Original Article

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Serum and Urinary Uric Acid and Creatinine Ratio as a Biomarker in Perinatal Asphyxia: A Prospective Observational Study

Paediatrics Section

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ABSTRACT

Introduction: Perinatal asphyxia is a major problem that substantially increases newborn morbidity and mortality. It is defined as the inability to establish breathing at birth. An estimated 23% of the approximately four million neonatal deaths and 26% of the 3.2 million stillbirths worldwide each year are due to perinatal asphyxia.

Aim: To determine serum uric acid, creatinine, urinary uric acid, and creatinine levels in neonates with perinatal asphyxia.

Materials and Methods: This was a prospective observational study conducted in a Level III-A Neonatal Intensive Care Unit (NICU), Department of Paediatrics, Shri B.M. Patil Medical College, Hospital and Research Centre, Vijayapura, Karnataka, India, from March 2023 to November 2024, with a sample size of 129 neonates. Renal parameters were assessed between 24 and 48 hours of life. The study included neonates born at ≥37 weeks' gestation with an Apgar score ≤7. Variables such as duration of oxygen therapy, renal function, length of NICU stay, duration of respiratory support (including mechanical ventilation) and complications during NICU stay were evaluated. Associations among qualitative variables were analysed using the Chi-squared test, and differences between quantitative groups were assessed using the t-test, with a significance level set at 5%.

Results: A significant association was observed between low Apgar scores at five minutes and elevated levels of serum and urinary biomarkers. Elevated serum and urinary UA/Cr ratios were significantly associated with lower Apgar scores (p-value <0.001). Both serum UA/Cr and urinary UA/Cr ratios were markedly elevated in neonates with lower Apgar scores, reinforcing their potential as early indicators of the severity of perinatal asphyxia.

Conclusion: Serum and urinary UA/Cr ratios show potential as biomarkers for perinatal asphyxia severity.

Keywords: Asphyxia neonatorum, Hypoxia-ischaemia of brain, Prognostic indicators

INTRODUCTION

According to the World Health Organisation (WHO), perinatal asphyxia is one of the main causes of early neonatal mortality and is defined as the inability to establish breathing at birth, estimated to be responsible for approximately 900,000 deaths annually [1]. Globally, birth asphyxia remains a prevalent and serious neonatal concern that significantly contributes to infant morbidity and mortality. Perinatal asphyxia is caused by insufficient oxygenation or impaired blood flow to the foetus or newborn, leading to a multisystem disorder of varying severity and duration, often culminating in multiple organ failure [2]. It has been reported that perinatal asphyxia accounts for an estimated 23% of the four million neonatal deaths and 26% of the 3.2 million stillbirths that occur worldwide each year [3].

Perinatal asphyxia is clinically defined as the inability to initiate and sustain breathing at birth. Newborns delivered outside hospital (outborn neonates) may be assessed based on whether they cried immediately after birth or exhibited gasping without crying. Apgar scores of 1-3 at one minute or 5 or below at five minutes were taken as severe perinatal asphyxia. Apgar scores of 4 and 5 at one minute of life are regarded as moderate perinatal asphyxia, while scores of 6 and 7 at one minute of life were taken as mild perinatal asphyxia. An Apgar score of 8-10 at one minute of life was taken as normal [4].

In neonates with normal renal function, creatinine and uric acid levels are elevated at birth and typically normalise within 24-48 hours. Uric acid and creatinine are considered biomarkers in this study because they reflect early renal dysfunction and systemic hypoxic injury in neonates with perinatal asphyxia. However, in cases of moderate to severe perinatal asphyxia, persistently elevated levels may suggest Acute Kidney Injury (AKI). The kidneys, second only to the central nervous system in sensitivity to hypoxia, are particularly vulnerable. Hypoxia, hypotension and exposure to nephrotoxic drugs during the perinatal period may lead to Acute Renal Failure (ARF), which is one of the most severe consequences of birth asphyxia. ARF has a poor prognosis and may result in irreversible renal impairment in up to 40% of affected neonates [5,6]. Electrolyte disturbances, such as abnormalities in calcium, potassium and sodium levels, can further complicate the clinical picture, contributing to convulsions, metabolic imbalances and haemodynamic instability [6].

Birth asphyxia often results in ischaemia of the renal proximal tubules, which can lead to acute tubular necrosis—usually reversible—but in more severe cases, cortical necrosis may occur, leading to irreversible renal damage. Both conditions result in elevated serum urea and creatinine levels. The underlying pathophysiology includes a shift to anaerobic metabolism, impaired ATP production, dysfunction of ion pumps and intracellular accumulation of calcium, sodium, chloride and water, along with extracellular potassium elevation, all contributing to the observed electrolyte imbalances [7].

Most existing studies evaluating AKI in the context of perinatal asphyxia focus primarily on the urinary Uric Acid-to-Creatinine (UA/Cr) ratio [8,9]. While healthy term neonates usually pass urine within 48 hours of life, this process is often delayed in asphyxiated newborns [5].

The present study aimed to evaluate the levels of serum uric acid and creatinine, as well as urinary uric acid and creatinine, in neonates diagnosed with perinatal asphyxia. Additionally, the study intends to examine the association between renal biomarkers and the severity of asphyxia, thereby providing insight into the prognostic significance of these markers in asphyxiated neonates.

MATERIALS AND METHODS

This prospective observational study was conducted in NICU of Department of Pediatrics, Shri B.M. Patil Medical College, Hospital and Research Centre, Vijayapura, Karnataka, India, from March 2023 to November 2024. The study was approved by the Institutional Ethics Committee (IEC) of BLDE Deemed to be University, Shri B.M. Patil Medical College (IEC Approval No.: BLDE(DU)/IEC/970/2022-23). Written informed consent was obtained from parents or legal guardians prior to enrollment.

Inclusion criteria: All term neonates born at ≥37 weeks of gestation with Apgar scores of ≤7 at 5 minutes (as per institutional protocol) were included as cases, whereas neonates with Apgar scores >7 at five minutes served as controls [4]. Staging of Hypoxic Ischaemic Encephalopathy (HIE) was performed according to Sarnat's staging [10].

Exclusion criteria: Neonates with major congenital anomalies were excluded from the study.

Sample size: The sample size was calculated using the formula $n=z^2 pq/d^2$, where z=1.96 for a 95% confidence level, p=0.092 (estimated prevalence of asphyxiated neonate admissions based on retrospective hospital records from the preceding year), q=1-p, and d=0.05 (margin of error). Substituting these values, the minimum required sample size was calculated to be 129. Of these, 68 neonates with Apgar scores ≤7 were included as cases and 61 neonates with Apgar scores >7 were included as controls (ethical constraints limiting selection of healthy neonates as controls and based on NICU availability and matching criteria).

Study Procedure

Neonates were monitored for severity of asphyxia (0-3: severe, 4-6: moderate and 7: mild asphyxia, as per institution protocol), duration of oxygen therapy and the modes of respiratory support, disturbances in serum sodium, potassium and lactate levels during the initial 48 hours, improvement/worsening/complications, follow-up till discharge or death. All asphyxiated babies in the NICU were evaluated for serum and urinary UA/Cr ratio within 24-48 hours of delivery.

STATISTICAL ANALYSIS

Data were compiled and analysed using Microsoft Excel and Statistical Package for the Social Sciences (SPSS) software version 26.0. Descriptive statistics were expressed as mean±Standard Deviation (SD) for continuous variables and as frequency (N) and percentage (%) for categorical variables. The comparison of continuous variables between cases and controls was performed using the Independent t-test. The Chi-square test was used to compare categorical variables. The Pearson correlation coefficient was applied to assess the correlation between serum and urinary biomarkers. A p-value of <0.05 was considered statistically significant.

RESULTS

Among the 68 neonates with perinatal asphyxia, 44 (64.7%) were male and 24 (35.3%) were female, while in the control group of 61 neonates, 22 (36.1%) were male and 39 (63.9%) were female. Low birth weight (<2.5 kg) was observed in 17 (25%) cases and 13 (21.3%) controls, whereas normal birth weight (>2.5 kg) was found in 51 (75%) cases and 48 (78.7%) controls. A significant maternal history was present in 22 (32.4%) mothers of asphyxiated neonates, compared to 12 (19.7%) in the control group. Caesarean section was the mode of delivery in 25 (36.8%) cases and 33 (54.1%) controls, with 13 (52%) primigravida and 12 (48%) multigravida in the case group. Vaginal delivery was noted in 43 (63.2%) cases and 28 (45.9%) controls, with 25 (58.1%) primigravida and 18 (41.8%) multigravida in the case group [Table/Fig-1].

Parameters		Cases (n=68)	Controls (n=61)
Sex			
Male		44 (64.7%)	22 (36.1%)
Female		24 (35.3%)	39 (63.9%)
Birth weight			
<2.5 kg		17 (25%)	13 (21.3%)
>2.5 kg		51 (75%)	48 (78.7%)
Significant maternal history			
Present		22 (32.4%)	12 (19.7%)
Absent		46 (67.6%)	49 (80.3%)
Mode of delivery			
Caesarean section	Total	25 (36.8%)	33 (54.1%)
	Primigravida	13 (52%)	11 (33.3%)
	Multigravida	12 (48%)	22 (66.6%)
Vaginal delivery	Total	43 (63.2%)	28 (45.9%)
	Primigravida	25 (58.1%)	11 (39.3%)
	Multigravida	18 (41.9%)	17 (60.7%)

[Table/Fig-1]: Baseline neonatal and maternal characteristics.

At one minute, APGAR scores of 0-3 were recorded in 13 (19.1%) cases, 4-6 in 35 (51.5%) cases, and 7 in 20 (29.4%) cases. All 61 (100%) controls had an APGAR score ≥8. At five minutes, 7 (10.3%) cases had an APGAR score of 0–3, 28 (41.2%) had scores of 4-6, and 33 (48.5%) had scores of 7. All controls (61; 100%) had APGAR scores >8 [Table/Fig-2].

APGAR score	Cases (n=68)	Controls (n=61)
At 1 minute		
0-3	13 (19.1%)	0
4-6	35 (51.5%)	0
7	20 (29.4%)	0
≥8	0	61 (100%)
At 5 minutes		
0-3	7 (10.3%)	0
4-6	28 (41.2%)	0
7	33 (48.5%)	0
≥8	0	61 (100%)

[Table/Fig-2]: Distribution of APGAR scores at 1 and 5 minutes.

Among the 68 asphyxiated neonates, 42 (61.7%) were categorised as HIE Stage I, 18 (26.5%) as HIE Stage II, and 8 (11.8%) as HIE Stage III. All controls (61; 100%) were classified as HIE Stage 0 [Table/Fig-3].

SARNAT stage	Cases (n=68)	Controls (n=61)
HIE 0	0	61 (100%)
HIE I	42 (61.7%)	0
HIE II	18 (26.5%)	0
HIE III	8 (11.8%)	0

[Table/Fig-3]: Sarnat staging among cases and controls [4].

Mean serum sodium was significantly higher in cases (142.47±6.35 mEq/L) than controls (138.39±3.19 mEq/L) (p-value <0.001). Mean serum potassium was also elevated in cases (4.50±0.40 mEq/L) compared to controls (4.17±0.51 mEq/L) (p-value <0.05). Serum lactate was markedly elevated in cases (5.22±3.32 mmol/L) versus controls (1.92±0.93 mmol/L) (p-value <0.001). Serum uric acid and creatinine levels were higher in cases (6.40±2.28 mg/dL and 1.04±0.20 mg/dL, respectively) than in controls (4.13±1.20 mg/dL and 0.95±0.31 mg/dL) (p-value <0.001 and p-value <0.05, respectively). Urinary uric acid and creatinine were significantly raised in cases (48.5±5.5 mg/dL and 42.21±4.7 mg/dL) compared to controls (18.66±4.15 mg/

dL and 17.48±3.78 mg/dL) (p-value <0.001). The serum UA/Cr ratio and urinary UA/Cr ratio were also significantly higher in cases (6.62±1.65 and 3.78±1.52, respectively) than in controls (5.06±1.46 and 0.70±0.49) (p-value <0.001) [Table/Fig-4].

Parameters	Cases (n=68)	Controls (n=61)	p-value
Serum sodium (mEq/L)	142.47±6.35	138.39±3.19	<0.001
Serum potassium (mEq/L)	4.50±0.40	4.17±0.51	<0.05
Serum lactate (mmol/L)	5.22±3.32	1.92±0.93	<0.001
Serum uric acid (mg/dL)	6.40±2.28	4.13±1.20	<0.001
Serum creatinine (mg/dL)	1.04±0.20	0.95±0.31	<0.05
Urinary uric acid (mg/dL)	48.5±5.5	18.66±4.15	<0.001
Urinary creatinine (mg/dL)	42.21±4.7	17.48±3.78	<0.001
Serum UA/Cr ratio	6.62±1.65	5.06±1.46	<0.001
Urinary UA/Cr ratio	3.78±1.52	0.70±0.49	<0.001

[Table/Fig-4]: Serum and urinary biomarkers in cases and controls.

A significant association was observed between low APGAR scores at five minutes and elevated levels of serum and urinary biomarkers. Neonates with APGAR scores ≤6 showed higher incidences of increased serum uric acid, serum creatinine, and urinary uric acid and creatinine levels (p-value <0.001). Both serum UA/Cr and urinary UA/Cr ratios were notably elevated in neonates with lower APGAR scores, reinforcing their potential as early indicators of perinatal asphyxia severity. These findings highlight the diagnostic value of these biomarkers in assessing renal involvement and hypoxic insult in asphyxiated neonates [Table/Fig-5].

Variables		APGAR score at 5 min			p-value
		0-3	4-6	7	
Serum uric acid level	Normal (2-6.2 mg/dL)	2 (4.2%)	15 (31.2%)	31 (64.6%)	<0.001
	Increased	5 (25.0%)	13 (65.0%)	2 (10.0%)	
Serum creatinine level	Normal (0.6-1.2 mg/dL)	3 (5.5%)	19 (34.5%)	33 (60.0%)	<0.001
	Increased	4 (30.7%)	9 (69.3%)	0	
Random urinary uric acid level	Normal (16-22 mg/dL)	2 (4.3%)	14 (30.4%)	30 (65.3%)	<0.001
	Increased	5 (22.8%)	14 (63.6%)	3 (13.6%)	
Random urinary creatinine level	Normal (2-20 mg/dL)	2 (4.3%)	14 (30.4%)	30 (65.3%)	<0.001
	Increased	5 (22.8%)	14 (63.6%)	3 (13.6%)	
Serum uric acid/serum creatinine ratio	Normal (3.33 to 5.16)	1 (4.0%)	6 (24.0%)	18 (72.0%)	<0.001
	Increased	6 (14.0%)	22 (51.2%)	15 (34.8%)	
Random urinary uric acid/urinary creatinine ratio	Normal (0.3 to 3.4)	1 (14.2%)	10 (35.7%)	31 (93.9%)	<0.001
	Increased	6 (85.7%)	18 (64.2%)	2 (6.06%)	

[Table/Fig-5]: Association between APGAR Scores at 5 minuts and renal biomarkers (Cases Only).

A weak positive correlation was observed between serum and urinary uric acid levels (r-value=0.238, p-value=0.05) and between serum and urinary UA/Cr ratios (r-value=0.249, p-value=0.040). No significant correlation was found between serum and urinary creatinine (r-value=0.065, p-value=0.600) [Table/Fig-6].

Biomarker pair	Correlation Coefficient (r)	p-value
Serum UA vs urinary UA	0.238	0.05
Serum Cr vs urinary Cr	0.065	0.600
Serum UA/Cr vs urinary UA/Cr	0.249	0.040

[Table/Fig-6]: Correlation between serum and urinary biomarkers (cases only).

Serum uric acid increased progressively with severity: 5.18±0.76 mg/dL in HIE I, 7.52±2.32 mg/dL in HIE II, and 9.85±3.31 mg/dL in HIE III (p-value <0.0001). Serum creatinine also showed a rising trend: 0.79±0.15 mg/dL (HIE I), 1.18±0.28 mg/dL (HIE II), and 1.31±0.41 mg/dL (HIE III) (p-value <0.0001). No statistically significant differences were observed in urinary uric acid, creatinine, or UA/Cr ratios across Sarnat stages [Table/Fig-7].

Biomarker	HIE I	HIE II	HIE III	p-value
Serum UA (mg/dL)	5.18±0.76	7.52±2.32	9.85±3.31	<0.0001
Urinary UA (mg/dL)	114.38±63.20	145.43±84.63	116.15±69.57	0.286
Serum Cr (mg/dL)	0.79±0.15	1.18±0.28	1.31±0.41	<0.0001
Urinary Cr (mg/dL)	44.00±60.13	40.84±23.97	35.59±32.25	0.903
Serum UA/Cr ratio	6.47±1.67	6.46±1.79	7.59±2.27	0.252
Urinary UA/Cr ratio	3.57±1.48	3.70±0.62	4.68±2.69	0.170

[Table/Fig-7]: Biomarker levels according to Sarnat Staging (Cases Only).

Among asphyxiated neonates, 32 (46.5%) developed convulsions, 2 (2.9%) died, and 66 (97.1%) were discharged. Improvement in clinical condition was observed in 39 (57.4%), while 27 (40.9%) required anticonvulsant therapy. All controls (61; 100%) were discharged in improved condition with no complications [Table/Fig-8].

Parameters	Cases (n=68)	Controls (n=61)
Neonatal convulsions	32 (46.5%)	0
Death	2 (2.9%)	0
Discharged	66 (97.1%)	61 (100%)
Improved	39 (57.4%)	61 (100%)
Required anticonvulsants	27 (40.9%)	0

[Table/Fig-8]: Neonatal outcomes and clinical status.

DISCUSSION

Perinatal asphyxia remains a significant contributor to neonatal morbidity and mortality and often necessitates intensive care in the NICU. Asphyxiated neonates are at higher risk of developing AKI, which may adversely affect overall prognosis. The APGAR score, particularly at five minutes, continues to be one of the most commonly used clinical markers for diagnosing and predicting the severity of asphyxia. However, its reliability may be limited in specific situations such as preterm infants or those with congenital anomalies, where the score may be low due to non asphyxia causes.

In the present study, a total of 129 term neonates were enrolled, including 68 cases and 61 controls. Male predominance was observed with 64.7% among cases and 63.9% among controls for female. At one minute, APGAR scores of 0-3 were recorded in 13 (19.1%) cases, 4-6 in 35 (51.5%) cases, and 7 in 20 (29.4%) cases. All 61 (100%) controls had an APGAR score ≥8. At five minutes, 7 (10.3%) cases had an APGAR score of 0-3, 28 (41.2%) had scores of 4-6, and 33 (48.5%) had scores >7. All controls (61; 100%) had APGAR scores >7. Another study by Manoj and Bhat V, reported APGAR scores at 1 minute in cases: 0-3 in 60, 4-6 in 20, and 6-7 in none; at five minutes, 0-3 in 11 neonates, 4-6 in 55, and 6-7 in 14 babies [11].

In the present study, mean serum uric acid was significantly higher in cases (6.40±2.28 mg/dL) compared to controls (4.13±1.20 mg/dL), and mean serum creatinine was significantly higher in cases (1.04±0.20 mg/dL) versus controls (0.95±0.31 mg/dL). The mean serum uric acid to creatinine ratio (UA/Cr) was significantly higher among cases (6.62±1.65) than controls (5.06±1.46) (p-value <0.001). Additionally, cases showed elevated mean values of urinary uric acid (uric acid excreted in urine) (48.5±5.5 mg/dL) and urinary creatinine (42.21±4.7 mg/dL), while none of the controls showed such elevations. A clear association was noted between lower 5-minute APGAR scores and elevated levels of biochemical markers, including serum uric acid, serum creatinine, and urinary

UA/Cr ratios. A similar study by Patel KP et al., reported that the mean urinary UA/Cr ratio was significantly higher in the asphyxiated group (2.75±0.18) than in controls (1.78±0.23) (p-value <0.0001) [9].

Supporting these findings, Gulati K et al., conducted a cross-sectional study on 100 term asphyxiated neonates and 100 controls, reporting a mean urinary UA/Cr ratio of 3.41±0.68 in the asphyxiated group versus 1.99±0.23 in controls (p-value <0.001). They also found a strong negative correlation between the 5-minute APGAR score and urinary UA/Cr ratio (r-value=–0.8806, p-value <0.001), indicating that higher biochemical ratios were associated with lower APGAR scores [12].

In the present study, convulsions developed in 46.5% of the asphyxiated neonates. Of these, 27 (84.4%) responded to antiepileptic therapy, while 2 (6.3%) had persistent seizures and died. One neonate died at 72 hours of life while undergoing therapeutic hypothermia, and another died on day five while on mechanical ventilation. A study by Chikkanna S et al., reviewed data from 100 newborns who experienced birth asphyxia and reported a mortality rate of 21%. The highest mortality (11%) was seen in those babies classified as HIE stage III. The study noted that a majority (22%) of the neonates who survived had some neurological issues and required long-term antiseizure medication [13].

Limitation(s)

This was a single-centre study, which may limit the generalisability of the findings to other settings with different neonatal care practices. Additionally, the study had limited follow-up and long-term neurodevelopmental outcomes were not assessed, which are crucial for understanding the full impact of perinatal asphyxia.

CONCLUSION(S)

This study highlights that the serum uric acid-to-creatinine ratio, like urinary levels, may serve as a useful biomarker for grading the severity of perinatal asphyxia. Given that serum collection is simpler and more feasible in NICU settings compared to urine collection, especially in critically ill neonates, serum biomarkers may offer a practical alternative. The significant correlation between low APGAR scores and elevated biochemical markers supports their utility in the early identification and prognostication of renal injury in asphyxiated neonates.

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