Research Article

Prognostic factors in severe and complicated malaria

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Abstract

Background: The spectrum of clinical picture of malaria ranges from the most benign febrile illness, which is completely curable with a simple course of chloroquine tablets to the most serious and life-threatening illness, even with very drastic therapeutic measures. That is the reason that has led to the studies from different parts the world to find out the clinical and laboratory parameters that may show a prognostic significance in this very common and frequently encountered condition.

Objective: (1) To identify the various clinical and laboratory parameters showing prognostic significance in severe and complicated malaria; (2) to study the relationship of these factors with mortality and morbidity; and (3) to find out the therapeutic outcome with various antimalarial drugs in such severe and complicated malaria cases.

Materials and Methods: A cross-sectional, observational study was carried out in LG Hospital, Ahmedabad. Adult patients of both the sexes admitted that clinical history suggestive of severe and/or complicated illness were included in the study.

Result: In this study, 100 adult male and female patients were studied. The male to female ratio was 3:2. The maximum number of patients was in the age range of 31–40 years. The overall mortality in this study was 10%, with more number (25%) of older patients showing fatal outcome with severe and complicated malaria. Anemia (35%) was the most common complication but with less mortality. Only one patient with *Plasmodium vivax* lead to fatal outcome, but he also showed very high parasitemia (grade IV), and the cause of death was acute respiratory distress syndrome.

Conclusion: Mortality is higher with *Plasmodium facliparum* malaria. Organ dysfunction is associated with higher mortality and is a sign of poor prognosis. Anemia, hypoglycemia, coma, convulsion, organ dysfunction, lactic acidosis hyperparasitemia, and leucocytosis are the prognostic factors in severe and complicated malaria as defined by the WHO. They are easily detectable and treatable and, hence, signify the importance of an early detection of these complications to decrease the morbidity and mortality owing to severe and complicated malaria.

KEY WORDS: Malaria, complicated, severe, prognostic factors, mortality

Introduction

Malaria is known to humanity since the ancient times, with the mention of its clinical features in Ayurvedic literature.

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Malaria, inspite of being preventable and curable, is still one of the most prevalent infectious diseases, especially, in the Asian and African countries. According to the recent reports in 2013, there are a total of 104 countries and territories in which malaria is presently considered endemic. Globally, the WHO estimates that 627,000 deaths (uncertainty range 473,000–789,000) occurred in 2012, with most deaths (77%) in children under 5 years of age.[1] Severe complicated malaria is mainly caused by *Plasmodium facliparum* infection and, in some cases, by *Plasmodium vivax*. Malaria affects almost every organ system of the body and can lead to various complications such as anemia, lactic acidosis, thrombocytopenia, hepatic dysfunction, acute respiratory distress

syndrome (ARDS), neurological symptoms, acute renal failure, gastrointestinal bleeding, and heart failure. The spectrum of clinical picture ranges from the most benign febrile illness, which is completely curable with a simple course of chloroquine tablets, to the most serious and life-threatening illness, even with very drastic therapeutic measures. That is the reason that has led to the studies from different parts the world to find out the clinical and laboratory parameters, which may show a prognostic significance in this very common and frequently encountered condition.

From all the studies and some suggestions of the just exports, the WHO has also implicated some factors showing some prognostic importance in the outcome of malaria. Some of these features are as follows:

Clinical features
- age <3 years
- coma
- convulsions-witnessed/reported
- absent corneal reflexes
- decerebrate rigidity
- clinical signs of organ dysfunction
- retinal hemorrhages

Laboratory examination
- hyperparasitemia
- peripheral schizontemia
- peripheral leucocytosis
- PCV <20%
- Hb <7 g%
- blood urea > 60 mg%
- serum creatinine > 3 mg%
- low CSF glucose
- SGOT increased by three times normal

Knowledge of these factors may help us in an earlier selection of drugs with lesser chances of resistance rather than waiting for a response from chloroquine or other newer less-toxic drugs.

Ours is a tertiary-care institute catering health services to the patients coming from overcrowded, lower socioeconomic society; hence, we encounter many cases of severe and complicated malaria who ultimately require higher therapeutic measures. Hence, a prospective study to find common prognostic factors will help in the management of such cases.

Objective

1. to identify the various clinical and laboratory parameters showing a prognostic significance in severe and complicated malaria.
2. to study the relationship of these factors with mortality and morbidity.
3. to find out the therapeutic outcome with various antimalarial drugs in such severe and complicated malaria cases.

Materials and Methods

A cross-sectional, observational study was carried out in LG Hospital, a tertiary-care teaching hospital attached with AMC MET Medical College, Ahmedabad, Gujarat, India. Adult patients of both the sexes admitted that clinical history suggestive of severe and/or complicated malaria served as the study material and was studied in detail by the following method. All such cases of malaria, irrespective of the status of smear examination for malarial parasites, that is, both the smear-positive and smear-negative cases (considered to be suffering from malaria on clinical ground and therapeutic response to antimalarial agents) were studied.

For categorization of the severe and complicated malaria, the WHO criteria was used.[2]

Signs	Manifestation
Cerebral malaria	Failure to localize or respond appropriately to noxious stimuli Coma persisting for > 30 min after generalized convulsions Coma not owing to any other cause
Convulsion	More than two generalized seizures in 24 h
Acidemia/acidosis	Manifested as labored deep breathing. Arterial pH <7.25 or plasma HCO3 < 15 mMol/L Venous lactate level > 15 mMol/L
Severe normocytic normochromic anemia	Hematocrit < 15% or Hb < 7 g% with a parasitemia level of > 1 lakh/unit.
Renal failure	Urine output of 24 h < 400 mL in adult No improvement with rehydration Serum creatinine > 3 g %
Pulmonary edema/ARDS	Noncardiogenic pulmonary edema often aggravated by overhydration
Hypoglycemia	Blood glucose level < 40 mg%
Hypotension/ shock	Systolic blood pressure < 80 mm Hg Core/skin temperature difference of > 10˚C
Bleeding/DIC	Significant bleeding and hemorrhage from gums, nose, and GIT Evidence of DIC
Hemoglobinuria	Macroscopic black, brown or red urine Not associated with effects of oxidant drugs and RBC enzyme defects
Extreme weakness	Prostration
Hyperparasitemia	Parasite level > 5% in nonimmune individuals
Jaundice	Serum bilirubin level > 3 mg %
Leucocytosis	WBC count > 15,000/ult

Detailed clinical history and physical examination were performed. Both the thick and thin peripheral blood smears

were examined for the malarial parasites, and grading was done as follows:

grade I: 1–10 parasites/1,000 fields examined
grade II: 10–100 parasites/1,000 fields examined
grade III: 1–10 parasites/field examined
grade IV: > 10 parasites/field examined

The kits for rapid diagnostic methods to detect malaria were obtained during the later part of the study, namely paracheck and optimal kits, to detect malarial parasite infection in mainly smear-negative patients.

Result

In this study, 100 adult male and female patients were studied. The male to female ratio was 3:2. The maximum number of patients was in the age range of 31–40 years, but the frequency distribution was found equal in all age groups, with slightly less incidences in patients older than 50 years of age. The overall mortality in this study was 10%, with more number of older patients (25%) presenting fatal outcome with severe and complicated malaria [Table1].

Various complications seen in this study are enumerated in Table 2 in the order of frequency of occurrence. Anemia was the most common complication but with less mortality and, ARDS was less common but was the most fatal. The majority of the patients (45%) with severe and complicated malaria presented fever lasting for more than 5 days, and mortality was also observed to be higher with longer duration of fever. But, no direct linear relationship was found with the duration of fever and development of fatal complications. As shown in Table 3, significantly higher percentage of patients with severe and complicated malaria showed fever either < 5 days (30%) or > 10 days (25%), but, in both these groups, the mortality was not very high (3.3% and 4%, respectively).

About 80% of the 100 cases of severe and complicated malaria showed smear-positive malaria and about 53% were *P. facliparum*, while two patients presented a combined infection with *P. facliparum* and *P. vivax*. None of the patients showed either ovale or malariae parasites [Table 4]

About 7% of smear-negative cases by peripheral smear examination were found to be positive by paracheck method, and 3% were found to be positive by optimal method.

In all, 10% of patients in this study were found to be negative for malarial infection by both the smear examination and other rapid diagnostic tests for malaria. These patients were included in the study on the basis of high clinical suspicion, and they were treated by antimalarial agents with good recovery in reasonable time frame, and none of them showed fatal outcome.

The laboratory parameters observations are shown in Table 5.

Prognostic factors observed in the study are shown in Table 6 in the order of frequency of their occurrence except for the duration of fever, as it is not included by the WHO list of prognostic factors. Coma was the commonest prognostic factor (50%) observed with a mortality of 4%, while the mortality was 100% in two patients with lactic acidosis.

The overall mortality in this study was 10% and 90% of which were male subjects. Only one patient with *P. vivax* presented a fatal outcome, but he also showed very high parasitemia (grade IV), and the cause of death was ARDS. One patient with mixed parasitemia showed acute renal failure with fatal outcome. The various causes of death are shown in Table 7 in the order of frequency of their occurrence.

Discussion

Many clinical studies have been published mentioning malaria as one of the important health hazard, particularly, the one caused by *P. facliparum*, as it mainly causes severe and complicated malaria, but *P. vivax* can also not be thought to be benign, as it also significantly causes mortality. The majority of the patients showed *P facliparum* malaria (53%) with a significant case of *P. vivax* too. Prognostic factors help to identify cases earlier and prompt an initiation of treatment to reduce mortality and morbidity.[2,3]

Malaria is commonly found in all age groups except for the first 3 months of life where maternal immunity may give some protection.[4] Extremes of age may be considered a important prognostic factor, as this study also showed a higher mortality (25%) in patients aged above 51 years. White[3] also reported the same figures in the study of complicated malaria and postulated that increased mortality in extremes of age was owing to diminished immunity, concomitant illness, and poor response to treatment.[3] In this study, we have not included pediatric patients. The mortality rate of 7% in the age group 21–40 years is comparable with other studies.[5,6] Thus complications of malaria may have fatal outcomes even in young adults and should not be considered benign at any age.

Male subjects are affected more commonly by malaria owing to clothing habits and outdoor work resulting in higher chances of mosquito bites.[7] Similarly, the occurrence of malaria was higher in male subject in this study, and the mortality when complications arise is higher in males (15%) when compared with the female subjects (2.5%). It also found, in this study, that those with severe and complicated malaria who presented with < 5 days of fever showed a lesser mortality of 3.33% when compared with a higher mortality of 17.7% in those who presented with 5–10 days of duration of fever, which is comparable with the other studies.[3,8] Thus, it implies that prompt diagnosis and initiation is essential to control mortality in severe and complicated cases of malaria.

As *P. facliparum* is the most serious form of disease, particularly, in tropics, peripheral smear is one of the most important prognostic factors. In this study, the maximum number of patients showed grade III (21%) or grade IV (44%) parasitemia index, and the mortality observed in these patients was 10%. Field et al. postulated that predominance of mature parasites indicates that a greater proportion are sequestered and carries a worse prognosis for any parasitemia

Table 1: Age and sex incidence

Age in years	Number of patients		Total	Mortality (%)
	Male	Female		
11–20	4	8	12	–
21–30	12	10	22	4.54
31–40	17	18	35	8.57
41–50	20	3	23	17.39
>51	7	1	8	25
Total	60	40	100	

Table 2: Complications seen in patients

Complication	No. of patients (%)	Mortality (%)
Anemia	35 (35)	8.57
Cerebral malaria	30 (30)	3.33
Hepatic dysfunction	25 (25)	20
Renal dysfunction	20 (20)	15
Hyperpyrexia	15 (15)	–
Hypoglycemia	10 (10)	–
ARDS/respiratory complication	5 (5)	60
Algid malaria	5 (5)	–
Others (bone marrow depression, CCF, DIC, septicemia)	5 (5)	20

Table 3: Duration of fever before hospitalization

Duration of fever (days)	No. of patients (%)	Death	Complication							Mortality (%)
			Cerebral malaria	Hypoglycemia	Anemia	ARF	Hepatic dysfunction	ARDS	Other	
<5	30 (30)	1	2	–	10	4	6	–	–	3.33
5–10	45 (45)	8	20	3	15	10	10	2	3	17.7
>10	25 (25)	1	8	7	10	6	9	3	2	4
Total	100	10	30	10	35	20	25	5	5	–

Table 4: Peripheral smear examination

Parasite	Smear examination					Total
	Positive				Negative	
	Grade I	Grade II	Grade III	Grade IV		
P. falciparum	5	5	15	28	–	53
P. vivax	–	3	5	15	–	23
Both	–	–	1	1	–	2
Total	5	8	21	44	20	100

Table 5: Laboratory parameters

Investigation	No. of patients (%)	Mortality (%)
Hemoglobin < 7g%	35 (35)	8
S. bilirubin > 3 g%	25 (25)	5
Blood urea > 60 mg%	20 (20)	3
S. creatinine > 3 g%	20 (20)	3
RBS < 40 mg%	10 (10)	0
Lactic acidosis (Serum HCO_3^- < 15 mMol/L)	2 (2)	

Table 6: Prognostic factors

Prognostic factor	Number of patients		Mortality (%)
	Male	Female	
Coma (all causes)	30	20	4
Organ dysfunction isolated and combined)	20	10	23.33
Hyperparsitemia (grades III and IV)	18	7	12
Convulsion	15	5	5
Anemia (isolated)	8	17	3
Hypoglycemia (with or without coma)	4	6	–
Hypotension	5	5	–
Lactic acidosis	2	–	100
Duration of fever (5–10 days)	30	15	17.7

Table 7: Causes of mortality

Causes of death	Total number of patients	Death			
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ARDS	5	3	1	–	4
Acute renal failure	20	2	–	1	3
Secondary septicemia	5	2	–	–	2
Cerebral malaria	30	1	–	–	1
Total		8	1	1	10

index; the same was found in this study too.[3] Thus, even with the availability of newer techniques today, peripheral smear still remains the main source of detection of malaria and an indicator of prognosis.

Parasitemia is one of the important factor indicating prognosis in malaria. In this study, only 25% of the study patients showed grade III/IV parasitemia index and of the ten subjects who died, only three showed grade III/IV parasitemia index. Moreover, in this study, there was a significant number of patients with severe and complicated malaria with lower grade parasitemia index; probably, a predominance of more mature parasites indicating that a greater proportion of parasites are sequestered, carrying worse prognosis for any parasitemia index.[6]

Prognostic factors postulated by the WHO in 1990 in severe and complicated malaria were found to be presenting prognostic significance in this study also.[2] The factors are hypoglycemia, anemia, ARDS, renal dysfunction, hepatic dysfunction, cerebral malaria, coma, leucocytosis, and lactic acidosis.

Mortality in this study was 10% and, as we included only severe and complicated malaria, this figure may not seem alarming, but the important aspect is that 2% of patients of *P vivax* infection also died even after hospitalization and treatment with antimalarial drugs. The majority of the patients was from poor socioeconomic class, who came late for the treatment, and some of them might have presented infection by chloroquine-resistant strains. Thus, this signifies that not only *P facliparum* but other features of infection also significantly affect the outcome of the disease.

Conclusion

Severe complicated malaria is common in tropics with high mortality especially in extremis of age with no sex predilection. Both *P facliparum* and *P. vivax* can cause severe and complicated malaria. Mortality is higher with *P facliparum* malaria. Organ dysfunction is associated with higher mortality and is a sign of poor prognosis. Anemia, hypoglycemia, coma, convulsion, organ dysfunction, lactic acidosis, hyperparasitemia, and leucocytosis are the prognostic factors in severe and complicated malaria as defined by the WHO. They are easily detectable and treatable and, hence, signify importance of early detection of these complications to decrease the morbidity and mortality owing to severe and complicated malaria.

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