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Predicting Outcomes in Neonatal Hypoxic-Ischemic Encephalopathy Treated with Therapeutic Hypothermia: Prognostic Values of Selected Real-World Markers from a Single- Centre Study

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Abstract

Background

To verify the accuracy and reliability of clinically applicable prognostic markers assessed by neonatologists—specifically, background amplitude-integrated electroencephalography (aEEG) at 24 and 36 hours and the presence of abnormal posterior limb of the internal capsule (PLIC) signaling on magnetic resonance imaging (MRI)—for predicting mortality and long-term morbidity in newborns undergoing therapeutic hypothermia.

Methods

This retrospective cohort study included newborns admitted to a tertiary perinatal center (2009–2020) for therapeutic hypothermia. Background aEEG recordings at 24 and 36 hours of life and the presence of abnormal PLIC imaging were evaluated. The ability of these markers to predict mortality and long-term neurodevelopmental outcomes was statistically tested.

Results

Of the 80 infants with complete follow-up data, 15 (18.75%) died, and 17 (21.25%) had an abnormal long-term neurodevelopmental outcome. The predictive ability was as follows: aEEG at 24 hours yielded a sensitivity of 0.81 and specificity of 0.90; aEEG at 36 hours yielded a sensitivity of 0.78 and specificity of 0.83; abnormal PLIC signaling yielded a sensitivity of 0.72 and specificity of 0.77.

Conclusions

The tested markers demonstrate good prognostic value and are readily applicable in routine clinical practice for multimodal prognostication without requiring highly specialized radiological or neurophysiological expertise.

Background

Perinatal asphyxia is a severe and feared complication of the perinatal period. Its primary neurological consequence, hypoxic-ischemic encephalopathy (HIE), is a significant cause of long-term neurodevelopmental morbidity in term infants. Until the early 21st century, no specific treatment was available; care centered on early stabilization and the maintenance of normal physiological parameters. Currently, therapeutic hypothermia (TH) is the standard of care for HIE in developed countries, demonstrably improving neonatal prognosis [1, 2].

However, the effectiveness of TH is relative, with a number needed to treat (NNT) between 7 and 9. Even with TH, the prognosis for infants following severe perinatal asphyxia remains uncertain. This prognostic ambiguity is highly stressful for both clinical staff and the infant's family. The availability of reliable prognostic markers can provide early reassurance in favorable cases, guide the early initiation of targeted developmental interventions for high-risk infants, or facilitate timely discussions regarding the redirection of care toward palliation.

To date, no single marker reliably predicts outcomes following TH. Research has explored various modalities, including severity of hypoxia (Apgar scores, umbilical cord blood), laboratory biomarkers of CNS damage, electrophysiological markers (continuous EEG, aEEG, evoked potentials), imaging (cranial ultrasound, MRI), and structured clinical exams [3, 4]. Electrophysiological and imaging methods offer the highest predictive accuracy [5–8]. However, many published protocols require specialized expertise or equipment often restricted to clinical trial settings. This study aims to test simple, clinically applicable prognostic markers whose evaluation does not depend on specialized sub-specialty expertise. Specifically, we assessed the prognostic value and inter-rater reliability of aEEG and basic MRI assessments performed directly by neonatologists following standard training.

Methods

This is a single-center, retrospective, observational cohort study. In accordance with the local ethics committee’s guidelines for retrospective anonymized analyses, specific informed consent was waived. The study included all newborns admitted to the Neonatal Intensive Care Unit (NICU) at the University Hospital Olomouc between 2009 and 2020 who were diagnosed with HIE and treated with TH. Exclusion criteria included gestational age < 36 weeks, severe chromosomal abnormalities, major congenital malformations, insufficient aEEG monitoring, lack of an MRI within the specified timeframe, or death before 72 hours of age precluding complete evaluation.

Therapeutic Hypothermia (TH) TH was indicated for newborns born at 36 + 0 weeks gestation or more and admitted within 6 hours of life with signs of severe birth asphyxia (Apgar 5 or less at 10 minutes, ongoing resuscitation at 10 minutes, or cord/infant blood pH < 7.0 or base excess − 16 mmol/L or more). Patients also required clinical signs of moderate-to-severe neonatal encephalopathy and an abnormal aEEG background. Whole-body TH (TECOterm NEO, Tec Com Medizintechnik GmbH) was initiated within 6 hours of birth, maintaining a target temperature of 33.5°C for 72 hours, followed by controlled rewarming.

Amplitude-Integrated Electroencephalography (aEEG) Continuous aEEG monitoring (CFM 6000 Olympic Medical; CFM Brainz monitor, Natus Medical) was maintained throughout TH and rewarming. Anonymized aEEG traces at 24 and 36 hours of life were extracted. Three experienced neonatologists (JH, VB, JL), blinded to clinical outcomes and each other’s evaluations, assessed the traces using Hellstrom-Westas criteria. Continuous normal voltage (CNV) and discontinuous normal voltage (DNV)

were classified as normal; burst-suppression (BS), low voltage (LV), and flat trace (FT) were classified as abnormal. Majority agreement was used in cases of discrepancy.

Magnetic Resonance Imaging (MRI) MRI was performed between days 8 and 14 of life using a 1.5T scanner (Magnetom Avanto, Siemens). Minimum sequences included axial/sagittal T1, axial T1 TIRR, axial T2 BLADE, axial DWI (with ADC maps), and axial SWI. Three neonatologists, blinded to clinical data and peer reviews, evaluated the posterior limb of the internal capsule (PLIC). Findings were classified as normal (favorable) if physiological myelination was present (increased signal in the dorsal half/third of the PLIC on T1-weighted images, or decreased signal on T2-weighted images). Absence of these signs was deemed abnormal.

Neurodevelopmental Outcome Long-term outcomes were assessed at 20–30 months using the Czech-validated Bayley Scales of Infant and Toddler Development, Second Edition (BSID-II). Children were examined by a pediatric neurologist (JH) for cerebral palsy (CP) and graded via the Gross Motor Function Classification System (GMFCS). An outcome was defined as "abnormal" if the BSID-II Psychomotor Development Index (PDI) or Mental Development Index (MDI) was < 70, or if CP was diagnosed regardless of GMFCS level.

Statistical Analysis Predictive performance was assessed using standard sensitivity and specificity measures without smoothing methods. Confidence intervals for sensitivity and specificity were calculated using the Wilson score method with a 95% confidence level. Sensitivity was defined as the proportion of true positive results among all subjects with the condition (TP/(TP + FN)), and specificity as the proportion of true negative results among all subjects without the condition (TN/(TN + FP)). Inter-rater reliability was calculated using Fleiss's kappa. Analyses were performed in MATLAB (R2024a, Update 6).

Results

Of 92 newborns treated with TH during the study period, 3 died within 72 hours, 2 missed MRI examinations, and 7 were lost to follow-up. A comparison of patient characteristics is shown in Table 1.

Table 1
Patient characteristics of the lost to follow-up sample vs included in study cohort (values presented as mean with range) (P-value: Pearson's Chi-square: SC, male; Mann-Whitney U test: gestational age, Apgar score, pH; Welchs t-test: birth weight)

Gestational age	**Included in study cohort (n = 80)**	**Not included in study cohort (n = 12)**	**P-value**
	39,0 (37–42)	**39,1 (37–41)**	**0,8913**
Birth weight	3235 (2000–4500)	2994 (2100–3860)	0,179
pH	6,89 (6,53–7,3)	6,86 (6,46–7,22)	0,6477
Apgar score at 5 minutes	3,41 (1–10)	2,83 (1–5)	0,7539
Caesarean section	37/80	6/12	0,512
Male	49/80	8/12	0,967

Eighty newborns were included in the final analysis. Fifteen (18.75%) died, and 17 (21.25%) were diagnosed with significant long-term neurodevelopmental impairment. CP was diagnosed in 16 children (13 severe, GMFCS 3 or higher – inability to walk independently). A PDI < 70 was recorded in 17 children, and an MDI < 70 in 15 children.

Predictor inter-rater reliability was excellent for aEEG and substantial for MRI. For aEEG at 24 hours (aEEG24), reviewers agreed in 71/80 cases (89%, Fleiss's kappa = 0.84). For aEEG at 36 hours (aEEG36), agreement was 72/80 (90%, kappa = 0.87). PLIC evaluation showed greater variability, with agreement in 62/80 cases (77%, kappa = 0.69).

Figure 2 illustrates predictive distribution based on birth weight, umbilical cord pH, and clinical outcome. Most newborns with normal outcomes displayed no abnormal markers, whereas almost all cases of death or severe impairment presented with at least one abnormality.

Defining "cases" as death or severe impairment, the predictive values were:

- aEEG24: Sensitivity 0.81 (95% CI 0.647–0.911), Specificity 0.90 (95% CI 0.778–0.955)
- aEEG36: Sensitivity 0.78 (95% CI 0.610–0.899), Specificity 0.83 (95% CI 0.700–0.919)
- PLIC: Sensitivity 0.72 (95% CI 0.546–0.844), Specificity 0.77 (95% CI 0.633–0.866)

When restricted to predicting motor impairment alone (PDI < 70), PLIC sensitivity increased to 0.75 (95% CI 0.505–0.898), specificity 0.77 (95% CI 0.635–0.867). Only 2 newborns with an abnormal PLIC and concurrent abnormal aEEG at both 24 and 36 hours experienced a favorable long-term outcome.

Conversely, only one newborn with an unfavorable outcome had normal ratings across all tested predictors.

Discussion

The prevalence of mortality (18.75%) and severe long-term impairment (21.25%) in our cohort aligns with published literature. Expanding indication criteria to include mild encephalopathy may lower adverse outcome rates in some modern cohorts [5, 9]; however, TH efficacy in mild HIE remains unproven and under investigation [10].

A key finding is the excellent inter-rater reliability among neonatologists evaluating aEEG recordings (kappa = 0.84–0.87). This confirms the accessibility of aEEG for real-world clinical practice, circumventing the lower reliability and specialized expertise demanded by standard continuous EEG [11]. While PLIC MRI evaluation showed lower agreement (kappa = 0.69), it remains a substantial and practically useful metric that could be optimized with targeted training [5, 12, 13].

The diagnostic value of background electroencephalography normalization during TH is well-documented [6]. In our study, surprisingly, early evaluation at 24 hours achieved the highest accuracy, though literature occasionally highlights 48-hour evaluations as highly predictive [8, 15]. Machine-learning algorithms now allow for automated background analysis even earlier, by 12 hours of life [3, 14]. A clinical caveat remains the impact of analgosedation, particularly midazolam, which can depress background EEG voltage [16, 17].

MRI represents another critical prognostic pillar. There are many classifications, schemes, and methodologies that, again with varying degrees of effectiveness, can predict the occurrence of serious complications. The individual markers described have varying predictive value and different “phenotypic” expressions. Some developed classification schemes have very high sensitivity regarding the occurrence of long-term complications but are insufficient in predicting specific clinical manifestations [5, 18]. Conversely, other assessment methods have lower overall sensitivity but, from a certain perspective, higher informational value for clinical practice (e.g., predicting the severity and phenotypic expression of the outcome: for example abnormalities in the basal ganglia/thalamus region—classically occur in sentinel events and reliably predict the occurrence of severe motor difficulties, “Watershed pattern” injury predicts the occurrence of primarily milder cognitive difficulties, near-total/Total brain injury – predicts very severe combined disability or the child’s death, focal/multifocal lesions – may be oligosymptomatic or depend on the extent and location of the lesions) [18, 19].

The timing of the examination is also important: early examination can provide valuable information that cannot be obtained if the examination is delayed (pseudo normalization); on the other hand, some changes take time to develop. Examination during therapy can be technically difficult and uncomfortable for the infant [18–23].

We demonstrated that a simplified evaluation of the PLIC signal in basic T1 and T2 projections by neonatologists yields solid diagnostic accuracy, independent of advanced sub-specialty input [12]. Though we did not replicate the near-perfect motor outcome prediction seen in older literature [24], our approach reflects the realities of unselected, real-world clinical settings. Emerging artificial intelligence technologies may eventually bridge the gap between simple visual interpretations and complex MRI scoring frameworks.

Limitations of this study include its retrospective nature and extended timeframe. We evaluated isolated segments of aEEG without accounting for specific medication burdens, and MRI timing varied broadly between days 8 and 14. Furthermore, abnormal aEEG was partially an inclusion criterion for TH, making the cohort inherently pre-selected for early electrographic abnormalities.

Conclusions

This longitudinal, single-center study validates the utility of streamlined, accessible testing. Background aEEG normalization at 24 and 36 hours, coupled with basic MRI PLIC signal assessment, provides highly predictive prognostic data. These modalities can be reliably interpreted by neonatologists following brief training, offering a robust foundation for multimodal prognostication in resource-constrained or real-world NICU environments.

Abbreviations

aEEG
amplitude-integrated electroencephalography
BS
burst-suppression
BSID
Bayley Scales of Infant and Toddler Development
cEEG
continuous electroencephalography
CNV
continuous normal voltage
CP
cerebral palsy
DNV
discontinuous normal voltage
FT
flat trace
GMFCS
gross motor function classification system
HIE

hypoxic-ischemic encephalopathy
LV
low voltage
MDI
mental development index
MRI
magnetic resonance imaging
NICU
neonatal intensive care unit
NNT
number needed to treat
PDI
psychomotor development index
PLIC
posterior limb of the internal capsule
TH
therapeutic hypothermia.

Declarations

Ethics approval and consent to participate

The research presented in this manuscript adheres to the ethical principles outlined by the University Hospital Olomouc, Czech Republic. All procedures involving human participants were conducted in accordance with the ethical standards of the University Hospital Olomouc and the Declaration of Helsinki (1964), as revised in 2013. In accordance with the local ethics committee's guidelines for retrospective anonymized analyses, specific informed consent to participate was waived by the Ethics Committee of University Hospital Olomouc.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

JH conception, design of the work, acquisition, analysis, drafted the work JL conception, design of the work; acquisition, substant. revisionMW conception, acquisitionVM acquisition, revisionVB acquisitionTF data analysis, interpretation of data

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Availability of data and materials

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

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Figures

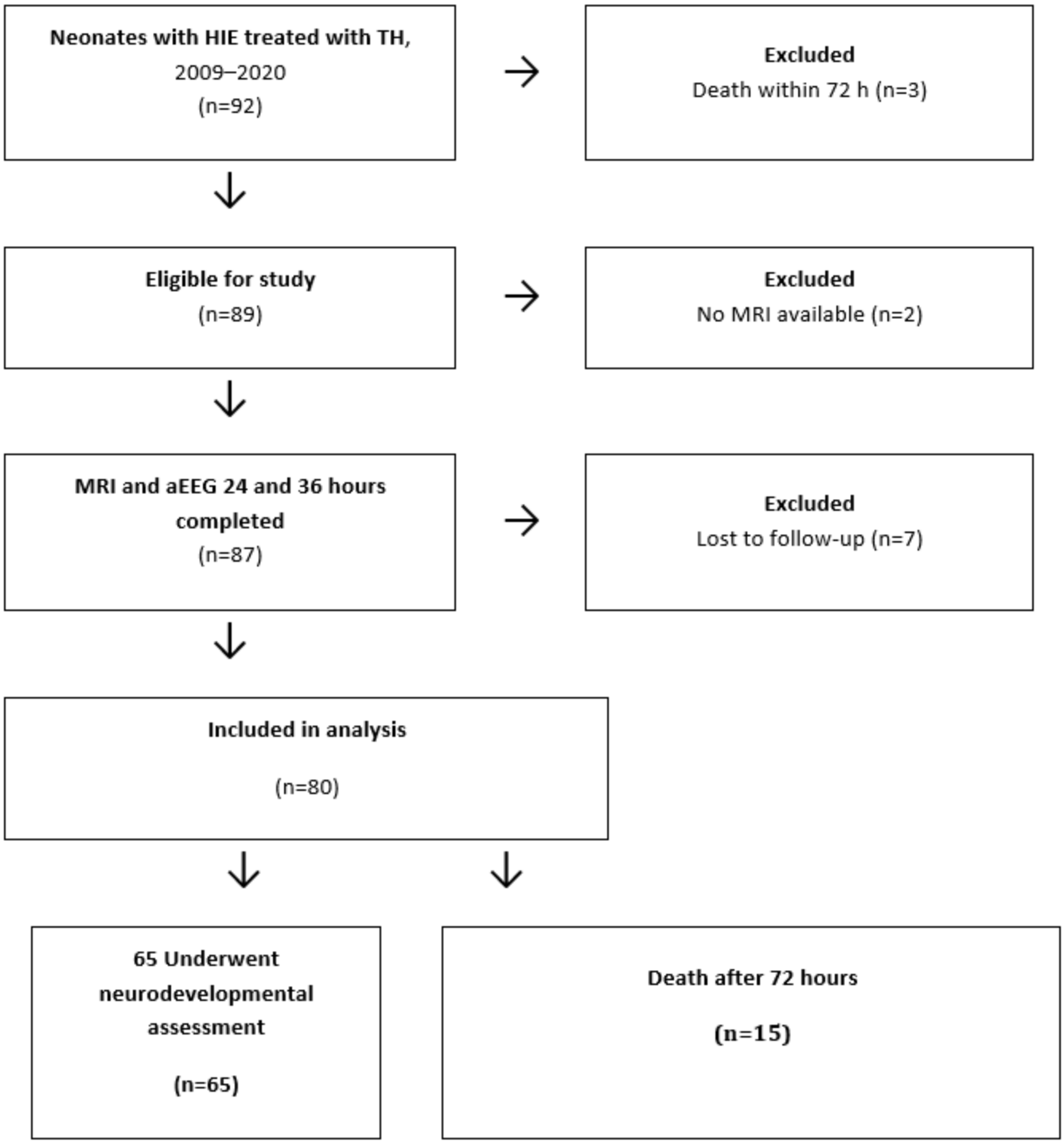


Figure 1

Flowchart showing study inclusion, exclusions and 2-year assessment of neonates with hypoxic-ischaemic encephalopathy treated with therapeutic hypothermia between 2009 and 2020.

HIE, hypoxic-ischaemic encephalopathy; **TH**, therapeutic hypothermia; **MRI**, magnetic resonance imaging.

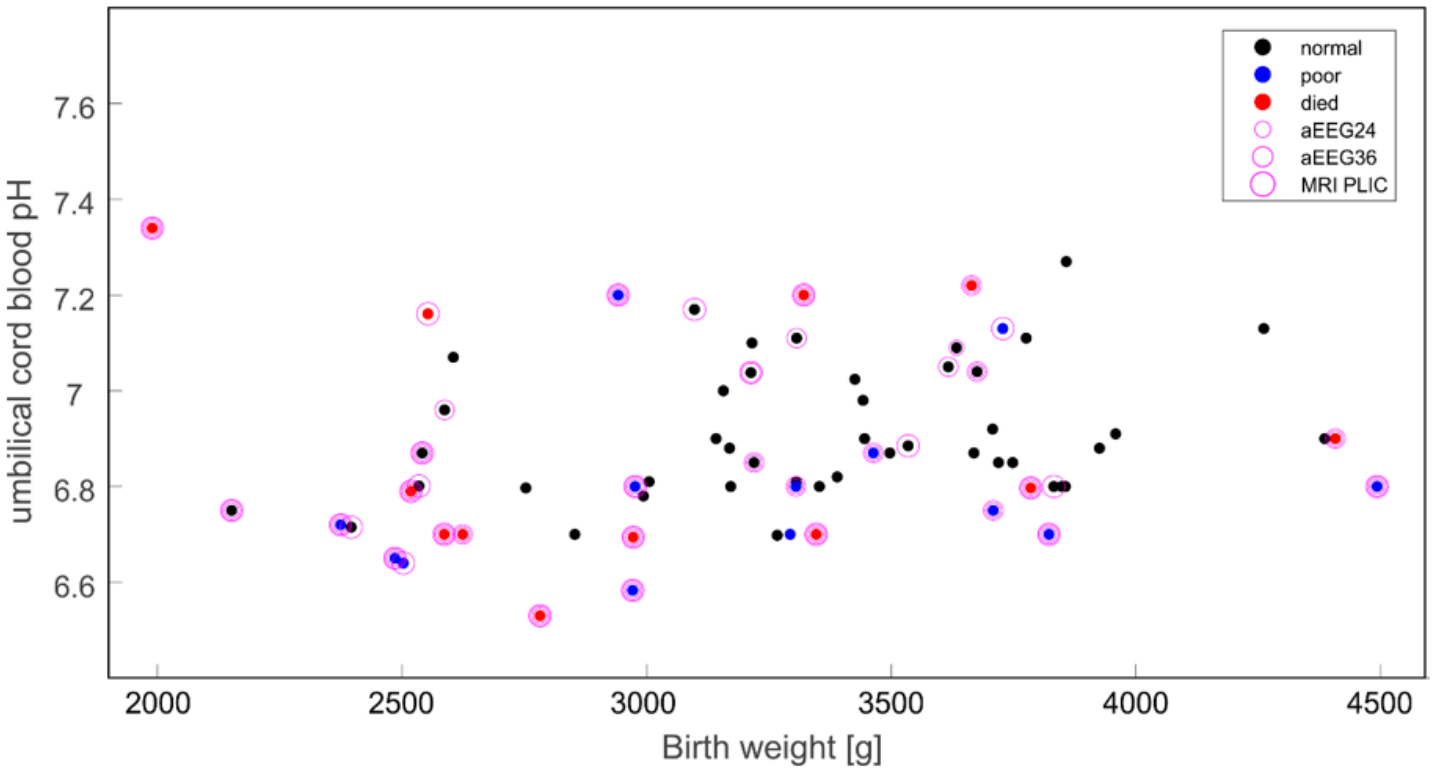


Figure 2

Graphical representation of the predictive capabilities of aEEG (background at 24 resp. 36 hours) and MRI (PLIC abnormality). Each newborn is represented with a single dot. The horizontal coordinate shows the birth weight and the vertical coordinate shows the pH of the umbilical cord blood (11 newborns are not shown due to missing acidity values). The color of the dot codes for the outcome. Abnormal values of the predictors are marked with concentric rings around the dots. The innermost ring represents abnormal aEEG24, the middle ring represents abnormal aEEG36, and the outermost ring represents abnormal PLIC. We observe that the three evaluated predictors have high sensitivity (i.e., almost all newborns with a poor outcome have at least one ring around their dots) and high specificity (i.e., most of newborns with a normal outcome have no rings around their dots).