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Original Research Article

A Study ON Clinical Presentation and Outcome of Malaria from an Underreported, P.vivax Predominant Region of North India.

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Abstract: P. falciparum is the most prevalent and dangerous species causing malaria worldwide. But in contrast to this P. vivax, known to cause benign malaria infection is the commonest species in our region (Uttar Pradesh) and is treated mainly with chloroquine. However in recent years many researchers have come up with the conclusion that P. vivax is changing its clinical pattern and has complications similar to P. falciparum. Due to paucity of studies from our region, poor health infrastructure and to know the present scenario of P. vivax clinical spectrum in our region we conducted a comparative study between different species causing malaria in our region. All febrile adult patients (> 18 years of age) admitted in medicine department, were tested for malaria parasites. Total 387 patients of malaria were enrolled who met both inclusion and exclusion criteria. Frequencies of alterations in clinical, biochemical parameters and outcome were determined in various plasmodium species. Data was analysed using appropriate statistical tests. Out of 387 patients, 297 were P. vivax, 54 were P. falciparum, and 36 were mixed infection. The complications seen in vivax malaria were: severe thrombocytopenia (39.4%), ARDS (15.33%), Hyperbilirubinemia (22.2%), AKI (12.3%), severe anaemia (21.21%), bleeding (6.06%), cerebral malaria (9.04%), seizure (3.03%) and death (3.5%). In our region also P. vivax is emerging to cause Severe and fatal malaria. Further molecular research, status of chloroquine sensitivity and clinical studies is required in the state to understand emergence of severe malaria in vivax mono-infection.
Keywords: Malaria, Plasmodium Falciparum, P. vivax, severe malaria, Comparative study, severe malaria, North India.

INTRODUCTION

Malaria is a potentially life-threatening parasitic disease caused by parasites known as Plasmodium vivax, Plasmodium falciparum, Plasmodium malaria and Plasmodium ovule. According to the latest estimates from WHO, there were 214 million new cases of malaria worldwide in 2015 (range 149–303 million). The African Region accounted for most global cases of malaria (88%), followed by the South-East Asia Region (10%) and the Eastern Mediterranean Region (2%). Among South East Asia region, India shares two-thirds of the burden (70%) followed by Myanmar (16%) and Indonesia (10%) (1). In India, the most common and deadliest species is P. Falciparum contributing to 66% of the total malaria cases in 2014 which is closely followed by P. Vivax.[1]. At present, official figures for malaria in India, available at NVBDCP [2] indicate 1.4 million confirmed cases and 561 deaths in 2014.[2].

The high mortality rate from P. falciparum is due to its ability to induce severe malaria, and in some cases, multiple organ dysfunction. The presenting symptoms and mortality patterns of severe malaria vary widely according to the geographical setting and therefore transmission intensity. Though P. vivax was considered a benign parasite compared with P. falciparum, recent research indicates patients with severe P. falciparum and P. vivax develop similar disease manifestations both in adults [4-9] and children [10-11]. Cho Naing *et al.;* in his study - Is Plasmodium vivax Malaria a Severe Malaria? A Systematic Review and Meta-Analysis concluded that the incidence of Severe malaria in patients infected with P. vivax was considerable [14].

Complications like cerebral malaria, anaemia, renal failure, ARDS, shock, bleeding/ DIC are usually

seen with falciparum Where as newer studies reveal that vivax is also associated with severe hepatic, acute kidney injury, respiratory, bleeding complications, cerebral malaria, seizures, thrombocytopenia[14-21].

Against a background of reports on severe malaria and the fact that there is not much information on malaria from this region, this comparative study between falciparum, vivax, and mixed infection, on the basis of their demographic characters, clinical Spectrum, biochemical Profile and outcome was planned among adults in a tertiary referral center in Kanpur, India.

MATERIAL AND METHODS

Setting and selection criteria

This was a cross sectional study conducted in the K P S Institute of Medicine, GSVM Medical College, Kanpur from July 2015 to Nov 2015.

Inclusion criteria:

All Febrile adult (>18yrs) patients admitted in the department were screened for malaria and those positive for P. vivax and/or P. falciparum were included in the study.

Exclusion criteria:

Following patients were excluded from the study: pregnant females, patients with age less than 18 yrs, Bacterial and viral meningitis, HIV/HBsAg positive patients, abnormal liver function test due to hepatotoxic drugs or any other cause, abnormal renal function test in acute or chronic renal failure due to any other cause, bleeding diathesis.

Malaria diagnosis

Malaria was diagnosed, and the species and number of parasites determined on Giemsa –stained thick and thin peripheral blood films examined under oil immersion. A slide was considered negative when there were no parasites in the 100 high power fields. Each blood film was reviewed by two experienced microscopists.

Clinical and laboratory assessment

After the diagnosis, Clinical evaluation was done by a physician. The patient demographics and clinical details were recorded in a standard proforma. These included name, age, sex, address, symptoms and signs of the patients. Other standard evaluation included assessment of blood pressure, axillary temperature, systemic examination and description of the other general examination of the patients. Complications and outcome of every patient was also noted. A complete blood count, RBS, liver function test, renal function test, serum electrolytes, USG- abdomen, were done in all patients.

Statistical Analysis

Data was compiled using Microsoft Excel. Percentages, proportion were calculated. χ^2 was used as test of significance.

RESULTS

A total of 387 malaria patients were admitted in the medicine department of GSVM Medical college, out of these 297 (76.74%) were positive for P. vivax, 54 (13.95%) were positive for P .falciparum and 36 (9.30%) patients were positive for both P. falciparum and P vivax. 270 (69.76%) malaria cases were males and 117 (30.24%) were females. Majority 144 (37.50%) malaria cases were from 21 to 30 years of age group followed by 90 (23.25%) cases in 11-20 years age group. Similar trend was seen in all the three groups.

Table1: Distribution of cases based on age and sex in our study

Age group	Males	Females	Total	%	P.vivax	%	P. falciparum	%	mixed infection	%
10-20 yr	72	18	90	23.25	72	24.24	9	16.5	9	25
21-30yr	108	36	144	37.5	99	33.33	18	33.5	27	75
31-40yr	18	9	27	6.9	18	6.06	9	16.5		
41-50yr	45	9	54	13.95	54	18.18				
51-60yr	9	18	27	6.9	27	9.09				
61-70yr	9	18	27	6.9	9	3.03	18	33.5		
71-80yr	9	9	18	4.6	18	6.07				
total	270	117	387	100	0	0	0	100	0	100
% sex	69.76	30.24		0						

	P.vivax	P.falciparum	Mixed infection	Probability
Males	216	36	18	0.017 (Not Significant)
Females	81	18	18	

Patients included in the study were from 10 districts of Uttarpradesh. Majority of the Patients 126 (32.22%) were from the Kanpur district followed by Fatehpur 81 (20.93%) as shown in the Fig-1.

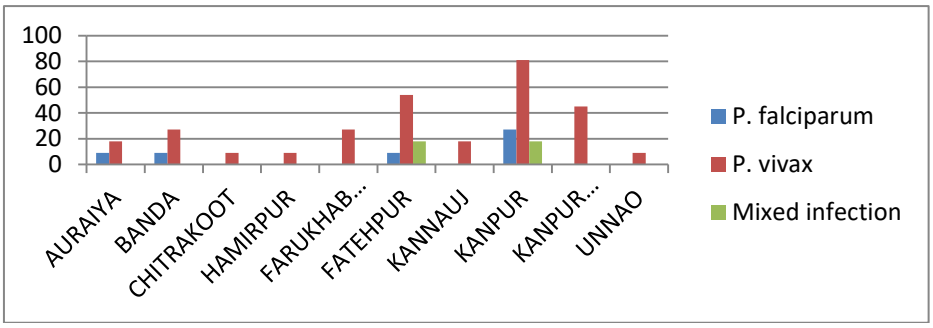

Fig 1: Distribution of cases based on their residence.

Table 2: Distribution of cases based on their residence

	P.vivax	P. falciparum	mixed infection	Probability
URBAN	90	36	18	0.00001 (Significant)
RURAL	207	18	18	

144 (37.02%) malaria cases were from urban area and 243 (62.79%) were from rural areas. Of the three groups, majority cases of P. vivax 207 (69.69%) were from rural area while in P. falciparum group majority cases 36 (66.66%) were from urban areas whereas in case of mixed infections rural to urban area patients were in the ratio of 1:1.

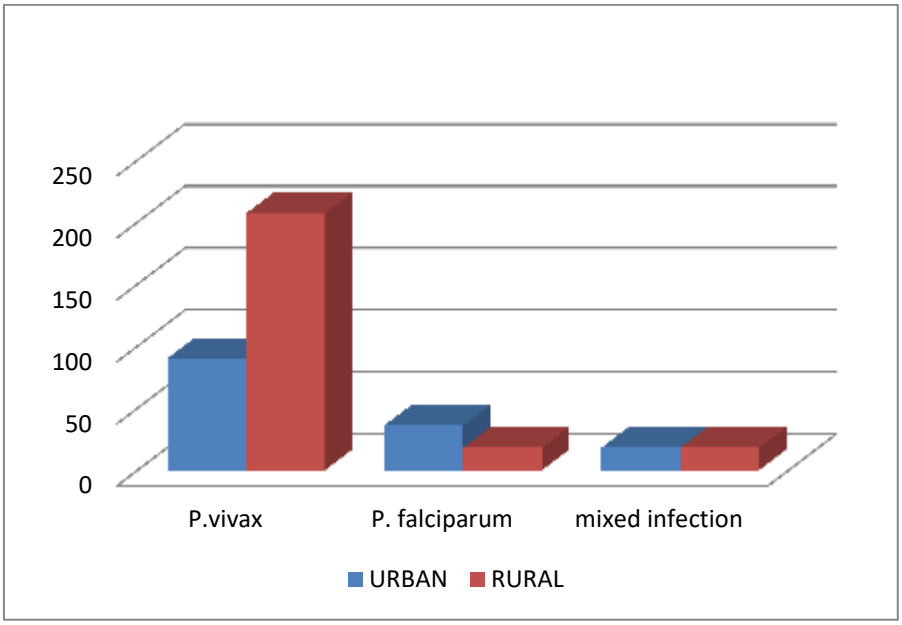

Fig 2: Showing distribution of cases based on urban and rural areas in our study.

Out of 387 malaria patients fever was present in all patients (100%) followed by chills and rigor in 75.12% and pallor in 52.71% of total patients. Fever was the chief presentation in all the groups [P vivax malaria – 297(100%), P falciparum – 54(100%), mixed infection 36(100%)] with a mean duration of 8.76 days.

Chills and rigor was most common in patients with mixed infection 30(83.33%) whereas it was similar in patients with P. Vivax 225(75.75%) and P. falciparum 36 (75%). Pallor was most common in P. vivax group 162 (54.3%) followed by P. falciparum 27(50%) and mixed infection 15 (41.5%). Generalized body ache symptom was presenting complaint in 33.33% mixed infection patients followed by 27.77% cases of P. falciparum and 18.3% p. vivax positive patients.

Out of 387 patients, Nausea and vomiting was observed in 96(24.08 %.) patients. It was most common in patients with mixed infection 18(50%) whereas it was equally present in P. vivax (66[22.3%])) and P falciparum (12[22.22%]) patients.

Table 3: Distribution of cases based on symptoms and signs in our study

		P.vivax (n=297)		**P.falciparum (n=54)**		**Mixed infection (n=36)**	
		No.	%	No.	%	No.	%
FEVER		297	100	54	100	36	100
CHILLS/RIGOR		225	75.75	36	75	30	83.33
PALLOR		162	54.3	27	50	15	41.5
GENRALIZED BODY ACHE		54	18.18	15	27.77	12	33.33
ABDOMINAL SYMPTOM AND SIGN	Nausea/Vomiting	66	22.3	12	22.22	18	50
	Pain abdomen	81	27.27	15	27.7	9	25
	loose stools	15	5.05	6	11.11	0	0
	Jaundice	66	22.3	3	5.55	18	50
	Hepatomegaly	54	18.3	12	22.22	9	25
	Spleenomegaly	27	9.32	3	5.55	6	16.6
BLEEDING	malena	6	2.02	0	0	3	8.3
	hematuria			3	5.55	0	0
	puerpura	6	2.02	3	5.55	0	0
	hematemsis	3	1.01	0	0	0	0
	epistasix	3	1.01	0	0	0	0
CNS	Headache	72	24.24	9	16.66	27	75
	Cerebral malaria	27	9.09	6	11.11	6	16.6
	Seizure	9	3.03	0	0	0	0
RESPIRATORY DISTRESS		45	15.33	15	16.66	9	25

Pain in abdomen was present in 105(27.13%) of total patients. It was present in 81[27.32%], 15(27.7%)] and 9(25%) patients of P. Vivax, P falciparum, mixed infection respectively.

Out of total patients, 19.37% had hepatomegaly and 9.03% splenomegaly. Of the three groups hepatomegaly was present maximum in mixed infection (25%) followed by P. falciparum (22.22%) and then P. vivax group (18.3%). Similarly Splenomegaly was also present maximum in mixed infection (16.6%) but followed by P Vivax group (9.32%) and then P. falciparum (5.55%).

Bleeding in the form of malena, purpura, epistasix, hematemsis and purpura was present in 11.1% patients of p. falciparum followed by cases with mixed infection (8.3%) and P. vivax (6.06%)

Diarrhoea was observed in 5.4% of the total cases. It was more common in P. falciparum malaria (11.11%) followed by P vivax (5.05%).

Headache was among chief complaint in 27.9% of our total malaria cases. It was present in 75% Patients with mixed infection followed by P. vivax (24.24%) and P falciparum (16.6%) cases.

10.07% of total patients had cerebral malaria. It was more common in mixed infection (16.6%) followed by 11.1% and 9.09% in P. falciparum and P. vivax malaria respectively. Out of these 9 patients of P vivax 3 patients had convulsions.

Breathlessness was more common with mixed infection (25%). It was seen in 16.6% and 15.33% patients of falciparum and vivax malaria respectively.

Laboratory parameters:

Table 4 shows various haematological abnormalities in different plasmodium species. Out of 387 total malaria cases, severe anaemia (i.e. haemoglobin <7mg %) was seen in 90(23.25%) patients. Severe anaemia was seen in 22.22% cases of P. falciparum, 21.21% cases of P. vivax cases, and maximum 25% cases with mixed infection.

Table 4: Hematological parameters of cases in our study

Hb		**P.vivax (n=297)**		**P. falciparum (n=54)**		**Mixed infection (n=36)**		Probability
		No.	%	No.	%	No.	%	
	<7mg/dl	63	21.21	12	22.22	15	25	
	7.0 - 10 mg/dl	99	33.33	15	27.7	6	16.6	
	>10mg/dl	135	45.3	27	50	21	58.33	0.0831
PLATELETS	<20000	27	9.2	0	0	0	0	
	20000 - 50000	90	30.2	6	66.66	9	25	
	50001- 100000	81	27.2	36	5.55	18	50	
	100001 - 150000	54	18.19	3	83.32	6	16.66	.00001
	>150000	15	15.21	9	16.68	3	8.34	
		Mean	SD	Mean	SD	Mean	SD	
Duration of fever		9.46	3.88	10.33	5.95	6.5	3.1	
TLC		7582.5	4465.2	7850	5535.1	9650	3323.4	
Neutrophil		64.35	13.62	64.25	15.56	69	12.72	
Lymphocyte		32.47	14.35	31.5	15.02	27.5	12.02	
Eosinophil		2.8	0.61	3	0.81	2.5	0.7	
Monocyte		1.65	0.48	1.5	0.57	1.5	0.7	

Out of 387 patients, 330 patients (i.e.85.27%) had thrombocytopenia (platelet count <150000/µL). It was present in 83.32% patients with P. falciparum, 84.79% patients with P. vivax malaria and 91.6% patients with mixed infection. Thrombocytopenia was more common with mixed infection group but moderate to severe thrombocytopenia(<50000) was most commonly seen among P vivax cases(39.4%) while platelet count between 50000 – 100000 was mostly seen in P. falciparum patients (66.66%). There were no other important differences in the haematological profile.

Of the total malaria cases 31.78% patients had raised serum bilirubin levels. It was more common in mixed infection group (41.66%) followed by P. vivax (33.5%) and P. falciparum (16.6%) cases.

Out of total 387, 77 patients (59.63%) had elevated levels of ALT and AST. 108 patients (27.9%) had ALT levels between 41-120 IU/L, and141 (31.78%) patients had ALT levels >120 IU/L. It was more deranged in P. vivax malaria (63.3%). It was seen in 50% and 41.6% patients of falciparum malaria and mixed infection respectively.

Table 5: Biochemical parameters in our study

		P.vivax (n=297)		**P. falciparum (n=54)**		**Mixed infection (n=36)**		
		No.	%	No.	%	No.	%	Probability
S. bilirubin	Normal(<1mg/dl)	198	66.5	42	77.7	21	44.4	
	Raised(1- 3 mg/dl)	33	11.11	8	14.8	15	41.66	0.000045
	>3mg/dl	66	22.2	4	7.04	5	13.88	
SGPT	Normal(10 - 40 u/l)	108	36.3	27	50%	12	33.3	
	Raised(41 - 120 u/l)	90	30.3	9	16.66	9	25	
	>121 u/l	99	33.3	18	33.33	15	41.6	0.1783
total raised		189	63.3	27	50%	24	41.6	
SGOT	Normal(10 - 40 u/l)	117	39.3	24	44.44	15	41.6	
	Raised(41 - 120 u/l)	117	39.3	18	33.33	9	25	
	>121 u/l	63	21.35	12	22.22	12	33.33	0.34866
Total (Raised)		180	60.65	30	55.55	21	58.33	
ALK PO4	Normal	99	33.5	36	75	27	75	
	Raised(>147iu/l)	198	66.5	18	25	9	25	0.00001
S. creatinine	Normal(0.5 - 1.5mg/dl)	234	78.78	33	61.11	21	58.33	0.0032
	Raised(1.5 - 3mg/dl)	27	9.09	12	22.2	9	25	
	>3mg/dl	36	12.3	9	16.6	6	16.6	

156 (37.2%) patients had AST levels between 40-120 IU/L, and 87 (22.48 %) patients had AST levels >120 IU/L. It was more deranged with P. vivax malaria (60.65%) It was seen in 58.33% and 55.55 % of patients with mixed infection and falciparum malaria respectively.

Acute kidney injury is suspected when oliguria is present and confirmed if serum creatinine is higher than 3.0mg/dl. Out of total 387 patients, 51 (13.17%) patients had serum creatinine > 3 mg/dl. Acute kidney injury was seen in 16.6% cases of both P. Falciparum and mixed infection while it was seen in 12.3% cases of P. vivax.

Out of total 387 patients, 18 (5.42%) expired. Maximum mortality was seen in mixed infection group (16.6%) followed by P. falciparum group (11.11%). It was least in P. vivax group (3.5%).

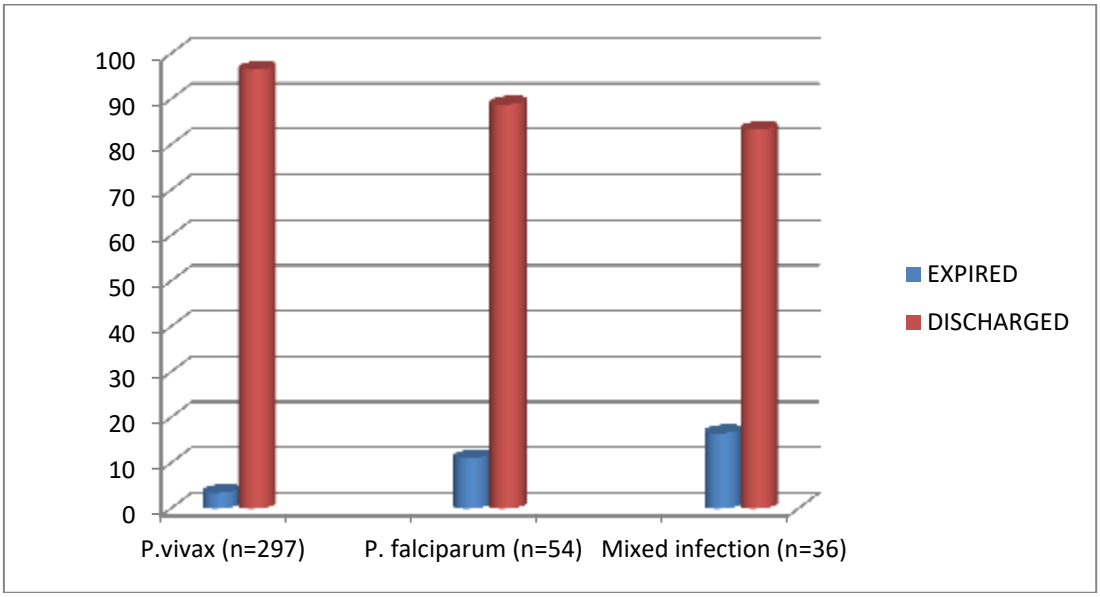

Fig 3: Showing No: of cases discharged/expired in our study.

DISCUSSION

We studied 387 diagnosed cases of malaria between July 2015 to November 2015. The most frequently implicated species was P vivax accounting for 76.74% while P. falciparum accounted for 13.95% and mixed infection for 9.30% of total cases. Our findings are supported by the data of NVBDC 2015 which reported the presence of only 351(0.85%) P .falciparum cases out of total 41264 malaria cases in Uttar Pradesh, the state where our institution is situated. But at national level (India) according to WHO report 2015 P. falciparum contributed 66% of total cases and according to NVBDC 65.55% of the total malaria cases in 2014. It is followed by P. vivax [1-3]. This indicates that P. vivax is the most widespread infection in Uttarpradesh [2, 22] which results in a pronounced morbidity. Species composition varies within the same country having different ecological condition with different types of breeding places and vectors. Recently, it had been reported that P. vivax also can cause life threatening complications and even death [14, 19, 20].

In our study, the male: female ratio was 2.3:1. This finding is similar to studies conducted by Muddaiah *et al.;* Gauravi Mishra *et al.;* Jadhav UM *et al.;* Bashawri LAM *et al.;* [23-26]. High infectivity in the male population has been attributed to high mobility and outdoor activities in contrast to females who are usually better clothed than men.

In the study conducted by Farogh A *et al.;* Muddaiah *et al.;* and Umm e Asha et al, majority of patients belonged to the age group of 21 -30 years[27, 23, 22]. In our study too, the age-wise distribution showed that the maximum number of patients were in the age group 21-30 years followed by 11-20 years, indicating that this is most active age in which maximum exposure could take place. Our finding further strengthens the fact that working group is predominantly affected, because this is the group which is exposed to mosquito bites especially in fields and outdoor. The study follows the age pyramid of our country; the base of age pyramid is formed by young people and apex by the older age group which constitutes lesser percentage of population.

In the present study it was observed that P. vivax infection was more common in rural areas where as P. falciparum cases were more common from urban areas as shown in graph no. Majority of the patients (32.66%) were from Kanpur district (place where the tertiary hospital is based) because of easy accessibility

where as 67.44% hailed from nearby 9 districts. Poor Health services in these areas needs to be developed, so that with the help of adequate vector control measures, active surveillance and efficient primary health care system- malaria transmission, severe morbidity and mortality of this disease can be reduced in this part of India.

Symptom analysis of all the patients showed that fever was the commonest symptom (100%) in all the cases with mean duration of 8.76 days. This was followed by chills and rigor (75.12%), Headache (27.9%), Pain abdomen (27.13%), Nausea and vomiting (24.08%), generalized body ache (20.93%). These findings are in accordance with several studies [23, 27, 28]. Diarrhoea an uncommon finding was seen in 5.05% of the total cases. Similar findings were observed in a study form bundelkhand and Mumbai [28, 30]. In both these studies diarrhoea was reported more in P falciparum cases.

As far as General physical signs are concerned 204 (52.71%) cases had pallor and 87 (22.48%) had Icterus. Systemic examination revealed splenomegaly in 36 (9.03%) and hepatomegaly in 75 (19.37%) patients.

Pallor as in many studies (Taksande *et al.;* Vinayak V Shela *et al.;*) [31, 7] is the commonest physical sign in our study too. We observed anaemia in 54.3% of p. Vivax, 50% of P. falciparum and 41.6% of mixed infection cases. In contrast to our finding much lower counts for anaemia of around 29.3%, 20.5% and 18.1% for P. Falciparum, P. Vivax and mixed infection respectively, were recorded from bundhelkhand [28]. Considering WHO criteria for severe malaria which is Hb < 7mg/dl for adults, severe anaemia was present in 90 (21.70%) cases. Kochar *et al.;* [32] in his study documented increased incidence of severe anaemia from (5.83%) in 1994 to 26.04% in 2004. Among different groups severe anaemia was present in 12(22.22%) cases with P. Falciparum infection, 63(21.21%) cases with P. vivax infection, and 9(25%) cases with mixed infection. Higher rates of severe anaemia have been reported in P. falciparum (39% and 60% respectively) and lower rates in P. vivax cases (15% &19% respectively) in patients of Aligarh and Saudi Arabia [22, 33] . Vidhan Jain *et al.;* in his study from central India reported that out of 22 cases of severe p. Vivax, severe anaemia was present in 32% cases [34]. Our study favours the concept that p. Vivax is no more benign. In contrast, much lower counts for severe anaemia of around 13% and 3% for P. falciparum and P. vivax, respectively, were recorded from Mumbai [9]. This variation might be due to the severity of infection and the level of immunity against the parasite in patients of falciparum and vivax malaria in different countries having endemic and non-endemic pockets. Severe anaemia may be due to red blood cell destruction, phagocytosis of non-parasitized red cells, increased splenic clearance, and dysery thropoiesis in bone marrow.

Of the total 387 patients hepatomegaly was present in 19.37% and splenomegaly in 9.03%. hepatomegaly was more common in P. falciparum group (22.22%) followed by P. vivax group (18.3%) whereas spleenomegaly was more common in P. vivax patients (9.32%) as compared to P. falciparum patients. one of the postulated reasons for this could be due to high incidence of relapses and chronic infection in P. vivax infection. Proportion of cases with splenomegaly is less in our study compared to others [37, 18], much higher rate of splenomegaly (71%) was recorded in falciparum malaria from the other parts of India [34] and Saudi Arabia [38, 39]. However these variations might be due to differences in the immune status of patients from different malaria transmission regions.

Thrombocytopenia (platelet count < 150000/µL) was the most common complication (85.25%) in our study. This value is similar to study by Faseela *et al.;* [41] (82.77%). Thrombocytopenia was seen more frequently in mixed (91.66%) and vivax infections(84.79%) than in falciparum infections(83.32%) as has been reported by Gupta *et al.;* [41] and other studies[42-43]; this is consistent with our findings. [42, 44]. Whereas studies from other part of India show higher percentage of thrombocytopenia in P. falciparum than P. Vivax patients [22,7]. Variations in values might be due to drug resistance and endemicity, as drug resistant parasites survive longer in their host and do more damages resulting in thrombocytopenia [45]. In our study severe thrombocytopenia (PLT < 50000) was associated more with P. vivax infection (30.2%) as compared to mixed infection (25%) and P. falciparum (11.11%). The elevated figure of thrombocytopenia in P. vivax infection showed that this species is also moving towards malignancy.

Bleeding is not uncommon in malaria [58]. Patients with mixed infection had the maximum bleeding manifestation followed by P. falciparum group. In our study, we found that signs of hepatic dysfunction were more frequent in cases of P falciparum, but that elevated liver enzymes were more frequent in P vivax. Of the total patients

One third cases had mild liver dysfunction (ALT & AST levels [41 – 120 Iu/l] was present in 27.9% and 37.2% respectively) whereas almost similar number of patients had moderate to severe liver dysfunction (ALT & AST levels > three times normal i.e. >121IU/L was present in 34.1% and 22.48% respectively). Mild liver dysfunction was majorly present in P. vivax cases while

severe liver dysfunction was predominantly seen in mixed infection cases. But overall elevated liver enzymes were found maximum in 60% of P. Vivax group. Other Studies from India (44, 11) also showed a lower percentage of patients with P. vivax had signs of hepatic dysfunction. Whilst previous studies (47, 11) have shown that there is an increase in liver enzymes in vivax cases. Hepatic dysfunction has been also described in 20–58% of patients with vivax malaria in Bikaner and Mumbai [44, 46].

The major complication of severe malaria include cerebral malaria, pulmonary edema, acute renal failure, severe anaemia and/ bleeding. Acidosis and hypoglycaemia are the two most common metabolic complications. Any of these complications can develop rapidly and progress to death within hours or days.

Table 6: Complications of malaria in our study

severe malaria						
	P. vivax (n=297)		P. falciparum (n= 54)		Mixed Infection (n=36)	
	No.	%	No.	%	No.	%
severe anaemia	63	21.21	12	22.22	15	25
Jaundice/ High Bilirubin	66	22.2	4	7.04	5	13.88
cerebral malaria	27	9.09	6	11.11	6	16.6
ARDS	45	15.33	15	16.66	9	25
AKI	36	12.3	9	16.6	6	16.6
Bleeding manifestation	18	6.06	6	11.1	3	8.3

In our study breathlessness was seen in 17.82%, renal dysfunction in 14.72%, altered sensorium in 7.75% and seizure in 2.32% of total patients.

Historically P. falciparum had been considered the notorious species causing all the above complications and Plasmodium vivax to cause benign tertian malaria. But now, several studies from different parts of India point out the changing clinical spectrum of p. vivax. There are growing evidences that P. vivax in causing severe malaria both in children (11, 15, 44, 47) and adults [16, 18, 48], and can cause severe life-threatening disease analogous to severe infection due to P. falciparum.

In our study breathlessness and altered behaviour is common finding in mixed infection and falciparum group but P. vivax is not too behind. Breathlessness was seen in 15.33% of P. vivax cases, although maximum cases of breathlessness were in mixed infection (25%) followed by P. falciparum group (16.66%). Cho naing *et al.;* [14] in his study reported three studies [35, 50, 51] that had higher incidence of acute respiratory distress (ARD) in P. vivax infection compared to P. falciparum mono or mixed infection. Two studies on adult participants [35, 50] reported a lower incidence of ARD in P. vivax infection compared to P. falciparum mono-infection and Only one study [35] provided data on ARD amongst adult participants, showing a significantly lower incidence of ARD in P. vivax infection compared with mixed infection (OR: 0.44, 95% CI: 0.2–0.96). In other reports from India, ARDs were reported in 6.6% in P. falciparum and 9.7% in P. vivax infections (by Rizvi et al and Hazra BR *et al.;*) [20, 32] whereas Umm-e Asma *et al.;* reported ARDS in 10% of P. falciparum and 3% of P.vivax infections. Vidhan Jain *et al.;* has reported respiratory distress as high as 32% in P. vivax cases. The aetiology describe is acute respiratory distress/ non cardiogenic pulmonary edema and secondly in both infections, this phenomenon occurs as parasites derive energy from anaerobic glycolysis of glucose which yields lactic acid, which may contribute to clinical manifestations of hypoglycaemia and lactic acidosis leading to respiratory distress in a few severely infected patients.

Acute renal failure is a common cause of morbidity and mortality in severe malaria patients of Southeast Asia and Indian subcontinent where transmission rate is low but there are occasional burst in malaria transmission in small pockets during post monsoon, resulting in an increased creatinine level in P. falciparum and P. vivax patients having high parasitaemia. Acute kidney injury was defined as serum creatinine >3 mg/dL and urine output <400 mL/24 hours with normal kidney size according to ultrasonography. In the present study, we observed AKI in 16.6% patients with P. falciparum and mixed infection each and 12.3% patients with P. vivax. Similar findings have also been reported in studies from India both in adults and children [16, 22, 53, 11, 44]. Our study further adds to the evidence that p. Vivax is emerging as a cause of acute kidney injury. Acute cortical necrosis is rare in patients with acute kidney injury from malaria [54]. The possible pathogenic factors are renal damage through renal hypo perfusion or endothelial injury through release of various circulating substances (intravascular haemolysis and sepsis).

Cerebral malaria defined by WHO as unarousable coma (GCS</= 10) or >/= 3 seizures in 24 hours is the most fatal complication of severe malaria. We observed impaired consciousness maximum in mixed infection group (16.6%) followed by p falciparum group (11.11%). 27(9.6%) patients of P.vivax had cerebral malaria out of which 3 patients (3.3%) had convulsions. Of these 9 cases, 3 patients expired. In a study by Neesha *et al.;* [18] cerebral malaria was present in 45.3% of falciparum cases, 15.1% in P.vivax cases and 9% of mixed infection cases. Cerebral malaria is possibly due to adherence of parasitized RBCs to the cerebral vascular endothelium leading to decrease cerebral blood flow [53]. Further production of TNF and subsequent cytokine imbalance are likely to play a role. P falciparum is the usual pathogen for cerebral malaria and our study too along with several studies [15, 22, 36, 11] shows the same finding. Besides we also report that P.vivax is no more benign and term "severe vivax malaria" suggested in a study by H singh *et al.;* [15] must be evaluated.

When properly treated, people with malaria can usually expect a complete recovery [56]. However, severe malaria can progress extremely rapidly and cause death within hours or days [57] in the most severe cases of the disease, mortality rate can reach 20%, even with intensive care and treatment [57].

In our study mortality rate was highest in mixed infection group (16.6%) followed by p falciparum (11.11%). Death was due to multiorgan dysfunction. They had deranged hepatic, haematological and renal parameters. Out of 99 patients 9 (3.3%) patients in P.vivax group expired. They all had cerebral malaria along with deranged hepatic, renal, respiratory and haematological manifestation. The mortality rate in severe vivax malaria ranged from 0.8% to 1.6% (29.) In a previous study from Bikaner mortality rate due to p falciparum was 11.09% similar to our study [32]. In a another study by D yadav from north India in children showed Malaria mortality highest in mixed infection (11.1%), followed by Pf (7.6%) and Pv (3%) group[10]. Case fatality rate due to P. vivax was between 1.6 and 3.8% among children [44, 35] however case fatality rate in adults was 9.5% in a tertiary care centre in Mumbai [49].

CONCLUSION:

In our region P. Vivax is the commonest species predominantly affecting the rural area. It may be surmised that, hepatomegaly, splenomegaly, Severe malaria, cerebral malaria, respiratory distress, AKI were more common in patients having mixed infection and severe P. Falciparum infection. However, several patients of P. Vivax monoinfection also had aforesaid complication which is comparable to monoinfection of p. Falciparum. Besides this, thrombocytopenia, Hepatic dysfunction and seizure were present more in P.vivax monoinfection. Respiratory distress, hepatic dysfunction, neurological involvement and renal impairments noted in P. Vivax are a matter of concern as they are the reasons for increased mortality in this Specie. This study highlights the change in the clinical spectrum of P.vivax malaria in Adults population of North India. Further molecular research, status of chloroquine sensitivity and clinical studies are required in the state to find out reasons for emergence of severe malaria in vivax mono-infection.

REFERENCES

1. World Health Organization. World Malaria Report, 2015. Available from: http://www.who.int/malaria/publications /world-malaria-report-2015. Last accessed on 2015 December 27].
2. Malaria, National Vector Borne Disease Control Programme (NVBDCP). Available from: http://www.nvbdcp.gov.in/malaria3.html . [Last accessed on 2015 Dec 27].
3. Available at: http://nvbdcp.gov.in/Doc/mal-situation-Nov15.pdf
4. Abdallah TM, Abdeen MT, Ahmed IS, Hamdan HZ, Magzoub M, Adam I; Severe Plasmodium falciparum and Plasmodium vivax malaria among adults at Kassala Hospital, eastern Sudan. Malar J 2013;12:148
5. Alessandro Bartoloni, Lorenzo Zammarchi; Clinical Aspects of Uncomplicated and Severe Malaria. Mediterr J Hematol Infect Dis. 2012; 4(1): e2012026. Published online 2012 May 4.
6. Aparup Das, Anupkumar R. Anvikar, Lauren J. Cator, Ramesh C. Dhiman, Alex Eapen, Neelima Mishra,Bhupinder N. Nagpal, *et al.;* Malaria in India: The Center for the Study of Complex Malaria in India. Acta Trop. 2012; 121(3): 267–273. Published online 2011 Nov 28.
7. Vinayak V Shela**t,** Harshal T Pandv**e,** Gayatri Pathak; Socio-demographic characters, clinical profile and laboratory parameters in malaria cases due Plasmodium falciparum and Plasmodium vivax: A comparative study. Journal of Medicine in the Tropics 2014; 16:2:76-80.
8. Muddaiah M, Prakash PS; A study of clinical profile of malaria in a tertiary referral centre in South Canara. J Vector Borne Dis 2006; 43:29-33.
9. Limaye CS, Londhey VA, Nabar ST; The study of complications of vivax malaria in comparision with falciparum malaria in Mumbai. J Assoc Physicians India 2012; 60: 15-18.

10. Yadav D, Chandra J, Aneja S, Kumar V, Kumar P, Dutta AK; changing profile of severe malaria in north Indian children**,** Indian J Pediatr. 2012; 79(4):483-7.
11. Rao, Y.K., Padhye A, Midha T, Martolia D.S, Kumar A, *et al.;* Variation in the clinical presentation of Plasmodium vivax and Plasmodium falciparum malaria in children: A hospital based study in Kanpur, India. Journal of Pediatric Infectious Diseases 2014; 9(4): 171-176.
12. Kaushik J S, Gomber s, Dewan P; Clinical and Epidemiological Profiles of Severe Malaria in Children from Delhi, India. J Health Popul Nutr. 2012; 30(1): 113–116.
13. Gehlawat VK, Arya V, Kaushik JS, Gathwala G; Clinical spectrum and treatment outcome of severe malaria caused by Plasmodium vivax in 18 children from northern India. Pathog Glob Health.2013; 107:210–4.
14. Cho Naing, Maxine A. Whittaker, Victor Nyunt Wai, Joon Wah Mak; Is Plasmodium vivax Malaria a Severe Malaria?: A Systematic Review and Meta-Analysis**.** PLoS Negl Trop Dis. 2014; 8(8): e3071. Published online 2014 Aug 14.
15. Singh H, Parakh A, Basu S, Rath B**;** Plasmodium vivax malaria: is it actually benign**?.** J Infect Public Health. 2011; 4(2):91-5.
16. Vivek B. Kute, Hargovind L. Trivedi, Aruna V. Vanikar, Pankaj R. Shah, Manoj R. Gumber, Himanshu V. Patel, *et al.;* Plasmodium vivax Malaria–associated Acute Kidney Injury, India, 2010–2011. Emerg Infect Dis. 2012; 18(5): 842–845.
17. D. K. Kochar, A. Das, S. K. Kochar; "Severe Plasmodium vivax malaria: a report on serial cases from Bikaner in northwestern India," American Journal of Tropical Medicine and Hygiene, 2009; 80(2):194–198.
18. Singh Neeshu, Mathur Aman, Naim Faran, Agarwal Nutan; The changing clinical spectrum of Malaria: a clinical study from Bundelkhand. IOSR journal of Dental and Medical Sciences (ISOR_JDMS) 2014; 13(6) Ver. II: 37-40.
19. Jagjit Singh, Bhargav Purohit, Anupama Desai, Lalita Savardekar; Clinical Manifestations, Treatment, and Outcome of Hospitalized Patients with Plasmodium vivax Malaria in Two Indian States: A Retrospective Study. Malaria Research and Treatment 2013; 2013: 5. http://dx.doi.org/10.1155/2013/341862.
20. Rizvi I, Tripathi DK, Chughtai AM, Beg M, Zaman S, Zaidi N; Complications associated with Plasmodium vivax malaria: a retrospective study from a tertiary care hospital based in Western Uttar Pradesh, India. Ann Afr Med 2013; 12: 155-159.
21. Wiwanitkit V; Overt bleeding in malarial patients: experience and review. Blood Coagul Fibrinolysis. 2008; 19(1):1-4.
22. Umm-e Asma, Farha Taufiq, Wajihullah Khan; Prevalence and Clinical Manifestations of Malaria in Aligarh, India. Korean j Parasitol 2014; 52(6):621-629.
23. Muddaiah M, Prakash PS; A study of clinical profile of malaria in a tertiary referral centre in South Canara. J Vector Borne Dis 2006; 43:29-33.
24. Mishra G; Hospital based study of malaria in Ratnagiri district, Maharashtra. J Vector Borne Dis 2003; 40:109-11.
25. Jadhav UM, Patkar VS, kadam NN; Thhrombocytopenia in malaria – co relation with type and severity of malaria. J Assoc Physicians India. 2004; 52:615-8.
26. Layla A. M. Bashawri, Ahmed A. Mandil, Ahmed A. Bahnassy, mirghani A. Ahmed; Malaria: HEMATOLOGICAL ASPECTS. Annals of Saudi Medicine, 2002; 22:5-6.
27. Farogh A, Quaaum A, aamir haleem, Ghaffar A; Haematological abnormalities in malaria. Biomedica 2009; 25: 52-55.
28. Singh Neeshu, Mathur Aman, Naim Faran, Agarwal Nutan; The changing clinical spectrum of Malaria: a clinical study from Bundelkhand. IOSR journal of Dental and Medical Sciences (ISOR_JDMS) 2012; 13(6) Ver. II: 37-40.
29. Piplani S; Clinical study of Falciparum malaria in Notheast. JAPI 2000; 48(1):110.
30. Yasmeen Khatib, Richa Patel, Karen Sequeira, Gaurav Agrawal, Nitin Chikhale; Hematological and biochemical alterations in malaria and their correlation with Parasitic Index. IOSR Journal of Pharmacy. 2015; 5(9): 53-56**.**
31. Taksande A, Vilhekar K, Jain M, Atkari S; Clinico-haematological profile of cerebral Malaria in a Rural hospital. J Indian Acad Clin Med 2006; 7: 308-12.
32. Kochar DK, Das A, Kochar SK, Saxena V, Sirohi P, Garg S, *et al.;* Severe Plasmodium vivax malaria: a report on serial cases from Bikaner in northwestern India. Am J Trop Med Hyg. 2009; 80:194–8.
33. Bashawri LA, Mandil AA, Bahnassy AA, Al-Shamsi MA, Bukhari HA; Epidemiological profile of malaria in a university hospital in eastern region of Saudi Arabia. Saudi Med J 2001; 22: 133-138.
34. Kochar DK, Kaswan K, Kochar SK, Sirohi P, Pal M, Kochar A, *et al.;* A comparative study

of regression of jaundice in patients of malaria and acute viral hepatitis. J Vector Borne Dis 2006; 43: 123-129.

35. Tjitra E, Anstey NM, Sugiarto P, Warikar N, Kenangalem E, Karyana M, *et al.;* Multidrug-resistant Plasmodium vivax associated with severe and fatal malaria: a prospective study in Papua, Indonesia. PLoS Med 2008; 5: e128. PMID: 18563962.
36. Malaria in a tertiary health care facility of Central India with special reference to severe vivax: implications for malaria control. Vidhan Jain, Avyact Agrawal, and Neeru Singh. Pathog Glob Health. 2013; 107(6): 299–304.
37. Taha K, Zein S; Hematological changes in Malaria: Relation to plasmodium Species. Kuwait Medical Journal 2007, 39 (3):262-7
38. Banzal S, Ayoola FA, El Sammani FE, Rahim SI, Subramanium P, Gadour MOE, *et al.;* The clinical pattern and complications of severe malaria in the Jazan region of Saudi Arabia. Ann Saudi Med 1999; 1: 378-380.
39. Malik GM, Seidi O, El-Taher AM, Mohammad AS; Clinical aspects of malaria in the Asir region, Saudi Arabia. Ann Saudi Med 1998; 18: 15-17.
40. Faseela TS, Roche R, Anita KB, Malli C, Rai Y. Diagnostic Value of Platelet count in Malaria. Journal of Clinical and Diagnostic Research. 2011; 5(3):464-6.
41. Narendra Kumar Gupta, ShyamBabuBansal, Uttam Chand Jain, Kiran Sahare; Study of thrombocytopenia in patients of malaria. Tropical parasitology. 2013; 3(1):58-61.
42. Jadhav UM, Patkar VS, Kadam NN; Thrombocytopenia in malaria-correlated with type and severity of malaria. J Assoc Physicians India 2004; 52: 615-618.
43. Yasmeen Khatib, Richa Patel, Karen Sequeira , Gaurav Agrawal, Nitin Chikhale; Hematological and biochemical alterations in malaria and their correlation with Parasitic Index. IOSR Journal of Pharmacy. 2015; 5(9): 53-56**.**
44. Kochar DK, Tanwar GS, Khatri PC; "Clinical features of children hospitalized with malaria—a study from Bikaner, Northwest India," American Journal of Tropical Medicine and Hygiene, 2010; 83(5):981–989.
45. Tjitra E, Anstey NM, Sugiarto P, Warikar N, Kenangalem E, Karyana M, *et al.;* Multidrug-resistant Plasmodium vivax associated with severe and fatal malaria: a prospective study in Papua, Indonesia. PLoS Med 2008; 5: e128.
46. Anvikar AR, Singh DK, Singh R, Das AP, Valecha N; Vivax malaria presenting with cerebral malaria and convulsions. Acta Parasitol 2010; 55: 96-98.
47. Patwari A, Aneja S, Berry AM, Ghose S; Hepatic dysfunction in childhood malaria. Arch Dis Chil 1979; 54(2): 139-141.
48. Malaria Research and Treatment Volume 2013 (2013), Article ID 341862, 5 pages http://dx.doi.org/10.1155/2013/341862 Research Article Clinical Manifestations, Treatment, and Outcome of Hospitalized Patients with Plasmodium vivax Malaria in Two Indian States: A Retrospective Study Jagjit Singh, Bhargav Purohit, Anupama Desai, Lalita Savardekar, Preeti Shanbag, and Nilima Kshirsagar.
49. Nadkar MY, Huchche AM, Singh R, Pazare AR; "Clinical profile of severe Plasmodium vivax malaria in a tertiary care centre in Mumbai from June 2010 -January 2011," Journal of the Association of Physicians of India, 2012; 60: 11–13.
50. Barber BE, William T, Grigg MJ, Menon J, Auburn S; A prospective comparative study of knowlesi, falciparum, and vivax malaria in Sabah, Malaysia: high proportion with severe disease from Plasmodium knowlesi and Plasmodium vivax but no mortality with early referral and artesunate therapy. Clin Infect Dis 009; 56: 383–397.
51. Barcus MJ, Basri H, Picarima H, Manyakori C, Sekartuti; Demographic risk factors for severe and fatal vivax and falciparum malaria among hospital admissions in northeastern Indonesian Papua. Am J Trop Med Hyg 2007; 77: 984–991.
52. Hazra BR, Chowdhury RS, Saha SK, Ghosh MB, Mazumder AK; changing scenario of malaria: a study at Calcutta. Indian J Malariol 1998; 35: 111-116.
53. Manan JA, Ali H, Lal M; Acute renal failure associated with malaria. J Ayub Med Coll Abbottabad 2006;18: 47-52.
54. Chugh KS, Jha V, Sakhuja V, Joshi K; Acute renal cortical necrosis—a study of 113 patients. Ren Fail. 1994; 16:37–47.
55. Tanwar GS, Khatri PC, Sengar GS, Kochar A, Kochar SK; Clinical profiles of 13 children with Plasmodium vivax cerebral malaria. Ann Trop Paediatr 2011; 31: 351–356.
56. "Frequently Asked Questions (FAQs): If I get malaria, will I have it for the rest of my life?". US Centers for Disease Control and Prevention. February 8, 2010. Retrieved2012-05-14. Trampuz A, Jereb M, Muzlovic I, Prabhu R (2003). "Clinical review: Severe malaria". Critical Care 2012; 7 (4): 315–23.
57. Nadjm B, Behrens RH; "Malaria: An update for physicians". Infectious Disease Clinics of North America 2012; 26 (2): 243–59.