

Perinatal events associated with birth asphyxia and hypoxic-ischemic encephalopathy in a middle-income country: A multicenter, observational study.

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Abstract

Background: Risk factors for neonatal encephalopathy differ across high- and low-income countries. Evidence of demographic characteristics and factors associated with perinatal hypoxia of infants who are at-risk for HIE in Southeast Asia is needed. Our primary objective was to investigate the intrapartum characteristics of infants ≥ 32 weeks' gestational age (GA) born with low Apgar scores. Secondary objectives were to determine perinatal hypoxic events, and the characteristics and outcomes of infants ≥ 35 weeks GA with hypoxic-ischemic encephalopathy (HIE).

Methods: A multicenter, retrospective, study was conducted. Individual charts were reviewed of infants with 5-minute Apgar scores ≤ 5 who were admitted to 4 tertiary centers in Thailand over 5 years. Events associated with perinatal hypoxia and outcomes were extracted. Variables were compared using chi-square, Fisher-exact test, two-independent sample t tests, ANOVA and Mann-Whitney. Data were analyzed using SPSS Statistics version 18.0. A p-value < 0.05 was considered statistically significant.

Results: Among 120235 infants, 454 had 5-minute Apgar scores ≤ 5 (average: 3.8 per 1000 live births). The estimated frequency of HIE in ≥ 32 weeks' GA infants was 1.5 per 1000 livebirths. Ninety-seven percent of the mothers' received antenatal care. After exclusions, 316 infants and 314 mothers comprised the final sample. Common intrapartum complications were abnormal fetal heart rate (38.5%) and meconium-stained amniotic fluid (19.1%). Infants ≥ 35 weeks GA had mean \pm standard deviation (SD) birthweight of 3003.4 ± 590.5 g; 10% were small-for-GA. Among ≥ 35 weeks GA infants with HIE, 42% had metabolic acidosis, 53% experienced sentinel, hypoxic perinatal events and advanced resuscitation was instituted in 92%. The severity of encephalopathy was reported in 99% of subjects. Eighty-five infants (62.5%) met all eligibility criteria for therapeutic hypothermia (TH) and 48 (56.5% of eligible infants) received treatment. The overall mortality rate was 29.4%.

Conclusion: Maternal and intrapartum characteristics of infants at-risk for perinatal asphyxia in Thailand were comparable to reports from high-income countries. To improve recruitment for TH in middle-income, South-East Asian countries, strategies to raise HIE awareness among practitioners and more simplified TH eligible criteria are warranted to encourage timely transfer to referral centers for treatment.

Background

Perinatal asphyxia is the leading cause of death in newborns, mostly in low- and middle-income countries (LMIC) [1-3]. Survivors are at-risk for long term adverse sequelae secondary to hypoxic-ischemic encephalopathy (HIE) [4]. Multidisciplinary strategies have been implemented to decrease the incidence and severity of perinatal asphyxia including the promotion of standardized antenatal care, improved management of intrapartum complications and birth resuscitation, and adequate postnatal supportive care [5].

Therapeutic hypothermia (TH) is proven to improve outcomes in late preterm and term infants with moderate or severe HIE [6, 7]. Robust meta-analyses of TH indicate a 25% reduction in the combined outcome of mortality or neurological disability [Risk Ratio (RR) 0.75; 95% confidence interval (95%CI) 0.68-0.83] [7]. The intervention has been universally adopted as standard of care where appropriate resources and multidisciplinary teams are available for neonatal follow-up [8, 9]. However the majority of studies were conducted in high-income countries while a meta-analysis from LMICs, although demonstrating the same trend of therapeutic effectiveness regarding mortality, did not reach statistical significance [RR 0.74 (95%CI 0.44, 1.25)] [10]. The current 2020 International Liaison Committee on Resuscitation (ILCOR) guideline states that TH for moderate or severe HIE should be implemented in accordance with established criteria [11].

Risk factors for neonatal encephalopathy differ across high- and low-income countries [12]. Apart from maternal socioeconomic status, several factors contribute to sub-optimal outcomes; full knowledge of the broad causation of hypoxic-ischemic events, intrapartum complications particularly fetal growth restriction or infections that accentuate the severity of brain injury [13], physician unawareness of TH eligibility criteria, late TH initiation [14], and lack of experienced caregivers to provide TH therapy [14]. The current HELIX trial is exploring the effectiveness of TH in LMICs, but it remains unclear whether TH should be labeled as a standard of care in these settings. The Malaysian National Neonatal Registry reported the incidence of HIE in term infants as 2.6 per 1000 livebirths, in a 1-year, retrospective study [15]. Hence, demographic characteristics of infants who are at-risk for HIE particularly in Southeast Asia (SEA) or other countries that have similar LMIC economic and health care systems is needed, to substantiate the incidence of HIE and factors associated with perinatal hypoxia.

In Thailand, the National Health Security Office manages the health economic system, via the Universal Health Coverage project, and has granted the use of TH in designated hospitals in each health region. However, the adoption of TH as standard of care across the country remains problematic for several reasons. These include identification of the leading causes of intrapartum hypoxia, social inequality between urban and rural regions, infants' demographic characteristics and associated comorbidities, and timely transfer of babies with HIE to treatment centers. Our primary objective was to investigate maternal demographic and intrapartum characteristics of infants ≥ 32 weeks gestational age (GA) with low Apgar scores. Secondary objectives were to determine the occurrence of perinatal hypoxic events, and the characteristics and outcomes of infants ≥ 35 weeks GA with hypoxic-ischemic encephalopathy (HIE).

Methods

This is a retrospective, multi-centered, observational study. Individual chart reviews were conducted of infants ≥ 32 weeks GA with birth asphyxia based on the ICD-10 World Health Organization definition [16], code P21 (1-minute Apgar score ≤ 7), who were admitted to a neonatal intensive care unit (NICU) at a referral center. These included: The Siriraj Hospital in Bangkok in the Center of Thailand or one of the 3 tertiary regional centers (Lampang Hospital in the North, Sunpasitthiprasong Hospital in the North East, and Chonburi Hospital in the East of Thailand). The centers had established TH for at least 1 year before the study period- January 1st 2013 to December 31st 2017. All 4 hospitals accept outborn infants and provide care for both low- and high-risk neonates. NICU admissions are overseen solely by neonatologists. There are no neonatal transport teams in government hospitals, and TH candidates are transferred to cooling centers by a reference team in the respective facilities. Servo-controlled devices are utilized for temperature management during TH. Amplitude electroencephalography (aEEG) is available in 3 out of the 4 hospitals.

Inclusion criteria for the study were all infants ≥ 32 weeks GA with perinatal asphyxia [17, 18]. We excluded infants with major congenital anomalies to preclude bias in the level of care administered and related outcomes [19].

Definitions

Perinatal hypoxic-ischemia encephalopathy (HIE) was defined as infants with perinatal asphyxia (Apgar score of ≤ 5 at 5 minutes) combined with signs of encephalopathy graded by the Sarnat-Sarnat classification [20]. Subjects for TH followed the modified inclusion criteria of the ICE trial [18] and comprised; 1) GA ≥ 35 weeks and birth weight ≥ 1800 g 2) signs of moderate or severe encephalopathy, and 3) at least 2 perinatal hypoxic-ischemic events: 10-minute Apgar score ≤ 5 or ≥ 2 persistently low Apgar scores, positive-pressure ventilation >10 minutes, umbilical cord or early blood gas (<1 hour) with metabolic acidosis, or intrapartum sentinel events [18]. The latter included events such as uterine bleeding or rupture, placental abruption, abnormal fetal heart rate, cord prolapse or shoulder dystocia [21]. For the purposes of this study, we defined level of income according to the Development Assistance Committee (DAC) list of countries eligible to receive official development assistance [22].

Data of pre-specified antenatal and intrapartum risk factors associated with neonatal encephalopathy [23-25], physical examinations and outcomes were extracted from individual charts by the respective hospital co-investigators (NT, RA, UT, and TW), using a customized template. Resuscitation practice followed the ILCOR guideline [26, 27]. Umbilical blood gas analysis was not universally obtained. Physical and neurological examinations performed by physicians were approved by the neonatologists. Cranial ultrasound or computerized tomography scans were performed at the discretion of the responsible physician. Brain magnetic resonance imaging scans were rarely done and there was no uniform protocol for aEEG during the study period. Seizures were observed clinically and those requiring anticonvulsant medications were included.

Statistical analysis

Descriptive data is presented as frequency and percentage for categorical variables and as mean (\pm standard deviation, SD) or median [25th percentile (P25), 75th percentile (P75)] for continuous data according to the data distribution. Risk factors for perinatal asphyxia across low-middle- and upper income countries were compared based on the published literature.

Variables were compared using chi-square or Fisher-exact test for categorical variables, two-independent sample *t* tests or one-way ANOVA for continuous variables, and Mann-Whitney U test for variables with non-normal distribution. All statistical analyses were performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). A *p*-value <0.05 was considered statistically significant.

Results

Over 5 years, 120235 infants ≥ 32 weeks' gestation were admitted to the study hospitals. The incidence of 1-minute Apgar score ≤ 7 was 3.2%. **Fig. 1** outlines recruitment for the study. The incidence of perinatal asphyxia ($n=454$) ranged from 2.6 to 6.7 (average 3.8) per 1,000 live births. One-hundred and thirty-eight infants were excluded due to major congenital anomalies or incomplete data. Therefore, 316 infants and 314 mothers comprised the final sample. **Table 1** presents maternal demographic characteristics. Eighty-nine percent of the mothers were Thai and 9% were from other SEA countries (Lao, Myanmar, and Cambodia). Two-hundred and ninety-nine mothers (97.4%) received antenatal care. The most common intrapartum complications were abnormal fetal heart rate (38.5%) and meconium-stained amniotic fluid (19.1%). Maternal fever or intraamniotic infection occurred in 2% respectively. Fifty-four percent ($n=169$) were delivered by cesarean section. Overall maternal characteristics were similar among centers except maternal age ($p<0.001$), multiple pregnancy ($p=0.002$), antepartum hemorrhage ($p=0.01$), abnormal fetal heart rate ($p<0.001$), shoulder dystocia ($p=0.003$), and emergency cesarean section ($p<0.001$)

Infants' GA ranged from 32 to 43 weeks (mean: 36.7 ± 2.7). Eighty-one infants (25.6%) were 32 to 34 weeks GA; 235 (74.4%) were ≥ 35 weeks. **Table 2** shows infant characteristics for the total and each GA group. Median [interquartile range; IQR] 1-minute Apgar score was 1 [1, 3] and 93.2% were intubated during resuscitation. Apart from GA, and birth parameters (birthweight, head circumference, and length), there was a significantly higher proportion of inborn infants in the 32- to 34-week GA group ($p<0.001$). **Table 3** shows the distribution of at-risk maternal and

infant characteristics for perinatal asphyxia across studies conducted in high- [18, 21, 28-30], middle- [15] (including this study)-and low-income countries [31-33].

Clinical encephalopathy was assessed in 215 (91.5%) and 221(94.0%) had documented encephalopathy. The frequency of HIE among infants ≥ 32 weeks GA was 1.5 per 1000 livebirths [43 infants 32-34 weeks GA (53.1%) and 136 infants (57.9%) ≥ 35 weeks GA]. **Table 4** shows characteristics and respective outcomes of infants ≥ 35 weeks GA with HIE (n=136). Perinatal insults were documented in: 41.9% based on metabolic acidosis (pH <7.0 or base deficit >16 mmol/L), 52.9% based on sentinel events, 99.3% by graded encephalopathy assessment, and 91.9% on need for advanced resuscitation. One-hundred and twenty-four (91.2%) had either moderate or severe encephalopathy. Eighty-five (62.5%) infants met all eligibility criteria for TH and it was provided in 48 (35.3%; 56.5% of eligible infants). The mortality rate was 29.4%.

Discussion

Although TH is an effective intervention to enhance survival without neurological deficit for infants with moderate to severe HIE, whether this therapeutic strategy should become the standard of care in middle-income countries remains problematic, because the treatment effect varies in high- versus low-resource settings [7, 10]. Reported incidences of HIE, associated demographics, and outcomes stem mostly from robust clinical trials conducted in either high-income countries or heterogeneous studies executed in LMIC settings, with recognized confounders. Data particularly from least developed or LMIC SEA countries that include Thailand, is limited.

The true national incidence, severity, and outcomes of infants with perinatal asphyxia is uncertain due to the lack of a uniform reporting system in Thailand and continuous immigration into the country. The ICD-10 definition identifies the status of infants at 1-minute but majority of the infants rapidly improve following resuscitation and achieve clinical stability. Our data shows that 12% of infants with an Apgar score of ≤ 7 at 1-minute remained at ≤ 5 at 5 minutes. Since we wanted to evaluate only infants at high-risk for HIE that were potential candidates for TH, we chose an Apgar score of ≤ 5 at 5 minutes for our definition of perinatal asphyxia and as a flag for the chart review [34]. Comparing incidences of perinatal asphyxia among regions is challenging because of inconsistent definitions and reports on pre-specified GA-groups [12]. In our study, the incidence of perinatal asphyxia ranged from 2.6 to 6.7 per 1000 live births with regional variation. The average incidence of 3.8 per 1000 live births is marginally higher than 2.6 per 1000 livebirths reported in Malaysia [15] but lies within the range reported by developed countries (1 to 8 per 1000 live births),[12] and is 4-fold lower than lower-income and developing countries (16%) [35, 36]. However, our hospital-based incidence using both inborn and outborn infants as a denominator, is potentially higher than the true population-based incidence due to selective bias since we only included referral hospitals and 35% of the subjects were outborn.

Twenty-one percent of the infants were born to immigrant SEA mothers but racial disparity did not influence management. Ninety-seven percent of the mothers had antenatal care and only 31% had complications. Overall demographic characteristics of the enrolled subjects were similar to many clinical trials of TH in developed countries. Our rates of major complications were comparable to the control group of the National Institute of Child Health and Human Development trial [21]; mean maternal age (27.9 vs. 27 years), maternal hypertension (11% vs. 13%), diabetes (11% vs. 8%), and antepartum hemorrhage (7% vs. 10-19%). Our rate of maternal fever was 2.2% which was also similar to clinical trials of TH (range:1.8% -12%) [18, 21, 28]. Meconium-stained amniotic fluid occurred in 19% of our study subjects while it was reported up to 29% in the neo.nEURO network randomized trial [29]. In the present study, a total of 54% of the subjects were born by cesarean section compared to reports of clinical trials from developed countries which varied from 46% to 75% [18, 21].

Apart from maternal factors, the mean birthweight of infants in the group ≥ 35 -weeks GA was 3009 g (10% were small for GA) which is slightly lower than approximately 3300g in several studies [18, 21, 29]. Pertinent demographic characteristics were similar except for the number of inborn infants which is one of the interesting factors related to outcome.[37] Overall, 65% of the infants in our study were inborn and 59% were ≥ 35 -weeks GA which was similar to the ICE and neo-nEURO network trials. The mean time to NICU admission was 2.8 hours and 91% were admitted to the referral hospitals within 6 hours of life. This is well within the golden, recommended period of 6 hours to initiate TH and positively influence outcomes [37, 38]. Although it is difficult to accurately compare the incidence of risk factors associated with perinatal asphyxia due to variable study definitions, gestational age categories selected apriori, and type and quality of included data, the overall baseline maternal and infant characteristics relating to outcomes show a similar trend between high- versus middle-income countries (**Table 3**).

Fifty-eight percent (136/235) of infants in the ≥ 35 -week GA with perinatal asphyxia had HIE. Only 85 (62.5%) met eligibility criteria for TH and 48 (35.3%) received treatment (62.5% of eligible infants). The reasons that 27.2% did not receive therapy was due to the unavailability of TH at the referral center at the time of birth, inability to refer to the cooling center within 6 hours of age, and non-familiarity with referral hospitals that performed TH. More than 90% of the enrolled subjects were clinically evaluated for TH based on Apgar scores, prolonged ventilation, or sentinel events. Umbilical cord or early blood gas analysis was performed in 77.9% of our cohort, and the availability of both have improved in rural Thai regions over time. We propose that the criteria for TH in LMIC settings should include intrapartum sentinel events as described and simpler HIE classification based on Apgar scores and clinically documented encephalopathy without mandatory blood gas analysis, which is inconsistently available.

To our knowledge, the true incidence of perinatal asphyxia in SEA countries remains undetermined. Our average frequency of HIE across the 4 institutions is similar to the Malaysian registry and high-income countries. However, the range suggests that in parts of Thailand the incidence is likely higher and the availability of TH could alter long-term adverse sequelae. Individual chart review by neonatologists using specific definitions for each variable relevant to current practice, ensures internal validity of our results. Moreover, we included major referral hospitals in different parts of Thailand to minimize selective bias and afford country-wide generalizability of the findings.

Nevertheless, some limitations related to the retrospective chart review merit consideration. First, complete chart data may not have been assembled, and we were unable to identify maternal socioeconomic and nutritional status which are reported risk factors for neonatal encephalopathy [24]. Hence, we utilized standard antenatal care as a proxy for the surveillance of good maternal health in 97% of the pregnancies. Second some variables were missing particular for infants who were outborn, such as maternal temperature and complete details of birth resuscitation. Third, as previously addressed, an umbilical cord gas or arterial blood gas analysis within the first few hours of life was either unavailable in some rural hospitals, or not considered part of standard practice in most hospitals during the study period. However, the total number of recruited infants should partially compensate for these limitations and maintain the validity of our results.

In summary, maternal and infant demographic characteristics and intrapartum risk factors for perinatal HIE in Thailand were comparable to published reports from high-income countries. Sixty-three percent of eligible infants received TH treatment. To improve access to country-wide TH, strategies need to be implemented to raise awareness of the eligibility criteria for therapy among obstetricians and allied perinatal health-care providers. Simplifying the criteria for TH in low-middle income countries may enhance accessibility to TH where transport of potential candidates can be expedited in a timely manner.

Abbreviations

aEEG: amplitude electroencephalography; GA: gestational age; HIE: hypoxic-ischemic encephalopathy; ILCOR: International Liaison Committee on Resuscitation; LMIC: low- and middle-income countries; NICU: neonatal intensive care unit; SEA: southeast asia; TH: therapeutic hypothermia

Declarations

The study protocol was approved by the Siriraj Institutional Review Board (Si 586/2018) and the local research ethics board of each institution. All methods were performed in accordance with the relevant guidelines and regulations.

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Authors' contributions

R.K. conceptualized, designed the study, and drafted the initial manuscript.

N.T., R.A., U.T., and T.W. conceptualized the study and performed data collection

BP critically reviewed and revised the manuscript into its final version.

All authors approved the final manuscript as submitted.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the Siriraj Institutional Review Board, the Institutional Review Board of Chonburi Hospital, the Lampang Human Ethics Research Subcommittee, and the Ethics Committee of the Sunpasitthiprasong Hospital. A waiver of informed consent was granted by the Siriraj Institutional Review Board, the Institutional Review Board of Chonburi Hospital, the Lampang Human Ethics Research Subcommittee, and the Ethics Committee of the Sunpasitthiprasong Hospital based on the retrospective study design without identification and assembly of individual, personalized data

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Maternal demographic characteristics across the four recruiting hospitals						
	Total (N= 314)	Siriraj (n=84)	Lampang (n=31)	Chonburi (n=109)	Surpasittiprasong (n=90)	P-value
Age (years)	27.9 ± 7.3	30.7 ± 6.7	28.4 ± 6.3	27.3 ± 7.3	25.6 ± 7.2	<0.001*
Nationality (n=314)						
Thai	280 (89.2)	73 (86.9)	30 (96.8)	94 (86.2)	83 (92.2)	0.25
Other SEA countries	27 (8.6)	11 (13.1)	1 (3.2)	14 (12.8)	1 (1.1)	0.03*
Other	7 (2.2)	-	-	1 (0.9)	6 (6.7)	0.02*
Received antenatal care (n=307)	299 (97.4)	81 (96.4)	31 (100)	106 (97.2)	81 (97.6)	0.96
Primigravida (n=307)	141 (45.9)	38 (45.2)	14 (45.2)	49 (45.4)	40 (47.6)	0.99
Multiple pregnancy (n=309)	22 (7.1)	13 (15.5)	2 (6.5)	7 (6.4)	0	0.002*
Pregnancy complications (n=302)						
Hypertension (n=303)	35 (11.6)	15 (17.9)	3 (9.7)	12 (11.0)	5 (6.3)	0.14
Diabetes (n=303)	33 (10.9)	8 (9.5)	3 (9.7)	11 (10.1)	11 (13.9)	0.81
Antepartum hemorrhage (n=302)	23 (7.6)	13 (15.5)	3 (9.7)	2 (1.8)	5 (6.4)	0.01*
Intrapartum complications						
Meconium-stained amniotic fluid (n=301)	60 (19.9)	14 (16.7)	7 (22.6)	25 (22.9)	14 (18.2)	0.68
Maternal temperature >38°C (n=301)	7 (2.3)	3 (3.6)	1 (3.2)	3 (2.8)	0	0.36
Intraamniotic infection (n=301)	6 (2.0)	2 (2.4)	0	4 (3.7)	0	0.29
Rupture of membranes >18h (n=301)	20 (6.6)	8 (9.5)	2 (6.5)	7 (6.4)	3 (3.9)	0.57
Abnormal fetal heart rate (n=302)	121 (40.1)	50 (59.5)	10 (32.3)	42 (38.5)	19 (24.4)	<0.001*
Shoulder dystocia (n=302)	34 (11.3)	6 (7.1)	7 (22.6)	6 (5.5)	15 (19.2)	0.003*
Delivery method (n=309)						
Emergency cesarean section	160 (51.8)	59 (70.2)	13 (41.9)	63 (57.8)	25 (29.4)	<0.001*
Non-emergency cesarean section	9 (2.9)	5 (6.0)	1 (3.2)	3 (2.8)	0 (0.0)	0.14
Data is presented in number (percentage) and mean ± standard deviation.						
* indicates $p < 0.05$.						
Abbreviations: SEA, South-East Asian						

Table 2 Demographic characteristics of infants with 5-minute Apgar score ≤ 5 grouped by gestational age				
	Total (N=316)	GA 32 to 34 weeks (n= 81)	GA 35 weeks or more (n=235)	P value
Gestational age (week)	36.7 \pm 2.7	32.9 \pm 0.9	38.1 \pm 1.6	<0.001*
Male sex	173 (54.7)	44 (54.3)	129 (54.9)	1.00
Inborn (n=311)	203 (65.3)	68 (84.0)	135 (58.7)	<0.001*
Age at NICU admission (hr)	2.8 \pm 4.6	2.8 \pm 6.1	2.9 \pm 3.9	0.93
Birthweight (g)	2718.2 \pm 739.0	1897.8 \pm 455.3	3003.4 \pm 590.5	<0.001*
Small-for-gestational age (n=314)	31 (9.9)	10 (12.3)	21 (9.0)	0.39
Large-for-gestational age (n=314)	21 (6.7)	2 (2.5)	19 (8.2)	0.12
Body length (cm)	48.2 \pm 4.6	43.1 \pm 4.4	49.9 \pm 3.2	<0.001*
Head circumference (cm)	32.3 \pm 2.3	29.9 \pm 2.2	33.2 \pm 1.5	<0.001*
Apgar scores				
1-minute (n=312)	1 [1, 3]	1 [1, 3]	1 [0, 3]	0.70
5-minute (n=313)	4 [1.5, 4.5]	4 [2, 5]	4 [2, 5]	0.08
10-minute (n=298)	6 [4, 7]	6 [4, 7]	6 [4.8, 6.3]	0.67
20-minute (n=136)	7 [5, 7.3]	7 [5, 8]	6 [1.8, 8.3]	0.57
Birth resuscitation				
Positive-pressure ventilation (n=308)	307 (99.7)	80 (100)	227 (99.6)	1.00
Nasal CPAP (n=305)	16 (5.2)	6 (7.6)	10 (4.4)	0.38
Tracheal intubation (n=308)	287 (93.2)	77 (96.3)	210 (92.1)	0.30
Chest compression (n=307)	144 (46.9)	39 (48.8)	105 (46.3)	0.80
Medication(s) (n=305)	109 (35.7)	30 (37.5)	79 (35.1)	0.79
Data is presented as mean (\pm standard deviation, SD), number (percentage), or median [P25, P75].				
P values were compared between GA 32- to 34-week group vs. GA ≥ 35 weeks'; * indicates <i>p</i> value <0.05.				
Abbreviations: CPAP, Continuous positive airway pressure; GA, Gestational age; NICU, Neonatal intensive care unit.				

Table 3 Distribution of maternal and infant characteristics at-risk for perinatal asphyxia based on level of income						
	High-income countries		Middle-income countries		Low-income countries	
Mean maternal age (years)	27-30	Jacobs SE et al. ¹⁸ Shankaran S et al. ²¹ Simbruner G et al. ²⁹	27.7 27.9	Boo NY et al. ¹⁵ This study	20-35	Abdo RA et al. ³¹ Babu BVA et al. ³² Ibrahim NA et al. ³³
Mean gestational age (weeks)	38-40	Jacobs SE et al. ¹⁸ Azzopardi DV et al. ²⁸ Simbruner G et al. ²⁹	38.8 36.7	Boo NY et al. ¹⁵ This study	>37	Ibrahim NA et al. ³³
Mean birthweight (kg)	3.3-3.5	Jacobs SE et al. ¹⁸ Shankaran S et al. ²¹ Azzopardi DV et al. ²⁸ Simbruner G et al. ²⁹	3.1 2.7	Boo NY et al. ¹⁵ This study	2.5-4.0	Ibrahim NA et al. ³³
Outborn	39-62%	Shankaran S et al. ²¹ Azzopardi DV et al. ²⁸ Simbruner G et al. ²⁹	16.4% 34.7%	Boo NY et al. ¹⁵ This study	24%	Ugwu GIM et al. ³⁵
Primigravida	38-49%	Jacobs SE et al. ¹⁸	45.9%	This study	32-55%	Abdo RA et al. ³¹ Babu BVA et al. ³²
Multiple pregnancy	0.9-1.8%	Jacobs SE et al. ¹⁸	1.6% 7%	Boo NY et al. ¹⁵ This study	3.3-8%	Babu BVA et al. ³² Ugwu GIM et al. ³⁵
Hypertension	13%	Shankaran S et al. ²¹	8.3% 11.1%	Boo NY et al. ¹⁵ This study	10-25%	Babu BVA et al. ³² Ibrahim NA et al. ³³
Diabetes	8%	Shankaran S et al. ²¹	14.7% 10.5%	Boo NY et al. ¹⁵ This study	2.4%	Ibrahim NA et al. ³³
Cesarean section	46-75%	Jacobs SE et al. ¹⁸ Shankaran S et al. ²¹ Simbruner G et al. ²⁹ Gluckman PD et al. ³⁰	31.2% 54.2%	Boo NY et al. ¹⁵ This study	17-52%	Babu BVA et al. ³² Ibrahim NA et al. ³³
Pyrexia or intrauterine infection	1.8-12%	Jacobs SE et al. ¹⁸ Shankaran S et al. ²¹ Azzopardi DV et al. ²⁸ Simbruner G et al. ²⁹	1.2% 4.1%	Boo NY et al. ¹⁵ This study	10-19%	Abdo RA et al. ³¹ Babu BVA et al. ³²
Shoulder dystocia	1-14%	Jacobs SE et al. ¹⁸	10.8%	This study		

		Shankaran S et al. ²¹				
Antepartum hemorrhage	10-19%	Jacobs SE et al. ¹⁸	2.9%	Boo NY et al. ¹⁵	6.9-10%	Babu BVA et al. ³²
		Gluckman PD et al. ³⁰	7.3%	This study		Ugwu GIM et al. ³⁵
MSAF	26-29%	Simbruner G et al. ²⁹	19%	This study	10-42%	Abdo RA et al. ³¹
						Babu BVA et al. ³²
Abnormal FHR	73-93%	Jacobs SE et al. ¹⁸	38.5%	This study	8%	Ugwu GIM et al. ³⁵
		Shankaran S et al. ²¹				
Abbreviations: FHR, fetal heart rate; MSAF: meconium-stained amniotic fluid.						

Table 4 Characteristics and outcomes of infants 35-weeks' gestation or more with hypoxic ischemic encephalopathy based on eligibility criteria for therapeutic hypothermia (N=136)	
Birth weight >1800g	135 / 135 (100)
Perinatal hypoxic events	
Apgar score ≤5 at 10 minutes	58 / 134 (42.6)
Require positive-pressure ventilation >10 minutes	125 / 134 (91.9)
Severe metabolic acidosis (pH <7.0 or base deficit >16)	57 / 106 (41.9)
Sentinel events	72 / 124 (52.9)
Clinical signs of encephalopathy (n=136)	
Seizure	77 / 131 (56.6)
Alteration of consciousness	112 / 127 (82.4)
Hypotonia	110 / 122 (90.2)
Abnormal primitive reflexes	101 / 107 (74.3)
Degree of encephalopathy (n=135)	
Mild	11 / 135 (8.1)
Moderate	60 / 135 (44.1)
Severe	64 / 135 (47.1)
NICU admission within 6 hours	117 / 128 (86.0)
Clinical outcomes	
Oxygen administration >24h	78 / 133 (57.4)
Non-invasive ventilation	13 / 133 (9.6)
Tracheal intubation	127 / 133 (93.4)
Intracranial hemorrhage	8 / 56 (5.9)
Therapeutic hypothermia	48/136 (35.3%)
Hospitalization days (n = 134)	13.0 [7.0, 25.25]
Death	40 / 136 (29.4)
Data is presented in number (percentage) or median [P25, P75].	
Abbreviations: NICU, Neonatal intensive care unit	

Figures

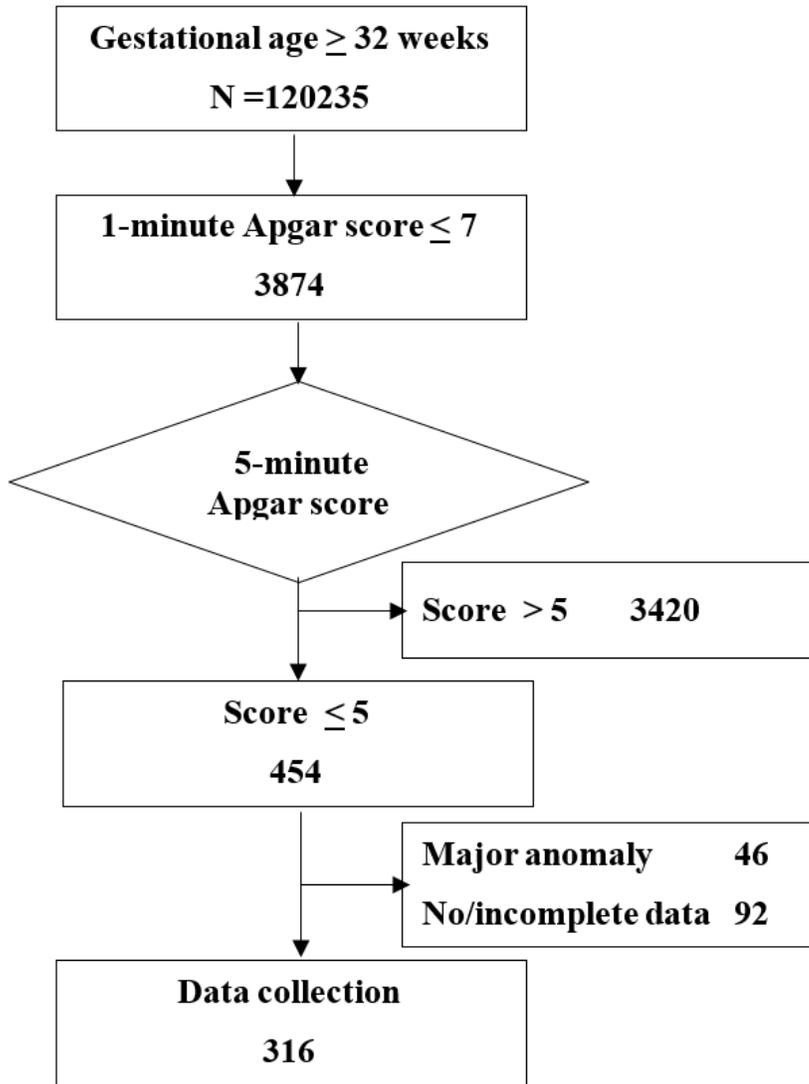


Figure 1

Flow chart of patient recruitment (Abbreviations: HIE, hypoxic-ischemic encephalopathy; TH, therapeutic hypothermia)