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Clinical and Laboratory Features of Human *Plasmodium knowlesi* Infection

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Abstract

Background—*Plasmodium knowlesi* is increasingly recognized as a cause of human malaria in Southeast Asia but there are no detailed prospective clinical studies of naturally acquired infections.

Methods—In a systematic study of the presentation and course of patients with acute *P. knowlesi* infection, clinical and laboratory data were collected from previously untreated, nonpregnant adults admitted to the hospital with polymerase chain reaction–confirmed acute malaria at Kapit Hospital (Sarawak, Malaysia) from July 2006 through February 2008.

Results—Of 152 patients recruited, 107 (70%) had *P. knowlesi* infection, 24 (16%) had *Plasmodium falciparum* infection, and 21 (14%) had *Plasmodium vivax*. Patients with *P. knowlesi* infection presented with a nonspecific febrile illness, had a baseline median parasitemia value at hospital admission of 1387 parasites/μL (interquartile range, 6–222,570 parasites/μL), and all were thrombocytopenic at hospital admission or on the following day. Most (93.5%) of the patients with *P. knowlesi* infection had uncomplicated malaria that responded to chloroquine and primaquine treatment. Based on World Health Organization criteria for falciparum malaria, 7 patients with *P. knowlesi* infection (6.5%) had severe infections at hospital admission. The most frequent complication was respiratory distress, which was present at hospital admission in 4 patients and developed after admission in an additional 3 patients. *P. knowlesi* parasitemia at hospital admission was an independent determinant of respiratory distress, as were serum creatinine level, serum bilirubin, and platelet count at admission ($P < .002$ for each). Two patients with knowlesi malaria died, representing a case fatality rate of 1.8% (95% confidence interval, 0.2%–6.6%).

Conclusions—Knowlesi malaria causes a wide spectrum of disease. Most cases are uncomplicated and respond promptly to treatment, but approximately 1 in 10 patients develop potentially fatal complications.

Five species of *Plasmodium* (*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium knowlesi)* cause naturally acquired malaria in

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humans. The most recently identified species is *P. knowlesi,* which we previously reported to be the most common cause of hospitalization for malaria in the Kapit Division of Sarawak in Malaysian Borneo [1]. Further studies of blood samples from patients presenting with malaria in Sarawak, Sabah, and Peninsular states confirmed a much wider distribution within Malaysia [2]. There have also been reports of locally acquired *P. knowlesi* infections from Southern Thailand, the Myanmar-China border, the Philippines, and Singapore [3-7], indicating that transmission occurs in many Southeast Asian countries.

P. knowlesi is primarily a chronic infection of the long-tailed *(Macaca fascicularis)* and pig-tailed *(Macaca nemestrina)* macaques [8]. It is easily confused with *Plasmodium malariae* on blood film microscopy in cases of human infection, because the morphologic appearances are almost identical [9, 10]. However, *P. knowlesi* is unique amongst the primate and human malarias in that it has a 24-h erythrocytic cycle [10], which is a characteristic that is likely to accelerate the development of complications [2]. Information on the characteristics of knowlesi malaria in humans, however, is restricted to single case reports [3, 5, 7]; our previous retrospective study of 94 patients with uncomplicated cases, in which we described available data relating to clinical features at presentation only [1]; and our report of 4 fatal cases [2]. We have, therefore, undertaken a detailed, systematic, prospective study of the presentation and clinical course of patients with a diagnosis of confirmed acute knowlesi malaria.

PATIENTS AND METHODS

Study site

This prospective study was conducted in the Kapit Division, which has a total population of 109,000 people of mostly Iban ethnicity [1]. A single World Health Organization (WHO) level 2 hospital serves the Division, together with 3 polyclinics and 22 rural health clinics. Health policy mandates that all patients with malaria are hospitalized until negative blood smear results are obtained on 2 consecutive days. Treatment for malaria is provided free of charge.

Subjects

Recruitment was consecutive and took place during 2 periods totalling 17 months from July 2006 through February 2008. All nonpregnant patients aged ≥15 years who were admitted to Kapit Hospital with a blood film result positive for any *Plasmodium* species were eligible, provided that there was no significant comorbid disease and that they had taken no antimalarial treatment within the previous 14 days. Subsequent confirmation of malaria species was determined by nested polymerase chain reaction assays [1]. All patients provided witnessed informed consent to the study procedures, which were approved by the Medical Research Ethics Subcommittee of the Malaysian Ministry of Health. In an initial 2-month pilot study, most cases of *P. vivax* and *P. falciparum* infection were among logging camp workers returning from long periods in Oceania or Equatorial Africa, respectively. Because the demographic characteristics and background immunity of these patients were significantly different from those of patients with knowlesi malaria, their clinical and laboratory data are presented but are not compared directly with data for patients with *P. knowlesi* infection.

Clinical procedures

Detailed demographic characteristics, history, and examination findings were recorded on a standard form. A baseline blood sample was obtained for routine biochemical and hematological testing, and regular monitoring of temperature, blood pressure, and pulse rate was started. Treatment was administered promptly according to the Malaysian Ministry of

Health Guidelines. Because there are no current guidelines for *P. knowlesi* malaria, the guidelines for *P. malariae* were used. Patients with uncomplicated knowlesi malaria received oral chloroquine (25 mg base/kg over a 3-day period) followed by primaquine (15 mg daily for 2 days) given as a gametocidal agent. Oral and/or intravenous hydration was administered at the discretion of the treating physician. Patients presenting with or developing features of severe malaria were treated in accordance with WHO guidelines [11] except that the thresholds for hyperparasitemia and anemia were changed to >100,000 asexual forms/μL of whole blood and <7.1 g of hemoglobin/dL, respectively, to allow for the low immunity levels of the local population. If indicated clinically, patients were transferred to Sibu Hospital for intensive care.

All patients were assessed clinically and by microscopic examination of blood films on each inpatient day. Additional laboratory tests were performed as indicated by the clinical state of the patient. Parasite clearance time and fever clearance time were taken as the number of days to the first of at least 2 follow-up assessments at which the patient had negative blood film results and was afebrile, respectively. When the patient was afebrile and had negative blood film results for 2 consecutive days, additional blood samples were obtained for routine biochemical and hematological tests before discharge. Patients returned on the 28th day after hospital admission for clinical review and blood tests.

Laboratory procedures

All blood films were examined by 2 experienced microscopists. The parasite density was first determined at Kapit Hospital on the basis of the number of parasites per 500 white blood cells and the total white blood cell count for each patient. Microscopic examination was repeated in Kuching, with the second microscopist blinded to the initial result. The mean of the 2 parasite densities was used in data analysis. Parasite DNA was extracted from blood spots that had been collected on filter paper, and the *Plasmodium* species was determined by nested polymerase chain reaction for *P. falciparum, P. vivax, P. malariae, P. ovale,* and *P. knowlesi,* as described elsewhere [1, 12].

Hematological profiles were determined on site using semi-automated methods (Sysmex model KX-21N). Serum sodium, potassium, glucose, creatinine, bilirubin, alanine aminotransferase (ALT), and albumin levels were either assayed on site (AVL 9180 and Hitachi 902; Roche/Hitachi, Roche Diagnostics) or serum samples were stored at −80°C before transfer on dry ice to the Biochemistry Department, Fremantle Hospital (Freemantle, Australia), for analysis (Cobas Integra 800; Roche Diagnostics). An additional uncuffed blood sample was collected into a chilled fluoride-oxalate tube, centrifuged immediately and separated plasma stored at −80 °C before transfer on dry ice to Fremantle Hospital for plasma lactate assay (COBAS INTEGRA 800). Other laboratory investigations, including blood cultures, urine dipstick testing, microscopic examination, and chest radiography were performed as indicated clinically.

Statistical analysis

Data were analyzed using SPSS software, version 15.0 (SPSS). Normally distributed variables were compared using the Student's *t* test or analysis of variance and the Scheffé post hoc test. All other data were analyzed using nonparametric methods (the Wilcoxon rank-sum test or Friedman test). Proportions were compared with use of Fisher's exact test. Multiple logistic or linear regression analysis using forward conditional modeling was performed to determine baseline associates of complications or markers of severity, respectively. Plausible predictive variables with a statistically significant ($P < .05$) univariate association with the specific severity outcome were selected for inclusion in the model. These variables were log-transformed prior to model entry if they were non-normally

distributed and a stepwise forward selection procedure was then performed to identify the significant independent associates in each case.

RESULTS

Baseline characteristics

The number of patients who participated in the study in relation to all malaria admissions to Kapit Hospital during the recruitment period is shown in figure 1. Their baseline demographic and clinical features are summarized in table 1. *P. knowlesi* infections were acquired locally by both sexes and across all age groups, with 93 (87%) of patients reporting recent activities in the jungle or forest-fringe in the Kapit Division. All regions along the Rejang River and its associated tributaries were represented, and there was no significant clustering of cases. Confirming our pilot study findings, most of the cases of vivax and falciparum malaria (31 cases; 69%) were imported, and the numbers were relatively small.

The overall median duration of symptoms prior to hospitalization was 5 days (interquartile range, 3–5 days), but 2 patients were unwell for >10 days before hospitalization. Symptoms were typically nonspecific. Fever and chills were present in almost all cases, and other frequent symptoms included abdominal pain, breathlessness, and productive cough. Tachypnea, pyrexia, and tachycardia were common clinical signs (table 1).

The results of baseline laboratory investigations are summarized in table 2. The level of parasitemia at hospital admission was relatively low in the *P. knowlesi* group, but there was a wide range that included 3 patients (2.8%) with parasite densities >100,000 parasites/μL and 33 patients (30.8%) with densities <500 parasites/μL. The most common abnormal laboratory finding was thrombocytopenia (<150,000 platelets/μL), which was present in 104 patients (98%), with 31 (29%) of 107 patients having a platelet count <50,000 platelets/μL. The 3 patients who did not have thrombocytopenia (155,000, 152,000, and 167,000 platelets/μL) had low parasitemias (5, 126, and 170 asexual forms/μL, respectively), and all became thrombocytopenic within 24 h (with nadir values of 90,000, 131,000, and 112,00 platelets/μL, respectively). Lymphopenia was found in 7 (6.5%) of patients at presentation, but all patients had normal values by the time of hospital discharge. Anemia was uncommon at hospital admission. Only 5 (4.6%) of the patients had a hemoglobin concentration <10 g/dL, whereas none of the patients met the criteria for severe anemia. Mild hepatic dysfunction, usually comprising an elevated serum ALT level and a low serum albumin level, was relatively common. Mild-to-moderate hyponatremia (range, 122–135 mmol/L) was evident in 29% of cases, all of which responded to rehydration and antimalarial therapy.

On the basis of WHO criteria for severe falciparum malaria [11], 8 (7.5%) of the patients with *P. knowlesi* infection had severe infections at presentation (table 3). The most frequent clinical presentations of severe infection were respiratory distress (diagnosed in 4 patients on the basis of a respiratory rate >30 breaths/min, oxygen saturation <94% by pulse oximetry, auscultatory findings, and radiographic changes), hyperparasitemia (3 patients), and jaundice (serum total bilirubin >43 μmol/L in 3 patients). There were 3 cases of renal failure (serum creatinine level ≥265 μmol/L despite fluid resuscitation), 2 cases of hypotension (systolic blood pressure ≤80 mmHg despite fluid resuscitation), and 1 case of hypoglycemia (venous plasma glucose level <2.2 mmol/L). There were no cases of unrousable coma. A combination of features was present at hospital admission in 3 patients.

Clinical course

Clinical and parasitological outcomes together with changes in key hematological and biochemical variables during hospitalization and at day 28 for patients with knowlesi malaria are summarized in tables 4 and 5. There was no clinical, laboratory, or radiological

evidence of other infections or conditions at study entry, during hospitalization, or at follow-up that would have influenced outcome. When patients with knowlesi malaria were discharged from the hospital, platelet counts had increased, and all patients had values that were within the normal range by day 28. Most of the remaining hematological and biochemical parameters had improved by hospital discharge. Abnormal laboratory values had resolved in all 87 patients with knowlesi malaria who attended for day 28 review.

Three patients, including 2 patients without complications at hospital admission, developed respiratory distress (table 3). A total of 7 (6.5%) of the 107 patients in the knowlesi group, all of whom were female, presented with or developed respiratory distress. Of those patients with evidence of severe knowlesi malaria either at presentation or during treatment, 2 died (table 3). Patient 1 had parasitemia at presentation (parasite density, 222,570 parasites/μL), evidence of multiorgan failure, hypoglycemia, and lactic acidosis. This patient died within 6 h after hospital admission despite intensive treatment with intravenous quinine, broad spectrum antibiotics, and ionotropic and ventilatory support. Patient 8 presented with symptoms and signs of a right hemiparesis and sensory inattention and had a history of uncontrolled hypertension. The patient's parasite density at hospital admission was 214,000 parasites/μL. She was treated with intravenous quinine but developed respiratory distress that required mechanical ventilation. After showing signs of improvement, she experienced neurological deterioration on the seventh day of hospitalization and died 24 h later. No neuroimaging studies were possible.

Baseline *P. knowlesi* parasitemia, complications, and markers of severity

Patients reporting breathlessness or vomiting had greater geometric mean parasite counts than did those who did not report these symptoms ($P = .025$ and $P = .038$, respectively). In a logistic regression model, presentation with or development of respiratory distress was positively and independently associated with the admission ln(parasitemia) and inversely associated with the admission hemoglobin level ($P = .004$ and $P = .015$, respectively). In multiple linear regression, (1) ln(parasitemia) and age were independent positive associates of ln(admission serum creatinine) ($P < .001$ and $P = .007$, respectively), (2) ln(parasitemia) and ln(plasma glucose) were independent associates of ln(admission serum total serum bilirubin) ($P = .003$ and $P = .008$, respectively), and (3) ln(parasitemia) was an independent associate of the ln(admission platelet count) and absolute differences between day 28 and hospital admission platelet counts ($P = .002$ and $P = .004$, respectively). In other multivariate models, ln(parasitemia) was not an independent associate of the admission hemoglobin level ($P = .49$) or serum ALT level ($P = .70$). In receiver operating characteristic curve analysis, parasitemia was a good predictor of complications after excluding hyperparasitemia (area under the receiver operating characteristic curve, 0.90 [95% confidence interval, 0.82–0.98]; $P < .001$). The prespecified 100,000/μL threshold was highly specific (specificity, 100%) but had a sensitivity of 30%.

DISCUSSION

The present study provides the first detailed, prospective evaluation of *P. knowlesi* infection in an area of Malaysian Borneo in which it is the most common locally acquired human malaria. Although there were demographic differences between the 3 groups of patients with malaria, there were no presenting symptoms or signs that distinguished knowlesi malaria from either falciparum or vivax malaria. Consistent with available—albeit, incomplete—retrospective data [1, 2], most cases of knowlesi malaria were uncomplicated and responded promptly to treatment with chloroquine and primaquine, but complications developed in nearly 1 in 10 patients. Because the number of cases of severe knowlesi malaria was small, an accurate case fatality rate is difficult to ascertain, but the case fatality rate was 1.8% (95% confidence interval, 0.2%–6.6%) in our sample. Malaria may have been a contributory

factor rather than the sole cause in our patient who presented with a stroke. Nevertheless, *P. knowlesi* infections occur in older as well as younger adult patients in the Kapit Division, and the vital organ dysfunction caused by this parasite may unmask underlying significant comorbidities.

Despite the significantly lower peripheral blood parasitemia, the patients with knowlesi malaria had clinical and laboratory profiles that were largely similar to those for patients with *P. falciparum* and *P. vivax* infection, with a wide spectrum of illness. The most frequent complication in our cohort was respiratory distress, which affected 1 in 15 patients. It is also a relatively common sequelum of severe falciparum malaria [13]. Respiratory distress can reflect pulmonary edema, acute respiratory distress syndrome, or metabolic acidosis. In our group, a pulmonary, rather than metabolic, etiology was the main cause, because we measured blood lactate concentrations and had access to chest radiographs and pulse oximetry. The strong association between parasitemia at hospital admission and the development of respiratory distress in our patients suggests that parasite-specific effects that increase pulmonary capillary permeability rather than iatrogenic fluid overload or the syndrome of inappropriate anti-diuretic hormone secretion are responsible, as in falciparum malaria [14]. Patients with falciparum malaria who develop respiratory distress have a relatively poor prognosis [13], and both of our patients who died developed this complication. Respiratory distress has also been reported as a rare complication of vivax [15-17] and ovale [18, 19] malaria. We cannot explain the disproportionate number of female patients with this complication in the *P. knowlesi* group. Although the women in our cohort, compared with the men, had lower serum albumin concentrations at presentation (34.5 g/L vs 38.0 g/L; $P < .001$), sex association has not been reported in the case of the other human malarias and is likely to be attributable to the play of chance in the present study.

The *P. knowlesi* parasitemia at hospital admission was also strongly and independently associated with renal dysfunction, and 3 patients developed renal failure despite resuscitation and rehydration. As with respiratory distress, this is another complication of falciparum malaria that could be mediated by the parasite [20], although the microvascular sequestration that may contribute to *P. falciparum*–associated renal dysfunction [21] is not known to occur in *P. knowlesi* infection. The presence of *P. knowlesi* parasitemia at hospital admission was also independently associated with the total serum bilirubin but not serum ALT level. This could reflect relatively brisk hemolysis associated with the short (24-h) erythrocytic cycle rather than abnormal liver function, but the median parasitemia was low, and there was no inverse association with hemoglobin level at hospital admission. It is still possible that hepatic dysfunction is a relatively late vital organ complication of *P. knowlesi* malaria but—as evidenced by patient 1, who presented with jaundice, hypoglycemia, and lactic acidosis—it is one with potentially devastating metabolic consequences.

Consistent with the nonsequestering nature of *P. knowlesi,* we did not observe significant neurologic sequelae except in patient 8, who had evidence of a stroke in the context of preexisting cerebrovascular risk. In addition, in contrast with the group of patients with *P. falciparum* infection, the group of patients with *P. knowlesi* included no patients with severe anemia. Both severe anemia and neurologic disturbance have been reported recently as common manifestations of severe vivax malaria [22, 23], but these complications were observed in patients who were younger than those in the present study and in areas of much greater malaria transmission of multiple *Plasmodium* species.

Despite the very high prevalence of thrombocytopenia among our patients with *P. knowlesi* infection (100%, compared with <80% in other human malarias [24-26]), none had a clinically evident coagulopathy. This is consistent with the relative infrequency of bleeding

episodes complicating severe falciparum malaria [11], but it is possible that a low platelet count (52,000 platelets/μL) and prolonged prothrombin time (17 sec) contributed to an intracerebral hemorrhage in the patient with knowlesi malaria who died of a probable stroke. The almost invariable presence of thrombocytopenia could facilitate diagnosis of knowlesi malaria. In addition, the significant association between platelet count and *P. knowlesi* parasite density and, in turn, the relationship between parasitemia and markers of severity, could imply that very low platelet counts are of prognostic significance. Such a relationship has been found among African children with falciparum malaria [27].

Although our study included relatively few patients with severe knowlesi malaria, we provide preliminary data relating to the incidence of severe disease. A larger study on the main complications and pathophysiology of knowlesi malaria is in progress, with the aim of establishing specific criteria for severity. It is likely that those for severe falciparum malaria, including neurologic sequelae, severe anemia, and hyperparasitemia [11], may not adequately address the unique biologic properties of *P. knowlesi.* In the case of falciparum malaria, ≥250,000 parasites/μL (or 5% parasitized erythrocytes) is conventionally used [11], but thresholds as low as 100,000/μL have been associated with increased mortality and have been used for nonimmune patients [28, 29]. It is therefore important to determine knowlesi-specific markers of disease severity, especially an accurate risk-associated threshold parasitemia.

Our study shows that knowlesi malaria is a significant cause of morbidity in the Kapit Division, extends available data to characterize the spectrum of illness and its clinical course, and confirms our previous observation that life-threatening complications can supervene [2]. Knowlesi malaria is widely distributed in Southeast Asia; it affects mainly people who enter forests or the forest fringe, but the transmission ecology of this potentially serious disease may be changing [30]. Recently, European travellers to Malaysia have received a diagnosis of knowlesi malaria following their return home [31, 32]. The increase in tourism in Southeast Asia may mean that more cases are detected in the future, including in Western countries. Clinicians assessing a patient who has visited an area with known or possible *P. knowlesi* transmission should be aware of the diagnosis, its clinical manifestations, and its course.

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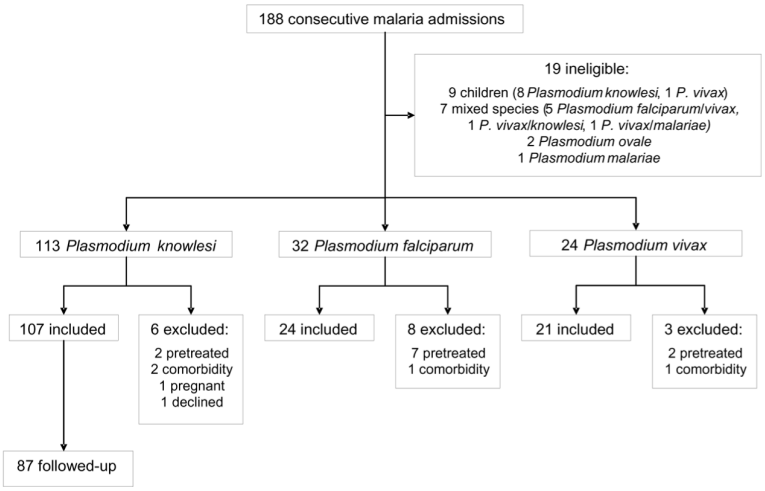

Figure 1.
Flow chart showing patient recruitment, exclusion, and follow-up in a study of human *Plasmodium knowlesi* infection in Malaysia.

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Table 1

Demographic and Clinical Characteristics of Patients Admitted to Kapit Hospital (Sarawak, Malaysia) with Untreated Malaria Categorized by *Plasmodium* Species

Variable	*Plasmodium knowlesi* (*n* = 107)	*Plasmodium falciparum* (*n* = 24)	*Plasmodium vivax* (*n* = 21)	*P*
Age, years				
Mean value (±SD)	44.9 ± 14.94[a]	38.7 ± 9.64	35.5 ± 10.61	.006
Range	16–79	15–53	15–51	
Male sex	56.1[b,c]	95.8	100	<.001
Iban ethnicity	91.6	95.8	76.2	.073
Occupation				<.001
Farmer	49.5	4.2	9.5	
Logging/plantation worker	27.1[b,c]	91.7	71.4	
Other	23.4	4.2	19	
Self-reported previous malaria	26.2[b,c]	75	57.1	<.001
Previous foreign travel	19.6[b,c]	91.7	71.4	<.001
Foreign travel within previous 4 weeks	0.9[b,c]	83.3	52.4	<.001
Duration of illness, median days (IQR)	5 (3–7)	2.5 (1–4.75)	3 (1–5)	<.001
Symptom				
Fever/chills	100	91.7	95.1	NA
Headache	94.4	87.5	52.4	NA
Rigors	89.7	79.2	85.7	NA
Malaise	89.7	91.7	66.7	NA
Anorexia	83.2	70.8	52.4	NA
Myalgia	87.9	79.2	90.2	NA
Cough	56.1	54.7	47.6	NA
Nausea	56.1	87.5	28.5	NA
Vomiting	33.6	41.7	19.0	NA
Abdominal pain	52.3	37.5	23.8	NA
Diarrhea	29.0	47.5	33.3	NA
Clinical findings				

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Variable	*Plasmodium knowlesi* (*n* = 107)	*Plasmodium falciparum* (*n* = 24)	*Plasmodium vivax* (*n* = 21)	*P*
Axillary temperature, median °C (IQR)	37.6 (37.0–38.5)	37.8 (37.0–38.5)	37.0 (36.8)	NA
Respiratory rate, median breaths/min (IQR)	26 (22–31)	25.5 (22.3–28.5)	27 (24.5–29.0)	NA
Pulse rate, mean beats/min (±SD)	95 ± 16	99 ± 17	97 ± 18	NA
Arterial blood pressure, mean mmHg (±SD)	89 ± 11	85 ± 9	89 ± 9	NA
Capillary refill time, median secs (IQR)	2 (2–3)	2 (2–3)	(2–3)	NA
Palpable liver	24.3	29.2	16.7	NA
Palpable spleen	15.0	20.8	23.8	NA

NOTE. Data are percentage of patients, unless otherwise indicated. IQR, interquartile range; NA, not assessed; SD, standard deviation.

[a] $P < .05$ vs *P. vivax.*

[b] $P < .01$ vs *P. falciparum.*

[c] $P < .01$ vs *P. vivax.*

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Table 2

Laboratory Results for Patients Admitted to Kapit Hospital with Untreated Malaria Categorized by *Plasmodium* Species

Variable	Normal range	*Plasmodium knowlesi* (*n* = 107)	*Plasmodium falciparum* (*n* = 24)	*Plasmodium vivax* (*n* = 21)
Parasite count, parasites/μL	NA	1387 (6–222,570)	26,781 (1840–271,760)	4258 (324–32,132)
Hemoglobin level, g/dL	11.3–15.7	13.3 (12.0–14.3)	12.9 (12.3–13.6)	13.5 (12.6–13.8)
White blood cell count, × 10^3 cells/μL	3.1–10.3	5.6 (4.7–7.0)	6.3 (5.3–8.6)	6.1 (4.9–7.8)
Neutrophil count, mean neutrophils × 10^3/μL (± SD)	.2–5.3	3.7 ± 1.8	4.6 ± 2.4	4.6 ± 2.2
Lymphocyte count, × 10^3 cells/μL	0.8–2.7	1.5 (1.1–2.0)	1.0 (0.8–1.4)	1.0 (0.6–1.7)
Platelet count, mean value × 10^3 platelets/μL (± SD)	150–450	71 ± 35	108 ± 59	118 ± 51
Prothrombin time, secs	NA	13 (12–15)	15 (13–16)	12 (12–14)
Blood group O, % of patients	NA	28.0	12.5	9.5
Serum creatinine level, μmol/L	<133	86 (73–100)	89 (80–97)	89 (76–98)
Serum sodium level, mmol/L	136–152	137 (135–140)	138 (135–140)	138 (135.5–141)
Serum total bilirubin, μmol/L	<21	13 (9–18)	17 (12–22)	16 (10–21)
Serum alanine aminotransferase level, IU/L	<40	36 (25–54)	26 (20–40)	27 (13–55)
Serum albumin level, g/dL	>36	36 (33–39)	38 (35–41)	41 (39–46)
Serum glucose level, mmol/L	4–8	6.2 (5.3–6.7)	6.4 (5.7–7.2)	6.2 (5.5–7.0)
Plasma lactate level, mmol/L	<2	1.6 (1.2–2.0)	1.5 (1.2–2.0)	1.5 (1.1–2.0)

NOTE. Unless otherwise indicated, data are median value (interquartile range). NA, not applicable.

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Table 3

Details of Knowlesi Patients Presenting with (Patients 1–8) or Developing (Patients 9 and 10) Severe Malaria

Patient	Age, years	Sex	Hyperparasitemia	Hypotension	Acute renal impairment	Jaundice	Hypoglycemia	Lactic acidosis	Severe anemia	Acute pulmonary edema or respiratory distress syndrome	Outcome
1	68	F	Yes (parasite count, 222,570 parasites/μL)	Yes (systolic blood pressure, 80 mmHg)	Yes (serum creatinine level, 320 μmol/L)	Yes (total serum bilirubin, 45 μmol/L)	Yes (plasma glucose level, <1.1 mmol/L)	Yes (plasma lactate level, 17.4 mmol/L)	No	Yes	Died
2	36	M	Yes (parasite count, 178,000 parasites/μL)	No	Yes (serum creatinine level, 385 μmol/L)	No	No	No	No	No	Discharged
3	50	F	No	No	No	Yes (total serum bilirubin, 87 μmol/L)	No	No	No	Yes	Discharged
4	71	M	No	Yes (systolic blood pressure, 79 mm/Hg)	No	No	No	No	No	No	Discharged
5	66	M	No	No	No	Yes (total serum bilirubin, 66 μmol/L)	No	No	No	No	Discharged
6	61	F	No	No	No	No	No	No	No	Yes	Discharged
7	69	F	No	No	Yes (serum creatinine level, 418 μmol/L)	No	No	No	No	Yes	Discharged
8	36	F	Yes (parasite count, 214,000 parasites/μL)	No	No	Yes (total serum bilirubin, 178 μmol/L)	No	No	No	Yes	Died
9	73	F	No	No	No	No	No	No	No	Yes	Discharged
10	54	F	No	No	No	No	No	No	No	Yes	Discharged

NOTE. Severe malaria was defined on the basis of World Health Organization criteria for severe falciparum malaria [11]. Hyperparasitemia was defined as >100,000 parasites/μL. Severe anemia was defined as hemoglobin concentration <7.1 g/dL. Hypotension was defined as systolic blood pressure ≤80 mmHg; Acute renal impairment was defined as a serum creatinine level >265 μmol/L despite rehydration. Jaundice was defined as serum bilirubin level >43 μmol/L. Hypoglycemia was defined as a serum glucose level <2.2 mmol/L. Hyperlactaemia was defined as a lactate level >6.0 mmol/L. Acute pulmonary edema or respiratory distress was defined as a respiratory rate >30 breaths/min plus oxygen saturation <94% on room air and/or pulmonary infiltrates visible on a chest radiograph.

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Table 4

Measures of Outcome in Patients Categorized by *Plasmodium* Species

Variable	*Plasmodium knowlesi* (*n* = 107)	*Plasmodium falciparum* (*n* = 24)	*Plasmodium vivax* (*n* = 21)
Fever clearance time, h	20 (12–31)	20 (11–37)	16 (4–28)
Parasite clearance time, days	1 (1–2)	3 (2–3.75)	3 (2–3)
Duration of hospitalization, days[a]	3 (3–4)	4 (4–5)	4 (3–4)

NOTE. Data are median value (interquartile range).

[a]Excludes 2 patients who died and 2 patients with hospital admission and day 1 data only.

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Table 5

Changes in Laboratory Test Results between Hospital Admission and Discharge and Hospital Admission and Day 28 in Patients with *Plasmodium knowlesi* Infections

Variable	Change from hospital admission to discharge (*n* = 103)	Change from hospital admission to day 28 (*n* = 87)
Hemoglobin level, g/dL	−1.3 ± 1.0	0 ± 1.3[a]
White blood cell count, × 10^3 cells/μL)	0.1 ± 1.8	1.2 ± 2.1[a]
Neutrophil count, median value × 10^3 cells/μL (IQR)	−0.6 (−1.5 to 0.6)[a]	0.5 (−0.5 to 1.45)
Lymphocyte count, median value × 10^3 cells/μL (IQR)	0.7 (0.40–1.3)[a]	0.9 (0.4–1.5)[a]
Platelet count, median value × 10^3platelets/μL (IQR)	65 (31–113) [a]	184 (144–222)[a]
Serum creatinine level, median μmol/L (IQR)	−8.5 (−19 to 1)[a]	−12 (−21 to 0)[b]
Serum sodium level, median mmol/L (IQR)	2 (0.1–5)[a]	3 (0–8)[a]
Serum total bilirubin, median μmol/L (IQR)	−6 (−15 to −3)[a]	−7 (−12.9 to −4.3)[a]
Serum alanine aminotransferase level, median IU/L (IQR)	−1 (−10 to 11)	−18 (−32.9 to −4)[a]
Serum albumin level, g/dL	−1.0 ± 2.8	4.8 ± 4.1[a]
Serum glucose, median mmol/L (IQR) (*n* = 56)	−0.4 (−1.1 to 0.8)	−0.6 (−1.21 to 0.37)[b]
Plasma lactate level, median mmol/L (IQR) (*n* = 56)	0.1 (−0.5 to 0.4)	−0.1 (−0.5 to 0.5)

NOTE. Unless otherwise indicated, data are mean value ± standard deviation. IQR, interquartile range.

[a] $P < .01$.

[b] $P \leq .05$.