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Original article

CONTEMPORARY BIOMARKERS OF BLOOD-BRAIN BARRIER INJURY AND NEUROINFLAMMATION IN PRETERM INFANTS WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY

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Abstract: **Background:** Hypoxic–ischemic encephalopathy (HIE) is a major cause of neonatal morbidity and long-term neurodevelopmental impairment, particularly in preterm infants. Early diagnosis remains challenging, and there is growing interest in biomarkers that reflect underlying mechanisms such as neuroinflammation and blood–brain barrier disruption.

Objective: To evaluate the diagnostic and prognostic value of selected circulating biomarkers in preterm infants with HIE, with emphasis on a multimarker approach.

Methods: This prospective cohort study included 120 preterm infants (gestational age 28–36 weeks), divided into HIE (n = 90) and control (n = 30) groups. Serum levels of NR2 antibodies, endothelin-1, glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL) were measured at 24–48 hours, day 5–7, and day 14. Statistical analysis included t-test, ANOVA, correlation analysis, logistic regression, and ROC curve analysis.

Results: Biomarker levels were significantly higher in the HIE group ($p < 0.001$). GFAP and NfL showed the highest diagnostic performance (AUC 0.86 and 0.88). The combined model achieved the best accuracy (AUC = 0.89). Biomarker levels correlated with disease severity.

Conclusion: A multimarker approach improves diagnostic accuracy and may support early risk stratification and individualized management in preterm infants with HIE.

Keywords: hypoxic–ischemic encephalopathy, preterm infants, biomarkers, GFAP, neurofilament light chain, endothelin-1, NR2 antibodies, neuroinflammation.

INTRODUCTION

Hypoxic–ischemic encephalopathy (HIE) remains a major cause of neonatal mortality and long-term neurodevelopmental impairment, particularly in preterm infants (1, 2). Despite advances in neonatal intensive care, early diagnosis and precise assessment of brain injury severity continue to represent significant clinical challenges.

The pathophysiology of HIE involves a complex cascade of events, including primary energy failure followed by secondary injury mechanisms such as excitotoxicity, oxidative stress, inflammation, and apoptosis (3, 4). Excessive glutamate release and NMDA receptor activation play a central role in neuronal injury, while disruption of the blood–brain barrier further contributes to disease progression (5, 6). In addition, endothelial dysfunction and impaired cerebral autoregulation, partly mediated by endothelin-1, exacerbate ischemic damage and worsen neurological outcomes (7, 8).

Conventional diagnostic approaches, including clinical assessment, neuroimaging, and electrophysiological monitoring, have important limitations, especially in the early phase of injury (5, 9). Therefore, increasing attention has been directed toward circulating biomarkers that may provide objective and early information about brain injury.

Recent studies have identified glial fibrillary acidic protein (GFAP) as a marker of astroglial injury and

blood–brain barrier disruption, while neurofilament light chain (NfL) reflects axonal damage (6, 10). Additional biomarkers, including NR2 antibodies, endothelin-1, and S100B, may further contribute to the evaluation of neuronal, glial, and vascular injury (11-14).

The aim of this study was to evaluate the diagnostic and prognostic value of selected biomarkers in preterm infants with HIE, with particular emphasis on the potential advantages of a multimarker approach.

MATERIALS AND METHODS

Subjects and Study Design

A prospective cohort study was conducted at the University Clinical Center Sarajevo, Clinic for Neonatology, over a 12-month period (January–December 2025). The study included a total of 120 preterm infants with a gestational age between 28 and 36 weeks.

The sample size was calculated based on an expected medium-to-large effect size (Cohen's d = 0.7), with a statistical power of 80% and a significance level of 0.05. The minimum required sample size was estimated at 102 participants; therefore, 120 infants were included to improve the robustness of the analysis and account for potential dropouts.

Participants were divided into two groups: preterm infants diagnosed with hypoxic–ischemic encephalopathy (HIE) (n = 90) and a control group of clinically stable preterm infants without evidence of perinatal asphyxia (n = 30).

The diagnosis of HIE was established based on a combination of clinical and laboratory criteria, including an Apgar score ≤ 5 at 5 minutes, the need for resuscitation at birth, evidence of metabolic acidosis (pH < 7.0 or base deficit ≥ 12 mmol/L), and neurological signs consistent with encephalopathy (1, 2).

The severity of HIE was classified according to the Sarnat and Sarnat staging system into three categories (1, 2):

• Stage I (mild): irritability, hyperreflexia, absence of seizures

• Stage II (moderate**):** lethargy, hypotonia, seizures, impaired reflexes

• Stage III (severe): coma, areflexia, severe central nervous system depression

Infants with major congenital anomalies, confirmed or suspected infections, or genetic syndromes were excluded from the study.

Methods

Blood samples were collected at predefined time points: within the first 24–48 hours of life, between days 5 and 7, and on day 14. Samples were obtained via venipuncture, centrifuged to separate serum, and stored at −80 °C until analysis.

The analyzed biomarkers included NR2 antibodies, endothelin-1, glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL). Quantitative measurements were performed using enzyme-linked immunosorbent assay (ELISA) kits (Elabscience Biotechnology Inc., Houston, TX, USA), in accordance with the manufacturer's instructions.

Based on receiver operating characteristic (ROC) curve analysis, optimal cut-off values for differentiating HIE from controls were determined as follows:

• GFAP: > 2.5 ng/mL
• NfL: > 3.0 ng/mL
• Endothelin-1: > 2.0 pg/mL
• NR2 antibodies: > 2.0 AU

All infants underwent serial cranial ultrasound examinations as part of routine clinical care. Magnetic resonance imaging (MRI) of the brain was performed in selected cases to further characterize the extent of brain injury. Continuous monitoring of cerebral activity was performed using amplitude-integrated electroencephalography (aEEG), which has proven value in early neurological assessment (5).

Clinical and demographic data, including gestational age, birth weight, Apgar scores, need for respiratory support, and the occurrence of complications (e.g., intraventricular hemorrhage), were collected prospectively from medical records.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages.

Normality of data distribution was assessed using the Kolmogorov–Smirnov test. Differences between groups were analyzed using Student's t-test or one-way analysis of variance (ANOVA), as appropriate. The chi-square test was used for categorical variables.

Pearson correlation analysis was applied to evaluate relationships between biomarker levels and clinical parameters. Multivariate logistic regression analysis was performed to identify independent predictors of HIE.

Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic performance of individual biomarkers and their combinations. The area under the curve (AUC), sensitivity, specificity, and 95% confidence intervals were calculated.

A post hoc power analysis confirmed that the study achieved a statistical power of 0.83 for detecting differences in primary biomarker outcomes.

A p-value < 0.05 was considered statistically significant.

Ethical approval

The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the institutional Ethics Committee. Written informed consent was obtained from the parents or legal guardians of all participants prior to inclusion in the study.

RESULTS

A total of 120 preterm infants were included in the study, of whom 90 (75%) were diagnosed with hypoxic–ischemic encephalopathy (HIE), while 30 (25%) served as controls. There were no statistically significant differences in gestational age between the groups (31.5 ± 2.1 vs 32.1 ± 1.8 weeks, p = 0.08) or birth weight (1650 ± 320 vs 1720 ± 290 g, p = 0.12). However, Apgar scores at 1 minute were significantly lower in the HIE group (4 ± 1 vs 8 ± 1, p < 0.001), indicating more severe perinatal distress (Table 1).

At 24–48 hours of life, all analyzed biomarkers were significantly elevated in the HIE group compared to controls. Mean GFAP levels were 4.2 ± 1.1 ng/mL in the HIE group versus 1.3 ± 0.5 ng/mL in controls (p < 0.001), while NfL levels were 5.1 ± 1.4 ng/mL versus 1.7 ± 0.6 ng/mL (p < 0.001). Endothelin-1 levels were also significantly higher (3.8 ± 1.0 vs 1.5 ± 0.4 pg/mL, p < 0.001), as well as NR2 antibodies (2.9 ± 0.9 vs 1.2 ± 0.3 AU, p < 0.001).

A decreasing trend in biomarker levels was observed over time; however, values remained significantly higher in the HIE group at all time points. By day 5–7, GFAP decreased to 3.6 ± 1.0 ng/mL, and further to 2.8 ± 0.9 ng/mL by day 14 (p < 0.001 for trend). Similarly, NfL levels decreased from 5.1 ± 1.4 ng/mL at baseline to 4.3 ± 1.2 ng/mL (day 5–7) and 3.5 ± 1.0 ng/mL (day 14), remaining significantly elevated compared to controls (p < 0.001) (Table 2).

Table 1. *Demographic and clinical characteristics*

Variable	HIE (n = 90)	Control (n = 30)	p
Gestational age (weeks)	31.5 ± 2.1	32.1 ± 1.8	0.08
Birth weight (g)	1650 ± 320	1720 ± 290	0.12
Apgar score (1 min)	4 ± 1	8 ± 1	< 0.001

Table 2. *Biomarker levels over time*

Biomarker	24–48 h	Day 5–7	Day 14	p
GFAP (ng/mL)	4.2 ± 1.1	3.6 ± 1.0	2.8 ± 0.9	< 0.001
NfL (ng/mL)	5.1 ± 1.4	4.3 ± 1.2	3.5 ± 1.0	< 0.001

Table 3. *Multivariate logistic regression analysis*

Variable	OR	95% CI	p
GFAP	2.8	1.9–4.1	< 0.001
NfL	3.2	2.1–4.8	< 0.001
Endothelin-1	2.1	1.4–3.2	0.002

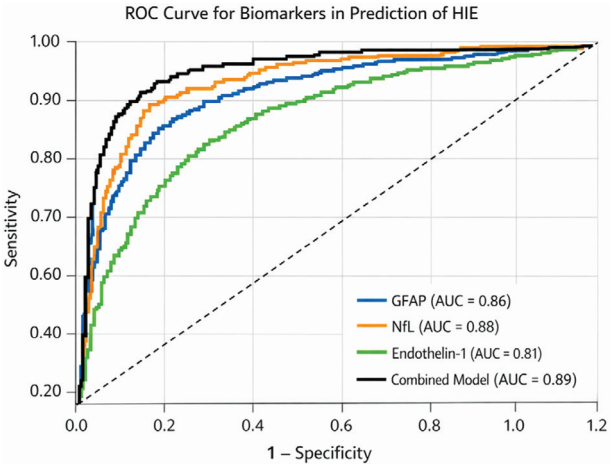

Figure 1. *Receiver operating characteristic (ROC) curves for GFAP, NfL, endothelin-1, and the combined biomarker model in predicting hypoxic–ischemic encephalopathy. The combined model demonstrated the highest diagnostic accuracy (AUC = 0.89)*

Subgroup analysis showed that infants with moderate-to-severe HIE (n = 52) had significantly higher biomarker levels than those with mild HIE (n = 38). Mean GFAP levels were 5.0 ± 1.2 ng/mL in the moderate-to-severe group compared to 3.2 ± 0.8 ng/mL in mild cases (p < 0.001), while NfL levels were 6.0 ± 1.5 ng/mL versus 4.0 ± 1.0 ng/mL (p < 0.001).

Correlation analysis demonstrated a significant negative correlation between Apgar score at 1 minute and biomarker levels: GFAP (r = –0.62, p < 0.001) and NfL (r = –0.68, p < 0.001).

Multivariate logistic regression analysis identified GFAP and NfL as independent predictors of HIE. GFAP showed an odds ratio (OR) of 2.8 (95% CI 1.9–4.1, p < 0.001), while NfL had an OR of 3.2 (95% CI 2.1–4.8, p < 0.001). Endothelin-1 was also a significant predictor (OR 2.1, 95% CI 1.4–3.2, p = 0.002) (Table 3).

Receiver operating characteristic (ROC) curve analysis demonstrated good diagnostic performance for individual biomarkers. GFAP achieved an area under the curve (AUC) of 0.86 (95% CI 0.79–0.92), while NfL showed slightly higher accuracy with an AUC of 0.88 (95% CI 0.82–0.94). Endothelin-1 demonstrated moderate diagnostic value (AUC 0.81, 95% CI 0.73–0.89).

The combined biomarker model (GFAP + NfL + endothelin-1) showed the highest diagnostic performance, with an AUC of 0.89 (95% CI 0.83–0.95), sensitivity of 87%, and specificity of 82% (Figure 1).

In terms of clinical outcomes, 34% of infants with HIE required mechanical ventilation, 48% required non-invasive respiratory support, and 29% developed intraventricular hemorrhage (grade II–IV). Higher biomarker levels were significantly associated with adverse outcomes, particularly in infants with severe HIE ($p < 0.001$).

DISCUSSION

The findings of this study highlight the clinical relevance of contemporary biomarkers in assessing brain injury in preterm infants with HIE. Biomarkers reflecting different pathophysiological pathways—neuronal, astroglial, inflammatory, and vascular—demonstrated significant diagnostic and prognostic value (15, 16, 17).

Consistent with previous studies, GFAP and NfL showed the strongest association with HIE severity. GFAP reflects astrocytic injury and blood–brain barrier disruption, while NfL serves as a sensitive indicator of axonal damage (17, 18). Their elevation in our cohort is in line with recent evidence demonstrating their role in early detection and severity assessment of neonatal brain injury (19, 20, 21).

In addition, NR2 antibodies demonstrated a significant increase in infants with HIE, supporting their role as markers of excitotoxic neuronal injury. NR2 subunits of the NMDA receptor are released following hypoxic–ischemic insult and reflect early glutamate-mediated neuronal damage (9, 18). Although their diagnostic performance was lower compared to GFAP and NfL, NR2 antibodies contributed additional pathophysiological insight, particularly in the early phase of injury, complementing the multimarker approach.

The observed decrease in biomarker levels over time likely reflects the dynamic nature of injury and repair processes. However, persistently elevated levels in the HIE group suggest ongoing secondary injury mechanisms, including neuroinflammation and delayed neuronal damage (18, 22).

Endothelin-1 also demonstrated significant diagnostic value, supporting the role of vascular dysfunction and impaired cerebral perfusion in HIE pathophysiology (18, 23). These findings reinforce the concept that neonatal hypoxic–ischemic injury involves not only neuronal damage but also vascular and endothelial components.

Importantly, the combined biomarker model showed the highest diagnostic accuracy. The multivariate model included GFAP, NfL, endothelin-1, and NR2 antibodies as independent variables, together with key clinical parameters such as Apgar score and gestational age. This integrative approach allowed simultaneous assessment of neuronal, glial, and vascular injury pathways, resulting in improved predictive performance compared to single biomarkers. These findings are consistent with studies suggesting that multimarker strategies provide superior clinical utility (3, 9, 18).

The strong correlation between low Apgar scores and elevated biomarker levels confirms their clinical relevance in reflecting the severity of perinatal hypoxia (1, 10). Furthermore, their association with adverse outcomes supports their potential use in prognostic stratification and individualized patient management (20).

From a clinical perspective, early identification of high-risk infants is essential, as timely interventions such as therapeutic hypothermia significantly improve outcomes (16, 17). Integration of biomarker profiling into clinical practice may enhance early decision-making and optimize treatment strategies.

Although our study provides valuable insights, further multicenter studies with long-term follow-up are needed to validate these findings and establish standardized biomarker thresholds for routine clinical use. Regional studies, including those reported in the *Sanamed* journal, also emphasize the importance of perinatal asphyxia as a significant contributor to neonatal morbidity (18, 21, 22).

Strengths and limitations

The strengths of this study include its prospective design and serial biomarker measurements. However, several limitations should be acknowledged. The study was conducted in a single center, which may limit generalizability. Additionally, long-term neurodevelopmental outcomes were not assessed, and future studies should explore the predictive value of these biomarkers for long-term prognosis.

CONCLUSION

Contemporary biomarkers, particularly when used in combination, represent a valuable tool for the early diagnosis and prognostic assessment of hypoxic–ischemic encephalopathy (HIE) in preterm infants. By reflecting multiple dimensions of brain injury, including astroglial damage, axonal disruption, and endothelial dysfunction, these biomarkers provide a more comprehensive understanding of the underlying pathophysiological processes.

The application of a multimarker model demonstrated high diagnostic accuracy and a strong associ-

ation with disease severity and clinical outcomes. Importantly, these findings suggest that biomarker profiling could enable earlier identification of infants at high risk for severe brain injury, even before overt clinical deterioration occurs.

In clinical practice, this approach has the potential to significantly modify current diagnostic and therapeutic strategies. Early biomarker-based risk stratification could support more timely initiation of neuroprotective interventions, including therapeutic hypothermia, as well as closer neurological monitoring and individualized supportive care. Furthermore, it may reduce reliance on delayed or less sensitive diagnostic modalities and improve decision-making in the critical early postnatal period.

Integration of biomarker assessment into routine neonatal protocols could also facilitate more precise prognostication, guide parental counseling, and optimize allocation of intensive care resources.

Although these results are promising, further multicenter studies with larger cohorts and long-term neurodevelopmental follow-up are necessary to validate these findings and to establish standardized cut-off values for routine clinical implementation.

Abbreviations

aEEG – Amplitude-Integrated Electroencephalography

GFAP – Glial Fibrillary Acidic Protein

HIE – Hypoxic–Ischemic Encephalopathy

MRI – Magnetic Resonance Imaging

NfL – Neurofilament Light Chain

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Note: Artificial intelligence was not utilized as a tool in this study.

Sažetak

SAVREMENI BIOMARKERI OŠTEĆENJA HEMATOENCEFALNE BARIJERE I NEUROINFLAMACIJE KOD NEDONOŠČADI SA HIPOKSIČNO-ISHEMIJSKIM OŠTEČENJEM MOZGA

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Uvod: Hipoksično-ishemijska encefalopatija (HIE) predstavlja značajan uzrok neonatalnog morbiditeta i dugoročnih neuroloških oštećenja, posebno kod nedonoščadi. Rana dijagnoza je otežana, a sve veći značaj pridaje se biomarkerima koji odražavaju patofiziološke procese poput neuroinflamacije i oštećenja hematoencefalne barijere.

Cilj: Proceniti dijagnostičku i prognostičku vrednost odabranih cirkulišućih biomarkera kod nedonoščadi sa HIE, s posebnim osvrtom na multimarker pristup.

Metode: Prospektivna kohortna studija obuhvatila je 120 nedonoščadi (gestacijska dob 28–36 sedmica), podeljenih u HIE (n = 90) i kontrolnu grupu (n = 30). Određivani su serumski nivoi NR2 antitela, endotelina-1, glijalnog fibrilarnog kiselog proteina (GFAP) i neurofilamentnog lakog lanca (NfL) u periodu 24–48 sati, 5–7 dana i 14. dana života. Statistička analiza uključivala je t-test, ANOVA, korelacijsku analizu, logističku regresiju i ROC analizu.

Rezultati: Vrednosti biomarkera bile su značajno više u HIE grupi ($p < 0,001$). GFAP i NfL pokazali su

najbolju dijagnostičku vrednost (AUC 0,86 i 0,88). Kombinovani model imao je najveću tačnost (AUC = 0,89). Vrednosti biomarkera korelirale su sa težinom bolesti.

Zaključak: Multimarker pristup poboljšava dijagnostičku tačnost i može doprineti ranoj proceni rizika i individualizaciji lečenja kod nedonoščadi sa HIE.

Ključne reči: hipoksično-ishemijska encefalopatija, nedonoščad, biomarkeri, GFAP, neurofilamentni laki lanac, endotelin-1, NR2 antitela, neuroinflamacija.

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