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Neurodevelopmental outcomes of mild neonatal encephalopathy treated with therapeutic hypothermia

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Abstract

Background Recent clinical practice has increasingly applied therapeutic hypothermia (TH) to mild neonatal encephalopathy (NE) to avoid missing the optimal treatment window. This study evaluates the efficacy and safety of TH for improving neurodevelopmental outcomes in infants with mild NE.

Methods This study comprised a retrospective cohort (2020-2022) and a prospective cohort (2022-2023). Neonates with mild NE were divided into TH and non-TH groups. The general condition, short-term and 2-year neurodevelopmental outcomes, incidence of adverse events, and hospitalization costs of the two groups were compared.

Results This study included 220 patients with mild NE: 147 in TH group and 73 in non-TH group. Compared with the non-TH group, TH group exhibited higher rates of vaginal delivery and lower umbilical cord blood pH (both $P<0.05$). The TH group experienced delayed first feeding, higher rates of arrhythmia or circulatory instability requiring inotropes/vasopressor support and greater hospitalization costs (all $P<0.05$).

As for the neurodevelopmental outcomes, compared with the non-TH group, the TH group exhibited a higher proportion of abnormal aEEG within 24 hours ($P=0.011$) but no significant differences emerged at 24-48 hours of age ($P=0.064$), 48-72 hours ($P=1.000$) or 4-7 days of age ($P=0.340$). There were no statistical significant differences in total MRI scores within 1-2 weeks of age (1 (0, 3) vs. 1.5 (0, 6), $P=0.362$), test of infant motor performance (TIMP) scores within 1-2 weeks

(-1.00 (-1.36, -0.72) vs. -1.20 (-1.46, -0.86), *P*=0.197) or at 4 months of age (-0.63 (-1.00, -0.31) vs. -0.63 (-0.90, -0.50), *P*=0.917), or 2-year-old Griffith scores between the TH and non-TH groups (all *P*>0.05). In telephone scripted interviews at 2-year-old, a total of 46 (20.9%) mild NE had abnormal outcomes: 25 (17.0%) in TH group, 21 (28.8%) in non-TH group (*P*=0.053). Logistic regression analysis revealed no independent association between TH and MRI abnormalities (OR=0.71, 95%CI: 0.25-1.86, *P*=0.493).

Conclusion Mild NE may leave neurological sequelae. TH did not significantly improve neurodevelopmental outcomes in mild NE cases, and may introduce adverse effects and increase hospitalization costs. Clinicians should exercise caution in applying TH for mild NE until robust evidence confirms its efficacy.

Trial registration: Chinese clinical trial registry, ChiCTR2200065304. Registered 1 November 2022 - Retrospectively registered, https://www.chictr.org.cn/index.html

Keywords: neonate, mild neonatal encephalopathy, therapeutic hypothermia, neurodevelopmental outcome.

Background

Therapeutic hypothermia (TH) is now part of standard care for moderate to severe neonatal encephalopathy (NE) worldwide [1-3], and remains the only proven neuroprotective treatment for NE. Multiple large-scale randomized controlled trials (RCTs) have demonstrated that TH could improve survival rates and reduce the incidence risk of long-term disabilities from infancy to mid-childhood in neonates with moderate to severe NE [4,5]. Notably, mild NE, accounting for approximately 50% of all NE cases, are not included in the initial RCTs due to perceived low risk of adverse outcomes and so do not meet current criteria for TH treatment. However, recent studies have

challenged this perception, which reported higher-than-expected rates of potential disabilities including learning and neuropsychological difficulties, autism, epilepsy, visual and sensory loss after mild NE [6-8]. There is already therapeutic creep, with many centers treating mild NE with TH despite the limited evidence for its efficacy and safety [9]. For instance, reports from the Canadian Neonatal Network [10], California Perinatal Transport System [11], and New South Wales in Australia [12] indicated that approximately 80% of mild NE cases were subjected to TH therapy.

Currently, there remains a paucity of high-quality studies evaluating the efficacy and safety of TH in mild NE, with only two ongoing clinical trials identified [13,14]. Therefore, this cohort study with a combined retrospective and prospective design aims to assess the effectiveness of TH in improving both short-term and two-year neurodevelopmental outcomes in mild NE cases, as well as the adverse reactions during TH treatment and hospitalization costs. The results could provide evidence-based support for refining the indications for TH in mild NE and optimizing healthcare resource allocation.

Methods

Study design and participants

This study employed a combined retrospective (January 2020 to August 2022) and prospective (September 2022 to May 2023) cohort design. The Department of Neonatology of Children's Hospital of Chongqing Medical University (CHCMU) is the largest neonatal referral center in Southwest China with 320 beds and approximately 8,000-10,000 annual discharges. The study was approved by the Institutional Review Board of CHCMU (Approval No. 2022-317). The requirement for informed consent was waived by the committee for the retrospective part, while signed informed consent was obtained from legal guardians of prospectively enrolled participants.

The inclusion criteria were the simultaneous fulfillment of conditions ①, ②, and ③. ① Gestational age at birth ≥35 weeks and birth weight ≥1800 g. ② Evidence of hypoxia-ischemia in the fetus or the successfully resuscitated neonates, meeting any one of the following four criteria: evidence of fetal distress such as uterine and/or placental rupture, placental abruption, umbilical cord prolapse, or severe fetal heart rate abnormalities (e.g., abnormal variability or late decelerations); 5-minute Apgar score ≤5; cord/arterial/venous/capillary blood gas analysis within 1 hour after birth showing pH ≤7.10 or base excess ≥ -12 mmol/L; requirement for positive pressure ventilation for >10 minutes after birth. ③ Neurological assessment indicated mild encephalopathy [1,2]. The modified Sarnat score within 6 hours after birth was used to diagnose mild NE, defined as: the presence of two or more abnormalities in any of the six categories, but fewer than three moderate/severe abnormalities as required to meet the definition of moderate to severe NE (Supplementary Table 1) [13,15,16]. Although the definitions of mild NE vary [15], studies have shown that the rate and severity of brain injury did not vary significantly on brain MRI when applied different definitions of mild NE currently being used [17]. Neonates with encephalopathy definitively attributed to non-hypoxic-ischemic etiologies, including severe intracranial hemorrhage, central nervous system infections, congenital neuromuscular disorders, major congenital malformations, or inherited metabolic disorders, were excluded.

The research retrospectively enrolled neonates diagnosed with mild NE admitted between January 2020 and August 2022, and they were stratified into TH and non-TH groups based on treatment allocation. Furthermore, from September 2022 to May 2023, eligible neonates with mild NE were prospectively recruited. The decision to administer TH was made through shared decision-making incorporating clinical recommendations and parental preferences.

Study implementation

According to TH protocol [1,2], TH was carried on the whole body of neonates with the Blanketrol® III temperature management device (Cincinnati, USA) or Comen P6 medical temperature-control instrument (Shenzhen, China) based on routine support for the symptomatic treatment. A rectal temperature of 33.5 ± 0.5℃ was maintained for the neonates in the TH group. Cooling was started within 6 hours of delivery and maintained for a period of 72 h. After the cooling phase neonates were slowly rewarmed within 10-12h (0.25-0.3℃/h). For the patients included in the non-TH group, routine supportive care was given, including thermal management, monitoring, and symptomatic treatment.

Magnetic resonance imaging (MRI) was performed on a 1.5-T magnet (GE Healthcare, Chicago, Illinois). Standard MRI protocol included axial T1-weighted images, T2-weighted images, and diffusion weighted imaging (DWI). Magnetic resonance spectroscopy (MRS) was not performed in our study due to the examination costs and time reasons. Brain MRIs were assessed independently by 2 experienced pediatric radiologist blinded to patient outcomes using Weeke scores, the total score was calculated by adding the 4 subscores (grey matter + white matter/cortical + cerebellum + additional; maximum score, 55) [18]. In each subitem, higher appointed scores indicated more extensive injury.

All neurodevelopmental assessments were conducted by certified examiners with extensive clinical experience.

Data collection and outcome measures

We collected demographic and perinatal information of neonates, maternal high risk pregnancy factors, clinical manifestations, the worst laboratory results of important systems within the first week of age, other supportive symptomatic treatments, as well as clinical outcomes, hospitalization duration and costs during neonatal intensive care unit (NICU) stay.

The primary outcomes of this study included short-term and 2-year neurodevelopmental outcomes. The measures for short-term neurological outcome included the worst NE grading based on modified Sarnat score within 6-72 hours of age, hearing screening results during NICU stay, amplitude-integrated electroencephalography (aEEG) grading (Supplementary Table 2) [19] within the first week of age, test of infant motor performance (TIMP) scores within 1-2 weeks and at 4 months of age, brain MRI Weeke scores within 1-2 weeks of age.

At the 2-year follow-up stage, standard neurodevelopmental assessment was performed using the Griffiths Development Scales-Chinese Edition (GDS-C), with the domain F (practical reasoning) excluded from evaluation as this ability remained underdeveloped in most children under 2 years of age. Meanwhile, standardized telephone interview questionnaires were administered for neurodevelopmental screening, with inquiries covering motor or language developmental delays, individual-social interaction difficulties, seizures, diagnosis of cerebral palsy (CP), receiving rehabilitation treatment, death, hearing loss, or blindness.

Statistical analysis

All analyses were conducted using SPSS 25.0 (IBM, Armonk, NY, USA). The continuous data was tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed continuous data were presented as mean ± *SD* and analyzed using Student's *t*-test; otherwise, the data were presented as median (*IQR)* and analyzed using the Mann-Whitney *U*-test. Categorical data were presented as *n* (%) and analyzed using the chi-squared test or Fisher's exact test. Univariable and multivariable logistic regression analyses were performed to identify the factors associated with MRI abnormalities as the dependent variable. Variables with $P<0.05$ in the univariable analyses were included in the multivariable analysis. The results were presented as odds ratio (OR) and confidence intervals (CIs). Two-sided $P<0.05$ were considered statistically significant.

Results

A total of 220 patients were enrolled in this study, comprising 135 neonates from a retrospective cohort and 85 from a prospective cohort. Among these 220 patients, 147 were subjected to TH (TH group), while 73 did not receive TH (non-TH group). The detailed process of follow-up is illustrated in Figure 1.

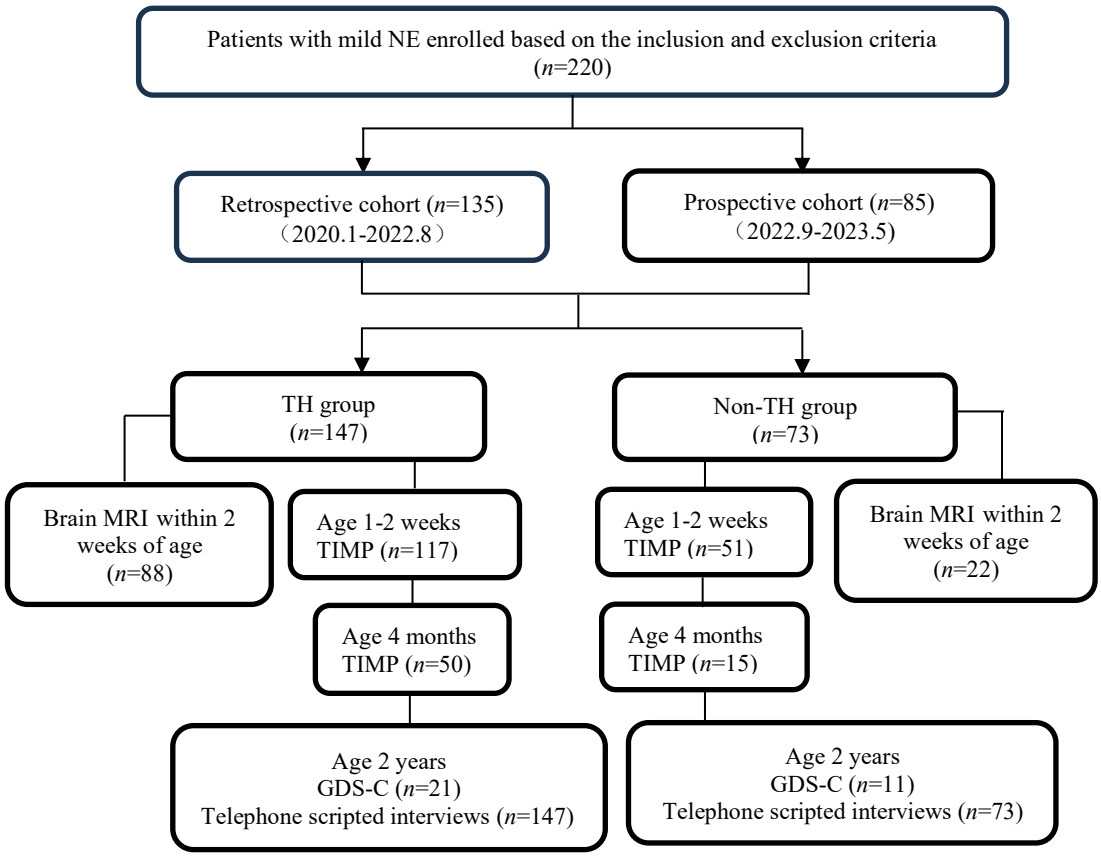


Figure 1 Flowchart for follow-up of mild neonatal encephalopathy cases

Characteristics of the patients

Compared with the non-TH group, the TH group exhibited higher rates of vaginal delivery and lower umbilical cord blood pH (P=0.001, P=0.032). Intracranial pressure-lowering medications (mannitol or furosemide) and sedatives (phenobarbital or midazolam) were administered more

frequently in the TH group (both P=0.000). There were no significant differences in the other perinatal and maternal characteristics between the TH and non-TH groups (all P>0.05) (Table 1).

Clinical outcomes and Health economics indicators during hospitalization

Compared with the non-TH group, the TH group exhibited delayed first feeding (P=0.007), shorter intubation duration (P=0.015), increased incidence of arrhythmia or circulatory instability requiring inotropes/vasopressor support (P=0.001). There were no significant differences in the functions of other organs except for creatinine, discharge status, or NICU hospitalization days between the two groups (all P>0.05). The median hospitalization costs of the TH group were significantly higher than non-TH group (P=0.000) (Table 2).

A total of 49 (22.3%) neonates with mild NE were discharged against medical advice. The most common adverse conditions involved abnormal neurological manifestations or examinations requiring continued treatment, feeding difficulties, supplemental oxygen dependence, or active infections.

Neurodevelopmental outcomes of mild NE

Compared with the non-TH group, the TH group exhibited a higher proportion of abnormal aEEG within 24 hours of age (P=0.011), but no significant differences emerged at 24-48 hours of age (P=0.064), 48-72 hours (P=1.000) or 4-7 days of age (P=0.340). Fewer infants progressed to moderate NE at 6-72 hours of age in the TH-group (P=0.042). There were no statistically significant differences in hearing screening results, TIMP scores within 1-2 weeks (-1.00 (-1.36, -0.72) vs. -1.20 (-1.46, -0.86)) or at 4 months of age (-0.63 (-1.00, -0.31) vs. -0.63 (-0.90, -0.50)), MRI total Weeke score (1 (0, 3) vs. 1.5 (0, 6)) or 4 subscores within 1-2 weeks of age, or 2-year-old GDS-C scores between the two groups (all P>0.05), despite the TH group showed marginally better original data (Table 3). The specific Weeke scoring items of brain MRI were shown in Table 4.

Telephone scripted interviews revealed abnormal neurodevelopmental outcomes at 2 years of age in 46 (20.9%) mild NE cases: 25 (17.0%) in the TH group and 21 (28.7%) in the non-TH group (*P*=0.053). The TH group exhibited 15 (10.2%) motor development delays, 17 (11.6%) language delays, 5 (3.4%) rehabilitation treatments, and 1 epilepsy diagnosis, whereas the non-TH group showed 14 (19.2%) motor delays, 15 (20.5%) language delays, 4 (5.5%) rehabilitation treatments, 1 epilepsy case, 1 CP diagnosis, and 2 suspected attention deficit hyperactivity disorder (ADHD) cases. No death, hearing loss, or blindness in the included cases.

Multivariable analysis for abnormal MRI

We intended to explore early warning indicators for adverse outcomes through regression analysis. Given the limited standard neurodevelopmental assessment data at 2-year follow-up and the subjective nature of telephone interviews, we selected MRI as the objective short-term outcome measure. No statistically significant differences emerged in clinical characteristics between neonates who underwent MRI in the TH and non-TH groups (Supplementary Table 3). Logistic regression analysis revealed that both gestational age (OR=0.73, 95% CI: 0.54-0.97, *P*=0.036) and intrauterine distress (OR=0.42, 95% CI: 0.19-0.94, *P*=0.036) were independently associated with MRI abnormalities, whereas TH was not (OR=0.71, 95%CI: 0.25-1.86, *P*=0.493) (Table 5).

Discussion

The development of NE is a dynamic process, with its severity potentially progressing from mild to moderate or even severe within days after birth [20,21]. Standard TH requires moderate to severe grading of NE and treatment initiation decisions within the 6-hour post-birth time window [1-3]. In recent years, given the potential risk of neurological sequelae in mild NE, clinical practice has gradually expanded TH indications to mild NE and even other patient populations to avoid missing the optimal treatment window [22]. However, high-quality evidence supporting the efficacy and

safety of TH in mild NE populations remains lacking. This combined retrospective and prospective cohort study revealed that 20.9% of infants with mild NE experienced adverse outcomes at 2 years of age. TH did not significantly improve short-term or 2-year neurodevelopmental outcomes of mild NE, while potentially introducing adverse effects and increasing hospitalization costs. Despite marginally more severe perinatal hypoxia and better original data of neurodevelopmental outcomes in the TH group, clinicians should exercise caution in applying TH for mild NE until robust evidence confirms its efficacy.

Clinically, neurodevelopmental assessments combined with neuroelectrophysiological monitoring and neuroimaging constitute a standard follow-up protocol for NE [2]. Among the neurological examinations, EEG/aEEG and MRI respectively play pivotal roles in the detection of cerebral functional and structural abnormalities. Furthermore, substantial evidence has demonstrated their high sensitivity and specificity in predicting long-term neurodevelopmental outcomes in NE [23,24]. As a bedside and simplified method of continuous brain monitoring, aEEG has been increasingly used to identify seizures and potential candidates for TH after a perinatal asphyxia insult. Several researches have demonstrated that the time required for aEEG normalization in asphyxiated infants effectively predicts neurodevelopmental outcomes. Normalization within 48 hours after birth correlates with favorable long-term neurological prognosis [24-26]. In cold environments, sleep quality deteriorates due to the weakened thermoregulatory function during quiet sleep phases. During TH treatment, the body actively avoids entering quiet sleep stages to circumvent physiological temperature reduction, which may cause delayed emergence of sleep-wake cycles (SWC) [26]. Studies have demonstrated that TH reduced the positive predictive value of abnormal aEEG patterns during the first 24-26 hours of age for adverse neurological outcomes in asphyxiated infants (59%) compared to non-TH group (84%), indicating that TH may alter early aEEG predictive accuracy [25, 26]. Furthermore, the prolonged half-life of sedative medications in TH-treated infants

may increase serum drug concentrations, potentially suppressing aEEG activity and delaying the emergence of normal waveforms or SWC [27]. Consequently, in this study, the higher proportion of abnormal aEEG patterns within 24 hours post-birth observed in the TH group may be resulted from the marginally more severe hypoxic insult, direct physiological effects of TH, or medication effects (particularly more frequent sedative administration). However, the proportion of abnormal aEEG findings beyond 24 hours of age in the TH group did not differ significantly from the non-TH group, suggesting that TH provide no measurable improvement in short-term neurological functional outcomes for mild NE.

MRI has been widely used to identify the structural brain injury pattern in patients with NE. Several MRI grading systems for brain injury after perinatal asphyxia have been developed and validated [28]. The Weeke score serves as a comprehensive brain MRI assessment system that evaluates all critical brain regions in neonates with perinatal asphyxia [18], enabling sensitive detection of subtle injuries [29] and greater prediction accuracy of long-term neurodevelopmental outcomes [28,30] in mild NE. Research by Andorka C et al. demonstrated that both the total score of the Weeke scoring system and gray matter injury grading were independent predictors of neurodevelopmental outcomes at 2 years of age [30]. In this study, although the original data revealed marginally lower total scores, reduced proportions of abnormalities in total items, grey matter subitem, white matter/cortex subitem and additional subitem in the TH group compared to the non-TH group, no statistically significant differences emerged between the two groups in total scores or any of the four subscores. Meanwhile, logistic regression analysis showed that TH was not independently correlate with MRI abnormalities. These observations suggested insufficient evidence to support the efficacy of TH in enhancing short-term neurological outcomes for neonates with mild NE. Studies had revealed that posterior limb of the internal capsule (PLIC) signal abnormalities were significantly associated with adverse outcomes [31,32]. In this study, the TH group exhibited a higher

incidence of PLIC abnormalities than the non-TH group, likely due to the more severe hypoxic insult prolonged secondary injury in PLIC axonal fiber tracts through wallerian degeneration [33]. In addition, gray matter injury prevalence exceeded white matter injury in both groups, indicating that infants diagnosed with mild NE within 6 hours after birth may still sustain severe brain injury. These may explain the remaining neurological problems such as motor and language development delays, cerebral palsy and seizures during 2-year follow-up.

Actually, multiple studies and meta-analyses have demonstrated that infants with mild NE face risks of adverse neurodevelopmental outcomes during long-term follow-up [6-8,15]. The meta-analysis by Kariholu U et al. [34] demonstrated that 20% of infants with mild NE developed adverse neurodevelopmental outcomes during follow-up from 10 days to 42 months. The incidence of neurological dysfunction increased from 20% at 12 months to 24% at 3 years of age as follow-up duration extended [35]. This increase is likely related to the improved diagnostic ability to detect academic delays and subtle cognitive problems at the older ages, highlighting the need for long-term follow-up of this population. In this study, the telephone scripted interviews revealed 20.9% incidence of neurodevelopmental abnormalities at 2-year follow-up in neonates with mild NE, including motor/language developmental delay, receipt of rehabilitation therapy, diagnosis of CP, and suspected ADHD. In addition, both the TH and non-TH groups exhibited the highest proportion of language developmental delay, consistent with the finding from the PRIME multicenter cohort study, which demonstrated that 40% of infants with mild NE scored <85 on the Bayley-III scales with predominant impairment in the language domain [15]. Lee BL et al. proposed that early childhood language developmental disorders might correlate with cognitive decline during adolescence [36], necessitating extended follow-up periods. Current literature reports on the effectiveness of TH in improving mild NE outcomes remain limited and inconsistent. Studies by Goswami IR et al. [10], Wang Z et al. [37], and Montaldo P et al. [38] suggested that TH may confer neuroprotective effects in neonates with mild

NE. However, a recent RCT also by Montaldo P et al. demonstrated that whole-body TH did not improve cerebral MR biomarkers in mild NE [39]. Another study focusing on mild NE cases that progressed to moderate NE revealed no significant differences in neurodevelopmental outcomes at 18-24 months of age between the TH and non-TH groups [40]. Consistent with the latter, our study detected no statistically significant differences in TIMP scores at 4 months of age or GDS-C scores at 2 years of age between the two groups, despite more severe hypoxia and marginally better original neurodevelopmental data in the TH group. These findings suggest that TH did not significantly improve long-term neurodevelopmental outcomes of mild NE.

In addition, TH is not a completely non-invasive intervention. It predisposes neonates to side effects such as arrhythmias, thrombocytopenia, coagulation dysfunction, and subcutaneous fat necrosis [41]. Moreover, TH leads to mother-infant separation, intensive care monitoring, concomitant invasive procedures and frequently sedative therapy [10]. This study showed increased hospitalization costs and higher incidence of potential adverse reactions in the TH group, including delayed first feeding, arrhythmia or hemodynamic instability. Collectively, clinicians should exercise caution in applying TH for mild NE until robust evidence confirms its efficacy and safety.

Our data demonstrated the spectrum of brain injury and disease severity within mild NE, early biomarkers are needed to identify infants with mild NE at risk of of adverse outcomes [42]. Multivariate analysis in this study revealed that gestational age and intrauterine distress were independent factors associated with MRI abnormalities. Current studies have confirmed that gestational age correlated with brain injury severity [43,44], while intrauterine distress might cause varying degrees of neonatal brain injury through factors including hypoxia duration, intensity, and specific brain regions involved [44]. This study proposes that gestational age and intrauterine distress may serve as potential reference indicators of early individualized treatment strategies for mild NE, though this conclusion requires validation through futher studies.

This study benefits from a population-representative sample of neonates with mild NE admitted to tertiary NICU, along with prospectively collected data that enhances variable control. The relatively large dataset enables comprehensive evaluation of the efficacy and safety of TH in mild NE, incorporating both short-term outcomes and 2-year neurodevelopmental follow-up across electrophysiological, imaging, clinical, and socioeconomic domains. As current evidence remains insufficient to establish TH effects and safety in mild NE cases, this observational cohort design better addresses medical ethical considerations.

This study has limitations. First, the baseline of the enrolled patients were inconsistent, with more severe perinatal hypoxia in the TH group, which may affect the judgment of the results. Second, the dataset contained numerous missing values, as not all infants underwent aEEG, MRI, or TIMP assessments, and 2-year neurological examination results were especially sparse. Incorporating brainstem auditory evoked potentials (BAEP) and visual evoked potentials (VEP) as additional assessment metrics could have strengthened the analysis. Third, the follow-up duration proved insufficient, extending observations to school age or adolescence may reveal latent issues like learning disabilities, intellectual impairment, or emotional disturbances. Finally, initial MRI scans were not uniformly completed within the first postnatal week, despite the known pseudonormalization of DWI signals by approximately day 8 [45]. The absence of MRS examinations represents another constraint, as this modality could identify metabolic abnormalities in deep brain nuclei undetectable by conventional MRI [39].

Conclusions

In conclusion, mild NE may result in neurological sequelae. TH demonstrated no significant improvement in neurodevelopmental outcomes of mild NE, and may cause adverse effects and increase hospitalization costs. Current evidence remains insufficient, clinicians should exercise

caution in applying TH for mild NE until its efficacy is confirmed by standardized multicenter prospective cohort studies with consistent baselines and extended follow-up through school age or adolescence.

Abbreviations

ADHD: Attention deficit hyperactivity disorder

AEEG: Amplitude-integrated electroencephalography

BE: Base excess

CHCMU: Children's Hospital of Chongqing Medical University

CI: Confidence interval

CP: Cerebral palsy

CSVT: Cerebral sinovenous thrombosis

DWI: Diffusion weighted imaging

EEG: Electroencephalography

GDS-C: Griffiths development scales-Chinese edition

IQR: Inter-quantile range

IVH: Intraventricular hemorrhage

MRI: Magnetic Resonance Imaging

MRS: Magnetic resonance spectroscopy

NE: Neonatal encephalopathy

NICU: Neonatal intensive care unit

OR: Odds ratio

pH: Potential of hydrogen

PLIC: Posterior limb of the internal capsule

PWML: Punctate white matter lesions

RCTs: Randomized controlled trials

SD: Standard deviation

SDH: Subdural hemorrhage

SI: Signal intensity

SWC: Sleep-wake cycle

TH: Therapeutic hypothermia

TIMP: Test of infant motor performance

Declarations

Ethics approval and consent to participate: The Institutional Review Board of CHCMU approved the study (Approval No. 2022-317). The requirement for informed consent was waived by the committee for the retrospective part, while signed informed consent was obtained from legal guardians of prospectively enrolled participants.

Consent for publication: Not applicable, this manuscript does not contain data from any individual person.

Availability of data and materials: The datasets generated and/or analysed during the current study are not publicly available as they are part of ongoing research, but they are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: Xiaolu Liu conceptualized and designed this study, performed data collection, analysis and visualization, and contributed to writing the draft and revising the manuscript. Xiaoling Duan and Tingsong Li contributed to patients' follow up and data collection. Chunyan Liu, Xiaoli Li and Enmei Zhan contributed to the neurodevelopmental assessments and data collection. Ying Deng and Ye Xu contributed to assessing brain MRIs Weeke scores and data collection. Xianming Xu contributed to data analysis. Kun Feng contributed to data collection, analysis and revising the manuscript. Lingling Xiang contributed to designed this study and data collection. Ziyu Hua supervised the study design, acquired the funding, conceptualized this study, contributed to data analysis and revised the manuscript. All authors approved the final manuscript as submitted.

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