STUDY OF RENAL FAILURE IN MALARIA

Girish Pamappa Vakrani[1], Nambakam Tanuja Subramanyam[2], Pawan Kumar Perugu[3]

[1]Assistant Professor, Department of Nephrology, Vydehi Institute of Medical Sciences and Research Center, Bengaluru.
[2]Assistant Professor, Department of General Medicine, Vydehi Institute of Medical Sciences and Research Center, Bengaluru.
[3]Junior Resident, Department of General Medicine, Vydehi Institute of Medical Sciences and Research Center, Bengaluru.

ABSTRACT

Renal failure is a serious complication of malaria, with a mortality of 14 to 33%. In view of the significant morbidity and mortality due to acute renal failure in malaria, there is need to identify patients at an early stage and to intensify care given to reduce morbidity and mortality.

AIMS

- To evaluate the clinical profile of Acute Renal Failure (ARF) in malaria.
- To evaluate the factors associated with adverse outcome, relation of severity of renal impairment on final outcome in patients with ARF due to malaria.

MATERIAL AND METHODS

This study was conducted at a tertiary care hospital over a period of 12 months.

STUDY DESIGN

- Type of study: Prospective Analytical, Observational Study.
- Sample Size: 50 patients admitted to ICU, Kidney Unit, and the Medicine Wards with Malaria and ARF.

Inclusion Criteria

Clinically screened patients with evidence of malarial parasites in the blood smears or by antigen detection with clinical features or biochemical evidence of acute renal failure.

Exclusion Criteria

- Presence of any disease or condition leading to ARF or affecting the outcome of malarial ARF.
- Other causes of Fever, Jaundice and Oliguria, like Leptospirosis, Dengue.

METHODOLOGY

Fifty patients who fulfilled the inclusion criteria were interrogated with regards to the complaints, clinical signs. Blood tests were sent on admission. Details were recorded as per the clinical proforma. The patients were followed until their discharge/death.

RESULTS

Oliguria was present in only 30% of patients. 30% of patients received haemodialysis. The mortality was 12% for severe renal failure. On Univariate analysis, Acidosis and Cerebral malaria were highly significant predictors of mortality. Other significant predictors were Renal failure, Oliguria, Shock, DIC, Hyperparasitemia, Leukocytosis (TLC). On Multivariate analysis, Oliguria, Cerebral malaria, Acidosis, Shock and two or more complications were the independent predictors of mortality.

CONCLUSIONS

- Acute renal failure was an important and life threatening complication of falciparum malaria having a male preponderance.
- Hyperbilirubinemia, Cerebral malaria, Metabolic acidosis, ARDS, DIC and Shock were the complications commonly associated with ARF in malaria.
- Oliguria, Cerebral malaria, Acidosis, Shock, TLC proved to be independent predictors of mortality.

KEYWORDS

Malaria, Renal failure, Oliguria, Hemodialysis.

HOW TO CITE THIS ARTICLE: Vakrani GP, Subramanyam NT, Perugu PK. Study of renal failure in malaria. J Evolution Med Dent Sci 2016;5(1):04-08, DOI: 10.14260/jemds/2016/2

Financial or Other, Competing Interest: None.
Submission 08-12-2015, Peer Review 09-12-2015,
Acceptance 29-12-2015, Published 01-01-2016.
Corresponding Author:
Girish Pamappa Vakrani,
A-29, Vydehi Hospital Staff Quarters,
#82, EPIP Area, Whitefield,
Bengaluru-560066.
E-mail: drvakranis@gmail.com, dr_vakranis@yahoo.co.in
DOI:10.14260/jemds/2016/2

INTRODUCTION

Malaria is caused by four species of the genus Plasmodium namely, Plasmodium vivax, Plasmodium falciparum, Plasmodium malariae and P. ovale. As per World Health Organisation, the major manifestations of severe malaria are cerebral malaria, severe anemia, jaundice, Acute Renal Failure (ARF), Acute Respiratory Distress Syndrome (ARDS), shock, disseminated major bacterial pathogens being isolated and

intravascular coagulation (DIC), convulsions, haemoglobinuria, impaired consciousness.[1] These occur mostly with Plasmodium falciparum malaria. Occurrences of acute renal failure in severe falciparum malaria is quite common in southeast Asia.[2] and Indian subcontinent.[3] Renal failure is a serious complication of malaria, with a reported total mortality of 14 to 33%.[4,5,6]

In view of the significant morbidity and mortality due to acute renal failure in malaria, there is an acute need to identify patients at an early stage and to intensify care given to these patients so that the burden of morbidity and mortality is reduced. This study is undertaken to evaluate the clinical profile and outcome of acute renal failure in malaria, admitted in our institute from January 2012 to December 2012.

MATERIAL AND METHODS

This study was conducted at a tertiary care hospital over a period of 12 months.

AIMS AND OBJECTIVES

- To evaluate the clinical profile of Acute Renal Failure in malaria.
- To evaluate the factors associated with adverse outcome, relation of severity of renal impairment on final outcome in patients with ARF due to malaria.

Study Period

January 2012 to December 2012.

Selection of Cases

Those patients admitted to ICU, kidney unit and the medicine wards in our institute with malaria and ARF were included in the study.

Study Design

- Type of Study: prospective analytical, observational study.
- Sample Size: 50 cases.

Inclusion Criteria

Clinically screened patients aged more than 18 years with evidence of malarial parasites in the blood smears or by antigen detection with clinical features or biochemical evidence of acute renal failure as follows:

1. Fever, nausea/vomitings, oliguria/anuria sometimes polyuria, jaundice, abdominal pain/tenderness, splenomegaly, shock, dyspnoea, altered sensorium, rarely convulsions.
2. Urine output less than 400ml/day despite of rehydration.
3. Serum creatinine more than 2mg/dl.

Exclusion Criteria

- Age less than 18 years.
- Presence of any disease or condition leading to ARF or affecting the outcome of malarial ARF.
- Any abnormalities of kidney on ultrasonography.
- Other causes of fever jaundice and oliguria, like leptospirosis, dengue.

METHODOLOGY

Fifty patients who fulfilled the inclusion criteria were enrolled in the study. Patients who fulfilled the inclusion criteria were thoroughly interrogated with regards to the presenting complaints like fever, jaundice, urine output, swelling of the body, breathlessness, bleeding tendency, altered sensorium, convulsions, etc. Vital parameters like temperature, pulse rate, blood pressure, respiratory rate were recorded. Clinical signs at admission like pallor, icterus, oedema, bleeding manifestations were noted and thorough systemic examination was done. The Glasgow coma score was also calculated. Blood investigations like peripheral smears, complete blood count, urea and creatinine levels, total bilirubin, SGOT, SGPT, blood glucose levels, electrolytes, arterial blood gases, were sent on admission. Parasite index was calculated for patients having positive peripheral smear as the number of parasites present per 100 red cells.

Details of treatment received by the patient before admission (At primary health centres) as well as in our hospital were recorded as per the clinical proforma. The patients were followed until their discharge/death and their outcome was noted as either Discharged (D) or Expired (E).

RESULTS

In our study, 35 (70%) patients had manifestation of severe malaria as per WHO. The observations made in our study were as follows:

1. The age of these 50 patients were over a range from 18 years to 60 years. The mean age of the patients in our study was 32.48±4.35 years.
2. Of these 50 patients, 43 (86%) patients were males.
3. All 50 presented with fever with chills and rigors. The other presenting complaints were vomiting 29 (58%), decreased urine output in 22 (44%), altered sensorium in 18 (36%), yellowness of eyes/dark yellow urine in 15 (30%), Convulsions in 11 (22%), breathlessness in 10 (20%) and bleeding tendencies in 6 (12%).
4. Pallor was the most dominant sign present in 37 (74%), followed by Splenomegaly in 26(52%), Icterus in 21 (42%), pedal edema in 16 (32%), Hepatomegaly in 15 (30%), Low GCS in 12 (24%) and Hepatosplenomegaly in 10 (20%). Bleeding tendency in the form of bleeding gums or hematuria in 6 (12%) and Hypotension in 5 (10%) were rare observations.
5. 47 (94%) patients had their HRP-2 test positive. While only 23 (46%) of these 50 patients had malarial parasites detected on their peripheral smear. In these 23 patients with peripheral smear positive for malaria, 16 (32%) of the patients had only Falciparum in their peripheral smear, Vivax was seen in 05 (10%) and both plasmodium falciparum and vivax in 02 (04%).
6. 34 (68%) patients had normal output i.e. 24 hr. urine output ≥400ml. Anuria was rare and present in only 1 (2%) patient. The mean urine output was 691.0±141.8ml.
7. Renal failure was divided into mild, moderate and severe depending upon the serum creatinine levels. 25 (50%) had mild renal failure, moderate renal failure was seen in 14 (28%) and severe renal failure was noted in 11 (22%).
8. Proteinuria >300mg/day was noted in 20 (40%) patients. Hemoglobinuria was seen in only 07 (14%) cases.
9. Moderate anemia [Hemoglobin: 07-10gm/dl] in 36 (72%), Severe anemia [Hemoglobin <07gm/dl] in 03 (06%). The mean WBC count was 9830.83±1285.5 per mm^3. Leukocytosis with total WBC count >13,000/mm^3 in 08 (16%) and 11000-13000/mm^3 in 09 (18%). The mean platelet count was 1.14±0.25 lakh/mm^3. Thrombocytopenia [Platelet count <1.5 lakh/mm^3] was seen in 37 (74%) of patients, severe thrombocytopenia

[Platelet count <0.5 lakh/mm^3] in 13 (26%). The mean Prolonged Prothrombin time was 14.84±1.03 sec. mildly prolonged prothrombin time [12 to 15 sec] in 33 (66%), Prolonged Prothrombin time [>15 sec] in 16 (32%).

10. The mean S. bilirubin was 2.93±0.61mg/dl. Hyperbilirubinemia [S. bilirubin >3mg/dL] was present in 21 (42%). The mean serum ALT was 53.37±49.63 IU/L. The mean Serum AST was 55.5±49/35 IU/L. Serum ALT [Serum ALT >120 IU/L] was noted in 04 (08%) of cases and elevated serum AST [serum AST >120 IU/L] in 04 (08%) of cases.
11. The mean arterial pH was 7.29±0.02. Arterial pH <7.25 was seen in 15 (30%) of patients, mean plasma Bicarbonate was 17.02±1.81mmol/L. Among these serum bicarbonate <15mmol/L was noted in 14 (28%) of patients.
12. The mean serum Sodium was 133.80±2.61meq/l. Hyponatremia [Sr. Na^+ <135meq/l] was seen in 27 (54%) cases. Hypernatremia [Sr. Na^+ >145meq/l] was uncommon, seen in 02 (04%) cases. The mean serum Potassium was 4.49±0.25meq/dl. In this study hypokalemia [Sr. K^+ <3.5meq/dl] was seen in 03 (06%) patients, while hyperkalemia [Sr. K^+ >5meq/dl] in 08 (16%) patients.
13. Among the factors associated in development of ARF. Hyperbilirubinemia was common, present in 21 (42%) of cases. While DIC, hypotension and hemolysis were rare, being present in 06 (12%), 05 (10%) and 03 (06%) cases respectively.
14. It was noted that 12 (24%) patients received artesunate and 16 (32%) patients received quinine only. While the combination antimalarial drugs artesunate and clindamycin was given to 8 (16%) of patients
15. 15 (30%) of patients received hemodialysis. Rest of the 35 (70%) patients were managed conservatively.
16. Out of the 50 patients, 44 (88%) survived, while the rest of the 06 (12%) of the patients succumbed to the disease. The mean duration of stay for the patients who recovered was 5.66±0.76. Death occurred at a mean time of 4.38±0.57 days (Range 1-6 days) after admission. The overall mortality in our study was 12% (06 patients out of 50 died) mortality was seen in patients with severe renal failure. Mortality in male patients was higher than the female patients, though the difference was statistically not significant.
17. Thus, mean urea, creatinine and serum potassium levels were significantly higher in patients who died as compared to those who survived (Table 1).
18. More than one complication was present in 34 (77%) patients in the survivor group and in 6 (100%) patients in the non-survivor group. Patients who had more than one complication mortality were significantly greater.

On univariate analysis (Table 2), significant predictors of mortality were: Cerebral malaria and Acidosis. At the end of multivariate analysis (Table 3), Oliguria, cerebral malaria, acidosis, DIC, shock and two or more complication were the independent predictors of mortality.

DISCUSSION

Acute Renal Failure (ARF) occurs as a complication of P. Falciparum malaria in 57% to 60%.[7], and the mortality in these cases may be between 14 to 33%.[4,5,6]

Diagnosis of Malaria

In the 23 patients with peripheral smear positive for malaria, Plasmodium falciparum was seen in 16 (92%). Prakash et al (2002) in a study of ninety-four patients of acute renal failure (ARF) complicating malaria over 5 years noted that Plasmodim falciparum and P.vivax were responsible for ARF in 76 (80.9%) and 11 (11.7%) patients respectively.[8]

DIAGNOSIS OF RENAL FAILURE

Serum Creatinine

Majority of patients 25 (50%) had mild renal failure. Mehta et al. (2001) in a study diagnosed ARF on the basis of serum creatinine >1.5mg/dl. They found 24 patients of malarial ARF over a 2 year period. Mild renal failure included serum creatinine <2mg/dl, moderate renal failure included serum creatinine 2-5mg/dl and severe renal failure included serum creatinine >5mg/dl. They noted 75% patients had severe renal failure, 25% had moderate renal failure and none had mild renal failure.[9]

Urine Output

Oliguria was noted in 16 (32%) patients. Mehta et al. (2001) noted 14 (58.33%) patients had non-oliguric ARF.[9] In the present study in the oliguric group the mean serum creatinine value was 5.40mg/dl, while in the non-oliguric group the mean serum creatinine value was 2.80mg/dl. Thus oliguric patients had more renal impairment.

Urine Examination

Proteinuria >300mg/day was noted in 20 (40%) of patients. Mehta et al (2001) noted Proteinuria (2+) in 28.26%, and microscopic haematuria in 21.74% patients.[10] Age distribution of patients: Patients age ranged from 18 to 60 years with average age was 32.48±4.32 years. Manan et al. (2006) studied patients who ranged in age from 16-65 years with a mean 32±12.61 years.[10]

SEX DISTRIBUTION OF STUDY SUBJECT

There was a male preponderance. Manan et al. (2006) in a study noted the male to female ratio was 3.6:1.

Clinical Profile

Symptom profile of study subjects: All 50 cases presented with fever with chills and rigors. Mehta et al. (2001) found the majority (91.66%) presented with fever followed by altered sensorium in 41.66% decreased urine output in 41.66%, convulsions in 8.33%, vomiting was present in 33.33% and loose stools in 12.5% of patients.[9] Thus, most of these finding are consistent with other studies.

Clinical Signs

Pallor was the most dominant sign, present in 37 (74%). Prakash et al. (2002) in a study, noted splenomegaly in 26.0%, hepatomegaly in 10.06% and hypotension in 32% patients.[8]

INVESTIGATIONS

Hematological Profile

Severe anaemia was seen in 3 (6%), Leukocytosis with total WBC count >13.000/mm^3 in 08 (16%), Thrombocytopenia [Platelet count <1.5 lakh/mm^3] in 24(48%) of patients, Prolonged prothrombin time [12-15 sec] in 33 (66%) of patients. Prakash et al. (2002) noted thrombocytopenia

12.76% patients.[8] Naqvi et al. (2003) found moderate reduction in haemoglobin was common.[11] Thrombocytopenia, <150,000/mm^3, was present in 87 patients by Naqvi et al. (2003).

In a study by Wilairatana (1999), it was noted total WBC count >10,000/mm^3 was seen in 60.7% of patients.[12]

Liver function tests: Hyperbilirubinemia was present in 21 (42%). Hyperbilirubinemia was present in 31 (32.97%) patients in a study by Prakash et al. (2002).[8]

Metabolic Acidosis

Metabolic acidosis was noted in 14 (28%) of patients. Manan et al. (2006) in a study found metabolic acidosis in 19.17% patients.[10]

Hypoglycaemia

Hypoglycaemia was noted in 04 (08%) of patients in the present study. Prakash et al. (1996) found hypoglycaemia in 11.5% of patients.[3]

Electrolyte Imbalance

It was noted that hyponatremia was common, seen in 27 (54%) cases. Hyponatremia was found in 57.7% of cases by Prakash et al. (1996).[3]

Complications of severe malaria and risk factors for ARF: Cerebral malaria (GCS <11) was present in 12 (24%). Acidosis was present in 15 (30%) patients, ARDS was present in 9 (18%), Severe anaemia was present in 04 (08%), Hypoglycaemia was present in 4 (8%).

Prakash et al. (2002) in a study of 94 patients of acute renal failure complicating malaria noted that multiple etiologic factors were contributing to the development of ARF and these included: Volume depletion 49 (51%), intravascular hemolysis 37 (39.4%), heavy parasitemia 34 (35%), hyperbilirubinemia 31 (33%), hypotension 29 (30.9%), sepsis 9(9.6%) and DIC 7 (7.4%).[8]

Antimalarial Treatment

We noted that 12 (24%) patients received artesunate and 16 (32%) patients received quinine only. A large randomized comparison of intra venous artesunate and quinine in 1461 patients with multiple complications including ARF by Dondorp et al. (2005) in Asia showed a significant survival benefit with artesunate. Mortality was 22% with quinine as compared with 15% with artesunate, a risk reduction of 34.7%.[13] They found no significant differences in the outcome and complications among the different drug regimens of 112 study patients.[12]

In the present study, it was noted out of 6 patients who died received combination antimalarial drugs. Mortality was 0.03% in patients receiving a single anti-malarial drug and was 23.52% in patients receiving a combination anti-malarial drug. It was noted that patients with severe malaria usually tend to receive combination therapy. This may explain the higher mortality seen in group receiving combination therapy.

Renal Replacement Therapy

15 (30%) of patients received haemodialysis. Mehta et al. (2001) study found 92% cases required dialysis of which 8 required haemodialysis.[9]

Supportive Treatment

Diuretics were given to 20 (40%) of patients. Blood or blood components were given to 25 (50%) of patients. Review by Bagshaw (2007) comparing loop diuretics with control in the management of ARF did not notice any association of diuretic use with reduction in mortality or requirement for renal replacement therapy. However, use of diuretics was associated with shorter duration of renal replacement therapy and increased urine output.[14]

Outcome

The mortality was 12% for severe renal failure. Mehta et al. (2001) in a study from Mumbai diagnosed ARF on the basis of serum creatinine more than 1.5mg/dl. In their study 75% patients had severe renal failure, 25% had moderate and none of them had minor renal failure. They noticed mortality was 29% malarial ARF.[9] The relatively low mortality in the present study may be attributed to the high proportion (50%) of patients with serum creatinine less than 3mg/dl.

Statistical Analysis

Univariate Analysis

On univariate analysis predictors of mortality in the present study were as follows: Highly significant predictors of mortality were: Cerebral malaria, Arterial pH and Plasma bicarbonate ($p<0.001$). Other significant predictors of mortality were: Oliguria, Shock, Disseminated intravascular coagulation, Total leucocyte count, Blood urea and Serum creatinine.

Multivariate Analysis

On multivariate analysis predictors of mortality were as follows: Oliguria, Cerebral malaria, Acidosis, TLC, Shock and presence of two or more complications apart from renal failure were the independent predictors of mortality. According to a study by Manan et al. (2006), Serum creatinine Leukocytosis, Hyperbilirubinemia, Cerebral malaria, DIC, Metabolic acidosis were the main causes of mortality in their patients.[10]

CONCLUSIONS

- Acute renal failure was an important and life threatening complication of falciparum malaria having a male preponderance.
- Non-oliguric renal failure was the most common pattern of renal failure.
- Other clinical manifestations being altered sensorium, jaundice, breathlessness and bleeding tendency.
- Hyperbilirubinemia, Cerebral malaria, Metabolic acidosis, ARDS, DIC and Shock were the complications commonly associated with ARF in malaria.
- Oliguria, Cerebral malaria, Acidosis, TLC, Shock and two or more complications proving to be independent predictors of mortality.

Limitations of the Study

- In the present study, the sample size was small.
- Majority of the patients had non-oliguric and mild-to-moderate renal failure. This could be responsible for the relatively low mortality.

- We evaluated only those patients who are admitted, so we missed those patients who died before reaching the hospital.
- It was not possible to evaluate the antimalarial treatment given to the patients before they were admitted in our hospital.

Sr. No.	Parameter	Survivors (n=44)	Non-Survivors (n=06)	p-value
1	Mean Blood urea (mg/dl)	94.5±22.37	175.83±107.09	0.0021*
2	Mean Serum Creatinine (mg/dl)	3.43±0.65	7.13±3.10	0.0046*
3	Mean Serum sodium (meq/dl)	134.11±2.87	131.55±8.05	0.3149
4	Mean Serum potassium (meq/dl)	4.35±0.21	5.48±1.12	0.0119

Table 1: Table showing RFT and mortality in Study Subjects (n=50)

Parameter	P-value
Oliguria	0.014
Mean Serum Creatinine (mg/dl)	0.0037
Mean Blood Urea (mg/dl)	0.01196
Mean WBC count (x103/L)	0.00553
Cerebral malaria	< 0.001
Acidosis	< 0.001
DIC	0.0048
Shock	0.01
Two or more complications apart from renal failure	0.002

Table 2: Showing Univariate Analysis of factors predicting mortality

Parameter	P-value
Oliguria	0.0012
Mean Serum Creatinine (mg/dl)	0.234
Mean Blood Urea (mg/dl)	0.0116
Mean WBC count (x103/L)	0.0049
Cerebral malaria	< 0.001
Acidosis	< 0.001
DIC	0.0063
Shock	0.0032
Two or more complications apart from renal failure	<0.001

Table 3: Showing Multivariate Analysis of factors predicting mortality

BIBLIOGRAPHY

1. World Health Organisation. Severe falciparum malaria. Trans R Soc Trop Med Hyg 2000;94:S1-S90.
2. Sitprija V. Nephrology forum. Nephropathy in falciparum malaria. Kidney int 1988;34:966.
3. Prakash J, Gupta A, Kumar O, Rout SB, Malhotra V and Srivastava PK. Acute renal failure in falciparum malaria-increasing prevalence in some area of India- A need for awareness. Nephrol dial Transplant 1996;11(12:2414–2416).
4. Naqvi R, Ahmad E, Akhtar F, et al. Predictors of outcome in malarial renal failure. Renal fail 1996;18(4):685-688.
5. Weber MW, Boker K, Horstmann RD, et al. Renal failure is a common complication in non-immune Europeans with Plasmodium falciparum malaria. Trop Med Parasitol 1991;42(2):115-118.
6. William J Stone, MD; James E Hanchett; M A J James H; et al. Acute renal insufficiency due to Falciparum malaria. Arch Intern Med 1972;129(4):620-628.
7. Barsoum RS. Malaria acute renal failure. J Am Soc Nephrol 2000;11:2147-54.
8. Prakash J, Singh AK, Gujrati S, et al. Acute renal failure in malaria: Changing trends.
   Indian J Nephrol 2002;12:113-117.
9. Mehtha KS, Halankar AR, Makwana PD, et al. Severe acute renal failure in malaria. J Postgrad Med 2001;47:24-26.
10. Abdul Manan J, Ali H, Lal M. Acute renal failure associated with malaria. J Ayub Med Coll Abbottabad 2006;18:47-52.
11. Naqvi R, Ahmad E, Akhtar F, et al. Outcome in severe acute renal failure associated with malaria. Nephrol Dial Transplant 2003;18:1820-3.
12. Wilairatana P, Westerlund EK, Aursudkij B, Vannapan S, Krudsood S, Viriyavejakul P, et al. Treatment of malaria acute renal failure by hemodialysis. Am J Trop Med Hyg 1999;60:233-7.
13. Dondrop A, Nosten F, Stepnieswaka K, et al. Artesunate versus Quinine for treatment of severe falciparum malaria: a randomized trial. Lancet 2005;366:717-25.
14. Bagshaw SM, Delaney A, Haase M, et al. Loop diuretics in the management of acute renal failure: a systematic review and meta-analysis. Crit Care Resusc 2007;9:60-8.