Diagnostic Value of Platelet and Leukocyte Counts in the Differential Diagnosis of Fever in the Returning Traveler

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Abstract. Malaria, arbovirus infection and travelers' diarrhea are among the most common etiologies of fever after a stay in the tropics. Because the initial symptoms of these diseases often overlap, the differential diagnosis remains a challenge. The aim of this study was to establish the effectiveness of platelet and leukocyte counts in the differential diagnosis of fever in the returning traveler. Between 2013 and 2016, patients with a clinical suspicion of malaria, who had thick blood smears performed were retrospectively included. The microbiological etiology of each episode was established based on molecular detection in the case of arbovirus infection, the detection of pathogens in stool samples for diarrhea and other gastrointestinal symptoms and the thick and thin blood smear results for malaria. A total of 1,218 episodes were included. Malaria, arbovirus infection, and diarrhea and other gastrointestinal symptoms caused 102 (8.4%), 68 (5.6%), and 72 (5.9%) episodes, respectively. The median platelet counts in malaria episodes were $89 \times 10^9/L$ and thrombocytopenia ($< 150,000 \times 10^9$ platelets/L) yielded a 98% negative predictive value to predict malaria. The median leukocyte counts in arbovirus infection episodes were $3.19 \times 10^9/L$ and leucopenia ($< 4 \times 10^9$ leukocytes/L) yielded a 97.9% negative predictive value to predict arbovirus infections. Platelet and leukocyte counts were not significantly altered in episodes caused by diarrhea and other gastrointestinal symptoms. Initial platelet and leukocyte counts might be useful for the clinical differential diagnosis of fever in the returning traveler. Although these results are insufficient to establish a diagnosis, they should be considered in the initial clinical assessment.

INTRODUCTION

Fever is one of the main reasons to attend emergency departments in travelers returning from tropical areas. Malaria, arbovirus infection, and travelers' diarrhea are among the most common etiologies of fever after a stay in the tropics.^{1–3} The initial clinical presentation for all these diseases is frequently unspecific and might include fever, arthralgia, headache, myalgia, and gastrointestinal symptoms. In consequence, the differential diagnosis based on clinical symptoms remains a challenge. Because of the increasing number of people travelling abroad and the difference in severity, outcome, and treatment of each condition, early diagnosis is crucial for the successful management of the patient, especially for life-threatening conditions such as malaria and severe dengue. Diagnostic predictors such as abnormalities in hematological parameters may be useful because they can suggest the etiology before the definitive microbiological diagnosis.

Acute malaria is often associated with mild or moderate thrombocytopenia in nonimmune adults and in children from malaria-endemic areas, and is a sensitive but nonspecific indicator of infection with malaria parasites. Profound thrombocytopenia is unusual. Malarial thrombocytopenia is rarely associated with hemorrhagic manifestations or disseminated intravascular coagulation either in nonimmune adults or children in endemic areas.^{4–6}

Arbovirus infections are commonly accompanied by thrombocytopenia and also by leucopenia. Potts and Rotham⁷ reviewed differences in laboratory indicators between patients with dengue and other febrile illnesses (measles, typhoid fever, leptospirosis, and severe acute respiratory syndrome)

in endemic areas and found that leukocyte and platelet counts were significantly lower among patients with dengue. Moreover, in endemic areas leukocyte parameters have been used for diagnostic models of dengue in combination with clinical symptoms.⁸ The same modifications in hematological parameters have been reported for Zika,⁹ chikungunya, and other arbovirus infections. These parameters are sensitive for arbovirus infection, but they lack specificity, as they vary among different arbovirus infections¹⁰ and they heighten in more severe cases.^{7,11}

Travelers' diarrhea and other gastrointestinal symptoms after a stay in a tropical or subtropical area can be caused by bacterial, viral, and parasitic pathogens. Laboratory indicators vary depending on the microbiological agent and its virulence. Few studies document abnormalities in hematological parameters as an indicator for travelers' diarrhea, except for enteric fever, which is commonly associated with thrombocytopenia and either leucopenia or leukocytosis.^{12–15}

The aim of this study was to establish the diagnostic effectiveness of leukocyte and platelet counts in the differential diagnosis of patients returning from tropical or subtropical areas with a clinical suspicion of malaria.

MATERIALS AND METHODS

Patients. The study was conducted at the Hospital Clinic i Provincial de Barcelona (an 800-bed teaching hospital in Barcelona, Spain). Following current clinical guidelines, screening for malaria in all febrile patients returning from tropical and subtropical areas is performed. This protocol includes fever measured using a thermometer and also a history of fever reported by the patient. Cases for this study were selected based on the thick and thin blood smear tests for malaria requested by the attending physician. All thick blood smears performed in the microbiology and parasitology

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department between 2013 and 2016 were retrospectively analyzed. Thick blood smears performed as a control of the evolution in already diagnosed patients were excluded, and only the first thick blood smear of each episode was analyzed. Date of analysis, last visited country, identified *Plasmodium* species, and parasite density were collected for each episode and patient. In addition, the results from the different diagnostic methods to detect arbovirus infections and data on bacterial and parasitic intestinal pathogens were collected retrospectively. Finally, platelet and leukocyte counts at the beginning of each malaria-suspected episode (± 3 days difference from the date of performance of the first thick and thin blood smear) were collected retrospectively.

Diagnostic procedures. The diagnosis of malaria was defined by the presence of *Plasmodium* trophozoites in the thick and thin blood smears. In addition, a rapid diagnostic test (BinaxNOW Malaria, Alere, Ireland) was performed in some cases depending on the last visited country and the chemoprophylaxis taken by the patient. In cases where the *Plasmodium* species could not be established solely by microscopy, a commercial nested polymerase chain reaction (PCR) with specific primers for *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale* was performed (BIOMALAR Gel Form Kit; BioTools, Madrid, Spain). PCR products were visualized in a 2% agarose gel.

Confirmed arbovirus infections were defined based on a positive specific real-time reverse transcription polymerase chain reaction (RT-PCR) for dengue, chikungunya, or Zika in serum or urine samples within the malaria suspected episode. An in-house multiplex real-time PCR was used for the molecular diagnosis of the four dengue serotypes using EXPRESS One-Step SuperScript qRT-PCR (Thermo Fisher, Madrid, Spain).¹⁶ For the molecular diagnosis of chikungunya and Zika, two different commercial real-time RT-PCR were performed: RealStar chikungunya RT-PCR (Altona Diagnostics, Hamburg, Germany) and RealStar Zika RT-PCR (Altona Diagnostics).

The diagnosis of travelers' diarrhea or presence of other intestinal pathogens was established with the detection of viral, bacterial, or parasitic pathogens in a stool sample collected during the same episode as the thick blood smear.

The routine methods for the detection of bacterial pathogens were cultures of the stool sample in Blood agar (Oxoid®; Thermo Fisher), MacConkey agar (Becton Dickinson®, Heidelberg, Germany), CCDA agar (Becton Dickinson®) for *Campylobacter* isolation, Salmonella Shigella (SS) agar (Becton Dickinson®) for *Shigella* and *Salmonella* isolation, Cefsulodin-Irgasan-Novobiocin (CIN) agar (Becton Dickinson®) for *Yersinia* isolation, and Rappaport-Vassiliadis *Salmonella* Enrichment Broth (Becton Dickinson®) for the recovery of *Salmonella* and latter planting onto SS agar. The isolated bacteria were identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker, Bremen, Germany), and the *Salmonella/Shigella* identified were serotyped by agglutination with commercial antisera (Bio-Rad®, Marnes-la-Coquette, France). An in-house multiplex PCR^{15,17} was used for the detection of virulence genes of diarrheagenic *Escherichia coli* targeted to CVD432 probe of enteroaggregative *E. coli* and the *lt* and *st* genes of enterotoxigenic *E. coli*. PCR products were visualized in a 2% agarose gel.

Parasitic pathogens were detected by direct microscopic observation from fresh and concentrated stool samples with

the merthiolate formalin ether method and the modified Kinyoun acid-fast stain from the concentrated samples for the detection of *Cryptosporidium* and *Cyclospora cayetanensis*.

The detection of rotavirus and adenovirus was performed with a rapid immunochromatographic test (bioNexia®; Rota-Adeno, Marcy-l'Etoile, France) from stool samples.

The different diagnostic techniques were performed based on diagnostic suspicion and clinical criteria. We should emphasize that there was no clinical request for Norovirus detection in the group of patients included in the study.

Statistical analysis. Clinical, epidemiologic, and laboratory data were collected on standardized forms and entered in a password protected database. Univariate and multiple logistic regression models were fitted for all clinical variables available using etiology as dependent variables. Interaction of independent variables was checked using the likelihood ratio test.

The area under the receiver operating characteristic (ROC) curves was used to compare the sensitivity and specificity of selected markers. Cutoff values were chosen based on the highest sensitivity and specificity to predict outcome using the "roctab/detail" function (Stata 11.0; Stata Corporation, College Station, TX). When the diagnostic performance was assessed for more than one variable, the estimates were derived from a logistic regression model using the selected markers or clinical features as independent variables and the condition to diagnose as the dependent variable. These analyses were carried out using the "Iroc," "Istat," and "roctab/graph" functions in Stata. Data were analyzed with STATA 11.

RESULTS

Characteristics of the study population and geographic distribution. During the study period, 1,218 episodes belonging to 1,185 patients returning from tropical or subtropical areas with a clinical suspicion of malaria were included in the study, and 46.8% were female. The most commonly visited area was sub-Saharan Africa (47.5%), followed by Southern Asia/Pacific (31.3%), Latin America (19.5%), and North Africa/Middle East (1.6%).

Among patients diagnosed with malaria, 85.3% had returned from sub-Saharan Africa; the single country with most malaria cases was Equatorial Guinea. Sub-Saharan Africa was the origin of 93% of patients diagnosed with *P. falciparum* malaria and all patients diagnosed with *P. malariae* and *P. ovale* malaria. Patients diagnosed with *P. vivax* malaria had arrived from South Asia/Pacific (55.6%) and Latin America (44.4%). Patients with arbovirus infection were mostly diagnosed after a stay in Southern Asia/Pacific (52.9%) and Latin America (44.1%), with Thailand and Indonesia as the most frequently visited countries. The distribution of patients with travelers' diarrhea and parasitic intestinal pathogens was more heterogeneous, although the most frequently visited region was sub-Saharan Africa (41.7%), and the most frequent visited country was India. Figure 1 shows the geographical distribution of the cases diagnosed with malaria and arbovirus infection.

Confirmed etiologic diagnosis. A confirmed etiologic diagnosis of arbovirus infection, malaria, or travelers' diarrhea and other intestinal pathogens was found in 238 (19.5%) cases. Malaria was responsible for 102 episodes (8.4%), arbovirus infection for 68 episodes (5.6%), and traveler's

FIGURE 1. Geographic destination of travelers included in the study with malaria and confirmed arbovirus infection from 2013 to 2016. This figure appears in color at www.ajtmh.org.

diarrhea and other gastrointestinal symptoms for 72 episodes (5.9%) (Table 1). Four patients were diagnosed with more than one tropical infection: three cases of malaria and an intestinal pathogen and one case of arbovirus infection and an intestinal pathogen.

Among the malaria-confirmed cases, the most common species was *P. falciparum*, followed by *P. vivax*, *P. ovale*, and *P. malariae*. In one case, neither microscopic nor molecular methods could determine the *Plasmodium* species. The median parasitemia was 0.6% (IQR: 0.05–3.6). The most frequently found arbovirus was dengue, followed by chikungunya and Zika.

Regarding gastrointestinal symptoms, 40 cases were caused by a bacterial pathogen and 32 by a parasitic pathogen. However, we did not perform molecular or serological investigations to look for potential viruses associated with gastrointestinal (GI) symptoms. Diarrheagenic *E. coli* was the most commonly identified bacterial agent and *Giardia lamblia* and *Blastocystis hominis* were the most commonly identified parasitic agents. The latter probably not being the cause of infection. Table 1 shows the etiology of all intestinal pathogens identified.

Leukocyte and platelet counts may help establish fever etiology. Figure 2 shows a scatter plot with the distribution of platelets and leukocytes counts according to the different etiologies, and Table 2 shows the median leukocyte and platelet counts according to the malaria and arbovirus etiologies. The four episodes with more than one etiology were

TABLE 1

Etiology of infection in travelers presenting with acute febrile illness with a suspected diagnosis of malaria

Aetiology	Number (%)	N	%
Unknown	979 (80.4)*		
Arbovirus	68 (5.6)*		
Dengue		50	73.5
Chikungunya		12	17.7
Zika		6	8.8
Malaria	102 (8.4)*		
<i>Plasmodium falciparum</i>		86	84.3
<i>Plasmodium vivax</i>		9	8.8
<i>Plasmodium ovale</i>		4	3.9
<i>Plasmodium malariae</i>		2	2.0
<i>Plasmodium</i> spp.		1	1.0
Traveller's diarrhea	40 (3.3)*		
EAEC		21	52.5
ETEC		10	25.0
ETEC + <i>Shigella flexneri</i>		1	2.5
<i>Campylobacter jejuni</i>		3	7.5
<i>Salmonella typhimurium</i>		2	5.0
<i>Salmonella</i> spp.		1	2.5
<i>Vibrio</i> spp.		1	2.5
<i>Shigella sonnei</i>		1	2.5
Intestinal parasites	32 (2.6)*		
<i>Blastocystis hominis</i>		10	31.3
<i>Cyclospora cayentanensis</i>		1	3.1
<i>Entamoeba histolytica/dispar</i>		3	9.4
<i>E. histolytica/dispar</i> + <i>Iodamoeba butschlii</i>		1	3.1
<i>E. histolytica/dispar</i> + <i>Chilomastix mesnili</i>		1	3.1
<i>E. histolytica/dispar</i> + <i>Giardia lamblia</i>		1	3.1
<i>G. lamblia</i>		11	34.4
<i>G. lamblia</i> + <i>C. mesnili</i>		1	3.1
<i>G. lamblia</i> + <i>C. mesnili</i> + <i>Cryptosporidium</i> sp.		1	3.1
<i>Hymenolepis nana</i>		1	3.1
<i>Schistosoma intercalatum</i> + <i>Trichuris trichiura</i>		1	3.1

EAEC = enteraggereactive *Escherichia coli*; ETEC = enterotoxigenic *E. coli*.

* Percentages may not total 100 because patients may have more than one diagnosis.

classified in the malaria and arbovirus infection group because it is known that these diseases cause more abnormalities in platelet and leukocyte counts. Although some overlap was found, malaria presented a major trend toward thrombocytopenia without affecting leukocyte counts. In the cases of arbovirus, both leucopenia and thrombocytopenia were observed.

Malaria. Figure 3A shows the platelet distribution among patients with and without malaria. Platelet counts were significantly lower ($P < 0.001$) in patients with malaria compared with patients without malaria. The ROC curve analysis for platelet count and malaria yielded an area under the curve of 0.89 (95% CI: 0.86–0.93, $P < 0.05$) (Figure 4B). Applying a cutoff value of $150,000 \times 10^9/L$ (thrombocytopenia), the sensitivity, specificity, negative and positive predictive values were 82.4%, 82.9%, 98.1%, and 30.6%, respectively. There was a higher tendency toward thrombocytopenia in episodes caused by *P. falciparum* than for the other *Plasmodium* species, but these differences were not statistically significant. A weak but significant inverse correlation between parasitemia levels and platelet counts was observed ($r = -0.31$, $P < 0.01$). Eighteen patients diagnosed with malaria did not have thrombocytopenia. In 16 cases, it was caused by *P. falciparum* in patients returning from sub-Saharan Africa, one case was caused by *P. vivax* in a patient returning from Pakistan, and one case was caused by *P. ovale* in a patient returning from

FIGURE 2. Distribution of white blood cell and platelet counts on admission in travelers with malaria and arbovirus infection. This figure appears in color at www.ajtmh.org.

Cameroon. Among the *P. falciparum* cases, three patients were travelers of sub-Saharan Africa origin living in a nonendemic area and visiting family or relatives in their country of origin, five patients had undergone previous episodes of malaria in previous travels to endemic areas, one patient was already under treatment when the platelet count was performed, and one patient was splenectomized.

Arbovirus infection. Both platelet and leukocyte counts in patients with arbovirus infection were significantly lower ($P < 0.001$) compared with patients without arbovirus infection (Table 2, Figure 4A). The ROC curve analysis for platelet and leukocyte counts and arbovirus infection yielded an area under the curve of 0.71 for platelet counts and 0.88 for leukocyte counts (Figure 4B). Applying a cutoff value of 4.00×10^9 leukocytes/L (leucopenia), the sensitivity, specificity, negative and positive predictive values were 72.1%, 87.3%, 98.1%, and 25.1%, respectively. The median platelet counts for patients with dengue, chikungunya, and Zika were 143, 223, and 155 ($\times 10^9/L$), respectively. The median leukocyte counts for patients with dengue, chikungunya, and Zika were 2.68, 3.24, and 3.55 ($\times 10^9/L$), respectively. The platelet and leukocyte levels were significantly lower in episodes caused by dengue ($P = 0.002$ and $P = 0.004$, respectively) compared with episodes caused by chikungunya.

The ROC curve for leukocyte counts, including only arbovirus infection and malaria cases, yielded an area under the curve of 0.78, and leucopenia had sensitivity, specificity, negative and positive predictive values of 72.1%, 59.8%, 78.4%, and 67.7%, respectively, to differentiate arbovirus infection from malaria.

TABLE 2

Platelet and leukocyte counts according to the etiology of fever in the returning traveler

Etiology (N)	Platelet counts ($10^9/L$)		Leukocyte counts ($10^9/L$)	
	Median	IQR	Median	IQR
Malaria (102)	89	52–135	4.75	3.73–6.00
Arbovirus infection (68)	154	120–1953	3.19	2.24–4.18
Travelers' diarrhea bacteria (40)	257	204–308	7.28	5.39–8.63
Intestinal parasites (32)	209	146–264	6.37	4.89–9.31
Unknown (979)	215	175–257	6.77	5.12–9.21

Travelers' diarrhea and other intestinal pathogens. No hematological parameter was significantly altered for patients, where a parasitic intestinal pathogen was identified. Platelet levels among patients with diarrhea of bacterial etiology were significantly higher ($P < 0.001$) compared with patients without this etiology. However, none showed a platelet count greater than $450,000 \times 10^9/L$ (thrombocythemia¹⁸). Leukocyte levels were not significantly altered in patients with travelers' diarrhea of bacterial etiology.

DISCUSSION

In this study, we have shown that an initial laboratory screening using hematological parameters such as platelet and leukocyte counts might assist the clinical differential diagnosis in returning travelers. Indeed, we show that in the case of malaria, platelet counts under $150,000 \times 10^9/L$ (thrombocytopenia) have sensitivity and specificity values of 82.4%, and 82.9%, respectively, and a negative predictive value of 98.1%. Although this diagnostic performance is not sufficient to establish a diagnosis, the clinician can use its high negative predictive value to consider diagnoses other than malaria in an initial assessment. Moreover, we show an inverse correlation between parasitemia levels and platelet count, indicating that levels of thrombocytopenia can be used as a predictive factor of severity in malaria. Few publications directly correlate parasitemia with lower platelet counts, and this correlation has mainly been presented in *P. vivax* malaria.^{19–21} Thrombocytopenia in the absence of significant bleeding is not considered a clinical manifestation for severe malaria.²² However, some studies correlate the levels of thrombocytopenia with malaria severity.^{23–25} Our results show a tendency for *P. falciparum* malaria to have lower platelet counts compared with other malaria species. These results agree with previous studies,^{25,26} although other publications²⁷ show that *P. vivax* infection presents higher rates of thrombocytopenia. Our study does not have enough cases of *non-falciparum* malaria to verify if thrombocytopenia is a discriminating feature for a particular type of malaria.

Among patients diagnosed with *P. falciparum* malaria without thrombocytopenia, we show a high rate of patients with previous episodes of malaria (8/16). It is known that the repeated exposure to malaria parasites is associated with semi-immunity against malaria and a reduced risk of severe malaria.²⁸ Some studies have shown that malaria severity is lower in patients of sub-Saharan Africa origin living in non-endemic areas and visiting family or relatives in their country of origin.^{29,30} In addition, different hematological patterns have been observed in semi-immune patients compared with nonimmune patients, including a lower rate of severe thrombocytopenia.^{23,30} These findings could explain the lack of thrombocytopenia in patients previously exposed to malaria.

We have shown that low platelet counts are not specific to malaria because they are also associated with arbovirus infections. However, in arbovirus infections, we usually find concomitant leucopenia.⁷ In this study, we observed statistically lower leukocyte and platelet levels associated with dengue, chikungunya, and Zika. In our sample, leukocyte levels show a better diagnostic performance than platelets because leukocyte levels are more specifically altered in arbovirus infections.

FIGURE 3. Platelet distribution in malaria and non-malaria cases (A) and diagnostic performance (area under the receiver operating characteristic [ROC] curve) for platelet counts to discriminate malaria and non-malaria cases (B). Dotted line indicates the cutoff value for thrombocytopenia. This figure appears in color at www.ajtmh.org.

Leukocyte counts of 4.00×10^9 leukocytes/L or less (leukopenia) have sensitivity and specificity values of 72.1% and 87.3%, respectively, and a negative predictive value of 98.1% for the detection of arbovirus infection. In addition, leukopenia showed a negative predictive value of 78.4% to differentiate malaria from arbovirus infection.

In agreement with previous studies,¹⁰ our results show that leukopenia and specially thrombocytopenia are more severe in dengue compared with chikungunya cases. No statistical significance in hematological parameters is shown for episodes caused by Zika due to the low number of included cases, since we only started testing for Zika virus in 2016, after the large 2015 Brazil outbreak.³¹ However, in agreement with previously reported cases, Zika cases in our study presented mild leukopenia.^{32,33}

No hematological parameter was significantly altered in episodes of travelers' diarrhea or where parasitic intestinal pathogens were identified, probably because of the lack of invasiveness of parasitic and bacterial agents causing gastrointestinal symptoms. *Blastocystis hominis* or *Hymenolepis nana* were identified in some episodes. Probably, in these cases the focus of fever was other than gastrointestinal but a parasitic study was additionally demanded by the clinician because of gastrointestinal symptoms or other epidemiological characteristics.

FIGURE 4. Leukocyte distribution in arbovirus and non-arbovirus cases (A) and diagnostic performance (area under the receiver operating characteristic [ROC] curve) for leukocyte counts to discriminate arbovirus and non-arbovirus infection cases (B). This figure appears in color at www.ajtmh.org.

In the cases included in our study, the country visited did not provide a major insight into the etiology. Most cases of *P. falciparum* malaria came from sub-Saharan Africa, particularly from Equatorial Guinea. However, because Equatorial Guinea is a former Spanish colony, and therefore a preferred destination, we do not consider it to reflect the severity of malaria in this country. Most cases of arbovirus infection arrived from Southern Asia/Pacific and Latin America. Our results show that the distribution of travelers' diarrhea and other gastrointestinal symptoms is more heterogeneous among tropical areas. These findings are in agreement with previously reported epidemiological information.³⁴

This study has several limitations. First, underlying conditions that could potentially alter leukocyte or platelet counts were not systematically investigated. Second, some of the selected cases may not correspond to acute febrile illness but rather to reported fevers. Finally, diagnoses other than malaria and arbovirus infection were not analyzed. These limitations would explain the large number of episodes of unknown etiology included in the study, although previous studies show a 25% rate of undiagnosed episodes of fever after travelling to the tropics.^{3,35} However, platelet and leukocyte counts were able to set apart malaria and arbovirus infections from other conditions. These indicators are inexpensive, easily available,

and can provide useful information in the differential diagnosis of returning travelers presenting with fever.

In conclusion, this study provides quantitative evidence for the potential role of platelet and leukocyte counts as diagnostic predictors of malaria and arbovirus infection, two of the most common causes of fever in the returning traveler and which may rapidly evolve into severe diseases. These parameters can be used as an initial guidance to accelerate the definitive diagnosis and administer the appropriate treatment.

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