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ORIGINAL RESEARCH

Hepatic and Renal Functions in HIV-Positive Children with Malaria in Western Kenya

Mambo FA[1], Shaviya N*[1], Were T[2]

[1]Department of Medical Laboratory Sciences, [2]Department of Microbiology and Parasitology, Masinde Muliro University of Science and Technology, Kakamega, Kenya

*Correspondence: Dr N. Shaviya, P.O. Box 190-50100, Kakamega, Kenya. E-mail: shavianathan@gmail.com; ORCID - https://orcid.org/0000-0001-7347-3130.

Abstract

Background: The burden of HIV and malaria co-infection lies disproportionately in the Sub-Saharan Africa region which bears most of the malaria endemic zones. While both malaria and HIV are known to dysregulate hepatic and renal functions, the combined effect of co-infection with malaria and HIV on hepatic and renal function among children remains poorly characterized.
Objective: To assess liver and renal functions in HIV-malaria co-infected children in Western Kenya.
Methods: A cross-sectional study was conducted among children aged 6-59 months with HIV and malaria coinfection at Kakamega County Referral Hospital, Western Kenya. A total of 138 children were enrolled. Microscopy and clinical chemistry analysers were used to diagnose malaria, and assay hepatic and renal function parameters respectively.
Results: HIV positive-malaria positive cases had significantly higher serum creatinine and urea levels compared to the HIV positive-malaria negative controls. Likewise, serum levels of the alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), total protein, albumin and globulin were significantly elevated in the HIV and malaria-positive cases compared to HIV-positive and malaria-negative controls. Significantly higher proportions of children with HIV and malaria coinfection also had elevated serum levels of ALT, ASP, GGT, total proteins, albumin and globulin compared to children without coinfection. Serum levels of Alkaline phosphatase (ALP) and Lactate dehydrogenase (LDH) were comparable in both groups.
Conclusion: Co-infection with HIV and malaria among children is generally associated with disrupted hepatic and renal function parameters.

Keywords: Alanine aminotransferase, Aspartate aminotransferase, Creatinine, HIV-Malaria coinfection, Plasmodium falciparum.

Introduction

Majority of people infected with HIV/AIDS and malaria reside in sub-Saharan Africa. [1] The overlap between these two infections and their geographical distribution results in co-infection which presents significant public health issues. [2,3] Recent studies have reported that over 2 million deaths were attributable to HIV and malaria co-infection in the year 2021.[4] Female

anopheles mosquitoes transmit plasmodium parasites, which cause malaria. Malaria is endemic in the majority of tropical and subtropical areas of the world. *Plasmodium falciparum* is the most virulent of the five plasmodium species that infect human beings, and it is also the one that causes the bulk of malaria-related illness and mortality [5] Close to one billion individuals are at risk for contracting malaria globally, majority of whom are children, with annual 247 million cases and 619,000 deaths. [4]

One in every five childhood deaths occurring in sub-Saharan African is attributable to malaria. [6] This situation is further complicated by the high prevalence of HIV/AIDS in the region. This high prevalence means that children born of HIV/AIDS infected parents are at higher risks of infection with the virus. Children are often vulnerable to malaria following the loss of maternally-acquired immunity and while they are yet to fully develop their innate immunity against the infection. [7] This is further complicated by HIV/AIDS, a disease that impairs immunity. [8]

The liver and kidney are vital organs in the body and dysregulation of their functions has serious consequences on the overall human health. [9] In addition, infections such as malaria and HIV affect hepatic and kidney functions. Liver disease has emerged as a major cause of death in HIV-infected individuals, [10] from HIV infection itself, drug toxicity and co-infections. HIV-infection is considered a cause of many hepatobiliary disorders, including elevated liver enzymes, hepatomegaly and liver steatosis. [11]

HIV-infected children are likely to experience proteinuria, impaired renal functions and end stage renal diseases. [12] Conversely, malaria has been shown to affect the glomeruli, tubules and the interstitial region. Kidney disease in malaria is primarily due to erythrocyte abnormalities. Parasitized red cells adhere to healthy erythrocytes, platelets and capillary endothelium, leading to formation of rosettes and clumps, which impair microcirculation. These events are probably contributing factors for kidney injury. [13] Moreover, the use of the Highly Active Anti-retroviral Therapy (HAART) in HIV-infected individuals has direct impact on kidney functions. [14] The combined effect of having both HIV and malaria infections on liver and kidney functions has not been fully understood, especially in children. Western Kenya is a malaria endemic region with malaria transmission occurring all year round. As such, HIV-infected children in this region are also likely to be infected with malaria. Therefore, this study aimed to assess liver and renal functions in HIV-malaria co-infected children in Western Kenya. Assessing liver and kidney functions in HIV-malaria co-infected children is key to disease monitoring.

Methods

Study design and population

The study was cross-sectional in design. The study participants were purposively recruited children comprising children aged 6 to 59 months, attending Kakamega County Referral Hospital, Western Kenya. Upon obtaining written informed consent, 138 children (male, n = 85 and female, n = 53) were recruited, categorized into HIV-positive malaria-negative (n = 69) and HIV-positive malaria-positive (n = 69) groups.

Sample collection and processing

Five millilitres of venous blood were drawn from the antecubital vein into a syringe. Three millilitres of the blood sample were transferred into an Ethylenediamine tetra-acetic acid vacutainer (EDTA) and 2ml was kept into plain BD vacutainer® tubes (Becton Dickinson, Franklin Lakes, USA). The tubes were then labelled with the participant's code, date and

sample collection time. The blood samples in EDTA tubes were used for CD4+ T-cell count immediately after blood collection. The blood in plain vacutainer tubes was allowed to clot for five minutes prior to serum extraction by centrifugation at 3000 r.p.m for five minutes. The serum obtained was used for hepatic function assays.

HIV-1 diagnosis

HIV-1 infection status was tested for using the rapid immunochromatographic test kit, *Determine*™ (Abbott Laboratories, Tokyo, Japan) and *First Response*™ (Trinity Biotech Plc, Bray, Ireland). In accordance with the Kenyan National HIV Testing algorithm, the participants were considered HIV-1-infected if they had HIV-positive results for *Determine* and HIV-1 positive results using the *First Response* kits.

Malaria diagnosis

Blood smears were prepared, stained with 3% Giemsa and parasitaemia determined by counting the number of asexual stage parasites per 200 White Blood Cells. The diagnosis of *P. falciparum* parasitaemia was confirmed microscopically after scanning a minimum of 200 high power fields. Variations in erythrocyte morphology, cell size, shape, and staining pattern were used to diagnose malaria infection.

Clinical chemistry measurements

Renal and liver function tests were performed using an automated Mindray™ BS-200 Clinical Chemistry analyser (Mindray Medical Intl, Shenzhen, China) as per manufacturer's instructions and standard operation procedures. Quality controls for the tests were done and parameters which failed were recalibrated. Briefly, 1000ul of serum was pitted into new, clean, unused Mindray™ BS-200 cuvettes and loaded inside the sample chamber of the machine. Subsequently, measurement of serum creatinine and urea was done for renal functions. Additionally, ALT, AST, GGT, ALP, LDH, bilirubin, albumin and total protein levels were performed using the same machine for liver function.

Definition of renal and hepatic ranges

Dysfunctions in hepatic function markers were defined based on previously established reference values are as follows:

a. Alanine aminotransferase (ALT) (high, >63.0 IU/L and normal, ≥6.0≤63.0 IU/L),
b. Aspartate aminotransferase (AST) (high, >95.0 IU/L and normal ≥15.0≤95.0 IU/L),
c. Alkaline phosphatase (ALP) (high, >392.0 IU/L and normal, ≥87.0≤392.0 IU/L),
d. Gamma Glutamyl Transferase (GGT) (high, >111.0 IU/l and normal, ≥4.0≤111.0 IU/l),
e. Hyperproteinaemia (serum total protein, >92.0 g/l); and normoproteinaemia (serum total protein, ≥50.0≤92.0 g/l),
f. Hyperalbuminaemia (serum albumin, >79.0 g/l); and normoalbuminaemia (serum albumin, ≥25.0≤79.0 g/l),
g. Hyperaglobulinaemia (serum globulins, >53.0 g/l); and normoglobuminaemia (serum globulins, ≥20.0≤53.0 g/l) and
h. Lactate Dehydrogenase (high, >170.0 IU/l and normal, ≥60.0≤63.0 IU/l).

Statistical analysis

All the statistical analyses were performed using SPSS version 24.0 (IBM). Descriptive characteristics of HIV-positive and HIV–negative children presenting with acute malaria are presented by median and range. Mann-Whitney-U statistics was used to compare means between groups for continuous variables.

Ethical considerations

Ethical approval for this study was obtained from the Masinde Muliro University of Science and Technology Institutional Ethical Review

Committee (MMUST/IERC/86/2022). Permission to carry out the study was obtained from the National Council of Science and Technology (NACOSTI). Written informed consent was obtained from the parents/guardians of the children before enrolment. Guidance and counselling were provided the caregivers of HIV positive children. Parents who are HIV-positive were also given medical education in addition to viral load testing and CD4+ T cell counts monitoring. Additionally, malaria-positive children were given oral artemether-lumefantrine medications according to WHO guidelines.

Results

Demographic and parasitological characteristics of the study patients

Age distribution of the study groups indicated that the 69 HIV-positive and malaria-positive children were significantly younger (median, 14.4; range, 5.0-48.0 months) compared to the 69 HIV-positive malaria-negative controls (median, 24.0; range, 6.0-54.0 months) (p = 0.039). Gender distribution was significantly different with the HIV-positive and malaria-positive cases having more females (64.2% *vs.* 35.8%) but fewer males (41.2% *vs.* 58.8%) compared to the HIV-positive malaria-negative controls (p = 0.014). Parasitological examination of the malaria-positive cases indicated a median parasitaemia level of 1870 parasites/µl of blood ranging from 1986-80,025 parasites/µl of blood. Further analysis of the parasitaemia levels in the malaria-positive cases indicated a rate of high density parasitaemia of 10.1% (7/69).

Renal function markers (Figures 1 and 2)

HIV-positive malaria-positive children had significantly higher serum creatinine (median, 93.0; range, 24.0-1935.0 µmol/L) and urea (median, 4.9; range, 1.4-34.5 mmol/L) in comparison to the HIV-positive malaria-negative controls (creatinine: median, 80.0; range, 46.0-205.0 µmol/L; p = 0.001 and urea: median, 3.7; range, 1.7-8.4 mmol/L; p <0.001). Notably, the proportions of children with elevated serum creatinine were similar between the cases (75.4%) and controls (71.0%) (p = 0.564). Additionally, the proportions of children with elevated serum urea were significantly higher in the cases (26.1%) relative to the controls (1.4%) (p <0.0001).

Liver function markers (Tables I and II)

Table II shows that median values of the serum levels of ALT, AST and GGT were significantly higher in children with HIV and malaria coinfection compared to those with HIV mono-infection (p = 0.031, 0.010 and <0.001 respectively). In addition, higher proportions of children with HIV and malaria coinfection had significantly higher elevated serum levels of ALT, AST and GGT (p = 0.001, <0.001 and 0.013 respectively) compared to the HIV-positive and malaria-negative group. However, the median serum levels of ALP and LDH were comparable in both groups (p = 0.262 and 0.113 respectively). Similarly, the proportions of children with HIV and malaria coinfection and those with HIV mono-infection who had elevated serum levels of ALP and LDH were comparable (p = 0.075 and 0.999 respectively).

Serum levels of total bilirubin (median, 20.5; range, 4.3-60.0 *vs.* median, 9.5; range, 3.5-26.0 µmol/L; p <0.001) and conjugated bilirubin (median, 6.7; range, 2.0-46.4 *vs.* median, 3.7; range, 0.9-13.4 µmol/L; p <0.001) were significantly higher in the HIV and malaria co-infected children compared to those without coinfection. In addition, the proportions of children presenting with hyperbilirubinaemia based on total serum bilirubin (49.3% *vs.* 5.8%; p <0.001) and conjugated bilirubin (68.1% *vs.* 30.4%; p <0.001) were significantly higher in the co-infected group compared to those without coinfection.

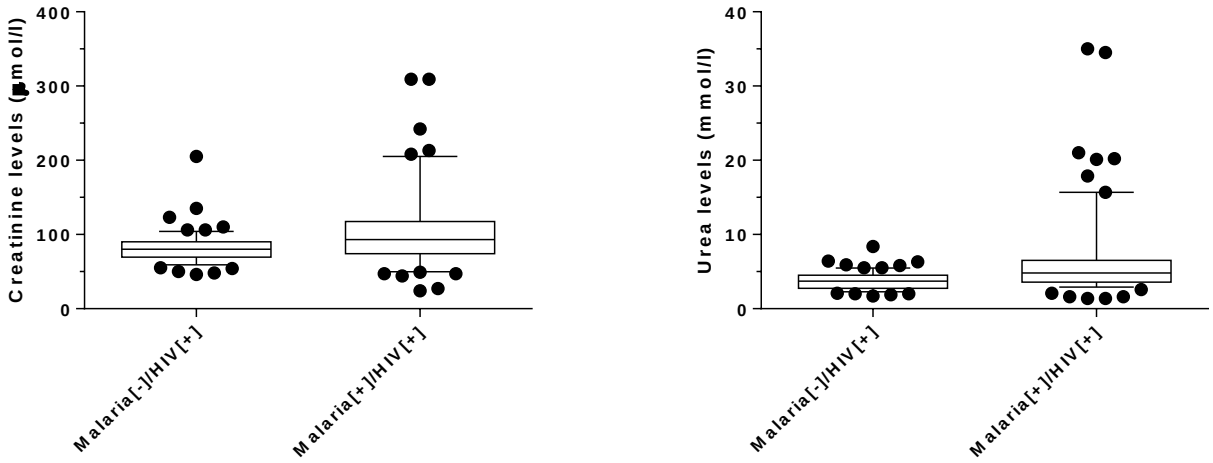

Figure 1: Pattern of median serum creatinine and urea levels in children with HIV and malaria coinfection and those with HIV mono-infection.

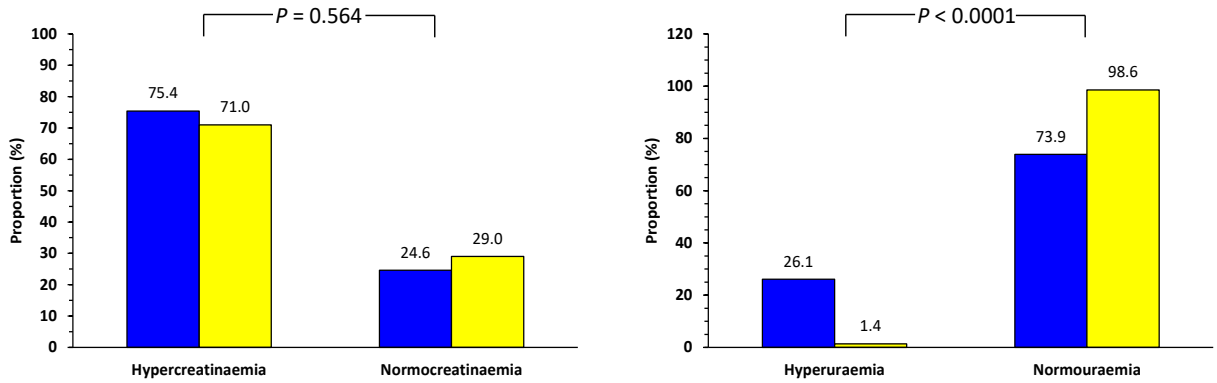

Figure 1: Proportions of children with elevated and normal serum creatinine and urea levels in the HIV and malaria coinfection group and the HIV mono-infection group.

The median values of serum total protein, albumin and globulin were significantly elevated in HIV-positive and malaria-positive children compared to HIV-positive and malaria-negative children (p< 0.001, <0.001, 0.006 respectively). In addition, significantly higher proportions of children HIV and malaria coinfection had elevated serum levels of total proteins, albumin and globulin compared to children without HIV and malaria coinfection (p = 0.018, <0.001 and 0.004 respectively).

Discussion

The present study found elevated levels of serum creatinine in the HIV and malaria co-infected children. This finding suggests renal dysfunction. Malaria alone has previously been associated with acute renal failure. [15] Contrary to the findings in the present study, elevated circulating creatinine levels in malaria are more likely to occur in adults compared to children. [16] However, it is not clear how HIV infection modulates creatinine levels in HIV mono-infected children.

Table I: Comparison of the median values of hepatic enzymes, serum bilirubin and serum proteins between the HIV and malaria coinfected group and the HIV mono-infected group

Marker	*HIV-positive and malaria-negative, n = 69*	*HIV-positive and malaria-positive, n = 69*	*p-value*
ALT, IU/L	11.0 (2.0-43.0)	16.0 (2.0-135.0)	0.031
AST, IU/L	16.5 (5.0-36.0)	19.5 (3.0-340.0)	0.010
ALP, IU/L	73.0 (28.0-559.0)	76.0 (29.0-572.0	0.262
GGT, IU/L	23.5 (6.0-170.0)	38.0 (5.0-423.0)	<0.001
LDH, IU/L	326.5 (95.5-720.3)	359.1 (75.6-1009.6)	0.113
Total bilirubin, µmol/L	9.5 (3.5-26.0)	20.5 (4.3-60.0)	<0.001
Conjugated bilirubin, µmol/L	3.7 (0.9-13.4)	6.7 (2.0-46.4)	<0.001
Total protein, g/L	82.0 (69.0-115.0)	90.0 (35.0-160.0)	<0.001
Albumin, g/L	50.0 (37.0-61.0)	55.0 (30.0-68.0)	<0.001
Globulins, g/L	29.5 (16.0-61.0)	36.0 (18.0-160.0)	0.006

HIV - Human Immunodeficiency Virus. µmol/L; ALT - Alanine aminotransferase; AST - Aspartate aminotransferase; ALP - Alkaline phosphatase; GGT - Gamma-glutamyl transferase; LDH - Lactate dehydrogenase.

Table II: Comparison of the proportion of children with elevated or normal serum levels of hepatic enzymes, serum bilirubin and serum proteins between the HIV and malaria coinfected group and the HIV mono-infected group

Marker	*Category*	*HIV-positive and malaria-negative, n = 69*	*HIV-positive and malaria-positive, n = 69*	*p-value*
ALT	Elevated	2 (2.9)	15 (21.7)	0.001
	Normal	67 (97.1)	54 (78.3)	
AST	Elevated	4 (5.8)	23 (33.3)	<0.001
	Normal	65 (94.2)	46 (66.7)	
ALP	Elevated	56 (82.4)	47 (68.1)	0.075
	Normal	13 (17.6)	22 (31.9)	
GGT	Elevated	35 (50.7)	50 (72.5)	0.013
	Normal	34 (49.3)	19 (27.5)	
LDH	Elevated	63 (91.3)	62 (89.9)	0.999
	Normal	6 (8.7)	7 (10.1)	
Total Bilirubin	Elevated	4 (5.8)	34 (49.3)	<0.001
	Normal	65 (94.2)	35 (50.7)	
Conjugated Bilirubin	Elevated	21 (30.4)	47 (68.1)	<0.001
	Normal	48 (69.6)	22 (31.9)	
Total protein	Elevated	38 (55.1)	53 (76.8)	0.018
	Normal	31 (44.9)	16 (23.2)	
Albumin	Elevated	2 (2.9)	17 (24.6)	<0.001
	Normal	67 (97.1)	52 (75.4)	
Globulin	Elevated	2 (2.9)	11 (15.9)	0.004
	Normal	67 (97.1)	58 (84.1)	

HIV - Human Immunodeficiency Virus. µmol/L; ALT - Alanine aminotransferase; AST - Aspartate aminotransferase; ALP - Alkaline phosphatase; GGT - Gamma-glutamyl transferase; LDH - Lactate dehydrogenase.
Figures in parentheses are percentages of the total in the respective column.

These findings seem to imply that HIV infection and malaria independently have adverse effects on renal functions in children. Creatinine is potentially a good indicator of renal functions in HIV and malaria co-infection since the levels in this category of patients are perhaps significantly higher than the mono-infected. On the other hand, normal serum creatinine levels vary depending on gender, age and race. Standard ranges in infants are between 41 to 85 µmol/L for females and 56 to 112 µmol/L for males. [17] This study reported a median value of 93 µmol/L in HIV and malaria co-infected children and 80 µmol/L in HIV mono-infected children. This is a clear elevation above the normal ranges for both HIV mono-infected as well as HIV-malaria co-infected groups. Since elevated serum creatinine is an indication of renal dysfunction, the mechanisms for the elevated serum levels in both HIV and malaria remain obscure. As such, renal dysfunction in malaria is primarily due to erythrocyte abnormalities. [15] Parasitized red cells tend to adhere to healthy erythrocytes, blood platelets and capillary endothelium, leading to formation of rosettes and clumps, which impair microcirculation, and these events are probable contributing factors to kidney injury, in association with haemodynamic instability, including hypovolaemia and shock. [15] HIV and malaria co-infection have additive effects on renal functions. They both modulate functions by different mechanisms ultimately leading to elevated serum creatinine levels. Consequently, it is critical to monitor creatinine levels in HIV-infected children in malaria endemic regions.

Similarly, this study established a significant elevation in serum urea levels in children with HIV and malaria co-infection compared with those with HIV alone. Urea is measured as blood urea nitrogen (BUN) and it is a key marker of renal functions. [13] Normal BUN ranges are generally between 2.1 and 8.5 mmol/l although these ranges are influenced by age and laboratory standards. [18] Malaria mono-infected children have been reported to present with elevated serum urea. For example, a study on determinants of mortality in *P. falciparum* infected children, high blood urea was reported and most of the children with elevated serum urea had acute kidney injury. [19] The precise mechanism by which falciparum malaria affects kidney functions resulting in elevation of serum urea is still not clear. However, just like in the case of creatinine, infected erythrocytes appear to play a key role in the actual obstruction of nephrons. [20] Likewise, elevated BUN in HIV mono-infected patients has been linked with renal dysfunction. A previous study has reported elevated serum urea levels in HIV mono infected -ART naïve patients. [21] Moreover, a previous study has also reported that HIV-associated nephropathies arise before the initiation of HIV seroconversion. [22]

The present study reports elevated serum ALT, AST, GGT and bilirubin (total and direct) in the HIV and falciparum malaria co-infected children compared to the HIV mono-infected children suggesting liver dysfunction in the former. The findings in the present study partly mirror previous findings among children with acute malaria and HIV infected children showing elevated serum activities of the liver enzymes AST, ALT, GGT. [23] Similarly, the higher levels of serum bilirubin and higher rates of hyperbilirubinaemia are consistent with findings in a previous study demonstrating that higher bilirubin levels were associated with severity of liver pathology, apoptosis, and NF-κB p65 activation in patients with falciparum malaria. [24] The underlying cause of the deranged hepatic functions in the HIV and malaria co-infected children may include malaria pigment deposition in the hepatocellular phagocytes, and altered inflammatory responses to both malaria and HIV infection. This assertion is supported by previous autopsy hepatic histologic studies in Malawi among children with falciparum malaria

illustrating increased numbers of haemozoin-laden Kupffer cells, that directly and indirectly alter hepatic functions. [25] Altogether, these findings illustrate increased hepatic pathology in HIV and malaria co-infected children.

Malaria-induced hepatocyte injury may manifest significant elevated serum level enzymes of ALT, AST, ALP and GGT. [26] The pathogenesis of hepatic dysfunction is not completely known; however, reduction in portal venous flow as a consequence of microvascular occlusion in the portal venous branches by parasitized erythrocytes, intrahepatic cholestasis due to reticuloendothelial blockage and hepatic microvilli dysfunction, suppression of bilirubin excretion due to the effect of parasitaemia or endotoxaemia or metabolic acidosis, apoptosis and oxidative stress, are all possible mechanisms involved in hepatic damage [27] HIV infection has also been shown to cause an elevation in the circulating enzymes - ALT, AST, ALP, GGT and LDH. A study assessing the prevalence and predictors of liver disease in HIV-infected children and adolescents reported a rise in the serum levels in both HIV–ART naïve and ART-experienced patients. [28] Additionally, the same study and others have revealed that HIV, ART and co-morbidities have a direct influence on serum levels of ALT, AST, ALP, GGT and LDH. A number of discrete mechanisms of hepatic injury due to HIV infection have been identified. These mechanisms include oxidative stress, mitochondrial injury, lipotoxicity, immune-mediated injury, cytotoxicity, toxic metabolite accumulation, gut microbial translocation, systemic inflammation, senescence and nodular regenerative hyperplasia. Disease states may use any number of these mechanisms to exert their effect on the liver leading to an elevation in circulating hepatic enzymes. [29]

The present study found significantly higher levels of both total and direct bilirubin in the HIV and malaria co-infected children compared with the HIV mono-infected group. Moreover, this study suggested higher rates of hyperbilirubinaemia in the HIV and malaria co-infected clinical group. Studies that have focused on paediatric malaria have reported hyperbilirubinaemia in patients. [30] Consequently, the total and direct serum bilirubin levels are often elevated. In patients with malaria, serum bilirubin has been shown to increase with increase in malaria parasite density. [31] Usually, in uncomplicated malaria, raised bilirubin is mainly due to haemolysis of parasitized and non-parasitized erythrocytes and/or hepatocytes damage. [24] On the other hand, HIV mono-infection has not been associated with hyperbilirubinaemia in ART-naïve patients. [32]

Consistent with the pattern of hepatic enzymes and serum bilirubin levels, the present study reported raised serum proteins in HIV and malaria co-infected subjects compared with the HIV mono-infected group. The study found higher levels of total proteins, albumin and globulins in HIV and malaria co-infected children. Besides, significantly higher rates of hyperproteinaemia, hyperalbuminaemia and hyperglobulinaemia were recorded in the co-infected clinical group. Likewise, other studies have found malaria and HIV infections to be independently associated with elevated serum proteins. Moreover, a cluster analysis of proteins in mild and severe malaria revealed an elevation of serum proteins in circulation with higher levels in the severe malaria group. [33]

Studies in HIV patients, both ART-naïve and ART-experienced, have revealed conflicting findings. For instance, electrophoresis of protein subunits including albumin and globulins have found elevated serum albumin, α-1, α -2, β and ɤ globulins. [34] Interestingly, a study among Iranian HIV-positive patients found no significant difference compared to normal subjects, in the circulating protein units. [35] HIV-

positive patients are at a higher risk of plasma cell disorders, ranging from polyclonal hypergammaglobulinaemia and monoclonal gammopathy to symptomatic multiple myeloma. [36] Generally, both HIV and malaria modulate serum hepatic enzymes, bilirubin and proteins. As is the case, the levels of these substrates are more elevated in the HIV and malaria co-infected groups compared with the HIV mono-infected group.

It appears that the two infections use different pathophysiological mechanisms to trigger renal dysfunction. Malaria is obviously a parasitic infection and HIV, viral. Therefore, if both mechanisms manifest in the same patient, then it is possible that the serum urea levels may be more elevated as indicated by the findings in this study. It is important to note that not so many recent studies have analysed paediatric HIV and malaria co-infection. This presents a complexity in understanding the mechanisms modulating renal dysfunction in the case of HIV and malaria co-infection. Nonetheless, higher serum creatinine and urea levels in the malaria and HIV co-infected children suggests higher nitrogen hypercatabolic state. This state could be as a result of the synergistic effect of the different complex pathophysiological mechanisms that the two infections use to impair renal functions.
Overall, derangements in protein metabolism characterized by hyper-catabolism with associated release of ammonia which subsequently leads higher urea and creatinine levels are possibilities. Hence, serum creatinine and urea may be important surrogate markers of HIV and malaria co-infection.

Conclusion

HIV and malaria coinfection in children is generally associated with elevated liver markers, renal markers and circulating proteins. The key laboratory parameters that are elevated include serum creatinine and urea for renal function and liver enzymes, serum bilirubin and total serum proteins for liver disease.

Limitation

This study did not account for HAART use and the duration of HAART treatment among HIV-positive children aged 0-59 months.

Authors' Contributions: MFA conceived and designed the study. All the authors did the literature review. SN and WT did data analysis. All the authors did data interpretation while SN drafted the manuscript. MFA and WT revised the manuscript for sound intellectual content. All the authors read and approved the final version of the manuscript.
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