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Case Report

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A RETROSPECTIVE STUDY ON THE INCIDENCE AND OUTCOMES OF ACUTE KIDNEY INJURY AMONG PATIENTS DIAGNOSED WITH MALARIA INFECTION IN SABAH – A TERTIARY CENTRE EXPERIENCE

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ABSTRACT

Introduction: Malaria infection is frequently complicated with acute kidney injury (AKI). Malaysia has an unique epidemiology – its malaria infections are primarily caused by the simian parasite *Plasmodium knowlesi*. Data is lacking on the incidence of AKI in *P. knowlesi* infection. Previous studies have suggested that *P. knowlesi* is associated with more severe features compared to *P. falciparum*.

Methods: We conducted a one-year retrospective cohort study to assess the incidence and outcomes of AKI among patients admitted for malaria infection at a state tertiary hospital.

Results: A total of 173 admissions for malaria infection was reported in Queen Elizabeth Hospital, Sabah in 2018. We excluded 53 cases from final analysis as clinical notes were unavailable. *Plasmodium knowlesi* infection was the organism reported in 97.5%. 19.2% (23/120) were classified as severe malaria. 31.7% (38/120) developed AKI as per KDIGO criteria. All incidences of acute kidney injury occurred within 48 hours of admission. After ruling out other causes, they were all attributed to be secondary to malaria infection. Among those with AKI, majority (50%) were Stage 1, 29% were Stage 2, while 21% had stage 3 acute kidney injury. 7.8% required temporary haemodialysis. Renal function normalised in 81.6% of AKI patients upon discharge. At 3 months followup, 13% of AKI patients had persistent renal impairment, with eGFR ranging from 44.2 – 51.9ml/min/1.73m2. Multivariate analysis showed that age more than 50 years old (OR 3.25; CI 1.37, 7.73; p=0.008), and high total bilirubin count (OR 5.6; CI 1.73, 18.12, p=0.004) were associated with the development of AKI.

Conclusion: AKI is common in malaria secondary to *Plasmodium knowlesi* infection. 13% of patients with AKI had persistent renal impairment at 3 months followup.

Keywords: *Malaria, Acute Kidney Injury, Plasmodium knowlesi*

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INTRODUCTION

The World Health Organisation (WHO) estimated that in 2016, 216 million cases of malaria occurred worldwide, among which 7% occurred in the South-East Asia region. This amounted to 15 million cases yearly (1). Malaria can be caused by any of the five *Plasmodium* species, namely, *Plasmodium falciparum, Plasmodium ovale, Plasmodium malariae, Plasmodium vivax*, and *Plasmodium knowlesi.*

Malaysia has an unique epidemiology – its malaria infections are primarily caused by the simian parasite *Plasmodium knowlesi* (2). This is not reported in other localities. Previous studies have suggested that *P. knowlesi* infection is associated with more severe features compared to *P. falciparum* infection (3).

Acute kidney injury (AKI) is a well-documented complication of malaria infection and it is associated with a higher case fatality rate (4,5). Globally reported incidences of AKI in malaria vary greatly, from 8% to 17.6% (6,7). In Southeast Asia, AKI is one of the most common complication in adults with *P. falciparum* malaria (8). A prospective study in west Pahang, Malaysia, has shown that malaria accounted for 3.3% of AKI in tropical acute febrile illness (9). A single centre report by a local tertiary hospital demonstrated AKI in 17.1% of patients diagnosed with malaria, among which 7.7% required dialysis (10).

There is a dearth of data on the incidence of AKI among *P. knowlesi* infection, as well as their long-term renal outcomes.

We reviewed all cases of malarial infection admitted to Queen Elizabeth Hospital from 1st January 2018 to 31st December 2018. We aim to assess the incidence, severity, and outcomes of AKI, as well as to identify any associations between sociodemographic or clinical factors and the occurrence of AKI.

MATERIALS AND METHODS

Queen Elizabeth Hospital (QEH) is an 800 bedded, tertiary care hospital located at the Malaysian state of Sabah, which serves a population of 3.9 million (11). As the main referral hospital in the region, it is funded by the Ministry of Health, and is equipped to provide intensive care service, renal replacement therapy services, and subspecialty consultations. The Malaysian Prevention and Control of Infectious Disease Act 1998 mandates notifying and reporting of all cases of malarial infections upon diagnosis. Upon research and ethical approval, the identifying particulars of all patients diagnosed with malaria infection and admitted to Hospital Queen Elizabeth during the study period (1st January 2018 to 31st December 2018) were retrieved from the Sabah State Health Department.

In the year 2018, QEH reported a total of 173 cases of malarial infection. They were all hospitalised, as per local protocol. Patient's clinical features upon initial presentation to any healthcare facility, blood investigations, and in-hospital ward allocation and progress were recorded. We excluded patients who were less than 18 years old, patients on regular renal replacement therapy and patients with history of renal transplant. This study was approved by the Malaysian Medical Research Ethics Committee (MREC).

DEFINITIONS

1. Acute kidney injury (AKI)

AKI is an acute reduction in kidney function, diagnosed via changes in serum creatinine and/or urine output. It is defined as a rise of serum creatinine of equal or more than 26.5μmol/L within 48 hours, or an increase in serum creatinine of equal or more than 1.5 times of baseline level; or urine volume of less than 0.5ml/kg/hour for 6 hours. The increase of serum creatinine from baseline must occur within prior 7 days(12). We classify severity of AKI based on the KDIGO classification (12). Patients with AKI will also be sub-classified into whether renal replacement therapy was required during the hospital stay.

The diagnosis of AKI requires the demonstration of rising serum creatinine trend. Since patients who present with an abnormal serum creatinine may not have a known baseline serum creatinine, a diagnosis and staging of AKI based on change of creatinine from baseline poses a limitation. We adopted the method described by the Acute Dialysis Quality Initiative (ADQI) group (13), whereby in patients without a baseline serum creatinine level, a normal premorbid renal function is assumed (GFR: 75ml/min/1.73m^2). The baseline creatinine level is then back calculated using the Modification of Diet in Renal Disease (MDRD) formula. This method has been used in previous studies (6).

In patients with confirmed AKI, serial creatinine taken in the ward would be recorded. We looked at onset of AKI after admission to determine whether it is a community-acquired (onset <48 hours after hospitalisation) or hospital-acquired AKI (onset after 48 hours of admission). We also took into consideration the clinical presentation, in an attempt to rule out other causes of AKI before deeming the AKI to be due to malarial infection. In patients who had persistent elevated/abnormal serum creatinine upon

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discharge, blood tests were done at 1 month and 3 months after discharge, to look for renal recovery (normalization of serum creatinine levels). The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Patients with an eGFR of less than 60ml/min/1.73m^2 at 3 months after discharge are deemed to have developed chronic kidney disease (CKD). They were subsequently staged as per KDIGO criteria (14)

2. Severe malaria

Severe malaria is diagnosed based on the criteria outlined by the World Health Organisation (WHO) in 2015 (15).

STATISTICAL ANALYSIS

Data were extracted from hospital case notes and computed into Statistical Package for Social Sciences (IBM Corp. Released 2013. IBM Statistics for Windows, Version 22.0. Armork, NY: IBM Corp.) for data analysis and interpretation.

Logistic regression was used to assess for factors associated with AKI. Univariate logistic regression was used to determine the unadjusted odds ratio between exposure variables and status of AKI. The simultaneous effects of capillary blood sugar, peripheral capillary oxygen saturation, age, respiratory rate, white blood cell count, aspartate transaminase (AST), total bilirubin, systolic and diastolic blood pressure, haemoglobin, platelet, serum bicarbonate and AKI status were determined via multivariate logistic regression analysis. Using automatic variable selection procedures, we identified significant factors by fitting all independent variables of interest into the model. We applied both forward and backward stepwise variable selection procedures with P value less than 0.05 as significant variable to include into the model. The assumptions of linearity in logit for each continuous variable were checked. The selected continuous variables linearity assumption was not met, thus the variables were categorized. The selected model in this step was considered preliminary main-effect model. Next, two-way interactions between selected independent variables were checked. The preliminary main-effect model was also checked for multicollinearity problem by obtaining variance-inflation-factor (VIF) for each independent variable. Goodness-of-fit statistics was used to assess the fit of the logistic model against the actual outcomes. Adjusted odds ratios and 95% confidence intervals were estimated. The P-value of 0.05 is considered significant.

RESULTS

Patient Characteristics

Queen Elizabeth Hospital reported 173 cases of malaria infection in the year 2018. Fifty three cases were excluded from analysis as case notes were incomplete or unavailable. Data analysis was done on the remaining 120 cases. The baseline demographic and clinical features upon presentation are summarised in Table I. Patients have a mean age of 43.5 years, predominantly male gender (83.3%), and are *Sabahan Bumiputras* in ethnicity (95%), Chinese (3.3%) and non-Malaysian (1.7%).

Table I: Baseline Demographic and Clinical Features upon Presentation to Hospital

Variables	
Age, years	43.5 (18.0)
Gender - Male - Female	 100 (83.3) 20 (16.7)
Ethnicity - *Sabahan Bumiputras* - Chinese - Others	 115 (95.0) 4 (3.3) 2 (1.7)
History of Malaria infection	14 (11.7)
Underlying medical comorbidities	34 (28.3)
Duration of unwell, days	5.7 (2.8)
Use of nephrotic drugs	8 (6.7)

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Table I: Baseline Demographic and Clinical Features upon Presentation to Hospital *(cont').*

Source of patient - Walk-in - Referred from district hospitals	 22 (18.3) 98 (81.7)
Malaria species - Plasmodium knowlesi - Plasmodium falciparum - Plasmodium vivax - Co infection (P knowlesi + P malariae)	 117 (97.5) 1 (0.8) 1 (0.8) 1 (0.8)
Severe malaria	23 (19.2)
Initial antimalarial treatment - Intravenous arthesunate - Oral riamet (artemether, lumefantrine) - Oral chloroquine and Intravenous clindamycin	 64 (53.3) 55 (45.8) 1 (0.8)
Patient disposition upon admission - Intensive care/High dependency ward - General ward	 18 (15.0) 102 (85.0)
Inotropic support on admission - No inotrope - One inotrope	 109 (90.8) 11 (9.2)
Intubation	1 (0.8)
Duration of hospitalisation, days	4 (2)
Systolic blood pressure, mmHg	120.2 (19.0)
Diastolic blood pressure, mmHg	70.8 (12.3)
Heart rate, beats per minute	96.6 (17.4)
Temperature, °C	38.0 (1.2)
Respiratory rate, breaths per minute	19.1 (2.6)
SPO2, %	98.2 (2.72)
Parasite count, parasites/µL	22126.56 (56156.4)
Haemoglobin, g/dL	13.2 (1.7)
White blood cell count, 10^3/µL	7.0 (2.3)
Platelet count, 10^3/µL	73.7 (85.5)
Creatinine, µmol/L	96.0 (74.5-115.6)**
Total bilirubin, µmol/L	29.7 (19.6)
Aspartate transaminase, U/L	45.5 (28.7)
Alanine transaminase, U/L	57.6 (44.1)
pH	7.4 (0.1)
Serum bicarbonate, mmol/L	23.3 (3.9)
Serum lactate, mmol/L	1.7 (0.8)
Capillary blood sugar level , mmol/L	6.9 (2.1)

**Continuous variables are described as Mean (+/- Standard Deviation), and categorical variables as n(%).*

*** median (IQR)*

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This cohort of patients were relatively well, with only 28.3% reported as having one or more underlying medical comorbidities. They presented after a mean of 5.7 days after feeling unwell. Most of the cases were referrals from district hospitals (81.7%). 11.7% volunteered a history of malaria infection. Eight cases (6.7%) had history of nephrotoxic drug consumption one week prior to presentation.

The majority of malaria infection is due to *P. knowlesi* (97.5%). One fifth (19.2%) of patients has severe malaria, as defined by WHO in 2015 (15). The main criteria used for diagnosis of severe malaria were shock (34.8%), acidosis (21.7%) and renal impairment (21.7%). They were hospitalised for a median of 4 days. There was no mortality reported in year 2018.

After admission, most of the patients were admitted to the General Ward (85%). Eighteenpatients were admitted to Intensive Care Unit (ICU). Artesunate (53.3%) was the most common initial antimalarial therapy given to the patients, followed by Riamet (Artemether/Lumefantrine) (45.8%) and Chloroquine plus Clindamycin (0.8%). During the clinical progression, only one patient has been intubated, whereas 11 patients required one inotropic support.

INCIDENCE OF AKI AND RENAL OUTCOMES

The median serum creatinine on presentation was 96.0µmol/L (IQR 74.5-115.6). Among the 120 cases analysed, 38 patients (31.7%) developed AKI based on KDIGO classification (Figure 1). All incidences of acute kidney injury occurred within 48 hours of admission. After ruling out other causes, they were all attributed to be secondary to malaria infection.Among those who developed AKI, 19 (50%) developed Stage 1, 11 (29%) developed Stage 2, and 8 (21%) developed Stage 3 AKI. Among those who developed Stage 3 AKI, 3 (7%) patients required temporary inpatient haemodialysis. One patient's renal function normalized at 1 month of follow-up, while 5 patients had persistent renal impairment at last review 3 months after discharge. Their eGFR ranged from 44.2 to 51.9ml/min/1.73m^2, which corresponds to CKD Stage 3.

FACTORS ASSOCIATED WITH AKI

Univariate analysis revealed patients who developed AKI were significantly older. On presentation, patients who developed AKI had significantly lower blood pressure, and a higher respiratory rate. Patients who developed AKI were also significantly more likely to have lower haemoglobin, higher white blood cell count, lower platelet count, higher total bilirubin, higher aspartate transaminase (AST) level, and lower serum bicarbonate. They are more likely to be admitted to the intensive care unit, and to be on inotropic support. There is no association between parasite load and incidence of AKI. (Table II).

Multivariate analysis showed that increasing age and elevated bilirubin conferred additional risk to the development of AKI. (Table III). The model fits well (Hosmer and Lemeshow test p= 0.934) and 71.4% of cases are predicted correctly if they have AKI or not. Area under the curve of receiver operating characteristic is 71.6% which indicate acceptable discrimination of the model's ability to discriminate between the two outcomes.

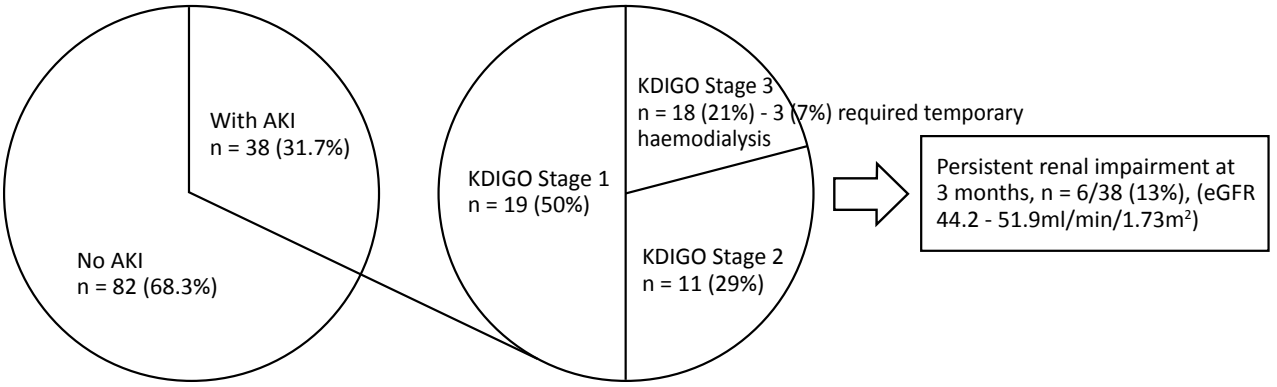

Figure 1: Incidence of AKI, severity and renal outcomes.

Table II: Selected factors associated with AKI by univariate analysis

Parameters	n	% with AKI	Unadjusted OR (95% CI OR)	P-value[a]
Gender - Male - Female	 100 20	 35 15	 3.05 (0.84, 11.13) 1	0.091
History of malaria - Yes - No	 14 106	 21.4 33	 0.55 (0.15, 2.11) 1	0.386
Comorbidities - Yes - No	 34 86	 44.1 26.7	 2.16 (0.94, 4.95) 1	0.068
Nephrotoxic drug - Yes - No	 8 112	 50 30.4	 2.29 (0.54, 9.71) 1	0.259
Inotropes - Yes - No	 11 109	 63.6 28.4	 4.40 (1.20, 16.01) 1	0.025
Intubated - Yes - No	 1 119	 100 31.1	 3.58 x 109 (0.00, -) 1	1.000
Patient disposition upon admission Intensive care/high dependency ward General	 18 102	 77.8 23.5	 11.38 (3.42, 37.83) 1	<0.001
Heart rate, beats per minute			1.00 (0.98, 1.02	0.922
Temperature			1.04 (0.76, 1.42)	0.830
Duration of unwell, days			1.02 (0.89, 1.16)	0.830
Parasite count			1.00 (1.00,1.00)	0.117
pH			1.26 (0.001,2.17x103)	0.952
Lactate			1.70 (0.88, 3.26)	0.112
SPO2			0.75 (0.61, 0.92)	0.006
Age			1.05 (1.02, 1.07)	<0.001
Respiratory rate (breath/min)			1.50 (1.17, 1.94)	0.002
White blood cells (x10^3/µL)			1.21 (1.02, 1.43)	0.032
Aspartate transaminase, AST (U/L)			1.02 (1.01, 1.04)	0.010
Alanine aminotransferase, ALT (U/L)			0.99 (0.98, 1.00)	0.221
Total bilirubin (µmol/L)			1.04 (1.02, 1.06)	0.002
Capillary blood sugar (mmol/L)			1.32 (1.01, 1.73)	0.041
Systolic BP			0.96 (0.94, 0.99)	0.002
Diastolic BP			0.94 (0.91, 0.98)	0.002
Haemoglobin (g/dl)			0.79 (0.63, 0.99)	0.038
Platelet (x10^3/µL)			0.97 (0.96, 0.99)	0.001
Serum bicarbonate (mmol/L)			0.79 (0.69, 0.90)	<0.001

[a] *Likelihood ratio (LR)*

**P values <0.05 are shown in bold.*

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DISCUSSION

In this cohort of relatively young (mean age 43.5, SD 18), and well (28.3% had at least one underlying medical comorbidity) patients, we noted an incidence of AKI of 31.7%. This is much higher than the 11%-17% as reported in the literature (10,16,17). We postulate several possible explanations.

Firstly, this study, to our knowledge, is one of the few cohort studies on renal outcomes of *P. Knowlesi* infection. It is possible that this species of Plasmodium is more virulent compared to other well studied species, causing more severe infection and organ involvement. More epidemiological studies and research looking into pathophysiology of *P knowlesi* infection are needed to confirm this.

Secondly, the *Sabahan bumiputras* is a group of people that are relatively less studied. It is possible that they may have certain unique biological traits that predispose them to develop AKI in the setting of infections. It is also possible that due to socioeconomic and logistical challenges which are endemic in this cohort, they present themselves relatively later to health facilities when they are unwell, thus increasing the risk of development of organ damage. In our cohort, the patients presented to the health facility after being unwell for a mean of 5.7 days (SD 2.8).

Thirdly, many patients had never had a serum creatinine checked before. The method we employed to diagnose AKI, as described by the ADQI group (13), assumes a normal premorbid renal function in this group of patients, and baseline creatinine is back calculated from GFR of 75ml/min/1.73m2). This method potentially overestimates the incidence of AKI by including patients with undiagnosed CKD in the analysis. A local population based study reported the prevalence of CKD as 9.07%, with only 4% of respondents with CKD being aware of their diagnosis (18).

In this study, through multivariate logistic regression analysis, we noted that the risk of development of AKI is significantly higher among patients who are 50 years old and older (OR 3.25; CI 1.37, 7.73; p=0.008), and high total bilirubin count (OR 5.6; CI 1.73, 18.12, p=0.004). These are important risk factors that have been similarly identified in other similar studies[6,7]. Recognising these risk factors will help identify population at risk of developing AKI, and thus facilitate early implementation of preventive therapy, monitoring and care.

Among the 38 patients who developed AKI due to malaria infection, 5 patients (13%) had persistent deranged renal function at 3 months after discharge. They have stage 3 CKD with eGFR of 44.2 – 51.9ml/min/1.73m^2. This is a large number and is quite alarming.

LIMITATIONS

Despite our best efforts, 53 out of 173 cases of malaria infection were excluded as their case notes were either incomplete or unavailable. This would be a significant source of bias, and highlights the importance of proper filing of case records. To improve the accuracy of reported incidence, we suggest extending this study to involve the whole state of Sabah, either by sampling all diagnosed malaria cases or by random sampling.

All the diagnosis of AKI in this cohort are made based on an increase in serum creatinine from baseline. The urine output of these patients were not meticulously charted, and, as urine output is one of the criteria for the diagnosis of AKI (12), that might have contributed to underestimation of the incidence of AKI. Furthermore, serum creatinine is a late marker of reduction of renal function. Renal damage

Table III: Adjusted Odds Ratio for factors associated with AKI

Parameters	n	% with AKI	Adjusted OR (95% CI OR)	P-value[a]
Age - Less than 50 years old - 50 years and above	 71 49	 21.1 46.9	 1 3.25 (1.37, 7.73)	0.008
Total bilirubin - Normal (≤17.1umol/L) - High (>17.1umol/L)	 33 79	 12.1 40.5	 1 5.60 (1.73, 18.12)	0.004

[a] *Likelihood ratio (LR)*

without overt functional changes would have been missed when diagnosing AKI based on serum creatinine and/or urine output alone (19). The incorporation of novel bio markers in identifying patients with subclinical renal damage is important, as it has been associated with adverse outcomes (20). Incorporating biomarkers to look for kidney injury would likely increase the incidence of AKI.

CONCLUSION

Acute kidney injury is common in malaria due to *Plasmodium* knowlesi infection. 13% of patients with AKI progress to chronic kidney disease at 3 months followup. Further research would be needed to confirm these findings, and if confirmed, would have far reaching implications in the management of malaria and kidney disease.

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