ORIGINAL ARTICLE

Factors associated with malaria and arboviral disease in patients with imported febrile syndrome: a retrospective cohort study

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Objective. To identify predictors of malaria and arboviral disease in patients with febrile syndrome who seek care after traveling from tropical or subtropical locations.

Methods. Observational retrospective cohort study. We collected demographic, epidemiologic, and clinical data; laboratory findings; and the clinical and final microbiologic diagnoses. Multivariate analysis was used to calculate indices of diagnostic accuracy (sensitivity, specificity, and predictive values) and coefficients of probability of combinations of variables.

Results. Data for 291 patients with febrile syndrome were included; 108 had malaria (37.1%), 28 had an arboviral disease (9.6%), and 155 had other causes of fever (53.3%). Multivariate analysis showed patients most likely to have malaria were those from sub-Saharan Africa, adjusted odds ratio (aOR) of 45.85 (95% CI, 9.45-222.49); immigrants who returned to visit friends and relatives (VFR), aOR of 3.55 (95% CI, 1.21-10.46); or had platelet concentrations <150 000/mm^3, aORa of 16.47 (95% CI, 5.46-49.70) or headache, aOR of 10.62 (95% CI, 3.20-35.28). The combination of these 4 variables gave a positive probability coefficient (PPC) of 23.72 (95% CI, 5.76-97.62). Patients with febrile syndrome most likely to have an arboviral disease were those from Central or South America, OR 5.07 (95% CI, 1.73-14.92), and those who had exanthems, OR 5.10 (95% CI, 1.72-17.02) or joint pain, OR 14.50 (95% CI, 3.05-68.80). The combination of these 3 variables gave a PPC of 20.66 (95% CI, 7.74-55.21).

Conclusions. Patients with febrile syndrome with the greatest probability of having malaria are those from sub-Saharan Africa, those who are VFR, and those with platelet concentrations under 150.000/µL or headache. Arboviral disease was more likely in patients from Central and South America who had exanthems or joint pain.

Keywords: Malaria. Dengue. Arboviral diseases. Fever. Travel. Travel medicine. Travel-related disease.

Factores asociados con malaria y arboviriasis en pacientes con síndrome febril importado: estudio de cohortes retrospectivo

Objetivos. Definir variables predictoras de malaria y arboviriasis en pacientes que consultan por síndrome febril tras la vuelta de un viaje a zonas tropicales/subtropicales.

Método. Estudio de cohortes retrospectivo. Se incluyeron variables demográficas, epidemiológicas, clínicas, analíticas y el diagnóstico final clínico y microbiológico. Se realizó un análisis multivariante y se calcularon los índices de exactitud diagnóstica (sensibilidad, especificidad, valores predictivos) y cocientes de probabilidad de la combinación de dichas variables.

Resultados. Se incluyeron 291 pacientes con síndrome febril, 108 tenían malaria (37,1%), 28 arboviriasis (9,6%) y 155 otras causas de fiebre (53,3%). En el análisis multivariante, los pacientes con síndrome febril con más riesgo de padecer malaria fueron los que procedían de África subsahariana [*odds ratio* ajustado (ORa): 45,85; IC 95%: 9,45-222,49], eran inmigrantes que visitan a familiares y amigos (VFA) (ORa = 3,55; IC 95%: 1,21-10,46), presentaban cifras de plaquetas < 150.000/mm^3 (ORa = 16,47; IC 95%: 5,46-49,70) o cefalea (ORa = 10,62; IC 95%: 3,20-35,28). La combinación de estas cuatro variables tiene un cociente de probabilidad positivo (CPP) de 23,72 (IC 95%: 5,76-97,62). Los pacientes con síndrome febril que tienen más riesgo de padecer arboviriasis eran los que procedían de Centroamérica y Sudamérica (OR = 5,07; IC 95%: 1,73-14,92), presentaban exantema (OR = 5,10; IC 95%: 1,72-17,02) o artromialgias (OR = 14,50; IC 95%: 3,05-68,80). La combinación de estas tres variables tiene un CPP de 20,66 (IC 95%: 7,74-55,21).

Conclusiones. Los pacientes con síndrome febril que tienen más riesgo de padecer malaria son los que procedían de África subsahariana, eran VFA, presentaban cifras de plaquetas < 150.000/µl o cefalea, y tenían mayor riesgo de padecer arboviriasis si procedían de Centroamérica y Sudamérica, presentaban exantema o artromialgias.

Palabras clave: Malaria. Dengue. Arboviriasis. Fiebre. Viajero. Medicina del viajero. Enfermedades relacionadas con el viaje.

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Introduction

Fever is the most frequent reason for consultation in travelers from tropical and subtropical regions after diarrhea, affecting 10-20%.[1-4] Fever usually occurs within 2 weeks of return, but in about 10% of cases, it occurs 6 months or even years after return.[5] Many travelers present to hospital emergency departments (ED) in the first instance, especially when the causative disease has a short incubation period, and symptoms present acutely.[6,7] Most health care professionals are often unsure when confronted with an imported febrile syndrome due to a lack of practice and acquired knowledge of tropical diseases, lack of protocols, broad differential diagnosis, and sometimes tricky access to rapid diagnostic tests.[8-10]

Some tropical diseases can be severe and potentially fatal when not diagnosed and treated correctly in time, such as malaria, typhoid fever, or leptospirosis.[11,12] Malaria is the leading cause of febrile syndrome in travelers from sub-Saharan Africa.[13-16] Some studies have evaluated predictors of malaria in patients with the imported febrile syndrome,[17-19] none of them were carried out in Spain.

Arboviruses are another frequent cause of fever in travelers, especially the dengue virus.[20]

The rest of the arboviruses presented increased cases in non-endemic areas following the Chikungunya epidemic in the Indian Ocean (2007). In the Caribbean, Central, and South America (2013), and subsequently, the Zika epidemic in 2015.[21,22] The clinical course is usually not severe. However, it is important to recognize arboviruses because of the comorbidity that they can generate, especially the Zika virus in pregnant women.

Knowledge of the variables predictive of malaria and arboviruses in patients with imported febrile syndrome may help to deal more logically with the problem in the ED, where these patients are usually present. The study aimed to define the epidemiological, clinical, or analytical variables that may be predictors of malaria and arboviruses in patients presenting with febrile syndrome after returning from a trip to tropical or subtropical regions.

Methods

Study design

Retrospective study of patients seen at the Imported Diseases and Clinical Parasitology Department of the Hospital General Universitario Doctor Balmis in Alicante from June 15, 2000, to December 31, 2020, with febrile syndrome after traveling to tropical or subtropical regions. Patients could be referred from the ED (directly or after hospital admission), primary care, foreign health care, or nongovernmental organizations (NGOs). Both adult and pediatric populations were included. Patients from non-tropical or subtropical regions or with incomplete medical records were excluded. No time limit was established after the onset of fever upon return.

Study variables

Demographic and epidemiological variables were collected (destination and type of travel, whether immigrants, travelers or immigrants with visits to friends and relatives -VFR-, compliance with antimalarial chemoprophylaxis in the indicated cases), clinical variables (symptoms accompanying fever at the time of consultation, such as headache, arthralgia or diarrhea, clinical signs such as hepatosplenomegaly, lymphadenopathy, exanthema or arthritis; clinical signs such as hepatosplenomegaly, lymphadenopathy, exanthema or arthritis); and analytical variables [leukocytes/mm^3, lymphocytes/mm^3, platelets/mm^3, hemoglobin (g/dl), lactate dehydrogenase (LDH) (IU/l), total bilirubin (mg/dl), creatinine (mg/dl), AST/ALT (IU/l), C-reactive protein (CRP) (mg/dl), Quick's index] and the final clinical and microbiological diagnosis.

Data were obtained from the practice's anonymized patient registration database and electronic medical records (ORION and MIZAR).

Definitions

Patients were classified as: (1) immigrants (born in tropical countries, but currently living in Spain), (2) VFR (immigrant population living in Spain but returning to their place of origin to visit family and friends) and (3) travelers (born in Spain or in another non-tropical country traveling for tourism, cooperation, work, or visits to relatives).

Microbiological diagnosis

A patient was considered to have malaria if 1) parasite forms of Plasmodium were visualized in the peripheral blood smear, 2) rapid *Plasmodium* antigen detection tests, or 3) a *Plasmodium* multiplex-CRP was positive. A diagnosis of arboviruses is defined as having compatible symptoms and the presence of IgM antibodies in the blood, seroconversion of two samples (one from the acute phase and one at 2-4 weeks) analyzed in parallel, positive CRP for dengue, Zika, or Chikungunya virus, or detection of dengue virus NS1 antigen.

Statistical analysis

A descriptive analysis was made of the categorical variables using percentages and continuous variables using means and standard deviations or medians and ranges, depending on whether they follow a normal distribution. The variables significant in the univariate analysis ($P < .05$) were included in a multivariate analysis through logistic regression with the stepwise regression method to identify the variables independently associated with the diagnosis of malaria and arboviruses. The measure of

association used was the adjusted odds ratio (ORa) with its 95% confidence interval (95% CI). Finally, diagnostic accuracy indices [sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR)] and COR (Receiver Operating Characteristic) curves were estimated for the variables found to be significant in the multivariate analysis. Likelihood ratios or likelihood ratios (LR) were calculated since these are not influenced by disease prevalence. The comparison of categorical variables was performed using Pearson's chi-square test. For the comparison of quantitative variables between more than two groups, the ANOVA or Mann-Whitney test (nonparametric test) was used, depending on whether they follow a normal distribution (according to the Kolmogorov-Smirnov test).

The variables that were significant in the univariate analysis ($P < .05$) were included in a multivariate analysis using logistic regression with the "stepwise regression" method to identify the variables independently associated with the diagnosis of malaria and arboviruses. Adjusted odds ratio (ORa) with its 95% confidence interval (95% CI) was used as the measure of association. Finally, diagnostic accuracy indices [sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR)] and ROC (Receiver Operating Characteristic) curves were estimated for the variables found to be significant in the multivariate analysis. Likelihood ratios or likelihood ratios (LR) were calculated, as these are not influenced by disease prevalence.

Statistical analysis of the results was performed with IBM SPSS version 22 (IBM Corp., Armonk, New York, USA), XLSTAT 2021 (Statistical Software for Excel, Addinsoft, New York, USA), and GraphPad Prism 9.4.1 (GraphPad Software, San Diego, California USA).

Ethical aspects

The study protocol was approved by the Ethics Committee of the Hospital General Universitario de Alicante (PI2021-086 ISABIAL 2021-0179) and, as it was a retrospective study, informed consent was waived. The Good Clinical Practice Guidelines and the Helsinki declaration were followed.

Results

Between 2000 and 2020, 1672 patients were seen in the office. In 398 patients, the reason for consultation was febrile syndrome. Of these, 107 were excluded (7 because they came from a trip to a non-tropical or subtropical area, 19 because it was not an imported disease, and 81 because there were insufficient data). Finally, a total of 291 patients were included. One hundred and eight (37.1%) were diagnosed with malaria, 28 (9.6%) with arboviruses, and 155 (53.3%) with other febrile illnesses. Of these, 204 (70.1%) were referred from the hospital emergency department. Table 1 shows the final diagnoses of the patients.

Table 1. Etiology of febrile syndrome in patients from tropical or subtropical countries

Diagnosis	Nº (%)
Malaria	**108 (37.1)**
Plasmodium falciparum	95 (32.6)
Plasmodium vivax	9 (3.1)
Plasmodium ovale	2 (0.7)
Plasmodium malariae	2 (0.7)
Arboviriasis[a]	**28 (9.6)**
Dengue	18 (6.2)
Chikungunya	10 (3.4)
Zika	1 (0.3)
Other diseases	**155 (53.3)**
Respiratory infection	60 (20.6)
Traveler's diarrhea	16 (5.5)
Urinary tract infection	16 (5.5)
Tuberculosis disease	15 (5.1)
Rickettsiosis	8 (2.7)
Leishmaniasis	6 (2.1)
Typhoid fever	6 (2.1)
Acute schistosomiasis	5 (1.7)
Q fever	5 (1.7)
Systemic disease	3 (1)
Hematological disease	3 (1)
Acute hepatitis	3 (1)
Acute monoarthritis	2 (0.7)
Skin and soft tissue infection	2 (0.7)
Brucellosis	1 (0.3)
Leptospirosis	1 (0.3)
Cysticercosis	1 (0.3)
Rubella	1 (0.3)
Toxoplasmosis	1 (0.3)

[a]One patient was diagnosed with two arboviruses as a cause of febrile syndrome

The epidemiological, clinical, and analytical characteristics of the patients included in the study are shown in Table 2. 54% of the patients were male, and the mean age was 36 years. Malaria patients were younger and were mostly VFR. The time to consultation and onset of fever was shorter for patients with malaria and arboviruses; regarding clinical variables, headache and hepatosplenomegaly predominated in the malaria group. Regarding laboratory parameters, malaria patients had more thrombopenia (platelets < 150 000/mm^3), anemia (hemoglobin < 12 g/dL), hyperbilirubinemia (total bilirubin > 1 mg/dL), increased LDH (LDH > 250 IU/L), increased CRP (CRP > 10 mg/dL) and altered Quick's index (< 70%) in a statistically significant manner. Patients with arboviruses presented more frequently with headache, rash, and arthromyalgia, and statistically significantly lower values of leukocytes, hemoglobin, and CRP.

Table 3 shows the univariate analysis of the clinical and analytical variables of the groups of patients with malaria and arboviruses, and Table 4 shows the multivariate analysis of the variables that were significant in the previous analysis. The diagnosis of malaria was associated with being from sub-Saharan Africa (ORa: 45.85; 95% CI: 9.45-222.49), being AFV (ORa: 3.55; 95% CI: 1.21-10.46), having a headache (ORa: 10.62; 95% CI: 3.20-

Table 2. Epidemiological, clinical, and analytical characteristics of the patients included in the study

	Aggregate sample N = 291 n (%)	Malaria N = 108 n (%)	Arboviruses N = 28 n (%)	Other diagnoses N = 155 n (%)	*P*
Sex					**.013**
Male	159 (54.6)	64 (59.3)	8 (28.6)	87 (56.1)	
Female	132 (45.4)	44 (40.7)	20 (71.4)	68 (43.9)	
Age [Mean (SD)]	36 (14)	32 (15)	39 (13)	38 (13)	**.001**
Type of patient					
VFR immigrant	116 (39.9)	64 (59.3)	12 (42.9)	40 (25.8)	< **.001**
Immigrant	64 (22)	16 (14.8)	1 (3.6)	47 (30.3)	< **.001**
Traveler	111 (38.1)	28 (25.9)	15 (53.6)	68 (43.9)	**.003**
Time in Spaina (days)	94 (106)	108 (118)	89 (81)	82 (96)	.273
Time to onset of symptoms (days) [Mean (SD)]	203 (632)	46 (248)	16 (19)	356 (821)	< **.001**
Time to consultation (days) [Mean (SD)]	14 (31)	8 (16)	5 (4)	20 (39)	**.001**
Continent					
Sub-Saharan Africa	172 (59.1)	100 (92.6)	2 (7.1)	70 (45.2)	< **.001**
Maghreb	16 (5.5)	1 (0.9)	0	15 (9.7)	**.004**
Latin America	69 (23.7)	3 (2.8)	21 (75)	45 (29)	< **.001**
Asia	34 (11.7)	4 (3.7)	5 (17.9)	25 (16)	**.005**
HIV infection	25 (8.6)	10 (9.3)	0	15 (9.7)	.232
Hospital admission	176 (60.5)	91 (84.3)	8 (28.6)	77 (49.7)	< **.001**
Incomplete chemoprophylaxis[b]	149 (81.9)	86/92 (94)	13/14 (93)	50/76 (65)	< **.001**
Clinical aspects					
Headache	118 (40.5)	55 (51)	16 (57)	47 (30)	**.001**
Exanthema	33 (13.3)	1 (0.9)	15 (53)	17 (11)	< **.001**
Arthromyalgia	114 (39.2)	36 (33)	26 (93)	52 (33)	< **.001**
Diarrhea	69 (23.7)	19 (17)	8 (28)	42 (27)	.167
Hepatomegaly	35 (12.1)	21 (19.6)	1 (3.6)	13 (8.4)	**.008**
Splenomegaly	28 (9.7)	20 (18.7)	0	8 (5.2)	< **.001**
Adenopathies	34 (11.8)	8 (7.5)	3 (11.5)	23 (14.8)	.201
Laboratory aspects					
Leukocytes (x 10^3/mm^3) [Mean (SD)]	6.753 (4.122)	6.047.8 (3.283)	5.206.4 (3.406)	7.524.8 (4.586)	**.002**
Lymphocytes (x 10^3/mm^3) [Mean (SD)]	1.713 (1.627)	1.519.5 (1.605.8)	1.766.5 (2.100)	1.843 (1.529)	.313
Platelets (x 10^3/mm^3) [Mean (SD)]	181 (110)	104 (64)	203 (95)	230 (108)	< **.001**
Hemoglobin (g/dL) [Median (IQR)]	12.9 (3.9-18.2)	12.1 (3.9-17.6)	14.1 (11.5-16.5)	13 (6.2-18.2)	**.003**
AST (UI/L) [Median (IQR)]	29 (3-1.011)	35 (3-283)	29 (13-279)	26 (8-1.011)	**.002**
ALT (UI/L) [Median (IQR)]	26.5 (5-622)	32 (7-396)	26.5 (10-356)	24 (5-622)	.076
Bilirubin[¥] (mg/dL) [Median (IQR)]	0.6 (0-21.5)	1.1 (0.2-21.5)	0.42 (0-2.3)	0.49 (0-12)	< **.001**
LDH[¥] (UI/L) [Mean (SD)]	375 (249)	449 (276)	289 (143)	339 (229)	**.020**
Cr (mg/dL) [Median (IQR)]	0.8 (0.3-10.1)	0.86 (0.3-10.1)	0.72 (0.4-1.3)	0.84 (0.3-4.3)	**.004**
CRP (mg/dL) [Mean (SD)]	7.2 (8.4)	9.6 (7.2)	2.2 (4.4)	6.3 (9.3)	< **.001**
Quick[¥] (%) [Median (IQR)]	87 (24-100)	83 (50-100)	100 (81-100)	88.5 (24-100)	**.006**
APTT[¥] (s) [Mean (SD)]	1.2 (2.4)	1.01 (0.33)	0.95 (0.12)	1.47 (3.55)	.535

[a]In the case of immigrant patients.
[b]Expressed over the total number of patients in whom it was indicated.
[¥]For these variables there are missing data in each of the groups.
HIV: human immunodeficiency virus; GOT/AST: aspartate aminotransferase; GPT/ALT: alanine aminotransferase; LDH: lactate dehydrogenase. Cr: Creatinine; CRP: C-reactive protein; LDH: lactate dehydrogenase; APTT: activated partial thromboplastin time.
Values in bold denote statistical significance ($P < .05$).

35.28) and having platelet counts < 150,000/mm^3 (ORa: 16.47; 95% CI: 5.46-49.7). In the case of arboviruses, the variables independently associated with this diagnosis were pro-ceding from Central and South America (ORa: 5.07; 95% CI: 1.73-14.92), exanthema (ORa: 5.10; 95% CI: 1.72-17.02) and arthromyalgia (ORa: 14.5; 95% CI: 3.05-68.80).

Table 5 shows the analysis of the sensitivity, specificity, predictive values, and likelihood ratios of the variables identified in the multivariate analysis and their combinations. In the case of malaria, the negative likelihood ratios are the most significant in the case of malaria.

Table 5 shows the analysis of the sensitivity, specificity, predictive values, and likelihood ratios of the variables identified in the multivariate analysis and their combinations. In the case of malaria, the negative likelihood ratios are the most significant for the variables taken individually. Thus, if the patient does not come from Africa, the probability of not having malaria is 7 times greater than that of having malaria (CP = 0.13). When combined variables are introduced, sensitivity is lost at the cost of increasing specificity and CPP. Thus, coming from a sub-Saharan African country, being a VFA immigrant, having headaches and thrombopenia, has a PPV of 93.3% (95% CI: 84.4-100) and a PCP of 23.72 (95% CI: 5.76-97.62).

Table 3. Univariate analysis of variables associated with the diagnosis of malaria and arboviruses

	Malaria		Arboviruses	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Sex (male)	1.35 (0.83-2.18)	.224	0.29 (0.13-0.69)	**.004**
Age < 35 years old	1.36 (0.85-2.20)	.224	0.52 (0.23-1.19)	.162
Sub-Saharan Africa	15.57 (6.87-35.33)	< **.001**	–	–
Central and South America	–	–	13.78 (5.54-34.31)	< **.001**
VFR tourists	3.67 (2.22-6.04)	< **.001**	1.15 (0.52-2.52)	.734
Exanthema	0.04 (0.01-0.33)	< **.001**	15.71 (6.49-37.99)	< **.001**
Artromialgias	0.67 (0.41-1.10)	.117	25.85 (5.99-111.41)	< **.001**
Cefalea	1.97 (1.22-3.21)	**.006**	2.11 (0.96-4.63)	.060
Diarrhea	0.57 (0.31-1.03)	.059	1.32 (0.56-3.16)	.525
Hepatomegaly	2.95 (1.43-6.08)	**.003**	0.25 (0.03-1.89)	.146
Splenomegaly	5.03 (2.13-11.87)	< **.001**	–	–
Adenopathies	0.5 (0.21-1.12)	.085	0.97 (0.27-3.41)	.959
Inadequate chemoprophylaxis	6.14 (2.39-15.76)	< **.001**	–	–
Leukocytes < 5000/mm^3	1.52 (0.94-2.48)	.089	2.01 (0.92-4.39)	.077
Lymphocytes < 1000/mm^3	1.95 (1.16-3.29)	**.012**	1.32 (0.59-2.95)	.499
Platelets < 150 000/mm^3	15.73 (8.60-28.75)	< **.001**	0.55 (0.24-1.25)	.150
Haemoglobin < 12 g/dL	3.00 (1.80-5.01)	< **.001**	0.15 (0.03-0.63)	**.003**
LDH ≥ 250 IU/L	3.59 (1.67-7.67)	**.001**	0.68 (0.18-2.65)	.575
Bilirubin > 1 mg/dL	2.90 (1.77-4.75)	< **.001**	0.44 (0.18-1.07)	.066
GOT > 50 IU/L	1.37 (0.79-2.39)	.248	0.89 (0.35-2.33)	.826
GPT > 50 IU/L	1.34 (0.78-2.29)	.224	1.18 (0.49-2.79)	.714
Quick index < 70%	1.52 (0.61-3.78)	.483	1.14 (1.08-1.21)	.132
CRP > 10 mg/dL	2.83 (1.59-5.01)	< **.001**	0.09 (0.01-0.72)	**.005**

VFR: Visiting friends and relatives; GOT: aspartate aminotransferase; GPT: alanine aminotransferase; LDH: lactate dehydrogenase; CRP: C-reactive protein. Values in bold denote statistical significance ($P < .05$).

In the case of patients with arboviruses, the combination of coming from Central and South America, having exanthema and arthromyalgiasis is the one that offers the highest PLR [20.66 (95% CI: 7.74-55.21)] with a PPV of 68.7% (95% CI: 46.0-91.5).

ROC curves were made, and the area under the curve (AUC) was calculated for the variables significant in the multivariate analysis (Figure 1). For malaria, the combination of coming from Africa, being AFV, having thrombopenia, and having headache has an AUC = 0.64 (95% CI = 0.57-0.70, $P < .001$), higher than if only the variables coming from Africa, being AFV and having thrombopenia are included (AUC = 0.61, 95% CI = 0.55-0.68, $P < .001$). For arboviruses, the combination of being from Latin America, having arthromyalgia, and exanthema had an AUC = 0.68 (95% CI = 0.60-0.76, $P < .001$), somewhat higher than if the variable exanthema was excluded (AUC = 0.63, 95% CI = 0.55-0.71, $P < .001$).

Table 4. Multivariate analysis for the diagnosis of malaria and arboviriasis

	Odds ratio	95% CI	*P*
Malaria			
Sub-Saharan Africa	45.85	9.45-222.49	< **.001**
Immigrant VFR	3.55	1.21-10.46	**.021**
Headache	10.62	3.20-35.28	**.000**
Thrombopenia	16.47	5.46-49.7	**.000**
Arboviruses			
Latin America	5.07	1.73-14.92	**.003**
Exanthema	5.10	1.72-17.02	**.004**
Arthromyalgia	14.50	3.05-68.80	**.001**

VFR: Visiting friends and relatives.
Bold p values denote statistical significance ($P < .05$).

Discussion

The present study shows results consistent with those described in the literature. Malaria is the leading cause of fever in patients from sub-Saharan Africa, and *Plasmodium falciparum* is the most frequent etiologic agent.[6,14,20] The causes of fever in patients not diagnosed with malaria or arboviruses are similar to the series of other studies.[2,3,14] In our study, respiratory infections, followed by diarrhea and urinary tract infections, are the leading causes.

The prevalence of malaria varies among studies, and in our work, it is one of the highest (37%). The patients in the malaria group are similar to those found in other studies, and most were AFV males from sub-Saharan Africa and younger than the other groups. It is known that being an FMDV is a risk factor as it is associated with a lower uptake of prophylactic measures. In patients with arboviruses, both the onset of fever after return and the time of consultation was shorter than in patients with other diagnoses, which is related to the pathogenesis of the disease. The clinical and laboratory variables described are concordant with the characteristics of the disease and with the rest of the studies. They presented more headaches, thrombopenia, elevated LDH, and CRP than the other groups. Patients with malaria and arboviruses had lower white blood cell counts than the rest. Headache is described as one of the typical symptoms of the disease (75-80%) and is related to the release of proinflammatory cytokines. There is no difference in frequency or intensity between malaria cases and those who develop cerebral malaria.

Table 5. Diagnostic accuracy rates for patients with malaria and for patients with arboviruses

	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	PLR % (95% CI)	NLR % (95% CI)
Malaria						
Africa	93.5 (86.9-97)	51.9 (44.7-59)	53.4 (46.3-60.6)	93.1 (88.2-98)	1.95 (1.66-2.28)	0.13 (0.06-0.26)
Immigrant VFR	59.3 (49.8-68)	71.6 (64.6-77.6)	55.2 (46.1-64.2)	74.9 (68.4-81.3)	1.52 (1.23-1.89)	0.42 (0.26-0.68)
Headache	50.9 (41.6-60.2)	65.6 (58.4-72.1)	46.6 (37.6-55.6)	69.4 (62.5-76.2)	1.48 (1.13-1.94)	0.75 (0.60-0.93)
Thrombopenia	82.4 (74-88.5)	76 (69.2-81.6)	66.9 (58.9-74.9)	88 (82.9-93)	3.43 (2.61-4.49)	0.23 (0.15-0.35)
Africa + VFR	56.5 (47.1-65.4)	89.1 (83.6-92.9)	75.3 (65.9-84.7)	77.6 (72-83.3)	5.17 (3.3-8.07)	0.49 (0.39-0.61)
VFR + Thrombopenia	51.9 (42.5-61)	90.7 (85.5-94.2)	76.7 (67-86.4)	76.1 (70.5-81.8)	5.58 (3.43-9.09)	0.53 (0.43-0.65)
Africa + Thrombopenia	75.9 (67-83)	90.2 (84.9-93.7)	82 (74.5-89.5)	86.4 (81.5-91.3)	7.72 (4.92-12.12)	0.27 (0.19-0.38)
Headache + Thrombopenia	41.7 (32.8-51.1)	91.8 (86.8-95)	75 (64-86)	72.7 (67-78.5)	5.08 (2.98-8.67)	0.64 (0.54-0.75)
Africa + VFR + Thrombopenia	49.1 (39.8-58.4)	96.7 (92.8-98.6)	89.8 (82.1-97.5)	76.3 (70.8-81.8)	14.97 (6.66-33.65)	0.53 (0.44-0.64)
Africa + VFR + Headache + Thrombopenia	25.9 (18.6-35)	98.9 (95.8-99.9)	93.3 (84.4-100)	69.3 (63.8-74.9)	23.72 (5.76-97.62)	0.75 (0.67-0.84)
Arboviruses						
Central and South America	75 (56.3-87.5)	82.1 (77-86.3)	30.9 (19.9-41.9)	96.9 (94.6-99.1)	4.2 (2.99-5.87)	0.30 (0.16-0.58)
Exanthema	53.6 (35.8-70.4)	93.2 (89.4-95.7)	45.5 (28.5-62.4)	95 (92.3-97.6)	7.83 (4.46-13.76)	0.49 (0.33-0.74)
Arthromyalgia	92.9 (76-99)	66.5 (60.6-72)	22.8 (15.1-30.5)	98.9 (97.3-100)	2.78 (2.27-3.39)	0.11 (0.03-0.41)
America + Exanthema	39.3 (23.6-57.6)	96.6 (93.5-98.3)	55.0 (33.2-76.8)	93.7 (90.8-96.6)	11.48 (5.21-25.29)	0.67 (0.47-0.85)
America + Arthromialgias	75 (56.3-87.5)	92.8 (88.9-95.4)	52.5 (37-68)	97.2 (95.2-99.2)	10.4 (6.4-16.8)	0.27 (0.14-0.51)
Exanthema + Arthromialgias	50.0 (32.7-67.3)	96.6 (93.5-98.3)	60.9 (40.9-80.8)	94.8 (92.1-97.4)	14.61 (6.96-30.66)	0.52 (0.36-0.75)
America + Exanthema + Arthromyalgia	39.3 (23.6-57.6)	98 (95.5-99.3)	68.7 (46.0-91.5)	93.8 (91.0-96.7)	20.66 (7.74-55.21)	0.62 (0.46-0.83)

PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative likelihood ratio.

Similarly, thrombopenia is classically associated with malaria and is of multifactorial etiology (hypersplenism, autoimmune, coagulation disorders). Regarding CRP elevation, there is a meta-analysis[28] that describes it as a biomarker for early detection and monitoring of malaria severity in a statistically significant way when compared with cases of mild malaria or fever due to other causes. However, they do not describe which diseases are included in the fever group from other causes. Bacterial and viral or systemic diseases have been included in our case.

Several studies have attempted to design a predictive model for malaria diagnosis in non-endemic areas.[15,17-19,23-25] The results of these studies are difficult to compare because of the heterogeneity of the population included (some include asymptomatic patients)[18] and because the variables chosen are sometimes subjective and not very reproducible. There is also variability in the time of fever development since the patient's return from travel. In some studies, it is limited to 3 months[19] and in others to 6 months.[17] It is known that infection by *P. vi-vax* and *P. ovale* can cause long-term fever due to the activation of hepatic hypnozoites and the release of merozoites into the blood, which can only be detected by testing during the febrile peak. Also, P. malaria and, less frequently, *P. falciparum* malaria can manifest clinically years after infection. For this reason, limiting the time of fever development could underestimate the prevalence of malaria.

In this study, as in that of Bottieau et al,[24] headache is a variable included in the final predictive model. However, it should be noted that since it is a symptom, and therefore subjective, it could be a limitation. In other studies, splenomegaly[19,24] (measured by physical examination) has been found to be a predictor variable; however, in our case it was not included in the final model. This is probably due to the low prevalence in our sample (only 9.7%), since only those patients in whom the presence or absence of this finding on physical examination was specified were included. Other clinical variables that have shown an association in other studies have been abdominal pain,[18] vomiting,[18,24] myalgias,[18] sweating[19] and fever without focus,[24] which were not included in our study.

Having performed inadequate chemoprophylaxis is also included in the multivariate analysis of other studies,[18,19,24] but not ours, due to the need for more information in the medical records. Regarding analytical variables, other studies are associated with anemia,[19] leukopenia,[19] low eosinophils (< 5%), and 19 elevated ALT and LDH.[24] In our case, anemia, leukopenia, and elevated LDH were significant in the univariate analysis but not in the multivariate analysis. Similarly, hyperbilirubinemia, a parameter that in other studies has been found to predict malaria,[15,24] was not included in our final model, probably due to a lack of data collection.

Arboviruses are an increasingly frequent cause of fever after travel,[20,21,26] especially dengue.[27] and it was the most frequent in our study. Probably related to the fact that the Zika and Chikungunya epidemics have been later, and the data collected is minor. In fact, among the studies that analyze predictive variables, Bottieu et al.[24] is the only one that includes arboviruses and exclusively Dengue.

A risk analysis is made for patients with dengue fever, comparing it with other causes of fever, excluding malaria. In this case, one is more likely to have the disease if one comes from Central and South America (PLR = 29), South Asia or the Pacific (PLR = 3.3), has leukopenia (PLR = 3.3), exanthema (PLR = 2.8) or thrombocytopenia (PLR = 2). In our study, arboviruses were up to 20 times more frequent in patients with arthromyalgia, exanthema, and from Central and South

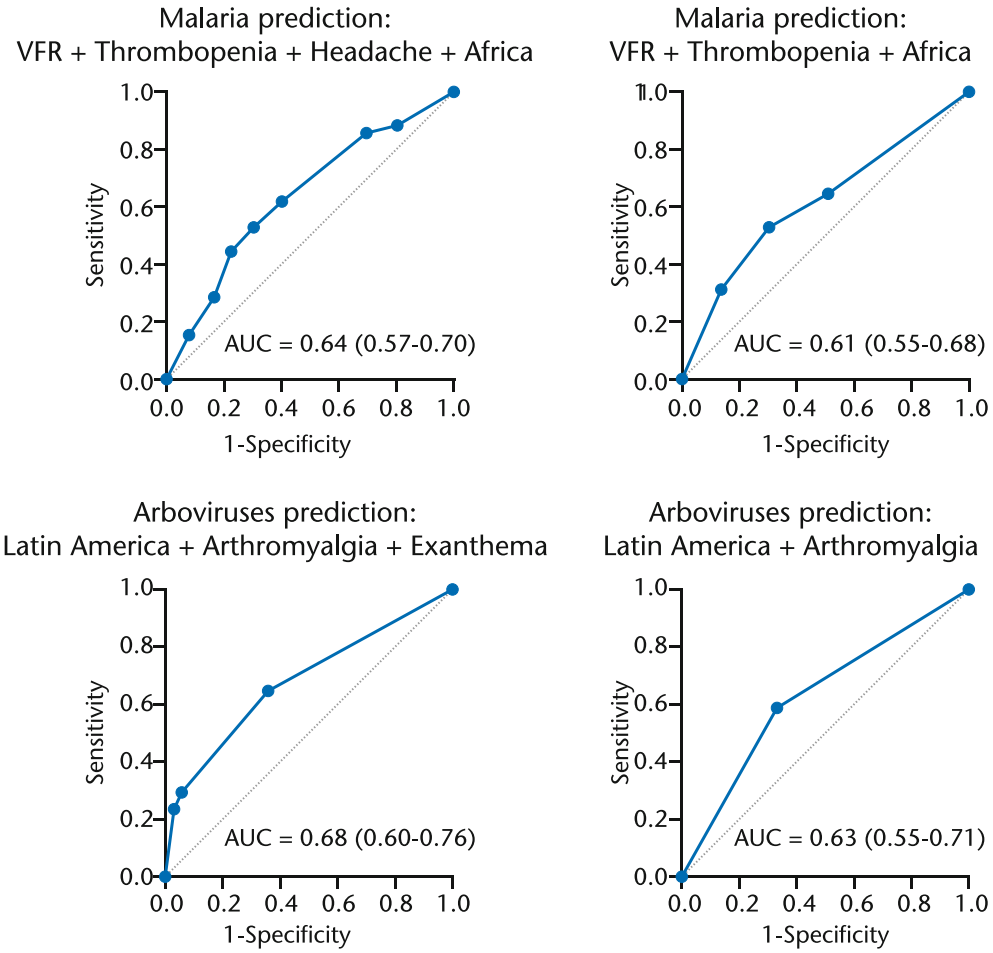

Figure 1. Receiver operating characteristic (COR) curves of the combined predictor variables for malaria and arboviruses.
VFR: immigrant visiting friends and relatives; AUC: area under the curve.

America so that a diagnostic approach could be made only with clinical variables. Although most cases are asymptomatic or have mild symptoms, the appearance of symptoms implies a greater risk of developing complications during or after the disease, such as severe dengue, Guillain-Barré syndrome, Zika-associated microcephaly, or post-chikungunya arthralgias,[29] so their recognition is essential, especially in the emergency department, which is often the first place of contact with the patient.

The AUCs, calculated for both predictive models, are halfway between no discrimination (AUC = 0.5) and perfect discrimination (AUC = 1). The only study that provides ROC curves is that of Casalino et al.[17]. However, it does not use a combined model. However, it provides one curve for clinical variables and others for laboratory variables. Their study concludes that none of the variables, alone or combined, has sufficient sensitivity or specificity to allow the diagnosis of malaria. The work of D'Acremont et al.[19] is the only one that speaks of initiating empirical antimalarial treatment if the post-test probability is greater than 80%. However, it recognizes that this threshold is arbitrary. In our case, the post-test probability is 89% for the combination of variables, with a higher PLR for malaria.

The main strength of our study is that it is the first, to our knowledge, to evaluate predictors of malaria in Spain and includes arboviruses. Regarding the limitations, firstly, this is a retrospective study of more than 20 years, so some data could not be collected because computerized histories were unavailable. Some patients were excluded because microbiological confirmation was unavailable due to the lack of current diagnostic techniques. Secondly, the sample size for arboviruses is small and probably influenced the association with some variables. Thirdly, although the population included is young, the number of children needs to be more to extrapolate the results to this population. Lastly, this is a single-center study, and the results obtained may not be extrapolated to other regions of Spain.

In conclusion, originating from sub-Saharan Africa, VFR, thrombopenia (platelets < 150 000/mm^3), and headache are independently associated with malaria. Patients with imported febrile syndrome presenting these four characteristics should be diagnosed parasitologically early. In the case of centers where the test is unavailable,

the diagnosis will be delayed, and if the patient is severe, empirical antimalarial treatment should be started. Travelers with the febrile syndrome who come from Central and South America and have arthromyalgia have a high probability of having arboviruses.

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