Study of Clinical Profile of Hospitalized Patients Diagnosed With Malaria

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Abstract :

Introduction : Malaria is a major health problem in India, predominantly caused by *Plasmodium vivax* and *Plasmodium falciparum*. The proportion of *P.vivax* to *P.falciparum* infection & the intensity of malaria transmission vary in different parts of India Objectives: We conducted this study of clinical profile of patients with *P.vivax* and *P.falciparum*, to study the diversity of features between the two and to see the clinical response to treatment. **Materials and Methods :** We studied 51 indoor patients who presented between June 2013 and November 2013 at a tertiary care level hospital. Malaria was confirmed by smear examination or Rapid Diagnostic Test (RDT). **Results:** *P.vivax* was the predominant species (78.43%). Most patients (90.19%) had up to grade 2 parasitemia. Most of the patients were in the 11-30 years age group. All patients had high grade fever followed by vomiting, nausea and headache. Splenomegaly was the commonest presenting sign followed by pallor. Moderate anemia was observed in 82.75% patients. The degree of anemia did not correlate with the infecting species. Thrombocytopenia was more severe in patients with *P.falciparum* malaria as compared to patients with P.vivax, when the cut off value of 50000/µl was considered. (62.5% vs 30%). Leucopenia was observed in 62.5% patients of *P.falciparum* vs. 32.5% of *P.vivax* patients. **Conclusion :** There was no case of severe malaria and no mortality in our study. All the patients responded well to standard therapy as per WHO guidelines and there was no early clinical failure observed.

Key words: Anemia, Leucopenia, Malaria, Parasitemia, Thrombocytopenia

Introduction :

Malaria is an endemic disease in India and a major health problem affecting 95% of the population residing in endemic zones. 20% of population residing in tribal, hilly and inaccessible areas consists of 80% of malaria patients. 564 deaths have been reported to health ministry of India in 2014 out of a total of 1.1 million total cases. Out of these, 65.5% of reported cases were of *P.falciparum*. It has been observed from the data that the incidence & prevalence of P. falciparum cases is subsequently increasing over the years. [1]

The proportion of *P.vivax* to *P.falciparum* varies in different parts of India. Also, the intensity of malaria transmission varies between states and from season to season. In India, 22% of people live in high transmission areas, 67% live in low transmission areas and 11% live in areas where there is no malaria.[2] Also contrary to the mistaken belief, that *P.vivax* presents as benign malaria, there is growing evidence that *P.vivax* can also present as complicated malaria.[3]

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Materials and Methods :

The aims of the present study were to study the clinical profile of patients presenting with *P.vivax* and *P.falciparum* malaria and to compare the diversity of clinical features and outcome between *P.vivax* and *P.falciparum* malaria. The clinical response of the treatment given to patients presenting with malaria was also judged. This was a retrospective, cross-sectional, observational study which was approved by the Institutional Ethics Committee of the concerned hospital. 51 patients of malaria, comprising of both P. vivax and *P.falciparum* infection were studied from the period of June 2013 to November 2013, as indoor patients. All patients underwent a routine complete blood count (CBC) and a peripheral smear examination for detection of malarial parasites on admission (Day 0). Some patients who had negative peripheral smears at the outset were subjected to rapid antigen detection tests. Patients with confirmed malaria by smear or RDT were included in the study. All patients were above 15 years of age. Apart from this, blood urea, serum creatinine, serum bilirubin and alanine transaminase

(ALT) were done in every patient. All patients were subjected to a repeat peripheral smear examination and CBC on the third day of admission (Day 3) to judge parasitological and hematological response to the antimalarial treatment started (on Day 0). Blood urea, serum creatinine, serum bilirubin, ALT was repeated when deemed necessary. Urine routine microscopy examination and S. widal was done on an individual case basis when found necessary. We divided our patients into five groups according to their platelet counts on admission. The groups were made as per NCI Common Terminology Criteria for Adverse Events version 3.0. [4]

Accordingly, patients were divided into five groups as follows:

Grade 0: Patients with normal platelet count of more than 1,50,000/µl

Grade 1: Patients with platelet count between 75000-1,50,000/µl

Grade 2: Patients with platelet count between 50,000-75,000/µl

Grade 3: Patients with platelet count between 25,000-50,000/µl

Grade 4: Patients with platelet count less than 25,000/µl

All patients were given treatment as per WHO guidelines according to the species identified.[5] Patients were said to have complicated or uncomplicated malaria as per WHO guidelines.[5] Patients with *P.vivax* were initiated with chloroquine unless the patients also had concomitant *P.falciparum* infection. All patients with *P.falciparum* were given Artemisin derivative combination therapy (ACT) in injectable form which was followed up with oral therapy as soon as the patient was stable.

Data of all patients was analyzed using SPSS version 20 software. Statistical tests of percentages, student's t-test of dependent and independent means, Spearman's rank correlation and chi square tests were employed as found appropriate.

Results :

Out of 51 patients, 29(57%) were males and 22(43%) were females. The median age of presentation was 35 years. Majority of patients, 26 out of 51 were between the age group of 15 and 30 years. There were only four patients between the age group of 61 to 80 years. There was no patient above the age of 80. The average duration of illness was 4.35 days, ranging from 2-15 days.

Table 1 : Presenting symptoms of malaria

Symptoms	n=51*(%)
Fever	51(100)
Vomiting	13(25.49)
Nausea	8(15.68)
Headache	7(13.73)
Abdominal pain	6(11.76)
Diarrhoea	4(7.84)
Giddiness	4(7.84)
Breathlessness	2(3.92)

* - Multiple responses

As shown in table 1, all patients had high grade fever followed by vomiting, nausea and headache as presenting complaints. Vomiting was present in 13 patients followed by nausea in 8 and headache in 7 patients. Only two patients had breathlessness but they had normal X-rays with rest of the respiratory parameters like saturation and respiratory rate being unaffected.

All patients were admitted to the ward and none of the patients needed ICU care subsequently also. Five patients had concomitant symptoms of urinary tract infection which was confirmed by urine routine micro examination. Pallor was present in 9 patients. Spleen was palpable in 10 patients. Three patients had icterus on presentation.

Out of all patients, 40(78.43%) patients had *P.vivax* malaria, 8 (15.68%) patients had P. falciparum malaria and 3 (5.88%) were found to have both. Two of smear negative patients were found to be positive for P. vivax by the rapid test. Out of 40 patients of *P.vivax* malaria,16 (40%)patients were found to have grade 1 parasitemia and 16(40%) patients had grade 2 parasitemia. Peripheral smears of 3(7.5%) patients of P. vivax showed occasional parasites and 3(7.5%)

patients of *P.vivax* had grade three parasitemia. Out of 8 patients with P.falciparum infection, 4 (50%) had grade 1 parasitemia, 3 (37.5%) had grade 2 parasitemia and 1(12.5%) had grade 3 parasitemia.

The mean Hb of males in the study was 11.26 gm/dl and that of females was 10.60 gm/dl. The difference was not statistically significant (p=0.28). 21 patients, 10 males and 11 females had moderate anemia defined as hemoglobin between 8.0-10.9 gm/dl. 3 patients had severe anemia defined as Hb less than 8.0 gm/dl, out of which two were females and one was a male. Out of the patients having severe anemia, 1 patient had P. vivax malaria, 1 had mixed infection and 1 patient had P. falciparum malaria. Two patients, one with P. vivax malaria and one with P. falciparum malaria required packed cell transfusions due to anemia.

Table 2 shows the mean hemoglobin, platelet and total leucocyte counts in *P.vivax* and *P.falciparum* malaria on presentation. It also demonstrates the significance between the difference in the means of hemoglobin, platelet and total leucocyte counts in *P.vivax* and P.falciparum malaria on presentation. The p-values here have been calculated using the unpaired t test between various hematological parameters of *P.vivax* and *P.falciparum* malaria.

As it is evident from table 2, mean Hb of patients with *P.vivax* infection was 11 gm/dl and that of patients with P. falciparum, was 11.13 gm/dl. We did not find any significant statistical association between severity of anemia and the type of infection (p=0.06).

Mean platelet count in *P.vivax* and P. falciparum patients was 79,225/µl and 40,900/µl, respectively.

Table 2: Comparison of hematological parameters between P.vivax and P.falciparum on presentation

Species/Hematological parameters	Hemoglobin gm/dl		Platelet count /µl		Total leucocyte count /µl	
	Mean	SD	Mean	SD	Mean	SD
P.vivax	11	1.79	79,255	39,984.93	4,778	1,801.86
P.falciparum	11.13	3.18	40,900	31,402.82	3,700	1,608.9
P-value	0.06		0.01		0.27	

Table 3 : Relationship between the parasitic grade and various hematological parameters

Hematologic parameters/parasitemia grade		Occasional	Grade 1	Grade 2	Grade 3	'p' value	r_s*
Hb g/dl	<8.0	0	0	2	0	0.70	-0.15
	8.0-10.9	1	9	6	2		
	>10.9	2	6	6	2		
	Normal	0	5	4	0		
Platelets /µl	>1,50,000	0	1	0	0	0.07	-0.24
	75000-1,50,000	0	9	9	0		
	50,000-75000	0	2	4	1		
	25,000-50,000	3	5	4	1		
	<25000	0	1	1	2		
Total WBC /µl	<4000	3	6	7	3	0.15	-0.14
	>4000	0	13	12	4		

* - Spearmann's rank correlation coefficient.

Table 4: Difference between various hematological parameters on day 0 (on day of presentation) and day 3

Statistical parameters	Hemoglobin g/dl		Total WBC count /µl		Platelet /µl	
	Day 0	Day 3	Day 0	Day 3	Day 0	Day 3
Mean	10.96	10.22	4627.84	5322.15	71827.45	119176.47
SD	2.13	2.06	1794.09	2000.37	40026.27	43077.93
t- value	5.48		3.07		7.35	
p-value	<0.00001		0.003		<0.00001	

On applying the appropriate statistical tests we found that there was a statistically significant association between the type of infection and the platelet count (p=0.01). Mean leucocyte count was 4,778/µl and 3,700/µl respectively, for *P.vivax* and P.falciparum patients. We however, did not find a statistically significant association between the infecting species and the presence of leucopenia (p=0.27).

We tried to find a correlation between the grade of parasitemia and the hematological parameters of hemoglobin, platelets and leucocyte counts using the Spearman's rank co-efficient. The corresponding p-value was derived from the Spearman's rank coefficient value (r_s) and was also separately derived using the chi square test. An inverse correlation was noted between hemoglobin levels and parasitic grade (r_s= -0.15). However the grade of parasitemia had no significant correlation with the severity of anemia (p=0.70). We also found an inverse correlation of the grade of parasitemia with platelet count (r_s = -0.24) and leucocyte count (r_s = -0.14). However this correlation was also not significant as shown by the p- values of platelet count (p=0.07) and leucocyte count (0.15). In inference, although all hematological parameters showed a negative correlation with the grade of parasitemia, they were not significantly affected by the parasitic grade.

In Table 4, mean hemoglobin, mean WBC count and mean platelet count have been shown on Day 0, the day of presentation and Day 3. The difference of means between these various hematological parameters on Day 0 and Day 3 was calculated using the paired t-test and the significance was derived from the t-value.The mean Hb on presentation of patients was 10.96 gm/dl and 10.22 gm/dl after treatment. The drop in Hb by 0.74 gm/dl after successful treatment of malaria was found to be statistically highly significant (p<0.00001).

Mean total WBC count on presentation was 4,627.84/µl which rose to a mean total count of 5,322.15/µl after treatment. The difference was statistically significant with p=0.003. Mean platelet levels on presentation were 71,827.45/µl. The mean platelet level rose to 1,19,176.47/µl after successful treatment with antimalarials. We found this difference in means to be statistically highly significant at p<0.00001. Five patients had an elevated bilirubin level, out of which four patients had P. vivax and one had P. falciparum. One patient was found to have cirrhosis of liver. No significant association of serum bilirubin was found with the grade of parasitemia (chi square 3.23, p=0.35) or type of parasitemia (chi square 0.04, p=0.83). Independent elevation of ALT without elevation of bilirubin was found in 2 patients. Elevated serum creatinine was found in only one patient with *P.falciparum* grade 3 (S.creat 1.6). Rest all patients had normal creatinine levels.

Thrombocytopenia was observed in all but 3 cases. All three patients with normal platelets had *P.vivax* malaria. All falciparum patients and those with mixed infection had thrombocytopenia. Mean platelet levels on presentation were 71,827.45/µl. 3 out of 8 (37.5%) falciparum patients had platelet counts less than 10,000/µl while only one out of 40 (2.5%) vivax patients had a similar platelet count. 62.5% (5 out of 8) of P.falciparum patients had platelet count less than 50,000/µl while only 42.5%(17 out of 40) of P. vivax patients had such a platelet count. One of three (33.3%) patients of mixed infection had a platelet count less

than 50,000/µl. About half (55%) of all patients had platelet counts in the range of 50,000-1,50,000/µl. None of the patients suffered from any kind of bleeding diathesis. Mean platelet count in *P.vivax* and P. falciparum patients was 79,225/µl and 40,900/µl, respectively. We however did not find significant statistical association between the platelet count and the grade of parasitemia. (Chi square 19.87,p=0.07).

Leucopenia was observed in 19 patients (37.25%). Mean leucocyte count was 4,778/µl and 3,700/µl respectively, for *P.vivax* and *P.falciparum* patients. Only one patient, having P.falciparum malaria had leucocytosis. It was observed in 5 out of 8 patients with *P.falciparum* malaria (62.5%) and 13 out of 40 patients with *P.vivax* (32.5%). 1 of 3 patients (33.3%) with mixed infections had leucopenia. There was no statistically significant association between the grade of parasitemia and the leucocyte count.(chi square 5.17,p=0.15) (Table 3) All our patients were smear negative on day 3 of diagnosis, having responded to treatment given as per WHO guidelines. We did not encounter any case of early treatment failure in our study, as defined by WHO. [5]

Discussion :

Small sample size and being a single centre study were the limitations of our study. Most of the patients we had were that of *P.vivax* malaria (78.43%) and they were cured with standard antimalarial therapy. *P.vivax* is the major species found in the state of Gujarat as per NVBDC data.[1]. Our data is also consistent with studies of Srivastava et al, Joshi et al, M.Muddaiah et al, Shelat V et al and Vishwanath K et al. [6 - 10] World-wide in other than African subcontinent, *P.vivax* happens to be the predominant species.[11] In our study, 25 out of 51(49%) patients were between 11 to 30 years age group(Lowest age was 15 years but this range considered for statistical analysis). Most other studies had the age groups between 21-30 years, having maximum patients. [7 - 10] In all these studies, there was a predominance of the younger population. [7 - 10]

There were more males 29(57%) in our study as compared to females 22(43%). However the male-female difference was not much compared to other studies. Other studies had a higher number of male patients as compared to females. [8, 9] However in the age group having the maximum number of patients we observed a higher number of males (68%) than females (32%). The high infectivity in males might be explained on the basis of the fact that males are more mobile and involved in outdoor activities and they also readily seek medical aid. [9] Anemia of moderate to severe variety was observed in 24 patients (82.75%). More percentage of females as compared to males were affected (54.5% vs. 41.3%). Several mechanisms have been implicated for the causation of anemia in patients of malaria. Accelerated RBC removal by the spleen, obligatory RBC destruction during parasite schizogony and ineffective erythropoiesis are some proposed mechanisms.[12,13] Severe anemia requiring transfusion is usually found in P. falciparum malaria but can also occur with *P.vivax* malaria.[5] In our study, three patients had severe anemia. Out of these, one had *P.vivax*, one had P.falciparum and one had mixed infection.

The difference in mean Hb levels between patients of *P.vivax* and *P.falciparum* were not found to be significant in our study which was consistent with the findings of Ranjini CY et al. [14] Hence, in our study it is difficult to say whether severe anemia occurs in *P.falciparum* alone. We also found a mean drop of 0.72 gm/dl in Hb on day 3 when a repeat CBC was carried out. The mean drop in Hb was found to be statistically significant. In malaria, the rate of development and the degree of anemia vary enormously. The Hb concentration may fall upto 2 gm/dl per day. Bone marrow dyserythropoiesis may last for days or weeks following acute malaria. Loss of unparasitized erythrocytes may also contribute to acute anemia following a single episode of uncomplicated malaria.[15] A drop in mean Hb concentrations, similar to our study was also found in a study conducted by Gonzales et al, where they showed a significant fall in mean Hb at day 8 of illness as compared to day 0.[16] In uncomplicated malaria, in low transmission settings anemia resolves slowly; the nadir of hematocrit is usually around one week after starting antimalarial treatment.[15] In P.falciparum malaria initially the hematocrit may be normal but may subsequently fall even after initiating anti-malarial therapy. In *P.vivax* infection the fall in Hb is attributed to parasitic activity. There is marked erythrocytic destruction at the beginning of infection, and their number may not return to pre-infection level till weeks even after

successful anti-malarial treatment.[3] This might explain the fall in mean Hb after antimalarial treatment in our study.

Thrombocytopenia was an important feature in our study. Thrombocytopenia is also considered to be commonly present in *P.falciparum* malaria but as studies show that it usually an equally important feature of *P.vivax* malaria also. [17,18,19] In our study, all but three patients had platelet counts less than 150000/µl. However when the cut off was taken as 50000/µl, 62.5% patients with P.falciparum malaria vs. 42.5% patients with *P.vivax* malaria had a platelet count less than 50000/µl. Overall 32 out of 51 (62.74%) patients had a platelet count of < 50000/µl. We found the association of species with the development of thrombocytopenia to be statistically significant in our study. This is consistent with the study conducted by Patel A et al, Ranjini CY et al, Khan et al and Jadhav et al.[13,14,18,20] We also found an inverse correlation between the parasitiemia grade and the platelet count, however it was not statistically significant. Kochar et al and Alfonzo Rodriguez et al also did not find an association between platelet count and parasitic grade in their study.[17,21] Bleeding was not observed in any of our patients who had thrombocytopenia even when the platelet count was as low as 10,000/µl. Thrombocytopenia in malaria is well tolerated. Platelet activation and enhanced hemostatic responses by hyperactive platelets are proposed mechanisms of few bleeding episodes despite significant thrombocyto penia in malaria patients. [22]

Several mechanisms are proposed for the development of thrombocytopenia in malaria in *P.falciparum* including sequestration of injured platelets by spleen as a result of immune complexes generated by malarial antigens.[10,13] Abnormalities in platelet structure and function have also been implicated and platelet invasion by the malaria parasite is also a suggested mechanism.[10] However, no particular mechanisms have been proposed for thrombocytopenia in *P.vivax* patients.[13] Also the occurrence of thrombocytopenia in vivax malaria needs further evaluation.[11]

There was a significant increase in mean platelet count on day 3 in our study which was also found in studies conducted by Gonzales et al and Taylor et al.[16,23] Leucopenia was observed in 37.25% of our patients. Both *P.vivax* and P.falciparum malaria patients were found to have leucopenia Leucopenia in malaria is thought to be due to localization of leukocytes away from the peripheral circulation and to spleen and other marginal pools and not due to depletion.[13] Leucocytosis in malaria is in fact associated with a poorer prognosis. In our study, 32.5% of *P.vivax* patients, 62.5% of *P.falciparum* patients and 33.3% patients with mixed infections had leukocyte counts less than 4000/µl. This shows that leucopenia is more prevalent with P.falciparum malaria. However, this difference was not found to be statistically significant. Two studies performed by Ranjini CY and Jadhav U et al also did not show any statistically significant association between total leucocyte count and the infecting plasmodium species.[14,24] Also the grade of parasitemia did not correlate with the decrease in leukocyte count statistically as demonstrated in a study conducted in western Thailand.[25]

An increase in mean leucocyte count was seen on day 3 in our patients which was statistically significant. Similar findings were demonstrated in studies conducted by Gonzales et al and Taylor et al. [16, 23] 90.19% patients had up to grade 2 parasitemia which as per one study might be associated with low transmission intensity in that area. [11] The same study also had a high prevalence of uncomplicated malaria as in our study. [11] The reason for this might be early presentation, prompt diagnosis and early institution of effective treatment as well as variable degrees of clinical immunity.[11]

Conclusion :

In conclusion of our study, hematological features of leucopenia and thrombocytopenia are important features of both types of malaria however thrombocytopenia is more significantly associated with *P.falciparum* infection. Fortunately in our region, *P.vivax* remains sensitive to chloroquine. The few cases of *P.falciparum* in our study were sensitive to standard ACT therapy. We did not have any mortality in our study and no patients had complicated malaria. The parasitemia in most cases was of moderate variety. Also RDT's might have a definitive role in diagnosing malaria that have negative peripheral smears with strong clinical suspicion. They help in early diagnosis and treatment when smears are negative and may prove useful in preventing the severity of disease.

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