

Research Article

TEMPORAL TRENDS, CLINICAL MANIFESTATIONS, AND PATIENT OUTCOMES OF FALCIPARUM MALARIA INFECTION AT WAD-MEDANI TEACHING HOSPITAL IN THE CENTRAL REGION OF SUDAN

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Received 09th January 2026; Accepted 05th February 2026; Published online 27th March 2026

Abstract

Background: Malaria is one of the most common diseases affecting humans worldwide. It remains a major global public health concern and a major cause of morbidity and mortality in tropical and subtropical countries. Plasmodium falciparum malaria is the most dangerous and fatal form of the illness, and it is the most common species prevalent in Sudan throughout the year. Gastrointestinal manifestations are common in malaria-endemic areas. Malaria occasionally presents with both typical and atypical symptoms and signs, and there is an increased burden on health services in hospitals due to the large spectrum of falciparum malaria presentation and outcome, especially in the Gezira area in Sudan. **Objectives:** To assess the trend, manifestations, and outcome of falciparum malaria infection in patients admitted to medical wards. **Methods:** This is a descriptive, prospective, cross-sectional hospital-based study, conducted in Wad Medani Teaching Hospital in the central region of Sudan during the period from December 2014 to May 2015. **Results:** A total of 160 patients were admitted with severe malaria during the period from December 2014 to May 2015. The age of the study population ranged from 15-80 years, with a mean age of 43.11 years, with the most affected patients in the age group 15-45 years. Males were 86 (53.8%) and females 74 (46.3%). The main manifestations and complications of severe falciparum malaria in this study were: hyperparasitemia, which was present in 90 patients (56.3%), followed by hypotension or circulatory collapse, which was observed in 52 patients (32.5%), hyperpyrexia was seen in 35 patients (21.9%), prostration and weakness seen in 33 patients (20.6%), cerebral malaria with loss of consciousness seen in 19 patients (11.9%), acute kidney injury (AKI) was seen in 18 patients (11.3%), hypoglycemia was seen in 18 patients (11.3%), repeated convulsions ≥ 3 frequency occurred in 14 patients (8.8%), severe anemia was seen in 10 patients (6.3%), abnormal bleeding occurred in 10 patients (6.3%), and hyperbilirubinemia also in 10 patients (6.3%). Pulmonary edema was found in 2 cases (1.3%), and disseminated intravascular coagulation (DIC) in 2 cases (1.3%), blackwater fever in one case (0.6%). Other complications like acute respiratory distress syndrome (ARDS) and acidosis were not reported in this study. Patients who received quinine hydrochloride salt via intravenous infusion were 153 (95.6%), and those who received artemether injection were 7 (4.4%). Some patients received supportive management according to their presentation. The main duration of hospital stay was 3-5 days in 87 patients (54.4%). The outcome was as follows: 154 patients (96.3%) improved and were discharged in good condition, and six patients (3.8%) died. **Conclusion:** Falciparum malaria is more common among younger adult age groups and males. The main manifestations and complications of severe falciparum malaria infection were hyperparasitemia, hypotension, hyperpyrexia, prostration and weakness, cerebral malaria, AKI, then hypoglycemia and repeated convulsions, and severe anemia. Most of the patients were treated with quinine with very good response, and the mortality rate was 3.8%.

Keywords: Plasmodium falciparum, Malaria, Clinical presentation, Complications, Outcome.

INTRODUCTION

Malaria is an endemic disease. According to the World Health Organization (WHO), there were an estimated 219 million cases of malaria in 2017 compared to 217 million the year before, with a mortality rate of 435,000 people, mostly children in the African Region. Malaria is caused by several Plasmodium (P) species. Plasmodium falciparum usually causes severe malaria in highly endemic areas [1]. Plasmodium genus are intraerythrocytic protozoa. There are four species of plasmodium: P. falciparum, P. vivax, P. ovale, and P. malariae. These parasites are usually transmitted by the bite of an infective female Anopheles species mosquito, but they can also be transmitted through exposure to infected blood products, congenital transmission, or laboratory exposure. P. falciparum is more prevalent in Sub-Saharan Africa and is the most

pathogenic malaria species, most commonly associated with severe illness and death, mainly in young children. Mixed infections with multiple species may occur in some areas if more than one species is present in circulation. P. knowlesi is mainly simian malaria found in Southeast Asia and may rarely affect humans. WHO defines severe malaria as a case of malaria with one or more of the following manifestations: neurologic symptoms, acute kidney injury, severe anemia (hemoglobin [Hb] $<7\text{g/dL}$), acute respiratory distress syndrome (ARDS), jaundice, or $\geq 5\%$ parasitemia. Cases also were counted as severe if the person received treatment for severe malaria (i.e., artesunate, quinidine, or an exchange blood transfusion) despite having no specific severe manifestations reported. All fatal malaria cases were classified as severe [2]. Sporozoites are inoculated into the bloodstream of an infected person when an anopheline mosquito bites them. The sporozoites enter hepatocytes within an hour, then divide and become exoerythrocytic merozoites (tissue schizogony). For P. vivax and P. ovale, forms called hypnozoites remain

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dormant in the liver and may later cause malaria; but *P. falciparum* does not produce hypnozoites. Later, merozoites leave the liver and invade erythrocytes and develop into early trophozoites, which are ring-shaped. When the trophozoites divide, they are called schizonts. The duration of each cycle in *P. falciparum* is about 48 hours. Destruction of erythrocytes and release of schizonts into the circulation is the main cause of clinical symptoms of malaria. Clinical presentation of malaria may be mild with nonspecific symptoms or could be severe. The majority of patients develop fever (>92% of cases), chills (79%), headaches (70%), and sweating (64%). Other common symptoms include dizziness, malaise, myalgia, abdominal pain, nausea, vomiting, mild diarrhea, and dry cough. Physical signs include fever, tachycardia, jaundice, pallor, orthostatic hypotension, hepatomegaly, and splenomegaly. Clinical examination may be unremarkable, especially in nonimmune persons [3]. Factors that contribute to the severity of malaria include the parasite species; age of the patient; immunity, general health, and nutritional status of the patient; chemoprophylaxis effects; and time of diagnosis and initiation of treatment. If not treated promptly, malaria may cause multiple organ damage resulting in altered consciousness (cerebral malaria), acute kidney injury and liver failure, respiratory distress, coma, and death.

Diagnosis of malaria is mainly by peripheral blood film microscopy (gold standard test), polymerase chain reaction, or rapid diagnostic tests. Thick and thin blood films can quickly detect the presence of malaria parasites, determine the species and percentage of red blood cells that are infected, and this is important for choosing the appropriate treatment. If three sets of thick and thin blood films were taken, spaced 12–24 hours apart and were negative for plasmodium, then malaria may be ruled out [2]. Other laboratory findings in malaria include: thrombocytopenia in 60% of cases, hyperbilirubinemia 40%, anemia 30%, and elevated hepatic aminotransferase levels 25%. The leukocyte count is usually normal or low. Cerebral malaria, pulmonary edema, acute renal failure, severe anemia, and/or bleeding are the major complications of malaria and may develop rapidly, leading to death if not treated appropriately. The most common metabolic complications are acidosis and hypoglycemia. So any patient with malaria should be assessed for symptoms and signs of severity and should be treated immediately [3]. Treatment should be initiated as soon as possible. Patients who have severe vomiting or severe malaria should receive parenteral therapy [4]. Chloroquine is used for treatment of *P. falciparum*, but in areas with chloroquine resistance, like the case in Sudan, there are four treatment options available. The first two options are atovaquone-proguanil (Malarone) or artemether-lumefantrine (Coartem). These are fixed-dose combination medicines that can be used for children and, for atovaquone-proguanil, non-pregnant adults. The third option is quinine sulfate plus doxycycline, tetracycline, or clindamycin. The combination option of quinine sulfate plus either doxycycline or tetracycline is generally preferred to quinine sulfate plus clindamycin because there is a lot of data about its efficacy. Treatment with quinine should continue for 7 days for infections. The fourth option is mefloquine; it has rare but serious side effects, which are severe neuropsychiatric reactions when used at treatment doses, so it should be given only if other options cannot be used [5]. The aim of this study was to assess the trend, manifestations, and outcome of *falciparum* malaria infection in patients admitted to medical wards.

METHODS

Study Setting

This study was conducted in Wad Medani Teaching Hospital, which is located in Gezira State in the central region of Sudan. The hospital serves as a major referral center for the region and provides comprehensive medical services to a large population.

Study Design

This is a descriptive, prospective, cross-sectional hospital-based study.

Study Period

The study was conducted during the period from December 2014 to May 2015.

Study Population

The study population included all patients admitted to the medical wards of Wad Medani Teaching Hospital with a confirmed diagnosis of severe *falciparum* malaria during the study period.

Inclusion Criteria

- Patients aged 15 years and above.
- Confirmed diagnosis of *falciparum* malaria by peripheral blood film microscopy.
- Patients meeting WHO criteria for severe malaria.

Exclusion Criteria

- Patients with other species of malaria (*P. vivax*, *P. ovale*, *P. malariae*).
- Patients who refused to participate in the study.

Data Collection

Data were collected using a structured questionnaire. Information was obtained from patient medical records, including demographic data (age, gender, residence), clinical symptoms and signs, laboratory results, treatment modalities, duration of hospital stay, and patient outcomes.

Laboratory Investigations

All patients underwent the following laboratory investigations:

- Peripheral blood film microscopy (thick and thin films) for malaria parasites.
- Complete blood count (CBC).
- Liver function tests (LFTs).
- Renal function tests (RFTs).
- Blood glucose level.
- Coagulation profile (PT, INR, APTT).
- Urinalysis.

Data Analysis

Data were entered and analyzed using the Statistical Package for Social Sciences (SPSS), version 20. Descriptive statistics,

including frequencies, percentages, means, and standard deviations, were used to summarize the data.

Ethical Considerations

Ethical approval was obtained from the University of Gezira's Ethical Committee. Informed consent was obtained from all participants. Confidentiality was maintained throughout the study.

RESULTS

A total of 160 patients were admitted with severe malaria during the period from December 2014 to May 2015. The age of the study population ranged from 15-80 years, with a mean age of 43.11 years. The most affected patients were in the age group 15-45 years. Males were 86 (53.8%) and females 74 (46.3%).

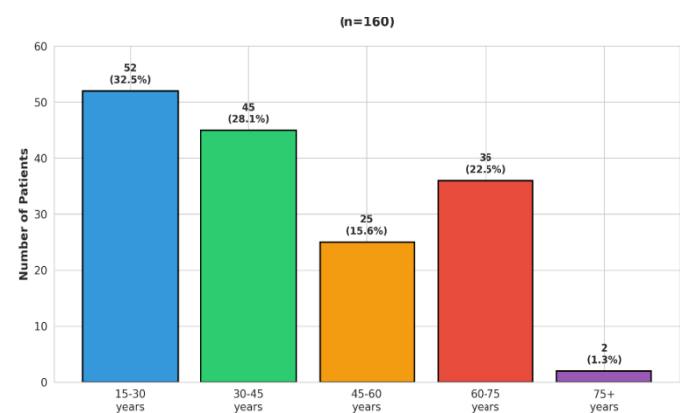


Figure 1. Age Distribution of Malaria Patients

Caption: Age distribution of 160 patients admitted with severe falciparum malaria to Wad-Medani Teaching Hospital, December 2014 to May 2015. The most affected age group was 15-45 years (52%), followed by 45-60 years (25%), 60-75 years (20%), and over 75 years (3%).

The main clinical manifestations and complications of severe falciparum malaria in this study are presented in Table 2.

Table 1. Clinical Manifestations and Complications of Severe Falciparum Malaria

Manifestation/Complication	Frequency	Percent
Hyperparasitemia	90	56.3
Hypotension/circulatory collapse	52	32.5
Hyperpyrexia	35	21.9
Prostration and weakness	33	20.6
Cerebral malaria	19	11.9
Acute kidney injury (AKI)	18	11.3
Hypoglycemia	18	11.3
Repeated convulsions (≥3)	14	8.8
Severe anemia	10	6.3
Abnormal bleeding	10	6.3
Hyperbilirubinemia	10	6.3
Pulmonary edema	2	1.3
DIC	2	1.3
Blackwater fever	1	0.6

Caption: Clinical manifestations and complications observed in 160 patients with severe falciparum malaria. Hyperparasitemia was the most common finding (56.3%), followed by hypotension/circulatory collapse (32.5%), hyperpyrexia (21.9%), and prostration/weakness (20.6%).

Cerebral malaria occurred in 11.9% of patients, and acute kidney injury in 11.3%.

Table 2. Laboratory Results Meeting WHO Criteria for Severe Malaria

Laboratory Parameter	Frequency	Percent
Positive blood film	156	97.5
Negative blood film	4	2.5
Hb ≤5 g/dl	10	6.3
HCT ≤15	10	6.3
Platelets <100	33	20.6
Serum bilirubin >2.5	10	6.3
Blood urea >80 mg/dl	25	15.6
Serum creatinine >3	18	11.3
Blood sugar <40 mg	17	10.6
Abnormal PT/INR	10	6.3
Abnormal APTT	5	3.0
Hemoglobinuria	2	1.3

Caption: Laboratory findings meeting WHO criteria for severe malaria among 160 patients. Positive blood film was found in 97.5% of patients. Key abnormalities included thrombocytopenia (20.6%), elevated blood urea (15.6%), elevated serum creatinine (11.3%), and hypoglycemia (10.6%).

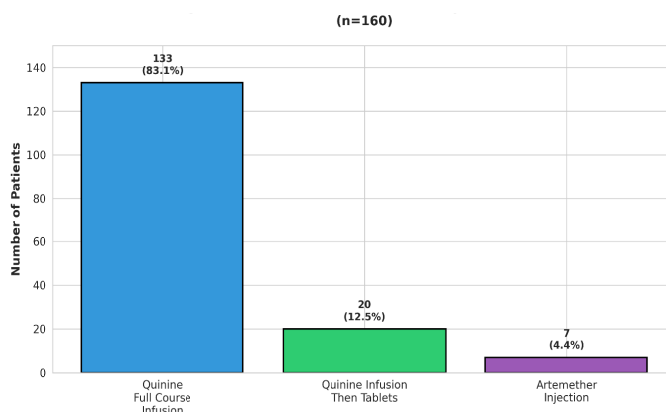


Figure 2. Treatment Modalities for Falciparum Malaria

Caption: Treatment modalities used for severe falciparum malaria patients. The vast majority (95.6%) received quinine hydrochloride via intravenous infusion, while 4.4% received artemether injection. Some patients also received supportive management according to their clinical presentation.

The main duration of hospital stay was 3-5 days in 87 patients (54.4%).

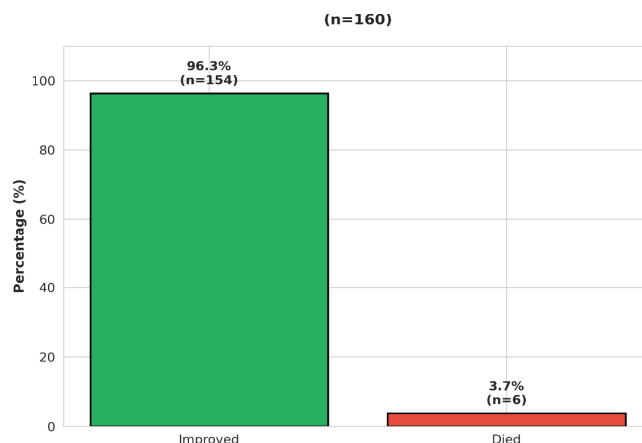


Figure 3. Patient Outcomes

Caption: Outcomes of 160 patients admitted with severe falciparum malaria. The majority (96.3%) improved and were discharged in good condition, while 6 patients (3.8%) died, resulting in a mortality rate of 3.8%.

The outcome was as follows: 154 patients (96.3%) improved and were discharged in good condition, and six patients (3.8%) died.

DISCUSSION

This prospective study conducted in Wad-Medani teaching hospital in Sudan included 160 patients who were admitted to medical wards with severe malaria during the study period. The age of the study population ranged between 15-80 years, with a mean age of 43.11 years, with the most affected patients in the age group 15-45 years, around 32.5% of patients. In comparison to the study which was done in a tertiary care hospital of India in 2016 by Saya RP et al, where they found that 63% of cases were in the age group of 15-30 years and the mean age was found to be 29.51 years [6]. In this study, 53.8% of patients were males and 46.3% were females. The high number of affected age group of 15-45 years and males affected more than females can be explained by the fact that these young adults and males stay outdoors until late evenings without protective measures against mosquitoes. Besides that, during nighttime, the mosquito-feeding activity is high, so they will be prone to mosquito bites. It was found that the main clinical presentation and complications of severe falciparum malaria were: hyperparasitemia, which was present in 56.3% of patients, followed by hypotension or circulatory collapse in 32.5% of patients, hyperpyrexia was seen in 21.9% of patients, and prostration and weakness seen in 30.6% of patients. In comparison to the above study conducted by Saya et al in India, the clinical presentations included nausea and vomiting (35, 35%), jaundice (34, 34%), oliguria (24, 24%), altered sensorium (24, 24%), breathing difficulty (10, 10%), and seizures (5, 5%) [6], while in this study, repeated convulsions ≥ 3 times occurred in 8.8% of patients.

In a study carried out by Wasnik P et al about the clinical profile of falciparum malaria in a tertiary referral center in Central India in 2012, they found that fever was the most common symptom followed by impaired consciousness. Other clinical manifestations of *P. falciparum* malaria in the same study included anemia in 52 (65%) patients, and out of these, 5 (6.25%) patients had severe anemia, and thrombocytopenia was found in 57.5% of patients. Abnormal kidney function tests were observed in 32.5% of patients [7]. In this study, complications of severe *P. falciparum* malaria were seen in 65% of patients as per WHO definition of severe falciparum malaria, compared to 46.25% of patients who were found to have severe *P. falciparum* malaria in the above study done by Wasnik et al in India [7]. In this study, the complications of severe falciparum malaria included cerebral malaria with loss of consciousness seen in 11.9% of patients. This finding was nearly similar to the findings of a study conducted in India by Ahmad et al in 2016, where they found that cerebral malaria due to *P. falciparum* occurred in 7.4% of patients [8]. Another complication of severe *P. falciparum* in this study was acute kidney injury (AKI), which was seen in 11.3% of patients. Severe malaria is mainly due to *Plasmodium falciparum* in highly endemic areas. Cerebral malaria and acute renal failure are criteria of malaria severity as defined by WHO and are mainly due to *P. falciparum* infection. Cerebral malaria and

AKI are serious complications of severe malaria. The exact direct causes of cerebral and kidney dysfunction are incompletely understood, but common pathophysiological pathways include impaired microcirculation due to sequestration of parasitized erythrocytes, systemic inflammatory responses, and endothelial activation. Early diagnosis of malaria and prompt early treatment with parenteral antimalarial therapy will decrease the mortality of these life-threatening conditions [9].

Tubular necrosis due to renal vascular obstruction by parasitized erythrocytes is the primary mechanism of renal failure, but other conditions associated with severe malaria, like hemolytic uremic syndrome and hemoglobinuric nephropathy, could be possible causes of renal failure in malaria. The outcome depends on early diagnosis and proper management. Acute kidney injury is a common complication of severe malaria and is associated with high mortality [10]. In this study, hypoglycemia was found in 11.3% of patients, which is a common metabolic complication of severe malaria and is associated with poor prognosis. Blackwater fever was found in one patient (0.6%). Blackwater fever is a rare but serious complication of malaria characterized by massive intravascular hemolysis and hemoglobinuria. It is usually associated with *P. falciparum* infection and can be triggered by quinine treatment [11]. Pulmonary edema was found in 2 cases (1.3%). Pulmonary complications, including pulmonary edema and acute respiratory distress syndrome (ARDS), are serious complications of severe malaria and are associated with high mortality [12].

In this study, most patients (95.6%) were treated with quinine hydrochloride salt via intravenous infusion, while 4.4% received artemether injection. The WHO recommends artesunate as the first-line treatment for severe malaria, but quinine remains an acceptable alternative, especially in settings where artesunate is not available [13]. The mortality rate in this study was 3.8%, which is comparable to other studies. A study conducted in India by Sarkar et al in 2012 reported a case fatality rate of 3.6% [14]. Another study conducted in Ghana and Uganda by Ampadu et al in 2019 reported a case fatality rate of 4.2% [15].

Conclusion

Falciparum malaria is more common among younger adult age groups and males. The main manifestations and complications of severe falciparum malaria infection were hyperparasitemia, hypotension, hyperpyrexia, prostration and weakness, cerebral malaria, AKI, then hypoglycemia and repeated convulsions, and severe anemia. Most of the patients were treated with quinine with very good response, and the mortality rate was 3.8%.

Recommendations

- Early diagnosis and prompt treatment of malaria are essential to prevent complications and reduce mortality.
- Health education campaigns should be conducted to raise awareness about malaria prevention measures, including the use of insecticide-treated bed nets and mosquito repellents.
- Healthcare facilities should ensure the availability of essential antimalarial drugs, including artesunate and quinine.

- Further research is needed to identify risk factors for severe malaria and to develop effective prevention strategies.

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