

Study About Poor Prognosis and Mortality Rate of *P. Falciparum* Malaria Infection in Children in Bihar

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Abstract: Background: The epidemiology of malaria in children is difficult to assess as most of clinical symptoms are non-specific and most of the cases occur in settings where no routine testing is available. The infection with the species *Plasmodium falciparum* is one of the leading causes of child death from infectious diseases worldwide. Malaria, a non-fatal disease if detected promptly and treated properly, still causes many deaths in malaria-endemic countries with limited healthcare facilities.

Objective: Study about poor prognosis and mortality rate of *p.falciparum* malaria infection in children in Bihar.

Materials & Methods: The study was carried out between Oct 2005 and Sept 2006 in the Department of Paediatrics PMCH Patna. All children (up to 18 yrs of age with fever of short duration visited to hospital either in OPD or indoor without any documented pre-existing systemic illness were included in this study. The cases for present study were selected on random basis amongst the case of malaria as per following protocol. Primary pool patients of all age groups, religion, presented with fever of short duration without any documented pre-existing illness and tested for malaria parasite via PBS (thick & thin smear) and rapid antigen test. Secondary pool cases from primary pool with definite diagnosis of *p. falciparum* malaria, were further divided into uncomplicated & complicated group according to WHO criteria 2000.

Results: About 150 cases were positive for *p.falciparum* malaria. Out of 150 cases under study 65 (43.33%) were complicated and 85 (56.67%) were uncomplicated cases of *p. falciparum* malaria. Incidence of *p. falciparum* malaria among febrile children was 84%. Incidence of *p. falciparum* was 16% of total malaria cases. Cerebral anemia was commonest complication (29.23%) of *p. falciparum* infection followed by jaundice (29.2%), hypoglycaemia (29.2%), and severe anemia (24.6%). MODS (21.33%), ARDS (3.07%), shock (3.07%), DIC (1.5%), acidosis (4.61%), ARF (6.15%) were uncommon complications. Number of mortality in complicated malaria was 8 which were 12.3% of complicated malaria and 5.33% of total *p.falciparum* malaria. Incidence of mortality rate in cerebral malaria was 21.05% which was 50% of total death, in severe anemia 6.25%, in ARF 50%, in shock 50%, pulmonary edema 100% and in MODS 35.71% respectively.

Conclusion: Children who were suffering with pulmonary edema, shock, ARF, and cerebral malaria have poor prognosis because mortality rate in the above complications is very high.

Keywords: *P. plasmodium*, MODS- multiorgan dysfunction syndrome, ARF-acute renal failure, DIC-disseminated intra vascular coagulation

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I. Introduction

Malaria is caused by *Plasmodium* parasites. The parasites are spread to people through the bites of infected female *Anopheles* mosquitoes, called "malaria vectors." There are 5 parasite species that cause malaria in humans, and 2 of these species – *P. falciparum* and *P. vivax* – pose the greatest threat.¹ In 2017, *P. falciparum* accounted for 99.7% of estimated malaria cases in the WHO African Region, as well as in the majority of cases in the WHO regions of South-East Asia (62.8%), the Eastern Mediterranean (69%) and the Western Pacific (71.9%). *P. vivax* is the predominant parasite in the WHO Region of the Americas, representing 74.1% of malaria cases.¹

According to the latest *World malaria report*, released in November 2018, there were 219 million cases of malaria in 2017, up from 217 million cases in 2016. The estimated number of malaria deaths stood at 435000 in 2017, a similar number to the previous year. The WHO African Region continues to carry a disproportionately high share of the global malaria burden. In 2017, the region was home to 92% of malaria cases and 93% of malaria deaths. In 2017, 5 countries accounted for nearly half of all malaria cases worldwide:

Nigeria (25%), the Democratic Republic of the Congo (11%), Mozambique (5%), India (4%) and Uganda (4%). Children under 5 years of age are the most vulnerable group affected by malaria; in 2017, they accounted for 61% (266 000) of all malaria deaths worldwide.¹

India is the major contributor to malaria burden in Southeast Asia.² In a recent study by “million death collaboration”, it was estimated that malaria accounts for 205,000 deaths per year in India, with 55,000 deaths occurring in early childhood.³ These numbers though have been questioned by some⁴ as they do highlight that the problem is much more than previously presumed.

Malaria due to *P. falciparum* has been historically associated with severe complications and mortality. However, *P. vivax* is now increasingly being reported as a cause of severe malaria from countries across the globe. Unusual manifestations like glomerulonephritis and gastroenteritis have also been reported.⁵

II. Materials & Methods

Longitudinal cohort study was carried out between Oct 2005 and Sept 2006 in the Department of PMCH, Patna. All children upto 18 yrs of age with fever of short duration visited to hospital either in OPD or indoor without any documented pre-existing systemic illness were included in this study. The cases for present study were selected on random basis amongst the case of malaria as per following protocol.

1. Primary pool- patients of all age groups, religion, presented with fever of short duration without any documented pre-existing illness and tested for malaria parasite via PBS (thick & thin smear) and rapid antigen test.
2. Secondary pool- cases from primary pool with definite diagnosis of *p. falciparum* malaria, were further divided into uncomplicated & complicated group according to WHO criteria 2000.

Relevant investigations done were: CBC, renal profile- blood urea, serum creatinine; liver function test- serum bilirubin, SGPT & SGOT, alkaline phosphatase, prothrombin time; blood sugar (random); serum fibrinogen & FDP; serum electrolytes- Na⁺, K⁺, HCO₃⁻; X-ray chest (PA view) and CT scan of brain (where needed). Final pool- those cases with *p.falciparum* either complicated or uncomplicated as per inclusion criteria were finally selected for present study.

III. Results

Out of 937 cases of malaria 150 (16%) were proved to be suffering from *p.falciparum* infection. Out of 150 cases of *p.falciparum* 65 cases (43.33%) were complicated according to WHO 2000 criteria and remaining 85 cases (56.7%) were uncomplicated.

Table 1: Different types of *p.falciparum* malaria complications

Types of complications	No. of cases	Male	Female
Cerebral malaria	19 (29.23%)	13 (68.42%)	6 (31.58%)
Hepatitis with jaundice	19 (29.23%)	11 (57.89%)	8 (42.11%)
Severe anemia	16 (24.61%)	7 (43.75%)	9 (56.25%)
Hypoglycaemia	19 (29.23%)	11 (57.89%)	8 (42.11%)
Shock	2 (3.07%)	1 (50%)	1 (50%)
ARDS	2 (3.07%)	2 (100%)	0
DIC	1 (1.53%)	0	1 (100%)
Acidosis	3 (4.61%)	2 (66.6%)	1 (33.94%)
ARF	4 (6.15%)	2 (50%)	2 (50%)
MODS	14 (21.53%)	8 (57.14%)	6 (42.86%)

Table 2: Mortality rate in cases under study in complicated and uncomplicated *p.falciparum* infection

	No. of cases	No. of deaths
Complicated <i>p. falciparum</i> malaria	65	8 (12.3%)
Total <i>p.falciparum</i> malaria	150	8 (5.33%)

Table 3: Age group distribution of mortality rate in severe *p.falciparum* malaria among cases under study (n=8)

	No. of cases	Cases of complicated <i>p.falciparum</i> malaria	Death
<1 yr	3	2	1 (50%)
1-5 yrs	40	19	2 (10.50%)
5-10 yrs	60	29	4 (13.8%)
10-15 yrs	38	13	1 (7.7%)
>15 yrs	9	2	0 (0%)

Table 4: Incidence of mortality rate in different types of complications in *p.falciparum* malaria

Types of complications	No. of cases	No. of died cases	Incidence of total death
Cerebral malaria	19	4 (21.05%)	50%
Pulmonary edema	2	2 (100%)	25%
Shock	2	1 (50%)	12.5%

Severe anemia	16	1 (6.25%)	12.5%
ARF	4	2 (50%)	25%
MODS	14	5 (5.7%)	62.5%

Table 5: Poor prognosis in types of complication in p.falciparum malaria among cases under study

Complications	No. of cases	Mortality
Pulmonary Edema	2	2 (100%)
Shock	2	1 (50%)
Cerebral malaria	19	4 (21.05%)
ARF	4	2 (50%)

IV. Discussion

A classic description would include fever with chills accompanied by constitutional symptoms consisting of headache, body ache, fatigue, dizziness and malaise.⁶ The salient differences from adults include, increased incidence of cough and respiratory distress (acidosis), convulsions, pretreatment hypoglycemia and neurological sequelae whereas, jaundice, pulmonary edema, renal failure and bleeding disturbances are less common.⁷

In the present study cerebral anemia was commonest complication (29.23%) of p. falciparum infection followed by jaundice (29.2%), hypoglycaemia (29.2%), and severe anemia (24.6%), MODS (21.33%), ARDS (3.07%), shock (3.07%), DIC (1.5%), acidosis (4.61%), ARF (6.15%) were uncommon complications. Cerebral malaria is the most common clinical presentation and cause of death in adults with severe malaria. The onset may be dramatic with a generalized convulsion, or gradual with initial drowsiness and confusion, followed by coma lasting from several hours to several days. The strict definition of cerebral malaria requires the presence of *P. falciparum* parasitemia and the patient to be unrousable with a Glasgow Coma Scale score of 9 or less, and other causes (e.g. hypoglycemia, bacterial meningitis and viral encephalitis) ruled out.⁸ The mortality of cerebral malaria ranges from 10% to 50% with treatment. Most survivors (>97% adults and >90% children) have no neurologic abnormalities on hospital discharge.⁹ Pulmonary edema is usually noncardiogenic and may progress to acute respiratory distress syndrome (ARDS) with an increased pulmonary capillary permeability. Volume overload and hypoalbuminemia may aggravate pulmonary capillary leakage. Chest radiograph abnormalities range from confluent nodules to basilar and/or diffuse bilateral pulmonary infiltrates. Noncardiogenic pulmonary edema rarely occurs with *P. vivax* and *P. ovale* malaria.¹⁰

Dhingra N et al¹¹ study revealed of all coded deaths at ages 1 month to 70 years, 2681 (3.6%) of 75 342 were attributed to malaria. Of these, 2419 (90%) were in rural areas and 2311 (86%) were not in any health-care facility. Death rates attributed to malaria correlated geographically with local malaria transmission rates derived independently from the Indian malaria control programme. The adjudicated results show 205 000 malaria deaths per year in India before age 70 years (55 000 in early childhood, 30 000 at ages 5–14 years, 120 000 at ages 15–69 years); 1.8% cumulative probability of death from malaria before age 70 years. Plausible lower and upper bounds (on the basis of only the initial coding) were 125 000–277 000. Malaria accounted for a substantial minority of about 1.3 million unattended rural fever deaths attributed to infectious diseases in people younger than 70 years.

Mittal M et al⁵ study showed overall, 198 cases were included, 128 (64.6%) were due to Plasmodium vivax, 66 (33.3%) due to P. falciparum and 4 (2%) had evidence of mixed infection of Pv + Pf. The clinical features on admission were similar in all the groups. In total, 64/128 (50%) patients with vivax infection had one or more complications with severe anemia in 33 (26%) and cerebral malaria in 16 (12.5%). Six deaths were reported in P. vivax cases. In the falciparum group, 52 (78.8%) had one or more complications with severe anemia in 37 (56.1%) and cerebral malaria in 24 (36.4%). Four deaths were reported in P. falciparum cases.⁵

P. falciparum was the most common etiologic agent in both severe and non-severe malaria causing 75% of all malaria cases overall. However, P. falciparum infection was the predominant causative agent of severe malaria, causing 85% of cases. Only 8.5% of severe malaria cases were caused by P. vivax, while 6.4 % were due to dual infection by both species of parasites. Therefore P. falciparum infection was more likely to cause severe malaria than P.vivax or mixed infection, and this was found to be statistically significant (P=0.0155).¹²

A prospective study done by N. Mohanty et al revealed 216 children with complicated falciparum malaria showed hepatopathy in 33.3% of cases with a higher incidence in children aged above five years. Bilirubin and alanine aminotransferase were moderately raised in most cases. No significant association with other common complications and no higher risk of mortality were observed.¹³ A prospective study done in 216 children with complicated falciparum malaria showed hepatopathy in 33.3% of cases with a higher incidence in children aged above five years. Bilirubin and alanine aminotransferase were moderately raised in most cases. No significant association with other common complications and no higher risk of mortality were observed.¹³

S. Bag et al¹⁴ study showed of the 50 cases, 4 patients (8%) had jaundice, and this is almost similar to the series of Ramchandran et al¹⁵ and Gupta et al¹⁶. Rise of serum bilirubin in falciparum malaria patients is considered to be due to hemolysis of peripheral parasitized red blood cell, and impairment in bilirubin transport because of reticulo endothelial blockage and disturbances of hepatocyte microvilli.¹⁷ Thus the conjugated, unconjugated and mixed type of hyperbilirubinemia observed in the present study might be due to aforementioned reasons. Fatty changes, liver cell necrosis, nuclear vacuolation and liver cell congestion have been observed in falciparum malaria infection.¹⁸

Renal manifestations in malaria include acute renal failure, glomerulonephritis and nephrotic syndrome.¹⁹ Study also encountered 2 children with severe disease with

hyperparasitaemia, presenting as generalized edema in absence of features of glomerulonephritis or significant proteinuria. This can probably be explained by increased capillary permeability, consequent to systemic inflammatory response.^{20,21} Subtle renal impairment in salt and water handling may also contribute.²²

Indications for hospitalization include cerebral malaria, severe anaemia, haemoglobinuria, renal failure, pulmonary oedema, coagulopathy, severe thrombocytopenia, shock, high parasitaemia, metabolic acidosis, hypoglycaemia, intractable vomiting, dehydration, seizures, or altered level of consciousness.²³ Among them, respiratory distress and impaired consciousness are indicators of a poor prognosis that should trigger immediate parenteral antimalarial treatment with any effective antimalarial first available. So eventually less efficacious as in non-malaria associated seizures²⁴, intravenous diazepam should be administered for any seizure lasting more than 5 minutes.²⁵

Falciparum malaria affect all ages with multiple-systemic complications which varies in different age group. Satpathy SK et al²⁶ studied 242 children with complicated Falciparum malaria with a median age of 6.5 years to look for occurrence of different complications in younger and older age groups and overall mortality picture. Unarousable coma (40.5%), severe anemia (26.03%), repeated seizures (46.2%) and hepatopathy (32.2%) were commonest complications. Under five children had higher risk of development of cerebral malaria (P<0.01), severe anemia (P<0.05) and seizures (P<0.001); whereas above five children had higher risk of acute renal failure (P<0.05) and malarial hepatopathy (P<0.02). Over all mortality was 9.9%, cerebral malaria being the commonest cause (6.6%). Multi-system involvement was seen in 58.4% cases of death. Children having pulmonary edema, shock and cerebral malaria had high case fatality rate.²⁶

Based on the results of Zeidan ZA et al²⁷ study, severe malaria in children was a disease of young children with a median age of 4 years; 75% of the children were below 6 years of age. The majority of mortalities (93%) occurred below the age of nine. This result agreed with a previous study by Imbert and Luxerborge,^{28,29} who reported that severe malaria cases and deaths decreased with increasing age.

Mundhe R et al³⁰ study revealed case fatality rate observed in our study was 13.63%. It was highest in multi organ involvement as compared to single organ involvement. Case fatality rate was highest in ARDS (81.81%) as compared to jaundice (22%), cerebral malaria (19.64%) and renal failure (10.71%). Similar findings were noted by Kochar D, et al³¹ and Patil VC³².

V. Conclusion

The clinical presentation of malaria depends on the severity and rapidity of infection and the immune response of the host. *P. falciparum* causes serious illness and children usually present early and undergo a rapid downhill course, if not diagnosed and treated early. The signs and symptoms in children range from asymptomatic infection to life threatening illness.

During this study, it was observed that children who were suffering with pulmonary edema, shock, renal failure and cerebral malaria have poor prognosis because mortality rate in the above complications was very high. So, it should be screened for any child present with fever along with hepatomegaly and or splenomegaly to diagnose early. Once diagnosed *p.falciparum* malaria, should be treated and managed urgently and appropriately to prevent dreaded complications.

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