Clinical Spectrum of Severe *Plasmodium falciparum* Malaria in a Tertiary Care Centre of Eastern India

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Authors' contributions

This work was carried out in collaboration between all authors. Authors PP, PKM and SP did the study design and wrote the protocol and final manuscript. Authors PP, AR, JH and AKB collected the patient's data. Authors PP, SD and SM performed laboratory works. Authors PP, SP and KD interpreted the laboratory results and clinical data. Authors PP, PKM and SP did the statistical analysis and literature searches. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Introduction: *Plasmodium falciparum* malaria is one of the major public health problem presented with varied clinical severity. This study was carried out to observe the clinical spectrum of severe *falciparum* malaria in a tertiary health care centre.
Methods: This study was undertaken in hospitalized adults with suspected severe malaria. Confirmation of *falciparum* infection was done by ICT/QBC and single-step-PCR. Diagnosis of severe malaria was done by WHO- guideline 2010.

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Results: 450 adult cases with *falciparum* infection were studied. Maximum number of cases was from 15-25 years age group depicting the high exposure to malaria. In these patients, acute renal failure (ARF) was the most common (36.2%) complication followed by cerebral malaria (35.3%), jaundice (27.8%), hepatic dysfunction (21.8%), respiratory distress (18.4%), severe malarial anemia (15.8%), thrombocytopenia (15.1%), and hypoglycemia (9.3%). Mortality was found in 6.0% of cases. Cerebral involvement and ARF were the common cause of death in these patients.
Conclusion: ARF is the most common type of clinical severity followed by cerebral malaria in adults and both are equally responsible for death along with other complications. Looking into the matter of varied clinical severity, accurate diagnosis, effective anti-malarial treatment along with supportive therapy is necessary to triumph over this deadly severe *falciparum* malaria.

1. INTRODUCTION

Plasmodium falciparum malaria is one of the most important causes of death and considered as a major global health concern. Regardless of many control strategies by national and international communities, *falciparum* malaria contributes to high morbidity and mortality amongst all the infectious diseases worldwide, accounting for 198 million positive cases of malaria and 584,000 deaths [1]. In India, of the 1.2 billion people, 80% live in malaria risk areas [2]. According to World Malaria Report, the number of cases of malaria reported from the country was 881,730 [1]. The number of deaths due to malaria is 8.75 times higher in subjects ≥ 5 years (42,000 deaths) compared to children < 5 years (4,800 deaths) [3].

Management of severe malaria cases is going to be a challenge for treating physician due to emergence of drug resistance parasites [4]. Various studies in adults with severe *P. falciparum* malaria showed a changing spectrum in last two decades. The clinical spectrum of severe *P. falciparum* varies with population and endemicity of malaria [5]. Studies undertaken in different parts of India on spectrum of severe *P. falciparum* malaria showed variation [4,6,7,8]. The present study was undertaken to define the spectrum of severe *P. falciparum* malaria in adults in a tertiary care centre.

2. MATERIALS AND METHODS

This prospective cohort study was undertaken in Sickle Cell Clinic and Molecular Biology Laboratory, Department of Medicine, Veer Surendra Sai Medical College, Burla (now renamed as Veer Surendra Sai Institute of Medical Sciences and Research, Burla) in the state of Odisha, eastern India. It is a tertiary care,

referral hospital for 12 million people residing in western Odisha and the state of Chhattisgarh. The state of Odisha is situated along the Bay of Bengal and extends from 17.78'N to 22.73'N latitude to 81.37'E to 87.53'E longitude. The study site is situated between the geographical co-ordinates of 21.50'N and 83.87'E. Malaria is the major public health problem in this geographical region. The state of Odisha is considered as a region for hyperendemic and low perennial transmission of malaria with a seasonal peak from July to October [9]. This state contributes to 23% of malaria positive cases, 50% of *P. falciparum* cases and 15% of malaria related deaths in India [10]. In the study area, *P. falciparum* alone accounted for 87.8% of malarial infections compared to 50% of *P. falciparum* infection in India [11].

2.1 Study Subjects

Patients aged ≥15 years with clinically suspected malarial infections, hospitalized in the Department of Medicine, Veer Surendra Sai Institute of Medical College Burla, between August, 2010 to December, 2014 were included in the study. All the cases were subjected to either immune chromatography test (SD, Bio Standard Diagnostics India) or Quantitative Buffy Coat (QBC) (BD, Becton Dickinson Diagnostics) followed by single step polymerase chain reaction in all cases for confirmation of *Plasmodium* species [12]. Severity of *P. falciparum* malaria was defined as per WHO criteria 2010 [13]. The most severe complication, cerebral malaria (CM) was defined as patients with any of the features like altered sensorium, convulsion or GCS (Glasgow Coma Score) of ≤ 10. Other complications like severe malaria anemia (SMA) (hemoglobin, < 5 g/dl), acute renal failure (ARF) (serum creatinine > 3 mg/dl), *jaundice* (serum bilirubin >3 mg/dl), hepatic

dysfunction (alanine transaminase (ALT)/ aspartate transaminase (AST) > 3 times of normal; 120 U/L), respiratory distress, hemoglobinuria (dark red or black colored urine positive for hemoglobin), thrombocytopenia (platelet count <50,000 /µL) and shock (systolic BP of < 80 mm Hg) were considered. Written informed consent was obtained from all the cases. This study was approved by institutional ethical committee of Veer Surendra Sai Medical College, Burla.

2.2 Exclusion Criteria

The following cases were excluded from the study (a) subjects co-infected with other *Plasmodium* species; (b) children <15 years of age; (c) subjects having chronic disease like tuberculosis, chronic renal failure, cirrhosis of liver and autoimmune diseases like systemic lupus erythematosus and rheumatoid arthritis; (d) patients with dengue fever; (e) pregnant women; (f) patients positive for hepatitis; (g) subjects who refused to consent for the study.

2.3 Laboratory Investigations

P. falciparum examination was made by either ICT or QBC and single step PCR. All the subjects were screened for sickle cell by sickling slide test. Those found positive were subjected to agarose gel Hb electrophoresis (pH 8.6). A complete blood count was done on an automated hematology analyzer (Sysmex pocH-100i; Sysmex Corporation, Kobe, Japan). Biochemical parameters such as serum bilirubin, creatinine, urea, alanine transaminase, aspartate transaminase, sodium, potassium, glucose were done in a semi auto-analyzer (Erba Chem 7; Erba Diagnostics Mannheim GmbH, Mannheim, Germany) as per the manufacturer's instructions.

2.4 Molecular Confirmation of *P. falciparum*

The molecular confirmation of *P. falciparum* was done by method described earlier [12]. Briefly, three primers namely PL3, PL4 and PL5 specific to the *P. falciparum* and *P. vivax* were used for confirmation of *Plasmodium* species. PL3 (5'-ATGGCCGTTTTTAGTTCGTG-3') and PL4 (5'-GGAAACGGTACGATAAGCCA-3') amplified a 346 bp product specific for *P. faciparum* where as PL3 (5'-ATGGCCGTTTTTAGTTCGTG-3') and PL5 (5'- ACGCGTGCAGCCTAGTTTAT-3') amplified a 266 bp product specific for *P. vivax*. A 25 µL of PCR reaction mixture contain 200 ng of genomic DNA, 2.5 µL of primer PL3 (10 picomole), 2 µL of each primer PL4 (10 picomole) and PL5 (10 picomole), 2.5 µL of 10 x PCR buffer, 2.5 µL of 25 mM $MgCl_2$ 0.5 units of DNA Taq polymerase (Merck Biosciencs Pvt. Ltd.). The PCR reaction mixture was heated initially at 94℃ for 4 minutes and was kept for 30 cycles each of denaturation at 94℃ for 30 seconds, annealing at 54℃ for 30 seconds and extension at 72℃ for 30 seconds followed by final extension at 72℃ for 5 minutes. The PCR amplified gene fragments were electrophoresed on 2% agarose gel, and visualized under Gel documentation system (Model: GelDoc XR; Make: BioRad Laboratories, USA) after ethidium bromide staining. This allowed the presence of *P. falciparum* or *P. vivax* by size of PCR product.

2.5 Statistical Analysis

Statistical analysis was done using Graph Pad Instat, window 3.00. $p < 0.05$ was considered statistically significant.

3. RESULTS

During the study period, 531 cases had suspected malarial infections. Of which, 377 (71.0%) were found positive either by ICT or QBC and 450 (84.7%) cases were positive for single step PCR. The entire lot of cases positive for ICT/QBC was found to be positive for single step PCR. Finally, 450 patients were included in the study. The mean age of the patients was 34.4±13.5 years (range, age 15 to 65 years) and majorities were males (315, 70.0%).

Complete blood count parameters showed 10.2% (46/450), 14.6% (66/450), 42.9% (193/450) and 31.8% (143/450) of patients had hemoglobin level <5 mg/dL, ≥ 5 to < 7 mg/dL, ≥ 7 to < 10 mg/dL and ≥ 10 mg/dL respectively. Individual data for red cell indices explained 43.1% of patients had microcytic (<76fL of MCV) and hypochromic (<27 pg of MCH) blood picture. The hematological and biochemical parameters have been presented in Table 1.

All the patients under this study were divided into 5 groups on the basis of increasing age (Table 2). The majority (151, 33.6%) of patients belonged to 15-25 years age group and minimum (40, 8.9%) were from >55 years age group. There was no difference in the sex distribution in five age groups (χ^2, 0.226; *p*, 0.63). Screening of sickle cell resulted 30 patients with sickle cell trait (HbAS) and 14 patients with sickle cell anemia

(HbSS). Majority of patients with sickle cell anemia and severe *falciparum* malaria were from 15 to 35 years of age (Table 2).

Clinical finding of the hospitalized patients showed fever in all the patients, where as vomiting, pallor and headache were present in 32.7%, 32.0% and 21.0% respectively. Shock was observed in 15 (3.3%) of patients. Majority of our cases had ARF in 36.2% followed by CM (35.3%), jaundice (27.8%), hepatic dysfunction (21.6%), respiratory distress (18.4%), thrombocytopenia (15.1%), SMA (10.2%) and hypoglycemia (9.3%). The detailed clinical parameters have been depicted in Fig. 1.

On comparison of age distribution of major clinical signs and symptoms the following were found. The incidence of SMA was highest (15.0%) in patients with age > 55 years. ARF was common in patients > 36 years of age. Hypoglycemia was in decreasing order with increasing age. Incidence of jaundice was high in patients with 36-45 years of age. CM was highest in patients with > 55 years of age group followed by 16-36 years age group and 36-55 years of age group. All other parameters were comparable in each age group. The incidence of major clinical signs and symptoms defining severe malaria in different age groups was depicted in Fig. 2. In 14 patients with malaria and sickle cell anemia, the incidence of ARF, CM, jaundice, hepatic dysfunction, respiratory distress and SMA was found to be 3, 4, 6, 5, 2 and 4

cases respectively. Episodes of painful crises were observed in 8 cases.

Severe malaria has been defined on the basis of presence of various complications. In this study, the severe malaria has been defined by presence of single complication in 194 patients (ARF in 51 (26.3%) cases, CM in 43 (22.2%) cases, hepatic dysfunction in 13 (6.7%) cases, hypoglycemia in 8 (4.1%) cases, jaundice in 26 (13.4%) cases, respiratory distress in 31 (16.0%) cases, SMA in 14 (7.2%) cases and thrombocytopenia in 8 (4.1%) cases) and more than one complication in 256 patients (two complications in 173 patients, three complications in 58 patients, four complications in 18 patients and five complications in 7 patients). Among the patients with multiple complications, 14.8% (38/256) patients had ARF with hepatic dysfunction followed by CM with ARF (5.9%, 15/256).

Death has been recorded in 27 (6.0%) patients in this study. The cause of death in different age groups has been illustrated in Table 2. Majority of patients were in 15-25 years of age group (44.4%, 12/27). Amongst the death patients, CM and ARF were the two important cause for death in 19 patients each (70.4%). The mortality in patients with multiple complications was significantly high compared to patients with single complication (Odd Ratio, 3.55; CI [1.321-9.564]; *p*, 0.0084). Three patients with sickle cell anemia had died.

Table 1. Hematological and biochemical parameters of severe *P. falciparum* malaria cases (n=450)

Parameters	Mean ± SD	Minimum	Maximum
Hemoglobin (g/dL)	8.9±3.0	2.1	23.9
White Blood Cells (x10^3/µL)	8.8±4.17	1.6	38.6
Red Blood Cells (x10^6/µL)	3.68±1.22	0.71	8.9
Mean Corpuscular Volume (fL)	78.3±10.0	43	120
Mean Corpuscular Hematocrit (pg)	26.0±3.6	10.9	36.8
Mean Corpuscular Hemoglobin Concentration (g/dL)	32.2±2.5	19.4	40
Platelets (x10^3/µL)	162.7±99.7	10	917
Lymphocytes (%)	27.3±13.3	3.7	73
Monocytes (%)	11.7±8.2	2.1	39.7
Neutrophil (%)	66.6±14.2	20	93
Glucose (U/L)	115.1±54.0	28	592
Serum Urea (mg/dL)	65.4±59.6	10	427
Serum Creatinine (mg/dL)	2.82±2.91	0.2	19.5
Serum Bilirubin (mg/dL)	3.47±4.7	0.07	54.3
Serum Aspartate Transaminase (AST) (mg/dL)	90.0±127.0	2.3	1524
Serum Alanine Transaminase (ALT) (mg/dL)	75.8±104.5	5.4	1307
Sodium (U/L)	132.9±7.9	96.4	171
Potassium (U/L)	4.22±1.2	2	6

Table 2. Age wise distribution of severe *P. falciparum* malaria cases with their sickle cell gene status, death and cause of death

Age groups (in years)	Total No. of cases Number (%)	Male Number (%)	Sickle cell trait (HbAS) / sickle cell anemia (HbSS) Number/number	Death Number (%)	Complications of patients resulting death	No. of patients died
15-25	151 (33.6)	105 (69.5)	10/6	12 (7.9)	1. CM+ARF+HD+RD	1
					2. CM+ARF+HD	1
					3. CM+ARF	2
					4. CM+ARF+SMA+T	1
					5. CM+RD (SCA)	2
					6. CM+J+RD+SMA (SCA)	1
					7. ARF+HD+SMA (SCA)	1
					8. ARF+HD	1
					9. ARF	1
					10. CM	1
26-35	114 (25.3)	78 (68.4)	6/6	5 (4.4)	1. CM+ARF+HD+SMA+T	1
					2. CM+ARF+HD	1
					3. CM+ARF+SMA	1
					4. CM+HYP	1
					5. ARF	1
36-45	89 (19.8)	63 (70.8)	6/0	3 (3.4)	1. CM+ARF+HD+SMA	1
					2. CM+ARF	1
					3. ARF+HD+SMA	1
46-55	56 (12.4)	40 (71.4)	5/1	3 (5.4)	1. CM+ARF+HD+SMA	1
					2. CM+HYPO+SMA	1
					3. ARF	1
>55	40 (8.9)	29 (72.5)	3/1	4 (10.0)	1. CM	1
					2. CM+J+RD+SMA	1
					3. CM+ARF+J	1
					4. ARF+RD+T	1
Total cases	450	315 (70.0)	30/14	27 (6.0)		27

Note: CM, Cerebral Malaria; ARF, Acute Renal Failure; SMA, Severe Malarial Anemia; HD, Hepatic Dysfunction; RD, Respiratory Distress; J, Jaundice; HYPO, Hypoglycemia;
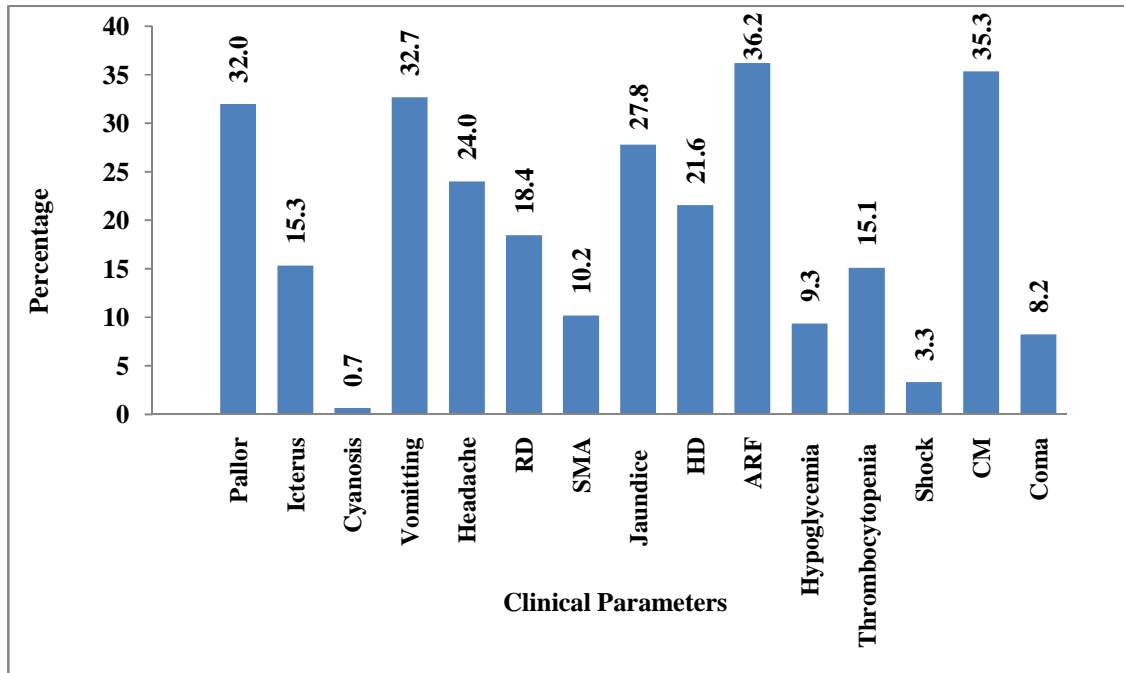*T, Thrombocytopenia; SCA, Sickle Cell Anemia*

Fig. 1. Incidence of different clinical parameters in severe *P falciparum* malaria cases (n=450)
Note: RD, Respiratory Distress; SMA, severe malarial anemia, HD, Hepatic Dysfunction; ARF, Acute Renal Failure; CM, Cerebral Malaria
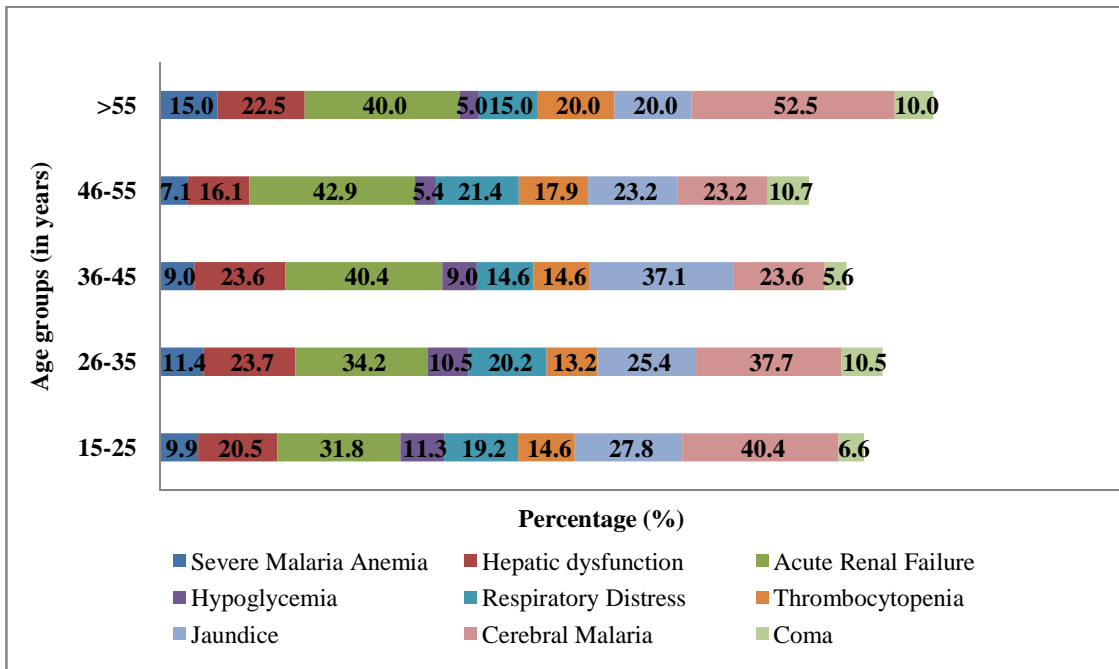

Fig. 2. Incidence of different clinical parameters in different age groups of severe *P. falciparum* malaria cases (n=450)

4. DISCUSSION

In this prospective hospital based study, we have included 450 patients with severe *P. falciparum* malaria. The mean age of the patients was 34.4±13.5 year with majority (70.0%) being males. It is not obvious that males were more prone to infection. It might be due to; first, the present study is based on patients admitted to the tertiary hare hospital. It is possible that some female patients were unable to reach our hospital due to logistic or socio-economic reasons. Second, as in an Indian family male is holding the economic status of the family, any health problem in males was given prior attention. Third, the exposure of males to the mosquitoes' bites is more compared to females. Of all the cases positive for single step PCR, 83.8% (377/450) of cases were found positive for *P. falciparum* by either ICT or QBC; resulting in 16.2% of more accuracy in PCR based detection of *P. falciparum.*

The sizable number of adults included in this study with severe malaria could be due to lack of premunition because of low and markedly seasonal transmission of malaria in this area. Another possibility could be due to concentration of severe cases being referred to this hospital for availing tertiary care facilities. Many patients attaining to this hospital may have administered anti-malarial treatments either from the health workers or from different health care facilities in the periphery. The finding of such positive cases in our study may have anti-malarial drugs resistant strains. Along with normal hemoglobin genotype (HbAA), we have found 30 patients with sickle cell trait and 14 patients with sickle cell anemia.

In this study we have found 15-25 years age group were more vulnerable to severe malaria and required hospitalization followed by 26-35 years of age group. Recently similar observations have been reported in two different studies from India [6,14]. In last two decades, the spectrum of severe malaria have been changed significantly [15]. Along with CM and SMA, other factors like jaundice, ARF and hepatic dysfunction are now contributing to malarial mortality. Studies on the spectrum of severity are necessary for better understanding of the dynamics of infection complexity and immune interaction in adults [16]. In the present study, fever along with ARF was the commonest clinical presentation followed by CM. The emergence of ARF as an important clinical manifestation of

severe *P. falciparum* malaria in adults has also been described in earlier studies from Vietnam and from different parts of India [14,15,17]. Several hypotheses such as mechanical obstruction by infected erythrocytes, immune mediated glomerular and tubular pathology, fluid loss due to multiple mechanisms and alterations in the renal microcirculation, etc, have been proposed as causative mechanism of ARF. It has been reported that ARF may be caused due to infection with *P. Malariae.* The presence of *P. malariae* in patients with ARF in our study population may not be ruled out as the prevalence of this species is high in Odisha [18]. In severe malaria cases usually ARF is associated with other complications [19]. In our study of 163 cases with ARF, CM was found in 49 cases, hepatic dysfunction in 62 cases, SMA in 14 cases, thrombocytopenia in 18 cases and respiratory distress in 16 cases.

SMA is the cause of fatal outcome in children rather than in adults [20]. Severe malaria with reduced level of hemoglobin (<5 mg/dL) was observed in 46 (10.2%) cases in our study. It has been suggested that *P. falciparum* glycosylphosphatidylinositol toxin interacts with the non parasitized red cells membrane contributing to malarial anemia [21]. The incidence of anemia in our patients is higher compared to 7.7% reported by Das LK et al. [4]. whereas lower compared to two studies in India [6,22]. The lower incidence of anemia with microcytic red cells in our patients might be due to presence of alpha thalassemia, a malaria protective hemoglobin disorder highly prevalent in study area [23].

Hepatic dysfunction characterized by increased level of liver enzymes was noticed in 21.6% of cases. This incidence was comparable in all age groups. Hepatic dysfunction occurs mainly due to sequestration of parasite infected red cells in the liver capillaries resulting ischemia [24]. In this study we have observed that along with the raised liver enzymes value, 79.4% of cases had raised bilirubin level (>2 mg/dL), while the incidence of jaundice alone without raised level of liver enzymes was 27.8% depicting the invasion of red cells by *P. falciparum* resulting hemolysis and increased bilirubin level. The incidences of jaundice in adults in other parts of India were 15.0% [6] and 18.8% [7] which were low comparable to our data. Asma et al. [6] and Croft AM et al. [25] have proposed the possible role of anti-malarial drug toxicity as an underlying

contributing factor for causing damage to hepatocytes and leakage of enzymes.

The other major clinical feature observed in this study was hypoglycemia in 42 (9.3%) cases. This finding is in accordance with 8.0 % incidence of hypoglycemia in South-East Asian adults [26]. Hypoglycemia was associated with CM (11, 26.2%), ARF (11, 26.2 %), Jaundice (9, 21.4 %) and SMA (5, 11.9 %) in our study. Hypoglycemia in *falciparum* malaria is usually ascribed to increased glucose use and impaired glucose production caused by the inhibition of gluconeogenesis. It has been reported that patients with prolonged fasting usually had hypoglycemia [27]. Though we have not investigated the duration of fasting in these patients during infection period, this might be a factor.

In severe *P. falciparum* malaria, respiratory distress develops in 25.0 % of adults due to respiratory compensation of metabolic acidosis, noncardiogenic pulmonary edema, concomitant pneumonia, and severe anemia [28]. In our study 18.4% of cases had respiratory distress with majority in the 46-55 years age group. Recently similar observation has been reported on eHealthMe study from FDA and social media reports [29].

Severe malaria is associated with thrombocytopenia. The various mechanism causing thrombocytopenia are coagulation disturbances, splenomegaly, bone marrow alterations, antibody mediated platelet destruction, oxidative stress etc. [30]. Many studies have reported the high incidence of thrombocytopenia with *P. falciparum* malaria. In our study, the incidence of thrombocytopenia was 15.1% which is very low compared to earlier studies [6,30-32,33]. Recently, in a multi institutional study thrombocytopenia was defined as a marker of disease severity and has a low prognostic utility, triage and management in adults with *falciparum* malaria [33].

Fourteen patients had *P. falciparum* malaria with sickle cell anemia presented with multiple clinical symptoms. The commonest symptom was vaso-occlusive crises (8/14) followed by jaundice (6/14), hepatic dysfunction (5/14), CM (4/14), SMA (4/14), ARF (3/14) and respiratory distress (2/14). The mean hemoglobin level was 7.6 mg/dL, ranging from 3.4 mg/dL to 10.9 mg/dL. During hospitalization 3 patients required blood transfusion. Surprisingly along with sickle cell anemia, we have registered 30 patients (6.7%) with sickle cell trait in severe *P. falciparum* malaria. The common causes of severity in these patients were CM and ARF. It has been hypothesized that, sickle cell trait protects against severity of disease due to *P. falciparum* malaria [34]. The finding of severe malaria with sickle cell trait in this region could be due to two reason; (1) the prevalent of sickle cell gene in the study area was found to be 21% [35]. (2) negative epistatic interaction between sickle cell trait and alpha thalassemia on *P. falciparum* malaria [36]. Though we have not analyzed the presence of alpha thalassemia in our patients, the prevalence of this inherited hemoglobin disorder in the study area is approximately 50% [23]. The presence of microcytic red cells picture in 41.3% of our patients also corroborated the presence of alpha thalassemia.

From all the above discussion, the incidence of SMA, CM and death was high in patients with > 55 years of age. This data is opposite to the hypothesis that in endemic area, the older age group developed partial immunity against malaria and got protection from severe disease. This severity in older age group might be due to the reduced immune protection in older age or different immune responses that are related to age may be responsible for the different outcomes [37].

We have recorded 27 (6.0%) deaths in this study. Both CM and ARF are major clinical complications responsible for death. In 22 (81.5%) cases, two or more complications were present indicating poorer prognosis and death as the number of complications increases. The highest percentage (10.0%, 4/40) of death was found in patients with > 55 years of age followed by 15-25 years of age group (7.9%, 12/151). This might be due to reduced immune mediated resistance against malarial infection in older age. The later might be due to over exposure to malaria infection. There were three deaths among patients with sickle cell anemia (21.4%, 3/14). All the three patients had repeated episodes of vaso-occlusive crises. Other causes responsible for death in these patients are CM and SMA. There were no studies describing the association of sickle cell anemia and malaria in India. Studies from Africa have represented that, though the protection afforded by sickle cell anemia is high compared to sickle cell trait, malaria is an important cause of death in patients with sickle cell anemia when affected [38,39].

We have certain limitations in this study. (1) We have not analyzed the effect of parasitemia with the clinical severity of malaria. (2) We have not recorded the number of cases diagnosed by either ICT or QBC separately in the initial screening procedure for *P. falciparum* infection, because the decision for diagnosis for *P. falciparum* infection by either ICT or QBC is depended upon treating physicians, so we have considered both the tests for infection.

5. CONCLUSION

The clinical severities of *P. falciparum* malaria may vary and depend upon the age of the patients, malaria endemicity, and transmission pattern. Of the various complications determining severity due to *P. falciparum* infection, CM and ARF were the two important factors responsible for fatality in these patients. It is important to prevent the exposure of malaria in adults in the age group of 15-25 years who are found to be most vulnerable for malarial infection. Along with early and appropriate anti-malarial drugs, exact diagnosis and management of complications are necessary to overcome the disease severity in a malaria endemic region.

CONSENT

Written informed consent was obtained from the patients (or from the guardian in case of minor). In case of unconscious patients, the consent has been obtained from patient's relative.

ETHICAL APPROVAL

This study was approved by Institutional Ethical Committee of Veer Surendra Sai Institute of Medical Sciences and Research, Burla.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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