

Severe Falciparum Malaria— Difference in Mortality among Male and Nonpregnant Females

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ABSTRACT

Background: There are many studies regarding the gender difference in severe falciparum malaria. But most of these studies indeed refer to pregnant females only. There are scanty and conflicting reports regarding the mortality trend in nonpregnant females.

Materials and Methods: This is a case control study which is open, single centre, single blind, prospective and interventional study. SPSS 19 was used at the end of the study for all statistical analysis. Student's t-test was used for nominal variables and chi-squared test was used for categorical variables.

Results: The mean pre hospitalization illness period is significantly lower in females. Incidence of convulsion is significantly higher in females. The mean haemoglobin

concentration in females is significantly lower. The mortality in females is significantly higher. Females over 40 years have higher mortality than females less than 40 years and also males over 40 years. Shock in female was associated with significantly high mortality.

Conclusion: The mortality in females is significantly higher in males. The females had lower haemoglobin level and increased incidence of convulsion than their male counterparts. Shock in females has significantly higher mortality. So prompt treatment can save many lives. The increased mortality in females cannot be explained by relative inaccessibility of females to health care system as previously explained, because they have reached hospital earlier than males. Causes of shock and their association with increased mortality in females need further studies.

Keywords: Acute renal failure, Acute respiratory distress syndrome, Falciparum malaria, Multi organ dysfunction syndrome

BACKGROUND

Malaria is the most important parasitic disease of human which affects nearly 219 million people in 104 malaria endemic countries. Excluding Sub-Saharan countries, South East Asian Region possesses most number of cases of malaria in the world [1]. India accounted for approximately 1.8 million cases of malaria in the year 2010. Most of the deaths in malaria are due to severe falciparum malaria [1-4]. Odisha is a unique state in eastern part, having 3% of population of India but contributing to more than 24% of total falciparum malaria cases of India. Though Odisha contributes only 4% land area of India 17% of deaths caused by malaria in the country have been reported from Odisha [3]. It is one of the most important public health disease in India and more so in Odisha.

In spite of being such an important disease, there are many areas of severe falciparum malaria where research work is scanty. One among them is effect of gender on severe falciparum malaria. It is well known that pregnant females with severe falciparum malaria fares badly with high mortality (30-50%) [1-4]. Non pregnant females are many times taken granted as males as regard to disease process and outcome. Average woman have lower body weight, smaller organs, increased fat and decreased body water than males [5]. There are also important sex differences in drug action and its metabolism. Gonadal steroid, menstruation, pregnancy and lactation may also alter the disease pathophysiology, drug action and their metabolism. So it will not be surprising to see gender differences in various diseases including malaria and their outcome.

In severe falciparum malaria there are contradictory reports published in literatures about the effect of gender. Kochar et al., from India while working on effect of pregnancy on malaria had observed mortality of 34% in pregnancy, 14% in non pregnant females and 8% in male [1]. Death in non pregnant female was higher than in male in this study. But Mengistu et al., from Ethiopia had observed no gender

differences in severe falciparum malaria [6]. He observed both the genders showing equal mortality of 28% (28.6% in male vs 28.3% in female). With these backgrounds this study was undertaken with the following aims and objectives; to determine the difference in clinical features in severe falciparum malaria with respect to gender, to determine the mortality trend in male and female and to determine the cause of difference in mortality if any in relation to gender.

MATERIALS AND METHODS

Patients suffering from severe falciparum malaria (as per WHO guideline 2010) and hospitalized were taken into the study. Detailed examination was conducted with a preset questioner. This is a case control study which is, single centre, single blind and prospective conducted in a tertiary health centre of eastern part of India over a period of 3 years.

Inclusion Criteria

1. Age more than 15 years.
2. Slide positive for *Plasmodium falciparum*.
3. Having one or more features of severe falciparum malaria (as per WHO guideline 2010).

Exclusion Criteria

1. Patients with other co-existing illness.
2. Pregnant females.
3. Mixed malarial infection.

After carefully considering the inclusion and exclusion criteria, all the patients were grouped into men and non pregnant women and relevant parameters were compared using SPSS 19 software. Student's t-test was used for nominal variables and chi-square test was used for categorical variables. Patient characteristics and outcome of interest was calculated with 95% confidence limits. The probability of <0.05 is considered to be significant.

Age group in year	Male	Female
≤19	12	6
20-29	34	22
30-39	22	22
40-49	19	18
50-59	11	10
≥60	17	12
Mean age ± SD	37.8 ± 16.7	38.1 ± 15.9

[Table/Fig-1]: Distribution of cases by age groups and gender, There was no difference in distribution of cases by age groups and gender ($p=0.777$) 66.9% of cases are between 20-49 years of age. The maximum numbers of cases are in the age group of 20-29

Complication	Male	Female	p-value
Cerebral	63	56	0.284
ARF	49	44	0.470
ARDS	44	28	0.287
Hepatopathy	30	24	0.880
Shock	16	11	0.722
Convulsion	19	28	0.014
hypoglycemia	0	01	0.272

[Table/Fig-2]: Incidence of complication, In both the genders cerebral malaria is the most common complication, followed by ARF, ARDS and hepatopathy

Gender	<40 year	≥40 year	p-value
Male	16	12	0.806
female	13	21	0.010
p-value	0.759	0.010	-

[Table/Fig-3]: Incidence of mortality in different age groups, There is significantly high mortality in females ≥40 yr in comparison to males ≥40 yr as well as females <40 yr

RESULTS

There was no difference between male and female in relation to mean age and age groups ($p=0.777$ [Table/Fig-1]). In both the genders nearly two-thirds of the patients were young (20-49 years). Contrary to the popular belief that females seek medical help later, in our study they came to hospital significantly earlier ($p=0.008$). In our study in both the genders the commonest presentation was multi organ dysfunction syndrome (MODS). The other complications (either occurring alone or part of MODS) in the decreasing order of frequency in both the genders are cerebral malaria, acute renal failure (ARF), (acute respiratory distress syndrome) ARDS, hepatopathy, shock and hypoglycemia. But there was no significant difference in these parameters in relation to gender [Table/Fig-2]. The most common MODS presentation in male patients was cerebral malaria + ARF + ARDS where as in females the most common presentation was cerebral malaria + ARF incidence of convulsion in females was significantly high. There was no significant difference among the male and female patients who survived, regarding the mean duration of hospital stay, total leukocyte count, blood urea nitrogen, serum creatinine, serum bilirubin, number of blood transfusion received and requirement of haemodialysis, suggesting equal distribution of organ damage. However the mean haemoglobin concentration among the female was significantly lower than male ($p=0.021$). Severe anaemia (haemoglobin <5 gm %) has not been found in any of the cases. But 6.1% of males and 8.5% of females had haemoglobin <7gm%.

In spite of equal treatment in both the genders (all received Artesunate as per WHO guideline), the mortality in females was significantly higher (24.3% in male vs 37.8% in female, $p=0.038$). Females aged ≥40 years had significantly higher mortality than males aged ≥40 ($p=0.010$) [Table/Fig-3]. Interestingly females ≥40 years had also

Complication	Male	Female	p-value
Cerebral	16	22	0.543
ARF	10	09	0.268
ARDS	12	13	0.712
Hepatopathy	06	12	0.580
Shock	02	09	0.047
convulsion	05	11	0.194

[Table/Fig-4]: Case fatality rate of various complications., Shock in female is a bad prognostic indicator and has significantly higher mortality than in males.

higher mortality than females <40 years ($p=0.010$). Both male and female had significantly higher mortality in cases of prior history of fever for ≤3 days than in cases of >3 days of fever. More than 80% of deaths in both the genders occurred within the first 48 hours. Comparing the various complications resulting in death in both the genders, it was observed that there was no difference in case fatality rate of cerebral malaria, ARF, ARDS hepatopathy, and convulsion [Table/Fig-4]. However shock in female had significantly higher mortality ($p=0.047$). Out of 16 cases of shock in male patients, 11 cases were present as solitary complication and five cases were component of MODS. In contrast, in females out of 11 cases of shock, 10 cases were associated with MODS. This suggests shock in female was having more severe manifestation resulting in higher death. MODS in female resulted in higher number of death in comparison to but not amounting to statistical significance. There was no statistically significant difference in death between males and females in MODS. However MODS with four organ dysfunction had very high mortality rate (100% in males vs 83.3% in females).

DISCUSSION

In our study more than two-thirds of the patients in both the genders were young (20-49 years). This is similar to the study by Mengistu et al., in Ethiopia where they observed 75% of the patients in this age group [6]. Younger people are more commonly affected probably because they stay outside home for more time for their livelihood in comparison to elders and are at greater risk for mosquito bite and acquisition of partial immunity to malaria in elders [7]. Previously some authors have explained that the mortality in female may be high because the females seek medical help later and their inaccessibility to health care facilities [8]. But in our study they came to the hospital significantly earlier ($p=0.008$). So the high mortality in females cannot be explained by this. Unfortunately there is no published data regarding the duration of illness prior to hospitalization with respect to gender. In our study in both the genders the commonest presentation was MODS, followed by cerebral malaria, ARF, ARDS, hepatopathy, shock and hypoglycaemia. The occurrence of various clinical features as observed by various workers is given below in a tabular form [Table/Fig-5]. Increasing evidence of MODS is also observed by Kochar et al., Mohapatra and Helbok et al., [9-12]. The incidences of other complications more closely resemble the rates observed by Mohapatra probably because both the studies are from same region [10]. We observed that incidence of convulsion in female was significantly high ($p=0.014$). Such difference in gender has not been reported earlier. In the absence of occurrence of differences in cerebral malaria, ARF, hypoglycaemia (which are common causes of convulsion in falciparum malaria), this significantly high occurrence of convulsion in females needs further study. The overall incidence of convulsion in male and female taken together is similar to that observed from Rajasthan and Vietnam but more than that has been observed in Ethiopia [6,7,9]. This geographical difference in convulsion should be studied further. The mean haemoglobin concentration among female was significantly lower than in male ($p=0.021$) which may be reflection of lower haemoglobin level in the general population of female because of low nutritional status

complication	Mohapatro et al., [10]	Kochar et al., [9]	Mengistu et al., [6]	Present study	
				Male	Female
Cerebral	88.3%	10.9%	28.7%	54.8%	62.2%
ARF	49.8%	06.2%	03.7%	45.4%	50.6%
ARDS	04.6%	03%	07.4%	38.3%	31.1%
Hepatopathy	52.9%	58.5%	21.3%	28.6%	27.6%
Shock	NA	03%	12.7%	13.9%	12.2%
Convulsion	NA	01.5%	12.5%	16.5%	31.1%
MODS	52.6%	22.4%	NA	54.8%	62.2%

[Table/Fig-5]: Comparative analysis of complications in various studies, Incidence of ARDS is comparatively higher in our study (NA*-data not available)

and the menstruation cycle. There is no published data regarding the difference of haemoglobin concentration between male and non pregnant female in severe falciparum malaria cases. Severe anaemia (haemoglobin <5 gm%) was not observed in any of the cases. But 6.1% of males and 8.5% of females had haemoglobin <7%. This is in accordance with previous observations that severe anaemia is uncommon in adult malaria cases [7].

Mengistu and Diro from Ethiopia had observed no differences in mortality with regard to gender in severe falciparum malaria (28.6% in male vs 28.3% in female) [6]. But Kochar et al., observed higher mortality in non pregnant females (34% in pregnancy, 14% in non pregnant females and 8% in male) [1]. They have not explained for this high mortality in non pregnant females. In our study females aged ≥ 40 years had significantly higher mortality than in males aged ≥ 40 ($P=0.010$). Interestingly females ≥ 40 years had also higher mortality than females <40 years ($p=0.010$). This observation has not been found in any published literature. Schwartz et al., noticed an increased mortality in patients of >40 years of age but they did not get any difference in mortality with respect to gender. Baird et al., hypothesized those different immune responses that are related to age may be responsible for the different outcome in elderly population [12]. Clark et al., postulated that the susceptibility of the aged population to the negative effect of cytokines expressed during the disease may be high [13]. Mengistu et al., have observed that those patients who died of severe falciparum malaria had a significantly higher age than the survivors [6]. They have proposed age ≥ 40 years as a bad prognostic indicator. Both male and female had significantly higher mortality in cases of prior history of fever for ≤ 3 days than in cases of >3 days of fever. But while comparing both the groups of fever in relation to gender the death rate in female is higher but not statistically significant. There is no published data regarding this observation. This may be related to severity of infection. In both male and female there was no difference in the hours of survival before death. More than 80% of deaths in both the genders occurred within in first 48 hours. Early death in severe falciparum malaria has also been observed by several other workers. Naqvi et al., from Pakistan, while studying malarial ARF observed that those patients who died of malaria ARF, they died within 1-2 days [14]. Brooks et al., had observed that death due to pulmonary oedema occur during the first 1-2 days of treatment [10]. Mengistu et al., from Ethiopia had observed that most deaths in severe malaria especially cerebral malaria occur within first 24-48 hours of hospitalization because of severity of infection and associated complication [6]. Our result is also in conformity with them. Therefore to prevent death in severe falciparum malaria the critical period is first 48 hours, when proper intervention can save most of the lives. Comparing the various complications resulting in death in both the genders, there was no difference in case fatality rate of cerebral malaria, ARF, ARDS, hepatopathy and convulsion [Table/Fig-4]. Out of 16 cases of shock in male patients, 11 cases were present as solitary complication and 5 cases were component

of MODS. In contrast in females out of total 11 shock cases only 1 case was found to be having solitary complication and 10 cases were associated with MODS. This suggests shock in female was having more severe manifestation resulting in higher mortality. Shock in female had significantly higher mortality in comparison to males ($p=0.047$). This has not been published in any literature. Postural hypotension is more common in female and has been postulated to be due to reduced sympathetic activity in female and diminished baroreceptor sensitivity for control of sympathetic outflow and lower peripheral resistance [7,15-16]. Critically ill patients have been found to be having relative adrenal deficiency. But there is no report of gender difference except in neurosurgical trauma cases [16]. Sheehan's syndrome is a common disease in females with varying severity which is a secondary cause of hypoadrenalism. These patients undergo acute adrenal failure in critically ill conditions unless steroids are supplemented. Some of the patients in this study might be suffering from milder forms of this disease, which needs further elaborate study.

CONCLUSION

In both the genders the commonest presentation was MODS, followed by cerebral malaria, ARF, ARDS, hepatopathy, shock and hypoglycaemia. At presentation females had significant lower haemoglobin level and increased incidence of convulsion. Females had significantly high mortality than in males. Females aged more than 40 years had significantly higher mortality when compared to either to females less than 40 years or males more than 40 years. The increased mortality in females cannot be explained by relative inaccessibility of females to health care system as previously explained, because they have reached hospital earlier. Shock in females had significantly higher mortality than in males. Causes of shock and their association with increased mortality in females need further studies. The first 24-48 hours is of paramount importance preventing the complications and death in severe falciparum malaria.

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