



Epidemiology, Clinical Features and Risk Factors for Imported Severe Malaria: Ten Years of Experience in a European Infectious Diseases Center

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Abstract

Background: Imported malaria remains a relevant clinical problem in Europe due to the rapid potential progression to severe and life-threatening disease, especially in non-immune patients and in the context in which diagnosis might be delayed due to lack of awareness among clinicians. In Portugal, malaria is a mandatory notifiable disease. In 2021, there were 79 cases reported to the Public Health System, but it is believed that cases are under-reported. **Materials and Methods:** In this retrospective observational study, we analysed the medical records of 163 patients with *Plasmodium spp* infection, admitted in the infectious disease ward between March 2013 and March 2023. We analysed epidemiology, clinical features and risk factors for imported severe malaria. **Results:** Being male (p value: 0.028), older age (p value: 0.013), underlying chronic medical conditions (p value: 0.005) and alcohol overuse (p value: 0.017) were identified as risk factors for severe malaria. Finding jaundice at presentation is also associated with severe disease (p value: <0.001), as well as polypnea (p value: 0.016), postural hypotension (p value: 0.005), impaired consciousness (p value: 0.015) and prostration (p value: <0.001). Blood test findings associated with severe malaria were the presence of anemia (p value < 0.001); elevation of transaminases (p value < 0.001); elevation of serum bilirubin (p value < 0.001); acute kidney injury (p value < 0.001) and leukocytosis (p value: 0.016). **Discus-**

sion and conclusion: Primary and secondary prevention measures, such as pre-travel consultations, chemoprophylaxis, and early diagnosis and treatment, should be emphasized and improved among high-risk prospective travelers to malaria endemic countries. This finding should prompt clinicians to advise men, older travelers and travelers with underlying chronic medical conditions on malaria prevention, and highlights the need for early diagnosis and treatment for patients with early symptoms of malaria.

Subject Areas

Infectious Diseases

Keywords

Severe Malaria, Epidemiology, Symptoms, Risk Factors, *Plasmodium spp*

1. Background

Malaria is an acute or subacute anthroponosis caused by at least one of six protozoan species of the genus *Plasmodium*, with almost all severe cases caused by *Plasmodium falciparum*. Due to increasing international travel and changing patterns of migration, malaria is still the most important tropical disease imported to Europe. Despite recent successful efforts to reduce the global malaria burden, this disease remains a significant global health problem. Malaria is endemic throughout most of the tropics; ongoing transmission occurs in 85 countries and territories [1]. The World Health Organization (WHO) reported 247 million cases and 63 thousand deaths from malaria in 2022 [2].

Most travelers to malarious areas have had no previous exposure to malaria parasites or have lost their immunity; they are at very high risk for severe disease, especially if infected with *Plasmodium falciparum* [3]. For this reason, it is important to consider malaria in all febrile patients with a history of travel to these areas and be aware of the risk factors for more severe disease.

In Portugal, malaria is a mandatory notifiable disease. In 2021 there were 79 cases reported to the Public Health System, but it is believed that cases are under-reported [4].

The definitive diagnosis of malaria is established in the setting of symptoms consistent with malaria and a positive malaria diagnostic test; diagnostic tools include light microscopy of blood smears and rapid diagnostic tests.

Criteria for the definition of severe malaria were amended by WHO over the last decade, particularly with regard to the definition of hyperparasitaemia. For epidemiological purposes, severe malaria is defined according to updated WHO guidelines [5] as one or more of the following, occurring in the absence of an identified alternative cause: Impaired consciousness with a glasgow coma score < 11 in adults; Prostration; Multiple convulsions; Acidosis (A base deficit of >8 mEq/L or, if not available, a plasma bicarbonate level of <15 mmol/L or venous

plasma lactate ≥ 5 mmol/L); Hypoglycaemia (blood or plasma glucose < 2.2 mmol/L or < 40 mg/dL); Severe malarial anemia (hemoglobin concentration ≤ 7 g/dL or a haematocrit of $\leq 20\%$ in adults) with a parasite count $> 10,000/\mu\text{L}$; Renal impairment (plasma or serum creatinine > 3 mg/dL or blood urea > 20 mmol/L); Jaundice (plasma or serum bilirubin > 3 mg/dL with a parasite count $> 100,000/\mu\text{L}$); Pulmonary edema (radiologically confirmed or oxygen saturation $< 92\%$ on room air with a respiratory rate $> 30/\text{min}$, often with chest indrawing and crepitations on auscultation); Significant bleeding (including recurrent or prolonged bleeding from the nose, gums or venipuncture sites; haematemesis or melaena); Shock and Hyperparasitaemia (*P. falciparum* parasitaemia $> 10\%$). Severe vivax and knowlesi malaria is defined as for falciparum malaria but with no parasite density thresholds. Severe knowlesi malaria is defined as for falciparum malaria but with two differences: *P. knowlesi* hyperparasitaemia is defined as parasite density $> 100,000/\mu\text{L}$ and jaundice and parasite density $> 20,000/\mu\text{L}$.

Mortality from untreated severe malaria, particularly cerebral malaria, approaches 100%. With prompt, effective antimalarial treatment and supportive care, the rate falls to 10% - 20% overall [5].

It is essential that full doses of effective parenteral antimalarial treatment be given promptly in the initial treatment of severe malaria. This should be followed by a full dose of effective ACT orally. Two classes of medicine are available for parenteral treatment of severe malaria: artemisinin derivatives (artesunate) and the cinchona alkaloids (quinine and quinidine). Parenteral artesunate is the treatment of choice for all severe malaria. The largest randomized clinical trials ever conducted on severe falciparum malaria showed a substantial reduction in mortality with intravenous or intramuscular artesunate as compared with parenteral quinine. The reduction in mortality was not associated with an increase in neurological sequelae in artesunate-treated survivors. Furthermore, artesunate is simpler and safer to use [5].

2. Materials and Methods

In this retrospective observational study, we analysed the medical records of all 163 patients who were at least 18 years old and had a laboratory-confirmed positive result for *Plasmodium spp* infection, admitted in the infectious disease ward (Serviço de Doenças Infeciosas of Hospital de Curry Cabral, Lisbon, Portugal) either in an outpatient or inpatient setting, between March 2013 and March 2023 (ten years).

For clinical purposes, severe malaria is defined according to updated WHO guidelines [5].

Confirmed cases were defined by a positive malaria diagnostic test; diagnostic tools include light microscopy of blood smears and rapid diagnostic tests.

Microscopic examination of blood films was the first technique used, and remains the “gold standard” and the most widely used method for the diagnosis of malaria. Thick and thin blood smears stained with Giemsa, Wright’s, or Field’s allow for rapid detection and differentiation, when possible, of the various species and the

parasite stages, and quantify the parasite density, known as parasitemia [6] [7].

Statistical analysis was performed using *IBM SPSS Statistics 28.0*. Continuous variables were described using arithmetic mean and range and categorical variables through absolute value and proportions. T-Student tests were performed to determine the statistical significance of continuous variables and chi-square (χ^2) and Fisher's exact tests for categorical variables. All statistical tests performed were two-tailed, with statistical significance reached at a $p < 0,05$ level.

3. Results

3.1. General Results

We report the findings relative to a total of 163 patients with confirmed Malaria infection from March 2013 to March 2023, all travel related. None of them was reported as acquired in the European Union, nor infected by blood transfusion, organ transplantation, needle sharing, or congenitally from mother to fetus.

Men were predominant (66,3%, 108/163) and the median age was 42,2 years old. The majority of the patients were from endemic countries (67,5%, 110/163), especially Angola (35%, 57/163). Underlying chronic medical conditions were found in 43% of patients (70/163) with a significant correlation with the severity of the disease (p value: 0.005). Prior history of malaria infection was found in 69 patients (42,3%, 69/163).

Sixty-seven patients (41,1%) were within the criteria of severe malaria. In this group, ages varied from 18 to 81, with a median value of 45 years old and with a standard deviation of 14.75 (p value: 0.013). They were mainly men (76%, 51/67) (p -value: 0,028). The majority of these patients were from African countries (64,2%, 43/67), especially from Angola (37,3%, 25/67), followed by Portuguese patients (32,9%, 21/67). Prior history of malaria infection was found in 22 patients (32,8%). Regarding comorbidities, cardiovascular risk factors like hypertension (23,90%, 16) and diabetes (14,9%, 10) were the most prevalent. Particular highlight for the significant association of alcohol overuse with severe forms of malaria (p value: 0.017) (**Table 1**).

Table 1. Characteristics of patients with imported malaria from 2013 to 2023.

Variable	All (n = 163)	Severe (n = 67)	Non-severe (n = 96)	p-value
Gender, n (%)				0.028
Male	108 (66.3)	51 (76.1)	57 (59.4)	
Female	55 (33.7)	16 (23.9)	39 (40.6)	
Age group (years)				0.013
Median (IQR)	42.2	45.01	39.74	
Nationality, n (%)				0.680
Endemic countries	110 (67.5)	44 (65.7)	66 (68.8)	
<i>Angola</i>	57	25	32	

Continued

<i>Bangladesh</i>	1	0	1	
<i>Brazil</i>	2	2	0	
<i>Cape Verde</i>	1	0	1	
<i>Democratic Republic of Congo</i>	2	1	1	
<i>Gambia</i>	1	0		
<i>Ghana</i>	2	2	1	
<i>Guinea Bissau</i>	22	6	0	
<i>Guinea Conakry</i>	4	1	16	
<i>India</i>	1	0	3	
<i>Mozambique</i>	7	3	1	
<i>Nigeria</i>	2	1	4	
<i>Pakistan</i>	3	1	1	
<i>Republic of Benin</i>	1	0	1	
<i>São Tomé and Príncipe</i>	1	1	0	
<i>Senegal</i>	2	0	2	
<i>South Africa</i>	1	1	0	
Non endemic countries	53 (32.5)	23 (34.3)	30 (31.2)	
<i>France</i>	5	1	4	
<i>Portugal</i>	47	22	25	
<i>Ukraine</i>	1	0	1	
Comorbidities, n (%)				
<i>Alcohol overuse</i>	7 (4.3)	4 (6)	3 (3.1)	0.017
<i>Hypertension</i>	32 (19.6)	16 (23.90)	16 (16.67)	0,301
<i>Diabetes</i>	16 (9.8)	10 (14.9)	6 (6.3)	0.079
<i>Hepatitis B</i>	5 (3.1)	3 (4.5)	2 (2.1)	0.407
<i>Hepatitis C</i>	3 (1.6)	2 (3)	1 (1)	0.383
<i>Human immunodeficiency virus</i>	11 (6.7)	6 (9)	5 (5.2)	0.381
<i>Dyslipidemia</i>	10 (6.1)	6 (9)	4 (4.2)	0.233
<i>Active smoking</i>	11 (6.7)	7 (10.4)	4 (4.2)	0.131
<i>Intravenous drug user</i>	2 (2.5)	1 (1.5)	3 (3.1)	0.24
<i>Depressive syndrome</i>	5 (3.1)	2 (3)	2 (2.1)	0.741
<i>Hematologic neoplasms</i>	2 (1.2)	1 (1.5)	1 (1)	0.816
<i>Asthma</i>	2 (1.2)	1 (1.5)	1 (1)	0.816
<i>Obesity</i>	9 (5.5)	4 (6)	5 (5.2)	0.873
<i>Chronic kidney disease</i>	2 (1.2)	1 (1.5)	1 (1)	0.398
<i>Drepanocytosis</i>	5 (3.1)	2 (3)	3 (3.1)	0.095
<i>Solid malignant neoplasm</i>	2 (1.2)	1 (1.5)	1 (1)	0.816

Continued

<i>None</i>	90 (55.2)	29 (30.2)	61 (67.8)	0.005
History of malaria infection. n (%)				0.04
Yes	69 (42.3)	22 (32.8)	47 (49)	
No	94 (57.7)	45 (67.2)	49 (51)	

IQR = Interquartile Range.

3.2. Trip Features

Our findings show that all malaria infections were acquired by traveling. None was reported as acquired in the European Union. In both groups the main travel purpose was visiting family (34,4%, 56/163). The majority of these patients traveled to African countries, especially Portuguese-speaking African countries (76%, 124/163). Concerning time of visit, the majority of the travels occurred between April and June (31,9%, 52/163), but in the non-severe group the most prevalent time was between October and December (33,3%, 31/96).

A pre-travel consultation was conducted in 14 patients (8,6%,14/163). Six patients (3,7%, 6/163) started malarial chemoprophylaxis before their trip, but all of them suspended it before medical indications (**Table 2**).

Table 2. Trip features of patients with imported malaria from 2013 to 2023.

Variable	All (n = 163)	Severe (n = 67)	Non-severe (n = 96)	p-value
Travel purpose, n (%)				0,231
<i>Leisure</i>	24 (14.7)	14 (20.9)	10 (10.4)	
<i>Refugee</i>	2 (1.2)	0 (0)	2 (2.1)	
<i>Resident</i>	36 (22)	14 (20.9)	22 (22.9)	
<i>Visit family</i>	56 (34.4)	18 (26.9)	38 (39.6)	
<i>Unknown</i>	4 (2.5)	2 (3)	2 (2.1)	
<i>Work</i>	41 (25.2)	19 (28.3)	22 (22.9)	
Travel destination, n				
<i>Angola</i>	86	39	47)	
<i>Bangladesh</i>	1	0	1	
<i>Republic of Benin</i>	1	0	1	
<i>Brazil</i>	2	2	0	
<i>Cameroon</i>	2	1	1	
<i>Chad</i>	1	0	1	
<i>Democratic Republic of Congo</i>	5	1	4	
<i>Equatorial Guinea</i>	1	0	1	
<i>Gambia</i>	1	0	1	

Continued

<i>Ghana</i>	4	3	1	
<i>Guinea Bissau</i>	22	6	16	
<i>Guinea Conakry</i>	5	1	4	
<i>India</i>	1	0	1	
<i>Ivory Coast</i>	1	0	1	
<i>Mozambique</i>	13	5	8	
<i>Nigeria</i>	4	3	1	
<i>Pakistan</i>	3	1	2	
<i>São Tomé and Príncipe</i>	3	1	2	
<i>Senegal</i>	3	0	3	
<i>Tanzania</i>	1	1	0	
<i>Togo</i>	3	3	0	
Time of visit, n (%)				0.542
<i>January-March</i>	40 (24.5)	20 (29.9)	20 (20.83)	
<i>April-June</i>	52 (31.9)	21 (31.3)	31 (32.3)	
<i>July-September</i>	22 (13.5)	9 (13.4)	13 (13.54)	
<i>October-December</i>	49 (30.1)	17 (25.4)	32 (33.33)	
Pre-travel consultation, n (%)				0.918
<i>Yes</i>	14 (8.5)	6 (9)	8 (8.3)	
<i>No</i>	130 (79.8)	54 (80.6)	76 (79.2)	
<i>Unknown</i>	19 (11.7)	7 (10.4)	12 (12.5)	
Malarial chemoprophylaxis, n (%)				0.086
<i>Yes</i>	6 (3.7)	5 (7.5)	1 (1)	
<i>No</i>	147 (90.2)	58 (86.5)	89 (92.7)	
<i>Unknown</i>	10 (6.1)	4 (6)	6 (6.3)	

3.3. Clinical Features

Our findings show that symptom onset occurred predominantly after returning to Portugal (84%, 137/163) with a median time from onset to diagnosis of 5 days.

Regarding clinical presentation, fever without specified pattern was the most prevalent symptom (91.4%, 149/163) in both groups, as well as headache (64.4%, 105/163).

On physical examination, fever was the most common finding in both groups (76.7%, 125/163), followed by jaundice in patients with severe malaria (29.9%, 20/67) and a normal physical examination in patients with non-severe disease (11.5%, 11/96).

Concerning blood test alterations, the most typical findings in both groups were elevation of C-reactive protein (91.4%, 149/163) and thrombocytopenia (87.1%, 142/163).

The mortality rate was 1.2%, which corresponds to two deaths, both with cerebral malaria (**Table 3**).

Table 3. Clinical features of patients with imported malaria from 2013 to 2023.

Variable	All (n = 163)	Severe (n = 67)	Non-severe (n = 96)	p-value
Symptom onset, n (%)				0,841
<i>Before returning to Portugal</i>	26 (16)	12 (17.9)	14 (14.6)	
<i>After returning to Portugal</i>	137 (84)	55 (82.1)	82 (85.4)	
Time from onset to diagnosis				
<i>Median (IQR)</i>	5	4 (1 - 19)	6 (1 - 30)	
Clinical manifestations, n (%)				
<i>Fever every 3 days</i>	3 (1.8)	1 (1.5)	2 (2.1)	1.000
<i>Fever without specified pattern</i>	149 (91.4)	60 (89.6)	89 (92.7)	0.594
<i>Shivering</i>	77 (47.2)	31 (46.3)	46 (47.9)	0.751
<i>Headache</i>	105 (64.4)	39 (58.2)	66 (68.8)	0.329
<i>Myalgia</i>	80 (49.1)	31 (46.3)	49 (51)	0.750
<i>Nausea</i>	59 (36.2)	23 (34.3)	36 (37.5)	<0.001
<i>Vomiting</i>	62 (38)	26 (38.8)	36 (37.5)	<0.001
<i>Abdominal pain</i>	42 (25.8)	17 (25.4)	25 (26)	0.924
<i>Diarrhea</i>	52 (31.9)	23 (34.3)	29 (30.2)	0.497
<i>Prostration</i>	18 (11)	18 (26.9)	0 (0)	<0.001
<i>Convulsion</i>	3 (1.8)	3 (4.5)	0 (0)	0.797
<i>Choluria</i>	5 (3.1)	2 (3)	3 (3.1)	0.691
<i>Asthenia</i>	8 (4.9)	3 (4.5)	5 (5.2)	0.081
Impaired consciousness	3 (1.8)	3 (4.5)	0 (0)	0.015
Physical examination findings, n (%)				
<i>Paleness</i>	22 (13.5)	12 (17.9)	10 (10.4)	0.168
<i>Jaundice</i>	27 (16.6)	20 (29.9)	7 (7.3)	<0.001
<i>Hepatomegaly</i>	13 (8)	5 (7.5)	8 (8.3)	0.840
<i>Splenomegaly</i>	3 (1.8)	1 (1.5)	2 (2.1)	0.782
<i>Hypotension</i>	9 (5.5)	1 (1.5)	8 (8.3)	0.005
<i>Polypnea</i>	10 (6.1)	8 (11.9)	2 (2.1)	0.016
<i>Fever</i>	125 (76.7)	53 (79.1)	72 (75)	0.852
<i>Prostration</i>	6 (3.7)	6 (9)	0 (0)	0.411
<i>Abdominal pain</i>	6 (3.7)	2 (3)	4 (4.2)	0.330
<i>Convulsion</i>	4 (2.5)	4 (6)	0 (0)	0.411
<i>Normal physical examination</i>	14 (8.6)	3 (4.5)	11 (11.5)	0.362

Continued

Blood test findings, n (%)				
<i>Anemia</i>	92 (56.4)	50 (74.6)	42 (43.8)	<0.001
<i>Trombocytopenia</i>	142 (87.1)	63 (94)	79 (82.3)	0.066
<i>Leukocytosis</i>	10 (6.1)	8 (11.9)	2 (2.1)	0.016
<i>Neutrophilia</i>	11 (6.7)	6 (9)	5 (5.2)	0.362
<i>Elevation of C-reactive protein</i>	149 (91.4)	63 (94)	86 (89.6)	0.438
<i>Elevation of transaminases</i>	67 (41.1)	42 (62.7)	25 (26)	<0.001
<i>Elevation of bilirubin</i>	61 (37.4)	42 (62.7)	19 (19.8)	<0.001
<i>Acute kidney injury</i>	48 (29.4)	32 (47.8)	16 (16.7)	<0.001
Mortality rate, n (%)	2 (1.2)	2 (3)	0 (0)	0.118

IQR = Interquartile Range.

3.4. Plasmodium Species

Plasmodium falciparum was the most predominant species (90.2%, 147/163) in all reported malaria cases. No significant association was found between species and severity (p value: 0.361) (Table 4).

Table 4. Plasmodium species identified in patients with imported malaria from 2013 to 2023.

Plasmodium species, n (%)	All (n = 163)	Severe (n = 67)	Non-severe (n = 96)	p-value
<i>Plasmodium malariae</i>	5 (3.07)	1 (1.5)	4 (4.2)	
<i>Plasmodium falciparum</i>	147 (90.18)	62 (92.5)	85 (88.5)	
<i>Plasmodium vivax</i>	6 (3.68)	1 (1.5)	5 (5.2)	0.361
Coinfection <i>Plasmodium falciparum</i> and <i>Plasmodium malariae</i>	5 (3.07)	3 (4.5)	2 (2.1)	

3.5. Criteria of Severe Malaria

For epidemiological purposes, severe malaria was defined according to October 2023 WHO guidelines [5].

Within the patients with severe malaria (n = 67), the most frequent criteria were jaundice (60.3%, 38/67), followed by prostration (41.3%, 26/67) and hyperparasitaemia > 10% (30.2%, 19/67) (Table 5).

Table 5. Criteria of severe malaria in patients with imported malaria from 2013 to 2023.

Variable	n (%)
Criteria of severe malaria, n (%)	
<i>Impaired consciousness: Glasgow Coma Scale < 11</i>	9 (14.3)
<i>Prostration</i>	26
<i>Multiple convulsions</i>	(41.3)

Continued

<i>Acidosis</i>	3 (4.8)
<i>Hypoglycemia: Blood or plasma glucose < 2.2 mmol/L (<40 mg/dL)</i>	15
<i>Severe malarial anemia: Hemoglobin concentration \leq 5 g/dL</i>	(23.8)
<i>Renal impairment: creatinine > 265 μmol/L (3 mg/dL) or blood urea > 20 mmol/L</i>	1 (1.6)
<i>Jaundice: bilirubin > 50 μmol/L (3 mg/dL) with a parasite count > 100,000/μL</i>	1 (1.6)
<i>Pulmonary edema</i>	11
<i>Significant bleeding</i>	(17.5)
<i>Shock</i>	38
	(60.3)
	8 (12.7)
	1 (1.6)
<i>Hyperparasitaemia: P. falciparum parasitaemia > 10%</i>	9 (14.3)
	19
	(30.2)

3.6. Management and Treatment

Treatment modalities of all patients are presented in **Table 6**.

Within the patients with severe malaria, 51 received intravenous quinine treatment at presentation (76.1%, 51/67), 22 received intravenous artesunate (22.4%, 15/63) and 1 patient received oral artemether/lumefantrine (1.5%, 1/67). In this group, 31 patients were admitted to the ICU (46.3%, 31/67), 16 patients for more than 3 days (51.6%, 16/31) and 15 patients during 3 or fewer days (48.8%, 15/31). During hospitalization, 15 patients had at least one blood transfusion (22.4%, 15/67) and 8 patients had haemodialysis (11.9%, 8/67). Of those who had haemodialysis, all recovered kidney function after an average of 4 sessions.

In the group of non-severe disease, 79 patients received intravenous quinine treatment at presentation due to the absence of an oral route or signs of severity that did not meet criteria for severe malaria (82.3%, 79/96); 10 patients received oral artemether/lumefantrine (10.4%, 10/96); 5 patients received artesunate (5.2%, 5/96), 1 patient received mefloquine (1%, 1/96) and 1 patient received atovaquone/proguanil (1%, 1/96). In this group, no patients were admitted to the UCI, had blood transfusions or haemodialysis.

3.7. Outcome

Two patients died, both of European origin (Portugal). One of them had been treated with intravenous quinine and the other with intravenous artesunate.

One death occurred within the first 24 hours of admission and the other 3 days after admission. In these patients the median time from onset to diagnosis was 9 days. Both had presented with hyperparasitaemia (19% and 50%) and symptoms of cerebral malaria (multiple convulsions and Glasgow coma scale < 11).

The mortality rate in our study was 1.2%.

Table 6. Management and treatment *in patients with imported malaria from 2013 to 2023.*

Variable	All (n = 163)	Severe (n = 67)	Non-severe (n = 96)	p-value
Initial therapy, n (%)				0.406
<i>Artesunate</i>	20 (12.3)	15 (22.4)	5 (5.2)	
<i>Artemether/Lumefantrine</i>	11 (6.7)	1 (1.5)	10 (10.4)	
<i>Quinine</i>	130 (79.8)	51 (76.1)	79 (82.3)	
<i>Mefloquine</i>	1 (0.6)	0 (0)	1 (1)	
<i>Atovaquone/proguanil</i>	1 (0.6)	0 (0)	1 (1)	
Admission in ICU, n (%)				0.287
Yes	31 (19)	31 (46.3)	0(0)	
<i>Yes, > 3 days</i>	16 (9.8)	16 (23.9)	0 (0)	
<i>Yes, 3 days or less</i>	15 (9.2)	15 (22.4)	0 (0)	
No	132 (81)	36 (53.7)	96 (100)	
Blood transfusion, n (%)				0.718
<i>Yes</i>	15 (9.2)	15 (22.4)	0 (0)	
<i>No</i>	149 (91.4)	53 (77.6)	96 (100)	
Haemodialysis, n (%)				0.510
<i>Yes</i>	9 (5.5)	8 (11.9)	0 (0)	
<i>No</i>	155 (95.1)	59 (88.1)	96 (100)	

3.8. Risk Factors for Severe Malaria

Being male (p value: 0.028), older age (p value: 0.013), underlying chronic medical conditions (p value: 0.005) and alcohol overuse (p value: 0.017) were identified as risk factors for severe malaria. However, no significant association was found between severe cases and nationality, travel purpose, time of visit, pre-travel consultation and chemoprophylaxis (p value > 0.05). On the other hand, prior malaria infections, regardless of the severity of the disease, appear to be a protective factor for severe malaria (p value: 0.04) (**Table 1, Table 2**).

Regarding clinical presentation, nausea and vomiting were associated with non-severe disease (p value < 0.001) and prostration and impaired consciousness were associated with severe forms of malaria (p value < 0.001) (**Table 3**). On physical examination the presence of jaundice (p value < 0.001), hypotension (p value: 0.005) or polypnea (p value: 0.016) was identified as risk factors for severe malaria. (**Table 3**) Anemia (p value < 0.001), leukocytosis (p value: 0.016), elevation of transaminases (p value < 0.001), elevation of bilirubin (p value < 0.001) and acute kidney injury (p value < 0.001) were identified as analytical risk factors for severe malaria. No other significant associations were found(**Table 3**).

4. Discussions and Conclusions

Imported malaria remains a relevant clinical problem due to the rapid progression

to severe and life-threatening disease, especially in non-immune patients and in the context in which diagnosis might be delayed due to lack of awareness of clinicians working in European countries.

This study added valuable information detailing epidemiology, clinical features and risk factors for imported severe malaria and offers a glimpse into the performance of the therapies used most recently.

Our results demonstrate that age was an independent risk factor for predicting severe malaria in adults (p value: 0.013). One explanation may be the underlying medical conditions of the elderly patients and our findings support such a theory (p value: 0.005). Also, the intrinsic failure of the physiologic regulatory mechanisms that occurs with age, puts this group of patients at risk of a greater imbalance caused by this parasitic disease, generating a severe phenotype of disease more seldom.

The risk of severe malaria was higher among men (p value: 0.028). Recent studies show that males had higher odds of developing renal failure and jaundice, which may lead to a more severe disease [8] [9].

The majority of patients with severe malaria in this study were Portuguese tourists or migrants acquiring the infection in West Africa. Our results demonstrate that ethnicity did not change the odds of severe malaria (p value > 0.05).

Alcohol overuse was identified as a risk factor for severe disease (p value: 0.017). Numerous studies have also demonstrated that abusive alcohol consumption can have strong immunosuppressive effects. Therefore, people are not only at higher risk of exposure to mosquito bites but could also be more vulnerable to *Plasmodium* parasites, thereby promoting the progression and severity of complications associated with malaria, which reinforces the idea that behaviors and preventive measures are important in tackling the risk of developing severe disease [10]. There is also the possibility that alcohol overuse is linked to worse self-care and may lead to later diagnosis due to neglecting disease signs.

Literature suggests that obesity, diabetes, and combinations of metabolic risk factors were associated with severe malaria [11]. In fact, cardiovascular risk factors like hypertension and diabetes were prevalent in patients within the criteria of severe malaria, although no significant association was found in this study (p value > 0.05).

Prior malaria infections, regardless of the severity, appear to be a protective factor for severe malaria in case of reinfection (p value: 0.04). Other studies also showed that patients with a history of previous clinical malaria, regardless of ethnicity, had a significantly reduced risk of WHO-defined severe *Falciparum* malaria [12]. Clinical immunity to malaria develops after exposure to parasites and varies with endemicity [13] [14]. In holoendemic regions, exposure to parasitemia is high enough that clinical immunity develops rapidly, and most adults and older children are clinically immune, whereas in hypoendemic regions, most people are not re-infected often enough to develop clinical immunity [13]. Even after it develops, clinical immunity can be lost without re-exposure. A person from a non-

endemic country who stays in malaria-affected areas for less than two years is considered non immune, and also at greater risk of more severe forms of the disease [15]. When individuals first develop clinical immunity, they are only immune to severe symptoms. If re-exposure continues, however, clinical immunity can result in asymptomatic or nearly asymptomatic disease.

4.1. Trip Features

The literature suggests that a substantial proportion of imported malaria cases in European countries occur among recent immigrants from malaria-endemic countries and more settled migrants who have traveled to visit friends and relatives in malaria-endemic countries [16]. They were less likely to seek pre-travel advice and take prophylaxis, and more likely to have a longer stay in a malaria endemic area and mimic risky behaviors of the locals. Most migrants are not aware of the waning of semi-immunity against malaria when they travel to their home countries [17]. This study indicated that travel to malaria-endemic countries for visiting relatives might be the most important risk factor associated with imported malaria cases in Lisbon (34.4%, 56/167). However, no significant association was found between travel purpose and severity of malaria (p value: 0.231).

A marked seasonal pattern was observed across European countries consistently reporting malaria from 2017 to 2019, with cases increasing during and immediately after the summer holiday months (July-September) [4]. Our findings could not support it since the majority of the cases occurred between April and June (31.9%, 52/163). No significant association was found between time of visit and severity of malaria (p value: 0.542).

In our study, pre-travel consultation was conducted in only 14 patients (8,6%). Six of those patients (3.7%, 6/163) started malarial chemoprophylaxis before their trip, but all of them suspended it before medical indications. Literature shows that this consultation, as well as chemoprophylaxis, has been associated with lower rates of malaria infection [18]. Our findings did not show a significant association between pre-travel consultation or chemoprophylaxis and the severity of the disease (p value > 0.05), possibly due to the small number of patients in these situations in this study.

4.2. Clinical Features

Our findings show that symptom onset occurred predominantly after returning to Portugal (84%, 137/163) with a median time from onset to diagnosis of 5 days.

Malaria has a broad range of clinical presentations. The first symptoms of malaria, common to all the different malaria species, are nonspecific and mimic a flu-like syndrome. Although fever represents the cardinal feature (93.2%, 152/163), clinical findings in malaria are extremely diverse and may range in severity from mild headache to serious complications leading to death, particularly in falciparum malaria. As the progression to these complications can be rapid, any malaria patient must be assessed and treated rapidly, and frequent observations are needed

to look for early signs of systemic complications [19]. There have been several reports of gastrointestinal symptoms, including nausea, vomiting, and diarrhea especially in patients with uncomplicated malaria [20]-[22].

In our study, significant association was found between uncomplicated malaria and clinical presentation with nausea (p value: <0.001) or vomiting (p value: <0.001). On the other hand, there was a significant association between severe malaria and impaired consciousness (p value: 0.015) and prostration (p value: <0.001). According to updated WHO guidelines, impaired consciousness with a Glasgow Coma Score < 11 in adults or a Blantyre coma score < 3 in children and prostration are criteria for severe malaria [5].

There is a wide variation in the report of jaundice in malaria in adults, with an incidence varying from 10% - 45% [23]. In our study with 163 patients with malaria, we have shown that jaundice occurs in 16,6% of all such cases. Jaundice is not an unusual accompaniment of malaria. It can occur due to intravascular hemolysis, disseminated intravascular coagulation, and, rarely, “malarial hepatitis”. Although the primary schizogony of the malarial parasite always leads to the rupture of the infected hepatocyte, alteration of the hepatic functions is uncommonly recorded due to this event [24]. According to our study, finding jaundice in physical examination of a patient diagnosed with malaria is associated with severe disease (p value: <0.001). Other physical signs can include polypnea (p value: 0.016) and postural hypotension (p value: 0.005).

Blood test findings associated with severe malaria were presence of anemia-hemoglobin (Hb) levels < 12.0 g/dL in women and <13.0 g/dL in men (p value < 0.001); elevation of transaminases (p value < 0.001); elevation of serum bilirubin (p value < 0.001); acute kidney injury (p value < 0.001) and leukocytosis (p value: 0.016).

It is no surprise that the association of these markers with severe disease as they are some of the analytical hallmarks of septic response, as renal impairment and elevation of serum bilirubin are also common end-organ dysfunctions related to severe sepsis.

4.3. *Plasmodium* Species

Plasmodium falciparum was the most predominant species imported (90.2%, 147/163). According to the literature, severe malaria is predominantly caused by *Plasmodium falciparum* [25]. However, no significant association was found between species and severity of malaria (p value: 0.361), probably due to the small number of *non-falciparum* cases. *Non-falciparum* infection might not always be sufficiently symptomatic to prompt individuals to seek care [25].

4.4. Management and Treatment

According to the literature, severe forms of malaria should be regarded as a medical emergency and managed in Intensive Care Units (ICU) [26] [27]. Our study did not show any significant association between ICU admission and outcome of

severe malaria.

Treatment must be initiated immediately after diagnosis (within two hours at the latest) [28]. Artesunate is now the first-line treatment of severe malaria. Unlike most conventional antimalarial drugs (quinine, mefloquine, pyrimethamine), artemisinin derivatives (dihydroartemisinin-DHA or artemimol, artemether, artemether, artesunate-artesunic acid, artelinate, artemotil) are active against all intraerythrocytic parasites, from early asexual blood stage parasites (circulating ring stages) to late blood stage parasites (mature trophozoites and schizonts responsible for cytoadherence) and immature sexual blood stage parasites (stages I - IV gametocytes) [28].

In our study, 76,1% patients with severe malaria were treated with quinine, followed by artesunate (22,4%) due to the later and lesser availability of artesunate in our hospital. Some studies showed that in comparison with quinine, parenteral artesunate reduced mortality from severe malaria by about 40% in adults [29]. Our study did not show any significant association between initial therapy with artesunate or quinine and outcome.

The mortality rate in our study was 1.2%. According to the Annual Epidemiological Report for 2021, the case fatality was 1.1% among all 1944 malaria cases with a known outcome [4]. In other reports, a case fatality rate of between 0.01% and 0.40% was applied to the estimated number of *P. falciparum* cases [30].

5. Conclusions

In conclusion, primary and secondary prevention measures, such as pre-travel consultations, chemoprophylaxis, and early diagnosis and treatment, should be emphasized and improved among high-risk prospective travelers to malaria endemic countries. Portugal maintains a close relationship with African countries, particularly former Portuguese colonies, and so malaria must be suspected in travelers who return from those countries.

This finding should prompt clinicians to advise men, older travelers and travelers with underlying chronic medical conditions on malaria prevention, and highlights the need for early diagnosis and treatment for patients with early symptoms of malaria.

Conflicts of Interest

The authors declare no conflicts of interest.

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