Survival of malarial acute kidney injury in children: A prospective analytical study

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ABSTRACT

Introduction: The renal involvement has been reported in *Plasmodium falciparum*, *Plasmodium malariae,* and recently in *Plasmodium vivax* infection. Although malaria is highly endemic in the rural locality of Odisha and a significant proportion of severe malaria causes acute renal complication, there is no definite study on the survival of malarial acute kidney injury (AKI) in children of the setup of the current study. **Objective:** The objective of the study was to find out the survival of malarial AKI in children. **Methods:** A prospective analytical study was conducted from October 2016 to September 2018 in the postgraduate department of pediatrics, of a tertiary care hospital in Odisha, after approval from the Institutional Ethics Committee. Children with smear-positive and/or quantitative buffy coat (QBC) positive malaria were included in the study. All the relevant data (age, gender, duration of hospital stays, stages of AKI, signs, and symptoms of AKI, serum urea and creatinine, electrolytes, and routine hemogram) were collected, validated and results were analyzed in terms of one-way ANOVA and Kaplan–Meier survival analysis. **Results:** Out of 202 malarial cases, 50.4% (102) cases were found to be suffering from malarial AKI. Out of 102 malarial AKI children, 68% were affected due to falciparum infection, 12% due to vivax, and rest 20% due to mixed infection. The median duration of survival in days between three stages of AKI was significant as evidenced by Tarone-Ware Chi-square=48.365 (df=2), p=0.000. **Conclusion:** Mortality was 6% and all of these deaths belong to Stage 3 AKI; furthermore, the morbidities are more in Stage 3 as compared to other stages.

Key words: *Acute kidney injury, Acute kidney injury network staging, Children, Kaplan–Meier survival, Malaria*

Malaria is caused by six species of the genus Plasmodium, namely, *Plasmodium vivax, Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale, Plasmodium knowles,* and *Plasmodium cynomolgi* [1]. Four species which are mostly responsible for malaria have common clinical features, i.e., periodic paroxysm, chills, rigors, sweating, bodyache, headache, nausea, general weakness, and prostration. Severe life-threatening complication such as cerebral malaria, severe anemia, acidosis, respiratory distress, jaundice, acute kidney injury (AKI), and acute respiratory distress syndrome occurs mostly with *P. falciparum* infection [2], rarely by *P. vivax* [3-5]. Renal involvement has been reported in *P. falciparum, P. malariae,* and recently in *P. vivax* infection. *P. malariae* associated nephropathy was reported, mainly from Africa [2].

Over a decade ago, cerebral malaria was the predominant manifestation of severe malaria whereas today, the combination of jaundice and renal failure is more common [6]. The clinical spectrum of renal involvement in malaria varies widely from urinary sediment abnormalities, mild proteinuria, and electrolyte changes to AKI with metabolic acidosis as well as a nephritic syndrome [7]. Although AKI is well-described complication of falciparum malaria in non-immune adult along with major contribution to their mortality in children, renal failure is not commonly encountered [8]. The overall incidence of AKI in children reported by various Indian authors ranges between 4 and 17.2% [7]. Studies have shown that incidence of AKI (serum creatinine >3 mg%) in pediatric population with complicated falciparum malaria is 7.7% in under-5 children and 18.4% in 5–14 years children [7,9].

AKI is associated with substantial morbidity and mortality worldwide, but data have been conspicuously missing from the global burden of disease study [10]. AKI refers to a syndrome in which a sudden deterioration in renal function results in the inability of the kidneys to maintain fluid and electrolyte homeostasis. It can be community-acquired, resulting from an injury or infection before admission to the hospital, or can be hospital-acquired, arising as a complication of hospital admission [11,12]. Despite the absence of data for disease burden, the drive toward providing universal dialysis for AKI, which can be life-saving, is growing [13]. Although malaria is highly endemic in our locality and a significant proportion of severe malaria causes acute renal complications, there is no definite study on the survival of these

children. Hence, the objective of this study was to find out the survival of malarial AKI in children.

METHODS

After approval from the Institutional Ethics Committee, a prospective analytical study was conducted from October 2016 to September 2018 in the postgraduate department of pediatrics, of a tertiary care hospital of Western Odisha. All the cases admitted to pediatrics ward with smear positive and/or QBC positive malaria cases, were included in the study. Cases without asexual form of plasmodium in the peripheral smear and with pre-existing renal diseases were excluded. After taking written informed consent from their parents or caregivers, a total of 202 malarial cases were enrolled in the study after satisfying the predefined inclusion and exclusion criteria.

All the malarial AKI cases were categorized as per the AKI network staging system (Table 1) [14] and were followed until their discharge or death from the hospital. All the relevant data such as age, sex, duration of hospital stay in days, stages of AKI, serum electrolytes (Na, K), signs and symptoms of malarial AKI (fever, chills and rigor, pain abdomen, convulsion, organomegaly, oliguria, anuria, jaundice, respiratory distress, and paleness), serum urea and creatinine, routine hemogram and outcome (death or discharge), were collected in a case report format and exported to the excel sheet. Our two major outcome measures were – the duration of hospital stay in days and time to event (death and discharge).

Data cleaning and validation were done manually, and results were analyzed in terms of one-way ANOVA and Kaplan–Meier survival analysis with the help of SPSS ver. 25 software (IBM, New York). For all statistical purpose, $p<0.05$ was considered to be significant.

RESULTS

Out of the total 202 malarial cases, 50.4% was the malarial AKI cases; their demographic, clinical, and laboratory profile are shown in Table 2. Out of 102 malarial AKI children, 68% of cases were affected due to falciparum infection, 12% due to vivax, and rest 20% due to mixed infection. The study participants were divided into three groups as per the stages of the AKI (Stages 1, 2, and 3).

Inter- and intra-group comparison of the mean duration of hospitalization was done among three groups of malarial AKI children and was statistically significant (F [2,100] = 172.057, p=0.000) as shown in Table 3. Mean duration of hospitalization in children with Stage-3 AKI (6.25±0.707 days) was significantly more than those in Stage-2 AKI (5.36±0.497 days), p=0.009, and Stage-1 AKI (2.756±0.121 days), p=0.000 (Fig. 1). Mean duration of hospitalization of children with Stage-2 AKI (5.36±0.497 days) was also significantly more than those in Stage-1 AKI (2.756±0.121 days) (p=0.0001).

Table 1: Staging of AKI

Stages of AKI	Serum creatinine	Urine output
1	↑ SCr≥26.5 µmol/L (≥0.3 mg/dL) or↑SCr≥150 a 200% (1.5 a×2)	<0.5 mL/kg/h (>6 h)
2	↑ SCr>200 a 300% (>2 a×3)	<0.5 mL/kg/h (>12 h)
3	↑ SCr>300% (×>3) or if baseline SCr≥353.6 µmol/L (≥4 mg/dL) ↑ SCr or anuria (12 h), ≥44.2 µmol/L (≥0.5 mg/dL)	<0.3 mL/kg/h (24 h) or anuria (12 h)

AKI: Acute kidney injury

Table 2: Characteristics of the study population

Parameters	Mean±SD (n=102)
Age in years	8.0±3.7
Sex (M/F ratio)	54/48 (1.1:1)
Weight (Kg)	21.6±8.9
Symptoms	
Fever (°F)	102
Chills and rigor	36
Headache	76
Altered sensorium	28
Respiratory distress	14
Ascites	6
Splenomegaly	93
Bleeding	3
Vomiting	68
Jaundice	8
Convulsion	17
Pain abdomen	42
Paleness	95
High colored urine	70
Anemia	98
Hepatomegaly	98
Flank pain	6
Edema	5
Dehydration	2
Oliguria	46
Laboratory parameters	
Malarial AKI (pf/pv/mixed)	69 (68%)/12 (12%)/21 (20%)
Na+ (Meq/L)	137.7 (±6.8)
K+ (Meq/L)	4.1 (±0.4)
Urea (mg/dl)	55.1 (±25.5)
Creatinine (mg/dl)	1.44 (±0.49)
Hb (g/dl)	8.5 (±1.2)
RBS (mg/dl)	93.0 (±26.9)
TLC (lacs/mm^3)	17573 (±4506)
TPC (lacs/mm^3)	1.7 (±0.6)
Duration of stay (days)	3.3
Stages of AKI (1/2/3)	102 (80/14/8)
Outcome (death)	6/102 (5.8%)
Death (pf/pv/mixed)	(5/0/1)

RBS: Random blood sugar, TLC: Total leukocyte count, TPC: Total platelet count, SD: Standard deviation, AKI: Acute kidney injury

Inter- and intra-group comparison of the mean duration of pre hospitalization illness was done among three groups and was found to be non-significant (F [2,100] = 0.854, p=0.429). The median duration of survival in children with Stage 1 AKI was 3 days while that in Stage 2 and Stage 3 were 5 and 7 days, respectively. The median duration of survival between three stages of AKI was significant (Tarone-Ware Chi-square=48.365 [df=2], p=0.000) (Fig. 2).

DISCUSSION

In spite of the severity of the disease, AKI can be reversible if detected early enough and managed properly. Some of the previous studies had reported 28.9% renal involvement in malaria cases [15] while other studies have also reported 4–70 % [7,16-19]. These variations were due to lack of awareness and late intervention of malaria, which lead to renal complication. Actually there was renal cortical vasoconstriction due to hypoperfusion, sequestration, and resultant acute tubular necrosis cause of lysis of parasite affected red blood cell (RBC) and microvascular obstruction. The present study reported 50.4% renal involvement due to lysis of affected RBC that lead to ineffective erythropoiesis, as result of which, ischemia of kidney occurred. The previous study had reported 58.2% renal involvement in falciparum malaria, 23% in vivax malaria [18].

Table 3: Inter- and intra-group comparison of hospital stay (one-way ANOVA)

Intragroup comparison	Mean±SD	Intergroup comparison	p value
Stage 1 AKI	2.756±0.121	Stage 1 versus Stage 2	<0.000
Stage 2 AKI	5.36±0.497	Stage 1 versus Stage 3	<0.000
Stage 3 AKI	6.25±0.707	Stage 2 versus Stage 3	<0.009

F (2,99)=172.057, p=0.000. SD: Standard deviation, AKI: Acute kidney injury

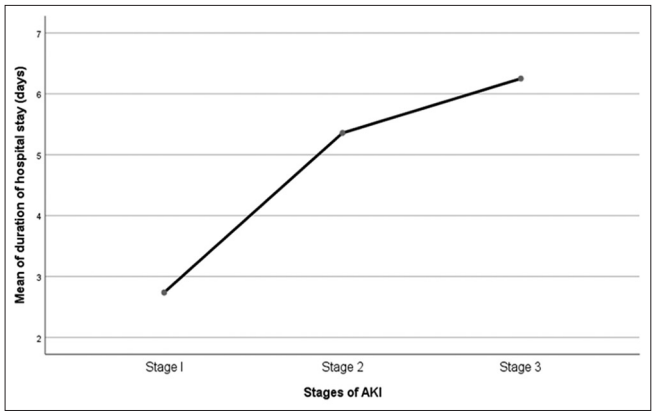

Figure 1: Mean plot showing variation in the duration of hospitalization in days among stages of acute kidney injury

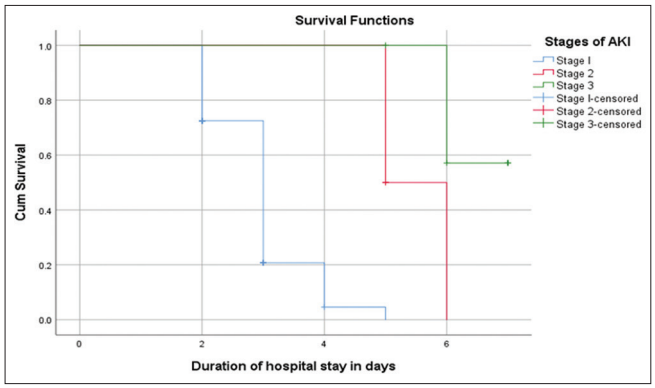

Figure 2: Kaplan–Meier survival analysis among stages of acute kidney injury

Kidney involvement was relatively more frequent in falciparum malaria than vivax malaria. The percentages of renal involvement were maximum in mixed infection group [19]. In this study, 61.7% renal involvement in falciparum malaria, 22.5% in mixed malaria, and 15.6% in vivax malaria were reported. The possible reason behind the obtained results could be due to falciparum malaria destroy more RBC as compared to other species of parasite. Some studies had reported 15–30% of mortality in malarial AKI [20] while in the present study, the mortality rate by malarial AKI was comparatively low (5.8%). The reduced mortality rate could be due to the education of people through the malarial program by the government.

Some inclusive measures of these government programs include awareness of malaria in the locality; early detection and intervention at the grass root level are mainly done by health workers in Odisha. AKI is a serious complication of malaria, with a reported mortality of 15–45% [19]. Another study had reported mortality of between 39.5% and 45% [21,22] in malarial AKI. As per the analysis, 6 cases had received dialysis but finally led to death after dialysis. Among them, all the cases were at Stage-3.

At present, there are no studies on survival analysis of malarial AKI affected children. This study was an approach toward the survival to know the status of these children. Time to event analysis demonstrated that the Stage 3 AKI children have got the maximum morbidities while the Stage 1 AKI children have the least morbidities. This study observed that AKI stages contribute to be the deciding factor when it comes to the future of the patient affect by malarial AKI.

Mean duration of hospitalization and time to event analysis (survival analysis) seems to be same but it is totally different as survival analysis counts for follow-up of the patients until final event is achieved, i.e., in our case discharge and/or death. As our center is a tertiary one, most of the cases are on a referral basis and we have got there is no effect of pre-illness duration on the outcome. However, there may be certain other influencing factors for which prediction analysis should be done to reach the best evidence.

The current study was also not devoid of limitations due to the small sample size and observer bias. We have only assessed the morbidities of AKI children, but it could have been better if we would have analyzed the AKI children on a daily basis so that the disease progression status could be known in more detail, extreme shortage of human resource was our main constraint. For better results, we suggest keeping all the above parameters in mind and a more robust approach supported with evidence can be opted.

CONCLUSION

The present study highlights the fact that morbidities and the median duration of survival are more in Stage 3 AKI as compared to the other two stages. Timely intervention, i.e., dialysis, is highly warranted to prevent renal complications. As there are no articles published on this emerging topic to date, detailed research with the best available evidence-based approach is needed.

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