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# Acute renal failure in severe falciparum malaria patients in an intensive care unit in Malaysia

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**ABSTRACT** *Objectives:* Identify the risk factors and the clinical impact of ARF in patients with severe falciparum malaria.

*Method:* Intensive care unit cases of severe falciparum malaria of Sarawak General Hospital were analysed.

*Results:* Out of 40 cases of severe falciparum malaria, 19 developed ARF. Patients with ARF were older (p=0·030), had higher AST (p=0·014), higher unconjugated bilirubin (p=0·041), and lower globulin (p=0·015). Aspartate transaminase level positively correlated with creatinine and urea level (log AST and urea: r=0·464, p=0·004; log AST and log creatinine: r=0·430, p=0·008); while unconjugated bilirubin level positively correlated with creatinine level with geometric transformation (r=0·402, p=0·020). Patients with ARF have higher mortality (p=0·004), and more failing organs (p = 0·0003). Patients with ARF that died had a higher number of organs failing compared with those that survived (p=0·043). Among patients with total parasite count of >300,000/μL, those patients treated with dialysis, haemofiltration or exchange transfusion developed less organ failure (p=0·050). Logistic regression with adjustment for age and malarial complications identified ARF to be the major predictor of mortality.

*Conclusions:* 1) Patients with severe falciparum malaria who developed ARF have higher rate of haemolysis, more organs failing and higher mortality rate. 2) Dialysis, haemofiltration or exchange transfusion may reduced the rate of organ failure among patients with parasite count >300000/μL.

**KEYWORDS** Acute renal failure, clinical outcome, severe falciparum malaria,

**LIST OF ABBREVIATIONS** Acute lung injury (ALI), acute renal failure (ARF), acute respiratory distress syndrome (ARDS) aspartate transaminase (AST), blood pressure (BP), continuous veno-venous haemofiltration (CVVH), disseminated intravascular coagulopathy (DIVC), daily percentage of dropping parasite count (DPDPC), haemodialysis (HD), intensive care unit (ICU), peritoneal dialysis (PD), *Plasmodium vivax* (*P. vivax*), *Plasmodium falciparum* (*P. falciparum*), *Plasmodium knowlesi* (*P. knowlesi*), statistical package for the social sciences (SPSS)

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## INTRODUCTION

Acute renal failure[1,2] is one of the major complications of malaria. This study aims to identify the risk factors and the clinical impact of ARF in patients with severe falciparum malaria, and to assess the outcome of clinical intervention.

## METHODS

Sarawak is a low malaria endemic area with around 2,700 cases reported each year. *P. vivax* infection contributed 67·4% of cases, *P. falciparum* 19·6%, *P. knowlesi* 11·4% and mixed infection 1·5%. Sarawak General Hospital has about 120 malarial admissions per year and 54·3% are *P. vivax*, 42·8% *P. falciparum*, 0·7% *P. knowlesi* and 2·3% are mixed infection.[2]

Cases of severe falciparum malaria admitted into our ICU from 1996 to 2004 were analysed retrospectively. Severe malaria is defined as a complicated falciparum malaria infection following WHO criteria.[3,4] Two ICU cases of *P. falciparum* infection were excluded as they did not fulfill the criteria for severe falciparum malaria. Twenty-two (55%) of the 40 cases were referred by a district hospital; eight (20%) were referred by outpatient clinics and ten (25%) presented directly to the hospital.

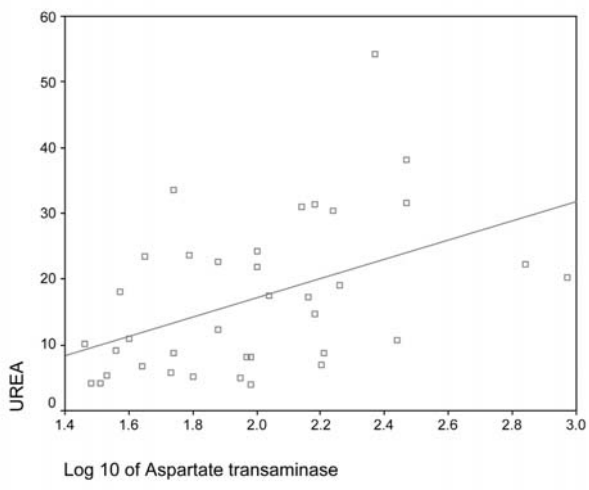


**FIGURE 1** Blood urea vs Log10 AST during admission in severe falciparum malaria. (r=0·464, p=0·004.)

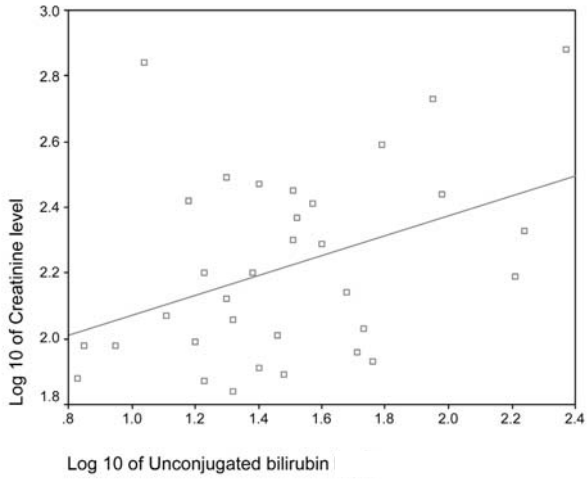


**FIGURE 3** Log10 creatinine vs Log10 unconjugated bilirubin level during admission in severe falciparum malaria. (r=0·402, p=0·020.)

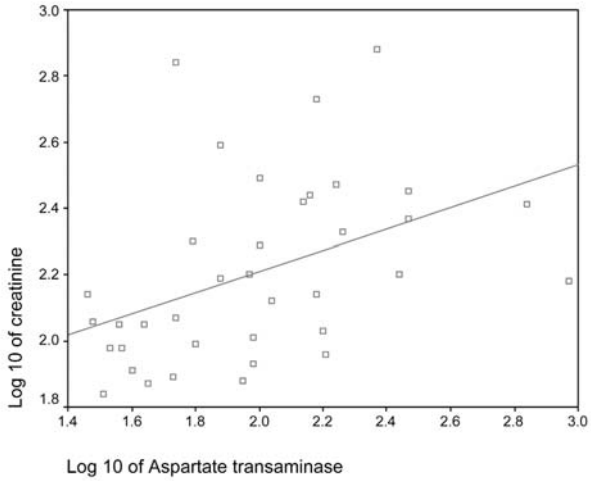


**FIGURE 2** Log10 creatinine vs Log10 AST during admission in severe falciparum malaria. (r=0·430, p=0·008.)

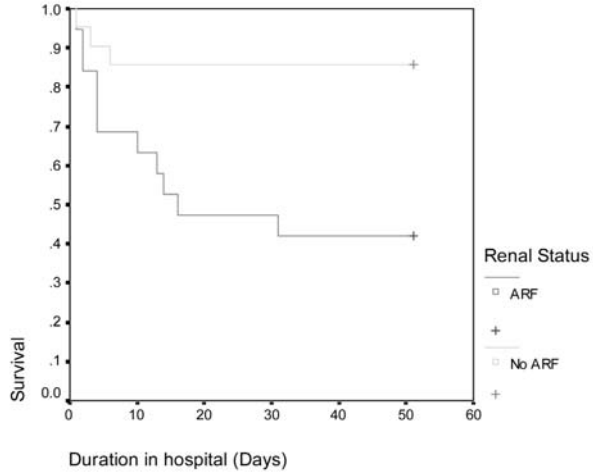


**FIGURE 4** Kaplan Meier survival curve showing patients grouped by renal status to compare survival between patients with and without ARF. (p=0·014).

### *Definition*

Acute renal failure[1,3] was defined in adults as urine output of less than 400 ml in 24 hours and serum creatinine of more than 265 µmol/L. Disseminated intravascular coagulopathy is defined as a platelet concentration of less than 20,000/µL, and a prothrombin time of more than twice the control, and a partial thromboplastin time more than 1·5 times the control, with or without other supporting measures, e.g. fibrinogen level, D-dimer and fibrin degradation product level.

Cerebral malaria is defined as deep coma not attributable to any other cause in patients with *P. falciparum* asexual parasitemia, i.e. the patient is unable to be aroused (>30 minutes if after convulsion), and unable to make a localising response.[3]

Acute respiratory distress syndrome and ALI were diagnosed based on the timing (acute onset), refractory hypoxaemia ($PaO_2/F_iO_2$ <200 mmHg for ARDS. $PaO_2/F_iO_2$ ≥ 200 mmHg but <300 mmHg for ALI) and typical chest radiography (bilateral lungs infiltrates).[5] We did not perform pulmonary capillary wedge pressure measurement in this series. Acute pulmonary oedema was diagnosed on clinical findings, chest radiography and the appropriate clinical circumstances (underlying aetiology).[6] It may be due to ARF, acute heart failure or overhydration.

Blood parasite count on thick film was calculated based on a WHO established method, i.e. converting the parasite count per µL in relation to the leukocyte count based on a standard figure of 8,000 leukocytes per µL of blood.[7]

We define DPDPC[2,8] as:

$$DPDPC = \left(1 - \text{day}\sqrt{\frac{\text{lower total parasite count}}{\text{highest total parasite count}}}\right) \times 100\%$$

Where the lower total count is defined as the first total parasite count once the asexual parasite count has dropped below 10,000/μL or, if not achievable, the last count before the patient died.

### *Statistical methodology*

The data were analysed using Microsoft excel and SPSS.[9] Demographic features, presenting illness, management and clinical course were studied to identify the risk factors for ARF, as well as the clinical impact of ARF and clinical intervention, in terms of morbidity and mortality.

The Kolmogorov-Smirnov test was used first to determine whether the data has a normal distribution. Logarithm transformation was performed to achieve a normal distribution in some data. Parametric test (e.g. student t-test) was used for comparison of data with normal distributions whereas non-parametric test (e.g. Mann-Whitney U test) were used in others.

Multivariate logistic regression was used to determine whether malarial complications remained significant after adjustment for age. Kaplan-Meier estimates were used to illustrate trends of survival and Cox-regression was used to verify the significance of the relationship between renal status and mortality trends.

## RESULTS

Out of 40 patients, 19 (47·5%) developed AR (see Table 1).

Patients with ARF were older, and had higher AST, and unconjugated bilirubin phosphate, and lower globulin.

Aspartate transaminase level correlated positively with urea (see Figure 1). Aspartate transaminase level also correlated positively with creatinine (see Figure 2). Unconjugated bilirubin correlated positively with creatinine (see Figure 3).

There were no significant differences in time of initiating anti-malarial treatment (both medians one day after admission), or in respect of the highest total parasite count and DPDPC[2,8] (see Table 2).

Patients with ARF had more severe uraemia and metabolic acidosis,, and also had more organ failure (see Table 3).

Higher mortality was observed among ARF patients (see Table 4). However, there were no significant differences in terms of cerebral malaria, ARDS or disseminated intravascular coagulopathy.

Hospital and ICU stays are longer in ARF patients (see Table 5).

In ARF patients, fatal cases have a higher number of failing organs in comparison to surviving cases (p=0·043).

Out of the 19 patients with ARF, 11 were treated with dialysis: 3 HD; 3 PD; 2 both HD and PD, and 3 CVVH.

Because of the high total parasite count of >300,000/μL, one non-ARF patient underwent 'prophylactic' CVVH with targeted plasma clearance of 1,100 ml/hour, while another had exchange transfusion. Both recovered without organ failure during admission.

Continuous haemofiltration was performed in four patients, with targeted plasma clearance ranging from 980 to 1,450 ml/hour.

Ten patients with a total parasite count of >300,000/μL developed less organ failure when treated with dialysis, heamo-filtration or exchange transfusion, with a median of one organ failing, in comparison to a median of three organs failing among those who have not undergone such treatment (p=0·050).

Logistic regression showed that ARF is the major mortality predictor among the complications of severe falciparum malaria, second only to cerebral malaria (see Table 6).

Figure 4 demonstrates lower survival severe falciparum malaria patients with ARF.

## DISCUSSION

Acute renal failure is one of the major organ complications of severe falciparum malaria and is associated with high morbidity and mortality despite renal replacement therapy. Forty-seven per cent of our patients with severe falciparum malaria developed ARF compared to 30·2% (91/301) in the series of Krishnan.[10]

Risk factors of ARF have been postulated to be high parasitaemia, haemolysis, dehydration[11] and rhabmyolysis.[12] In our study, ARF occured more frequently in older patients. Haemolysis is a prominent feature in ARF patients, as evidenced by high AST and high unconjugated bilirubin although anaemia on presentation was not significantly different among ARF patients.[13,14] Unfortunately, most patients did not have lactate dehydrogenase to support further the relationship of haemolysis to ARF.

Rhabdomyolysis is another possible cause of ARF. However, most patients did not have severe myalgia and thus the serum creatine phosphokinase and myoglobinuria were not included in their investigations.

High phosphate can be explained by both haemolysis and reduced renal excretion of phosphate in ARF patients. Lower globulin is an unexplained feature in our ARF patients and needs to be verified by larger patient data. The immunological response of patients should be studied as another possible risk factor.

**TABLE 1** Mean values for clinical features and laboratory measurements on admission in severe falciparum malaria with and without ARF.

| Clinical features | Unit | ARF | Non-ARF | p value |
|---|---|---|---|---|
| Number of patients | | 19 | 21 | |
| Age | Year | 48·0 | 36·7 | 0·030 |
| Onset* | Day | 6 | 6 | |
| Pulse rate | /min | 96 | 96 | |
| Systolic BP | mHg | 111 | 62 | 0·252 |
| Diastolic BP | mmHg | 102 | 59 | 0·244 |
| Urine output on admission day | ml/hour | 66 | 85 | 0·294 |
| Haemoglobin | g/dL | 9·7 | 9·8 | 0·857 |
| Total white blood cell | /μL | 8,058 | 6,657 | 0·190 |
| Platelet* | /μL | 32,599 | 29,806 | 0·703 |
| Prothrombin time | second | 17 | 15 | 0·265 |
| Partial thromboplastin time | second | 46 | 41 | 0·419 |
| Fibrinogen level | mg/dL | 301 | 287 | 0·895 |
| AST* | U/L | 140 | 72 | 0·014 |
| ALT* | U/L | 63 | 44 | 0·133 |
| Unconjugated bilirubin* | μmol/L | 45 | 23 | 0·041 |
| Conjugated bilirubin* | μmol/L | 64 | 43 | 0·313 |
| Albumin | g/L | 24 | 23 | 0·786 |
| Globulin | g/L | 26 | 33 | 0·015 |
| Corrected Calcium** | mmol/L | 2·21 | 2·28 | 0·231 |
| Phosphate | mmol/L | 1·56 | 0·86 | 0·043 |
| Sodium | mmol/L | 129 | 131 | 0·355 |
| Potassium | mmol/L | 4·2 | 4·2 | 0·965 |
| Blood Urea | mmol/L | 22·6 | 13·3 | 0·010 |
| Creatinine* | μmol/L | 228 | 120 | 0·001 |

*Geometric mean was used.

** Corrected calcium = (40 g/L – [plasma albumin]) × 0.02 + [serum calcium] in mmol/L

Not all ARF patients are dialysed, as they may die before dialysis. Fifty-seven point nine percent (11/19) of our patients were dialysed whereas Krishnan reported 36·3% (33/91). Some ARF patients passed spontaneously into the polyuric phase of ARF without needing dialysis. Thus, the threshold for dialysis is dependent on the clinical condition of the patients, and the choice of dialysis modalities depends on available facility.

Acute renal failure predicts high mortality. In our series, 57·9% of such patients (11/19) died. Acute renal failure was identified as a major predictor of mortality among the complications of severe falciparum malaria, second only to cerebral malaria in our observational study. Early dialysis has been suggested as one way to reduce the complications of severe falciparum malaria.[15,16]

In our study, renal replacement therapy seemed particularly beneficial for patients with high parasitaemia of >300,000/ul, resulting in a fewer number of organs failing. Prophylactic continuous haemofiltration or exchange transfusion, by removing toxic metabolites in acute haemolysis associated with malaria infection and its treatment,[17] may reduce the number of organs failing. Only four of the patients in this study have undergone continuous haemofiltration and further studies are needed to confirm its potential benefits.

**TABLE 2** Parasite counts of severe falciparum malaria in ARF and non-ARF patients.

| Parasite counts | Unit | Mean ARF | Mean Non-ARF | p value |
|---|---|---|---|---|
| Highest total parasite count | /µL | 195,411 | 167,875 | 0·507 |
| DPDPC | | 0·846 | 0·788 | 0·371 |

**TABLE 3** Arterial metabolic acidosis findings and organ failures in ARF and non-ARF patients

| Parameters | Mean ARF | Mean Non-ARF | p value |
|---|---|---|---|
| Arterial pH | 7·25 | 7·35 | 0·175 |
| Arterial base excess | -12·4 | -8·3 | 0·124 |
| Number of organs failed* | 3 | 1 | 0·0003 |

*Median is measured and p-value was derived with Mann-Whitney U test.

**TABLE 4** Survival Rate in ARF and non-ARF patients.

| | Number of patients ARF | Non-ARF | Total |
|---|---|---|---|
| Fatal | 11 (57·9%) | 3 (14·3%) | 14 (35%) |
| Survived | 8 | 18 | 16 |
| Total | 19 | 21 | 40 |

Chi Square, p= 0·004

**TABLE 5** Hospital and ICU stay in ARF and non-ARF surviving patients.

| Duration (Days) | Mean ARF | Mean Non-ARF | p-value* |
|---|---|---|---|
| Hospital stay | 18 | 14 | 0·375 |
| ICU Stay | 8 | 6 | 0·176 |

*t-test

**TABLE 6** Malarial complications and the odds ratio of a fatal outcome after adjustment for age.

| Complications | Number of patients | Odds ratio | 95% Confidence interval | p-value |
|---|---|---|---|---|
| ARF | 19 | 20·1 | 1·95–225 | 0·012 |
| Cerebral malaria | 10 | 35·1 | 2·62–470 | 0·007 |
| DIVC | 13 | 6·86 | 0·684–68·8 | 0·102 |
| ARDS | 15 | 1·85 | 0·253–13·5 | 0·546 |

Acute renal failure could be part of the multi-organ failure syndrome. This would explain the observation of a higher number of failing organs in severe falciparum malaria patients with ARF in comparison to other patients.

Multivariate analysis demonstrated that both ARF and cerebral malaria independently correlated with mortality in severe falciparum malaria. Thus the prevention and management of these two complications should be thoroughly studied in order to improve survival.

Finally, this study demonstrates that ARF is a common major complication of severe falciparum malaria with high mortality rate, possibly caused by haemolysis, and should be managed promptly. High parasitaemia >300,000/µL may be another indication for early renal replacement therapy.

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