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Malaria Severity in Mangaluru City in the Southwestern Coastal Region of India

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Abstract. Dakshina Kannada district in the Southwestern region of Karnataka state, India, including Mangaluru city is endemic to malaria. About 80% of malaria infections in Mangaluru and its surrounding areas are caused by *Plasmodium vivax* and the remainder is due to *Plasmodium falciparum*. Malaria-associated clinical complications significantly occur in this region. Here, we report the pathological conditions of 41 cases of fatal severe malaria, admitted to the district government hospital in Mangaluru city during January 2013 through December 2016. The results of clinical, hematological, and biochemical analyses showed that most of these severe malaria cases were associated with thrombocytopenia, anemia, metabolic acidosis, acute respiratory distress, and single or multi-organ dysfunction involving liver, kidney, and brain. Of the 41 fatal malaria cases, 24, 10, and seven patients had *P. vivax*, *P. falciparum*, and *P. vivax* and *P. falciparum* mixed infections, respectively. These data suggest that besides *P. falciparum* that is known to extensively cause severe and fatal malaria illnesses, *P. vivax* causes fatal illnesses substantially in this region, an observation that is consistent with recent findings in other regions.

INTRODUCTION

Malaria is a major global public health problem in most parts of the tropical region, contributing to an estimated 216 million clinical cases and approximately 445,000 deaths in 2016 alone.[1,2] Besides a huge health burden, malaria morbidity is a substantial hindrance to socioeconomic development of a country because of loss of manpower.[3,4] Malaria is endemic in most parts of India, accounting for ~70% of the total cases reported in Southeast Asia.[5–7] In 2014, more than one million clinical cases were reported in India.[8] The extent of malaria prevalence varies in different parts of India, that is, the eastern, northeastern, central, and southwestern regions of India, including several parts of Karnataka state.[9,10] Although five species of malaria parasites infect humans in Southeast Asia,[10] infection by *Plasmodium vivax* predominates (60–80%) compared with *Plasmodium falciparum* (20–40%); other species are rarely found.[11,12] In some parts of India, ~52% of infections are caused by *P. falciparum* and the remainder by *P. vivax*.[6]

Malaria is a highly complex disease that displays a multitude of pathological conditions. Even the early stages of malaria infection present a wide variety of systemic clinical conditions, including the characteristic periodic fever, chills, headache, dizziness, malaise, abdominal discomfort, nausea, and muscle and joint aches.[13,14] Prolonged infections lead to extreme anemia, metabolic acidosis, hemoglobinuria, splenomegaly, hepatomegaly, and other severe illnesses. *P. falciparum* infection is well known to cause single and multi-organ–related fatal conditions, including cerebral malaria, renal failure, hepatic dysfunction and failure, and acute respiratory distress syndrome (ARDS).[15,16] Although, until recently, *P. vivax* infection has been thought to be mostly benign and rarely fatal, in recent years, *P. vivax* is increasingly being identified as considerably virulent and causes severe illnesses and mortality.[17–23] This is evident from the report that in several subregions of Peru, where malaria transmission is almost exclusively due to *P. vivax*, critical illnesses occur considerably.[23]

Although several parts of the southwestern India are endemic to malaria, very little has been reported on the extent of disease severity and clinical complications in the Mangaluru region. Mangaluru city, the government headquarter of Dakshina Kannada district situated along the coastal area of Arabian Sea in Karnataka state, South India, is also endemic to malaria. The city and its surrounding areas have warm and humid climate with high rainfall during monsoon seasons. This region harbors high vector density and is disposed to efficient malaria transmission. The relative proportions of *P. vivax* and *P. falciparum* infections in this region are ~80% and ~20%, respectively.[24]

The medical records at the Dakshina Kannada District Health Office (DKDHO) indicate that, in 1990, the incidences of malaria in the Mangaluru area were very low, a total of only 19 cases. In 1992, malaria started emerging at a significant rate with the increased urbanization through road and building construction activities. This emergence appears to be because of the migrant infected workers who came from northern parts of India, where malaria infection is relatively high, and spreading infection. Thus, malaria prevalence has steadily increased from 1992, showing peak levels of annual parasite index (API) of 35.2 recorded in 1996 at the DKDHO, coinciding with the increased growth rate of construction activity in the area. The heightened governmental control measures and the dedicated local community awareness programs during this period substantially brought down the API to 6.4 in 2000. However, once again the incidence exponentially increased to a peak API level of 46.7 in 2005 that also coincided with the rapid expansion and growth of construction and the road infrastructure activities. Although from 2005 the API has decreased considerably, malaria is still a substantial problem in the Mangaluru area; the DKDHO-recorded clinical cases in

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2016 were 5,182 with an API of 10.3. The disease incidence and fatal malaria cases are likely to be considerably higher than these numbers, as the malaria-infected individuals treated at private clinics and some hospitals might not have been reported to the DKDHO and a sizable number of infected people do not even go to hospitals for diagnosis and treatment. In efforts to gain insight into the extent of fatal severe malaria prevalence in this region, we examined the medical records at a major referral hospital in Mangaluru and analyzed severe malaria cases. Herein, we report the results of this analysis.

METHODS

We analyzed medical records of confirmed cases of severe malaria patients admitted to the Wenlock District Hospital, a major Karnataka state government tertiary care hospital in Mangaluru city, during January 2013 to December 2016. The hospital's archived medical records were analyzed for gender and age information, and radiological, clinical, biochemical, and hematological laboratory data. Malaria was diagnosed by microscopic examination of Giemsa-stained thick and thin blood smears. The records indicate that on inpatient admission to the hospital, the clinical symptoms and central nervous system manifestations were recorded, and hematological and serum biochemical analyses were performed. The severity of malaria was classified according to the World Health Organization criteria for *P. falciparum* illnesses.[25] All cases were treated for malaria as per the guidelines of the National Vector Borne Disease Control Program, India.

Parasitemia was assessed by counting the number of parasites under a ×100 microscopic field and given a score of 1 to 4: score 1, 1–10 parasites per 10 microscopic fields; score 2, 11–100 parasites per 10 fields; score 3, 1–10 parasites per one field; score 4, more than 10 parasites per one field. In the cases reported here, most *P. falciparum* infections received a score of 3 or 4, whereas *P. vivax* infections received a score of 1 or 2.

RESULTS

A total of 18,936 malaria cases were diagnosed and treated during January 2013 to December 2016 at the Wenlock District Hospital. Of these total cases, 15,334 and 2,456 cases were due to *P. vivax* and *P. falciparum* infections, respectively, and 1,146 had *P. vivax* and *P. falciparum* mixed infections. During 2013–2016, the total number of fatal severe malaria cases recorded at this hospital was 41 and the case fatality rate was 0.22%. Of the 41 severe malaria cases analyzed in this study, 14 males and 10 females had *P. vivax* infection (58.5%), seven males and three females had *P. falciparum* infection (24.4%), and six males and one female had *P. vivax* and *P. falciparum* mixed infection (17.1%) (Table 1). When the cases were distributed to different age groups, the distribution was as follows: four in 0–14 years, 10 in 15–30 years, 11 in 31–45 years, nine in 46–60 years, and seven in > 60 years old groups (Table1). Thus, most fatal clinical complications were in adults. Interestingly, the relative proportion of *P. vivax* and *P. falciparum* infections in the 41 severe malaria cases analyzed here was, respectively, 84% and 16%. This relative proportion is similar to the relative proportion of ~82% *P. vivax* and ~18% *P. falciparum* infection in this endemic area.[24] Thus, the frequency of severe illnesses in *P. falciparum*– and *P. vivax*–infected patients is directly proportional to the proportion of *P. falciparum* and *P. vivax* infection. This observation suggests that in this endemic area, *P. vivax* causes fatal illnesses at a rate almost similar to that caused by *P. falciparum*.

TABLE 1
Gender and age of fatal malaria cases analyzed in this study

		Plasmodium vivax, *n* (%)	*Plasmodium falciparum*, *n* (%)	Mixed infection, *n* (%)
Gender	Male	14 (34.1)	7 (17.1)	6 (14.6)
	Female	10 (24.4)	3 (7.3)	1 (2.4)
Age (years)	0–14	1 (2.4)	0	3 (7.3)
	15–30	5 (12.1)	3 (7.3)	2 (4.8)
	31–45	6 (14.6)	4 (9.7)	1 (2.4)
	46–60	6 (14.6)	2 (4.8)	1 (2.4)
	≥ 60	6 (14.6)	1 (2.4)	0

The patients exhibited varying degrees of malaria clinical symptoms and disease complications, including intermittent fever, chills, headache, vomiting, difficulty in breathing, and altered consciousness. The malaria parasitemia was scored based on the density of parasites in blood smears as defined under "Methods." Blood parasitemia in *P. falciparum* infection was much higher than that in *P. vivax* infection.[26] Analysis of blood samples indicated altered biochemical parameters, including serum urea, creatinine, direct and indirect bilirubin, level of electrolytes (sodium, potassium, chloride, and bicarbonate), and liver enzymes, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) (Table 2). These results revealed significantly altered parameters in all three types of malaria infections. Notably, compared with normal values, higher levels of AST, ALT, urea, and bilirubin and lower levels of bicarbonate and platelets were observed in *P. vivax* infections (Table 2), whereas AST and ALT were at higher levels and bicarbonate and platelets levels were lower in *P. falciparum* infections (Table 2). In the case of mixed infections, higher levels of leukocytes, urea, creatinine, bilirubin, AST, ALT, and ALP, and much lower levels of platelets and bicarbonates were seen (Table 2).

Overall, the results of this study indicated that the most common clinical conditions were thrombocytopenia, metabolic acidosis, and low platelet counts (< 150,000) and plasma bicarbonate levels (< 17 mmol/L) (Table 2). All patients had hyponatremia, most likely due to dehydration from vomiting and diarrhea, and low bicarbonate levels due to high levels of metabolic acidosis, a principal pathologic feature in severe malaria. Five of the 41 patients exhibited neurological symptoms characteristic of cerebral malaria, including seizures, altered sensorium, upper motor neuron signs (hypertonia), and opisthotonus posturing. Three of these five cases had mixed infection, one had *P. falciparum*, and one patient had only *P. vivax* infection.

High levels of ALT due to liver injury were observed in 14 (58.3%) of 24 *P. vivax* infections compared with eight (80%) of 10 *P. falciparum* infections and five (71.4%) of seven mixed infections. Jaundice with serum bilirubin levels of > 3.0 mg/dL was observed in six (25%) of 24 *P. vivax* infections compared with three (30%) of 10 *P. falciparum* infections and six (85.7%) of seven mixed infections (Table 2). The metabolic acidosis condition associated with plasma bicarbonate level of < 15 mmol/L was observed in 22 (91.7%) of 24 *P. vivax* infections compared with six (60%) of 10 *P. falciparum* infections

TABLE 2
Hematological and biochemical parameters of 41 severe malaria cases treated at Wenlock Hospital in Mangaluru city (values are mean ± SD).

Clinical parameters (normal reference range)	*Plasmodium vivax* (*n* = 24)	*Plasmodium falciparum* (*n* = 10)	Mixed infection (n = 7)	*P*-value
Hemoglobin (Hb) (11–15 gm/dL)	9.8 ± 3.2	10.8 ± 1.9	8.8 ± 2.3	0.358
Total leukocyte count (4,000–10,000/μL)	8,409 ± 3,900	6,466 ± 2,464	13,785 ± 9,368	0.020
Platelet counts (150,000–400,000/μL)	63,791 ± 72,480	81,555 ± 67,797	15,714 ± 9,655	0.133
Urea (10–45 mg/dL)	86.0 ± 60.7	67.6 ± 36.8	150.9 ± 139	0.075
Creatinine (0.4–1.4 mg/dL)	2.3 ± 1.85	2.13 ± 1.32	4.45 ± 5.7	0.176
Na^+ (136–149 mmol/L)	135 ± 6.6	132.8 ± 7.4	133.1 ± 5.6	0.621
K^+ (3.5–5.3 mmol/L)	7 ± 10.2	4.08 ± 0.91	5.4 ± 0.87	0.345
Cl^- (98–111 mmol/L)	92.7 ± 18.7	93.6 ± 9.4	98.3 ± 7.2	0.785
HCO_3^- (23–27 mmol/L)	14.8 ± 5.9	16.5 ± 3	9.4 ± 4.8	0.074
Total bilirubin (0.2–1.2 mg/dL)	3.0 ± 4	3.2 ± 3.8	15.3 ± 11.3	< 0.0001
Direct bilirubin up to 0.3 mg/dL	2.1 ± 3.4	2.2 ± 3	10.1 ± 6.8	0.002
Aspartate aminotransferase (5.0–40 IU/L)	101.2 ± 104.9	220.8 ± 143.8	113.1 ± 11.8	0.022
Alanine aminotransferase (5.0–40 IU/L)	87.3 ± 88.5	95.5 ± 62.3	62.7 ± 43.4	0.676
Alkaline phosphatase (40–129 IU/L)	135.3 ± 94	88.5 ± 64.5	252 ± 148.7	0.019
Albumin (3.2–5.5 g/dL))	2.7 ± 0.8	3.2 ± 0.6	2.4 ± 0.6	0.118
Total protein (6.0–8.3 g/dL)	5.9 ± 1.51	6.0 ± 1.1	5.08 ± 0.4	0.406

and seven (100%) of seven mixed infections (Table 2). Thrombocytopenia/low platelet count of < 150,000 was observed in 23 (95.8%) of 24 *P. vivax* infections compared with eight (80%) of 10 *P. falciparum* infections and seven (100%) of seven mixed infections (Table 2).

Acute renal failure (ARF)/acute kidney injury with altered serum creatinine levels of > 3 mg/dL was found in 18 (75%) of 24 *P. vivax* infections compared with six (60%) of 10 *P. falciparum* cases and five (71.4%) of seven mixed infections. There were no differences in these parameters between *P. falciparum* and *P. vivax* (odds ratio [OR]: 0.8; confidence interval [CI]: 0.2–2.6; *P*-value 0.71) (Table 3).

Acute respiratory distress syndrome exhibiting pulmonary edema and difficulty in breathing was found in 18 (75%) of 24 *P. vivax* infections compared with five (50%) of 10 *P. falciparum* infections and six (85.7%) of seven mixed infections (OR: 0.6; CI: 0.9–2.2; *P*-value 0.52) (Table 3).

Shock with systolic blood pressure of < 80 mm Hg was observed in 18 (75%) of 24 *P. vivax* infections compared with seven (70%) of 10 *P. falciparum* infections and three (42.8%) of seven mixed infections (OR: 0.9; CI: 0.2–2.9; *P*-value 0.90) (see Table 3).

The multi-organ dysfunction was observed in 21 (87.5%) *P. vivax* infections, six (60%) *P. falciparum* infections, and six (85.7%) mixed infections, with biochemical and radiographic evidence indicating involvement of more than two organs (OR: 0.6; CI: 0.2–2.2; *P*-value 0.52) (Table3).

CONCLUSION

The findings of this study are as follows: 1) Both *P. vivax* and *P. falciparum* infections are common in Mangaluru city and surrounding areas,[24] and severe *P. vivax* malaria is a significant health problem in this region. 2) Overall, the malaria case fatality rate is about 0.22%. 3) The rate of infections progressing to severe disease is similar to *P. falciparum* and *P. vivax* infection groups. This is consistent with the observed number of severe cases being higher in *P. vivax* than in *P. falciparum* infection, suggesting that severe malaria in vivax infection is substantial. In this region, it is likely that malaria fatalities, including those associated with comorbidity, are much higher than that reported here based on the records available from one major district hospital in Mangaluru city. This is because a significant number of infected people in this region and elsewhere in India do not go to hospital for diagnosis, and do not seek hospital admission when they are seriously ill and eventually die. Also, malaria cases that are treated at certain clinics and hospitals that eventually resulted

TABLE 3
Association between parasite species and clinical conditions in severe malaria cases treated at Wenlock Hospital in Mangaluru city

Clinical condition as per WHO criteria	Description	*Plasmodium vivax* (*n* = 24)	*Plasmodium falciparum* (*n* = 10)	Mixed infected (*n* = 7)	Odds ratio, confidence interval: *P. falciparum* vs. *P. vivax*	*P*-value
Impaired consciousness	Disorientation or confusion	20 (83.3%)	9 (90%)	6 (85.7%)	1.08, 0.3–3.1	0.880
Renal impairment (acute renal failure/ acute kidney injury)	Serum creatinine > 3 mg/dL	18 (75%)	6 (60%)	5 (71.4%)	0.8, 0.2–2.6	0.710
Pulmonary edema/acute respiratory distress syndrome	Respiratory distress and bilateral diffuse infiltrates on chest radiograph, O_2 saturation < 92% on room air with a respiratory rate > 30/min	18 (75%)	5 (50%)	6 (85.7%)	0.6, 0.9–2.2	0.52
Hemoglobinuria	Hb in urine	0	0	2 (28.5%)	–	–
Shock	Systolic blood pressure < 80 mm Hg	18 (75%)	7 (70%)	3 (42.8%)	0.9, 0.2–2.9	0.900
Multi-organ dysfunction	Biochemical and radiographic evidence of > 2 organs involvement	21 (87.5%)	6 (60%)	6 (85.7%)	0.6, 0.2–2.2	0.520

in death are not reported. Therefore, the malaria deaths are likely to be higher than the recorded numbers. This prediction is consistent with the report by Dhingra et al.[27] that the actual deaths due to malaria in India is nearly 14 times more than the reported numbers. 4) Finally, as observed in endemic regions outside of Africa, the proportion of malaria deaths in children in this area is considerably lower than those in adults. This observation is consistent with the previous findings that adults are more exposed to malaria and are also more vulnerable to severe disease.[28,29]

Regardless of infecting *Plasmodium* species, commonly observed clinical illnesses in malaria patients in Mangaluru region were cerebral malaria, metabolic acidosis, respiratory distress, ARF, liver dysfunction, thrombocytopenia, and multi-organ dysfunction. Although the number of cases analyzed was less and statistical analysis using large numbers of samples is needed to reach a definitive conclusion, the results of the present study suggest that fatal illness appears to be common in both *P. falciparum* and *P. vivax* infections in Mangaluru region. This scenario is not surprising given that many studies elsewhere that have carefully ruled out the possibility of co-infection with *P. falciparum* by using polymerase chain reaction-based diagnosis found that severe illnesses due to *P. vivax* infection are not as rare as it has been thought to be.[26–32]

A note of caution regarding the conclusion made previously regarding the extent of severe malaria cases that were attributed exclusively to *P. vivax* mono-infection is that because the diagnosis was based only on microscopy, coinfection with *P. falciparum* in some of the cases cannot be completely ruled out. In *P. falciparum* infection, the trophozoite- and schizont-stage–infected red blood cells are sequestered in microvascular capillaries of the brain and other organs and, thus, are usually absent in the circulation, leading to misdiagnosis. Although the ring-stage *P. falciparum*–infected red blood cells are likely to present in the circulation, a careful examination by highly skilled and specially trained experts is required to accurately identify parasite species. In addition, sensitive diagnostic methods such as rapid diagnostic tests and polymerase chain reaction will provide the exact extent of *P. vivax* mono-infection contributing to malaria fatality.

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