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Laboratory markers of disease severity in *Plasmodium knowlesi* infection: a case control study

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Abstract

Background: *Plasmodium knowlesi* malaria causes severe disease in up to 10% of cases in Malaysian Borneo and has a mortality rate of 1 - 2%. However, laboratory markers with the ability to identify patients at risk of developing complications have not yet been assessed as they have for other species of Plasmodium.

Methods: A case control study was undertaken in two hospitals in Sarikei and Sibu, Malaysian Borneo. One hundred and ten patients with uncomplicated (n = 93) and severe (n = 17) *P. knowlesi* malaria were studied. Standardized pigment-containing neutrophil (PCN) count, parasite density and platelet counts were determined and analysed by logistic regression and receiver operating characteristic (ROC) analysis.

Results: The PCN count was strongly associated with risk of disease severity. Patients with high parasite density (≥ 35,000/μl) or with thrombocytopaenia (≤ 45,000/μl) were also more likely to develop complications (odds ratio (OR) = 9.93 and OR = 5.27, respectively). The PCN count yielded the highest area under the ROC curve (AUC) estimate among all markers of severity (AUC = 0.8561, 95% confidence interval: 0.7328, 0.9794). However, the difference between all parameter AUC estimates was not statistically significant (Wald test, p = 0.73).

Conclusion: Counting PCN is labour-intensive and not superior in predicting severity over parasitaemia and platelet counts. Parasite and platelet counts are simpler tests with an acceptable degree of precision. Any adult patient diagnosed with *P. knowlesi* malaria and having a parasite count ≥35,000/μl or ≥1% or a platelet count ≤45,000/μl can be regarded at risk of developing complications and should be managed according to current WHO guidelines for the treatment of severe malaria.

Keywords: Plasmodium knowlesi, Severity markers, Malaria pigment, Parasitaemia, Platelet count

Background

Human infection with *Plasmodium knowlesi* was thought to be a rare event until an unexpected high incidence of cases was revealed in the Kapit division of Sarawak, Malaysian Borneo in 2004 [1]. Subsequent reports of mixed and mono-infections with *P. knowlesi* from other locations in Sarawak and Sabah, Malaysian Borneo [2], and also from Vietnam, Myanmar, Thailand and the Philippines show a much wider distribution than initially presumed [3-7]. A clinical cohort study on adult patients demonstrated a severity rate of up to 10% and a case fatality rate about 2% [8]. Typical complications include respiratory distress, jaundice and acute renal failure which are features of multiple organ failure also seen in adult *Plasmodium falciparum* infections [9]. In contrast, coma does not appear to be a presenting feature of *P. knowlesi* malaria.

Despite a relatively high rate of complications, markers for identifying *P. knowlesi* malaria patients at risk of severe disease have not been properly assessed. However, higher peripheral blood parasitemia and lower platelet counts are proposed as markers of severity but precise cut-offs are not available [8]. The malaria pigment

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