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# Unpleasant Souvenir: Imported *Plasmodium falciparum* Malaria in Türkiye

## *Nahoş Hatıra: Türkiye'de Yurtdışı Kaynaklı Plasmodium falciparum Sıtması*

Ahmet Özbilgin[1], Varol Tunalı[2], Şebnem Şenol Akar[3], İbrahim Çavuş[1], Orçun Zorbozan[4], Ahmet Yıldırım[1], Nevin Turgay[4]

[1]Manisa Celal Bayar University Faculty of Medicine, Department of Parasitology, Manisa, Türkiye
[2]Eşrefpaşa Municipality Hospital, Clinic of Emergency Medicine, İzmir, Türkiye
[3]Manisa Celal Bayar University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Manisa, Türkiye
[4]Ege University Faculty of Medicine, Department of Parasitology, İzmir, Türkiye

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## ABSTRACT

**Objective:** Each year, approximately 125 million people visit malaria-endemic countries. This study aimed to investigate the clinical characteristics of imported *Plasmodium falciparum* malaria infections in Türkiye.
**Methods:** The study included patients diagnosed with *P. falciparum* malaria between 1996 and 2022. A retrospective evaluation was conducted on whole blood samples and/or blood smears, as well as detailed medical histories, clinical manifestations, and laboratory findings. A total of 131 imported cases of *P. falciparum* were included in the study.
**Results:** Among the patients, 121 were male. Of these, 101 had traveled to Africa, while 30 had visited Asia. Among the patients, 109 were returned travelers, and 22 were refugees/migrants. Early trophozoites were observed in all patients, while gametocytes were detected in 30 patients. Cerebral malaria developed in 15 patients, resulting in the death of two individuals. Additionally, 10 patients received preventive chemoprophylaxis.
**Conclusion:** Turkey is situated on migration routes that connect two continents to Europe, where more than 95% of the global malaria burden exists. The importation of malaria through returned travelers poses a risk of malaria reintroduction in our country, given the presence of suitable vectors, climate conditions, and environmental factors. Importantly, 30 patients (22.9%) exhibited gametocyte forms of *P. falciparum*, which have the potential to infect Anopheles species, thus establishing a basis for local malaria transmission.
**Keywords:** Travel medicine, fever, Türkiye, migration, malaria

## ÖZ

**Amaç:** Her yıl yaklaşık 125 milyon kişi sıtmanın endemik olduğu ülkeleri ziyaret etmektedir. Bu çalışmada Türkiye'ye dışarıdan gelen *Plasmodium falciparum* sıtma enfeksiyonlarının klinik özelliklerinin araştırılması amaçlanmıştır.
**Yöntemler:** Çalışmaya 1996-2022 yılları arasında *P. falciparum* sıtması tanısı konan hastalar dahil edildi. Tam kan örnekleri ve/veya kan yaymaları, ayrıntılı tıbbi öyküler, klinik belirtiler ve laboratuvar bulguları retrospektif olarak değerlendirildi. Çalışmaya toplam 131 dışarıdan gelen *P. falciparum* olgusu dahil edildi.
**Bulgular:** Hastaların 121'i erkekti. Bunlardan 101'i Afrika'yı, 30'u Asya'yı ziyaret etmişti. Hastalar arasında 109'u turist/ziyaretçi ve 22'si mülteci/göçmendi. Tüm hastalarda erken dönem trofozoitler gözlenirken, 30 hastada gametositler tespit edildi. On beş hastada serebral sıtma gelişti ve iki kişinin ölümüyle sonuçlandı. Ayrıca 10 hastaya koruyucu kemoprofilaksi uygulandı.
**Sonuç:** Türkiye, küresel sıtma yükünün %95'inden fazlasının bulunduğu iki kıtayı Avrupa'ya bağlayan göç yolları üzerinde yer almaktadır. Uygun vektörlerin varlığı, iklim koşulları ve çevresel faktörler göz önüne alındığında, sıtmanın geri dönen yolcular aracılığıyla ithal edilmesi, ülkemizde sıtmanın yeniden ortaya çıkması riski oluşturmaktadır. Daha da önemlisi, 30 hastanın (%22,9) *P. falciparum*'un Anopheles türlerini enfekte etme potansiyeline sahip gametosit formlarına sahip olması, yerli sıtma bulaşı açısından önemli bir risk faktörü olarak değerlendirilmiştir.
**Anahtar Kelimeler:** Seyahat sağlığı, ateş, Türkiye, göç, sıtma

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**Address for Correspondence/Yazar Adresi:** Varol Tunalı, Eşrefpaşa Municipality Hospital, Clinic of Emergency Medicine, İzmir, Türkiye
**E-mail/E-Posta:** varoltunali@gmail.com **ORCID ID:** orcid.org/0000-0003-1799-2539



Türkiye PARAZİTOLOJİ Dergisi

## INTRODUCTION

Ninety-one designated malaria-endemic countries are visited by more than 125 million people annually. A serious proportion of these travelers fall ill during their travel and over 10,000 malaria cases are reported on the return. The actual number of cases can rise to thirty thousand with the addition of unrecorded cases (1). Visitors from non-endemic countries who have not encountered malaria before, lack semi-immunity against it and therefore are at higher risk for malaria (2). In this context, it is recommended for returned travelers who had fever during the 3 months after departure to be examined for malaria (3).

It is estimated that 10-15 million European travelers visit malaria-endemic areas, and 12-15 thousand cases of malaria are imported into European Union countries every year (4). An eight-fold increase in the number of imported malaria cases is reported in Europe between 1972 and 1999 (from 1,500 to 13,000 cases) (5). Most of the imported cases of malaria in Europe are due to *Plasmodium falciparum* comprising more than 70% of all imported malaria cases, mostly acquired in the western and central parts of Africa by travelers who were visiting friends and relatives (VFR) (6,7). In this context, human mobility and migration play a pivotal role in malaria re-introduction and transmission, as infected individuals can inadvertently introduce malaria parasites, potentially including drug-resistant strains, into new regions, creating challenges for elimination efforts in low-transmission areas (8). Natural disasters and migration, such as those triggered by earthquakes and flooding, can exacerbate malaria transmission by leading to changes in behavior, such as sleeping outdoors due to housing loss or safety concerns, as well as disrupting normal healthcare services and disease control activities (9).

In Türkiye, 1,651 imported malaria cases were reported between the years 1990 and 2009 with an average of 45-50 cases annually. Three hundred one (18%) were single *P. falciparum* cases and 22 were mixed *P. vivax* and *P. falciparum* (10). In the year 2009, the number of imported cases (n=46) exceeded the number of autochthonous cases (n=38) for the first time. This prompted a need for special interest to survey and control imported malaria cases in Türkiye (11). Türkiye reported 9 relapsing cases in 2010 and 4 relapsing cases in 2011. An outbreak of 208 *P. vivax* cases, both imported and local, was detected in the south-eastern province of Mardin in 2012. Investigation indicated that the outbreak was due to importation by lorry drivers arriving from malaria-endemic countries and delayed diagnosis of index cases. The outbreak was rapidly controlled, and surveillance intensified in the south-eastern part of the country (12). Between 2012 and 2022, there has only been a report of 3 autochthonous cases of *P. falciparum*/*P. vivax* mixed infection seen in Kayseri province in 2022 (13).

Artemisinin combination therapies are used for uncomplicated *P. falciparum* malaria cases in Türkiye according to World Health Organization (WHO) guidelines (14). Artemether-lumefantrine combination therapy is the treatment of choice for this patient group.

The aim of this study is to present the epidemiological status of imported *P. falciparum* malaria in Türkiye with clinical and laboratory features.

## METHODS

### Ethical Approval

The ethical committee approval for this study was obtained from Manisa Celal Bayar University Faculty of Medicine Health Sciences Ethics Committee (20.478.486-1893/21.06.2023) and Manisa Celal Bayar University Faculty of Medicine Health Sciences Ethics Committee (decision no: 192/05.07.2021).

### Patients and Microscopy Methods

In total, 131 patients who were admitted to Manisa Celal Bayar University Faculty of Medicine Parasitology Department or consulted from another hospital, between January 1st, 1996, and December 30th, 2022, and diagnosed with *P. falciparum* malaria by microscopy were included in the study. Blood smears and detailed anamneses obtained from patients were evaluated retrospectively. Malaria was diagnosed with the detection of *P. falciparum* on light microscopic examination of Giemsa stained thin and thick smear of fingertip blood samples on x100 magnification (Figure 1). The diagnosis was made with the observation of a minimum of 200 microscopic fields on thin and 100 microscopic fields on thick smears. Differential diagnosis of *P. falciparum* malaria was made according to WHO guidelines (15). The detailed anamneses of the patients were evaluated.

### Sample Obtaining for Molecular Analysis and Real-Time PCR

The Giemsa-stained preparations of both thick drops and thin smears from all patients were immersed in methanol twice for a duration of 1-2 minutes each time. Following this process, all preparations were thoroughly rinsed with distilled water and left to dry. Once dried, the preparations were delicately scraped off the slide using a sterile scalpel and transferred to a sterile Petri dish. This material contained the *Plasmodium* spp.

The collected material was then carefully transferred to a 1.5 mL Eppendorf tube, and 200 µL of sterile phosphate buffered saline was added. Subsequently, DNA isolation was carried out using the ROCHE High Pure PCR Template Preparation Kit, enabling the extraction of DNA from the collected material.

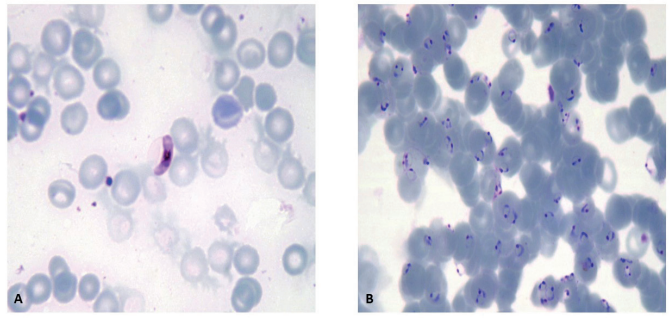


**Figure 1.** Images of microscopical findings in thin blood smears A. Gametocytes of *P. falciparum* on thin blood smear B. Early trophozoites of *P. falciparum* on thin blood smear

For further analysis, a specific primer, designed for the Plasmodium apicoplast gene region, was employed to conduct reverse transcription-quantitative polymerase chain reaction (RT-qPCR) analysis.

F: CGAAAGTTAAGGGAGTGAAGACG

R: AATACTCGCCCCAGAACCC

The total reaction volume was 25 µL, comprising 1 µL of forward primer, 1 µL of reverse primer, 12.5 µL of QuantiTect Probe PCR Kit Master, 1 µL of EvaGreen, and 6.5 µL of PCR-grade water (H20). To perform the RT-qPCR analysis, 5 µL of DNA was added to the reaction mixture.

The applied protocol consisted of an initial denaturation step at 95 ˚C for 15 minutes, followed by 40 cycles of denaturation at 95 ˚C for 15 seconds, annealing at 60 ˚C for 30 seconds, and extension at 72 ˚C for 20 seconds. Subsequently, a melting analysis was conducted.

The melting analysis results were used to perform species differentiation by comparing the melting curves of the control samples (*P. falciparum, P. vivax, P. ovale*, and *P. malaria* control samples) with those of the patient samples.

### Statistical Analysis

A descriptive data set was prepared based on the patients'records. The data were then analyzed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). To evaluate the data set, descriptive statistics such as frequency, percentage, and mean ± standard error were employed.

## RESULTS

A total of 131 patients diagnosed with *P. falciparum* malaria were included in the study. The age range of the patients was 18-65 years, with a mean age of 34 years. Among the patients, 121 were male and 10 were female.

Microscopic, clinical, and laboratory findings were evaluated and are presented in Table 1. In the microscopic examinations, early trophozoites of *P. falciparum* were detected in all samples, while gametocytes were observed in 30 cases (22.9%). Schizonts of *P. falciparum* were detected in peripheral blood smears from 3 patients. According to WHO criteria, hyperparasitemia was observed in 86 samples (65.6%).

A total of 101 patients had traveled to Africa (77%), while 30 had visited Asia (23%). Among the patients, 109 were returned travelers (83.2%), and 22 were refugees or asylum seekers (16.8%).

The most common presenting symptom was fever with chills (n=131). Fatigue was reported by 114 patients, and prodromal findings such as malaise and headache were observed in 102 patients. Other complaints included poor appetite (n=68), headaches (n=55), myalgia/arthralgia (n=43), gastrointestinal symptoms (n=45), sore throat and cough (n=32), and weight loss (n=26) (Table 1).

The most frequent physical examination finding was splenomegaly (n=82), followed by hepatomegaly in 60 patients. Icterus was the least common finding (n=34). Cerebral malaria was diagnosed in 15 patients, and unfortunately, two of them succumbed to the disease (Table 1).

Serum lactate dehydrogenase levels were elevated above 400 IU in 91 patients, while elevated serum aspartate transaminase aspartat aminotransferaz levels were observed in 78 patients.

**Table 1.** Characteristics, clinical and laboratory findings of *Plasmodium falciparum* patients

| **Characteristics** | **(n=131)** | **%** |
|---|---|---|
| **Age** (mean)* | 34 | |
| **Gender** (female/male) | 10/121 | 7.6/92.4 |
| **Travel region** | | |
| Africa | 101 | 77.0 |
| Asia | 30 | 23.0 |
| Returned traveller (tourism, business visit, education, family/friend visit) | 109 | 83.2 |
| Refugee/asylum seeker | 22 | 16.8 |
| Complaints | | |
| Fevers, chills | 131 | 100.00 |
| Fatigue | 114 | 87.0 |
| Prodromal findings (malaise, headache) | 102 | 77.8 |
| Poor appetite | 68 | 51.9 |
| Headaches | 55 | 41.9 |
| Myalgia/arthralgia | 43 | 32.8 |
| Gastrointestinal symptoms (diarrhoea, stomach ache) | 45 | 34.3 |
| Sore throat and cough | 32 | 24.4 |
| Weight loss | 26 | 19.8 |
| **Physical examination findings** | | |
| Splenomegaly | 82 | 62.5 |
| Hepatomegaly | 60 | 45.8 |
| Icterus | 34 | 25.9 |
| Laboratory findings | | |
| LDH >400 IU | 91 | 69.4 |
| AST >60 IU | 78 | 59.5 |
| WBC <4,000 cell/mm$^3$ | 59 | 45.0 |
| Hyperbilirubinemia (total bilirubin >1.2 mg/dL) | 54 | 41.2 |
| **Microscopy** (Giemsa-stained peripheral blood smears) | | |
| Early trophozoites | 131 | 100.00 |
| Hyperparasitemia | 86 | 69 |
| Gametocytes | 30 | 22.9 |
| **Cerebral malaria** | 15 | 11.4 |
| Coma | 7 | 5.3 |
| Confusion | 4 | 3.0 |
| Convulsions | 2 | 1.5 |
| Dead | 2 | 1.5 |
| Chemoprophylaxis | 10 | 7.6 |

*Age range was 18-65 years; LDH: Lactate dehydrogenase, AST: Aspartate transaminase, WBC: White blood cell

Leukopenia and hyperbilirubinemia were present in 59 and 54 patients, respectively (Table 1). Among the 131 patients, only 10 received chemoprophylaxis.

RT-qPCR analysis of all samples confirmed the presence of *P. falciparum*.

## DISCUSSION

Türkiye stands at the crossroads of Europe, Asia, and Africa and is located in the subtropical zone near the Balkans, Caucasia, and the Middle East. There are 10 *Anopheles* species identified in Türkiye; *An. sacharovi* is the most important vector of malaria, followed by *An. superpictus*, *An. maculipennis* and *An. Subalpinus* (11). Historically, autochthonous cases of *P. vivax* and *P. falciparum* malaria have been reported in Anatolia (16). *P. vivax* has been the main causative agent of malaria in Türkiye but according to WHO data, since 2010 Türkiye is malaria-free, and all the cases are imported malaria cases (17).

It is worth noting that there have been reports of autochthonous mixed cases of *P. vivax* and *P. falciparum* in Türkiye. For instance, in Kayseri province, three malaria cases caused by *P. falciparum* and *P. vivax* were reported, despite the absence of travel history to endemic regions (13). These cases involved individuals without known chronic diseases who presented with symptoms such as high fever, chills, and sweating, along with hepatosplenomegaly and thrombocytopenia. The diagnosis was confirmed through real-time polymerase chain reaction analysis and treatment with artemether-lumefantrine and primaquine was administered. All three patients exhibited mixed parasitemia and responded well to treatment, with no recurrence of parasitemia observed.

Although malaria elimination has been achieved in Türkiye, researchers agree on the risk of autochthonous infection in Türkiye due to *P. malariae* and *P. falciparum* based on the presence of suitable vectors and climate conditions (18,19). In the presented study, 23% of the patients had gametocyte forms of *P. falciparum*, which can infect *Anopheles* species. It has been reported that female *An. superpictus* mosquitoes in Türkiye can be experimentally infected with *P. falciparum* in the laboratory (20). In addition, it should be kept in mind that there may be an increase in *P. vivax* malaria cases, as the increase in temperature will accelerate the sporogonic period in the mosquito (21). A particular concern is the presence of asymptomatic malaria patients with sub-microscopic parasitemia, as they pose a significant risk for the re-introduction of malaria in areas where competent vectors and suitable climatic conditions exist (22).

Hyperparasitemia in *P. falciparum* malaria is associated with higher mortality and morbidity (23). According to the Centers for Disease Control and Prevention, hyperparasitemia itself is considered a manifestation of severe malaria (24). Particularly in non-endemic areas, hyperparasitemia has been found to be a sensitive and specific indicator of severe malaria and consequently, mortality and morbidity rates (25,26). However, in our study, hyperparasitemia was present in 86 (65.6%) of the samples, whereas cerebral malaria was observed in 15 (11.4%) patients, and 2 patients (1.5%) succumbed to the disease. This finding contradicts the literature, as Türkiye is a non-endemic country for *P. falciparum* malaria, and its population lacks semi-immunity. Some studies have suggested updating the definition of hyperparasitemia (27), and our study results also support this notion.

We believe that one of the reasons for the high rates of hyperparasitemia in our study is the late diagnosis of *P. falciparum* malaria, which is a common occurrence in non-endemic countries (28). In our study, a majority of the patients were returned travelers (83%), who were Turkish nationals, while most imported *P. falciparum* cases in Europe are found among migrants or European nationals VFR in Africa (29,30). VFRs in Europe tend to make less effort to seek healthcare services (31). Similarly, in Türkiye, patients experience delays in being diagnosed with malaria, even though they present at health centers. Supporting this, a recent study showed insufficient travel medicine awareness among medical doctors in Türkiye. These factors may have contributed to the high percentage of hyperparasitemia, while morbidity and mortality rates remained relatively low. This can be attributed to the aggressive nature of *P. falciparum* malaria, which prompts individuals to seek medical care.

### Study Limitations

Our study has several limitations. Although the Parasitology Department of Manisa Celal Bayar University is a leading laboratory in Türkiye, it is not the national reference center. While we receive many malaria-suspected samples from all over Türkiye, we do not have access to all samples. Therefore, our results may not fully represent the entire epidemiology of imported *P. falciparum* malaria in Türkiye. However, we have sufficient grounds to believe that our findings accurately reflect the current situation of imported *P. falciparum* malaria in Türkiye. Another limitation is the absence of diagnostic molecular methods, as microscopy remains the gold standard for malaria diagnosis (33). The under-representation of females in our study (6.4% of all patients) could not be explained, and its coincidental nature cannot be ruled out. All the samples mentioned in this study are cryopreserved and stored in the Manisa Celal Bayar University Parasite Bank for future studies.

## CONCLUSION

Climate change and human mobility present significant threats that can potentially facilitate the transmission of *P. falciparum* in regions that were previously non-endemic, such as Türkiye and Mediterranean countries in Europe. The detection of gametocytes in 22.9% of the samples, coupled with the expanding distribution of vectors due to climate change, amplifies the potential risk of autochthonous transmission of *P. falciparum* malaria in Türkiye and possibly in the surrounding region.

In order to mitigate this risk, it is crucial to recommend chemoprophylaxis for all travelers visiting high-risk regions for malaria. Moreover, malaria should be considered a priority diagnosis in the differential diagnosis of fever in returned travelers who have visited malaria-endemic regions. It is imperative to incorporate travel medicine, particularly malaria, into the curriculum of healthcare workers to enhance their preparedness in dealing with returned travelers.

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### * Ethics

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### * Authorship Contributions

Concept: A.Ö.; Design: A.Ö., V.T., İ.Ç., N.T.; Data Collection or Processing: A.Ö., Ş.Ş.A., İ.Ç., A.Y.; Analysis or Interpretation: A.Ö., Ş.Ş.A., O.Z.; Literature Search: A.Ö., V.T.; Writing: A.Ö., V.T., İ.Ç., N.T.

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