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Original Research Article

A study of clinical profile of malaria with special reference to complications and outcome

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ABSTRACT

Background: Malaria has a wide clinical spectrum ranging from uncomplicated disease to a fatal one. The objectives were to study clinical profile of Malaria with special reference to its complications and outcome.
Methods: A prospective observational study was done in a tertiary care hospital including total of 300 patients diagnosed with *Vivax* or *Falciparum* Malaria. Data on patients' clinical details with investigations, complications, and outcome was recorded and analysed using SPSS version 17.
Results: Out of 300 patients, 179 had *Vivax* and 121 had *Falciparum* Malaria. Oliguria, high coloured urine, altered sensorium, convulsion, breathlessness, bleeding was more common in *Falciparum* malaria. Hypoglycaemia, thrombocytopenia, renal and hepatic involvement and ALI/ARDS were also more common in falciparum group. However, ALI/ARDS was more fatal in vivax group. Complications, outcome and biochemical parameters were correlated with parasite index and the correlations were statistically significant. Out of 22 deaths, 12 patients were from falciparum and 10 were from vivax group. Most common complication leading to death was ARDS/ALI, followed by AKI, convulsion, hepatic involvement and bleeding in decreasing order in both types of Malaria. Three patients with parasitic index <5% and 19 patients with parasitic index >5% died.
Conclusions: Clinical profile of Falciparum Malaria was more complicated. Metabolic complications with multi organ involvement, ALI/ARDS and mortality were more in Falciparum Malaria. Correlation of parasitic index with complications, biochemical parameters and outcome in both the groups was statistically significant.

Keywords: Complications, Malaria, Outcome, Parasitic index

INTRODUCTION

Malaria presents a major public health problem in the developing world owing to the high rates of morbidity and mortality.[1] According to the WHO estimates, released in September 2015, there were 214 million cases of malaria in 2015 and 438, 000 deaths. Malaria represents a medical emergency and without prompt and appropriate treatment it may rapidly progress to complications and death.[2]

Residents in temperate and sub-tropical regions of Asia and Latin America of all ages have low levels of naturally acquired immunity, and thus typically present with acute or severe disease to mild and more chronic infections, particularly in adult men.[3]

Malaria infections may cause vital organ dysfunction and death. Severe malaria which is caused mostly due to P. falciparum species is defined by clinical or laboratory evidence of vital organ dysfunction. The manifestations of severe malaria include: Unarousable coma/ cerebral malaria, acidemia/acidosis, severe normochromic normocytic anaemia, renal failure, pulmonary edema/ adult respiratory distress syndrome, hypoglycaemia, hypotension/ shock, bleeding/ disseminated intravascular

coagulation and convulsions. Other manifestations include haemoglobinuria, extreme weakness, hyperparasitaemia and jaundice.[4,5]

Compared to *P. falciparum* infection, *P. vivax* infection is much less likely to progress to severe malaria. Symptoms of severe vivax malaria are quite like those of severe *P. falciparum* malaria and can be fatal. Severe anaemia and respiratory distress occur at all ages, although severe anaemia is particularly common in young children.[5] There are very limited studies on Indian population describing the clinical profile, outcome and complications in malaria.

Objectives of the study were to study clinical spectrum and outcome of Malaria and to study the complications and their correlation with parasitic index.

METHODS

It was a prospective observational study for 18 months. Patients admitted in Medicine general wards and Medical Intensive care unit of tertiary care teaching public hospital. And study sample size was 300 patients.

Inclusion criteria

Patients of either gender above 18 years of age diagnosed with *Vivax* or *Falciparum* malaria on peripheral smear and admitted in hospital were included in study.

Exclusion criteria

Patients diagnosed with chronic liver, kidney/CNS disease, concurrent infections like dengue, leptospirosis, typhoid etc. and mixed malaria were excluded.

Study procedure

The study was initiated after obtaining the approval from the Ethics committee of hospital. The patients were selected based on the inclusion and exclusion criteria of the study protocol.

A detailed clinical history was taken. Thorough clinical examination was done. Patients were investigated and treated as per the protocol of hospital. The patients were followed up until their death or discharge from the hospital. The results were interpreted as per the history, clinical examination and investigation findings. All information about diagnosis on peripheral smear, type of infection, duration of hospital stay, laboratory investigations and patient outcome at discharge was recorded.

Statistical analysis

Qualitative data was represented in form of frequency and percentage. Association between qualitative variables was assessed by chi-square test with continuity correction for all 2X2 tables and without continuity correction in rest and Fischer exact test for all 2X2 tables, where p-value of chi-square test was not valid due to small count (E.g.-Association between vivax and falciparum cases and mortality). Quantitative data was represented using mean and median and IQR (Interquartile range). Analysis of Quantitative data between a qualitative variable with two subgroups was done using unpaired t-test if data passes 'Normality test' and by Mann-Whitney test if data fails 'Normality test' (e.g.-Comparison of day's admission between vivax and falciparum cases.

Results were graphically represented where necessary. SPSS version 17 was used for analysis of the data.

RESULTS

A total of 300 patients were divided into 2 groups, viz. Group A having 179 (60%) patients of vivax and Group B, having 121 (40%) patients with falciparum malaria. The mean ± SD age of the patients was 37±15 years. (Figure 1).

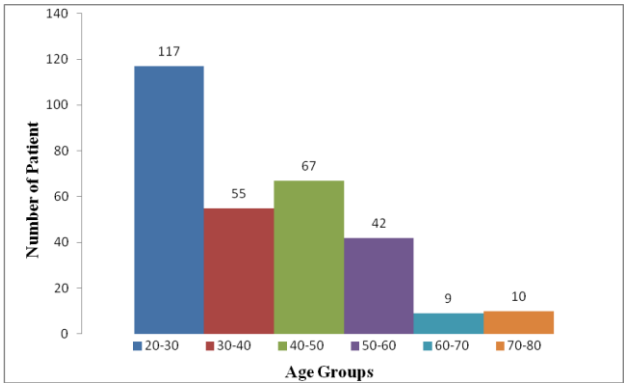

Figure 1: Age wise distribution.

There were 193 (65.67%) males and 103 (34.44%) females. Using binomial test, it was found that there were significantly greater number of males than females ($p<0.0001$).

Fever was reported in all 300 patients. Body ache was reported by 231 (77%) patients. Oliguria and breathlessness was seen in 24 (8%) patients. High coloured urine was reported by 32 (10.67%) patients. Bleeding was reported by 33 (11%) patients. Convulsions and altered sensorium was seen in 22 (7.33%) patients while loose motion was the least frequent complaint presented by the patients and was seen in only 1 (0.33%) patient.

The signs reported were pallor present in 13 (4.33%) patients, icterus in 24 (8%) patients, pedal oedema in 21 (7%) patients, petechiae in 27 (9%) patients, hepatomegaly and splenomegaly in 15 (5%) patients. There was a considerable difference seen between the presence and absence of signs in the patients diagnosed with malaria, most number of patients demonstrated the

absence of signs (p<0.0001). There were 169 patients with normal Hb levels and using binomial test, indicated that there was significantly greater number of patients who had normal Hb (p=0.0325). There were 222 patients with abnormal levels of WBC, the mean + SD of abnormal WBC was 6791 + 2670 per cu.mm. There were 221 patients with abnormal levels of platelets. There were 268 patients with normal levels and 32 patients with abnormal levels of total and indirect bilirubin. The mean + SD of abnormal total and indirect bilirubin levels was 5.43±1.23 g/dL and 2.022±0.62 g/dL respectively.

SGOT and SGPT were abnormal in 33 patients. The mean + SD of abnormal SGOT and SGPT was 408.45±182.56 IU/L and 538.21±192.57 IU/L respectively. Alkaline phosphatase (ALP) was normal in 269 patients. Prothrombin time (PT)/ INR was abnormal in 33 patients. Random blood sugar (RBS) was abnormal in 25 patients with the mean + SD of 104.6±38.2 mg/dL. The mean + SD of abnormal serum creatinine of 5.04±1.15 mg/dL was seen in 30 patients. Abnormal level of blood urea nitrogen (BUN) with the mean + SD of 56.38±14.34 mg/dL was seen in 29 patients. Serum sodium was abnormal in 29 patients with the mean + SD of 134.52±2.43 mEq/L. Serum potassium was abnormal in 30 patients with the mean + SD of 4.85±0.54 mEq/L. Using binomial test, indicated that there was significantly greater number of patients having abnormal levels of the aforementioned parameters (p<0.0001).

The ABG characteristics was reported to be normal in 255 (85%) of the cases while 45 (15%) cases presented with hypoxia/metabolic acidosis. It was noted that significantly greater number of patients showed normal urine. Chest X-ray findings showed B/L fluffy shadows in 18 (6%) patients. All 300 patients had sinus tachycardia and no other abnormal findings on ECG. The USG findings were found to be normal in 281 (95.25%) patients 11 (3.73%) patients demonstrated hepatosplenomegaly. CT-brain was done in 37/300 patients, it was normal. CSF examination was done in 23/300 patients, it was normal. Schizonts were present in all 300 patients' peripheral smear; RMA test detected 179 (59.67%) patients of *P. vivax* while 121 (40.33%) patients of *P. falciparum*.

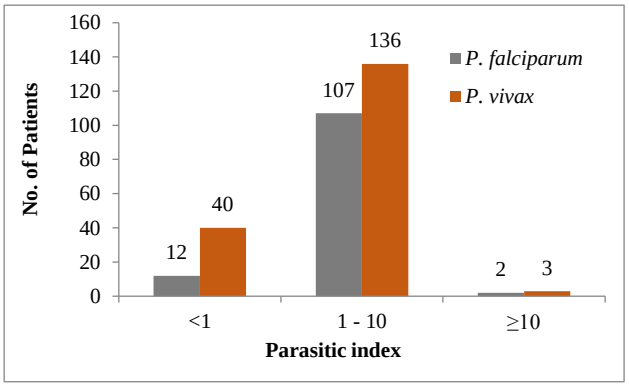

Figure 2: Parasitic index.

Out of the 179 patients belonging to group A, 40 (22.35%) patients had a parasite index (PI) of <1, 136 had a PI of 1-10 and 3 had a PI of >10. Amongst 121 patients belonging to group B, 12 (9.92%) patients had a PI of <1, 107 (88.43%) had a PI of 1-10 and 1 (1.65%) had a PI of >10 (Figure 2).

Table 1: Ventilator support.

Ventilator support	*P. falciparum*	*P. vivax*	P value
Required	18	13	0.0452 (using Chi Square test)
Not required	103	166	
Total	121	179	

Thirteen patients from group A compared to 18 patients from group B required ventilatory support. The difference in 2 groups was statistically significant using a Chi square test (Table 1). There were 10 deaths in group A compared to 12 in group B (Figure 3).

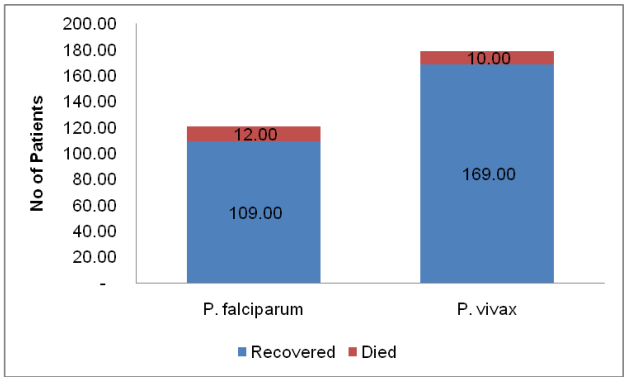

Figure 3: Outcome.

Outcome was better with *Vivax* malaria as compared to Falciparum malaria. Both the groups were comparable for anemia, leucopenia and thrombocytopenia. Hepatic involvement was significantly greater in *falciparum* group. (p=0.0069). Number of patients with raised INR was significantly greater in Falciparum group (p=0.0005). Renal involvement in the form of Acute Kidney Injury (AKI) was not statistically different among the males and females of both the groups. Though pulmonary involvement in the form of ALI or ARDS was more in *falciparum* group, the difference was not statistically significant (Table 2).

Table 2: Pulmonary involvement.

Parameter	Group B (%)	Group A (%)	P value
No. of patients with ALI/ARDS	13 (10.74)	5 (2.79)	0.0516 (using Fisher's exact test)
No. of patients with no ALI/ARDS	108 (89.25)	174 (97.21)	

Out of 13 patients with pulmonary involvement in *falciparum* group, 5 patients survived. However, mortality due to pulmonary involvement in *vivax* group was 80% as compared to 61.53% in *falciparum* group. There were 106 patients from *falciparum* group with neurological involvement in the form of altered sensorium whereas only 7 patients from *vivax* group had altered sensorium. Convulsions were observed in 15 from *Falciparum* as compared to 7 from *vivax* group and the difference was statistically significant.

PI of <5% was observed in 152 patients in *vivax* as compared to 58 in *falciparum* group. PI of >5% was observed in 63 patients in *falciparum* group as compared to 27 patients from *vivax* group. Only 3 patients with PI of <5% died whereas 19 patients with PI of >5% died from both the groups. Higher PI was associated with more mortality and this finding was statistically significant (Table 3).

Table 3: Association of parasitic index with deaths.

Parasitic index (PI)	Group B (%)	Group A (%)	P value (using chi-square test)	Patients died
<5%	58	152	<0.0001	3
>5%	63	27	<0.0001	19
Total patients	**121**	**179**		**22**

When we looked at the clinical profile of patients who died, it was observed that bleeding and hepatic involvement were not seen in any patient of *vivax* group. It was also noted that some patients in *falciparum* group had more than one complication. There was statistically significant association of various parameters like ARDS, AKI, leucopenia and Thrombocytopenia with mortality.

PI of both groups was correlated with various parameters. The correlation coefficient was calculated using Spearman's correlation coefficient (SCC). In *vivax*, there was a significant low negative correlation between PI and platelets (SCC=-0.2086, p=0.0051), significant intermediate correlation (p<0.0001) between PI and SGOT (SCC=0.3518), SGPT (SCC=0.3518), total bilirubin (SCC=0.3281), BUN (SCC=0.3225) and TLC (SCC= 0.5008).

In *falciparum* group, there was a significant high negative correlation between PI and platelets (SCC=-0.7561, p<0.0001), significant intermediate correlation (p= 0.0002) between PI and SGOT (SCC=0.3516), SGPT (SCC=0.3516), total bilirubin (SCC=0.3548), BUN (SCC=0.4633) and TLC (SCC=0.2797). There was a significant moderate positive correlation between PI of *falciparum* and bleeding tendency, occurrence of conclusions, presence of altered sensorium and hypoxia/metabolic acidosis (p<0.0001).

There was a significant intermediate positive correlation between PI and bleeding tendency, convulsions, altered sensorium, ARDS for both the groups.

DISCUSSION

Worldwide, an estimated 300-500 million people contract malaria each year, resulting in 1.5-2.7 million deaths annually. Thus, malaria remains a devastating global health problem.[2] The first symptoms of malaria, common to all the different malaria species, are nonspecific and mimic a flu-like syndrome. Although fever represents the cardinal feature, clinical findings in malaria are extremely diverse and may range in severity from mild headache to serious complications leading to death, particularly in falciparum malaria. As the progression to these complications can be rapid, any malaria patient must be assessed and treated rapidly, and frequent observations are needed to look for early signs of systemic complications.[6]

The mean ± SD age of the patients was 37±15 years. The mean age of the patients reported by Nand N et al, was 32.7±14 years.[6] The age wise distribution reported in a study by Muddaiah M, et al was 65.6% s between 15-30 years, 14.65% between 31-40 years, 9.23% between 41-50 years, 5.73% between 51-60 years, 3.82% between 61-70 years and 0.95% patients between 71-80 years.[7] These reports were somewhat similar to our study; the difference seen may be due to the difference in the study area.

There were 193 (65.67%) males and 103 (34.44%) females. It was found that there was significantly greater number of males than females. In a study by Nandwani S et al there were 55% males and 45% females, these were comparable to present study.[8]

Clinical features reported by Rajkumar A et al were more or less comparable to our study.[9] Another study by Nand N et al reported the presenting clinical features that included fever (100%), body aches (45%), headache (55%), diarrhoea (10%), dark urine (10%), altered sensorium (46.6%), and oliguria (11.6%). These reports were more or less similar to our study.[6] The temperature reported by Nandwani S et al in patients with malaria was 38.49±1.27ºC; this was more or less similar to present study.[8]

A study by Muddaiah M et al reported that there were 14.73% patients with icterus, 11.5% with pallor, 15.7% with splenomegaly, 13.6% with hepatomegaly, and 13.6% with hepatosplenomegaly. These reports showed a higher percentage of patients with the presenting signs.[7]

There was significantly greater number of patients who had abnormal levels of CBC, LFT, RFT parameters. However, there are a few published data on the number of patients with normal and abnormal levels of the laboratory parameters. It was demonstrated that significantly greater number of patients had normal ABG. Nayak KC et al reported that metabolic acidosis/hypoxia was reported in 7% patients, the percentage of patients was less as compared to present study.[10]

In 2012, Rajkumar A et al reported 11% patients with high coloured/dark urine which was similar to this study.[9] Nayak KC et al reported that there were 11% patients with abnormal chest X-ray findings.[10] These findings were more or less similar to this studies. Muddaiah M et al reported that there were 15.7% with splenomegaly, 13.6% with hepatomegaly, and 13.6% with hepatosplenomegaly.[7] Present study reported less percentage of patients with hepatomegaly, splenomegaly and hepato-splenomegaly.

In a study by Singh G et al 62.5% patients were infected with *P. vivax* and 25% were infected with *P. falciparum*. The reports were comparable to present study.[11] There are very few studies reporting the parasitic index in *P. falciparum*.

In a study by Rajkumar, the parasitic load in patients infected with *P. falciparum* group was 0-5% in 5 patients, 6-10% in 7 patients, 11-20% and >20% in 2 patients each, while for the P. vivax group was 0-5% in 22 patients, 6-10% in 4 patients, 11-20% in 1 patient, while no patients had a parasitic load of >20% in the *P. vivax* group. This reports somewhat differed from this study, this may be due to the sample size, difference in study population and area.[9] There is little published data available that reports the number of patients that require ventilator support in patients.

There is very little published data available that reports the recovery and death in the patients infected with P. falciparum and *P. vivax*. In a study by Gupta NK, there were 76.9% patients with in the *P. vivax* group and 77.78% patients in *P. falciparum* group who were detected with thrombocytopenia.[12] These results differed from present study which showed no significant difference between the two groups.

In a study by Jadhav UM et al reported the WBC count in the patients infected with *P. vivax* and *P. falciparum* which was 15.5% and 10.7% respectively for WBC count of <4000 and 1.7% vs 6.8% for WBC count >11000. Also a significant difference in the WBC count was seen between the two groups.[13] These results contradicted our study; this may be due to the difference in the endemic area and study population. In a study by Basawaraj G et al, there were 22.2% patients in the *P. vivax* group and 47.2% patients in the *P. falciparum* group who had serum creatinine >3mg%.[14] There was a significant difference between the two groups. This difference may be attributed to the fact that all cases of malaria including the mixed type were included in their study.

There are very few literatures available that reports and compares the hepatic involvement in patients belonging to the *P. vivax* group and *P. falciparum* group. In a study by Shiva Kumar BG et al there were 8% patients reported from each of *P. vivax* and *P. falciparum* group with raised ALP levels. These reports were similar to this study.[15] There are no studies which report the INR in *P. vivax* and *P. falciparum* infected patients.

In a study by Basawaraj G et al, there were 5.45% patients reported with hepatomegaly and 42.7% patients reported with splenomegaly.[14] The percentage of patients with hepatomegaly was comparable to this study while there were more patients diagnosed with splenomegaly. Basawaraj G et al reported that there were 50% patients in the *P. falciparum* group while there were no patients in the *P. vivax* group who were reported to have ARDS.[14] There were less number of patients with ARDS in both the groups as compared to present study. There are no studies that report the number of deaths in patients diagnosed with either *P. vivax* or *P. falciparum* with pulmonary involvement.

Using Fisher's exact test indicated that the proportion of patients with altered sensorium was significantly greater in P. falciparum group (p=0.0069). The results from a study by Shivakumar15 were similar to this study. There are no studies which report the incidence of convulsions for *P. vivax* and *P. falciparum*. Nayak et al reported similar findings in parasite index as compared to present study.[10] There are no studies available to our knowledge that analyses and compares the clinical symptoms and laboratory parameters in patients infected either with *P. vivax* or *P. falciparum*. There are no studies to our knowledge that report and compare the incidences of the clinical profile of both groups of malaria and their PI.

This was a prospective observational study conducted to study the clinical profile of malaria with special references to complication and outcome in Indian population. Present study has a limitation of a small sample size, although the data was being prospectively collected to further describe the evolving pattern of severe malaria at our centre. However, this study will help to form the basis for similar studies in the future.

CONCLUSION

The present study highlights the clinical profile of malaria caused by *P. falciparum* and *P. vivax*. The comparison of clinical parameters between these two

species of Plasmodium showed no significant difference in the clinical and laboratory parameters. Several studies have reported that *P. falciparum* is a complicated malaria involving multisystem organ failure. However, in this study even *P. Vivax* malaria was associated with fatal complications. The drawback of the study was the small sample size and shorter study duration. Thus, there is a need of prospective studies with bigger sample size to find out any changing trends over years.

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