Original Article

Performance of Serum Neutrophil–Gelatinase Associated Lipocalin (NGAL) in the Diagnosis of Pregnancy-Related Acute Kidney Injury (PRAKI) in Delta, State Nigeria: A Prospective Study

EP Orhewere[1], AB Odonmeta[1], OA Adejumo[2], OC Okoye[1,3]

[1]Department of Internal Medicine, Delta State University Teaching Hospital, Oghara, Delta State, [2]Department of Internal Medicine, University of Medical Sciences, Ondo State, [3]Department of Internal Medicine, Delta State University, Abraka, Delta State, Nigeria

Abstract

Background: Pregnancy-related acute kidney injury (PRAKI) is associated with poor maternal and perinatal outcomes if not promptly recognized. Diagnosis of PRAKI is currently based on serum creatinine, which delays diagnosis and, inevitably, treatment. **Aims:** To determine the performance of serum NGAL in the diagnosis of PRAKI among women in the peripartum period and determine the normal serum NGAL levels in nonpregnant women. **Methods:** A prospective study involving 162 pregnant women who presented in labor in two hospitals in Delta State and 150 nonpregnant controls. Serum creatinine and NGAL were assayed using blood samples collected from study participant at 0, 6, 12, 24, and 48 hours and 7 days postdelivery. Diagnosis of PRAKI was based on both serum creatinine and NGAL. The diagnostic performance of NGAL was determined by performing a receiver operation curve and determining the area under the curve (AUC). **Results:** The prevalence of AKI using creatinine-based KDIGO criteria was 22.2% and 50% using serum NGAL. The optimal diagnostic accuracy for serum NGAL was at the 12th hour, using a cut off of 142 ng/dl determined by Youden's index. The reference range for nonpregnant women was 12.77 – 135.67 ng/dl. The sensitivity and specificity of serum NGAL at a cut off 142 ng/ml were 77.2% and 75.4% (AUC = 0.79), respectively while using 135.67 ng/ml (upper limit determined from nonpregnant women) as cut-off, sensitivity was 77.78% and specificity was 70.63%. **Conclusion:** Serum NGAL is a promising marker for early diagnosis of PRAKI with high sensitivity and specificity.

Keywords: *Creatinine, diagnostic utility, NGAL, pregnancy-related acute kidney injury*

Received: 10-May-2024;
Revision: 16-Jan-2025;
Accepted: 04-Mar-2025;
Published: 26-Apr-2025

Introduction

The burden of pregnancy related acute kidney injury (PRAKI) is still high and associated with significant maternal and perinatal outcomes in most low- and middle income countries.[1] The maternal and perinatal mortality associated with PRAKI in Africa is as high as 34.4% and 60.5%, respectively.[1] PRAKI is more common in low- and middle-income countries (LMICs) compared with high income countries (HICs).[2] The reported incidence in HICs is 1–2.8% compared with 4–26% reported in LMICs.[1,2] Early diagnosis of PRAKI is important to reducing the associated burden and improving overall outcome.

Diagnosis of PRAKI is currently based on serum creatinine, but this marker has significant limitations. The use of creatinine as a marker of kidney injury, although most widely used and accepted, is fraught with some limitations. Serum levels of creatinine may be affected by factors such as diet, muscle bulk, glomerular

Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_326_24

Address for correspondence: Dr. OC Okoye, Department of Internal Medicine, Delta State University Teaching Hospital, Oghara, Delta State, Nigeria.
E-mail: ogonwosu2002@yahoo.com

How to cite this article: Orhewere EP, Odonmeta AB, Adejumo OA, Okoye OC. The performance of serum neutrophil-gelatinase associated lipocalin (NGAL) in the diagnosis of pregnancy-related acute kidney injury (PRAKI) in Delta, State Nigeria: A prospective study. Niger J Clin Pract 2025;28:525-30.

filtration rate (GFR), tubular secretion of creatinine, gender and race.[3] In addition, the diagnosis of kidney injury is delayed because serum creatinine accumulation lags behind kidney injury.[4] The half-life of creatinine increases as GFR decrease; hence, it may take up to 24 hours before the serum creatinine value rises after an acute insult to the kidneys.[4] This inevitably delays diagnosis and initiation of treatment.

The lack of reliable biomarkers of early structural kidney injury results in an unacceptable delay in the clinical diagnosis, which severely limits prompt therapeutic intervention. Therefore, there is an urgent need for a biomarker that can promptly detect PRAKI. Neutrophil gelatinase-associated lipocalin (NGAL) is an emerging biomarker for early diagnosis of acute kidney injury (AKI). It has been shown to detect AKI earlier than serum creatinine.[5] Neutrophil gelatinase-associated lipocalin, unlike creatinine, is a marker responsive to tissue stress and nephron injury, but less so to adaptive hemodynamic responses. At a cutoff value of 130 ng/ml NGAL, sensitivity and specificity of serum NGAL for detecting acute injury were 90% and 99.5%, respectively.[5] The marker is noninvasive, clinically actionable and reliably measurable on available standardized clinical platforms. Furthermore, NGAL incrementally adds value to the baseline clinical risk assessment, potentially enabling physicians to intervene early to limit the extent of renal injury.[6]

Despite the promising data and information on NGAL, a majority of the studies have been conducted in developed countries. Furthermore, at the time of this study, there was no existing nomogram of serum NGAL in Nigeria. Therefore, this study was aimed at determining the performance of serum NGAL compared with serum creatinine in the detection of PRAKI among Black pregnant women in a LMIC; in addition, determine a normal reference range for serum NGAL in a nonpregnant female population.

Subjects and Methods

This prospective study was carried out over a 5-week period between March and April, 2020 in two public health institutions in Delta State, Nigeria. The two institutions are 40 km apart and provide high level obstetric care for women in Delta State and environs, in addition to serving as training institutions for undergraduate and postgraduate students. Inclusion criteria were booked and unbooked women in labor with known baseline creatinine values; pregnant women diagnosed with chronic kidney disease, but with stable eGFR higher than 15 ml/min/1.73 m^2; and those who gave consent to participate in the study. Pregnant women who had end stage renal disease and those who require renal replacement therapy were to be excluded, but no such cases were encountered.

Sample size estimation and data collection

The sample size was calculated using Cochran's formula[7] for a population less than 10,000 because the hospitals' statistics showed that about 500 pregnant women deliver yearly. The prevalence of 16.9% was used for the calculation based on a previous study on PRAKI by Sivakumar *et al*.[8] After inclusion of 10% attrition rate, the minimum sample size was 165.

Consenting patients who met the inclusion criteria were recruited consecutively from the labor ward unit. Patients' records were checked to confirm booking status. Healthy nonpregnant hospital staff and medical colleagues were recruited as controls, age and parity matched with patients who gave informed consent.

Researcher administered proforma was used to obtain socio-demographic and clinical information from the study participants. Six milliliters of whole blood was collected from study participants at 0 hr, 6 hrs, 12 hrs, 24 hrs, and 48 hrs and 7 days postdelivery. Blood samples were separated, and the sera were stored at -20°C. Serum creatinine for each timed period was determined using the ARCHITECT c4000 clinical chemistry analyzer manufactured by Abbot. Serum NGAL was assayed using the sandwiched ELISA principle, where the optical density of the complex of human NGAL and its antibodies were measured through spectrophotometry at 450 nm wavelength. The concentration of human NGAL in serum was calculated by comparing the optical densities of the samples to the standard curve. The Quickey human NGAL ELISA kit Catalog-No: E-TSEL-H0003, 96T, manufactured by ELABSCIENCE was used. The kit was stored at 2–8°C and was warmed to room temperature just before usage.

Definition of terms

PRAKI was defined as a decline in kidney function evidenced by an increase in serum creatinine by a level higher than 0.3 mg/dl (26.5 μmol/l) within 48 hours or increase in serum creatinine to 1.5 times baseline, which was known or presumed to have occurred within the prior 7 days.[9] PRAKI was also defined by serum NGAL above cut-off value determined for nonpregnant women in this study

Ethical consideration

Ethical approval was obtained from the Health Research and Ethics Committee of Delta State University Teaching Hospital (HREC/PAN/2019/070/0320). A duly signed/thumb printed informed consent, or a recorded verbal consent was obtained from participants before

they were recruited for the study. This study was conducted in accordance with the ethical guidelines set by the Delta State University Teaching Hospital HREC.

Data analysis

Data was collated and analyzed with the International Business Machines Statistical Package for Social Sciences (IBM-SPSS) version 22.0. Discrete variables were presented as frequencies and percentages. Continuous data were presented as means and standard deviation. Student's *t*-test was used to compare means between two groups while analysis of variance was used to compare means for more than two groups. The primary outcome for the study was PRAKI defined as 0.3 mg/dl rise in serum creatinine from baseline within 48 hours and a rise in serum NGAL above cut-off determined for nonpregnant women in this study. The sensitivity, specificity, negative predictive value, positive predictive value and accuracy of serum NGAL using serum creatinine as gold standard were calculated as using Med Calc statistical software. The discriminatory power of NGAL was determined by performing receiver operation curve and determining the AUC. Statistical significance was set at a probability level of <0.05.

Results

We studied 162 pregnant women and 150 nonpregnant controls with a mean age of 30.1 ± 1.3 years, respectively. A majority (93.2%) of the participants were married, ninety-seven (59.9%) had primary level of education while 124 (76.5%) were assigned International Standard Classification of Occupation (ISCO) level 1 based on self-report [Table 1]. Of the 162 pregnant women, 58 (35.8%) were nulliparous, 17 (10.5%) primiparous and 87 (53.7%) multiparous. Among the 150 nonpregnant women, 45 (30.0%) were nulliparous, 20 (13.3%) primiparous and 85 (56.7%) multiparous.

Among the 150 nonpregnant women, serum NGAL ranged from 10-144 ng/ml (median 49 ng/ml). The normal reference intervals determined using the nonparametric percentile method CLSI C28-A3 was 12.77 ng/dl (95%CI: 10.00-15.00) to 135.67 ng/ml (95%CI: 126.00-144.00). The frequency of PRAKI using the determined normal upper limit (135.67 ng/ml) was 50% (sensitivity = 77.78%, specificity = 70.63%). The optimal diagnostic accuracy for serum NGAL was at the 12th hour, using the cut off of 142 ng/ml determined by Youden's index (sensitivity = 77.78%, specificity = 75.40%, positive predictive = 39.2%, negative predictive value = 94.3%, AUC = 0.795, $P < 0.001$), Table 2, Figure 1. The frequency of PRAKI using serum creatinine was 22.2%.

The mean serum NGAL level (ng/ml) in patients with PRAKI were statistically significantly greater than NGAL levels in patients without PRAKI at all the time points [Table 3]. Although the mean serum NGAL level was statistically significantly higher at all-time intervals in those who developed PRAKI except at baseline, the mean serum creatinine level, was only statistically significantly higher at 24 hours, 48 hours and 7th day as shown in Table 4.

The intra-profile changes of serum NGAL levels in patients with PRAKI show that there were significant differences

Table 1: Socio-Demographic Characteristics of the Respondents

Variable	Pregnant women (*n* (%)/Mean±SD)
Age category (years)	
21-30	81 (50.0%)
31-40	69 (42.6%)
>40	12 (7.4%)
Mean Age	30.07±1.29
Marital Status	
Married	151 (93.7%)
Single	11 (6.3%)
Level of Education	
Primary	97 (59.9%)
Secondary	49 (30.2%)
Tertiary	16 (9.9%)
ISCO Occupational level	
Level 1	124 (76.5%)
Level 2	11 (6.8%)
Level 3	21 (13.0%)
Level 4	6 (3.7%)
Parity	
0	58 (35.8%)
1	17 (10.5%)
2	52 (32.1%)
3	35 (21.6%)

SD=Standard deviation, ISCO=International Standard Classification of Occupation

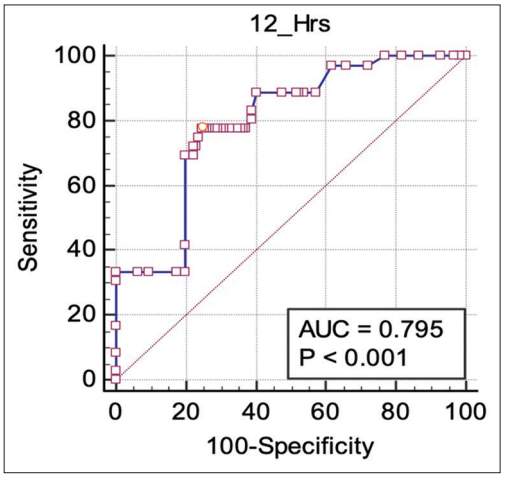

Figure 1: ROC curves for NGAL values at 12 hours (original)

Table 2: Criterion values and coordinates of the ROC curve at 12 hours

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR	+PV	95% CI	-PV	95% CI
≥47	100.00	90.3-100.0	0.00	0.0-2.9	1.00		16.9	16.9-16.9		
>75	100.00	90.3-100.0	23.02	16.0-31.4	1.30	0.00	20.9	19.4-22.6	100.0	
>77	97.22	85.5-99.9	27.78	20.2-36.5	1.35	0.10	21.5	19.6-23.7	98.0	87.4-99.7
>79	97.22	85.5-99.9	38.10	29.6-47.2	1.57	0.073	24.3	21.7-27.1	98.5	90.6-99.8
>80	88.89	73.9-96.9	42.86	34.1-52.0	1.56	0.26	24.1	20.8-27.7	95.0	88.0-98.0
>100	88.89	73.9-96.9	59.52	50.4-68.2	2.20	0.19	30.9	26.0-36.3	96.3	91.2-98.5
>110	83.33	67.2-93.6	61.11	52.0-69.7	2.14	0.27	30.4	25.1-36.2	94.7	89.5-97.4
>112	80.56	64.0-91.8	61.11	52.0-69.7	2.07	0.32	29.7	24.4-35.7	93.9	88.7-96.8
>120	77.78	60.8-89.9	62.70	53.6-71.1	2.09	0.35	29.8	24.2-36.1	93.3	88.1-96.3
>142	77.78	60.8-89.9	75.40	66.9-82.6	3.16	0.29	39.2	31.2-47.8	94.3	90.0-96.9
>143	75.00	57.8-87.9	76.19	67.8-83.3	3.15	0.33	39.1	30.8-48.1	93.7	89.4-96.4
>150	72.22	54.8-85.8	76.98	68.6-84.0	3.14	0.36	39.0	30.5-48.3	93.1	88.8-95.9
>170	72.22	54.8-85.8	77.78	69.5-84.7	3.25	0.36	39.9	31.1-49.3	93.2	88.9-95.9
>173	69.44	51.9-83.7	77.78	69.5-84.7	3.12	0.39	38.9	30.1-48.5	92.6	88.3-95.4
>180	69.44	51.9-83.7	80.16	72.1-86.7	3.50	0.38	41.7	32.1-51.9	92.8	88.6-95.5
>188	33.33	18.6-51.0	80.16	72.1-86.7	1.68	0.83	25.5	16.1-38.0	85.5	82.2-88.3
>200	33.33	18.6-51.0	100.00	97.1-100.0		0.67	100.0		88.0	85.4-90.3
>285	0.00	0.0-9.7	100.00	97.1-100.0		1.00			83.1	83.1-83.1

Table 3: Variation in serum NGAL levels on Assessment Days

	ALL	Disease condition		*F*	*P*
		No PRAKI	PRAKI		
Baseline	64.35±1.6	64.05±1.85	65.39±3.2	6.73	0.001
6 Hrs.	98.34±3.31	89.79±3.07	128.25±8.76	1181.16	<0.0001
12 Hrs.	127.65±4.34	114.29±4.4	174.44±8.22	2079.89	<0.0001
24 Hrs.	137.78±5.5	119.85±5.28	200.56±11.56	2246.31	<0.0001
48 Hrs.	130.27±7.1	108.41±5.46	206.78±21.34	1565.33	<0.0001
7 Days	111.64±8.23	87.76±4.2	195.19±30.4	1141.03	<0.0001

Table 4: Comparison of variation in serum creatinine and serum NGAL levels at various time intervals in patients that developed PRAKI

Time intervals	Serum creatinine	*P*	Serum NGAL	*P*
Baseline	0.65±0.02	0.06	65.39±3.2	0.72
6 Hrs.	0.68±0.02	0.22	128.25±8.76	<0.001
12 Hrs.	0.72±0.01	0.50	174.44±8.22	<0.001
24 Hrs.	1.07±0.06	<0.001	200.56±11.56	<0.001
48 Hrs.	1.96±0.22	<0.001	206.78±21.34	<0.001

between the NGAL levels at baseline and NGAL levels at other time points, (p = <0.001). Similarly, the intra-profile changes of NGAL levels in patients without PRAKI show that there were significant differences between the NGAL levels at baseline and NGAL at other time points (P = <0.001), however, the absolute values were much higher in women with PRAKI.

Figure 2 shows the variation in mean NGAL levels across the time intervals for patients with PRAKI, without PRAKI and all the patients. Serum NGAL increased steeply from baseline, peaked at 48 hours and decline thereafter in patients who developed PRAKI. In contrast, serum NGAL increased slowly from baseline, peaking at 24 hours and declined thereafter in patients without PRAKI.

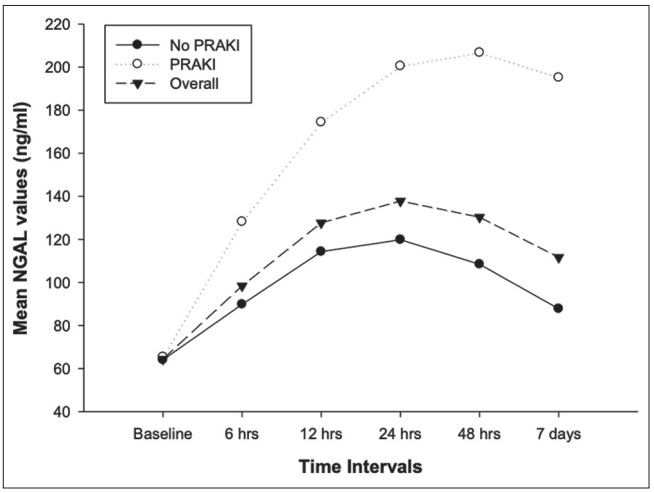

Figure 2: Variation of NGAL levels across the time intervals (original)

Discussion

This study determined the performance of serum NGAL

in the diagnosis of PRAKI among women in peripartum period and a normal reference range for serum NGAL in nonpregnant women. The frequency of PRAKI was 50% using a serum NGAL cut-off of 135.6 ng/dl. Serum NGAL detected PRAKI earlier than serum creatinine, with optimum performance at the 12th hour.

The median serum NGAL level among nonpregnant women was 49 ng/ml (10 ng/ml – 144 ng/ml), which is similar to 50 ng/ml reported by Kafkas *et al*.[10] in Greece. However, Kümpers *et al*.[11] reported a lower median of 39.0 ng/ml. The reference interval recorded in this study (12.75 – 135.67 ng/ml) is similar to 21.4 -142.5 ng/ml reported by Makris *et al*.[12] However, the lower limit of the reference value in this study is far lower than 73.2 ng/ml reported in a healthy female population living in Caribbean using manual ELISA method.[13]

The difference noted may be explained by population and methodological differences such as the serum NGAL assay methods and the specific NGAL kits. NGAL can be measured in urine, plasma and serum using ELISA, immunoblotting system and most recently with a commercial kit like particle enhanced turbimetric immunoassay (PETIA) that uses automated analyzer.[12] Although, ELISA was used in the present study and the study conducted in the Caribbean,[13] the NGAL kits were made by different manufacturers. Makris *et al*.[12] used PETIA in their own study. There are no published studies yet in Nigeria and Africa to draw reference from to the best of our knowledge. Thus, our findings should serve as a reference for normal serum NGAL level for healthy nonpregnant women in Nigeria.

The frequency of PRAKI was 50% using the cut-off value of serum NGAL obtained in this study. This was higher than 22.2% using serum creatinine in the same study participants, suggesting that serum NGAL is more sensitive in the diagnosis of PRAKI compared with serum creatinine. Serum creatinine is probably inferior to NGAL, partly because serum creatinine level rises only after significant damage has occurred in the nephron, hence the need for newer diagnostic biomarkers. This study provides evidence that supports NGAL as a promising biomarker for early diagnosis of PRAKI amongst Blacks living in Africa.

The limitation of this study was that other clinical conditions such as malignancies, lung diseases that may alter NGAL levels were not objectively excluded in the participants as comprehensive evaluations were not conducted. However, this study has a number of strengths. First, this study provides data and information regarding a specific susceptible population for whom the literature is relatively scarce in the study region. Second, this study is probably the first prospective diagnostic study on PRAKI in Nigeria using serum NGAL and additionally reports a reference value for serum NGAL in nonpregnant women in Nigeria.

In conclusion, our findings suggest that serum NGAL is an earlier biomarker of PRAKI compared with serum creatinine. We recommend further studies to determine the feasibility of its use over serum creatinine in the diagnosis of PRAKI in low resource settings. Specifically, a cost-benefit or cost-utility analysis may provide useful information to foster practice changes and improvement in patient outcomes.

Acknowledgement

The authors would like to acknowledge Dr. Kingsley Agholor, Obstetrician and Gynaecologist at Central Hospital, Warri, for volunteering his expertise and helping to secure a supportive research environment for the team and study participants. We acknowledge all health professionals who provided care for our partcipants during this study.

Ethical approval

Ethical approval was obtained from the Health Ethics and Research Committee of the Delta State University Teaching Hospital, Oghara Delta State with reference number DELSUTH/HREC/2019/070/0320.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Shalaby AS, Shemies RS. Pregnancy-related acute kidney injury in the African continent: Where do we stand? A systematic review. J Nephrol 2022;35:2175-89.
2. Davidson B, Bajpai D, Shah S, Jones E, Okyere P, Wearne N, *et al*. Pregnancy-associated acute kidney injury in low-resource settings: Progress over the last decade. Semin Nephrol 2022;42:151317.
3. Makris K, Spanou L. Acute kidney injury: Diagnostic approaches and controversies. Clin Biochem Rev 2016;37:153-75.
4. Ostermann M, Joannidis M. Acute kidney injury 2016: Diagnosis and diagnostic workup. Crit Care 2016;20:299.
5. Simonazzi G, Capelli I, Curti A, Comai G, Rizzo N, Manna GLA. Serum and urinary neutrophil gelatinase-associated lipocalin monitoring in normal pregnancy versus pregnancies complicated by pre-eclampsia. *In Vivo* (Brooklyn) 2015;122:117-21.
6. Nickolas TL, O'Rourke MJ, Yang J, Sise ME, Canetta PA, Barasch N, *et al*. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase–Associated lipocalin and acute kidney injury. Ann Intern Med 2008;148:810-9.
7. Cochran WG. The estimation of sample size. In: Sampling Techniques. 3rd ed. John Wiley and Sons. New York City; 2004.

p-89-94.
8. Sivakumar V, Sivaramakrishna G, Sainaresh VV, Sriramnaveen P, Kishore CK, Rani CS, *et al*. Pregnancy-related acute renal failure: A ten-year experience. Saudi J kidney Dis Transplant 2011;22:352-3.
9. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Workgroup. KDIGO Clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1-138.
10. Kafkas N, Demponeras C, Zouboulоglou F, Spanou L, Babalis D, Makris K. Serum levels of gelatinase associated lipocalin as indicator of the inflammatory status in coronary artery disease. Int J Inflam 2012;2012:189797.
11. Kümpers P, Hafer C, Lukasz A, Lichtinghagen R, Brand K, Flisher D, *et al*. Serum neutrophil gelatinase-associated lipocalin at inception of renal replacement therapy predicts survival in critically ill patients with acute kidney injury. Crit Care 2010;14:R9.
12. Makris K, Stefani D, Makri E, Panagou I, Lagiou M, Sarli A, *et al*. Evaluation of a particle enhanced turbidimetric assay for the measurement of neutrophil gelatinase-associated lipocalin in plasma and urine on Architect-8000: Analytical performance and establishment of reference values. Clin Biochem 2015;48:1291-7.
13. Idris S, Ezenwaka C, Davis G. Reference interval for serum neutrophil gelatinase-associated lipocalin in apparently healthy caribbean population. Trop J Nephrol 2020;15:17-24.