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RENAL AND HEPATIC DYSFUNCTION IN HIV AND MALARIA CO-INFECTION: A COMPARATIVE ANALYSIS OF BIOMARKERS AND THEIR DIAGNOSTIC ACCURACY

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ABSTRACT

Background: **The aim of the study was to find the diagnostic and clinical meaning of renal and hepatic biochemical indicators in HIV-1-infected children with and without *Plasmodium falciparum* malaria infection in Western Kenya.**
Methods: **A cross-sectional study was carried out. Renal markers (creatinine, urea) and hepatic (ALT, AST, GGT, ALP, LDH, total and direct bilirubin, total protein, albumin and globulins) enzymes in the serum and plasma were measured. Diagnostic performance was rated with the help of ROC analysis and Youden index in order to separate the cases co-infected with HIV and HIV-only controls.**
Results: **Co-infection of malaria-HIV resulted in a much higher serum creatinine level (93.0 umol/L, median) and urea level (4.9 mmol/L, median) as compared to non-co-infected HIV children (creatinine: 80.0 umol/L, p = 0.001; urea: 3.7 mmol/L, $p < 0.0001$). Both groups were similar in terms of hypercreatinemia (75.4% vs. 71.0%, $p = 0.564$) and more severely infected children had hyperuremia (26.1% vs. 1.4% $p < 0.0001$). Hepatic parameters, such as ALT, AST, GGT, bilirubin ratio, total protein, albumin, and globulins, were**

highly increased in the co-infected group and the rates of abnormal values were higher. It was found that co-infection and hyperbilirubinemia were strongly correlated with an odds ratio of 15.8 (95% CI: 5.18-48.12, $p < 0.0001$). There were no significant differences in ALP and LDH. Diagnostic analysis revealed average ROC-AUC total bilirubin (0.7-0.8), poor performance in a number of markers (0.6-0.7) and failed performance in creatinine, ALP, and LDH (0.5-0.6). However, LDH was shown to be of high diagnostic utility (Youden, index: 82.2, sensitivity: 91.2, specificity: 91.0).

***Conclusions: P. falciparum* -HIV co-infection in children is related to significant renal and hepatic biochemical abnormalities. Despite the low diagnostic value of the majority of markers, LDH was the most accurate one. The close correlation with hyperbilirubinemia highlights the clinical benefit of co-infection and promotes the application of combined diagnostic strategies to impacted pediatric patients.**

***Key words*: Renal function tests, liver function markers, diagnostic accuracy, biochemical markers, dysfunctions, Youden index**

INTRODUCTION

Malaria and HIV are among the most devastating infectious diseases globally, particularly in sub-Saharan Africa, where their epidemiological and pathophysiological overlaps result in compounded health burdens, especially in children. Malaria, primarily caused by *Plasmodium falciparum*, is transmitted via the bite of infected female *Anopheles* mosquitos, leading to hepatocytic and subsequent erythrocytic cycles that are responsible for clinical disease manifestations[1]. In parallel, HIV, transmitted through body fluids or vertically from mother to child, targets the immune cells such as CD4+ T lymphocytes, leading to immunosuppression[2]. In 2021, 247 million malaria cases were recorded globally, with 95% occurring in the African region. The disease accounted for 619,000 deaths, predominantly among children under five years[3]. Kenya reported 6.7 million malaria cases, with 70% of its population being at risk, particularly children in the coast and lake endemic regions[4]. Concurrently, HIV/AIDS remains a major health threat, with 39 million people globally living with HIV in 2022, 1.5 million of whom were children under fifteen. Of these, many were infected via vertical transmission, with only a fraction on antiretroviral therapy[5].

Co-infection with malaria and HIV exacerbates morbidity and mortality. Studies have demonstrated higher malaria parasitemia, increased severity of disease (including cerebral malaria), and elevated HIV viral loads in co-infected children[6-7]. Furthermore, co-infection has been linked to increased mortality and severe anemia[8-9]. Despite WHO recommendations for presumptive antimalarial treatment in febrile children, declining malaria transmission rates raise concerns about overdiagnosis and missed alternative diagnoses[3,10].

Fever alone, previously used as a key diagnostic criterion, shows limited predictive value, with studies highlighting the need for a combination of clinical signs and laboratory confirmation[11-13]. Laboratory

diagnostics, including microscopy and rapid diagnostic tests (RDTs), along with hematological and biochemical markers, have improved diagnostic accuracy[14-15]. HIV infection may complicate malaria diagnosis due to overlapping symptoms with other opportunistic infections and the protective effects of medications like cotrimoxazole prophylaxis. Additionally, asymptomatic parasitemia in endemic regions further challenges diagnosis[4,13,16]. This current study, therefore, evaluated a number of renal and hepatic biochemical markers changes associated with malaria parasitemia in HIV-positive children and assessed their diagnostic implications in HIV-malaria co-infection in febrile children.

Materials and Methods

Design: Mixed cross-sectional and case control. Data was collected from a sample at a single point in time. Case control because there was comparison between two groups; malaria positive and HIV positive co-infected (n=69) as the cases and the malaria negative and HIV positive (n=69) as the controls.

Sampling: Convenient consecutive random and purposive sampling

Cases and Controls: Participants included HIV-positive children with and without confirmed malaria infection. Serum samples were collected and analyzed for renal and hepatic biomarkers profile levels. sample size was determined by the patients who were presented to the health facility by their parents or guardians during the study period. Fischer's formula (1998)

$$\frac{N = (z^2pq)/D^2}{n}$$

was used to arrive at a total of 138 patients, who were divided equally thus, 69 cases and 69 controls, and were thus a representative of the cases observed at the health facility at that time.

Inclusion/Exclusion Criteria

Children aged between 6-59 months, whose guardians/parents gave consent, with malaria positive slides were recruited into the study. Children whose parents/guardians declined to give consent and those on anti-malarial and antiretroviral treatments at the time of sampling were excluded, including those who were HIV negative and malaria negative since these were considered being normal individuals. Also excluded were malaria positive but HIV negative were excluded since the research focused on the co-infected.

Informed Consent and ethical approval: The parents or guardians of the children gave informed consent for screening and enrolment into the study. Research permit was obtained from National Commission for Science, Technology and Innovation (NACOSTI), Ref No. NACOSTI/P/22/16599 after approval by the Masinde Muliro University of Science and Technology's Institutional Ethics and Review Committee (MMUST IERC), Ref No. MMUST/IERC/027/2022.

Parasitological analyses: Thick and thin blood smears were prepared using blood samples obtained from the children, stained by the Giemsa and observed microscopically to confirm the presence of *Plasmodium falciparum* parasites in addition to the clinical diagnosis of malaria. Blood was also tested using a malaria rapid diagnostic test (One Step™ Malaria Test Kit – mRDT with inbuilt control bands). To ensure assay validity and quality assurance, the positive slides for malaria parasites were subjected to a review

by another qualified parasitologist/medical laboratory technologist.

HIV-1 Testing:
Two rapid immunochromatographic kits, Determine™ and First Response™ were used to test the presence of HIV-1antibodies. One rapid kit was used as the screening test while the second rapid kit was used as the tie-breaker and as a confirmatory test. 50 µl of whole blood was applied to the rapid test kit cassette followed by 5 drops of the chase buffer to complete the test. The test kits have inbuilt control bands to ensure validity and assure quality.

Serum for Biochemical Markers: Renal and hepatic function markers were tested using an automated Mindray™ BS-200 clinical chemistry analyzer as per the manufacturer's instructions and the standard operating procedures at the Kakamega County Teaching and Referral Hospital laboratory. 1000 µl of serum was pipetted into a clean unused Mindray™ BS-200 cuvette for each specimen and loaded into the sample chamber of the machine, subsequently measuring the renal and hepatic biochemical profiles. Quality control procedures were performed as per the manufacturer's requirements.

Statistical Analyses: Descriptive characteristics of malaria-HIV positive and malaria negative-HIV positive were illustrated by medians and ranges and compared using the Mann–Whitney U test. Differences in proportions of the measured indices were compared using Chi-square test. Diagnostic performance was evaluated via Receiver Operating Characteristic (ROC) curves' Area Under the Curve (AUC), and Youden's index.

RESULTS

Renal biochemical markers

Renal Dysfunction was defined as follows; Hypercreatinemia as creatinine of >59.0 µmol/L and Hyperuricemia as of urea >12.4 mmol/L. Children co-infected with HIV and malaria exhibited significantly elevated serum creatinine (median: 93.0 µmol/L; range: 24.0–1935.0) compared to the levels in HIV mono-infected children (median: 80.0 µmol/L; range: 46.0–205.0; p=0.001). Serum urea was similarly elevated compared to the levels in HIV mono-infected children (Median: 4.9 mmol/L vs. 3.7 mmol/L; p<0.0001), (Fig. 1). While the prevalence of hypercreatinemia did not differ significantly between groups (75.4% vs. 71.0%; P=0.564), hyperuricemia was more frequent in co-infected children (26.1% vs. 1.4%; p < 0.0001), (Fig. 2).

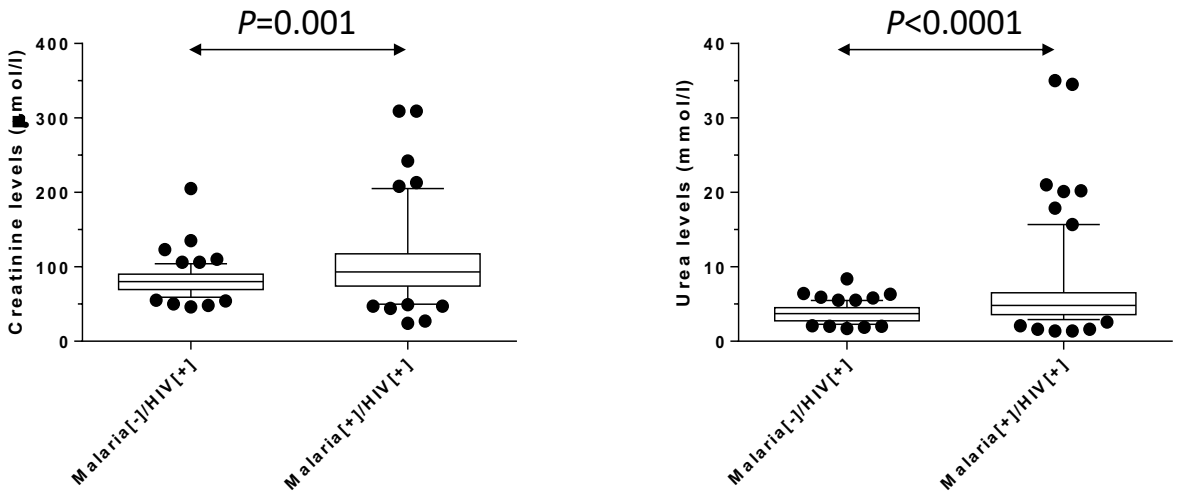

Figure 1: *Concentrations and alteration in serum creatinine and urea levels between HIV mono-infected and malaria-HIV co-infected children*

Results were presented as number (n) and proportion (%) and as median (range) for serum creatinine and urea levels. HIV, human immunodeficiency virus. µmol/l, micromole/litre. mmol/l, millimole/litre. p-values ≤ 0.05 indicate significant difference.

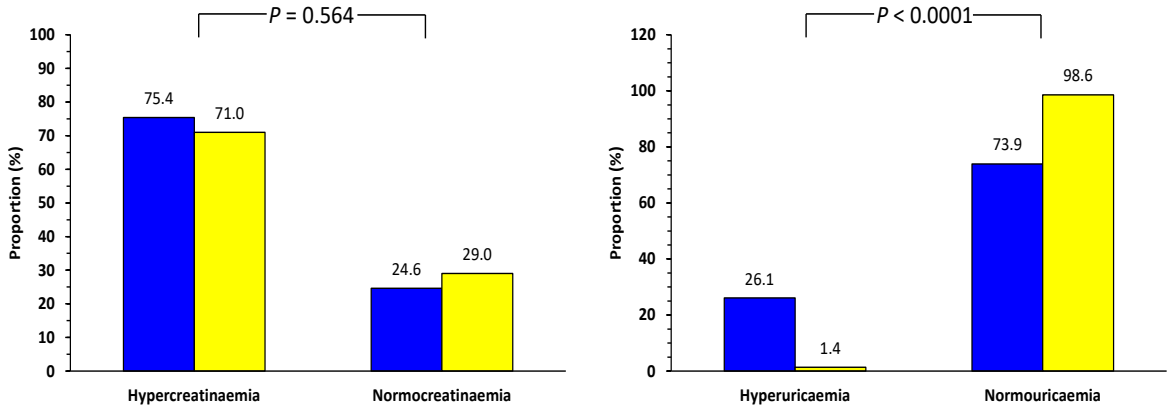

Figure 2: *Rates of dysfunction in renal biochemical markers*

Dysfunctions in creatinine levels were defined as hypercreatinemia (serum creatinine, >59.0 µmol/l); and normocreatinemia (serum creatinine, ≤59.0 µmol/l). Dysfunctions in urea levels were defined as hyperuricemia (serum urea, >12.4 mmol/l); and normouricemia (serum urea, ≤12.4 mmol/l). Blue bars represent Malaria¬ [+] HIV [+] and yellow bars indicate Malaria¬ [-] HIV [+]. P-values ≤ 0.05 indicate significant difference.

Hepatic biochemical markers

Hepatic Dysfunction was defined as follows: ALT > 63 IU/L; AST > 95 IU/L; ALP > 392 IU/L; GGT >111 IU/L, Hyperproteinemia: total protein > 92 g/L, Hyperalbuminemia: albumin > 79 g/L, Hyperglobulinemia: globulins > 53 g/L and Hyperbilirubinemia: total bilirubin > 20.5 µmol/L; direct bilirubin > 5.1 µmol/L. Table 1 shows ALT, AST, and GGT levels which were significantly increased in malaria-HIV co-infected

children: ALT: 16.0 vs. 11.0 IU/L (p = 0.031), AST: 19.5 vs. 16.5 IU/L (p=0.010) and GGT: 38.0 vs. 23.5 IU/L (p < 0.0001). Elevated enzyme proportions were also higher in the co-infected group: ALT: 21.7% vs. 2.9% (p = 0.001), AST: 33.3% vs. 5.8% (p < 0.0001) and GGT: 72.5% vs. 50.7% (P = 0.013). ALP and LDH levels did not differ significantly between groups. As indicators of hemolysis, Total bilirubin (20.5 vs. 9.5 µmol/L; p < 0.0001) and direct bilirubin (6.7 vs. 3.7 µmol/L; p < 0.0001) were elevated in malaria-HIV co-infected children. Prevalence of hyperbilirubinemia was higher in malaria-HIV co-infection: Total bilirubin: 49.3% vs. 5.8% (p < 0.0001) and Direct bilirubin: 68.1% vs. 30.4% (p < 0.0001). For protein metabolism, Total Protein, Albumin, and Globulin were significantly elevated in the co-infected group: Total protein: 90.0 vs. 82.0 g/L (p < 0.0001), Albumin: 55.0 vs. 50.0 g/L (P < 0.0001) and Globulins: 36.0 vs. 29.5 g/L (P = 0.006). The corresponding abnormalities in protein metabolism were as follows: Hyperproteinemia: 76.8% vs. 55.1% (p = 0.018), Hyperalbuminemia: 24.6% vs. 2.9% (p < 0.0001) and Hyperglobulinemia: 15.9% vs. 2.9% (P = 0.004).

Table 1:

Concentration levels of hepatic enzymes and proteins comparisons between co-infected HIV-malaria positive and HIV mono-infected children

Marker	**HIV-positive and malaria-negative, n=69** **(%, conc., Med. range)**	**HIV-positive and malaria-positive, n=69** **(%, conc. Med. range)**	***P***
ALT, IU/l	11.0 (2.0-43.0)	16.0 (2.0-135.0)	**0.031**
High	2 (2.9)	15 (21.7)	**0.001**
Normal	67 (97.1)	54 (78.3)	
AST, IU/l	16.5 (5.0-36.0)	19.5 (3.0-340.0)	**0.010**
High	4 (5.8)	23 (33.3)	**<0.0001**
Normal	65 (94.2)	46 (66.7)	
ALP, IU/l	73.0 (28.0-559.0)	76.0 (29.0-572.0	0.262
High	56 (82.4)	47 (68.1)	0.075
Normal	13 (17.6)	22 (31.9)	
GGT, IU/l	23.5 (6.0-170.0)	38.0 (5.0-423.0)	**<0.0001**
High	35 (50.7)	50 (72.5)	**0.013**
Normal	34 (49.3)	19 (27.5)	
LDH, IU/l	326.5 (95.5-720.3)	359.1 (75.6-1009.6)	0.113
High	63 (91.3)	62 (89.9)	0.999
Normal	6 (8.7)	7 (10.1)	
Total bilirubin, µmol/l	9.5 (3.5-26.0)	20.5 (4.3-60.0)	**<0.0001**
Hyperbilirubinaemia	4 (5.8)	34 (49.3)	**<0.0001**
Normobilirubinaemia	65 (94.2)	35 (50.7)	
Direct bilirubin, µmol/l	3.7 (0.9-13.4)	6.7 (2.0-46.4)	**<0.0001**
Hyperbilirubinaemia	21 (30.4)	47 (68.1)	**<0.0001**
Normobilirubinaemia	48 (69.6)	22 (31.9)	
Total protein, g/l	82.0 (69.0-115.0)	90.0 (35.0-160.0)	**<0.0001**
Hyperproteinaemia	38 (55.1)	53 (76.8)	**0.018**
Normoproteinaemia	31 (44.9)	16 (23.2)	
Albumin, g/l	50.0 (37.0-61.0)	55.0 (30.0-68.0)	**<0.0001**
Hyperalbuminaemia	2 (2.9)	17 (24.6)	**<0.0001**
Normoalbuminaemia	67 (97.1)	52 (75.4)	

Globulins, g/l	29.5 (16.0-61.0)	36.0 (18.0-160.0)	**0.006**
Hyperglobulinaemia	2 (2.9)	11 (15.9)	**0.004**
Normoglobulinaemia	67 (97.1)	58 (84.1)	

Results were presented as number (n) and proportion (%) and as median (range) for liver function tests parameters levels. HIV, human immunodeficiency virus. µmol/l, micromole/litre. g/l, g/litre. ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; GGT, Gamma-glutamyl transferase; LDH, Lactate dehydrogenase. p-values in bold indicate significant difference.

Diagnostic utility of the biochemical markers

Diagnostic performance analysis revealed balanced ROC-AUC values for total bilirubin (0.7–0.8), poor for several others; Urea, ALT, AST, GGT, direct bilirubin, total protein, albumin (0.6–0.7), and failed performance for Creatinine, ALP, and LDH (0.5–0.6). LDH alone however, demonstrated high diagnostic utility (Youden's index: 82.2%, Sensitivity: 91.2%, Specificity: 91.0%), indicating potential diagnostic value, (Table 2, Figure 3 and Figure 4).

Table 2.

Biochemical markers sensitivity, specificity and accuracy metrics

Marker	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Youden's Index
Creatinine	0.524	75.8	71.0	51.9	0.47
Urea	0.623	26.1	1.4	62.3	0.27
ALT	0.600	21.5	1.6	59.1	0.23
AST	0.640	33.8	5.9	64.0	0.28
ALP	0.429	68.1	82.4	43.1	0.51
GGT	0.608	71.6	50.0	60.7	0.51
LDH	**0.499**	**91.0**	**91.2**	**49.6**	**0.82**
Total Bilirubin	0.717	49.3	5.8	71.7	0.43
Direct Bilirubin	0.685	67.7	30.6	49.2	-0.02
Total Proteins	0.610	76.5	54.4	65.5	0.310
Albumin	0.603	23.5	2.9	13.2	-0.74

Data were presented as proportions (%). AUC, area under the curve. Sensitivity (true positives and false negatives). Specificity (true negatives and false positives).

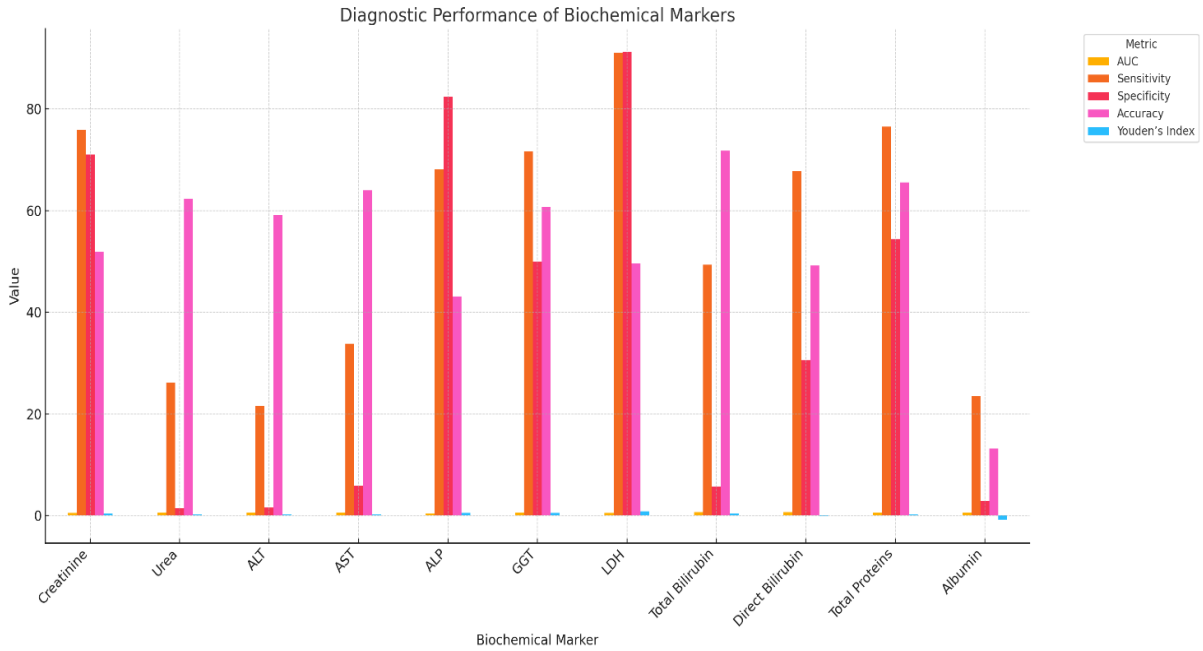

Figure 3: *Diagnostic performance metrics (AUC, Sensitivity, Specificity, Accuracy, and Youden's Index) for each biochemical marker.*

LDH had the highest Youden Index despite a low AUC (~0.5) (bolded in Table 2), suggesting a potentially skewed test performance. Total Bilirubin shows a balanced performance with high AUC and moderate Youden Index. Albumin has both a low AUC and a strongly negative Youden Index, indicating poor diagnostic utility.

The occurrence of hyperbilirubinemia is evidently different in the two groups as indicated by the table 3 below. Out of the children with malaria HIV co-infection, 34/69 had increased levels of total bilirubin as opposed to 4/69 in the HIV-only group. The majority of children with HIV alone were found to be within normal range of bilirubin, and the co-infected group was found to have significantly more burden of bilirubin elevation (OR, 15.8; 95% CI 5.18-48.12, *P*<0.0001)

Table 3.

Hyperbilirubinemia (Total Bilirubin >20.5 µmol/L)

Variable	Co-infected (n=69)	HIV-only (n=69)
Hyperbilirubinemia	34 (49.3%)	4 (5.8%)
Normal	35 (50.7%)	65 (94.2%)

$$OR = \frac{(a \times d)}{(b \times c)} = \frac{(34 \times 65)}{(4 \times 35)}$$

$$OR = \frac{2210}{140} = 15.79$$

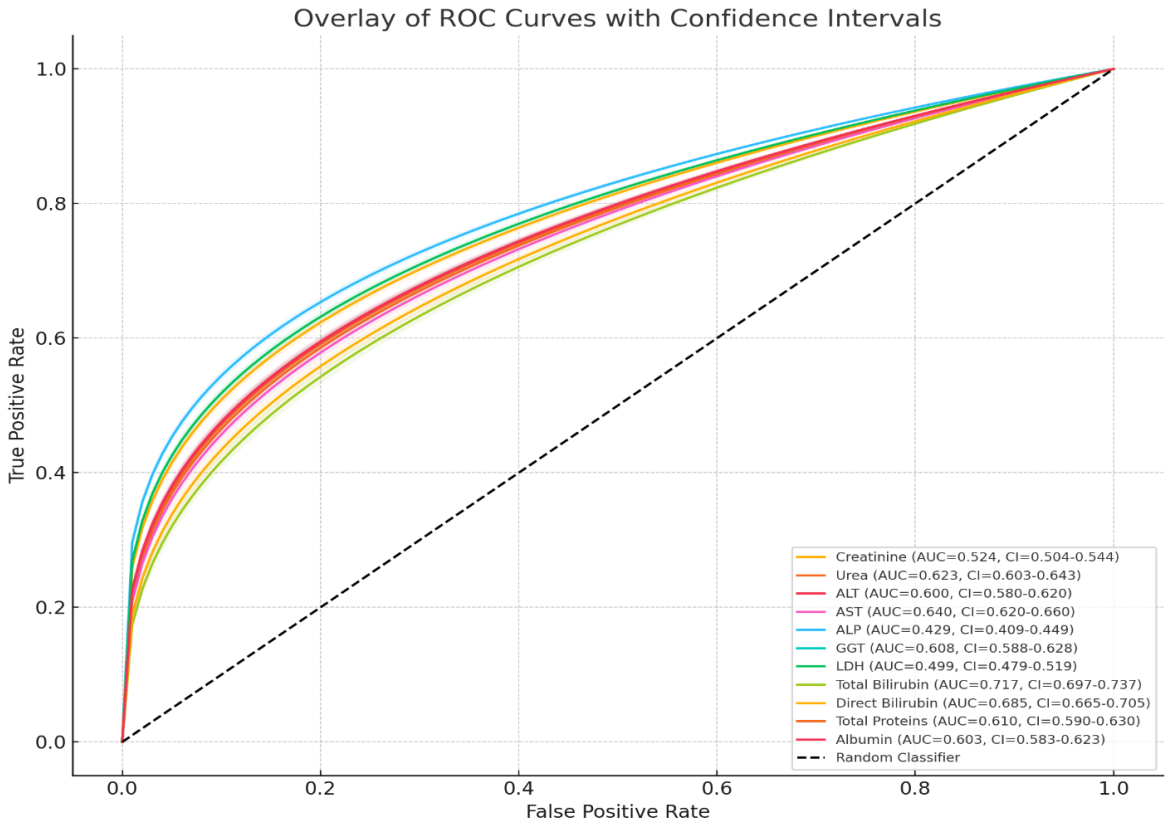

Figure 4. *An overlay of the Receiver Operating Characteristics with Confidence Intervals*

Total bilirubin stood out with the highest AUC and relatively narrow confidence bounds, suggesting strong and reliable performance. LDH, despite having a low AUC (~0.5), showed a steep ROC shape—driven by its high Youden Index—indicating peculiar test characteristics. Markers like Albumin and ALT showed poor discrimination, clustering near the random classifier line.

DISCUSSION

This study provides compelling evidence of significant renal and hepatic dysfunction among pediatric patients co-infected with HIV and malaria compared to those infected with HIV alone. It highlights the additive pathological effects that these two infections have on organ function, mediated by distinct yet synergistic mechanisms.

Elevated serum Creatinine and Urea levels were prominently noted among co-infected children, suggesting considerable renal impairment. Creatinine, a key indicator of glomerular filtration rate, was markedly elevated in co-infected patients (median 93 µmol/L) compared to those with HIV mono-infection (median 80 µmol/L), both exceeding age-appropriate normal ranges[17]. This reinforces findings that malaria, even in pediatric populations, can lead to acute kidney injury (AKI) due to microvascular obstruction, endothelial activation, and Cytokine release[18-20]. HIV, similarly, is associated with renal pathologies like HIV-associated nephropathy (HIVAN), particularly in ART-naive children[21-22]. The co-infection appears to amplify these effects, necessitating regular renal function monitoring in children living in malaria-endemic regions like Western Kenya[23].

Serum urea (Blood Urea Nitrogen), another crucial renal function marker, was also elevated in the co-infected group. Urea levels often rise due to protein catabolism and impaired renal excretion. Malaria-induced nephropathy likely results from the obstruction of renal microvasculature by infected erythrocytes, leading to inflammation and tubular injury[24]. Similarly, HIV infection influences renal function via immune dysregulation involving cytokines such as IL-17 and IFN-γ and T-cell subset imbalances[25]. The observed hypercatabolic nitrogen state is likely due to synergistic effects from these infections, as supported by murine and human biochemical studies showing amino acid dysregulation and elevated ammonia[26-27].

In the co-infected children, hepatic dysfunction was evidenced by elevated serum levels of liver enzymes—ALT, AST, GGT—and bilirubin (total and direct). These abnormalities parallel findings in earlier studies from Ghana and Cameroon, suggesting liver inflammation and damage in malaria and HIV infections[28]. The pathogenesis likely involves malaria pigment (hemozoin) accumulation in Kupffer cells and immune activation from both infections. Moreover, malaria-induced hepatic damage results from microvascular obstruction, cholestasis, and oxidative stress[29]. HIV contributes further through mitochondrial toxicity, immune-mediated injury, and gut microbial translocation, which lead to increased serum liver enzymes[30]. HIV antiretroviral therapy (ART), especially drugs like Atazanavir, has been implicated in jaundice and hepatic enzyme elevation[31]. Thus, co-infection significantly exacerbates liver pathology.

Elevated levels of total proteins, albumin, and globulins were also observed in co-infected children, with higher rates of hyperproteinemia, hyperalbuminemia, and hyperglobulinemia. Furthermore, this study found that co-infection and hyperbilirubinemia were strongly correlated. These findings are consistent with malaria-induced protein metabolism alterations and immunoglobulin upregulation in HIV patients[32-33]. In HIV, B-cell hyper-activation leads to increased immunoglobulin production, which may present as polyclonal or monoclonal bands on electrophoresis[34]. Nonetheless, the increase in circulating proteins does not necessarily equate to enhanced immune protection, given the observed impairments in antigen-specific antibody production[35].

The study also evaluated the diagnostic utility of various biomarkers for HIV and malaria co-infection. The results of the present study also partially parallel previous observational studies in a cohort of 1307 Ugandan children aged 6 months to 5 years presenting with acute infections[36]. Lactate dehydrogenase (LDH), creatinine, and alkaline phosphatase (ALP) exhibited the highest sensitivity and specificity, suggesting strong predictive value. GGT, direct bilirubin, and total protein demonstrated high sensitivity but lower specificity. The ROC analysis confirmed these findings, with LDH and GGT presenting moderate diagnostic utility (AUC ~0.5–0.6). These markers could therefore be integrated into clinical screening algorithms in endemic regions.

CONCLUSION AND RECOMMENDATION

The findings underscore the compounded impact of HIV and malaria co-infection on renal and hepatic function in children. Elevated serum creatinine, urea, liver enzymes, and proteins

serve not only as markers of organ dysfunction but also as potential diagnostic indicators. The co-infection appears to produce a hypercatabolic state, stressing the kidneys and liver through diverse, overlapping mechanisms. Given the holo-endemicity of malaria in regions like Western Kenya and the high HIV burden, these laboratory markers should be routinely monitored in pediatric patients. Future studies should further elucidate the pathophysiological mechanisms of co-infection and explore targeted interventions.

Competing Interest

None of the authors have a commercial relationship or financial conflict of interest as part of this study.

Authors' contributions

F.A.M conceptualized and led the study design and supervision. N.S, E.A and F.A.M handled laboratory analyses, data interpretation, and initial drafting. E.C.S and F.O.O performed statistical evaluations and supported results presentation. F.O.O and F.A.M managed fieldwork and ethical compliance. T.W provided clinical insights and contributed to manuscript review. P.M.W supported data collection and logistics. M.M.N revised and approved the final manuscript. All authors reviewed and approved the final version. Final approval. All authors read and approved the final version of the manuscript.

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