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Therapeutic hypothermia for neonatal encephalopathy in developing countries: Current evidence

Deepak Chawla

Department of Neonatology, Government Medical College Hospital, Chandigarh, India

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ABSTRACT

Problem considered: Birth asphyxia and resultant brain injury are an important cause of neonatal mortality and morbidity in resource-limited countries. Prevention of birth asphyxia needs effective coverage of evidence-based interventions during antenatal care, childbirth, and high-risk pregnancies, close intrapartum monitoring, access to emergency obstetric care, and neonatal resuscitation. Therapeutic hypothermia is the only specific therapy proven to reduce the incidence of death and disability in neonates with hypoxic-ischemic encephalopathy (HIE). While therapeutic hypothermia is the standard of care in high-income contours, its benefit in low- and middle-income countries remains unproven.

Methods: This article analyzes the evidence from randomized controlled trials conducted in different settings. As systematic reviews of these trials have shown significant statistical heterogeneity in the efficacy of therapeutic hypothermia, this article examines the reasons behind heterogeneity in the outcome of death before discharge from the hospital.

Results: The following factors were found to be associated with the loss of efficacy of therapeutic hypothermia – the absence of objective evidence of acute birth asphyxia, suboptimal care during transport of extramural neonates, uncontrolled hypothermia before admission to a neonatal unit, and the severity of HIE.

Conclusion: A sufficiently powered randomized controlled trial that takes into account these effect modifiers needs to be conducted in rescue-limited settings.

1. Introduction

Birth asphyxia is an important cause of neonatal mortality and morbidity in low- and middle-income countries (LMIC). Intrapartum-related events account for more than 10 % under-five and about one-fifth of neonatal deaths.[1] The proportion of neonatal deaths due to asphyxia is still higher in settings with high neonatal mortality. Reliable estimates of the burden of encephalopathy due to birth asphyxia are not available. A systematic review restricted to studies from LMIC reported an incidence range of 1.5–20.3 per 1000 live births with a case fatality rate of 19.2 % (45 studies, n = 3307).[2] About 45 % (19 studies, n = 1595) of neonates with encephalopathy died or developed moderate to severe neurodevelopmental disability by 1–3.5 years of age (see Table 1).

The incidence of birth asphyxia can be reduced by early detection and evidence-based management of high-risk pregnancies, close intrapartum monitoring, access to emergency obstetric care, and appropriate neonatal resuscitation. However, therapeutic hypothermia is the only specific therapy available for neonates who have suffered from birth asphyxia and have developed hypoxic-ischemic encephalopathy (HIE). Therapeutic hypothermia is initiated in eligible neonates within 6 h of birth. The core body temperature is brought down to 33.5 + 0.5 °C, maintained at this level for the next 48–72 h, and then slowly brought back to the euthermic level of 37.0 + 0.5 °C. In high-income countries, therapeutic hypothermia significantly reduces the combined outcome of mortality or major neurodevelopmental disability by 18 months of age (number needed to treat: 7; 95 % CI: 5 to 10).[3] However, the benefit of therapeutic hypothermia in LMIC remains unconvincing with different studies and systematic reviews reporting conflicting results.[4–7] This paper discusses the evidence for the use of therapeutic hypothermia for neonates with HIE in LMIC.

2. Methodology

A literature search was conducted (PubMed and Cochrane Register of Controlled Trials, last updated on 15 November 2023) to find the most recent systematic review of studies evaluating the efficacy of therapeutic hypothermia in term or late preterm neonates with birth asphyxia. The

E-mail address: drdeepak@gmch.gov.in.

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Table 1
Randomised controlled trials investigating therapeutic hypothermia.

Author/Study	Eligibility criteria	Enrolled		Outborn		Mean cord pH		HIE-1		HIE-2		HIE-3		Cooling methods	Cooling device	Target temp		Duration	Rewarming rate
		I	C	I	C	I	C	I	C	I	C	I	C			I			
Aker (THIN)[9]	Gestation >35 weeks, birth weight>1800 g Apgar score <5 at 5 minutes Cord pH<7 or base excess> -12 Need of PPV for at least 10 minutes (if outborn - no cry at birth) Age less than 5 h Moderate or severe HIE	25	25	12	8	6.81	6.93							WBC	MiraCradle	33-34	72	0.2-0.5
Akisu[13]	Gestation >37 weeks Apgar score <6 at 5 minutes Cord pH<7.1 or base excess> -10 ???Age less than 6 h Moderate to severe HIE	11	10			7.02	7.03	2	1	7	5	3	3	HC	Not mentioned	33-33.5	72	0.5
Bharadwaj[14]	Gestation >37 weeks Apgar score <7 at 10 minutes Cord pH<7 or base excess> -12 Two of the 5 criteria - Apgar score, fetal distress, assisted ventilation for at least 10 min, sentinel event and organ dysfunction Age less than 6 h Moderate to severe HIE	65	65	0	0	7.09	7.08	0	0	55	54	7	8	WBC	Gel packs	33-34	72	0.5
Bhat[17]	Inclusion criteria not specified	20	15											WBC		33.5	72	
Catherine[8]	Gestation >37 weeks Apgar score <6 at 10 minutes Cord pH<7 or base excess> -12 Cord ABG + 2 of the 4 criteria - Apgar score, clinical evidence of fetal distress, assisted ventilation for at least 10 min, organ dysfunction Age less than 6 h Moderate to severe HIE	78	84	0	0									WBC	MiraCradle	33.5	72	0.5
Gluckman/CoolCap[29]	Gestation >35 weeks, birth weight >1800 g. Apgar score <5 at 10 minutes or need of resuscitation at 10 minutes Cord pH<7 or base excess> -16 Age less than 5.5 h Abnormal aEEG Moderate or severe HIE	116	118			6.9	6.9	0	0					HC	Olympic	34-35	72	0.5
Eicher[23]	Gestation >34 weeks, birth weight >1999 g Cord pH<7 or base excess> -12 Apgar score at 10 minutes <6 or need of resuscitation at 5 minutes Age less than 6 h Any HIE	32	33	26	23	6.95	0.19	1	1	5	5	25	25	WBC	Gel pack + Blanketerol	33	48	0.5
Gane[30]	Gestation >37 weeks Apgar score <5 at 10 minutes Cord pH<7 or base excess> -16 Cord ABG + 2 of the 4 criteria - Apgar score, clinical evidence of fetal distress, assisted ventilation for at least 10 min, organ dysfunction Age less than 6 h Moderate to severe HIE	61	61	0	0	6.89	6.85	0	0	45	44	15	16	WBC	Gel packs	33-34	72	0.25
Gunn[24]	Gestation >36 weeks Cord pH<7.1 Apgar score at 5 minutes <7 Age less than 6 h Moderate or severe HIE	12	10			6.96	6.79	0	0					HC	Silclear tubing	36-36.5 (n-6), 35.5-35.9 (n=6)	72	0.5
Jacob/ICE[25]	Gestation >34 weeks, birth weight >1999 g Cord pH<7 or base excess> -12 Apgar score at 10 minutes <6 or need of resuscitation at 5 minutes Age less than 6 h Moderate or severe HIE (Enrolled neonates had mild HIE also - 17 in intervention and 25 in control group)	110	111	68	66	6.9	6.9	17	25	63	54	30	29	WBC	Gel pack	33.5	72	0.25
Jose[10]	Moderate to severe HIE after an acute perinatal event, with acidosis or resuscitation	77	79	35	32	6.7	6.6			51	39	22	28	WBC	Gel packs	33	72	
Joy[15]	Gestation >37 weeks Apgar score <6 at 10 minutes	58	58	0	0	7.06	7.09	0	0	49	51	9	7	WBC	Gel packs	33-34	72	0.5

	Cord pH<7 or base excess> -12 Two of the 4 criteria - Apgar score, fetal distress or sentinel event, assisted ventilation for at least 10 min, and organ dysfunction Age less than 6 h Moderate or severe HIE																	
neo.nEURO[27]	Gestation >35 weeks, birth weight >1799 g. Apgar score <5 at 5 minutes or need of resuscitation at 10 minutes Cord pH<7 or base excess> -16 Age less than 5.5 h Abnormal aEEG Moderate or severe HIE	64	65	39	42	6.9	6.9	0	0	24	17	38	46	WBC	Tecotherm TS Med 200	33.5	72	0.5
NICHD[26]	Gestation >35 weeks, birth weight >1800 g Cord pH<7 or base excess> -16 If pH 7.01-7.15 or BE 10-15.9 or NA- then needed to have acute perinatal event and Apgar score at 10 minutes <6 or positive pressure ventilation for at least 10 minutes Age less than 6 h Moderate or severe HIE	102	106	47	42	6.9	6.8	0	0	69	66	32	32	WBC	Blanketrol II	33.5	72	0.5
Rakesh[11]	Gestation >37 weeks Apgar score <6 at 10 minutes Cord pH<7 or base excess> -12 Two of the 4 criteria - Apgar score, fetal distress, assisted ventilation for at least 10 min, and organ dysfunction Age less than 6 h Any grade of HIE	60	60	0	0	6.94	6.92	1	2	41	44	18	14	WBC	MiraCradle	33-34	72	
Robertson[19]	Gestation >36 weeks, birth weight >2000 g. Apgar score <6 at 5 minutes or need of resuscitation at 5 minutes Age less than 3 h Any HIE	21	15	0	0									WBC	Water bottle	33-34	72	
Tanigasalam[12]	Gestation >37 weeks Apgar score <6 at 10 minutes Cord pH<7 or base excess> -12 Two of the 4 criteria - Apgar score, fetal distress, assisted ventilation for at least 10 min, and organ dysfunction Age less than 6 h Any grade of HIE	60	60	0	0	6.95	6.93	1	4	42	41	17	15	WBC	Gel packs	33-34	72	0.5
Thayyil[21]	Gestation >36 weeks, birth weight >1800 g. Thompson score>5	17	16											WBC	PCM			
Thayyil (HELIX)[4]	Gestation >36 weeks, birth weight >1800 g. Apgar score <6 at 5 minutes or need of resuscitation/absence of cry at 5 minutes Age less than 6 h Moderate to severe HIE	202	206	140	145	6.94	6.97	0	0	161	167	41	39	WBC	Tecotherm Ne0	33.5	72	0.5
TOBY[16]	Gestation >35 weeks Cord pH<7 or base excess> -16 Apgar score at 10 minutes <6 or continued need of resuscitation at 10 minutes Age less than 6 h Abnormal aEEG Moderate or severe HIE	163	162					0	0	65	67	98	95	WBC	Tecotherm TS 200	33.5	72	0.5
Zhou[31]	Gestation >36 weeks, birth weight >2499 g. Apgar score <6 at 5 minutes or need of resuscitation at 5 minutes Cord pH<7 or base excess> -16 Age less than 6 h Any HIE	100	94	77	77			21	18	41	41	38	35	HC	Henyang	34.5-35	72	spontaneous

I: Intervention, C: Control, HIE: Hypoxic-ischemic encephalopathy.[29–31]

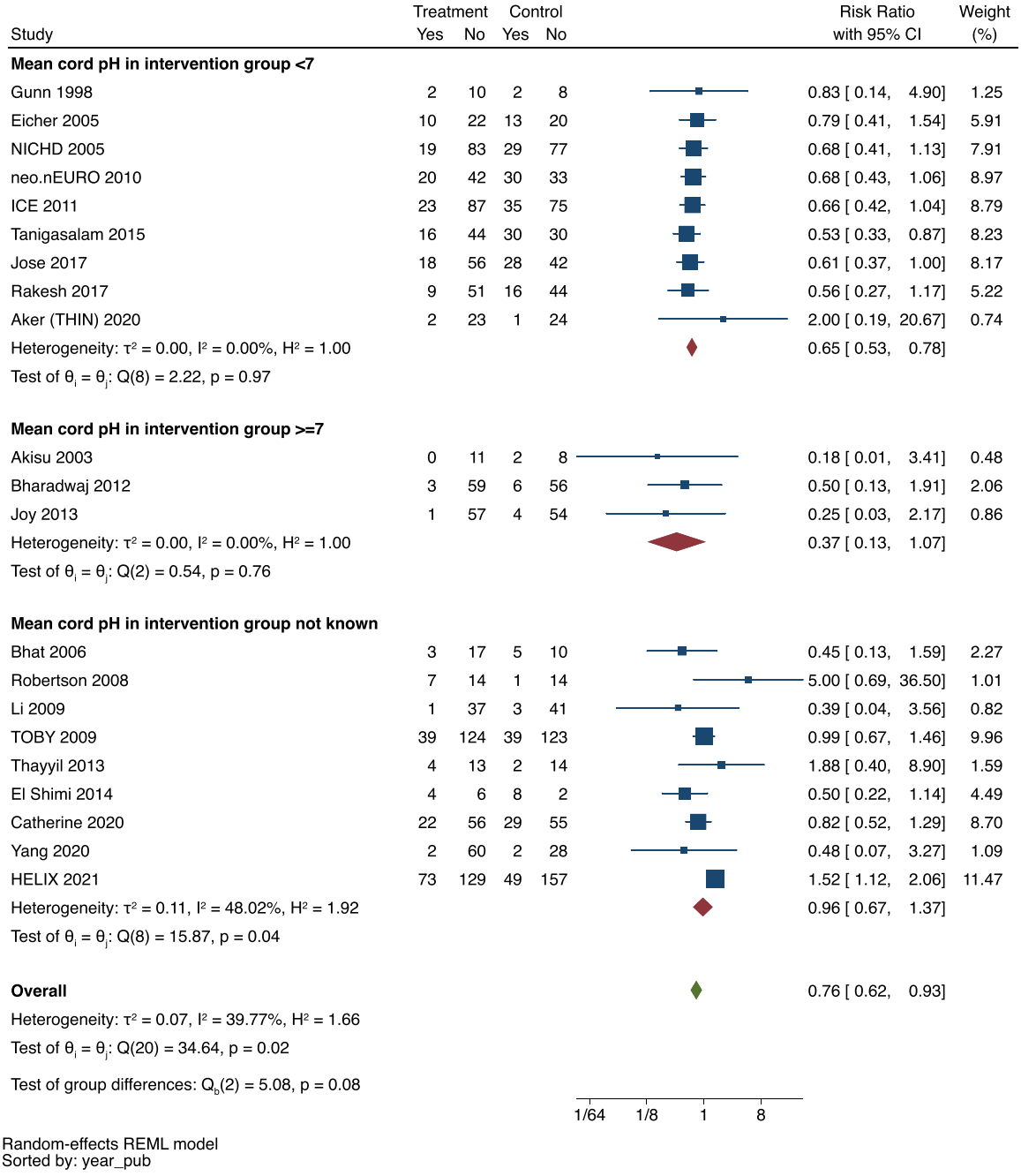

Fig. 1. Forest plot depicting the effect of therapeutic hypothermia on death before discharge with subgroup analysis based on cord pH.

literature was also searched for randomized controlled trials published after the date of the literature search in the most recent systematic review. Primary studies enrolling term and later preterm neonates with birth asphyxia were eligible for inclusion if eligible neonates were randomized to a control group or therapeutic hypothermia (manual or servo-controlled, whole body or selective head cooling). We planned to update the most recent systematic review by including the newly published studies. The following information was extracted from the studies included in the systematic review: trial setting, risk of bias, cord pH, the proportion of extramural neonates, admission temperature, and the proportion of neonates with different grades of severity of HIE. If not reported in the systematic review, subgroup analysis was conducted to evaluate the effect of these factors on the efficacy of therapeutic hypothermia. Data analysis was done using Stata 16.1 (Stata Corp, College Station, TX).

3. Results and discussion

The most recent systematic review and meta-analysis on therapeutic hypothermia's efficacy in birth asphyxia was published in 2022 with the literature search updated till October 31, 2021.[5] The review included 39 publications from 29 RCTs and 2926 participants. In the pooled estimates, therapeutic hypothermia was associated with a significant reduction in the composite outcome of mortality or disability at 18–24 months of age (10 studies, RR: 0.78; 95 % CI: 0.72 to 0.86) The pooled estimates showed a trend toward reduction in all-cause mortality till 28 days (22 studies, RR: 0.87; 95 % CI: 0.75 to 1.00), 18–24 months (11 studies, RR: 0.88; 95 % CI = 0.78 to 1.01), and 5–10 years (2 studies, RR:

0.81; 95 % CI: 0.62 to 1.04) of age. A significant reduction was noted in the incidence of disability at 18–24 months (11 studies, RR: 0.62; 95 % CI: 0.52 to 0.75) and at 5–10 years (3 studies, RR: 0.68; 95 % CI: 0.52 to 0.90) of age. Neonates receiving therapeutic hypothermia also had a significantly lower risk of being diagnosed with cerebral palsy at 18–24 months of age (8 studies, RR: 0.63; 95 % CI: 0.50 to 0.78) and later in childhood (3 studies RR: 0.63; 95 % CI: 0.46 to 0.85). However, hidden in these pooled estimates is wide variation in the outcomes observed in trials conducted in different care settings or with varying methodological rigor. **1. Trial setting:** Of the studies included in the systematic review ten were conducted in LMIC and five in upper-middle-income countries (UMIC). While the composite outcome of death or disability at 18–24 months of age is reported in all the studies from HIC, only two of ten studies from LMIC report this outcome.[4,8] Due to the lack of power, it is difficult to interpret the difference in this important outcome based on the trial setting. Still, the studies conducted in LMIC show no reduction in the incidence of death or disability with therapeutic hypothermia (RR: 0.92; 95 % CI: 0.77 to 1.09). Also, no reduction is observed in neonatal mortality (RR: 0.89; RR: 0.74 to 1.09) that is reported by all trials from LMIC. Pooled estimates from two trials that reported disability at 18–24 months of age show a significant reduction (RR: 0.49; 95 % CI: 0.30 to 0.80) in this outcome. However, one of these trials has shown a significant increase in mortality before discharge (RR: 1·50; 95 % CI: 1·10 to 2·04) and by 18 months of age (RR: 1·35; 95 % CI: 1·04–1·76) in the therapeutic hypothermia group.[4] **2. Trial rigor:** Of the studies included in the systematic review by Mathew et al.,[5] one-third

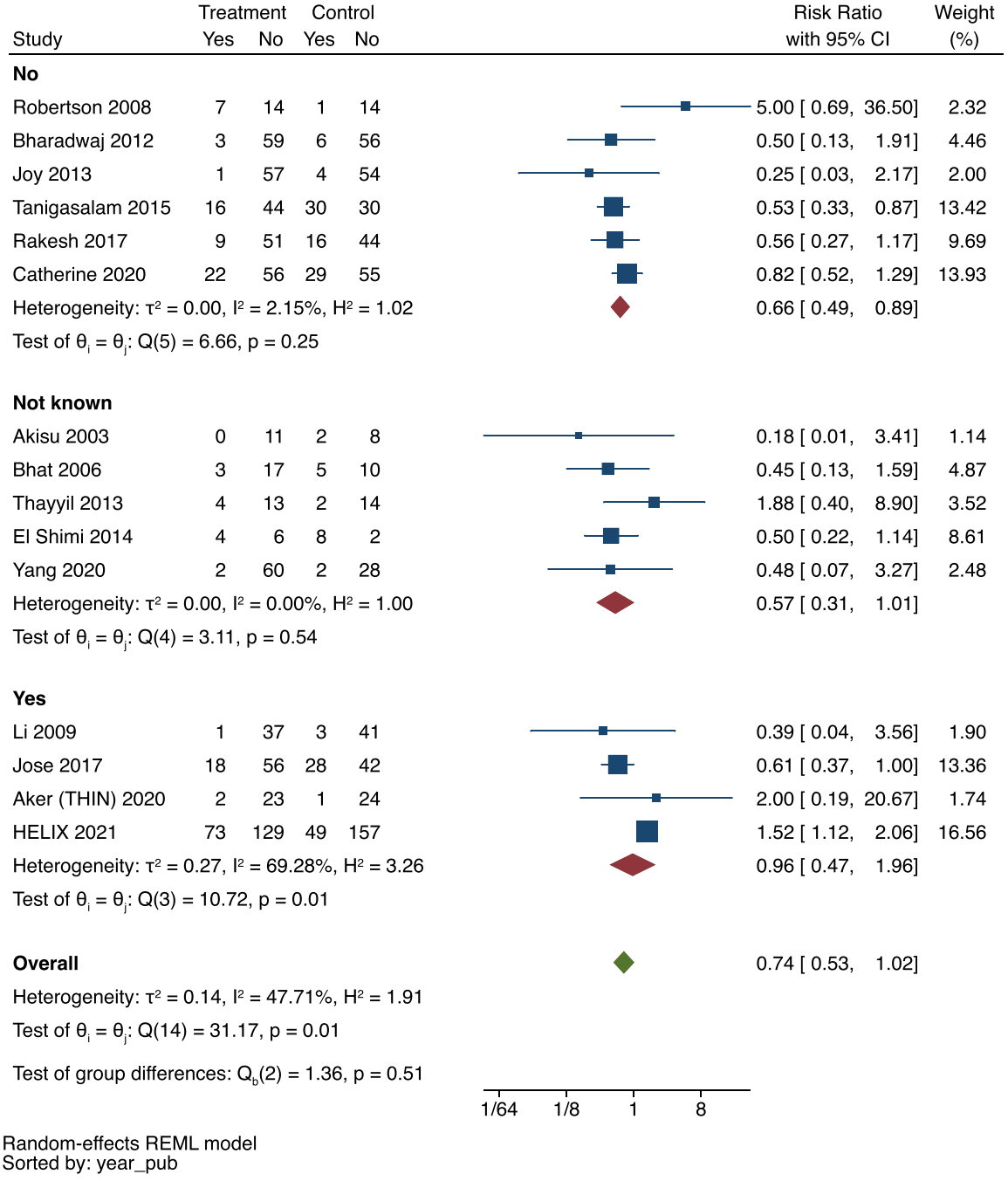

Fig. 2. Forest plot depicting the effect of therapeutic hypothermia on death before discharge with subgroup analysis based on inclusion of extramural neonates a) Studies from low- and middle-income countries b) Studies from high-income countries.

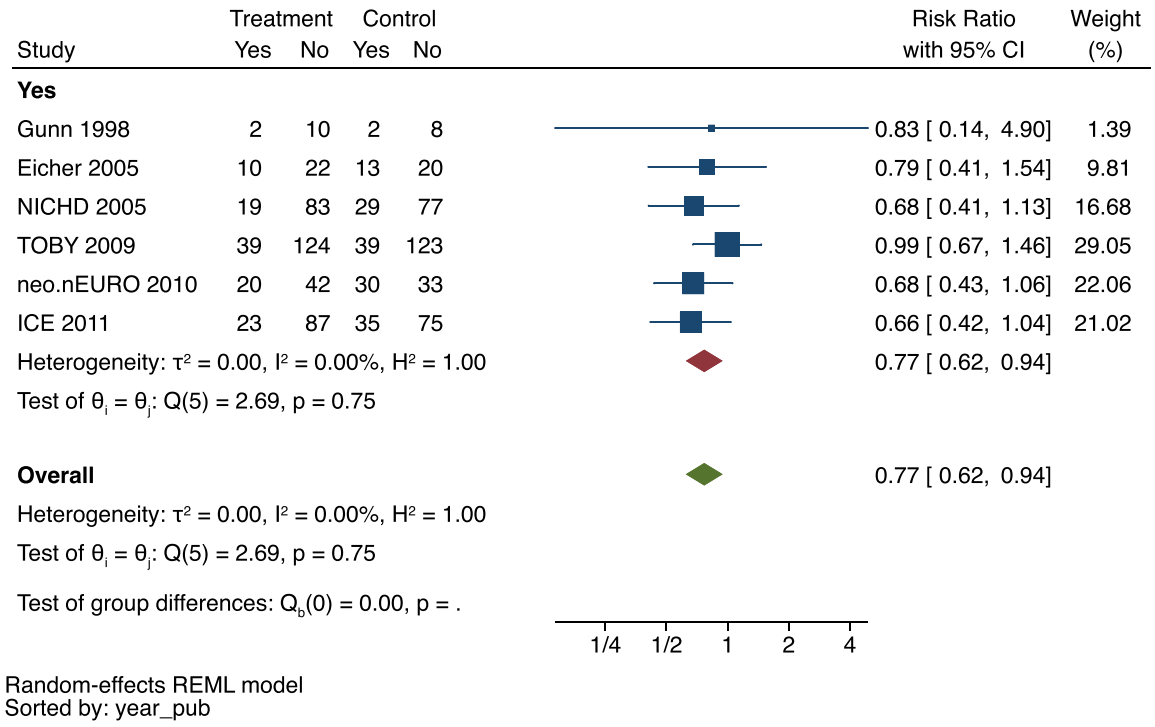

Fig. 2. (*continued*).

were at low risk of bias while two-thirds were at moderate and high risk of bias. Interestingly, pooled estimates from the trials at moderate and high risk of bias show a greater effect size (more benefit) of therapeutic hypothermia for the outcomes of neonatal mortality, disability, and the composite outcome of death or disability at 18–24 months of age. Although this is not unexpected for subjective or patient-reported outcomes, such an effect on an outcome like mortality is perplexing.

An important observation from the above-mentioned systematic review is a high degree of statistical heterogeneity observed for most outcomes reported from the LMIC. Many reasons can explain this heterogeneity. First, LMIC itself is a broad category that clubs widely varying types of health facilities - ranging from the pediatric ward in a sub-district hospital with poor infrastructure to a well-equipped neonatal intensive care unit in an apex tertiary care institute. Studies from the latter would resemble the studies from HIC more closely than the studies from truly resource-limited settings. Yet, making this distinction among different types of health facilities from LMIC is not easy for the authors of a systematic review who only have access to published study reports. Second, an important predictor of the outcome in sick neonates is the need for transporting from one to another health facility. Such neonates called 'extramural' or 'outborn' neonates have a higher risk of adverse outcomes than 'intramural' or 'inborn' neonates because of ongoing respiratory or circulatory compromise and a higher risk of uncontrolled temperature fluctuations during the transport. Varying proportions of extramural neonates in different studies can explain some of the heterogeneity observed in the outcomes. Third, birth asphyxia itself is a condition with varying severity. Identifying candidates for therapeutic hypothermia can be based on objective (e.g., cord pH, aEEG) or subjective (e.g., history of delayed cry at birth, Apgar score) criteria. Most trials from LMIC have relied on subjective criteria to identify candidates for therapeutic hypothermia. Administration of therapeutic hypothermia to neonates without significant birth asphyxia can increase the risk of mortality. In addition, combined with a small sample size, enrolling a heterogeneous group of neonates in a trial can lead to an unrecognizable imbalance of prognosis in the study groups. Fourth, healthcare workers may have varying skills or application of skills for the identification of HIE, a necessary criterion to administer therapeutic hypothermia. Misclassification of HIE can be associated with loss of efficacy or increased adverse events with therapeutic hypothermia. Next, we examine the role of some of the above-mentioned factors in accounting for heterogeneity in the outcomes of trials reported from HIC and LMIC/UMIC settings. The role of the following prognostic factors is examined: cord pH, the proportion of extramural neonates, the proportion of neonates with severe HIE, and admission temperature. Ideally, the role of these factors is examined in an individual patient data meta-analysis and meta-regression. However as individual patient data is not available, we examine the role of these factors by sub-group analysis of studies in which these variables have been reported. Further, as most studies from LMIC have reported only short-term outcomes, we assess the impact of these factors only on neonatal death before discharge from the hospital.

1. **Cord** pH**:** Based on this variable, the studies can be divided into three categories: mean cord pH of enrolled neonates <7.0, mean cord pH of enrolled neonates >7.0, and cord pH not reported. When meta-analysis is restricted to studies that have reported a mean cord pH < 7.0 in the enrolled neonates,[9–12] studies from LMIC and HIC have a similar pooled risk ratio with a significant reduction in the incidence of death before discharge (Fig. 1). Three studies, all from LMIC, included neonates that had a mean cord pH of 7.0 or more.[13–15] Due to the small sample size and low event rate (probably because babies were less severely asphyxiated), the pooled effect size showed a lack of significant effect and a wide CI. One study from HIC[16] and eight from LMIC[4,8,17–22] did not report cord pH of included neonates (the HELIX trial is included as a study in which cord pH is not reported as it was available in only about 11 % of enrolled neonates). As evident from the forest plot and accompanying I2 value, substantial heterogeneity was observed in the event rate.
2. **Extramural neonates:** Six studies were conducted only on intramural neonates.[8,11,12,14,15,19] Of these five were conducted in a single institute in India.[8,11,12,14,15] The pooled effect size shows a significant reduction in death before discharge (RR: 0.66; 0.49 to 0.89,

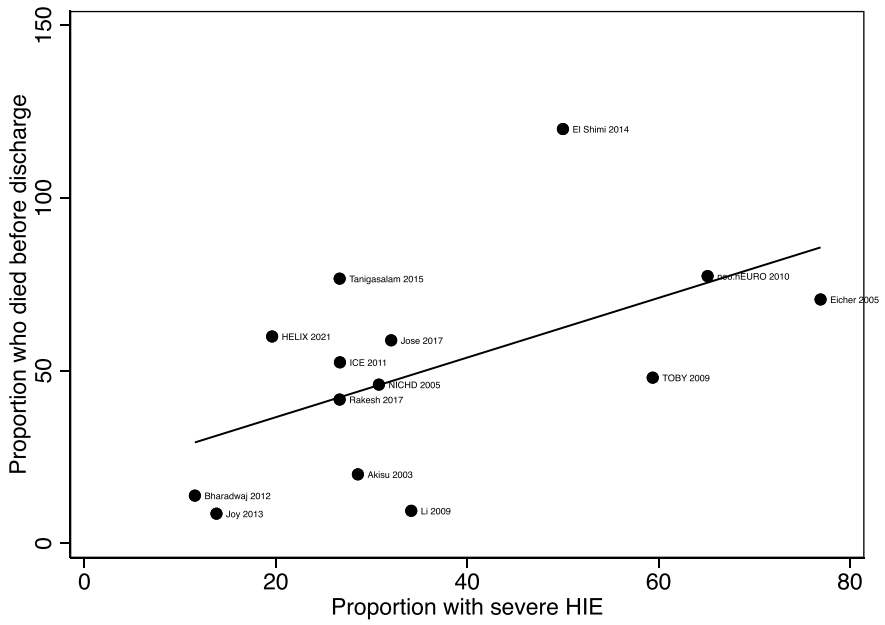

Fig. 3. A scatter plot depicting the correlation between the proportion of enrolled neonates with severe hypoxic-ischemic encephalopathy and death before discharge.

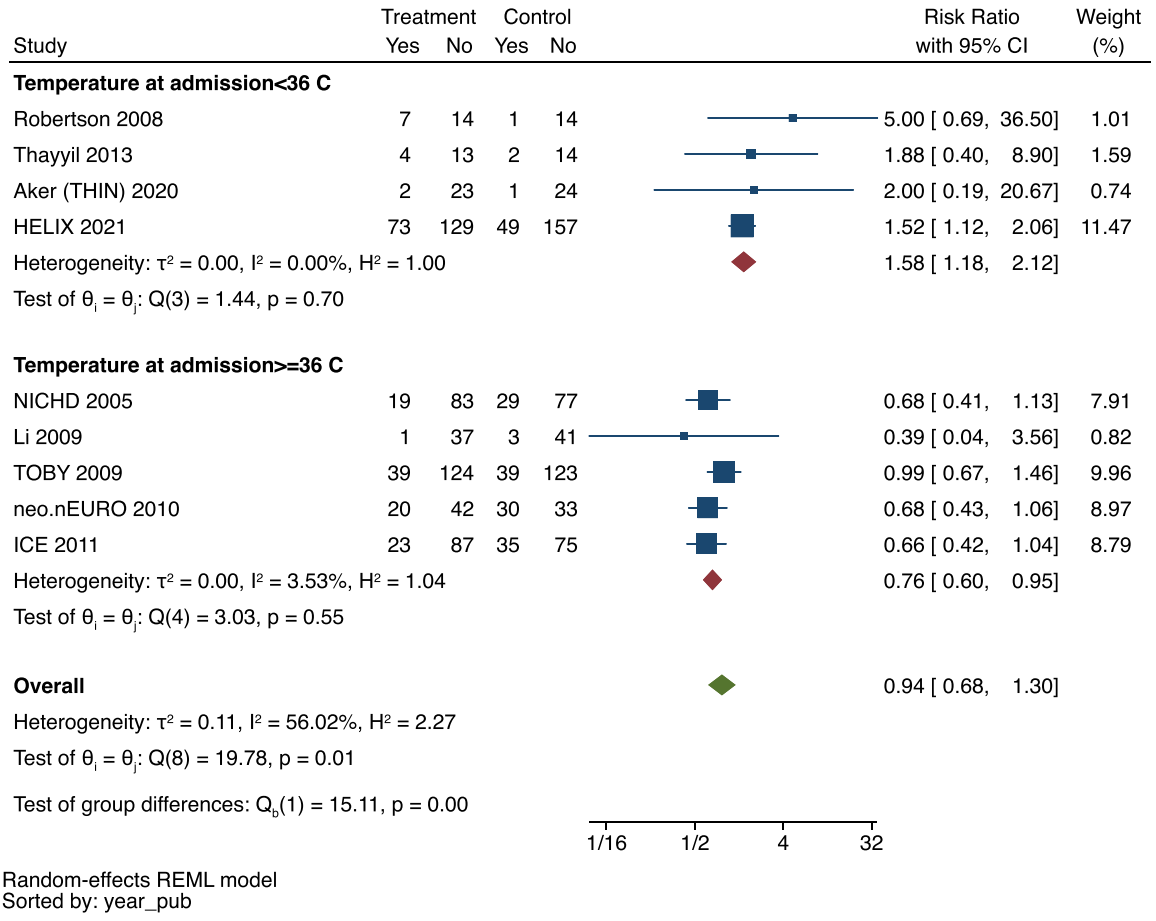

Fig. 4. Forest plot depicting the effect of therapeutic hypothermia on death before discharge with subgroup analysis based on admission temperature.

Fig. 2a). Six studies from HIC included extramural neonates and the pooled effect size is similar to that observed with overall analysis (Fig. 2b).[16,23–27] Four studies from LMIC enrolled extramural neonates.[4,9,10,18] The outcome shows significant heterogeneity and a non-significant pooled effect size (RR: 0.96; 0.47 to 1.96, I2 = 69.3 %).

3. **Severity of HIE:** An analysis of the correlation between the proportion of neonates with severe HIE (average of the two groups) and the proportion of neonates (average of the two groups) who died before discharge in each group was performed (Fig. 3). A linear correlation can be observed between the proportion of neonates with severe HIE and the proportion of neonates who died.
4. **Admission temperature:** The effect of admission temperature on the outcome can be investigated by dividing the studies into two groups: mean temperature at admission being above or below 36.0 °C in the intervention group. A total of nine studies reported mean admission temperature. In four studies, all from LMIC, the admission temperature in the intervention group was less than 36 °C.[4,9,19,21] The pooled estimate shows a significant increase in the risk of death before discharge (RR: 1.58; 1.18 to 2.12). It may however be noted that a single trial contributed to 92.6 % of the pooled data.[4] In five studies, four from HIC and one from LMIC, the admission temperature in the intervention group was >36 °C.[16,18,25–27] The pooled estimate shows a significant decrease in the risk of death before discharge (Fig. 4, RR: 0.76; 0.60 to 0.95, I2 = 3.5 %). An increase in mortality with hypothermia may be caused by the following two reasons: the direct effect of hypothermia on mortality and hypothermia being an indirect marker of more severe birth asphyxia and lower basal metabolic rate.

Reasonable doubts have been raised on the efficacy of therapeutic hypothermia in neonates born in LMIC. However, it is evident from the analysis given above that the effect of therapeutic hypothermia may be influenced by many factors that are more likely to operate in resource-limited settings. The absence of objective evidence of acute birth asphyxia (cord pH), suboptimal care during transport of extramural neonates leading to ongoing tissue injury, uncontrolled hypothermia before admission to a neonatal unit, and severity of HIE are some of these factors. The biology of brain injury due to hypoxia-ischemia remains similar whether a neonate is born in an HIC or an LMIC. Previous claims about the possible interaction between asphyxia and co-existing perinatal infection leading to poor effect of therapeutic hypothermia have not been found to be true.[4] It is very likely that when selected rigorously taking care of the above-mentioned factors, therapeutic hypothermia may work even in LMIC. However, till this is proven in a sufficiently power randomized controlled trial, newborn care practitioners need to be more careful in the use of therapeutic hypothermia.[28]

Ethical approval statement

Ethical approval was not needed as this article is secondary research on published and deidentified primary research.

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Author statement

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Author contribution statement

DC planned the study, conducted the literature search and analysis, and wrote the first draft of the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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