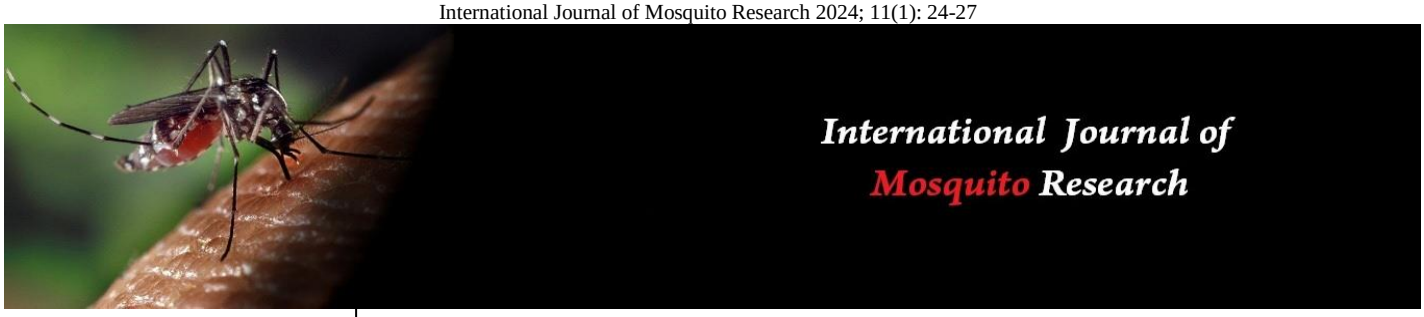

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Hospital based evaluation of the cardiovascular involvement in severe malarias

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Abstract
Aim: The aim of the present study was to evaluate the involvement of cardiovascular system in severe malaria.
Methods: This prospective study was conducted on patients of severe malaria who were admitted in the hospital. Informed consent was taken from patient or patient's relatives. In total, 200 cases of severe malaria (*P. falciparum* 120; *P. Vivax* 60; and mixed 20) diagnosed by peripheral blood smear examination, rapid card test and PCR were studied. Evaluation of cardiovascular system was done by clinical examination, chest X- ray and ECG.
Results: The severe manifestations of malaria included severe anaemia (Hb <5 g%) in 26% of patients, hepatitis in 25% of patients, respiratory distress in 20% of patients, cerebral malaria in 24% of patients, hypoglycemia in 2% of patients, acute renal failure in 10% of patients, abnormal bleeding in 16% of patients, circulatory failure in 10% of patients, pulmonary edema in 2% of patients, and hemoglobinuria in 4% of patients. Among the 200 instances of severe malaria, 35 individuals had cardiovascular symptoms, 20 experienced circulatory failure, 15 had congestive heart failure, and 5 had pulmonary edema. Cardiovascular involvement was more prevalent in cases of *P. falciparum* malaria compared to *P. Vivax* or mixed malaria. While some echocardiographic measures were within the normal range, there was a notable difference between individuals with and without cardiovascular involvement.
Conclusion: Our work determines that severe malaria exhibits cardiovascular system engagement, as seen by alterations in ECG and cardiac markers, suggesting myocardial participation. This association is linked to heightened morbidity and fatality rates.

Keywords: Cardiac markers, circulatory failure, congestive cardiac failure, falciparum malaria, pulmonary edema, vivax malaria

Introduction
Malaria is a disease characterized by a distinct and intricate pathogenesis. Both parasitized and non-parasitized red blood cells (RBC) have reduced flexibility and stick to the endothelium [1]. The result is a gradual blockage of the microcirculation. At the same time, there is a noticeable widespread inflammation in the body, accompanied by impaired functioning of the blood vessels and a rise in their permeability [2]. The parasite biomass in falciparum malaria undergoes a 6- to 20-fold increase throughout each replication cycle. The rapid and continuous increase in the amount of parasite tissue every 48 hours is a significant factor contributing to the range of severe and potentially fatal complications that can occur suddenly and unexpectedly within a few hours of infection. This makes *Plasmodium falciparum* the most hazardous among the five species that can infect humans. From a prognostic standpoint, the two most significant factors indicating severe malaria are metabolic acidosis and cerebral malaria [3]. Presently, about 90 nations and territories are susceptible to malaria transmission. In non-endemic nations, malaria often constitutes the foremost imported tropical ailment. Malaria is endemic in various groups. The frequency of international travel to nations with prevalent malaria is consistently rising. These travelers include not just immigrants from countries where a disease is common who are visiting friends and family, but also a growing number of elderly tourists with several chronic illnesses [4]. There are four species of malaria parasites that infect humans: *P. falciparum*, *P. malariae*, *P. ovale*, and *P. Vivax*.[5,6] *Plasmodium falciparum* is the very pathogenic species. Malaria mostly affects children below the age of 5 years and pregnant women, particularly in underdeveloped nations.

Pregnant women are at a heightened risk due to their compromised immune system during pregnancy, posing a threat to both the mother and the fetus [7]. An analogous issue arises with children under the age of five, as their immune systems are not yet fully matured. Upon reviewing the literature, it was found that malaria can be further complicated by cardiac involvement. Similar to cerebral malaria, cardiac involvement is primarily restricted to acute infections caused by *P. falciparum* [8].

The objective of this study was to assess the impact of severe malaria on the cardiovascular system.

Materials and Methods

This prospective study was conducted on patients of severe malaria who were admitted in the hospital. Informed consent was taken from patient or patient's relatives. In total, 200 cases of severe malaria (*P. falciparum* 120; *P. Vivax* 60; and mixed 20) diagnosed by peripheral blood smear examination, rapid card test and PCR were studied. Evaluation of cardiovascular system was done by clinical examination, chest X- ray & ECG.

Inclusion criteria

Only those cases of severe malaria having the asexual forms of Plasmodium in the blood by smear examination were included in the study. The diagnosis of severe malaria was done as per WHO 2006 guidelines [9].

Exclusion criteria

Patients who refused to give the written consent or had other concurrent illness or pre-existing diseases like cardiac diseases, hypertension, diabetes mellitus, COPD, hepatitis B and C, typhoid fever, HIV, tuberculosis, etc. was not included in the study.

Diagnostic methods used to detect malaria parasite

The diagnosis of malaria was confirmed using the gold standard method of examining thick and thin smears of peripheral blood under a microscope to detect the presence of the asexual form of the Plasmodium parasite. The RDTs utilized the identification of particular Plasmodium spp. through the detection of lactate dehydrogenase (OptiMal test; Diamed AG, Cressier sur Morat, Switzerland) and histidine rich protein 2 (Falcivax test; Zephyr Biomedical Systems, Goa, India). The presence of *Plasmodium* spp. was also verified using PCR analysis. The PCR analyses were directed towards the 18S ribosomal RNA gene of the parasite and employed one genus-specific 5′ primer and two species-specific 3′ primers in the identical reaction mixture. Each patient was assessed according to the proforma (CRF). The assessment for cardiovascular involvement included: (a) A comprehensive clinical examination of the cardiovascular system; (b) A chest X-ray to detect any signs of an enlarged heart or lung congestion; and (c) A standard 12-lead ECG. The following 14 points were meticulously examined in every electrocardiogram (ECG): (1) standardization (calibration) and technical features (including lead placement and artifacts); (2) rhythm; (3) heart rate; (4) PR interval/AV conduction; (5) QRS interval; (6) QT/QTc interval; (7) mean QRS electrical axis; (8) P-waves; (9) QRS voltages; (10) precordial R-wave progression; (11) abnormal Q waves; (12) ST segments; (13) T-waves; and (14) U-waves. Serial electrocardiograms were recorded for all patients until they were discharged. Cardiac markers, including Troponin-I and CPK-MB, were assessed in all patients with severe malaria. Patients who originally exhibited elevated blood levels of these indicators were reassessed following a 21-day follow-up period.

High-resolution transthoracic echocardiograms: An extensive echocardiographic examination was conducted using the conventional approach, using transducers with frequencies of 2.5 and 5.0 MHz. Cardiac ultrasound was performed on a total of 200 individuals. The examination was conducted with the simultaneous recording of a reference electrocardiogram (ECG) lead. Left parasternal, short axis, apical four-chamber, and subcostal images were acquired to provide optimal visibility of all four cardiac chambers, major blood arteries, and the pericardium. The measurements and computations were conducted using M-mode tracings from three cardiac cycles, following the guidelines of the American Society of Echocardiography. The following parameters were measured: left ventricular internal dimension-end systolic (LVESD) and end diastolic (LVEDD), interventricular septal thickness (end diastolic, DIVST), left ventricular posterior wall thickness (end diastolic, DLVPWT), left ventricular ejection fraction (EF%), peak velocity of early filling phase (Ei), peak velocity of atrial filling phase (Ai), and Ei/Ai ratio.

Additional laboratory tests were conducted, including a complete blood count (CBC) which assessed the total leukocyte count (TLC), differential leukocyte count (DLC), hemoglobin (Hb), packed cell volume (PCV), and platelet counts. Blood glucose level, blood urea and serum creatinine, serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, serum protein, albumin and globulin levels were also measured. Furthermore, urine examination was performed for all cases. Dengue serology was performed to exclude the possibility of dengue fever. In all instances where there was question, lumbar puncture and cerebrospinal fluid (CSF) analysis were performed to exclude the presence of other conditions such as meningitis and encephalitis. Additional diagnostic procedures were performed to exclude any other systemic or heart conditions.

Statistical analysis

The statistical analysis was conducted using MS Excel and SPSS version 22. The data was analyzed by conducting a Chi-square ($\chi 2$) test to assess the statistical significance of different factors. A p-value of less than 0.05 was considered to indicate significance. The calculation of parasite density was performed using the geometric mean method for data analysis.

Results

Table 1: Manifestations of severe malaria

Severe manifestations	N	%
Severe anaemia	52	26
Hepatitis	50	25
Respiratory distress	40	20
Cerebral dysfunction	48	24
Hypoglycemia	4	2
Acute renal failure	20	10
Bleeding disorder	32	16
Circulatory failure	20	10
Pulmonary edema	4	2
Hemoglobinuria	8	4
Multi-organ failure	22	11

Manifestations of severe malaria were severe anaemia (Hb <5

g%) in 26% patients, followed by hepatitis in 25%, respiratory distress in 20%, cerebral malaria in 24%, hypoglycemia in 2%, acute renal failure in 10%, abnormal bleeding in 16%, circulatory failure in 10%, pulmonary edema in 2% and hemoglobinuria in 4% patients.

Table 2: Distribution of cardiovascular manifestations in severe malaria

Malaria type	Total cases of cardiovascular manifestations (n=35)	Circulatory failure (n=20)	Congestive heart failure (n=15)	Pulmonary edema (n=5)
Severe *P. falciparum*	18	12	6	2
Severe *P. Vivax*	10	4	6	-
Severe mixed	6	6	2	2

Out of these 200 cases of severe malaria, 35 were found to be suffering from cardiovascular manifestations 20 from circulatory failure, 15 from congestive heart failure and 5 from pulmonary edema. Cardiovascular involvement was more commonly found in *P. falciparum* malaria as compared to *P. Vivax* or mixed malaria.

Table 3: Echocardiographic parameters in severe malaria

Echocardiographic parameter	With cardiac involvement n=35	Without cardiac involvement n=165	P Value
LVEDD (cm)	4.06±0.4	3.77±0.44	0.0001
LVESD (cm)	2.56±0.42	2.44±0.36	0.0001
DIVST (cm)	0.54±0.16	0.55±0.12	0.7
DLVPWT (cm)	0.48±0.07	0.48±0.08	0.01
EF (%)	58.32±1.04	59.14±1.16	0.01

M-mode echocardiography showed mean left ventricular end diastolic diameter (LVEDD) of 4.06±0.4 cm (ranging from 3–4.4 cm), left ventricular end systolic diameter (LVESD) of 2.56±0.44 cm (ranging from 2–3 cm), mean interventricular septal thickness (end diastolic) was 0.54±0.14 cm (ranging from 0.3–0.7 cm) and left ventricular post-wall thickness (end diastolic) of 0.48±0.08 cm (ranging from 0.3–0.6 cm). Left ventricular ejection fraction was 58±1.04% and ranged from 55–65%. No patient had any evidence of pericardial effusion and regional or global hypokinesia. Although various echocardiographic parameters were within the limit of normal range but there was a significant difference between patients with or with- out cardiovascular involvement.

Discussions

The severe form of falciparum malaria is characterized by cardiovascular symptoms such as low blood pressure, sudden accumulation of fluid in the lungs (acute pulmonary edema), inflammation of the heart muscle (toxic myocarditis), and irregularities in the electrical conduction of the heart [10, 11]. Cardiovascular difficulties in malaria may be caused by several factors, including severe falciparum parasitemia, sequestration, secondary infections, severe anaemia, hypoxia, hyperpyrexia, dehydration/fluid overload, metabolic acidosis, and disseminated intravascular coagulation [12].

Manifestations of severe malaria were severe anaemia (Hb <5 g%) in 26% patients, followed by hepatitis in 25%, respiratory distress in 20%, cerebral malaria in 24%, hypoglycemia in 2%, acute renal failure in 10%, abnormal bleeding in 16%, circulatory failure in 10%, pulmonary edema in 2% and hemoglobinuria in 4% patients. An increase in the cardiac index can occur when there is reduced peripheral vascular resistance and when ventricular filling pressures are low to normal. The reduced pressures may also be attributed to hypovolemia, which can result from decreased fluid intake, high-grade fever, excessive sweating, vomiting, and diarrhea. Orthostatic hypotension is prevalent. Septicemia, metabolic acidosis, and hypoxia can lead to a decrease in cardiac index [13]. The underlying mechanisms responsible for myocardial injury in falciparum malaria are not well understood. Myocardial damage may be caused by ischemia, acidosis, toxic effects of substances such as falciparum glycosyl-phosphatidyl-inositol, or Plasmodium-triggered mechanisms like apoptosis [12-14].

Among these 200 instances of severe malaria, 35 individuals were diagnosed with cardiovascular manifestations. 20 individuals died as a result of circulatory failure, 15 individuals died due to congestive heart failure, and 5 individuals died from pulmonary edema. Cardiovascular involvement was more typically seen in *P. falciparum* malaria as compared to *P. Vivax* or mixed malaria. The current investigation indicated congestive heart failure in seven individuals, all of them having Hb ≤5 g% and cardiomegaly. Although cardiac enlargement is generally found in chronic anemia, however, if it is present in acute anaemia it is a consequence of existence of other cardiovascular illness, may be acute malarial myocarditis in our patients [15]. M-mode echocardiography showed mean left ventricular end diastolic diameter (LVEDD) of 4.06±0.4 cm (ranging from 3–4.4 cm), left ventricular end systolic diameter (LVESD) of 2.56±0.44 cm (ranging from 2–3 cm), mean interventricular septal thickness (end diastolic) was 0.54±0.14 cm (ranging from 0.3–0.7 cm) and left ventricular post-wall thickness (end diastolic) of 0.48±0.08 cm (ranging from 0.3–0.6 cm). Left ventricular ejection fraction was 58±1.04% and ranged from 55–65%. No patient had any indication of pericardial effusion with regional or global hypokinesia. Although different echocardiographic values were within the limit of normal range yet there was a significant difference between individuals with or with-out cardiovascular involvement.

ECG alterations reported in our research may suggest early myocardial involvement because electrophysiology of cardiac myocytes modifies before changes could be noticed on echocardiography. Although it may also be explained by the existence of severe anaemia, these variations can also be attributable to a range of other causes such hyperventilation, anxiety, body posture, diet, neurogenic effects, temperature, electrolyte imbalance, allergic responses. Similarly, prior

research has indicated a range of abnormalities on ECG but they hold questionable link with clinical and functional condition of heart [16]. Mohapatra *et al.* [17] revealed involvement of the myocardium in cerebral malaria, it may induce myocardial damage, reversible global hypokinesia comparable to cardiac stunning and widespread myocardial necrosis as shown by increased Troponin-T, echo, and autopsy.

Conclusion

Our research findings indicate that severe malaria affects the cardiovascular system, as shown by alterations in electrocardiogram (ECG) readings and cardiac markers, which suggest myocardial involvement. This cardiovascular impact is linked to higher rates of illness and death. Our research also shown that severe *vivax* malaria, which includes cardiovascular complications, is linked to a comparatively lower level of parasite density when compared to falciparum and mixed infections. We were the first to report this, and our findings indicate that *vivax* malaria is no longer considered benign. Therefore, a re-evaluation of the pathophysiology of vivax malaria is necessary.

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