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Correlating Thompson score and cardiac dysfunction in neonates suffering from perinatal asphyxia – A prospective observational study

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ABSTRACT

Background: Perinatal asphyxia continues to be a leading cause of neonatal morbidity and mortality worldwide. It causes multiorgan failure with brain involvement as the major organ of concern (hypoxic-ischemic encephalopathy). Cardiac dysfunction is also a feature of perinatal asphyxia. **Aims and Objectives:** The study and to correlate cardiac dysfunction detected by cardiac biomarkers and echocardiography with the severity of perinatal asphyxia as graded by the Thompson score. **Materials and Methods:** In this prospective observational study, babies with Apgar score <7 at 1 min received in the sick newborn care unit of a tertiary care hospital in West Bengal, India, were enrolled over 6 months. Thompson's score was assessed on the 1st day with the estimation of creatine phosphokinase MB (CPK-MB) and troponin (Trn) T within 24 h of birth. Thompson score assessment was continued twice daily till discharge or death. Transthoracic echocardiography was done at the earliest within the 1st week. **Results:** Of the 81 neonates enrolled, 28 neonates had cardiac dysfunction detected by positive Trn T and raised CPK-MB. Echocardiography showed 15 neonates (18.5%) had systolic dysfunction whereas 13 (16.0%) had tricuspid regurgitation. There was a strong association between Thompson score and Trn T and CPK-MB (rpb = 0.85, rho = 0.97, respectively, P ≤ 0.001). Thompson score was highly sensitive and specific in detecting the need for mechanical ventilation, and fluid restriction in inotrope-resistant cardiac dysfunction (sensitivity 90%, 78.4%, respectively; and specificity 95.8%, 97.7%, respectively), in predicting initiation of feeding and final outcome (sensitivity 82.9% and 100%, respectively, specificity 97.8%, 89%, respectively). **Conclusion:** Clinical assessment by the Thompson score can predict the degree of cardiac dysfunction, mechanical ventilation requirement, feed initiation, and final outcome in perinatal asphyxia.

Key words: Perinatal asphyxia; Newborn; Cardiac dysfunction; Thompson score

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INTRODUCTION

The issue of neonatal mortality continues to be one of the major healthcare concerns globally. As of the 2022 data recorded by the World Health Organisation (WHO), 2.3 million children died in the first 20 days of life.[1] It was seen that children dying within the first 28 days of birth suffered from conditions and diseases associated with lack of quality care at birth or skilled care and treatment immediately after birth and in the 1st days of life. The lack of quality care or skilled care in most low- and middle-income countries makes perinatal asphyxia one of the most common causes of neonatal mortality in today's time.[1]

Perinatal asphyxia is defined as failure to initiate and sustain breathing at birth by the WHO.[2] It acts first on the central nervous system, but also on the heart, by hypoxia and subsequent ischemia-reperfusion injury.

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Myocardial development at birth is still incomplete and cannot adequately respond to this hypoxic insult. Cardiac dysfunction, including low ventricular output, bradycardia, and pulmonary hypertension, complicates the already compromised circulatory status of the newborn with perinatal asphyxia. Multiorgan and especially cardiovascular failure seem to play a crucial role in the secondary phase of hypoxic-ischemic encephalopathy (HIE) and its high mortality rate.[3]

The data available on the incidence and severity of myocardial dysfunction in neonates with perinatal asphyxia are limited.[4] Most of the studies assessing the effects of perinatal asphyxia focus primarily on the neurological involvement, and only a few studies assess the role of cardiac involvement.[5] Electrocardiography and serum levels of cardiac enzymes can be used to demonstrate myocardial dysfunction.[6] Cardiac biomarkers play a crucial role in myocardial injury and heart failure in adult patients, but their clinical relevance in neonatology has not been established.[7] Troponin (Trn) I and T, creatine phosphokinase- MB (CPK-MB), and myoglobin are markers of cardiac injury.[8] CPK-MB has been found to be both specific and sensitive for diagnosing acute myocardial infarction in adults until recently being replaced by highly selective Troponins.[9,10] CPK-MB has been found to correlate well with the degree of myocardial involvement in perinatal asphyxia in the neonatal period and is also associated with poor outcomes.[11] The Trn complex, part of the sarcomere, regulates cardiac and skeletal muscle contraction. Trn I exists only in three isoforms (one specific to the myocardium) and Trn T has four isoforms/specific to the cardiac muscle.[12] After a cardiac injury, Trn s become detectable in the blood around the 2nd to the 4th h, with a peak at 12 h, and remain high for 7–10 days.[13] Troponin levels in both term and preterm infants show higher values than the adult reference ranges, probably due to the presence of cardiorespiratory compromise associated with adaptation to post-natal circulation, particularly in preterm.[14] A meta-analysis of 67 studies studying the role of cardiac biomarkers in neonatology has concluded that Trn I/T can be clinically relevant in perinatal asphyxia as a marker of myocardial injury and a reliable indicator of severity and mortality.[7]

Bedside assessment and regular monitoring of neonates with perinatal asphyxia for identification of HIE is of utmost importance. The Thompson score is one such tool which comprises various clinical parameters such as consciousness, posture, tone, presence of seizures, neonatal reflexes, and respiration to detect HIE.[15] Unlike Sarnat and Sarnat staging,[16] it can determine the level of HIE through a numerical score. Thompson score has been seen to have high sensitivity and specificity for predicting adverse outcomes (death or severe disability).[15,17] Therefore, this study aims to document the incidence of cardiac dysfunction in neonates with perinatal asphyxia through cardiac biomarkers such as CPK-MB and Trn T. It also attempts to study the utility of Thompson score in predicting myocardial dysfunction, mechanical ventilation requirement, feeds initiation, final outcome in perinatal asphyxia.

Aims and objectives

To study the utility of clinical scoring in perinatal asphyxia. To correlate cardiac dysfunction caused by perinatal asphyxia detected by cardiac biomarkers and echocardiography, with the severity of perinatal asphyxia graded by Thompson score.

MATERIALS AND METHODS

This prospective observational study was conducted in the Sick Newborn Care Unit (SNCU) of a tertiary care hospital over 6 months. After ethical clearance granted by the Institutional Ethical Committee on December 16, 2023, registration number ECR/71/Inst/WB/2015/RR18 of Calcutta National Medical College and Hospital, Kolkata, West Bengal, India, and informed consent from the parents, the neonates with perinatal asphyxia with Apgar score <7 at 1 min were enrolled over a period of 6 months. The National Neonatal Perinatal Database definition II of South East Asian Region, WHO defines perinatal asphyxia as an Apgar score of <7 at 1 min of age, moderate perinatal asphyxia as Apgar score between 4 and 6 at 1-min of age, and severe perinatal asphyxia as Apgar score of 3 or < 1-min of age.[18] Cases of perinatal asphyxia which were admitted on or beyond day 2 of life, neonates suspected to have congenital heart diseases, major central nervous system malformations, and neonatal sepsis were excluded from the study. Apgar score was recorded for inborn neonates by junior residents present in the delivery room with an Apgar timer of servo-controlled radiant heat warmer. Another junior resident was assigned to note down the Apgar scores in the delivery room. Thompson score of the studied neonates to detect HIE was used for monitoring these neonates twice daily till they were discharged or to death by a 3rd-year postgraduate trainee posted in the SNCU. HIE following perinatal asphyxia can be categorized as mild, moderate, and severe when Thompson's score ranges from 0 to 10, 11 to 14, and ≥15, respectively.[15] All the neonates were managed in the SNCU as per hospital protocol. They were given oxygen by hood (5–6 L/min), nasal continuous positive airway pressure, mechanical ventilation (based on saturation of oxygen), intravenous fluids, Vitamin K, inotropes (dopamine and/or dobutamine each by 1–20 μg/kg/min), and anticonvulsants (phenobarbitone

20 mg/kg as loading dose, followed by 3–5 mg/kg/day, and levetiracetam was also added with same loading dose with 20–60 mg/kg/day in non-responder to phenobarbitone), wherever required. Intravenous nitroglycerine infusion in the dose of 4–5 μg/kg/min and fluid restriction was advised for neonates with cardiac dysfunction who were not responding to inotrope.[19] Feeding was started once the patient showed improvement, initially started as nasogastric feeding and then followed by spoon or breastfeeding. The final outcome of discharge and death was also noted.

The blood for CPK-MB and Trn T was tested within 24 h of birth by collecting 2–3 mL of venous blood. CPK-MB was quantitatively measured using the immuneinhibition International Federation of Clinical Chemistry methodology using the Konelab™ Clinical Chemistry Analyzer. Trn T was detected using the Cobas H 232 bedside kit produced by Roche which employs the principle of qualitative immunological test for the detection of Trn T in heparinized venous blood.

Transthoracic echocardiography was performed using the Esaote MyLab™X7 ultrasound system with the pediatric P2 5-13 probe. Every neonate had a first echocardiogram within 72 h or at least before being discharged by the same experienced Pediatric Cardiologist. Standard echocardiographic views such as subcostal (coronal and sagittal), apical, parasternal long- and short-axis and high parasternal and suprasternal views were used as per the American Heart Association guidelines. Two-dimensional, M-mode, pulsed-Doppler, continuous-wave Doppler, color Doppler, and tissue Doppler imaging were used in all and relevant images/data were recorded. Features suggestive of myocardial dysfunction such as systolic dysfunction (primarily left ventricular dysfunction expressed by both reduced fractional shortening and peak aortic velocity), and tricuspid regurgitation were noted.

Statistical analysis

A minimum sample size of 50 was needed to get a correlation coefficient of 0.50 between Thompson's score and cardiac biomarkers with a power of 80%. Therefore, a total of 81 neonates were enrolled over a period of 6 months. Data were collected in a pre-designed data sheet and entered in Microsoft Excel Worksheet 2019 and analyzed using International Business Machines Corporation Statistical Product and Service Solutions (SPSS) Software version 29 of September 2022 (SPSS Inc., Chicago, Illinois). Demographic parameters of neonates of various grades of HIE were compared by the Chi-square test, Kruskal–Wallis test, and Fischer's exact test. The correlation between cardiac enzymes and the severity of birth asphyxia was determined using the point biserial correlation coefficient and Spearman's rank correlation coefficient. Comparison of biochemical parameters and findings of 2D Echocardiography were made by analysis of variance. A $P<0.05$ was considered as statistically significant.

RESULTS

A total of 81 neonates were enrolled over a period of 6 months. The mean gestational age of the enrolled neonates was 36.38±3.31 weeks, ranging from 30 to 42 weeks. The majority of the neonates were male (n=50, 61.7%). The mean birth weight (Kg) was 2.33±0.63 kg. Normal vaginal delivery was seen to be the most common mode of delivery (56.8%) with 7.4% of deliveries being assisted vaginal deliveries, and the remaining by lower uterine cesarean section (35.8%). Table 1 enumerates the basic characteristics of the study participants.

As per the Thompson score 67.9% (n=55), 17.3% (n=14), and 14.8% (n=12) of the neonates were categorized into mild, moderate, and severe HIE respectively. The various parameters studied and the outcome of the neonates as per Thompson score categorization of HIE are given in Table 2.

Cardiac dysfunction as detected by positive Trn T and raised CPK-MB was seen in 28 neonates. A total of 33 neonates had Trn T positive but only 28 of them had CPK-MB detectable above 150 U/L. The mean CPK-MB was 204.68±262.34 U/L. CPK-MB was found to be in the range of 0-150 U/L in 53 (65.4%) of the participants. This was further confirmed by 2D Echocardiography which showed

Table 1: Basic characteristics of studied neonates

All parameters	Mean±SD||Median (IQR)
Gestational age (Weeks)	36.38±3.31||37.00 (33.00–39.00)
Gestational age	**n (%)**
<37 Weeks	31 (38.3)
≥37 Weeks	50 (61.7)
Gender	**n (%)**
Male	50 (61.7)
Female	31 (38.3)
Birth weight (kg)	2.33±0.63||2.60 (1.80–2.80)
Birth weight	n (%)
<2.5 kg	36 (44.4)
≥2.5 kg	45 (55.6)
Mode of delivery	**n (%)**
NVD	46 (56.8)
AVD	6 (7.4)
LUCS	29 (35.8)
APGAR (1 min)	3.38±1.56||4.00 (2.00–5.00)
APGAR (5 min)	5.77±2.35||7.00 (3.00–8.00)

NVD: Normal vaginal delivery, AVD: Assisted vaginal delivery, LUCS: Lower uterine caesarean section

Table 2: Cardiac biomarkers, clinical parameters, and outcome as per Thompson score grading of HIE

Parameters	HIE category as per Thompson score			
	Mild (n=55) (%)	Moderate (n=14) (%)	Severe (n=12) (%)	P-value
APGAR (1 min)***	4.18±1.16	2.00±0.78	1.33±0.49	<0.001[1]
APGAR (5 min)***	7.07±1.29	3.57±1.74	2.33±0.98	<0.001[1]
Troponin T (Positive)***	7 (12.7)	14 (100.0)	12 (100.0)	<0.001[2]
CPK-MB (U/L)***	70.42±38.33	248.21±116.14	769.25±192.62	<0.001[1]
CPK-MB Category***				<0.001[3]
0–150 U/L	53 (96.4)	0 (0.0)	0 (0.0)	
150–300 U/L	2 (3.6)	12 (85.7)	0 (0.0)	
≥300 U/L	0 (0.0)	2 (14.3)	12 (100.0)	
2D-ECHO***				<0.001[3]
No abnormality detected	51 (92.7)	2 (14.3)	0 (0.0)	
Systolic dysfunction	1 (1.8)	3 (21.4)	11 (91.7)	
Tricuspid regurgitation	3 (5.5)	9 (64.3)	1 (8.3)	
Feeding within 48 h (yes)***	46 (83.6)	0 (0.0)	0 (0.0)	<0.001[2]
Fluid restriction (yes)***	11 (20.0)	14 (100.0)	12 (100.0)	<0.001[2]
Inotrope (yes)***	0 (0.0)	13 (92.9)	12 (100.0)	<0.001[3]
Anticonvulsant (yes)***	9 (16.4)	13 (92.9)	8 (66.7)	<0.001[2]
Nitroglycerine (yes)***	1 (1.8)	3 (21.4)	9 (75.0)	<0.001[3]
Mechanical ventilation (yes)***	0 (0.0)	1 (7.1)	9 (75.0)	<0.001[3]
Outcome***				<0.001[3]
Discharged	52 (94.5)	3 (21.4)	1 (8.3)	
Discharged with anticonvulsant	3 (5.5)	11 (78.6)	7 (58.3)	
Death	0 (0.0)	0 (0.0)	4 (33.3)	

***Significant at P<0.05, 1: Kruskal Wallis test, 2: Chi-squared test, 3: Fisher's exact test, HIE: Hypoxic-ischemic encephalopathy, CPK-MB: Creatine phosphokinase MB

Table 3: Comparison of changes in cardiac enzymes and 2D echo findings as per Thompson score grading of HIE

Cardiac markers	HIE category based on Thompson score					Adjusted P value		
	Mild (%)	Moderate (%)	Severe (%)	χ^2	P-value	Mild versus moderate	Mild versus severe	Moderate versus severe
Troponin T				55.696	<0.001	<0.001	<0.001	1.00
Positive	7 (12.7)	14 (100.0)	12 (100.0)	55.696	<0.001	<0.001	<0.001	1.00
Negative	48 (87.3)	0 (0.0)	0 (0.0)					
CPK-MB								
(Mean [SD])	70.42 (38.33)	248.21 (116.14)	769.25 (192.62)	54.206	<0.001	<0.001	<0.001	0.429
0–150 U/L	53 (96.4)	0 (0.0)	0 (0.0)	128.067	<0.001	<0.001	<0.001	<0.001
150–300 U/L	2 (3.6)	12 (85.7)	0 (0.0)					
≥300 U/L	0 (0.0)	2 (14.3)	12 (100.0)					
2D ECHO								
No abnormality	51 (92.7)	2 (14.3)	0 (0.0)	87.319	<0.001	<0.001	<0.001	0.001
Systolic dysfunction	1 (1.8)	3 (21.4)	11 (91.7)					
Tricuspid regurgitation	3 (5.5)	9 (64.3)	1 (8.3)					

HIE: Hypoxic-ischemic encephalopathy, CPK-MB: Creatine phosphokinase MB

53 (65.4%) of the participants had no abnormality, whereas 15 (18.5%) had systolic dysfunction and 13 (16.0%) had tricuspid regurgitation. The categorization of HIE as per Thompson score correlated well with the cardiac enzymes and 2D echocardiography findings. Table 3 shows the corrected P-value and comparison of changes in cardiac enzymes and 2D echocardiography findings in the various grades of HIE.

The association between Thompson score and CPK-MB and Trn T was studied, and a strong correlation was seen between them. The strength of association between Thompson score and Trn T was 0.85 Point-Biserial Correlation, using the Wilcoxon–Mann–Whitney U Test to compare the two variables (W=1571.000, P≤0.001). Figure 1 depicts the scatter plot showing the association between the Thompson score and CPK-MB. Non-parametric tests (Spearman Correlation) were used for comparison and a very strong positive correlation between CPK-MB and Thompson score was seen which was statistically significant (rho=0.97, P≤0.001).

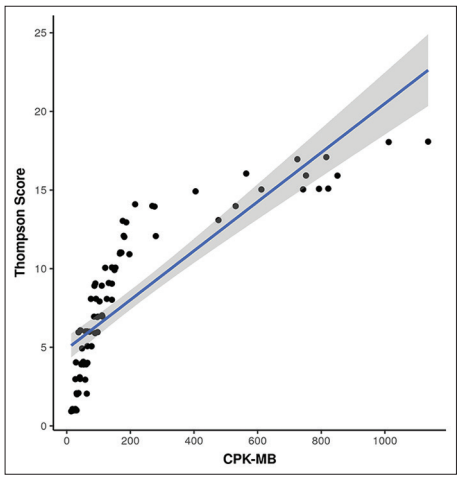

Figure 1: Association between Thompson score and creatine phosphokinase MB

The utility of the Thompson score in predicting the clinical course and outcome of neonates with cardiac dysfunction in perinatal asphyxia was also studied. To test the sensitivity and specificity of Thompson's score in predicting the course of neonates with cardiac dysfunction, reviewer operator curves (ROC) were used for analysis. It was seen that the Thompson score was highly sensitive and specific in detecting need for mechanical ventilation and fluid restriction in inotrope-resistant cardiac dysfunction (sensitivity 90% and 78.4%, respectively, specificity 95.8% and 97.7%, respectively). It was also sensitive and specific in predicting initiation of feeding and outcome (sensitivity 82.9% and 100%, respectively, and specificity 97.8% and 89.6%, respectively). The ROC of the aforementioned clinical parameters are depicted in Figure 2.

The association between the Thompson score and the three outcome groups- "discharged," "discharged with anti-convulsant" and "death" was also studied. Using the Kruskal–Wallis non-parametric test a significant difference between the three groups in terms of Thompson Score (χ^2=43.108, P≤0.001) was found, with the median Thompson Score being highest in the Death group. The strength of Association using Kendall's Tau was 0.62, indicating a large effect size. The density plot shown in Figure 3 depicts the distribution of the Thompson Score in the three different groups of Outcome.

DISCUSSION

Myocardial injury as a component of the spectrum of multi-organ dysfunction in perinatal asphyxia has been identified as early as in the nineteen seventies.[20] Despite the preferential perfusion seen in perinatal asphyxia, myocardial ischemia does occur leading to myocardial dysfunction.[11] Progression of ischemia beyond 20 min leads to damage to the myocardial cell membrane and releases CPK-MB and Trn T into the bloodstream. CPK-MB levels although significantly elevated in asphyxiated infants they do not appear to discriminate well those infants with cardiovascular compromise.[21-23] Cardiac dysfunction, as detected by both raised Trn T and CPK-MB and confirmed by echocardiography was seen in 28 out of 81 neonates (34.57%). In the current study, CPK-MB was raised in all the neonates with a mean value of 204.68±262.34 U/L. Rajakumar et al., had reported a mean value of 121±77.4 IU/L, and Agrawal et al., had reported it to be 147.5 IU/l in their study.[24,25] In this study, CPK-MB was raised higher in the neonates suffering from severe perinatal asphyxia and HIE. The mean value of CPK-MB ranged from 70.42±38.33 U/L to 769.25±192.62 U/L between mild to severe HIE cases. In the study by Barberi et al., the range was from 127±94.2 IU/L to 334±239 IU/L between mild to severe asphyxia neonates, and Singh et al. also reported a mean value range of 54.58±30.48 U/L to 350.75±238.12 U/L in mild to severe perinatal asphyxia neonates.[11,26] On associating CPK-MB level to the Thompson score the strength of association was high with a Spearman correlation coefficient of 0.97.

Trn concentration in the myocardium is much higher compared to CPK-MB, although negligible in the plasma in healthy humans. The Trn levels raise within a few hours after the acute ischemic episode and remain high for 10–14 days, thus increasing the diagnostic time range.[27] In the current study Trn T level was raised in 33 neonates (47.74%) neonates, indicating a lower threshold for detecting even mild cardiac dysfunction not detected by echocardiography. Yellanthoor and Rajamanickam found elevated Trn T levels in 71.9% of asphyxiated neonates.[23] Rajakumar et al., demonstrated a linear relationship between raising levels of Trn T and cardiac dysfunction and mortality.[24] In a meta-analysis on cardiac biomarkers in neonatology, Trn T was seen to correlate well with echocardiographic findings of myocardial dysfunction.[7,28-30] Due to the qualitative nature of the bedside diagnostic kit, the current study could not ascertain the level of Trn T in all the neonates with cardiac dysfunction. However, its strength of association with the severity of HIE as per Thompson's score was high (0.85 points biserial correlation coefficient).

Echocardiography is helpful in the early identification of tricuspid regurgitation, compromised left ventricular output, and stroke volume in neonates suffering from perinatal asphyxia. In the current study, 13 neonates (16%) had tricuspid regurgitation and 15 neonates (18.5%) had systolic dysfunction which correlated directly with increasing severity of asphyxia. In contrast to this, Yellanthoor and Rajamanickam found tricuspid regurgitation at a significantly higher rate (14.03% had

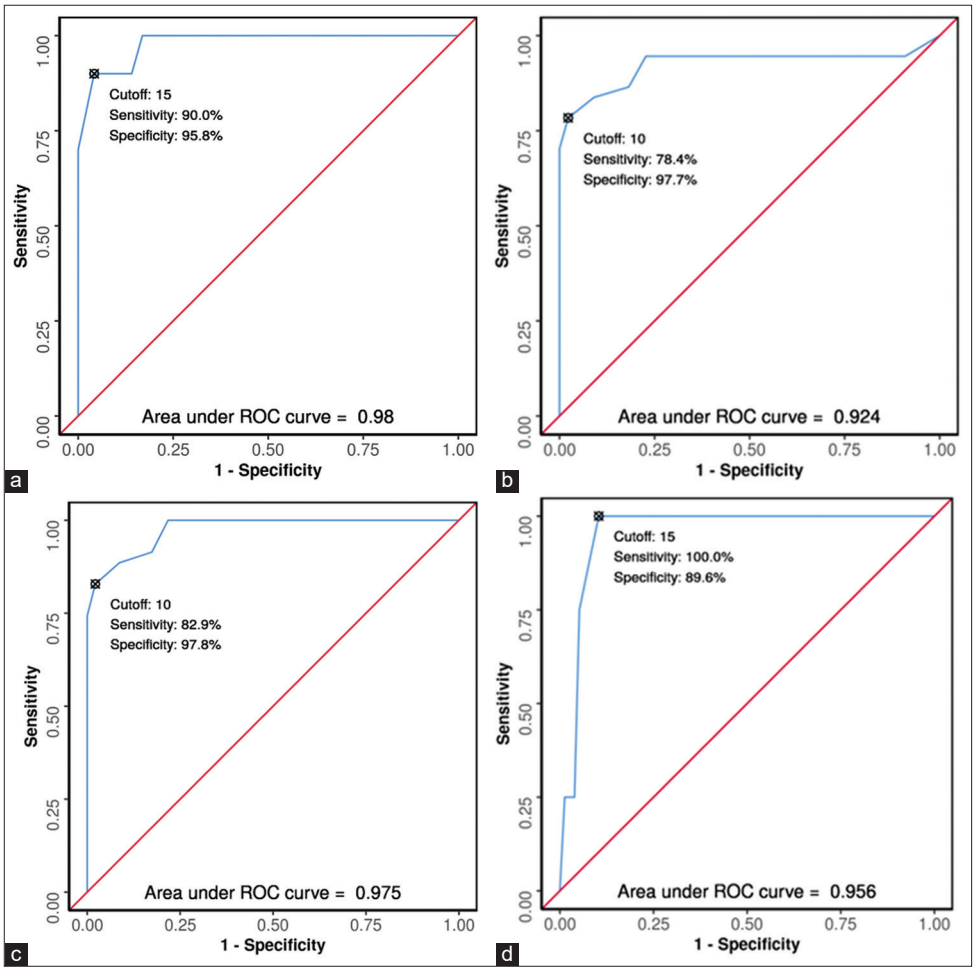

Figure 2: Reviewer operator curve analysis showing diagnostic performance of Thompson score in predicting. (a) Mechanical ventilation, (b) Fluid restriction in inotrope-resistant cardiac dysfunction, (c) Initiation of feeding within 48 h, (d) Final outcome

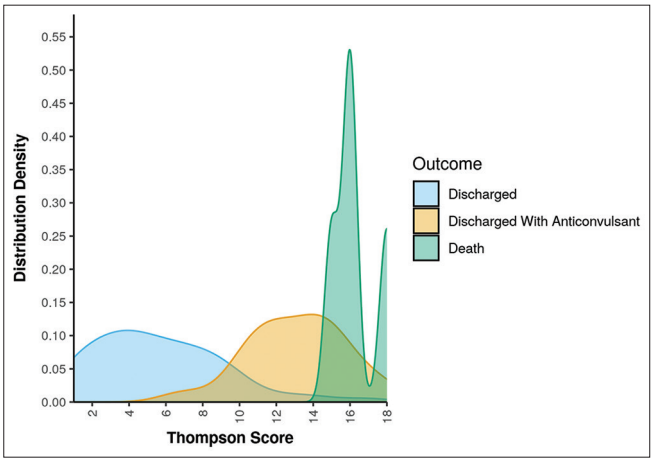

Figure 3: Association between outcome and Thompson score

tricuspid regurgitation alone whereas 28.07% had tricuspid regurgitation with pulmonary artery hypertension) in asphyxiated neonates and more frequently with increasing severity of asphyxia.[23] Rajakumar et al., found the incidence of tricuspid regurgitation to be 23.3% and ventricular dysfunction as 30% in their study.[24]

Thompson score and its correlation with morbidity and mortality have been seen in various studies. In the study by Bhagwani et al., the Thompson score showed a statistically significant correlation between morbidity and day 1 Thompson score (P=0.024) and mortality and day 1 Thompson score (P=0.001).[31] However, its role in identifying or predicting multi-organ dysfunction is not well defined. In the study by Thorsen et al., 59.2% of the patients had multiple organ failure but the Thompson score was not associated with it.[17] In our study, Thompson's score correlated well with the cardiac biomarkers, echocardiography findings, clinical parameters monitored, and outcome. The review operator curves in Figure 2 depict the same.

Limitations of the study

The limitation of the study was not documenting all the multi-organ involvement in the studied neonates, and thus not taking into account the confounding effect of multi-system involvement in mortality of the neonates. Cord blood pH could have been a better option than Apgar Score for initial enrollment. Follow up of discharged neonates was required.

CONCLUSION

The above finding of the correlation of the Thompson score with cardiac dysfunction in birth asphyxia can be further tested with the varied components of multi-organ failure in birth asphyxia. The sensitivity and specificity of the Thompson score correlate well with the changes in cardiac biomarkers, echocardiography, and outcome, thus possibly aiding in faster identification of comorbidities of perinatal asphyxia and HIE.

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AN- Conceptualized the study and undertook data collection; **BG**-Conceptualized and designed the study, coordinated and supervised the analysis, and substantially reviewed and revised the manuscript for important intellectual content; **MS**- Wrote, revised the manuscript, and coordinated the analysis.

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