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Clinical and histopathological profile of acute renal failure caused by falciparum and vivax monoinfection : An observational study from Bikaner, northwest zone of Rajasthan, India

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ABSTRACT

Background & objectives: Acute renal failure (ARF) is a known manifestation of severe *Plasmodium falciparum* (*Pf)* malaria but recently it has also been observed with *P. vivax* (*Pv)* monoinfection. A clinical observational study has been conducted to evaluate the clinical and histopathological profile of ARF in malaria.

Methods: This study was conducted on 288 consecutive cases of malaria with monoinfection (*Pf* 191 and *Pv* 97) diagnosed by peripheral blood film examination and rapid card test. ARF was diagnosed as per WHO criterion (serum creatinine >3 mg%). The data were analysed by Standard *t*-test using ANOVA software.

Results: ARF was seen in 52 cases of *Pf* and 14 cases of *Pv* malaria. Mean age was 32.58 yr (ranging 15–65; *Pf* 33.37 and *Pv* 29.14) and male to female ratio was 2:1 (*Pf* 3:1 and *Pv* 1:1). Most of the cases developed ARF within 10 days of onset of the disease. Associated severe manifestations were jaundice (53 cases: *Pf* 44 and *Pv* 9), cerebral malaria (28 cases: *Pf* 25 and *Pv* 3), severe anemia (18 cases: *Pf* 17 and *Pv* 1), hypotension (16 cases: *Pf* 11 and *Pv* 5), bleeding manifestations (16 cases: *Pf* 14 and *Pv* 2), multiorgan failure (12 cases: *Pf* 9 and *Pv* 3) and ARDS (6 cases: *Pf* 5 and *Pv* 1). Kidney biopsy (16 *Pf* and 2 *Pv*) showed acute tubular necrosis (5 *Pf* and 1 *Pv*), mesangioproliferative glomerulonephritis (2 *Pf*) or both (9 *Pf* and 1 *Pv*). Haemodialysis was done in 7 (*Pf* 4 and *Pv* 3) cases, out of which four survived. Most of the cases (48.49%) recovered within two weeks (range 3–20 days). Total mortality was 27.27% (*Pf* 28.85% and *Pv* 21.43%).

Interpretation & conclusion: ARF can also be caused by vivax monoinfection with similar clinical and histopathological features although outcome is less severe as compared to falciparum monoinfection.

Key words Acute tubular necrosis; malarial acute renal failure; mesangioproliferative glomerulonephritis; *Plasmodium falciparum; Plasmodium vivax*

INTRODUCTION

Acute renal failure (ARF) is one of the important manifestations of severe falciparum malaria; although it can occur rarely with vivax also[1–4]. Recently, high incidence of ARF caused by monoinfections with *Plasmodium falciparum* and *P. vivax* has been reported from various parts of the world including India[5–11]. It can occur as an isolated complication or as a component of multiorgan involvement[12–16].

The precise mechanism of ARF in malaria is not clearly known. Several hypotheses including mechanical obstruction caused by cytoadherence and sequestration of infected erythrocytes, immune-mediated glomerular pathology, alteration in renal and systemic hemodynamics, release of cytokines, reactive oxygen intermediates and nitric oxide have been proposed. In addition to the above, restricted blood flow to the kidneys due to less intake and increased loss of fluids can cause dehydration and renal ischemia[1, 8, 17].

There are various histopathological alterations reported in renal biopsy from ARF caused by acute malaria including acute tubular necrosis, acute glomerulonephritis, mesangioproliferative glomerulonephritis (MPGN) and membranoproliferative glomerulonephritis (in chronic malaria)[18–22]. Our endeavour was to evaluate the clinical and histopathological profile of ARF in falciparum and vivax malaria monoinfection.

MATERIAL & METHODS

This was a prospective study conducted on malaria patients admitted in a classified malaria ward under the Department of Medicine, S.P. Medical College and P.B.M. Hospital, Bikaner, Rajasthan, India. It included the patients of both sexes belonging to all age groups ex-

cept the pediatric range. The study protocol was approved by the Institutional Ethics Committee. Informed consent was taken from patients or legal guardian for participation in the study and for kidney biopsy separately.

The diagnosis of malaria was done on the basis of conventional thick and thin peripheral blood smear stained with Giemsa stain and examined under oil immersion lens of the microscope along with rapid diagnostic tests (RDTs) based on detection of specific *Plasmodium* species lactate dehydrogenase (OptiMal test; Diamed AG, Cressier sur Morat, Switzerland). Classification of type of malaria was based on the identification of species by peripheral blood smear as well as RDTs.

Patients suffering from either *P. falciparum* or *P. vivax* monoinfection diagnosed by peripheral blood smear as well as RDTs were included in the study, whereas patients suffering from mixed infection (*Pf* + *Pv*), patients already suffering from other pre-existing underlying disease like hypertension, diabetes mellitus, chronic renal failure, tuberculosis, nephrotic syndrome, chronic liver disease, etc. and patients who did not give consent were not included in the study.

ARF in malaria was diagnosed as per WHO criteria, i.e. serum creatinine >3 mg/dl with 24 h urine output <400 ml in spite of adequate rehydration[23]. Acute renal failure in malaria is usually oliguric (<400 ml/day) or anuric (<50 ml/day) but urine output may be normal or increased. Serum creatinine play an important role in determining the ARF in malaria patients.

Thorough clinical and biochemical examination was done for each patient which includes tests like haemoglobin, total and differential leukocyte count, total platelet count, bleeding time, clotting time, prothrombin time, blood sugar, serum bilirubin, SGOT/SGPT, serum alkaline phosphatase, blood urea, serum creatinine, serum electrolytes, urine analysis including microscopy, ECG and X-ray chest. Sonography of abdomen was done for size and echo texture of liver and kidneys and to mark the site and depth for renal percutaneous needle biopsy. Patients of ARF were further divided into two groups, namely oliguric and nonoliguric renal failure based on daily urine output of <400 ml (or <0.5 ml/kg/h over >6 h) or above, respectively.

Glomerular filtration rate (GFR) was measured at the time of admission by Cockcroft and Gault formula[24]:

$$\text{Creatinine clearance} = \frac{140\text{-age} \times \text{Wt}}{\text{Serum creatinine (mg/dl)}} \times 72$$

Where, creatinine clearance is in ml/min; and Wt is lean body weight in kg. This value is multiplied by 0.85 for women since lower fraction of body weight is composed of muscle mass.

Renal biopsy/necropsy was performed in 18 (16 *Pf* and 2 *Pv*) cases. About 9 (8 *Pf* and 1 *Pv*) patients having oliguric renal failure and six patients (all *Pf*) of nonoliguric renal failure who died during the course of treatment were subjected to trucut percutaneous needle necropsy done by surface marking for renal histopathology. Biopsy samples were collected immediately after death of the patients. Besides these, two patients (both *Pf*) of oliguric renal failure and one (*Pv*) patient of nonoliguric renal failure who survived were subjected to percutaneous trucut needle biopsy under ultrasound during treatment. Renal biopsies and necropsies were analyzed and interpreted with the help of a histopathologist and nephrologist.

Daily urine output was measured and daily progress of the patients was monitored during the course of management. All patients were treated according to the WHO guidelines[23]. Fluids were given according to urine output plus one litre (insensible loss, as Bikaner is having hot climate). Blood transfusion or packed cell transfusion were given to patients with Hb <5 g%. Patients were subjected to haemodialysis when oliguria persisted or deteriorated, in the presence of signs of fluid overload or when rapid serial rise in serum creatinine (RIFLE criteria, RIFLE is an acronym for risk, injury, failure, loss and end-stage) was observed[25]. Contraindication to haemodialysis included hypotension and bleeding manifestations. Data were analysed by standard *t*-test using ANOVA software. P-value of <0.05 is taken as significant.

RESULTS

A total of 288 consecutive patients of malaria with monoinfection (191 *P. falciparum* and 97 *P. vivax*) were studied. ARF was present in 52 (27.22%) cases of *Pf* and 14 (14.43%) cases of *Pv* malaria ($p < 0.05$). Mean age in cases of *Pf* was 33.37 ± 12.59 yr (age ranging 15–65 yr) while in *Pv* it was 29.14 ± 13.93 yr (age ranging 17–65 yr). Majority of these patients 51 (77.27%) cases were between 20–40 yr of age. Male predominance (M:F = 3:1) was observed in *Pf* cases while those were equally affected in *Pv* cases.

At the time of presentation mean duration of illness (mean of duration since onset of fever) was 7.90 ± 3.47 days (range 4–20 days) in *Pf* cases while it was 6.366 ± 2.53 days (range 3–10 days) in the cases of *Pv* malaria. All six (*Pf*) cases were symptomatic for >10 days, 39

Table 1. Clinical profile of ARF in malaria (n = 66)

S.No.	Parameter	Falciparum ARF (n = 52)	Vivax ARF (n = 14)	*p*-value
1.	Type of ARF			
	Oliguric	11	5	<0.05*
	Nonoliguric	41	9	
2.	Age (mean ± SD)	33.37 ± 12.59	29.14 ± 13.93	0.280
3.	Sex (Male : Female)	39 : 13	7 : 7	0.072
4.	Duration of illness (Days)	7.90 ± 3.47	6.36 ± 2.53	0.124
5.	Cerebral malaria	25	3	0.04*
6.	Multiorgan failure	9	3	0.390
7.	ARDS	5	1	0.476
8.	Hypotension	11	5	0.215
9.	Urine analysis			
	Albuminuria	27	4	0.014*
	RBCs	21	3	0.16
	Pus cells	11	2	0.441
	Casts	9	2	0.574
10.	GFR (<20 ml/min)	19	3	0.238
11.	Haemoglobin (<5 g%)	17	1	0.05*
12.	S. creatinine (mg%)	3.87 ± 1.07	4.04 ± 2.14	0.710
13.	Blood sugar (<70 mg%)	12	3	0.694
14.	S. bilirubin (>2.5 mg%)	44	9	0.027*
15.	Recovery period (days)	9.13 ± 4.24	8 ± 3.41	0.422
16.	Outcome—Deaths	15	3	0.427

*Significant values.

(30 *Pf* and 9 *Pv*) for 6–10 days while 21 (16 *Pf* and 5 *Pv*) cases were symptomatic for up to five days only. Most of the patients were having other associated severe manifestations of malaria (more commonly with falciparum infection) like jaundice (53 cases: 44 *Pf* and 9 *Pv*), cerebral malaria (28 cases: 25 *Pf* and 3 *Pv*), severe anemia (18 cases: 17 *Pf* and 1 *Pv*), bleeding manifestations in the form of epistaxis and hematemesis (16 cases: 14 *Pf* and 2 *Pv*), multiorgan failure (12 cases: 9 *Pf* and 3 *Pv*), hypotension (16 cases: 11 *Pf* and 5 *Pv*), and ARDS (6 cases: 5 *Pf* and 1 *Pv*). Isolated ARF was seen in 8 (5 *Pf* and 3 *Pv*) cases. Clinical profiles of these patients are shown in Table 1.

Out of 52 cases of *Pf* ARF, 11 had oliguric renal failure and 41 nonoliguric renal failure while out of 14 cases of *Pv* ARF, five had oliguric renal failure and nine nonoliguric renal failure. Thus, nonoliguric renal failure was more commonly seen in both *Pf* and *Pv* ARF. Glomerular filtration rate (GRF) on admission was <20 ml/min in 22 (19 *Pf* and 3 *Pv*) patients, out of which 13 (11 *Pf* and 2 *Pv*) patients died while it was 20–50 ml/min in rest of the 44 cases, out of which only 5 (4 *Pf* and 1 *Pv*) died.

Regarding on urine analysis, albuminuria was present in significantly more number of cases of *Pf* malaria as compared to *Pv* ($p = 0.014$). While haematuria, pus cells, bile pigments and casts were present in urine sediment with no statistically significant difference found between *Pf* and *Pv* cases.

Laboratory investigations showed that blood urea was higher in *Pf* cases (mean 107.57 ± 31.78, range 72–252 mg%) as compared to *Pv* cases (mean 96 ± 19.06, range 66–100 mg%). Mean serum creatinine was 3.87 ± 1.07 mg% in *Pf* cases (range 3.1–8.6 mg%) while it was 4.04 ± 2.14 mg% in *Pv* cases (range 3.1–11 mg%), however, the difference was not found statistically significant. Haemoglobin <5 g% was present in 32.69% cases of *Pf* as compared to 7.14% cases of *Pv* malaria ($p <0.05$). About 22.73% (18.18% *Pf* and 4.55% *Pv*) cases had blood sugar <70 mg%. Total serum bilirubin >2.5 mg% was found in 84.62% cases of *Pf* as compared to 64.29% cases of *Pv* ($p <0.027$).

Dialysis was done on seven cases (all oliguric) as per indication and contraindication (4 *Pf* cases = dialysis session 1, 2, 2, 5 respectively, and 3*Pv* cases = dialysis session 2, 3, 5 respectively); 4 of them (57.14%; 1 *Pf* and 3 *Pv*) survived, whereas only one (*Pf*) survived (11.11%) in non-dialysis group in oliguric renal failure.

Out of 66 patients, 18 (27.27%) of ARF died, 15 (83.33%) were suffering from falciparum malaria and 3

Table 2. Profile of patients dying of malarial ARF (n = 18)

S.No.	Age/Sex	Illness (Days)	Type of malaria	Type of ARF	GFR	Dialysis (Session)	Associted severe manifestation	Admission (Days)	Histopathology
1	20/M	10	*Pf*	O	9.68	2	ARDS+J	5	–
2	34/M	15	*Pf*	O	14.81	–	CM+HEM+J+SA	3	ATN+MPGN
3.	30/M	5	*Pf*	N	24.18	–	MOF+CM+J	1	ATN+MPGN
4.	18/F	5	*Pf*	N	14.13	–	MOF+J+SA	3	ATN
5.	22/M	8	*Pf*	O	18.03	–	MOF+CM+J	2 h	ATN
6.	16/M	7	*Pf*	O	18.05	–	MOF+CM+J+SA	2 h	MPGN
7.	4/M	15	*Pf*	O	16.92	–	ARDS+CM+J	4 h	MPGN
8	45/M	15	*Pf*	N	16.55	–	MOF+J+SA	1	ATN+MPGN
9.	55/M	7	*Pf*	O	21.99	–	MOF+CM+J+SA	1	ATN+MPGN
10.	32/M	4	*Pf*	O	25.5	1	MOF+CM+J	2	ATN+MPGN
11.	40/M	6	*Pf*	N	24.6	–	ARDS+J	6	ATN+MPGN
12.	40/M	5	*Pf*	N	18.69	–	ARDS+J	5	ATN
13.	32/M	10	*Pf*	N	20	–	ARDS+J	6	ATN
14.	26/M	10	*Pf*	O	17.73	–	MOF+CM+J	1	ATN+MPGN
15.	28/F	8	*Pv*	O	13.28	2	MOF+CM+J+SA	3	ATN+MPGN
16.	20/F	3	*Pv*	O	5.15	–	MOF+CM+J+HT	2	ATN
17.	35/F	5	*Pv*	O	10.39	–	MOF+CM+J+SA	1	–
18.	25/F	7	*Pv*	N	21.56	–	MOF+J	1	–

GFR—Glomerular filtration rate; O—Oliguric; N—Nonoliguric; ARDS—Acute respiratory distress syndrome; CM—Cerebral malaria, HEM—Haemetemesis; MOF—Multiorgan failure; J—Jaundice; SA—Severe anemia; HT—Hypotension; ATN—Acute tubular necrosis; MPGN—Mesangioproliferative glomerulonephritis.

(16.67%) from vivax; 11 (61.11%) had oliguric renal failure (9 *Pf* and 2 *Pv*) and 7 (38.89%) had nonoliguric renal failure (6 *Pf* and 1 *Pv*). Mortality was highest within 72 h of admission, three died within 4 h (all *Pf*), six died in 4–24 h (5 *Pf* and 1*Pv*), and five died in 24–72 h (3 *Pf* and 2 *Pv*). All the four (*Pf*) patients died after 72 h of hospitalization. About 12 (66.67%; 9 *Pf* and 3 *Pv*) had multiorgan failure as cause of death. All the 5 (35.71% *Pf*) paitens died of ARDS, out of which two died after recovery of renal functions and one (*Pf*) died due to massive upper GI bleed (Table 2).

A majority of 42 patients (87.5%; 32 *Pf* and 10 *Pv*) out of 48 (37 *Pf* and 11 *Pv*) who survived, their renal functions recovered within two weeks of starting antimalarial treatment. Patients having oliguric renal failure who survived due to dialysis support, their renal functions recovered within three weeks to normal. Mean duration of recovery was 9.13 ± 4.24 days (range 3–20 days) in *Pf* cases while it was 8 ± 3.41 days (range 4–15 days) in *Pv* cases.

Renal histopathology

Renal histopathology was done in 18 (16 *Pf* and 2 *Pv*) cases under light microscopy by pathologist. MPGN was seen in 12 cases. Two cases (both falciparum oliguric renal failure) had isolated MPGN while it was seen along with changes of acute tubular necrosis (ATN) in 10 cases (falciparum 9 out of those 6 were oliguric, 3 nonoliguric and one case of nonoliguric vivax malaria). ATN alone was seen in 6 cases (5 falciparum: 2 oliguric, 3 nonoliguric and one with vivax oliguric renal failure) (Table 3). Details of histopathological changes were as follows:

Mesangioproliferative glomerulonephritis: The glomeruli were diffusely involved showing varying de-

Table 3. Renal histopathological findings in patients of renal failure

Histopathology	Falciparum malaria			Vivax malaria			Total
	Oliguric	Nonoliguric	Total	Oliguric	Nonoliguric	Total	
ATN	2	3	5	1	–	1	6
MPGN	2	–	2	–	–	–	2
MPGN + ATN	6	3	9	–	1	1	10
Total	10	6	16	1	1	2	18

ATN— Acute tubular necrosis; MPGN— Mesangioproliferative glomerulonephritis.

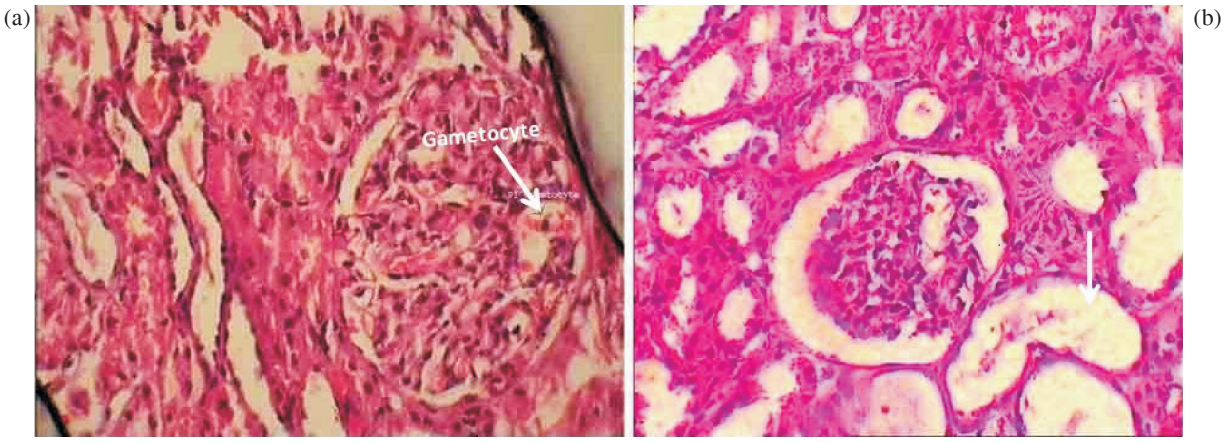

Fig. 1: Renal tissue from a patient of renal failure due to *Plasmodium falciparum* monoinfection showing: (a) mesangioproliferative glomerulonephritis —note gametocyte of *Pf* in one of the tuft; and (b) acute tubular necrosis.

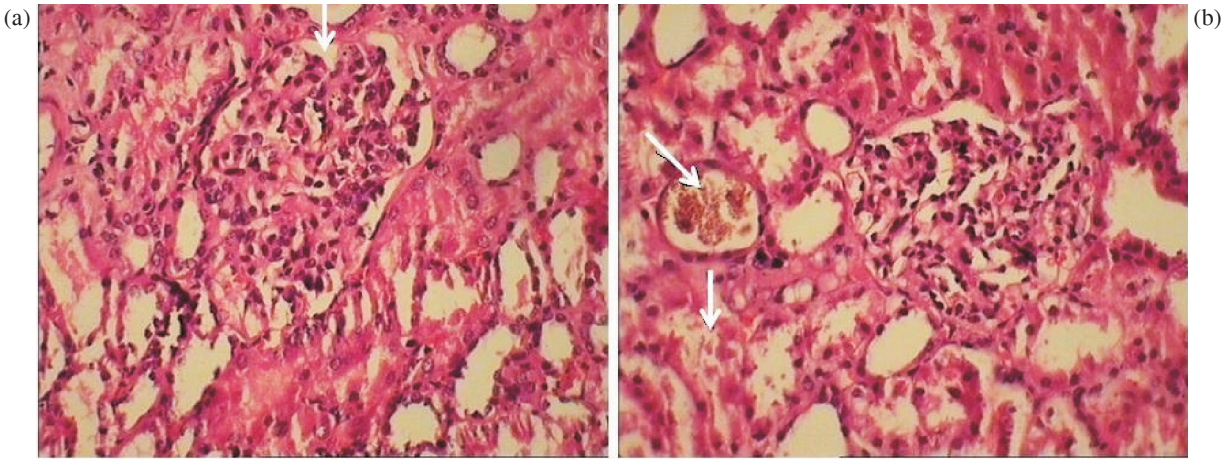

Fig. 2: Renal tissue from a patient of renal failure due to *Plasmodium vivax* monoinfection showing: (a) mesangioproliferative glomerulonephritis; and (b) tubules exfoliation and loss of brush border.

gree of proliferative changes (increase in mesangial matrix and mesangial cells). The glomeruli were congested showing RBCs in capillary lumina and Bowman's space, presence of pigment was noted in glomerular capillaries and in RBCs. Blood vessels showed congestion and were full of RBCs showing presence of pigments. Interstitium was in general unremarkable showing only focal collection of lymphocytes. Tubules showed RBCs with presence of pigment. There was no significant difference found in the histopathology of renal biopsy of falciparum and vivax malaria except that gametocyte of *Pf* was noted in one of the tuft in one *Pf* case (Fig. 1a & 2a).

Acute tubular necrosis (ATN): Tubules showed features of acute necrosis in the form of exfoliation of epithelial cells and loss of brush borders. Large number of RBCs and RBC casts were present showing presence of pigment, in some cases hyaline casts were also present and in one case complete denudation of tubular basement membrane was seen. There were no significant histopathological differences found in cases of falciparum and vivax malaria (Fig. 1b & 2b).

DISCUSSION

Renal failure is an important manifestation of severe malaria most commonly occurring in falciparum cases and its incidence is gradually increasing during last few years[4–16]. Tran *et al*[26] reported that approximately 50% of patients of malaria had biochemical evidence of renal involvement (serum creatinine >2 mg/dl) but only 30% fulfilled the stricter WHO criteria of acute renal failure. Mehta *et al*[17] found that *P. falciparum* was responsible for acute renal failure in 66.66%, *P. vivax* in 12.5% and 20.83% cases had mixed infection with *P. vivax* and *P. falciparum*. Our study shows ARF in 22.92% cases out of 288 who were admitted in the hospital; monoinfection

with falciparum was responsible for 78.79% and mono-infection with vivax for 21.21% cases, thus, we also observed increasing incidence of ARF in malaria from 2.07% in 1997[27]. Although this does not show true incidence of ARF in malaria as this study involved only those cases of malaria who were admitted in our tertiary care hospital referred from periphery because of severity of illness or intolerability of drugs.

We found nonoliguric renal failure (75.76%) as most common presentation both in falciparum (78.85% out of 52 cases) as well as vivax (64.29% out of 14 cases) as compared to oliguric renal failure. This is in contrast to previous studies which reported oliguric renal failure as more common in presentation[1, 17, 22].

Our study showed malarial ARF is often associated with other manifestations of severe malaria similar to previous reports[1, 12–16] although 12.12% cases in this study had ARF (7.58% *Pf* and 4.55% *Pv*) as the only manifestation of severe malaria.

It was found that the mortality was more in patients with falciparum renal failure (28.85%) as compared to vivax renal failure (21.43%). Similar observations had been made by other workers who found that mortality was high in patients of falciparum malaria having renal failure [1, 22]. We also found that most of the patients who died were also having other potentially fatal complications of malaria like cerebral malaria, ARDS, multiorgan failure, etc. similar to previous reports[1, 22].

Mortality in patients was directly related to their glomerular filtration rate at the time of admission. Those having GFR <20 ml/min on admission had a poor outcome and the outcome was more poor in patients of oliguric renal failure. This could probably be explained by advanced derangements in renal functions, associated multiorgan dysfunction, electrolyte imbalance and delay in seeking medical attention. Patients of nonoliguric renal failure did not require dialysis support and their renal functions returned to normal within two weeks of starting antimalarial treatment.

In our study, haemodialysis was done on seven cases (5 falciparum and 2 vivax all with oliguric renal failure), out of which 42.85% (3 cases, all falciparum) died while mortality was 88.89% in rest of the oliguric renal failure cases in whom haemodialysis could not be done. Thus, our study showed dialysis reduced mortality by 50% in oliguric renal failure and it should be done as soon as possible for better outcome. Similar observations have been made by other workers[1, 22]. Haemodialysis could not be done in 59 patients because of no-indication (like good response to conservative treatment, no serial rapid rise in serum creatinine and improvement in urine output) or contraindication (like hypotension or bleeding manifestations) or very short stay in the hospital.

Histopathological studies showed MPGN+ATN in maximum number of cases followed by ATN and MPGN alone. Although MPGN is usually seen in chronic conditions but we found it in cases of acute malaria as well, recently, it has also been reported in acute infection[28] including acute malaria[18]. Tran *et al*[26] concluded that renal failure in malaria results from acute tubular necrosis but not because of glomerulonephritis. The role of glomerular pathology is unclear, clinical presentation and urine sediment finding do not suggest glomerulonephritis although histopathological evidence of glomerular changes has been reported in some studies on acute falciparum malaria[1]. Nguansangiam *et al*[21] did study on electron microscopic examination of renal tissues in fatal cases of falciparum malaria and found PRBC sequestration in glomeruli and tubulointerstitial vessels, acute tubular changes, mild glomerular hypercellularity and monocyte infiltrate in glomerular and peritubular capillaries.

Brooks *et al*[29] have reported the presence of iron positive pigment in the epithelium of tubules and in interstitial cells on microscopic examination of percutaneous biopsy specimens from patients of renal insufficiency due to malaria. Renal histopathology in our study also showed the presence of pigment in glomerular capillaries, interstitium and tubules. Thus, it can be postulated that hyperparasitization of young RBCs with increased sequestration in vital organs, haemolysis, haemoglobinuria and release of haemozoin pigment directly or indirectly lead to release of inflammatory mediators, causing damage to the structure and function of the organ including kidneys.

Interstitium was unremarkable in our study. This is in contrast to previous reports where interstitium inflammation was a common histopathological association in malarial ATN[1]. Acute renal failure in vivax malaria may also be a manifestation of severe systemic inflammatory response syndrome as happens in sepsis[30–31]. Marked inflammatory imbalance in severe vivax malaria has been reported by Andrade *et al*[32].

Thus, our study showed that not only *P. falciparum* but *P. vivax* is also becoming an important cause of ARF due to malaria. Awareness and early recognition is very important to reduce morbidity and mortality as we have observed that ARF in malaria can occur within five days of onset of symptoms of malaria in about one-third of the cases. It is mostly associated with other severe manifestations of malaria. Renal histopathology was not remarkably different in falciparum and vivax malarial ARF al-

though it was just light microscopy study further large and advance study including electron microscopy and immunofluroscent studies are required to understand the pathology of ARF in malaria.

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