial injury in asphyxiated neonates, despite its apparently high specificity (86.4%) in ROC curve analysis. A limited number of studies have examined the diagnostic utility of myoglobin in the setting of birth asphyxia, and myoglobin levels are mainly associated with renal failure and renal tubular damage.<sup>27</sup> To the best of our knowledge, this is one of the few studies to compare the use of myoglobin with that of specific cardiac markers (CK-MB, hs-cTnI, and BNP) for detecting myocardial injury in asphyxiated neonates.

The major limitation of this study is the small sample size. A larger study is required to fully verify our results, confirm appropriate cutoff values, and establish which test or combination of tests has the best clinical utility in diagnosing myocardial injury caused by neonatal asphyxia. Additionally, no comparisons were made with other diagnostic information, such as that obtained from Doppler echocardiography. Such data should be included in future studies to determine whether serum levels of the four biomarkers might predict the degree of myocardial injury. Further research is also required to discover whether hs-cTnI could be used as a prognostic marker.

In summary, serum hs-cTnI levels significantly increase during the acute phase of neonatal asphyxia. ROC curve analysis shows that the diagnostic value of hs-cTnI is higher than that of CK-MB, myoglobin, or BNP. Consequently, serum hs-cTnI levels may be a useful biomarker for early prediction of myocardial injury caused by neonatal asphyxia. Confirmation of the results is necessary using a larger sample size.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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