Clinical Profile and Prognostic Indicators in Adults Hospitalized with Severe Malaria Caused by Different *Plasmodium* Species

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ABSTRACT

INTRODUCTION: Severe malaria remains a major cause of death and morbidity among adults in the Asiatic tropics. This study was planned to evaluate clinical profile and prognostic indicators of severe malaria in adults so as to improve insight into this highly prevalent disease.

MATERIALS AND METHODS: This prospective observational study was conducted on 60 confirmed cases of malaria. Cases were divided into two groups: (a) study group: suffering from severe malaria and (b) control group: no severe manifestations. All cases were thoroughly studied for clinical features, laboratory evaluation, and outcome. Prognostic evaluation was also done by different score systems.

RESULTS: In all, 40 cases suffer from severe malaria (study group), while 20 cases belong to the control group. The majority of our cases were males of age 21–40 years. The most common species of malaria in the study group was *vivax* (52.5%), followed by *falciparum* (25%) and mixed malaria species (22.5%). The clinical predictors for severe malaria were rural habitat, longer duration of fever, marked chills, tiredness, giddiness, nausea, vomiting, decreased urine output, jaundice, and altered sensorium. Extreme weakness (80%), jaundice (55%), renal failure (50%), and severe anemia (27.5%) were the most common presenting features in severe malaria. Two patients died of severe mixed malaria. The mortality rate was significantly associated with lower hemoglobin level ($P = 0.002$); higher total leukocyte count ($P = 0.006$), blood urea ($P < 0.001$), serum creatinine ($P < 0.001$), SGOT ($P = 0.001$), SGPT ($P < 0.007$), serum bilirubin ($P = 0.003$), and parasite density ($P = 0.033$); lower platelet count ($P = 0.043$); and those who had more APACHE II score ($P = 0.003$), SOFA score ($P = 0.04$), and Multiple Organ Dysfunction Score ($P < 0.001$) and lower Glasgow Coma Scale ($P < 0.001$).

CONCLUSIONS: Manifestations of severe malaria is becoming increasingly more prevalent specifically in *vivax* and mixed malaria cases. Our study proposes that there are certain clinical predictors and prognostic indicators that should be kept in mind for better management of severe malaria.

KEYWORDS: severe malaria, clinical predictor, prognostic indicators, *Plasmodium vivax, Plasmodium falciparum*, mixed malaria

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Introduction

Malaria continues to create menace in developing countries, especially Indian subcontinent.[1] The spectrum of disease has changed worldwide, and there is an increasing trend for multiple organ dysfunctions attributed to *Plasmodium falciparum* as well as *Plasmodium vivax*.[2–5] While many data have been published on severe malaria among children[6,7] only a few studies have been published regarding severe malaria among adults. Furthermore, these studies had a greater emphasis on *P. falciparum* malaria. Until recently, *P. vivax* was considered a benign parasite compared with *P. falciparum*. Now, there are increasing reports on severe *vivax* and mixed malaria.[8,9] Such data are of paramount importance to health care givers, health planners, and researchers.

Although clinically, *P. vivax* is causing similar manifestations of severe malaria as has been known to occur with *P. falciparum* infection, their pathophysiology in likely to be different. The determinants of severe malaria and its pathophysiology are not completely understood. The epidemiological studies of severe malaria and its related deaths may provide additional understanding of the disease course and eventually lead to improved case management. Therefore, this study was planned to evaluate clinical profile and prognostic indicators of severe malaria caused by different species of plasmodium (*P. vivax*, *P. falciparum*, and mixed infection) in adults.

Material and Methods

This study was conducted among patients of malaria admitted in classified malaria and other medical wards of the Department of Medicine, Sardar Patel Medical College and Associated Groups of Hospitals, Bikaner, India. We included

the patients of both sexes belonging to age more than 15 years. The study was approved by the Ethics Committee of Sardar Patel Medical College and AG Hospitals, and the research was conducted in accordance with the principles of the Declaration of Helsinki. Patients who gave their written, informed consent to participate were included and examined in detail. A patient complaining of *marked chills* means he/she was feeling chills even after covering with three to four blankets and the one complaining of *extreme weakness* means he/she was feeling so weak that he/she was not able to walk independently.

The diagnosis of malaria was confirmed by examination of thick and thin peripheral blood smear test and rapid diagnostic test. Diagnosis of species of plasmodium was further confirmed by polymerase chain reaction (PCR). The parasite density was calculated in all the patients as per World Health Organization (WHO) guidelines.[10] Other investigations done were complete blood count; liver function test; renal function test; amount of Na^+, K^+, Ca^{++}, LDH, and blood sugar; urine complete and microscopic test; blood culture/sensitivity test; abdominal ultrasonography, especially for kidneys, spleen, and liver; chest X-ray (PA view), electrocardiography; 24-hour urine protein; PCR; presence of leptospirosis; C-reactive protein test; type of blood group; and prevalence of human immunodeficiency virus, hepatitis B surface antigen, and hepatitis C virus.

The patients were divided into two groups: (A) study group (patients with severe malaria) and (B) control group (patients without severe manifestations of malaria). Diagnosis of severe malaria was done as per WHO criteria.[11] Both groups were compared to evaluate clinical profile and prognostic indicator of severe malaria. The assessment of various prognostic factors was also done by using different score systems such as APACHE II score,[12] Multiple Organ Dysfunction Score (MODS),[13] SOFA score,[14] and Glasgow Coma Scale (GCS).[15]

All patients were treated as per WHO guidelines.[10] Daily clinical evaluations of all the patients were done during their hospital stay.

Statistical analysis. Statistical analysis was done using MS Excel and SPSS version 11. Numerical variables were represented in mean ± SD, and ordinal variables in percent. Unpaired *t*-test or chi-square test (χ^2) was used to compare two groups, while analysis of variance and chi-square tests were used to compare multiple groups. A *P*-value of <0.05 was considered as significant.

Results

This observational prospective study was conducted using 60 consecutive confirmed cases of malaria who were admitted in various wards of Department of Medicine, Sardar Patel Medical College, Bikaner, from July 2013 to June 2014, out of which 40 had severe malaria as per WHO criteria (study group) and 20 did not had severe malaria (control group).

The epidemiological profile is shown in Table 1. Males were affected more than females in both the groups (57.5% vs 42.5% in the study group and 60.0% vs 40.0% in the control group). The mean age was 29.08 ± 15.18 in the study group and 35.45 ± 15.33 in the control group, and most patients were between 21 and 40 years (52.5% vs 43.3%). Among females, most patients were housewife (30.0% vs 35.5%), and among males, most were farmer (25.0% vs 20.0%) by occupation. Most patients belonged to rural area as compared to urban area in both the groups (rural 80% and 55% vs urban 20% and 45%, respectively).

Table 1. Epidemiological profile.

	STUDY GROUP (NO. = 40)	CONTROL GROUP (NO. = 20)	χ^2	*P*
Sex				
Male	23 (57.5%)	12 (60.0%)	0.303	0.582
Female	17 (42.5%)	8 (40.0%)		
Age group (yrs.)				
<20	9 (22.5%)	4 (20.0%)		
21–40	21 (52.5%)	9 (43.3%)		
>40	10 (25.0%)	7 (35.0%)		
Mean	29.08 ± 15.18	35.45 ± 15.33	*t* = 1.528	0.132
Occupation				
Driver	4 (10%)	0		
Farmer	10 (25%)	4 (20.0%)		
Housewife	12 (30%)	7 (35.0%)		
Labour	11 (27.5%)	0		
Student	3 (7.5%)	9 (45.0%)		
Residential area				
Rural	32 (80%)	11 (55.0%)	4.104	0.043*
Urban	8 (20%)	9 (45.0%)		

The clinical profile is shown in Table 2. The most common species was *P. vivax* (52.5% vs 55.0%) followed by *P. falciparum* (25.0% vs 35.0%) and mixed infection (22.5% vs 10.0%) in both the groups. Although all the patients presented with complain of fever in both the groups, the mean duration of fever was more in the study group as compared to the control group (10.98 ± 7.6 vs 3.90 ± 0.97, $P < 0.001$). All patients (100%) of control group presented with fever for less than five days, whereas in the study group, only 35% of patients presented with fever for less than 5 days, 25% had it for 6–10 days, and 40% had it for more than 10 days. Other presenting symptoms were chills, tiredness, giddiness, body ache, nausea, headache, anorexia, vomiting, jaundice, oliguria, altered sensorium, seizures, respiratory distress, and diarrhea. The symptoms of marked weakness and tiredness, marked chills, nausea, jaundice, decreased urine, and altered sensorium at the time of presentation were indicative of severe malaria.

The laboratory profile is shown in Table 3. The study group had significantly lower mean Hb (7.31 ± 2.17 g% vs 8.68 ± 2.63 g%, $P = 0.037$), higher total leukocyte count (TLC)

Table 2. Clinical profile at the time of presentation.

SYMPTOMS	STUDY GROUP (n = 40)		CONTROL GROUP (n = 20)		χ^2	*P*
	NO.	%	NO.	%		
Fever	40	100	20	100		
<5 days	14	35	20	100	4.131	<0.001*
5–10 days	10	25	0			
>10 days	16	40	0			
Type of Malaria						
Vivax	21	52.5	11	55	1.6226	0.4442
Falciparum	10	25	7	35		
Mixed	9	22.5	2	10		
Tiredness	40	100	16	80	4.615	0.032*
Giddiness	40	100.0	16	80	4.615	0.032*
Chills	40	100	11	55.0	12.857	<0.001*
Body ache	34	85.0	16	80.0	0.240	0.624
Nausea	34	85.0	9	45.0	10.506	0.001*
Headache	32	80.0	17	85.0	0.223	0.637
Anorexia	32	80.0	15	75.0	0.196	0.658
Vomiting	24	60.0	5	25.0	6.541	0.011*
Jaundice	22	55.0	4	20.0	6.652	0.010*
Oliguria	20	50.0	0	–	15.000	<0.001*
Altered sensorium	12	30.0	0	–	7.500	0.006*
Diarrhea	2	5.0	0	–	1.034	0.309

(13.78 ± 12.66 thousand/cmm vs 4.55 ± 1.53 thousand/cmm, $P = 0.002$), lower platelet count (67.99 ± 53.37 thousand/cmm vs 123.95 ± 43.76 thousand/cmm, $P < 0.001$), higher parasite density (88.87 ± 56.89 thousand/cmm vs 41.85 ± 16.63 thousand/cmm, $P = 0.001$), higher LDH (652.43 ± 254.82 vs 263.75 ± 188.33, $P < 0.001$), higher RDW (28.88 ± 15.33 vs 14.13 ± 0.74, $P < 0.001$), higher serum bilirubin (5.53 ± 5.64 vs 2.46 ± 2.84, $P = 0.026$), higher SGOT (88.78 ± 100.02 vs 40.10 ± 27.49, $P = 0.038$), higher SGPT (110.08 ± 148.24 vs 39.75 ± 26.51, $P < 0.001$), higher blood urea (80.58 ± 4.52 vs 33.25 ± 5.39, $P < 0.001$), and higher serum creatinine (2.79 ± 3.89 vs 0.68 ± 0.08, $P = 0.019$).

The assessment of various prognostic factors is also shown in Table 3. The study group had higher APACHE II score (12.24 ± 2.46 vs 2.40 ± 1.19, $P < 0.001$), higher SOFA score (17.92 ± 2.82 vs 2.78 ± 0.04, $P < 0.001$), higher MODS (7.30 ± 1.14 vs 2.95 ± 1.23, $P < 0.001$), and lower GCS (13.3 ± 2.61 vs 14.75 ± 0.55, $P = 0.018$) as compared to the control group.

Among the various manifestations of severe malaria, the most common were extreme weakness (80%) followed by jaundice (55%), renal failure (50%), severe anemia (27.5%), altered sensorium (15%), hyperparasitemia (10%), hypotension (7.5%), hypoglycemia (5%), convulsion (5%), and acute respiratory distress syndrome (ARDS) (2.5%) (Table 4).

The mean duration of hospital stay was more in the study group as compared to the control group (7.78 ± 3.58 vs

Table 3. Laboratory profile at the time of admission.

PARAMETERS	STUDY GROUP (n = 40)		CONTROL GROUP (n = 20)		T	*P*
	MEAN	SD	MEAN	SD		
Hb (gm%)	7.31	2.17	8.68	2.63	2.132	0.037*
TLC (thousands)	7.04	3.95	4.55	1.53	2.703	0.009*
Platelet count (thousands)	67.99	53.37	123.95	43.76	4.052	<0.001*
Parasite density (thousands)	88.87	56.89	41.85	16.63	3.606	0.001*
LDH	652.43	254.82	263.75	188.33	6.036	<0.001*
RDW	28.88	15.33	14.13	0.74	4.283	<0.001*
Serum bilirubin	5.53	5.64	2.46	2.84	2.286	0.026*
SGOT (IU/L)	88.78	100.02	40.10	27.49	2.128	0.038*
SGPT (IU/L)	110.08	148.24	39.75	26.51	3.614	0.001*
Blood sugar (mg/dl)	102.98	16.16	98.05	10.56	1.357	0.180
Blood urea (mg/dl)	80.58	45.52	33.25	5.39	4.614	<0.001*
S. creatinine (mg/dl)	2.79	3.89	0.68	0.08	2.423	0.019*
Sodium (mmol/L)	138.25	21.34	140.00	0.00	0.365	0.716
Potassium (mmol/L)	4.48	1.63	4.05	0.08	1.177	0.244
APACHE II	12.24	2.46	2.40	1.19	16.867	<0.001*
SOFA	17.92	2.82	2.78	0.04	23.883	<0.001*
MODS	7.30	1.14	2.95	1.23	13.580	<0.001*
GCS	13.30	2.61	14.75	0.55	2.444	0.018*

Table 4. Distribution of cases in the study group according to severe manifestation of malaria.

SEVERE MANIFESTATION	*P. vivax* (*n* = 21)	*P. falciparum* (*n* = 10)	*MIXED* (*n* = 9)	TOTAL	%
Extreme weakness	18 (86%)	7 (70%)	7 (78%)	32	80.0
Jaundice (SB >3 mg/dl)	10 (48%)	10 (100%)	2 (22%)	22	55.0
Renal failure (SC >3.0)	12 (57%)	6 (60%)	2 (22%)	20	50.0
Severe anemia (Hb <5 gm/dl)	3 (14%)	4 (40%)	4 (44%)	11	27.5
Altered sensorium	6 (28.5%)	4 (40%)	2 (22%)	12	15.0
Hyperparasitemia (PD >1 lacs/μl)	2 (9.5%)	1 (10%)	1 (11%)	4	10.0
Hypotension (SBP <80)	3 (14%)	0	0	3	7.5
Hypoglycemia (RBS <40)	2 (9.5%)	0	0	2	5.0
Convulsion (>2GS 24 hrs)	0	0	2 (22%)	2	5.0
ARDS	1 (4.7%)	0	0	1	2.5

5.10 ± 1.55, $P < 0.001$). Out of 40 cases of severe malaria, 2 (5%) patients expired; both were having mixed infection. These expired patients had significantly lower mean Hb (2.70 ± 0.42 g% vs 7.94 ± 2.24 g%, $P = 0.002$), higher TLC (12.8 ± 0.63 thousand/cmm vs 5.98 ± 3.37 thousand/cmm, $P = 0.006$), lower platelet counts (7.50 ± 7.07 thousand/cmm vs 89.37 ± 55.61 thousand/cmm, $P = 0.043$), higher parasite density (150.0 ± 30.11 thousand/cmm vs 70.54 ± 51.08 thousand/cmm, $P = 0.033$), higher serum bilirubin (16.05 ± 3.18 vs 4.48 ± 5.16, $P = 0.003$), higher SGOT (260.0 ± 21.51 vs 66.09 ± 79.84, $P = 0.001$), higher SGPT (320.0 ± 29.42 vs 78.59 ± 120.21, $P = 0.007$), higher blood urea (185.0 ± 18.79 vs 60.86 ± 37.78, $P < 0.001$), higher serum creatinine (11.3 ± 2.12 vs 1.99 ± 3.34, $P < 0.001$), higher APACHE II score (19.27 ± 1.37 vs 8.60 ± 4.83, $P = 0.003$), higher SOFA score (23.5 ± 0.71 vs 12.47 ± 7.36, $P = 0.040$), higher MODS (12.0 ± 0.00 vs 5.64 ± 2.11, $P < 0.001$), and lower GCS (3.50 ± 0.71 vs 14.14 ± 1.19, $P < 0.001$) as compared to patients who survived (Table 5).

Increased blood urea and serum creatinine ($P < 0.001$), increased MODS ($P < 0.001$), and decreased GCS ($P < 0.001$) were more strongly associated with poor prognosis.

Discussion

Despite intensive efforts over the last century to understand and control malaria, it remains a leading cause of morbidity and mortality in humans. Severe malaria has been associated with high morbidity and mortality.[16] In the present study of 60 consecutive cases of malaria, 40 had severe manifestations of malaria. In these 40 patients, the most common species

Table 5. Statistical analysis of different parameters according to prognosis in the study group.

PARAMETERS	OUTCOME				T	*P*
	SURVIVAL (n = 38)		EXPIRED (n = 2)			
	MEAN	SD	MEAN	SD		
Hemoglobin (gm%)	7.94	2.24	2.70	0.42	3.281	0.002*
TLC (thousands)	5.98	3.37	12.80	0.63	2.840	0.006*
Blood urea (mg/dl)	60.66	37.78	185.00	18.79	4.616	<0.001*
Serum creatinine (mg/dl)	1.99	3.34	11.30	2.12	3.894	<0.001*
SGOT (IU/L)	66.09	79.84	260.00	21.51	3.406	0.001*
SGPT (IU/L)	78.59	120.21	320.00	29.42	2.817	0.007*
Serum bilirubin	4.48	5.16	16.05	3.18	3.133	0.003*
Parasite density (thousands)	70.54	51.08	150.00	30.11	2.181	0.033*
Platelet count (thousands)	89.37	55.61	7.50	7.07	2.065	0.043*
APACHE II score	8.60	4.83	19.27	1.37	3.093	0.003*
SOFA score	12.47	7.36	23.50	0.71	2.100	0.040*
MODS	5.64	2.11	12.00	0.53	4.232	<0.001*
GCS	14.14	1.19	3.50	0.71	12.486	<0.001*

was *P. vivax*, 21 (52.5%); followed by *P. falciparum*, 10 (25%); and *mixed* malaria species, 9 (22.5%), which was similar to findings by Erhart et al[17] and Jadhav et al,[18] whereas earlier studies done by Rojanasthien et al[19] and Bashawri et al[20] reported higher *falciparum* prevalence when severe malaria caused by *vivax* was not known.

We found that the maximum numbers of cases belong to age group of 21–40 years (mean 32.26 years). Most other studies[18,20] have mean age groups between 25 and 40. The young adult age group is more affected due to their greater mobility and greater risk of exposure due to more outdoor activity. The present study had 58.75% males as compared to 41.25% females, which is similar to Erhart et al[17] (69% males) and Bashawri et al[20] (75.9% males). Although we did not find much of the statistically significant difference in epidemiological characteristics of study and control groups, we did find that rural patients were more affected and more severely affected as compared to urban patients, which may be because of illiteracy, unawareness, nonavailability of nearby medical facilities, and delay in seeking medical help. We also found that the labor class was more prone to develop severe malaria; this may be because of poor nutrition, less health awareness, and delay in seeking medical help due to economic reasons. Students were less prone to develop severe malaria; this may be because of health awareness.

In our studies, all patients presented with complain of fever in both the groups, followed by body ache, chills, tiredness, giddiness, nausea, headache, anorexia, vomiting, jaundice, oliguria, altered sensorium, and diarrhea in order. We found that those who had longer duration of fever are more likely to develop severe manifestation of malaria ($P < 0.017$). Thus, our study suggests that any fever in the malaria prone area should not be taken lightly and should be evaluated vigorously for malaria.

The present study shows severe anemia (Hb <5 g%) in 27.5% of cases of the study group. The other studies conducted by different workers[17,20,21] showed severe anemia in 5.5–15.83% of cases. The studies conducted in developing countries show higher levels of anemia. Most patients in these areas have iron and folate deficiency due to inadequate dietary intake along with parasitic and bacterial infections that themselves can contribute to significant amount of anemia.

In our study, renal failure was observed in 50% of cases of the study group, and it was seen almost equally among severe *P. vivax* (57%) and severe *P. falciparum* (60%) malaria. It was seen in 22% cases of severe mixed malaria. We found that 60% of malarial ARF were due to *vivax* infection and 30% due to *falciparum*. Gupta et al[22] studied 74 patients of ARF in Bikaner and found that 70% of malarial ARF was due to *P. falciparum*, 18.9% due to *P. vivax*, and 10.8% due to mixed infection. Prakash et al[23] studied 94 patients of malarial ARF in Varanasi and found that 80.9% of malarial ARF was due to *P. falciparum* and 11.7% due to *P. vivax*. Thus, our study shows changing patterns of severe manifestations of malaria. We are observing increasing incidence of malarial ARF. This is because of increasing number of *P. vivax* malaria presenting with severe manifestations.

In the present study, the occurrence of liver dysfunction as measured by serum bilirubin >3 mg% was 37%, which is similar to observations made by other workers.[24] Over the last decade, the clinical manifestations of malaria have undergone a significant change in our region. Our present study revealed that extreme weakness was present in 80% of the cases of severe malaria, jaundice in 55%, renal failure in 50%, severe anemia in 27.5%, altered sensorium in 15%, hyperparasitemia in 10%, hypotension in 7.5%, cerebral malaria in 5%, hypoglycemia in 5%, convulsion in 5%, and ARDS in 2.5%. This shows that the incidence of cerebral malaria has decreased, while that of jaundice, renal failure, and severe anemia has increased. Important causes of mortality in our study were renal failure, multiple organ dysfunction, and cerebral malaria.

As we compared different parameters in patients who died and survived, we found that severe anemia; high parasite density; severe thrombocytopenia; leukocytosis; increased blood urea and creatinine; increased serum bilirubin; raised SGOT and SGPT; high APACHE II score, SOFA score, and MODS; and lower GCS were associated with poor outcome. Similar observations had been noted by Sahu et al[25] in severe *falciparum* malaria. Therefore, we suggest that these parameters should be considered as poor prognostic indicators and should be evaluated meticulously in clinically indicated patients so as to recognize early life-threatening conditions.

Conclusion

Our study suggests that there are certain clinical predictor and prognostic indicators of severe malaria that should be kept in mind for better management. Patients presenting with longer duration of fever, marked tiredness, marked chills, nausea, vomiting jaundice, decreased urine, and altered sensorium and patients with mixed *vivax and falciparum* infections must be thought of having severe malaria. Severe anemia, high parasite density, severe thrombocytopenia, leukocytosis, increased blood urea and creatinine, increased serum bilirubin, raised aminotransferase, increased APACHE II score, increased SOFA score, increased MODS, and decreased GCS are poor prognostic factors of severe malaria. Renal failure, increased MODS, and decreased GCS are more strongly associated with poor prognosis.

Author Contributions

Designed the study and analyzed the data and their interpretation: BKG and AG. Drafted the manuscript: BKG and HRN. Approved the final version to be published: BKG. Carried out clinical assessment: HRN, HRB, SLM, and SK. Evaluated and analyzed laboratory data and their interpretation: AG. All authors read and approved the final manuscript. Guarantors of the paper: HRN and BKG.

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