Original Paper

Neonatology

Neonatology 2018;114:341–347
DOI: 10.1159/000490721

Received: November 14, 2017
Accepted after revision: June 6, 2018
Published online: August 21, 2018

# Predictive Value of Thompson-Score for Long-Term Neurological and Cognitive Outcome in Term Newborns with Perinatal Asphyxia and Hypoxic-Ischemic Encephalopathy Undergoing Controlled Hypothermia Treatment

Marc R. Mendler[a] Ines Mendler[b] Mohammad A. Hassan[c] Benjamin Mayer[d] Harald Bode[e] Helmut D. Hummler[a, f]

[a]Division of Neonatology and Pediatric Critical Care, Department of Pediatrics and Adolescent Medicine, Ulm University, Ulm, Germany; [b]Department of Child and Adolescent Psychiatry and Psychotherapy, University Hospital Ulm, Ulm, Germany; [c]Department of Pediatrics, Sohag University, Sohag, Egypt; [d]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany; [e]Department of Pediatrics and Adolescent Medicine, Division of Social Pediatrics and Child Neurology, Ulm University, Ulm, Germany; [f]Department of Pediatrics, Division of Neonatology, Sidra Medical and Research Center, Doha, Qatar

**Keywords**
Hypothermia · Thompson-score · Perinatal asphyxia · Hypoxic-ischemic encephalopathy · Newborns · Outcome

**Abstract**
***Background:*** The so-called Thompson-score (TS) for newborns with hypoxic-ischemic encephalopathy (HIE) was developed before the introduction of controlled hypothermia as clinical routine. Information on the predictive value of TS in newborns undergoing therapeutic hypothermia to estimate long-term outcome is limited. ***Objectives:*** To determine the predictive value of TS to estimate long-term cognitive and neurological outcome in newborns with perinatal asphyxia treated with controlled hypothermia. ***Methods:*** Thirty-six term newborns with HIE undergoing controlled hypothermia were followed using Wechsler Preschool and Primary Scale of intelligence III test and standardized neurological examination. The primary outcome was survival without cognitive impairment, defined as an IQ ≥85. Secondary outcomes were motor outcomes, survival without relevant neurological impairment, death and epilepsy. ***Results:*** Follow-up was done in 33 out of 36 (91.6%) infants at 53 ± 12 months (mean ± SD). For all investigated parameters, a statistically significant relationship with peak TS was demonstrated. A one-point increase in peak TS indicated an OR (95% CI) of 1.5 (1.1–2.0, $p = 0.006$) for death or cognitive impairment, an OR (95% CI) of 2.2 (1.3–3.8, $p = 0.004$) for death or relevant neurologic impairment, an OR (95% CI) of 2.1 (1.3–3.5, $p = 0.005$) for death or epilepsy and an OR (95% CI) of 1.5 (1.1–2.1, $p = 0.02$) for death. Although the TS for newborns with adverse outcome (death or cognitive impair-



E-Mail karger@karger.com
www.karger.com/neo

Marc R. Mendler, MD
Division of Neonatology and Pediatric Critical Care
Department of Pediatrics and Adolescent Medicine
Ulm University, Eythstrasse 24, DE–89075 Ulm (Germany)
E-Mail marc.mendler@uniklinik-ulm.de

ment) compared to normal outcome tended to be higher (13 [4–16] vs. 9 [0–13], d1; 15 [5–19] vs. 9 [1–14], d2; 14 [5–21] vs. 8 [2–15], d3; median [range]), there was a considerable overlap during the first 3 days of life between both groups. ***Conclusions:*** The TS seems to be a prognostic tool for predicting the long-term outcome in asphyxiated term newborns undergoing controlled hypothermia after the third day of life. A higher score appears to be significantly associated with an adverse outcome. 

## Introduction

Perinatal asphyxia is associated with a high risk of death or permanent disability for the newborn infant. If hypoxic-ischemic encephalopathy (HIE) occurs, prediction of outcome is extremely important for further management and for parental counseling. Furthermore, decisions for the use of neuroprotective therapeutic interventions, such as the controlled hypothermia, and for neuro-developmental follow-up have to be made to use resources effectively for those neonates who need these interventions and for close follow-up. Many clinicians currently use the so-called Thompson-score (TS) in clinical routine to estimate clinically neuro-developmental outcome along with other indicators, such as EEG and/or MRI. The TS published by Thompson et al. [1] in 1997 is based on the longitudinal clinical assessment of 9 signs. Each sign is scored from 0 to 3 and the sum score for each day is calculated (Table 1). However, the TS was validated initially only with a small sample size of only 35 neonates who did not receive controlled hypothermia because this treatment option was not yet available. To our knowledge there is only one study evaluating the TS in neonates undergoing hypothermia. This study from Thorsen et al. [2] focused on short-term outcomes. Therefore, the aim of this study was to assess the predictive value of the TS for adverse cognitive and neurological outcome, epilepsy, and death in a cohort of newborns with HIE undergoing a standardized hypothermia treatment protocol.

## Methods

*Study Design*

The protocol was approved by the ethical review committee of the University of Ulm (No.300/13). This is a retrospective analysis of infants of ≥35 weeks' gestation, born between 04/2007 and 07/2011 with perinatal asphyxia and HIE treated in the perinatal center, University of Ulm, with controlled hypothermia and assessed with a minimum of one recorded TS after birth. Whole body hypothermia was used according to the study protocol of Shankaran et al. [3] using a cooling mattress and aiming for a rectal temperature of 33 to 34 °C for 72 h, followed by slow rewarming.

Infants with malformations or inborn errors of metabolism were excluded. After written parental consent was obtained, 1 child psychiatrist and 1 pediatrician performed all follow-up assessments in a standardized examination room to minimize potential bias from different environments. Associations between the peak value of TS and outcome variables were assessed.

The primary outcome for this study was survival without cognitive impairment defined as a general IQ ≥85. Secondary outcomes were survival without relevant neurological impairment, death and epilepsy. We defined different grades of adverse neurological outcome: normal or mild, moderate, and severe disability (see definition in online suppl. material; for all online suppl. material, see www.karger.com/doi/10.1159/000490721), with moderate and severe disability classified as "relevant."

A detailed psychometric assessment and a neurologic examination were performed with the children accompanied by at least one of the parents, unless this seemed undesirable during the testing process. For evaluation of the general cognitive performance, the Wechsler Preschool and Primary Scale of intelligence III (WPPSI-III) test, standardized for children in Germany (2009) was used. Results on this test include a general measure of IQ (the primary outcome) with quotients for verbal and nonverbal performance and processing speed. All results are expressed as an age-standardized score, with a population mean of 100 and a standard deviation of 15. To detect neurologic dysfunction and signs of cerebral palsy, a structured neurologic examination was performed by one of 2 investigators. Neuromotor function was assessed using the Gross Motor Function Classification System with scores on the assessments ranging from 1 to 5, with higher scores indicating greater impairment

*Statistical Analysis*

Descriptive analyses were conducted for all continuous variables using mean ± SD and median (interquartile range). Categorical variables were described using frequencies and percentages. For all outcomes variables, logistic regression models were applied to evaluate the prognostic impact of the maximal TS observed for each patient by means of OR and their 95% CI. Furthermore, standard measures of diagnostic test validity, such as sensitivity and specificity, were calculated for different cut-off levels of the TS. The optimal cut-off was selected by maximizing the Youden index [4]. The receiver operating characteristics curve was used for a graphical visualization of the diagnostic analyses. A $p < 0.05$ was considered statistically significant.

## Results

Our study included 36 infants with asphyxia/HIE treated with controlled hypothermia. Seven infants died and 3 infants were lost to follow-up. Demographic characteristics of the infants at the time of admission to our NICU are presented in Table 2. Primary outcome data were available for 33/36 (91.6%). The mean age at follow-

**Table 1.** Thompson-score

| Sign | Score | | | |
|---|---|---|---|---|
| | 0 | 1 | 2 | 3 |
| Tone | Normal | Hyper | Hypo | Flaccid |
| Level of consciousness | Normal | Hyper alert, stare | Lethargic | Comatose |
| Fits | None | Infrequent <3/day | Frequent >2/day | |
| Posture | Normal | Fisting, cycling | Strong, distal flexion | Decerebrate |
| Moro-reflex | Normal | Partial | Absent | |
| Grasp-reflex | Normal | Poor | Absent | |
| Suck-reflex | Normal | Poor | Absent | |
| Respiratory pattern | Normal | Hyperventilation | Brief apnoea | IPPV (apnoea) |
| Fontanelle | Normal | Full, not tense | Tense | |

up was 53 ± 12 months. Approximately two-thirds of the infants were male, 23 out of 33 (70%) were out born, and 20 out of 36 (61%) had a 10-min APGAR score ≤5.

Twenty-two infants could be assessed using the WPPSI-III test for the primary outcome (survival without cognitive impairment). For 1 infant, the test was incomplete because of poor cooperation. Four infants were unable to perform the test because of severe mental retardation or physical handicap. In those infants, the IQ-level was specified using criteria of ICD 10 classification and estimated to be less than 85 in the final analysis. Overall, there were 18 (55%) infants with an IQ ≥85. The mean IQ among surviving infants undergoing the WPPSI-III was 98.

Almost all surviving infants with a maximal TS ≤10 had a normal IQ and almost all infants who showed an impaired IQ (<85) had a TS ≥11; there was only 1 infant with an IQ of 81 and a TS <10. In contrast, there were 7 infants with a normal IQ with a TS between 11 and 15. Logistic regression analysis revealed an OR (95% CI) of 1.5 (1.1–2.0, $p = 0.006$), that is, a 1-unit increase in maximal TS was associated with a 1.5-fold increased probability of an adverse outcome. Regarding secondary outcomes, we observed 20 infants surviving without relevant neurological impairment with a maximal TS of ≤15. Six infants with TS between 11 and 21 had an adverse neurological outcome. The OR (95% CI) for an adverse neurological outcome associated with maximal TS was 2.2 (1.3–3.8, $p = 0.004$). Three survivors had epilepsy. They had a maximal TS of at least 13. Modeling the probability of death or being affected by epilepsy related to maximal TS was estimated as an OR (95% CI) of 2.1 (1.3–3.5, $p = 0.005$).

Seven infants had died, and all had a maximal TS of at least 15. The corresponding OR (95% CI) of maximal TS was 1.5 (1.1–2.1, $p = 0.02$). The receiver operating characteristic analysis for all outcome variables demonstrated a high prognostic accuracy of the maximal TS (Fig. 1). The optimal cut-off values of maximal TS for the 4 investigated outcomes ranged from 11 to 15, and a value of 15 seems to be a useful predictor. The corresponding sensitivities and specificities ranged from 60 to 94%. For cognitive outcome, 2 optimal cut-off values were identified (maximal TS equal to 11 and 15), where the lower one was associated with higher sensitivity and the higher one with higher specificity. Although the TS for infants with adverse outcome (death or adverse cognitive outcome as compared to normal survivors) tended to be higher (13 [4–16] vs. 9 [0–13], d1; 15 [5–19] vs. 9 [1–14], d2; 14 [5–21] vs. 8 [2–15], d3; median [range]), there was a considerable overlap during the first 3 days of life between both groups (Fig. 2). Furthermore, the TS for infants with ad-

**Table 2.** Patient demographics

| Total ($n = 33$) | Mean ± SD/*n* |
|---|---|
| Gestational age, weeks | 39.4±1.7 |
| Birth weight, g | 3,343±594 |
| Male gender, *n* (%) | 20/33 (61) |
| Apgar Score ≤5 at 10 min, *n* (%) | 20/32 (61) |
| Missing data, *n* | 1 |
| First rectal temperature in the NICU, °C | 35.0±1.8 |
| pH (birth, or within 1 h) | 6.89±0.2 |
| Worst base excess within 1 h, mmol/L | –20.5±4.2 |
| Missing data | 13 |
| Sarnat-Score/HIE, *n*/total, *n* (%) | |
| Mild, *n* | 0 |
| Moderate | 18/33 (55) |
| Severe | 15/33 (45) |
| Inborn, *n* (%) | 10/33 (30) |

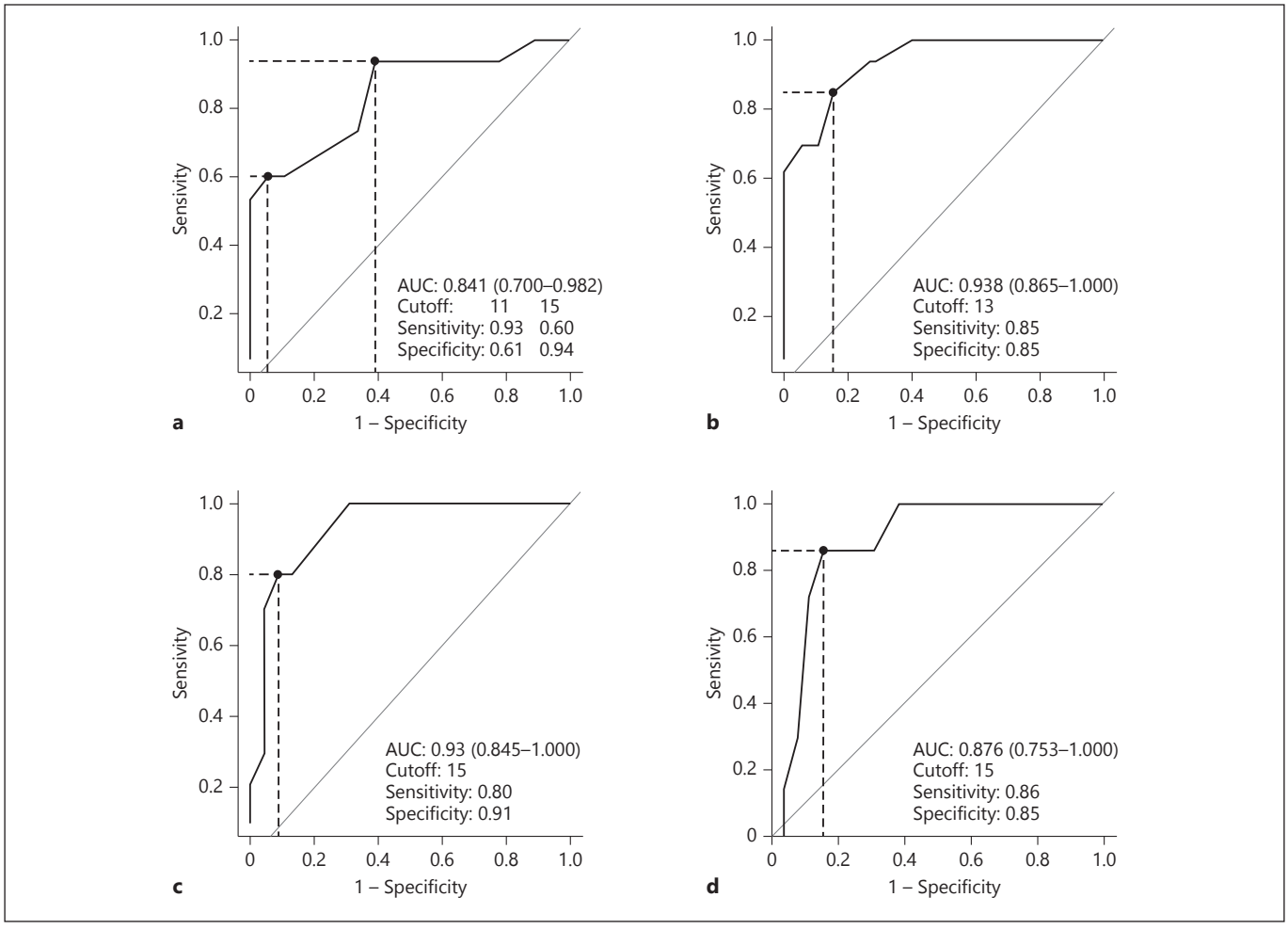
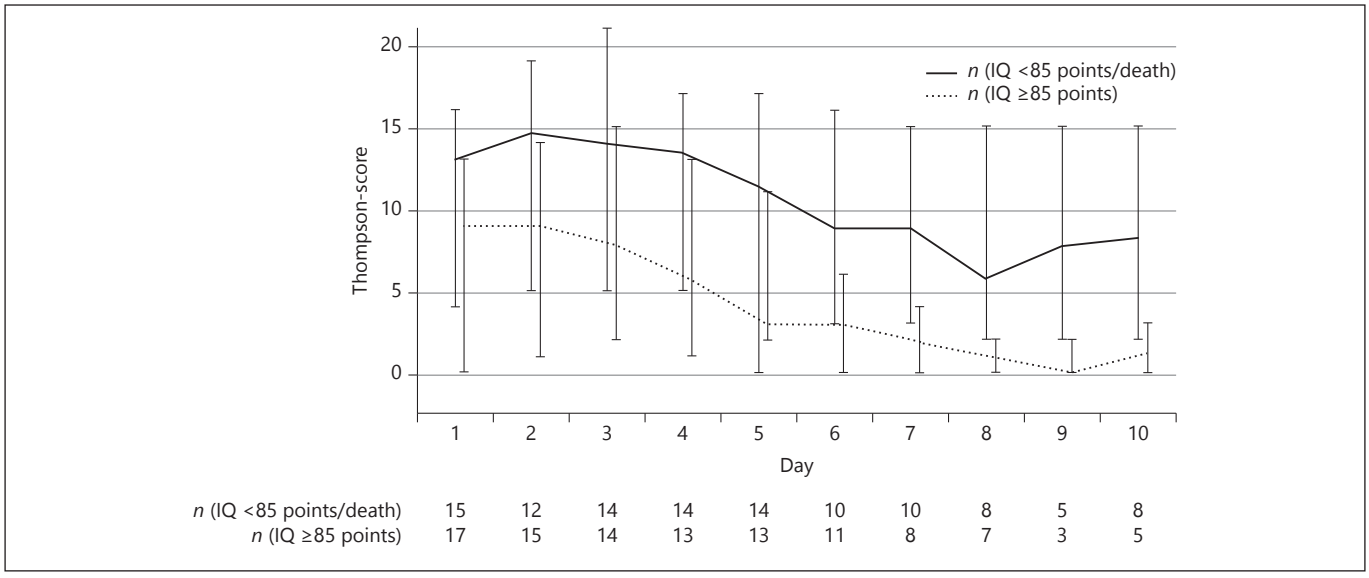



**Fig. 1.** ROC analysis for diagnostic accuracy of maximal Thompson-score for (**a**) surviving without cognitive impairment (alive and IQ ≥85), (**b**) surviving without relevant neurological impairment, (**c**) surviving without development of epilepsy, (**d**) surviving (outcome "death"); area under the ROC curve = AUC and corresponding 95% CI, cut-off: optimal cut-off for maximal Thompson-score relying on Youden index. AUC, area under curve.

verse outcome (death or relevant neurological impairment as compared to normal survivors) tended to be higher (13 [8–16] vs. 9 [0–13], d1; 15 [5–19] vs. 9 [1–14], d2; 15 [5–21] vs. 8 [2–15], d3; median [range]; Fig. 3).

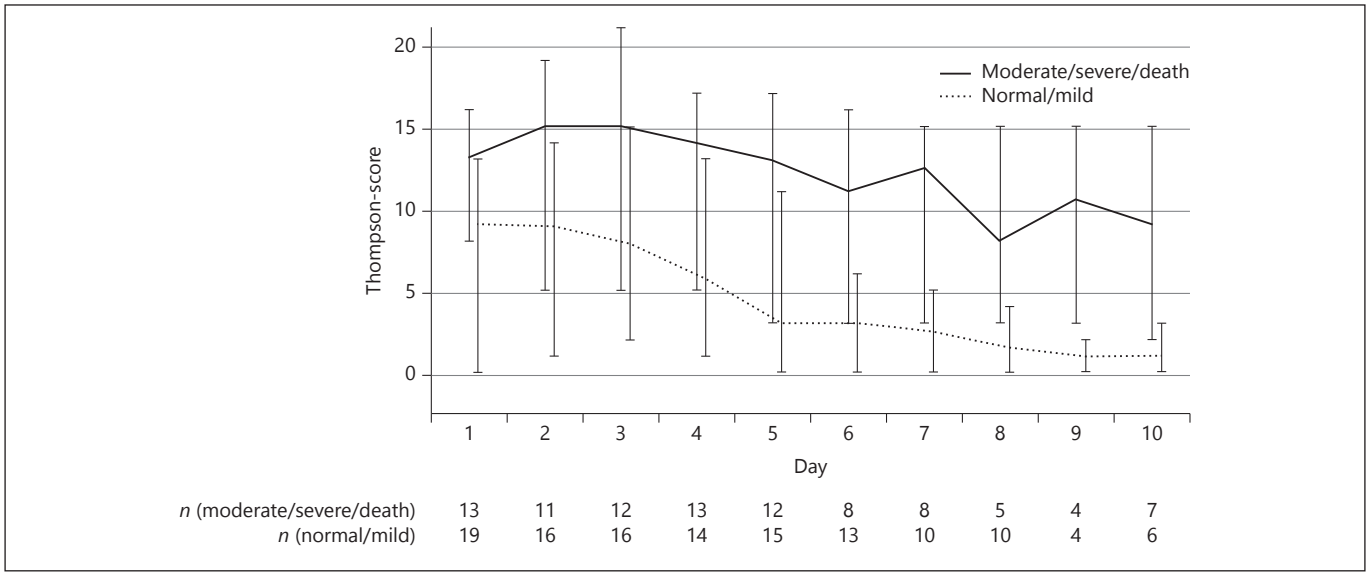
## Discussion

In our study, the TS, a widely used instrument in the clinical routine, showed a strong association between higher values of the score and adverse long-term outcome. This scoring system was first described in 1997 by Thompson et al. [1] as a clinical method for prediction of outcome of newborns with HIE, which requires little time for the assessment, no comprehensive training for the clinical personnel, and no specific equipment. Further studies report a high sensitivity and specificity to predict outcome [5]. Meanwhile, therapeutic hypothermia became an established standard treatment of neonatal HIE. Since hypothermia itself and/or associated pharmacologic interventions such as sedation may influence the TS, its value during hypothermia treatment was unclear. However, we need to point out on the fact that besides hypothermia, which may influence TS values by itself, all our newborns, except for one, received morphine during hypothermia, usually using a continuous infusion, which may increase the TS. Furthermore, in two thirds of the newborns phenobarbital was used as well for sedation. Only one newborn was completely paralyzed during the hypothermia phase, but the maximal TS was 15 in that case thereafter.




| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *n* (IQ <85 points/death) | 15 | 12 | 14 | 14 | 14 | 10 | 10 | 8 | 5 | 8 |
| *n* (IQ ≥85 points) | 17 | 15 | 14 | 13 | 13 | 11 | 8 | 7 | 3 | 5 |

**Fig. 2.** Thompson-scores for infants with death or IQ <85 (straight line) and for surviving infants with an IQ ≥85 (dotted line). Values are presented as median and range.




| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *n* (moderate/severe/death) | 13 | 11 | 12 | 13 | 12 | 8 | 8 | 5 | 4 | 7 |
| *n* (normal/mild) | 19 | 16 | 16 | 14 | 15 | 13 | 10 | 10 | 4 | 6 |

**Fig. 3.** Thompson-scores for infants with death or moderate to severe neurological outcome (straight line) and for surviving infants with mild or normal neurological outcome (dotted line). Values are presented as median and range.

To our knowledge, there is only 1 study evaluating the TS in neonates treated with hypothermia. Beyond short-term outcomes, this study from Thorsen et al. [2] provided death before discharge and development of severe epilepsy as the primary outcome. The authors showed that a score >12 as compared to a lower score is strongly associated with adverse outcome. Our study is the first study to investigate the correlation of TS with potential adverse long-term effects in neonates treated with hypothermia and thus provides new information.

There are many potential ways to look at longitudinally obtained TS values. We used the peak-TS because it was demonstrated by Thompson et al. [1] that this approach provides the best correlation with outcome. We

identified a statistically significant correlation between the peak TS and our primary outcome and identified 2 cut-off points of 11 and 15, depending on whether a high sensitivity or specificity is required by the user. Investigators use different definitions for "normal outcome." Thompson et al. [1] defined no clinical evidence of cerebral palsy and a Griffith's GQ ≥70 as "normal." Our primary outcome included survival without cognitive impairment and we differentiated between cognitive and neurologic impairment. Nevertheless, Thompson et al. [1] also reported that all infants with a score <11 were normal with a sensitivity of 100%. With a score >15, all infants were abnormal with a specificity of 96%. These results correspond almost with our values (93 and 94%) and our cutoff value of 13 for survival without relevant neurologic impairment fits quite well to the original dataset and to another report on cognitive and neurologic data from Mwakyusa et al. [6] although other definitions (only developmental delay, only cerebral palsy) and no hypothermia were used in their study.

The only study providing data on the TS in relation to the development of severe seizures/epilepsy is available from Thorsen et al. [2] who described a significant increased risk for this outcome for individuals with a TS >12. In our study, we found a statistically significant correlation with a cutoff point of 15 in the TS. Mwakyusa et al. [6] also report a higher incidence of neonatal seizures with higher TS values, although they examined their infants at a different age and assessed only infants without hypothermia treatment.

A relationship between a higher TS and death as the single outcome variable was described in earlier studies without hypothermia. Mwakyusa et al. [6] described a statistically significant correlation of TS with mortality and reported for a value ≥15 a sensitivity of 88% and a specificity of 99%. Biselele et al. [7] reported a good correlation between TS and mortality. Thorsen et al. [2] showed a nonlinear relationship between TS and death in their infants undergoing hypothermia treatment. This is comparable with our study findings describing a statistically significant correlation with TS and survival with a TS cutoff of 15.

In general, we were able to establish a statistically significant relationship with the TS as a continuous predictor in all investigated parameters. It is also interesting that our cutoff values are in the same range as already described by Thompson et al. [1] who suggested limits of >10 and >15 on different postnatal ages. Comparisons with previously published data is difficult because different ways to analyze the data were used and almost always a day 1 score was used, in comparison to the peak score, for which Thompson et al. [1] themselves reported the best correlation. The range of scores for infants with good versus adverse outcome seems to separate during the first days of life in the original paper, whereas they show considerable overlap during the first 3 days for cognitive outcome. Since our study infants received hypothermia treatment, almost all infants received opioids and sedatives during the initial 3 days of life, which may result in inappropriately high values of TS. Therefore, we decided to look also at the peak TS, which occurred uniformly after the hypothermia treatment phase.

There are several other limitations in our study. First, the study has a retrospective design. Second, evaluation of the infants using TS was done by different physicians in a typical NICU setting, and sometimes was not done every day. However, this corresponds to the clinical practice, and the score was developed exactly for this setting. Furthermore, the timing of the first evaluation of the TS was not standardized, and often done later in outborn infants, which may have influenced the values, as suggested by Biselele et al. [8] but also represents the typical clinical practice. In addition, follow-up was not done with the same age in our study participants. Therefore, the WPPSI-III test was used which allows cognitive assessments between 3 and 7:2 years of age.

## Conclusions

In summary, using the Thomson Score as a prognostic tool for predicting the long-term outcome in asphyxiated term newborns with HIE may be useful also when applied in newborns undergoing a controlled hypothermia treatment protocol. This information is novel and may be important for counseling parents. A higher score appears to be significantly associated with an adverse outcome. The cut-off limits studied suggest that a peak value of >15 is associated with a substantially higher risk for adverse outcome. During the first 3 days of life, there is considerable overlap in TS values comparing infants with good versus adverse outcomes. Further studies are needed to validate our results in a larger number of infants with HIE undergoing hypothermia treatment.

## Disclosure Statement

This study was supported by our parental support group "Förderkreis für intensivpflegebedürftige Kinder Ulm e.V."

## References


1 Thompson CM, Puterman AS, Linley LL, Hann FM, van der Elst CW, Molteno CD, Malan AF: The value of a scoring system for hypoxic ischaemic encephalopathy in predicting neurodevelopmental outcome. Acta Paediatr 1997;86:757–761.

2 Thorsen P, Jansen-Van Der Weide MC, Groenendaal F, Onland W, Van Straaten HLM, Zonnenberg I, Vermeulen JR, Dijk PH, Dudink J, Rijken M, van Heijst A, Dijkman KP, Cools F, Zecic A, van Kaam AH, de Haan TR: The thompson encephalopathy score and short-term outcomes in asphyxiated newborns treated with therapeutic hypothermia. Pediatr Neurol 2016;60:49–53.

3 Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, Fanaroff AA, Poole WK, Wright LL, Higgins RD, Finer NN, Carlo WA, Duara S, Oh W, Cotten CM, Stevenson DK, Stoll BJ, Lemons JA, Guillet R, Jobe AH; National Institute of Child Health and Human Development Neonatal Research Network: Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005;353:1574–1584.

4 Youden WJ: Index for rating diagnostic tests. Cancer 1950;3:32–35.

5 Bhagwani DK, Sharma M, Dolker S, Kothapalli S: To study the correlation of thompson scoring in predicting early neonatal outcome in post asphyxiated term neonates. J Clin Diagnostic Res 2016;10:SC16–SC19.

6 Mwakyusa SD, Manji KP, Massawe AW: The hypoxic ischaemic encephalopathy score in predicting neurodevelopmental outcomes among infants with birth asphyxia at the Muhimbili National Hospital, Dar-es-Salaam, Tanzania. J Trop Pediatr 2009;55:8–14.

7 Biselele T, Naulaers G, Bunga Muntu P, Nkidiaka E, Kapepela M, Mavinga L, Tady B: A descriptive study of perinatal asphyxia at the University Hospital of Kinshasa (Democratic Republic of Congo). J Trop Pediatr 2013;59:274–279.

8 Biselele T, Naulaers G, Tady B: Evolution of the Thompson score during the first 6 h in infants with perinatal asphyxia. Acta Paediatr 2014;103:145–148.