

## Original Research Article

# Complicated malaria: relationship of complications and parasite load to outcome

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### ABSTRACT

**Background:** The incidence of complicated malaria cases is increasing day by day. Complicated malaria present in different ways in different places globally. If malaria is diagnosed and treated immediately, then the death rate is less than one percent. The objective was to study the relationship of complications and parasite load to outcome (mortality) among patients with complicated malaria.

**Methods:** The present hospital based Prospective Observational study was carried out among 100 cases of “Complicated malaria.” The present study was carried out at Department of General medicine, Kamineni hospitals, L. B. Nagar, Hyderabad.

**Results:** 71% patients were infected with *Plasmodium falciparum*, 25% with *Plasmodium vivax* and 4% with both *Plasmodium falciparum* and *vivax*. 12% patients deceased and 88% survived. The relationship between GCS, convulsions, pH, bicarbonate, lactate, hemoglobin, creatinine, SBP, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, PT, INR, aPTT, and outcome was statistically highly significant (p=0.000). The relationship between Total Bilirubin, RBS and outcome was statistically not significant (p=0.351). Multivariate analysis using logistic regression model, to determine the effect of studied variables on the final outcome, revealed no significant influence of studied variables in predicting the outcome (p>0.05). The relationship between increasing parasite load and outcome was studied, and it showed it was statistically highly significant (p=0.000).

**Conclusions:** The prognosis and outcome of patients with complicated malaria worsen as the parasite load increases and the probability of death increases markedly in such patients. The presentation of inappropriate parameters at admission, aid us in predicting poor outcome and appropriate treatment plan.

**Keywords:** Complicated malaria, Diagnosis, Falciparum, Vivax

### INTRODUCTION

Female Anopheles mosquito is known for transmitting malaria. Malaria is caused mainly by *vivax* and *falciparum* species in India.<sup>1</sup>

Globally, a significant proportion of the population is infected by malaria parasite annually. Nearly up to two million dies annually. Tropical Africa constitutes around

90% of the worldwide burden. Out of the remaining 10% of the worldwide burden, 66% of the cases are occurring from India, Brazil, and Sri Lanka. 80% of the total cases from Southeast Asia Region is seen in India.<sup>2</sup>

Of the most common species causing malaria in India, i.e., *falciparum* and *vivax*, *falciparum* is associated with complicated malaria, which results in various organ failures. The commonly encountered complications are

cerebral malaria (most common), black water fever, ARF, ARDS, DIC, hypotension, and shock. Morbidity and mortality are increased in associated HIV infection and pregnancy.<sup>3</sup>

The incidence of complicated malaria cases is increasing day by day. This is mainly due to mosquitoes becoming more and more resistant to insecticides. The parasite is also becoming more and more resistant to drugs like chloroquine.<sup>3</sup>

Large-scale migration of human population and increased travel to endemic areas from non-endemic areas and lack of proper caretaking behaviour is contributing to the spread of resurgence. Hence malaria remains a cause of constant threat to the public health.<sup>1</sup>

Complicated malaria present in different ways in different places globally. Presentation of complicated malaria seen at one place may not be same at another place. In endemic areas, cerebral malaria is very common among the pediatric population with increased mortality and morbidity. When compared to age group below five years, incidence of cerebral malaria is less common in the older age group due to immune-mediated response.<sup>2</sup>

If malaria is diagnosed and treated immediately, then the death rate is less than one percent. But in complicated malaria involving the vital organs, mortality increases significantly.<sup>1</sup> Early diagnosis and treatment reduces mortality and morbidity.<sup>3</sup>

Hence the present study was carried out to study the relationship of complications and parasite load to outcome among patients with complicated malaria.

## METHODS

**Study group, place and sample size:** The present hospital based Prospective Observational study was carried out among 100 cases of "Complicated malaria." The present study was carried out at Department of General medicine, Kamineni hospitals, L. B. Nagar, Hyderabad

### *Study period*

August 2011 and September 2013.

### *Study design*

Prospective Observational study

### *Inclusion criteria*

- Confirmed cases of complicated malaria as per the definition of "WHO 2000 criteria for Severe malaria",
- Patients willing to participate in the present study.

### *Exclusion criteria*

Patients with history of alcoholism, hepatotoxic drugs usage (Ex: Statins, Antituberculosis Therapy (ATT), Antiretroviral Therapy (ART), Paracetamol, etc), liver disease (Ex:- Wilson's disease, Hemochromatosis, Hepatocellular Carcinoma (HCC), positive viral serology (Ex:- Hepatitis B) are excluded from the present study.

### *Methodology*

All the patients included in the study group underwent a complete clinical and laboratory evaluation. The clinical evaluation consisted of making a note of age, sex, clinical symptoms of the patient, GCS (Glasgow Coma Scale) estimation, recording vital data-pulse rate, blood pressure, respiratory rate, and temperature. The laboratory evaluation consisted of Rapid diagnostic card test for *Plasmodium falciparum* and *vivax*, Peripheral Blood Smear (PBS)-Thick and Thin Blood Smear, Complete Blood Picture (CBP)-Hemoglobin (Hb), TLC (Total Leucocyte Count), Platelet count, Renal function tests-Blood Urea, Serum Creatinine, Random Blood Sugar (RBS), Coagulation profile-PT (Prothrombin Time), aPTT (activated Partial Thromboplastin Time) and INR (International Normalized Ratio), Liver function tests-Total Bilirubin (Direct and Indirect), SGOT, SGPT, ALP, Total Protein, Albumin, Globulin, Arterial Blood Gas (ABG) analysis-pH, PaO<sub>2</sub>, PaCO<sub>2</sub>, Bicarbonate, Venous Lactate level. Parasitic Load is estimated by counting the number of asexual parasites per high-power field (HPF) on a thick blood film. (1+ = 1-10 parasites per 100 HPF, 2+ =11-100 parasites per 100 HPF, 3+ =1-10 parasites per each HPF, 4+ = more than 10 parasites per each HPF).<sup>4</sup> The Outcome of this study is measured in terms of Mortality (Alive/Deceased)

### *Data analysis*

All the collected data was compiled in Microsoft Excel database. The data was presented as frequency tables, cross tables, simple bar charts, stacked bar charts, mean and standard deviation. Statistical analysis was performed using IBM SPSS version 21 software. The statistical significance of the relationship between variables under study and outcome, parasite load and outcome were determined by using Fisher's exact test. To determine effect of variables under study and the outcome, multivariate analysis using logistic regression model was done.

## RESULTS

In our study group out of 100 patients, 71 patients were infected with *Plasmodium falciparum* (71%), 25 patients were infected with *Plasmodium vivax* (25%) and 4 patients were infected with both *plasmodium falciparum* and *vivax* (4%) as shown in Table 1.

**Table 1: Species distribution of the present study.**

Patients infected with type of organisms		
Species	No. of patients	%
Patients infected with plasmodium falciparum	71	71.0
Patients infected with plasmodium vivax	25	25.0
Patients infected with plasmodium falciparum and plasmodium vivax	4	4.0
Total	100	100.0

In our study group out of 100 patients, 23 patients (23%) had Glasgow Coma Scale (GCS) <9, out of which 12 patients (52%) deceased and 77 patients (77%) had GCS >9, out of which 0 patients (0%) deceased. The relationship between GCS and Outcome was statistically highly significant (p-value = 0.000) as shown in Table 2.

**Table 2: Relationship between GCS and outcome.**

Glasgow coma scale (GCS)	Deceased	
	No. of patients	%
GCS > 9	77	77.0
GCS ≤ 9	23	23.0
Total	100	100.0

In our study group out of 100 patients, 16 patients (16%) had convulsions, out of which 11 patients (69%) deceased and 84 patients (84%) did not have convulsions, out of which 1 patient (1%) deceased. The relationship between Convulsions and Outcome was statistically highly significant (p-value = 0.000) as shown in Table 3.

**Table 3: Relationship between convulsions and outcome.**

Convulsions (GTCS)	Deceased	
	No. of patients	%
Absent	84	84.0
Present	16	16.0
Total	100	100.0

In our study group out of 100 patients, 12 patients (12%) deceased and 88 patients (88%) survived as shown in Table 4.

**Table 4: Survival rate of subjects in the present study.**

Outcome	No. of patients	Percent
Alive	88	88.0
Deceased	12	12.0
Total	100	100.0

**Table 5: Relationship between various complications and outcome.**

Complications	WHO Criteria	Deceased	Total	p-value (Fishers exact test)	RR	95% CI of RR	
						Lower	Upper
SBP	SBP < 80	3 (60%)	5	0.012	6.33	2.454	16.342
	SBP ≥ 80	9 (90%)	95				
GCS	GCS < 9	12 (52%)	23	0.000			
	GCS > 9	0	77				
Convulsions	Yes	11 (69%)	16	0.000	57.57	8.005	416.29
	No	1 (1%)	84				
Hemoglobin	< 5 gm/dl	3 (50%)	6	0.020	5.222	1.896	14.381
	≥ 5 gm/dl	9 (10%)	94				
Creatinine	> 3 mg/dl	9 (24%)	37	0.008	5.108	1.475	17.687
	≤ 3 mg/dl	3 (5%)	63				
RBS	<40 mg/dl	3 (75%)	4	0.500	8	3.451	18.546
	≥40 mg/dl	9 (9%)	96				
PT	> 20 sec	4 (57%)	7	0.004	6.643	2.641	16.706
	≤ 20 sec	8 (9%)	93				
INR	> 1.33	4 (57%)	7	0.004	6.643	2.641	16.706
	≤ 1.33	8 (9%)	93				
aPTT	> 40 sec	5 (50%)	10	0.002	6.429	2.502	16.515
	≤ 40 sec	7 (8%)	90				
Total Bilirubin	> 3 mg/dl	12 (14%)	88	0.351			
	≤ 3 mg/dl	0	12				
pH	< 7.25	9 (69%)	13	0.000	20.077	6.235	64.654
	≥ 7.25	3 (3%)	87				
PaO2/FiO2 ratio	< 200	11 (65%)	17	0.000	53.706	7.419	388.785
	≥ 200	1 (83%)	83				
Bicarbonate	< 15	11 (34%)	32	0.000	23.375	3.152	173.33
	≥ 15	1 (1%)	68				
Lactate	> 5	5	7	0.000	9.490	4.045	22.261
	≤ 5	7	93				

In our study, relationship between GCS, Convulsions, pH, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, plasma Bicarbonate, Lactate level (p-value = 0.000), Hemoglobin level (p-value = 0.020), serum Creatinine level (p-value = 0.008), SBP (p-value = 0.012), PT, INR (p-value = 0.004), aPTT (p-value =

0.002) and the Outcome was statistically highly significant.

In our study, relationship between serum Total Bilirubin (p-value = 0.351), RBS (p-value = 0.500) and the Outcome was statistically not significant.

**Table 6: Significance of complications in predicting the outcome (logistic regression).**

Significance of complications in predicting the outcome (logistic regression)						
	B	S. E.	Wald	df	Significance p-value	Exp (B)
SBP	0.820	207.156	0.000	1	0.997	2.269
GCS	14.131	1590.233	0.000	1	0.993	1370814.173
Convulsions	0.078	10024.451	0.000	1	1.000	1.081
Hemoglobin	-3.111	2028.510	0.000	1	0.999	0.045
Creatinine	-8.036	2157.514	0.000	1	0.997	0.000
RBS	-0.455	72.589	0.000	1	0.995	0.634
PT	-61.933	19323.743	0.000	1	0.997	0.000
INR	903.403	286047.854	0.000	1	0.997	0.000
aPTT	-0.656	1826.593	0.000	1	1.000	0.519
Total Bilirubin	1.232	485.332	0.000	1	0.998	3.428
pH	211.548	75440.488	0.000	1	0.998	7.486E+091
PaO <sub>2</sub> / FiO <sub>2</sub> ratio	-0.085	93.216	0.000	1	0.999	0.919
Bicarbonate	-3.982	2099.411	0.000	1	0.998	0.019
Lactate	-2.002	2069.600	0.000	1	0.999	0.135
Constant	-1507.779	454580.568	0.000	1	0.997	0.000

To determine the effect of the studied variables on final outcome (mortality), Multivariate analysis using Logistic regression model was done. On analysis of data, all p-

values were found to be “>0.05” hence there is no significant influence of the studied variables in predicting the outcome as shown in Table 6.

**Table 7: Relationship between parasite load and outcome.**

Relationship between Parasite Load and Outcome					
		Outcome		Total	
		Deceased	Alive		
Parasite Load	1+	Count	0	34	34
		% within Outcome	0.0%	38.6%	34.0%
	2+	Count	5	48	53
		% within Outcome	41.7%	54.5%	53.0%
	3+	Count	6	3	9
		% within Outcome	50.0%	3.4%	9.0%
	4+	Count	1	3	4
		% within Outcome	8.3%	3.4%	4.0%
Total	Count	12	88	100	
	% within Outcome	100.0%	100.0%	100.0%	

In our study group out of 100 patients, 34 patients (34%) had 1+ parasite load, 53 patients (53%) had 2+ parasite load, 9 patients (9%) had 3+ parasite load and 4 patients (4%) had 4+ parasite load. In our study group out of 100 patients, 12 patients deceased (100%). 0 patients out of 34 deceased in 1+ parasite load group (0%), 5 patients

out of 53 deceased in 2+ parasite load group (41.7%), 6 patients out of 9 deceased in 3+ parasite load group (50%) and 1 patient out of 4 deceased in 4+ parasite load group (8.3%) as shown in Table 7. Table 8 shows the relationship between increasing Parasite Load and

Outcome was statistically highly significant (p-value = 0.000).

**Table 8: Significance of parasite load and outcome.**

Tests	Value	Exact Significance (2-sided) P-value
Fisher's Exact Test	22.558	0.000
N of Valid Cases	100	

## DISCUSSION

71% patients were infected with *Plasmodium falciparum*, 25% with *Plasmodium vivax* and 4% with both *Plasmodium falciparum* and *vivax*. 12% patients deceased and 88% survived. The relationship between GCS, convulsions, pH, bicarbonate, lactate, hemoglobin, creatinine, SBP, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, PT, INR, aPTT, and Outcome was statistically highly significant (p-value = 0.000). The relationship between Total Bilirubin, RBS and outcome was statistically not significant (p-value = 0.351). Multivariate analysis using logistic regression model, to determine the effect of studied variables on final outcome (mortality), revealed no significant influence of studied variables in predicting the outcome (p-value >0.05). The relationship between increasing Parasite Load and Outcome was studied, and it showed it was statistically highly significant (p-value = 0.000).

The various complications of "Complicated malaria" seen in our study group were Jaundice (88%), Renal failure (37%), Acidemia/Acidosis-pH <7.25 (13%)/Bicarbonate < 15m.mol/l (32%)/Lactate >5m.mol/l (7%), Cerebral malaria (23%), Pulmonary edema/ARDS (17%), Convulsions (16%), Bleeding/DIC-PT > 20 seconds (7%)/INR >1.33 (7%)/aPPT >40 seconds (10%), Severe anemia (6%), Hypotension/Shock (5%) and Hypoglycemia (4%).

The relationship of various complications of complicated malaria with outcome was studied and statistical significance was calculated.

In our study relationship between GCS and Outcome was statistically highly significant (p-value = 0.000). This result was comparable to other studies by Mishra SK et al, Bruneel F et al, Soni PN et al, and Newton PN et al.<sup>5-8</sup>

In our study relationship between Convulsions and Outcome was statistically highly significant (p-value = 0.000). This result was comparable to other studies by Newton PN et al.<sup>8</sup>

In our study relationship between pH, plasma Bicarbonate, Lactate level, and Outcome were statistically highly significant (p-value = 0.000). These results were comparable to other similar studies by Bruneel F et al, Newton PN et al, and Soni PN et al.<sup>6-8</sup>

In our study relationship between Hemoglobin level and Outcome was statistically significant (p-value = 0.020). This result was comparable to other studies by Newton PN et al and Mishra SK et al.<sup>8,5</sup>

In our study relationship between serum Creatinine level and Outcome was statistically significant (p-value = 0.008). This result was comparable to other studies by Newton PN et al, Soni PN et al, and Mishra SK et al.<sup>8,7,5</sup>

In our study relationship between SBP (hypotension/shock) and outcome was statistically significant (p-value = 0.012). This result was comparable to other studies by Bruneel F et al, and Newton PN et al.<sup>6,8</sup>

In our study relationship between the PaO<sub>2</sub>/FiO<sub>2</sub> ratio (Pulmonary edema/ARDS) and Outcome was statistically highly significant (p-value = 0.000). This result was comparable to other studies by Bruneel F et al, and Mishra SK et al.<sup>6,5</sup>

In our study relationship between PT, INR (p-value = 0.004), aPTT (p-value = 0.002) (Bleeding/DIC) and Outcome was statistically significant. This result was comparable to other studies by Bruneel F et al.<sup>6</sup>

In our study relationship between serum Total Bilirubin and Outcome was statistically not significant (p-value = 0.351). This result was comparable to other studies by Soni PN et al, and Mishra SK et al.<sup>7,5</sup>

In our study relationship between RBS level and Outcome was statistically not significant (p-value = 0.500). This result was comparable to other studies by Bruneel F et al, Newton PN et al, and Mishra SK et al.<sup>6,8,5</sup>

In our study, all the various complications of complicated malaria had no significant influence (p-value > 0.05) on the final outcome (mortality). It could probably be attributed to all the complications together playing a significant role in determining the outcome.

The relationship between increasing Parasite load and Outcome was studied, and it showed it was statistically highly significant (p-value = 0.000). This result was comparable to other similar studies by John W. Field et al.<sup>9</sup>

Peripheral blood density of parasites is the single best parameter of disease severity and is regarded as the reference standard, although it may not adequately reflect the total number of parasites involved in the pathophysiologic process.<sup>10</sup>

## CONCLUSION

The prognosis and outcome of patients with complicated malaria worsen as the parasite load increases and the probability of death increases markedly in such patients.

The presentation of inappropriate parameters at admission, aid us in predicting poor outcome and appropriate treatment plan.

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