

Characteristics of Travel-Related Severe *Plasmodium vivax* and *Plasmodium falciparum* Malaria in Individuals Hospitalized at a Tertiary Referral Center in Lima, Peru

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Abstract. Severe *Plasmodium falciparum* malaria is uncommon in South America. Lima, Peru, while not endemic for malaria, is home to specialized centers for infectious diseases that admit and manage patients with severe malaria (SM), all of whom contracted infection during travel. This retrospective study describes severe travel-related malaria in individuals admitted to one tertiary care referral hospital in Lima, Peru; severity was classified based on criteria published by the World Health Organization in 2000. Data were abstracted from medical records of patients with SM admitted to Hospital Nacional Cayetano Heredia from 2006 to 2011. Of 33 SM cases with complete clinical data, the mean age was 39 years and the male/female ratio was 2.8. Most cases were contracted in known endemic regions within Peru: Amazonia (47%), the central jungle (18%), and the northern coast (12%); cases were also found in five (15%) travelers returning from Africa. *Plasmodium vivax* was most commonly identified (71%) among the severe infections, followed by *P. falciparum* (18%); mixed infections composed 11% of the group. Among the criteria of severity, jaundice was most common (58%), followed by severe thrombocytopenia (47%), hyperpyrexia (32%), and shock (15%). *Plasmodium vivax* mono-infection predominated as the etiology of SM in cases acquired in Peru.

INTRODUCTION

The World Health Organization (WHO) estimated that 3.4 billion people are at risk of malaria worldwide, and more than 200 million individuals are infected in 2012.¹ Infections were primarily in sub-Saharan Africa, resulting in over 600,000 deaths annually, most of whom were children under 5 years of age.¹ The clinical spectrum of symptomatic malaria in endemic areas ranges from mild to severe, lethal disease.^{2,3} It is important to recognize severe malaria (SM) because it is associated with high mortality. Criteria for SM include high levels of parasitemia and/or major signs of organ dysfunction, but their prevalence in malaria cases varies from region to region and between children and adults.^{4–7}

In 2014, the WHO and partners updated the 1990, 2000, and 2010 clinical classifications of SM^{5–7} to include three groups with a gradation of severity.⁴ SM includes various clinical presentations, particularly, hypoglycemia, lactic acidosis, respiratory distress, severe thrombocytopenia ($< 50,000/\text{mm}^3$), jaundice, neurological dysfunction (coma, seizure), and multiple organ failure.^{6,7} Most clinicians traditionally consider *Plasmodium falciparum* to be the parasite species responsible for SM. However, this clinical paradigm has been challenged in the last decade⁸ by numerous reports of symptoms and signs of severe disease, and even deaths due to *Plasmodium vivax* mono-infection.^{9–12}

In Peru, malaria remains an important public health problem; about half the population is potentially exposed to malaria or lives in areas with ecological factors favorable to transmission. Three main areas with different transmission patterns can be identified, that is, the Amazon region, the central jungle, and the northern coast, currently accounting for 80%, 18%,

and 2% of all cases in the country, respectively.¹³ *Plasmodium vivax* is the predominant species in Peru (~85% of the infections) followed by *P. falciparum* (~15% of the infections), which is almost exclusively reported in the Amazon Region.¹⁴

Lima, the largest city in Peru located in the desert-like central coast of Peru, is not endemic for malaria, but has emerged as a place where travel-related malaria (imported malaria) is seen. Peruvian and international travelers who acquired infection in malaria-endemic areas travel through the city either to return home or in transit. Similar to other non-endemic areas, imported malaria is often not diagnosed in a timely way at health facilities and clinics in Lima. Such late diagnosis is likely the reason for referral of severe cases to specialized health facilities (tertiary medical centers).

The Hospital Nacional Cayetano Heredia (HNCH) in Lima, the national referral center for management of malaria, hospitalized 42 patients for malaria between 2006 and 2011. This study aimed to determine the frequency of SM and, particularly, clinical features of the malaria during this period, with the goal of contributing to a better knowledge of the clinical manifestations of SM in the developing world but non-endemic setting. We anticipate that this analysis will allow for better identification and management of malaria in such settings.

METHODS

This retrospective case series study was conducted at HNCH. As a high-complexity hospital care provider (complexity level III-1), HNCH is responsible for meeting the health needs of the population of the north area of Lima, offering specialized inpatient and outpatient comprehensive care, with emphasis on recovery and rehabilitation of health problems through highly specialized medical and surgical units. HNCH is affiliated with the Instituto de Medicina Tropical Alexander von Humboldt, whose activities comprise clinical care, training, and research in infectious and tropical diseases.

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This affiliation allows the hospital to be a national reference center for malaria and other infectious diseases.

Available clinical records of individuals with malaria infection admitted to HNCH from January 1, 2006 to December 31, 2011 were reviewed. Each case of malaria was evaluated individually, and those patients who met the WHO criteria for SM⁶ were included in the study. Sociodemographic (age, gender, and occupation), epidemiological (place of origin, place of infection, and time of the disease), clinical (impaired consciousness, prostration, multiple convulsions, respiratory distress [acidotic breathing], shock, abnormal bleeding, pulmonary edema [radiological], and jaundice), and laboratory (hypoglycemia, metabolic acidosis, severe anemia, hyperparasitemia, hyperlactatemia, and renal impairment) data were registered from identified patients with SM using a study form previously validated by malaria clinical experts. The time of disease was the period between the beginning of symptoms and the admission of the patient to the hospital.

Parasite density was measured through the semiquantitative method of crosses.¹⁵ The reading of the smear is done with the 100× oil immersion objective and the density is determined by examining 100 high-powered fields. The number of crosses reflects an estimate of the number of parasites per field: 1+ is 1 parasite per field in 100 fields; 2+ is 2–20 parasites per field in 100 fields; 3+ is 21–200 parasites per field in 100 fields; and 4+ is more than 200 parasites per field in 100 fields.¹⁵

Data were entered twice by independent data entry clerks, and validated and cleaned in Excel (Microsoft Corp, Redmond, WA). Data analysis was performed with SPSS 13.0 for Windows® (SPSS Inc., Chicago, IL). Descriptive statistics were used for numerical (median, mean, interquartile range, and standard deviation) and categorical (absolute and relative frequencies) variables. Comparisons between proportions were assessed using Fisher's exact test, considering a value of $P < 0.05$ as statistically significant.

Permission for the review of clinical records was received from hospital authorities after explaining the purpose and procedures of the study. Ethical clearance was obtained from the Ethics Review Board of the Universidad Peruana Cayetano Heredia, Lima, Peru (SIDISI code: 0000059594).

RESULTS

Thirty-three individuals admitted to HNCH between 2006 and 2011 met the newly published WHO criteria (2014) for the diagnosis of SM. Seven additional SM cases were registered during the study period, but their clinical records were incomplete. Two of these cases died. The first patient was a 19-year-old woman, 29 weeks pregnant, who was admitted to the emergency department. The patient had mixed malaria infection (*P. vivax* and *P. falciparum*) and severe, refractory shock and died within 24 hours of admission. The second case was a 33-year-old male veterinarian who acquired the infection by *P. falciparum* in French Guyana. He was transferred to HNCH from an outside hospital, where he had been misdiagnosed, delaying appropriate treatment. His condition deteriorated and he was transferred to our institution with multiorgan failure and shock leading to death 18 days later despite aggressive therapy and intensive care unit support.

The demographic and epidemiological features of individuals with SM in our hospital fit the well-known clinical

TABLE 1
Demographic and epidemiological features of patients with SM

Variable	Value
Age	
Mean (±SD)	40 (±15.8)
Sex	
Male, <i>n</i> (%)	24 (72.7)
Female, <i>n</i> (%)	9 (27.3)
Place of residence	
Lima, <i>n</i> (%)	18 (54.5)
Loreto, <i>n</i> (%)	3 (9.1)
Madre de Dios, <i>n</i> (%)	2 (6.1)
Piura, <i>n</i> (%)	3 (6.1)
Other, <i>n</i> (%)	8 (24.2)
Region of infection	
Peruvian Amazonia, <i>n</i> (%)	15 (45.4)
Peruvian central jungle, <i>n</i> (%)	6 (18.2)
Africa, <i>n</i> (%)	5 (15.2)
Peruvian north coast, <i>n</i> (%)	4 (12.1)
Other, <i>n</i> (%)	3 (9.1)
Previous episode of malaria	
Yes, <i>n</i> (%)	9 (27.3)
No, <i>n</i> (%)	24 (72.7)

SD = standard deviation; SM = severe malaria.

features of this disease (Table 1). The average age was 40 ± 15.8 years (range = 14–64 years), with a male/female ratio of 2:7. Only nine (26.5%) individuals had a previous episode of malaria. Although most individuals acquired malaria in Peruvian endemic areas (Amazon region [45%], central jungle [18%], and northern coast [12%]), five individuals acquired *P. falciparum* abroad, Africa being most common (15%).

The median duration of illness before presentation was 10 days (interquartile range [IQR] = 5–15 days); only one patient presented with less than 48 hours of disease. All patients sought medical care at other (public and private) health facilities before being transferred to HNCH, and most of them were properly diagnosed only after their admission at HNCH. The most common symptoms from the onset of disease to the admission to hospital were fever (100%), chills (89%), malaise (70%), and headache (67%). The most common signs at the time of admission were hepatomegaly (76%) and splenomegaly (45%) (Table 2).

On the basis of microscopy results, 23 (70%) patients had *P. vivax* mono-infection, six (18%) had *P. falciparum* mono-infection, and four (12%) had mixed infection with *P. vivax* and *P. falciparum*. Although patients with *P. vivax* mono-infection predominated with parasite densities of 1–2 crosses (70%), those with *P. falciparum* mono-infection had higher parasite densities of 3–4 crosses (66.7%) ($P = 0.03$) (Table 3), reflecting the known red cell tropisms and biology of these parasites.

The 2014 clinical classification of SM was used to analyze patient severity (Tables 4 and 5). Here, 67% (22/33) of patients were classified in group 1 with no difference between mono-infection by *P. vivax* and/or *P. falciparum* (including mixed infections). In this group, all but one of the patients were prostrate or obtunded, four (19%) had impaired consciousness but not deep coma. Of these four patients, two had mono-infection by *P. vivax*. Respiratory distress was present in 61% (20/22) of SM patients, although 90% of these cases were classified as mild. Half of the patients who developed shock (27%) had *P. vivax* mono-infection. Alternative causes of shock, for example, bacteremia, were not determined in these patients.

TABLE 2
Clinical features of patients with SM

Variable	Value (N = 33)	<i>Plasmodium vivax</i> (N = 23)	<i>Plasmodium falciparum</i> (N = 6)	Mixed (N = 4)
Time of disease (days), median (IQR)	10 (5–15)	10 (7.5–15)	7.5 (5–14)	32 (11.5–52.5)
SBP (mmHg), mean ($\pm$ SD)	101 ($\pm$ 17.1)	104 ($\pm$ 17.5)	97.5 ($\pm$ 13.3)	87.5 ($\pm$ 15)
DBP (mmHg), mean ($\pm$ SD)	62 ($\pm$ 12)	62.2 ($\pm$ 11.7)	65.5 ($\pm$ 13.2)	55 ($\pm$ 12.9)
Temperature ($^{\circ}$ C), mean ($\pm$ SD)	39 ($\pm$ 1.2)	39.1 ($\pm$ 1.3)	38.6 ($\pm$ 0.9)	39.2 ($\pm$ 1.2)
Fever, n (%)	25 (75.8)	19 (82.6)	4 (66.7)	3 (75)
Chills, n (%)	29 (88.9)	22 (95.6)	4 (66.7)	3 (75)
General malaise, n (%)	23 (69.7)	14 (60.9)	5 (83)	4 (100)
Hepatomegaly, n (%)	25 (75.7)	18 (78.3)	5 (83)	2 (50)
Splenomegaly, n (%)	15 (45.4)	11 (47.8)	3 (50)	1 (25)
Headache, n (%)	22 (66.7)	15 (65.2)	4 (66.7)	3 (75)
Petechiae/ecchymosis, n (%)	5 (15.1)	5 (21.7)	0	0
Oliguria, n (%)	3 (9.1)	1 (4.3)	2 (33)	0

DBP = diastolic blood pressure; IQR = interquartile range; SBP = systolic blood pressure; SD = standard deviation; SM = severe malaria.

Using the 2014 WHO classification, there were no major differences in severity between *P. vivax* and *P. falciparum* malaria cases, except patients infected by *P. falciparum* more often had jaundice (Table 5). In those with jaundice, the mean total bilirubin level was 3.3 mg/dL (1.4–6.25), while the mean platelet counts and hemoglobin levels were 60,000 platelets/mm³ and 11.3 g/dL, respectively (Table 6).

Antimalarial therapies administered to the patients with SM at HNCH during the study period reflect international norms of practice at the time. Most patients with *P. vivax* mono-infection (19/23, 83%) received oral antimalarial treatment, mainly chloroquine plus primaquine. In contrast, half of patients with *P. falciparum* (mono-infection or mixed infection) were given intravenous artesunate, while the other half received oral treatment with artesunate and mefloquine.

DISCUSSION

This study is the first to describe clinical features of SM in patients admitted to an infectious diseases referral center in a non-malaria-endemic region of a developing country. *Plasmodium vivax* was the most frequent cause of SM during the study period. Cases with SM mostly involved young adult men from endemic regions within Peru (primarily the Amazon region) and outside Peru (travelers returning from Africa). The 11-day mean duration of illness before hospital admission indicates a long period in which appropriate interventions (diagnostics, drug treatment) could improve patient outcome.

Vulnerability to SM has been associated with transmission intensity and age-dependent development of immunity.¹⁶ In areas with high transmission (such as sub-Saharan Africa), the most vulnerable groups are ranked as follows: young children who have not yet developed partial immunity to malaria; pregnant women, whose immunity is decreased by pregnancy; and travelers or migrants coming from areas with little or

no malaria transmission, who lack any form of antimalarial immunity. On the other hand, in areas with lower transmission (such as Latin America and Asia), residents are less frequently exposed and infected; hence, there is a higher prevalence of malaria-naïve individuals among this population. Many may reach adulthood without having developed relative protective immunity and are thus susceptible to more severe and sometimes fatal malarial illness. Further, clinical immunity to malaria—even if acquired by residence in an endemic region—diminishes rapidly after leaving such a region. In Peruvian endemic areas as the Amazon Region, adolescents and young adults (as in this study) with partial and non-protective immunity are more vulnerable to severe disease when they typically start to work in high risk, outdoor activities bringing them into contact with infected vector mosquitoes.¹⁷

Recent reports of severe disease and deaths have challenged the dogma that *P. vivax* is benign,^{7–10} alerting clinicians on the potential severity of the disease. However in Peru, malaria guidelines have not yet been updated taking into account the new evidence, and continue to consider that SM is only associated with *P. falciparum*.¹⁵ This underestimation of the importance of *P. vivax* as potentially responsible for SM could lead to a delayed diagnosis and inappropriate management of cases by health personnel.

Another issue is the understanding of SM, its definition and classification, since the lack of an adequate characterization can lead to errors and delays in identifying cases requiring more intensive clinical attention and parenteral therapy. In this analysis, we adopted the recent classification of SM proposed by WHO in 2014.⁴ Notably, two-thirds of the patients were classified into the highest severity group (group 1), while one-third to group 2. There were no differences between *P. vivax* and/or *P. falciparum* (as mono-infection or mixed). Most patients were prostrate but conscious and none were severely comatose (Glasgow Coma Scale < 11) or psychotically agitated, reflecting the rarity of cerebral malaria in this patient population. Respiratory distress was a frequent finding, but not severe. Neither *P. vivax* nor *P. falciparum* patients who developed shock (27%) often had acidosis. Mild jaundice (total bilirubin > 3 g/dL) was common; none of our patients had levels above 8 g/dL, which has been associated with increased mortality. More than half of *P. vivax* and all of *P. falciparum* cases of SM were associated with jaundice, which generally does not predict death. Only 3/33 of patients had

TABLE 3
Parasite density by species

Parasite density	Total (N = 33)	<i>Plasmodium vivax</i> (N = 23)	<i>Plasmodium falciparum</i> (N = 6)	Mixed (N = 4)
1+, n (%)	7 (21.2)	5 (21.7)	1 (16.7)	1 (25)
2+, n (%)	14 (42.4)	11 (47.8)	—	3 (75)
3+, n (%)	7 (21.2)	4 (17.4)	3 (50)	—
4+, n (%)	2 (6.1)	1 (4.3)	1 (16.7)	—
Unknown	3 (9.1)	2 (8.6)	1 (16.7)	—

TABLE 4
Clinical classification of patients with SM by species

Group	Total (N = 33) (%)	<i>Plasmodium vivax</i> (N = 23) (%)	<i>Plasmodium falciparum</i> (N = 6) (%)	Mixed (N = 4) (%)
Group 1	22 (66.7)	16 (69.6)	3 (50)	3 (75)
Prostrated or obtunded	21 (63.6)	15 (65.2)	3 (50)	3 (75)
Prostrate but fully conscious	17 (51.5)	13 (56.5)	2 (33.3)	2 (50)
Prostrate with impaired consciousness, but not in deep coma (GCS > 11)	4 (12.1)	2 (8.7)	1 (16.7)	1 (25)
Confusion and agitation (GCS > 11)	0 (0)	—	—	—
Coma (GCS < 11)	0 (0)	—	—	—
Respiratory distress	20 (60.6)	14 (60.9)	3 (50)	3 (75)
Mild	18 (54.5)	13 (56.5)	2 (33.3)	3 (75)
Severe	2 (6.1)	1 (4.3)	1 (16.7)	0
Shock (BP < 80 mmHg)	9 (27.3)	5 (21.7)	2 (33.3)	2 (50)
Anuria	0 (0)	—	—	—
Significant upper gastrointestinal hemorrhage	1 (3)	1 (4.3)	—	—
Group 2	11 (33.3)	7 (30.4)	3 (50)	1 (25)
Severe anemia (Hb < 7 g/dL or hematocrit < 20%)	3 (9.1)	2 (8.7)	—	1 (25)
Seizures (one or more within a 24-hour period)	0 (0)	—	—	—
Hemoglobinuria (blackwater)	4 (12.1)	3 (13)	1 (16.7)	—
Jaundice	10 (30.3)	6 (26.1)	3 (50)	1 (25)
Group 3	0 (0)	—	—	—

BP = blood pressure; GCS = Glasgow Coma Scale; Hb = hemoglobin; SM = severe malaria.

severe anemia while none had hemorrhagic manifestations. Two patients—one with *P. vivax* and one with *P. falciparum*—required renal replacement therapy.

The severity of malaria in Amazonia is less than in Africa, as a recent comparison of patients from India and Brazil showed.³ In this study, differences in presentation, such as hyperlactatemia, respiratory distress, hypoglycemia, and disseminated intravascular coagulopathy were more frequently reported in Brazilian cases, although the overall fatality rate was 20-fold higher in India.³ Several comorbidities, socioeconomic differences, health-care access, and infrastructure were some of the factors that could influence the outcome between these two populations.

Most patients had typical manifestations of malaria (62% with the triad of fever, chills, and headache, and 88% with only fever and chills) combined with a history of living in or traveling to an endemic malaria area. However, this information was not routinely recorded or clearly ascertained in a clinically actionable way that would raise the index of suspicion for malaria to allow for timely diagnosis and treatment (median of 11 days), thus increasing the risk for increased malaria severity.¹⁸

Even though the pathogenesis of malaria due to *P. vivax* and *P. falciparum* differs fundamentally (the latter known to include *P. falciparum* erythrocyte membrane protein 1-mediated

parasite sequestration, faster parasite growth rates, and a wider range of erythrocyte age preferences),¹⁹ systematically validated criteria to assess severe *P. vivax* malaria remain lacking, particularly the presence of comorbidities such as bacteremia or other medical conditions. The 2014 WHO criteria for SM remain based on *P. falciparum*-caused disease. Future studies should validate the usefulness of these criteria for *P. vivax* and other species as well.²⁰

After the diagnosis of SM, parenteral antimalarial treatment should be started without delay. Parenteral artesunate is the treatment of choice, with parenteral artemether or quinine as acceptable alternatives when parenteral artesunate is not available.⁷ In this retrospective analysis, only five (14.7%) patients received intravenous artesunate, while most received oral antimalarial treatment. The low rate of use of parenteral treatment in patients with SM can be explained by the lack of availability of such treatment at most general hospitals in Peru, running out of supplies at the Ministry of Health, the lack of trained physicians in the identification and management of SM, and the lack of recognition of SM caused by *P. vivax*.

This study has limitations. Being retrospective, collection of clinical data was not standardized and diagnosis was done by using microscopy only; molecular diagnostic testing might have detected mixed infections that could have been missed in this study. Clinical care differed because of the physicians in

TABLE 5
Epidemiological and research definition of patients with SM by species

	Total (N = 33) n (%)	<i>Plasmodium vivax</i> (N = 23) n (%)	<i>Plasmodium falciparum</i> (N = 6) n (%)	Mixed (N = 4) n (%)
Impaired consciousness	0 (0)	—	—	—
Severe anemia	5 (15.2)	3 (13)	—	2 (50)
Hypoglycemia (blood or plasma glucose < 40 mg/dL)	0 (0)	—	—	—
Acute kidney injury (creatinine > 3 mg/dL)	2 (6.1)	1 (4.3)	1 (16.7)	—
Jaundice (plasma or serum bilirubin > 3 mg/dL)	18 (54.5)	12 (52.2)	6 (100)	—
Pulmonary edema	3 (9.1)	2 (8.7)	1 (16.7)	0
Significant bleeding	7 (21.2)	7 (30.4)	—	—
Shock	9 (27.3)	5 (21.7)	2 (33.3)	2 (50)
Acidosis (N = 12)	2 (16.7)	1 (11)	1 (16.7)	0
Renal replacement therapy	2 (6.1)	1 (4.3)	1 (16.7)	—

SM = severe malaria.

TABLE 6
Laboratory features of patients with SM

Variable	Value
Hematocrit (%), median (IQR)	33 (29.5–36.4)
Hemoglobin (g/dL), median (IQR)	11.3 (10.1–12.3)
Platelets ($\times 1,000/\text{mm}^3$), median (IQR)	60 (32–93.25)
Bicarbonate (mmol/L), median (IQR)	19.4 (17.4–20.2)
Glucose (mg/dL), median (IQR)	96 (87.5–112)
Creatinine (mg/dL), median (IQR)	1 (0.8–1.2)
Total bilirubin (mg/dL), median (IQR)	3.3 (1.4–6.25)

IQR = interquartile range; SM = severe malaria.

charge of the patient's care during the study period, including the lack of updated guidelines for managing SM including *P. vivax* as a potential cause of SM. The lack of standardized laboratory testing and data recording may also bias interpretation of data obtained. Finally, the numbers of cases are low and subject to referral bias. However, because SM in Lima is under-recognized—and the same may be true of other major cities in the developing world where malaria is not transmitted but where malaria patients may be present²¹—this clinical scenario is important for clinicians and public health professionals to know.

Herein, we report that severe *P. vivax* malaria in patients admitted to a specialized hospital in a non-malaria endemic area of Peru is an important clinical syndrome. Physicians should consider *P. vivax* as a potential cause of SM, and approach this disease aggressively. Despite the small number of cases in this report, the data do suggest differences in the clinical manifestations and complications of SM by *P. vivax* and *P. falciparum*. These data highlight the need for prospective studies to standardize laboratory and clinical data and clinical management that will allow for a better understanding of the wide range of features of SM.

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