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Liver injury in malaria infected patients in Douala-Cameroon and its association with poor medical practice

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Abstract

Background Malaria is an endemic mosquito-borne disease in sub-Saharan regions, including Cameroon. Due to the obligatory hepatic stage of its pathogenic agents, malaria can induce liver damage if not properly treated. Hence, we assessed the impact of malaria infection on liver transaminases among febrile patients consulting at the Deido District Hospital, Douala-Cameroon, in regard to their attitude towards the practice of preventive measures, treatment, and management of malaria.

Methods Over 10 weeks, 150 febrile patients and 28 healthy individuals serving as the control group were enrolled and their blood samples screened for *Plasmodium* species by Giemsa Staining and liver injury evaluated by measuring the serum level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities. The socio-demographic characteristics of participants and their attitude towards the practice of preventive measures, treatment, and management of malaria were collected using a structured- questionnaire.

Results Among tested febrile patients, 113 (75%) were malaria-positive. Females were more affected (65.5%) than males; the most affected age group were adults between 30-60 years (55.8%). A significant association ($p<0.05$; relative risk [RR] = 1.424 or $p<0.05$; RR = 1.947) was found between malaria infection and non-use of mosquito nets or insecticides, respectively. The serum level of ALT and AST activities in malaria-positive were significantly ($p<0.05$) increased, compared to healthy or malaria-negative individuals. Furthermore, transaminase activity was significantly ($p<0.05$) elevated in non-practitioners of preventive measures; and in patients who engaged in auto-medication or traditional medication, compared to those who sought treatment from health centers.

Conclusion Our findings demonstrated that non-practice of preventive measures, improper treatment and management of malaria infection can lead to an abnormal increase in serum level of transaminases which may reflect liver injury.

Keywords Febrile patients, Malaria infection, Liver injury, Transaminases, Deido District Hospital

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Background

Malaria, transmitted through the bite of an infected female *Anopheles* mosquito, is an acute febrile illness caused by the *Plasmodium* parasite [1]. There are 5 parasites species namely: *Plasmodium falciparum, Plasmodium malariae, Plasmodium vivax, Plasmodium ovale and Plasmodium knowlesi*. The predominant species of *Plasmodium* responsible for malaria infections in humans are *P. falciparum and P. vivax* [2]. This infection remains a major health problem in the world. According to the annual World Health Organization (WHO) report for 2021, there were an estimated 241 million cases worldwide in 2020. Malaria is endemic in South America, Asia, and Sub-Saharan Africa. In this latest area, 165 million cases have been documented, with 313 500 deaths. Children under the age of five and pregnant women are the most sensitive populations to the sickness. In 2018, for example, under-five children accounted for 67 % (272 000) of all malaria deaths globally [3]. In 2020, the number of reported cases and deaths in Cameroon were 2 974 819 and 4 000 people respectively, with 53% of deaths occurring among under-five children [4, 5]. Cameroon has initiated preventive measures against malaria through the practice of good environmental hygiene and the use of long-lasting treated mosquito nets, artemisinin-based combination (ACT) therapies at a subsidized cost for first-line treatment for uncomplicated malaria cases and intermittent preventive therapy with sulphadoxine-pyrimethamine. Despite the considerable reduction of its prevalence, malaria is still responsible for 26% of consultations and 46% of hospital admissions.

It is well established that the pathogenic agent of malaria infection interferes with the liver, a key organ that plays many vital functions in the body [6, 7]. Indeed, in humans, the life cycle of the *Plasmodium* species has 2 main stages: hepatic and erythrocytic stages. During the hepatic stage, invasion of liver cells by malaria parasites can cause organ congestion, sinusoidal blockage, cellular inflammation and necrosis [8]. When these happen, as consequence of hepatic injury, liver enzymes such as transaminases, alkaline phosphatase and gamma glutamyl-transpeptidases enzymes leak out into the circulation, therefore increasing their activities [9–11]. Also, cases of clinical jaundice were reported in 5.3% to 62% patients with falciparium malaria in endemic countries like India [12–14]. Unfortunately, in these endemic regions, information regarding the negative impact of malaria parasites on the liver is poorly disseminated. In addition, many people ignore the fact that improper management of malaria can lead to the development of liver injury with the risk of the occurrence of liver failure, susceptible to being fatal for the patients [15, 16]. Accordingly, there is a need to continuously assess the impact of malaria infection on the liver to sensitize the population to the considerable risk of developing severe liver injury or liver failure during malaria infection, if poorly managed. Thus, the purpose of this study was to investigate the influence of malaria infection on liver injury indicators among feverish patients consulting at the Deido District Hospital in Douala, Cameroon, in regard to their attitude toward the practice of malaria prevention, treatment, and management.

Material and Methods

Ethical consideration

Administrative Authorization (N° 0219/AR/MINSANTE/DRSPL/SSDD/HDD) to undertake this study was issued by the Director of Deido District Hospital Douala amplified by the Regional Health Office of the Littoral Region, Ministry of Public Health, Cameroon. Before starting the study, an ethical clearance (N° 2022/1829-05/SG/IRB/FHS) was issued by the Institutional Review Board of the Faculty of Health Sciences of the University of Buea.

Study area

The study was conducted at the Deido District Hospital, Douala, Littoral Region-Cameroon. Deido is one of the most populated neighborhoods of Douala, the largest city and economic capital of the country. The hospital is located at latitude 4° 4' 4.0" North and longitude 9° 42' 59.0" (Fig. 1), bordered to the North by the 9th District police station, to the South by civilian residents, to the East by the MRS fuel station and to the West by Hotel *le Bosquet*. This hospital covers a surface area of 4 600 m^2, has several units and a bed space capacity of 65 beds.

Study design and participants

A cross-sectional study, accompanied by laboratory tests, was carried out from the 15th of March to the 16th of May 2022, at the Laboratory Unit of the Deido District Hospital. The target population of this investigation comprised of febrile patients consulting at the Deido District Hospital in Douala, Littoral Region of Cameroon. The study included any febrile patients, who agreed to take part in this study by signing the informed consent form. The study excluded febrile patients with different conditions other than malaria. Also, patients with liver-related diseases were excluded from the study. For participants aged 18 years or less, the informed consent form was signed by a guardian or parent.

Sampling method and sample size

A convenient sampling method was used to recruit patients. Potential participants were approached and the goal of the study first explained to them. Then, if they agree to take part in the study, a consent form was

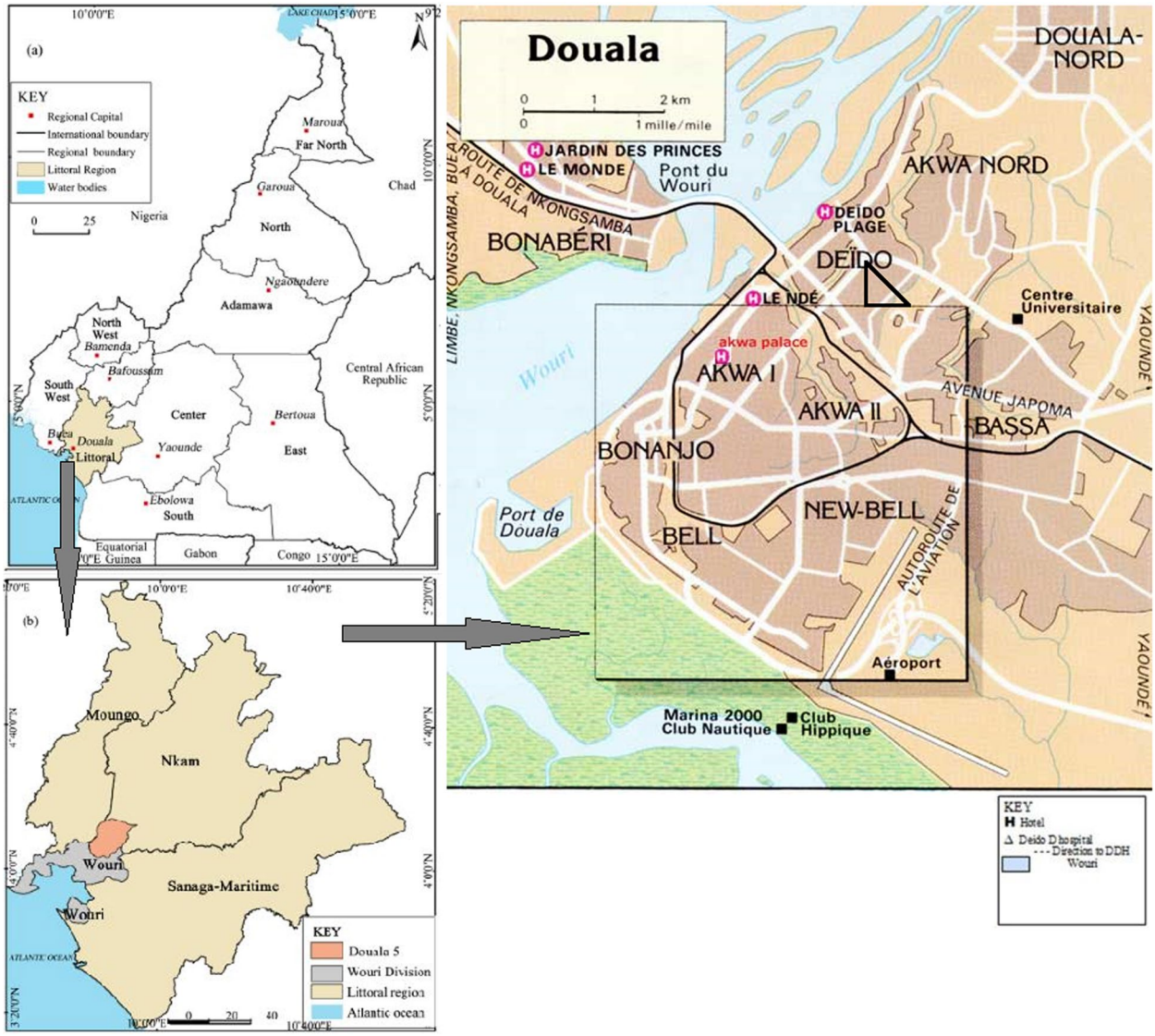

Fig. 1 Adapted map of Deido Health District Area

given to them, afterwards, a structured questionnaire was used to collect the information before collecting the blood. A total of 150 febrile participants were enrolled, in addition to 28 healthy individuals (free from any diseases) who served as a control group when assessing liver aminotransferases.

Data collection

Assessment of the knowledge and attitude of febrile patients towards preventive measures, treatment and management of malaria

The knowledge and attitude of febrile patients regarding the preventive measures, treatment, and management of malaria infection were assessed by using a structured- questionnaire (Supplementary file). The questionnaire consisted of 36 questions divided into two sections. The first section had 13 questions regarding the socio-demographic status of the patient, and the second section contained 23 questions regarding the methods of prevention, management, and treatment of malaria. The questionnaires were assigned codes to make patients' information enrolled in the study anonymous and confidential.

Determination of malaria infection rate among febrile patients at Deido District Hospital

Laboratory analysis was carried out to determine the prevalence of malaria infection among febrile patients

enrolled in the study. Briefly, capillary blood samples from febrile patients were collected and screened for the presence of the *Plasmodium* trophozoites by the Giemsa stain. The materials required for this procedure include glass slides, 10% Giemsa stain, smear stick, pipette, lancet, dropper, and tap water. A lancet was used to prick the finger and the blood droplet was collected on the labeled glass slide. By a circular motion, the blood droplet was spread on the glass slide using smear stick and allowed to air dry at room temperature. The dried glass slide was then stained with Giemsa reagent for 15 min. The glass slide was rinsed with tap water to remove excess Giemsa stain and dried at 60°C in an oven. Finally, immersion oil was added to the slide and mounted for viewing under a light microscope.

Assessment of serum liver transaminases activity of febrile patients

The impact of malaria infection on the markers of liver injury in febrile patients was assessed by measuring the levels of serum activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Blood samples (≈ 5 mL) from the median cubital vein were aseptically collected in the red cap dry labeled tubes, allowed to settle at room temperature for 30 min, and centrifuged (3000 rpm/min, 10 min, 25°C) to obtain serum. The serum was then transferred into labeled Eppendorf vials for ALT and AST activities measurement in a semi-auto-analyzer spectrophotometer (Genrui) using a kit produced by SGM Company (Roma, Italia) according to the manufacturer's instructions.

Statistical analysis

Extracted data from questionnaire and laboratory test results were recorded and processed using Microsoft Excel 2013 (Microsoft Corporation, USA). Descriptive statistics were used and data were expressed in the form of mean plus or minus standard deviation (mean ± SD), frequencies, or percentages. Analysis was performed using GraphPad Prism 8.0.2 software. Comparisons of quantitative data between malaria-infected patients, and non-infected patients or the control group (healthy individuals) were made by the non-parametric Student *t*-test followed by the Mann-Whitney U test. Fisher's Exact Test was used and the Relative Risks were calculated from contingency tables to evaluate the association between malaria infection and the socio-demographic characteristics of febrile patients as well as their attitude towards the practice of preventive measures, treatment, and management of malaria. Differences between compared groups were considered significant at $p< 0.05$.

Results

Knowledge and attitude of participants regarding the preventive measures against malaria

Socio-demographic characteristics of the studied population

The socio-demographic data of the patients enrolled in this study are summarized in Table 1. A total of 150 febrile patients (mean age 38.6 ± 21.6) were enrolled. Among them, 93(62%) were female. The greater proportion of participants was aged between 30-60years (76; 50.7%) and 14 patients were under five years. Ninety-three (62.0%) participants were married while 45 (30.0%) were university attendants, and 48 (32.2%) engaged in business activities.

Attitudes of febrile patients enrolled in the study towards the practice of preventive measures against malaria

The attitude of febrile patients consulting at Deido District Hospital towards the practice of preventive measures against malaria is presented in Table 2. It appears that the greater proportion (89) of the studied population live in cement houses (59.3%), with gable spaces (65.3%), and with ceiling (58.7%). Ninety-eight (65.3%)

Table 1 Socio-demographic characteristics of febrile patients enrolled in the study

Variables	Category	Number (n =150)	Percentage (%)
Gender	Male	57	38.0
	Female	93	62.0
Age range (Years)	[0-5]	14	9.3
	[5-30]	39	26.0
	[30-60]	76	50.7
	[>60]	21	14.0
Marital status	Married	93	62.0
	Single	40	26.7
	Divorced	4	2.6
	Widow	10	6.7
	Widower	3	2.0
Education	Never attended school	14	9.3
	Primary school	26	17.3
	Secondary school	35	23.4
	High school	30	20
	University	45	30
Occupation	Farmer	11	7.3
	Teacher	26	17.3
	Health care worker	19	12.6
	Business	48	32.2
	Others	46	30.6
	Total	150	100

Table 2 Attitudes of febrile patient enrolled in the study toward the practice of preventive measures against malaria

Variables	Category	Number (n =150)	Percentage %
House type	Mud	14	9.3
	Cement	89	59.3
	Wood	47	31.4
Gable space	Yes	98	65.3
	No	52	34.7
Ceiling house	Yes	88	58.7
	No	62	41.3
Stay out late at night	Yes	52	34.7
	No	98	65.3
Regular use of mosquito nets	Yes	70	46.7
	No	80	53.3
Regular use of insecticides	Yes	48	32.0
	No	102	68.0
Regular use of malaria prophylaxis	Yes	45	30.0
	No	105	70.0

participants did not stay out late at night, while 70 (46.7%) regularly used mosquito nets. Also, 102 (68%) of the participants were not regular users of insecticides, and 105 (70%) did not take prophylaxis against malaria.

Attitude of febrile patients toward management and treatment of malaria infection

The attitude of participants regarding the management and treatment of malaria presented in Table 3 shows that none of the febrile patients enrolled in the study visited the hospital on the same day or three days after the appearance of the first symptoms. One hundred and ten (73.3%) attended the hospital after 7 days while 40 (26.7%) visited the hospital after 30 days. A greater proportion of the participants (77) practiced auto-medication (51.3%) while only 27 (18.0%) received treatment from a health center. Also, 91 (60.7%) of the patients declared to take artemisinin-based combination therapy as a treatment option while 29 (19.3%) opted for traditional medication from herbalists.

Malaria infection rate among febrile patients

Prevalence of malaria infection among febrile patients enrolled in the study

Figure 2A depicts the prevalence of malaria infection among the studied population. Over 150 febrile patients enrolled in the study, 113 (75%) were tested positive for the presence of *P. falciparum* and 37 (25%) tested negative.

Distribution of malaria infection in relation to gender and age of the participants

The distribution of malaria infection according to the gender and age group of infected participants of the study is presented in Table 4. Of the 113 patients who were tested positive for malaria, 74 (65.5%) were female and 39 (34.5%) were male. The greater proportion of infected patients (63; 55.8%) were between 30 and 60 years old. Seven (6.2%) infected patients were under five years.

Distribution of malaria infection in febrile patients according to the practice of preventive measures

Table 5 presents the association of malaria infection with the attitude of febrile patients towards the practice of preventive measures. Among a total of 113 malaria-positive participants, 43 (38.1%) were regular users of mosquitos net, while 70 (61.9%) did not use mosquito nets. Regarding the regular use of insecticides, up to 91 (80.5%), malaria-infected participants did not use insecticides as a preventive measure whereas 22 (19.5%)

Table 3 Attitudes of febrile patients enrolled in the study toward management and treatment of malaria infection

Variables	Category	Number (n =150)	Percentage %
Time to get to the hospital after appearance of the first symptoms	Same day	0	0.0
	Three days	0	0.0
	Seven days	110	73.3
	Thirty days	40	26.7
Take treatment from	Health center	27	18.0
	Pharmacy	17	11.3
	Herbalist	29	19.4
	Auto-medication	77	51.3
Type of malaria drug	ACT	91	60.7
	Quinine	30	20.0
	Traditional medication	29	19.3

ACT Artemisinin-based Combination Therapy

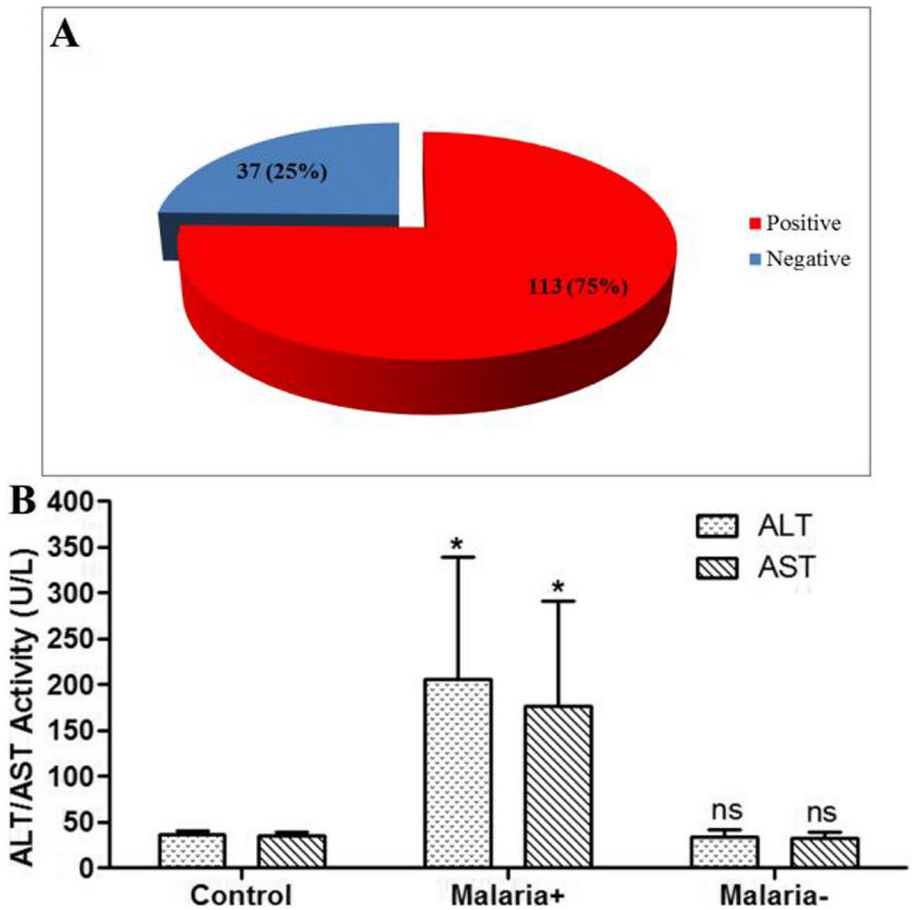

Fig. 2 Prevalence of malaria infection (**A**) and variation of serum level of ALT and AST activities (**B**) of febrile patients enrolled in the study. Data are expressed as mean ± SD of two independent analyses in duplicate. ***** Values significantly ($p<0.05$) different when compared to control group. **NS** Values non-significantly ($p>0.05$) different when compared to control group. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase SD: Standard Deviation; Malaria+: infected febrile patients; Malaria-:non-infected febrile patients

Table 4 Association between malaria infection, gender and age group of febrile patients

Variables	Category	Malaria + (%) (*n* =113)	Malaria - (%) (*n* = 37)	Strength of Association		
				RR	RR [95% CI]	*p* value
Gender	Male	39 (34.5)	18 (48.6)			
	Female	74 (65.5)	19 (51.4)	1.163	[0.94-1.42]	$=0.1714^{ns}$
Age range (years)	[0-5]	7 (6.2)	7 (18.9)	1		
	[5-30]	24 (21.2)	15 (40.5)	1.231	[0.69-2.19]	$=0.5343^{ns}$
	[30-60]	63 (55.8)	13 (35.2)	1.658	[0.97-2.82]	=0.0124*
	[>60]	19 (16.8)	2 (5.4)	1.810	[1.05-3.11]	=0.0111*

Malaria+: Malaria infected febrile patients; Malaria-: Malaria non-infected febrile patients; RR: Relative risk value determined by Fisher's Exact Test; CI: Confidence Interval; *: indicate *p* value statistically significant ($p<0.05$); ^{ns}: indicate *p* value statistically non-significant ($p>0.05$)

frequently used insecticides. Finally, the number of malaria-infected participants who did not consider taking malaria prophylaxis as a preventive measure was 95 (84.1%) while those on malaria prophylaxis were 18 (15.9%). From Table 5, it emerges that people that do not regularly use mosquito net (RR= 1.42 vs 1, 95%CI= 1.16-1.74, $p = 0.0002$), do not frequently use insecticides (RR= 1.947, 95%CI= 1.42-2.67, $p<0.0001$), and do not use prophylactic measures (RR = 2.26 vs 1, 95%CI=

Table 5 Association between malaria infection and the attitude of febrile patients towards preventive measures

Variables	Category	Malaria + (%) (*n* =113)	Malaria - (%) (*n* =37)	Strength of Association		
				RR	RR [95% CI]	*p* value
Regular use of mosquito net	Yes	43 (38.1)	27 (73.0)	1		
	No	70 (61.9)	10 (27.0)	1.424	[1.16-1.74]	=0.0002*
Regular use of insecticides	Yes	22 (19.5)	26 (70.3)	1		
	No	91 (80.5)	11 (29.7)	1.947	[1.42-2.67]	<0.0001*
Regular use of prophylaxis	Yes	18 (15.9)	27 (73.0)	1		
	No	95 (84.1)	10 (27.0)	2.262	[1.57-3.25]	<0.0001*

Malaria+: Malaria infected febrile patients; Malaria-: Malaria non-infected febrile patients; *RR* Relative risk value determined by Fisher's Exact Test, *CI* Confidence Interval; ***:** indicate *p* value statistically significant ($p<0.05$)

1.57-3.25, $p<0.0001$) were more significantly associated with malaria infection than those who use it

Distribution of malaria infection according to the attitude of febrile patients towards the management and treatment of malaria

The frequency of malaria infection concerning the attitude of participants towards the management and treatment of malaria is presented in Table 6. Regarding the time to seek medical assistance after the appearance of the first symptoms, 98 (86.7%) infected participants attended the hospital after 7 days while 15 (13.3%) came after 30 days. Sixty-two (54.9%) infected patients were under auto-medication, and 19 (16.8%) and 20 (17.7%) took treatment from a health care center and herbalist, respectively. Concerning the type of medication, 72 (63.7%) infected patients were under ACT whereas 22 (19.5%) took traditional medication from herbalists.

Impact of malaria infection on liver injury among infected patients enrolled in the study

Variation of serum levels of liver transaminases of malaria-infected and non-infected patients

Signs of hepatic injury in malaria-infected and non-infected patients were assessed by measuring serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities, whose results are presented in Fig. 2B. Compared to the control group (healthy individual) whose mean values were 35.8 ± 4.9 U/L, range from 29.2-41.9 U/L and 34.7 ± 4.1 U/L, range 29.0-39.5 U/L respectively for ALT and AST activities, infection by *P. falciparum* significantly ($p<0.05$) increase both ALT and AST activities to 205.3 ± 134.1 U/L, values ranging from 37.3 to 1904.9 U/L and 176.5 ± 114.8 U/L, values ranging from 33.7 to 1823.4 U/L respectively for ALT and AST activities. There was no significant ($p>0.05$) difference between ALT and AST activities (33.9 ± 7.8

Table 6 Association between malaria infection and the attitude of febrile patients towards management and treatment of malaria

Variables	Category	Malaria + (%) (*n* =113)	Malaria - (%) (*n* =37)	Strength of Association		
				RR	RR [95% CI]	*p* value
Time to get to the hospital after appearance of the first symptoms	Same day	0(0.0)	0(0.0)	/	/	/
	Three days	0(0.0)	0(0.0)	/	/	/
	Seven days	98(86.7)	12(32.4)	2.376	[1.58-3.56]	<0.0001*
	Thirty days	15(13.3)	25(67.6)	1		
	Total	113(100)	37(100)			
Take treatment from	Health center	19(16.8)	8(21.6)	1		
	Pharmacy	12(10.6)	5(13.5)	1.003	[0.67-1.48]	$=0.6302^{ns}$
	Herbalist	20(17.7)	9(24.4)	0.980	[0.69-1.38]	$=1.000^{ns}$
	Auto-medication	62(54.9)	15(40.5)	1.144	[0.87-1.49]	$=0.2029^{ns}$
	Total	113(100)	37(100)			
Type of malaria drug	ACT	72(63.7)	19(51.4)	1		
	Quinine	19(16.8)	11(29.6)	0.800	[0.59-1.07]	$=0.0703^{ns}$
	Traditional medication	22(19.5)	7(19.0)	0.958	[0.76-1.20]	$=0.4454^{ns}$
	Total	113(100)	37(100)			

ACT Artemisinin-based Combination Therapy, *Malaria+* Malaria infected febrile patients, *Malaria-* Malaria non-infected febrile patients, *RR* Relative risk value determined by Fisher's Exact Test, *CI* Confidence Interval, ***** indicate *p* value statistically significant ($p<0.05$), **^{ns},** indicate *p* value statistically non-significant ($p>0.05$)

U/L, ranging from 22.7 to 50.2 U/L, and 32.2 ± 6.4 U/L, ranging from 20.2 to 43.7 respectively) of non-infected patients and those of healthy individuals.

Variation of serum levels of liver aminotransferases in malaria infected patients in relation to gender and age

Table 7 presents the variation in the means of serum level of ALT and AST activities in malaria-infected patients with respect to their age and gender. Regarding the gender, the mean values in males were 102.4 ± 55.1 U/L ranging from 44 to 320 U/L and 88.7 ± 45.4 UI/L ranging from 40 to 240 respectively for ALT and AST activities whereas in females, the mean values were 249.4 ± 151.7 U/L ranging from 37 to 1904.9 and 214.9 ± 128.3U/L ranging from 33 to 1823.4 respectively for ALT and AST activities. These values were 6 and 5 times greater than the upper limit of their respective normal range regarding ALT and AST activities respectively and were significantly (p<0.05) different when compared to the corresponding values observed in the control group. For the age, the highest values of ALT (265.1 ± 157.7 U/L) and AST (228.4 ± 128.2 U/L) were seen in the age range between 30 and 60 years.

Variation of serum level of liver transaminases in malaria-infected patients in respect to their attitude toward preventive measures against malaria

The variation in the means of serum levels of ALT and AST activities in malaria-infected patients according to their attitude toward the practice of preventive measures against malaria is presented in Fig. 3. Firstly, regarding the use of mosquito nets, there was a significant increase (p<0.05) in ALT and AST activities in non-users of mosquitos net (247.3 ± 184.9 U/L; range [71-1904.9] and 215.8 ± 154.7U/L; range [68.9-1823.4] respectively for ALT and AST) compared to regular users (51.4 ± 10.1 U/L; range [37.3-70.9] and 49.8±9.4 U/L; range [33.7-50.2] respectively for ALT and AST). Secondly, concerning the regular use of insecticides, a significant increase (p<0.05) in ALT and AST activities was observed in non-users of insecticides (223.4 ± 156.2U/L; range [51.4-1904.9] and 192.1 ± 132.4 U/L; range [50.3-1823.4] respectively for ALT and AST) compared to users (43.0 ± 3.6 U/L; range [37.3-50.1] and 42.3 ± 5.1 U/L; range [40-1830] respectively for ALT and AST). Finally, concerning the regular taking of malaria prophylaxis, there was a significant increase (p<0.05) in ALT and AST activities in non-users of malaria prophylaxis (219.7 ± 151.6 U/L; range [47.6-1904.9] and 189.4 ± 128.8 U/L; range [47.7-1823.4] respectively for ALT and AST) compared to users (41.7 ± 3.5 U/L; range [37.3-44.74] and 40.8 ± 4.4 U/L; range [33.7-47.6] respectively for ALT and AST).

Variation of serum levels of liver transaminases in malaria infected patients in respect to their attitude toward management and treatment of malaria

The variation in the mean values of serum levels of ALT and AST activities in malaria-infected patients concerning their attitude toward management and treatment against malaria is shown in Table 8. Firstly, regarding the time taken to get to the hospital after the appearance of first symptoms, there was a significant increase (p<0.05) in ALT and AST activities in patients who took 30 days to get to the hospital (470 ± 435.8 U/L; range [189-1904.9] and 409.2 ± 361.5 U/L; range [170-1823] respectively for ALT and AST) compared to patients who went to the hospital after 7 days (82.7 ± 33.5 U/L range [37-182] and 77.1 ± 31.1 U/L range [33-160] respectively for ALT and AST). Secondly, concerning the health facility in which they

Table 7 Variation in the mean and range values of serum level of ALT and AST activities assessed in malaria infected patients in respect with the gender and age

Variables	Category	Parameters	
		ALT	AST
		Mean±SD [range]	Mean±SD [range]
Gender	Male (*n*=39)	102.4±55.1* [44-320]	88.7±45.4 [40-240]
	Female (*n*=74)	249.4±151.7* [37-1904.9]	214.9±128.3* [33-1823.4]
Age range	[0-5] (*n*=7)	61.2±20.1ns [40-96]	57.6±13.0 ns [45-85]
	[5-30] (*n*=24)	130±96.5* [47-390]	105.5±77.5* [36-350]
	[30-60] (*n*=63)	265.1±157.7* [37-1904.9]	228.4±128.2* [33-1823.4]
	[>60] (*n*=19)	91.7±43.0 ns [39-180]	104.3±65.0* [37-270]
Control (*n*=28)		35.8±4.9 [29.2-41.9]	34.7±4.1 [29.0-39.1]
Normal range		[31-41]	[31-38]

Data are expressed as mean ± SD of two independent analyses in duplicate. * Values significantly p<0.05) different when compared to control group. **ns** Values non-significantly (p>0.05) different when compared to control group. *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase

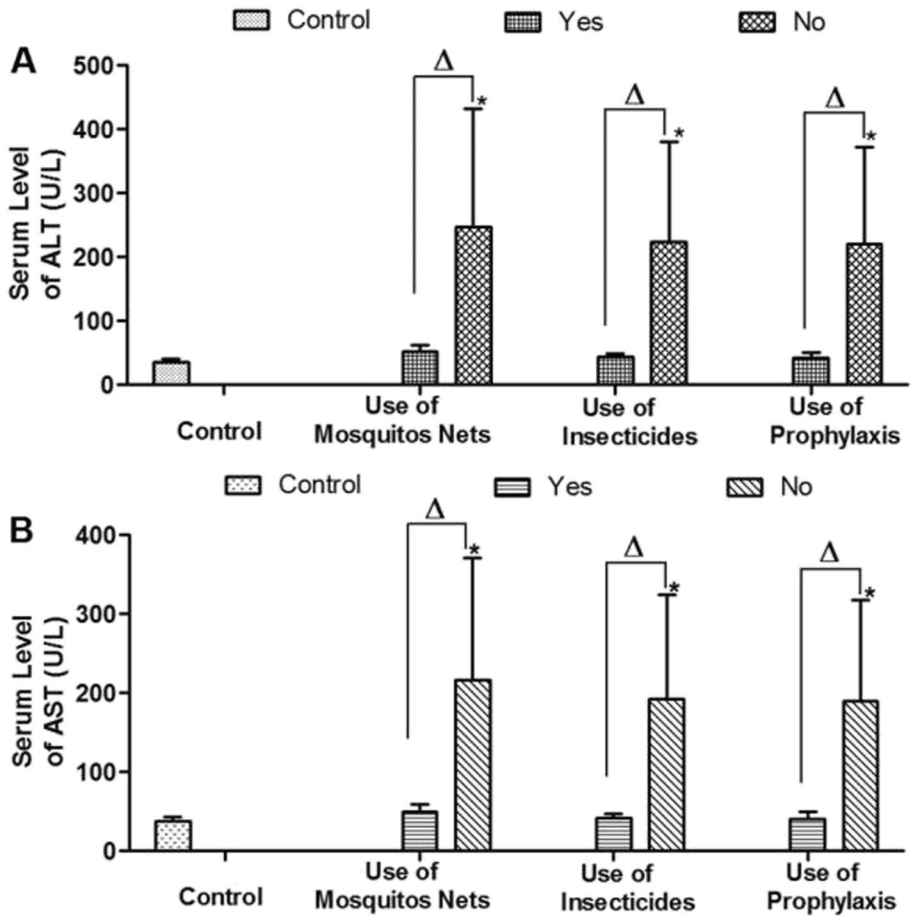

Fig. 3 Variation of liver transaminases activities assessed on malaria infected patients in respect to their attitude towards preventive measure against malaria infection. (**A**) Serum level of alanine aminotransferase; (**B**) Serum level of aspartate aminotransferase. Data are expressed as mean ± SD of two independent analyses in duplicate. ***** Values significantly ($p<0.05$) different when compared to control group. **Δ** Values significantly ($p<0.05$) different when compared between two category within the same variables

seek health care after the appearance of the first symptoms of the disease, a significant increase ($p<0.05$) in ALT and AST activities was observed in patients who engaged in auto-medication (260.4 ± 199.2 U/L; range [86-1904.9] and 226.6 ± 165.3 U/L; range [74-1823] respectively for ALT and AST) compared to patients who seek for care in health centers (42.07 ± 2.8 U/L range [37-48] and 41.2 ± 4.6 U/L range [33-48] respectively for ALT and AST). Finally, regarding the medication taken against malaria, there was a significant increase ($p<0.05$) in ALT and AST activities in traditional medication users as a treatment against malaria (387.6 ± 367.6 U/L; range [130-1904.9] and 349.7 ± 292.6 U/L; range [120-1823] respectively for ALT and AST) compared to ACT users (66.7 ± 21.1 U/L range [36-100] and 61.9 ± 16.9 U/L range [33-95] respectively for ALT and AST).

Discussion

Malaria is one of the most common endemic mosquito-borne diseases in the sub-Saharan region, including Cameroon. Unfortunately, diagnostic procedures do not consider evaluating biomarkers of liver injury, although all species of malaria parasites possess an obligatory hepatic stage, which can increases morbidity and mortality, as a consequence of complications arising from liver impairment [10, 15, 17]. Accordingly, assessing bio-indicators of liver injury or identifying risk factors that can induce liver dysfunction may contribute to preventing or reducing the occurrence of severe forms of malaria infection and related death. Hence, this study aimed to contribute to the epidemiological surveillance of the impact of malaria infection among febrile patients consulting in an urban area, particularly at the Deido District Hospital, located in Douala, the economic capital of Cameroon,

Table 8 Variation in the mean and range values of liver transaminases activities assessed on malaria infected patients in respect with their attitude towards management and treatment against malaria infection

Variable	Category	Parameters	
		ALT	AST
		Mean ± SD [Range]	Mean ± SD [Range]
Time to get to the hospital after the appearance of the first symptoms	Seven days (*n*=98)	82.7±33.5 [37-182]	77.1±31.1 [33-160]
	Thirty days (*n*=15)	470±435.8^{*P1} [189-1904.9]	409.2±361.5^{*P1} [170-1823]
Take treatment from	Health center (*n*=19)	42.07±2.8 [37-48]	41.2±4.6 [33-48]
	Pharmacy (*n*=12)	53.1±3.0 [48-58]	51.6±2.5 [47-56]
	Herbalist (*n*=20	69.4±7.6 [57-85]	66.2±6.1 [65-74]
	Auto-medication (*n*=62)	260.4 ± 199.2^{*P2} [86-1904.9]	226.6 ±165.3 ^{*P2} [74-1823]
Type of malaria drug	ACT (*n*=77)	66.7±21.1 [36-100]	61.9±16.9 [33-95]
	Quinine (*n*=19)	119.2±10.1^{*P3} [100-130]	109.5±11.4^{*P3} [94-125]
	Traditional medication (*n*=22)	387.6±367.6^{*P4} [130-1904.9]	349.7±292.6^{*P4} [120.-1823]
Control (*n*=28)		35.8±4.9 [29.2-41.9]	34.7±4.1 [29.0-39.1]
Normal range		[31-41]	[31-38]

Data are expressed as mean ± SD of two independent analyses in duplicate. * Values significantly ($p<0.05$) different when compared to control group. ^{P1} Values significantly ($p<0.05$) different when compared between seven and thirty days; ^{P2} Values significantly ($p<0.05$) different when compared between health center and auto-medication; ^{P3} Values significantly ($p<0.05$) different when compared between ACT and Quinine; ^{P4} Values significantly ($p<0.05$) different when compared between ACT and traditional medication. *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase. *ACT* Artemisinin-based Combination Therapy

with their practice towards preventive measures, treatment, and management of malaria infection.

Blood analysis, carried out on 150 febrile patients enrolled in this study showed 113 (75%) positive cases of malaria infection (Fig. 2A). This high prevalence is close to that recently reported by Galani et al. [18] who found an infection rate of 77% (134/174) among febrile patients consulting at the regional hospital of Ngaoundéré, another urban zone, located at the Adamawa Region of Cameroon. These findings suggest that Female *Anopheles* mosquitoes, the vector responsible for malaria transmission is highly proliferating in urban areas, likely due to poor sanitary conditions, therefore confirming that malaria is effectively endemic in Cameroon. Indeed, Malaria still represents 26% of consultations and 46% of hospital admissions, with the number of cases reported in 2020 being 2.9 million, with 4000 deaths [4].

To gain an insight into why such a high infection rate of malaria is found among febrile patients in Cameroon, we assessed their attitudes towards the practice of preventive measures, as recommended by the Cameroonian Ministry of Public Health through the National Malaria Control Program. The assessed preventive measures included regular use of long-lasting treated mosquito nets and insecticides for vector control and intermittent preventive therapy for prophylaxis. Our results showed a significant ($p<0.05$) association between malaria infection and the non-use of mosquito nets, insecticides, or prophylaxis drugs; with the prevalence being 61.9, 80.5, and 84.1% respectively (Table 5). Compared to febrile patients who declared themselves as regular practitioners of the abovementioned preventive measures, the relative risk (RR) for contracting malaria, as determined by Fisher's Exact Test, were 1.424; 1.947 and 2.262 respectively for non-users of mosquito nets, non-users of insecticides and non-users of prophylaxis drugs. These findings, on one hand, revealed that in urban zones, people did not pay attention to the preventive measures against malaria; on other hand, suggested that more community health campaigns should be organized in other to sensitize the population about the effective practice of preventive measures against malaria.

Proper case management of malaria requires early diagnosis and prompt treatment with effective antimalarials [3]. Thus, we assessed the attitude of febrile patients enrolled in this study towards the management and treatment of malaria. Our results showed that malaria-infected patients continue to adopt risky behaviors regarding recommended management and treatment of malaria. Indeed, we found that none of the malaria-infected patients sought medical help before one week after the appearance of first the symptoms, which is a behavior contrary to early diagnosis as advocated by WHO. Also, we found that 62 (52.9%) of infected patients were under auto-medication and 22 (19.5%) took traditional medication from herbalists (Table 6) before attending the hospital. Such risky attitudes are very often the cause of the development of severe forms of malaria, which could justify the high mortality observed in these regions where malaria remains endemic.

In humans, the lifecycle of plasmodium species is divided into 2 phases. The pre-erythrocytic phase and then the erythrocytic phase that is responsible for the clinical manifestations of malaria [13, 19]. The pre-erythrocytic phase, also known as the hepatic stage, usually affects the liver. The invasive form of malaria parasites, known as sporozoites, is transmitted to humans through a bite of female Anopheles mosquitos. These sporozoites reach the liver via the bloodstream and then infect hepatocytes, where they mature into tissue schizonts to produce hundreds of merozoites, which after rupture, invade erythrocytes [7, 19]. Rupture of infected hepatocytes coincidentally occurs with clinical symptoms of malaria, accompanied by a moderate increase in serum level of aminotransferases enzymes [20, 21]. However, severe forms of malaria which mimic hepatic failure with a marked increase in serum level of transaminases have been also reported [9, 17]. In this study, we found that compared to healthy individuals whose ALT and AST values were 35.8 ± 4.9 U/L and 34.7 ± 4.1 U/L respectively, or non-infected febrile patients with ALT and AST values of 33.9 ± 7.8 U/L and 32.2 ± 6.4 U/L, infection by Plasmodium species significantly (p<0.05) increases serum level of ALT and AST to 205.3 ± 134.1 U/L and 176.5 ± 114.8 U/L, respectively (Fig. 2B). This abnormal increase of serum level of transaminases which are cytosolic enzymes, could be the consequence of massive necrosis of hepatocytes induced by schizonts ruptures. Similar findings have been also reported in Nigeria, a neighboring country where malaria is also endemic [22].

As earlier mentioned, good practice of preventive measures, early diagnosis, and effective antimalarial are necessary to prevent or cure malaria. Indeed, when poorly treated, Plasmodium species can remain dormant for weeks or months after initial infection, before they mature into tissues schizonts and produce symptomatic infection [2, 7, 17]; that increase the risk of developing severe liver injury characterized by abnormally elevated serum level of transaminases [9, 11]. In this study, to evidence the impact of the poor practice of preventive measures or improper management of malaria on the liver, we first compared the serum level ALT and AST activities between infected patients who effectively practice preventive measures and infected patients who did not integrate these preventive measures in their lifestyle. We noticed a significant (p<0.05) in serum level of ALT and AST activities in non-users of mosquito nets, non-users of insecticides, or non-users of malaria prophylaxis when compared to regular users of mosquito nets, insecticides, or prophylaxis against malaria respectively (Fig. 3). These observations suggest that non-practice of preventive measures can represent risk factors for developing severe liver injury during malaria infection. Secondly, regarding the management and treatment of malaria, infected patients who seek medical attention 30 days after the appearance of first symptoms presented a significant (p<0.05) elevated level of serum transaminases when compared to those who attended the hospital after 7 days. Also, a significant (p<0.05) increase in serum level of ALT and AST was observed between those who took treatment from a health care center (42.07 ± 2.8 U/L and 41.2 ± 4.6 U/L respectively for ALT and AST) and patients under auto-medication (260.4 ± 119.2 U/L and 226.6 ± 165.3 U/L, respectively for ALT and AST). Similarly, infected patients who took traditional medication from herbalists presented a significant (p<0.05) elevated serum level of transaminases (387.6 ± 367.6 U/L and 349.7 ± 292.6 U/L, respectively for ALT and AST) when compared to infected patients under Artemisinin-based Combination Therapy (66.7 ± 21.1 U/L and 61.9 ± 16.9 U/L, respectively for ALT and AST) (Table 8). From these findings, it can be suggested that delay before seeking proper medical care, auto-medication, or non-efficient traditional medicine obtained from herbalists represent risky behaviors that can lead to the development of a complicated form of malaria, characterized by the occurrence of severe liver injuries susceptible to lead to the death of patients [17].

As the limitation of this study, the sample size can be pointed out and could be therefore increased in further study to obtain more representative data. Also, it will be interesting to extend sampling during the entire year instead of only 2-3 months. Also, we were not able to assess all indicators of liver damage, including total bilirubin, conjugated bilirubin, alkaline phosphatase, or gamma-glutamyl-trans peptidase, due to resource constraints.

Conclusion

Malaria is still considered a major health threat in many developing countries, including Cameroon. The progression of this disease affects the liver and is associated with the elevation of serum liver of liver enzymes such as ALT and ALT. This study demonstrated that abnormal serum level of liver aminotransferases found in positive cases of malaria among febrile patients consulting at Deido District Hospital, Douala-Cameroon, is associated with non-practice of preventive measures, and improper management and treatment of malaria infection, suggesting that if not properly handled, malaria can cause severe damage to the liver, which can lead to the death of the patients.

Abbreviations

ALT Alanine aminotransferase
AST Aspartate aminotransferase

ACT Artemisinin-based Combination Therapy
WHO World Health Organization
RR Relative Risk

Supplementary Information

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Additional file 1.

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Authors' contributions
AFK, PDDC, FNN and PFM defined the research subject and its aims, conceived and designed the methodological approach. AFK, ZW, NASN, AGKF, NEN, and EN performed the experiments. AFK, NASN, BRTG, AGKF, EN and NEN analyzed the data and wrote the paper. All the authors read and approved the final version of this manuscript.

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Declarations

Ethical approval and consent to participate
The ethical clearance (N° 2022/1829-05/SG/IRB/FHS) to undertake this study was issued by the Institutional Review Board of the Faculty of Health Sciences of the University of Buea. Administrative Authorization (N° 0219/AR/MINSANTE/DRSPL/SSDD/HDD) was obtained from the Director of Deido District Hospital Douala, amplified by the Regional Health Office of the Littoral Region, Ministry of Public Health, Cameroon. Written informed consent was signed by all participants of this study, after they had understood the purpose and procedure of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Sutherland CJ (2016) Persistent Parasitism: The Adaptive Biology of Malariae and Ovale Malaria. Trends Parasitol 32:808–819
2. Sato S (2021) Plasmodium—a brief introduction to the parasites causing human malaria and their basic biology. J Physiol Anthropol 40:1
3. WHO W. World malaria report 2021. 2021. https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021. Accessed 6 Jul 2022.
4. Ngouakam H, Akongem MA, Cagetan TT, Ngueugang ALW, Tientche B, Nsagha DS (2021) Assessment of Knowledge and Attitude Regarding Risk Factors of Malaria Among Caregivers of Under-Five Children in the Buea Health District, South West Region, Cameroon. Int J Trop Dis. Health:36–50
5. Nyasa RB, Fotabe EL, Ndip RN (2021) Trends in malaria prevalence and risk factors associated with the disease in Nkongho-mbeng; a typical rural setting in the equatorial rainforest of the South West Region of Cameroon. Plos One 16:e0251380
6. Autino B, Corbett Y, Castelli F, Taramelli D (2012) PATHOGENESIS OF MALARIA IN TISSUES AND BLOOD. Mediterr J Hematol Infect Dis 4:e2012061
7. Talwani R, Gilliam BL, Howell C (2011) Infectious Diseases and the Liver. Clin Liver Dis 15:111–130
8. Viriyavejakul P, Khachonsaksumet V, Punsawad C (2014) Liver changes in severe Plasmodium falciparum malaria: histopathology, apoptosis and nuclear factor kappa B expression. Malar J 13:106
9. Cheaveau J, Marasinghe D, Akakpo S, Deardon R, Naugler C, Chin A et al (2019) The Impact of Malaria on Liver Enzymes: A Retrospective Cohort Study (2010–2017). Open Forum Infect Dis 6:ofz234
10. Murthy GL, Sahay RK, Sreenivas DV, Sundaram C, Shantaram V (1998) Hepatitis in falciparum malaria. Trop Gastroenterol Off J Dig Dis Found 19:152–154
11. Woodford J, Shanks GD, Griffin P, Chalon S, McCarthy JS (2018) The Dynamics of Liver Function Test Abnormalities after Malaria Infection: A Retrospective Observational Study. Am J Trop Med Hyg 98:1113–1119
12. Anand AC, Ramji C, Narula AS, Singh W (1992) Malarial hepatitis: a heterogeneous syndrome? Natl Med J India 5:59–62
13. Anand AC, Puri P (2005) Jaundice in malaria. J Gastroenterol Hepatol 20:1322–1332
14. Mazumder R, Mishra RK, Mazumder H, Mukherjee P (2002) Jaundice in falciparum malaria--some prospective observations. J Indian Med Assoc 100:312–314
15. Das SN, Mohapatra B, Mohanty R, Dash PC, Kar K, Dash PK (2007) Malarial hepatitis as a component of multiorgan failure--a bad prognostic sign. J Indian Med Assoc 105:247–250
16. Sung YH, Park JM (2010) A case of malarial hepatitis by Plasmodium vivax. Korean J Gastroenterol Taehan Sohwagi Hakhoe Chi 56:329–333
17. Rupani AB, Amarapurkar AD (2009) Hepatic changes in fatal malaria: an emerging problem. Ann Trop Med Parasitol 103:119–127
18. Galani BRT, Mapouokam DW, Simo FBN, Mohamadou H, Chuisseu PDD, Njintang NY et al (2021) Investigation of dengue–malaria coinfection among febrile patients consulting at Ngaoundere Regional Hospital. Cameroon. J Med Virol 93:3350–3361
19. Cunha BA (1988) Systemic infections affecting the liver. Postgrad Med 84:148–168
20. Abro AH, Ustadi AM, Abro HA, Abdou AS, Younis NJ, Akaila SI (2009) Jaundice with hepatic dysfunction in P. falciparum malaria. J Coll Physicians Surg--Pak JCPSP 19:363–366
21. Shah S, Ali L, Sattar RA, Aziz T, Ansari T, Ara J (2009) Malarial hepatopathy in falciparum malaria. J Coll Physicians Surg--Pak JCPSP 19:367–370
22. Enemchukwu BN, Ibe CC, Udedi SC, Iroha A, Ubaoji KI, Ogundapo SS (2014) Liver function assessment in malaria, typhoid and malaria-typhoid co-infection in Aba, Abia State, Nigeria. Pak J Biol Sci PJBS 17:860–863

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