Clinical Utility of Rapid Plasma Neutrophil Gelatinase-Associated Lipocalin Assays for Diagnosing Acute Kidney Injury in Critically Ill Newborn Infants

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ABSTRACT

Purpose: Neutrophil gelatinase-associated lipocalin (NGAL) has been identified as an early marker of acute kidney injury (AKI). This study was designed to evaluate the clinical utility of the rapid plasma NGAL assay for diagnosing AKI in critically ill newborn infants in the neonatal intensive care unit (NICU).

Methods: The medical records of 178 critically ill newborn infants >34 weeks of gestational age who underwent plasma NGAL measurement during the first week of life in the Korea University Ansan Hospital NICU from February 2011 to August 2015 were retrospectively reviewed. Plasma NGAL levels were measured at bedside by using a commercial competitive immunoassay kit simultaneously with serum creatinine (Cr) level determination.

Results: Of 178 newborn infants enrolled in this study (study group), 25 infants had AKI (AKI group) while 153 infants had no AKI (control group). The plasma NGAL level in the AKI group (114.0 [76.5–281.5] ng/mL) was significantly higher than that in the control group (74.0 [52.5–122.5] ng/mL, $P=0.001$). Moreover, plasma NGAL levels were found to be correlated with serum Cr levels in the study group ($r=0.208$, $P=0.005$). Plasma NGAL achieved an area under the receiver operating characteristic curve of 0.705 for detecting AKI (95% confidence interval: 0.593–0.817). The best cut-off plasma NGAL level for AKI diagnosis was 100 ng/mL.

Conclusion: The rapid plasma NGAL assay has diagnostic value for AKI in critically ill newborn infants >34 weeks of gestational age. Further investigations with a larger population are needed to confirm the potential use of plasma NGAL levels for diagnosing AKI in newborn infants.

Key Words: Neutrophil gelatinase-associated lipocalin, Acute kidney injury, Serum creatinine, Newborn infants

INTRODUCTION

Acute kidney injury (AKI) is a serious condition that damages the tubular function of the

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kidney¹⁾. It is frequently found in infants in the neonatal intensive care unit (NICU), with poor outcome associated with increased length of stay and mortality²⁾. Critically ill infants in the NICU are at a high risk of having AKI because they have multiple risk factors³⁻⁵⁾.

Current studies have shown that serum creatinine (Cr) level is widely used for diagnosing neonatal AKI^{6,7)}; however, it has many disadvantages. For example, serum Cr levels can vary depending on age, gender, muscle mass, medication, and intravascular volume status⁸⁾. Furthermore, elevation of serum Cr level is not a marker but a consequence of kidney injury. It is not present in patients before 25–50% loss of kidney function. The unique renal physiology of preterm and term infants, associated with renal immaturity, also creates challenges for using serum Cr level as an AKI marker⁹⁾. Furthermore, in the first few days of life, serum Cr reflects the maternal value. It differs widely depending on weight and gestational age^{10,11)}. Therefore, novel neonatal AKI criteria with new biomarker need to be established owing to the possibility of delayed diagnosis and misclassification of AKI by using serum Cr levels. As a result, a significant amount of research has been conducted to identify novel biomarkers of damage to allow for the earlier identification of neonates with AKI. These novel biomarkers include neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, kidney injury molecule-1, and others¹²⁻¹⁵⁾.

NGAL, a 25-kD protein of the lipocalin superfamily, is a promising early biomarker of AKI. It is released in kidney tissue and upregulated in kidney tubule cells. In addition, renal expression of NGAL is increased dramatically after renal ischemia¹⁶⁾. The NGAL concentration in blood has been demonstrated to be a sensitive and specific early marker of AKI¹⁷⁾. In addition, it is useful for heterogeneous groups of children and adults^{18,19)}. Serum and urine NGAL levels have also shown good performance in newborn infants with AKI^{13,20,21)}.

In infants, using urine samples for NGAL measurement has a limitation because collecting urine for AKI evaluation is difficult owing to anuria, oliguria, or impaired urine-concentrating ability in infants⁸⁾. To overcome such limitation in collecting urine sample, studies using blood NGAL measurement have been performed for several neonatal groups^{13,17,22)}. Recently, rapid plasma NGAL assay has provided clinicians an opportunity to explore its potential usefulness at bedside within 20 min. Therefore, the objective of this study was to evaluate the clinical utility of the rapid plasma NGAL assay for diagnosing AKI in critically ill newborn infants >34 weeks of gestational age.

MATERIALS AND METHODS

1. Study population

This study was performed retrospectively by reviewing the medical records of critically ill newborn infants admitted to the NICU of Korea University Ansan Hospital between February 2011 and August 2015. During the study period, 178 critically ill newborn infants >34 weeks of gestational age who underwent plasma NGAL measurement during the first week of life were enrolled.

Measurement of plasma NGAL was performed simultaneously with serum Cr level determination for critically ill newborn infants with a high risk of having AKI owing to their multiple risk factors. The study group comprising 178 newborn infants was divided into two groups according to the AKI criteria, as follows: 1) infants with AKI (AKI group) and 2) infants without AKI (control group). This study was approved by the Institutional Review Board (IRB) of Korea University Ansan Hospital (IRB no.: AS17137).

2. Diagnosis and staging of AKI

The diagnosis of AKI was based on serum Cr ≥ 1.5 mg/dL on the first week of life (normal renal function in the mother of the neonate) or on the neonatal modified Kidney Disease: Improving Global Outcome (KDIGO) Cr criteria during the first week of life^{7,23,24)}. The neonatal modified KDIGO Cr criteria are as follows:

- Stage I AKI was diagnosed when the serum Cr level increased by ≥ 0.3 mg/dL within 48 h or the serum Cr level increased by $\geq 1.5 - 1.9 \times$ the reference level (lowest previous serum Cr value) within 7 days.
- Stage II AKI was diagnosed when the serum Cr level increased by $\geq 2.0 - 2.9 \times$ the reference level.
- Stage III AKI was diagnosed when the serum Cr increased by $\geq 3 \times$ the reference serum Cr, or when the serum Cr level was ≥ 2.5 mg/dL, or when the infant was receiving dialysis.

3. Measurement of plasma NGAL

Plasma NGAL levels were measured with a commercial competitive immunoassay kit (Alere Triage[®] NGAL test; Alere Inc., San Diego, CA, USA) at bedside. The assay has a detection range of 60–1,300 ng/mL with a coefficient of variation of 10–15%. All samples were simultaneously tested once the sampling was completed, including plasma NGAL level, serum Cr level, and other routine tests.

4. Clinical data collection

Maternal and neonatal data were collected from medical records through a retrospective review. The collected data included gestational age, birth weight, height, gender, Apgar score (at 1 and 5 min), antenatal steroid administration, mode of delivery, and maternal pregnancy complications. Neonatal outcomes were also collected, including perinatal asphyxia, persistent pulmonary hypertension of the newborn (PPHN), respiratory distress syndrome (RDS), meconium aspiration syndrome (MAS), patent ductus arteriosus (PDA), neonatal sepsis, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and mortality. Patients with congenital renal abnormalities detected with abdominal ultrasound were excluded. The definitions of neonatal outcomes in this study are as follows:

- Perinatal asphyxia was defined as pH <7.2 and Apgar score ≤7 at 5 minutes of the infants at birth.
- PPHN was defined as the need for nitric oxide treatment for infants with ventilator care.
- RDS was defined as infants the need for intratracheal surfactant instillation.
- MAS was defined as meconium aspiration and requirement for ventilator care.
- PDA was defined as two-dimensional echocardiogram-proven PDA treated with ibuprofen.
- Sepsis was defined as pathogen-proven sepsis.
- NEC was evaluated using abdominal radiography and physical examination, and defined as stage II and stage III of the modified Bell's staging criteria.
- IVH was defined as a Papile-Burstein classification grade of II or higher.
- PVL was defined by brain sonography-proven PVL.

Clinical laboratory results such as serum Cr level, white blood cell (WBC) count, platelet count, and C-reactive protein (CRP) level were recorded for each infant as part of routine care. Leukocytosis was defined as WBC count >21,000/mm³. CRP positivity was defined as CRP level >0.5 mg/dL. Urine output was recorded during the first week of life. Urine output of <0.5 mL·kg⁻¹·hour⁻¹ indicated oliguria. In the AKI group, the test results of plasma NGAL and serum Cr levels were used at the time of AKI diagnosis.

5. Statistical analysis

Categorical variables are expressed as number (percentage), whereas continuous variables are expressed as mean±standard

deviation or median [25th–75th percentile]. Continuous variables between two groups were compared with Mann-Whitney's rank sum *U* test. Categorical variables were compared with Pearson's chi-square test or Fisher's exact test as appropriate. Correlations between plasma NGAL and serum Cr levels were analyzed using Spearman's rank correlation analysis. Receiver operator characteristic (ROC) analysis was performed to determine the best cutoff value for plasma NGAL level to detect neonatal AKI and assess discrimination ability (by calculating the area under the ROC curve [AUC]) of plasma NGAL to recognize infants with AKI. The cutoff value was estimated using the Youden index ($J = \text{sensitivity} + \text{specificity} - 1$), with the two right-hand quantities being sensitivity and specificity. Statistical analysis was performed using IBM SPSS Statistics version 20.0 for Windows (IBM Corp., Armonk, NY, USA). A *P*-value of <0.05 was considered statistically significant.

RESULTS

Of the 178 infants (study group), 25 infants fulfilled the criteria for AKI (AKI group). A total of 12 infants had serum Cr level ≥1.5 mg/dL (2 on the first day of life, 7 on the second day, 1 on the third day, 1 on the fourth day, and 1 on the sixth day of life). On the other hand, 23 infants developed AKI according to the modified neonatal KDIGO Cr criteria (2 on the first day of life, 16 on the second day, 3 on the third day, 1 on the fourth day, and 1 on the sixth day of life). All these 23 infants were classified as having stage I AKI according to the modified neonatal KDIGO Cr criteria. Ten infants fulfilled both criteria (serum Cr ≥1.5 mg/dL and neonatal modified KIDGO Cr criteria). The remaining 153 infants did not meet the criteria for AKI (control group).

The demographic and clinical characteristics of these two groups are summarized in Table 1. The gestational age at birth was 36.9±2.2 weeks in the AKI group and 37.3±2.1 weeks in the control group, with no significant difference between the two groups. The birth weight was 2,533±695 g in the AKI group and 2,890±641 g in the control group. The height was 46.6±4.4 cm in the AKI group and 48.3±3.6 cm in the control group. Both birth weight and height were significantly different between the two groups. Birth weight, height, and Apgar scores (at 1 and 5 min) were significantly different between the two groups. However, there were no significant differences in gestational age or small for gestational age (SGA) status between the two groups. A

Table 1. Demographic and Clinical Characteristics of Infants in the Acute Kidney Injury Group and the Control Group

	AKI group (N=25)	Control group (N=153)	P-value
Gestational age (wks)	36.9±2.2	37.3±2.1	0.345
Birth weight (g)	2,533±695	2,890±641	0.011
Height (cm)	46.6±4.4	48.3±3.6	0.037
Gender (male)	15 (60.0%)	90 (58.8%)	1.000
Perinatal characteristics			
Apgar score, 1 min	5 [2-6]	8 [7-9]	<0.001
Apgar score, 5 min	7 [6-8]	9 [8-9]	<0.001
Antenatal steroid administration	2 (8.0%)	8 (5.2%)	0.929
Caesarean section	18 (72.0%)	107 (70.4%)	1.000
Small for gestational age	6 (24.0%)	15 (9.9%)	0.091
Maternal characteristics			
Chorioamnionitis	1 (4.0%)	0 (0.0%)	0.299
Gestational diabetes mellitus	2 (8.0%)	9 (5.9%)	1.000
Pregnancy-induced hypertension	3 (12.0%)	9 (5.9%)	0.483
Preeclampsia	0 (0.0%)	3 (2.0%)	1.000
Neonatal outcomes			
Perinatal asphyxia	11 (32.0%)	15 (6.5%)	<0.001
Persistent pulmonary hypertension of the newborn	2 (8.0%)	5 (3.3%)	0.566
Respiratory distress syndrome	5 (20.0%)	27 (17.6%)	0.997
Meconium aspiration syndrome	4 (16.0%)	11 (7.2%)	0.279
Patent ductus arteriosus	5 (20.0%)	20 (13.1%)	0.539
Sepsis	1 (4.2%)	1 (0.7%)	0.635
Necrotizing enterocolitis	0 (0%)	0 (0%)	N/A
Intraventricular hemorrhage	1 (4.0%)	6 (3.9%)	1.000
Periventricular leukomalacia	1 (4.2%)	1 (0.7%)	0.635
Mortality	2 (8.0%)	2 (1.3%)	0.172
Oliguria	3 (12.0%)	0 (0.0%)	0.002

Categorical variables are expressed as number (in percentages) while continuous variables are expressed as mean±standard deviation or median [25th–75th percentile].

Abbreviation: AKI, acute kidney injury.

greater proportion of SGA infants were identified in the AKI group than in the control group; however, the difference was not statistically significant.

In neonatal outcomes, the incidence of perinatal asphyxia was higher ($P<0.001$) in the AKI group than in the control group. Oliguria only appeared in the AKI group ($P=0.002$). However, there were no difference in other characteristics or neonatal outcomes between the two groups.

The incidence of leukocytosis or CRP elevation showed no significant difference between the AKI group and the control

Table 2. Laboratory Findings of Infant in the Acute Kidney Injury Group and the Control Group

	AKI group (N=25)	Control group (N=153)	P-value
Age at exam (d)	2 [2-2]	2 [1-2]	0.059
WBC (/mm ³)	23,254±29,210	17,178±8,575	0.312
Leukocytosis (>21,000/mm ³)	9 (36.0%)	37 (24.2%)	0.211
Platelet (/mm ³)	214,040±85,916	243,529±69,928	0.060
CRP (mg/dL)	0.4±0.9	0.5±1.2	0.726
CRP positivity rate (>0.5 mg/dL)	4 (16%)	28 (18.3%)	1.000
Serum Cr (mg/dL)	1.27 [1.06-1.70]	0.78 [0.60-0.90]	<0.001
Plasma NGAL (ng/mL)	114.0 [76.5-281.5]	74.0 [52.5-122.5]	0.001

Categorical variables are expressed as number (in percentages) while continuous variables are expressed as mean±standard deviation or median [25th–75th percentile].

Abbreviations: AKI, acute kidney injury; WBC, white blood cell; CRP, C-reactive protein; Cr, creatinine; NGAL, neutrophil gelatinase-associated lipocalin.

Figure 1. Serum creatinine versus plasma neutrophil gelatinase-associated lipocalin levels in the study group. Abbreviations: NGAL, neutrophil gelatinase-associated lipocalin; Cr, Creatinine.

group. The median serum Cr level in the AKI group was significantly higher than that in the control group (1.27 [1.06–1.70] mg/dL vs. 0.78 [0.60–0.90] mg/dL, $P<0.001$). The median plasma NGAL level in the AKI group was also significantly higher than that in the control group (114.0 [76.5–281.5] ng/mL vs. 74.0 [52.5–122.5] ng/mL, $P=0.001$, Table 2).

The plasma NGAL levels were found to be weakly correlated with serum Cr levels in the study group ($r=0.208$, $P=0.005$, Figure 1).

Figure 2. Receiver operating characteristic curve used to determine plasma neutrophil gelatinase-associated lipocalin (plasma NGAL) cutoff value for detecting acute kidney injury. The area under the curve value for plasma NGAL was 0.705; 95% confidence interval: 0.593–0.817 and $P=0.001$.

Table 3. Diagnostic Accuracy of Plasma Neutrophil Gelatinase-Associated Lipocalin Levels for Detecting Acute Kidney Injury According to Various Cutoff Values

Cutoff value for plasma NGAL (ng/mL)	Positive predictive value (%)	Negative predictive value (%)	Sensitivity (%)	Specificity (%)
70	21.2	94.9	84.0	49.0
80	20.9	92.4	72.0	55.6
90	23.4	93.1	72.0	61.4
100	25.0	92.7	68.0	66.7
110	22.4	90.0	52.0	70.6

Abbreviation: NGAL, neutrophil gelatinase-associated lipocalin.

The AUC for the detection of AKI with plasma NGAL level was 0.705 (95% confidence interval: 0.593–0.817, $P=0.001$, Figure 2). The best cutoff plasma NGAL level for the detection of AKI, estimated using Youden index, was found to be 100 ng/mL. At this cutoff value, the sensitivity was 68.0%, the specificity was 66.7%, and the positive predictive value was 25.0% (Table 3).

DISCUSSION

Serum Cr level is still widely used in current clinical studies to define neonatal AKI^(6,7) despite its limitations of being influenced by maternal-fetal transplacental transfer, body mass, and maturation variability^(8–11). Furthermore, elevation of serum Cr level is a reflection of decreased renal function, not a marker of kidney

injury. It is not appear in patients before 25–50% loss of kidney function^(8,11). In addition, it takes time for serum Cr level changes to be detected after kidney injury, thus limiting its usefulness for early detection of AKI^(25,26).

As a novel diagnostic marker for AKI, serum and urine NGAL levels have shown good performance in newborn infants with AKI who undergo cardiopulmonary bypass or those with perinatal asphyxia^(13,20). Also, elevation of NGAL takes only two hours after kidney injury, while elevation of serum Cr takes at least one day^(20,25).

For the last two decades, urine NGAL level has been studied extensively because NGAL is released directly into the urine by kidney tubules after renal injury. However, collecting urine for AKI evaluation is difficult owing to anuria, oliguria, or impaired urine-concentration ability in infants⁽⁸⁾. Considering that urinary NGAL levels are correlated with the plasma or serum levels of NGAL regardless of the cause of increased NGAL production⁽²⁷⁾, many studies have evaluated the value of blood NGAL levels in neonatal groups^(13,17,22).

This study aimed to assess whether increased plasma NGAL level might be useful as a diagnostic marker of AKI in critically ill newborn infants diagnosed as having AKI based on serum Cr levels. Our results revealed that plasma NGAL levels were increased significantly in the AKI group, suggesting that kidney injury might be a possible cause of elevated plasma NGAL level. Moreover, the AUC was moderately accurate and statistically fair. Therefore, plasma NGAL showed good performance in AKI diagnosis in critically ill newborn infants in the NICU.

Compared with previous studies on newborn infants with AKI^(13,17,20,22,28,29), our study included a neonatal population in the late preterm period with a gestational age of 34–36 weeks. In addition, the AKI population of our study was composed of infants with mild AKI because all cases were classified as stage I AKI.

The plasma NGAL and serum Cr levels showed weak correlations in the study group ($r=0.208$, $P=0.005$). With this tendency, plasma NGAL level might have some relationship with serum Cr level to be a biomarker for diagnosing AKI. Similarly, in the study of El-Farghali et al.⁽¹⁷⁾ on critically ill newborn infants, serum NGAL levels showed a significant correlation with subsequent serum Cr levels measured within 48 h after admission ($r=0.78$, $P=0.0001$)⁽¹⁷⁾. Therefore, plasma NGAL level could be a diagnostic marker comparable to serum Cr level.

Recently, it has been reported that blood NGAL level can help define AKI in various neonatal groups^(13,17,20,22,28,29). Jiang and Cui⁽²⁸⁾ performed a meta-analysis concerning the accuracy of using

NGAL level in the diagnosis of AKI to clarify the definition of AKI. The studies included in their meta-analysis used various diagnostic criteria of AKI (serum Cr ≥ 1.5 mg/dL or serum Cr increase from baseline of >0.3 mg/dL, or both). The results of their bivariate model for diagnostic meta-analysis showed summary AUC, pooled diagnostic odd ratio, pooled sensitivity, and pooled specificity of 0.87, 27.20, 81%, and 86% respectively, indicating that NGAL level could be used to diagnose AKI in infants. After the diagnostic meta-analysis, a prospective study on asphyxiated neonates by Baumert et al.²⁹⁾ also showed that serum NGAL level has a high specificity as an AKI marker (AUC= 0.93, $P=0.01$, specificity=95%).

In our study, the results of statistical analysis showed lower sensitivity, specificity, and AUC compared with those of previous studies^{13,17,20,22,28,29)}. This might be because most of the infants with AKI included in our study showed mild disease (stage I). However, in the study of El-Farghali et al.¹⁷⁾ which is the only study classified and reported AKI stage, 25 of 34 infants showed stage II or III AKI in the Acute Kidney Injury Network (AKIN) Cr criteria. Their AUC (0.95) was higher than that of the present study. It seems to be owing to the fact that study of El-Farghali et al. contained more infants with high stage of AKI than present study.

In our study, the best cutoff value for plasma NGAL to diagnose AKI was 100 ng/mL, with a sensitivity of 68.0% and a specificity of 66.7%. The meta-analysis performed by Jiang and Cui²⁸⁾ reported a cutoff value ranging from 66.6 to 157 ng/mL. Baumert et al.²⁹⁾ reported a cutoff value of 140.7 ng/mL for AKI diagnosis in patients with asphyxia. These differences could be related to the inclusion of late preterm infants between 34 and 36 weeks of gestational age, difference in patient characteristics in each study, difference in the test method, and component difference of blood. The use of different AKI criteria in each study could also influence the result of the best cutoff value for blood NGAL level.

Oliguria that fulfilled the urine output criteria occurred in about 12% of our AKI group. Many studies have reported that $>50\%$ of AKI cases are nonoliguric, highlighting the insensitivity of oliguria to predict AKI in newborns^{30,31)}. For example, El-Farghali et al.¹⁷⁾ reported that, of 60 full-term infants, 34 infants were found to have AKI according to the criteria proposed by the AKIN. This is consistent with our study showing a lower rate of oliguria than other studies because our AKI group was composed of infants with a milder stage of AKI.

However, the present study also has limitations. First, the diagnosis of AKI based on serum Cr level is limited by the late res-

ponse of serum Cr to AKI. Therefore, infants with elevated plasma NGAL level before serum Cr elevation might have been missed as having neonatal AKI. El-Farghali et al.¹⁷⁾ reported that serum NGAL levels are significantly increased in neonates with evolving AKI before serum Cr elevation, and that serum NGAL levels are significantly correlated with subsequent serum Cr levels, not the initial serum Cr levels. Second, this study was performed at a single center, thus limiting the number of the enrolled newborn infants with AKI. Therefore, a large multicenter randomized trial on the clinical application of plasma NGAL for newborn infants with AKI is needed. Further investigations with larger patient groups are also required to better assess the role of rapid plasma NGAL assay for AKI diagnosis in critically ill newborn infants at bedside. Third, to verify a better biomarker for AKI, simultaneous examination of other serum biomarkers is desirable^{24,32)}. Recent studies have unveiled other AKI biomarkers including interleukin-18¹⁴⁾ and cystatin C¹⁵⁾. Fourth, our study could not evaluate the power of NGAL level to diagnose AKI before serum Cr level owing to the limitation of the retrospective chart review. Therefore, a prospective study with a larger group should be performed in the future with serial NGAL and serum Cr tests for critically ill newborn infants who are likely to develop AKI.

In conclusion, the rapid plasma NGAL assay has diagnostic value for AKI in critically ill newborn infants >34 weeks of gestational age. Further investigations with a larger population are needed to confirm the potential application of plasma NGAL level for diagnosing and managing AKI in newborn infants.

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