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Risk factors for fatal outcome of malaria: A hospital-based study in PyinOoLwin District

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A hospital-based prospective study was conducted to identify risk factors influencing malaria mortality in PyinOoLwin district from 1st September, 2005 to 31st August, 2006. Face-to-face interview with patients or attendants using pre-tested, closed-ended questionnaire was conducted for all admitted malaria cases during study period. Among 822 cases, 47.4% were severe and complicated malaria cases and 56 patients expired at hospital. Patients aged above 13 years, being male with history of traveling to malaria endemic area, who denied past history of malaria attack, with duration of illness more than five days before hospitalization, who sought treatment from untrained practitioners as second healthcare provider, presented with fits, heavy parasitaemia, deep jaundice, and without clinical spleen enlargement were significant risk factors for malaria death ($p<0.05$). Prompt and adequate treatment at the community level, early referral and specific treatment at hospital should be ensured to reduce malaria mortality.

INTRODUCTION

Malaria has been ranked as one of the top priority diseases in Myanmar. Malaria accounted for more than 10% of out-patient attendance in 2004 [1]. Malaria mortality became declined gradually during last 14 years. It reduced from 12.6 to 3.7 per hundred-thousand populations during 1990 to 2004. Although the trend of malaria mortality is declining, reported number of deaths is still high. Malaria mortality rate in Myanmar was highest in South East Asia Region [2].

Malaria control program in Myanmar sets the objective of reducing malaria morbidity and mortality 50% by 2010 taking the year 2000 as base year [3]. In planning and implementing the disease management components, understanding the risk factors of severe and complicated malaria cases is paramount important. Identifying and combating risk factors at their earliest stage of manifestation can prevent further deteriorations and mortality.

This study was conducted to find out the risk factors for malaria fatality among admitted patients in Madayar, Singu and Moegoke township hospitals in PyinOoLwin District, Myanmar.

MATERIALS AND METHODS

The study was a hospital-based cross-sectional one. The study population was malaria patients admitted to 3 township hospitals (Madayar, Singu and Moegoke) in PyinOoLwin District.

Data were collected using a pre-coded and pre-tested questionnaire which composed of closed-ended questions on patient personal data, history of present malaria attack, health care seeking behavior, clinical features on admission, parasitological diagnosis in hospital, treatment in hospital, and outcome of patient.

In each township hospital, the civil assistant surgeons (CAS) assigned in medical wards were trained for data collection. The team

spent at least two days with each CAS to ensure that the questionnaire was filled as required. CAS obtained a written informed consent from each malaria patient or attendant before collecting data. CAS filled up the forms by asking either the patients or their attendants during their hospital stay. Final diagnosis and clinical outcomes were recorded by CAS only after discharge or death of the patients. Collected data in hospitals were gathered on monthly basis. The responses in the questionnaires were compiled, coded, and entered into computer by using Epi-data 3.01 software. Data analysis was done using SPSS version 11.5 computer software. Frequency and percentage tables were used to describe background characteristics of patients. Bivariate and multivariate binary logistic regression analyses were done to find out the risk factors for malaria fatality. The level of significant was set at p-value <0.05.

RESULTS

Characteristics of admitted malaria patients

A total of 822 malaria cases were admitted to township hospitals of PyinOoLwin District during one year study period. The mean age of admitted patients was 24.6 years. Majority (54.1%) were young adults aged between 18 and 40 years while 13.7 % were under five children and only 2.7% over 60 years. Male patients accounted for 56% and the female patients 44%. Among female patients, 14 cases were admitted for pregnancy with malaria. Regarding occupation, 28.6% were farmers followed by gold-digging laborers (27.3%), ruby-digging laborers (16.2%), dependent housewives and children (11.9%), forest related workers (3.1%), students (3.4%), government servants including soldiers and polices (9.0%), and wandering traders (0.6%). As regard the education level, 9.4% were preschool children. Illiterates accounted for 5.6%. Forty-seven per cent of cases can read and write or primary school followed by completed up to middle school (28.4%). Completed high school, university student, graduates, and post graduates accounted for 5.3%, 3.0%, 1.2%, and 0.2%, respectively (Table 1).

Table 1. Background characteristics of malaria patients

Variables	Frequency	Percent
Age (years) (n=822)		
<5	113	13.7
5 - 17	156	19
18 - 39	445	54.1
40 - 60	86	10.5
>60	22	2.7
Mean ± SD	24.6 ± 15.1	Range (1 to 67)
Gender(n=822)		
Male	460	56
Female	362	44
Occupation (n=802)		
Farmers	229	28.6
Gold-digging laborers	219	27.3
Ruby- digging laborers	130	16.2
Dependents	13	1.6
Children	82	10.2
Government servants	72	9
Students	27	3.4
Forest related workers	25	3.1
Wandering traders	5	0.6
Education (n=809)		
Illiterate	45	5.6
Preschool	77	9.5
Primary	379	46.8
Middle	230	28.4
High	43	5.3
University	24	3
Graduate	10	1.2
Postgraduate	1	0.2

Clinical presentation

Among total 822 admitted malaria cases, 69.7% of patients had history of traveling to malaria endemic area. Past history of malaria attack was revealed by 33.9% of patients. Among them, 30% suffered from more than three malaria attacks within one year. Only 0.7% of cases gave history of blood transfusion. The mean duration of fever before admission was 5.3 days on average and ranged from 1 to 22 days. Among recorded 809 cases, 66.2% presented with fever of 37.7 to 39 degree Celsius, 24% with hyperpyrexia of 39.4 degree Celsius and above, and 9.8% with normal temperature. The mean body temperature of patient on admission was 38.7 with SD of 1.04 degree Celsius.

Sensorial changes ranged from impaired consciousness up to deep coma were presented in 45.5% of total admitted cases. According to modified Glasgow coma scale (GCS), 34.2% of cases were GCS scores more than seven while the remaining 65.8% with GCS scores seven or less (unrousable coma) at the time of admission. The time between impaired consciousness and admission varied from 3 hours to 48 hours with an average duration of 8.1 with SD of 5.8 hours. History of fit was investigated in 36.6% of unconscious cases.

Of total admitted cases, clinical anemia was recorded in 88.3% of patients. Among them, only 201 cases (29.4%) were tested for hemoglobin level. The mean hemoglobin concentration was 5.3 gram% with SD of 2.4 gram%. Clinical jaundice was detected in 13.8% of admitted cases.

All malarial hepatitis cases (n=38), all hepato-renal failure cases (n=3), 35.7% (5/14) of malaria with pregnancy cases, 12.3% (37/302) of cerebral malaria cases, 18.3% (3/16) of black water fever cases, 8.3% (1/12) of hyperpyrexia cases, 60% (3/5) of algid malaria cases, and 5.3% (23/432) of uncomplicated malaria cases presented with jaundice.

Liver enlargement was detected in 37.8% of cases with mean of 4 cm with SD of 2 cm below the costal margin. Splenomegaly was detected in 15.9% of all cases with a mean size of 5 cm with SD of 2 cm below the costal margin. Dark urine was recorded in 44 cases. All 16 black water fever cases, 5.6% (17/302) of cerebral malaria cases, and 28.9% (11/38) of malaria hepatitis cases passed dark urine.

Shock occurred in nine cases of cerebral malaria (including two cases of cerebral malaria with pregnancy and two cases of cerebral malaria with pulmonary edema), five cases of algid malaria, and two cases of black water fever. Eight cases presented with shock expired at hospital and one case of malaria with pregnancy with shock was referred to Mandalay specialist hospital.

Treatment seeking behavior before admission

Among all cases, the main sources of initial treatment were basic health staff (BHS) (28.9%), taking anti-malarial drugs mentioned by drug shop owners (26.9%), general practitioners (GP) (21.4%), quacks (9.8%), indigenous medical practitioners (5.3%), self treatment at home (5%), and volunteer health workers (VHW) (2.7%). Second source of treatment was revealed by 602 cases. The second malaria treatment providers were GP (32.1%), self treatment (25.7%), BHS (15.6%), indigenous medical practi- tioners (14.8%), VHW (4.8%), local drug shops (3.8%), and quacks (3.2%). Third source of treatment was also revealed by 183 patients. They sought treatment from GP (73.8%) and BHS (12.6%) as third health care provider just before admission to hospital.

The majority of cases were referred to hospital by GP and BHS, 56.6% and 22.9% respectively. Only 12.3% of cases came to hospital on their own decision. Among cases referred by GP, 51% showed referral chip paper on admission while only 5.4% of cases referred by BHS attached with referral chips. As regards drugs used before admission, answers were obtained only from 62.1% of all admitted cases. Drugs used were chloroquine tablets, quinine tablets, artesunate tablets, and sulfadoxine-pyrimethamine (SP): 45.8%, 18.3%, 12.7%, and 10.6% respectively. The remaining 12.6% of patients received complicated combinations of drugs including antimala-rials, antibiotics and symptomatic drugs.

Treatment at hospital

Diagnosis

In 64.2% of admitted patients, malaria diagnosis was confirmed by blood for malaria parasite microscopy (MP), and 35.8% by Rapid Diagnostic Test (RDT). Blood slides for MP were taken from 37.6% of patients within 30 minutes after admission. It was between 30 minutes to 1 hour in 32.3% of patients, between 1 to 12

hours in 12.3%, and over 12 hours in 17.8% of patients. Interval between blood for MP taken and MP results returned from laboratory varied from within one to twenty-four hours with mean duration of 4.9 ± 4.2 hours.

Parasite density was expressed in terms of 1+, 2+, 3+, and 4+ [6]. Parasite density was stated in 513 out of 528 results. Among them, 9.0% were 1+, 50.9% were 2+, 24.0% were 3+, and 10.1% were 4+. Follow-up MP examination was done in none of the cases. Results from laboratory stated that: 74.2% were *Plasmodium falciparum*, 22.5% were *Plasmodium vivax*, and 3.3% showed mixed infection.

Treatment

Among 610 *Plasmodium falciparum* cases confirmed by microscopy or RDT, 42.8% received quinine alone, 4.4% received quinine plus artemisinin, and 26.6% received artemisinin-based combination therapy. The remaining 26.2% of cases were treated with miscellaneous combinations of anti-malarial drugs.

Majority (88.2%) of *Plasmodium vivax* confirmed cases by microscopy, received chloroquine plus antibiotics while remaining cases received SP, primaquine, and clindamycin.

Of all admitted cases, 34.5% of patients received antibiotics. Frequently using antibiotics included tetracycline, septrin, quinolones (ciprofloxacin & norfloxacin), chloramphenicol, amoxicillin, and ampicillin.

Glucose, steroids (hydrocortisone, and dexamethasone), mannitol, and nootrophil were used as ancillary treatments in severe and complicated malaria cases. Blood transfusion was given in 14 severe anemia cases (1.7% of total cases). Plasma expenders were also used in three patients presented with shock.

The average duration of stay in hospital was 5.8 days with SD of 6.3 days with a range of 0 to 32 days. The mean duration of stay for 56 expired cases was 1.4 days with SD of 3.7 days with a range of 0 to 6 days. Among 56 expired cases, 28.6% died within 24 hours after admission.

Category specific outcomes of severe malaria cases

Among 822 admitted cases, 52.6% were uncomplicated while 47.4% were severe and complicated malaria (SCM). Of SCM cases, 74.9% survived and discharged from hospital and only 14.4% cases expired at hospital. Among SCM cases, most of the patients were cerebral malaria (77.4%) followed by malarial hepatitis (9.7%), black water fever (4.1%), severe anemia (3.6%), hyperpyrexia (3.1%), algid malaria (1.3%) and hepato-renal failure (0.8%). Among cerebral malaria cases, outcomes were recorded as survived and discharged (72.2%), expired (14.9%), and signed and left (11.3%). Only one pregnancy with cerebral malaria was referred to hospital.

Among malarial hepatitis cases (n=38), six cases expired and the remaining were survived and discharged from hospital. Among black water fever cases, two patients died in hospital and other two patients signed and left. One malaria case presented with hyperpyrexia absconded while all others survived. One case out of 14 severe anemia cases and one out of five algid malaria cases died in hospital.

Factors responsible for malaria fatality

To execute the logistic analysis, the outcomes were categorized into discharged and death. Deaths included ‘deaths in hospital’ plus ‘sign & left’ cases i.e. the latter outcome was assumed to be expired at home. Referred case (n=1) and absconded cases (n=5) were excluded from analysis since the exact outcomes were unknown. Therefore, 384 SCM cases were analyzed.

In bivariate analysis, there was no significant difference in death of malaria due to occupation, education, initial and final treatment provider, high fever, clinical anemia, and liver enlargement. The crude

odds ratios of malaria death were higher in patients aged above 13 years [OR=2.0 (95%CI 1.1 to 3.4), p=0.012], being male [OR=2.3 (95%CI 1.6 to 3.6), p=0.000], with history of traveling to malaria endemic area [OR=1.8 (95%CI 1.1 to 3.2), p=0.061], who denied past history of malaria attack [OR=3.8 (95%CI 2.3 to 6.6), p=0.000], with deep jaundice [OR=4.3 (95%CI 2.0 to 9.5), p=0.000], and without clinical spleen enlargement [OR=3.0 (95%CI 1.2 to 12.5), p=0.003].

Table 2. Associations between risk factors and outcomes of SCM

Variables	No. of SCM	% Death	Crude OR (95%CI)	p	Adjusted OR (95%CI)	p
Background characteristics						
Age						
≤ 13 years	81	34.6	1.0		1.0	
> 13 years	303	21.1	2.0 (1.1-3.4)	0.012	0.4 (0.1-1.9)	0.308
Gender						
Female	191	14.1	1.0		1.0	
Male	193	33.7	2.3 (1.6-3.6)	0.000	1.1 (0.4-3.2)	0.874
Occupation						
High-risk	259	26.3	1.0			
Low-risk	122	18.9	1.5 (0.9-2.6)	0.114	-	-
Education						
High	155	30.3	1.0			
Low	159	23.9	1.37 (0.8-1.8)	0.200	-	-
History of present illness						
Past history						
Yes	270	17.0	1.0		1.0	
No	102	44.1	3.8 (2.3-6.6)	0.000	7.5 (2.6-21.9)	0.000
Travel history						
No	148	17.6	1.0			
Yes	236	27.9	1.8 (1.1-3.2)	0.061	-	-
Duration of illness						
≤ 5 days	225	11.6	1.0		1.0	
> 5 days	157	42.0	5.6 (3.2-9.7)	0.000	8.2 (2.8-24.5)	0.000
History of fits						
No	259	15.1	1.0		1.0	0.000
Yes	125	42.4	4.2 (2.5-6.89)	0.000	3.2 (2.7- 6.2)	
Treatment seeking behavior						
1st provider						
GP/BHS	188	23.5	1.0			
Others	153	26.6	1.1 (0.8-1.6)	0.517	-	-
2nd provider						
GP/BHS	146	11.6	1.0		1.0	
Others	161	37.9	4.6 (2.6-8.4)	0.000	4.7 (1.6-13.6)	0.005
3rd provider						
GP/BHS	84	25.0	1.0			
Others	92	38.1	1.5 (1.0-2.4)	0.061	-	-
General conditions on admission						
Anemia						
No / Mild	261	22.1	1.0			
Severe	114	22.2	1.0 (0.6-1.8)	0.901	-	-
Jaundice						
No / mild	352	21.0	1.0		1.00	
Deep	28	53.6	4.3 (2.0-9.5)	0.000	1.2 (0.03-2.4)	0.243
Fever						
<39.4 · C	276	23.9	1.0			
≥39.4 · C	105	22.9	0.9 (0.6-1.6)	0.828	-	-
Spleen size						
Not palpable	106	34.9	3.0 (1.2-12.5)	0.003	1.6 (0.1-12.2)	0.126
Palpable	247	19.8	1.0		1.0	
Liver						
Not palpable	92	17.4	1.0			
Palpable	71	26.8	1.7 (0.8-3.7)	0.149	-	-
Treatment at hospital						
Parasite density						
1+ , 2 +	178	7.3	1.0		1.0	
3+ & 4+	179	39.1	8.2 (4.2-16.8)	0.000	4.7 (1.5-14.3)	0.007
Hospital treatment						
Simple	344	22.4	1.00			
Compli-cated	40	37.5	2.1 (1.1-4.1)	0.054	-	-

In the multiple logistic regression analysis, the factors significantly associated with increased likelihood of malaria death were patients who presented with history of fits [OR=3.2 (95%CI 2.7 to 6.2)], treated with untrained practitioners as second health care provider [OR= 4.7 (95%CI 1.6 to 13.6)], duration of illness more than five days before admission [OR=8.2(95%CI 2.8 to 24.5)], and heavy parasite load (3+ and above) [OR= 4.7 (95%CI 1.5 to 14.3)] (Table 2).

DISCUSSION

Our study aimed to identify the factors responsible for malaria fatality in order to reduce malaria mortality by eliminating or modifying those factors. Combating risk factors at their earliest stage of manifestation may prevent further deteriorations.

The overall case-fatality rate (CFR) among the admitted malaria cases was 6.8%. It did not include 36 'signed and left' cases that might likely have died at home. Therefore, CFR might go up to 11.2% if the outcome of 'signed and left' cases could be

confirmed as expired. The fatality rate among severe cases was 14.36%. It might go up to 23.59% if the 'sign and left' cases were regarded as mortality.

Our results revealed that duration of illness more than five days before admission is significantly associated with high fatality of malaria. A study in Myanmar reported that the highest proportion of deaths occurred if mean duration of illness ≥8.5 days while the lowest proportions of deaths occurred in mean duration of illness ≤3.13 days before hospitalization [4].

Our study showed that treating with untrained providers during second healthcare seeking leading to delay in effective, prompt and timelessness of anti-malarial management and increase severity and death of malaria. Therefore, the stage of disease when the patient usually search for second treatment should be considered as 'critical stage' that may determine the outcome. A study in Myanmar reported malaria mortality among the adult population was associated with a long delay in seeking treatment [4]. Studies done in Philippine, Kenya and Guinea [5] [6] [7] supported that severity of malaria is associated with use of official health sectors and hospitals. Patients sought treatment from untrained practi-tioners in early stage. They were admitted to hospitals when disease became more severe and complicated in late stage.

In present study, malaria patients presented with fits were three to four times increase in risk of death. Similar finding regarding cerebral manifestation of malaria as one of the major causes of death was reported in Myanmar [4] as well as global literature [8]. Fits might be partly due to hyperpyrexia, especially in children. However, neither relations between fits and age of patients, nor between fits and hyperpyrexia (≥39.4 degree Celsius) were found. There was no significant relation between high parasite density and fits.

Our results revealed that the factor significantly associated with increased likelihood of malaria death was patients with heavy parasite load. The results of a program trial conducted in France [9] also reported that high-level parasitaemia was associated with increased risk for death among malaria patients.

In univariate analysis, the results from this study showed that malaria death was higher in patients aged above 13 years, being male gender, with history of traveling to malaria endemic area, who denied past history of malaria attack and without clinical spleen enlargement. In a study of Myanmar, adults were 2.8 times more likely to die from malaria than children [4]. Increasing age as a risk factor for death of malaria has been reported in Europeans [10], and France [11]. In a study in France [9] reported increased likelihood of malaria death is associated with age and male sex.

The non-immunes with history of travel to malaria endemic areas were also more prone to malaria death. Many rural and sub-urban areas in PyinOoLwin District are malaria endemic areas. Migratory non-immune floating populations incidentally entered into malaria endemic areas acquired malaria were more likely to suffer from severe malaria and more prone to die of malaria. A study in France also reported that traveling to malaria endemic area in East Africa is significantly associated with death of malaria [9]. A study in United States [12] suggested that travelers to malaria-endemic areas were resulting in potentially severe illness and high CFR.

Regarding treatment, hospital treatment should be strictly in line with latest national anti-malarial treatment guidelines (NAM TG). Township hospitals in PyinOoLwin District obeyed NAMTG such as diagnosis using microscopy (64.2%) and RDT (35.8%) and use of ACT (26.6%) in confirmed *Plasmodium falciparum* cases. However, minor deviations such as use of non-recommended combinations of anti-malarial drugs, over use of antibiotics, and ancillary treatments e.g. steroids, mannitol, and nootrophil should be abandoned in

order to improve compliance with NAMTG in hospitals. In conclusion, risk factors impeding prompt and adequate treatment at the community level, early referral and specific treatment at hospital should be revised to reduce malaria mortality.

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