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Imported Malaria in Portugal: A Retrospective Analysis from a Tertiary Public Hospital

Malária Importada em Portugal: Uma Análise Retrospetiva de um Hospital Público Terciário

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ABSTRACT

Imported malaria remains a clinical and public health challenge in non-endemic countries. This retrospective study analyzed all adult malaria cases diagnosed at Hospitais da Universidade de Coimbra between 2020 and 2024, and the aim was to characterize the epidemiological profile, assess the impact of previous malaria history, and identify biomarkers associated with disease severity. A total of 88 patients were included, mostly male expatriates, with exposure primarily in Angola. Previous malaria history was reported in 52.3% of cases. Severe malaria was diagnosed in 25.0% of patients, being significantly more frequent among those without a prior history of the disease ($p = 0.027$). These patients had significantly higher creatinine ($p = 0.009$) and lactate dehydrogenase ($p = 0.038$) levels, suggesting an increased risk of complications. Urea and parasitemia were independently associated with longer hospital stay ($p < 0.001$ and $p = 0.016$, respectively), used here as a proxy for severity. These findings support the hypothesis of semi-immunity in previously exposed individuals and highlight the potential of laboratory biomarkers for clinical risk stratification. Continuous surveillance and targeted prevention strategies for non-immune and semi-immune travelers remain essential, especially in countries like Portugal, where malaria reintroduction can be a real concern.
Keywords: Communicable Diseases, Imported/epidemiology; Emigrants and Immigrants; Immunity; Malaria/epidemiology; Portugal

RESUMO

A malária importada continua a representar um desafio clínico e de saúde pública em países não endémicos. Este estudo retrospetivo analisou todos os casos de malária diagnosticados em adultos nos Hospitais da Universidade de Coimbra, entre 2020 e 2024, com o objetivo de caracterizar o perfil epidemiológico, avaliar o impacto da história prévia de malária e identificar biomarcadores associados à severidade da doença. Foram incluídos 88 doentes, maioritariamente homens expatriados, expostos sobretudo em Angola, dos quais 52,3% apresentava história prévia de malária. Classificaram-se 25.0% dos casos como malária severa, sendo esta mais frequente nos doentes sem história prévia ($p = 0,027$). Nestes, os níveis de creatinina ($p = 0,009$) e desidrogenase lática ($p = 0,038$) foram significativamente mais elevados, sugerindo maior risco de complicações. Ureia e parasitémia mostraram associação independente com a duração do internamento ($p < 0,001$ e $p = 0,016$, respetivamente), utilizadas como marcadores indiretos de gravidade. Estes dados apoiam a hipótese de semi-imunidade em doentes previamente expostos e realçam o potencial de marcadores laboratoriais na estratificação do risco clínico. A vigilância contínua e estratégias de prevenção dirigidas a viajantes não imunes e semi-imunes permanecem essenciais, especialmente em países como Portugal, onde a reintrodução da malária pode ser uma preocupação real.
Palavras-chave: Doenças Transmissíveis Importadas/epidemiologia; Emigrantes e Imigrantes; Imunidade; Malária/epidemiologia; Portugal

Malaria, caused by *Plasmodium* spp. and transmitted by *Anopheles* mosquitoes, is endemic to tropical regions, but globalization and climate change have increased the risk of reintroduction in malaria-free areas, including Europe.[1,2]

In Portugal, endemic malaria transmission ceased in 1959.[2] In recent decades, international travel to tropical destinations and migratory flows between Portugal and malaria-endemic regions, particularly from lusophone African countries, have contributed to the occurrence of imported malaria.[3] Among migrants and expatriates who spend extended periods in endemic areas, repeated exposure to the parasite can occur. Such cumulative exposure may lead to partial immunity (semi-immunity), reducing disease severity, while differences in immunity can affect presentation, treatment, and prognosis.[4]

Across Portugal, competent *Anopheles* vectors coexist with imported malaria cases. Clusters combining high vector density and imported infections have been documented in Condeixa-a-Nova (Coimbra) and other regions of the country. Given that Condeixa-a-Nova falls within our hospital's catchment area, this case underscores the local relevance of investigating imported malaria.[2,5]

The aim of this study was to characterize imported malaria cases diagnosed at Hospitais da Universidade de Coimbra (HUC) between 2020 and 2024. We focused on geographic origin, prior malaria history, as well as disease severity. In addition, we explored the association between laboratory markers and hospitalization outcomes, under the hypothesis that specific biomarkers may reflect severity and predict length of stay. These insights may ultimately support better clinical practice in a setting with a considerable burden of imported malaria, where reintroduction remains a concern.[5]

This retrospective cohort study included every adult (≥ 18 years) patient with laboratory-confirmed malaria diagnosed at HUC, Portugal, between 2020 and 2024. Data was

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extracted from the hospital electronic records.

The diagnosis of malaria was made by microscopic examination of thick/thin blood smears, with parasitemia as percentage of infected red blood cells. The diagnosis of severe *Plasmodium falciparum* malaria was defined according to current World Health Organization (WHO) criteria.[6]

Descriptive statistics were used to summarize demographic, clinical, and laboratory data. Comparisons used chi-square/Fisher's for categorical and t-test/Mann-Whitney for continuous variables. Variables associated with hospitalization length in univariate analysis were entered into linear regression; due to multicollinearity, blood creatinine and lactate dehydrogenase (LDH) were excluded. The model included urea, bilirubin, platelets, age, and parasitemia. Linear regression assumptions were verified.

Analyses were two-tailed, with $p < 0.05$ considered significant, and performed in SPSS v29.

A total of 88 malaria cases were recorded between 2020 and 2024. Fig. 1 shows the annual trend in total and severe malaria cases and Table 1 details the demographic, biological, and clinical characteristics of the study population according to previous malaria history. The cohort (mean age 47.4 years) was mostly male (86.4%), Portuguese (75.0%), with exposure mainly in Sub-Saharan Africa (97.7%). Angola accounted for 59 cases (67.1%), followed by Mozambique (6; 6.8%) and the Ivory Coast (3; 3.4%). Uganda, Central African Republic, Mali, Equatorial Guinea, Gabon, and Ghana each contributed two cases (2.3%), while single cases were imported from Tanzania, Democratic Republic of Congo, Sierra Leone, Guinea-Bissau, Nigeria, São Tomé and Príncipe and India. A previous history of malaria was reported in 46 (52.3%) patients; among expatriates, 58.3% had previous episodes of malaria.

Lower blood LDH ($p = 0.038$) and creatinine ($p = 0.009$) levels were significantly associated with previous malaria episodes. Severe malaria was diagnosed in 25.0% of patients, most commonly due to jaundice and hyperparasitemia (50.0% and 41.0% of severe cases, respectively), as defined by WHO criteria; and was significantly more frequent in those without a prior history of malaria ($p = 0.027$). All severe malaria cases were due to *P. falciparum*.

Hospitalization length was positively associated with urea, LDH, creatinine, bilirubin, parasitemia and age, and negatively with platelet count in univariate analysis (all $p < 0.05$). In the multivariate model, urea ($p < 0.001$) and parasitemia ($p = 0.016$) remained independently associated with longer stays.

Between 2020 and 2024, we observed a rising number of imported malaria cases at our hospital, with a marked increase post-COVID-19. This trend reflects Portuguese and European data, where malaria resurged after travel restrictions eased.[7]

Prior malaria exposure influenced disease presentation. In our expatriate group, 58.3% had a history of malaria, in line with findings from another Portuguese study.[3] Consistent with the semi-immunity hypothesis, our data indicate that patients with a prior history of malaria were more likely to present with milder disease, aligning with previous reports.[4,8,9]

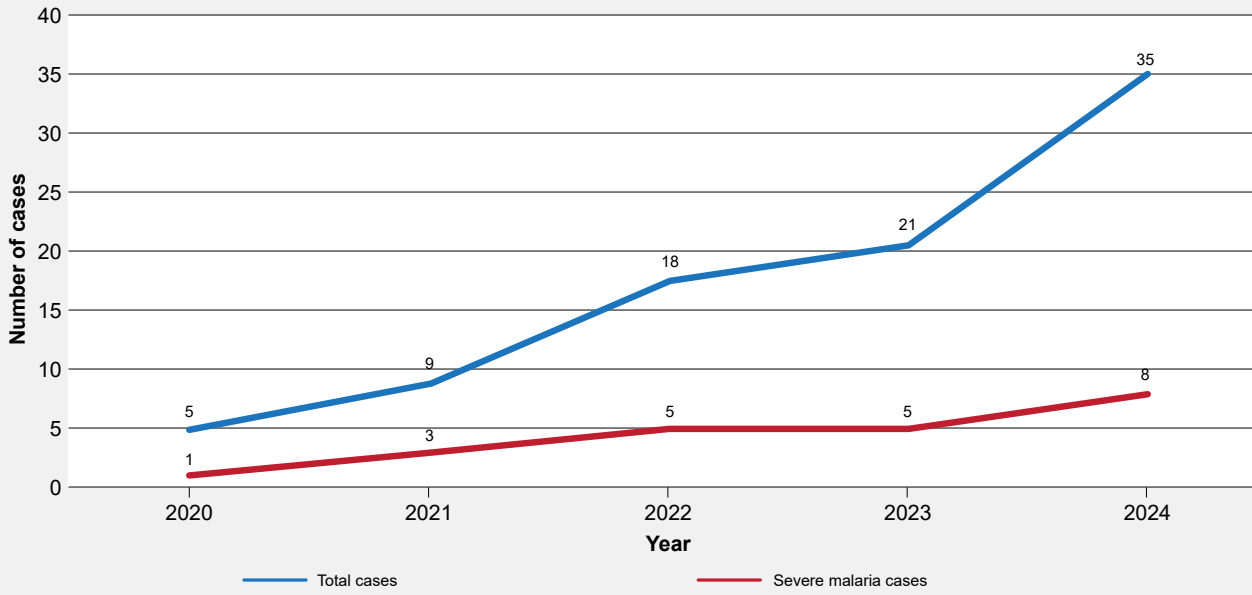

Figure 1 – Trends in total and severe malaria cases, by year, at Unidade Local de Saúde Coimbra (2020 - 2024)

Table 1 – Demographic, biological characteristics and outcomes of malaria cases diagnosed at HUC, all and according to history of malaria (section 1 of 2).

Analytical markers, treatment and outcomes	All	Previous malaria	No previous malaria	*p*-value
Number of cases, n (%)	88	46 (52.27)	42 (47.73)	
Age in years, Mean (SD)	47.44 (14.29)	49.17 (13.29)	45.55 (15.24)	0.237
Age group, n (%)				
18 - 24	6 (6.82)	2 (4.35)	4 (9.52)	0.419
25 - 34	14 (15.91)	5 (10.87)	9 (21.43)	0.245
35 - 44	17 (19.32)	11 (23.91)	6 (14.29)	0.253
45 - 54	21 (23.86)	10 (21.74)	11 (26.19)	0.625
55 - 64	21 (23.86)	13 (28.26)	8 (19.05)	0.311
> 64	9 (10.23)	5 (10.87)	4 (9.52)	1
Male, n (%)	76 (86.36)	41 (89.13)	35 (83.33)	0.429
Country of exposure, n (%)				
Angola	59 (67.05)	31 (67.39)	28 (66.67)	0.942
Others	28 (31.82)	14 (30.43)	14 (33.33)	0.771
Unknown	1 (1.14)	1 (2.17)	0 (0.00)	1
Nationality, n (%)				
Portuguese	66 (75.00)	34 (73.91)	32 (76.19)	0.805
Angolan	15 (17.00)	9 (19.57)	6 (14.29)	0.511
Other	6 (6.82)	3 (6.52)	3 (7.14)	1
Unknown	1 (1.14)	0 (0.00)	1 (2.38)	0.477
Type of traveler, n (%)				
Expatriates	48 (54.55)	28 (60.87)	20 (47.62)	0.284
Short trip	22 (25.00)	8 (17.39)	14 (33.33)	0.093
Mission	4 (4.55)	2 (4.35)	2 (4.76)	1
Recent immigrant	10 (11.36)	6 (13.04)	4 (9.52)	0.603
Unknown	4 (4.55)	2 (4.35)	2 (4.76)	1
Species, n (%)				
P. falciparum	73 (82.95)	35 (76.09)	38 (90.48)	0.073
P. ovale	6 (6.82)	4 (8.70)	2 (4.76)	0.678
P. vivax	3 (3.41)	2 (4.35)	1 (2.38)	1
P. malariae	2 (2.27)	2 (4.35)	0 (0)	0.495
P. falciparum + P. ovale	2 (2.27)	2 (4.35)	0 (0)	0.495
Unknown	2 (2.27)	1 (2.17)	1 (2.38)	1
Symptoms evolution, days **Median** (IQR)	4.00 (2.00 - 4.00)	4.00 (2.25 - 5.00)	4.00 (2.00 - 6.75)	0.521
Parasitemia, % **Median** (IQR)	1.50 (0.30 - 5.00)	1.50 (0.25 - 3.95)	1.00 (0.48 - 5.50)	0.809
Platelet count, 10^3/(µL) **Median** (IQR)	56.00 (35.00 - 100.00)	64.70 (38.75 - 101.75)	48.00 (26.00 - 96.00)	0.073
Hemoglobin, g/dL **Mean** (SD)	13.46 (2.20)	13.18 (2.00)	13.77 (2.40)	0.216
Creatinine, mg/dL **Median** (IQR)	0.94 (0.83 - 1.13)	0.90 (0.83 - 0.99)	1.05 (0.85 - 1.79)	**0.009***
Urea, mmol/L **Median** (IQR)	2.80 (2.13 - 3.88)	2.75 (2.08 - 3.60)	2.85 (2.15 - 4.25)	0.561
Bilirubin, mg/dL **Median** (IQR)	1.60 (1.10 - 2.69)	1.55 (1.10 - 2.78)	1.70 (1.00 - 2.66)	0.808
Creatine kinase, U/L **Median** (IQR)	72.00 (41.00 - 113.00)	55.00 (40.00 - 99.00)	73.00 (46.00 - 128.50)	0.192
LDH, U/L **Median** (IQR)	355.00 (270.00 - 519.00)	326.00 (252.00 - 458.00)	400.50 (293.00 - 551.25)	**0.038***

A/L: artemeter-lumefrantine; ICU: intensive care unit; IMCU: intermediate care unit; IQR: interquartile range; P.: *Plasmodium*; SD: standard deviation

*: *p*-value < 0.05 and therefore statistically significant. The tests performed are the Student's *t*-test or the non-parametric Wilcoxon-Mann-Whitney test, Pearson's chi-squared test or Fisher's exact test depending on the type of variables.

Table 1 – Demographic, biological characteristics and outcomes of malaria cases diagnosed at HUC, all and according to history of malaria (section 2 of 2).

Analytical markers, treatment and outcomes	All	Previous malaria	No previous malaria	*p*-value
Cases with severe malaria at admission, n (%)	22 (25.00)	7 (15.22)	15 (35.71)	**0.027***
Outcome, n (%)				
Outpatient	15 (17.05)	10 (21.74)	5 (11.90)	0.220
Ward	52 (59.09)	28 (60.87)	24 (57.14)	0.722
IMCU	15 (17.05)	5 (10.87)	10 (23.81)	0.107
ICU	6 (6.82)	3 (6.52)	3 (7.14)	1
Length of hospitalization, days **Median** (IQR)	4.00 (3.00 - 7.00)	4.00 (3.00 - 6.00)	5.00 (3.00 - 7.50)	0.308
Antimalarial treatment, n (%)				
Artesunate, then A/L	42 (47.73)	17 (36.96)	25 (59.52)	**0.034***
A/L alone	39 (44.32)	26 (56.52)	13 (30.95)	**0.016***
Other combinations	5 (5.68)	2 (4.35)	3 (7.14)	0.666
Unknown	2 (2.27)	1 (2.17)	1 (2.38)	1

A/L: artemeter-lumefrantine; ICU: intensive care unit; IMCU: intermediate care unit; IQR: interquartile range; P.: *Plasmodium*; SD: standard deviation
*: *p*-value < 0.05 and therefore statistically significant. The tests performed are the Student's *t*-test or the non-parametric Wilcoxon-Mann-Whitney test, Pearson's chi-squared test or Fisher's exact test depending on the type of variables.

Our results indicated that patients without prior *Plasmodium* spp. exposure showed a higher risk of organ complications, such as acute kidney injury (AKI), with elevated creatinine levels. This aligns with reports showing that non-immune patients are more prone to AKI.[10] Similarly, patients without prior malaria had higher LDH levels.

We also evaluated whether admission laboratory values could predict outcomes, using length of hospital stay as a surrogate for severity. Urea and parasitemia emerged as independent predictors in multivariate analysis. Elevated urea and hyperparasitemia are recognized by the WHO as severity markers for malaria.[6] Our findings align with these definitions, as both biomarkers were independently associated with longer hospital stays.

Beyond individual clinical management, these findings have broader implications. The predominance of expatriates and exposure mainly in Angola highlight the need for targeted preventive strategies for high-risk groups. Strengthening awareness among healthcare providers and travelers could contribute to earlier diagnosis and improved outcomes. At the public health level, continuous surveillance is essential to promptly detect imported cases and mitigate the risk of local reintroduction.

This study has limitations. Its retrospective, single-center design may limit generalizability. Prior malaria history was self-reported and not verified serologically.

This short article updates the profile of imported malaria in Portugal, showing that patients without prior malaria episodes had more severe disease and worse biomarker profiles, suggesting partial protection from semi-immunity. Urea and parasitemia were independently associated with the outcome and may serve as useful markers for clinical risk stratification. Pre-travel counselling should be strengthened not only for tourists and business travelers, but also for expatriates and immigrants returning to endemic regions, as they remain at risk and may contribute to the reintroduction of malaria in Portugal.

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The authors have declared that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

TVF: Data collection, analysis and interpretation, drafting of the manuscript.

GAS: Data analysis and interpretation, critical review of the manuscript.

VD: Data analysis, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

ETHICS

The study was approved by the Ethics Committee of the ULS Coimbra (170/25 CE).

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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