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Comparison of urine neutrophil gelatinase-associated lipocalin to serum creatinine to assess kidney function in neonatal asphyxia

Winston Leonardo Tanzil, Rocky Wilar, Max F. J. Mantik, Adrian Umboh, Suryadi N. N. Tatura

Abstract

Background Infants with neonatal asphyxia have multiorgan damage, such as to the kidneys (50%), central nervous system (28%), cardiovascular system (25%), and lungs (23%). Neonatal asphyxia reduces kidney perfusion, often leading to acute kidney injury (AKI) after asphyxia. Neutrophil gelatinase-associated lipocalin (NGAL) levels in the blood, urine and kidney tissue increased rapidly in AKI. Urinary NGAL is proposed to have better performance in diagnosing AKI than creatinine due to its earlier, rapid level increase and it is less invasive.

Objective To compare urinary NGAL to serum creatinine as a marker to assess kidney function in neonatal asphyxia.

Methods Diagnostic comparison study with cross-sectional design was performed at neonatal intensive care unit (NICU) of Prof. Dr. R. D. Kandou Hospital, Manado from November 2015 to February 2016. All subjects had neonatal asphyxia. Data were analyzed using descriptive analysis, receiver-operator characteristic (ROC) curve, and Z-test.

Results Urinary NGAL with cut-off point of 652.24 ng/mL can predict AKI in neonates with asphyxia with 100% sensitivity, 75% specificity, 52.3% positive predictive value, and 100% negative predictive value. Chi-square test resulted in a value of $x^2 = 20.036$, P=0.0001). This shows that urinary NGAL levels >652,24 ng/mL can predicts AKI by 20 times in infants with neonatal asphyxia. So, urinary NGAL performs better than serum creatinine, therefore it can replace serum creatinine as an alternative non-invasive diagnostic test for diagnosing AKI in infants with neonatal asphyxia.

Conclusion The diagnostic value of urinary NGAL is higher than that of serum creatinine in assessing kidney function in neonatal asphyxia. [Paediatr Indones. 2016;56:356-9. doi: 10.14238/pi56.4.2016.356-9].

Keywords: neonatal asphyxia, urinary NGAL, serum creatinine, kidney function

Neonatal asphyxia has an incidence of 0.5-2% in newborns, and is the main cause of neonatal mortality in the NICU. Asphyxia causes hypoxia and ischemia in infants, leading to multiple organ failure affecting the kidneys (50%), central nervous system (28%), cardiovascular system (25%), and lungs (23%). Neonatal asphyxia decreases renal perfusion. As such, AKI often occurs after severe asphyxia. Acute kidney

From the Department of Child Health, Sam Ratulangi University Medical School/Prof Dr. R. D. Kandou Hospital, Manado, Indonesia.

Reprint requests to: Winston Leonardo Tanzil, Department of Child Health, Sam Ratulangi University Medical School/Prof Dr. R. D. Kandou Hospital, Jl. Raya Tanawangko, Manado, Indonesia. Tel. +62 (431) 821652. Fax. +62 (431) 859091. E-mail : officus@yahoo.com.

injury (AKI) is a complex syndrome, with various clinical manifestations, from minimal serum creatinine increases to renal failure with anuria.[1-5]

Serum creatinine is a biomarker commonly used to diagnose AKI. However, creatinine examination is not particularly sensitive or specific for diagnosing AKI, as other non-renal factors regulate creatinine, distribution volume, and creatinine excretion. Past studies have suggested that urinary NGAL may be a more accurate biological marker to assess renal function. NGAL, a component of the neutrophil secondary granules, is specifically released in serum and urine in response to a stimulus. In addition, NGAL levels can be detected up to 48 hours before elevated creatinine levels can be detected. Hence, we aimed to compare urinary NGAL to serum creatinine as a marker to assess kidney function in neonatal asphyxia.[6-9]

Methods

This comparative diagnostic study with cross-sectional design was performed in the NICU, Prof. Dr. R.D. Kandou Hospital, Manado from November 2015 to February 2016. Subjects were neonates with neonatal asphyxia, born at full term with body weight ≥2,500 grams, and fulfill the *American Academy of Pediatrics/ American College of Obstetricians And Gynecologists* (AAP/ACOG) criteria for neonatal asphyxia: a 5-minute Apgar score ≤3.[10] Subjects' parents provided informed consent and approval for medical action. Neonates with suspected sepsis, low birth weight, premature birth, congenital anomalies, or birth trauma were excluded from this study. Upon NICU admission, blood and urine sample were collected. Blood sample (3 mL) was withdrawn from neonates that fulfill the inclusion criteria, using a needle that connected to a

vacuumtainer. The blood sample then sent to laboratory for serum creatinine examination. Meanwhile, we also collected 15 mL urine sample using urine collector bag. After collection, samples were immediately stored in an icebox and transported to laboratory for urine NGAL examintaion. This study was approved by the Medical Ethics Committee of Sam Ratulangi Medical School. Data were analyzed by descriptive analysis, ROC curve, and Z-test, using *SPSS version 22* software.

Results

Of 79 neonates who experienced neonatal asphyxia, 28 were excluded due to suspected sepsis (18), low birth weight (4), premature birth (3), congenital anomalies (2), or birth trauma (1). Hence, 51 infants met the inclusion criteria. Of these, 11 neonates were diagnosed with AKI, based on increased serum creatinine levels of >1.5 mg/dL (**Table 1**).

Eleven neonates had increased serum creatinine levels (>1.5 mg/dL) accompanied by increased urinary NGAL levels. The AKI diagnose in this 11 neonates was based on creatinine level increse. Of the 40 subjects with serum creatinine level ≤1.5 mg/dL, 13 neonates had elevated urinary NGAL levels but without increased serum creatinine (not diagnosed as AKI) (**Table 2**).

ROC curve analysis revealed an area under the curve (AUC) value of 0.886 for obtaining a urinary NGAL cut-off point 652.24 ng/mL (**Figure 1**). Using

Table 1. Subject distribution by gender and AKI based on serum creatinine concentration >1.5 mg/dL

Gender	AKI (n=11)	Not AKI (n=40)	Total (N=51)
Male, n	7	28	35
Female, n	4	12	16

Table 2. Comparison of serum creatinine and urinary NGAL for diagnosing AKI

Classification based on NGAL level, n	Classification based on creatinine level AKI (n=11)	Not AKI (n=40)	Total (N=51)
AKI	11	13	24
Not AKI	0	27	27

Chi-square test, we got $X^2 = 20.036$ with P < 0.001.
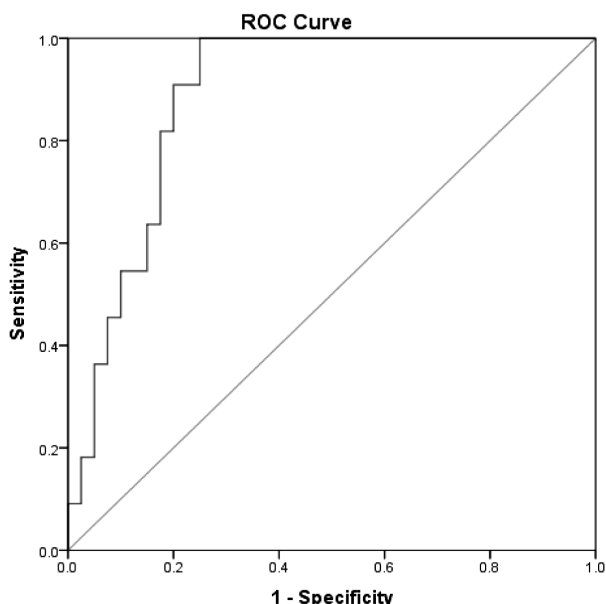

Figure 1. ROC curve analysis for urinary NGAL levels

A urinary NGAL cut-off point of 652.24 ng/mL had a sensitivity of 100%, specificity 75%, positive predictive value (PPV) 52.3%, and negative predictive value (NPV) 100%. Using this urinary NGAL cut-off point, 21 neonates were diagnosed to have AKI, comprising 15 (71.4%) males and 6 (28.6%) females (**Table 3**). The mean urinary NGAL level in asphyxiated neonates with AKI in our study was 2,134.16 ng/mL, ranging from 681.19 ng/mL to 2,631.18 ng/mL.

Table 3. Urinary NGAL levels and the incidence of AKI in neonatal asphyxia

NGAL level, n	AKI (n=11)	Not AKI (n=40)	Total (N=51)
≥ 652.24 ng/mL	11	10	21
< 652.24 ng/mL	0	30	30

Discussion

Using serum creatinine >1.5 mg/dL as a biomarker to define AKI, we found 11 neonates diagnosed with AKI of whom 7 (64%) were male and 4 (36%) were female. However, using urine NGAL with a 652.24 ng/mL cut-off point, we surmised that 21 neonates had AKI, of whom 15 (71.4%) male and 6 (28.6%) were female. Chiabi *et al*. found more males with neonatal asphyxia in Cameroon (54% with a male: female ratio of 1.3:1).[11]

The ROC analysis had an AUC of 0.886, using the urinary NGAL cut-off point of 652.24 ng/mL to diagnose AKI in neonates with neonatal asphyxia had a sensitivity of 100%, specificity 75%, PPV 52.3%, and NPV 100%. In contrast, Haase *et al*. obtained a urinary NGAL cut-off point of 193.2 ng/ml, with 77.8% sensitivity and 84.3% specificity. This difference may have been due to different etiologies of AKI. In our study, all subjects had neonatal asphyxia, while their study was conducted in critically ill patients with AKI.[12]

The mean urinary NGAL level in asphyxiated neonates with AKI in our study was higher than the cut-off point (2,134.16 ng/mL), ranging from 681.19 ng/mL to 2,631.18 ng/mL. The 652.24 ng/mL urinary NGAL cut-off point could be used detect the incidence of AKI in subjects with neonatal asphyxia, with a sensitivity of 100% (Z = 1.915; P=0.028) and a specificity of 75% (Z = -0.01; P=0.05). We also found a PPV of 52.3%, NPV of 100%, positive likelihood ratio of 1.33, and negative likelihood ratio of zero. These results suggest that the incidence of AKI in neonates with asphyxia may be underdiagnosed.

A limitation of this study was not comparing the degree of asphyxia severity to urinary NGAL levels, so we could not determine if there was a positive association between the two variables. In addition, due to the cross-sectional design of the study, further research on serum and urinary NGAL levels must be done to further assess their usefulness in diagnosing AKI in neonatal asphyxia.

Chi-square test revealed a X^2 value of 20.036 (P<0.001). This result suggests that urinary NGAL level > 652.24 ng/mL can predict AKI by 20 times in neonates with neonatal asphyxia. In conclusion, examination of urinary NGAL has a higher diagnostic test value than serum creatinine. As such, it can be used as an alternative, non-invasive diagnostic test to diagnose AKI in neonates with neonatal asphyxia.

Acknowledgments

Conflict of interest

None declared.

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