

Predictive Factors of Malaria in Travelers to Areas Where Malaria Is Endemic

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Background: The differentiation of malaria from other causes of fever is difficult. The development of tools for rapid and specific clinical diagnosis is of paramount importance for the identification of individuals infected with malaria.

Method: A 4-year prospective study to identify the clinical and biological variables associated with malaria included all patients suspected of having malaria who presented in the emergency department (ED) of a French hospital.

Results: Of 783 patients admitted to the ED with suspected malaria, 145 had positive findings of a thick smear for *Plasmodium* species, mainly *Plasmodium falciparum* (90.3%). In univariate analysis, the following 12 variables were significantly associated with diagnosis of malaria: older than 30 years, male sex, immigration to France from an area where malaria is endemic, a visit to sub-Saharan Africa, insufficient antimalaria prophylaxis, fe-

ver, chills, absence of diarrhea, a leukocyte count within the reference range, thrombocytopenia, and increased lactate dehydrogenase and bilirubin levels. In multivariate analysis, the factors predictive of malaria included a visit to sub-Saharan Africa (odds ratio [OR], 7.7; 95% confidence interval [CI], 2.8-21.3), a temperature of at least 38.5°C (OR, 6.2; 95% CI, 2.8-13.3), chills (OR, 3.0; 95% CI, 1.4-6.6), thrombocytopenia (OR, 16.5; 95% CI, 7.1-38.3), and abnormally high total bilirubin levels (OR, 21.5; 95% CI, 6.4-72.5). However, alone or combined, these features had insufficient sensitivity (95.0%) and low specificity (55.0%) for the diagnosis of malaria.

Conclusions: Malaria should be suspected in all patients presenting with complaints after travel to an area where malaria is endemic, and these patients should undergo blood microscopy.

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MALARIA IS still a major public health problem in many countries. More than 90 countries are affected, and more than one third of the world population is exposed to the risk for contracting malaria.¹ The number of cases in the world is estimated at 300 million to 500 million each year, and the number of deaths at 1.5 million to 2.7 million. Malaria remains the first cause of death in sub-Saharan Africa, where 90% of all cases occur.

In the United States, Europe, and Australia, imported cases of malaria are diagnosed among travelers to areas where the disease is endemic. Such cases have been increasing worldwide, with more than 16 000 diagnosed in Europe annually, 5000 of them in France, and more than 1500 cases annually in the United States.²⁻⁵

Rapid diagnosis of malaria is essential for the reduction of morbidity and mortality. However, clinical diagnosis of ma-

laria is difficult in areas where malaria is endemic, and malaria is not easily distinguished from other causes of fever. Some studies have evaluated causes of fever and factors predictive of malaria in areas where malaria is endemic, mostly in children.⁶⁻⁹

Similarly, in areas where malaria is not endemic, imported malaria may be missed in 40% to 60% of patients presenting with fever after trips to areas where malaria is endemic, and the clinical presentation of malaria is often nonspecific.¹⁰⁻¹⁵ To our knowledge, no previous prospective study has evaluated the clinical variables associated with malaria in this setting. Consequently, the development of tools for rapid and specific clinical diagnosis is of paramount importance for the identification of individuals infected with malaria.

The goal of the present study was to assess the value of clinical and easy available biological variables for the diagnosis of malaria among patients returning from areas where malaria is endemic.

PATIENTS AND METHODS

SETTING

This study was conducted in the Bichat-Claude Bernard Hospital, a 1300-bed university-affiliated teaching hospital that serves as a referral center and primary care facility in the metropolitan area of Paris, France. More than 60000 patients visit the hospital's emergency department (ED) each year.

PATIENTS

We included all patients presenting to the Bichat-Claude Bernard ED who underwent laboratory tests for the diagnosis of malaria during the 4 years from August 1, 1995, through July 31, 1999.

METHODS

Clinical and demographic data were obtained from the patients' medical charts and from the Parasitology Department. Diagnosis of malaria was obtained by means of thick and thin-smear microscopy. Quantitative buffy-coat analysis was performed overnight and during weekends, but results of thick and thin smears were obtained in all cases as soon as possible. If these results were negative, a new parasitological test was performed if clinically indicated.

Optimal prophylaxis was defined as the use of an adequate drug (a combination of chloroquine diphosphate plus chloroguanide hydrochloride or mefloquine hydrochloride for patients visiting sub-Saharan Africa) with good

compliance (respect of drug scheduling and dosage) during the stay in the area where malaria is endemic and 4 weeks after the return to an area where the disease is not endemic.

To explore the possible relationship between clinical or biological variables and malaria diagnosis, we used the Kruskal-Wallis 1-way analysis of variance for continuous variables and the χ^2 test with the Fisher 2-tailed exact test for categorical variables. If necessary, continuous variables were classified by choosing their median or clinically relevant value. A *P* value of no greater than .05 was used to determine statistical significance.

The variables found to be significant and those with a *P* value of less than .25 by univariate analysis were included in a logistic regression model and eliminated one by one in a backward fashion on the basis of the adjusted odds ratio (OR) to develop a model with the strongest possible relationships. From these results, a prediction model was proposed. Clinical features at admission and laboratory data were assigned weights based on the results of the values found by univariate and multivariate analysis to determine the best predictor of malaria in an individual patient. The sensitivity and specificity of the model for predicting malaria in the population studied were determined for each score value. After stratification, the performance of the malaria prediction model was assessed by means of the receiver operating characteristics (ROC) curve.

Data are presented as mean \pm SD. Median values and ranges are presented when necessary.

We used Statistica 5.1 (StatSoft, Inc, Tulsa, Okla) and EPI-INFO 6 (World Health Organization, Geneva, Switzerland) software for data collection and analysis.

RESULTS

PATIENT CHARACTERISTICS

We included 783 consecutive patients during the 4-year study. Patient characteristics are given in **Table 1**. More than half of the patients were born in regions where malaria is endemic.

MALARIA PROPHYLAXIS

Malaria prophylaxis was used by 39.0% of the patients, but only 44.9% of them complied with their treatment while visiting the area where malaria is endemic and after their return to France; thus, only 17.5% of the entire population had optimal prophylaxis.

The following factors were associated with good antimalaria prophylaxis: age (≤ 30 or > 30 years, 31.3% vs 9.7%, respectively [$P < .001$]); sex (female or male, 25% vs 12.4%, respectively [$P = .03$]); and patients' origin (area where malaria is not or is endemic, 30.3% vs 5.8%, respectively [$P < .001$]). Differences in prophylaxis use were found according to the following visited areas: Asia, 45%; sub-Saharan Africa, 18.7%; and North Africa, 0% ($P = .01$).

MALARIA DIAGNOSIS

Malaria was diagnosed in 145 patients (18.5%). *Plasmodium falciparum* was identified in 131 cases (90.3%); *Plas-*

modium ovale, in 8 (5.5%); and *Plasmodium vivax*, in 7 (4.8%). One patient had coinfection by *P falciparum* and *P vivax*. Of the 131 patients infected by *P falciparum*, 127 contracted their infection in sub-Saharan Africa (mostly French-speaking west Africa) and the other 4 in Indonesia, Southeast Asia, or South America. All 8 cases of *P ovale* infections were contracted in sub-Saharan Africa. The 7 cases of *P vivax* infections were contracted in India, Central America, and north and sub-Saharan Africa. More than 90% of cases of malaria were acquired in sub-Saharan Africa.

The following diagnoses were assigned to patients in whom malaria was not detected: febrile diarrhea (12.5%), urinary tract infection (6.2%), lower respiratory tract infection (9.6%), upper respiratory tract infection (6.8%), acute meningitis (3.4%), acute hepatitis (2.8%), and cutaneous infection (3.4%); the remaining patients (55.3%) had fever without any identified cause (except for 1 patient with an acute Epstein-Barr virus infection).

PREDICTIVE FACTORS OF MALARIA

The clinical and biological features associated with a diagnosis of malaria are shown in **Table 2** and **Table 3**. Patients with malaria were significantly older than the others. Most were male and came from areas where malaria is endemic. More had visited sub-Saharan Africa, and

Table 1. Characteristics of 783 Patients Suspected of Having Malaria

Patient Characteristic	Data
Age, mean ± SD, y	37.1 ± 12.3
Sex, No. M/F (ratio)	462/321 (1.43)
Origin, No. (%)	
Sub-Saharan Africa	388 (49.6)
France/European Union	383 (48.9)
Asia	12 (1.5)
Patients from regions where malaria is endemic, No. (%)	418 (53.4)
Residing in France	380 (90.9)
Residing in France for >10 y	121 (52.2)
Area visited, No. (%)	
Sub-Saharan Africa	616 (78.7)
Asia	104 (13.3)
North Africa	31 (4.0)
South and Central America	32 (4.1)
Antimalaria chemoprophylaxis, No. (%)	305 (39.0)
Optimal chemoprophylaxis, No. (%)	137 (17.5)
Time from first symptoms to hospital arrival, mean ± SD, d	8.3 ± 21.3*
Time from return to France to hospital arrival, mean ± SD, d	36.7 ± 75.5†
Fever before admission to hospital, No. (%)	642 (82.0)
Chills, No. (%)	407 (52.0)
Digestive disturbances, No. (%)	253 (32.3)
Diarrhea	180 (22.3)
Temperature, mean ± SD, °C	38.3 ± 1.2
Diagnosis of malaria, No. (%)	145 (18.5)
<i>Plasmodium falciparum</i>	131 (90.3)
<i>Plasmodium ovale</i>	8 (5.5)
<i>Plasmodium vivax</i>	7 (4.8)

*Median was 3 days (range, 1-210 days).

†Median was 7 days (range, 0-360 days).

more had received nonoptimal prophylaxis. Most patients with malaria had a history of fever before arrival in our ED, presented with chills but not with diarrhea, had fever on arrival in the ED, and had lower leukocyte and platelet counts and higher lactate dehydrogenase and bilirubin concentrations.

The results of multivariate analysis (**Table 4**) disclosed 5 independent factors predictive of malaria: a visit to sub-Saharan Africa (OR, 7.7; 95% confidence interval [CI], 2.8-21.3); a temperature of at least 38.5°C on arrival in the ED (OR, 6.2; 95% CI, 2.8-13.3); chills (OR, 3.0; 95% CI, 1.4-6.6); a platelet count below 130 000 cells/ μ L (OR, 16.5; 95% CI, 7.1-38.3); and total bilirubin levels of at least 1.05 mg/dL (>18 μ mol/L) (OR, 21.5; 95% CI, 6.4-72.5).

Figure 1 presents the scatterplots of temperature at admission, platelet count, and total bilirubin levels according to malaria diagnosis. The reference range for total bilirubin level is less than 1.4 mg/dL (<24 μ mol/L). **Figure 2** shows the ROC curve for malaria diagnosis according to clinical variables at admission. **Figure 3** shows the ROC curve for clinical and biological variables.

COMMENT

In the present study, the need for parasitological tests for malaria was used as the inclusion criterion. We found

Table 2. Comparison of Continuous Variables Between Patients With and Without Malaria*

	Malaria	Other Diagnosis	P Value
Age, y	40.1 ± 11	35.8 ± 14	.005
Time from first symptoms to hospital arrival, d	4.6 ± 4	9.5 ± 24.2	NS
Time from arrival to area where malaria is not endemic to hospital arrival, d	21.9 ± 54.6	42.2 ± 81.3	<.001
Temperature, °C	39.1 ± 1.3	38 ± 1.2	<.001
Hemoglobin, g/dL	13.3 ± 2.0	13.4 ± 2.2	NS
Leukocyte count, cells/ μ L	5890 ± 4880	7910 ± 5120	.002
Platelet count, cells/ μ L	102 520 ± 58 230	235 410 ± 102 300	<.001
Urea nitrogen, mg/dL†	13.7 ± 5.3	12.9 ± 4.2	NS
Creatinine, mg/dL‡	1.2 ± 0.2	1.1 ± 0.5	NS
Lactate dehydrogenase, U/L	652 ± 258	514 ± 248	.01
Total bilirubin, mg/dL§	1.6 ± 0.8	0.7 ± 0.7	<.001
Free bilirubin, mg/dL§	1.0 ± 0.8	0.3 ± 0.7	<.001

*Data are given as mean ± SD.

†To convert to millimoles per liter, multiply by 0.357.

‡To convert to micromoles per liter, multiply by 88.4.

§To convert to micromoles per liter, multiply by 17.1.

that these tests had been prescribed for patients who had returned from areas where malaria is endemic during the past year and who exhibited nonspecific symptoms such as fever, chills, headache, myalgia, and abdominal complaints. We found that imported malaria is a frequent consultation reason in the emergency setting; that *P falciparum* is the most frequent causative *Plasmodium* species in France; that some patients seeking medical care after a visit in an area where malaria is endemic had not received optimal antimalaria prophylaxis; and that the diagnosis of malaria remains a clinical difficulty.

Our study included patients with different degrees of immunity to malaria depending on their origin and, for immigrant non-French patients, their period of residence in an area where the disease is not endemic. In the present study, immune and semi-immune immigrant patients, defined as those with a history of a malaria attack or those born in rural areas where malaria is endemic, accounted for more than 50% of all patients undergoing testing for malaria and of those with a diagnosis of malaria, as reported by other authors in studies of imported malaria.^{3,5,16-23} Despite the large number of patients included, our study population probably did not correspond to the total number of those traveling to areas where malaria is endemic. However, it probably corresponded fairly well to the population of subjects who are symptomatic after a journey to a tropical region and who live in a large city located in an area where malaria is not endemic. Otherwise, there are some differences between the patients with malaria identified in the present study compared with those seen in the United States, where *P vivax* is more frequent and where a greater number of cases are acquired outside of Africa.⁵

An important result of our study was that only 17.5% of the entire population complied with the currently ac-

Table 3. Clinical Variables Associated With the Diagnosis of Malaria*

	Prevalence of Malaria, %	OR (95% CI)	P Value	Positive Predictive Value, %	Negative Predictive Value, %	Maximum Likelihood Ratio
Age, y			<.001	29.0	86.2	1.7
≤30	13.8	1.0				
>30	29.1	2.6 (1.8-3.7)				
Sex			<.001	26.1	92.5	1.6
Female	7.4	1.0				
Male	26.2	4.4 (2.7-7.2)				
Patient's origin			<.001	23.7	87.4	1.4
Area where malaria is not endemic	12.6	1.0				
Other area where malaria is endemic	23.6	2.2 (1.4-3.2)				
Area visited			<.001	21.1	95.2	1.3
Other area where malaria is endemic	4.8	1.0				
Africa	22.2	5.7 (2.6-12.8)				
Chemoprophylaxis			<.001	21.1	93.4	1.2
Optimal	6.6	1.0				
Nonoptimal	21.1	3.8 (1.8-8.2)				
Fever before hospital arrival			<.001	21.5	95.0	1.2
No	5.0	1.0				
Yes	27.4	5.2 (2.3-12.5)				
Chills			<.001	27.5	91.2	1.7
No	8.8	1.0				
Yes	27.5	4.0 (3.6-6.1)				
Diarrhea			.007	11.6	79.4	3.4
Yes	11.6	1.0				
No	20.6	2.0 (1.2-3.3)				
Temperature ≥38.5°C			<.001	39.1	88.5	2.0
No	11.5	1.0				
Yes	39.0	5.0 (3.3-7.5)				
Platelet count ≤130 000/μL			<.001	67.1	87.7	5.8
No	10.1	1.0				
Yes	67.9	18.0 (11.1-29.4)				
Total bilirubin level ≥1.05 mg/dL (≥18 μmol/L)			<.001	72.0	90.7	5.3
No	9.3	1.0				
Yes	72.0	25.0 (11.8-54.0)				

*OR indicates odds ratio; CI, confidence interval.

Table 4. Independent Predictive Factors of Malaria Disclosed by Multivariate Analysis

	Parameter Estimate, β	Odds Ratio	SE of β	95% Confidence Interval
Visited sub-Saharan Africa	2.040566	7.7	0.518211	2.8-21.3
Temperature ≥38.5°C	1.815757	6.2	0.393315	2.8-13.3
Chills	1.107806	3.0	0.398892	1.4-6.6
Platelet count ≤130 000/μL	2.804889	16.5	0.428626	7.1-38.3
Total bilirubin level ≥1.05 mg/dL (≥18 μmol/L)	3.066796	21.5	0.620458	6.4-72.4

cepted chemoprophylactic regimens for travelers in areas where malaria is endemic, which is consistent with previously published data.^{10,17,19,21,24-26} We found that non-compliance with antimalaria chemoprophylaxis was associated with the immigrants' origin (as previously reported^{23,27}), age greater than 30 years, and male sex.

Malaria was diagnosed in 18.5% of the patients in the present study. Previous reports indicated propor-

tions of 4% to 36%.^{11,28} *Plasmodium falciparum* was identified in 90% of our malaria cases, and in 10% to 76% by others.^{5,11-13,15,28,29} The areas visited and the world distribution of *Plasmodium* species are closely related to *Plasmodium* strain identification and the proportion of patients with *P falciparum*.⁴

The diagnosis of imported malaria remains a challenge for most clinicians. In industrialized countries, malaria may be initially missed in up to 60% of patients attending hospital consultations,^{10,11,13,15} and the disease is still associated with a high fatality rate.³ Although it is currently accepted that the clinical presentation of malaria is often nonspecific, some clinical features have been frequently associated with its diagnosis, especially visits to sub-Saharan Africa,³⁰ thrombocytopenia (reported in 43%-75% of patients with malaria), and increased bilirubin levels (in 30%-64%).¹³ Fever is also frequently associated with malaria, but may be absent in 2.4% to 51% of cases.^{13,31-33}

The present study includes a very large number of patients with complaints that may be related to malaria and a large number with a documented diagnosis of malaria. We found that certain easily available clinical and biological features may be predictive of the disease. Univariate analysis showed that the factors significantly associated with the diagnosis of malaria were age greater

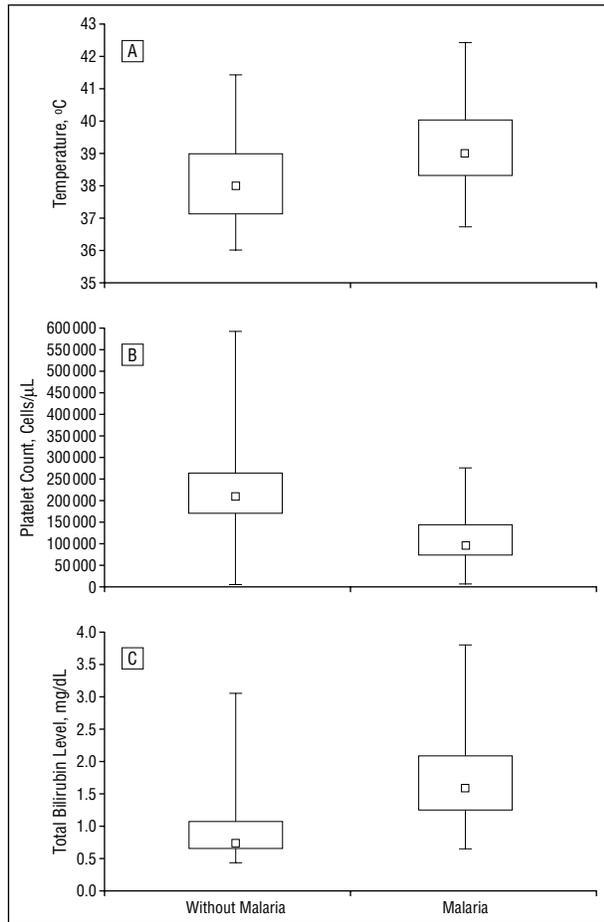


Figure 1. Scatterplots of temperature (A), platelet counts (B), and total bilirubin levels (C) according to malaria diagnosis. Bars indicate range; large boxes, 25th to 75th percentiles; and small boxes, median values. To convert total bilirubin level from milligrams per deciliter to micromoles per liter, multiply by 17.1.

than 30 years, male sex, foreign origin, a visit to sub-Saharan Africa, noncompliance with chemoprophylaxis, a fever before arrival in the hospital, chills, the absence of diarrhea, a temperature of at least 38.5°C, a leukocyte count within the reference range, thrombocytopenia, and mild elevation of lactate dehydrogenase and bilirubin levels. However, the positive and negative predictive values of these factors were low.

Although we found, on multivariate analysis, that a visit to sub-Saharan Africa, a temperature of at least 38.5°C, chills, thrombocytopenia, and high total bilirubin levels were independent predictors of malaria, these signs were not sufficiently sensitive or specific to differentiate malaria from other diseases. In addition, ROC curves showed that, alone or in combination, these features were not sensitive or specific enough to permit the diagnosis of malaria. Our data are consistent with the results of a previous report on the diagnosis of malaria in travelers.³⁴ When the ROC curves in Figures 1 and 2 were compared, laboratory tests for thrombocytopenia and high total bilirubin levels displayed poor sensitivity gain but greater specificity.

Consequently, we believe that, if on arrival in the hospital or in a prehospital setting, a visit to sub-Saharan Africa, absence of prophylaxis for malaria, fever (especially

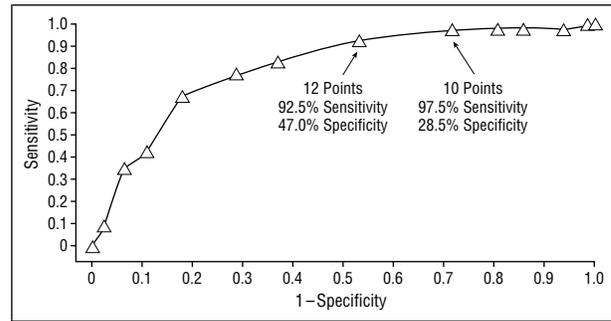


Figure 2. Receiver operating characteristic curve for the diagnosis of malaria according to clinical features at admission. The curve includes the following variables: older than 30 years, a visit to sub-Saharan Africa, inadequate prophylaxis for malaria, fever before arrival in the emergency department (ED), chills, absence of diarrhea, and temperature on arrival in the ED of at least 38.5°C. For all variables except the last one, we used the odds ratio obtained by univariate analysis; for the last variable, we used the odds ratio obtained by multivariate analysis.

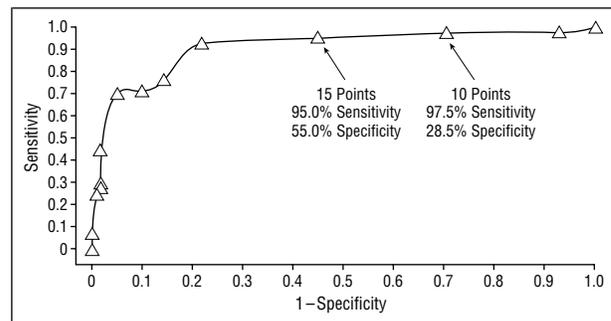


Figure 3. Receiver operating characteristic curve for the diagnosis of malaria according to clinical features at admission and laboratory data. This curve included the clinical variables used in Figure 2, plus thrombocytopenia and high total bilirubin levels. For the 2 new variables, the odds ratios obtained by multivariate analysis were used to calculate the final score.

high fever), and chills are present, a diagnosis of malaria should be considered, and patients should undergo testing for malarial parasites. On the other hand, if biological features such as thrombocytopenia or increased bilirubin levels are found, malaria should be suspected, patients' characteristics should be reevaluated, and parasitological tests for malaria should be prescribed if the subject has a history of travel to an area where malaria is endemic.

CONCLUSIONS

Malaria remains a challenge for clinicians. According to past and present data, all symptomatic patients with a history of travel to an area where malaria is endemic should undergo microscopic examination or testing for a rapid diagnosis of malaria. Certain clinical and laboratory features may be predictive of malaria, but their sensitivity and specificity are insufficient. Our results strongly suggest that patients who return from areas where malaria is endemic and who present with clinical and biological variables suggestive of malaria but with negative findings of a blood film test should undergo clinical and parasitological reevaluation to exclude a diagnosis of malaria.

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