

Clinical and Laboratory Features Associated with Acute Kidney Injury in Severe Malaria

Hiren Anghan, Prayas Sethi, Manish Soneja, Sandeep Mahajan¹, Naveet Wig

Departments of Medicine and ¹Nephrology, All India Institute of Medical Sciences, New Delhi, India

Abstract

Introduction: Critically ill severe malaria constitutes one of the major hospital admissions in Indian setting. Clinical studies identifying the factors associated with acute kidney injury (AKI) in malaria are lacking. This study aimed to identify these factors. **Methods:** This prospective observational study was conducted in a tertiary care center of North India. All adult patients with severe malaria were studied during 2012–2014. **Results:** The study included 79 patients and AKI was observed in 36 patients. Of these 79 patients, 52.7% were *Plasmodium falciparum* positive and 47.2% were *Plasmodium vivax* positive. In AKI patients, thrombocytopenia and jaundice were the most common other complications seen. Among *P. vivax* malarial patients, 17 (36%) patients had AKI. Features associated with AKI among patients admitted with *P. vivax* malaria were as follows: tachycardia (adjusted relative risk [RR]: 3.9; 95% confidence interval [CI]: 1.1–13.7), direct hyperbilirubinemia (adjusted RR: 4.7; 95% CI: 1.4–15.2), anemia (adjusted RR: 6; 95% CI: 1.7–22.4), and sepsis (adjusted RR: 3.3; 95% CI: 1.1–13.7). The presence of tachycardia, acidosis, cerebral malaria, acute respiratory distress syndrome/acute lung injury, hypotensive shock, and poor Glasgow Coma Scale were associated with higher mortality in patients with AKI. Patients who required mechanical ventilation and/or vasopressor support had higher mortality. **Conclusion:** *P. vivax* is an important cause of severe malaria with AKI in our setting. Various other clinical features are associated with AKI and related mortality.

Keywords: Acute kidney injury, critically ill, severe malaria

INTRODUCTION

Tropical countries, including India, carry the major burden of malaria. Severe malaria is diagnosed by demonstrating asexual forms of the malaria parasites in the blood in a patient with a potentially fatal manifestation or complication of malaria in whom other diagnoses have been excluded. Our intensive care team deals routinely with malaria complications as they require critical care management. These complications, as defined by the WHO, include cerebral malaria, pulmonary edema, acute renal failure, acidosis, hypoglycemia, severe anemia, bleeding, jaundice, and shock. Recent evidence is that the overall burden, economic impact, and severity of *Plasmodium vivax* have been underestimated.^[1]

Malaria contributes 2%–39% to overall hospital admissions for acute kidney injury (AKI). In endemic areas, the incidence of AKI may be >4% of malaria cases. Among those with severe parasitemia, as many as 60% develop AKI. Renal involvement has been reported in *Plasmodium falciparum*, *Plasmodium*

malariae, and recently in *P. vivax* infections. AKI is usually seen at the end of the 1st week and is nonoliguric in 50%–75%.^[2] In view of the high mortality rates associated with AKI, it is critical to identify the clinical and laboratory parameters associated with AKI in a patient with malaria, to avoid progression to renal failure. Good hydration, monitoring of urine output, and renal function with careful use of nephrotoxic medications are the bedrock of supportive care. Timely transfer for dialysis is particularly important and is a challenging issue in resource-limited settings.

Our study was designed to estimate the incidence and analyze the parameters associated with AKI in severe malaria. Such data from Indian settings are scarce.

Address for correspondence: Prof. Naveet Wig,
Room No 3097, Department of Medicine, All India Institute of Medical
Sciences, New Delhi, India.
E-mail: naveetwig@gmail.com

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METHODS

Ours was a prospective observational study conducted in a tertiary care center of North India from 2012 to 2014. All patients >12 years with confirmed severe malaria who were willing to participate were studied. A total of 64 severe malaria cases without AKI were needed to estimate the incidence with 95% confidence interval (CI) and 25% relative precision. Patients on nephrotoxic drugs, with other chronic diseases, or patients not giving consent were excluded from the study. Patients were followed up till a month after discharge or death. The diagnosis of malaria was made on all patients screened for acute febrile illness by a positive plasmodium lactate dehydrogenase antigen-based rapid diagnostic test and peripheral blood film confirmed on Giemsa stain.

Apart from the parasite density, percentage of parasitized red blood cells (parasitemia percentage) and the presence of one or more schizonts in the Giemsa-stained smear were also noted. Blood samples were taken on the day of admission for full blood count, renal function, liver function, glucose, and arterial blood gas analysis. A chest radiograph was obtained, and blood was collected for bacterial culture sensitivity, Widal test, HIV, hepatitis profile, NS1 antigen for dengue, *Leptospira* serology, and other specific tests (i.e., lumbar puncture) to exclude any other infection according to symptoms as clinically indicated.

AKI network (AKIN) criteria to define AKI in patients with severe malaria were used as these criteria are more sensitive and specific. It differs from RIFLE (Risk, injury, failure, loss and end stage kidney disease) classification, in that it reduces the need for baseline creatinine but requires two creatinine values within 48 h.^[3] Serum creatinine 1.5–2 times from baseline or 25 µmol/L from baseline increase or urine output <400 mL/24 h or <0.5 mL/kg/h were taken to be indicative of AKI. Renal replacement therapy was given in the form of hemodialysis as indicated.

Data were analyzed using STATA 12.1 software. Descriptive statistics for continuous variables were represented as mean ± standard deviation as well as median and range (minimum to maximum). Categorical variables were reported in terms of the number and percentage of patients affected. The incidence of AKI was calculated with 95% CI in severe malaria. In case of continuous variable, *t*-test/Wilcoxon rank sum test was applied as appropriate to calculate the difference in average between the groups. The Chi-square test was used to calculate the association of categorical variables with outcome. Receiver operating characteristic curve analysis was done to find the cutoff of variables where not available. Univariate logistic regression and stepwise multiple logistic regression were applied to calculate the unadjusted and adjusted odds ratio (OR). This was consequently converted to relative risk (RR).

RESULTS

From the 100 patients screened, 79 with severe malaria were recruited. Among these, 47 (59.5%) had *P. vivax* malaria and

32 (40.5%) had *P. falciparum* malaria. The most common associations were thrombocytopenia (71, 89.8%), jaundice (50, 63.2%), and renal failure (36, 45.6%). Sepsis was present in 25 (31.6%) patients. Cerebral malaria, severe anemia, and acute respiratory distress syndrome (ARDS) were present in 15 (18.9%), 12 (16%), and 10 (12.6%), respectively.

Of the 36 patients with AKI, 19 (52.7%) were *P. falciparum* positive compared to 17 (47.2%) were *P. vivax* positive. None were positive for both *P. falciparum* and *P. vivax*. However, polymerase chain reaction-based tests were not performed in our study. Patients with AKI were classified into three stages on the basis of the AKIN classification. On the day of onset of AKI, 9 (25%) were in Stage 1, 8 (22%) in Stage 2, and 19 (53%) in Stage 3. The final AKI stage recorded (i.e., the uppermost stage of AKI that developed before improvement began) were as follows: 4 (13%) in Stage 1, 11 (30%) in Stage 2, and 21 (57%) in Stage 3.

The comparison between the clinical and laboratory parameters of AKI versus non-AKI group is shown in Table 1. On univariate analysis, vomiting was significantly higher in patients with AKI. Patients with AKI were more likely to have tachycardia (>96/min), tachypnea (>20 per min), and pallor. Anemia (hemoglobin [Hb] <70 g/L), leukocytosis, levels of direct bilirubin >1.5 mg/dl, lactate >5 mmol/L, transaminase >40 IU/L, and infection with *P. falciparum* species were significantly associated with AKI. Sepsis was significantly more frequent in 18/36 (50%) with AKI than in 7 (16%) without.

On multivariate analysis, higher prevalence ratio (adjusted RR: 3.9; 95% CI: 1.1–13.7), direct hyperbilirubinemia (adjusted RR: 4.7; 95% CI: 1.4–15.2), lower Hb (<70 g/L) (adjusted RR: 6; 95% CI: 1.7–21.4), and sepsis (adjusted RR: 3.3; 95% CI: 1–10.5) were significantly associated with AKI.

Thrombocytopenia was seen in 33 (91%) of those with and 38 (88%) without AKI. Complications that were significantly higher in AKI included ARDS (OR: 5.85; 95% CI: 1.85–29.66), sepsis (OR: 5.14; 95% CI: 1.81–14.55), acidosis (OR: 4.9; 95% CI: 1.66–14.5), and shock (OR: 2.69; 95% CI: 1–7.25). Comparing the two species, 14 (78%) *P. falciparum* patients with AKI required dialysis as compared to 6 (35%) with *P. vivax*; this difference was statistically significant ($P = 0.02$).

A total of 11/79 severe malaria patients died. Features on admission associated with a fatal outcome are shown in Table 2.

The association of different complications of malaria in AKI patients with mortality is shown in Table 3.

Acidosis ($P = 0.001$), sepsis ($P = 0.016$), and renal failure ($P = 0.042$) were more common in *P. falciparum* than *P. vivax* malaria. Several patients with *P. vivax* malaria also had these complications. No patient had a mixed infection with both *P. vivax* and *P. falciparum*. The frequency of various complications in the two types of malaria is shown in Table 4.

Table 1: Clinical and laboratory features compared between acute kidney injury and nonacute kidney injury group

Variable	With AKI, frequency (%) (n=36)	Without AKI, frequency (%) (n=43)	P	Univariate RR (95% CI)
Pulse rate				
>96	25 (59.5)	17 (39.5)	0.008	3.5 (1.4-8.9)
Respiratory rate				
>20	30 (83.4)	19 (44.2)	0.001	6.3 (2.2-18.2)
Nausea and vomiting				
Yes	32 (88.9)	30 (69.8)	0.039	3.5 (1.01-11.8)
Pallor				
Yes	27 (75)	22 (51.5)	0.030	2.9 (1.1-7.5)
Hemoglobin (g/l)				
>70	19 (52.7)	34 (79.1)	0.012	3.38 (1.2-9)
Conjugated bilirubin				
>26.6	24 (66.7)	15 (34.8)	0.007	3.7 (1.5-9.5)
SGOT				
>40	23 (64)	12 (28)	0.002	4.6 (1.7-11.8)
Lactate				
>5	14 (39)	7 (16.8)	0.023	3.3 (1.1-9.3)
Species				
<i>Plasmodium falciparum</i>	19 (47.2)	13 (30)	0.042	2.6 (1.02-6.5)
Sepsis				
Yes	18 (50)	7 (16)	0.001	5.1 (1.8-14.5)

Univariate analysis (values expressed in terms of RR with 95% of CI on univariate analysis). AKI: Acute kidney injury; CI: Confidence interval; RR: Relative risk; SGOT: Serum glutamic-oxaloacetic transaminase

Table 2: Statistically significant “clinical features in acute kidney injury fatalities”

Variables	AKI died (n=9)	AKI survived, (n=27)	P
PR (per min), mean±SD	112.4±4.8	101.9±11.1	0.01
SBP (mm Hg), mean±SD	82.4±6.2	99±14	0.009
TLC (per cu mm)	13,000 (6100-25,000)	9000 (1500-23,000)	0.03
GCS, mean±SD	7.1±3.8	14.2±1.5	0.001
APACHE II score	26.2±7	11.9±5.8	0.002
Mechanical ventilation (%)	7 (78)	4 (14)	0.001
Vasopressor support (%)	7 (78)	4 (14)	0.001

AKI: Acute kidney injury; SD: Standard deviation; PR: Prevalence ratio; SBP: Systolic blood pressure; GCS: Glasgow Coma Scale; APACHE: Acute Physiology and Chronic Health Evaluation; TLC: Total leucocyte count

DISCUSSION

P. falciparum has been a major cause of complicated malaria, but over the years, there have been numerous cases of *P. vivax* malaria- causing severe complications. The disturbing fact is that the most common and widespread species of malaria is *P. vivax*. The exact pathogenesis, parasite-host interactions, and reasons for multi-organ dysfunction due to *P. vivax* are unclear.^[4]

In our study, 47 (59.49%) patients had *P. vivax* malaria who satisfied the WHO criteria for severe malaria indicating the underestimated severe presentation of *P. vivax* malaria. The presence of *P. falciparum* malaria has not shown statistically significant difference in risk of increased mortality as compared to *P. vivax*, and even though the falciparum has shown statistically significant increased chances of complications associated with malaria, the absolute number of patients with these complications is high. This is consistent with the globally increased complicated *P. vivax* malaria. In a systematic review and meta-analysis by Rahimi et al., on severe *P. vivax* malaria, there has been an

increasing trend in the prevalence of complications in *P. vivax* malaria.^[5] Among the 77 studies reporting severe *P. vivax* malaria, severe thrombocytopenia (<50,000/mm³) was the most common “severe” manifestation (888/45,775 with pooled prevalence of 8.6%). The case fatality was 0.3% (353/46,411). Likewise, there have been various isolated case reports and series on fatalities seen in *P. vivax* malaria.

Numerous criteria for diagnosing AKI are available such as the WHO, RIFLE, and AKIN. AKIN criteria for AKI was used keeping in view that small change in serum creatinine is associated with adverse outcomes, and consequent to its increased sensitivity, it estimated the AKI prevalence of 45% which is higher than the studies done earlier. Different studies have shown variable prevalence of AKI in malaria ranging from 6% to 40%. Ratanarat et al. found that AKIN criteria improved sensitivity for detection of AKI, and prediction of inhospital mortality was better than that of RIFLE criteria in critically ill patients with multi-organ dysfunction syndrome.^[6]

Table 3: Statistically significant “complications of malaria associated with mortality” in acute kidney injury

Complications	Died (n=9)	Survived (n=27)	P	OR (95% CI)
Cerebral malaria				
Yes	6	4	0.012	11.5 (2.007-65.9)
ARDS/ALI				
Yes	7	2	0.002	43.7 (5.91-368.7)
Acidosis				
Yes	7	9	0.049	7 (1.2-40.82)
Sepsis				
Yes	8	10	0.018	13.6 (1.47-143.5)
Hypotensive shock				
Yes	2	7	0.004	28 (2.89-270.5)
Poor GCS				
Yes	6	1	<0.001	52 (4.57-591)

OR: Odds ratio; CI: Confidence interval; GCS: Glasgow Coma Scale; ARDS: Acute respiratory distress syndrome; ALI: Acute lung injury

Table 4: Species-related frequency of complications in the study population

Complications	<i>Plasmodium falciparum</i> frequency (percentage of n=32)	<i>Plasmodium vivax</i> frequency (percentage of n=47)	P	OR (95% CI)
Hyperpyrexia				
Yes	13 (40.7)	19 (40.4)	0.98	1 (0.4-2.25)
Cerebral malaria				
Yes	9 (28.1)	6 (12.8)	0.08	3.12 (0.62-15.69)
ARDS/ALI				
Yes	5 (15.6)	6 (12.8)	0.71	0.41 (0.07-2.39)
Jaundice				
Yes	21 (65.3)	31 (66)	0.97	0.9 (0.3-2.66)
Renal failure				
Yes	19 (59.3)	17 (36.1)	0.042	2.57 (1.02-6.49)
Severe anemia				
Yes	7 (21.9)	5 (10.6)	0.17	2.32 (0.57-9.40)
Bleeding/DIC				
Yes	12 (37.5)	15 (31.9)	0.60	0.88 (0.28-2.77)
Rash				
Yes	3 (9.3)	3 (6.3)	0.62	1.44 (0.23-8.90)
Thrombocytopenia				
Yes	27 (84.38)	44 (93.6)	0.18	0.32 (0.06-1.62)
Acidosis				
Yes	16 (50)	6 (12.8)	0.001	7.06 (2.22-22.50)
Hypotensive shock				
Yes	11 (34.4)	9 (19.1)	0.12	2.25 (0.49-10.25)
Sepsis				
Yes	15 (46.9)	10 (21.2)	0.016	3.26 (1.21-8.74)
Seizure				
Yes	3 (9.3)	2 (4.2)	0.39	2.5 (0.39-15.92)
>5% parasitemia				
Yes	0	0	-	-
Poor GCS				
Yes	5 (15.6)	5 (10.6)	0.52	0.41 (0.05-3.42)

OR: Odds ratio; CI: Confidence interval; GCS: Glasgow Coma Scale; ARDS: Acute respiratory distress syndrome; ALI: Acute lung injury; DIC: Disseminated intravascular coagulation

A systematic review and meta-analysis by Xiong *et al.* found that the AKIN criteria can identify more patients in classifying AKI in intensive care unit (ICU) patients compared to RIFLE criteria; however, the AKIN criteria did not show a better

ability in predicting hospital mortality in both ICU and cardiac surgery patients compared to RIFLE criteria.^[7]

Tachycardia, direct hyperbilirubinemia, and anemia (<7 g/dl) were associated with AKI. The etiology of AKI in the presence

of these factors can be attributed to hemolysis, parasite load, dehydration and fever *per se*, sepsis and Disseminated intravascular coagulation (DIC), etc. Cytokine response to severe infection could also be contributory. Hence, an anemic and icteric acute febrile patient in endemic area who tests positive for malaria merits serial monitoring of kidney functions. Severe anemia with Hb <5 g/dL and/or hematocrit <15% is one of the well-known complications and poor predictor of severe malaria. Apart from the WHO criteria for severe malaria, this predictive value of Hb and hematocrit level was also reported in studies done by Mishra *et al.* and von Seidlein *et al.*^[8,9] The present study has also shown the statistically significant value of low Hb level and hematocrit level in patients of AKI in severe malaria. In a study done by Saravu *et al.* for risk factors and outcome stratified by severity of AKI showed, increasing age, higher heart rate, lower diastolic blood pressure, icterus, and hepatomegaly were identified risk factors of AKI.^[10]

The overall mortality rate among those with kidney injury ranges from 15% to 50% in different series.^[11] A total of 11/79 severe malaria patients died in our study which is almost in accord with the worldwide mortality rate.

The presence of tachycardia, acidosis, cerebral malaria, ARDS/acute lung injury, hypotensive shock, and poor Glasgow Coma Scale (GCS) was associated with higher mortality in patients with AKI. Patients who required mechanical ventilation and/or vasopressor support had higher mortality. It is needless to say that these conditions are associated with poor outcomes in all critically ill patients, and the presence of AKI can worsen these conditions. AKI can contribute to encephalopathy due to uremia, metabolic acidosis can be worsened, and superadded infections can worsen sepsis and may lead to ARDS. The presence of cerebral malaria is the main cause behind the low GCS score or impaired sensorium. Other factors that can cause similar poor sensorium are presence of hypoglycemia, electrolyte imbalance, and severe shock. The significant predictive value of low GCS score in severe malaria was also shown in a study done by Hanson *et al.*^[12] They also developed a scoring system Coma, Acidosis, Malaria (CAM score) using this parameter as one of the components. The low GCS score was also one of the significant predictors of mortality in a study done by Dondorp *et al.*^[13] Studies by Tangpukdee *et al.* in Thailand on adult malaria patients showed tachycardia as a predictor of mortality.^[14] Frequent presence of severe anemia and shock in patients who died may have contributed to the significant difference of pulse rate in the two study groups in our study.

Strength and limitations of study

This is probably the only study done using AKIN criteria to define AKI in malaria. However, the sample size was small with a referral bias.

Only admitted patients with suspected severe malaria were studied and that the size of denominator populations of people with *P. falciparum* and *P. vivax* infections was unknown (those not reaching a health facility; those managed in

outpatients clinic; and those admitted but not severe) nor the proportion of them that reached hospital and were admitted.

CONCLUSION

The prevalence of AKI among patients admitted to hospital with severe malaria was 45.6% in our study. Direct hyperbilirubinemia, anemia, tachycardia, and sepsis were associated risk factors in these patients. This information can be applied in any resource-limited health-care setting at primary health-care level to identify patients who have a high likelihood of AKI in the presence of severe malaria and can be timely referred.

Future studies should investigate if even earlier detection with novel biomarkers, before rise in serum creatinine, would alter the epidemiology of this preventable complication. The present study shows that there is rising trend of complicated *P. vivax* malaria.

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Conflicts of interest

There are no conflicts of interest.

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