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Study of early detection of renal impairment in patients with malaria

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Abstract
Background: Establishment of prevalence of malaria-associated renal impairment in Nigeria is important for proper prognosis and management of malaria and its associated complications. Using biuret method for protein estimation, alkaline picrate-slot method for creatinine and urea estimation, and flame photometry and titrimetric method for electrolytes estimation, selected kidney function parameters.
Objective:
1. To identify cases of severe malaria by performing urine dipstick test.
2. To suggest early intervention in patients with renal dysfunction because of complicated malaria.
3. To correlate findings of urine dipstick with serum creatinine level.
4. To follow up cases if serum creatinine level is more than 1.3 mg/dl or in the presence of positive hematuria and proteinuria in urine dipstick.

Methods: A duration based cross sectional study which enrolled 100 cases of smear positive malaria attending Shadan Institute of Medical Sciences, Hyderabad, Telangana, India for 18 months duration. Urine dipstick was performed in all cases to detect hematuria and proteinuria and findings were correlated with serum creatinine level. Acute kidney injury was graded on the basis of serum creatinine level. Hematuria, proteinuria, and creatinine level was reassessed after starting antimalarial treatment and fluid therapy. Early intervention was suggested in patients with renal dysfunction.
Results: In the present study, 46 patients were female and 154 were male suggesting male predominance which can also be explained by other studies done in past out of 200 patients, 42 were found to have hematuria (24 patients with AKI and 18 patients with normal renal function) and 62 had proteinuria (24 patients with AKI and 38 with normal renal function). Though significantly higher values of hematuria and proteinuria were observed in patients with renal impairment than those without renal impairment.
Conclusion: *P. falciparum* and *P. Vivax* malaria associated with acute kidney injury is therefore a life threatening condition, so early diagnosis and intervention with appropriate anti- malarial drugs, fluid therapy and hemodialysis is required to revert AKI, reduce mortality and morbidity. Presence of microscopic haematuria and proteinuria in urine dipstick can be a good parameter for the early detection of renal impairment in patients with malaria even when serum creatinine is normal, which also has a statistical significance ($p < 0.01$).

Keywords: Renal impairment, *P. falciparum* and *P. Vivax*, malaria-associated renal, Nigeria

Introduction
Malaria is a life threatening disease with nearly half of the world population being vulnerable to infection. Malaria accounts for an estimated 2-3 million deaths annually and it is also responsible for untold morbidity in approximately 300-500 million people annually. Malaria is caused by *plasmodium*, which is transmitted by mosquitoes. Four species of *plasmodium* cause malaria in humans. These are *Plasmodium falciparume*, *P. Vivax*, *P malaria*e and *P. ovale. P. falciparum* is responsible for most deaths and most of the severe complications, including cerebral malaria, anemia and renal failure [1-4].
Individuals with mild or uncomplicated malaria typically present clinically with fever and perhaps one or more of the following symptoms: chills and sweats, headache, vomiting, watery diarrhea, anemia, jaundice, and splenomegaly, but do not generally have any of the features identified in severe or complicated malaria. If properly diagnosed and treated, recovery success is high for patients with uncomplicated malaria.

Patients with *P. falciparum* infection are prone to develop severe malaria in 30% of cases, which resulted in case fatality rate of 20% [5]. In Southeast Asia, acute renal failure (ARF) is one of the most common complications in adults with falciparum malaria. The incidence of ARF in patients with severe malaria varies widely ranging from 15% to 48% [8-14] which resulted in a high fatality rate of over 70% in untreated patients [15]. The availability of renal replacement therapy (RRT) and appropriate antimalarial chemotherapy has been shown to reduce case fatality rate as well as enhance the recovery of renal function. Serum creatinine is the mainstay of the diagnosis of AKI. However, altered serum creatinine concentration is only observed when the glomerular filtration rate falls below 50%. The detection of haematuria using a dipstick seems to be a highly specific and sensitive method of observing renal impairment in malaria [5].

Therefore this study is aimed at detecting early renal dysfunction in malaria patients using urine dipstick method, in the form of hematuria and proteinuria.

Aim

To study early detection of renal impairment in patients with malaria

Objective

1. To identify cases of severe malaria by performing urine dipstick test.
2. To suggest early intervention in patients with renal dysfunction because of complicated malaria.
3. To correlate findings of urine dipstick with serum creatinine level.
4. To follow up cases if serum creatinine level is more than 1.2 mg/dl or in the presence of positive hematuria and proteinuria in urine dipstick.

Material and methods

Present study primarily aims to study early detection of renal impairment in patients with malaria. This study was approved by the institutional ethics committee prior to the commencement of data collection.

Study design

Cross sectional study

Source of data

All the patients with smear positive malaria presenting to Medicine Department at Shadan Institute of Medical Sciences, who satisfy the inclusion criteria were studied from January 2014 to June 2015.

Duration of the study

This study was conducted over a period of 18 months, from JANUARY 2014 to JULY 2015.

Sample size

100 cases of smear positive malaria satisfying the inclusion criteria

Inclusion criteria

1) Patients with smear positive *P. falciparum* or *P. Vivax* malaria visiting the hospital for treatment.
2) Patients aged >15 yrs (both genders are included).

Exclusion criteria

1) Pregnant women
2) Patients with known renal dysfunction
3) Other identifiable causes of hematuria and proteinuria

Methodology

200 smear positive malaria patients who fulfilled the inclusion criteria were enrolled in the study.

An informed written consent was taken from all the subjects. A prestructured proforma is used to collect the baseline data.

Detailed clinical history was taken and though examination was done on participating individuals.

On admission, urine was collected and analyzed within 30 minutes to detect microscopic hematuria or proteinuria by dipstick test.

Patient was asked to submit random midstream urine sample prior to admission in a 50 mL urine container for laboratory analysis for random urine dipstick test (for hematuria and proteinuria). The dipstick analysis was done using the uriplus 900 urine analysis strip. The following are the grades of proteinuria as provided by the manufacturers:

Negative- absent Trace- 15 to 30 mg/dl
1+: 30 to 100 mg/dl
2+: 100 to 300 mg/dl
3+: 300 to 1000 mg/dl
4+: greater than 1000 mg/dl

The following are the grades of hematuria Negative- absent
Trace- 10 cells/microlitres
1+: 25 cells/microlitres (small)
2+: 80 cells/microlitres (moderate)
3+: 200 cells/microlitres (large)

Hematuria, proteinuria, and renal function status was reassessed after starting antimalarial treatment and fluid therapy.

Peripheral smear examination

Preparation of Thick smear: Wipe away first drop of blood at the finger prick site. Then touch a clean microscope slide near one end to the next drop that forms.

Spread drop of blood with corner of another slide to make an area about 1 cm in diameter. Correct thickness is attained when newsprint is barely legible through the smear. Air dry, allowing 30 minutes for the thick smear. The thick film is first deheamoglobinised in water and then stained with Giemsa. Prepare a 10% Giemsa in buffered water at pH 7.1. Immerse the slide in the stain for 5 minutes. Rinse gently for 1 or 2 seconds in a jar of tap water. Drain, dry and examine.

The thick smear of correct thickness is the one through which newsprint is barely visible. It is dried for 30 minutes and not fixed with methanol. This allows the red blood cells to be hemolysed and leukocytes and any malaria parasites present will be the only detectable elements. However, due to the hemolysis and slow drying, the plasmodia morphology can get distorted, making differentiation of species difficult. Thick smears are therefore used to detect infection, and to estimate parasite concentrations.

HRP-2 test

HRP-2 test was done by immunochromatography method using Paracheck-Pf test kit, manufactured by Orchid Biomedical Systems, India. Since only

P.falciparum releases HRP-2, this test will give negative results with patients infected with *P.vivax*, *P.ovale*, or *P.malariae*. Non-falciparum malaria may therefore be misdiagnosed as malaria negative.

Sensitivity

Different studies showed a global sensitivity of over 90% in the detection of P.falciparum compared with microscopy. False negative results were associated with low parasitaemia under 100 parasites/µl: often these patients are asymptomatic. False negative results have reported in patients with severe condition and very high parasitaemia (> 20% of red cells parasitized) [4]. This phenomenon (prozone event) is rare but severe malaria should not be excluded on the sole basis of a negative test.

Specificity

The specificity of Paracheck – Pf is high (>90%)[4]. False positive results are partly explained by the fact that the body slowly eliminated HRP-2 after parasite clearance: HRP-2 tests can remain positive for up to one month (mean time being about 2 weeks) after parasite clearance. HRP-2 clearance time is function of many factors and not well-understood yet[4]. False positive occurs also because microscope cannot detect less that 10^8 parasites in the body; however rapid antigen tests can if HRP-2 (or pLDH) is still hanging in the circulation. False positive HRP-2 results are also reported in patient with autoimmune diseases like rheumatoid factor.

Blood urea estimation

The sample of blood is collected in the chemistry bulb (containing potassium oxalate as anticoagulant). Urea of oxalate is allowed to react with the enzyme urease; urea is split up into ammonia. By adding Nessler's reagent (An alkaline solution of a double iodide of mercury and potassium iodide) to ammonia a colored compound is produced. The color is compared in photoelectric colorimeter, with that of a standard urea solution treated in the same manner as the blood sample.

Serum Creatinine estimation

The method used for the estimation of creatinine is Jaffe's reaction, the production of a red color with the alkaline picrate solution. The color is compared in photo electric colorimeter, with that of a standard solution treated in the same manner as the blood sample.

Statistical analysis

Individual case data from study subjects of malaria was transferred on MS Excel sheet and analyzed further using standard statistical techniques.

The collected data was analysed with SPSS 16.0 version. To describe about the data descriptive statistics frequency analysis, percentage analysis, cross tabulation were used for categorical variables and the mean & S.D were used for continuous variables. To find the significance in categorical data Chi-Square test was used. In the above statistical tool the probability value .05 is considered as significant level.

Results

The present study "early detection of renal impairment in malaria patients" was carried out in Vydehi institute of medical sciences and research centre.

It included a total of 200 patients. The observations noted in the present study are as follows.

Table 1: Gender distribution in study subjects

Sex		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Female	46	23.0	23.0	23.0
	Male	154	77.0	77.0	100.0
	Total	200	100.0	100.0	

Out of 200 cases, 46 were females and 154 males.

Table 2: Malaria patients with splenomegaly (clinically)

Splenomegaly (clinically)		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Absent	138	69.0	69.0	69.0
	Present	62	31.0	31.0	100.0
	Total	200	100.0	100.0	

Out of 200 smear positive patients, 62 patients had splenomegaly (clinically).

Table 3: Malaria patients with hepatomegaly

Hepatomegaly		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	A	146	73.0	73.0	73.0
	P	54	27.0	27.0	100.0
	Total	100	100.0	100.0	

Out of 200 smear positive patients, 54 patients had hepatomegaly

Table 4: Prevalence of malarial parasite species

Malarial parasite	Study population (100 patients)
P. Vivax	72
P. falciparum	124
Mixed	4

Out of 200 patients of established malaria, 124 had *P. falciparum*, 72 had *P. Vivax* and 4 had mixed infection

Table 5: Hematuria and Proteinuria in malaria smear positive patients at the time of admission (before treatment).

	Patients with AKI	Patients without AKI
Hematuria	**24**	**18**
Proteinuria	**24**	**38**

In our study 42 patients were found to have hematuria and 62 had proteinuria.

Total 24 patients had ARF (out of 200 study subjects). Hematuria was also seen in 18 patients and proteinuria in 38 patients with normal renal function

Table 6: Hematuria and its grades in the study group (total 100 patients)

Hematuria		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1+	16	8.0	8.0	8.0
	2+	4	2.0	2.0	10.0
	3+	8	4.0	4.0	14.0
	Neg	158	79.0	79.0	93.0
	trace	14	7.0	7.0	100.0
	Total	200	100.0	100.0	

In our study, out of 200 malaria smear positive patients, 42 patients were found to have hematuria.

Table 7: Proteinuria and its grades in the study group (total 200 patients)

Proteinuria		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1+	18	9.0	9.0	9.0
	2+	12	6.0	6.0	15.0
	3+	4	2.0	2.0	17.0
	4+	8	4.0	4.0	21.0
	Neg	138	69.0	69.0	90.0
	trace	20	10.0	10.0	100.0
	Total	200	100.0	100.0	

In our study, out of 200 malaria smear positive patients, 62 patients were found to have proteinuria.

Table 8: Proteinuria and its grades in malarial AKI patients (24 patients) & the involvement of malarial parasite (at the time of admission) (Proteinuria 2)

Malaria parasite	Trace	1+	2+	3+	4+
Vivax	-	2	6	2	2
Falciparum	-	-	2	2	6
Mixed	-	-	2	-	-

In our study, out of 24 malarial AKI patients, 4+ proteinuria was observed in 8 patients (2 vivax, 6 falciparum), 3+ proteinuria in 4 patients (I2vivax, 2 falciparum), 2+ proteinuria in 10 patients (6vivax, 2 falciparum, 2 mixed), 1+ proteinuria in 2 patient (vivax)

Discussion

In the present study, 46 patients were female and 154 were male suggesting male predominance which can also be explained by other studies done in past.

Venugopalan P et al in a study noted that out of the total population of 2196 studied (including children) in Mangalore, where 1631 (74.27%) were males and 565 (25.72%) females [5].

Luo EP et al studied 5,069 malaria cases where 3,809 (75.14%) were males cases and 1,260 (24.85%) were females, with a sex ratio of 3.02:1 [7].

Parajuli K et al studied 32 malaria positive cases where 75% were males and 25% were females [8].

Muddaiah M et al found that males (81%) outnumbered females (19%) out of total 314 malaria cases [9].

In the current study of 200 patients of established malaria, 124 had *P. falciparum*, 72 had *P. Vivax* and 4 had mixed infection.

Aishwarya et al studied a total of 31 patients, out of them 19 (61.29%) patients were smear positive for *P .falciparum* malaria, 11 had *P.vivax* (35.48%) malaria and one had mixed infection [10].

In present study out of 200 patients, 42 were found to have hematuria (24 patients with AKI and 18 patients with normal renal function) and 62 had proteinuria (24 patients with AKI and 38 with normal renal function). Though significantly higher values of hematuria and proteinuria were observed in patients with renal impairment than those without renal impairment.

Pati ss et al studied 77 malaria patients and noted twenty-three (29.8%) had haematuria and 52 (67.5%) had urinary protein > or = 300 mg/L. Renal impairment (plasma creatinine > or = 1.2 mg/dL) was observed in 17 (22.07%) patients [11]. Aishwarya S et al in their study noted prevelance of microscopic hematuria which was 13% out of total 31 patients, and only 3 patients had AKI.

In current study 24 patients (12%) had ARF out of which 12 had P vivax, 10 with *P. falciparum* and 2 with mixed infection).

In a study from Karachi, Naqvi et al diagnosed ARF (due to malaria) on the basis of serum creatinine > 2mg/dl. They noted 124 (5.97%) patients of malarial ARF over a 10 year period out of 2098 patients.

In the above mentioned study by Naqvi et al, renal impairment was considered when serum creatinine was greater than 2 whereas in present study its equal to or more than

1.3 mg/dl and was also for a short duration comparatively, which explains the difference in the prevalence of AKI.

Prakash et al (2002) from North India, included patients having serum creatinine > 3 mg/dl in a study on malarial ARF. They found 94 patients of malarial ARF over a 5 year period [12].

In the current study 24 patients had ARF (12%) (12 with P vivax, 10 with falciparum and 2 with mixed infection). Out of 24 patients there were 6 cases of severe AKI with creatinine >4mg/dl (2 vivax and 4 falciparum), 6 cases of moderate AKI with creatinine 3-4mg/dl (2 vivax and 4 falciparum) and 12 cases of mild AKI with creatinine 1.3-2.9 (8vivax, 2falciparum and 2 mixed infection).

It very well suggests that Plasmodium falciparum is mainly associated with moderate to severe renal impairment whereas mild malarial AKI patients were found to be infected with Plasmodium vivax and is also strongly supported by other studies.

Naqvi et al in their study observed that that out of 124 patients of malarial ARF, 121 were found to have *P. falciparum* and 3 *P. Vivax*.

Mehta et al in their study noted that out of 24 patients of malarial ARF, Six patients (25%) had moderate renal failure. *P. falciparum* was detected in four while *P. Vivax* and mixed infection were noted in one each. Eighteen patients (75%) had severe renal failure. Twelve (67%) of these were PF positive, two (11%) were PV positive while four (22%) showed mixed infection.

Dialysis has improved the survival of the cases when instituted early in the course. Adequacy of dialysis is considered when the post dialysis creatinine and urea decrease to 50% or less of the pre-dialysis values.

In the present study, 8 patients (33% of malarial AKI) were subjected to HD.

The reason for having less number of malarial AKI who required hemodialysis could be due to exclusion criteria in the current study where cases with known renal dysfunction were excluded. It can be explained that malarial AKI can worsen renal function in a patient if there are other comorbidities associated with renal dysfunction are present.

In another study by Prakash et al dialysis therapy was required in 57.7% as they had severe renal failure.

Manan et al (2006) noted 78.26% required dialysis.

Prakash et al (2002) in their study found that 76.6% cases required dialysis support [95].

In this study, 4patients (16.66%) with severe AKI (both with *P. falciparum* infection) succumbed to illness.

The various other studies have reported mortality between 14 – 33% from different countries

Prakash et al (2002) in their study on malarial ARF included patients having serum creatinine more than 3 mg/dl. They observed a mortality of 20.2% in malarial ARF [86].

Conclusion

Incidence of acute renal failure in malaria in India has led to increase in morbidity and mortality, particularly if its associated with *P. falciparum*.

Acute renal failure is an important and life threatening complication of falciparum malaria having a male preponderance.

Early detection and prompt treatment are the keys to proper management of malaria patients.

So this study was carried out for early diagnosis of renal dysfunction using urine dipstick method to detect hematuria and proteinuria even if serum creatinine level is normal.

Current study is also statistically significant ($p < 0.01$).

The urine dipstick method is a simple, rapid and cost-effective method convenient for use in rural and remote areas, and patients with positive result can be referred to higher centre for further evaluation and management.

Conclusion

Out of these 8 patients, 6 were infected with falciparum and 2 had vivax infection. 4 patients with severe AKI (both with *P. falciparum* infection) succumbed to illness. major public health problem in tropical developing countries like India.

P. falciparum and *P. Vivax* malaria associated with acute kidney injury is therefore a life threatening condition, so early diagnosis and intervention with appropriate anti-malarial drugs, fluid therapy and hemodialysis is required to revert AKI, reduce mortality and morbidity.

Presence of microscopic haematuria and proteinuria in urine dipstick can be a good parameter for the early detection of renal impairment in patients with malaria even when serum creatinine is normal, which also has a statistical significance ($p < 0.01$).

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Conflict of Interest: None

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