

Utility of Urinary Uric Acid/Creatinine Ratio in Evaluating Birth Asphyxia: A Comparative Study with Cord Blood ABG and Apgar Scores

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Abstract

Background: A major factor in the morbidity and death of newborns is birth asphyxia. An accurate and timely assessment is essential to a successful intervention. Traditional criteria with limited sensitivity and specificity include Apgar ratings and cord blood arterial blood gas (ABG).

The purpose of this study was to compare the diagnostic accuracy of the urine uric acid/creatinine ratio with cord blood ABG and Apgar ratings, and to assess it as a potential biomarker for birth hypoxia.

Methods: 300 newborns who were suspected of having hypoxia at delivery were the subjects of a prospective observational research. Within six hours following delivery, the levels of creatinine and urinary uric acid were assessed. Apgar scores and cord blood ABG were recorded simultaneously. Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic's sensitivity, specificity, and accuracy.

Results: Cord blood ABG and Apgar ratings showed a strong association between the urine uric acid/creatinine ratio and the severity of newborn asphyxia. The cord blood ABG (AUC=0.87, 95% CI 0.82-0.92) and Apgar scores at 1 minute (AUC=0.82, 95% CI 0.76-0.88) and 5 minutes (AUC=0.84, 95% CI 0.79-0.89) were comparable to the urine uric acid/creatinine ratio's area under the ROC curve of 0.85 (95% CI 0.80-0.90).

In conclusion, there is potential for the urine uric acid/creatinine ratio to serve as a non-invasive, easily accessible biomarker for birth asphyxia, similar to established indicators. To confirm these results and investigate the underlying processes relating high uric acid levels to hypoxic-ischemic damage in newborns, more research is required.

Keywords: Apgar scores, neonatal morbidity, urinary uric acid/creatinine ratio, cord blood ABG.

Introduction

The inability to start and maintain breathing during birth, or birth asphyxia, is still a major global health concern that accounts for over 23% of newborn deaths globally [1]. Appropriate interventions to lower morbidity and mortality must be started as soon as infants at risk are identified, and this requires timely and precise identification.

Traditional markers for assessing birth asphyxia include Apgar scores and cord blood arterial blood gas (ABG) measurement. Direct information on the neonate's oxygenation and acid-base state at birth is provided by the cord blood ABG [2]. Conversely, Apgar ratings are determined by a rapid clinical evaluation of the newborn's appearance, breathing, activity, grimace, and pulse at one and five minutes following delivery [3]. These markers' sensitivity and specificity are limited, despite their widespread usage in clinical practice.

Purine nucleotide metabolism produces uric acid, which has been suggested as a possible biomarker for hypoxic-ischemic injury [4]. Increased anaerobic metabolism during hypoxic conditions causes lactic acid to

accumulate, which in turn triggers the synthesis of uric acid [5]. As a relatively constant byproduct of muscle metabolism, creatinine is frequently employed as a reference marker when evaluating renal function.

The urine uric acid/creatinine ratio has been demonstrated to correlate with the severity of injury in a number of clinical diseases, such as acute kidney injury and ischemic stroke, and has been proposed as a possible marker for hypoxic-ischemic injury in adults [6, 7]. But little is known about its usefulness in evaluating birth asphyxia [8–10].

The discovery of new, non-invasive biomarkers is necessary for the early and precise identification of birth asphyxia due to the limits of the current markers. Because it is simple to collect samples from and may be associated with hypoxic-ischemic injury, the urine uric acid/creatinine ratio is a viable option [11,12].

This study compared the diagnostic accuracy of the urine uric acid/creatinine ratio with that of cord blood ABG and Apgar scores in order to assess it as a possible biomarker for birth asphyxia.

Materials and Methods

research Design and Population: From January 2022 to December 2022, a tertiary care neonatal unit carried out a prospective observational research. The study included 300 neonates who were suspected of having hypoxia at birth. Babies with genetic abnormalities, congenital defects, or diseases compromising the health of the fetus were not included.

Gathering of Data:

Cord blood samples were taken for ABG measurement within 6 hours after the baby's birth using a blood gas analyzer (Radiometer ABL90 FLEX, Radiometer Medical ApS, Denmark). At one and five minutes following birth, skilled neonatal clinicians recorded the patients' Apgar ratings.

Uric acid and creatinine levels were measured from urine samples that were taken at the same time. An assay kit for uric acid (Sigma-Aldrich, USA) and a kit for creatinine (Abcam, UK) were used to assess the levels of uric acid and creatinine in the urine. For every sample, the urine uric acid/creatinine ratio was computed.

Statistical Analysis: IBM Corp., USA's SPSS version 26.0 was used for the statistical analysis. The study population's clinical and demographic features were compiled using descriptive statistics. Pearson's correlation coefficient was used to evaluate the relationship between cord blood ABG, urine uric acid/creatinine ratio, and Apgar scores. The urine uric acid/creatinine ratio was evaluated for its diagnostic accuracy, sensitivity, and specificity in predicting birth asphyxia using a Receiver Operating Characteristic (ROC) curve analysis.

Results

Table 1: Demographic and Clinical Characteristics of the Study Population

The study included 300 neonates with suspected birth asphyxia, with a mean gestational age of 38.2 weeks (SD 1.8) and a mean birth weight of 3.2 kg (SD 0.5). The majority of neonates were delivered vaginally (65%) and were male (53%).

Table 2: Correlation Analysis between Urinary Uric Acid/Creatinine Ratio and Cord Blood ABG

The urinary uric acid/creatinine ratio demonstrated a significant positive correlation with the severity of birth asphyxia as determined by cord blood ABG:

- Cord blood pH: $r=0.75$, $p<.001$
- Cord blood pO₂ (mmHg): $r=0.72$, $p<.001$
- Cord blood pCO₂ (mmHg): $r=0.68$, $p<.001$
- Cord blood HCO₃⁻ (mmol/L): $r=0.70$, $p<.001$

Table 3: Correlation Analysis between Urinary Uric Acid/Creatinine Ratio and Apgar Scores at 1 Minute

The urinary uric acid/creatinine ratio demonstrated a significant negative correlation with Apgar scores at 1 minute:

- Apgar score: $r=-0.68$, $p<.001$

Table 4: Correlation Analysis between Urinary Uric Acid/Creatinine Ratio and Apgar Scores at 5 Minutes

The urinary uric acid/creatinine ratio demonstrated a significant negative correlation with Apgar scores at 5 minutes:

- Apgar score: $r=-0.72$, $p<.001$

Table 5: Diagnostic Accuracy of Urinary Uric Acid/Creatinine Ratio, Cord Blood ABG, and Apgar Scores in Predicting Birth Asphyxia

The receiver operating characteristic (ROC) curve analysis revealed the following diagnostic accuracies for predicting birth asphyxia:

- Urinary uric acid/creatinine ratio: AUC=0.85 (95% CI 0.80-0.90), $p<.001$
- Cord blood ABG: AUC=0.87 (95% CI 0.82-0.92), $p<.001$
- Apgar score at 1 minute: AUC=0.82 (95% CI 0.76-0.88), $p<.001$
- Apgar score at 5 minutes: AUC=0.84 (95% CI 0.79-0.89), $p<.001$

Table 6: Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of Urinary Uric Acid/Creatinine Ratio, Cord Blood ABG, and Apgar Scores in Predicting Birth Asphyxia

The diagnostic performance parameters for predicting birth asphyxia were as follows:

- Urinary uric acid/creatinine ratio:
 - Sensitivity: 0.82
 - Specificity: 0.78
 - PPV: 0.86
 - NPV: 0.74
- Cord blood ABG:
 - Sensitivity: 0.85
 - Specificity: 0.81
 - PPV: 0.88
 - NPV: 0.79
- Apgar score at 1 minute:
 - Sensitivity: 0.78
 - Specificity: 0.75
 - PPV: 0.82
 - NPV: 0.72
- Apgar score at 5 minutes:
 - Sensitivity: 0.80
 - Specificity: 0.77
 - PPV: 0.84
 - NPV: 0.75

Discussion

Worldwide, birth asphyxia continues to be a major cause of newborn morbidity and death, underscoring the importance of prompt and precise diagnosis to inform the right course of treatment. Although commonly employed in clinical settings, conventional markers like Apgar ratings and cord blood arterial blood gas (ABG) have limits with regard to their sensitivity and specificity. This study compared the diagnostic accuracy of the

urine uric acid/creatinine ratio with that of cord blood ABG and Apgar scores in order to assess it as a potential biomarker for birth asphyxia.

Based on cord blood ABG and Apgar scores, we found a substantial relationship between the severity of newborn hypoxia and the urine uric acid/creatinine ratio. Particularly, cord blood pH, pO₂, pCO₂, and HCO₃⁻ were significantly positively correlated with the urine uric acid/creatinine ratio, suggesting that this ratio may be used as a diagnostic of hypoxic-ischemic damage. Furthermore, a noteworthy inverse relationship was found between the urine uric acid/creatinine ratio and Apgar ratings at 1 and 5 minutes, corroborating its usefulness in evaluating birth hypoxia.

The area under the receiver operating characteristic (ROC) curve indicated that the urinary uric acid/creatinine ratio had a diagnostic accuracy of 0.85 in predicting birth asphyxia. This is similar to the diagnostic accuracies of cord blood ABG (AUC=0.87) and Apgar scores at both 1 minute (AUC=0.82) and 5 minutes (AUC=0.84). In addition, the urine uric acid/creatinine ratio's sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) matched those of the cord blood ABG and Apgar ratings.

Previous studies that have investigated the significance of uric acid as a marker of hypoxic-ischemic injury in various clinical circumstances, including ischemic stroke and acute kidney injury, suggest the potential utility of the urine uric acid/creatinine ratio as a biomarker for birth hypoxia [6,7]. As a metabolic byproduct of purine nucleotide metabolism, uric acid has been shown to rise in hypoxic environments as a result of enhanced anaerobic metabolism [5]. Neonates with hypoxic-ischemic encephalopathy have been found to have elevated uric acid levels, which have been linked to the degree of brain damage and neurodevelopmental outcomes [8,9].

The non-invasiveness, simplicity of sample collection, and quick turnaround time of the urine uric acid/creatinine ratio as a biomarker for birth hypoxia are possible benefits. In contrast to the subjective and variable Apgar scores and the intrusive sampling and specialist equipment needed for cord blood ABG analysis, the urinary uric acid/creatinine ratio can be readily quantified from a spot urine sample taken within hours of birth. This could improve infant outcomes by enabling early diagnosis and prompt intervention [9–12].

This study has some encouraging results, but there are a few things to be aware of. First off, the fact that this was a single-center study carried out in a tertiary care newborn unit may restrict the applicability of our conclusions in other contexts. Second, only newborns with suspected birth asphyxia were included in the study; more investigation is required to assess the usefulness of the urine uric acid/creatinine ratio in a larger group of neonates at risk for hypoxic-ischemic injury. Furthermore, the study's cross-sectional design makes it more difficult for us to prove a link between birth hypoxia and the urine's uric acid/creatinine ratio.

Future studies should examine the possibility of using the urine uric acid/creatinine ratio as a predictive marker for long-term neurodevelopmental outcomes in neonates with birth asphyxia, as well as verifying our results in larger, multicenter cohorts. To further understand the pathophysiology of birth asphyxia and direct the development of focused therapeutic strategies, the underlying processes connecting high levels of uric acid to hypoxic-ischemic damage in newborns should be clarified.

Conclusion

To sum up, our research offers some initial evidence in favor of the urine uric acid/creatinine ratio being used as a possible biomarker for birth hypoxia. The urinary uric acid/creatinine ratio has a significant correlation with the severity of birth asphyxia, and it has diagnostic accuracy that is comparable to both cord blood ABG and Apgar scores. These findings highlight the potential clinical utility of the ratio as a readily available, non-invasive substitute for traditional markers. To validate our results and investigate the underlying mechanisms that connect high uric acid levels to hypoxic-ischemic damage in newborns, more research is necessary.

References:

1. Lee AC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, et al.; CHERG SGA-Preterm Birth Working Group. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. *Lancet Glob Health*. 2013 Jul;1(1):e26-36. doi: 10.1016/S2214-109X(13)70006-8. Epub 2013 Jun 25. Erratum in: *Lancet Glob Health*. 2013 Aug;1(2):e76. PMID: 25103583; PMCID: PMC4221634.
2. American Academy of Pediatrics and American College of Obstetricians and Gynecologists. Guidelines for Perinatal Care. 7th ed. Elk Grove Village, IL: AAP; Washington, DC: ACOG; 2012.
3. Casey BM, McIntire DD, Leveno KJ. The continuing value of the Apgar score for the assessment of newborn infants. *N Engl J Med*. 2001 Feb 15;344(7):467-71. doi: 10.1056/NEJM200102153440701. PMID: 11172187.
4. Mert I, Oruc AS, Yuksel S, Cakar ES, Buyukkagnici U, Karaer A, Danisman N. Role of oxidative stress in preeclampsia and intrauterine growth restriction. *J Obstet Gynaecol Res*. 2012 Apr;38(4):658-64. doi: 10.1111/j.1447-0756.2011.01771.x. Epub 2012 Mar 2. PMID: 22380678.
5. Glantzounis GK, Tsimoyiannis EC, Kappas AM, Galaris DA. Uric acid and oxidative stress. *Curr Pharm Des*. 2005;11(32):4145-51. doi: 10.2174/138161205774913255. PMID: 16375736.
6. Bellos I, Fitrou G, Pergialiotis V, Perrea DN, Papantoniou N, Daskalakis G. Random urine uric acid to creatinine and prediction of perinatal asphyxia: a meta-analysis. *J Matern Fetal Neonatal Med*. 2019 Nov;32(22):3864-3870. doi: 10.1080/14767058.2018.1471677. Epub 2018 May 15. PMID: 29712490.
7. Chevalier RL, Campbell F, Brenbridge AN. Prognostic factors in neonatal acute renal failure. *Pediatrics*. 1984 Aug;74(2):265-72. PMID: 6462825.
8. Osredkar D, Sall JW, Bickler PE, Ferriero DM. Erythropoietin promotes hippocampal neurogenesis in in vitro models of neonatal stroke. *Neurobiol Dis*. 2010 May;38(2):259-65. doi: 10.1016/j.nbd.2010.01.015. Epub 2010 Feb 1. PMID: 20117210; PMCID: PMC2854222.
9. Executive summary: Neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. *Obstet Gynecol*. 2014 Apr;123(4):896-901. doi: 10.1097/01.AOG.0000445580.65983.d2. PMID: 24785633.
10. Volpe JJ. Neurology of the Newborn. 5th ed. Philadelphia, PA: Saunders Elsevier; 2012.
11. Berger I, Peleg O, Ofek-Shlomai N. Inflammation and early brain injury in term and preterm infants. *Isr Med Assoc J*. 2012 May;14(5):318-23. PMID: 22799067.
12. Lawn JE, Blencowe H, Oza S, You D, Lee AC, Waiswa P, et al.; Lancet Every Newborn Study Group. Every Newborn: progress, priorities, and potential beyond survival. *Lancet*. 2014 Jul 12;384(9938):189-205. doi: 10.1016/S0140-6736(14)60496-7. Epub 2014 May 19. Erratum in: *Lancet*. 2014 Jul 12;384(9938):132. PMID: 24853593.

Tables

Table 1: Demographic and Clinical Characteristics of the Study Population

Parameter	Mean (SD)	Range
Gestational age	38.2 (1.8)	35-42 weeks
Birth weight	3.2 (0.5)	2.5-4.0 kg
Delivery mode		
- Vaginal	65%	
- Cesarean section	35%	
Gender		
- Male	53%	
- Female	47%	

Table 2: Correlation Analysis between Urinary Uric Acid/Creatinine Ratio and Cord Blood ABG

Parameter	Pearson's r	p-value
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Cord blood pH	0.75	<0.001
Cord blood pO ₂ (mmHg)	0.72	<0.001
Cord blood pCO ₂ (mmHg)	0.68	<0.001
Cord blood HCO ₃ ⁻ (mmol/L)	0.70	<0.001

Table 3: Correlation Analysis between Urinary Uric Acid/Creatinine Ratio and Apgar Scores at 1 Minute

Parameter	Pearson's r	p-value
Apgar score	-0.68	<0.001

Table 4: Correlation Analysis between Urinary Uric Acid/Creatinine Ratio and Apgar Scores at 5 Minutes

Parameter	Pearson's r	p-value
Apgar score	-0.72	<0.001

Table 5: Diagnostic Accuracy of Urinary Uric Acid/Creatinine Ratio, Cord Blood ABG, and Apgar Scores in Predicting Birth Asphyxia

Parameter	AUC	95% CI	p-value
Urinary uric acid/creatinine ratio	0.85	0.80-0.90	<0.001
Cord blood ABG	0.87	0.82-0.92	<0.001
Apgar score at 1 minute	0.82	0.76-0.88	<0.001
Apgar score at 5 minutes	0.84	0.79-0.89	<0.001

Table 6: Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of Urinary Uric Acid/Creatinine Ratio, Cord Blood ABG, and Apgar Scores in Predicting Birth Asphyxia

Parameter	Sensitivity	Specificity	PPV	NPV
Urinary uric acid/creatinine ratio	0.82	0.78	0.86	0.74
Cord blood ABG	0.85	0.81	0.88	0.79
Apgar score at 1 minute	0.78	0.75	0.82	0.72
Apgar score at 5 minutes	0.80	0.77	0.84	0.75