



Diagnostic & Prognostic Evaluation of Urinary Abnormalities for Malaria Associated Kidney Disease

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Abstract

Background: Malaria is a multi-organ illness due to plasmodium species and involves the brain, liver and kidneys¹. Urinary abnormalities are frequently found in malaria patients and may be associated with a wide spectrum of renal injury including chronic kidney disease⁷.

Objective: To correlate urinary abnormalities in malaria patients with the occurrence of kidney disease and its clinical outcomes.

Methods: A prospective study was conducted in 458 patients of confirmed malaria, to measure urinary abnormalities including proteinuria and hematuria at presentation, and correlate them with kidney injury reflected by a falling creatinine clearance rate $<60 \text{ mg/m}^2$. Patients were treated using standard care pathways and followed for 6 months after discharge from hospital. Persistence or resolution of kidney injury was identified using the parameters mentioned above. Statistical analyses were done using standard tests and a 'p' value <0.05 was considered significant.

Results: Urinary abnormalities were found in 230 of 458 (50.21%) patients, and were equally divided between both plasmodium species. Older patients (age >30 years) were more frequently affected, and there were no gender difference in urinary abnormalities in either species infestation. The average number of dialysis sessions was also similar, while hospital length of stay was significantly greater at 7.29 ± 2.94 days in the *P. falciparum* patients vs. 6.18 ± 3.11 days for *P. vivax* ($p < 0.05$, 198/230). 198 patients survived and 6 months follow up was completed in 142 patients. Complete resolution of kidney disease occurred in 70/142 patients, while 72/142 had residual disease progressing to chronic kidney disease (CKD). There was a significant correlation between urinary abnormalities in malaria patients and renal disease at follow up ($p < 0.05$), which had a negative predictive value of 57.98% with a sensitivity of 20.22% and specificity 69.50%.

Conclusion: Presence and persistence of urinary abnormalities in patients with malaria may be early markers of renal injury. Absence of these urinary abnormalities at follow up suggests resolution of renal insult associated with malaria and low likelihood of progression to CKD.

Keywords: urinary abnormalities, kidney disease, and malaria.

Introduction

Malaria is a vector borne illness caused by the parasite species Plasmodium and spread by the

female Anopheles mosquito¹. It is endemic in warm humid tropical and subtropical countries, and affects both children and adults. Fever is the

initial presentation and may be intermittent or continuous. It rises rapidly and is characteristically associated with shaking chills and rigor, profuse sweating, headache, muscle and joint pain, nausea, vomiting and loss of appetite. Other symptoms may include diarrhea, skin rash, abdominal pain and features of upper respiratory tract infection².

Severe malaria may present as altered consciousness, convulsions, respiratory distress, renal impairment³, jaundice, abnormal bleeding or shock⁴. Laboratory investigations may reveal anaemia, hypoglycemia, acidosis, raised creatinine, hyperbilirubinaemia and hyperparasitaemia. Several factors influence the progression of uncomplicated malaria to severe malaria, including plasmodium species, age and gender of the patient, host immunity, parasitic load, and availability of timely and effective treatment. In recent years hepatic and renal complications have replaced cerebral malaria as the predominant manifestation of severe malaria⁸.

Urinary abnormalities like albuminuria (71.2%), pyuria (53.8%), hematuria (45%) and granular casts (71.4%) have been demonstrated in patients with malaria⁷. Proteinuria and hematuria have been shown to be predictors of end-stage renal disease in mass screening of population⁵. However, urinary abnormalities may be present in malaria even in the absence of renal disease.

Malaria associated renal impairment has a wide spectrum, including asymptomatic proteinuria or hematuria, acute glomerulonephritis, acute kidney injury, nephritic or nephrotic syndrome⁶ and chronic kidney disease. In India, four species of Plasmodium have been identified to cause malaria. *P. vivax* infection occurs in 60-75% of patients while *P. falciparum* accounts for 35-40% of malaria cases⁸. The latter is implicated in severe malaria and is thought to be more often associated with renal dysfunction. However, *P. vivax* is increasingly being seen to cause kidney injury. Other species of plasmodium are less common and their contribution to cases of severe malaria is relatively low.

We attempted to study the correlation of urinary abnormalities with kidney injury in malaria patients infected with *P. falciparum* or *P. vivax*. Our objective was to evaluate proteinuria and hematuria as potential diagnostic and prognostic predictors of kidney disease and its outcomes.

Methods

A prospective study was conducted in the KPS Institute of Medicine, GSVM Medical College, Kanpur. A total of 458 adult patients of *P. falciparum* and *P. vivax* malaria presenting between January 2016 and October 2018 were included in the study. Diagnosis of malaria was established using a thick and thin peripheral blood smear stained with Leishman's stain, and the rapid malarial antigen card test².

Inclusion Criteria

1. Confirmed diagnosis of malaria
2. Urinary abnormalities with or without decline of age and weight adjusted creatinine clearance below normal

Exclusion Criteria

1. Patients <18 years of age
2. Mixed infections with more than one plasmodium species
3. Known history or clinical/laboratory evidence of kidney disease
4. Pregnant women

All patients underwent a detailed history and clinical examination including recording of vital parameters, and their blood and urine samples were collected at presentation. A complete blood count (CBC), renal function test (RFT), serum electrolytes (SE), liver function test (LFT), random plasma glucose (RPG) and urinalysis were performed in our standardized laboratory. Triple screening for HIV, HBsAg and HCV was done for all patients using the card test. A baseline creatinine clearance (CrCl) was calculated for each patient using the Cockcroft-Gault equation⁹: $CrCl = \frac{Sex * ((140 - Age) / (Serum Creatinine)) * (Weight / 72)}$.

Malaria treatment was given using oral or parenteral medication as indicated, according to

the 2014 guidelines provided by the National Institute of Malaria Research². Renal replacement therapy was offered to patients with features of severe renal injury not responding to conservative treatment. These included severe hyperkalemia, intractable acidosis, fluid overload or oliguria. A 6 months follow-up for all patients was conducted after discharge and blood tests and urinalysis were repeated at this time.

Statistical Analysis

Statistical analyses were conducted using standardized tests. Difference in proportions was compared by chi-square test (significant ‘p’ value <0.05). The sensitivity, specificity, positive and negative predictive values were calculated, along with relative risk for malaria patients developing kidney disease in the presence of urinary abnormalities.

Results

The data from 458 patients of malaria including 190 (41.5%) of *P. falciparum* and 268 (58.5%) of *P. vivax* malaria are shown below.

Table 1: Presence of urinary abnormalities (proteinuria and/or hematuria) in malaria patients.

	Urinary Abnormalities	Present	Absent	Total
Malaria (n=458)	Yes	230 (50.21%)	228 (49.79%)	458 (100%)

Almost half of the patients of malaria in the study had urinary abnormalities, while the remainder had normal urine routine and microscopy results.

Table 2: Number of patients with urinary abnormalities according to species of the malarial parasite.

Type of Malaria ↓	Urinary Abnormalities ⇒		Total (%) (n = 458)
	Present (%) (n = 230)	Absent (%) (n = 228)	
<i>P. falciparum</i>	101(43.91)	89 (39.04)	190 (41.48)
<i>P. vivax</i>	129 (56.09)	139 (60.96)	268 (58.51)

$X^2 = 0.1454, p = 0.1454$

P. vivax malaria was slightly more common than *P. falciparum*, but the percentage of malaria

patients presenting with urinary abnormalities was statistically similar.

Tables 3 and 4 below show the appearance of urinary abnormalities in *P. falciparum* and *P. vivax* malaria patients respectively, as a function of age.

Table 3: Age distribution in *P. falciparum* malaria patients

Age (years) ↓	Urinary Abnormalities ⇒		Total (%)
	Present (%)	Absent (%)	
< 30	9 (8.91)	18 (20.22)	27 (14.21)
31 – 60	48 (47.52)	39 (43.82)	87 (45.79)
>60	44 (43.57)	32 (35.96)	76 (40)
Total	101	89	190

$X^2 = 5.088, p = 0.67854$ (not significant), Df = 2

Table 4: Age distribution in *P. vivax* malaria patients

Age (years) ↓	Urinary Abnormalities ⇒		Total (%)
	Present (%)	Absent (%)	
< 30	5 (3.87)	14 (10.07)	19 (7.00)
31 – 60	66 (51.67)	73 (52.52)	139 (51.86)
>60	58 (44.96)	52 (37.41)	110 (41.05)
Total	129	139	268

$X^2 = 0.1454, p = 0.1015$ (not significant), Df = 2

Three age groups were compared including young patients <30 years of age, adults 31–60 years and older patients >60 years. There was no statistically significant difference in the occurrence of urinary abnormalities between the three age groups. However, patients younger than 30 years had lower, while patients older than 30 years had a higher incidence of urinary abnormalities in malaria from both species (p<0.05).

Table 5: Gender distribution of patients according to Plasmodium species

Plasmodium species ⇒ Patient gender ↓	<i>P. falciparum</i> (n=101)	<i>P. vivax</i> (n=129)
Male	57	73
Female	44	56

$Z = 0.1518, p = 0.8793$

Urinary abnormalities were commoner in males (56.5%) than females (43.5%), but the gender ratio (females:males) was similar between the

Plasmodium species. (*P. falciparum* 1:1.3 and *P. vivax* 1:1.3)

The spectrum of urinary abnormalities and clinical kidney disease in patients with malaria is shown below in tables 6 & 7, respectively.

Table 6: Frequency of urinary abnormalities and features of kidney disease:

	<i>P. falciparum</i>	<i>P. vivax</i>
Proteinuria (only)	38 (38%)	31 (24%)
Proteinuria + Haematuria	15 (15%)	10 (8%)
Decreased urine output		
- Oliguria (<500 ml/24h)	61 (60%)	49 (38%)
- Anuria (<50 ml/24h)	18 (18%)	9 (7%)

Proteinuria alone was the commonest finding on urinalysis, while that associated with haematuria was relatively less frequent. The majority of patients with kidney disease presented with oliguria, although anuria was not infrequent. These results were comparable in infections due to either plasmodium species (p=NS).

Table 7: Clinical features of malaria associated kidney disease

Clinical Features	<i>P. falciparum</i>	<i>P. vivax</i>
Proteinuria	18 (17.9%)	15 (11.6%)
Decreased urine output	56 (55.6%)	14 (10.8%)
Metabolic acidosis	19 (18.8%)	15 (11.6%)
Hyperkalemia	16 (15.8%)	16 (12.4%)
Volume overload	16 (15.8%)	17 (13.2%)
Uremic encephalopathy	4 (4%)	3 (2.3%)

Decreased urine output with or without other clinical findings was the most frequent complaint in patients of *P. falciparum* malaria. Those presenting with other features like isolated proteinuria, hyperkalaemia, metabolic acidosis and fluid overload were similarly distributed across both groups, and uremic encephalopathy was uncommon.

Clinical Intervention

Treatment of malaria-associated kidney disease was done according to guidelines², including parenteral administration of anti malarial drugs, antipyretics, antibiotics and anticonvulsants, and supportive measures like maintaining fluid and electrolyte balance. Laboratory services were available along with facilities for intensive care, oxygen supply, mechanical ventilation, blood

transfusion, and dialysis and specialized nursing care.

Conservative

1. Artemisin based therapy: artesunate 2.4 mg/kg intravenously after dilution as recommended
2. Antibiotics (where indicated)
3. Intravenous fluids
4. General supportive treatment

Conservative (as above) + Intravenous

1. Low dose Frusemide - 20 mg BD
2. High dose Frusemide - 60 mg TID

Renal replacement therapy

Criteria for hemodialysis:

1. Decreased urine output (urine output<500 ml/24 hours)
2. Severe acidosis (pH<7.20)
3. Hyperkalemia (>6 meq/L)
4. Persistently declining creatinine clearance (>30% of baseline/24 hours)

Rationale for hemodialysis

To allow the kidney to recover from the malarial pathophysiological insult, including:

1. Correction of acidosis and electrolyte imbalance
2. Increased clearance of uremic toxins
3. Treatment of fluid overload

Table 8 below, shows the number of patients of malaria with kidney disease, which required renal replacement therapy and the average number of hemodialysis sessions, average length of stay, and in hospital mortality.

Table 8: Renal replacement therapy for kidney disease in malaria

Outcome	<i>P. falciparum</i> (n = 101)	<i>P. vivax</i> (n = 129)
# Of patients for dialysis	25 (24.7%)	26 (20.2%)
# Of dialysis sessions	3.38 ± 1.26	3.24 ± 1.21
Length of stay (days)	7.29 ± 2.94	6.18 ± 3.11 [†]
In hospital mortality	11 (10.9%)	17 (13.2%)

[†]p<0.05

Patients in the *P. vivax* group fared marginally better than *P. falciparum* in the requirement and length of dialysis, and in-hospital mortality, although this difference was not statistically

significant. The length of stay, however, was longer for *P. falciparum* than for *P. vivax* affected patients ($p < 0.05$).

Table 9: Patients with malaria associated urinary abnormalities and kidney disease

Urinary Abnormalities⇒	Present	Absent	Total
Impaired renal function (age adjusted eGFR < 60 ml/min) ↓			
Present	18	43	61
Absent	71	98	169
Total	89	141	230

$X^2 = 2.941$, $P < 0.05$ (significant)

The above table shows the frequency of kidney disease, reflected by a falling creatinine clearance <60ml/min, as a function of urinary abnormalities in malaria patients. The Mantel Haenszel chi-square test shows a statistically significant association between these two variables. The overall risk of developing kidney disease in malaria is 38.70%, while a relative risk of 0.69 predicts the likelihood of renal sparing in the absence of urinary abnormalities. The sensitivity of the association is low at 20.22% while the specificity is moderate at 69.50%, and the positive predictive value is 29.50%. However, a negative predictive value of 57.98% makes it a favourable indicator of preserved kidney function, in the absence of urinary abnormalities in patients with malaria.

Of the 230 malaria patients with kidney disease 198 survived and were followed up for 6 months after discharge from the hospital. At the end of the follow up period, data was available for 142 patients. The following table shows the results:

Table 10: Patients at 6 months follow up

	Normal – (n=70) eGFR > 60 mg/min	CKD – NDD ⁺ (n=62)	CKD – DD ⁺⁺ (n=10)
CrCl (eGFR) mg/min	72+/-8	45+/-16	12+/-7
Proteinuria	<0.1 g/day	>0.5g/day	0.1 – 0.5 g/day
Proteinuria + Haematuria	<4RBC/hpf	5-10 RBC/hpf	5-10 RBC/hpf

⁺NDD - non-dialysis dependent (eGFR range 15-60 mg/m²),

⁺⁺DD - dialysis dependent (eGFR range <15 mg/m²)

Of the 142 patients with a 6 months follow-up, 72 patients had residual renal dysfunction of which

62 patients were managed conservatively, and 10 developed chronic kidney disease requiring haemodialysis. 70 patients recovered completely and regained normal kidney function with no urinary abnormalities or signs of renal dysfunction.

Discussion

Malaria is a common tropical illness spread widely across the Indian subcontinent. It is often associated with a single or multiple system dysfunctions, leading to significant morbidity and mortality. *P. falciparum* is known to cause more severe disease, associated with anaemia, hemodynamic compromise, severe oliguria, neurological dysfunction and sepsis. *P. vivax* on the other hand, is complicated by liver injury, blood dyscrasias, splenomegaly and sepsis.

In the last decade or so the pattern of malarial complications in both plasmodium species appears to have changed, and a higher incidence of sepsis, electrolyte abnormalities, acid base disturbances and kidney injury are seen. The reason for this is not clear but the outcomes in these complicated malaria patients are poor.

The malarial parasite can cause direct kidney injury, inflammation and consequent glomerulonephritis. Renal complications may also result from altered host immune response to the parasite, hyperbilirubinaemia, electrolyte imbalance and hemodynamic compromise. Acute kidney injury including acute tubular necrosis and acute interstitial nephritis may require hemodialysis, and occasionally lead to chronic kidney disease¹¹.

Patients presenting with fever may have urinary abnormalities like proteinuria and hematuria as a part of the systemic illness, and the renal function remains normal (age and weight matched CrCl > 60). In severe malaria kidney affection may manifest as a spectrum of abnormalities, including rising creatinine, metabolic acidosis, hyperkalemia and oliguria¹². The risk factors for renal injury includes older age, hypotension,

superadded infection, altered sensorium and decreased urine output¹³.

Hyperparasitemia and host immune response can both cause renal tubular damage. Low perfusion pressure due to hypovolemia and shock adds to the insult and may lead to acute tubular injury, while a damaged endothelium in the capillaries causes proteinuria and hematuria, which in turn may further occlude the microcirculation. The resultant release of inflammatory cytokines like endothelins, interleukins and thromboxane, leads to formation and deposition of immune complexes, causing glomerulonephritis or acute interstitial nephritis. Cortical necrosis is an uncommon but usually irreversible manifestation of kidney disease in malaria¹¹.

It has been shown that one third of patients with malaria associated kidney injury have normal age matched creatinine clearance at presentation. Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) are early biomarkers for acute kidney injury, and can be detected earlier than rise in creatinine levels¹⁴. Early diagnosis and prompt initiation of renal replacement therapy is shown to be associated with improved clinical outcome and survival¹⁵.

Limitations

- 1) The study was conducted at a teaching hospital where the sickest patients are admitted. The occurrence of asymptomatic urinary abnormalities in patients with fever and malaria might be significantly higher.
- 2) Kidney injury could not be characterized accurately as only clinical and laboratory data were collected. A kidney biopsy could provide deeper insight into the nature of kidney disease, improving our diagnostic, therapeutic and prognostic capabilities.
- 3) Follow up data could not be captured in its entirety, as some patients were lost to follow up.

Conclusion

A significant number of malaria patients present with urinary abnormalities and develop complications needing specialized care in a hospital. Renal involvement poses a substantial disease burden in severe malaria, and most patients respond well to conservative therapy and supportive measures. Renal replacement therapy may be required in half to two thirds of the patients with severe kidney disease, and treatment outcomes are good with a reasonable likelihood of regaining complete renal function.

Recommendations

- 1) Primary care physicians most commonly diagnose malaria and its complications. They must maintain a high index of suspicion to detect signs and symptoms suggestive of severe disease, and refer to a well-equipped hospital to manage complications.
- 2) Baseline hematological and biochemical parameters like complete blood count, serum creatinine, electrolytes, should be monitored at presentation and followed through to recovery, as a diagnostic and prognostic tool for complications of malaria.

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