Serum creatinine and urea lack diagnostic accuracy for predicting malaria co-infection in HIV-positive children

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ABSTRACT

Children under the age of five years in malaria-endemic regions of sub-Saharan Africa face a dual threat from Plasmodium falciparum malaria and HIV-1 infection. Both infections independently cause renal dysfunction, yet the diagnostic value of renal biomarkers in differentiating co-infected from mono-infected children remains uncertain. The objective of this study is to determine whether renal functional markers can predict malaria co-infection among HIV-positive children aged less than five years in Western Kenya. A cross-sectional case–control study involving 138 HIV-positive children (69 malaria-positive, 69 malaria-negative) attending Kakamega County Teaching and Referral Hospital was conducted. Malaria was confirmed by microscopy and rapid diagnostic tests. Serum creatinine and urea were quantified using an automated clinical chemistry analyzer. Parasitemia levels, age, and gender were compared between groups using the Mann-Whitney U and chi-square tests. Diagnostic performance of the renal functional markers was evaluated using ROC curve analysis. Children co-infected with malaria and HIV were younger (median 14.4 months in the co-infected vs. 24.0 months in the mono-infected group, $p = 0.039$). A higher proportion of co-infected children were female (64.2%) compared to the mono-infected group (35.8%, $p=0.014$). The median parasite density among co-infected children was 1,870 parasites/µL (range 1,806–80,025). Serum creatinine (93.0 µmol/L vs. 80.0 µmol/L, $p = 0.001$) and urea (4.9 mmol/L vs. 3.7 mmol/L, $p < 0.0001$) were significantly higher in the co-infected than mono-infected children. However, ROC analysis revealed poor discriminative ability (AUC < 0.70) for both markers. Despite elevated renal markers among co-infected children, creatinine and urea lack sufficient diagnostic accuracy to predict malaria co-infection in HIV-positive pediatric populations. Integrating parasitological testing with routine renal monitoring remains essential for accurate case management in co-endemic regions.

Keywords: Creatinine, Children, Co-Infection, HIV, Malaria, Parasitemia, Renal Biomarkers, ROC, Urea

I. INTRODUCTION

Malaria and HIV remain two of the most significant co-endemic public health challenges in sub-Saharan Africa, particularly affecting children under five years of age, who experience the highest vulnerability to infection, severe disease, and mortality. In many regions with intense *Plasmodium falciparum* transmission, the overlap between malaria and pediatric HIV infection creates a clinical and epidemiological environment in which co-infection is common, synergistic, and difficult to manage. Immune suppression associated with pediatric HIV heightens susceptibility to malaria, increases parasite densities, and contributes to more severe clinical outcomes than in HIV-negative children. As a result, the dual burden of malaria and HIV continues to complicate child health interventions, treatment algorithms, and long-term survival in endemic settings.[1,2]

Co-infection with *P. falciparum* and HIV has been consistently associated with increased morbidity, severe anemia, prolonged hospitalization, and higher mortality rates.[3] The biological interaction between the two pathogens amplifies systemic inflammation, disrupts immune regulation, and predisposes infected children to multi-organ dysfunction—among which renal impairment remains a clinically significant but often under-investigated outcome. Both malaria and HIV can independently compromise renal function, and their combined effect may be additive or synergistic. Malaria-associated acute kidney injury (AKI) may occur through mechanisms such as microvascular obstruction by parasitized erythrocytes, hemolysis leading to tubular injury, and deposition of immune complexes in renal tissues. HIV infection contributes additional renal insults, including HIV-associated nephropathy (HIVAN), chronic inflammation, cytokine dysregulation, and direct viral effects on renal epithelial cells.[4,5]

Despite this biological plausibility, uncertainty persists regarding the extent to which renal biomarkers—such as serum creatinine, urea, electrolytes, and emerging injury markers—accurately reflect the presence or severity of malaria co-infection among children living with HIV (CLHIV). These biomarkers, which represent key dependent variables, may fluctuate due to infection-related renal stress, immune activation, or hemodynamic instability. Conversely, malaria co-infection status (presence, absence, or severity/parasite density) functions as the primary independent variable influencing biomarker levels. Understanding this relationship is essential because renal biomarkers guide clinical decision-making, early detection of kidney injury, and prognostication. However, most existing studies have focused on adult cohorts, severe malaria presentations, or advanced HIV disease, thereby leaving substantial knowledge gaps in the pediatric population. This gap underscores the need for targeted investigation to clarify how malaria co-infection affects renal biomarker profiles in CLHIV, ultimately informing improved diagnostic pathways and integrated pediatric care in high-burden settings.

1.2 Research Objectives

To assess the diagnostic accuracy of serum creatinine and urea for predicting malaria co-infection in HIV-positive children.

III. METHODOLOGY

A cross-sectional case–control study was conducted at Kakamega County Teaching and Referral Hospital, Western Kenya, between July 2021 and June 2023. This study design was most appropriate because it allowed precise, ethical, and efficient comparison of renal biomarkers between malaria-infected and uninfected HIV-positive children. It aligned well with the study objectives, the nature of the population, and the feasibility constraints of conducting clinical research in a resource-limited, high-burden setting. A total of 138 HIV-positive children aged 6–59 months were consecutively recruited until the desired sample size was reached. A total of 138 children were sampled and grouped into two groups, HIV-positive malaria-negative (n = 69) as the controls and HIV-positive malaria-positive (n = 69) as the cases. For a case-control study such as this one, statistical reference comes from power analysis principles such as Cohen's effect size theory (1988) – used for estimating minimum sample size required to detect a significant difference between two means or proportions with acceptable power (80%), significance level (a=0.05) and effect size (small, medium and large). Our sample size determination was relevant since we tested group differences in biomarkers. Malaria was confirmed by microscopy of Giemsa stained thick and thin peripheral blood smears and also malaria rapid diagnostic tests using *Pf*HRP2-based malaria RDTs. Parasitemia levels were categorized as low density (≤ 999 parasites/µl blood), medium density (1000-49,999 parasites/µl blood) and high density (≥50,000 parasites/µl blood) based on recent studies by Wasena *et.al*., 2025.[6] HIV infections were determined using RDT as per the national testing guidelines.[7] Serum creatinine and urea were analyzed using an automated clinical chemistry analyzer (Mindray™ BS-200 Clinical Chemistry Analyzer – Mindray Medical International, Shenzhen, China). Data were analyzed using SPSS v24, with significance at $p < 0.05$. Youden index was used to determine the optimal cut-off points to evaluate the performance of the renal biomarkers. Youden index is calculated as the sum of the true positive rate (sensitivity) and the true negative rate (specificity) minus one (J = Sensitivity + Specificity – 1) and represents the maximum vertical distance between the ROC curve and the random chance line. A higher value of Youden index, closer to 1, indicates a better performing test, whereas a value of 0 means the test is no better than random chance and a value of -1 indicates a perfect inverse relationship.

IV. FINDINGS & DISCUSSION

4.1 Findings

Co-infected children were significantly younger (median 14.4 months; range 5–48) compared to controls (24.0 months; range 6–54; p = 0.039). A higher proportion of co-infected children were females (64.2%) compared to the mono-infected group (35.8%, p=0.014). The median parasite density was 1,870 parasites/µL (range 1,806–80,025) with 7 (10.1%) of the co-infected children having high density parasitemia. Serum creatinine (93.0 µmol/L for the co-infected compared to 80.0 µmol/L for the mono-infected, p = 0.001) and Blood Urea Nitrogen (4.9 mmol/L for the co-infected compared to 3.7 mmol/L for the mono-infected, p < 0.0001) were higher in co-infected children, Table 1, but both showed poor predictive ability (AUC < 0.70) of malaria and HIV co-infection. No significant correlation was found between parasitemia and renal markers.

Table 1
Comparative Demographic, Parasitological, and Renal Function Profiles of HIV-Positive Children with and without Malaria Co-Infection

Variable	HIV+ Malaria– (n=69)	HIV+ Malaria+ (n=69)	p-value
Median age (months)	24.0 (6–54)	14.4 (5–48)	0.039
Female (%)	35.8	64.2	**0.014**
Parasite density (parasites/µL)	–	1,870 (1,806–80,025)	–
Low density parasitemia		0 (0.0)	
Medium density parasitemia		62 (89.9)	
High density parasitemia		7 (10.1)	
Serum creatinine (µmol/L)	80.0	93.0	**0.001**
Serum urea (mmol/L)	3.7	4.9	**<0.0001**

Table 1 provides a summary of the parasitemia levels and demographic characteristics of the study subjects. Children who were both HIV-infected and malaria-positive were significantly younger than the HIV-infected but malaria-negative controls (median age 14.4 months, range 5–48 months vs. median 24 months, range 6–54 months;p =0.039). Out of the 138 children enrolled in the study, there were notable gender differences between the groups. Among the HIV-infected malaria-positive cases, females were the majority (64.2%) compared to males (35.8%), while in the HIV-infected malaria-negative controls, males were more (58.8%) than females (41.2%) - a difference that was statistically significant (p = 0.014). Microscopic examination of malaria-positive cases showed a median parasite density of 1,870 parasites per microliter of blood, with counts ranging from 1,806 to as high as 80,025 parasites /µL blood. Within this group, there were zero patients under the low density parasitemia, however, 62 of 69 co-infected representing 89.9% had medium density parasitemia and 7 of the 69 co-infected representing 10.1% of the children had high-density parasitemia.

Table 2
ROC Analysis for Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value for Renal Markers

Marker	AUC (95% CI)	Cut-off levels of the marker	Sensitivity (%)	Specificity (%)	+PV (%)	-PV (%)	Accuracy (%)
Creatinine	0.661 (0.426-0.681)	71.0	75.8	71.0	50.5	55.6	51.9
Urea	0.703 (0.529-0.717)	6.4	1.4	26.1	94.7	57.1	62.3

The ROC-AUC analysis results were moderate (0.6-0.7) for both urea and creatinine, Table 2, but were however below the optimal threshold ROC-AUC cut off value (≥0.75). The sensitivities and specificities were, respectively: creatinine (75.8% and 71.0%), urea (1.4% and 26.1%). The positive predictive value and negative predictive value for the markers were: creatinine (50.5% and 55.6%), urea (94.7% and 57.1%). The accuracy to correctly identify malaria in HIV infection was creatinine (51.9%) and urea (62.3%).

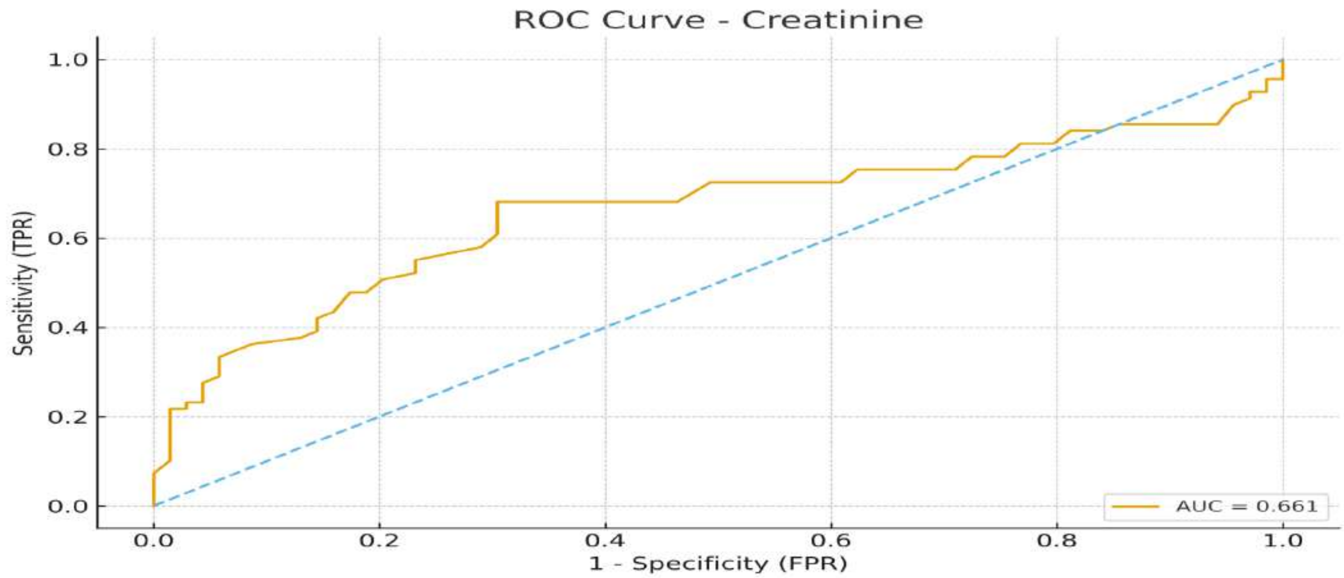

Figure 1
Creatinine AUC=0.661; cut-off=71.0 µmol/L; sensitivity=75.8%; specificity=71.0%

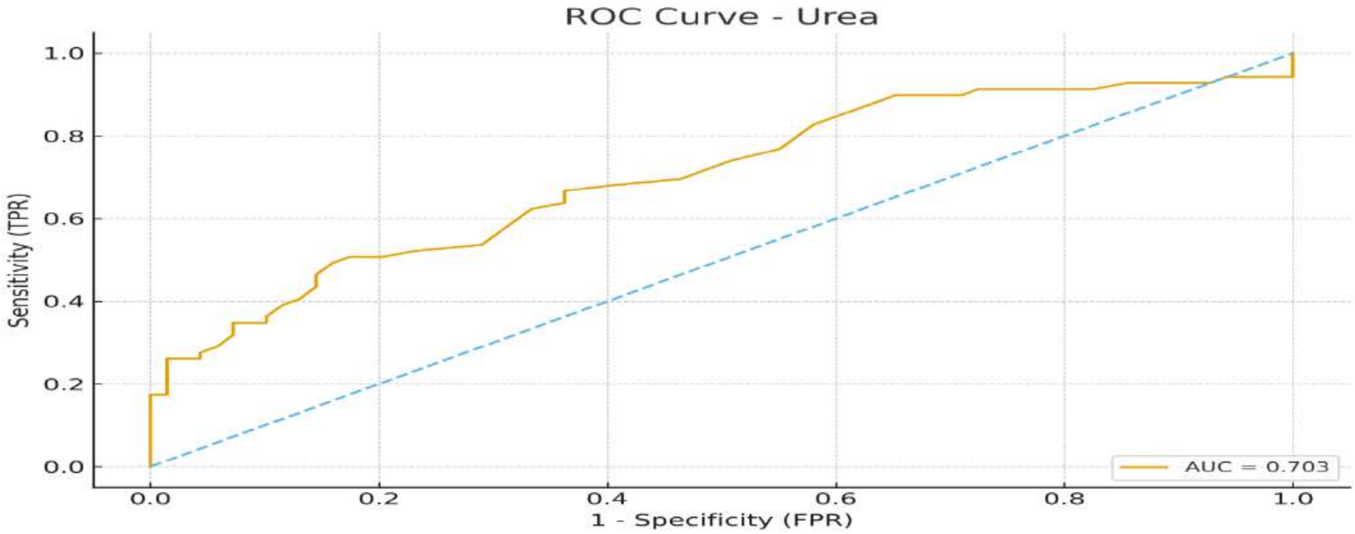

Figure 2
Urea AUC=0.703; cutoff=6.40mmol/L; sensitivity= 26.1%; specificity= 1.4%

ROC analysis revealed modest discriminative ability for renal markers. Creatinine showed an AUC of 0.661 (95% CI 0.426–0.681), Figure 1, while urea demonstrated slightly higher accuracy with an AUC of 0.703 (95% CI 0.529–0.717), Figure 2. Using the Youden index, the optimal thresholds were 87.0 µmol/L for creatinine and 4.90 mmol/L for urea. Alternative threshold evaluation showed that lowering the creatinine cutoff to 69.0 µmol/L improved sensitivity to 81.2% but reduced specificity to 23.2%. Conversely, a urea threshold of 4.70 mmol/L achieved high specificity of 79.7% at the expense of sensitivity (50.7%). These findings indicate limited utility of renal biomarkers for reliably detecting malaria co-infection in HIV-positive children. The PPV and NPV were highly dependent on disease prevalence and as a limitation, these values may not reflect their real world performance in a clinical setting.

4.2 Discussion

This study demonstrates that renal functional markers are not reliable predictors of malaria co-infection among HIV-positive children. Although creatinine and urea were elevated in co-infected participants,[8-10] these elevations were non-specific and showed poor diagnostic performance. Younger and female children were disproportionately affected, suggesting demographic vulnerability. Restrictive gender norms pose unique challenges to females in accessing preventive treatment and care. These trends support previous observations that incomplete immune maturation and social caregiving patterns increase malaria exposure and susceptibility in early childhood, particularly among the female gender in low-income settings.[11] The demographic skew underscores that co-infection is not purely biological, it is shaped by age- and gender-linked vulnerabilities within the pediatric population, however, this may require further investigations. This may also point to the impact of age and muscle mass on creatinine levels, especially given the significant age difference between the groups. The findings align with reports from Tanzania and Nigeria showing non-specific renal changes in pediatric malaria.[12,13]

Although elevations in serum urea and creatinine were observed among co-infected children, diagnostic performance remained weak across multiple threshold strategies. Based on the Youden's index of ≤50.0% which denotes inability of the marker to detect disease or health,[14] all the renal laboratory markers had no diagnostic value. Creatinine performed particularly poorly, regardless of whether sensitivity or specificity was prioritized. Urea showed borderline utility as a rule-in test at higher cutoffs and as a rule-out indicator at lower cutoffs but still lacked sufficient reliability for standalone use. There are multiple non-renal factors such as dehydration, diet and the urea catabolic state that may influence the urea levels. Inter-laboratory differences in assay calibration, sample handling, and reference methods (e.g., Jaffe vs. enzymatic assays) can affect results and reproducibility.[15] Many studies use one measurement, missing temporal changes. Renal function fluctuates, and serial trends are more reliable than isolated values. If the study population includes mixed disease etiologies (e.g., acute vs. chronic kidney injury), biomarker accuracy naturally declines because cutoff thresholds may not generalize. Using empirically derived thresholds (like 71 µmol/L or 6.4 mmol/L) may not optimize discrimination for any specific cohort. ROC-based cutoffs derived from population-level data often underperform in smaller, clinical subgroups. These results support the continued reliance on parasitological malaria diagnosis, with renal markers maintained strictly for patient monitoring rather than case detection.

V. CONCLUSION & RECOMMENDATIONS

5.1 Conclusion

Malaria disproportionately affects vulnerable and marginalized population subgroups, including girls. Despite significant elevations in serum creatinine and urea among HIV and malaria co-infected children, these renal markers lack predictive accuracy for co-infection. Malaria testing therefore should remain parasitology-based, complemented by renal monitoring for disease management. The study highlights the compounded burden of infection, emphasizing the need for integrated pediatric HIV–malaria care in endemic regions. Therefore, renal indices should be used to monitor, not diagnose, co-infection severity.

5.2 Recommendations

The findings of this study highlight the need to strengthen pediatric HIV care by incorporating routine malaria testing into clinical follow-up, particularly in regions where both infections are highly prevalent. In addition, renal function markers should be utilized primarily for ongoing monitoring rather than as standalone diagnostic tools, given their variable sensitivity in detecting early renal impairment in the context of co-infection. Finally, future research should prioritize longitudinal studies with larger cohorts to better characterize renal function dynamics over time and to evaluate how treatment interventions influence biomarker trends in children living with HIV who experience malaria co-infection.

REFERENCES

[1] Kwenti TE. Malaria and HIV coinfection in sub-Saharan Africa: prevalence, impact, and treatment strategies. Res Rep Trop Med. 2018;9:123–136.

[2] Talapko J, Škrlec I, Alebić T, Jukić M, Včev A. Malaria: the past and the present. Microorganisms. 2019;7(6):179.

[3] Lacey H, Patel K, Ngugi J, et al. Combating malaria in Kenya through collaborative population health education: a systematic review and pilot case study. Infect Dis (Lond). 2023;55(10):664–683.

[4] Roberds A, Walker K, Louis M, et al. HIV-1 impact on malaria transmission: a complex and relevant global health concern. Front Cell Infect Microbiol. 2021;11.

[5] Zandstra J, van Houten CB, Carrol ED, et al. Future biomarkers for infection and inflammation in febrile children. Front Immunol. 2021;12.

[6] Wasena SA, Obala AA, Otieno K, et al. Diagnostic accuracy of PfHRP2-based malaria rapid diagnostic tests and antigenemia persistence in Kenyan children from a holoendemic region: implications for case management and surveillance. Exp Biol Med. 2025;250:10585.

[7] Ministry of Health (Kenya). Kenya HIV Testing Services Operational Manual. Nairobi: Ministry of Health; 2022. p.29.

[8] Batte A, Stadelmann C, Kuteesa W, et al. Malaria-associated acute kidney injury in African children: prevalence, pathophysiology, impact, and management challenges. Int J Nephrol Renovasc Dis. 2021;14:235–253.

[9] Seki M, Inaguma D, Imai E, et al. Blood urea nitrogen is independently associated with renal outcomes in Japanese patients with stage 3–5 chronic kidney disease: a prospective observational study. BMC Nephrol. 2019;20(1):115.

[10] Olusola BA, Bamidele O, Okonko IO, et al. Early HIV infection is associated with reduced proportions of gamma delta T subsets as well as high creatinine and urea levels. Scand J Immunol. 2020;91(5):e12976.

[11] Atobrah D, Dzah SM, Mba C, et al. Conceptualization of gender in published malaria and gender research: a systematic descriptive review. Int J Equity Health. 2025;24:211.

[12] Esezobor CI, Solarin AU, Akintan P, et al. Kidney function of HIV-infected children in Lagos, Nigeria: using Filler's serum cystatin C-based formula. J Int AIDS Soc. 2010;13:17.

[13] Fredrick F, Kamuhabwa A, Matee M, et al. Renal abnormalities among HIV-infected children at Muhimbili National Hospital, Dar es Salaam, Tanzania. BMC Nephrol. 2016;17(1):30.

[14] Rota M, Bellocco R, Rizzi S, et al. Optimal cut-point definition in biomarkers: the case of censored failure time outcome. BMC Med Res Methodol. 2015;15(1):24.

[15] Osmic-Husni A, Begić E, Halilović E, Softić A, Avdagić N. Comparison of Jaffe method and enzymatic method at measuring serum creatinine level, creatinine clearance and estimated glomerular filtration rate. J Acad Med Sci BiH. 2023;35(2):113–117.