Contents lists available at ScienceDirect

Journal of Acute Disease

journal homepage: www.jadweb.org

Document heading doi:

Oliguric and non-oliguric acute renal failure in malaria in west zone of rajasthan, India-A comparative study

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ARTICLE INFO

Article history:
Received 19 February 2012
Received in revised form 30 March 2012
Accepted 7 April 2012
Available online 20 November 2012

Keywords:
Malarial acute renal failure
Non-oliguric acute renal failure
Oliguric renal failure
Acute tubular necrosis
Mesangioproliferative glomerulonephritis

ABSTRACT

Objective: To report a comparative clinical and histopathological study on oliguric and non-oliguric acute renal failure (ARF) in malaria. **Method:** 311 consecutive cases of malaria out of which 74 (23.79%) had ARF as per WHO criteria were conducted. Mean age was 32.58 (range 15-60 years) and male: female was 2:1. **Result:** Most of the cases developed ARF within 10 d of onset. 18 cases (11 falciparum, 2 mixed, 5 vivax) presented with oliguric and 56 (41 falciparum, 6 mixed, 9 vivax) with non-oliguric renal failure. Associated major manifestations were jaundice (75.68%), cerebral malaria (41.89%), bleeding manifestations (32.43%), severe anemia (27.03%), hypotension (25.68%), multi-organ failure (18.92%), severe thrombocytopenia (12.16%), and ARDS (8.11%). Kidney biopsy (n=20) showed acute tubular necrosis (n=7), Mesangioproliferative glomerulonephritis (n=4) or both (n=9). Hemodialysis was done in 8 cases of oliguric renal failure out of which 4 survived (average no. of session 2.9). **Conclusion:** Most of the cases recovered within 3 weeks. Total mortality was 28.38% (n=21) and mortality was more in oliguric renal failure (72.22%) as compare to non-oliguric renal failure (14.29%).

1. Introduction

While acute renal failure (ARF) due to leptospiral infection is on decline, malaria has become the emerging cause of ARF[1,2]. Acute renal failure is one of the important manifestations of severe falciparum (pf) malaria, although it can occur rarely with vivax (pv) also[3]. Recently high incidence of ARF has been reported from various parts of the world including India both in cases of falciparum as well as vivax malaria[1-11]. It can occur as an isolated complication or as a component of multi-organ involvement[3].

Precise mechanism of ARF in malaria is not clearly known. Several hypothesis including mechanical obstruction caused by cytoadherence and sequestration of infected erythrocytes, immune-mediated glomerular pathology, alteration in renal and systemic homodynamics, release of cytokines, reactive oxygen intermediates and nitric oxide have been proposed. In addition to above, restricted blood flow to the kidneys due to less intake and increase loss of fluids can cause dehydration and renal ischemia[3,5,9].

Various histopathological alterations has been reported in the renal biopsy of malarial ARF include acute tubular necrosis, acute glomerulonephritis, Mesangioproliferative glomerulonephritis and nephrotic syndrome especially due to membranoproliferative glomerulonephritis in chronic malaria[3,9,12,13].

ARF in malaria is usually associated with oliguria and in severe cases even anuria. Occasionally ARF may be non-oliguric which make the diagnosis difficult unless serum creatinine is estimated[3]. Therefore this study was planned to evaluate renal functions in malaria and compare clinically and histopathologically oliguric ARF and non-oliguric ARF.

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2. Material and method

This was a prospective study conducted on patients of malaria who were admitted in a classified malaria ward during August-October 2003 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 except the pediatric range.

The study protocol was approved by 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 microscopy along with rapid diagnostic test (RDT) 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 identification of species by peripheral blood smear as well as RDTs.

2.1. Exclusion criteria

Patients already suffering from other preexisting 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.

Acute renal failure 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[14]. Acute renal failure in malaria is usually oliguric (<400 mL/d) or anuric (<50 mL/d) but urine output may be normal or increased. Serum creatinine play important role in determining the ARF in malaria patients. Therefore we divided patients into two groups-Group A. Oliguric ARF= Patients with serum creatinine >3 mg/dL and 24 h urine output <400 mL (or <0.5 mL/kg/h over >6 h) in spite of adequate rehydration and Group B. Non-oliguric ARF= Patients with serum creatinine >3 mg/dL and normal urine output.

Thorough clinical and biochemical examination was done for each patient which includes tests like hemoglobin, 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.

Glomerular filtration rate (GFR) was measured at the time of admission by Cockcroft-Gault Formula[15]

Creatinine clearance = (140-age) × Wt / Serum creatinine (mg/dL) × 72

(Creatinine clearance is in ml/min, 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 20 cases (12 oliguric, 8 non-oliguric). 10 patients having oliguric renal failure (8 pf, 1 mixed, 1 pv) and 7 patients (6 pf, 1 mixed) of nonoliguric renal failure who died during course of treatment were subjected to trucut percutaneous needle necropsy done by surface marking for renal histopathology. Besides these, 2 patient of oliguric renal failure (1 pf, 1 mixed) 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 WHO guidelines[14]. Fluids were given according to urine output plus 1 L (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 haemodiaysis when oliguria persisted or deteriorated, in the presence of signs of fluid overload or when rapid serial rise in serum creatinine (RIFLE criteria) was observed[16]. Contraindication to hemodialysis included hypotension and bleeding manifestations.

3. Results

A total of 311 consecutive patients of malaria were studied (191 pf, 97 pv and 23 with pf+pv mixed infection). ARF was present in 74 cases (23.79%) out of which 56 (75.68%) had non-oliguric renal failure (41 pf, 6 mixed, 9 pv) and 18 (24.32%) had oliguric renal failure (11 pf, 2 mixed, 5 pv). Mean age in cases of non-oliguric ARF was (33.36±2.89) yrs (age ranging 15-65 yrs) while in oliguric ARF it was (28.44±2.21) (age ranging 17-55 yrs). Majority of these patients (58 cases, 78.38%) were between 15-40 years of age (43 non-oliguric, 15 oliguric). Male to female ratio was 2:1 with slightly more male predominance (M:F=2.6:1) in cases of oliguric ARF as compare to non-oliguric cases (M:F=1.95:1).

At the time of presentation mean duration of illness was (7.41±3.39) d (range 3-20) in non-oliguric cases while it was

(7.94±3.33) (range 3–15 d) in oliguric ARF. 7 cases (5 non–oliguric=4 pf, 1 mixed; 2 oliguric=2 pf) were symptomatic for more than 10 d, 42 (31 non–oliguric=23 pf, 2 mixed, 6 pv; 11 oliguric= 7 pf, 2 mixed, 2 pv) for 6–10 d while 25 cases (20 non–oliguric=14 pf, 3 mixed, 3 pv; 5 oliguric= 2 pf, 3 pv) were symptomatic for up to 5 d only.

Most of the patients were having other associated manifestations of severe malaria (more commonly with falciparum infection) like jaundice (serum bilirubin >2.5 mg%) was present in 75.68% (56 cases; 43 non–oliguric=34 pf, 5 mixed, 4 pv; 13 oliguric= 8 pf, 2 mixed, 3 pv), cerebral malaria 41.89% (31 cases; 19 non–oliguric= 15 pf, 3 mixed, 1 pv; 12 oliguric=10 pf, 2 pv), bleeding manifestations in form of epistaxis, hemetemesis 32.43% (24 cases;15 non–oliguric=10 pf, 3 mixed, 2 pv; 9 oliguric= 7 pf, 1 mixed, 1 pv), severe anemia (Hb <5 gm%) in 27.03% (20 cases;14 non–oliguric= 12 pf, 1 mixed, 1 pv; 6 oliguric= 4 pf, 1 mixed, 1 pv), hypotension 25.68% (19 cases; 12 non–oliguric= 8 pf, 2

Table 1
Clinical profile of non–oliguric & oliguric ARF in Malaria (*n*=74).

SN.	Parameter	Non–oliguric ARF (*n*=56)	Oliguric ARF (*n*=18)	*P*–value
1	Type of infection PF	41	11	0.529
	Mixed	6	2	–
	PV	9	5	–
2	Age (mean ± sd)	33.36 ± 2.89	28.44 ± 2.21	0.158
3	Sex (M:F)	37:19	13:5	0.430
4	Duration of illness (d)	7.41 ± 3.39	7.94 ± 3.33	0.124
5	Cerebral malaria	19(33.93%)	12(66.67%)	0.183
6	Multi–organ failure	5(8.93%)	9(50.00%)	0.495
7	ARDS	3(5.36%)	4(22.22%)	0.533
8	Hypotension	12(21.43%)	7(38.89%)	0.123
9	Bleeding manifestations	15(26.79%)	9(50.00%)	0.281
10	GFR(<20 mL/min)	12(21.43%)	12(66.67%)	<0.001*
11	Recovery period (mean):	(8.31± 3.86) d	(13.20 ± 3.27) d	<0.009*
	<1 week	17	0	–
	1–2 weeks	28	2	–
	2–3 weeks	3	2	–
13	Out–come: total deaths:	8	13	–
	Deaths in <4 h	0	4	–
	4–24 h	3	3	<0.001*
	24–72 h	1	5	–
	>72 h	3	2	–

*Significant values.

Table 2
Laboratory investigations and histopathological profile of non–oliguric & oliguric ARF in malaria (*n*=74).

SN.	Parameter	Non–Oliguric ARF (*n*=56)	Oliguric ARF(*n*=18)	*P*–value
1	Urine analysis:–Albuminuria	29(51.79%)	7(38.89%)	0.248
	RBCs	21(37.50%)	6(33.33%)	0.490
	Pus cells	11(19.64%)	3(16.67%)	0.541
	Casts	10(17.86%)	2(11.11%)	0.396
2	Hemoglobin (<5 gm%)	14(25.00%)	6(33.33%)	0.342
3	Leucocytosis	16(28.57%)	7(38.89%)	0.258
3	Thrombocytopenia (Platelets<50 000/mm^3)	8(14.29%)	1(5.56%)	0.470
4	Blood urea	102.34± 25.33	120.91± 52.41	<0.021*
5	S. creatinine (mg%)	3.58± 0.75	4.88± 2.22	<0.001*
6	Blood sugar (<70 mg%)	10(17.86%)	5(27.78%)	0.276
7	S. bilirubin(>2.5 mg%)	43(76.79%)	13(72.22%)	0.458
8	Histopathology (*n*=20):–	8(5 pf+2 mixed+1 pv)	12(10 pf+1 mixed+1 pv)	
	MPGN	1(mixed)	3(2 pf+1 mixed)	
	ATN	4(3 pf+1 mixed)	3(2 pf+1 pv)	
	MPGN+ATN	3(2 pf+1 pv)	6(pf)	

*Significant values.

Table 3.
Profile of patients dying of malarial non-oliguric ARF (n=8).

S.N	Age & sex	Duration of illness (d)	Type of malaria	GFR	Dialysis (session)	Associated severe manifestation	Hospital stay (d)	Histopathology
1	30M	5	PF	24.18	–	MOF+CM+J	1	ATN+MPGN
2	18F	5	PF	14.13	–	MOF+J+SA	3	ATN
3	45M	15	PF	16.55	–	MOF+J+SA	1	ATN+MPGN
4	40M	6	PF	24.60	–	ARDS+J	6	ATN+MPGN
5	40M	5	PF	18.69	–	ARDS+J	5	ATN
6	32M	10	PF	20.00	–	ARDS+J	6	ATN
7	50F	10	MIXED	15.15	–	MOF+CM+J	1	MPGN
8	25F	7	PV	21.56	–	MOF+J	1	–

Table 4.
Profile of patients dying of malarial oliguric ARF (n=13).

S.N	Age & sex	Duration of illness (d)	Type of malaria	Gfr	Dialysis (session)	Associated severe manifestation	Hospital stay (d)	Histopathology
1	20M	10	PF	9.68	2	ARDS+J	5	–
2	34M	15	PF	14.81	–	CM+HEM+J+SA	3	ATN+MPGN
3	22M	8	PF	18.03	–	MOF+CM+J	2 h	ATN
4	16M	7	PF	18.05	–	MOF+CM+J+SA	2 h	MPGN
5	45M	15	PF	16.92	–	ARDS+CM+J	4 h	MPGN
6	55M	7	PF	21.99	–	MOF+CM+J+SA	1	ATN+MPGN
7	32M	4	PF	25.50	1	MOF+CM+J	2	ATN+MPGN
8	26M	10	PF	17.73	–	MOF+CM+J	1	ATN+MPGN
9	28F	8	PF	13.28	2	MOF+CM+J+SA	3	ATN+MPGN
10	36M	10	MIXED	15.60	3	ARDS+J	5	
11	15M	6	MIXED	5.88		MOF+J+HT	1 h	MPGN
12	20F	3	PV	5.15	–	MOF+CM+J+HT	2	ATN
13	35F	5	PV	10.39	–	MOF+CM+J+SA	1	–

mixed, 2 pv; 7 oliguric= 3 pf, 1 mixed, 3 pv), multi-organ failure 18.92% (14 cases; 5 non-oliguric= 3 pf, 1 mixed, 1 pv; 9 oliguric= 6 pf, 1 mixed, 2 pv), severe thrombocytopenia (total platelet count <50 000/mm3) 12.16% (9 cases; 8 non-oliguric= 6 pf, 1 mixed, 1 pv; 1 oliguric pf) and ARDS in 9.46% (7 cases; 3 non-oliguric= 3 pf; 4 oliguric= 3 pf, 1 mixed). Isolated ARF was seen in 16.21% cases (12 patients; 10 non-oliguric= 6 pf, 1 mixed, 3 pv; 2 oliguric= 2 pv). Clinical profiles of these patients are shown in Table 1 and Table 2.

GFR on admission in the cases of non-oliguric ARF was higher (mean (24.99±46.45); ranging 13.22-49.13) as compared to oliguric ARF (mean (16.88±41.35); ranging 5.15-26.75; P<0.00007) and it was <20 mL/min in 32.43% patients (24 cases; 12 non-oliguric= 10 pf, 2 mixed; 12 oliguric= 7 pf, 2 mixed, 3 pv) out of which 66.67% patient died (16 cases; 5 non-oliguric= 4 pf, 1 mixed; 11 oliguric= 7 pf, 2 mixed, 2 pv) while it was 20-50 mL/min in rest of the 67.57% (50 cases; 44 non-oliguric= 31 pf, 4 mixed, 9 pv; 6 oliguric= 4 pf, 2 pv) out of which only 10% died (5 cases; 3 non-oliguric= 2 pf, 1 pv; 2 oliguric= 2 pf).

On urine analysis, albuminuria was present in 48.65% cases (36 cases; 29 non-oliguric; 7 oliguric) while microscopic hematuria was present in 36.49% (27 cases; 21 non-oliguric; 6 oliguric), pus cells in 18.92% (14 cases; 11 non-oliguric; 3 oliguric) and casts in 16.22% cases (12 cases; 10 non-oliguric; 2 oliguric) in urine sediment with no statistically significant difference between non-oliguric and oliguric cases.

Laboratory investigations revealed leucocytosis in 31.08%(23 cases; 16 non-oliguric, 7 oliguric) whereas leucopenia was found in 3(4.05%) cases of non-oliguric renal failure, blood urea was higher in oliguric cases (mean (120.91 ±52.41), ranging 90-265 mg%) as compared to non-oliguric cases (mean (102.34±25.33), ranging 66-207 mg%; P=0.021) and mean serum creatinine was also higher in oliguric cases (mean (4.88±2.22), ranging 3.2-11 mg%) as compared to non-oliguric cases (mean (3.58±0.75), ranging 3.1-6.6 mg%;

P=<0.001). Blood sugar was <70 mg% in 20.27% (15 cases; 10 non-oliguic, 5 oliguric; P=0.276)

Hemodialysis was done on 8 cases (all oliguric) as per indication and contraindication (4 pf cases=dialysis session 1,2,2,5 respectively, 1 mixed case= dialysis session 3 and 3 pv cases=dialysis session 2,3,5 respectively); 4 of them (50%; 1 pf, 3 pv) survived where as only one (pf) survived (5.56%) in non-dialysis group in oliguric renal failure.

21 out of 74 patients of acute renal failure died (total mortality 28.38%). 8 of them were suffering from non-oliguric renal failure (mortality 14.29% out of 56 cases) and 13 from oliguric renal failure (mortality 72.22% out of 18 cases). Mortality was highest within 72 h of admission, 4 died within 4 hours (all oliguric), 6 died in 4-24 h (3 non-oliguric and 3 oliguric) and 6 died in 24-72 h (1 non-oliguric and 5 oliguric). 5 patients (3 non-oliguric and 2 oliguric) died after 72 h of hospitalization. 66.67% (14 cases; 5 non- oliguric, 9 oliguric) had multi-organ failure as cause of death while 38.89% (7 cases; 3 non-oliguric,4 oliguric) died of ARDS out of which 2 died after recovery of renal functions and 1 died (oliguric pf) due to massive upper GI bleed.

A majority of 47 patients (88.69%; 45 non-oliguric, 2 oliguric) out of 53 who survived, their renal functions recovered within 2 weeks of starting antimalarial treatment. Patients having oliguric renal failure who survived due to dialysis support, their renal functions recovered within 3 weeks to normal. Mean duration of recovery was (8.31 ± 3.86) d (ranging 3-16 d) in non-oliguric cases while it was (13.20 ± 3.27) days (ranging 8-20 d) in cases of oliguric renal failure (P<0.009).

3.1. Renal histopathology

Renal histopathology was done in 20 cases (8 non-oliguric= 6 pf, 1 mixed, 1 pv and 12 oliguric= 9 pf, 2 mixed, 1 pv) under light microscopy by pathologist. MPGN was seen in 13 cases. 4 cases (1non-oliguric mixed malaria and 3oliguric renal failure; 2 pf, 1 mixed) had isolated MPGN while it was seen along with changes of ATN in 9 cases (3 non-oliguric; 2 pf, 1pv and 6 oliguric all pf). Acute tubular necrosis alone was seen in 7 cases (4non-oliguric; 3 pf, 1 mixed and 3 with oliguric renal failure 2 pf, 1 pv). Details of histopathological changes were as follows:

3.1.1.Mesangioproliferative glomerulonephritis (MPGN)

The glomeruli were diffusely involved showing varying degree 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 in the histopathology of renal biopsy of non-oliguric ARF and oliguric ARF and falciparum, mixed and vivax malaria.

3.1.2. 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 was no significant histopathological difference in cases of non-oliguric ARF and oliguric ARF or falciparum, mixed and vivax malaria.

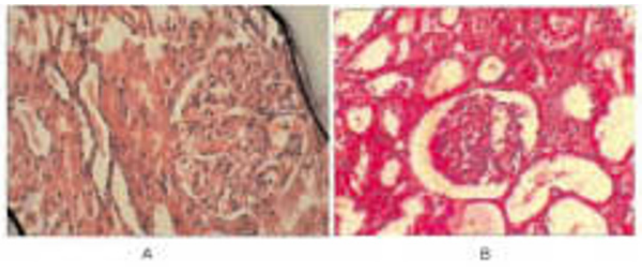

Figure 1. Renal tissue from a patient of oliguric renal failure due to *Plasmodium falciparum* malaria showing mesangioproliferative glomerulonephritis along with acute tubular necrosis.
A: The glomeruli are diffusely involved showing increase in mesangial matrix and increase in mesangial cells. Capillary lumina and bowmans space show presence of RBC. Interstitium is unremarkable except for focal lymphocytic collection. Gametocyte of Pf was noted in one of the tuft (as shown by arrow).
B: Tubules show features of acute necrosis in the form of exfoliation of epithelial cells and loss of brush borders. Large number of RBC and RBC casts are present showing presence of pigment.

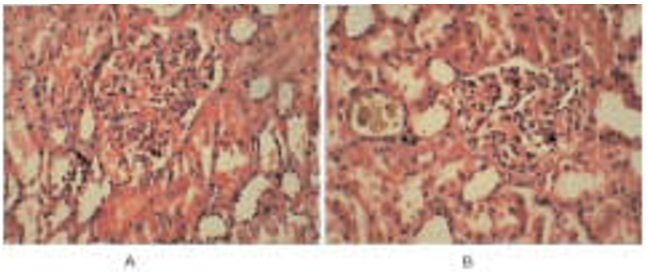

Figure 2. Renal tissue from a patient of Non-oliguric renal failure due to *Plasmodium vivax* infection showing mesangioproliferative glomerulonephritis and acute tubular necrosis.
A: The glomeruli are diffusely involved showing proliferative changes of mostly mesangial cells. Glomeruli are congested showing red blood cells in capillary lumina and in Bowmans space. Presence of pigment is noted in the glomerular capillaries and in red blood cells. Interstitium is unremarkable showing only focal collection of lymphocytes. B: Tubules show exfoliation and loss of brush border.

4. Discussion

Renal failure is an important manifestation of severe malaria most commonly falciparum and its incidence is gradually increasing since last few years[1-3]. Tran Tin Hien et al reported that approximately 50% of patients of malaria had biochemical evidence of renal involvement (*S. creatinine* > 2 mg/dL) but only 30% fulfilled the stricter WHO criteria of acute renal failure.17 Most of the reports on ARF in malaria considered oliguric ARF[1,5,6,17]. Our study also shows increasing incidence of ARF in malaria from 2.07% in 1997 to 23.47% in the present study[18]. Although this does not show true incidence of ARF in malaria as it 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. Rise in incidence of ARF in malaria may be because of screening of cases of malaria for renal functions as we have found non-oliguric renal failure (75.76%) to be the most common presentation of malarial ARF as compared to oliguric renal failure however possibility of changes in the antigenicity and pathogenicity (virulence) of the parasite can not be rule out.

Our study shows malarial ARF is often associated with other manifestations of severe malaria (more commonly with oliguric ARF) similar to previous reports[3] although 16.21% of our cases had ARF (13.51% non-oliguric and 2.70% oliguric) as the only manifestation of severe malaria.

We found that mortality was more in patients with oliguric renal failure (72.22%) as compared to non-oliguric renal failure (14.29%) and most of the patients who died were also having other potentially fatal complications of severe malaria like cerebral malaria, ARDS, multi-organ failure etc. similar to previous reports[3].

Mortality in our 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. Patient of non-oliguric renal failure did not require dialysis support and their renal functions returned to normal within two weeks of starting antimalarial treatment.

In our study, hemodialysis was done on 8 cases of oliguric renal failure out of which 50% died while mortality was 90% in rest of the oliguric renal failure cases in whom hemodialysis could not be done. Thus similar to previous observations our study also shows dialysis reduced mortality by 50% in oliguric renal failure and it should be done as soon as possible for better out come[3]. Hemodialysis 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 in our cases showed MPGN+ATN in maximum number of the cases followed by ATN and MPGN alone. 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[3]. Nghansangian et al did study on electron microscopic examination of renal tissues in fatal cases of falciparum malaria and found PRBC sequestration in glomeruli and tubulo-interstitial vessels, acute tubular changes, mild glomerular hypercellularity and monocyte infiltrate in glomerular and peritubular capillaries[19].

Brooks M.H. et al 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[20]. Renal histopathology in our study also shows 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, hemolysis, hemoglobinuria and release of hemozoin 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[3].

Looking at the short history of the illness, association of various other organ dysfunction, similar clinical presentation and renal histopathological findings in various types of malaria, pathogenesis of ARF in malaria may also be a manifestation of severe systemic inflammatory response syndrome such as happens in other severe infections[21-23].

Thus, our study shows incidence of ARF due to malaria is on rise and non-oliguric renal failure is more common manifestation. Awareness and early recognition is very important to reduce morbidity and mortality as we have observed that ARF in malaria can occurs within 5 d of

onset of symptoms in about one third of the cases. It is mostly associated with other manifestations of severe malaria. Renal histopathology was not remarkably different in different types of malarial ARF although it was just light microscopy study further large and advance study including electron microscopy and immunofluroscent studies are required to understand pathology of ARF in malaria.

Conflict of interest statement

We declare that we have no conflict of interest. KCN and BKG designed the study, analysis of data and their interpretation. BKG drafted the manuscript. KCN approved final version to be published. SK1, SK2, PP carried out clinical assessment. AG evaluated and analyzed laboratory data and their interpretation. All authors read and approved the final manuscript. KCN and BKG are guarantors of the paper. Ethical Approval: Prior approval has been taken from the Institution Ethics Committee to carry out this work and informed consent taken from the subjects enrolled in the study.

References

[1] Jayakumar M, Prabahar MR, Fernando EM, Manorajan R, Venkatraman R, Balaraman V. Epidemiologic trend changes in acute renal failure-a tertiary center experience from South India. *Ren Fail* 2006; **28**: 405–10.

[2] Abdul Manan J, Ali H, Lal M. Acute renal failure associated with malaria. *J Ayub Med Coll Abbottabad* 2006, **18**:47–52.

[3] Das BS. Renal failure in malaria. *J Vect Born Dis* 2008; **45**(2): 83–97.

[4] Wasiu AO, Kayode AA. Pediatric acute renal failure in southwestern Nigeria. *Kidney Int* 2004; **66:** 1541–8.

[5] Mehta KS, Halankar AR, Makwana PD, Torane PP, Satija PS, Shah VB. Severe acute renal failure in malaria. *J Postgrad Med* 2001; **47**: 24–6.

[6] Prakash J, Singh AK, Gujrati S, Maheshwari A. Acute renal failure in malaria: Changing trends. *Indian J Nephrol* 2002; **12**: 113–117.

[7] Sanghai SR, Shah I. *Plasmodium vivax* with acute glomerulonephritis in an 8 years old. *J Vector Borne Dis* 2010; **47**: 65–6.

[8] Prakash J, Singh AK, Kumar NS, Saxena RK. Acute renal failure in *Plasmodium vivax* malaria. *J Assoc Physicians India* 2003; **51**: 265–7.

[9] Zaki SA, Shanbag P. Atypical manifestations of malaria. *Res Rep Trop Med* 2011; **2**: 9–22.

[10] Maheshwari A, Singh AK, Sinha DK, Tripathi K, Prakash J. Spectrum of renal disease in malaria. *J Indian Med Assoc* 2004;**102**: 143–6.

[11] Kaur D, Wasir V, Gulati S, Bagga A. Unusual presentation of *Plasmodium vivax* malaria with severe thrombocytopenia and acute renal failure. *J Trop Pediatr* 2007; **53**: 210–2.

[12] Hartenbower, DL, Kantor GL, Rosen VJ. Renal failure due to acute glomerulonephritis during falciparum malaria. *Case Rep Military Med* 1972, **137**: 74–6.

[13] Barsoum R. Malarial Nephropathies. *Nephrol Dial Transplant* 1998; **13**: 1588–97.

[14] World Health Organization (WHO). Severe Falciparum Malaria. *Trans Royal So Trop Med Hyg* 2000; **94**: 1–90.

[15] Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.

[16] Bellomo R, Kellum JA, Mehta R, Palevsky PM, Ronco C. Acute Dialysis Quality Initiative II: the Vicenza conference. *Curr Opin Crit Care* 2002; **8**(6): 505–8.

[17] Tran TH, Day NP, Nguyen HP, Nguyen TH, Waller D, Peto TE and white NJ. A controlled trail of artemether or quinine in Vietnamese adults with severe falciparum malaria. *New Engl J Med* 1996; **335**: 70–83.

[18] Kochar, D, Kumawat BL, Karan, S, Kochar SK, Agarwal, RP. Severe and complicated malaria in Bikaner (Rajasthan), Western India. *Southeast Asian J Trop Med Public health* 1997; **28**(2): 259–67.

[19] Nguansangiam S, Day NPJ, Hien TT, Mai NTH, Chaisri U, Riganti M, et al. A quantitative ultrastructural study of renal pathology in fatal *Plasmodium falciparum* malaria. *Trop Med Int Health* 2007; **12**(9): 1037–1050.

[20] Brooks MH, Malloy JP, Bartelloni PJ, Tigertt WD, Sheehy TW, Barry KG. Pathophysiology of acute falciparum malaria. I. Correlation of clinical and biochemical abnormalities. *Am J Med* 1967; **43**(5): 735–44.

[21] Eiam-Ong S. Malaria nephropathy. *Semin Nephrol* 2003; **23**: 21–33.

[22] Clark IA, Budd AC, Alleva LM, Cowden WB. Human malarial disease: a consequence of inflammatory cytokine release. *Malar J* 2006; **5**: 85. doi: 10.1186/1475 -2875-5-85, 10 October.

[23] Andrade BB, Reis-Filho A, Souza-Neto SM, Clarêncio J, Camargo LMA, Barral A, et al. Severe *Plasmodium vivax* malaria exhibits marked inflammatory imbalance. *Malar J* 2010; **9**: 13–20.