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Original Article

Potential of Neutrophil Gelatinase-Associated Lipocalin and N-Acetyl-Beta-D-Glucosaminidase Biomarkers in Diagnosing Acute Kidney Injury in Pediatric Cases of Severe Malaria

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Abstract

Background: Acute kidney injury (AKI) constitutes a severe complication of malaria in the context of severity, often contributing to higher rates of morbidity and mortality in children. Traditional biomarkers, such as serum urea, creatinine, and estimated glomerular filtration rate (eGFR), remain too insensitive to detect very early renal impairments.

Objectives: The present study investigated the potential of N-acetyl-beta-D-glucosaminidase (NAG) and neutrophil gelatinase-associated lipocalin (NGAL) to serve as alternative markers for AKI detection in malaria-infected children.

Methods: A comparative cross-sectional study involving 85 children (30 severe malaria, 25 mild malaria, and 30 controls) aged 1–15 years was performed in a Nigerian tertiary healthcare facility. Renal function markers (urea, serum creatinine, and eGFR) and electrolytes were analyzed. NAG and NGAL assays were performed as well. Finally, ANOVA, correlation, and receiver operating characteristic curve analysis were employed for data analysis.

Results: Significant hyponatremia ($P<0.05$) and metabolic acidosis were noted among the malaria-infected children. There were significantly elevated levels of NAG and NGAL in severe malaria cases compared with controls ($P<0.05$). NAG was highly correlated with creatinine ($r=0.478$, $P=0.007$), while NGAL distinguished between conditions with excellent accuracy (AUC: 0.975 and 0.855 for mild and severe malaria).

Conclusion: NAG and NGAL are superior to the traditional renal markers since they are sensitive and specific biomarkers for AKI in children with malaria. Routine use of these parameters could facilitate the early detection of AKI in the clinical setting, leading to improved patient outcomes in resource-poor environments.

Keywords: Acute kidney injury, Malaria, NAG, NGAL, Pediatrics

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Background

Malaria is a severe parasitic illness and a major global health challenge, especially in developing countries. *Plasmodium falciparum*, a protozoan from the genus Plasmodium, causes the most severe forms of the disease (1). In addition, climatic and socioeconomic factors greatly affect the endemicity of malaria, limiting its distribution to tropical and subtropical areas between latitudes 62°N and 40°S (2,3). Until now, 96% of the 228 million malaria cases and 98% of the 603 thousand deaths worldwide occurred in Africa; children under five remain the most vulnerable, owing to a lack of immunity. Accordingly, malaria has extensive public health importance globally, and in Nigeria, it contributes as much as 23% of total global cases (4).

According to White (5) and Oshomah-Bello et al (6), organ dysfunction, including acute kidney injury (AKI), frequently complicates severe malaria, a multi-system disease that arises from host-parasite interactions. AKI is the abrupt decline in renal function, resulting in the inability of the kidneys to maintain fluid and electrolyte balance. Moreover, it is a major cause of morbidity and mortality in severe malaria (7,8). As defined by the Kidney Disease Improving Global Outcomes criteria, AKI affects

approximately 13 million people annually, with 85% of cases (and > 2.3 million deaths) occurring in low-income and middle-income countries. Additionally, AKI is a significant contributor to mortality in patients with severe malaria, exacerbating the already high burden of the disease. It is also associated with increased mortality rates, particularly in children, underscoring the urgent need for more reliable and early diagnostic strategies to mitigate the fatal outcomes of this complication (9,10).

Malaria-induced AKI is a result of the direct and indirect processes that are involved in the malaria-related pathophysiology. Afolayan et al (11) reported that secondary effects (e.g., parasites occluding the small blood vessels of the kidneys, severe anemia, and high parasite burden) can result in ischemic injury and damage to kidney tubules. There is a critical need for more sensitive and specific biomarkers to enable the early diagnosis of AKI in the vulnerable pediatric population infected with malaria. Serum creatinine (SCr), urea, and estimated glomerular filtration rate (eGFR) are traditional and well-established markers; however, they are limited by insensitivity to early renal damage and dependence on age, muscle mass, and dietary factors (12). Although eGFR, derived from SCr, has been commonly used to assess kidney function, it can be inadequate in detecting AKI early, especially in pediatric patients. The dependency on these markers thus necessitates newer markers that might detect renal impairment at its earliest stages, especially in pediatric cases, given that the AKI is mostly fast progressing owing to limited clinical signs in the early phase. The early detection of AKI is critical, especially in the pediatric population infected with malaria, for which there is an urgent need for more sensitive and specific biomarkers. SCr and urea are commonly utilized, but they can be inadequate to detect AKI early since both rise late after an initial period of renal injury. The delay in diagnosis also inhibits timely interventions, resulting in a worsening of the outcome. This makes it imperative to find newer markers of renal dysfunction to detect it in its earliest stages, especially in children, where AKI is frequently fast progressing because of the paucity of clinical symptoms in the early phase.

N-acetyl-beta-D-glucosaminidase (NAG) and neutrophil gelatinase-associated lipocalin are two potential biomarkers for AKI early diagnosis that are being investigated in this study. NAG is a lysosomal enzyme primarily present in proximal tubular epithelial cells; its increased excretion in urine implies early proximal tubular injury preceding alterations in the conventional markers of renal damage (13). NGAL, however, is a 25-kDa protein mainly secreted by distal tubular cells. In addition, its plasma and urine levels rapidly increase within 2–6 hours following tubular injury, indicating a more encompassing range of renal epithelial stress. NGAL is more reflective of injury to the distal nephron and systemic inflammatory responses, whereas NAG is concerned with damage to the proximal tubule (14,15). Therefore, the two biomarkers provide complementary information in renal injury, and their combined use may remarkably improve the early detection, risk stratification, and patient management of AKI during pediatric malaria.

Electrolytes, such as sodium (Na^+), potassium (K^+), chloride (Cl^-), and bicarbonate (HCO_3^-), work toward fluid balancing, acid-base equilibrium maintenance, and cellular functions. Electrolyte disturbances (e.g., hyponatremia and hyperkalemia) in severe malaria greatly contribute to kidney involvement and increase the severity of the disease (10,16). NGAL and NAG are useful urinary markers indicating the presence of renal tubular injury long before the diagnosis is established by the rise of the usual blood markers of kidney function, such as SCr and urea (17). This research intends to clarify the potential function of NGAL and NAG in the diagnosis of AKI in children suffering from malaria, thus making early detection possible and improving clinical outcomes, leading to the reduction of morbidity and mortality in at-risk children.

Materials and Methods

Study Design

This comparative cross-sectional study was performed to compare the performance of NAG and NGAL as biomarkers for AKI in children with severe malaria between January and July 2024. In total, fifty-five pediatric patients aged 1–15 years who were confirmed to have malaria were recruited from the Children's Emergency Ward of the Federal Medical Centre (FMC) in Owo, Nigeria. It should be noted that only those patients who had undergone strict diagnostic procedures to confirm cases were enrolled in this study. The study population was divided into three different groups: one group of 30 children with severe malaria, another group with mild malaria consisting of 25 children, and the control group of 30 healthy children who were matched for age and gender and had no history of malaria infection. This categorization facilitates a comparative study of the biomarker levels between different disease severities and the control population.

Study Site

The research was conducted at FMC Owo, a tertiary hospital in Ondo State, Nigeria. The hospital is properly equipped and staffed to offer complete diagnostic and therapeutic services. Moreover, it is a referral hospital for the neighboring communities. Owo is located at 5°35′E longitude and 7°11′N latitude, and as per the national census performed in 2006, there were approximately 218,886 people living in this area (18). The site was chosen for the study because of the high number of pediatric malaria cases and the hospital's significant role in treating severe malaria complications, including AKI. The demographic features of the population served by FMC Owo are highly relevant to this study since the area is characterized by a high prevalence of malaria and

has a younger population, with children under 5 years being very much prone to severe malaria. Given the poor access to modern diagnostic technology in rural areas, this research is vital in testing out the inexpensive early diagnostic markers (e.g., NGAL and NAG) for improving the situation in underserved populations.

Inclusion and Exclusion Criteria

Case Group (Children with Severe Malaria)

Inclusion Criteria

The research consisted of children aged 1–15 years old who were recognized as suffering from a severe case of malaria by World Health Organization standards (19). Clinical features confirming this diagnosis included prostration, multiple convulsions, deep breathing, jaundice, hypoglycemia, metabolic acidosis, and/or hyperparasitemia with a parasite count ≥ 250,000 parasites/μL of blood.

Generally, the assent process is performed with children from the age of 7 years and above, depending on their maturity level and understanding, by explaining the study in age-appropriate language and obtaining their agreement to participate. Along with the assent, parental or guardian consent was obtained when necessary, thereby acquiring the ethical approval for the child's participation in the research.

Exclusion Criteria

Children who had concurrent renal diseases, along with hypertension, diabetes, cardiac diseases, or human immunodeficiency virus infection, were not included in the study, as these illnesses could influence the outcomes. Moreover, children with severe infections (e.g., sepsis or tuberculosis) who were already on treatment were not recruited since this could confound data interpretation. Additionally, those children who received nephrotoxic drugs before the hospital admission were excluded from the study so that the assessment of renal function would not be biased.

Control Group (Healthy Children)

Inclusion Criteria

The control group consisted of children in the age range of 1–15, matched with respect to their ages and genders with the case group. They were all apparently healthy children without a history of malaria, any chronic illness, or ongoing infection. Informed consent was required from the parent or guardian, and assent from the appropriately aged child was necessary for the ethical approval of the kid's participation in the study.

Exclusion Criteria

Children with confirmed malaria, acute infections, or chronic conditions (e.g., kidney diseases and metabolic disorders) were not allowed in the controls. A history of nephrotoxic drug use and hospitalization for any disease in the preceding month were also considered exclusion criteria in the process of obtaining the most accurate findings for the study.

Sample Collection and Handling

From each participant, the blood sample was aseptically drawn through venipuncture, taking all the precautions to avoid contamination. These blood samples, meant for malaria diagnosis, were collected in an ethylenediaminetetraacetic acid tube and stained with Giemsa for thick and thin smear examination (10), a very efficient method for observing parasites. The blood for renal function tests and biomarker study was centrifuged at 4,000 rpm for 5 minutes to separate and obtain serum, which was stored at −20°C until further analysis.

Laboratory Analysis

Malaria diagnosis was confirmed by the microscopic examination of Giemsa-stained thick and thin blood smears. In addition, parasite density was graded according to counts of *Plasmodium falciparum* parasites in a high-power field as low parasite density: ≤ 50,000 parasites/μL (mild infection), moderate parasite density: 50,001–250,000 parasites/μL (moderate infection), and high parasite density: > 250,000 parasites/μL (severe infection) (19). Based on the parasite count/high-power field, each subject's malaria parasite density was assigned to one of these categories. Further, the number of study subjects falling into each density category was tabulated to provide a more representative distribution of malaria severity in the study population.

SCr concentrations were assessed via the Jaffe reaction, while urea concentrations were evaluated via the urease-Berthelot procedure, both of which are highly well accepted in assessing kidney function (20). The concentrations of Na^+, K^+, Cl^-, and HCO_3^- were measured by ion-selective electrode methods (12). Furthermore, NGAL and NAG serum assays were performed by enzyme-linked immunosorbent assay kits, all assays being conducted in duplicates to increase reproducibility, reduce variability, and enhance the accuracy of biomarker quantification (21).

The pediatric eGFR formula by the revised Schwartz equation (22) is as follows:

$$\text{eGFR (mL/min)} = 0.413 \times \frac{\text{Height (cm)}}{\text{Serum creatinine}\left(\frac{\text{mg}}{\text{dL}}\right)}$$

Statistical Analysis

All the data were processed using IBM SPSS (IBM Corporation, Armonk, NY) software, version 25.0. Descriptive statistics were used to summarize the data, and the results were expressed as means ± standard deviations. In addition, a one-way analysis of variance was applied, and Tukey's post hoc test was performed for multiple comparisons to determine the differences among the groups. Moreover, the Spearman correlation

was utilized to evaluate any correlations among renal function parameters and biomarkers. To evaluate the diagnostic ability of the biomarkers, a receiver operating characteristic (ROC) curve analysis was plotted, and the corresponding area under the ROC curves (AUCs) for sensitivity and specificity underwent calculation. Any *P* value less than 0.05 was considered statistically significant.

Results

The research included a total of 85 pediatric patients, who were then split into children with severe malaria (n = 30), children with mild malaria (n = 25), and controls (n = 30) who were healthy and of the same age as the children with the disease. This categorization allowed the comparison of renal functions and marker levels among the different diseases according to their severity. The ages of the participants were between 1 year and 15 years, with the mean age being 7.2 ± 3.5 years ($P > 0.05$, Figure 1). The renal function data of the groups in the study are summarized in Table 1. There were statistically significant differences between the two groups of children with severe and mild malaria, as their $Na^+$and HCO_3^- levels were lower than those of healthy controls ($P < 0.05$). Further, the mean values for children with severe malaria were 129.20 ± 3.24 mmol/L for $Na^+$and 12.91 ± 3.16 mmol/L for HCO_3^-, indicating a considerable disruption of the body's electrolytes. Although K^+levels were higher in children with malaria, statistical analysis revealed no significant difference when compared to healthy children ($P > 0.05$), implying that K^+disturbances might be indirectly related to malaria severity. In the same vein, Cl^- levels were the same across the groups without any significant differences ($P > 0.05$). Urea, SCr, and eGFR levels, which are indicators of kidney function, were higher in both malaria-infected groups than in controls. However, the differences were not statistically significant ($P > 0.05$).

Figure 2 presents the mean levels of NAG among

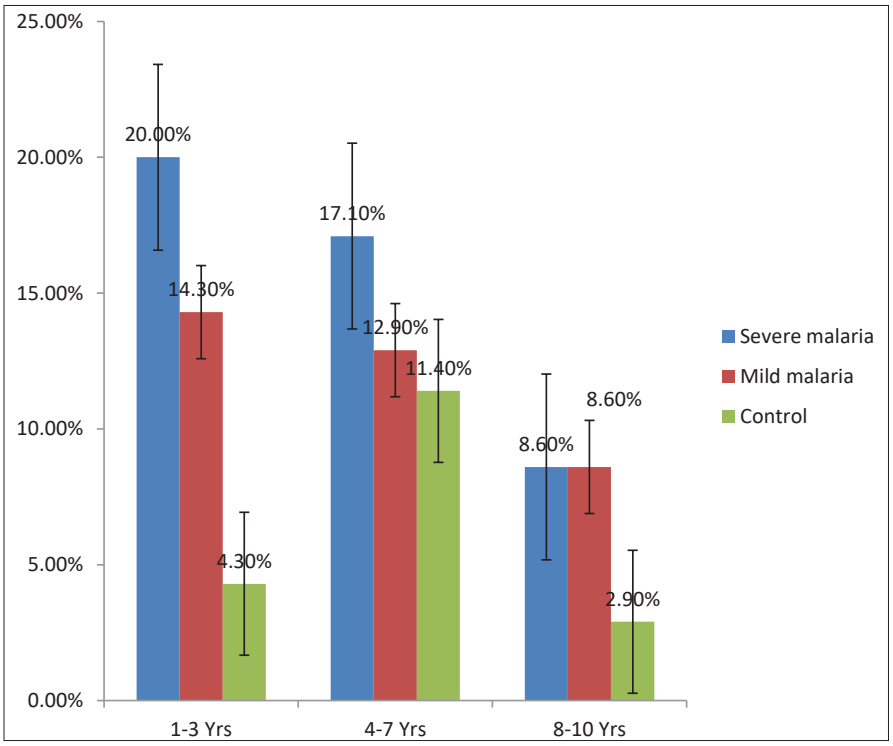

Figure 1. Age Group Distribution of the Subject Population in Percentage

Table 1. Comparison of Mean Renal Function Parameters in Both Children With Severe and Mild Malaria Infection With Control Groups

	Severe malaria (n = 30)	Mild malaria (n = 25)	Control group (n = 30)	*P* Value
Na^+(mEq/L)	129.20 ± 3.24 [a,c]	131.80 ± 3.97 [bc]	135.20 ± 3.43 [bc]	0.000*
K^+(mEq/L)	3.45 ± 0.43	3.40 ± 0.47	3.28 ± 0.30	0.441
Cl^- (mEq/L)	100.40 ± 2.58	100.36 ± 2.98	100.92 ± 2.76	0.800
HCO_3^- (mEq/L)	12.91 ± 3.16 [a]	14.66 ± 3.15 [a]	19.39 ± 1.79 [bc]	0.000*
Urea (mg/dL)	10.17 ± 3.67	10.99 ± 4.35	10.37 ± 3.35	0.725
SCr (mg/dL)	0.52 ± 0.12	0.53 ± 0.12	0.53 ± 0.08	0.943
eGFR (mL/min)	146.64 ± 43.83	153.77 ± 51.40	155.66 ± 54.14	0.797

Note. Na^+: Sodium; K^+: Potassium; Cl^-: Chloride; HCO_3^-: Bicarbonate; SCr: Serum creatinine; eGFR: Estimated glomerular filtration rate. * Significant at $P \leq 0.05$. a = Significantly different from control, b = Significantly different from severe malaria, and c = Significantly different from mild malaria.

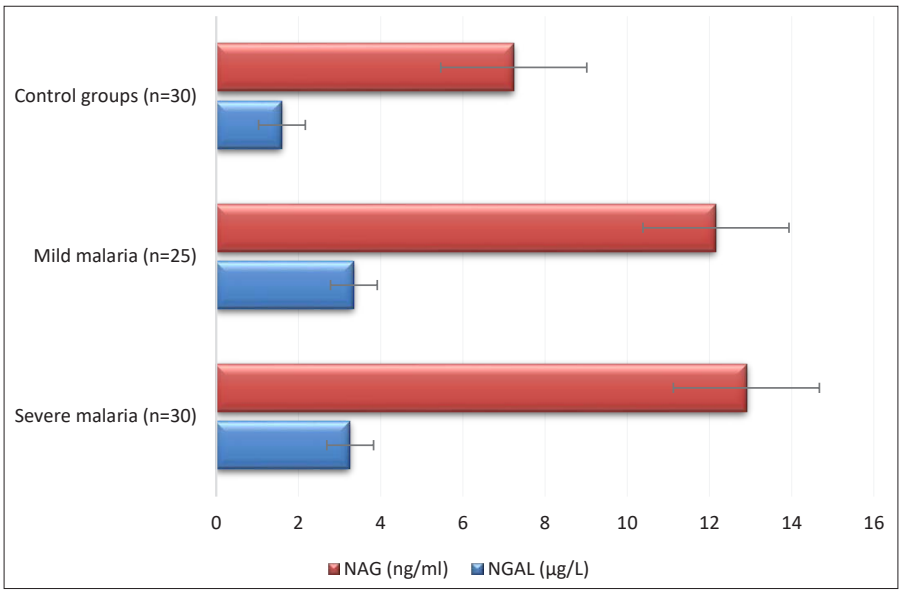

Figure 2. Standard Error Bar Chart Showing NAG and NGAL Among the Study Participants. *Note*. NAG: N-acetyl-beta-D-glucosaminidase; NGAL: Neutrophil gelatinase-associated lipocalin

the groups. Children with severe malaria exhibited significantly higher NAG levels (12.90 ± 3.03 ng/mL) compared to the mild malaria (12.15 ± 1.90 ng/mL) and control (7.24 ± 2.15 ng/mL, $P < 0.05$) groups. Based on the post hoc analysis, there were significant differences between the severe malaria and control groups, demonstrating the ease of using NAG as a sign of renal tubular injury due to the malaria infection. The levels of NGAL were also very high in children with malaria. An average NGAL level of 3.26 ± 0.62 ng/mL was recorded for the severe malaria cases, followed by 3.34 ± 0.60 ng/mL and 1.60 ± 0.58 ng/mL for mild malaria cases and controls, respectively. The difference in NGAL levels between children with malaria and controls was statistically very significant ($P < 0.05$). Spearman correlation analysis revealed that there was a significant positive correlation between NAG and creatinine levels in children with severe malaria (r = 0.478, $P = 0.007$). A similar pattern was observed in children with mild malaria (r = 0.448, $P = 0.025$), suggesting that NAG levels are indicative of renal impairment (Table 2 and Figure 3). Conversely, NGAL showed high diagnostic accuracy, with the ROC curve analysis yielding an AUC of 0.687 in mild malaria. However, NAG demonstrated 0.574 in severe malaria (Figures 4 and 5).

Table 2. Correlation of NAG and NGAL with Renal Function Parameters in Mild Malaria Infections

Pairs of variables	Correlation coefficient (r)	*P* value
NGAL vs. Na+	0.019	0.927
NGAL vs. K+	0.025	0.907
NGAL vs. Cl-	0.169	0.419
NGAL vs. HCO_3-	-0.08	0.703
NGAL vs. Urea	-0.181	0.388
NGAL vs. SCr	-0.158	0.451
NAG vs. Na+	0.468	0.018
NAG vs. K+	0.042	0.841
NAG vs. Cl-	0.149	0.478
NAG vs. HCO_3-	0.448	0.025
NAG vs. Urea	-0.148	0.481
NAG vs. SCr	0.448	0.025

Note. Na^+: Sodium; K^+: Potassium; Cl^-: Chloride; HCO_3^-: Bicarbonate; SCr: Serum creatinine; NAG: N-acetyl-beta-D-glucosaminidase; NGAL: Neutrophil gelatinase-associated lipocalin. * The correlation is significant at the 0.05 level (2-tailed).

Discussion

Our findings confirmed that malaria-infected children, especially those with severe malaria, exhibit disturbances in electrolytes and elevated biomarker levels, highlighting the systemic and renal involvement of the disease. Hyponatremic and low HCO_3^- levels were among the most frequent electrolyte disturbances experienced by the children, which is consistent with the findings of some previous studies that have established these serum electrolyte imbalances to be malaria complications (2, 16). Na^+ levels are deranged, and the dilutional type of hyponatremia is a hallmark. Normally, vasopressin secretion is increased in this condition, which retains water and dilutes the Na^+ (23). Na^+ imbalance could, however, also be caused by parasite-induced renal dysfunction in which Na^+ ions are sequestered by the infected red blood cells, thereby contributing to reduced plasma Na^+ levels (24). Metabolic acidosis, as detected with the depletion of HCO_3^-, reflects the systemic effects of malaria on the renal and cardiovascular systems. The disruptive processes behind malaria-induced acidosis are thought to be linked with the anaerobic metabolism and impaired renal excretion of acid metabolites, thereby worsening electrolytic imbalance (25, 26). Thus, such a complex interplay between parasite activity, electrolyte imbalance, and renal dysfunction is necessary for the

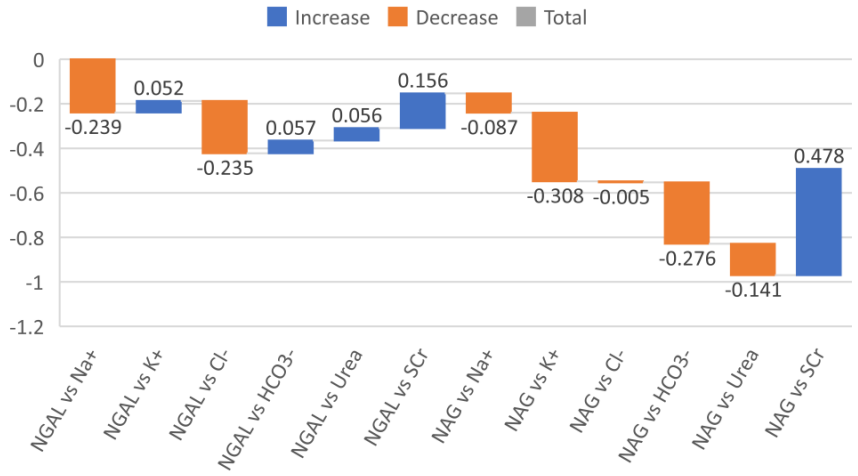

Figure 3. Correlation of NGAL and NAG With Renal Function Parameters in Severe Malaria Infection. *Note*. Na^+: Sodium; K^+: Potassium; Cl^-: Chloride; HCO_3^-: Bicarbonate; SCr: Serum creatinine; NAG: N-acetyl-beta-D-glucosaminidase; NGAL: Neutrophil gelatinase-associated lipocalin

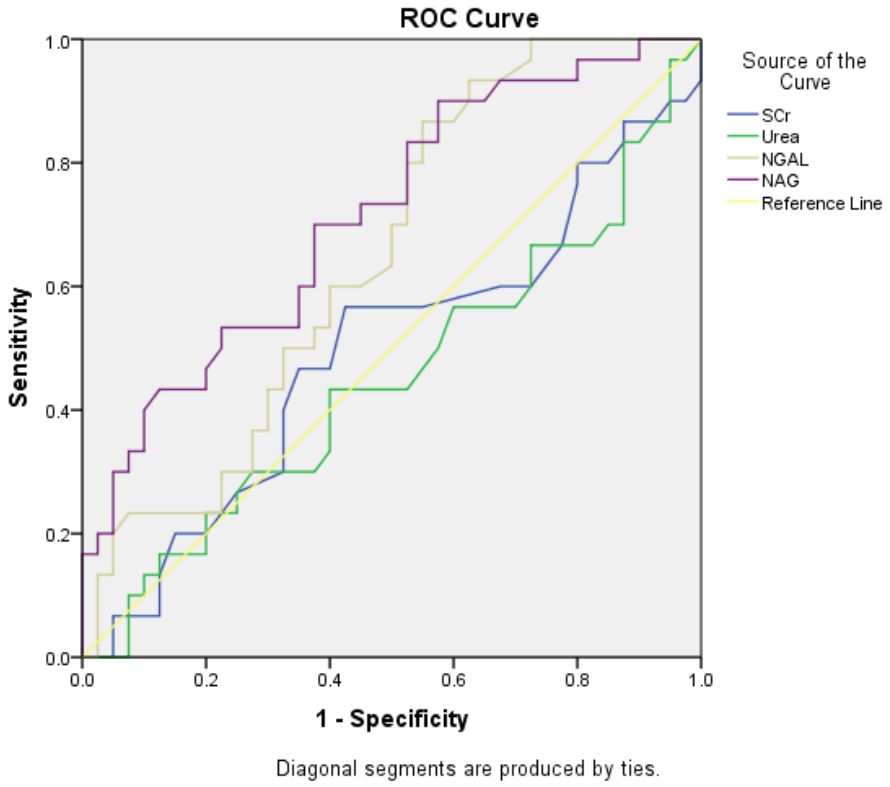

Figure 4. The ROC Curve of NGAL, NAG, Urea, and SCr as a Diagnostic Tool in Severe Malaria Subjects. *Note*. ROC: Receiver operating characteristic; NGAL: Neutrophil gelatinase-associated lipocalin; NAG: N-acetyl-beta-D-glucosaminidase; SCr: Serum creatinine

regular monitoring of renal functions and acid-base balance investigations in children afflicted by malaria.

Although there were elevated values for conventional renal markers (e.g., SCr and urea) in the malaria-infected group, no significant differences were observed. According to these results, it can be concluded that these traditional biomarkers are not sensitive enough to detect early renal injury. Many factors affect SCr and urea levels but are not directly linked to the extent of the renal damage, including age, diet, muscle mass, and hydration status. Secondly, these markers are usually late responders to tubular injury and are even occasionally only reported to rise after considerable renal dysfunction has set in (12, 27). The eGFR, derived from SCr, also faces similar limitations in detecting early AKI. Hence, just depending upon SCr, urea, or eGFR for diagnosing AKI may lead to late diagnosis, and if brought early, it could avoid further damage to the kidneys and all other associated complications.

Meanwhile, malaria-infected children showed significantly elevated levels ($P < 0.001$) of NAG and NGAL in comparison with the controls, with the highest levels observed in severe malaria ($P = 0.034$). NAG, a lysosomal

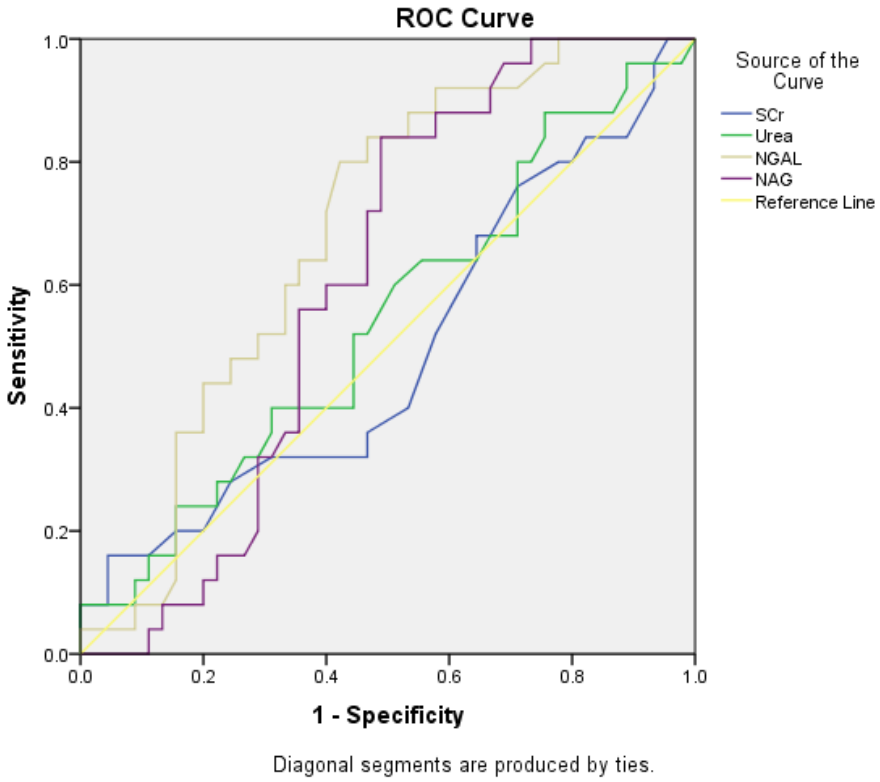

Figure 5. ROC Curve of NGAL, NAG, Urea, and SCr as a Diagnostic Tool in Mild Malaria Subjects. *Note*. ROC: Receiver operating characteristic; NGAL: Neutrophil gelatinase-associated lipocalin; NAG: N-acetyl-beta-D-glucosaminidase; SCr: Serum creatinine

enzyme secreted by proximal tubular cells during the injury of tubular cells, is a marker of tubular dysfunction and has been associated with renal damage in malaria-induced AKI (13). The increased levels of NAG provided an AUC of 0.574, which is moderate at best and suggests that it lacks both sensitivity and specificity. Nevertheless, it remains a valuable indicator of ongoing tubular injury. The correlation between NAG and SCr in the severe and mild malaria cases suggests that tubular injury plays a significant role in NAG measurement, further supporting previous works on NAG as a diagnostic marker in malaria-induced AKI (11, 28). NGAL is a small protein that is primarily secreted by distal tubular cells and possesses high diagnostic accuracy due to the very rapid increase of its plasma and urine levels after undergoing tubular injury, with an AUC value indicating better sensitivity for early renal injury detection. Due to this quick rise, NGAL is considered an early biomarker for AKI (15, 29). It is noteworthy that NGAL levels were quite high even in mild malaria, which could be a sign of kidney dysfunction or damage that would not be detected through conventional urea or creatinine testing. The combination of NAG-based and NGAL-based techniques is indeed great support in the diagnosis of renal dysfunction, even though diagnostics relying on AUC and overall performance have certain limitations. NAG is an indicator of tubular damage, while NGAL represents the renal dysfunction more quickly. The combination of the two biomarkers provides a broader and more accurate approach to AKI staging, which, in turn, leads to better-informed clinical management and individualized treatment (30, 31).

The use of NGAL and NAG for early AKI diagnosis in malaria patients, particularly in places where contemporary, advanced diagnostic methods are unavailable, implies new and interesting diagnostic possibilities. In regions where malaria is prevalent, due to the challenge in the detection of AKI, the application of NGAL and NAG tests enables early diagnosis, thus allowing early interventions for the patient's improved prognosis (10, 32). These biomarkers are helpful not just from the perspective of diagnosis but also for monitoring renal recovery and treatment response (6, 33). Additionally, an elevated level of NGAL and NAG may be prognostic with respect to a patient's longer-term renal state in malaria survivors. The introduction of routine testing for these biomarkers into clinical practice can further improve management by providing early clues to alterations in renal function (34, 35). Nevertheless, this study had some limitations, including the small sample size, which limits generalizability, and the lack of baseline creatinine levels, which interferes with assessing the accuracy of AKI staging. Therefore, future studies should include larger multicenter trials to validate these biomarkers and analyze their cost-effectiveness in order to ascertain whether their routine use is feasible. Additionally, longitudinal studies are required to understand the long-term renal outcomes of children with malaria and thus evaluate the predictive capacity of NGAL and NAG.

Conclusion

Our results indicated that NAG and NGAL were appropriate markers of AKI in malaria. Although urea, eGFR, and SCr remain valuable traditional renal damage markers in clinical practice, the lack of AKI sensitivity implies the necessity of more advanced clinical biomarkers. NAG and NGAL had pragmatic evidence of merit for diagnostic performance for AKI, with NGAL being identified as highly sensitive and specific for early diagnosis of AKI in a cohort of pediatric patients with malaria. In the clinical setting, these biomarkers can be used to broaden the detection of malaria-associated AKI, which could ultimately reduce mortality while enhancing the quality of life of infected children.

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Writing–review & editing: Adedeji David Atere, Yekeen Adebisi Kosamat, Adekunle Abiodun Adesiyan.

Competing Interests

Authors declare no conflicts of interest.

Consent to Publications

The manuscript was read and approved by all authors. The consent for publication is available on request.

Data Availability Statement

Available on request.

Ethical Approval and Consent to Participate

All procedures performed in this study were in accordance with the ethical standards of the Declaration of Helsinki. Institutional Review Board (IRB) of the FMC, Owo (IRB No. FMC/OW/380/VOL.CCXVII/37) gave ethical approval. Informed consents of the pediatric's parents or caregivers were obtained before enrolment after due explanation of the aims and procedures of the research that guaranteed confidentiality and voluntary participation.

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