

**SEVERE FALCIPARUM MALARIA PATIENTS TRANSFERRED "LATE" TO A HIGH LEVEL ICU IN INDIA REPRESENTS A DIFFICULT RESEARCH CAPTURE POINT TO COMMENT ON PREDICTORS OF MORTALITY AND RELATED ORGAN DYSFUNCTION**

Dear Sir,

We read with interest the study by Sahu and associates,<sup>(1)</sup> whose primary aim was to examine the association of organ dysfunction with intensive care unit (ICU) mortality in patients with severe falciparum malaria who attended the Kalinga Hospital, Bhubaneswar, India over a ten-year period. Specifically, the authors reported a 35.4% incidence of ICU mortality. Mortality was associated with a higher prevalence of renal failure with or without liver dysfunction and the need for ventilator support.<sup>(1)</sup>

Overall, this is an interesting study.<sup>(1)</sup> However, the inability to determine the prior complete medical and pathology history of many patients transferred to the ICU makes the interpretation of the results and outcomes difficult. The additional discussion points comparing mortality results with critical reports of epidemiological field studies may be limited due to the way the data was captured. Potential problems emerge when defining a select patient population with organ dysfunction subtypes that would be common to a high level ICU. In particular, this relates to the suggestion of case load "stability" over a ten-year period. This latter aspect of the study likely strayed away from the authors' primary aim, which was to determine the association between individual malaria organ complications and related mortality in an ICU. We discuss these study issues in the context of organ dysfunction in the ICU.

Firstly, we observed that the ICU study described by Sahu et al<sup>(1)</sup> was carried out in a high-dependency level three private hospital unit, and would therefore provide best practice and supportive therapy outcomes such as haemodialysis. On the other hand, a significant number of patients with renal failure would have been referred to the unit because of the need for intensive support. Therefore, the study inadvertently biases a high organ dysfunction sub-population. The outcomes would also depend in part on the treatments available and the sample sizes for individual organ dysfunction clusters. For example, facilities for haemofiltration are seldom available in most rural hospitals, or to the poor in India. Although peritoneal dialysis is an alternative method that is available to a greater number of patients across Indian hospitals, this treatment is only half as effective as haemodialysis at reducing acidosis and serum creatinine concentration levels. In addition, peritoneal dialysis is associated with significantly higher mortality when compared to haemodialysis.<sup>(2-4)</sup>

Secondly, the issue of patient transfer from a low-intensity medical setting to the Kalinga Hospital ICU is not a trivial one. The time taken to present at the Kalinga Hospital ICU as a result of stay in another ICU or general hospital ward was likely to have been considerable given that parasite blood films were negative in the majority of patients. Hypothetically, this raises the possibility that significantly reduced or rapid clearance of blood parasite load may have increased the need for renal support and the development of organ dysfunction,<sup>(1,5)</sup> although patients with and without positive blood films were not stratified on this basis in the study.<sup>(1)</sup> On the other hand, it is well known that patients who present with acute renal failure have a higher parasite load.<sup>(6,7)</sup> For example, hypercatabolic acute renal failure in cerebral malaria is associated with heavy parasitaemia and hyperbilirubinaemia.<sup>(6)</sup>

Renal failure in cerebral malaria likely reflects a longer duration of illness before referral or treatment.<sup>(4)</sup> The early management of acute renal failure does have a significant impact on outcomes. For example, the Centre for severe cases of malaria for South Vietnam, a specialist team, has managed malaria-associated renal failure with peritoneal dialysis, and the mortality rate has fallen from 75% (78 out of 104) to 26% (27 out of 104).<sup>(3)</sup>

Thirdly, the sample sizes for individual organ involvement or combinational groupings (range 4–42) were small and likely lacked significant statistical power. Although 44.5% of the overall patient sample presented with acute renal failure, only 1.3% of patients presented with renal failure as the sole organ system affected.<sup>(1)</sup> This important finding shows that renal failure in this ICU group was associated with other organ system failures.<sup>(1)</sup> If we were to exclude patients with no organ failure from the study, the number of patients presenting with acute renal failure would be greater than 65%. It is interesting that cerebral involvement with renal failure or liver dysfunction carried a 50%–60% mortality rate, but when combined with all three organ dysfunctions (cerebral, liver and renal), there was a 20%–30% reduction in mortality, possibly due to chance.<sup>(1)</sup>

Finally, it is not surprising that organ dysfunction patterns for individual patients were stable over two five-year analysis periods in Sahu et al's study.<sup>(1)</sup> We understand why the authors have carried out a comparison of two five-year cohort periods; the emerging literature highlights increasing peripheral organ dysfunction with decreasing rates of cerebral involvement. However, Sahu and associates could not contribute to this debate as they had a select sub-sample population, where the rate of renal failure would be expected to be high because the patients either presented very late to their ICU unit, or represented a high-risk organ dysfunction cohort. Additionally, this component of the study design does not address the primary aim of determining the association between individual and combinational organ complications with severe malaria-related ICU mortality.

In summary, the authors were correct in reflecting on an emerging concept for increasing numbers of severe malarial patients presenting with acute renal failure in relation to epidemiological case studies.<sup>(7)</sup> Renal injury is considered to be quite common in Southeast Asia and in the Indian subcontinent, where the intensity of malaria transmission is usually low with occasional microfoci of intense transmission.<sup>(7)</sup> The authors also presented an interesting patient sub-sample, where the blood parasite levels were low or absent. However, we feel that it would be difficult to compare the mortality rates and provide comparisons with the cited mortality rates of 10%–25% in large field studies.<sup>(2)</sup> In particular, the patient mortality rate in broader fields or ICU studies is likely to be diluted as a result of the larger number of patients with no organ dysfunction, and/or as a result of partial immunity. One would expect a high-dependency ICU unit to present with more complex cases of multi-organ dysfunction.

Yours sincerely,

Craig S McLachlan

Colman B Taylor

Yang Li

Lynsey Willenberg

Slade Matthews

Parisa Glass

John Myburgh

The George Institute for Global Health Australia  
Division of Critical Care  
Level 7  
341 George Street  
Sydney  
New South Wales 2000  
Australia  
Email: reperfusion@hotmail.com

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