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OPEN ACCESS ORIGINAL ARTICLE

Impact of Malaria Severity on Selected Liver Function Markers in Aden, Yemen: A Pilot Study

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ABSTRACT

Background: Malaria remains a significant public health concern, with *Plasmodium falciparum* and *P. vivax* infections often leading to systemic complications, including hepatic dysfunction.
Objective: This study investigates the relationship between malaria severity and liver function abnormalities, particularly bilirubin and liver enzyme elevations, in malaria patients in Aden, Yemen.
Method: A retrospective observational study was conducted among 150 malaria patients from September to December 2024 in multiple private and public hospitals in Aden, Yemen. Malaria severity was classified based on WHO criteria into severe, moderate and mild. Liver function markers, including (ALT), (AST), (T. Bilirubin), and (D. Bilirubin), were measured using spectrophotometry. Statistical analyses were performed using SPSS version 26 with significance set at $p < 0.05$.
Results: Males (61%) were more affected than females (39%), with *Plasmodium falciparum* accounting for 68% of cases. Severe malaria was observed in 56% of patients. Liver enzyme levels were markedly elevated in severe malaria cases, with mean ALT at 80.29 ± 45.11 U/L and ALT at 78.46 ± 46.67 U/L. Bilirubin levels were also significantly increased (T. Bilirubin: 3.00 ± 2.3 mg/dL, D. Bilirubin: 1.19 ± 1.1 mg/dL), with a strong association between disease severity and hepatic dysfunction ($p < 0.001$). However, no statistical relationship was found between malaria severity and demographic characteristics, including gender ($p = 0.318$), place of residence ($p = 0.438$), and participant age ($p = 0.869$).
Conclusion: Severe malaria is associated with significant hepatic dysfunction, characterized by elevated liver enzyme levels and hyperbilirubinemia. These findings underscore the importance of continuous liver function monitoring in malaria patients to prevent severe hepatic complications. Further research is needed to elucidate the underlying mechanisms and potential long-term impacts of malarial hepatopathy.

Keywords: Malaria, Liver Function, Bilirubin, Hepatic Dysfunction, Malaria Severity, Aden, Yemen.

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INTRODUCTION

Malaria remains a major global health challenge, particularly in tropical and subtropical regions where it is endemic (1). The World Health Organization reports that during 2022 the disease caused 247 million cases of malaria and 619,000 deaths worldwide wherein the African region bore 96 percent of fatalities (2). Malaria remains endemic in Yemen due to climatic challenges, ongoing conflict, and limited healthcare resources (3, 4). *Plasmodium falciparum* and vivax infections being the main malaria agent Yemen records 90% of its total malaria cases and seasonal transmission reaches its highest levels from October through March in the southern governorates (5). The endemic malaria infection throughout the region creates additional disease challenges because poverty coupled with malnutrition together with healthcare service disruptions make managing malaria more complex (2). The study of hepatic dysfunction as a severe complication of malaria has become more important because it strongly affects patient outcomes and disease severity (6). Plasmodium lifecycle initiation takes place inside the liver where the parasite develops before red blood cell invasion occurs according to research (7). The mechanisms responsible for liver involvement in malaria consist of direct parasitic invasion along with immune-mediated damage and hemolysis and microvascular alterations (9). Liver disease processes cause hepatocellular damage that leads to biochemical problems including elevated liver enzyme levels and hyperbilirubinemia along with hepatomegaly while acute liver failure develops as a severe manifestation (9). The clinical signs of hepatic complications due to malaria appear as liver problems with jaundice along with coagulation disorders and metabolic problems that boost disease severity and death rates (9).

Different malaria-endemic territories have demonstrated conflicting patterns regarding both how often patients develop hepatic problems from malaria and the extent of their severity. A Canadian research study by Cheaveau J et al. (10) determined elevated liver enzymes in most malaria patients because the disease heavily affects the liver. Mala W et al. (11) performed a large meta-analysis study that reported non-severe malaria patients presented with less hyperbilirubinemia incidents because of healthcare access variations and different disease manifestations. Research that evaluates malaria-associated hepatic dysfunction in Yemen remains scarce even though global evidence exists. Every patient benefit from knowing hepatic complications in malaria because social economic issues and healthcare system problems remain major problems in Yemen. Research focused on assessing the hepatic dysfunction levels in malaria-infected patients who seek medical care at healthcare facilities located in Aden, Yemen.

The research evaluated liver function disorders by reviewing changes in alanine aminotransferase (ALT) and aspartate aminotransferase (ALT) with bilirubin levels to detect hepatic involvement. This analysis also investigated severe liver dysfunction prevalence rates along with identifying risk factors that affect malaria patients through evaluation of parasite species and disease severity combined with patient comorbidities. The study presented data about malaria which helps health services in Yemen develop both effective guidelines along with clinical treatment methods. The improvement of both awareness and diagnostic capacities for hepatic complications from malaria would lead to earlier interventions which decrease severe malaria consequences within endemic areas.

METHODOLOGY

Study Design

This study was designed as a retrospective or observational study, conducted to assess the hepatic complications associated with malaria in patients presenting to healthcare facilities in Aden, Yemen.

Study Site and Duration

The study was conducted across multiple private and public hospitals in Aden, Yemen. The data collection period spanned four months, from September to December 2024.

Study Population

The study population included patients diagnosed with malaria during the study period. Diagnosis was confirmed through blood smear microscopy or rapid diagnostic tests.

Inclusion Criteria

- Patients aged 6 years and above.

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- Patients with a confirmed diagnosis of malaria (*Plasmodium falciparum*, *Plasmodium vivax*).
- Patients willing to provide informed consent.

Exclusion Criteria

- Patients with a history of chronic liver disease or known hepatic comorbidities.
- Patients with concurrent infections such as hepatitis B or C.
- Pregnant women, due to differing physiological responses.
- Patients who had received antimalarial treatment prior to hospital presentation.

Sample Size Calculation

The sample size was calculated using the formula for retrospective studies:

$$n = Z^2 \times P\,(1-P) / d^2$$

Where:

- Z is the Z-score corresponding to a 95% confidence level (1.96).
- P is the expected prevalence of hepatic complications in malaria patients (assumed to be 50% due to lack of prior regional data).
- d is the margin of error (0.09).

$n = (1.96)^2 \times 0.50(1-0.50) / (0.09)^2 = 119$

Thus, the target sample size was set at 150 patients to account for potential dropouts and missing data.

Data Collection Procedure

Patients meeting the inclusion criteria were enrolled consecutively from the participating hospitals. Data were collected through:

- Clinical records: Patient demographic and clinical information, including age, sex, residence.
- Laboratory tests: Results for liver enzymes (ALT, AST) and bilirubin levels were obtained from hospital laboratories.

Data were extracted on patient demographics, clinical presentation, liver enzyme levels (ALT, AST), bilirubin levels, and outcomes. Additional data included sex, age, residence (village or city), and malaria severity. Severe malaria was defined according to WHO criteria, including hyperbilirubinemia (≥ 3 mg/dL), liver enzyme elevation (≥ 2× the upper limit of normal), and multi-organ dysfunction (2).

Sample analysis method

Liver function markers, including ALT, AST, T. Bilirubin, and D. Bilirubin, were measured using an automated biochemical analyzer (e.g., Roche Cobas c311 or equivalent), which utilizes spectrophotometric methods for enzyme quantification.

- ALT and AST levels were determined using the International Federation of Clinical Chemistry (IFCC) method without pyridoxal phosphate activation, ensuring standardized enzyme activity measurement.
- Bilirubin levels (T. Bilirubin and D. Bilirubin) were assessed via the diazo reaction method, which provides high sensitivity for detecting bilirubin fractions.

Data Collection Process

- **Blood Sample Timing**: Venous blood samples were collected in the morning (between 7:00 AM and 10:00 AM) to minimize the impact of diurnal variations on liver enzyme levels, as ALT and AST levels have been reported to fluctuate throughout the day.
- **Malaria Severity Classification**: Malaria severity was classified based on the WHO 2015 criteria, which define severe malaria as the presence of at least one of the following:
  - Hyperparasitemia (> 5% parasitized erythrocytes).
  - Severe anemia (Hemoglobin < 7 g/dL).
  - Hyperbilirubinemia (Total bilirubin >3 mg/dL).
  - Acidosis/metabolic disturbances (plasma bicarbonate <15 mmol/L).
  - Impaired consciousness (Glasgow Coma Score <11).
  - Renal impairment (Creatinine > 3 mg/dL).
  - Severe thrombocytopenia (< 50,000 platelets/μL).

Confounder Control

- **Potential Confounders**: The study accounted for potential confounding factors, including malnutrition, concurrent infections (e.g., viral hepatitis, bacterial sepsis), and pre-existing liver diseases.

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- **Control Methods**
  - Patients with a known history of liver disease, or hepatotoxic drug intake were excluded to minimize confounding effects.
  - Nutritional status was assessed using BMI and serum albumin levels, allowing for stratification based on malnutrition risk.
  - A detailed clinical history and serological tests (Hepatitis B and C screening) were performed to rule out alternative causes of liver dysfunction.

Ethical Considerations
Ethical approval was obtained from the University of Science and Technology, Aden Yemen (MEC/0AD68). Written informed consent was obtained from all participants before enrollment in the study.

Data Analysis
Descriptive statistics summarized patient characteristics and liver enzyme levels. Chi-square and t-tests compared variables between groups with and without hepatic complications. Logistic regression identified predictors of severe hepatic involvement. P-values <0.05 were considered statistically significant.

Statistical Adjustment: Multivariate logistic regression analysis was conducted only to adjust for confounders. The mean difference with 95% confidence intervals (CIs) of independent t tests were reported for key associations between malaria severity and hepatic dysfunction and also age.

RESULTS
Patient Characteristics
Among the 150 malaria patients included in the study, males (61%) were more affected than females (39%). *Plasmodium falciparum* was the predominant species (68%), which is consistent with its well-documented association with severe malaria and complications. Most patients (77%) resided in urban areas, while 23% lived in villages. The age distribution was nearly even, with 49% of patients under 20 years and 51% over 20 years. Notably, severe malaria cases (56%) outnumbered mild cases (44%), indicating a significant disease burden.

Table 1: Demographic Characteristics of Malaria Patients, n= 150

Characteristic		Number (%)
Sex	Males	91 (61%)
	Female	59 (39%)
Age	Less than 20	74 (49%)
	More than 20	76 (51%)
Residence Status	Rural Areas	34 (23%)
	City	116 (77%)
Malaria Severity	Mild	66 (44%)
	Severe	84 (56%)

Liver Enzyme and Bilirubin Levels
The mean values of liver enzymes and bilirubin were markedly elevated in malaria patients. Alanine aminotransferase (ALT) and aspartate aminotransferase (ALT) had mean values of 80.29 U/L and 78.46 U/L, respectively, exceeding the normal reference ranges. Similarly, total bilirubin (T. Bilirubin) and direct bilirubin (D. Bilirubin) levels were significantly elevated, suggesting hepatic dysfunction, which is a recognized complication of malaria, particularly in severe cases.

Table 2: Liver Enzymes and Bilirubin Levels in Malaria Patients, n= 150

Marker	Normal Range	Mean Value (SD)
ALT(GPT)	10-41 U/L	80.29 (45.11)
ALT(GPT)	10-40 U/L	78.46 (46.67)
T. Bilirubin	0.1-1 mg/dL	3.00 (2.3)
D. Bilirubin	0.1-0.25 mg/dL	1.19 (1.1)

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Association of Risk Factors with Malaria Severity

Statistical analysis (Table 3) indicated no significant association between sex (p=0.318), residence (p=0.438), or age (p=0.869) with malaria severity. This suggests that while these demographic factors may contribute to malaria incidence, they do not significantly influence the severity of the disease.

Table 3: Association of Risk Factors with Malaria Severity, n= 150

Risk Factor		Malaria Severity		
		Mild	Severe	P-value
Sex	Male	37 (56.1%)	54 (64.3%)	0.318
	female	29 (43.9%)	30 (35.7%)	
Residence	Rural Areas	13 (19.7%)	22 (26.2%)	0.438
	City	53 (80.3%)	62 (73.8%)	
Age	Less than 20	33 (50.0%)	40 (47.6%)	0.869
	More than 20	33 (50.0%)	44 (52.4%)	

*P-values <0.05 were considered statistically significant

Relationship between Malaria Severity and Liver Function Abnormalities

Table 4 presents independent t-test results comparing liver function markers between mild and severe malaria cases. The findings indicate that severe malaria is associated with significantly higher levels of direct bilirubin (p=0.00), total bilirubin (p=0.00), ALT (p=0.00), and ALT (p=0.00), confirming substantial hepatic involvement in severe cases. These findings align with existing literature demonstrating malaria-induced hepatocellular injury, likely due to immune response activation, hemolysis, and parasite sequestration in hepatic sinusoids.

Table 4: Independent T test between malaria severity and variables, n= 150

Variables	Malaria Mild (n =66) Mean (SD)	Malaria Severe (n =84) Mean (SD)	Mean diff. (95% CI)	t-stats (df)	*P* value
Age	20.54 (8.40)	21.17 (7.67)	-0.63 (3.26-2.0)	0.476	0.635
DB	0.48 (0.28)	1.77 (1.20)	-1.29 (1.56-1.02)	9.541	0.00
TB	1.6 (0.68)	4.11(2.53)	2.51 (3.08-1.93)-	8.688	0.00
SGPT	55.83 (23.04)	96.25 (52.67)	-40.40 (53.1-27.7)	6.312	0.00
SGPT	58.80 (22.71)	97.18 (50.94)	38.37 (50.7-26.1)-	6.169	0.00

*P-values <0.05 were considered statistically significant.

DISCUSSION

This study presents comprehensive data on the demographic characteristics, malaria severity, liver function markers, and associated risk factors among 150 malaria patients. A detailed discussion of these findings, including comparisons with existing literature and national malaria surveillance data, is provided below.

The study observed a higher prevalence of malaria among males (61%) compared to females (39%). However, national malaria surveillance data from Yemen should be referenced to determine whether this male predominance aligns with broader epidemiological trends. Future studies should incorporate national registry data to provide a more contextualized comparison. A study in Uganda reported a higher incidence of malaria among males,

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potentially due to occupational exposure and behavioral factors (12). However, this study did not collect data on occupation or behavior, making such claims speculative and unsupported by the current dataset. Future studies should explicitly assess these factors to draw definitive conclusions.

Contrasting evidence from Ethiopia indicates a higher incidence of malaria among females, particularly those aged 15–39 years, attributed to increased healthcare-seeking behavior and biological factors (13). These discrepancies highlight the influence of regional, cultural, and occupational factors on malaria prevalence. The age distribution in this study was nearly equal, with 49% of patients under 20 years and 51% over 20 years. Notably, age was not significantly associated with malaria severity (p=0.869). This finding contrasts with a large multicenter study in Asia, which demonstrated a stepwise increase in malaria mortality with age, from 6.1% in children under 10 years to 36.5% in patients over 50 years (14). However, the age classification used in this study (<20 and >20 years) does not align with standard epidemiological age groupings (e.g., <5, 5–14, 15–44, 45+), limiting direct comparability with other studies. Future research should adopt internationally recognized age brackets to facilitate meaningful comparisons.

A majority of patients (77%) resided in urban areas. However, residence status did not significantly influence malaria severity (p=0.438). This finding suggests that urbanization may not necessarily confer protection against severe malaria, possibly due to factors like population density and vector breeding sites in urban settings.

The study reported elevated liver enzyme and bilirubin levels among malaria patients, indicating hepatic dysfunction. Malarial hepatopathy is a condition in which *Plasmodium falciparum* infection leads to liver dysfunction through multiple mechanisms, including parasite sequestration in hepatic sinusoids, oxidative stress, inflammatory cytokine release, and the deposition of malarial pigment (hemozoin).

The hepatic involvement in malaria has been well-documented. Similar findings were reported in a study assessing liver function in malaria patients, which found significant increases in ALT, AST, and bilirubin levels compared to healthy controls (15). However, the study did not screen for pre-existing liver diseases such as hepatitis, which could have also contributed to liver dysfunction. This is a major limitation that should be addressed in future research.

Plasmodium falciparum affects liver cells through multiple pathological mechanisms:

1. Oxidative Stress: The parasite induces excessive production of reactive oxygen species (ROS), leading to oxidative damage in hepatocytes.
2. Cytokine Storm: The immune response triggers elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which contribute to hepatocellular damage.
3. Hemozoin Deposition: Malarial pigment (hemozoin), a byproduct of hemoglobin digestion by Plasmodium parasites, accumulates in liver macrophages (Kupffer cells) and disrupts normal hepatic function. Hemozoin-laden macrophages impair bilirubin clearance, contributing to hyperbilirubinemia and hepatic inflammation.

The study demonstrated that severe malaria cases had significantly higher levels of direct bilirubin, total bilirubin, ALT, and AST compared to mild cases (p=0.00 for all comparisons). This finding is consistent with the concept of malarial hepatopathy, where severe malaria is associated with marked hepatic dysfunction (16). A study on liver changes in severe *Plasmodium falciparum* malaria corroborated these findings, reporting significant elevations in liver enzymes and bilirubin levels (17).

However, attributing liver dysfunction solely to malaria is challenging. Without laboratory confirmation of pre-existing liver disease, some cases of liver dysfunction may be due to underlying hepatic conditions rather than malaria alone. This is a key limitation that should be acknowledged.

Study Limitations

Several limitations should be acknowledged:

1. Exclusion of liver disease patients: While this helped isolate malaria-related hepatic dysfunction, it may have led to selection bias.
2. Reliance on hospital data: The findings may not be generalizable to the broader population, especially asymptomatic malaria cases.

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3. No laboratory confirmation of pre-existing liver disease: The study did not screen for underlying liver conditions such as viral hepatitis, which could have influenced liver enzyme elevations. Therefore, this study cannot definitively attribute liver dysfunction solely to malaria.
4. Short study duration: The study was conducted over a limited timeframe, potentially affecting seasonal variability in malaria incidence and severity.
5. Gender bias: The study design may have inadvertently introduced gender bias due to variations in healthcare-seeking behavior.

CONCLUSION

The findings underscore the importance of early liver function monitoring in malaria patients to prevent severe hepatic complications. Future studies should incorporate a longer study duration, broader population-based sampling, and laboratory screening for co-existing liver diseases to improve result validity. Additionally, further research into the mechanistic pathways of malaria-induced liver dysfunction, including the role of oxidative stress, cytokine storms, and hemozoin deposition, is warranted.

Conflict of Interest

The authors declare that no conflict of interest.

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