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Evaluation of Clinical Predictors and Prognostic Indicators of Acute Renal Failure Caused by Different *Plasmodium* Species in Hospitalized Adult Patients in North West Zone of Rajasthan, India

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Abstract

Aims & Objectives: Recently high incidence of acute renal failure (ARF) in malaria has been reported from various parts of world including India. This study was planned to evaluate the clinical predictors and prognostic indicators of ARF in malaria. *Methods:* This prospective observational study was done on 60 consecutive confirmed cases of malaria admitted in the department of medicine. 40 had ARF (study group) and 20 did not (control group). All cases were thoroughly studied for clinical features, laboratory evaluation and outcome. Diagnosis of ARF was made as per WHO criteria. RIFLE criteria were used to stratify severity of acute kidney injury. Prognostic evaluation was also done by different Score system. *Results:* Out of 40 patients who had ARF 57.6% had *P. vivax* infection, 32.5% *P. falciparum* while 10% had mixed infection, thus we observed significantly high number of cases of ARF due to vivax malaria. Clinical predictors for ARF were longer duration of fever, marked chills, severe tiredness, nausea, vomiting, jaundice, altered sensorium, decrease urine, low GFR , low hemoglobin, high parasite density, TLC, RDW, LDH, bilirubin, SGOT, SGPT, urea, creatinine, APACHE II, SOFA, MODS and low GCS score. There was no difference in age and sex distribution but rural patients were more affected by ARF. 65% of our cases had non-oliguric ARF. Other manifestations of severe malaria like cerebral malaria (20%), malarial hepatitis (42.5%) and severe anemia (20%) were commonly associated with ARF. 15 cases of ARF needed dialysis. Two patients died both with mixed malaria, RIFLE-F category. Poor prognostic indicators were severe anemia ($p<0.01$), higher TLC ($p<0.01$), Blood urea ($p<0.001$), serum creatinine ($p<0.001$), SGOT ($p=0.001$), SGPT ($p<0.01$), serum bilirubin ($p<0.01$), parasite density ($p<0.05$), lower platelet count ($p<0.05$), and those with higher APACHE II score ($p<0.01$), SOFA score ($p<0.05$) and MODS score ($p<0.001$) and lower GCS score ($p<0.001$). *Conclusions:* Our study shows clinical predictors associated with increased risk for development of ARF and poor prognostic indicators associated with serious morbidity and mortality in ARF caused by malaria , if we give due attention to these factors at the time of clinical presentation we can reduce morbidity and mortality due to ARF caused by malaria.

Keywords: Acute Renal Failure; Clinical Predictor; Prognostic Indicators; *P. Vivax; P. Falciparum;* Mixed Malaria; RIFLE Criteria.

Introduction

Acute renal failure (ARF) is one of the important manifestations of severe falciparum malaria and there is increasing reports on ARF associated with vivax also.[1]Recently, high incidence of ARF has been reported from various part of world including India [2-4].

WHO has defined ARF in malaria as serum creatinine >3 mg/dl with 24 hr urine output<400ml, in spite of rehydration in patients [5]. Acute renal failure in malaria is usually oliguric (urine output <400 ml/day) or anuric (urine output <50 ml/day) but it may also be normal or increased [2]. Daily

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measurement of serum creatinine is most important investigation [1].

Precise mechanism of renal failure in falciparum malaria is not clearly known. Several hypotheses including mechanical obstruction by infected erythrocytes, immune mediated glomerular pathology, fluid loss due to multiple mechanisms and alterations in the renal microcirculation, etc have been proposed [6-8]. Cytoadherence of *P. falciparum* infected red blood cells (IRBCs) to the vascular endothelial cells of different host organs along with rosette formation is considered as a most important mechanism of severe malaria. Parasite proteins referred to as variant surface antigens (VSA) expressed on the IRBC surface mediate adhesion of infected erythrocytes to host vascular endothelial receptors.[7,8] Significantly more IRBCs were seen in renal vasculature of malaria patients with ARF than those without ARF [9]. Although the pathogenesis of ARF in malaria caused by different *plasmodium species* may be different but various studies has reported similar histopathological findings of renal biopsy [10,11].

ARF in malaria is associated with serious morbidity and high mortality but we could find only few reports on prognostic factors related to outcome of renal failure associated with malaria [12,13]. Therefore this study was planned to evaluate the clinical predictors of ARF in malaria and to evaluate prognostic indicators regarding outcome of such cases.

Material and Methods

This study was conducted on patients of malaria admit-ted in classified malaria and other medical wards of the Department of Medicine, Sardar Patel Medical College and Associated Groups of Hospitals, Bikaner, India. We included the patients of both sexes belonging to age more than 15 years. Approval of ethics committee was taken for this study. All the consequent patients of malaria given consent for participation in the study were included and examined in detail as per Performa. A patient complaining of *marked chills* means he / she was feeling chills even after covering with three to four blankets and the one complaining of *extreme weakness* means he / she was feeling so weak that he / she was not able to walk independently.

The diagnosis of malaria was confirmed by examination of thick and thin peripheral blood smear and RDT test. Diagnosis of species of plasmodium was further be confirmed by PCR. Parasite Density was calculated in all the patients as per WHO guidelines (WHO 2006) [14]. Diagnosis of Acute Renal Failure was made as per WHO criteria that is serum creatinine >3 mg / dl with 24 hr urine output of less than 400 ml despite rehydration [15]. Other Investigations done were CBC, Liver Function Test, Renal Function Test, Na^+, K^+, Ca^{++}, LDH, Blood Sugar, Urine complete and microscopic, Blood culture / sensitivity, Ultrasonography abdomen specially for kidneys, spleen and liver, Chest X- ray PA View, ECG, 24 hour urine protein, leptospirosis, Blood Group, HIV, HBsAg and HCV etc.

These cases were divided into two groups:- (A)Study group: Patient of malaria with ARF and (B) Control group: Patient of malaria with no ARF. RIFLE (**R**isk **I**njury **F**ailure **L**oss **E**SKD) criteria was used to stratify severity of acute kidney injury (AKI) [16]. Glomerular filtration rate (GFR) was measured by Cockcroft-Gault Formula [17]. The assessment of vari-ous prognostic factors were also done by using different score systems such as APACHE II (Acute Physiology Age and Chronic Health Evaluation II) score [18], Multiple Organ Dys-function Score (MODS) [19], SOFA (Sequential Organ Failure Assessment) score [20], and Glasgow Coma Scale (GCS) [21].

All patients were treated as per WHO guidelines [15]. Supportive management was provided as per need including tepid sponging, antipyretics (for fever), packed cell transfusion (when hematocrit <20%), fluids were given according to urine output +600ml (insensible loss) + other form of fluid loss (vomiting / sweating / diarrhea). Renal Replacement Therapy (RRT) was provided whenever indicated. Daily clinical evaluations of all the patients were done during their hospital stay.

Statistical Analysis

Statistical analysis was done using MS Excel and SPSS version 11. Numerical variables were represented in mean ± SD, and ordinal variables in percent. Unpaired *t*-test or chi-square test (c^2) was used to compare two groups, while analysis of variance and chi-square tests were used to compare multiple groups. A *p*-value of <0.05 was considered as significant.

Observations

This observational prospective study was conducted on 60 consecutive confirmed cases of malaria who were admitted in various wards of the department of medicine S.P. Medical college and Associated Groups of Hospitals, Bikaner during July 2013 to June 2014 out of which 40 had ARF as per

WHO criteria (study group) and 20 did not (control group). Both groups were compared and evaluated for clinical predictor of ARF in malaria.

The epidemiological profile is shown in table-1. Maximum number of cases were found between age group 21-40 years in both the groups (42.5% vs 45.0%). 37.5%. cases of study group and 20% cases of control group were below the age of 20 years while 20% vs 35% cases belonged to >40 years of age. Mean age was 29.08±15.18 vs 35.45±15.33 showing relatively younger age group was more affected by ARF although statistically not significant (p=0.132). Male: Female ratio was 21:19 vs 12:8 (p=0.582). In females most patients were housewife (37.5% vs 35.0%) and in males most were farmer (25.0% vs 20.0%) by occupation, labour class was more affected by ARF and students least. Most patients belong to rural area (80% vs 55) as compared to urban (20% vs 45%) in both the groups (p=0.043).

The clinical profile is shown in Table 2. Most common species was *P. vivax* (57.5 vs 55.0%) followed by *P. falciparum* (32.5 vs 35.0%) and mixed infection (10.0% vs 10.0%) in both the groups. Although fever was presenting complain in all the patients of both the groups but mean duration of fever was more in study group as compared to control group (10.98±7.6 vs 3.90±0.97; p<0.001). All patients of control group (100%) presented with fever for less than 5 days whereas only 35% of study group had fever for less than 5 days while 25% had it for 6 to 10 days and 40% for more than 10 days. Other presenting symptoms were chills, tiredness, giddiness, bodyache, nausea, headache, anorexia, vomiting, jaundice, oliguria, altered sensorium, seizures, respiratory distress and diarrhea. Marked weakness and tiredness, giddiness, marked chills, nausea, vomiting, jaundice, decreased urine and altered sensorium were the symptoms at the time of presentation indicative of ARF in malaria.

Overall prevalence of ARF in our study as per WHO criteria was 66.67% (40 out of 60 cases; 38.3% *vivax* malaria, 21.7% *falciparum* and 6.7% mixed malaria). Species wise overall prevalence of ARF was 67.65% in *vivax* malaria (23 out of 34 cases), 65% in *falciparum* malaria (13 out of 20) and 66.67% in mixed malaria (4 out of 6). Out of 40 cases of study group 14(35%) were having oliguric ARF (6 *vivax*, 5 *falciparum* and 3 mixed malaria) while 26(65%) had normal urine output (non-oliguric) ARF (17 *vivax*, 8 *falciparum* and 1 mixed malaria). We used RIFLE criteria to assess severity of the AKI in the study group and found that 17.5% of the cases were belong to RIFLE-R category (7 / 40; all *vivax*), 27.5% to RIFLE-I (11 / 40; 5 *vivax*, 6 *falciparum*) and 55% to RIFLE-F (22 / 40; 11 *vivax*, 7 *falciparum* and 4 mixed malaria). Thus we observed that although ARF was highly prevalent in *vivax* malaria but it was most severe in mixed malaria followed by *falciparum* and *vivax* malaria (Table 3).

The laboratory profile at the time of admission is shown in Table 4. Study group had significantly lower mean Hb (6.13± 2.17 gm% vs 8.68±2.63 gm%, P=0.037), higher TLC (13.78±12.66 thousand / cmm vs 4.55±1.53 thousand / cmm, P=0.002), lower platelet count (67.99± 53.37 thousand / cmm vs 123.95±43.76 thousand / cmm, P<0.001), higher parasite density (88.87±56.89 thousand / cmm vs 41.85±16.63 thousand / cmm, P=0.001), higher LDH (732.381±381.46 vs 125.75±39.68, P<0.001), higher RDW (20.70±10.62 vs 14.13±0.74, P<0.008), higher serum bilirubin (5.53±5.64 vs 2.46±2.84, P=0.026), higher SGOT (94.85±65.91 vs 40.10±27.49, P=0.001), higher SGPT (105.70±79.13 vs 39.75±26.51, P<0.001), higher blood urea (150.78±61.25 vs 33.25±5.39, P<0.001), higher serum creatinine (5.89±3.05 vs 0.68±0.08, P=0.001)and low GFR (31.47±18.27 vs 95.00±3.03, P=0.001).

Assessment of various prognostic factors at the time of admission is also shown in Table 4. Study group had higher APACHE II score (9.90±6.45 vs 2.40±1.19, P<0.001), higher SOFA score (9.43±1.93 vs 2.78±0.04, P<0.001), higher MODS score (7.75±4.67 vs 2.95±1.23, P<0.004), and lower GCS score (12.90±3.97 vs 14.75±0.55, P=0.022), as compared to control group.

Mean duration of hospital stay was more in study group as compared to control (7.83±3.58 vs 5.10±1.55, p<0.002). 15 patients needed dialysis (7*vivax*, 5 *falciparum* and 3mixed malaria) out of which one died of mixed malaria with multi-organ failure. Patients suffering from ARF with *vivax* malaria recovered fast and their hospital stay was less (Table 5).

Out of 40 cases of ARF 2(5%) patients expired, both were suffering from severe mixed malaria with multi organ failure and GFR 10.1 and 11.9 respectively and belonging to RIFLE-F category. These expired patients had significantly lower mean Hemoglobin (3.40± 1.41 gm% vs 7.51±2.16 gm%, P=0.012), higher TLC (12.8±0.63 thousand / cmm vs 5.98±3.37 thousand / cmm, P=0.006), lower platelets count (37.50±7.07 thousand / cmm vs 89.37±55.61 thousand / cmm, P=0.043), higher parasite density (150.0±30.11 thousand / cmm vs 69.97±50.24 thousand / cmm, P=0.033), higher serum bilirubin (16.05±3.18 vs 4.48±5.16, P=0.003), higher SGOT (245.0±21.21 vs 86.95±57.31, P=0.001), higher SGPT (242.50±109.60 vs 98.50±72.18, P=0.01), higher blood urea (222.50±53.03 vs 147.00±59.87, P<0.089), higher serum creatinine(11.30±2.12 vs 5.75±2.95, P=0.001),

lower GFR (11.0±0.9 vs 32.55±14.53, P<0.001) higher APACHE II score (22.50±0.71 vs 9.24±5.90, P=0.003), higher SOFA score (16.50±2.12 vs 9.05±0.99, P<0.001), higher MODS score (16.0±2.830 vs 7.32±4.35, P=0.009), and lower GCS score (5.00±0.71 vs 13.32±3.62, P=0.003), as compared to patients who were survived (Table 6).

Table 1: Epidemiological profile

	Study group (No.=40)	Control group (No.=20)	χ^2	p
Sex				
Male	21(52.5%)	12 (60.0%)	0.303	0.582
Female	19(47.5%)	8 (40.0%)		
Age Group (yrs.) <20	15 (37.5%)	4 (20.0%)		
21-40	17(42.5%)	9 (45.0%)		
>40	8 (20.0%)	7 (35.0%)	t=1.528	0.132
Mean	29.08±15.18	35.45±15.33		
Occupation				
Driver	4 (10%)	0		
Farmer	10 ((25%)	4 (20.0%)		
Housewife	12 (30%)	7 (35.0%)		
Labour	11 (27.5%)	0		
Student	3 (7.5%)	9 (45.0%)		
Residential area				
Rural	32(80%)	11 (55.0%)	4.104	0.043*
Urban	8(20%)	9 (45.0)		

Table 2: Clinical profile at the time of presentation

Symptoms	Study group (n=40)		Control group (n=20)		χ^2	p
	No.	%	No.	%		
Fever	40	100	20	100		
< 5 days	14	35	20	100		
5-10 days	10	25	0		4.131	<0.001*
>10 days	16	40	0			
Type of Malaria:						
Vivax	23	57.5	11	55.0		
Falciparum	13	32.5	7	35.0	0.040	0.980
Mixed	4	10.0	2	10.0		
Tiredness	40	100	16	80	4.615	0.032*
Giddiness	40	100.0	16	80	4.615	0.032*
Chills	40	100	11	55.0	12.857	<0.001*
Bodyache	37	92.5	20	100	1.579	0.209
Nausea	34	85.0	9	45.0	10.506	0.001*
Headache	28	70.0	17	85.0	1.600	0.206
Anorexia	32	80.0	15	75.0	0.196	0.658
Vomiting	28	70.0	5	25.0	10.909	0.001*
Jaundice	20	55.0	4	20.0	5.000	0.025*
Oliguria	14	35.0	0	-	9.130	0.003*
Altered Sensorium	8	20.0	0	-	4.615	0.032*
Diarrhea	2	5.0	0	-	1.034	0.309

Table 3: Distribution of cases according to oliguric/non-oliguric ARF and RIFLE criteria in study group (No=40)

	P.vivax (No.= 23)	*P. falciparum* (No.= 13)	*Mixed* (No.= 4)	Total (No.= 40)
Oliguric/Non-Oliguric				
➢ Oliguric	6(15%)	5(12.5%)	3(7.5%)	14(35%)
➢ Non-Oliguric	17(42.5%)	8(20%)	1(2.5%)	26(65%)
➢ Total	23(57.5%)	13(32.5%)	4(10%)	40(100%)
RIFLE criteria				
➢ RIFLE-R	7(17.5%)	0	0	7(17.5%)
➢ RIFLE-I	5(12.5%)	6(15%)	0	11(27.5%)
➢ RIFLE-F	11(27.5%)	7(17.5%)	4(10%)	22(55%)
➢ Total	23(57.5%)	13(32.5%)	4(10%)	40(100%)

Table 4: Laboratory profile at the time of admission

Parameters	Study Group (n=40)		Control Group (n=20)		t	p
	Mean	SD	Mean	SD		
Hb (gm%)	6.13	2.17	8.68	2.63	2.732	0.037*
TLC (thousands)	13.78	12.66	4.55	1.53	3.237	0.002*
Platelet Count (in thousands per µL)	67.99	53.37	123.95	43.76	4.052	<0.001*
Parasite Density (in thousands per µL)	88.87	56.89	41.85	16.63	3.606	0.001*
LDH (U/L)	732.93	381.46	125.75	39.68	7.069	<0.001*
RDW (%)	20.70	10.62	14.13	0.74	2.752	0.008*
Serum Bilirubin(mg/dl)	5.53	5.64	2.46	2.84	2.286	0.026*
SGOT (IU/L)	94.85	65.91	40.10	27.49	3.552	0.001*
SGPT (IU/L)	105.70	79.13	39.75	26.51	3.614	0.001*
Blood Sugar (mg/dl)	98.05	10.56	102.98	16.16	1.131	0.263
Blood Urea (mg/dl)	150.78	61.25	33.25	5.39	8.529	<0.001*
S. Creatinine (mg/dl)	5.89	3.05	0.68	0.08	7.597	<0.001*
Sodium (mmol/L)	139.50	4.38	140.00	0.00	0.508	0.613
Potassium (mmol/L)	4.48	1.63	4.05	0.08	1.177	0.244
GFR	31.47	18.27	95.0	3.03	15.386	<0.001*
APACHE II	9.90	6.45	2.40	1.19	5.135	<0.001*
SOFA	9.43	1.93	2.78	0.04	15.294	<0.001*
MODS	7.75	4.67	2.95	1.23	4.499	<0.004*
GCS	12.90	3.97	14.75	0.55	2.354	0.022*

Table 5: Distribution of cases according to hospital stay, dialysis and outcome

	Study Group(No.=40)				Control Group	
	P. vivax	*P. falciparum*	*Mixed*	Total	(No.=20)	
Hospital stay(days)						
≤5	7(17.5%)	3(7.5%)	0	10(25%)	16(80%)	
6-10	15(37.5%)	8(20%)	2(5%)	25(62.5%)	4(20%)	t=3.187
>10	1(2.5%)	2(5%)	2(5%)	5(12.5%)	0	p=0.002*
Mean± SD	7.86±3.36	12.71±2.58	10.75±6.18	7.83±3.58	5.1± 1.55	
Dialysis	7(17.5%)	5(12.5%)	3(7.5%)	15(37.5%)		
Death	0	0	2(5%)	2(5%)	0	

Table 6: Statistical analysis of different parameters according to prognosis in study group

Parameters	Outcome				t	p
	Survival (n=38)		Expired (n=2)			
	Mean	SD	Mean	SD		
Hemoglobin (gm%)	7.51	2.16	3.40	1.41	2.639	0.012*
TLC (Thousands)	5.98	3.37	12.80	0.63	2.840	0.006*
Blood Urea (mg/dl)	147.00	59.87	222.50	53.30	1.743	0.089*
Serum Creatinine (mg/dl)	5.75	2.95	11.30	2.12	3.894	<0.001*
SGOT (IU/L)	86.95	57.31	245.00	21.21	3.846	<0.001*
SGPT (IU/L)	98.50	72.18	242.50	109.60	2.704	0.010*
Serum Bilirubin(mg/dl)	4.48	5.16	16.05	3.18	3.133	0.003*
Parasite Density (in thousands per µL)	69.97	50.24	150.00	30.11	2.181	0.033*
Platelet Count (in thousands per µL)	89.37	55.61	7.50	7.07	2.065	0.043*
GFR	32.55	14.53	11.0	0.90	3.914	<0.001*
APACHE II Score	9.24	5.90	22.50	0.71	3.140	0.003*
SOFA Score	9.05	0.99	16.50	2.12	9.957	<0.001*
MODS	7.32	4.35	16.00	2.83	2.773	0.009*
GCS	13.32	3.62	5.00	0.00	3.211	0.003*

Table 7: Evaluation of various parameters with respect to severity of acute kidney injury as per RIFLE criteria in study group (No.=40)

S. N.	Parameter	RIFLE-F (No.=22) Mean±SD	RIFLE-I (No.=11) Mean±SD	RIFLE-R (No.=7) Mean±SD	p
1.	Hospital Stay (days)	8.86±4.36	6.36±1.69	6.71±1.25	0.108
2.	Parasite Density(per µL)	87045.46±62013.42	67909.09±18894.44	61285.71±20295.44	0.09
3.	TLC(per µL)	13672.73±8192.92	6363.64±3993.31	8328.57±4671.8	0.04*
4.	Platelet count(per µL)	124954.5±128854.5	37363.64±14389.39	154857.1±156121.1	0.07
5.	RDW (%)	20.93±11.51	17.09±1.77	16.68±2.95	0.33

S. N.	Parameter	RIFLE-F (No.=22) Mean±SD	RIFLE-I (No.=11) Mean±SD	RIFLE-R (No.=7) Mean±SD	p
1.	Hospital Stay (days)	8.86±4.36	6.36±1.69	6.71±1.25	0.108
2.	Parasite Density(per µL)	87045.46±62013.42	67909.09±18894.44	61285.71±20295.44	0.09
3.	TLC(per µL)	13672.73±8192.92	6363.64±3993.31	8328.57±4671.8	0.04*
4.	Platelet count(per µL)	124954.5±128854.5	37363.64±14389.39	154857.1±156121.1	0.07
5.	RDW (%)	20.93±11.51	17.09±1.77	16.68±2.95	0.33
6.	SGOT(IU/L)	121.09±95.46	93.55±39.49	108.29±100.26	0.67
7.	SGPT(IU/L)	134.46±105.35	95.81±43.62	107.71±98.04	0.46
8.	Serum Bilirubin (mg%)	7.18±6.15	4.46±4.10	4.58±5.78	0.56
9.	Blood Urea(mg%)	159.59±63.60	116.09±76.11	118.01±117.67	0.12
10.	Serum Creatinine(mg%)	6.57±2.83	5.54±2.86	4.81±1.87	0.27
11.	LDH (U/L)	759.27±470.83	739.11±223.26	640.43±272.53	0.78
12.	Urine output (ml in 24 hrs)	637.46±593.04	781.82±535.85	1276.71±695.39	0.05*
13.	GFR	18.13±4.47	33.27±8.55	64.71±4.57	0.04*
14.	APACH -II	15.23±3.88	13.36±3.41	9.43±4.65	0.005*
15.	SOFA	10.68±2.26	9.09±1.13	7.71±0.95	0.001*
16.	MODS	9.77±3.98	7.82±2.32	5.14±3.53	0.01*
17.	GCS	9.05±2.46	13.18±4.05	13.85±14.16	0.002*

Discussion

Despite intensive efforts over the last century to understand and control malaria it remain a leading cause of morbidity and mortality in humans. Acute renal failure (ARF) is one of the important manifestations of severe *falciparum* malaria and recently it has also been reported with increasing incidence in *vivax* malaria [1-4].

In the present study out of 60 consecutive cases of malaria studied, 40 had acute renal failure. Thus we observed high prevalence (66.67%) of ARF in adults and this high prevalence of ARF was seen in all types of malaria caused by different *plasmodium* species (*vivax* malaria 23 out of 34 cases 67.65%; *falciparum* malaria 13 out of 20 cases, 65%; and mixed malaria 4 out of 6, 66.67%). The overall prevalence of renal failure in *P. falciparum* is reported to vary from 1–60%.[1] The increasing incidence of malarial acute renal failure represent a serious challenge [22]. In our region also, the prevalence of ARF in malaria has increased from 2.07% (in 1994) [23] to 66.67% in present study. This is because increasing number of *vivax* malaria is also presenting with severe manifestation as has been seen in *falciparum malaria*.

We found that maximum numbers of cases belongs to age group of 21-40 (mean 29.08) years. The young adult age group is more affected due to their greater mobility and greater risk of exposure due to more outdoor activity. We also found that rural patients were more affected with malaria and also with more incidence of ARF as compared to urban which may be because of illiteracy, unawareness, non availability of nearby medical facilities and delay in seeking medical help. Similarly we found that the labour class was more prone to develop ARF; this may be because of poor nutrition, less health awareness, and delay in seeking medical help due to economic reasons. Students were less prone to develop ARF; this may be because of health awareness.

Although fever was presenting complain in all patients in both the groups but we found that those who had longer the duration of fever were more prone to develop ARF ($p<0.001$). Thus our study suggest that longer the duration of illness more the chances of development of ARF. Among other presenting symptoms marked weakness and tiredness, marked chills, nausea, vomiting, altered sensorium, decrease urine (oliguria) and jaundice were found to be significantly associated with ARF thus these symptoms should be considered as clinical predictor of malarial ARF and patients presenting with these symptoms should be evaluated for renal functions.

We compared various laboratory parameters between study and control Group at the time of admission in the hospital to find out which were the parameters associated with ARF and found that leucocytosis, high parasitemia, elevated RDW, elevated SGOT and SGPT level, high bilirubin, raised LDH, decreased GFR, high APACHE II, SOFA, MODS and low GCS sores were the indicator of ARF. Hyperbilirubinemia in falciparum malaria possibly predisposes for ARF, which may remain unnoticed.[24] We also found that other manifestation of severe malaria like cerebral malaria (20%), malarial hepatitis (42.5%), severe anemia (20%) were commonly associated with ARF.

As we compared different parameters in patients who died and survived we found that severe anemia, high parasite density, severe thrombocytopenia, leucocytosis, increase blood urea and creatinine, increased serum bilirubin, raised SGOT and SGPT, high APACHE II score, SOFA score and MODS score and lower GCS score were associated with poor outcome. Similarly Kute et al (2012) also found that

mortality in malaria-associated acute kidney injury was associated with higher APACHE II, SOFA, MODS scores and low GSC score [12]. ARF associated with jaundice had high mortality in comparison to non-jaundiced ARF patients [25]. Jaundice is probably associated with toxicity to tubular cells with more risk of development of acute tubular necrosis. Similar observations had also been made by Sahu et al(2010) in severe falciparum malaria [26].

Thanachartwet et al (2013) by using RIFLE criteria demonstrated that the requirement for renal replacement therapy (RRT) and in-hospital mortality in severe *falciparum* malaria was increased significantly with severity of AKI [3]. Basu et al (2011) reported that AKI diagnosed using RIFLE criteria was associated with the requirement for RRT and case fatality rate in patients with tropical acute febrile illnesses such as scrub typhus, falciparum malaria, enteric fever, dengue, and leptospirosis [27]. However, these RIFLE criteria have never been evaluated among a cohort of patients with ARF caused by different *plasmodium species*. In our study, we also evaluated AKI in the study group using the RIFLE criteria and various parameters were assessed with respect to RIFLE category. We observed that higher parasite density, thrombocytopenia, leucocytosis, higher APACHE II score, higher SOFA score, higher MODS score and lower GCS score were significantly associated with more severe AKI. We also found that higher RDW, higher levels of SGOT, SGPT, serum bilirubin, blood urea, serum creatinine and LDH were also related with higher degree of AKI although statistically not significant (Table 7). Therefore we suggest that these parameters should be considered as poor prognostic indicators and should be evaluated meticulously in clinically indicated patients so as to recognize early and manage promptly this life threatening condition.

Conclusion

Acute renal failure (ARF) is emerging as an important serious manifestation of malaria with increasing incidence. Besides that *plasmodium vivax* is increasingly presenting with acute renal failure. Our study suggests that there are certain clinical predictor and prognostic indicators of ARF in malaria. Patients presenting with longer duration of fever, marked tiredness, marked chills, nausea, vomiting, jaundice, decrease urine and altered sensorium are the clinical predictor of ARF in malaria. Severe anemia, High Parasite Density, Severe Thrombocytopenia, Leucocytosis, Increase blood urea and creatinine, Increased serum bilirubin, Raised SGOT and SGPT, high APACHE II score, high SOFA score, high MODS score, low GCS score and high category of RIFLE criteria are the poor prognostic indicators of ARF in malaria. Therefore knowledge and early recognition of these clinical predictors and prognostic indicators may help us in identifying each malaria patients likely to develop ARF or likely to worsen with ARF so early appropriate management may help in better outcome of these patients.

Declaration

Authors Contribution

Designed the study and analyzed the data and their interpreta-tion: BKG and AG. Drafted the manuscript: BKG and SLM. Approved the final version to be published: BKG. Carried out clinical assessment: SLM, RB, HRN and LMS. Evaluated and analyzed laboratory data and their interpretation: AG. All authors read and approved the final manuscript. Guarantors of the paper: BKG and SLM.

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Competing Interest

None declared

Ethical Approval

A prior approval has been taken from the Institutional Ethics Committee to carry out this work, and an informed consent was obtained from the subjects enrolled in this study.

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