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Epidemiological and clinical characteristics of imported falciparum malaria in the Republic of North Macedonia

A 13-year experience

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Summary
Background *Plasmodium falciparum* is the leading cause of imported malaria and the most common cause of death in returning travellers.
Aim To identify the main epidemiological and clinical characteristics of patients with imported falciparum malaria in the Republic of North Macedonia.
Material and methods Retrospectively analyzed were the epidemiological and clinical features of 34 patients with imported falciparum malaria who were diagnosed and treated at the university clinic for infectious diseases and febrile conditions in Skopje from 2010 to 2022. Malaria diagnosis was based on the microscopic detection of parasites in thick and thin blood smears.
Results All patients were male, with a median age of 36 years and a range of 22–60 years. Of the patients 33 (97.1%) acquired the disease in Sub-Saharan Africa. All patients except one stayed in endemic regions for work/business purposes. Chemoprophylaxis was completely applied in 4 (11.8%) patients. The median time of onset between the symptoms and diagnosis was 4 days, with a range of 1–12 days. Prevailing clinical manifestations were fever, chills, and splenomegaly in 100%, 94%, and 68% of patients, respectively. Severe malaria was noticed in 8 (23.5%)

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patients. In 5 (14.7%) patients the initial parasitemia was higher than 5%. On admission, thrombocytopenia, hyperbilirubinemia, and elevated alanine aminotransferase were registered in 94%, 58%, and 62% of patients, respectively. Out of the 33 patients with adequate follow-up, the outcome was favorable in 31 (93.9%).
Conclusion In every febrile traveller returned from Africa, imported falciparum malaria should be an essential part of differential diagnostic considerations.

Keywords Africa · Fever · Outcome · *Plasmodium falciparum* · Treatment

Introduction

Malaria is a life-threatening, mosquito-borne disease caused by protozoan parasites of the genus *Plasmodium* [1]. As the most important parasitic disease in the world [2], and the most common potentially fatal tropical parasitic infection [3], malaria remains a significant public health problem globally [4]. Malaria is endemic throughout most of the Tropics, with an ongoing transmission that occurs in 85 countries and territories [5]. In 2020, the World Health Organization (WHO) reported 241 million malaria cases with 627,000 deaths. Furthermore, about 90% of malaria-related deaths in Sub-Saharan Africa [5, 6]. An estimated 3.3 billion people around the globe are at risk of being infected with malaria [6, 7].

Malaria can be imported from malaria-endemic to non-endemic countries by international travellers, migrants and asylum-seekers [2, 8]. Also, it can have adverse diagnostic and therapeutic outcomes owing to the unfamiliarity of healthcare providers with this tropical infection [8]. In non-endemic countries, the reported incidence of imported malaria varies widely due to variability in disease recognition, diagnostic capabilities, reporting protocols and adherence to those protocols, and population travel patterns [9]. The risk to travellers of acquiring malaria depends on the areas of endemicity visited, the season, the purpose of travel, travel conditions, risk behavior, the intensity of exposure, and the success of protective measures [2, 7, 10, 11]. Imported malaria is a diagnostic challenge with initial misdiagnosis rates of 40% or greater [9], and at the same time it is the most common cause of death in returning travellers [12]. Also, malaria imported to non-endemic countries can sometimes cause secondary local transmission if competent vectors are present in specific areas [7, 9].

Among the *Plasmodium* species pathogenic to humans, *P. falciparum* is the leading cause of imported malaria [6, 13]. Imported falciparum malaria is acquired mainly in Africa [1, 14, 15] and is a serious health hazard and the most common cause of fatal infections in returning travellers [8, 13, 16, 17]. The reported global case fatality rate of imported falciparum malaria varies from 0 to 3.8%; furthermore, 2–16% of imported falciparum malaria are severe cases with a mortality of 10–15% [2, 12, 13]. This results from the absence of immunity, failure to use chemoprophylaxis or delays in seeking medical attention, misdiagnosis or delayed diagnosis, and inappropriate treatment [2, 11, 18].

In Europe, including the Republic of North Macedonia (2 million population), autochthonous malaria was eradicated in the 1970s using extensive and consistent measures, such as early detection and treatment of the infected individuals, insecticide treatment of vector habitats, irrigation measures in marshy areas, and mass chemoprophylaxis of the populations living in high-risk areas [14, 19]. Since then, only imported cases of malaria have been reported in Europe, except for several cases of autochthonous transmission [7, 15].

This study aimed to identify the main demographic, epidemiological, and clinical characteristics, treatment, and outcomes in patients with imported falciparum malaria that have been observed in recent years in the Republic of North Macedonia.

Material and methods

Study design and participants

This descriptive, retrospective, observational cohort study presents demographic, epidemiological, and clinical features, treatment, and outcomes of 34 consecutive patients with microbiologically confirmed imported falciparum malaria. The patients were travellers who had returned from malaria-endemic areas and were diagnosed and treated at the university clinic for infectious diseases and febrile conditions in Skopje from January 2010 to August 2022, knowing that this tertiary hospital is the only referral hospital that provides diagnosis and treatment to malaria patients in the whole country.

Diagnosis

The malaria diagnosis was based on existing symptoms and signs, the travel history, and the parasite demonstration by microscopic examination of the Giemsa-stained peripheral thick and thin blood smears that were examined by experienced laboratory personnel. If the initial smear was negative in the presence of strong clinical suspicion, the examination was repeated in at least three additional smears within 48 h. The number of parasites was counted as trophozoites per 100 erythrocytes in the thin blood smear. In some of the patients, and depending on the availability, a rapid immunochromatographic diagnostic test (RDT) based on the detection of *P. falciparum* histidine-rich protein 2 (ALL Test Malaria P.f/P.v/Pan Rapid Test Cassette, Hangzhou AllTest Biotech CO., LTD. Hangzhou, China) was performed in parallel or on the detection of *Plasmodium* lactate dehydroge-

nase (OnSite Malaria Pf/PvAb Combo Rapid Test, CTK Biotech, Inc. San Diego, CA, USA).

Data collection

The medical records data of all patients were obtained retrospectively from the hospital records archive. Data collected included demographic, epidemiological, clinical, and laboratory indicators and outcomes. For statistical analysis, the collected data was entered into an SPSS database (SPSS version 15.0, SPSS Inc., Chicago, IL, USA).

The following parameters were systematically recorded: a) age, gender, and nationality, b) the exposure history (country of malaria exposure, duration of exposure, reason for travel, chemoprophylaxis), the time interval between the return date from a malaria-endemic area and the onset of symptoms, a patient's and healthcare delay, the time elapsed between the onset of symptoms and the diagnosis, the presence of comorbidities, and a history of malaria in the past, c) clinical data, fever, chills, malaise, sweats, anorexia, headache, arthralgia, vomiting, diarrhea, cough, jaundice, oliguria, bleeding disorders, mental disorders, hepatomegaly, splenomegaly, d) laboratory profile composed of hemogram, glycemia, hepatic and renal functional tests, e) *P. falciparum* species identification and quantification of parasites, f) prescribed antimalarial treatment, g) defervescence, days of parasitological clearance and the hospitalization duration and h) outcome. In some cases, lactate, blood gas, cerebrospinal fluid (CSF) analysis, cultures and other microbiological, chest radiograph and/or ultrasound investigations were additionally obtained (data not presented).

Definitions

Falciparum malaria was considered when *P. falciparum* was detected in a blood smear or with positive RDT. Imported malaria refers to malaria acquired in a malaria-endemic country and brought and diagnosed in a malaria-nonendemic territory. The country of infection is a malaria-endemic country in which the patient stayed during the incubation period. A patient's delay is defined as a period between the onset of symptoms and first contact with a doctor, while the healthcare delay is the number of days from first healthcare contact until malaria diagnosis.

The definition of abnormalities in hematological tests was based on established reference values: hemoglobin (Hb) level less than 11 g/L and 7 g/L for moderate and severe anemia, respectively, leucocytes (WBC) less than 4.0×10^9/L for leucopenia, platelets levels less than $150{,}000 \times 10^9$/L and $50{,}000 \times 10^9$/L for mild and severe thrombocytopenia, respectively. Hypoglycemia is defined as glucose blood levels less than 4 mmol/L, elevated blood urea, creatinine, bilirubin, alanine aminotransferase (ALT) and C-reactive protein (CRP) were defined with levels higher than 10 mmol/L, 140 µmol/L, 30 µmol/L, 50 U/L and 15 mg/L, respectively. Adequate prophylaxis was defined as enough long and proper use of an adequate drug with good compliance before visiting the malaria-endemic region, during the stay and after return from the endemic region. Severe malaria was defined according to the World Health Organization criteria [20]. Defervescence was defined as the interval between the start of antimalarial treatment and the first normal temperature in a patient who then subsequently remained without fever. Parasite clearance time is defined as the time between the start of antimalarial treatment and the disappearance of trophozoites of *P. falciparum* from the blood. The outcome was assessed according to survival.

Treatment

Patients were treated immediately after admission to the hospital. Therapeutic regimens were chosen according to the disease severity and drug availability. Patients with uncomplicated falciparum malaria received orally a single mefloquine dose or either artemether-lumefantrine or atovaquone-proguanil, both for 3 days. Some patients also received doxycycline for 7 days concomitantly with the abovementioned drugs. Intravenous quinine dihydrochloride plus clindamycin was given to patients with severe disease, and if it was not available, some oral regimens were used. In cases of severe course and concurrent superinfections, additional drugs were used, including mannitol, antibiotics, blood, erythrocyte or platelet substitution, and catecholamines.

Follow-up

Patients were hospitalized and remained there until parasitemia was absent and they felt clinically improved. The temperature was monitored four times a day. In addition, standard laboratory tests and blood smears were performed daily until both the fever and parasites were cleared. A follow-up consultation was systematically offered to all patients for clinical, hematological, laboratory re-evaluation, and control malaria slides on days 7, 15, and 28 after the start of treatment.

Data analysis

Categorical variables were described using frequencies and percentages. Numerical variables were summarized by median and range.

Ethics approval

The study was approved by the Ethics Committee of the Faculty of Medicine in Skopje. The study was conducted in accordance with the ethical principles for

medical research in humans and the Declaration of Helsinki; however, written informed consent was not provided, given its retrospective observational design.

Results

During the study period, 34 male patients with imported falciparum malaria were diagnosed and treated at the University Clinic for Infectious Diseases and Febrile Conditions in Skopje, with a median age of 36 years and a range of 22–60 years. Of the patients 29 (85.3%) were citizens of the Republic of North Macedonia, while the remaining 5 (14.7%) were from other nationalities. The yearly distribution of imported falciparum malaria was median 2, range 0–7 cases. Imported falciparum malaria was diagnosed during all months except in March, with the highest frequency in July–August with 10 (29.4%) and December–January with 8 (23.5%) cases. Except for 1 patient (2.9%) who was infected in Afghanistan, the remaining 33 patients (97.1%) acquired the disease in Africa. In nine cases, the country of infection was the Central African Republic, in six it was Ghana, three in Sierra Leone, two patients each acquired malaria in Nigeria, Mali, Mozambique and Tanzania, and one each in Zanzibar, Liberia, Chad, Angola, Cameroon, South Sudan and Equatorial Guinea.

The median duration of exposure was 82.5 days with a range of 14–180 days. In contrast, the purpose for traveling in endemic regions was work for 28 (82.4%) and tourism for 1 (2.9%) of the Macedonian citizens and military duties for 3 (8.8%), marine and trade with coffee for 1 (2.9%) each of foreign citizens (of whom 4 had spouses from the Republic of North Macedonia). Chemoprophylaxis was initiated in 13 (38.2%) patients, in 8 cases mefloquine, doxycycline in 3 cases and atovaquone-proguanil in 2 cases; however, chemoprophylaxis was completed in only four patients (11.8%), and all of them had used mefloquine. The time interval median between the date of return from the malaria-endemic area and the onset of symptoms was 6 days, with a range of 0–90 days. The median of the patient's delay was 2 days with a range of 0–7 days, while the healthcare delay median was 2 days with a range of 0–10 days. Finally, the median time elapsed between the onset of symptoms and diagnosis was 4 days, with a range of 1–12 days. Comorbidities and a history of malaria in the past were evident in 3 (8.8%) and 8 (23.5%) patients, respectively.

As presented in Fig. 1, the prevailing clinical manifestations in patients were fever (100%), chills (94.1%), headache (82.4%), arthralgia (58.8%), and splenomegaly (67.6%). Also, other manifestations were noticed, such as malaise, sweats, anorexia, hepatomegaly, vomiting, diarrhea, cough, and jaundice. Severe malaria was detected in 8 (23.5%) patients and manifested with oliguria, bleeding, and mental disorders in 8 (23.5%), 3 (8.8%), and 6 (17.6%) patients, respectively.

Initial peripheral blood parasitemia was median 1.3%, range 0.3–10%. In 16 (47.0%) patients, parasitemia was up to 1%, between 1% and 2% in 8 patients (23.5%), between 2% and 5% in 5 patients (14.7%) and in the remaining 5 patients (14.7%) the parasitemia was higher than 5%. Malaria rapid diagnostic tests were performed in 17 (50%) patients, where the infection was confirmed in all cases. Some of the more pronounced hematological and biochemical laboratory characteristics are illustrated in Fig. 2. The prevailing manifestations were thrombocytopenia (in 94.1%, with severe thrombocytopenia in 55.9%), hyperbilirubinemia (in 57.6%), and elevated ALT (in 61.8%). Initially, CRP was elevated in 33 out of 33 (100%) examined patients and in 17 (53.1%) patients CRP was higher than 100 mg/L. Elevated blood urea nitrogen, creatinine, hypoglycemia, anemia, and leucopenia were seen in 17.6%, 15.6%, 2.9%, 8.8%,

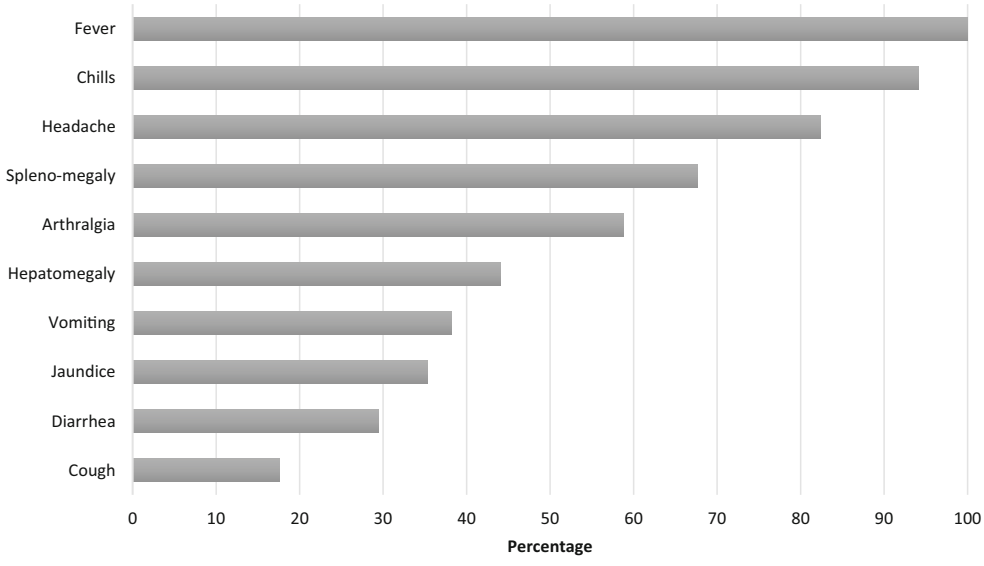

Fig. 1 Clinical characteristics in patients with imported falciparum malaria

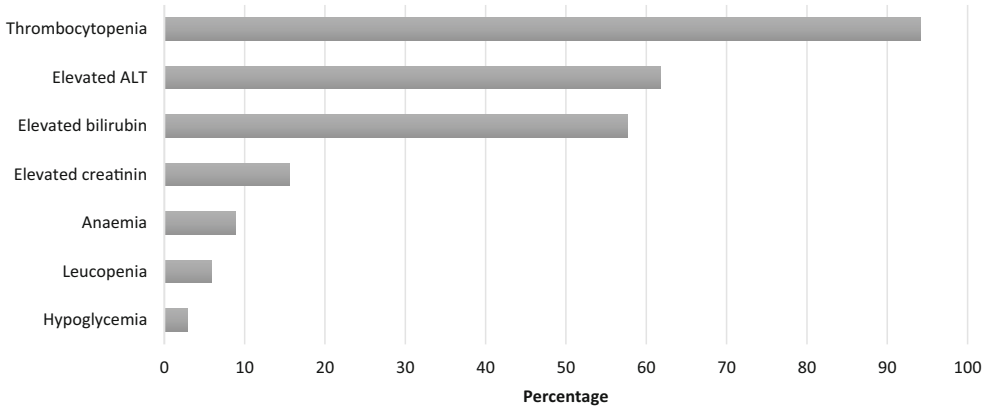

Fig. 2 Hematological and biochemical features in patients with imported falciparum malaria

and 5.9%, respectively. All 18 patients tested for HIV infection were negative.

Although anemia was initially present in 8.8% of our patients, on the second and seventh days of the treatment it reached 34.4% and 41.9%, respectively and on the 15th day it was 30.0% in patients who were followed up. On the second hospital day, the number of patients with elevated serum urea and creatinine levels was increased (from 17.6 to 28.6% and from 15.6 to 28.0%, respectively); as well as the number of patients with hyperbilirubinemia higher than 100 µmol/L and ALT higher than 100 U/L (from 15.1 to 31.6% and from 23.5 to 31.8%, respectively). Until the seventh day of hospitalization, the elevated urea, creatinine, hyperbilirubinemia higher than 100 µmol/L and ALT higher than 100 U/L gradually decreased to 13.3%, 14.3%, 12.0%, and 21.4% of the monitored patients, respectively. Also, the number of patients with severe thrombocytopenia was significantly reduced (6.4%).

Of the patients 21 (61.8%) were treated with atovaquone-proguanil, 9 of them (26.5%) in parallel with doxycycline. Artemether-lumefantrine was administered to 6 patients (17.6%), mefloquine to 5 patients (14.7%), concomitantly with doxycycline to 2 patients, and 1 severe case (a foreign patient) was treated with quinine dihydrochloride plus clindamycin. The foreign patient was transported abroad on day 3, and was lost to follow-up. Also, one of the patients died soon after admission without starting treatment.

Out of the 33 patients with known outcomes, it was favorable in 31 (93.9%) and 2 (6.1%) patients died, both on the day of admission. In one patient, recrudescence was observed with elevated parasitemia after the treatment applied with mefloquine, and he was retreated with atovaquone-proguanil with a favorable outcome. The medians of defervescence, parasite clearance, and length of hospital stay were 3 days, 3 days, and 8 days, with ranges of 1–10, 1–10, and 1–21 days, respectively, whereas the survived patients were followed-up for a median 10 days and a range of 3–28 days.

Discussion

Imported malaria is a heterogeneous clinical entity, which depends on *Plasmodium species,* the region where it was acquired, the country from where it is imported (with all its social and economic characteristics, infrastructure, and medical resources), different patient groups (determined by the age, immunity, reasons for travel, applied protective measures), etc. Therefore, even if speaking only of imported falciparum malaria, as in our case, due to the diversity of the mentioned features and specifics, the current knowledge cannot be universally applied and cannot be adequately subjected to comparison in all circumstances and areas.

Our series of patients consisted of a rather homogeneous group of exclusively male patients of young and middle age, with imported falciparum malaria, which, with some exceptions was acquired in Africa during a stay for existential professional activities, mainly on oil platforms or work in civil engineering. Although imported falciparum malaria affects people of all ages [10, 13, 16, 21–23], many studies have demonstrated a similar age distribution to ours [8, 18, 23–26]. Imported falciparum malaria has been found in 58–91% of male patients [8, 22, 27, 28], and to our knowledge our study is the only one where all patients were male. This kind of age and gender distribution was due to work-related reasons for which our patients stayed in malaria-endemic areas. Africa is considered the most important risk factor for acquiring malaria [14, 29], having in mind that 70–100% of imported falciparum malaria is acquired in Sub-Saharan Africa [13, 22, 24, 30, 31]. Furthermore, countries where our patients were infected have been reported in other studies [32, 33]. In general, the main reasons for travelling in endemic regions were visiting friends and relatives in 14–78% [25, 31], immigration/refugees in 12–75% [10, 16, 34], tourism in 4–60% [10, 31, 34], and rarely missionary/volunteer/humanitarian aid, research/education and military activities [10]. Work was an essential reason for our patients' stay in malaria-endemic regions. It has been presented in 39% and up to 94% of imported malaria and in 14–27% of imported

falciparum malaria [24, 31], mainly in reports from East European countries and China. These countries like the Republic of North Macedonia are not attractive destinations for immigrants and because the majority of their citizens cannot afford touristic travels to exotic destinations; however, they offer competent and cheap labor [1, 14, 29, 32]. Patients from these countries are highly susceptible to acquiring malaria due to a lack of immunity, poor education, lack of awareness of malaria risk as well as their exposed working and living conditions [4].

Although imported falciparum malaria is present throughout the year, the peak seasonal distribution in Europe is mainly during the late summer and around New Year, when holidays or prolonged festive days are used for traveling home. This period also coincides with the rainy season in malaria-endemic countries [7, 8, 29]. Similar to other studies [18, 21, 25], most of our patients were healthy people with almost no comorbidities, a rare history of previous malaria, as well as a small percentage of adequate chemoprophylaxis [16, 24, 35]. Previous malaria was found in 24–61% [25–27] and was more common in populations of immigrants from endemic areas and in visiting friends and relatives, which influence milder disease manifestations. The adequate chemoprophylaxis, which was used by 3–64% of travellers [10, 15, 21, 22, 27], along with timely recognition and appropriate treatment of imported malaria, are prerequisites for a favorable outcome [11].

In patients with imported falciparum malaria, the median exposure time in malaria-endemic areas was 21–32 days, with a range of 7–150 days [13, 16, 18, 22]. The median time between returning from a malaria-endemic area and symptoms starting was 6–9 days, with a range of 0–180 days [6, 22, 30, 36]. About 15% of patients had symptoms more than 30 days after returning [37]. In one study, patient's and healthcare delay medians were 2 and 0, with a range of 0–30 and 0–25 days, respectively [22], while another study reported that 66% of patients with falciparum malaria had healthcare delays of more than 1 day [21]. In the study of Wangdahl et al. healthcare delay among patients with imported falciparum malaria was reported to be 83%, 8%, 4%, and 2% on days 0, 1–2, 3–6, and >6, respectively [38]. Finally, the median time between the onset of symptoms and diagnosis was 3–8 days, with a range of 0–42 days [2, 6, 12, 18, 22, 39].

Clinical manifestations in our patients included a high diversity of symptoms and signs that are not pathognomonic for malaria. As shown in Fig. 1, we noticed a large percentage of organomegaly; however, some studies showed even higher rates than ours [1, 6]. In the literature, severe malaria was found in 4% [16], 9% [35, 38], 27% [36], and up to 36–38% of patients [24, 30]. In one study, 38 out of 64 patients (59.3%) with severe imported falciparum malaria were travellers who stayed in an endemic-malaria region for less than 6 months [21]. These results are in agreement with our findings where severe malaria was evident in 7 out of 8 patients with a stay in an endemic region of 4 months or shorter. Also, in our series, only one of the patients with severe malaria had adequate chemoprophylaxis and a history of previous malaria.

Initial laboratory analyses of our patients, compared to the previous series, revealed a higher prevalence of thrombocytopenia, an absence of severe anemia, and rare cases of leucopenia and hypoglycemia [25, 27, 34]. In addition, our patients demonstrated increased levels of bilirubin, ALT and CRP, findings that are well known in malaria patients [6, 8]. Interestingly, in the first days after the onset of treatment, we also noticed a significant reduction in hemoglobin, as previously reported [18, 25]. The initial parasitemia in imported falciparum malaria was found to be median 0.1–4.8%, range 0.002–20% [21, 30, 38, 40], and was very similar to that found in our patients [22, 34, 35].

Having in mind that malaria is not an endemic disease in the Republic of North Macedonia and that the doctors do not have much experience in managing this disease, we intend to use inpatient management, regardless of their clinical condition. The lack of sufficient experience and the absence of a national protocol for the treatment of malaria are the reasons why quite often standard antimalarial treatment is modified with the addition of doxycycline. Outpatient treatment of uncomplicated imported falciparum malaria is a field of debate; however, French national guidelines allow the option of outpatient management of uncomplicated falciparum malaria [17]. Access to antimalarial drugs is also a serious problem, especially for those aimed at severe malaria [15], which in our circumstances is explained by the small market and the limited number of malaria cases. The availability of antimalarial drugs for parenteral use in our country is more of an exception than a rule. The choice of treatment for our patients was primarily determined by the current availability of drugs. However, our treatment regimens were in accordance with therapeutic courses used in other studies [21, 25, 28, 36].

Literature data about defervescence from 1.1 to 3.5 days [23, 28], parasite clearance duration of up to 7 days [41], and a hospital stay of median 3–4.6 days, range 1–29 days [8, 18, 22], are very similar to the results obtained in our study. The frequency of case fatality rate was reported from 0% [22] up to 9% [27], showing our data are within this range. The principal reasons for the high prevalence of severe malaria and death in our patients, in addition to certain patient and healthcare delays, were low adherence to adequate chemoprophylaxis [1, 7, 12, 15, 33, 36] and low immunity against the disease [12, 26]. According to Nilles and Arguin two thirds of the deaths due to imported malaria are associated with medical errors, including failure to diagnose malaria on initial presentation, failure to prescribe the correct

chemoprophylaxis regimen, failure to initiate treatment promptly on diagnosis, or treatment with an inappropriate antimalarial drug [9].

Conclusion

The presence of imported falciparum malaria in the Republic of North Macedonia was mostly encountered in young and adult males who acquired the disease during their work activities in Africa. Every febrile traveller returned from Africa should be a constituent part of differential diagnostic considerations about imported falciparum malaria, whereas splenomegaly, thrombocytopenia, elevated bilirubin, and ALT, should just be considered additional supportive factors. Severe clinical courses and deaths can be significantly prevented by combining a high compliance rate with antimalarial chemoprophylaxis, a high index of suspicion among physicians evaluating febrile illnesses in returned travellers, and prompt and adequate treatment.

Author Contribution Mile Bosilkovski: concept, design, acquisition of data, interpretation of data, drafting the article, final approval of the version to be submitted. Bachir Khezzani: design, revising the article critically for important intellectual content, drafting the article, final approval of the version to be submitted. Kostadin Poposki: acquisition, analysis, and interpretation of data, final approval of the version to be submitted. Vesna Semenakova-Cvetkovska, Ivan Vidinic, Arlinda Osmani Lloga, Dejan Jakimovski, Marija Dimzova: acquisition, analysis, and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

Declarations

Conflict of interest M. Bosilkovski, B. Khezzani, K. Poposki, V. Semenakova-Cvetkovska, I. Vidinic, A.O. Lloga, D. Jakimovski and M. Dimzova declare that they have no competing interests.

Ethical standards The study was approved by the Ethics Committee of the Faculty of Medicine in Skopje. The study was conducted in accordance with the ethical principles for medical research in humans and the Declaration of Helsinki. However, written informed consent was waived given its retrospective observational design.

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