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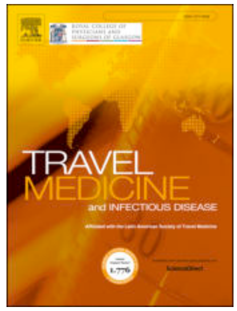

Malaria in Turkey: A Comprehensive Analysis of Diagnosis, Treatment, and the Impact of COVID-19, Ten Years After Malaria Elimination (2012–2023)

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Abstract

Background: The characteristics, diagnosis, and treatment stages of malaria in Turkey in the last ten years are not known except few case reports. We aimed to describe the details of the diagnosis and treatment practices of malaria cases in various hospitals across Turkey between 2012 and 2023 after the declaration of the elimination of malaria.

Methods: We collected the patient data from 30 centers by using Qualtrics Survey Software. The patients were categorized according to the WHO Malaria Severe Disease Symptoms guidelines.

Results: We detected 299 malaria cases. Of these patients, 23.7% experienced misdiagnosis, with 77.5% of misdiagnosed cases receiving antibiotics. Among the patients, 9 (3%) had no travel history. Additionally, 28 (9.4%) patients required admission to the intensive care unit (ICU) during hospitalization. There is a significant association between misdiagnosis and subsequent ICU admissions. Additionally, the duration between malaria diagnosis and the initiation of treatment significantly affected ICU admissions. Furthermore, the number of cases with severe malaria (according to WHO criteria) and ICU admissions increased after the COVID-19 period. In multivariate analysis, initial misdiagnosis was found to be associated with ICU admission (OR: 2.8, $p < 0.05$), while each day's treatment delays post-diagnosis increased ICU admissions (OR: 1.26, $p < 0.05$).

Conclusion: Misdiagnosis is common which delays the treatment and is correlated with higher admissions to ICUs. Post-COVID-19, there was a notable increase in both ICU admissions and cases of severe malaria, suggesting an escalation in disease severity that warrants further investigation. The resurgence of rare malaria cases with no travel history to abroad highlights the necessity of continued vigilance for new malaria cases. Efforts to promptly treat upon diagnosis and improve diagnostic accuracy in Turkey, where malaria is uncommon, are crucial. Enhancing diagnostic methods and treatment strategies remains essential, especially in significant events like COVID-19.

Introduction

The World Health Organization (WHO) launched the "Global Technical Strategy for Malaria 2016-2030," building upon the successes of its preceding 15-year plan by prioritizing global collaboration and focus[1]. The WHO's malaria elimination strategy has three main bases. First, it aims to secure universal access to malaria prevention, diagnosis, and treatment by encouraging insecticide nets, indoor residual spraying, quality-assured microscopy or rapid diagnostic tests, and WHO-recommended antimalarial medicines. Second, it emphasizes strengthening efforts to achieve malaria-free status. Third, it seeks to make surveillance a core intervention that guides resource distribution and responses. The first target was to reduce malaria incidence and death by 40% in 2020 compared to 2015. However, the elimination target outlined in the 2020 report shows an increase in deaths and domestic incidents[2].

Globally, in 2021, there were an estimated 247 million malaria cases in 84 malaria-endemic countries [3]. Since 2016, malaria cases have increased; the most significant annual increase of 13 million cases was observed between 2019 and 2020 during the first year of the COVID-19 pandemic. Thereafter, an increase of 2 million new cases was recorded in 2021 compared to 2020. Overall, an estimated additional 13.4 million cases were attributed to the impact of the COVID-19 pandemic[3].

Even though Malaria was known to have been eliminated[4] in Turkey in 2010, clinicians working in different regions report sporadic local cases. These cases pose novel challenges to the healthcare system such as increased misdiagnoses and higher rates of malaria-related mortality and morbidity. Despite the increasing trend in malaria cases, the characteristics, diagnosis, and treatment of malaria in Turkey in the last 10 years are not fully known. In this multicenter longitudinal study, we aim to investigate diagnostic challenges, treatment strategies, and complication management across Turkey over a decade. Our results may provide data for decision-makers to establish strategies for prevention, treatment, and management of complications.

Methods

Data Collection

In this multicenter study, an online survey in alignment with the WHO Malaria Severe Disease Symptoms guidelines[5] was distributed to physicians in infectious diseases clinics/centers. Researchers shared the survey individually with physicians via Qualtrics Survey Software. The survey covers information regarding the institution, demographics of malaria patients, patient travel history, symptoms, clinical findings, laboratory values, examination, treatment regimens, complications, and patient outcomes.

Study Sites and Population

All the healthcare institutions throughout Turkey were invited to join the study. Thirty healthcare institutions, comprising 15 university hospitals, 9 training and research hospitals, 3 city hospitals, and 3 private hospitals, voluntarily participated in the research. From these 30 healthcare institutions, data from 310 individuals were collected. However, 11 patients were excluded from the analysis as they were under the age of 18 during the treatment period. Figure 1 shows a map of the distribution of malaria cases across different provinces in Turkey. It is important to note that out of the 299 patients included in the study, 131 (43.8%) individuals were diagnosed in Istanbul.

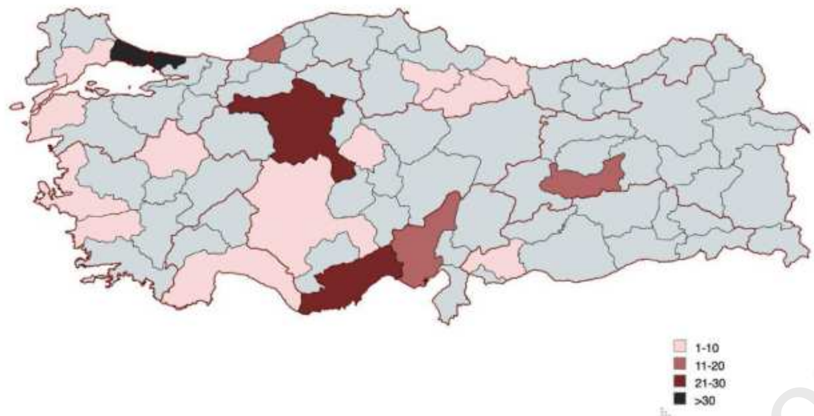

Figure 1: Geographical Distribution of Malaria Cases Included in This Study Across Provinces in Turkey by a Color-Coded Map

Data Analysis
The statistical analyses were performed by using SPSS and Stata software. Univariate analyses were performed to explore the relationships between various factors and critical outcomes such as intensive care unit (ICU) admission, rehospitalization, and severe malaria. The severity of the cases was defined according to WHO Severe Malaria standards[5]. In the univariate analysis, we used the Mann-Whitney U test as a non-parametric test. In multivariate analysis for the prediction of outcomes, logistic regression was performed.

Ethics Statement
The study was approved by the institutional review board of Koç University (no: 2023.017.IRB1.005) and from each study center.

Results

Patient Demographics

In total, 299 patients were included in this study. The gender of 296 of them was specified, 1 was marked as other, and the remaining 2 were not marked. Out of 299 patients, 278 (93%) of them were men. The mean age was 36.3 years (SD: 11.1, min: 18 and max: 72). 239 (79.9%) of the patients claimed to be Turkish in origin and the remaining 60 (20.1%) were from other nationalities. The nationalities of 47 out of 60 patients were identifiable, 14 patients from Nigeria, 7 from Afghanistan, 5 from Cameroon, 3 from Chad and Pakistan, 2 patients from Sudan, Congo, and Egypt, one patient from Guinea, Bangladesh, Burundi, Ivory, Finland, Kenya, Mali, Senegal and Tunisia. Eleven people had immigrant or temporary protection status.

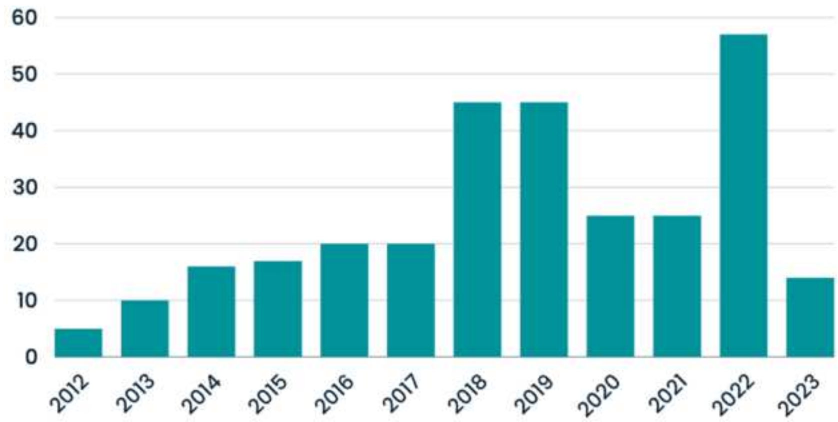

Figure 2: Number of patients diagnosed with Malaria by years

Initial Healthcare Engagement and Misdiagnoses

Out of 299 patients, 111 (37.1%) applied to another health institution before diagnosis of malaria. In 299 patients, 71 (23.7%) were misdiagnosed (Figure 3). In patients with misdiagnosis, 29 (40.8%) were misdiagnosed with URTI (upper respiratory tract infection), 7 (9.9%) were misdiagnosed with gastroenteritis, 8 (11.3%) were misdiagnosed with pneumonia, 3 (4.2%) were misdiagnosed with acute hepatitis, 4 (5.6%) were misdiagnosed with COVID-19, 2 (2.8%) were misdiagnosed with hematologic malignancy, 2 (2.8%) were misdiagnosed with UTI (urinary tract infection), 4 (5.6%) were misdiagnosed with typhoid fever. The other group of misdiagnosed patients has 12 (16.9%) patients. It included cases of 5 of unknown origin, 1 of acute appendicitis, 1 of volvulus, 1 of dengue fever, 1 of rickettsiosis, 1 of myocardial infarction, 1 of sepsis, and 1 of bacterial infection.

Notably, antibiotics were prescribed to 55 of 71 misdiagnosed patients (77.5%). Out of these groups, 48 (87.3%) of the prescribed antibiotics are known. (12 amoxicillin/clavulanic acid, 6 ciprofloxacin, 5 levofloxacin, 3 piperacillin-tazobactam, 2 ampicillin sulbactam, 2 cefazolin, 2 ceftriaxone, 2 cefuroxime, 2 cefixime, 1 ciprofloxacin, 1 azithromycin, 1 clarithromycin, 1 clindamycin and ceftriaxone combined, 1 levofloxacin and metronidazole combined, 1 meropenem and moxifloxacin combined, 1 moxifloxacin, 1 penicillin, 1 ceftriaxone and metronidazole combined, 1 ciprofloxacin and metronidazole combined, 1 ciprofloxacin and ceftriaxone combined, 1 doxycycline).

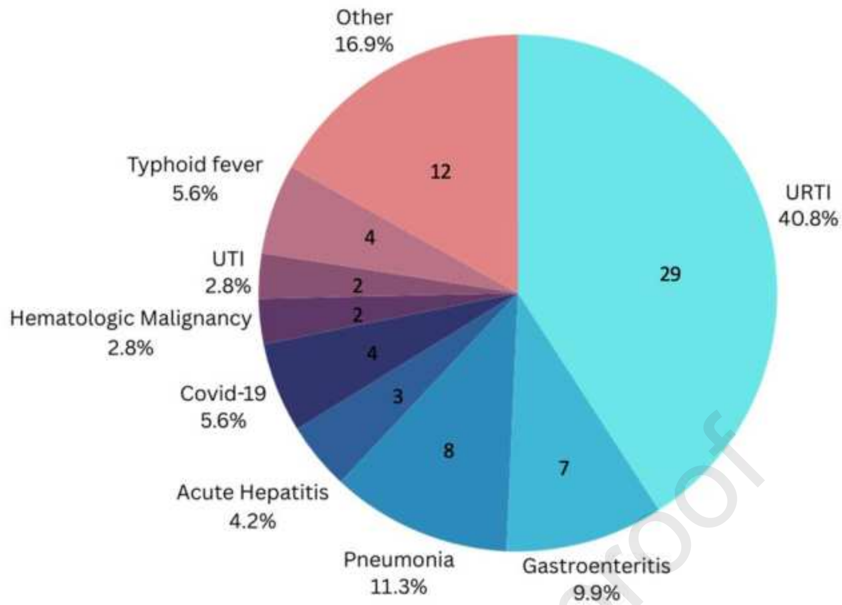

Figure 3: Distribution of Initial Misdiagnoses Among Patients

Nine patients (six male and three female) were reported with no history of traveling abroad. In eight of these patients, *P. vivax* and in one patient *P. falciparum* were detected. Diagnosis of *P. falciparum* was confirmed via peripheral smear and plasmodium rapid diagnostic test. These cases were from Edirne, Mardin, Mersin, and Istanbul, and the distribution by year was as follows: two cases in 2012, one in 2013, two in 2014, and one case each in 2018, 2019, 2020, and 2022.

Travel History and Chemoprophylaxis

Among the 290 patients with international travel history, 186 (64.1%) declared receiving chemoprophylaxis, of whom 18 received full doses, and 24 did not complete chemoprophylaxis. It is unknown whether the rest of the individuals received pre-travel chemoprophylaxis. The number of patients who were informed about chemoprophylaxis before travel was 66 (60,6%), and it is not known whether 181 patients were informed about chemoprophylaxis.

The mean duration from the onset of symptoms to admission to a clinical center was 5.5 days (min: 0 and max: 39 days), and the mean duration from admission to diagnosis was 0.54 days.

Diagnostic Methods and Treatment Approaches

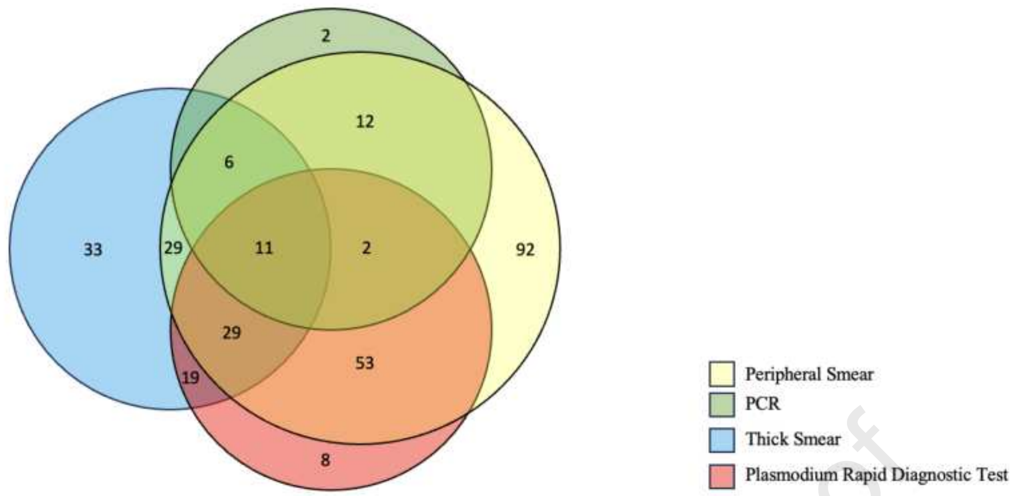

Figure 4: Distribution of four diagnostic tests for malaria, including peripheral smear, Polymerase Chain Reaction (PCR), thick smear, and plasmodium rapid diagnostic test

Among the diagnostic methods, the peripheral smear was the most commonly used one and the PCR was the least commonly used as shown in Figure 4. Each malaria case was approved by the Malaria Control Department of the Ministry of Health of Turkey, as a part of an obligatory procedure. Anti-malarial medications were obtained from either the Ministry of Health or Provincial Health Directorates. In total 270 patients received artemether-lumefantrine (264 orally and 6 intravenously), 63 patients received primaquine (orally), 26 patients received artesunate (10 orally and 16 intravenously), 11 patients received doxycycline, seven patients received artemisinin (three orally and four intravenously), four patients received chloroquine (orally), two patients received atovaquone and proguanil combination (orally). Clindamycin, quinine, sulometapyrazine, pyrimethamine, artequick, hydroxychloroquine, piperaquine, and a combination of quinine and clindamycin were administered to a total of 8 patients, 7 patients received a single one of these aforementioned medications, and 1 patient received a combination of quinine and clindamycin.

Distribution of Plasmodium Species and Outcomes

P. falciparum was detected in 203 patients (67.9%), *P.vivax* in 39 (13%), and *P. falciparum* and *P. ovale* were identified together in 9 patients, *P. falciparum* and *P. vivax* were identified together in 8 patients, *P. malariae* was identified in 2 patients, *P. ovale* was identified in 5 patients. In 33 (11%) patients, the species was not detected.

28 patients (9.36%) were admitted to the ICU during hospitalization, with reported ICU stays ranging from 1 to 28 days. Among these, 25 patients were infected with *P. falciparum* (2 of them had *P. vivax* infection along with falciparum), 1 was infected with *P. vivax*, and the plasmodium species could not be identified in the remaining 2 patients. One of the *P. falciparum* cases that was admitted to the ICU had no travel history of abroad.

Out of 299 patients, 19 (6.4%) patients were readmitted to the hospital. Among 19 patients, 3 (15.8 %) of them required previous ICU admission. Four of 299 patients (1.3%) died during treatment. Two out of the four initially received incorrect diagnoses, four had kidney failure, and three developed cerebral malaria as a complication.

Complications

In terms of complications during the patients' hospital stay, as Figure 5 shows major three complications were severe anemia, renal failure, and cerebral malaria. Renal failure was reported in 32 (10.7%) cases, severe anemia in 35 (11.7%), cerebral malaria in 14 (4.7%), splenic rupture in 4, thrombocytopenia in 11, and cerebral ischemia and hearing loss were each reported in a single patient. Among cerebral malaria patients, confusion was observed in 13 cases, coma in 3, speech disorders in 9, signs of intracranial hypertension in 2, and drowsiness and convulsions in one patient each.

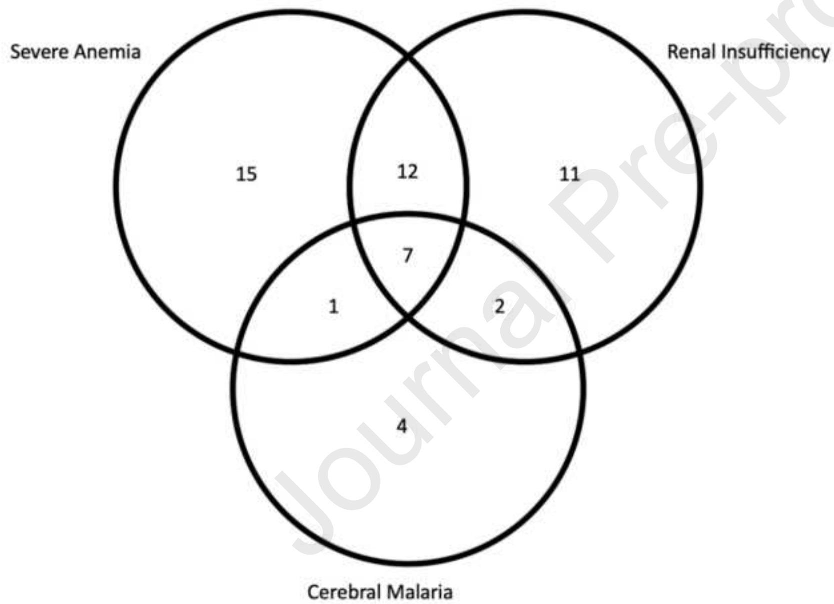

Figure 5: Distribution of the most common complications among patients, including severe anemia, renal insufficiency, and cerebral malaria

Although steroid therapy has no proven effect on malaria[6], it was administered to 10 patients for the management of the complications that developed during their hospital stay. Erythrocyte suspension transfusion was required for 34 patients (11.4%). The mean amount of transfusion was 4 units (min:1, max:16 units). During hospitalization, 7 patients underwent plasmapheresis and 5 underwent exchange transfusion. Antibiotics were administered to 58 patients during hospital stays due to secondary bacterial infection. Only 11 (19%) of bacterial infections had laboratory confirmation (culture, PCR, etc.). Among the 120 patients diagnosed with malaria during the COVID-19 era, 2 were reported to be coinfected with SARS-CoV-2 during their hospitalization.

Table 1: Distribution of patients with post-malaria sequela and their durations (PMNS: Post-malaria Neurological Syndrome)

Sequels/Month	1	2	3	4	5	6	7	8	9	10	11	12	Total Number
Headache	10	3	2	2						1			18
Restlessness	2	2	4		1							1	10
Depression	3	2	1		1	1					1		9
Anxiety	4	2	1		1							1	9
Personality Change	1		1		1						1		4
PMNS		2						1					3
Speech Problems		1										1	2
Nystagmus	1	1											2
Myopathy	1	1											2
Tremor	1												1
Memory Loss											1		1
Hallucinations												1	1
Polyneuropathy						1							1
Ataxia	1												1
Paresthesia						1							1
Hemiplegia										1			1

Associations with ICU Admission and WHO severity criteria

Table 2: Categorization of the patients according to WHO severity criteria

Criteria	Number of patients
Impaired consciousness: Glasgow Coma Scale score <11	19
Prostration: The condition where a person becomes unable to sit without assistance, stand, or walk	62
Seizures:More than 2 convulsive seizures within 24 hours	3
Acidosis: (> 8 mEq/L if base excess measurement is not available, or plasma bicarbonate level < 15 mmol/L, or venous plasma lactate level ≥ 5 mmol/L)	14
Hypoglycemia: Blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL)	7

Severe malaria anemia: In adults with a parasite count > 10,000/µL, respectively, hemoglobin concentration < 7 g/dL or hematocrit < 20%.	27
Kidney failure: Plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea level > 20 mmol/L	27
Jaundice: Plasma or serum bilirubin > 50 µmol/L (3 mg/dL), and parasite count > 100,000/µL	30
Pulmonary edema: Radiologically confirmed or oxygen saturation at room air < 90%, along with frequent chest retractions and crepitations on auscultation	11
Severe bleeding: Recurrent or prolonged bleeding from the nose, gums, or blood vessels, or hematemesis or melena	4
Shock: Compensated shock is defined by a capillary refill ≥ 3 seconds or a temperature gradient in the leg (middle and proximal extremities) without hypotension. Decompensated shock is defined by a systolic blood pressure in adults < 80 mmHg accompanied by impaired perfusion (cold peripheral extremities or prolonged capillary refill)	6
Hyperparasitemia: *P. falciparum* parasitemia > 10% (This criterion is specific to *P. falciparum*; for *P. knowlesi*, hyperparasitemia is defined as a parasite density > 100,000/µL)	25

The rehospitalization of the patients was not related to their severity which was represented by being in ICU in their first admission ($p>0.05$). Of the patients needing readmission, 2 had *P. malaria*, 2 had *P. falciparum* and *P. ovale* co-infection, and 15 were infected with *P. falciparum*. An association between rehospitalization and jaundice at the initial admission was revealed with univariate analyses ($p <0.05$).

In univariate analysis, shortness of breath and respiratory distress, hypotension, jaundice, hepatomegaly, hypoglycemia, confusion, seizures, syncope, anuria/oliguria, dark urine, and coma were found to be associated with ICU admission ($p <0.05$). No correlation between ICU admission and factors such as being an imported case, immigration status, and use of chemoprophylaxis was found. There was no correlation of the time between the symptom onset date and the date of admission to the clinic compared to ICU admissions. However, it was observed that the time between the date of malaria diagnosis and the start of treatment significantly affected ICU admissions (p<0.001).

Patients who received chemoprophylaxis were compared with those who did not receive or did not complete chemoprophylaxis, separately. Local cases were excluded from the data set since they do not have a travel history and in Turkey, malaria chemoprophylaxis is provided only for individuals traveling to malaria-endemic regions. Among 18 patients who received a full dose of chemoprophylaxis, 4 of the patients were admitted to the ICU. 14 patients with no chemoprophylaxis use and one with incomplete use were admitted to the ICU. There is no data regarding chemoprophylaxis use for the rest 10 patients admitted to the ICU. No relationship was found between ICU admission and chemoprophylaxis use.

Table 3: Characteristics of the patients according to ICU admission

Grouping Variable	ICU n=28 (%)	Non-ICU n=271 (%)	p Value
Patient applied to another institution before diagnosis	35,7	37,3	0,871
Patient received any other diagnosis before being diagnosed with malaria	39,3	22,1	0,042
Patient been given antibiotics before being diagnosed with malaria	25	17,7	0,328
Person have immigration or temporary protection status	3,6	3,7	0,58
Patient is an imported case	96,4	97	0,546
WHO Severity-Impaired consciousness	57,1	1,1	<0.001
WHO Severity-Prostration	75	15,1	<0.001
WHO Severity-Seizures	10,7	0	<0.001
WHO Severity-Acidosis	46,4	0,4	<0.001
WHO Severity-Hypoglycemia	17,9	0,7	<0.001
WHO Severity-Severe malaria anemia	46,4	5,2	<0.001
WHO Severity-Kidney failure	64,3	3	<0.001
WHO Severity-Jaundice	50	5,9	<0.001
WHO Severity-Pulmonary edema	25	1,1	<0.001
WHO Severity-Severe bleeding	10,7	0,4	<0.001
WHO Severity-Shock	21,4	0	<0.001
WHO Severity-Hyperparasitemia	39,3	5,2	<0.001
Confirmed secondary bacterial infection developed	14,3	2,6	0,02
Administration of antibiotics considering a secondary bacterial infection	50	16,2	<0.001
Patient is coinfected with COVID-19	0,7	0,7	0,648
Patient is given steroids	25	0,7	<0.001
Patient received plasma exchange	21,4	0,7	<0.001
Transfusion done for the patient's anemia	67,9	5,5	<0.001
Exchange transfusion performed on the patient	17,9	0	<0.001

Table 4: Laboratory Results

The median values in parentheses represent the median for ICU-admitted patients (first value) and non-ICU-admitted patients (second value)

Laboratory Values	**Total Number**	**Median (ICU-Non ICU)**	**Min and Max Value**
Lowest Hemoglobin Count (g/dl)	295	11.4 (7.45-11.8)	4.40-17.60
Lowest Leukocyte Count (10^9/L)	298	4555 (4730-4515)	1500-25650
Lowest Thrombocyte Count per mcL	297	65000 (25000-72150)	7000-351000
Highest creatin value (mg/dL)	292	1 (2.8-1)	0.35-20.40
Highest ALT value (U/L)	294	52.5 (74-50)	10-789
Highest AST value (U/L)	290	53.8 (106-49)	17-1262
Highest LDH value (units/L)	252	457 (932-439)	58-3700
Highest CRP value (mg/L)	275	101 (189.5-92)	1-568
Highest procalcitonin value (ng/ml)	124	3.9 (15.5-3.2)	0.05-270.69

Table 4 displays laboratory results for various parameters in a study population. Laboratory values were compared between patients admitted to the ICU and those who were not, as well as between patients meeting at least one of the WHO severe disease criteria and those who did not. Since all of the laboratory value distribution was non-parametric, the Mann-Whitney U test was utilized. Laboratory values other than leukocyte count were observed to be affected by ICU admission. Notably, the median of lowest hemoglobin levels, lowest thrombocyte counts, and highest levels of creatine, ALT, AST, LDH, CRP, and Procalcitonin all exhibited highly significant differences ($p<0.001$) between patients admitted to the ICU and those who were not. Furthermore, elevated ALT levels also showed a significant association ($p=0.011$).

Specifically, the lowest hemoglobin levels, lowest thrombocyte counts, and highest levels of creatine, ALT, AST, LDH, and CRP demonstrated highly significant distinctions ($p< 0.001$) among patients categorized based on WHO severity criteria. The highest procalcitonin levels also exhibited a noteworthy association with severity ($p=0.037$). Conversely, the lowest leukocyte counts did not show statistical significance ($p=0.111$).

Univariate analysis was performed to see whether there was a relationship between patients who met at least one of the WHO severe disease criteria and patients who were admitted to the ICU, and a statistically significant relationship was found. ($p <0.05$) While 27 of 28 patients admitted to ICU met this criterion, it was observed that only one patient did not comply. It was found that the sensitivity of the WHO severity criteria was 99.9%, and the specificity was 80.6% in predicting ICU admission of patients in the data set. The ROC area value is 0.904.

Multivariate logistic regression analysis was performed between ICU admission and age, gender, misdiagnosis, proven secondary infection, and the time between diagnosis and initial treatment given to account for confounding variables. The study revealed that initial misdiagnosis led to a 2.8-fold increase in ICU admissions ($p < 0.05$). Additionally, each day delayed for treatment after diagnosis was associated with a 1.26-fold increase in ICU admissions per day ($p < 0.05$). Furthermore, the development of secondary bacterial infections was found to be linked with a significant 9.5-fold increase in ICU admissions ($p < 0.05$).

Impact of COVID-19 on Malaria Cases and ICU Admission

The number of malaria cases diagnosed after the first COVID-19 case emerged in Turkey (March 2020) [7] was 120, of whom 18 were admitted to the ICU. Among 179 patients who were diagnosed before COVID-19, 10 were admitted to the ICU. There was a significant increase in ICU admissions among patients diagnosed after the COVID-19 period compared to those diagnosed before ($p < 0.05$). Of 299 patients, 93 (31.1%) were observed to meet at least one of the severe illness criteria defined by the WHO in the study. Furthermore, when considering whether patients met any of the WHO severe disease criteria, it is evident that these criteria were more frequently observed among patients admitted after March 2020 ($p < 0.05$).

Discussion

Since the Ministry of Health has not publicly reported malaria cases in Turkey since the pandemic, data collected from various hospitals across the country are especially important.
According to the latest available data in Turkey, it is known that between 135 and 280 imported cases of malaria occur annually[8]. Therefore, this study covers approximately 10% of the malaria cases observed in Turkey between 2012 and 2023.

Nine patients were local cases with no history of traveling abroad, and there was no evidence indicating a connection between them. The number of local malaria cases in Turkey, which was 11,378 in 2000, dropped to 2,036 in 2005 as a result of the successful elimination program[9]. According to the Turkish Health Statistical Yearbooks, no local cases have been reported in Turkey since 2010[9].

When the cases with no history of abroad were examined, *P. vivax* was diagnosed in 8 cases and *P. falciparum* was diagnosed in one. Although local *P. falciparum* cases were frequently observed in Turkey during the malaria epidemic in the early 1900s, it has become a scarce condition in the last 50 years. Since there have been no reported local cases in the past 14 years, according to the Ministry of Health, it is crucial to implement necessary precautions to prevent future local cases. Notably, in 2023, after a 20-year gap, two local cases were reported in the United States, underlining the sporadic nature of such occurrences globally[10].

Although the Ministry of Health has not reported any local malaria cases since 2010, according to various media sources[11], there was a malaria epidemic in Mardin in 2012, and infection was detected in 99 people. The Ministry of Health stated that 2 of these cases had a history of traveling abroad but did not make a statement about the remaining cases.

Three cases of malaria by *P. falciparum* and *P. vivax* were reported in Kayseri province in 2022[12]. All were presented with typical malaria symptoms and confirmed via laboratory studies.

Moreover, all of them were reported through the provincial health directorate's infectious diseases unit, and the reference laboratory of the General Directorate of Public Health of Turkey confirmed their malaria diagnoses. Additionally, this[13] study refers to a local malaria case in Manisa, initially diagnosed as leukemia. Similarly, two patients in our study were initially suspected of having hematological malignancy, but their diagnosis was later confirmed as malaria. A well-known individual who recently traveled to Nigeria was diagnosed with malaria in Kocaeli Province, Turkey, and died, possibly due to a delay in diagnosis[14].

Prior data from the late 1990s and early 2000s shows that the most common species of Plasmodium was *P. vivax* [15]. However, because of the decrease in local cases, imported *P. falciparum* cases in the last decade surpassed the number of *P. vivax* cases [9].

P. falciparum and P. vivax are the most prevalent malarial pathogens globally, transmitted by female Anopheles mosquito vectors[16]. In Turkey, ten Anopheles species have been found; the most significant malaria vector is Anopheles sacharovi, which is followed by Anopheles superpictus, Anopheles maculipennis, and Anopheles subalpinus. The presence of these vectors can lead to locally transmitted malaria cases, especially with increasing global mobility and changing environmental conditions[17]. Massive population changes, a rise in imported cases, and the potential threat of climate change could all lead to future malaria epidemics, unavoidably resulting in serious public health problems in Turkey[18].

It is noteworthy that in our study 278 of 299 patients (93%) were male. In various other studies that have been conducted in Turkey after 2010, this rate varies between 69% and 98.7%[19-22]. Similar studies in Germany, France, and Spain report male rates as high as 75.7% (between 2014 and 2016), 62.4%, and 56.8%, respectively[23-25]. Before the malaria elimination, the proportion of females was much higher[26,27]. Only seven out of 18 female patients were of Turkish origin, of whom 3 had no history of traveling abroad, thus; it can be observed that the gender gap among Turkish-origin citizens who traveled abroad and contracted malaria is even more pronounced. The higher proportion of men compared to studies conducted in other countries may be related to the fact that trips to Africa from Turkey are mostly business trips which are male-dominated.

A total of 66 patients were informed about the use of chemoprophylaxis. Notably, all individuals adhering to chemoprophylaxis were of Turkish origin, with 64 being Turkish and 2 having foreign nationality among those informed about it. Out of the 66 individuals informed about the treatment, 24 discontinued the prescribed regimen prematurely. While various demographic and psychological reasons for non-adherence to chemoprophylaxis exist, there is a noticeable absence of specific studies addressing this issue in Turkey. It creates an opportunity to investigate the factors contributing to non-adherence among the local population.

The fatality rate was 1.3%, with 4 deaths among 299 patients. However, it is important to consider that there may be reporting bias, as some fatal cases might not have been documented. The tendency to report surviving cases might be higher.

In multivariate analysis, the longer lag time before initiation of treatment after diagnosis, misdiagnosis at previous health centers, and secondary bacterial infection during the patient's hospital stay were found to be associated with ICU admission ($p < 0.05$). Various previous studies also emphasize that it is of utmost importance to start treatment as early as possible after the initial malaria diagnosis[28]. Even though the lack of availability of medication is one of the critical reasons for the delayed initiation of treatment, no issue regarding drug supply was reported by the centers from which we received the data[29]. The initial misdiagnosis is a variable that directly affects the diagnosis and treatment process and also increases the likelihood of being admitted to ICU by almost 3 times (OR: 2.8, P: 0.027). According to the results, 71 patients (23.7%) were initially misdiagnosed, which by itself delays the treatment process. With malaria being a rare occurrence in present-day Turkey and officially declared absent in local cases since 2010, it has been observed that misdiagnosis could be more common, especially in local cases (66.6%).

Malaria can be confused with various diseases as patients present with a myriad of different signs/symptoms and is a rare diagnosis in non-endemic countries. In our study, these diseases can vary from lower or upper respiratory tract infections (n=41, 57.7%) to hematologic malignancies (n=2, 2.8 %). In addition, considering that 4 of 31 misdiagnosis cases (12.9%) seen after COVID-19 were wrongfully concluded to be COVID-19 infection cases, it would not be wrong to assume COVID-19 had some effect on misdiagnosis rates of malaria.

Among Organisation for Economic Co-operation and Development (OECD) countries, Turkey ranks first in antibiotic resistance rate[30]. When the antibiotic usage data of the patients were examined, it was determined that up to 77.5 % of misdiagnosed patients were given antibiotic treatment. Upon reviewing the antibiotics administered during hospitalization, it was determined that antibiotics were given to 58 patients. However, bacterial infection was only detected in 11 of these patients. These findings indicate unnecessary use of antibiotics and treatment of patients without proper diagnosis.

In our study, the median level of procalcitonin was 3.9, which is a value that could be detected in bacterial sepsis. Although higher procalcitonin values were found to be associated with ICU admissions and severe disease according to WHO, procalcitonin is not one of the frequently used tests to examine the course of malaria disease and has no place in the WHO Severe Disease Classification scale. Although various studies have concluded that procalcitonin is elevated in severe malaria, the meta-analysis conducted by Mahittikorn and colleagues concluded that "using PCT alone may not effectively differentiate between severe and uncomplicated malaria cases or infected and uninfected individuals." [31]. Conducting prospective studies to explore PCT levels in malaria cases could provide valuable insights. Subsequently, this research may support the consideration of procalcitonin inclusion within the WHO criteria for severe disease.

Our study comprised 93 patients who met at least one of the WHO Severe Disease Criteria. Although it is recommended to follow up these patients in the ICU by WHO, our study showed that only 27 of these patients were admitted to the ICU and followed up. Interestingly, one of the patients admitted to the ICU did not meet any of the severe disease criteria initially. However, this patient experienced a relapse: the patient's condition was initially stable upon admission but deteriorated after discharge, leading to readmission to the hospital and subsequent ICU admission. It was highlighted that the data entered for the WHO severe disease criteria for this patient could have been from the patient's initial admission.

WHO Severe Disease Criteria for Malaria consists of 12 items[5]. While all these criteria are based on objective data, “prostration” is a relatively subjective criterion and cannot be measured in any specific way. Interestingly, none of the cases where “prostration” was solely observed resulted in ICU admission. Prostration was marked in 62 out of 93 patients (66.7%). Among the 27 patients admitted to the ICU, 21 had prostration as a criterion. Additionally, apart from prostration, no other severe disease criteria were examined in 25 cases, and none of these patients were admitted to the ICU. Our findings indicate that the prostration criteria lack specificity and sensitivity, being notably subjective. Therefore, further comprehensive studies can be conducted on this criterion in the future, and it could potentially be revised.

In our study, the most common sequela was headaches, which can persist for up to 10 months. This is often followed by psychological symptoms like restlessness, depression, anxiety, and personality changes, subsequently leading to neurological sequela. Among the 299 patients, 28 (9.4%) experienced sequela lasting at least 1 month. These observations highlight that malaria, with its various complications during and after treatment, can significantly impact a patient's life, extending beyond the phase of diagnosis and treatment.

A study shows that during the COVID-19 pandemic in 2020, millions of excess malaria cases and tens of thousands of additional deaths occurred globally, and malaria incidence rates increased in over 50% of malaria-endemic countries in addition to an approximate 70% increase in mortality rates where malaria deaths were reported[32]. The WHO 2021 report discusses COVID-19's impact on malaria prevention, attributing disruptions in the delivery of malaria prevention, diagnosis, and treatment during the pandemic as causative factors[33]. The COVID-19 pandemic has had various impacts on malaria prevention. Similar symptoms of COVID-19 and malaria have increased the possibility of misdiagnosis and contributed to the overlook of potential co-infections[34,35]. The pandemic led to decreased capacity in healthcare systems and affected the logistics and supply chains crucial for malaria control measures[36,37]. Moreover, patients had to consider the risks of seeking medical care during the pandemic because of possible exposure to COVID-19 which may lead to potential delays in treatment[36].

We have observed a significant increase in ICU admissions and severe disease according to WHO among patients after the initiation of the COVID-19 period. ($p < 0.05$) The heightened severity of malaria cases and the rise in ICU admissions before and after the initiation of the COVID-19 era might be attributed to negligence. However, a more detailed analysis could elucidate the specific factors contributing to this trend.

Conclusion

One of the most prominent highlights of our research is the increase in malaria cases and their severity following the COVID-19 pandemic. Additionally, our study underlines the challenge of cases with no travel history of abroad. This emphasizes the importance of educating healthcare professionals on this issue, especially given the difficulty in diagnosis. Furthermore, our investigation demonstrates that misdiagnosis and delays in initiating treatment contribute to a worsened disease course, leading to increased ICU admissions. Our study underscores the challenges of malaria cases in Turkey, especially post pandemic period, indicating the need for better diagnosis and treatment. With further research for addressing the complexities of malaria management and advancing public health initiatives, we can improve patient healthcare practices to yield better outcomes.

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Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Onder Ergonul reports was provided by Koç University. Onder Ergonul reports a relationship with Koç University that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.