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A study of renal manifestations in children with malaria

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Abstract
Aim: Our study was to evaluate the renal manifestations and relationship between various renal manifestations with severity of disease of malaria in children patient.
Methodology: Renal function was assessed by urine examination, urine sodium, FeNa, blood urea, serum creatinine and GFR and severity of malaria was assessed by parasite count. Results: Frequencies, percentages, Mean, standard deviation, Chi-square test and Anova test were used and P value was taken less than 0.05 for significant differences.
Conclusions: Renal dysfunction and electrolyte imbalance were not uncommon with Plasmodium vivax infection. And it was common with Plasmodium falciparum infection.

Keywords: malaria, children patient, renal dysfunction

1. Introduction

Malaria is caused by four species of the genus Plasmodium namely, Plasmodium vivax, P. falciparum, P. malariae and P. ovale. Common clinical presentations of infection with all four Plasmodia species are periodic paroxysm, chills, rigors, sweating, body aches, headache, nausea, general weakness and prostration. Severe life-threatening complications such as cerebral malaria, severe anemia, acidosis, respiratory distress, jaundice, acute renal failure (ARF), acute respiratory distress syndrome (ARDS), etc occur mostly with P. falciparum infection. A few reports have appeared indicating association of severe complications of malaria with P. vivax infection. Malaria is a potentially life threatening disease in tropics, as it affects over 400 million people per year, most of whom live in Africa, South east Asia, and Latin America. India is one of the major contributors to malaria mortality and morbidity in South and Southeast Asia region. Malaria accounts for more than one million child deaths globally every year. Renal involvement in malaria varies from mild protein urea to severe renal failure. Clinically significant renal and renal related disorders are commonly seen in infection with plasmodium falciparum and recently in P. vivax infections. The knowledge of renal function is important for clinical management of patients with malaria, including monitoring of drug dosage and fluid balance. Renal involvement has been reported in P. falciparum, P. malariae, and recently in P. vivax infections. Publications on P. vivax renal failure are too few and inconclusive to merit a detailed review. Therefore, renal failure related to P. falciparum malaria will be reviewed in detail while renal involvement in P. malariae and P. vivax will be mentioned briefly. Renal involvement in P. malariae infection: Incidence of progressive glomerulonephritis was significantly higher in malaria-endemic areas of Africa. P. malariae was considered an important cause of chronic malarial nephropathy (quartan malarial nephropathy) The incidence of glomerulonephritis gradually declined along with eradication of malaria in many parts of Africa. The disease affected mostly children and presented as steroid-resistant nephrotic syndrome. The pathogenesis of renal involvement is possibly mediated through immune complex deposition. Histopathologic observations include features of mesangiocapillary glomerular, and subendothelial immune complex deposits containing IgG, C3, and malarial antigens. The disease progresses to renal failure even after successful eradication of the infection. Quartan malarial nephropathy was reported mainly from Africa 6–12. However, most evidences in favour of quartan malaria nephropathy have been circumstantially linked with P. malariae infection. Another recent review on nephrotic syndrome in quartan malaria inferred that the association between renal involvement and P. malariae infection was only coincidental and reported mostly before 1975. Currently, there is no evidence of chronic malarial glomerulopathy in African children with nephritic syndrome, Renal involvement in P. vivax malaria has been reported mostly from Indian subcontinent. Our study was to evaluated the renal manifestations and relationship between various renal manifestation with severity of disease of malaria in children patient.

2. Materials & Method

The patients were diagnosed to have malaria on the basis of peripheral blood smear examination and data collected by using purposive sampling technique. Renal manifestations in children with malaria were carried out in the upgraded department of Pediatrics, Katihar medical college, Katihar, Bihar “between” October 2013 to September 2015. The attendant of entire subjects signed an informed consent approved by institutional ethical committee of Katihar Medical College, Katihar, Bihar, India was sought.

Method

A total of 60 patients with ages 0 to 15 years were taken for the study. A full assessment of patient was taken and detailed history regarding various clinical manifestations were elicited. Detailed clinical examination and investigations were done. Renal function was assessed by urine examination, urine sodium, Fe Na, blood urea, serum creatinine and GFR. GFR was calculated by using Schwartz formula. This method avoids need for a collection of urine and is more accurate than creatinine clearance. Severity of malaria was assessed by parasite count. Various renal manifestations were compared with severity of infection.

Statistical Analysis: The data was analyzed by statistical methods, by using frequencies, percentages, Mean, standard deviation, Chi-square test and Anova test. P value was taken less than 0.05 for significant differences.

Observations

A detailed history was taken followed by a detailed clinical examination to assess clinical severity and complications. Total 60 children ages 0-15 years with malaria were included in our study. All the patients in this study were proved to be cases of malaria by Peripheral smear examination. These investigations were done before the antimalarial treatment was started. There were 25 healthy children age 25 years sex matched, taken as controls. The presenting symptoms in 60 children were febrile at the time of presentation. Vomiting was one of the frequent symptoms after fever. It was seen in 28% of the total cases. Headache was the third common presenting symptom along with fever. It was noted in 22% of Patients. Abdomen pain, dysuria and reduced urine output were present in 10% cases less than 5 years age group, 10% noted in 5-9 years and 7% of cases were 10 to 14 years age of children. Two cases were convulsion at the time of presentation and both of them were diagnosed as febrile seizure. Pallor was noted in 53% of the total cases. It was documented in 53% of vivax cases, 36% of falciparum cases and 43% of mixed infection Icterus was noted in 4 (7%) patients. Three cases were falciparum infection and one case was mixed infection.

Twenty cases were only splenomegaly, four cases were only hepatomegaly and thirteen cases were both hepatomegaly and splenomegaly. Weights of the patients were assessed according to percentage of expected weight for present age of the child. 48% of patients were weight more than 80% of expected weight for their age, 28% were weight between 71 to 80% of expected weight for their age, 17% were weight between 61 to 70% and 5% cases were weight between 51 to 60% of expected weight for their age. Only one child was weight less than 50% for its age.

Plasmodium vivax was the most frequently observed species. It was seen in more than half the cases i.e. 53.3%. Both Plasmodium falciparum and mixed infection consisting of Plasmodium vivax and falciparum infection were observed in 23.3% cases.

29 patients were hemoglobin less than 10gm/dl. Out of which 26 cases were hemoglobin between 7- 10 gm/dl and only three patients were hemoglobin (Hb) < 7 gm/dl. Mean Hb in our study was 10.5±1.86 g/dl. 53% Plasmodium vivax, 42% Plasmodium falciparum and 42% percent of mixed infected children were hemoglobin less than 10 g/dl , but severe anemia i.e. Hb <7 gm% was seen only with falciparum and mixed infection.

In our study thrombocytopenia was observed in 72% (43 out of 60) of the patients. Out of these 43 patients, 10 patients had severe thrombocytopenia (<50,000/comm.), 13 patients were moderate thrombocytopenia (platelet count between 50000 and 100000) and 20 patients were mild thrombocytopenia (platelet count between 100000 and 150000).

93% of the patients with falciparum malaria were associated with thrombocytopenia, in that 43% of the patients were platelet count <50,000/mm^3. Incidence of severe thrombocytopenia documented in vivax and mixed infection were 6% and 14% respectively. Proteinuria was documented in 42% of malaria cases, proteinuria was common in malaria cases compare to control (P<0.05), Proteinuria was common with falciparum and mixed malaria infection than vivax infection (p<0.05), hematuria was noticed in 13% of cases, pyuria was observed in 12% of cases, Both hematuria and pyuria were no clinical significant association with malaria compare to control.

77% of the cases were FeNa less than one. 13% cases were FeNa between 1 to 2 and 10% case were FeNa more than two. There was no statistical difference in values of FeNa between various species or with severity of infection.

21 out of 60 patients were serum sodium level between 135-140 meq/dl, 18 patients were sodium level between 130 to 135 meq/l, 19 patients were serum sodium level between 125-130 meq/l and only two patients were serum sodium below 125 meq/l.

Sodium level below 130 meq/1 were more common with falciparum and mixed infection than vivax infection (p<0.05)

Majority of the patients (81.7%) were potassium level between 3-5 meq/I, 42.9% of falciparum cases were hyperkalemia (> 5 meq/I) but it was documented only in 12.5% of vivax malaria. Hyperkalemia was not seen in mixed malaria cases in present study.

More than half of the patient were serum bicarbonate level more than 20 meq/l. Almost one third of patient were bicarbonate level between 15-20 meq/l. Only small percentage of cases (10%) were bicarbonate level below 15 meq/l.

Mean sodium and mean bicarbonate level was significantly low in patients with malaria compare to controls. Mean potassium level was high in malaria cases compare to controls.

Mean sodium and mean bicarbonate decrease as the severity increases. Mean potassium increases as severity of infection increases.

Mean sodium was low in falciparum malaria then vivax and mixed infection. High mean potassium and low mean bicarbonate level was documented with falciparum infections. However it was not statistically significant, More than half of the cases had blood urea level between 20-40 mg/dl. 16 out of 60 patients had blood urea level below 20 mg / dl and 11 out of 60 patients had blood urea m level above 40 mg/dl.

Falciparum malaria was significantly increased level of creatinine compare to vivax and mixed infection.

Low GFR (<90 ml/Kg/1.73 M^2) was more common with falciparum malaria. However it was not statistically significant.

Blood urea, serum creatinine was significantly high in malaria cases compared to control. Mean glomerular filtration rate was significantly low in malaria cases compare to control. Mean blood urea and mean serum creatinine level was significantly high in falciparum species compare to vivax and mixed infection. Though Mean GFR was low with falciparum and mixed infection, it was not statistically significant.

Table 1: Comparison of mean levels of blood urea, serum creatinine and GFR levels with severity of malaria

Severity	<100/mm³ N=1	100- 1000/mm³ N=21	10001-10000/mm³ N=29	>10000 / mm³ N=10	p value
Mean blood urea	28±0	21.80±9.2	28.76±9.22	57.10±29.286	<0.001 Vhs
Mean Serum creatinine	0.6±0	0.665±0.013	0.74±0.21	1.07±0.28	<0.001 Vhs
Mean GFR	112±0	96.5±22.2	96.88±29.1	64.79±12.224	=0.006 Hs

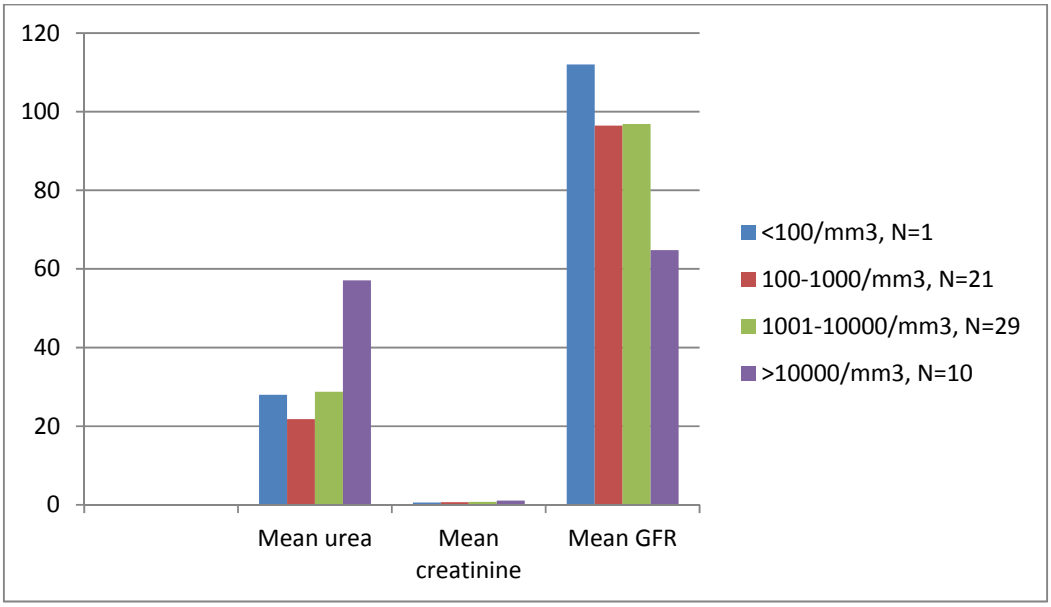

Fig 1: Comparison of mean levels of blood urea, serum creatinine and GFR levels with severity of malaria.

As severity of malaria increases, mean blood urea and mean serum creatinine was spontaneously increased and mean GFR decreased

Table 2: Comparison of serum electrolytes and renal function in with age.

GROUP		N	Mean	Std Deviation	P
Case Na	<5	18	133.056	3.686	
	5-9	22	133.909	3.753	
	10-14	20	131.100	4.400	0.07
K	<5	18	4.350	.584	
	5-9	22	4.373	.542	
	10-14	20	4.570	.677	0.45
HCO3	<5	18	19.833	3.276	
	5-9	22	21.077	2.694	
	10-14	20	20.285	3.581	0.46
GFR	<5	18	78.983	26.561	
	5-9	22	97.782	19.251	
	10-14	20	95.650	31.756	0.06
B. Urea	<5	18	33.000	22.904	
	5-9	22	26.000	10.323	
	10-14	20	35.150	21.627	0.26
B. Creatinine	<5	18	0.700	.214	
	5-9	22	0.714	.196	
	10-14	20	0.895	.278	0.06

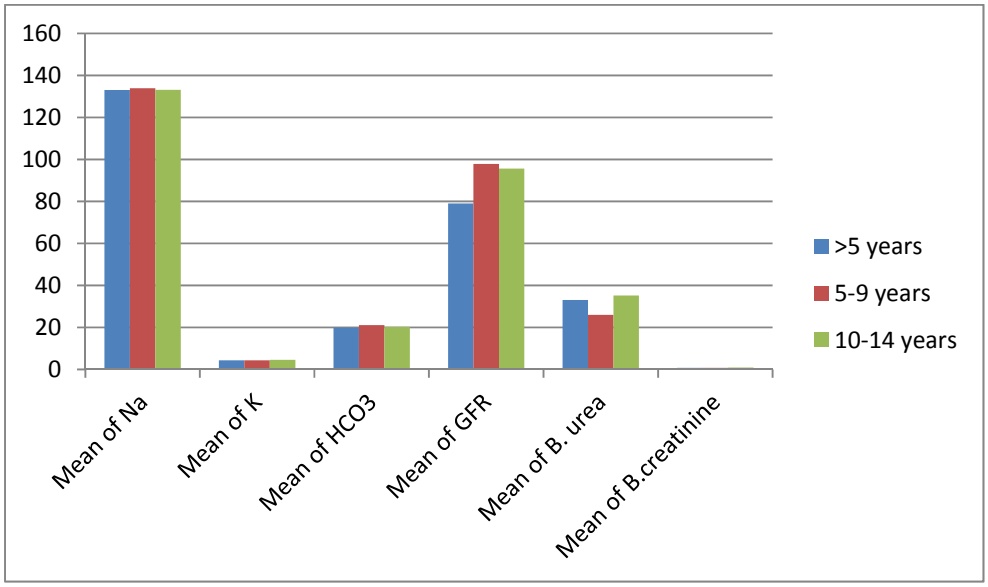

Fig 2: Comparison of serum electrolytes and renal function in with age.

There was no statistical significant difference in mean levels of sodium, potassium, bicarbonate, GFR, blood urea and serum creatinine in malaria cases of different age groups.

3. Discussion

Malaria is endemic in the tropics and subtropics causing 247 million infections worldwide and 3.3 billion world's population were at risk in 2006. The burden of malaria in Southeast Asia has been underappreciated, despite recent evidence suggesting that the continent contributes almost 40% of the world's malaria. India contributes 77% of the total malaria in Southeast Asia and about 95% of the population of moderate to high risk of malaria in SEA Region is living in India.

Though we are familiar with various presentations and complications of malaria, renal complications are not frequently encountered. There are only few studies on renal manifestations in children with malaria. Our study was a hospital based comparative study of renal functions in sixty children with malaria.

In our study the male to female children patient ratio was 1.14:1. In other study high male predominance was attributed to higher health seeking behavior for male children, but in our study both male and female children were almost equally affected.

Children between 5-9 years of age were commonly affected by malaria. This may be due to increased exposure to mosquito bites outdoors compared to children less than 5 yrs. Jasani JH *et al.* [9] observed similar results in their study. Studies by Okwara FN *et al.* [6] and Marsh K *et al.* [10] reported that preschool children were more commonly affected by malaria.

Presenting Symptoms of malaria children patient of our study were similar with the finding of Muddaiah M *et al.* [1] 10% of patients of our study were dysuria, 10% was reduced urine output and 2% of cases were hematuria.

In our finding Incidence of pallor was 53%, while study conducted by Malhotra OP *et al*, [12] pallor was found 73%.

Splenomegaly was seen in 55% of the patients in our study Similarly Taha K *et al.* [13] concluded that 60% children patient were splenomegaly. Hepatomegaly was noted in 28% of the patients in the present study. Study by Taha K *et al* was shown a similar incidence of hepatomegaly (30%) in their work. Sowunmi A14 has reported that hepatomegaly was more common than splenomegaly in acute falciparum infection in children. This observation was contrary to my findings wherein splenomegaly was more common.

The clinical findings in vivax, falciparum and mixed infections were more or less similar. There was no statistically significant difference in clinical presentation of various types of malaria.

In the our study the incidence of vivax malaria was 54% and both falciparum and mixed infection were incidence of 23%. Finding of Shetty G *et al.* [15] was similar to our study. Jadav UM *et al*, [8] Lathia TB *et al.* [7] and Goyal S *et al.* [17] was similar incidence of vivax malaria in their studies. Rasheed A *et al.* [11] had higher incidence of falciparum infection, which was attributed to higher incidence of falciparum infection in the area in which study was conducted. Study by Faseela TS *et al.* [16] observed higher incidence of mixed infection simillar to our study, which was attributed to endemicity for malaria in that area.

48% of the study population was Hb less than 10gm%, only 5% was severe anemia i.e. Hb less than 7gm%. Mean hemoglobin in my study was 10.5±1.86gm%, which was less compare to Rasheed A *et al.* [11] study, where mean Hb was 12.87±1.88gm%. Marsh K [10] was reported an incidence of 17% of severe anemia in his study group, which is higher than what we observed (6%).

In our study thrombocytopenia was observed in 72% of the patients. 33% was mild thrombocytopenia, 22% was moderate and 17% was severe degree thrombocytopenia. Shetty G *et al.* [15] and Jamal *et al.* were reported similar results, but few studies were reported slightly lower incidence of thrombocytopenia like 40% and 58.97%.

Proteinuria was documented in 42% of malaria children patient of our study, which was similar to study done by Sowunmi A[3] in which proteinuria was reported in 40% acute falciparum malaria cases. Ahmad SH *et al.* 18 was documented 4 out of 23 patients having proteinuria in his study. In contrary Buchard GD *et al.* [24] was concluded 85% protein urea and Nityananda *et al.* [25] reported 78% higher incidence proteinuria in their studies. Incidences of proteinuria in these studies were 85%

and 78% respectively. In these studies proteinuria was estimated quantitatively, but in the present study only qualitative testing of urine protein was done.

In our study proteinuria was significantly more common with falciparum and mixed infection. Ugwuja EI. [19] Was supported the finding of our study.

Ekeanyanwu RC *et al.* reported significant higher incidence of proteinuria in age group between 1 to 5 years in children affected with malaria, but in present study such difference was not found.

Ogbadoyi EO *et al.* [2] and Ekeanyanwu RC *et al.* in their studies reported that presence of proteinuria in malaria depends on severity of infection. But in our study such difference was not found.

Fever may have contributed to the proteinuria in our study, but study done by Sowunmi A [3] and Ehrich JH *et al.* [20] showed that proteinuria was not related to body temperature at presentation and there was no correlation between the level of fever and proteinuria.

Studies have shown that proteinuria in malaria is both tubular and glomerular types due to aggressive immune mediated glomerular and tubulointerstitial dysfunction. This immuno pathogenetic hypothesis is supported by microscopic examination of renal biopsy tissue in adult patient with malaria showing mesangial proliferation and mesangial deposition of immunoproteins.

In our study mean urine sodium level was significantly higher in malaria cases compared to control. Mean urine sodium was significantly high in falciparum malaria cases. Sowunmi A. [3] was reported similar results in his study. In that same study there was a positive correlation between urine sodium excretion and degree of parasitemia, both during and after recovery from the illness, but such relation was not found in our study.

In our study 77% of the cases were FeNa less than one. 13% cases were FeNa between 1 to 2 and 10% case were FeNa more than 2. There was no statistical difference in FeNa between different species or severity of malaria infection. Sowunmi A was reported FeNa value greater than 2 in 25% of cases and Ahmad SH was reported in 4% of cases. Both these results were contradicts to our finding related to FeNa. Urine sodium and fractional excretion of sodium are good indicators of renal tubular function. These changes in urine sodium and fractional excretion of sodium in our study suggest that there was a renal tubular dysfunction during acute malarial illness.

In our study 30% cases were mild hyponatremia (Na level between 135-131 meq/l), 32% patients were moderate hyponatremia (Na level between 125-130meq/l) and only 3% patients were severe hyponatremia (Na<125 meq/l). Hyponatremia was more common with falciparum and mixed infection than vivax infection. In our work serum sodium less than 130meq/l was seen in 65% of cases in comparison to studies by English MC *et al.* Wolfswinkel ME *et al.* [21] and Yadav KS *et al.* [22] in which it was seen in 55%, 46% and 34% of malaria cases respectively.

Studies done by Ogbadoyi EO *et al.* [2] and Uzuegbu UE [23] showed that, there was no significant differences between the levels of sodium in male malaria patients and individuals without malaria. However in females, there was significant variation in sodium compare to controls. But our study was failed to show any such relationship with gender of the child.

Ebele JI *et al.* in their study reported that hyponatremia was common with children aged less than 10yrs. But our study was not shown any such relationship.

Recent systematic analysis on Dysnatremia in malaria by the study of Brown S showed that hyponatremia was common in falciparum malaria and less frequently reported in non-falciparum malaria. The extent of hyponatremia was also more extreme in falciparum malaria than it was in non-falciparum malaria. Our study was shown such similar results. Our study also showed that mean sodium decreases as severity of malaria increases.

In our work 42.9% of falciparum patients were hyperkalemia (>5meq/l) while vivax patients were only 12.5% hyperkalemia. Our studies shown that as mean potassium increases as severity of infection increases. Sowunmi A also reported higher serum potassium level during acute falciparum illness.

Jasani JH *et al.* and Ebele JI *et al.* contradicts to the finding of potassium level in malaria cases of our study and concluded that hypokalemia in children with malaria.

Impaired renal function might be the cause for hyperkalemia in our study, but it needs more studies to know the exact pathogenesis.

In our study mean blood urea, mean serum creatinine was significantly higher in malaria cases compared to control. Ekeanyanwu RC *et al.*, but Ogbadoyi EO *et al.*, they failed to show any significant difference between the serum creatinine levels in malaria patients when compare to healthy controls.

Studies by Ogbadoyi EO *et al.* [2] and Idonije BO *et al.* also reported that serum urea changes seen commonly with female patients who was malaria. This observation was not seen in our study. Ekeanyanwu RC *et al.* in their study also observed that Children between 1 - 5 years were higher levels of serum urea and creatinine when compared with children between 6 - 12 years. Such relationship between age group and serum urea or serum creatinine levels were not observed in our study.

Study done by Umboh A *et al*, [4] they reported that blood urea increases with severity of infection, but not creatinine. However our study showed mean Blood urea and mean serum creatinine increases as severity of malaria increases. In contrary, study done by Adenosun OG *et al.* [5] showed that there was no significant correlation between blood urea with severity of infection.

Our study also showed that patients with Falciparum malaria was significantly increased level of serum creatinine compare to vivax and mixed infection. It was said that renal impairment was commonly seen with falciparum cases, but no more studies have been compared renal function between vivax and falciparum malaria.

In our study 53% of cases were renal impairment during acute illness. It was near about contradicts the study done at Aligarh (India) by Ahmad SH, [18] where 83% of cases were impairment of renal function during acute illness. The study conducted by Sowunmi A [3] revealed that impairment of renal function was seen in 45% of cases. My study was not showed any significant relationship between low GFR (<9**0** ml/kg/1.73 m^2) level and malaria species or severity of infection. It was concurrence with findings of Umboh A *et al*.

It was a general consensus that impaired renal function was common in falciparum malaria. Contrary to the popular belief, vivax infection can impair renal function as was seen in our study.

4. Summary

Our study shows that, Plasmodium vivax malaria was the predominant form of malaria. It was seen in 54% of cases. Highest number of cases were seen in school going children. There was a slight male preponderance for malaria with male to female to ratio being 1.14:1. Majority of the cases were from rural areas. All patients were febrile at admission. The other common presenting complaints were vomiting (28%) and headache (22%). Dysuria (10%), reduced urine output (10%) and hematuria (2%) were the common urinary complaints in malaria cases. Commonest clinical finding were splenomegaly (55%), pallor (53%) and hepatomegaly (28%). Icterus was seen in only 6% of case. Anemia was present in 48% of patients, only 5% of cases had severe anemia. Thrombocytopenia was most common (72%) haematological abnormality. Severe thrombocytopenia was seen in 17% of cases. Proteinuria was documented in 42% of cases, and it was common with falciparum and mixed malaria than vivax infection. Elevated urine sodium excretion was seen 50% of cases. Mean urine sodium was high with falciparum infection. Hyponatremia was seen in 65% of cases. It was common with falciparum and mixed infection. Mean sodium decreases as severity of infection increases. Blood urea and serum creatinine were significantly higher in malaria cases compare to controls. Falciparum cases were higher levels of serum creatinine than vivax and mixed malaria infection. Mean serum urea and serum creatinine increases as severity of infection increases. Low glomerular filtration rate was seen 53% of cases.

5. Conclusion

Our study also showed that renal dysfunction and electrolyte imbalance was not uncommon with plasmodium vivax infection, and impaired renal function was common in Plasmodium falciparum infection. And it may facilitate safer use of fluids and drugs. In order to establish true picture of the incidence, prevalence and causes of malaria associated kidney dysfunction and electrolyte imbalance requires further extensive clinical studies and research.

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