Original Article

# Analysis of the Clinical Profile in Patients with *Plasmodium falciparum* Malaria and Its Association with Parasite Density

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## Abstract

**Background:** Malaria remains a major health hazard in the modern world, particularly in developing countries. In *Plasmodium falciparum* malaria, there is a direct correlation between asexual erythrocytic stage parasite density and disease severity. Accordingly, the correlations between parasite density and various clinical presentations, severity, and outcome were examined in falciparum malaria in India. **Materials and Methods:** The study was conducted in a tertiary health-care center in North India. Of 100 cases of falciparum malaria, 65 patients were male and 35 were female. A total of 54 patients were in the uncomplicated group and 46 patients were in the complicated malaria group. **Results:** Fever, anemia, icterus, splenomegaly, hepatomegaly, and hepatosplenomegaly were common clinical findings. All clinical findings were significantly more common in the complicated malaria group and patients with a high parasite density than in the uncomplicated group and those with a low parasite density. All patients in the uncomplicated malaria group had a parasite density of <5% while most patients in the complicated malaria group had a parasite density of >5%, and the difference between groups was statistically significant. The incidence of cerebral malaria was significantly higher in cases with a high parasite density; 58.33% mortality was observed in these cases. Cerebral malaria and hyperbilirubinemia was the most frequently encountered combination of complications. **Conclusions:** In *P. falciparum* malaria, parasite density was associated with complications and poor clinical outcomes. These results may inform treatment decisions and suggest that a threshold parasite density of 5% is informative.

**Keywords:** Malaria, parasite density, *Plasmodium falciparum*

## Introduction

Malaria remains, as it has been for centuries, one of the most serious parasitic diseases worldwide, affecting 300–500 million people and causing over 1 million deaths annually.[1] *Plasmodium falciparum* accounts for nearly 50% of reported malaria cases. The major endemic areas in India are in the Northeastern states. *P. falciparum* infection can lead to cerebral malaria, acute renal failure, acute malarial hepatitis, hypoglycemia, hyperpyrexia, noncardiogenic pulmonary edema, adult respiratory distress syndrome, adrenal insufficiency-like syndrome, hyperparasitemia, blackwater fever, cardiac arrhythmias, and gastrointestinal syndromes.[2-4] Typically, a higher parasite count is associated with a more severe infection[5] and increased mortality. Accordingly, correlations between *P. falciparum* density and various clinical presentations, complications, and outcome were examined in malaria patients.

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## Materials and Methods

This open prospective study was conducted in the Department of Medicine in a tertiary healthcare center in North India. The study included 100 consecutive patients with *P. falciparum* malaria who were admitted to the department between June 2009 and May 2010. Adult patients of >18 years old, either male or female, presenting with fever, headache, body ache, and confirmed *P. falciparum* based on the detected of the asexual form of *P. falciparum* in a blood smear were included in the study. Those with a negative peripheral smear for

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*P. falciparum*, mixed plasmodium infection, or evidence of any coexisting morbid disorder that could affect the outcome, for example, diabetes mellitus, chronic renal disease, chronic liver disease, rheumatic heart disease, and coronary artery disease were excluded from the study.

Written consent was obtained from all patients. A detailed history was obtained, and a clinical examination was performed for all patients. Various parameters were investigated in all patients, including a complete blood count, peripheral blood smear (thin and thick), blood sugar, serum bilirubin, aspartate aminotransferase, alanine aminotransferase, urea, creatinine, serum proteins, serum electrolytes, chest X-ray, and arterial blood gas, if needed. The parasite density was estimated by an experienced pathologist. All slides obtained for all patients were examined by the same pathologist to prevent observation error.

Microscope examination of blood films is the current gold standard for the diagnosis of malaria. Blood obtained by pricking a finger or earlobe is ideal because the density of developed trophozoites or schizonts is greater in blood from these capillary-rich areas. Both thick and thin smears were prepared separately for each patient. The blood films were air dried, and thin blood films were fixed with methanol. Blood films were stained with Field's/Giemsa stain. The initial thick smear was declared negative only if no malarial parasites were seen after the examination of a 100 × 1.25 oil immersion high-power field. After the detection of malarial parasites, thin smears were used to identify the parasite species. Parasite density was then estimated from the thin blood smears. All patients were followed in the hospital until recovery or death.

Parasite density was estimated as follows:

Parasite density = Number of parasitized RBCs × *X*/200 WBCs

Where *X* = Total WBC count/200; WBC: White blood cell; RBC: Red blood cell.

Parasite density was calculated as the % parasitemia. All patients were categorized into three groups based on parasite density as follows:

1. Group A: Parasite density <5%
2. Group B: Parasite density 5%–10%
3. Group CL Parasite density >10%.

The parasite density was estimated daily for 3 days. Mean parasite density was calculated and used to estimate correlations with clinical manifestations, complications, and outcome in *P. falciparum* malaria patients.

### Statistical analysis

Data were analyzed using SPSS version 16 (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.). Quantitative variables are described as mean ± standard deviation. Analyses of variance (Fisher's test) were performed to compare mean values among the groups of patients. The categorical data are presented as percentages and differences among groups were evaluated using Chi-square test of proportions. Differences in mean values between groups for two variable strata were evaluated using *t*-tests. A $P < 0.05$ was considered significant for all statistical analyses.

## Observations

A total of 100 patients with *P. falciparum* malaria who fulfilled the inclusion criteria were enrolled in the study. There were 65 males and 35 females. Blood films were observed for parasite species [Figures 1 and 2]. All cases of uncomplicated malaria had a parasite density of <5%. Most cases of complicated malaria had a parasite density of 5%–10%. The difference between groups was statistically significant [Table 1 and Chart 1].

Fever was the most common symptom and was present in all patients at the time of admission, irrespective of parasite density. Nausea and vomiting (66%), headache (62%), jaundice (22%), impaired consciousness (17%), oliguria or anuria (13%), and bleeding (4%) were also observed. Convulsions were not present in any case.

The impact of increasing parasite density on clinical disease parameters in the three groups is summarized in Table 2 and Chart 2. Impaired consciousness and oliguria or anuria were more common in patients with a parasite density of >10% than in patients with lower parasite densities, and this difference was statistically significant. Hepatosplenomegaly and hypotension were significantly more common in patients with a parasite density of >10% than in the other groups [Table 3].

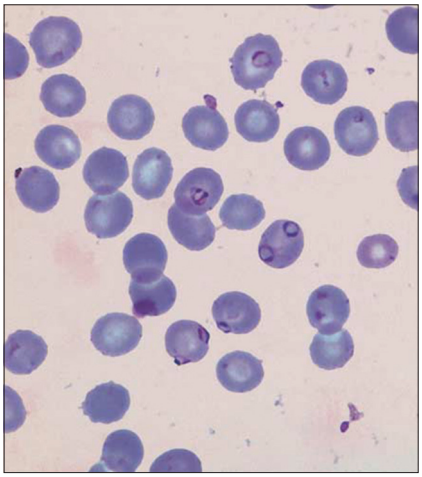

**Figure 1:** Ring form of *Plasmodium falciparum* (100×, Leishman stain)

**Table 1: Severity of Falciparum Malaria with Respect to Parasite Density**

| Parasite density (%) | Uncomplicated (*n*=54), *n* (%) | Complicated (*n*=46), *n* (%) | *P* |
|---|---|---|---|
| <5 | 54 (100) | 14 (30.43) | 0.001 |
| 5-10 | 0 | 18 (39.13) | 0.001 |
| >10 | 0 | 14 (30.43) | 0.001 |

**Table 2: Association between Parasite Density and Clinical Characteristics of 100 Studied Patients**

| Clinical features | Group A <5% (*n*=68), *n* (%) | Group B 5%-10% (*n*=18), *n* (%) | Group C >10% (*n*=14), *n* (%) | *P* |
|---|---|---|---|---|
| Fever | 68 (100) | 18 (100) | 14 (14) | - |
| Nausea and vomiting | 41 (60.29) | 13 (72.22) | 12 (85.71) | 0.15 |
| Headache | 41 (60.29) | 11 (61.11) | 10 (71.42) | 0.73 |
| Jaundice | 11 (16.17) | 5 (27.27) | 6 (42.85) | 0.70 |
| Cough | 11 (16.17) | 2 (11.11) | 3 (21.42) | 0.73 |
| Pain in the abdomen | 16 (23.52) | 1 (11.11) | 3 (21.42) | 0.51 |
| Impaired consciousness | 2 (2.94) | 7 (38.88) | 8 (57.14) | 0.001 |
| Oliguria/anuria | 2 (2.94) | 4 (22.22) | 7 (50) | 0.001 |
| Convulsions | 0 | 0 | 0 | - |
| Hepatosplenomegaly | 9 (13.23) | 9 (50) | 8 (57.14) | 0.001 |
| Bleeding | 1 (14.70) | 1 (5.55) | 2 (14.28) | 0.58 |

**Table 3: Comparisons between Parasite Density and Laboratory Parameters of 100 Studied Patients**

| Laboratory parameters | Parasite density | | | *P* |
|---|---|---|---|---|
| | Group A <5% (*n*=68) | Group B 5-10% (*n*=18) | Group C >10% (*n*=14) | |
| Age | 33.45±16.39 | 32.38±11.98 | 42.28±19.05 | 0.1 |
| Duration of illness (days) | 8.11±6.85 | 7.61±4.04 | 7.5±2.3 | 0.9 |
| Hemoglobin (g/dL) | 9.97±2.06 | 7.84±2.48 | 7.33±2.29 | 0.001 |
| WBC count | 8852.20±6513.44 | 7594.44±5020.01 | 12864.28±7064.71 | 0.05 |
| Platelet count (lacs) | 1.15±0.64 | 0.88±0.63 | 0.83±0.52 | 0.09 |
| Total bilirubin (mg/dL) | 1.37±0.876 | 4.14±5.96 | 4.40±3.52 | 0.001 |
| Serum SGOT (U/L) | 49.74±23.96 | 78.91±43.70 | 270.28±530.84 | 0.001 |
| Serum SGPT (U/L) | 45.59±27.05 | 57.28±42.51 | 394.71±827.53 | 0.001 |
| Total proteins (mg/dL) | 6.71±0.84 | 6.58±0.62 | 5.25±0.75 | 0.001 |
| Serum albumin (g/dL) | 3.09±0.73 | 2.95±0.47 | 2.75±0.59 | 0.20 |
| Blood urea (mg/dL) | 38.15±19.97 | 86.47±78.58 | 90.56±67.04 | 0.001 |
| Serum creatinine (mg/dL) | 1.01±0.63 | 1.41±0.93 | 2.34±1.92 | 0.001 |
| Serum Na+ (mEq/L) | 139.42±4.23 | 137.75±4.43 | 135.14±7.75 | 0.01 |
| Serum K+ (mEq/L) | 4.55±3.49 | 4.08±0.66 | 3.97±0.83 | 0.70 |
| Parasite density (%) | 2.16±1.35 | 7.44±1.43 | 14.55±3.09 | 0.001 |
| RBS (mg/dL) | 101.37±38.28 | 114.94±64.03 | 83.35±29.31 | 0.12 |

WBC: White blood cell, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic-pyruvic transaminase, RBS: Random blood sugar

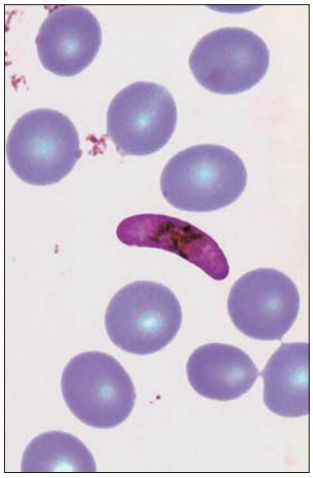

**Figure 2:** Gametocyte of *Plasmodium falciparum* (100×, Leishman stain)

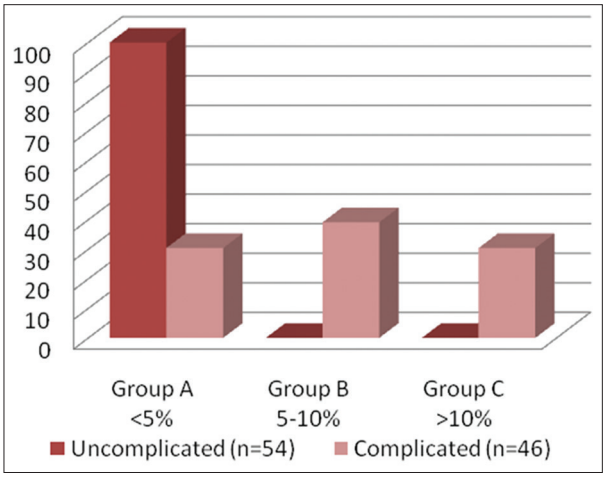


**Chart 1:** Severity of falciparum malaria with respect to parasite density

The hemoglobin (Hb), platelets, serum total protein, serum albumin, and random blood sugar levels decreased as parasite density increased from <5% to >10%. Total leukocyte count, blood urea, serum creatinine, serum aspartate aminotransferase,

and serum alanine aminotransferase increased as parasite density increased from <5% to >10% [Table 3].

Patients with *P. falciparum* malaria developed complications at a parasite count of >5%, and the severity of complications increased when the parasite count was >10%. The difference between groups was statistically significant [Table 4 and Chart 3].

Mortality was most commonly associated with cerebral malaria (58.33%), followed by hypotension (57.14%) [Table 5 and Chart 4]. All patients who died had a parasite density of >10%. The majority of patients who died had cerebral malaria and hyperbilirubinemia as complications.

## Discussion

Infection with *P. falciparum* is more serious than infections with other malarial species owing to the high frequency of severe complications. In *P. falciparum* malaria, parasite density is directly correlated with the severity of clinical disease. Patients with high parasite counts have more severe and complicated courses.[6,7]

In this study, the major symptoms observed were fever, followed by nausea and vomiting, headache, jaundice, cough, pain in the abdomen, impaired consciousness, and oliguria or anuria.

Shaikh *et al*.[8] reported fever in all patients, rigor in 96% of patients, and vomiting and headache in 62% of patients. Ali *et al*.[9] also observed fever in 100% of cases. Murthy *et al*.[6] reported fever with chills and rigor (98.10%), altered sensorium (48.10%), algid malaria (18.35%), and jaundice (27.12%).

In the present study, anemia was found in 58% of cases, hepatomegaly in 32% of cases, splenomegaly in 66% of cases, and hepatosplenomegaly in 27% of cases. Anemia results from accelerated RBC removal by the spleen, obligatory RBC destruction during parasite schizogony, and ineffective erythropoiesis. Enlargements of the liver and spleen result from the inflammatory response to plasmodia and are more severe in cases of *P. falciparum* infection.

Shaikh *et al*.[8] reported anemia in 58% of cases, disseminated intravascular coagulation in 4% of patients, hepatosplenomegaly in 20% of patients, and bacterial septicemia in 18% of patients. Murthy *et al*.[6] and Ali *et al*.[9]

**Table 4: Complications with Respect to Parasite Density**

| Complications | Group A (*n*=68) | Group B (*n*=18) | Group C (*n*=42) | *P* |
|---|---|---|---|---|
| Cerebral malaria | 0 | 3 | 9 | 0.001 |
| Severe anemia | 2 | 1 | 2 | 0.20 |
| Acute renal failure | 2 | 1 | 3 | 0.02 |
| Hypotension | 1 | 1 | 5 | 0.001 |
| Hyperbilirubinemia | 7 | 7 | 4 | 0.001 |
| Bleeding | 1 | 1 | 2 | 0.07 |

**Table 5: Distribution of Complicated form of Falciparum Malaria with Mortality**

| Complications | Number of cases | | Mortality | | Percentage |
|---|---|---|---|---|---|
| | Male | Female | Male | Female | |
| Cerebral malaria | 9 | 3 | 5 | 2 | 58.33 |
| Severe anemia | 3 | 2 | 0 | 1 | 20 |
| Acute renal failure | 5 | 1 | 2 | 0 | 33.33 |
| Hypotension | 5 | 2 | 3 | 1 | 57.14 |
| Hyperbilirubinemia | 20 | 2 | 6 | 1 | 31.81 |

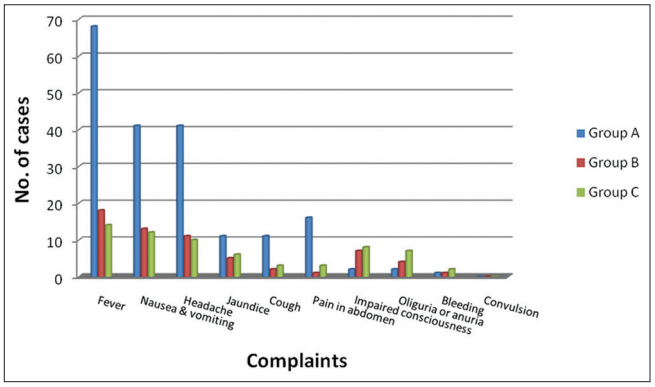


**Chart 2:** Parasite density with respect to various clinical presentations

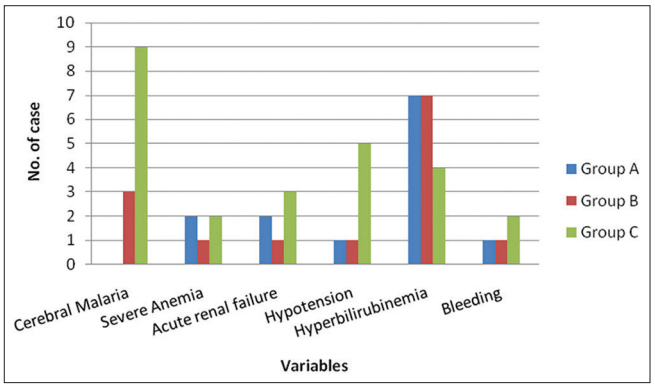


**Chart 3:** Showed pattern of complications with parasite density

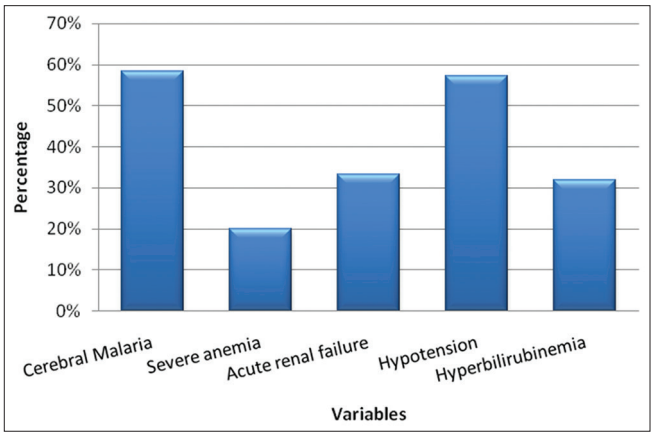


**Chart 4:** Distribution of complicated form of falciparum malaria with mortality

reported similar results, but Muddaiah and Prakash[10] reported anemia in 14.27% of cases.

The relationship between the severity of falciparum malaria and parasitemia is complex. In the present study, 68% of patients had a parasite density of <5% (Group A), 18% had a parasite density of 5%–10% (Group B), and 14% had a parasite density of >10% (Group C). All the uncomplicated malaria cases had a parasite density of <5% while most of the complicated malaria cases (32/46) had a parasite density of >5%. The difference between these groups was statistically significant.

As per WHO criteria, in the present study, out of 100 cases, 46 were complicated malaria. Among these 46 patients, 22 had hyperbilirubinemia (serum bilirubin >3 mg%), 12 had cerebral malaria, 7 had hypotension (systolic blood pressure <80 mmHg), 6 had acute renal failure, and 5 patients had severe anemia (Hb <5 mg%).

Cerebral malaria may be defined strictly as an unarousable coma (i.e., a nonpurposeful response or no response to a painful stimulus) in falciparum malaria. Cerebral malaria was present in 12 out of 46 cases (26.08%) of complicated malaria. All patients with cerebral malaria had a parasite density of >5%, and 9 out of 12 (75%) patients had a parasite density of >10%. This difference was statistically significant ($P$ = 0.000). In total, 7 out of 12 patients (58.33%) with cerebral malaria in the study died. The mortality rate was highest in patients with cerebral malaria.

Murthy *et al*.[6] observed cerebral malaria in 45.56% of cases. Bajiya and Kochar[11] reported a mortality rate of 33.5% while Ahmad *et al*.[12] reported a mortality rate of 23%, which was similar to the results of our study.

Hyperbilirubinemia was found in 22 out of 100 cases in the study. These patients were in the complicated malaria group. No patient in the uncomplicated malaria group had serum bilirubin levels exceeding 3.0 mg%. The incidence of hyperbilirubinemia increased from 10.29% in Group A to 57.14% in Group C as parasite density increased from <5% to >10%. This difference between groups was statistically significant ($P$ = 0.00096) [Table 3]. Seven out of 22 patients (58.33%) with hyperbilirubinemia died in the study.

Wasnik *et al*.[13] observed hyperbilirubinemia in 35% of patients while Muddaiah and Prakash[10] observed it in 14.73% of cases.

Thrombocytopenia is a common observation in falciparum malaria. Thrombocytopenia is thought to be caused by increased splenic sequestration, immune-mediated destruction, and shortened platelet survival. The degree of thrombocytopenia is associated with the severity of falciparum malaria. In the present study, the incidence of severe thrombocytopenia was significantly higher in the complicated malaria group than the uncomplicated malaria group ($P$ = 0.000).

Wasnik *et al*.[13] observed thrombocytopenia in 46 (57.5%) patients while Ali *et al*.[9] reported thrombocytopenia in 95.65% of patients with a parasite density of >10% and 58.06% of patients with a parasite density of <5%.

*P. falciparum* malaria is one of the most common causes of acute renal failure in adults. In the present study, 92.64% (63 out of 68) of cases in the uncomplicated malaria group had serum creatinine levels of <1.5 mg/dL while only 62.5% (20 out of 32) in the complicated malaria group had serum creatinine levels of <1.5 mg%. This difference between groups was statistically significant ($P$ = 0.0001). The occurrence of renal failure in cases of complicated falciparum malaria was also reported previously. Bajiya and Kochar[11] reported a high incidence (21.7%), and similar results were observed by Gopinathan and Subramanian,[14] Hazra *et al*.,[15] and Prakash *et al*.[16]

*P. falciparum* is the most dangerous form of malaria, with a mortality exceeding 20% depending on the degree of parasitemia and the development of complications. High parasitemia, even without complications, can lead to high mortality.

In the present study, an overall mortality of 10% was observed. All cases of mortality were in the complicated malaria group. No death occurred in the uncomplicated malaria group. All patients who died had a parasite density of >10%.

## Conclusions

The detection of *P. falciparum* in a peripheral smear can be used to diagnose malaria, but the assessment of the malaria parasite index helps determine the prognosis. It can serve as a good prognostic marker combined with other established factors. Owing to its low cost and effectiveness, the parasite index should be evaluated in all malaria patients. The results of study are consistent with those of previous studies. The parasite index of *P. falciparum* is a good prognostic marker.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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