







Risk for infantile spasms after acute symptomatic neonatal seizures

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Abstract

Objective: Infantile spasms (IS) is a severe epilepsy in early childhood. Early treatment of IS provides the best chance of seizure remission and favorable developmental outcome. We aimed to develop a prediction rule to accurately predict which neonates with acute symptomatic seizures will develop IS.

Methods: We used data from the *Neonatal Seizure Registry*, a prospective, multi-center cohort of infants with acute symptomatic neonatal seizures born from July 2015 to March 2018. Neonates with acute symptomatic seizures who received clinical electroencephalography (EEG) and magnetic resonance imaging (MRI) and were younger than 2 years of age at the time of enrollment were included. We evaluated the association of neonatal EEG, MRI, and clinical factors with subsequent IS using bivariate analysis and best subsets logistic regression. We selected a final model through a consensus process that balanced statistical significance with clinical relevance.

Results: IS developed in 12 of 204 infants (6%). Multiple potential predictors were associated with IS, including Apgar scores, EEG features, seizure characteristics, MRI abnormalities, and clinical status at hospital discharge. The final model included three risk factors: (a) severely abnormal EEG *or* ≥ 3 days with seizures recorded on EEG, (b) deep gray *or* brainstem injury on MRI, and (c) abnormal tone on discharge exam. The stratified risk of IS was the following: no factors 0% (0/82, 95% confidence interval [CI] 0%-4%), one or two factors 4% (4/108, 95% CI 1%-9%), and all three factors 57% (8/14, 95% CI 29%-83%).

Significance: IS risk after acute symptomatic neonatal seizures can be stratified using commonly available clinical data. No child without risk factors, vs >50% of those with all three factors, developed IS. This risk prediction rule may be valuable for clinical counseling as well as for selecting participants for clinical trials to prevent post-neonatal epilepsy. This tailored approach may lead to earlier diagnosis and treatment and improve outcomes for a devastating early life epilepsy.

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Funding information This work was supported by the Pediatric Epilepsy Research Foundation and the Patient-Centered Outcomes Research Institute (2015C2-1507-31187).

KEYWORDS

EEG, infantile spasms, MRI, neonatal seizures

1 | INTRODUCTION

The neonatal period carries the highest risk for seizures across the life span with an incidence of approximately 1-4/1000 live births.¹ More than 70% of neonatal seizures are caused by an acute symptomatic cause such as hypoxic-ischemic encephalopathy (HIE), ischemic stroke, or intracranial hemorrhage.² These acute symptomatic seizures are typically self-limited in the neonatal period; however, $\geq 25\%$ of affected children develop post-neonatal epilepsy (chronic unprovoked seizures).³⁻⁷ Up to 10% of children with clinically diagnosed neonatal seizures will develop infantile spasms, a severe form of early life epilepsy that can lead to developmental regression, intellectual disability, and lifelong epilepsy.^{3,4,8}

Prompt diagnosis and early successful treatment of infantile spasms provide the best opportunity for protection of neurodevelopment and remission of epilepsy, even in the setting of perinatal brain injury.⁹⁻¹² Conversely, delayed treatment of infantile spasms increases the risk of poor neurodevelopmental outcomes.¹³ Despite this, clinical follow-up for survivors of neonatal seizures is highly variable. Close clinical follow-up, education, and counseling for the families and primary care providers of children at highest risk could improve early recognition of infantile spasms, expedite treatment, and optimize developmental trajectory. For families of children at low risk, the burden of multiple visits could be reduced.

Reports of infantile spasms after neonatal seizures are limited by single-center enrollment, small sample sizes, and lack of gold standard continuous neonatal electroencephalography (cEEG) monitoring or detailed brain magnetic resonance imaging (MRI). We enrolled and followed neonates who survived acute symptomatic seizures

Key Points

- Survivors of neonatal seizures are at risk for infantile spasms (IS); individualized risk prediction could improve time to diagnosis and treatment.
- Three risk factors predicted IS: (a) severely abnormal EEG *or* ≥ 3 days with seizures recorded on EEG, (b) deep gray *or* brainstem injury on MRI, and (c) abnormal tone on discharge exam.
- The stratified risk of IS was: no factors 0% (0/82, 95% confidence interval [CI] 0%-4%), one or two factors 4% (4/108, 95% CI 1%-9%), and all three factors 57% (8/14, 95% CI 29%-83%).
- IS risk after acute symptomatic neonatal seizures can be stratified using commonly available clinical data.

to develop a risk model using neonatal cEEG, brain MRI, and clinical characteristics, to stratify the risk of infantile spasms after acute symptomatic neonatal seizures. Our goal was to develop a model that is accurate, parsimonious, and clinically relevant.

2 | METHODS

2.1 | Study design

This was a multicenter cohort of surviving infants with acute symptomatic neonatal seizures born between July 2015 and

March 2018 and enrolled at one of seven *Neonatal Seizure Registry* sites (NCT02789176). Each site has a level IV neonatal intensive care unit (NICU) and follows the American Clinical Neurophysiology Society (ACNS) guidelines for cEEG in neonates.¹⁴ All sites also have a level IV comprehensive pediatric epilepsy program. No study-specific treatment guideline was provided. Seizure treatment, including anti-seizure medication selection, dosing, and duration of therapy, was at the discretion of the clinical team. Five of the seven sites had local institutional guidelines, pathways, or workflows for neonatal seizure management during the entire study period.

2.2 | Standard protocol approvals, registrations, and patient consents

Neonates were enrolled after informed, written parent consent. The local institutional review board for every site approved the study protocol.

2.3 | Inclusion and exclusion criteria

Neonatal Seizure Registry enrollment criteria were: (a) neonate with EEG-confirmed seizure at the study site or referring hospital, or (b) neonate treated with anti-seizure medication for clinical events suspected to be seizures with clinical history, including event semiology supporting the diagnosis of seizures, and (c) acute symptomatic cause of seizure (eg, HIE, ischemic stroke, intracranial hemorrhage [ICH], or other brain injury). Neonates with events that were determined *not* to be seizures based on history, semiology, or cEEG were not enrolled. Neonates with transient cause for seizures (eg, hyponatremia, hypocalcemia, hypoglycemia without brain injury), or neonatal onset epilepsy were not enrolled.

For the current analysis, we included infants based on availability of clinically acquired, diagnostic quality MRI and EEG, as well as a minimum of 12 months of follow-up. We excluded children for the following reasons: lack of consent for additional follow up about infantile spasms, brain MRI unavailable, or uninterpretable EEG.

2.4 | Measurements

2.4.1 | Clinical data

Neonatal demographic and clinical data were determined by systematic chart review. Study site investigators established the primary seizure etiology based upon medical record review.

2.4.2 | EEG

The most abnormal EEG background documented in the clinical record during the first 24 hours of recording at the study center was determined by the study site investigator and was categorized as: (a) normal (clearly stated as such in the report), (b) mild/moderately abnormal (not normal but not severe), or (c) severely abnormal (including burst-suppression, flat trace, depressed and undifferentiated, or electrocerebral inactivity).¹⁵ EEG background patterns were confirmed by central review of both the neonatal EEG trace and EEG reports; where these differed, a final determination was made by consensus between two board-certified clinical neurophysiologists (NAM and RAS) who were blinded to the clinical outcomes and followed a published background classification scheme.¹⁶ Seizures were defined as sudden, abnormal EEG events with a repetitive and evolving pattern with amplitude ≥ 2 μ V and duration ≥ 10 seconds, with or without a clinical correlate.¹⁵ Seizure burden was extracted from cEEG reports at the study center, confirmed by blinded central review of the first 24 hours of cEEG, and categorized as follows: (a) high burden: status epilepticus, frequent recurrent seizures without status epilepticus, many (>7) isolated seizures, or (b) low burden: <7 seizures.² Status epilepticus (defined as >30 minutes of seizure within any 1-hour epoch¹⁵) within the first 24 hours of cEEG was confirmed by central review of the neonatal EEG trace.

2.4.3 | MRI

The first clinically acquired neonatal MR images obtained after seizure onset were reviewed and interpreted by a board-certified, fellowship-trained pediatric neuroradiologist (YL) who was blinded to the clinical data. A quality score was assigned based on the degree of patient motion degradation (diagnostic, limited, or not interpretable). Studies were scored based on location of signal abnormality on available sequences (T1, T2, diffusion weighted imaging [DWI], fluid-attenuated inversion recovery, susceptibility weighted imaging, arterial spin labelling), pattern, and severity of injury. Locations included cortex, white matter, deep gray nuclei, posterior limb of the internal capsule, cerebellum, brainstem, specific lobes, and whether the process was unilateral or bilateral. Patterns of injury included focal, multifocal, global, watershed, or no injury. Hypoxic ischemic injury and germinal matrix hemorrhage were scored using established severity scales.^{17,18} Ischemic stroke was scored based on the fraction of hemispheric involvement by thirds. Clinical reports were scored for brainstem and deep gray nuclei injury.

2.4.4 | Primary outcome

Infantile spasms were defined according to International League Against Epilepsy (ILAE) criteria as seizures characterized by “epileptic spasms... a sudden flexion, extension, or mixed extension–flexion of predominantly proximal and truncal muscles” occurring in clusters during infancy.¹⁹ Infantile spasms diagnosis was determined by parent report at 12 months corrected gestational age and corroborated by local study investigator systematic chart review (ie, documented diagnosis of infantile spasms in keeping with ILAE definition by a pediatric neurologist in the child's medical record).

2.5 | Statistical analysis

In bivariate analyses, we compared characteristics of infants who developed infantile spasms to infants who did not. We used Fisher exact test for categorical variables, and the Wilcoxon rank-sum test for continuous variables. To create a clinically relevant, parsimonious, multivariable model, we collected all variables with a bivariate association with infantile spasms at a significance level of $P < .1$ and with $\leq 10\%$ missing data among participants who developed infantile spasms. We then created variations of these variables to enhance clinical applicability. For example, we created new binary variables from continuous variables using different thresholds (ie, converted one variable—“number of days with seizures”—into multiple variables such as “two or more days with seizures,” “three or more days with seizures”). As another example, we combined variables from the same modality using “or” (ie, combined two variables “MRI brainstem abnormality” and “MRI deep gray abnormality” into one variable “MRI brainstem or deep gray abnormality”). Through discussion and consensus among three clinical experts (ZMG, RAS, HCG), we selected a subset of the variables that we judged would be easy to implement in a clinical setting and robust to variations in practice across centers. This subset is referred to as the *Curated Variable Pool*.

We used the best subsets algorithm with logistic regression to identify the best fitting one, two, and three variable models (ie, lowest Akaike information criteria [AIC]) using both variable pools with the a priori specification that no children without the risk factors in the final model developed infantile spasms (ie, specificity 100%). We limited to three variables because there were only 12 subjects who developed infantile spasms, and we did not want to create an overfit model. When the models included only binary variables, we considered each variable to be a risk factor and calculated the observed likelihood of infantile spasms as a function of the number of risk factors. When models included a continuous variable, we used the regression coefficients to create a scoring system.²⁰

We quantified model performance using metrics to assess the overall model fit (AIC), the ability to rule out low risk neonates (specificity), and the ability to correctly identify high-risk neonates (positive predictive value). To demonstrate the improvements in fit of models as more variables were added, we also report McFadden adjusted R squared.²¹

To assist with variable selection, and to provide reassurance that selected variables would provide robust predictive performance, we performed a sensitivity analysis using a bootstrap technique. To do so, we created 1000 bootstrap populations from the final analytic data set. In each bootstrap population we used the best subsets algorithm to find the five best-fitting (ie lowest AIC) logistic regression models that used three variables (ie, 5000 total models).²² We then tabulated how often each variable appeared in each of these models and used this rank as a measure of variable importance. In selecting the final model, we considered small AIC differences (< 1) to be negligible, and preferred variables with high variable importance in the bootstrap analysis.

We conducted analysis using the R statistical programming language (version 3.4.4, Vienna, Austria; <https://www.r-project.org/>).²³

2.6 | Approach to missing data

Children with missing data for neonatal MRI or EEG were excluded from all analyses.

To understand the effect of missing data on the final model, we used multiple imputation for missing values in abnormal tone. We created and analyzed 1000 data sets with imputed values and pooled the estimates, using the fully conditional specification technique (chained equations),²⁴ assuming data were missing at random and using a logistic regression to impute abnormal tone. We also provide additional information on the group with missing values for abnormal tone.

3 | RESULTS

There were 222 potentially eligible participants in the cohort, and we excluded 18: one did not consent to this arm of the *Neonatal Seizure Registry*, 2 were excluded post hoc as they were later determined not to have had acute symptomatic neonatal seizures (one with a genetic diagnosis and one with seizure onset > 44 weeks corrected gestational age), and three died after discharge home and before age 12 months. Eleven patients were excluded for inadequate imaging (for eight, MRI was not available; for three, MRI was not of sufficient quality for interpretation) and one child was excluded who did not have an interpretable neonatal EEG (Figure 1). The 12 infants who were excluded for incomplete MRI or EEG data were more likely to have had a complex medical

course (low birthweight, preterm, congenital heart disease), abnormal EEG, older age, abnormal tone, and difficulty feeding at the time of hospital discharge as compared to the 204 with complete available data (Table S1).

Among 204 infants included in the present analysis, cEEG was initiated at the study site at a median of 33 hours (interquartile range [IQR] 11 to 83 hours) and MRI was acquired at a median of 4 days (IQR 3 to 8 days). Neonatal seizure etiology was HIE in 87 (43%), ischemic stroke in 54 (26%), intracranial hemorrhage in 36 (18%), hypoglycemia in 4 (2%), and other varied etiologies in 23 (11%).

Twelve children developed infantile spasms (6%) with onset at a median of 5.9 months (IQR 4.8 to 8.4 months). Clinical characteristics, seizure etiologies, and EEG and MRI findings of the children with infantile spasms are presented in Table 1. Neonatal seizure etiology was HIE in six (50%), intracranial hemorrhage in three (25%), ischemic stroke in two (17%), and hypoglycemia with brain injury in one infant (8%). There was no statistically significant difference in seizure etiology among children with and without infantile spasms ($P = .6$).

In the bivariate analysis, multiple variables distinguished neonates who subsequently developed infantile spasms from those who did not go on to have spasms (Tables 2 and 3). From these variables, we selected 17 for the *Curated Variables Pool* (Table S2).

The one-variable model with the lowest AIC used a constructed variable from clinically documented EEG findings: “worst EEG background on the first day was severely abnormal *or* EEG confirmed seizures recorded on three or more days” (AIC 76.2; adjusted R^2 0.21; Sensitivity 83% and PPV 19%). The best two-variable model added a constructed MRI variable from the research neuroradiology review: “Brain MRI has either deep gray *or* brainstem abnormality on T2 or DWI” (AIC 65.1; adjusted R^2 0.35; Sensitivity 75% and PPV 36% for both risk factors present). The three-variable models added a clinical factor to the EEG and MRI variables. Several three-variable models performed similarly (top 10 models: AIC 55.9-59.6). After review and discussion of the models, we added “abnormal tone at discharge” to the best two variables as it had the highest variable importance in the bootstrap analysis (Table S3). The three-variable model

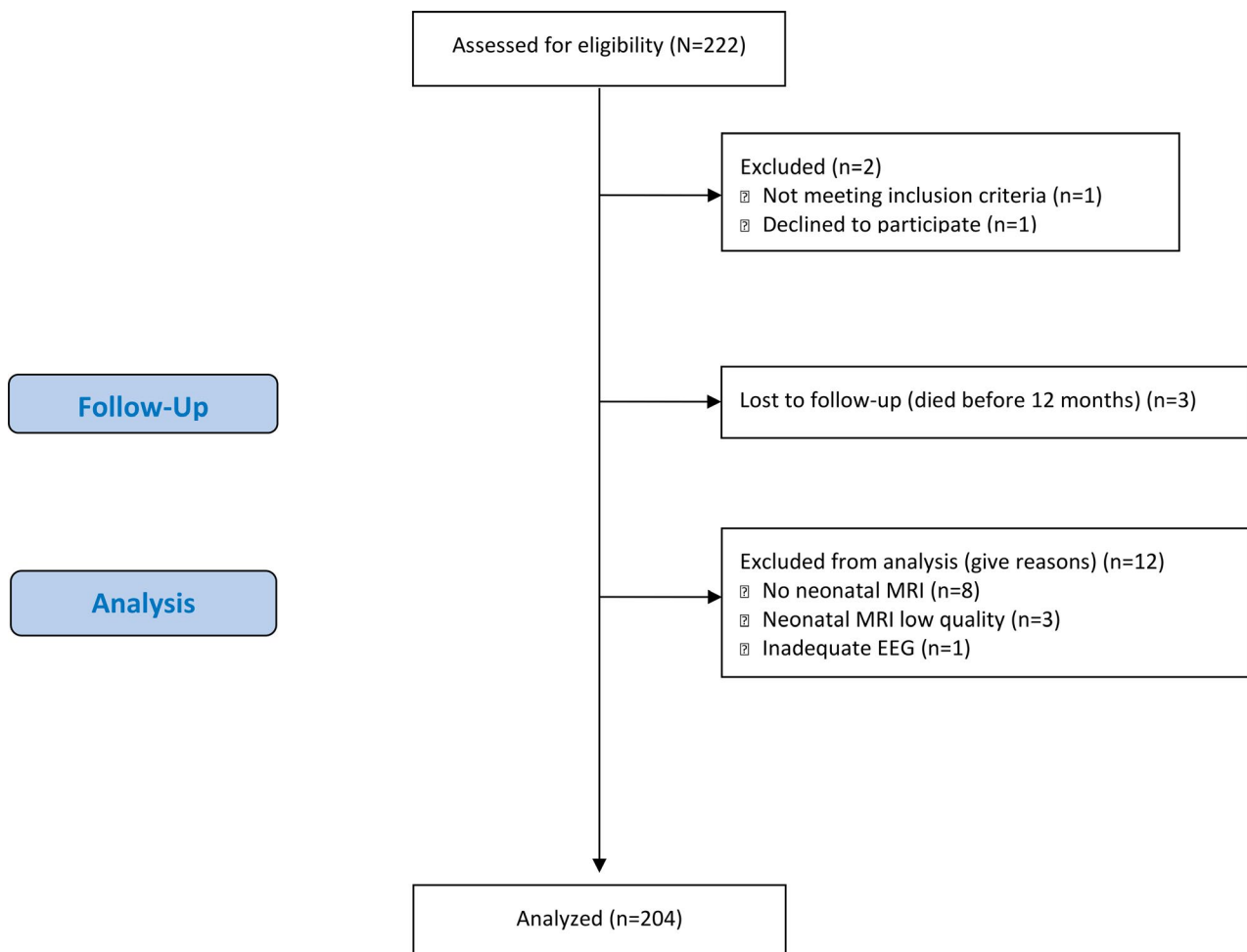


FIGURE 1 Flow diagram of study participants

TABLE 1 Clinical, EEG, MRI, and discharge characteristics of 12 children with acute symptomatic neonatal seizures who subsequently developed infantile spasms

| Clinical Factors | | EEG factors | | | | MRI injury (research read) | | | | MRI injury (clinical report) | | | | Clinical factors at discharge | | | |
|------------------|------|------------------------|-------------------------|------------------|------------------------|----------------------------|------------|-----------|------------|------------------------------|------------|------------|--------|-------------------------------|------|--------------|--|
| | | Worst background Day 1 | Therapeutic hypothermia | Seizure etiology | Days with EEG seizures | Deep gray | Brain-stem | Deep gray | Brain-stem | Deep gray | Brain-stem | Age (days) | G-Tube | PO feeds? | Tone | Risk factors | |
| M | 39.1 | 2.9 | No | HIE | 3 | Y | Y | Y | N | Y | 31 | Yes | None | Increased | 3 | | |
| F | 40.1 | 3.3 | No | HIE | 1 | Y | N | Y | N | Y | 20 | No | All | Mixed | 3 | | |
| F | 39.9 | 3.3 | No | HIE | 3 | Y | Y | Y | Y | Y | 27 | No | All | Increased | 3 | | |
| F | 40.4 | 3.9 | Yes | HIE | 0 | Y | Y | Y | Y | Y | 33 | No | Some | Mixed | 3 | | |
| M | 35.4 | 2.1 | No | HIE | 0 | Y | Y | Y | Y | Y | 12 | No | None | Decreased | 3 | | |
| F | 39.1 | 2.5 | No | HIE | 2 | N | Y | Y | Y | Y | 16 | Yes | None | Normal | 1 | | |
| M | 29.7 | 1.7 | No | ICH | 1 | Y | Y | U | U | U | 131 | No | None | Increased | 3 | | |
| M | 37.7 | 2.9 | Yes | ICH | 12 | Y | N | N | N | N | 101 | Yes | Some | Increased | 3 | | |
| M | 39.1 | 3.2 | No | ICH | 15 | N | N | N | Y | Y | 38 | No | Some | Unknown | 1 | | |
| M | 32.7 | 1.7 | No | Stroke | 5 | Y | Y | Y | N | Y | 59 | No | All | Normal | 2 | | |
| M | 41.1 | 2.9 | No | Stroke | 2 | Y | Y | Y | Y | Y | 10 | No | All | Decreased | 3 | | |
| M | 40.3 | 3 | No | Hypoglycemia | 1 | Y | N | Y | N | Y | 21 | No | All | Increased | 2 | | |

Note: Abbreviations: BW, birth weight; GA, gestational age; G-Tube, gastrostomy tube; PO, by mouth; U, Unknown.

TABLE 2 Bivariate associations of neonatal factors with subsequent infantile spasms among 204 children with acute symptomatic neonatal seizures

| Factors | No Infantile spasms ^a , N = 192 | Infantile spasms ^a , N = 12 | P-value ^b | Missing data (N) |
|--|---|---|----------------------|------------------|
| <i>Delivery/ Birth Factors</i> | | | | |
| Apgar score at 1 min | 4 [2-8] | 1 [1-2] | .004 | 6 ^c |
| Birth weight (kg) | 3.2 [2.8-3.6] | 2.9 [2.4-3.2] | .06 | 3 ^c |
| <i>EEG/ Seizure Factors</i> | | | | |
| Worst background, first day of recording at study center (clinical report) | | | | |
| Normal | 18 (9%) | 0 | .0003 | None |
| Mild/moderately abnormal | 129 (67%) | 3 (25%) | | |
| Severely abnormal | 24 (13%) | 8 (67%) | | |
| Electrographic status epilepticus at onset | 21 (11%) | 1 (8%) | | |
| Seizures (clinical report) | | | | |
| Days with EEG seizures | 1 [1-2] | 2 [1-4] | .11 | None |
| EEG Seizures on \geq 3 days | 23 (12%) | 5 (42%) | .01 | None |
| Research interpretation of EEG | | | | |
| Burst suppression OR severe discontinuity | 53 (28%) | 8 (67%) | .007 | None |
| <i>MRI Brain Factors</i> | | | | |
| Deep gray injury (clinical report) | 79 (41%) | 9 (82%) | .03 | 1 ^d |
| Brainstem injury (clinical report) | 28 (15%) | 6 (55%) | .004 | 1 ^d |
| Deep gray injury, DWI or T2 (research read) | 67 (35%) | 10 (83%) | .001 | None |
| Brainstem injury, DWI or T2 (research read) | 28 (15%) | 8 (67%) | .0001 | None |
| PLIC injury, DWI or T2 (research read) | 45 (23%) | 8 (67%) | .003 | None |
| Subarachnoid abnormality, T1 (research read) | 31 (16%) | 5 (42%) | .04 | None |
| <i>Discharge factors</i> | | | | |
| Age at NICU discharge (days) | 12 [8-22] | 29 [19-43] | .002 | None |
| Age at hospital discharge (days) | 13 [9-24] | 29 [20-43] | .003 | None |
| Feeding | | | | |
| No enteral feeds (NPO) | 1 (0.5%) | 1 (8%) | .002 | None |
| No PO feeds (tube fed) | 10 (5%) | 3 (25%) | | |
| Some PO feeds (tube top-up) | 24 (13%) | 3 (25%) | | |
| All PO feeds | 157 (82%) | 5 (42%) | | |
| Not all PO feeds at discharge | 35 (18%) | 7 (58%) | .003 | None |
| Gastrostomy tube | 10 (5%) | 3 (25%) | .03 | None |
| Tone | | | | |
| Normal | 139 (72%) | 2 (17%) | .00001 | 11 |
| Increased (hypertonic) | 13 (7%) | 6 (50%) | | |
| Decreased (hypotonic) | 26 (14%) | 2 (17%) | | |
| Mixed (hyper and hypotonic) | 3 (2%) | 2 (17%) | | |
| Unknown | 11 (6%) | 0 (0%) | | |
| Level of consciousness | | | | |
| Normal | 184 (96%) | 9 (75%) | .009 | 7 |
| Irritable | 1 (0.5%) | 0 (0%) | | |
| Depressed | 1 (0.5%) | 2 (17%) | | |
| Unresponsive | 0 (0%) | 0 (0%) | | |
| Not specified/Unknown | 6 (3%) | 1 (8%) | | |

Abbreviations: DWI, diffusion weighted imaging; EEG, electroencephalography; Hosp, hospital; NICU, neonatal intensive care unit; PLIC, posterior limb of the internal capsule; PO, by mouth.

^aAll values are N (column percent) or median [interquartile range];

^bFisher exact test for categorical variables; Wilcoxon test for continuous variables;

^cInfants with unknown 1-min Apgar and unknown weight occurred in the group that did not develop infantile spasms.

^dMissing in a child with infantile spasms.

performed as follows: AIC 59.3; adjusted R^2 0.44; sensitivity 67%, and PPV 57% for all three risk factors present.

A missing value for tone (5% of participants) was assigned as normal for the initial analysis, based on our clinical experience that tone is sometimes not reported if it is normal. No subjects with missing tone data subsequently developed infantile spasms. Six infants (54%) with missing tone had the EEG risk factor (seizures on ≥ 3 days or severely abnormal background) and five (45%) had the imaging risk factor. A sensitivity analysis using multivariate imputation by chained equations (mice) indicated similar coefficients and odds ratios, indicating no effect of these missing data on the overall model (data not shown).

Using the variables selected for the three-variable model, we stratified individuals into three risk categories: Children with no risk factors had a very low probability of infantile spasms (0 of 82, 0%, 95% confidence interval [CI] 0%-4%); those with one or two factors had a small probability of infantile spasms (4 of 108, 4%, 95% CI 1%-9%); and children

with all three risk factors had a high probability of infantile spasms (8 of 14, 57%, 95% CI 29%-83%). Among infants with infantile spasms (9 of 12), 75% had severely abnormal EEG or ≥ 3 days with seizures recorded on EEG and deep or brainstem injury on MRI as compared to 16 of 192 (8%) without infantile spasms ($P \leq .0005$).

Selecting a different third variable led to the following risk stratifications. If, instead of “abnormal tone at discharge,” the third risk factor was “had a gastrostomy tube at discharge,” the risk stratification was as follows: no risk factors very low risk (0 of 88, 0%, 95% CI 0%-4%), one risk factor small risk (2 of 85, 2%, 95% CI 0.3%-8%), or two or three risk factors moderate risk (10 of 30, 33%, 95% CI 17%-53%). If the third risk factor was “not full oral feeds,” the risk stratification was as follows: no risk factors very low risk (0 of 79, 0%, 95% CI 0%-5%), one risk factor small risk (1 of 81, 1%, 95% CI 0%-7%), two or three risk factors moderate risk (11 of 44, 25%, 95% CI 13%-40%).

TABLE 3 Neonatal factors not associated with subsequent infantile spasms ($P \geq .1$) among 204 children with acute symptomatic neonatal seizures

| Category | Variables |
|----------------------|--|
| Study/center | Study site, setting of seizure onset (ie, ICU, labor and delivery, well baby nursery, home, study center vs referral center) |
| Demographics | Sex, ethnicity, race, maternal education, maternal insurance |
| Delivery Factors | Gestational age at delivery, 5- and 10-min Apgar scores, head circumference at birth, use of hypothermia, age at admission |
| EEG/ Seizure Factors | Indication for EEG, subclinical seizures, EEG seizures on outside EEG, seizure etiology, seizure burden, research read as a multi-level categorical variable based on the first 24 h of EEG recording |
| NICU Course | Anti-seizure medication choice for seizures, congenital heart defect, congenital diaphragmatic hernia, ECMO |
| Discharge data | Where discharged (ie, home vs elsewhere), need for respiratory support, abnormal reflexes, discharge on anti-seizure medications |
| MRI | Research review of images: DWI or T2 abnormalities in other locations (occipital, temporal, frontal, parietal, any cortex); T1 abnormalities in other locations (white matter, subdural, other); SWI abnormalities in any location (focal, multifocal, subarachnoid, subdural, epidural, hemosiderosis, other) |

Abbreviations: DWI, diffusion weighted imaging; ECMO, extracorporeal membrane oxygenation; EEG, electroencephalography; ICU, intensive care unit; SWI, susceptibility weighted imaging.

4 | DISCUSSION

In this large, multicenter study of neonates who survived acute symptomatic seizures, 6% of children developed infantile spasms before age 12 months. Three neonatal risk factors identified infants with a high risk of infantile spasms: (a) Severely abnormal neonatal EEG background on the first day of recording *or* electrographic seizures on three or more days of recording; (b) MRI with deep gray *or* brainstem injury; and (c) abnormal tone on hospital discharge neurological examination. None of the infants without these three risk factors developed infantile spasms, whereas those with one or two factors had a risk that was similar to the baseline risk of the cohort. More than half of children with all three risk factors developed infantile spasms. Of interest, many clinical variables (eg, demographics, seizure etiology, and duration of neonatal seizure treatment) were not related to the risk of infantile spasms.

The rate of infantile spasms in this *Neonatal Seizure Registry* cohort is lower than that reported in most prior studies.^{3,4,8} This could be due to widespread use of hypothermia for HIE. A recent study that included 178 infants with HIE (not necessarily with neonatal seizures) reported ~4% incidence of infantile spasms (95% CI 1.6-7.9). In that study, infants with severe HIE had a very high rate of infantile spasms (25%) if they did not receive therapeutic hypothermia when compared with children who did receive therapeutic hypothermia (<5%), although the difference was not significant.²⁵ In addition, the rate of infantile spasms might be influenced by early initiation of cEEG as per ACNS guidelines²⁶ and EEG-based treatment of seizures at the *Neonatal Seizure Registry* centers (vs clinical diagnosis and treatment of seizures)—both of which may improve speed of treatment and

reduce seizure burden. Furthermore, including mixed etiologies of acute symptomatic neonatal seizures and excluding infants with neonatal-onset epilepsies may have affected the overall frequency of infantile spasms.

Our findings align with two potential mechanisms by which neonatal brain injury may lead to infantile spasms. First, our findings echo prior work implicating severe neonatal brain injury,²⁷ especially to the brainstem^{28,29} or deep gray structures^{28,30} as a precursor to the development of post-neonatal epilepsy, regardless of the etiology of the injury. This is somewhat counterintuitive, as epilepsy is often conceptualized as a cortical phenomenon. However, dysfunction in subcortical structures underlies several other epilepsies, such as childhood absence epilepsy³¹ and hypothalamic hamartoma.³² Thus epileptogenesis after neonatal brain injury may rely on the development of abnormal networks between deep and superficial neuronal structures, with injury to the deep structures as the primary driver of the abnormality.

Second, our model lends credence to the hypothesis that neonatal seizures are an important risk factor for future epilepsy,^{7,33} and that seizure burden is an independent predictor of developmental outcome.³⁴ However, the causal relationship between neonatal seizures and post-neonatal epilepsy remains uncertain. Seizure burden may be a marker of brain injury severity or may be itself a cause epileptogenic injury. The predictive value of abnormal EEG background for post-neonatal epilepsy has also been described,^{30,35,36} particularly if abnormalities persist at 21 days.³⁷ However, the best timing of predictive EEG for infantile spasms is not known and deserves further exploration.

The third variable in the model, muscle tone at discharge, is novel, although statistically less robust than the variables related to EEG and MRI. Two other clinical variables—inability to take full oral feeds by the time of neonatal hospital discharge and placement of gastrostomy tube—performed similarly. It is unclear if these three variables are merely markers of brain injury severity or if they carry additional significance. For example, problems with feeding and abnormal tone may be attributable to brainstem or deep gray injury, although these clinical-anatomical links are not specific. From a practical standpoint, any of the three clinical variables may present challenges to uniform assessment. Tone and other neurological examination findings may depend on the expertise of the clinician who performs the examination, and these findings are often incompletely documented. Gastrostomy-tube placement is rare in the neonatal period, and practice may vary from center to center, which could limit the number of high-risk children identified. Finally, lack of full oral feeds at discharge or transfer may depend on hospital policies regarding transfer to a community hospital for convalescence and duration of hospitalization in the acute care setting. Modeling with these or other clinical variables would be of interest in validation cohorts.

We note that no demographic variables were associated with subsequent development of infantile spasms in this closely followed cohort. Given known demographic disparities in US pediatric epilepsy care,^{20,38,39} the absence of these associations serves as a baseline for monitoring outcome disparities in future work.

Although early treatment of infantile spasms provides an opportunity to optimize neurodevelopment and limit later epilepsy,^{9-11,13} correct diagnosis and adequate treatment are often delayed—by one week or more in 70% of children, according to a recent report.⁴⁰ Treatment delays have a direct association with cognitive outcomes, with an estimated drop in intelligence quotient of eight points attributed to a 1 week lag in recognition and treatment of infantile spasms. This estimated reduction increased to 15 points when the treatment delay exceeded 8 weeks.⁴⁰ These data suggest that family education and close clinical monitoring for children who are at high risk, such as those identified by our risk prediction model, may lead to improved outcomes through earlier diagnosis and rapid treatment initiation.

Several limitations merit discussion. First, a diagnosis of infantile spasms was a rare outcome (12 of 204, 6%), which prevented splitting our cohort into model building and validation data sets. Second, EEG monitoring, while applied according to ACNS criteria, was at the discretion of the treating physician. Furthermore, monitoring reports and EEG studies were only reviewed from study center recordings, and some seizures may have occurred prior to transfer to the study center or prior to placement of EEG leads. Third, the timing and sequences of MRI were not standardized; although all of the children we present had studies that were of adequate diagnostic quality, we opted to include centralized research neuroimaging review data in the final models because it improved the predictive value, the clinical MRI report was missing for one of the children with infantile spasms, and, in our experience, relevant data (eg, presence of absence of brainstem injury) are not always available in clinical reports. We suggest that clinicians who are concerned about infantile spasm risk inquire with their radiology colleagues if assessment of deep gray or brainstem injury is not included in a clinical MRI report, and that centers make efforts to standardize neuroradiology reads to include this important feature. Fourth, neonatal seizure treatment was at the discretion of the clinical team and varied among study sites, although phenobarbital was by far the most commonly prescribed medication at every site. Fifth, we recognized the challenges and limitations in accurately assessing tone based on chart review and suggest that future studies implement prospective, standardized assessment of tone, as well as additional relevant clinical factors, particularly time to achieve full oral feeds. Finally, 11 children had missing or uninterpretable MRI data and these children were excluded from the analysis. Although we do not know the reasons for failure to obtain MRI (or repeat MRI

in the case of initial low-quality scan), we speculate that this may be due to underlying complex medical conditions such as prematurity and congenital heart disease. Our data highlight the importance of imaging for counseling families about risk of infantile spasms.

5 | CONCLUSIONS

Understanding the risk factors for infantile spasms after acute symptomatic neonatal seizures will facilitate opportunities for prompt diagnosis and treatment of infantile spasms to maximize neurodevelopmental potential. Children who survived acute symptomatic neonatal seizures and had *all three* of the following risk factors: (a) severely abnormal neonatal EEG background on the first day of recording *or* seizures on three or more days of recording; (b) MRI with deep gray *or* brainstem injury; and (c) abnormal tone on discharge neurological examination had >50% risk of infantile spasms in our cohort. Although these findings must be replicated in additional cohorts, it is likely that children with acute symptomatic neonatal seizures and all three risk factors will benefit from specific counseling about infantile spasms and intensive neurology follow-up, as well as parent and primary care physician counseling to facilitate recognition of infantile spasms. Children with only one or two of these risk factors also require careful clinical follow-up, as is provided in current typical clinical practice. However, parents of children with acute symptomatic neonatal seizures who do not have any of the risk factors can be reassured that the risk of infantile spasms is very low.

Identifying children at high risk for infantile spasms is important for counseling, clinical monitoring, and clinical trials designed to test novel agents to prevent post-neonatal epilepsy. Understanding which children are at the highest risk for infantile spasms is also crucial for future studies designed to prevent infantile spasms. A high-risk category with a 50% chance of developing of infantile spasms is attractive for targeted trial design, although large networks like the *Neonatal Seizure Registry* will be needed to enroll sufficient numbers of high-risk children. Future studies will be important to validate these variables and to test the negative predictive value of the model more robustly in the low risk groups.

ACKNOWLEDGMENTS






The Pediatric Epilepsy Research Foundation and Patient Centered Outcomes Research Institute supported this study but did not participate in design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. The authors would like to acknowledge Drs. Donna Ferriero and Faye Silverstein for their seminal contributions to the *Neonatal*

Seizure Registry, as well as the research assistants and parent partners at each study site.

CONFLICT OF INTEREST

Zachary Grinspan, MD, MS, has done consulting work for Alpha Insights and Bio-Pharm Solutions Co., Ltd. (South Korea) and medicolegal consulting. Renée A. Shellhaas, MD, MS, is a consultant for the Epilepsy Study Consortium and receives royalties from UpToDate for authorship of topics related to neonatal seizures. She serves as an associate editor for *Neurology*. The remaining authors have nothing to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines affirm that this work is consistent with the Journal's guidelines for ethical publication.

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REFERENCES

1. Glass HC, Wu YW. Epidemiology of neonatal seizures. *J Pediatr Neurol.* 2009;7:13–7.
2. Glass HC, Shellhaas RA, Wusthoff CJ, *et al.* Contemporary profile of seizures in neonates: a Prospective Cohort Study. *J Pediatr.* 2016;174(98–103):e101.
3. Garfinkle J, Shevell MI. Cerebral palsy, developmental delay, and epilepsy after neonatal seizures. *Pediatr. Neurol.* 2011;44:88–96.
4. Nunes ML, Martins MA, Barea BM, Wainberg RC, da Costa JS. Neurological outcomes of newborns with neonatal seizures. *Arq Neuropsiquiatr.* 2008;66:168–74.
5. Pisani F, Cerminara C, Fusco C, Sisti L. Neonatal status epilepticus vs. recurrent neonatal seizures: clinical findings and outcome. *Neurology.* 2007;69(23):2177–85.
6. Billingham LL, Beslow LA, Abend NS, *et al.* Incidence and predictors of epilepsy after pediatric arterial ischemic stroke. *Neurology.* 2017;88(7):630–7.
7. Fox CK, Glass HC, Sidney S, Smith SE, Fullerton HJ. Neonatal seizures triple the risk of a remote seizure after perinatal ischemic stroke. *Neurology.* 2016;86(23):2179–86.
8. Ronen GM, Buckley D, Penney S, Streiner DL. Long-term prognosis in children with neonatal seizures: a population based study. *Neurology.* 2007;69:1816–22.
9. Knupp KG, Coryell J, Nickels KC, *et al.* Response to treatment in a prospective national infantile spasms cohort. *Ann Neurol.* 2016;79:475–84.
10. Eisermann MM, DeLaRaillere A, Dellatolas G, *et al.* Infantile spasms in Down syndrome—effects of delayed anticonvulsive treatment. *Epilepsy Res.* 2003;55(1–2):21–7.
11. Goh S, Kwiatkowski DJ, Dorer DJ, Thiele EA. Infantile spasms and intellectual outcomes in children with tuberous sclerosis complex. *Neurology.* 2005;65(2):235–8.

12. Widjaja E, Go C, McCoy B, Snead OC. Neurodevelopmental outcome of infantile spasms: a systematic review and meta-analysis. *Epilepsy Res.* 2015;109:155–62.
13. Oc FJ, Lux AL, Darke K, *et al.* The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study. *Epilepsia.* 2011;52(7):1359–64.
14. Shellhaas RA, Chang T, Tsuchida T, *et al.* The American Clinical Neurophysiology Society's Guideline on Continuous Electroencephalography Monitoring in Neonates. *J Clin Neurophysiol.* 2011;28(6):611–7.
15. Tsuchida TN, Wusthoff CJ, Shellhaas RA, Abend NS, Hahn CD, Sullivan JE, *et al.* American clinical neurophysiology society standardized EEG terminology and categorization for the description of continuous EEG monitoring in neonates: report of the American Clinical Neurophysiology Society critical care monitoring committee. *J Clin Neurophysiol.* 2013;30(2):161–73.
16. Shellhaas RA, Gallagher PR, Clancy RR. Assessment of neonatal electroencephalography (EEG) background by conventional and two amplitude-integrated EEG classification systems. *J Pediatr.* 2008;153(3):369–74.
17. Barkovich AJ, Hajnal BL, Vigneron D, *et al.* Prediction of neuro-motor outcome in perinatal asphyxia: evaluation of MR scoring systems. *AJNR Am J Neuroradiol.* 1998;19(1):143–9.
18. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr.* 1978;92(4):529–34.
19. Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, *et al.* Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia.* 2017;58(4):531–42.
20. Grinspan ZM, Patel AD, Hafeez B, Abramson EL, Kern LM. Predicting frequent emergency department use among children with epilepsy: a retrospective cohort study using electronic health data from 2 centers. *Epilepsia.* 2018;59(1):155–69.
21. McFadden D. Quantitative methods for analysing travel behaviour of individuals: some recent developments. London, UK: Croom Helm; 1979.
22. Royston P, Sauerbrei W. Bootstrap assessment of the stability of multivariable models. *Stata J.* 2009;9(4):547–70.
23. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <http://www.R-project.org/>. Published 2013. Accessed April 6, 2020
24. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate Imputation by Chained Equations in R. *J Stat Softw.* 2011;45(3):67.
25. Abu Dhais F, McNamara B, O'Mahony O, McSweeney N, Livingstone V, Murray DM, *et al.* Impact of therapeutic hypothermia on infantile spasms: an observational cohort study. *Dev Med Child Neurol.* 2020;62(1):62–8.
26. Shellhaas RA, Chang T, Tsuchida T, *et al.* The American Clinical Neurophysiology Society's Guideline on continuous electroencephalography monitoring in neonates. *J Clin Neurophysiol.* 2011;28(6):611–7.
27. Nevalainen P, Metsäranta M, Toiviainen-Salo S, Marchi V, Mikkonen K, Vanhatalo S, *et al.* Neonatal neuroimaging and neurophysiology predict infantile onset epilepsy after perinatal hypoxic ischemic encephalopathy. *Seizure.* 2020;80:249–56.
28. Gano D, Sargent MA, Miller SP, Connolly MB, Wong P, Glass HC, *et al.* MRI findings in infants with infantile spasms after neonatal hypoxic-ischemic encephalopathy. *Pediatr Neurol.* 2013;49(6):401–5.
29. Jung DE, Ritacco DG, Nordli DR, Koh S, Venkatesan C. Early anatomical injury patterns predict epilepsy in head cooled neonates with hypoxic-ischemic encephalopathy. *Pediatr Neurol.* 2015;53(2):135–40.
30. McDonough TL, Paolicchi JM, Heier LA, Das N, Engel M, Perlman JM, *et al.* Prediction of future epilepsy in neonates with hypoxic-ischemic encephalopathy who received selective head cooling. *J Child Neurol.* 2017;32(7):630–7.
31. Blumenfeld H. Consciousness and epilepsy: why are patients with absence seizures absent? *Prog Brain Res.* 2005;150:271–86.
32. Kuzniecky R, Guthrie B, Mountz J, *et al.* Intrinsic epileptogenesis of hypothalamic hamartomas in gelastic epilepsy. *Ann Neurol.* 1997;42(1):60–7.
33. Glass HC, Hong KJ, Rogers EE, *et al.* Risk factors for epilepsy in children with neonatal encephalopathy. *Pediatr Res.* 2011;70(5):535–40.
34. Glass HC, Glidden D, Jeremy RJ, Barkovich AJ, Ferriero DM, Miller SP. Clinical neonatal seizures are independently associated with outcome in infants at risk for hypoxic-ischemic brain injury. *J Pediatr.* 2009;155(3):318–23.
35. Garfinkle J, Shevell MI. Prognostic factors and development of a scoring system for outcome of neonatal seizures in term infants. *Eur J Paediatr Neurol.* 2011;15(3):222–9.
36. Pisani F, Sisti L, Seri S. A scoring system for early prognostic assessment after neonatal seizures. *Pediatrics.* 2009;124(4):e580–587.
37. Kato T, Okumura A, Hayakawa F, *et al.* Prolonged EEG depression in term and near-term infants with hypoxic ischemic encephalopathy and later development of West syndrome. *Epilepsia.* 2010;51(12):2392–6.
38. Pestana Knight EM, Schiltz NK, Bakaki PM, Koroukian SM, Lhatoo SD, Kaiboriboon K. Increasing utilization of pediatric epilepsy surgery in the United States between 1997 and 2009. *Epilepsia.* 2015;56(3):375–81.
39. Gregerson CHY, Bakian AV, Wilkes J, *et al.* Disparities in pediatric epilepsy remission are associated with race and ethnicity. *J Child Neurol.* 2019;34(14):928–36.
40. Hussain SA, Lay J, Cheng E, Weng J, Sankar R, Baca CB. Recognition of infantile spasms is often delayed: the ASSIST Study. *J Pediatr.* 2017;190:215–21.e211.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Glass HC, Grinspan ZM, Li Y, *et al*; the Neonatal Seizure Registry Study Group. Risk for infantile spasms after acute symptomatic neonatal seizures. *Epilepsia.* 2020;61:2774–2784. <https://doi.org/10.1111/epi.16749>