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Original Research Article

To Analyse the Clinical Characteristics of Falciparum, Vivax, and Mixed Infections of Malaria: A Retrospective Study

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Abstract

Aim: To analyse the clinical characteristics of falciparum, vivax, and mixed infections of malaria in a tertiary care hospital in Bihar, India.

Material and Methods: A retrospective study was conducted in the Department of general medicine, Netaji subhas medical college and hospital, Bihta, Patna, Bihar, India for one year .All adult patients (>15 years of age) admitted with the diagnosis of P. vivax malaria, P. falciparum, and mixed malarial infection. The diagnosis of malaria was made based on the detection of malaria parasites by conventional thick and thin peripheral blood films, stained with Giemsa stain, and rapid diagnostic tests (RDTs). The RDTs were based on the detection of specific Plasmodium antigen, lactate dehydrogenase. The Care Start™ malaria parasite lactate dehydrogenase/histidine-rich protein 2 (pLDH/HRP2) combo (Pf/Pv) test was used. It consists of a conjugate pad dispensed with two monoclonal antibodies, which are specific to pLDH of P. vivax and HRP 2 of P. falciparum.

Results: The most common species was vivax (62%), followed by falciparum (29%) and mixed plasmodium spp. (9%). The mean age of the patients was 34.23 ± 15.7 years. The predominant age group affected was between 21 and 40 years. There was no statistically significant difference in the age of cases in the uncomplicated or severe malaria. Males were predominantly affected, constituting 64.4%, while females were 35.6%. Fever (100%) was the most common symptom observed among the study population, followed by chills (73.4%), headache (48%), icterus (46.2%), vomiting (46%), abdominal pain (29%), decreased urine output (20%), and altered sensorium (16%), while pallor (60.9%) and splenomegaly (34.6%) were the common physical findings present in study participants. Comparison of different laboratory parameters between various types of malaria. In the present study, Hb was significantly lower in falciparum malaria as compared to vivax and mixed malaria and leukocyte count was significantly lower in mixed malaria as compared to vivax and falciparum malaria. However, no statistically significant differences were observed in other haematological and biochemical parameters. Presence of comorbid conditions was observed in a significant proportion (32%) of patients.

Conclusion: Malaria is still an important public health issue despite a consistent decline in its incidence. *P. vivax* is the plasmodium species which is responsible for most of the cases. Its potential to cause life-threatening illness is the cause of concern. The role of comorbid conditions in influencing the clinical outcome of malaria should be further explored.

Keywords: Clinical profile, Falciparum, Mixed, Vivax

Introduction

Malaria is a protozoan disease caused by infection with parasites of the genus plasmodium and transmitted to man by certain species of infected female anopheline mosquito. [1] Six species of the genus plasmodium cause nearly all malarial infections in humans. These are P. falciparum, P. vivax, two morphologically identical sympatric species of P. ovale (as suggested by recent evidence), P. malaria, and in Southeast Asia the Malaria monkey malaria parasite P. knowlesi. [2] World health organisation released latest world malaria report which was released on 19 November 2018 an estimated 219 million cases and 435000 deaths in 2017. Data from 2015-2017 shows that no significant progress in reducing global malaria cases was made in this period. [3] Between year 2000 and 2015, malaria incidence among population at risk decreased by 37% globally; during the same period malaria mortality rates among population at risk decreased by 60%. In 2016, there were estimated 216 million malaria cases, an increase of about 5 million cases over 2015. Deaths reached 445000,

similar number 2015. [4] Malaria continues to be major public health threat in India particularly due to Plasmodium falciparum which is prone to complications. In India about 21.98% population lives in malaria high transmission areas. About 91% of malaria cases and 99% of deaths due to malaria is reported from north eastern states Chhattisgarh, Jharkhand, Gujarat, Rajasthan, West Bengal and Karnataka and their states also vulnerable with local and focal out breaks of malaria and much of these areas are remote and inaccessible. [5] The malaria Incidence and deaths due to malaria have reduced significantly in recent years during the period 2000 to 2015, cases declined by 44% from 2.03 million to 1.13 million and deaths declined by 69% from 932 to 287 annually. Falciparum percentage remained around 50% from 2000 to 2013 but rose to 65.6% in 2014 and 67.1% in 2015 in India. [6] In 2017 total cases reported are 0.84 million and falciparum contributes to 63.39% with total deaths about 109.

Material and Methods

A retrospective study was conducted in the Department of general medicine, Netaji subhas medical college and hospital, Bihta, Patna, Bihar, India for one year. This study was conducted in all malaria-positive patients presented in outpatient departments admitted in the medical wards, high dependency and intensive care unit. written informed consent was obtained from all the study participants.

Inclusion Criteria

All adult patients (>15 years of age) admitted with the diagnosis of *P. vivax* malaria, *P. falciparum*, and mixed malarial infection. The diagnosis of malaria was made based on the detection of malaria parasites by conventional thick and thin peripheral blood films, stained with Giemsa stain, and rapid diagnostic tests (RDTs). The RDTs were based on the detection of specific *Plasmodium* antigen, lactate dehydrogenase. The Care Start™ malaria parasite lactate dehydrogenase/histidine-rich protein 2 (pLDH/HRP2) combo (Pf/Pv) test was used. It consists of a conjugate pad dispensed with two monoclonal antibodies, which are specific to pLDH of *P. vivax* and HRP 2 of *P. falciparum*.

National Vector Borne Disease Control Programme (NVBDCP) criteria for the definition of severe malaria were followed and all the patients were treated according to the NVBDCP guidelines which are the same as the WHO criteria.[6,7]

Clinical features of severe malaria

- Cerebral malaria as characterized by impaired consciousness or coma, convulsions, or both
- Acute respiratory distress syndrome (ARDS)
- Circulatory collapse (systolic blood pressure <80 mmHg)
- Jaundice in the setting of other organ dysfunction (serum bilirubin >3 mg/d)
- Haemoglobinuria
- Abnormal spontaneous bleeding.

Laboratory features of severe malaria

- Hypoglycaemia (blood glucose <40 mg/dl)
- Severe anaemia (haemoglobin [Hb] <5 g/dl, packed cell volume <15%)
- Metabolic acidosis (plasma bicarbonate <15 mmol/L or pH <7.35)
- Hyperlactataemia (lactate >5 mmol/L)
- Acute kidney injury (serum creatinine >3 mg/dl).

In all the patients, detailed history and demographic profile were recorded and general and systemic examination was done. Haematological and biochemical investigations were carried out which included complete blood count, erythrocyte sedimentation rate, highly sensitive C-reactive protein, blood glucose, liver function test, renal function test, serum electrolytes, urine examination, prothrombin time, procalcitonin, arterial blood gas analysis, blood and urine cultures, chest X-ray, and electrocardiogram. Cerebrospinal fluid analysis was G6PD screening test which was also done as required. Other specific tests, brain and abdominal imaging, were done as per the clinical judgment. Exclusion criteria comprised positive serology for dengue, leptospirosis, scrub typhus, typhoid, hepatitis B, hepatitis C, and HIV. All pregnant females were also excluded from the study.

Statistical Analysis

Data analyses were performed using SPSS for Windows, version 11.5 (SPSS, Chicago, IL, USA). Data were expressed as mean ± standard deviation or number and percentage. The normal data distribution was analysed with the Kolmogorov–Smirnov test. Baseline clinical parameters were compared between the subgroups by Chi-square or Student's test. $P < 0.05$ was considered significant.

Results

A total of 295 patients with peripheral smear and/or antigen-based RDT positive for *P. vivax*, *P. falciparum*, or mixed were observed in the study. The most common species was *vivax* (62%), followed by *falciparum* (29%) and *mixed plasmodium* spp. (9%). Demographics and clinical characteristics of all malaria cases of the present study are shown in Table 1. The mean age of the patients was 34.23 ± 15.7 years. The predominant

age group affected was between 21 and 40 years. There was no statistically significant difference in the age of cases in the uncomplicated or severe malaria. Males were predominantly affected, constituting 64.4%, while females were 35.6%. Fever (100%) was the most common symptom observed among the study population, followed by chills (73.4%), headache (48%), icterus (46.2%), vomiting (46%), abdominal pain (29%), decreased urine output (20%), and altered sensorium (16%), while pallor (60.9%) and splenomegaly (34.6%) were the common physical findings present in study participants.

Table 1 Demographics and clinical characteristics of malaria(*n*=295)

	Frequency (%)
Sex	
Female	105 (35.6)
Male	190 (64.4)
Clinical features	
Fever	295 (100)
Chills	217 (73.4)
Vomiting	134 (45.5)
Diarrhea	29 (9.9)
Abdominal pain	86 (29.2)
Headache	142 (48.1)
Pallor	180 (60.9)
Icterus	136 (46.2)
Convulsion	11 (3.8)
Altered sensorium	90 (30.4)
Shock	19 (6.4)
Decreased urine output	58 (19.6)
Splenomegaly	102 (34.6)

Table 2 depicts the comparison of different laboratory parameters between various types of malaria. In the present study, Hb was significantly lower in *falciparum* malaria as compared to *vivax* and *mixed* malaria and leukocyte count was significantly lower in *mixed* malaria as compared to *vivax* and *falciparum* malaria. However, no statistically significant differences were observed in other haematological and biochemical parameters. Presence of comorbid conditions was observed in a significant proportion (32%) of patients. The most common disease was type 2 diabetes in the study participants (n = 295), as shown in Table 3.

Table 2 Comparison of different laboratory parameters between different types of malaria

Characteristics	**Plasmodium falciparum (n=85)**	**Plasmodium vivax (n=183)**	**Mixed (n=27)**	**Total**	**P**
Hb (g/dl)	7.87±0.7	9.06±2.5	8.08±2.2	8.29±2.6	0.002
Total leukocyte count (/mm^3)	9476±7490	9038±5182	7514±4380	9157±6553	0.015
Platelet counts (/mm^3)	79768±54979	77771±60371	79230±62373	79036±57337	0.962
Blood glucose (mg/dl)	115.9±61.0	114.4±44.2	96.37±30.7	113.6±53.8	0.190
Serum sodium (mEq/l)	135.0±7.8	135.9±6.0	136.8±8.3	135.5±7.3	0.386
Serum potassium (mEq/l)	4.07±0.7	4.15±0.7	3.74±0.7	4.07±0.7	0.06
Serum urea (mg/dl)	84.01±71.7	76.34±54.5	61.77±49.1	79.44±64.6	0.261
Serum creatinine (mg/dl)	2.03±2.1	1.77±1.6	1.62±1.6	1.91±1.97	0.484
Serum bilirubin (mg/dl)	3.73±4.8	3.23±4.4	2.29±2.4	3.43±4.5	0.224
Alanine transaminase (IU/L)	124.07±154.6	108.85±95.8	61.57±40.2	113.06±131.0	0.131
Aspartate transaminase (IU/L)	101.14±157.0	74.57±73.5	61.87±39.4	88.60±127.4	0.264
Glucose (mg/dl)	68.22±17.3	67.88±15.5	77.75±15.3	69.29±16.3	0.33

Hb: Haemoglobin

Table 3 Prevalence of comorbidities(*n*=295)

Comorbid condition	Frequency (%)
Diabetes mellitus	26
Hypertension	9
Chronic kidney disease	8
Chronic liver disease	8
Malignancy	6

Out of all patients, 23% of patients had at least one component of severe malaria. Clinical characteristics and laboratory parameters of uncomplicated and severe malaria patients are described in Table Table4a4a and andb.b. Inflammatory markers were significantly higher in patients with severe malaria in addition to the prevalence of comorbidities, acute kidney injury, altered sensorium, anaemia, thrombocytopenia, and transaminitis. It was noted that nearly equal proportion of *P. vivax* and *P. falciparum* patients had severe malaria. None of the patients with mixed infection had severe malaria. Various manifestations and their prevalence in different species are summarized in Table 5. Severe anomia (Hb <5 mg/dl), thrombocytopenia (platelet count <1 lac/cmm), and acute kidney injury were significantly greater in patients with *P. vivax*. Superficial haemorrhages in the form of subconjunctival haemorrhage and gum bleeding were present in 2% of patients who required platelet transfusions and 8% were given packed red blood cell transfusions. Renal replacement therapy in the form of haemodialysis was given in 5% of patients.

Table 4a Clinical features according to the severity of malaria

Characteristics	Uncomplicated malaria (n=227)	Severe malaria (n=68)	P
Age (years)	32.8±12.6	40±8.4	0.01
Gender (male)	64	63.5	0.56
Fever	100	100	0.4
Headache	76	74	0.8
Vomiting	32	30	0.12
Abdominal pain	23	24	0.6
Altered sensorium	0	29	0.001
Decreased urine output	12	26	0.01
Presence of comorbidity	5	27	0.001
Pallor	42	66	0.001
Icterus	27	47	0.002
Hepatomegaly	31	32	0.5
Splenomegaly	33	30	0.4

Table 4b Laboratory parameters according to the severity of malaria

Characteristics	Uncomplicated malaria (n=227)	Severe malaria (n=68)	P
Hb	12.2±2.8	10.4±4.6	0.02
Total leukocyte count (cells/mm^3)	5100±2350	5600±3200	0.01
Platelet count (cells/mm^3)	89000±14000	52500±27000	0.001
Hs CRP	24±8	42±14	0.002
ESR	19±12	36±17	0.01
Total bilirubin	1.6±0.8	2.4±1.3	0.03
Alanine transaminase (IU/L)	46±12	58±14	0.04
Aspartate transaminase (IU/L)	42±11	56±12	0.01
Blood urea	27±7	42±11	0.001
Serum creatinine	1.2±0.6	1.8±1.0	0.02

ESR: Erythrocyte sedimentation rate, Hs CRP: High-sensitivity C-reactive protein, Hb: Haemoglobin

Table 5 Manifestations of severe malaria according to the *Plasmodium* species

Characteristics	Plasmodium vivax (n=47), n (%)	Plasmodium falciparum (n=21), n (%)	P
Coma	26	29	0.17
Shock	10	21	0.042
Respiratory distress/ARDS	8	16	0.01
Hb (<5 g/dl)	43.30	17	0.001
Thrombocytopenia (<100,000/mm^3)	67.0	48	0. 01
Hypoglycemia (<50 mg/dl)	2.70	1.8	0.56
Serum creatinine (>3 mg/dl)	34.50	12.30	0.01
Serum bilirubin (>3 mg/dl)	32.45	33.30	0.22
Multiorgan dysfunction	15	13.30	0.13

ARDS: Acute respiratory distress syndrome, Hb: Haemoglobin

Discussion

Malaria is a major public health problem, endemic in over hundred countries across the world. [8] The burden of malaria in India is complex because of the highly variable geographical and epidemiological profiles and transmission factors. Severe malaria is historically caused by *P. falciparum*, but it has been increasingly observed that *vivax* malaria and mixed infection malaria can also cause similar complications and death. [9] This is an important notable point that since there are no separate severity criteria exist for *P. vivax* malaria, criteria of severe malaria which were advocated for falciparum malaria, all parameters exept parasite severity index have been adopted for other plasmodium species as well. The WHO criteria for *P. falciparum* malaria which has been endorsed by NVBDCP also seems to be applicable for *P. vivax*. The present study had a similar proportion of *Plasmodium species* as reported by other authors from North India. The results are in accordance with the earlier findings in which *P. vivax* and *P. falciparum* were reported to be 56.5% and 39.1%, respectively. [10] Others have also observed a higher prevalence of *vivax* than *falciparum* in our country. [11] We had noted that maximum patients in the age group 21–40 years with male gender predominantly affected similar to other reports. [12] The possible explanation for both might be the greater outdoor exposure. Common clinical features such as fever, chills, headache, and abdominal complaints observed in the present study were the same as found in the other studies. [13] Splenomegaly was noted in 34% of all cases. Spleen enlargement occurs due to phagocytosis of parasitized red blood cells and their accumulation in the spleen for clearance. There was no statistically significant difference in splenomegaly in severe malaria and uncomplicated malaria. We observed that the patients with uncomplicated malaria and with severe malaria were present in equal proportions. This indicates that *P. vivax* is the most widespread infection in India which results in a profound morbidity. [11-15] In recent times, it has been reported that *P. vivax* has immense potential to cause life-threatening complications. [16] Exact pathogenesis and organ-specific morbidity caused by *P. vivax* infection remain unrecognized and poorly defined because of a paucity of research in this area. Out of different manifestations of severe malaria, cerebral malaria was observed in 26% and 29% of *vivax* and *falciparum* malaria.

Hyperbilirubinemia and multi-organ dysfunction were also not significantly different among the two species. These complications have been observed by other researchers.[17] Hyperbilirubinemia and cerebral malaria are believed to be due to sequestration of infected red blood cells in microvasculature of visceral organs.

Anaemia was a major clinical finding present in our study. Severe anaemia was noted in43% *vivax* malaria in comparison to 17% in *falciparum* malaria. In contrast, much lower counts for anaemia of around 13% and 3% for *P. falciparum* and *P. vivax*, respectively, were reported by Limaye *et al*. [18] which might be due to the severity of infection and the level of immunity against the parasite in patients of *falciparum* and *vivax malaria* and difference in endemicity. Poor nutrition and coexisting helminthiasis can aggravate anaemia in our patients, as reported by others. [19] *Plasmodium species* invade red blood cells and make them rigid and less pliable which get homolysed. Thrombocytopenia is another haematological parameter which was present in 67% and 48% of severe malaria patients, same as reported by others. [20-22] Thrombocytopenia is considered a sensitive marker of malaria. Mechanisms causing thrombocytopenia have been proposed as peripheral destruction, bone marrow alteration, and excessive removal of platelets by splenic pooling and antibody-mediated platelet destruction.

Acute renal failure is a common cause of morbidity and mortality in severe malaria. Acute kidney injury was significantly higher in patients with *vivax* malaria (34.5%) than *falciparum* malaria

(12%) cases. Similar results were recorded from the patients of other parts of the country. [23,24] High levels of parasitaemia, immune-mediated and hypoxic glomerular injury by the circulating parasites which causes inflammation and alters renal microcirculation are the probable mechanisms of acute kidney injury which is escalated by coexisting dehydration and hypotension in these patients. [25]

ARDS was observed in 8% *P. vivax* cases and 16% of *P. falciparum* cases. In other reports of India, it was 10% and 3%. [26] ARDS occurs due to sequestration of parasites in lung microvasculature. In *vivax* malaria, it has been postulated to be due to sequestration, cytokine-mediated injury, or nitric oxide production. [27] In the present study, it was noted that a significantly higher number of patients with comorbidities had severe malaria as compared to those who had uncomplicated malaria. This might be an indicator of the overall host immune status. There has been some evidence in literature which suggests that comorbidities, specifically obesity and diabetes, are risk factors for severe malaria in adults. [28] More evidence is needed to confirm this finding. Two patients in the present study died who had *vivax* malaria. They had Type 2 diabetes, multi-organ failure and secondary sepsis due to ventilator-associated pneumonia. One patient with *falciparum* malaria died as he had glioblastoma multiforme.

Conclusion

Malaria is still an important public health issue despite a consistent decline in its incidence. *P. vivax* is the plasmodium species which is responsible for most of the cases. Its potential to cause life-threatening illness is the cause of concern. The role of comorbid conditions in influencing the clinical outcome of malaria should be further explored.

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