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HEMATOLOGIC AND CLINICAL INDICES OF MALARIA IN A SEMI-IMMUNE POPULATION OF WESTERN THAILAND

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Abstract. This study examines hematologic profiles of persons with acute *Plasmodium falciparum* or *P. vivax* infection in Maesod on Thailand's western border with Myanmar compared with febrile, non-parasitemic persons also reporting to malaria clinics. Nine hundred seventy-nine subjects were malaria-negative, 414 were infected with *P. falciparum*, and 646 were infected with *P. vivax.* Persons with patent parasitemia tended to have significantly lower white blood cell, red blood cell, platelet, and hemoglobin levels than those who were malaria-negative. For the first time, a parallel trend in thrombocytopenia with parasitemia was found to be associated with both *P. falciparum,* and *P. vivax* infection. Using logistic regression, persons with platelet counts < 150,000/μL were 12–15 times more likely to have malaria than persons with platelet counts ≥ 150,000/μL. This study supplements previous literature on the hematologic effects of malaria and helps define those alterations for a semi-immune population. Thrombocytopenia is identified as a key indicator of malaria in these febrile patients.

INTRODUCTION

The prevalence of malaria in Thailand has decreased dramatically from previous levels, but regions of the country are still affected. Approximately 40% of the 150,000 malaria cases detected in Thailand annually are foreign migrants and among them 97% are from Myanmar and Cambodia (Thai Ministry of Public Health Malaria Statistics, 2000). Tak province, on the central part of the Thailand-Myanmar border, is the most common destination for ethnic minorities from Myanmar who migrate into Thailand and become engaged in agricultural work. This province has had the highest number of malaria cases for 10 consecutive years. *Plasmodium vivax* and *P. falciparum* are both common.

Hematologic changes associated with malaria infection are well recognized, but specific changes may vary with level of malaria endemicity, background hemoglobinopathy, nutritional status, demographic factors, and malaria immunity.[1] This study examines the hematologic effects of acute malaria on adults in Tak Province. Specifically, the hematologic profiles of persons infected with *P. falciparum* or *P. vivax* are compared with expected normal values, as well as with the profiles of otherwise similar febrile persons without microscopically detectable parasitemia. Additionally, the clinical symptoms and hematologic parameters most predictive of malaria in this population are identified.

SUBJECTS AND METHODS

Data used in this study were collected as part of a series of study to evaluate malaria rapid diagnostic devices.[2] The study was reviewed and approved by the Thai Ministry of Public Health Ethical Review Committee for Research in Human Subjects and the U.S. Army's Human Subjects Research Review Board. Patients were recruited from May 18, 2001 through June 29, 2001 from malaria clinics operated by the Thai Ministry of Public Health in the Mae Ku, Maesod, and Phob Phra Districts of Tak Province, Thailand. The study population is composed largely of migrant workers from Myanmar. Inclusion criteria were presentation to a participating clinic site for malaria diagnosis and treatment; age ≥ 20 years; and at least one of the following: an oral temperature ≥ 38°C, headache, or a history of fever within the past 72 hours. Severely ill patients were referred to district hospitals; therefore, complicated malaria cases were excluded in practice. Each patient was assigned a unique patient identifier. All enrolled patients were interviewed in their own vernacular language, Thai, Burmese, or Karen, for information on current symptoms and previous malaria episodes and treatments. Venous blood was drawn into EDTA-filled tubes to be used for preparation of blood film slides and automated complete blood counts (CBCs). Two slides for study purposes were promptly prepared at the field site, each with a thin and thick smear. A third smear was prepared and provided immediately to the local clinic staff to be stained and interpreted according to routine clinic procedures for therapeutic purpose.

Tubes were transported on ice within two hours to the field laboratory, where cell counts were performed using a Coulter T-890 automated cell counters (Beckman-Coulter, Inc, Fullerton, CA). Daily quality assurance checks were performed and recorded, and commercial standards were used in accordance with the manufacturer's recommendations. The cell counters provided data on the white blood cell count (WBC), red blood cell count (RBC), hemoglobin level (Hb), hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, lymphocyte count, and lymphocyte percent.

Blood smear slides were stained with Giemsa. One slide from each study participant was examined independently by two experienced microscopists. They determined the presence or absence of *Plasmodia* parasites, the species, and the number of asexual parasites per 200 WBCs. If fewer than 10 asexual parasites per 200 WBCs were observed, counting continued to 500 WBCs. Parasite densities were calculated as parasites per microliter of blood (parasites/WBCs counted × total WBCs in 1 μL of blood), and the results of the two readings were averaged. Concordance between the two blinded microscopists' interpretations was assessed and cases of species discordance from the two readings, mostly associ-

ated with very low parasitemia, were excluded from this analysis.

Data were analyzed using SAS version 8.1 (SAS Institute, Cary, NC). Patients were categorized based on microscopy results: no malaria (control group), *P. falciparum* detected, *P. falciparum* at densities greater than 1,000 parasites/μL, *P. vivax* detected, *P. vivax* at densities greater than 1,000 parasites/μL, mixed *P. falciparum*/*P. vivax* infection, or *P. malariae* detected. Mean hematologic parameters were calculated by sex for the control group (who also presented with fever, headache, or a history of fever). Hematologic parameters were compared between the control group and the specific malaria groups using independent-sample *t*-tests. Parasite densities for single-species infections were divided into quartiles, and their associations with the hematologic parameters were detected using analysis of variance.

To test for an association between malaria and symptoms or specific hematologic values, categorical variables were created for platelets, RBCs, and WBCs. Bivariate associations were examined between these variables or clinical symptoms and various outcomes: any malaria, *P. falciparum*, *P. vivax*, mixed infection, *P. malariae*, *P. falciparum* > 1,000 parasites/μL, *P. vivax* > 1,000 parasites/μL, or the lower densities for either species. Variables significant in any of these analyses were fit into logistic regression models to identify factors that were collectively predictive of malaria. Each malaria outcome was modeled separately, and stepwise selection was used to identify the variables with the most predictive value for each outcome.

RESULTS

Two thousand one hundred forty-nine subjects were enrolled in the study. Their mean age was 28 years (range = 20–70 years), and 69% were men. Seventy participants were excluded from the analysis because only gametocytes were detected (n = 6) or because of species discordance in the readings of the two microscopists (n = 64). Asexual malaria parasites were observed in the blood smears of 1,100 participants, and 979 had negative blood films. Of the malaria-positive slides, 646 (59%) were *P. vivax*, 414 (38%) were *P. falciparum*, 23 (2%) were mixed *P. falciparum* and *P. vivax* infections, 15 (1%) were *P. malariae*, and 2 (0.2%) were *P. ovale*.

The mean values of selected hematologic parameters for the negative (control) group were determined for this population, stratified by sex (Table 1). T-tests showed that RBCs, Hb, platelet count, and lymphocyte count were significantly different between men and women without malaria, so subsequent analysis of continuous variables was stratified by sex. For comparison, Table 1 also includes published normal values, although derived from a population from the United States and with relatively wide ranges.[3] All the values from this study population fall within the acceptable normal limits.

Hematologic parameters of participants in each of the malaria outcomes were compared with those of the sex-specific control group using independent-sample *t*-tests. Results are shown by sex and parasite species in Table 2. For *P. falciparum* and *P. vivax*, the mean values of WBCs, RBCs, platelet counts, and lymphocyte counts were significantly lower for the infected groups than for the uninfected groups among both men and women. The exclusion of persons with parasite densities less than 1,000 parasites/μL did not yield substantially different results. Although sample sizes for *P. malariae* and mixed infections were small, similar trends were observed in these groups.

TABLE 1

Comparison of mean values of hematologic parameters for non-malarious subjects by sex

Parameter		No.*	Mean	*P*	Published values†
White blood cells	Men	615	8.27		4.5–11.0
(10^3/μL)	Women	363	8.49		4.5–11.0
	Difference		–0.22	0.23	
Red blood cells	Men	615	4.97		4.6–6.2
(10^6/μL)	Women	363	4.52		4.2–5.4
	Difference		0.45	< 0.0001	
Hemoglobin	Men	615	13.77		13.5–18.0
(g/dL)	Women	363	11.91		12.0–16.0‡
	Difference		1.86	< 0.0001	
Platelets	Men	615	245.0		150–400
(10^3/μL)	Women	363	290.6		150–400
	Difference		–45.6	< 0.0001	
Lymphocytes	Men	615	2.43		1.0–4.8
(10^3/μL)	Women	363	2.73		1.0–4.8
	Difference		–0.30	< 0.0001	

* One subject had missing sex information.
† Mazza.[3]
‡ Anemia is sometimes defined as a hemoglobin level < 12 g/dL for men and < 10 g/dL for women.[6]

Parasitemias for *P. falciparum* ranged from 10 to 687,622 parasites/μL; parasitemias for *P. vivax* ranged from 9 to 225,006 parasites/μL. Analysis of variance was used to identify relationships between hematologic parameters and parasite densities. Platelet count was the only parameter for any group that showed a trend across quartiles of parasite densities. The mean platelet count was significantly lower in men and women with higher parasitemia for either *P. falciparum* or *P. vivax* (Table 3 and Figure 1).

Categorical variables were created from three of the hematologic parameters: WBC, RBC, and platelet counts. Along with age and clinical symptoms, these variables were tested for independent associations with type of malaria as shown in Table 4. A WBC < 5,000/μL, a RBC < 4,000,000/μL, a platelet count < 150,000/μL, an oral temperature ≥ 38.5°C, a history of fever in the past 72 hours, malaise, and chills were all significantly more likely to occur in persons with any malaria, *P. falciparum*, or *P. vivax*, than in persons with a negative blood film. Low WBC, RBC, and platelet counts were also significant for persons with *P. malariae*, despite the small sample size for this group. Vomiting was a significant predictor in persons with any malaria or *P. falciparum*. Myalgias and lack of cough were significant for any malaria and *P. vivax*. Analysis of persons with high levels of parasitemia produced very similar results to any parasitemia; the lower parasitemia categories showed similar tendencies but with reduced strength and significance.

Factors significant for any of the malaria categories were fit to a logistic regression model using stepwise selection to determine the most significant predictors of malaria for each outcome and the results are shown in Table 5. The three hematologic parameters were significant predictors for the presence of malaria, with the exception of RBCs in *P. vivax* infections. Platelet count showed the strongest association and had the greatest predictive power in each of the models;

TABLE 2
Hematologic values in persons with positive malaria smears compared to the negative control group by sex

Parameter		Men		Women	
		No.*	Mean (median)	No.*	Mean (median)
White blood cells ($10^3/\mu L$)	Negative	615	8.27	363	8.49
	P. falciparum	325	6.22†	89	6.28†
	P. vivax	459	6.71†	186	6.39†
	Mixed *Pf/Pv*	19	6.58‡	4	5.88
	P. malariae	14	5.57†	1	–
Red blood cells ($10^6/\mu L$)	Negative	615	4.97	363	4.52
	P. falciparum	325	4.62†	89	4.34§
	P. vivax	459	4.79†	184	4.28†
	Mixed *Pf/Pv*	19	4.76	4	3.68‡
	P. malariae	14	4.41†	1	–
Hemoglobin (g/dL)	Negative	615	13.77	363	11.91
	P. falciparum	325	12.93†	89	11.51
	P. vivax	459	13.44‡	186	11.59§
	Mixed *Pf/Pv*	19	13.00	4	10.93
	P. malariae	14	11.85†	1	–
Platelets ($10^3/\mu L$)	Negative	615	245.0 (240.0)	363	290.6 (278.0)
	P. falciparum	325	126.3† (114.0)	89	133.6† (130.0)
	P. vivax	459	140.4† (131.0)	186	160.7† (141.0)
	Mixed *Pf/Pv*	19	125.2†	4	228.8
	P. malariae	14	139.1†	1	–
Lymphocytes ($10^3/\mu L$)	Negative	615	2.43	363	2.73
	P. falciparum	325	1.56†	89	1.42†
	P. vivax	459	1.77†	186	1.81†
	Mixed *Pf/Pv*	19	1.52†	4	2.18
	P. malariae	14	2.04	1	–

* Two subjects had missing sex information, one in the negative group and the other in the *Plasmodium vivax* group.
† $P < 0.001$, infected versus control group.
‡ $P < 0.01$, infected versus control group.
§ $P < 0.05$, infected versus control group.

persons with platelet counts < 150,000/μL were 12.5–14.7 times more likely to have any of these malaria outcomes than persons with platelet counts ≥ 150,000/μL. Fever and being ill for less than three days were also indicators in all the final models. Vomiting was a significant predictor in the *P. falciparum* models; malaise and lack of cough were predictors in the *P. vivax* models. A history of fever in the past 72 hours was a significant predictor of any malaria model only. For *P. malariae* infections, only low platelet and RBC counts were significant when controlling for the other factors, and only low platelet count and fever were significant for mixed infections.

DISCUSSION

The decreases observed in this study in WBC and lymphocyte counts associated with malaria infection are striking. While not all studies have found a decrease in leukocytes during malaria infection,[4,5] this alteration is certainly not unprecedented, either for *P. falciparum*[5,6] or for *P. vivax*.[5,7] The decreased levels of circulating lymphocytes were also expected from prior studies.[6–8]

Low platelet counts have been consistently found for both *P. falciparum*[4–6,8,9] and *P. vivax*.[4,7,10–13] A substantial proportion of cases in this study had very low platelet counts,

TABLE 3
Association between parasite densities (parasites/μL) and platelet count($\times 10^3/\mu L$)

	Parasite density range	Men		Women	
		No.*	Mean platelet count	No.*	Mean platelet count
Negative	0	615	245.0	363	290.6
P. falciparum	1–2,225	84	158.5	15	169.4
	2,226–10,300	77	122.9	26	131.0
	10,301–37,000	82	117.5	25	137.3
	>37,000	82	105.2	23	109.0
		Model F value = 8.23 $P < 0.0001$		Model F value = 3.06 $P = 0.03$	
P. vivax	1–525	93	197.0	50	220.7
	526–3,400	131	139.4	43	158.3
	3,401–9,500	108	131.3	52	142.9
	>9,500	127	107.8	41	112.3
		Model F value = 37.94 $P < 0.0001$		Model F value = 19.2 $P < 0.0001$	

* Two subjects had missing sex information, one in the negative group and the other in the *Plasmodium vivax* group.

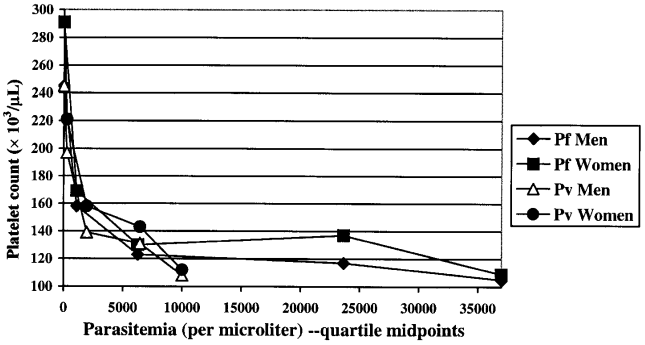

FIGURE 1. Platelet count by parasitemia in the study population. Pf = *Plasmodium falciparum*; Pv = *P. vivax*. The x-axis is truncated and the uppermost Pf quartile midpoint is 268,500.

especially among those with *P. falciparum* infection, 39% of whom had platelet counts less than 100,000/μL. *Plasmodium falciparum* cases with platelet levels below this count have also been documented in other populations of semi-immune[4,5] and non-immune patients.[6]

The trend of decreasing platelet count with increasing levels of parasitemia observed in this study has been previously noted for *P. falciparum*,[4,6] but to our knowledge, has not been documented in the literature for *P. vivax*. Decreased platelet production has been ruled out.[5,11,14] Thrombocytopenia is a result of peripheral destruction and consumption. Immune complexes generated by malarial antigen lead to sequestration of the injured platelets by macrophages in the spleen.[15–18] Platelet consumption in disseminated intravascular coagulation contributes to thrombocytopenia in complicated *P. falciparum* malaria; however, this process is not relevant to the present study population. Platelet dysfunction resulting in hyperaggregation is another alteration occurring in association with malaria resulting in hyperaggregation.[19] During malaria infection, there are several factors that activate platelets, among which are formation of immune complexes and damage to endothelial cells. Surface contact of platelet membrane to with parasitized RBCs is another stimulator.[20] Intravascular lysis of the activated platelets may also occur.[9] Trends between increasing parasite density with a decrease in the level of hematologic parameters other than platelet count were not observed in this study, nor have they been consistently noted in the literature.

Anemia has frequently been associated with malaria. In regions of sub-Saharan Africa with stable, high malaria transmission, severe anemia is common among children or pregnant women infected with *P. falciparum*.[21] Studies among non-immune or semi-immune populations outside Africa have also found statistically significant levels of mild anemia in falciparum malaria patients.[4,5,22,23] *Plasmodium vivax* has been associated with mild anemia in some studies,[7,10,12,24,25] but not in others.[4] Two possible causes of this anemia are increased hemolysis or a decreased rate of erythrocyte production.[26,27] Despite the extensive documentation of anemia in malaria, only mild decreases in Hb were observed in this study. This discrepancy may be related to the multifactorial etiology of anemia. The impact of malaria anemia is greatest in regions of sub-Saharan Africa where underlying anemia and poor nutrition are common. Although a few cases of very low Hb were observed among our study participants, only 16% of all participants had even mild anemia (Hb level < 11.0 g/dL). Furthermore, some observers have suggested that malaria-related anemia is more severe in areas of intense malaria transmission and in younger children rather than in older children or adults.[21,27] While this study and others in southeastern or eastern Asia have noted Hb decreases or mild anemia among malaria cases,[4,7,10,23] the small degree of Hb change observed in this study population may reflect a lower prevalence of underlying anemia, better nutritional status, and/or better access to treatment.

Fever and history of fever are fairly sensitive measures of malaria, but they lack specificity or positive predictive value, especially in regions where malaria is less prevalent. The identification of signs or constellations of signs indicative of malaria could also help to improve appropriate treatment in areas where most people are parasitemic, but malaria diagnosis is still based solely on fever in the presence of any parasitemia.[28]

Studies from various areas have failed to identify factors that can substantially improve upon current measures. The lack of specificity of malaria-associated signs and symptoms has led some researchers to conclude that only fever and history of fever have any real diagnostic value.[29,30] A history of fever in the absence of another major symptom was the best predictor of malaria-positive blood slides in adults in Papua New Guinea,[31] and a study in Zimbabwe concluded that only microscopy could improve diagnostic capabilities beyond those "unknown decision rules" used by health care workers.[29] Combinations of factors have proved slightly better at identifying malaria. In Ethiopia, fever, previous malaria, and pallor was the measure with the best combined sensitivity and specificity.[32] The identification of additional criteria helpful in diagnosing malaria would be of use in this field.

The symptoms found in this study to be independently associated with the presence of malaria parasites have been well recognized: oral temperature ≥ 38.5°C, history of fever in the past 72 hours, malaise, chills, and (for *P. falciparum*) vomiting. Associations between low WBC, RBC, or platelet counts and malaria infection are not as widely acknowledged, in part because they are not routinely obtained at malaria clinics. These parameters, however, appear to have the strongest independent measures of association besides fever; crude odds ratios as high as 23 are observed for low platelet count and the presence of *P. falciparum*. Even when controlling for other clinical factors, platelet count still has a higher predictive value for malaria infection than any symptoms. A person from this study population infected with *P. falciparum* is almost 15 times more likely to have a low platelet count (< 150,000/μL) than a malaria-negative one, adjusting for fever, vomiting, days ill, RBCs, and WBCs.

Platelet count may be of limited diagnostic applicability in settings where health care workers must operate without even the benefits of a microscope. However, in Thailand, capability of a routine CBC is available at all district-level hospitals. Interestingly, malaria diagnosis at those hospitals is sometimes less accurate than at malaria clinics because of reliance on only thin blood films or the limited experience of hospital microscopists in detecting malaria parasites or in reading a thick smear compared with specially-trained malaria clinic microscopists. Also, patients presenting to district hospitals often have prior self-treatment with ineffective or sub-

TABLE 4
Independent associations between symptoms or hematologic parameters and malaria infection*

		Negative (n = 979)	*P. falciparum* (n = 414)			*P. vivax* (n = 646)			*P. malariae* (n = 15)		
		No.	No.	OR	95% CI	No.	OR	95% CI	No.	OR	95% CI
Age (years)	< 40	833	364	Ref		566	Ref		14	Ref	
	≥ 40	146	50	0.8	(0.6, 1.1)	80	0.8	(0.6, 1.1)	1	0.4	(0.1, 3.1)
White blood cells/μl	< 5,000	67	112	4.2	(3.0, 5.8)†	135	3.0	(2.2, 4.1)†	5	5.3	(1.8, 15.9)‡
	5,000–10,000	709	284	Ref		474	Ref		10	Ref	
	> 10,000	203	18	0.2	(0.1, 0.4)†	37	0.3	(0.2, 0.4)†	0	–	–
Red blood cells/μL	< 4,000,000	75	80	2.9	(2.1, 4.1)†	81	1.7	(1.2, 2.4)‡	7	10.5	(3.7, 29.9)†
	≥ 4,000,000	904	334	Ref		565	Ref		8	Ref	
Platelets/μl	< 150,000	79	279	23.5	(17.3, 32.1)†	377	16.0	(12.1, 21.1)†	11	31.3	(9.7, 101)†
	≥ 150,000	900	135	Ref		269	Ref		4	Ref	
Headache	No	14	5	Ref		11	Ref		2	Ref	
	Yes	965	409	1.2	(0.4, 3.3)	635	0.8	(0.4, 1.9)	13	0.1	(0.02, 0.5)†
Fever (°C)	< 38.5	850	195	Ref		412	Ref		13	Ref	
	≥ 38.5	129	219	7.4	(5.7, 9.7)†	234	3.7	(2.9, 4.8)†	2	1.0	(0.2, 4.5)
History of fever, past 72 hours	No	67	7	Ref		17	Ref		1	Ref	
	Yes	912	407	4.3	(1.9, 9.4)†	629	2.7	(1.6, 4.7)†	14	1.0	(0.1, 7.9)
Vomiting	No	792	259	Ref		510	Ref		14	Ref	
	Yes	187	155	2.5	(2.0, 3.3)†	136	1.1	(0.9, 1.4)	1	0.3	(0.03, 2.3)
Malaise	No	433	105	Ref		165	Ref		5	Ref	
	Yes	546	309	2.3	(1.8, 3.0)†	481	2.3	(1.9, 2.9)†	10	1.6	(0.5, 4.7)
Myalgias	No	58	15	Ref		20	Ref		2	Ref	
	Yes	921	399	1.7	(0.9, 3.0)	626	2.0	(1.2, 3.3)‡	13	0.4	(0.1, 1.9)
Cough	No	788	340	1.1	(0.5, 1.5)	559	1.6	(1.2, 2.1)‡	12	1.0	(0.3, 3.5)
	Yes	191	74	Ref		87	Ref		3	Ref	
Diarrhea	No	957	403	Ref		634	Ref		15	Ref	
	Yes	22	11	1.2	(0.6, 2.5)	12	0.8	(0.4, 1.7)	0	–	–
Chills	No	227	48	Ref		75	Ref		2	Ref	
	Yes	752	366	2.3	(1.6, 3.2)†	571	2.3	(1.7, 3.0)†	13	2.0	(0.4, 8.8)
Days ill	≤ 3	719	311	1.1	(0.8, 1.4)	500	1.2	(1.0, 1.6)	9	1.8	(0.6, 5.2)
	> 3	260	103	Ref		146	Ref		6	Ref	

* OR = odds ratio; CI = confidence interval; Ref = referent.
† $P < 0.001$.
‡ $P < 0.01$.

therapeutic doses of antimalarials. Such treatment may suppress the parasites or distort their morphology, but not fully eliminate them. Therefore, in this malaria-endemic area, an acutely febrile patient with low platelet count and a reduced WBC count, irrespective of a malaria smear report, should always be thoroughly re-evaluated for malaria. A recent study also identified a prognostic value for thrombocytopenia in African children, with a lower platelet count associated with more severe illness or outcome.[33] While prognosis could not be evaluated in this study, platelets might play a similar role in this population.

This study used very rigorous microscopy procedures, which should minimize misclassification of malaria status. Additionally, the large sample size and high proportion of malaria cases give this analysis substantial power to detect differences between cases and controls. Daily quality control checks of the automated cell counters maintained the accuracy and precision of the hematologic measurements.

One limitation of this study is that the controls are symptomatic, febrile individuals, and therefore do not represent a healthy population. They are likely to have had a diverse collection of bacterial and viral ailments that could affect the

TABLE 5
Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for parameters associated with malaria infection

	Any malaria		*P. falciparum*		*P. vivax*	
	OR	95% CI	OR	95% CI	OR	95% CI
White blood cells < 5000/μL	1.6	(1.1, 2.2)	1.2	(0.8, 1.9)	1.6	(1.1, 2.4)
White blood cells > 10,000/μL	0.3	(0.2, 0.5)	0.2	(0.1, 0.4)	0.4	(0.2, 0.5)
Red blood cells < 4,000,000/μL	1.7	(1.2, 2.5)	1.9	(1.2, 3.1)		–
Platelets < 150,000/μL	12.8	(9.7, 16.9)	14.7	(10.4, 21.3)	12.5	(9.3, 16.9)
Fever ≥ 38.5°C	2.4	(1.8, 3.1)	3.3	(2.3, 4.6)	1.8	(1.3, 2.5)
Days ill ≤ 3	1.9	(1.5, 2.5)	2.2	(1.5, 3.2)	2.0	(1.5, 2.8)
History of fever, 72 hours	1.9	(1.0, 3.3)		–		–
Malaise	1.5	(1.2, 1.9)		–	1.9	(1.4, 2.5)
No cough	1.4	(1.0, 1.8)		–	1.5	(1.1, 2.1)
Vomiting		–	1.9	(1.3, 2.7)		–
Logistic regression	Model $R^2 = 0.35$ Wald $\chi^2 = 523$ $P < 0.0001$		Model $R^2 = 0.36$ Wald $\chi^2 = 383$ $P < 0.0001$		Model $R^2 = 0.31$ Wald $\chi^2 = 396$ $P < 0.0001$	

measured hematologic variables in different ways. Nonetheless, the mean hematologic parameters for the control group fell within the standard normal ranges measured in other populations. Another caution in interpreting our data is that the statistically significant differences found between malaria cases and controls in many of the measured parameters do not necessarily indicate clinical significance.

Although these basic hematologic changes in association with malaria are not new to the subject, our data add more detailed information to the limited body of knowledge. The observations of thrombocytopenia and lymphopenia are in accordance with those reported in non-immune individuals,[6] and are unlike observations reported from sub-Saharan Africa. This study implies that malaria must always be a key differential diagnosis in acutely febrile patients with thrombocytopenia and leukopenia from this endemic area. This is the first documentation that the parallel trend in thrombocytopenia with parasitemia is not only unique for infection with *P. falciparum*, but also with *P. vivax*. Greater exploration of the strong, inverse relationship between platelet levels and malaria infection may afford means to improve diagnosis and alleviate the clinical severity of or accelerate recovery from this disease.

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