EARLY BIOMARKERS OF NEURODEVELOPMENTAL DISORDERS IN PRETERM INFANTS: A PROSPECTIVE MULTIMODAL COHORT STUDY

Mamadaliyev Boburjon Odiljon o‘g‘li
4th-year undergraduate student in Pediatrics, Group 222, Central Asian Medical University e-mail: boburjonmamadaliyev038@gmail.com

Abstract: *Background*

Preterm birth remains one of the strongest risk factors for neurodevelopmental disorders (NDDs), including cerebral palsy, autism spectrum disorder, and cognitive impairment. Early identification of high-risk infants through reliable biomarkers may enable timely intervention and improve long-term outcomes. However, clinically validated early predictors remain insufficiently integrated into neonatal practice.

Methods

A prospective cohort study was conducted among preterm infants born at <32 weeks’ gestation and admitted to a tertiary neonatal intensive care unit. Multimodal biomarkers were evaluated, including serum neuroinflammatory markers (IL-6, S100B), amplitude-integrated electroencephalography (aEEG), cranial MRI metrics, and standardized neurological examinations. Neurodevelopmental outcomes were assessed at corrected age of 24 months using validated developmental scales. Multivariate logistic regression was applied to determine independent predictors of adverse outcomes.

Results

Among 162 enrolled infants, abnormal aEEG patterns within the first week of life, elevated S100B concentrations, and reduced white matter fractional anisotropy on MRI were significantly associated with later neurodevelopmental impairment ($p<0.01$). A combined biomarker model demonstrated improved predictive accuracy compared with single markers (AUC 0.87 vs. 0.68–0.74). Early systemic inflammation correlated with delayed motor and cognitive development.

Conclusion

Multimodal early biomarkers integrating neurophysiological, biochemical, and neuroimaging parameters show strong potential for early risk stratification in preterm infants. Implementation of combined screening algorithms may facilitate personalized follow-up and early neuroprotective interventions.

Keywords

Preterm infants; Neurodevelopmental disorders; Early biomarkers; aEEG; MRI; Neuroinflammation; Neonatal neurology

Introduction

Preterm birth represents a major global health concern and accounts for a substantial proportion of neonatal morbidity and long-term neurological disability. Advances in neonatal intensive care have improved survival rates among extremely preterm infants; however, the prevalence of neurodevelopmental disorders (NDDs) remains high. These

disorders encompass a wide clinical spectrum, including cognitive delay, motor impairment, attention deficits, and autism spectrum conditions. Early identification of vulnerable infants is essential for initiating neuroprotective strategies during critical developmental windows.

Neurodevelopmental vulnerability in preterm infants is closely linked to the immaturity of the central nervous system, susceptibility to hypoxic-ischemic injury, inflammation, and disturbances in synaptogenesis and myelination. Emerging evidence suggests that early biomarkers—measurable biological or physiological indicators—may allow clinicians to predict neurodevelopmental outcomes before clinical manifestations become evident.

Traditional assessment tools, such as neurological examination or developmental screening scales, often lack sufficient sensitivity during the neonatal period. Consequently, attention has shifted toward integrated approaches combining neurophysiological monitoring, neuroimaging, and molecular markers. Despite promising findings, there remains a lack of consensus regarding which biomarkers provide the highest predictive value in routine clinical practice.

The present study aims to evaluate the predictive utility of early multimodal biomarkers in identifying preterm infants at risk of neurodevelopmental disorders. The objectives were: (1) to analyze associations between early biochemical, electrophysiological, and neuroimaging markers and developmental outcomes; (2) to develop a combined predictive model; and (3) to assess clinical applicability for early screening programs.

Methods

Study Design

This was a prospective observational cohort study conducted in a tertiary neonatal intensive care unit between January 2022 and December 2024.

Study Population

Eligible participants included preterm infants born at <32 weeks’ gestation or with birth weight <1500 g. Exclusion criteria comprised major congenital anomalies, chromosomal disorders, or severe perinatal infections known to independently affect neurodevelopment.

Clinical Variables and Biomarkers

The following parameters were collected:

1. Biochemical Markers

- Serum S100B protein
- Interleukin-6 (IL-6)
- C-reactive protein (CRP)

2. Neuroimaging

- Cranial MRI at term-equivalent age
- White matter integrity assessed using diffusion tensor imaging metrics

3. Neurological Examination

- Standardized neonatal neurological assessment scores

4. Neurophysiological Monitoring

- Amplitude-integrated EEG recorded during the first 72 hours of life
- Background pattern classification and seizure activity

Outcome Measures

Primary outcome: neurodevelopmental impairment at corrected age of 24 months, defined as cognitive or motor score below −2 SD on standardized developmental testing.

Ethical Considerations

Ethical approval was obtained from the Institutional Review Board (Approval No. 4). Written informed parental consent was secured for all participants.

Statistical Analysis

Continuous variables were analyzed using Student’s t-test or Mann–Whitney U test. Categorical variables were compared using chi-square analysis. Multivariate logistic regression identified independent predictors. Predictive performance was evaluated using receiver operating characteristic (ROC) curves.

Results

Participant Characteristics

A total of 162 preterm infants were included, with a mean gestational age of 29.1 ± 1.8 weeks and mean birth weight of 1240 ± 260 g. Neurodevelopmental impairment was identified in 36 infants (22.2%) at follow-up.

Biochemical Biomarkers

Infants with adverse outcomes demonstrated significantly higher early S100B levels and elevated IL-6 concentrations compared with the control group ($p<0.01$). These findings suggest a link between systemic inflammation and later neurological dysfunction.

Neurophysiological Findings

Abnormal aEEG background patterns during the first week of life were strongly associated with later developmental delay (OR 3.8; 95% CI 1.7–8.4).

Neuroimaging Outcomes

MRI analysis revealed reduced fractional anisotropy in periventricular white matter regions among infants with poor outcomes, indicating disrupted myelination processes.

Combined Predictive Model

(Table 1. Multimodal biomarker predictors of neurodevelopmental impairment in preterm infants)

A composite model integrating S100B levels, aEEG abnormalities, and MRI findings achieved an area under the ROC curve of 0.87, outperforming single-parameter models.

Discussion

This study demonstrates that early multimodal biomarkers significantly enhance prediction of neurodevelopmental outcomes in preterm infants. Elevated S100B protein levels likely reflect astroglial injury and blood–brain barrier disruption, while abnormal aEEG patterns indicate early disturbances in cortical activity. Structural MRI findings further support the role of white matter vulnerability in preterm brain injury.

The findings align with previous research highlighting the contribution of neuroinflammation and disrupted neural connectivity to later developmental deficits.

Integration of electrophysiological monitoring with biochemical markers may offer a more comprehensive representation of early brain health compared with isolated assessments.

One of the major strengths of this study is the longitudinal follow-up to 24 months, enabling evaluation of clinically meaningful developmental endpoints. Additionally, the combined biomarker model reflects a practical clinical approach that could be implemented within neonatal intensive care settings.

Nevertheless, several limitations should be acknowledged. The single-center design may limit generalizability, and biomarker thresholds require validation in larger populations. Furthermore, long-term neurodevelopment beyond early childhood was not assessed.

From a clinical perspective, early risk stratification using multimodal biomarkers may guide individualized neuroprotective strategies, including early rehabilitation programs, parental counseling, and targeted follow-up. Future research should explore integration of genetic and metabolomic markers to further refine predictive accuracy.

Conclusion

Early multimodal biomarkers combining biochemical, electrophysiological, and neuroimaging parameters provide a robust framework for predicting neurodevelopmental disorders in preterm infants. Adoption of integrated screening models may enable earlier intervention and improve long-term neurological outcomes. Larger multicenter studies are warranted to validate standardized biomarker algorithms for routine neonatal practice.

REFERENCES:

[1] Volpe JJ, Brain injury in premature infants, Lancet Neurology, 2019, 18(1):110-124.

[2] Glass HC, Early biomarkers of neonatal brain injury, Pediatrics, 2018, 142(6):e20180642.

[3] Back SA, White matter injury in preterm infants, Nature Reviews Neurology, 2017, 13(6):331-345.

[4] O’Shea TM, Neurodevelopmental outcomes after preterm birth, Journal of Pediatrics, 2020, 218:6-12.

[5] Murray DM, aEEG monitoring in neonates, Clinical Neurophysiology, 2016, 127(1):1-11.

[6] Inder TE, MRI biomarkers in preterm brain injury, Pediatric Research, 2018, 84(3):372-380.

[7] Hintz SR, Neurodevelopmental follow-up of extremely preterm infants, Pediatrics, 2020, 145(2):e20191505.

[8] Hagberg H, Inflammation and brain injury in preterm infants, Nature Reviews Neurology, 2015, 11(4):192-208.

[9] Ment LR, Imaging predictors of outcome, Neurology, 2017, 88(9):890-898.

[10] Doyle LW, Long-term outcomes of prematurity, Seminars in Fetal & Neonatal Medicine, 2019, 24(2):101-107.

[11] Glass HC, Seizure biomarkers in neonates, Neurology, 2017, 88(10):978-986.

[12] Thompson DK, Diffusion MRI in neonatal brain development, NeuroImage, 2019, 185:112-123.

[13] Spittle AJ, Early intervention after preterm birth, Early Human Development, 2018, 125:1-7.

[14] Ahearne CE, Predictive modeling in neonatal neurology, Frontiers in Neurology, 2021, 12:645321.

[15] Anderson PJ, Neurobehavioral outcomes of preterm infants, Lancet Child & Adolescent Health, 2020, 4(9):713-724.