

## Short-term Outcome and Predictors of Survival Among Neonates With Moderate or Severe Hypoxic Ischemic Encephalopathy: Data From the Indian Neonatal Collaborative

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**Background:** Among term and late preterm infants, hypoxic ischemic encephalopathy (HIE) is an important cause of mortality, and neurologic morbidity among survivors.

**Objective:** The primary objective was to study the incidence of survival to discharge among late preterm and term infants with moderate or severe HIE. Secondary objectives were to explore variation in the management of HIE across participating sites and to identify the predictors of survival.

**Setting:** Indian Neonatal Collaborative (INNC), a network of 28 neonatal units in India.

**Study design:** Retrospective cohort.

**Participants:** Late preterm (34-36 weeks) and term (37-42 weeks) infants with moderate to severe HIE from 2018-2019.

**Outcome:** The primary outcome was survival to discharge (including discharged home and transfer to other hospital). A

multivariate logistic regression model was constructed to identify the predictors of survival.

**Results:** Of 352 infants with moderate or severe HIE, 59% received therapeutic hypothermia. Survival to discharge among infants with moderate or severe HIE was 82%. Severe HIE (aOR 0.04; 95% CI 0.02-0.10), persistent pulmonary hypertension (PPHN) (aOR 0.22; 95% CI 0.08-0.61) and requirement of epinephrine during resuscitation (aOR 0.21; 95% CI 0.05-0.84) were independently associated with decreased odds of survival to discharge.

**Conclusion:** Survival to discharge among infants with moderate or severe HIE was 82%. Severe HIE, requirement of epinephrine during resuscitation and PPHN decreased the odds of survival.

**Keywords:** *Asphyxia, Hypothermia, Management, Outcome.*

Among term and late preterm infants, hypoxic ischemic encephalopathy (HIE) is an important cause of mortality, and neurologic morbidity among survivors [1]. In 2002-2003, the National Neonatal Perinatal Database (NNPD), a network of neonatal units in India comprising of 18 units across the country, reported that the incidence of HIE was 1.4% among institutional deliveries, and perinatal asphyxia was the commonest primary cause of neonatal mortality (28.8%) and stillbirth (45.1%) [2]. A recent systematic analysis of global, national, and regional causes of child mortality identified HIE as the third important cause (20%) of neonatal deaths in India [3,4]. However, data about the various factors influencing the outcome are lacking. Therapeutic hypothermia (TH) is the

standard of care for HIE in developed countries, but the adoption rate and techniques may differ in low- and middle-income countries (LMICs) [5]. Since the management of the neonates with HIE has undergone major changes in the last decade and nationally representative data were lacking, we

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planned this study to look at short term outcomes and factors associated with decreased survival in late preterm and term infants with HIE.

### METHODS

We used data from the Indian Neonatal Collaborative (INNC), a network of 28 tertiary care neonatal intensive care units

(NICUs) from both public and private sectors across India, contributing real time data anonymously to a common database. This was a retrospective cohort study including late preterm (34-36 weeks) and term (37-42 weeks) infants with moderate or severe HIE admitted between January, 2018 and December, 2019. The demographic details, clinical data including resuscitation details, Apgar score, and Score for Neonatal Acute Physiology with Perinatal Extension-II (SNAPPE-II) score were recorded. Modified Sarnat and Sarnat staging was used to categorize HIE. The primary objective was to study the incidence of survival to discharge, which was defined as either discharged home or transferred to other hospital. The secondary objective was to explore variation in the management of HIE across participating sites and to identify the predictors of survival.

**Statistical analysis:** Proportion and frequency statistics were used for the baseline characteristics. Chi-square tests were used for the association between categorical variables and outcome. A multivariable logistic regression model for identifying the predictors of survival was created by including independent variables based on biological plausibility, and the results of univariate analysis ( $P < 0.1$ ).  $P$  value  $< 0.05$  was considered significant. Stata 14.0 was used for analysis.

## RESULTS

Participating units differed in terms of admission characteristics, with predominantly intramural admissions at

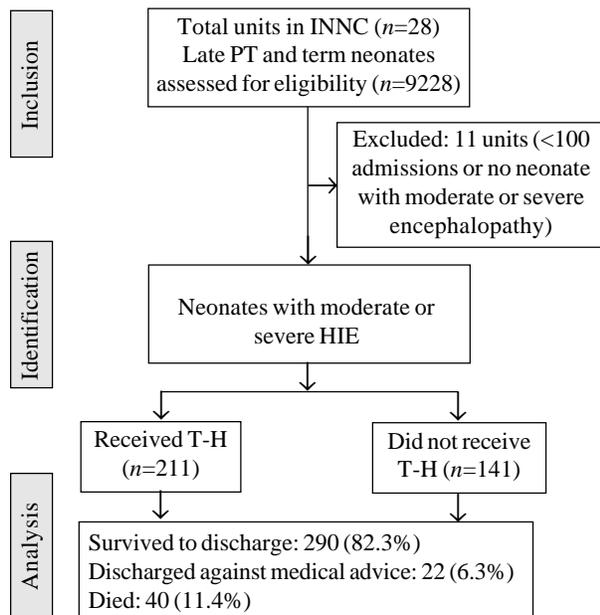
some sites, and exclusively extramural admissions at other. Of the 9228 late preterm and term infants enrolled in the database during the study period, 352 (3.8%) infants (65.3% male) developed moderate or severe encephalopathy (**Fig. 1**). The median gestational age was 39 weeks and mean (SD) birth weight was 2844 (467) gram; 305 (86%) had moderate encephalopathy (**Table I**). Sixty-two (17%) infants received mechanical ventilation support and the median duration of ventilation was  $< 1$  day in infants with moderate encephalopathy while this was  $> 1$  day in infants with severe encephalopathy ( $P < 0.001$ ). Only 12 out of 28 centres were providing TH to these infants (**Web Table I**). Around 60% ( $n = 211$ ) of the infants received TH as a part of management, most commonly (87%) with phase change material (PCM) (**Table I**).

The mortality was 11.4% ( $n = 40$ ) in the study population. A total of 290 (82.3%) infants survived to discharge, while 22

**Table I Characteristics of Neonates With Hypoxic Ischemic Encephalopathy (N=352)**

Neonatal characteristics	Value
Gestation wk <sup>a</sup>	39 (37-40)
Birth weight, g <sup>a</sup>	2900 (2526-3137)
Intramural births	270 (76.7)
Male sex	230 (65.3)
Multiple birth	1 (0.3)
Meconium-stained liquor	122 (34.7)
SNAPPE II	33 (18.45)
<i>Cord blood gas<sup>b</sup></i>	
pH <sup>a</sup>	7.18 (7.00-7.28)
pH $< 7$	48 (22)
Base excess <sup>a</sup>	-14.0 (-11 to -17)
<i>Hypoxic ischemic encephalopathy</i>	
Moderate	305 (86.6)
Severe	47 (13.4)
Therapeutic hypothermia	211 (59.9)
<i>Mode of cooling<sup>c</sup></i>	
Servo-controlled	20 (9.4)
Phase change material	184 (87.2)
Ice packs	5 (2.3)
Persistent pulmonary hypertension	29 (8.2)
Seizures requiring $\geq 2$ anticonvulsants	77 (21.9)
Duration of hospital stay, d	8 (6-12.7)
<i>Disposition</i>	
Discharged home	274 (77.8)
Transferred to other hospital	16 (4.5)
Discharge against medical advice	22 (6.3)
Death	40 (11.4)

Data presented as no. (%) or <sup>a</sup>median (IQR). SNAPPE II, score for neonatal acute physiology with perinatal extension-II; BE, base excess; <sup>b</sup>cord blood gas available for 220 infants; <sup>c</sup>Used other modes in 2 neonates.



INNOC: Indian neonatal collaborative; PT: preterm; HIE: hypoxic ischemic encephalopathy; TH: therapeutic hypothermia.

**Fig. 1** Study flow diagram.

**Table II Predictors of Survival to Discharge Among Late Preterm and Term Infants With Moderate to Severe HIE**

Predictor	Adjusted OR (95% CI)	P value
Female sex	1.17 (0.58-2.37)	0.64
Extramural birth	1.34 (0.55-3.24)	0.51
Meconium-stained liquor	0.82 (0.40-1.69)	0.60
Severe HIE	0.04 (0.02-0.10)	<0.001
Therapeutic hypothermia	1.22 (0.58-2.57)	0.59
PPHN	0.22 (0.08-0.61)	0.004
Seizures requiring ≥2 anticonvulsants	1.54 (0.64-3.70)	0.33
Epinephrine during resuscitation	0.21 (0.05-0.84)	0.02

HIE, Hypoxic ischemic encephalopathy; PPHN, Persistent pulmonary hypertension.

(6.3%) infants left against medical advice. Data regarding the neurological status at disposition were lacking due to variable assessment protocol at discharge; however, information about the feeding status was available. Most infants (76%) were on direct breastfeeds at discharge.

A multivariate logistic regression model was created by including variables based on the results of univariate analysis and biological plausibility. After adjusting for confounders, severe HIE (aOR 0.04; 95% CI 0.02-0.10), persistent pulmonary hypertension (PPHN) (aOR 0.22; 95% CI 0.08- 0.61), and requirement of epinephrine during resuscitation (aOR 0.21; 95% CI 0.05-0.84) were independently associated with decreased odds of survival to discharge (**Table II**). Therapeutic hypothermia (aOR 1.22; 95% CI 0.58-2.57) was not a significant predictor.

## DISCUSSION

The incidence of asphyxia could not be calculated from the INNC data, as all live births are not captured in the database. However, the neonatal and postnatal characteristics and outcomes are available. Survival to discharge among infants with moderate or severe HIE was >80% in most centers. The case fatality rate was 11.4% among moderate or severe HIE.

Therapeutic hypothermia for perinatal asphyxia in LMICs has not been shown to be associated with a statistically significant reduction in neonatal mortality or neurodevelopmental morbidity [6]. The results of a multicentre study (HELIX trial) from LMICs was recently published [7]. In this study, therapeutic hypothermia was not a significant predictor of survival. The apparent lack of impact of TH on outcomes could be due to differences in clinical management protocols or related to factors like perinatal infection, fetal growth restriction, differences in inborn/outborns (differences in obstetric management) and

nurse:patient ratio, which were not assessed in the current study. Cost of the cooling device is a significant factor for providing TH. A multicentre study has earlier shown the feasibility and safety of a phase change material-based cooling device in Indian neonatal units [8]. A recent study from India has confirmed that therapeutic hypothermia induced by phase changing material reduced brain injury detected on magnetic resonance imaging (MRI) in infants with moderate HIE [10].

After adjusting for confounders, severe HIE, PPHN, and requirement of epinephrine during resuscitation were independently associated with decreased odds of survival to discharge. The reason for the pulmonary hypertension in these infants was not assessed in the current study. Large studies looking at the predictors of survival in HIE in the TH era are lacking. However, a few small studies have reported severe HIE [11], low birthweight, preterm, intramural birth, severe asphyxia, and no formal/primary education of parents [12] as independent predictors. A study from Japan reported outborn births, low Apgar score at 5 minute, use of epinephrine, low cord blood pH and abnormal brain magnetic resonance imaging as significant factors associated with poor outcome [12]. Similarly, a recent study suggested that MRI and neurophysiologic tests (EEG or aEEG) were potential predictors of adverse outcome [13]. However, data on these investigations were not available for this cohort.

The strength of the study is the use of data collected in real time from the largest network of tertiary care NICUs in India, including public and private centers. Limitations include the lack of data regarding cause-specific neonatal mortality and inability to calculate the incidence of HIE. Another limitation was the lack of uniform protocol amongst the participating units for the management of the infants with moderate or severe HIE, which could have affected the overall efficacy of TH.

To conclude, moderate or severe encephalopathy due to perinatal asphyxia was an important reason for admission to the NICU among late preterm and term infants. Around 60% of these infants received TH, but the device used differed between centres. Survival to discharge among infants with moderate or severe HIE was 82%. Severe HIE, epinephrine during resuscitation and PPHN decreased the odds of survival to discharge, while TH was not a significant factor.

*Ethics clearance:* The participation in the INNC database was approved by Institutional ethics committee at individual centers. No personal identifiers were retained.

*Contributors:* CK, NP: conceptualized and designed the study. CK, GP, NP: designed the data collection tools; NP, TPO, ASA, BT, DC, SR, MS, NSK, AAM, SK, BS, SM, PK: coordinated and supervised the data collection at respective centers and interpreted the data. CK, NP: performed the statistical analysis; CK, GP, NP:

drafted the initial manuscript; NP, TPO, ASA, SM, PK: critically reviewed the manuscript for important intellectual content. NP and PK revised the final manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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**Web Table I Admissions and Survival to Discharge Among Individual Centers for Neonates with Hypoxic Ischemic Encephalopathy (N=352)**

Site	Moderate or severe encephalopathy	Received therapeutic hypothermia (n=211)	Survived to discharge (n=290)
Site 1	6	4 (67)	3 (50)
Site 2	3	1 (33)	1 (33)
Site 3	7	6 (85)	7 (100)
Site 4	11	3 (27)	4 (36)
Site 5	16	6 (37)	15 (93)
Site 6	13	0	11 (84)
Site 7	12	6 (50)	11 (91)
Site 8	12	6 (50)	11 (91)
Site 9	34	5 (14)	26 (76)
Site 10	2	1 (50)	2 (100)
Site 11	6	0	3 (50)
Site 12	7	0	6 (85)
Site 13	196	168 (85)	164 (83)
Site 14	3	0	3 (100)
Site 15	3	2 (67)	3 (100)
Site 16	17	0	17 (100)
Site 17	4	3 (75)	3 (75)

Note: Eleven units had fewer admissions so not analysed. Data presented as no. (%).