ORIGINAL RESEARCH ARTICLE

To Study the Role of Urinary Uric Acid to Creatinine Ratio as a Marker of Perinatal Asphyxia and Its Severity in Newborns

Sunita Arora[1], Arshpuneet Kaur[2], Mandeep S Khurana[3], Jaskiran K Sandhu[4]

Abstract

Objective: To compare urinary uric acid and creatinine ratio (UUA/Cr) among asphyxiated and nonasphyxiated neonates.

Background: Perinatal asphyxia is the leading cause of neonatal morbidity and mortality. The last few decades have seen many improvements in modern medicine but still, there is a lack of easily available biochemical markers to diagnose perinatal asphyxia more so in institutional deliveries.

Study design: Cross-sectional, comparative study.

Setting: NICU and postnatal wards of tertiary care center.

Participants: Forty asphyxiated and 40 healthy term newborns were enrolled in the study. Two milliliters of cord arterial blood was collected for a blood gas analysis in asphyxiated neonates only. Spot urine samples were collected within the first 24 hours of life in both asphyxiated and nonasphyxiated groups and analyzed for UUA/Cr ratio.

Results: The mean UUA/Cr ratio was found to be higher in asphyxiated (2.41 ± 0.58) than in nonasphyxiated neonates (1.58 ± 0.17) ($p < 0.001$). There was a positive correlation between the UUA/Cr ratio and the severity of hypoxic–ischemic encephalopathy among asphyxiated neonates ($p < 0.001$). A negative correlation was found of UUA/Cr ratio with Apgar score and umbilical cord blood pH. The cutoff value of the UUA/Cr ratio of 1.36 has 97.5% sensitivity, 100% specificity, 100% positive predictive value, 97.5% negative predictive value, and 98.7% accuracy.

Conclusion: This ratio can be used as a reliable diagnostic marker to detect perinatal asphyxia in neonates where adequate birth history is not available.

Keywords: Asphyxia, HIE (Hypoxic–ischemic encephalopathy), UUA/Cr (Urinary uric acid to creatinine ratio).

AMEI's Current Trends in Diagnosis & Treatment (2021): 10.5005/jp-journals-10055-0133

Introduction

Perinatal asphyxia is derived from the Greek word asphyxos, which means born without an evident pulse. Perinatal asphyxia is defined as a condition during the first and second stages of labor in which inadequate gas exchange causes fetal hypoxemia and hypercarbia, characterized by cord blood pH less than 7 with an Apgar score of 4–6 at 1 minute of birth.[1] Asphyxia is defined pathologically as the fusion of both hypoxia and hypoperfusion causing inadequate tissue gas exchange leading to metabolic acidosis and elevated lactate levels. Birth asphyxia is defined by World Health Organization as "failure to initiate and sustain breathing at birth" with Apgar Score less than 7 at 1 minute of life.[2] Globally, hypoxia of the newborn accounts for 23% of the 4 million newborn deaths and 26% of 3.2 million stillbirths per year.[3] Approximately 20–25% of asphyxiated neonates with severe hypoxic–ischemic encephalopathy (HIE) die during the newborn period. In India, 2.5–3.5 lac neonatal deaths occur every year due to birth asphyxia, maximally within the first 72 hours of life.[4] National Neonatal–Perinatal Database in India suggests that birth asphyxia causes approximately 20% of newborn deaths and 8.4% of newborn babies in India have a 1 minute Apgar score <7, of which 1.4% exhibits HIE.[5] Asphyxia in term neonates causes renal, neurological, cardiac, and pulmonary dysfunction in 50, 28, 25, and 25%, respectively. As a result of decreased oxygenation and hypoperfusion, perinatal asphyxia affects the functioning of various organ systems like renal, central nervous, cardiovascular, respiratory, gastrointestinal, and hematological.[6] HIE causes permanent neurological damage that can lead to neonatal deaths or is manifested later as cerebral palsy, epilepsy, mental retardation, or developmental delay. Asphyxia during labor and delivery can occur due to insufficient umbilical cord blood flow (cord compression), impaired gas exchange across the placenta (abruptio placenta), inadequate blood flow to the maternal side of the placenta (severe maternal hypotension), transient, intermittent hypoxia of normal labor (anemia/growth retarded fetus), and failure to expand the lungs and complete the changes in ventilation and lung perfusion that are crucial at birth.

Due to the failure of gas exchange in the fetus and newborn, blood and tissue pH and pO_2 fall but tissue oxygen utilization persists causing a further fall in pO_2. Anaerobic metabolism occurs due to hypoxic damage to cerebral oxidative metabolism and produces two molecules of ATP as compared to 32 molecules of ATP during aerobic metabolism. Oxidative phosphorylation

[1–3]Department of Paediatrics, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India

[4]Department of Biochemistry, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India

Corresponding Author: Arshpuneet Kaur, Department of Paediatrics, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India, Phone: +91 9872282617, e-mail: puneeteleven11@gmail.com

How to cite this article: Arora S, Kaur A, Khurana MS, *et al*. To Study the Role of Urinary Uric Acid to Creatinine Ratio as a Marker of Perinatal Asphyxia and Its Severity in Newborns. AMEI's Curr Trends Diagn Treat 2021;5(2):85–88.

Source of support: Nil

Conflict of interest: None

and ATP production fail further due to prolonged asphyxia. ATP is degraded with increased formation of ADP and AMP that are further catabolized to adenosine, inosine, and hypoxanthine. If tissue hypoxia persists further with consequent reperfusion injury, hypoxanthine is degraded by xanthine oxidase into xanthine and uric acid.[7] So, the formation of uric acid increases and it enters the blood from ischemic tissues and then is excreted in the urine where uric acid can be quantified easily.[8]

Apgar score plays a limited role in predicting neurological sequelae that are influenced by various factors like prematurity, maternal infections, maternal sedations, etc.[9] The signs of birth asphyxia are not specific and overlap with other illnesses. So, there is a need for an easily available biochemical marker to delineate an asphyxiated and nonasphyxiated etiology. Hence, we conducted this study with an objective to compare urinary uric acid to creatinine (UUA/Cr) ratio in term neonates with and without perinatal asphyxia and study its correlation with the severity of HIE, cord blood pH, and Apgar scores if any.

Methods

The study was done in NICU and postnatal wards of tertiary care center in a time duration of 18 months (February 2019–October 2020) after getting approval from the institutional ethics committee. Written informed consent was taken from parents/guardians.

Inclusion Criteria

Total 80 newborns born at 37–42 weeks, AGA (appropriate for gestational age) delivered via a normal vaginal delivery or through a C-section were enrolled in the study. Of 80 neonates, 40 had evidence of perinatal asphyxia and 40 did not show any evidence of perinatal asphyxia.

Perinatal asphyxia was diagnosed when at least three out of the following were present:

- Apgar score at 1 minute of life was <7.
- Need of resuscitation for >1 minute with positive pressure ventilation (PPV) before stable spontaneous respiration develops.
- HIE as defined by Levene staging (mild, moderate, or severe).
- Intrapartum signs of fetal distress, such as nonreactive nonstress test (NST) on continuous electronic fetal Doppler monitoring or thick meconium-stained amniotic fluid (MSAF).
- Severe metabolic or mixed acidosis (pH <7) in an umbilical artery cord blood sample.

Exclusion Criteria

- Congenital abnormalities.
- Maternal drug abuse.
- Magnesium sulfate or opioids given to mother within 4 hours prior to delivery (pharmacological depression).
- Erythroblastosis fetalis.
- Mothers consuming alcohol.
- Mothers who smoke.
- Mothers on antiepileptics.

Apgar score was recorded at 1 and 5 minutes. ABG was done by collecting 2 mL of umbilical cord blood sample of asphyxiated neonates only at birth. After admission to NICU, the predesigned pro forma was filled that included antenatal risk factors for perinatal asphyxia, intrapartum factors like mode of delivery, prolonged rupture of membranes, and history of meconium-stained liquor, and details of birth events like Apgar score, gender, weight, and gestational age of newborns. Examination including vitals and anthropometry with a complete neurological and systemic examination was conducted. The asphyxiated group was monitored for CNS complications attributable to perinatal asphyxia. Grading of HIE was done by Levene staging. Spot urine samples within the first 24 hours of life were collected in sterile containers by using a pediatric urine collecting bag in both asphyxiated and nonasphyxiated groups.

UUA/Cr was measured by an automated biochemistry analyzer (Siemens Dimension RXL Max). Uric acid was measured by URCA flex cartridge method which was the modification of the uricase method. Urine creatinine was measured by using CRE-2 (Creatinine Assay kit)method.

Statistical Analysis

The analysis was done using 23.0 Version of SPSS software. Student *t* test, correlation coefficient, and Chi-square test were applied to test the statistical significance.

Results

Baseline characteristics like birth weight, mode of delivery, and maternal parity were comparable in both groups. There was overall male preponderance in both the groups, more so in the nonasphyxiated group. Nonreactive NST and thick MSAF were observed only in asphyxiated neonates (p <0.001). One minute Apgar score was 4 ± 1 and mean 5 minute Apgar score was 7 ± 1 in asphyxiated neonates. All neonates in the nonasphyxiated group had Apgar score more than 7 at 1 and 5 minutes (Table 1).

Most asphyxiated neonates required bag and mask ventilation (BMV) (18, 45%) followed by intubation with PPV and physical stimulation (11 each, 27.5%). In the asphyxiated group, the umbilical cord blood pH was 7.06–7.15 in 22 neonates (55%) followed by 7.00–7.05 in 11 (27.5%) and 6.70–6.90 in 7 (17.5%) cases. Mean cord blood pH was 7.03 ± 0.08. Most cases in our study had HIE 1 (57.5%) and 5% had HIE 3. Twelve asphyxiated neonates (30%) did not show any signs of encephalopathy in the first 24 hours of life (Table 2).

Mean UUA/Cr ratio was found to be significantly higher in asphyxiated neonates (2.41 ± 0.58) as compared to nonasphyxiated neonates (1.58 ± 0.17) (Table 3).

Table 1: Baseline characteristics of neonates

Baseline characteristics	*Asphyxiated (n = 40)*	*Nonasphyxiated (n = 40)*	*p value*
Male/female	22/18	31/9	0.033
Mean birth weight	2.89 ± 0.37	2.92 ± 0.34	0.633
Normal vaginal delivery/ lower-segment cesarean section	18/22	24/16	0.262
Primipara/multipara	26/14	22/18	0.361
Reactive/nonreactive NST	24/16	40/0	0.001
Thick MSAF	23/17	40/0	0.001
Apgar score			
1 minute	4 ± 1	>7	0.001
5 minute	7 ± 1	>7	0.001

UUA/Cr ratio was high in babies requiring intubation and PPV (2.90 ± 0.45) and low in those requiring physical stimulation (1.96 ± 0.51). UUA/Cr ratio was high (2.8 ± 0.483) in babies with cord blood pH between 6.70–6.90 and low (2.40 ± 0.64) in babies with a cord blood pH of 7.00–7.05. There was a significant negative correlation between the UUA/Cr ratio and umbilical cord blood pH (Fig. 1).

In neonates with a 1 minute Apgar score of 0–3, the UUA/Cr ratio was 2.660 ± 0.336. The ratio was 2.374 ± 0.60 and 2.82 ± 0.38 in neonates with Apgar scores of 4–6 at 1 and 5 minutes of life, respectively. A significant negative correlation exists between the UUA/Cr ratio and Apgar score at 1 and 5 minutes (Figs 2 and 3).

The UUA/Cr ratio was high (3.60 ± 0.14) in HIE 3 followed by (3.25 ± 0.07) and (2.61 ± 0.18) in HIE 2 and 1, respectively. Those neonates who did not exhibit any sign of HIE had a UUA/Cr ratio of 1.66 ± 0.20 (Table 4).

Table 2: Mode of resuscitation, umbilical cord blood pH, and stages of HIE among the asphyxiated group

	Asphyxiated neonates	
Mode of resuscitation	*No.*	*%age*
Physical stimulation	11	27.5
Bag and mask ventilation	18	45.0
Bag and tube ventilation	11	27.5
Cord blood pH		
6.70–6.90	7	17.5
7.00–7.05	11	27.5
7.06–7.15	22	55
No HIE	12	30
HIE 1	23	57.5
HIE 2	3	7.5
HIE 3	2	5

Table 3: Comparison of UUA/Cr ratio among both groups

	UUA/Cr		
Group	*Range*	*Mean ± SD*	*p value*
Asphyxiated neonates	1.3–3.7	2.410 ± 0.58	0.001
Nonasphyxiated neonates	1.3–2.0	1.588 ± 0.17	

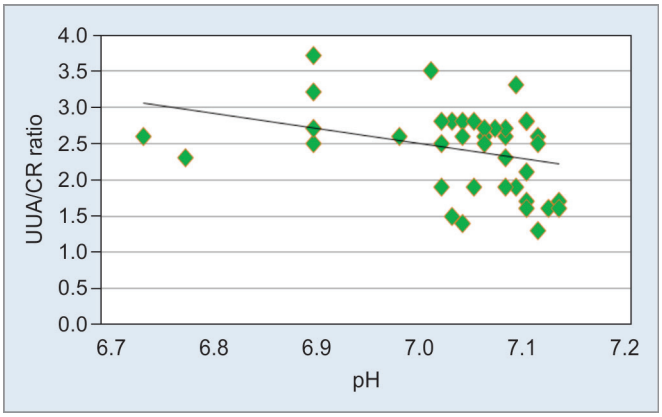

Fig. 1: Scatter plot showing a significant negative correlation between UUA/Cr ratio and cord blood pH

The cutoff value of the UUA/Cr ratio of 1.36 was found to be 97.5% sensitive, 100% specific with 100% positive predictive value, 97.5% negative predictive value, and 98.7% accuracy (Table 5).

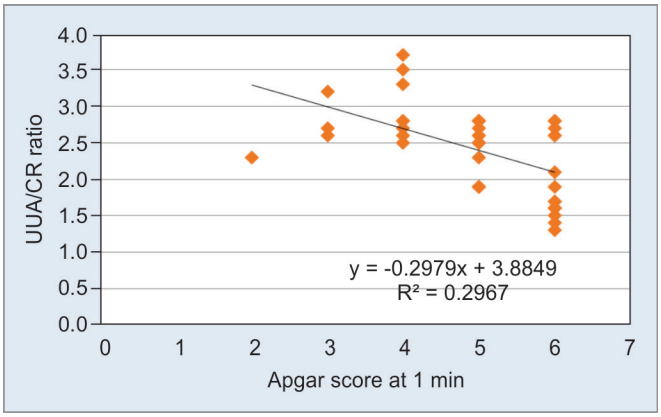

Fig. 2: Scatter plot showing a significant negative correlation between the UUA/Cr ratio and 1 minute Apgar score

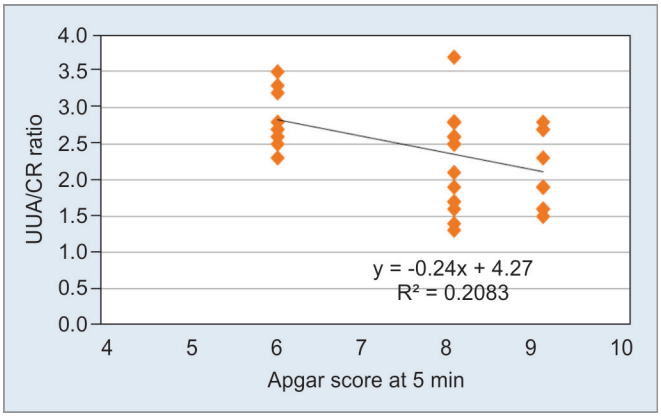

Fig. 3: Scatter plot showing a statistically significant negative correlation found between the UUA/Cr ratio and 5 minute Apgar score

Table 4: Correlation of UUA/Cr with modes of resuscitation, Apgar score, cord blood pH, and stages of HIE among the asphyxiated group

Mode of resuscitation	*N*	*Mean ± SD*	*p value*
Physical stimulation	11	1.96 ± 0.51	0.001
Bag and mask ventilation	18	2.38 ± 0.46	
Bag and tube ventilation	11	2.40 ± 0.45	
1 minute Apgar score			
0–3	5	2.66 ± 0.33	0.001
4–6	35	2.37 ± 0.60	
5 minute Apgar score			
4–6	10	2.82 ± 0.38	0.003
>7	30	2.27 ± 0.57	
Cord blood pH			
6.70–6.90	7	2.80 ± 0.48	0.036
7.00–7.05	11	2.40 ± 0.64	
7.06–7.15	22	2.43 ± 0.47	
No HIE	12	1.66 ± 0.20	
HIE 1	23	2.61 ± 0.18	
HIE 2	3	3.25 ± 0.07	0.001
HIE 3	2	3.60 ± 0.14	

Table 5: Diagnostic value of UUA/Cr ratio in the prediction of perinatal asphyxia

UUA/Cr cutoff	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*	*Accuracy*
1.36	97.5	100	100	97.5	98.7

Area under ROC	*Std error*	*p value*
0.995	0.005	<0.001

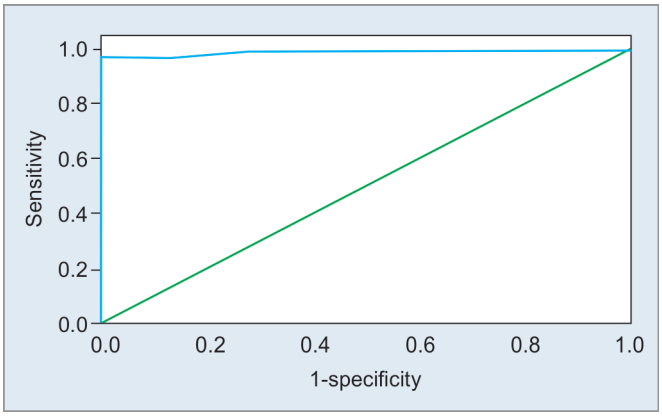

Fig. 4: ROC curve

On plotting the ROC curve, area under curve was 0.995 with a standard error of 0.005 (Fig. 4).

Discussion

In our study, we observed a significantly higher UUA/Cr ratio in asphyxiated neonates (2.4 ± 0.58) than in the nonasphyxiated group (1.5 ± 0.17). Mahmoud and El Abd observed the UUA/Cr ratio (2.41 ± 0.58) in asphyxiated neonates which was higher than in nonasphyxiated neonates (1.58 ± 0.17).[10] Baseline characteristics resembled the study conducted by Darshan et al., Palit et al., Kinjal et al., and Krishnana et al.[11–13,3] There was a significant negative correlation of UUA/Cr ratio with Apgar score and cord blood pH in our study. Gubbala et al. and Shenoy et al. also observed a negative correlation with cord blood pH. We found a positive correlation of the UUA/Cr ratio with the severity of HIE. The ratio was high in babies requiring intubation and PPV (2.90 ± 0.45) and low in physical stimulation (1.96 ± 0.51) in the present study. Nariman et al. also observed a negative correlation with 1 and 5 minutes of Apgar scores.[14] The UUA/Cr ratio correlated well with stages of HIE. Correlation of ratio with the severity of HIE was also observed by Mahmoud and El Abd and Sarayna et al.[15] The cutoff value of the UUA/Cr ratio was found to be 1.36 which is 97.5% sensitive, 100% specific with 100% positive predictive value, 97.5% negative predictive value, and 98.7% accuracy. Similarly, the cutoff value of the UUA/Cr ratio was >1.22 with 86% sensitivity, 92% specificity, and 89% accuracy in a study done by Akisu et al.[16]

UUA/Cr ratio is a reliable, rapid, cheap, noninvasive, and easy screening method for the early detection of birth asphyxia and its severity and deciding about the level of care needed by the newborn.[17] A large number of oxygen radicals are formed in the re-oxygenation period following birth asphyxia and profound levels of uric acid are generated and excreted in urine within the first day of life. Therefore, the assay should be performed on the earliest void samples after the asphyxiating event. This lab marker assumes the importance in evaluating symptomatic neonates in whom birth history including the presence or absence of asphyxia, meconium staining of liquor, Apgar score, and modes of resuscitation are not known as in the case of home deliveries.

References

1. Snyder EY, Cloherty JP. Perinatal asphyxia and hypoxic ischemic encephalopathy. In: Cloherty JP, Stark Ann R, Eichenwald EC, et al., editors. Manual of neonatal care. 7th ed. Wolters Kluwer; p. 711.
2. WHO: perinatal mortality–a listing of available information. FRH/MSM.96.7. Geneva: WHO; 1996.
3. Krishnana E, Ponnusamy V, Sekar SP. Study of urinary uric acid and creatinine ratio as a marker of neonatal asphyxia for babies born in tertiary care hospital. Int J Res Med Sci 2017;5(12):5418–5423. DOI: 10.18203/2320-6012.ijrms20175466.
4. Choudhary L, Palsanis S, Berwal PK, et al. Study of urinary uric acid and creatinine as a marker of perinatal asphyxia and its correlation with different stages of HIE. J Preg Child Health 2017;4:336. DOI: 10.4172/2376-127X.1000336.
5. Yaswanth K, Babu MS, Srinivas K. Study of urinary uric acid to creatinine ratio in assessing the severity of birth asphyxia. IOSR-JDMS 2017;16(10):69.
6. Agarwal R, Jain A, Deorari AK, et al. Post resuscitation management of asphyxiated neonates. Ind J Pediatr 2008;75(2):175–180. DOI: 10.1007/s12098-008-0026-5.
7. Rieselbach RE, Steele TH. Influence of the kidney upon urate homeostasis in health and disease. Am J Med 1974;56(5):665–669. DOI: 10.1016/0002-9343(74)90633-0.
8. Pietz J, Guttenberg N, Gluck L. Hypoxantine: a marker for perinatal asphyxia. Obstet Gynaecol 1988;72(5):762–766. PMID: 3140152.
9. Dennis J, Johnson A, Mutch L. Acid-base status at birth and neurodevelopmental outcome at four and one-half years. Am J Obstet Gynecol 1989;161(1):213–220. DOI: 10.1016/0002-9378(89)90269-x.
10. Mahmoud R, El Abd D. Urinary uric acid/creatinine ratio in term infants with perinatal asphyxia. Small 2016;32:80.
11. Kataria D, Joshi K, Singh J. Spot urine uric acid level as early marker of kidney injury in birth-asphyxiated newborns. Int J Sci Study 2019;6(11):24–28. DOI: 10.17354/ijss/2018/6.
12. Palit S, Wilar R, Runtunuwu A, et al. Blood pH and urinary uric acid-creatinine ratio in newborns with asphyxia. J Paediatr Indonesiana 2015;55(6):352–356. DOI: 10.14238/pi55.6.2015.
13. Patel KP, Makadia MG, Patel VI, et al. Urinary uric acid/creatinine ratio–a marker for perinatal asphyxia. J Clinic Diag Res 2017;11(1):SC08. DOI: 10.7860/JCDR/2017/22697.9267.
14. Nariman S, Mosayebi Z, Sagheb S, et al. Urinary uric acid and creatinine ratio as a marker of mortalityand unfavourable outcome in NICU admitted neonates. Iran J Pediatr 2016;26(4):e5739. DOI: 10.5812/ijp.5739.
15. Rajmoham T, Sarayna R. Study of urinary uric acid and creatinine as a marker for neonatal asphyxia. IP Int J Med Pediatr Oncol 2019;5(2):66–68. DOI: 10.18231/j.ijmpo.2019.015.
16. Akisü M, Kültürsay N. Value of the urinary uric acid to creatinine ratio in term infants with perinatal asphyxia. Pediatr Int 1998;40(1):78–81. DOI: 10.1111/j.1442-200x.1998.tb01408.x.
17. Nagdy N, Komen W, Ko HK. Early biochemical indicators of hypoxic ischemic encephalopathy after birth asphyxia. Pediatr Res 2001;49(4):502–506. DOI: 10.1203/00006450-200104000-00011.