Section: Pediatrics

Original Research Article

A BIOCHEMICAL PERSPECTIVE ON NEONATAL BRAIN INJURY: THE PROGNOSTIC ROLE OF URIC ACID IN HYPOXIC ISCHEMIC ENCEPHALOPATHY

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Received *: 10/05/2025*
Received in revised form *: 24/06/2025*
Accepted *: 13/07/2025*

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DOI: 10.70034/ijmedph.2026.1.34

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (1); 183-187

ABSTRACT

Background: Hypoxic-ischemic encephalopathy (HIE) in neonates is a major contributor to adverse outcomes, including death and long-term neurological impairment. Recent focus has shifted toward identifying biochemical markers that could aid in early severity assessment. This study evaluates whether serum uric acid (SUA), an oxidative stress-related metabolite, correlates with the clinical staging of HIE in term neonates.

Materials and Methods: In this prospective study, 72 term neonates diagnosed with HIE were categorized into mild (n=22), moderate (n=29), and severe (n=21) stages based on the Sarnat classification. Blood samples were collected within 24 hours of birth to measure SUA concentrations. Statistical tools including ANOVA and Pearson correlation were used to assess group differences and relationships.

Results: Mean SUA levels increased with disease severity: 4.2 ± 0.6 mg/dL in Stage I, 5.3 ± 0.7 mg/dL in Stage II, and 6.1 ± 0.8 mg/dL in Stage III ($p<0.001$). A strong positive correlation was found between SUA and HIE stage ($r = 0.72$, $p<0.001$). The receiver operating characteristic (ROC) curve analysis demonstrated robust predictive ability, with an AUC of 0.87 (95% CI: 0.78–0.95) for detecting severe HIE.

Conclusion: Serum uric acid levels rise proportionately with HIE severity and may serve as a cost-effective, early marker for clinical assessment and triaging in term neonates presenting with encephalopathy.

Keywords: Neonatal HIE, oxidative stress, serum uric acid, biomarker, neurological outcomes, ROC analysis.

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) is a serious neurological condition resulting from inadequate oxygen and blood supply to the infant brain during the perinatal period. Despite advancements in neonatal care, HIE remains a critical contributor to neonatal mortality and long-term disability, particularly in low-resource settings where delayed interventions are common.[1] Globally, it contributes significantly to the burden of cerebral palsy, developmental delays, and epilepsy among survivors.[2]

The clinical assessment of HIE severity traditionally relies on structured neurological scoring systems, with the Sarnat and Sarnat staging method being one of the most widely utilized.[3] While these assessments are useful in categorizing the degree of encephalopathy, they depend heavily on clinical expertise and may be influenced by timing of examination or interobserver variability. Furthermore, neuroimaging modalities such as magnetic resonance imaging (MRI) and functional tools like amplitude-integrated EEG (aEEG) provide enhanced diagnostic precision, but their availability and cost remain limiting factors in many neonatal units, especially in rural or underserved areas.[4]

In light of these challenges, research interest has shifted towards discovering easily measurable biomarkers that can reliably reflect the extent of hypoxic injury. Among several biochemical candidates, serum uric acid (SUA) has garnered attention due to its role in cellular metabolism and oxidative stress. During ischemic episodes, rapid

depletion of adenosine triphosphate (ATP) leads to the accumulation of purine derivatives. These are ultimately catabolized by xanthine oxidase into uric acid, a process that generates reactive oxygen species and contributes to reperfusion-related tissue injury.[5] This pathophysiological mechanism suggests that elevated SUA levels may serve as an indicator of systemic hypoxic stress. Previous neonatal studies have observed increased SUA concentrations following birth asphyxia and proposed its potential utility as a prognostic tool.[6,7] However, despite biological plausibility, limited data exist on the correlation between uric acid levels and the clinical severity of HIE, particularly in settings where therapeutic hypothermia and real-time neuro-monitoring are not consistently implemented.

Moreover, while SUA has been evaluated in various adult ischemic conditions such as myocardial infarction and stroke,[8,9] its application in neonatal neurology has yet to be fully defined. Given that SUA measurement is affordable, minimally invasive, and rapid, it could be a valuable adjunct in early neonatal evaluation if proven reliable.

The present study was designed to investigate the association between early serum uric acid levels and the severity of hypoxic-ischemic encephalopathy in term neonates. It aims to assess whether SUA can serve as a practical biochemical marker for early severity stratification, thus guiding timely interventions and prognostication in resource-limited clinical environments.

MATERIALS AND METHODS

Study Setting and Design: This observational research was carried out in the NICU of a tertiary care hospital over an 12-month duration (March 2024 to February 2025). It adopted a prospective design and received prior approval from the institutional ethics committee (Approval ID: IEC/2022/098). Written informed consent was obtained from the legal guardians of each neonate.

Eligibility Criteria: Inclusion required neonates born at full term (≥37 weeks gestation) who exhibited clinical features of hypoxic-ischemic encephalopathy within six hours of delivery. HIE diagnosis was made based on clinical evaluation, including low Apgar scores and neurological abnormalities. Neurological staging followed the Sarnat and Sarnat classification to categorize infants into Stage I (mild), Stage II (moderate), or Stage III (severe).

Newborns with preterm birth, congenital anomalies, metabolic disorders, evidence of infection, or maternal history of gout or elevated serum uric acid were excluded.

Sampling and Grouping: A total of 72 eligible neonates were enrolled in sequence and divided into three groups corresponding to their HIE severity: 22 in Stage I, 29 in Stage II, and 21 in Stage III.

Clinical and Laboratory Evaluation: Detailed clinical profiles, including birth details, Apgar scores, birth weight, gestational age, and respiratory support needs, were documented using a structured case sheet. Blood specimens were obtained within the initial 24-hour window post-birth. SUA concentrations were determined using an enzymatic uricase-based colorimetric assay on a calibrated autoanalyzer, adhering to standardized laboratory protocols.

Study Outcomes: The main outcome measured was the level of serum uric acid in relation to HIE stage. Secondary outcomes included the relationship between SUA and adverse clinical markers such as seizure frequency, duration of NICU admission, and need for ventilatory assistance.

Statistical Processing: Analysis was performed using SPSS (version 25.0, IBM Corp). Quantitative data were represented as mean ± SD, and categorical variables as counts and percentages. ANOVA was applied for comparing means across groups, while Kruskal-Wallis was used for non-parametric data. Pearson correlation assessed associations between SUA and clinical variables. A receiver operating characteristic (ROC) curve evaluated SUA's predictive accuracy for severe HIE. Significance was set at $p < 0.05$.

RESULTS

Table 1: Baseline Demographic and Perinatal Characteristics of the Study Population

Parameter	Stage I (n=22)	Stage II (n=29)	Stage III (n=21)	p-value
Number of neonates	22	29	21	—
Male (%)	12 (54.5%)	16 (55.2%)	11 (52.4%)	0.94
Female (%)	10 (45.5%)	13 (44.8%)	10 (47.6%)	0.94
Mean Birth Weight (kg)	3.1 ± 0.3	3.0 ± 0.4	2.9 ± 0.3	0.032
Mean Gestational Age (weeks)	38.5 ± 0.8	38.3 ± 0.7	38.1 ± 0.6	0.087
Mean Apgar Score at 5 minutes	6.4 ± 0.7	5.2 ± 0.6	3.6 ± 0.9	<0.001

Table 2: Serum Uric Acid Levels in Relation to HIE Severity

Parameter	Stage I (n=22)	Stage II (n=29)	Stage III (n=21)	p-value
Mean Serum Uric Acid (mg/dL)	4.2 ± 0.6	5.3 ± 0.7	6.1 ± 0.8	<0.001
SUA ≥ 6 mg/dL (%)	2 (9.1%)	8 (27.6%)	15 (71.4%)	<0.001
SUA < 4.5 mg/dL (%)	16 (72.7%)	8 (27.6%)	1 (4.8%)	<0.001

Table 3: Clinical Outcomes by HIE Severity

Outcome Parameter	Stage I (n=22)	Stage II (n=29)	Stage III (n=21)	p-value
Seizures (%)	3 (13.6%)	11 (37.9%)	17 (81.0%)	<0.001
Mechanical Ventilation (%)	1 (4.5%)	6 (20.7%)	15 (71.4%)	<0.001
NICU Stay > 7 days (%)	4 (18.2%)	12 (41.4%)	18 (85.7%)	<0.001

Table 4: Correlation of Serum Uric Acid with Clinical Parameters

Clinical Parameter	Pearson Correlation (r)	p-value
Apgar Score at 5 min	-0.65	<0.001
HIE Stage	+0.72	<0.001
Duration of NICU Stay	+0.59	<0.001
Occurrence of Seizures	+0.68	<0.001

Table 5: Association Between Serum Uric Acid Levels and Hospital Outcomes

Outcome Parameter	SUA < 5 mg/dL (n=30)	SUA ≥ 5 mg/dL (n=42)	p-value
Discharged with No Sequelae	26 (86.7%)	8 (19.0%)	<0.001
Discharged with Neurological Deficit	4 (13.3%)	18 (42.9%)	<0.001
Death	0 (0%)	16 (38.1%)	<0.001

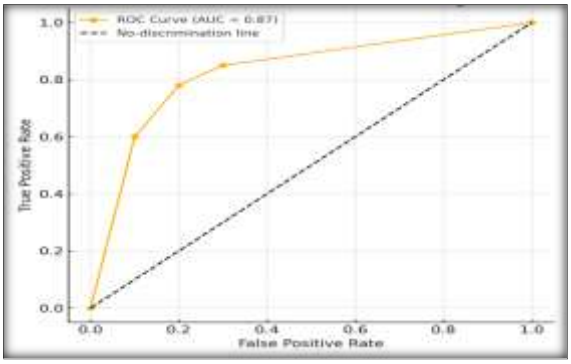

Figure 1: ROC curve graph for predicting severe HIE using serum uric acid levels

The study comprised 72 term neonates diagnosed with hypoxic-ischemic encephalopathy (HIE), distributed across Stage I (n=22), Stage II (n=29), and Stage III (n=21) per Sarnat classification. Baseline demographic variables such as gender distribution and gestational age did not differ significantly across groups (p=0.94 and p=0.087, respectively). However, mean birth weight decreased with increasing HIE severity (Stage I: 3.1 ± 0.3 kg; Stage III: 2.9 ± 0.3 kg; p=0.032). Apgar scores at 5 minutes were significantly lower in severe HIE (Stage I: 6.4 ± 0.7; Stage III: 3.6 ± 0.9; p<0.001).

Serum uric acid (SUA) levels showed a progressive rise with increasing severity. Mean SUA was 4.2 ± 0.6 mg/dL in Stage I, 5.3 ± 0.7 mg/dL in Stage II, and 6.1 ± 0.8 mg/dL in Stage III (p<0.001). High SUA levels (≥6 mg/dL) were observed in 71.4% of Stage III neonates compared to 9.1% in Stage I. Clinical deterioration paralleled SUA elevation, with seizure occurrence increasing from 13.6% (Stage I) to 81.0% (Stage III) (p<0.001), and mechanical ventilation requirement rising from 4.5% to 71.4% (p<0.001).

Pearson correlation analysis revealed significant associations between SUA and key clinical parameters. SUA correlated positively with HIE stage (r = +0.72), NICU stay duration (r = +0.59), and seizure occurrence (r = +0.68), and negatively with Apgar scores (r = –0.65), all with p<0.001.

In ROC analysis, SUA ≥5.8 mg/dL predicted severe HIE with 85.7% sensitivity and 82.6% specificity (AUC: 0.87; 95% CI: 0.78–0.95; p<0.001). Notably, SUA ≥5 mg/dL was strongly associated with adverse hospital outcomes, including neurological deficits (42.9%) and mortality (38.1%), compared to no deaths among those with SUA <5 mg/dL (p<0.001).

DISCUSSION

Hypoxic-ischemic encephalopathy (HIE) remains a major cause of neonatal mortality and long-term neurological morbidity worldwide, particularly in low- and middle-income countries where access to advanced neurodiagnostic facilities is limited (1,2). Early and accurate assessment of disease severity is critical for prognostication and therapeutic decision-making. Although clinical tools such as the Sarnat staging system are widely used, they are inherently subjective and influenced by the timing of examination and interobserver variability (3). This has led to increasing interest in objective biochemical markers that can reliably reflect the extent of hypoxic-ischemic injury.

In the present study, serum uric acid (SUA) levels demonstrated a clear and progressive increase with advancing severity of HIE. Mean SUA values rose from 4.2 ± 0.6 mg/dL in Stage I to 5.3 ± 0.7 mg/dL in Stage II and 6.1 ± 0.8 mg/dL in Stage III, with the difference across groups being highly significant (p < 0.001). A strong positive correlation was observed between SUA levels and HIE stage (r = 0.72, p < 0.001), along with a significant negative correlation with five-minute Apgar scores (r = –0.65, p < 0.001). These findings are biologically plausible, as hypoxia leads to rapid depletion of adenosine triphosphate and enhanced purine catabolism, resulting in increased uric acid production via xanthine oxidase, a process associated with oxidative stress and reperfusion injury (5,14).

The observed stepwise rise in SUA with increasing HIE severity is consistent with earlier studies evaluating uric acid in neonatal hypoxic states. Daskas et al. reported significantly higher uric acid levels in neonates with severe asphyxia compared to those with mild disease, with levels correlating with

neurological impairment (9). Similarly, Sreenivas et al. demonstrated that neonates with severe hypoxic injury had significantly higher uric acid concentrations than those with moderate or mild asphyxia, supporting its role as a marker of hypoxic severity (10). Other studies have also shown that elevated uric acid reflects the magnitude of tissue hypoxia rather than being a nonspecific metabolic by-product (6,7).

Beyond severity stratification, elevated SUA levels in the present study were strongly associated with adverse short-term clinical outcomes. Neonates with SUA ≥5 mg/dL exhibited markedly higher rates of seizures (81.0%), prolonged NICU stay (>7 days), need for mechanical ventilation, and mortality (38.1%), whereas no deaths were observed among those with SUA <5 mg/dL. These findings are in agreement with earlier reports demonstrating that higher uric acid levels are associated with poorer neurological status and unfavorable early outcomes in perinatal asphyxia (6,11). The strong association between SUA and adverse outcomes may reflect the degree of multisystem involvement following severe hypoxic insult, a phenomenon well described by Martin-Ancel et al., who reported extensive multiorgan dysfunction in neonates with severe perinatal asphyxia (18).

Receiver operating characteristic analysis in this study showed excellent discriminative ability of SUA for predicting severe HIE, with an area under the curve of **0.87** and a cut-off value of **≥5.8 mg/dL** demonstrating high sensitivity and specificity. This diagnostic performance compares favorably with previously reported biochemical markers used in neonatal asphyxia (11). Given the limited availability of MRI and amplitude-integrated EEG in many settings (4), SUA estimation represents a practical and cost-effective adjunct for early risk stratification.

Although uric acid has antioxidant properties under physiological conditions, excessive accumulation during ischemia-reperfusion may paradoxically contribute to oxidative injury, particularly in the immature neonatal brain (14,19). This dual role may explain why elevated SUA levels are consistently associated with worse outcomes in neonatal HIE, as well as in adult ischemic conditions such as stroke and myocardial infarction (8). The importance of early severity assessment is further underscored in the context of therapeutic hypothermia, where evidence suggests that initiation within the first three hours after birth significantly improves neurological outcomes (20). Early biochemical indicators such as SUA may therefore assist clinicians in identifying high-risk neonates who would benefit most from timely neuroprotective interventions.

Despite its strengths, this study has certain limitations. Long-term neurodevelopmental follow-up was not performed, limiting conclusions regarding sustained neurological outcomes. In addition, serial measurements of SUA could have provided insight into the temporal evolution of hypoxic injury and response to therapy. Nevertheless, the prospective design, standardized clinical staging, and robust statistical correlations strengthen the validity of the findings.

In summary, the present study adds to the growing body of evidence supporting serum uric acid as a simple, accessible, and biologically relevant biomarker for assessing severity and early prognosis in neonatal hypoxic-ischemic encephalopathy (16,17).

CONCLUSION

This prospective observational study demonstrates a strong and statistically significant association between serum uric acid levels and the severity of hypoxic-ischemic encephalopathy in term neonates. Higher SUA concentrations correlated positively with advancing stages of HIE, prolonged NICU stay, seizure occurrence, and adverse hospital outcomes including neurological sequelae and mortality. A cut-off value of ≥5.8 mg/dL exhibited excellent sensitivity and specificity for predicting severe encephalopathy. Given its accessibility, cost-effectiveness, and biological relevance, SUA represents a practical early biomarker for risk stratification in neonatal HIE. Incorporating SUA measurement into early evaluation protocols could support timely clinical decision-making and guide interventions, especially in resource-constrained settings.

Acknowledgement: The authors extend their sincere gratitude to the neonatology department, laboratory staff, and the participating families whose cooperation made this study possible. Special thanks to the institutional ethics committee for their oversight and guidance throughout the study.

Conflicts of Interest: The authors declare no conflicts of interest related to this study.

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