# Original Article Construction of an early diagnostic model for brain injury in premature infants based on combined amplitude-integrated electroencephalography and cranial ultrasound parameters

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**Abstract:** Objective: To develop and evaluate an early diagnostic model for brain injury in premature infants (BIPI) using combined amplitude-integrated electroencephalography (aEEG) and cranial ultrasound (CUS) parameters, aiming to enhance the accuracy of early BIPI detection. Methods: This single-center retrospective cohort study included 350 premature infants admitted to the Neonatal Intensive Care Unit (NICU) of the First Affiliated Hospital of Xi'an Medical University between August 2018 and October 2023. Key aEEG parameters (upper boundary voltage, lower boundary voltage, narrow bandwidth, and aEEG score) and CUS parameters (systolic blood flow velocity, diastolic blood flow velocity, and resistance index) were collected. Feature selection was performed using Lasso regression, and a combined risk prediction model was developed. Model performance was assessed using receiver operating characteristic (ROC) curves and the area under the curve (AUC). Results: Significant differences were observed in both aEEG and CUS parameters between the brain injury group (n = 145) and the non-injury group (n = 205) (all P < 0.05). Lasso regression identified seven key parameters for model construction. The combined model achieved an AUC of 0.89, with a sensitivity of 86.21% and specificity of 79.51%, significantly outperforming models based on aEEG or CUS parameters alone (P < 0.001). Conclusion: The combined aEEG and CUS model significantly improves the early detection of BIPI and may facilitate timely interventions to reduce the risk of long-term neurodevelopmental impairments in premature infants.

**Keywords:** Premature infants, brain injury, amplitude-integrated electroencephalography, cranial ultrasound, early diagnosis, lasso regression

#### Introduction

Recent advancements in resuscitation and monitoring technologies have markedly improved the survival rates of critically ill premature infants [1]. For instance, the survival rate of infants born between 26 and 32 weeks of gestation increased from 40.9% in 2012 to 63.6% in 2017. Similarly, the survival rate for infants weighing less than 1000 grams has reached approximately 42.3% [2]. Despite these gains, premature infants remain highly susceptible to brain injury due to the immaturity of their developing brains. Hypoxia, hyperoxia, ischemia, and infections are major contributors to brain injury, collectively referred to as Brain Injury in Premature Infants (BIPI) [3]. BIPI can result from prenatal, perinatal, or postnatal insults such as cerebral hypoxia-ischemia and intracranial hemorrhage, often manifesting with specific clinical signs [4]. Severe cases may lead to long-term neurological complications including intellectual disabilities, cerebral palsy, and epilepsy, imposing significant burdens on affected families [5]. Due to the immature vascular, neural, and endocrine systems, premature infants have limited tolerance to hypoxic events, where even brief episodes of asphyxia can cause irreversible brain damage. The two primary forms of BIPI are intracranial hemorrhage and white matter damage (WMD) [6]. Intracranial hemorrhage often presents as periventricular-intraventricular hemorrhage, whereas WMD commonly results in periventricular leukomalacia, both causing severe and lasting neurological deficits [7]. Currently, no specific treatments for BIPI exist, and the early mortality rate and risk of sequelae remain high. However, the relative plasticity of the premature brain offers opportunities for early intervention. Identifying risk factors and initiating timely management such as oxygen therapy, blood pressure and glucose control, and neuroprotection can significantly mitigate long-term damage [8]. Therefore, early detection and diagnosis of BIPI are critical for improving outcomes.

Due to underdeveloped nervous and muscular systems, the clinical signs of BIPI are often subtle and difficult to detect [9]. This underscores the need for objective and practical diagnostic methods, particularly those involving cerebral function monitoring and neuroimaging. Continuous and non-invasive cerebral function monitoring (CFM) technologies play an essential role [10], including Near-Infrared Spectroscopy (NIRS) [11], Brainstem Auditory Evoked Response (BAER) [12], conventional Electroencephalography (EEG), and Amplitude-Integrated EEG (aEEG) [13]. Among these, aEEG is particularly suited for the Neonatal Intensive Care Unit (NICU) due to its simplicity and capacity for real-time monitoring.

As a simplified form of EEG, aEEG requires only a single-channel electrode, offering intuitive graphical output for continuous bedside monitoring [14]. It has been widely employed in neonatal hypoxic-ischemic encephalopathy (HIE) to predict injury severity and guide interventions [15]. Although research on aEEG application in BIPI is still evolving, early studies suggest its utility in assessing neurodevelopmental maturity and detecting brain injury. For neuroimaging, cranial ultrasound (CUS) remains a noninvasive, cost-effective, and widely used technique in the NICU [16], particularly effective for identifying midline and periventricular abnormalities, including intraventricular hemorrhage. However, CUS is limited by its lower resolution for peripheral lesions, restricted diagnostic range, and operator dependence, which may affect diagnostic accuracy [17].

The diagnostic value of aEEG or CUS alone is limited by suboptimal sensitivity and specificity. Therefore, this study aims to integrate aEEG and CUS parameters using a multiparameter approach to enhance diagnostic performance. By employing a Lasso regression model, a predictive model is constructed to improve early BIPI detection. This multi-parameter strategy seeks to overcome the limitations of single-modality diagnostics, offering clinicians a more comprehensive tool for early identification of high-risk infants and enabling timely interventions to reduce long-term neurodevelopmental impairments.

# Materials and methods

## Study design

This single-center retrospective cohort study aimed to evaluate the early diagnostic value of aEEG and CUS parameters for BIPI. Clinical data were retrospectively collected from 350 premature infants admitted to the Neonatal Intensive Care Unit (NICU) at the First Affiliated Hospital of Xi'an Medical University between August 2018 and October 2023. They were divided into a brain injury group (n = 145) and a non-injury group (n = 205). The study was approved by the Ethics Committee of The First Affiliated Hospital of Xi'an Medical University. As a retrospective study, the requirement for informed consent from guardians was waived.

## Inclusion and exclusion criteria

*Inclusion criteria:* (1) Gestational age < 37 weeks. (2) Admission within 24 hours after birth. (3) Meeting the diagnostic criteria for BIPI [18]. (4) Complete clinical data available.

*Exclusion criteria*: (1) Admission > 24 hours after birth or hospital stay < 1 week. (2) Diagnosed with bilirubin encephalopathy, hypoglycemic encephalopathy, brain injury from inherited metabolic disorders, TORCH infections, congenital neurological malformations, chromosomal abnormalities, or central nervous system infections. (3) Inability to complete ultrasound cerebral blood flow assessment, cranial MRI, aEEG, or NBNA scoring. (4) Incomplete clinical data. (5) Death within 12 hours of intensive care treatment after admission. (6) Presence of congenital brain malformations. (7) Severe metabolic disorders.

## Clinical data collection

Demographic data included sex, birth weight, gestational age, delivery method, and 1-minute and 5-minute Apgar scores. Imaging and physiological parameters included aEEG metrics (upper boundary voltage, lower boundary voltage, narrow bandwidth, and aEEG score) and CUS measurements (systolic blood flow velocity [Vs], diastolic blood flow velocity [Vd], and resistance index [RI]).

#### Detection methods

aEEG monitoring: Brain electrical activity was assessed using the Olympic CFM 6000 brain function monitor. The device was calibrated before use, and the infant's scalp was prepared with fine sandpaper paste and alcohol. Electrodes were placed on the bilateral parietal bones (P3-P4) according to the international 10/20 EEG system, with a 75 mm interelectrode distance. The midpoint between the electrodes was located 50 mm posterior to the vertex, and the reference electrode was placed 25 mm anterior to the vertex along the forehead midline (Fp1-Fp2). Electrodes were secured with adhesive tape and an elastic cap, ensuring impedance was maintained below 5 kΩ.

*CUS examination:* Bedside CUS was performed on the second day after birth and weekly thereafter until a corrected gestational age of 40 weeks was reached. Using a Mindray M9 color Doppler ultrasound system, infants in the supine position were scanned via the anterior fontanelle to obtain coronal views of the frontal lobe, anterior horns of the lateral ventricles, third ventricle, and occipital lobe regions. The probe was rotated 90° to obtain mid-sagittal and bilateral sagittal images to assess the anterior horns, central regions, and posterior horns of the lateral ventricles. Cranial injury findings were recorded, and bilateral cerebral Vs, Vd, and RI values were documented.

## Functional scoring

*aEEG scoring:* Brain activity was evaluated using the Hellström-Westas five-point classification system, categorizing patterns into continuous normal voltage, discontinuous normal voltage, burst-suppression, sustained low voltage, and electrical silence. Scores were adjusted based on gestational age: (1) 27-28 weeks: 2 points. (2) 29-30 weeks: 6 points. (3) 31-32 weeks: 8 points. (4) 33-35 weeks: 10 points. (5) 36-37 weeks: 11 points. The maximum score was 13 points [19].

Apgar scoring: The Apgar score assessed newborn health based on heart rate, respiration, muscle tone, reflex response, and skin color. Scores ranged from 0 to 10, with higher scores indicating better health status [20].

#### Outcome measures

*Primary outcomes:* Development of a predictive model for BIPI using aEEG and CUS parameters, and evaluation of its diagnostic effectiveness and accuracy.

Secondary outcomes: Recording of functional scores, including aEEG and Apgar scores, to assess the neurodevelopmental and immediate health status of the infants.

Data processing and statistical analysis

All statistical analyses were performed using SPSS version 26.0, and figures were generated using R version 4.2.2. Data entry and verification were conducted independently by two researchers before uploading to an electronic database.

• Categorical variables were expressed as frequencies and percentages and compared using the Chi-square test.

• Continuous variables were presented as mean  $\pm$  standard deviation and compared using independent samples t-tests. Variables not normally distributed were expressed as median (P25, P75).

• Logistic regression analysis was used to identify risk factors for BIPI.

• Feature selection for model construction was conducted using the Lasso regression model.

• The diagnostic performance of the predictive model was evaluated using Receiver Operating Characteristic (ROC) curves and the Area Under the Curve (AUC).

• A *P*-value < 0.05 was considered statistically significant.

Factor	Brain Injury Group (n = 145)	Non-Injury Group (n = 205)	Statistic	P-value
Sex				
Male	83	102	1.901	0.167
Female	62	103		
Delivery Method				
Cesarean Section	61	96	0.778	0.378
Vaginal Delivery	84	109		
Premature Rupture of Membranes				
Yes	52	59	1.967	0.161
No	93	146		
Apgar Score (1 min)				
$\leq$ 3 Points	22	6	17.304	< 0.001
> 3 Points	123	199		
Apgar Score (5 min)				
$\leq$ 7 Points	17	9	6.643	0.01
> 7 Points	128	196		
Gestational Age (days)	244.00 [240.00, 249.00]	244.00 [240.00, 247.00]	-0.068	0.946
Birth Weight (g)	2083.86 ± 347.86	2151.00 [1975.00, 2378.00]	-1.708	0.088

 Table 1. Comparison of clinical data

#### Results

#### Comparison of clinical data

As shown in **Table 1**, clinical characteristics were compared between the groups. No significant differences were observed in gender distribution (P = 0.167), delivery method (cesarean section vs. vaginal delivery, P = 0.378), or incidence of premature rupture of membranes (P = 0.161). Gestational age (P = 0.946) and birth weight (P = 0.088) were also comparable between groups.

However, a significantly higher proportion of infants in the brain injury group had a 1-minute Apgar score  $\leq$  3 compared to the non-injury group (P < 0.001), indicating a strong association between low 1-minute Apgar scores and brain injury. Similarly, a higher proportion of infants in the brain injury group had a 5-minute Apgar score  $\leq$  7 (P = 0.010). Additionally, the average gestational age and birth weight were significantly lower in the brain injury group than in the non-injury group (both P < 0.001).

## Comparison of aEEG parameters and scores

As shown in **Figure 1**, significant differences in aEEG parameters and scores were observed between the two groups. The brain injury group

exhibited significantly lower upper boundary voltage, lower boundary voltage, and narrower bandwidth values (all P < 0.001) compared to the non-injury group.

## Comparison of CUS parameters between

As illustrated in **Figure 2**, significant differences in CUS parameters were noted. Infants in the BIPI group had significantly lower Vs and Vd values and a significantly higher RI (all P < 0.001) compared to those in the non-injury group.

# Correlation analysis between Apgar scores and aEEG and CUS parameters

As shown in **Figures 3** and **4**, correlation analyses were conducted between Apgar scores and aEEG and CUS parameters. A significant negative correlation was found between the upper boundary voltage and the 5-minute Apgar score (r = -0.108, P = 0.043). No other significant correlations were observed between aEEG or CUS parameters and either the 1-minute or 5-minute Apgar scores. While the upper boundary voltage may reflect changes in the 5-minute Apgar score, this does not imply that other parameters are unrelated to brain injury, as they may influence outcomes through mechanisms not captured by Apgar scoring.



**Figure 1.** Comparison of aEEG Parameters and Scores. A. Comparison of upper boundary voltage between brain injury and non-injury groups. B. Comparison of lower boundary voltage between brain injury and non-injury groups. C. Comparison of narrow bandwidth values between brain injury and non-injury groups. D. Comparison of overall aEEG scores between brain injury and non-injury groups. Note: aEEG: Amplitude-Integrated Electroencephalography.

# Predictive value of aEEG and CUS parameters in BIPI

As shown in **Figure 5**, aEEG and CUS parameters demonstrated varying predictive abilities for BIPI. The aEEG score achieved an AUC of 0.709, with a sensitivity of 85.52% and a specificity of 54.15%, indicating high sensitivity for detecting brain injury. Similarly, Vs (AUC = 0.724) and Vd (AUC = 0.688) demonstrated high sensitivities of 84.14% and 89.66%, respectively, supporting their utility in early detection. In terms of specificity, the lower boundary voltage (76.10%, AUC = 0.719) and RI (71.71%, AUC = 0.672) performed relatively well, highlighting their diagnostic value in distinguishing non-injury cases.

## Construction of the lasso regression model

As depicted in **Figure 6**, a Lasso regression model was employed to identify significant parameters for constructing a predictive model for BIPI. The final model formula was as follows.

Model formula = 1.634267971 + (0.10717217) Upper Boundary Voltage (µV) + 0.339154982



**Figure 2.** Comparison of CUS Parameters Between. A. Comparison of Vs (systolic blood flow velocity) between brain injury and non-injury groups. B. Comparison of Vd (diastolic blood flow velocity) between brain injury and non-injury groups. C. Comparison of resistance index (RI) between brain injury and non-injury groups. Note: CUS: Cranial Ultrasound, RI: Resistance Index, Vs: Systolic Blood Flow Velocity, and Vd: Diastolic Blood Flow Velocity,  $\mu$ V: microvolts.

# Application of aEEG and CUS in early diagnosis of BIPI



**Figure 3.** Correlation Analysis Between aEEG and CUS Parameters with 1-Minute Apgar Scores. A. Correlation between 1-minute Apgar score and upper boundary voltage. B. Correlation between 1-minute Apgar score and narrow bandwidth. D. Correlation between 1-minute Apgar score and aEEG score. E. Correlation between 1-minute Apgar score and aEEG score. E. Correlation between 1-minute Apgar score and Vs. F. Correlation between 1-minute Apgar score and resistance index (RI). Note: aEEG: Amplitude-Integrated Electroencephalography, CUS: Cranial Ultrasound, RI: Resistance Index, Vs: Systolic Blood Flow Velocity, Vd: Diastolic Blood Flow Velocity, and µV: microvolts.

# Application of aEEG and CUS in early diagnosis of BIPI



**Figure 4.** Correlation Analysis Between aEEG and CUS Parameters with 5-Minute Apgar Scores. A. Correlation between 5-minute Apgar score and upper boundary voltage. B. Correlation between 5-minute Apgar score and lower boundary voltage. C. Correlation between 5-minute Apgar score and narrow bandwidth. D. Correlation between 5-minute Apgar score and aEEG score. E. Correlation between 5-minute Apgar score and Vs. F. Correlation between 5-minute Apgar score and Vd. G. Correlation between 5-minute Apgar score and resistance index (RI). Note: aEEG: Amplitude-Integrated Electroencephalography, CUS: Cranial Ultrasound, RI: Resistance Index, Vs: Systolic Blood Flow Velocity, Vd: Diastolic Blood Flow Velocity, and µV: microvolts.



**Figure 5.** Predictive Value of aEEG and CUS Parameters in BIPI. A. ROC curve of upper boundary voltage, illustrating its diagnostic performance in predicting BIPI. B. ROC curve of lower boundary voltage, illustrating its diagnostic performance in predicting BIPI. C. ROC curve of narrow bandwidth, illustrating its diagnostic performance in predicting BIPI. D. ROC curve of aEEG score, illustrating its diagnostic performance in predicting BIPI. F. ROC curve of Vd, illustrating its diagnostic performance in predicting BIPI. G. ROC curve of resistance index (RI), illustrating its diagnostic performance in predicting BIPI. Note: ROC: Receiver Operating Characteristic, aEEG: Amplitude-Integrated Electroencephalography, CUS: Cranial Ultrasound, RI: Resistance Index, Vs: Systolic Blood Flow Velocity, Vd: Diastolic Blood Flow Velocity, μV: microvolts, AUC: Area Under the Curve, and BIPI: Brain Injury in Premature Infants.



**Figure 6.** Lasso Regression Model Construction of aEEG and CUS Parameters. A. Regularization path, showing the effect of different  $\lambda$  values on model complexity, thereby selecting the optimal  $\lambda$  value. B. Coefficient path plot, illustrating the changes in feature coefficients across different  $\lambda$  values. Note: Lasso: Lasso Regression, aEEG: Amplitude-Integrated Electroencephalography, CUS: Cranial Ultrasound, and  $\lambda$ : Regularization Parameter.

Lower Boundary Voltage ( $\mu$ V) + (0.051914416) Narrow Bandwidth ( $\mu$ V) + (0.372943544) aEEG Score + 0.23099412 Vs (cm/s) + 0. 420342285 × Vd (cm/s) + (-5.359420584) × RI. The optimal regularization parameter ( $\lambda$ ) was set at 0.0053963 to balance model complexity and prevent overfitting. Seven key parameters - upper boundary voltage, lower boundary voltage, narrow bandwidth, aEEG score, Vs, Vd, and RI - were selected as significant predictors. The model demonstrated strong predictive performance, substantially enhancing diagnostic accuracy.

#### Comparison of diagnostic efficacy between the combined model and individual indicators

As shown in Figure 7 and Table 2, the Lasso risk score model outperformed models based on individual aEEG or CUS parameters. The combined model achieved an AUC of 0.89, significantly higher than individual indicators such as the upper boundary voltage (AUC = 0.653) and lower boundary voltage (AUC = 0.719). It also exhibited high sensitivity (86.21%) and specificity (79.51%), reflecting excellent diagnostic accuracy.

In contrast, individual parameters demonstrated imbalanced performance. For example, while the lower boundary voltage showed relatively high specificity (76.10%), it had lower sensitivity (59.31%). Vd, conversely, exhibited high sensitivity (89.66%) but low

specificity (43.90%). The Lasso model also achieved the highest Youden's index (65.72%) and overall diagnostic accuracy, offering a better balance between sensitivity and specificity. These results highlight the superiority of the combined model in reducing both false positives and false negatives, making it a more effective tool for early BIPI detection.

#### Discussion

Recent advancements in NICU technologies have significantly improved the survival rates of



In this study, both aEEG and CUS parameters effectively differentiated between infants with and without brain iniury. Specifically, infants with BIPI exhibited significantly lower upper boundary voltage, lower boundary voltage, and narrow bandwidth values on aEEG, indicating substantial alterations in brain function status. Regarding CUS findings, infants with BIPI had significantly lower Vs and Vd values and higher RI values, suggesting hemodynamic disturbances associated with brain injury. These results are consistent with previous studies, including Griesmaier et al. [26], who reported significant correlations between aEEG scores and brain injury severity as detected by MRI, and Boswinkel et al. [27], who evaluated BIPI characteristics

Figure 7. ROC Curve of the Combined Model. Note: ROC: Receiver Operating Characteristic.

premature infants; however, this improvement has also coincided with an increased incidence of BIPI [21]. Brain injury in premature infants can result in long-term neurodevelopmental sequelae, including intellectual disabilities and cerebral palsy, imposing substantial burdens on families and society. Therefore, early identification and intervention are critical [22]. Nonetheless, due to immature nervous and muscular systems, clinical manifestations of BIPI are often atypical, complicating early diagnosis and underscoring the need for effective diagnostic tools.

Given their practicality in the NICU setting, aEEG and CUS have been increasingly adopted for early brain injury assessment. However, the limited sensitivity and specificity of either method alone emphasize the need for a combined diagnostic approach [23]. Variane et al. [24] reviewed the extensive application of aEEG in NICUs, highlighting its important role in neonatal brain injury assessment. Similarly, De Wel et al. [25] explored the association between early, continuous aEEG monitoring and brain development or injury, further supporting its diagnostic value. using CUS and MRI in moderate to late preterm infants, further validating the diagnostic utility of CUS.

In addition, this study utilized a Lasso regression model to identify seven key features associated with brain injury: upper boundary voltage, lower boundary voltage, narrow bandwidth, aEEG score, Vs, Vd, and RI. The predictive model constructed using these parameters achieved an AUC of 0.89, with a sensitivity of 86.21% and a specificity of 79.51%, significantly outperforming models based on individual aEEG or CUS parameters. This demonstrates that the combined use of aEEG and CUS provides a more comprehensive and accurate diagnostic framework for BIPI. Lin et al. [5] similarly emphasized the predictive value of aEEG parameters in brain injury assessment, while Wang et al. [28] highlighted the utility of early aEEG-EEG monitoring for predicting long-term neurodevelopmental outcomes in extremely preterm infants.

Compared to previous studies, the findings of this study further validate the combined application of aEEG and CUS in the early diagnosis of BIPI. For example, O'Muircheartaigh et al.

Marker 1	Marker 2	Z value	P value	AUC Difference	CI Lower Upper			
Upper Boundary Voltage (µV)	Lasso risk score	-7.779	< 0.001	-0.237	-0.2960.177			
Lower Boundary Voltage (µV)	Lasso risk score	-6.81	< 0.001	-0.17	-0.2190.121			
Narrow band width ( $\mu V$ )	Lasso risk score	-8.989	< 0.001	-0.293	-0.3570.229			
aGGE score	Lasso risk score	-6.925	< 0.001	-0.181	-0.2320.129			
Vs (cm/s)	Lasso risk score	-6.618	< 0.001	-0.165	-0.2140.116			
Vd (cm/s)	Lasso risk score	-7.312	< 0.001	-0.202	-0.2560.148			
RI	Lasso risk score	-7.28	< 0.001	-0.217	-0.2760.159			

Table 2. Comparison of diagnostic efficacy between combined model and individual indicators

Note: aEEG: Amplitude-Integrated Electroencephalography, CUS: Cranial Ultrasound, RI: Resistance Index, Vs: Systolic Blood Flow Velocity, Vd: Diastolic Blood Flow Velocity, µV: microvolts, AUC: Area Under the Curve, and CI: Confidence Interval.

[29] employed Bayesian regression techniques to construct a model for detecting focal white matter injury in neonates, achieving high accuracy in estimating brain tissue intensity and morphology. Sjöbom et al. [30] explored the predictive role of Neurofilament Light (NfL) as a biomarker for adverse neurodevelopmental outcomes in premature infants, underscoring the potential of biomarkers in brain injury diagnostics. Xu et al. [31] identified a positive correlation between PLAGL1 gene methylation levels in cord blood and the occurrence of BIPI. suggesting its potential as a diagnostic marker. Similarly, Lloyd et al. [32] evaluated the predictive value of multi-channel EEG for 2-year neurodevelopmental outcomes in preterm infants, while Patel et al. [33] proposed a risk-factorbased CUS screening protocol that improved resource utilization and brain injury detection rates. Other studies have demonstrated the value of aEEG in predicting the severity of HIE and guiding early interventions. By integrating aEEG and CUS parameters, this study addresses the limitations of single-modality approaches, further enhancing diagnostic accuracy.

Moreover, this study reaffirms the clinical value of CUS parameters (Vs, Vd, and RI) in differentiating between infants with and without brain injury. These findings are consistent with previous reports on the application of CUS in assessing cerebral blood flow, further emphasizing its predictive utility for brain injury. Wang et al. [28] also supported the association between aEEG parameters and brain injury prognosis. Hüning et al. [34] combined aEEG and MRI to assess brain function and structure, demonstrating the predictive value of integrated modalities for neurodevelopmental outcomes in preterm infants. Furthermore, O'Muircheartaigh et al. [29] illustrated the value of MRI-based brain models in detecting white matter injury, highlighting the importance of multimodal neuroimaging in brain injury assessment.

The combined diagnostic model based on aEEG and CUS parameters offers clinicians an effective tool for the early identification of BIPI. In the NICU environment, the non-invasive nature of aEEG and CUS allows for repeated assessments as the infant's condition evolves. making these methods practical and reliable. The risk score model constructed using Lasso regression enables more accurate prediction of brain injury, supporting timely interventions such as oxygen therapy and blood pressure or glucose management. These measures can help mitigate the long-term neurodevelopmental impacts of brain injury in premature infants. Zhu et al. [17] demonstrated the potential of a radiomics model combined with CUS in predicting white matter injury in BIPI, further supporting the clinical value of multi-parameter approaches. Similarly, Patel et al. [33] emphasized the role of CUS protocols in optimizing resource allocation and improving detection rates, reinforcing the importance of multimodal diagnostic strategies.

Despite its strengths, this study has several limitations. First, as a single-center retrospective study, it is susceptible to selection bias. Multi-center, large-sample prospective studies are needed to validate the model's generalizability and robustness. Second, this study primarily focused on aEEG and CUS parameters, excluding other potential factors such as genetic and metabolic biomarkers. Future research should incorporate additional biological and imaging markers to develop more comprehensive predictive models. Finally, the relatively short follow-up period limited the evaluation of long-term neurodevelopmental outcomes. Extending the follow-up duration in future studies will provide a more thorough assessment of the long-term effects of BIPI and the efficacy of early interventions.

In conclusion, this study successfully developed an early diagnostic model for BIPI based on the combined use of aEEG and CUS parameters, significantly improving diagnostic efficacy. The model enables clinicians to better identify high-risk infants and implement timely interventions, thereby reducing the long-term neurodevelopmental impacts of brain injury. With further validation in multi-center studies, this model holds promise as a valuable tool for the early diagnosis and intervention of BIPI, ultimately improving the prognosis of premature infants.

#### Disclosure of conflict of interest

None.

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#### References

- [1] Kaempf JW and Gautham K. Do small baby units improve extremely premature infant outcomes? J Perinatol 2022; 42: 281-285.
- [2] Helenius K, Sjörs G, Shah PS, Modi N, Reichman B, Morisaki N, Kusuda S, Lui K, Darlow BA, Bassler D, Håkansson S, Adams M, Vento M, Rusconi F, Isayama T, Lee SK and Lehtonen L. Survival in very preterm infants: an international comparison of 10 national neonatal networks. Pediatrics 2017; 140: e20171264.
- [3] Spinillo A, Dominoni M, Mas FD, Cesari S, Fiandrino G and Gardella B. Placental fetal vascular malperfusion, neonatal neurologic morbidity, and infant neurodevelopmental outcomes: a systematic review and meta-analysis. Am J Obstet Gynecol 2023; 229: 632-640.e632.
- [4] Ma LM, Si X, Zhai SF, Wu XL, Li N and Liu XH. Recombinant erythropoietin protective and related effects on brain injury in premature infants. Eur Rev Med Pharmacol Sci 2023; 27: 10958-10967.

- [5] Lin C, Chen B, Wang Z, Zou A and Ke M. Assessment of neural function recovery in premature infants at high risk of brain injury using amplitude integrated electroencephalography and GMs scales. J Neurosci Methods 2024; 410: 110246.
- [6] Armstrong RC, Sullivan GM, Perl DP, Rosarda JD and Radomski KL. White matter damage and degeneration in traumatic brain injury. Trends Neurosci 2024; 47: 677-692.
- [7] Hadi E, Haddad L, Levy M, Gindes L, Hausman-Kedem M, Bassan H, Ben-Sira L, Libzon S, Kassif E, Hoffmann C, Leibovitz Z, Kasprian G and Lerman-Sagie T. Fetal intraventricular hemorrhage and periventricular hemorrhagic venous infarction: time for dedicated classification system. Ultrasound Obstet Gynecol 2024; 64: 285-293.
- [8] Malwade S, Chalipat S, Shah P and Mane S. The role of early intervention therapy in neurodevelopmental outcomes of premature infants. Cureus 2024; 16: e68618.
- [9] Majumdar A, Jana A, Jana A, Biswas S, Bhatacharyya S and Bannerjee S. Importance of normal values of CSF parameters in term versus preterm neonates. J Clin Neonatol 2013; 2: 166-168.
- [10] Jain P, Saini SS, Sahu JK, Madaan P, Sundaram V and Dutta S. Predictive ability of amplitude integrated electroencephalography for adverse outcomes in neonates with sepsis-associated encephalopathy: a cohort study. Indian J Pediatr 2025; 92: 73-75.
- [11] Roldán M and Kyriacou PA. Near-infrared spectroscopy (NIRS) in traumatic brain injury (TBI). Sensors (Basel) 2021; 21: 1586.
- [12] Rossetti E, Pro S, Picardo S, Longo D and DI Capua M. Brain auditory evoked potentials in pediatric intensive care unit: diagnostic role on encephalopathy and central respiratory failure on infants. Minerva Pediatr (Torino) 2024; 76: 197-200.
- [13] Zhu D, Wang M, Feng F, Nan N, Liu Y, Shi J and Mao B. Correlation between clinical features and total maturation score by magnetic resonance imaging in very low birth weight premature infants with brain injury. Ann Palliat Med 2021; 10: 2089-2097.
- [14] Singh A, Saluja S, Kler N, Garg P, Soni A and Thakur A. Amplitude integrated EEG: how much it helps in prognostication in neonatal encephalopathy? J Matern Fetal Neonatal Med 2022; 35: 7748-7755.
- [15] Meder U, Cseko AJ, Szakacs L, Balogh CD, Szakmar E, Andorka C, Kovacs K, Dobi M, Brandt FA, Szabo M, Szabo AJ and Jermendy A. Longitudinal analysis of amplitude-integrated electroencephalography for outcome prediction in

hypoxic-ischemic encephalopathy. J Pediatr 2022; 246: 19-25.e15.

- [16] Liu L. Application of brain ultrasound in premature infants with brain injury. Front Neurol 2023; 14: 1095280.
- [17] Zhu T, Zhang S, Jiang W, Chai D, Mao J, Wei Y and Xiong J. A multiplanar radiomics model based on cranial ultrasound to predict the white matter injury in premature infants and an analysis of its correlation with neurodevelopment. J Ultrasound Med 2024; 43: 899-911.
- [18] Neonatal Professional Committee of Chinese Medical Doctor Association. Experts' consensus on the diagnosis, prevention and treatment of brain injury in premature infants in China. Zhongguo Dang Dai Er Ke Za Zhi 2012; 14: 883-884.
- [19] Luo F, Chen Z, Lin H, Wang C, Ma X and Shi L. Evaluation of cerebral function in high risk term infants by using a scoring system based on aEEG. Transl Pediatr 2014; 3: 278-286.
- [20] Zou F, Fang Y, Lin Y, Feng Z, Cai S, Huang J, Zheng S and Li J. Pathway analysis of the impact of family function and self-efficacy on depression and anxiety in patients undergoing in vitro fertilization-embryo transfer. BMC Psychol 2024; 12: 749.
- [21] Yates N, Gunn AJ, Bennet L, Dhillon SK and Davidson JO. Preventing brain injury in the preterm infant-current controversies and potential therapies. Int J Mol Sci 2021; 22: 1671.
- [22] Xie Y, Yang Y and Yuan T. Brain damage in the preterm infant: clinical aspects and recent progress in the prevention and treatment. CNS Neurol Disord Drug Targets 2023; 22: 27-40.
- [23] Zhang Q and Zhou X. Review on the application of imaging examination for brain injury in premature infants. Front Neurol 2023; 14: 1100623.
- [24] Variane GFT, Rodrigues DP, Pietrobom RFR, França CN, Netto A and Magalhães M. Newborns at high risk for brain injury: the role of the amplitude-integrated electroencephalography. J Pediatr (Rio J) 2022; 98: 565-571.
- [25] De Wel O, Van Huffel S, Lavanga M, Jansen K, Dereymaeker A, Dudink J, Gui L, Hüppi PS, de Vries LS, Naulaers G, Benders M and Tataranno ML. Relationship between early functional and structural brain developments and brain injury in preterm infants. Cerebellum 2021; 20: 556-568.
- [26] Griesmaier E, Schreiner C, Winkler I, Posod A, Sappler M, Kiechl-Kohlendorfer U and Neubauer V. Association of aEEG and brain injury severity on MRI at term-equivalent age in preterm infants. Acta Paediatr 2024; 113: 229-238.

- [27] Boswinkel V, Krüse-Ruijter MF, Nijboer-Oosterveld J, Nijholt IM, Edens MA, Mulder-de Tollenaer SM, Smit-Wu MN, Boomsma MF, de Vries LS and van Wezel-Meijler G. Incidence of brain lesions in moderate-late preterm infants assessed by cranial ultrasound and MRI: the BIMP-study. Eur J Radiol 2021; 136: 109500.
- [28] Wang X, Trabatti C, Weeke L, Dudink J, Swanenburg de Veye H, Eijsermans R, Koopman-Esseboom C, Benders M and Tataranno ML. Early qualitative and quantitative amplitude-integrated electroencephalogram and raw electroencephalogram for predicting long-term neurodevelopmental outcomes in extremely preterm infants in the Netherlands: a 10-year cohort study. Lancet Digit Health 2023; 5: e895e904.
- [29] O'Muircheartaigh J, Robinson EC, Pietsch M, Wolfers T, Aljabar P, Grande LC, Teixeira R, Bozek J, Schuh A, Makropoulos A, Batalle D, Hutter J, Vecchiato K, Steinweg JK, Fitzgibbon S, Hughes E, Price AN, Marquand A, Reuckert D, Rutherford M, Hajnal JV, Counsell SJ and Edwards AD. Modelling brain development to detect white matter injury in term and preterm born neonates. Brain 2020; 143: 467-479.
- [30] Sjöbom U, Hellström W, Löfqvist C, Nilsson AK, Holmström G, Pupp IH, Ley D, Blennow K, Zetterberg H, Sävman K and Hellström A. Analysis of brain injury biomarker neurofilament light and neurodevelopmental outcomes and retinopathy of prematurity among preterm infants. JAMA Netw Open 2021; 4: e214138.
- [31] Xu L, Jin X, Lu Y, Zheng B, Zheng Z, Chen L and Zhu H. Increased PLAGL1 gene methylation in cord blood is positively correlated with brain injury in chorioamniotic preterm infants. Biochem Genet 2024; 1-15.
- [32] Lloyd RO, O'Toole JM, Livingstone V, Filan PM and Boylan GB. Can EEG accurately predict 2-year neurodevelopmental outcome for preterm infants? Arch Dis Child Fetal Neonatal Ed 2021; 106: 535-541.
- [33] Patel S, Martel-Bucci A, Wintermark P, Shalish W, Claveau M and Beltempo M. Optimizing timing and frequency of head ultrasound screening for severe brain injury among preterm infants born <32 weeks' gestation. J Matern Fetal Neonatal Med 2022; 35: 10330-10336.
- [34] Hüning B, Storbeck T, Bruns N, Dransfeld F, Hobrecht J, Karpienski J, Sirin S, Schweiger B, Weiss C, Felderhoff-Müser U and Müller H. Relationship between brain function (aEEG) and brain structure (MRI) and their predictive value for neurodevelopmental outcome of preterm infants. Eur J Pediatr 2018; 177: 1181-1189.