

ASSOCIATION OF HEPATOMEGALY AND JAUNDICE WITH ACUTE RENAL FAILURE BUT NOT WITH CEREBRAL MALARIA IN SEVERE FALCIPARUM MALARIA IN THAILAND

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Abstract. We conducted a case record study comparing liver tests abnormalities in 20 malaria-related acute renal failure cases without cerebral malaria, 52 cerebral malaria cases without other organ impairment, 189 cases of non-severe malaria associated with a high parasite burden, and 131 cases of mild *Plasmodium falciparum* malaria. Jaundice and hepatomegaly were significantly associated with renal failure (adjusted odds ratio [AOR], 3.3, 95% confidence interval [CI], 1.3–8.6, $P = 0.01$; and AOR, 1.7 95% CI, 1.13–2.4, $P = 0.01$) but not with cerebral malaria (AOR, 1, 95% CI, 0.5–2, $P = 0.8$; and AOR, 1.08, 95% CI, 0.8–1.8, $P = 0.5$). Patients with acute renal failure were significantly older and had increased liver abnormalities compared with other groups. Although an increase in the proportion of mature schizonts over ring forms was significantly associated with cerebral malaria, it did not seem to have affected acute renal failure. These results suggested that cytoadherence was not the main determinant for renal failure and that jaundice itself may have potentiated the effects of hypovolemia.

INTRODUCTION

Malaria still kills > 1 million people every year.¹ Numerous specific and nonspecific effectors of the immune system are involved in the host response to control the multiplication of *Plasmodium falciparum*. Among these, the liver and the reticuloendothelial system in general have a role in phagocytosis, soluble mediator release, and initiation of the humoral response. During mild malaria, it is common to observe nonspecific hepatitis, indicated by a slight hepatomegaly and liver enzyme elevation.^{2,3} Jaundice is common in adults with severe malaria. Notably, it has often been reported in patients with cerebral malaria, acute renal failure, or both.^{1,4} Jaundice in patients with malaria can result from hemolysis of parasitized and nonparasitized red blood cells and liver dysfunction.¹

Few studies have focused on hepatomegaly during severe malaria.⁵ Hepatic failure is exceptional, but decreased hepatic blood flow⁶ and microsomal activity are common during severe malaria.⁷ There are several clinical manifestations of severe malaria, which may differ in pathophysiology. From a pragmatic perspective, these manifestations have in common the following: they are life-threatening, and they are often grouped as a multifaceted entity requiring intensive care.¹ However, in research, this may hamper progress in the elucidation of underlying pathogenesis. Definition of both cases and controls is of paramount importance in the design of epidemiological studies.⁸ We therefore split the definition of severe malaria into nonoverlapping subgroups and conducted a cross-sectional case record study to determine whether liver abnormalities had any preferential association with different manifestations of disease severity.

MATERIAL AND METHODS

Study site. The study took place at the Hospital for Tropical Diseases, Bangkok, Thailand. We chose mutually exclusive clinical categories that are common entities in Thailand. We conducted a cross-sectional study on 20 patients with malarial acute renal failure without neurological impairment,

52 patients with cerebral malaria without renal failure, 189 patients with nonsevere malaria despite a high parasite biomass, and 131 patients with mild *P. falciparum* malaria. All were admitted between January 1998 and December 1999. The duration of illness was recorded. The liver size was measured in centimeters below the ribcage on the midclavicular line on a supine patient. As others,^{2,3} we considered the measure of a palpable liver as a reflection of hepatomegaly. However, liver span and tenderness were not recorded. All patients underwent clinical examination and had blood smear, blood count, and blood chemistry analyses performed at the time of admission.

Definitions. Cases. Because acute renal failure and cerebral malaria may not have the same pathophysiology, we decided to create a separate group for each of them. Acute renal failure was defined as a serum creatinine level > 3 mg/dL; cerebral malaria was defined as a Glasgow Coma Scale < 10.

Controls. Moderately severe controls were patients with no cerebral or renal complications despite having a high parasite biomass, which was defined as the presence of asexual parasitemia > 5% or 200,000 parasites/ μ L, or the presence of circulating schizonts⁹ and the absence of any severity-defining criteria.

Mild controls had mild falciparum malaria, defined as the presence of *P. falciparum* on the blood smear and the absence of any of the above criteria.

Patients with mixed *Plasmodium* infections were excluded from the study.

Comparison groups. It has been suggested that at a population level, the relative rarity of severe complications of malaria reflects that of the most virulent strains.¹⁰ In this perspective, the best control group to study host factors related to severe complications of malaria would have been patients infected by the same strain who did not develop severe complications of malaria. In the absence of known stable virulence markers, and because there is a positive correlation between parasite biomass and complications, we chose “moderately severe controls” with a high parasite bio-

TABLE 1
Clinical, parasitological, and liver test differences between different groups

Variable	Acute renal failure	Cerebral malaria	Moderately severe malaria	Mild malaria
Mean (\pm SD) [range] age (years)	34 (\pm 12) [14–59]	27 (\pm 9) [16–52]	26 (\pm 11) [3–65]	25 (\pm 11) [6–60]
Median (IQR) fever duration (days)	6 (4–7)	5 (4–10)	4 (3–6)	4 (2–7)
Median (IQR) parasites/ μ L	224,110 (13,350–468,200)	46,930 (11,955–178,150)	138,000 (42,800–279,680)	19,435 (5,810–49,740)
Median (IQR) schizonts/ μ L	73 (0–149)	31 (0–73)	25 (0–41)	–
Schizonts (IQR) per 10,000 trophozoites	3.9 (0–14.3)	2.2 (0–33)	1.6 (0–7.6)	0
Mean (\pm SD) hemoglobin level (g/dL)	10.9 (\pm 2.5)	10.2 (\pm 3)	12 (12 \pm 2.4)	11.5 (\pm 2.5)
Median (IQR) aspartate aminotransferase level (IU)	95 (62–168)	53 (32–83)	58 (34–99)	32 (23–46)
Median (IQR) alanine aminotransferase level (IU)	50 (32–102)	36 (19–81)	45 (25–80)	28 (18–44)
Median globulin level (g/dL) (IQR)	31.5 (27–35)	28 (25–31)	28 (24–31)	28 (24–32)
Median (IQR) albumin level (g/dL)	30 (28–34)	35 (32–40)	36 (32–41)	40 (36–43)
Median (IQR) alkaline phosphatase level (IU)	68 (48–100)	76 (39–119)	82 (59–110)	–
Median (IQR) conjugated/total bilirubin ratio	0.53 (0.40–0.67)	0.37 (0.25–0.5)	0.34 (0.25–0.49)	0.24 (0.21–0.31)
Median (IQR) unconjugated bilirubin level (mg/dL)	3.2 (1.95–7.6)	1.63 (1.16–2.7)	1.6 (1.1–2.45)	0.81 (0.51–1.27)
Median conjugated bilirubin level (mg/dL) (IQR)	3.5 (2.2–9.9)	0.85 (0.45–2)	0.8 (0.45–2)	0.28 (0.15–0.54)
Jaundice (%)				
Yes	18 (90)	21 (41)	71 (38)	11 (8)
No	2 (10)	31 (59)	118 (62)	120 (92)
Liver size, [†] centimeters below the ribcage (%)				
0	4 (20)	22 (32)	107 (57)	85 (65)
1	5 (25)	6 (12)	20 (11)	23 (18)
2	3 (15)	10 (20)	35 (19)	14 (11)
3	5 (25)	7 (13)	11 (6)	5 (3)
4	5 (15)	7 (13)	16 (8)	4 (3)
Correlation between liver size and evolution duration [‡]	+0.21 (P = 0.0001)	+0.06 (P = 0.6)	+0.27 (P = 0.0002)	+0.1 (P = 0.25)

* IQR = interquartile range; SD = standard deviation.

[†] There was a linear trend when comparing cerebral malaria with moderately severe malaria (P = 0.034), and with mild malaria (P < 0.0001). There was a linear trend when comparing malarial acute renal failure with moderately severe malaria (P = 0.002) and mild malaria (P < 0.0001). When comparing moderately severe malaria with mild malaria, there was also a linear trend (P = 0.009).

[‡] Spearman's rho coefficient.

mass and then adjusted for symptom duration. Patients thus had parasites of comparable growth kinetics and only differed from the clinical status reflecting presence or absence of cerebral or renal dysfunction. Thus, after frequency matching for parasite biomass and adjusting for the time we assume this reduced the specific effect of the strain, we therefore facilitated the detection of host-related protective or risk factors. A previous study showed that in addition, in our setting, choosing controls with no complications despite a high parasite biomass allows the reduction of referral hospital bias.¹¹ Nevertheless, we also used a more classical control group: mild malaria.

Statistical methods. Data were analyzed by STATA version 6.0 (College Station, TX). To compare medians, we used the Wilcoxon rank-sum test. To compare means, we used Student's t -test. We obtained crude odds ratios and then included relevant variables in multiple logistic regression models. To quantify the relationship between quantitative variables, we used Spearman's correlation. To adjust for po-

tential confounders, we used quantile regression (nonparametric regression). Statistical significance was set at 5%. Some correlations were similar in all groups; therefore, we reported them as a global value for all patients.

RESULTS

Table 1 shows that the mean age was significantly higher in the acute renal failure group (P = 0.005). The most mature infections, in terms of the stage of parasite development as reflected by the early trophozoite/schizont ratio,⁹ were observed in the cerebral malaria group, whereas the highest parasite counts were in the renal failure group (Table 1). Patients with renal failure and cerebral malaria had significantly lower hemoglobin concentrations than moderately severe malaria (P = 0.05 and P < 0.0001, respectively).

Liver tests. Patients with acute renal failure often had abnormal liver tests; 90% of them had jaundice (Tables 1 and 2). There was a significantly higher proportion of con-

TABLE 2
Crude and adjusted odds ratios for palpable liver size and jaundice using different comparison groups

Comparison groups	Exposure	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)	P value
CM/moderately severe malaria	Palpable liver	1.8 (0.96–3.3)	1.08 (0.8–1.8)†	0.5
CM/moderately severe malaria	Jaundice	1.1 (0.6–2.1)	1.0 (0.5–2)†	0.8
ARF/moderately severe malaria	Palpable liver	5.2 (1.8–15.5)	1.7 (1.13–2.4)†	0.01
ARF/moderately severe malaria	Jaundice	15 (3.7–∞)	3.3 (1.3–8.6)†	0.01
ARF/CM	Palpable liver	2.9 (0.9–9.5)	1.35 (0.9–2)‡	0.13
ARF/CM	Jaundice	12.1 (2.8–∞)	13.3 (2.6–64)‡	0.002
CM/mild	Palpable liver	2.5 (1.3–4.8)	1.1 (0.8–1.6)§¶	0.5
ARF/mild malaria	Palpable liver	7.4 (2.4–22.2)	3 (1.24–7.5)§#	0.01
Moderately severe malaria/mild malaria	Palpable liver	1.4 (0.9–2.2)	1.3 (0.99–1.7)§	0.055

* AOR = adjusted odds ratio; ARF = malaria with acute renal failure; CI = confidence interval; CM = cerebral malaria.

† Adjusted using a logistic regression model with liver size, jaundice, spleen size, parasitemia, schizont counts, and symptom duration as independent variables. Interaction terms were created but did not show significant interaction.

‡ Model including jaundice and liver size as independent variables.

§ Adjusted using a logistic regression model with liver size, spleen size, direct bilirubin, parasitemia, and symptom duration as independent variables.

¶ AOR for direct bilirubin level, 1.4 (95% CI, 1.1–1.7) ($P = 0.002$).

AOR for direct bilirubin level, 1.6 (95% CI, 1.16–2.2) ($P = 0.004$).

jugated bilirubin in renal failure than in cerebral malaria ($P = 0.002$) and in mild or moderately severe malaria ($P < 0.0001$). No significant difference between the proportion of conjugated bilirubin in cerebral malaria and moderately severe malaria was observed ($P = 0.7$). Among patients with acute renal failure, there was also a significantly higher aspartate aminotransferase level ($P = 0.005$) than in patients with cerebral malaria or in moderately severe controls (Table 1). Among patients with acute renal failure, there was also a significantly higher globulin level than in patients without renal failure ($P = 0.005$) (Table 1). Among patients with acute renal failure, there was a significantly lower albumin level than in patients with cerebral malaria or in moderately severe controls ($P = 0.02$) (Table 1). However, there was no difference in total protein level between groups ($P = 0.21$). Alkaline phosphatase seemed lower in the acute renal failure group, but this difference was not significant ($P > 0.5$) (Table 1).

Adjusted odds ratios. Table 2 shows that jaundice and increased liver size were associated with acute renal failure, but not with cerebral malaria. In the logistic regression models, when comparing cerebral malaria with moderately se-

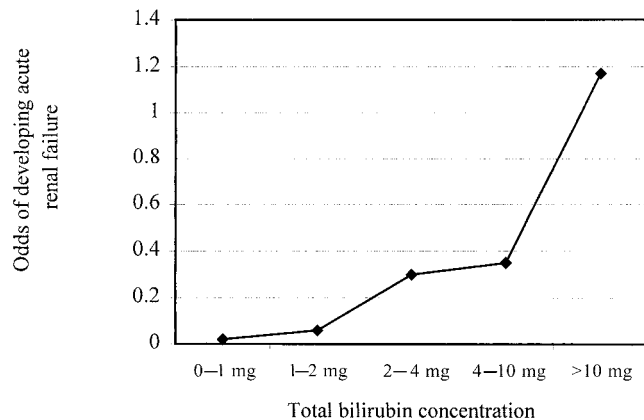


FIGURE 1. Odds of developing malaria-associated acute renal failure for different total bilirubin concentrations, with moderately severe malaria used as the control.

vere malaria and adjusting for parasitemia, schizont counts, and evolution duration, we observed that splenomegaly was associated with cerebral malaria (adjusted odds ratio [AOR], 1.4, 95% confidence interval [CI], 1.04–1.9, $P = 0.02$). A longer evolution duration (in days) (AOR, 1.14, 95% CI, 1.05–1.25, $P = 0.002$) and increased schizont counts (AOR, 1.12, 95% CI, 1.02–1.24, $P = 0.02$) were associated with cerebral malaria. We then replaced parasitemia and schizont counts with the schizont/trophozoite ratio, a reflection of the percentage of parasites expressing cytoadherence-mediating knobs.⁹ After transforming the schizont/trophozoite ratio into a categorical variable with equivalent patient numbers in each group, the increase in the proportion of mature schizonts over young asexual forms was associated with cerebral malaria (AOR, 1.76, 95% CI, 1.15–2.7, $P = 0.009$). When comparing acute renal failure with moderately severe malaria, neither evolution duration (AOR, 0.97, 95% CI, 0.8–1.2, $P = 0.7$) nor parasite counts (AOR for parasitemia, 1, 95% CI, 0.99–1, $P = 0.6$; AOR for schizont counts, 1.04, 95% CI, 0.9–1.2, $P = 0.6$) were significant. The proportion of mature schizonts or young forms was not associated with significant risk for renal failure (AOR, 1.3, 95% CI, 0.6–2.6, $P = 0.4$). The most parsimonious model comparing acute renal failure and moderately severe malaria retained jaundice and increased liver size as risk factors and splenomegaly, which was associated with protection from acute renal failure (AOR, 0.38, 95% CI, 0.14–1, $P = 0.05$). Recoding bilirubin in categorical variables showed that there was a linear trend between the concentration of total bilirubin and acute renal failure (chi-square, 27, $P < 0.0001$) (Figure 1). Liver enzymes and albumin levels were removed from the models because after adjustment, they did not predict either cerebral malaria or acute renal failure (data not shown).

Liver size. Because the palpable portion of the liver is not the most appropriate measure of hepatomegaly, we defined hepatomegaly as when patients had a palpable liver of > 2 cm. By use of this definition, hepatomegaly was significantly associated with acute renal failure (AOR, 5.4, 95% CI, 1.8–16.6, $P = 0.003$) but not with cerebral malaria (AOR, 1.4, 95% CI, 0.6–4, $P = 0.4$) when we used moderately severe malaria as the control. There was a positive

correlation between liver size and spleen size (Spearman's rho = +0.42, $P < 0.0001$). Liver size increased with parasitemia and schizont counts (Spearman's rho, respectively, +0.14, $P = 0.003$, and +0.29, $P < 0.0001$). Liver size was not correlated with the ratio of trophozoites/schizonts (Spearman's rho = 0.02, $P = 0.7$). There was a positive correlation between liver size and both conjugated (Spearman's rho = +0.30, $P < 0.0001$) and unconjugated bilirubin (Spearman's rho = +0.28, $P < 0.0001$). Adjusting for parasitemia and schizont counts did not alter these associations ($P < 0.0001$). After excluding patients with renal failure, there was a positive correlation between liver size and creatinine level (Spearman's rho = +0.17, $P = 0.006$). Adjusting for parasitemia and schizonts did not alter this association ($P < 0.0001$), but after adding bilirubin to the model, the correlation between elevated creatinine level and liver size disappeared ($P = 0.22$).

Bilirubin, creatinine, and age. Both conjugated and unconjugated bilirubin median concentrations were higher among patients with acute renal failure (Table 1, $P < 0.001$); this remained significant after adjusting for parasitemia and schizont counts. The conjugated bilirubin/total bilirubin ratio was significantly higher in the acute renal failure group (Table 1). There was a positive correlation between age and conjugated bilirubin (Spearman's rho = 0.25, $P < 0.0001$) and between age and unconjugated bilirubin (Spearman's rho = 0.19, $P = 0.0001$). After excluding patients with acute renal failure and adjusting for weight and parasite counts (nonparametric regression), we observed that the median creatinine level was not influenced by age ($P = 0.66$). After excluding patients with acute renal failure and adjusting for weight and parasite counts (nonparametric regression), we observed that the median creatinine concentration was positively correlated with conjugated bilirubin ($P = 0.005$) but not unconjugated bilirubin ($P = 0.14$). Among patients with jaundice, those with acute renal failure had significantly higher median concentrations of conjugated bilirubin, 6.5 IU (interquartile range [IQR] = 2.34–13.2) than moderately severe controls with jaundice, 3 IU (IQR = 1.6–6.3) ($P = 0.008$). After adjusting for parasitemia and schizont counts, this remained significant ($P = 0.01$).

Bilirubin in patients with jaundice. After excluding acute renal failure, the proportion of conjugated bilirubin/total bilirubin was significantly higher in patients with jaundice (ratio = 0.55, IQR = 0.4–0.62) than in those without jaundice (ratio = 0.27, IQR = 0.22–0.36) ($P < 0.0001$).

Among patients with jaundice, the median unconjugated bilirubin level was slightly higher among patients with renal failure (3.5 mg/dL; IQR = 2.4–7.7) than among moderately severe controls with jaundice (2.8 mg/dL; IQR = 2.1–4.3), but this failed to reach statistical significance ($P = 0.06$) before and after adjustment for parasitemia and schizont counts ($P = 0.26$). Similarly, in patients with jaundice, there was no significant difference in the median conjugated/total bilirubin concentrations ratio between patients with acute renal failure (ratio = 0.61; IQR = 0.52–0.67) and moderately severe controls (ratio = 0.55; IQR = 0.39–0.63) ($P = 0.08$).

Bilirubin, parasite counts, and trophozoite/schizont ratio. Levels of conjugated and unconjugated bilirubin were positively correlated with parasitemia (Spearman's rho = +0.36, $P < 0.0001$, and Spearman's rho = +0.33, $P <$

0.0001, respectively) and schizont counts (Spearman's rho = +0.43, $P < 0.0001$, and Spearman's rho = +0.42, $P < 0.0001$, respectively).

By use of nonparametric regression analysis in data for the patient groups without renal failure, we observed that conjugated bilirubin was positively correlated with early trophozoite counts ($P = 0.036$) and schizont counts ($P = 0.02$), but not by the early trophozoite/schizont ratio ($P = 0.5$). Similarly, after adjusting for the patient's weight, we observed that the creatinine level was positively correlated with parasite counts ($P = 0.037$), but not by the early trophozoite/schizont ratio ($P = 0.4$).

Predictive values. We placed patients with cerebral malaria, acute renal failure, and moderately severe malaria into one group: patients with a high parasite biomass. In this group, the sensitivity of having a palpable liver for predicting acute renal failure was 76% (95% CI, 54–90), the specificity was 54% (95% CI, 47–60), the positive predictive value was 14% (95% CI, 8–21), and the negative predictive value was 96% (95% CI, 91–98). In the same group, the sensitivity of jaundice to predict for acute renal failure was 92% (95% CI, 73–99), the specificity was 61% (95% CI, 54–67), the positive predictive value was 19% (95% CI, 12–27), and the negative predictive value was 99% (95% CI, 95–100).

DISCUSSION

In Thailand, malaria transmission is low, and all ages may develop severe malaria.¹² In adults, jaundice and acute renal failure are common presentations of severe malaria. Here, when we used homogenous case definitions, we observed that jaundice and hepatomegaly were associated with acute renal failure, but not with cerebral malaria. Among patients with acute renal failure, there seemed to be an increase in liver test abnormalities. A notable difference was the higher percentage of both conjugated and unconjugated bilirubin in patients with renal failure than in patients in other groups. Although renal failure itself may increase conjugated bilirubin, the significant increase of the conjugated bilirubin proportion among patients with jaundice with and without renal failure suggests that patients with jaundice and malaria had cholestasis. The linear relationship between renal failure and total bilirubin and studies on the renal consequences of obstructive jaundice¹³ could therefore support a possible causal relationship.

The pathophysiology of renal failure in malaria is still unclear.¹ It is thought that cytoadherence, multifactorial changes in cortical perfusion, cytokine release, and hypovolemia lead to tubular necrosis. The association between renal failure and jaundice is a recurrent finding in studies on severe malaria.^{14–17} Acute renal failure can be found both in patients with and without cerebral malaria.¹⁵ In the case of isolated acute renal failure, considering cytoadherence as the major mechanism would imply that it must be organ selective, because cerebral function is highly sensitive to vascular disturbances. However, in our logistic regression models, schizont counts and their relative proportion to ring forms, which reflect the proportion of sequestered parasites,⁹ were not risk factors when compared with moderately severe con-

trols. This suggested that sequestration was not the most important determinant of acute renal failure.

On the contrary, schizont counts and their relative proportion to ring forms were risk factors for cerebral malaria, supporting the hypothesis of cytoadherence-related neurological impairment. We also observed that creatinine increased with parasite counts, but that the proportion of mature forms did not seem to influence its concentration. In other words, a high parasite biomass was a prerequisite for acute renal failure, but whether most parasites were sequestered or not was not a crucial determinant. Severe malaria results from a combination of host and parasite factors.¹ Parasite virulence can be defined as its intrinsic ability to cytoadhere and to upregulate endothelial cytoadherence receptors and escape splenic destruction; in addition, virulence must also be assessed in terms of its multiplicative dynamics.¹⁶ Our results suggested that the parasites' multiplicative dynamics were an important element in patients with renal failure, whereas the ability to cytoadhere seemed more important for cerebral malaria.

This is consistent with a pathological study on severe malaria showing that the presence of parasitized red blood cells in the kidney was much lower in the kidneys than in the brains of patients with cerebral malaria.¹⁷ An extension of this would be that parasites that have both cytoadhesive and multiplicative dimensions of virulence would lead to the association of cerebral malaria and acute renal failure. Host factors also seem important: we observed here that patients with acute renal failure were significantly older than the rest. Age-related differences of liver function may explain this. Given the increase of both conjugated and unconjugated bilirubin with age, a hypothesis would be that the hepatic (and maybe renal) function of older patients was more fragile under the stress of infection and hemolysis. In these patients, jaundice may have resulted from both an increase in bilirubin production due to massive hemolysis and some degree of retention. An increased stimulation of liver macrophages in patients with high parasite burdens may have generated intra hepatic cholestasis.³ Bilirubin in general is toxic for tubular cells, but it has been shown that patients with obstructive jaundice have a high risk of tubular necrosis when exposed to hypovolemia and hypoxia.¹³ Here, patients with acute renal failure had hypoalbuminemia, which may have contributed to hypovolemia.

The correlation between hepatomegaly and splenomegaly suggested that in patients with a high biomass, there is a global activation of the reticuloendothelial system. Here, we found that splenomegaly seemed protective against renal failure but was associated with cerebral malaria. It is possible that splenic destruction of parasitized red blood cells reduced intravascular and intrahepatic red blood cell destruction, thus reducing hepatic inflammation and protecting the patient from renal failure. On the contrary, increased splenic activity may have selected cytoadhesive clones of *P. falciparum*, increasing the risk for cerebral malaria.¹⁸ This may have explained why in patients with cerebral malaria there was no correlation between liver size and symptom duration.

Reports of renal failure and jaundice during severe malaria originate mainly from Asian countries, probably because of differences in malaria transmission. However, regional differences in the prevalence of liver enzyme defects,

notably for glucuronidation, could also contribute to these differences.

Among patients with a smear suggesting high parasite biomass, having jaundice or a palpable liver had low positive predictive value. Nevertheless, given the strong association between jaundice and renal failure, a question arises: how useful would chelating agents be in the prevention of renal failure among patients with jaundice? Similarly, it has been shown that careful rehydration in patients with obstructive jaundice could significantly reduce acute renal failure.¹⁹ These simple measures could prevent a complication that is associated with both high mortality and increased costs.

Acknowledgments: We thank Mr. John Butler Prizer for his help with the study.

Financial support: Financial support was received from the Bureau Régional and Scientific Cooperation Department at the French Embassy in Bangkok. Financial support was also received from Mahidol University and NAID, grant U01A135827. M.N. received the Lavoisier Grant, French Ministry of Foreign Affairs.

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