

To study the laboratory profile of severe malaria in a tertiary care centre of North India

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Abstract

Introduction: Malaria ranks third among the major infectious diseases in causing deaths- after pneumococcal acute respiratory infections and tuberculosis. It is expected that by the turn of the century malaria would be the number one infectious killer disease in the world. It is the most widely distributed and is responsible for up to 400 million infections every year. The aim of the study was to describe the laboratory parameters and their correlation with mortality in Malaria. **Methods:** This was a one year retrospective and one and half year prospective study. All patients diagnosed to have Malaria were included in this study. **Results:** Laboratory parameters were recorded carefully and the data was analyzed by the appropriate statistical methods. A total of 124 patients were studied 92 patients of Plasmodium vivax, 21 patients of Plasmodium falciparum and 11 patients of Mixed malaria. Complications observed were severe anemia (< 7 gm/dl), thrombocytopenia, renal dysfunction (S.creat > 1.2mg/dl), raised bilirubin > 3mg%, metabolic acidosis, and acute respiratory distress syndrome (ARDS). Thrombocytopenia and jaundice were the most frequent complications in the severe cases. 10/124 patients (8.06%) expired. 8/10 patients who expired had four or more organ dysfunction. **Conclusion:** ARDS had the most significant correlation with mortality. Other significant factors contributing to death were jaundice, severe anemia and renal failure.

Key words: Laboratory parameters, mortality, outcome, severe malaria

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Introduction

India contributes to about 70% of Malaria in the South East Asia region. Annually India reports about two million cases and 1,000 deaths attributable to Malaria [1]. There exists heterogeneity and variability in the transmission between and within the states of the country as many ecotypes / paradigms of Malaria have been recognized. Among the four species of Plasmodium, Plasmodium falciparum and vivax are commonly found in our country. Disease caused by Plasmodium vivax Malaria used to be called benign tertian. In contrast Plasmodium falciparum causes severe Malaria and often produces multi-organ failure unless treated early with multiple drugs. Recently there have been some isolated reports showing severe Plasmodium vivax Malaria associated with

thrombocytopenia, cerebral malaria, acute respiratory distress syndrome, acute renal failure and hepatic dysfunction. Kochar et al in a study reported several cases of vivax Malaria with multi-organ dysfunction syndrome [2]. Profound thrombocytopenia is a well-recognized complication of falciparum malaria but recently there have been several reports of vivax malaria with thrombocytopenia [3,4] Direct lytic effect, immunological reactions, splenic sequestration and oxidative stress are some of suggested mechanisms for thrombocytopenia [5,6]. Acute respiratory distress syndrome (ARDS), hepatic involvement and renal involvement are common in Plasmodium falciparum Malaria; these complications also have been reported in Plasmodium vivax Malaria [7-12]. Morbidity and mortality of Plasmodium vivax have increased recently due to the serious complications associated with it. There are very few prospective studies on laboratory

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profile of Malaria. Taking this background, we planned a study to document the association of laboratory parameters with changing clinical profile of this common disease.

Materials and Methods

This was a descriptive study, which was done in the Department of Medicine, Christian Medical College and Hospital, Ludhiana, over a period of two and half years (one and a half year prospective and one year retrospective study). In retrospective study, data was collected from case records of all cases admitted to Christian Medical College and Hospital, Ludhiana, with diagnosis of Malaria from 1st October 2008 to 30th September, 2009. In prospective study (1st October 2009 to 31st March, 2011), all patients admitted and diagnosed as Malaria were included. Diagnosis of Malaria was made by examining the peripheral blood smear (thick and thin smear). Parasite index will be calculated in all cases. All cases enrolled in the study underwent OptiMAL malarial antigen test to rule out falciparum-vivax co-infection (mixed malaria). OptiMAL is a rapid (10 minutes) malaria detection test which utilizes a dipstick coated with monoclonal antibodies against the intracellular metabolic enzyme

parasite lactate dehydrogenase. Differentiation of malaria parasite was based on antigenic difference between pLDH isoforms. OptiMAL has sensitivity of 95.3% and specificity of 100% for *Plasmodium falciparum* and sensitivity of 96% and specificity of 100% for *Plasmodium vivax*. Complete blood count, renal function test, liver function test, arterial blood gases analysis, chest x-ray conducted. Imaging (CT scan, MRI) wherever required. Treatment was given to all patients as per WHO guidelines. Patient's clinical features, laboratory parameters and response to treatment were recorded as per data collection sheet. Patients were categorized into *Plasmodium vivax*, Malaria, *Plasmodium falciparum* Malaria and mixed infection. The study was approved by hospital ethics committee and the information obtained from this study were tabulated in a master chart and then analyzed to obtain measurable data. Percentages were calculated for a number of patients in different groups to convey appropriate statistical information.

Statistical Analysis- To compare mean values of a variable between more than two groups, we used analysis of variance [ANOVA] and to compare two proportions of subjects we applied Z-test.

Results

This was a descriptive study, done in the Department of Medicine, Christian Medical College and Hospital, Ludhiana. Study was done over a period of 2½ years (one year retrospective from 1st October, 2008 to 30th September 2009 and one and half year prospective from 1st October, 2009 to 31st March, 2011). All patients admitted at Christian Medical College and Hospital, Ludhiana with a diagnosis of Malaria were included and following observations were made. A total of 124 patients were studied 92 patients of *Plasmodium vivax*, 21 patients of *Plasmodium falciparum* and 11 patients of mixed malaria [Table:1]. Male: Female ratio was 3.8 :1. Pallor and jaundice were seen significantly more in *Plasmodium falciparum* and Mixed malaria. 49/124 patients had hemoglobin < 10gm/dl and 119/124 (95.92%) had thrombocytopenia [Table:2]. Severe malaria was observed in 39/124 patients of which 25 (27.12%) were of *Plasmodium vivax*, 9 (42.86%) were of *Plasmodium falciparum* and 5 (45.45%) were of Mixed malaria. Thrombocytopenia and jaundice were the most frequent complications in the severe cases. Mixed malaria was found in 11 cases. 5 of them were severe cases [Table: 3]. 54/92 of *Plasmodium vivax* cases responded to chloroquine alone. 31 patients (33.7%) required artesunate or combinations. 10/124 patients (8.06%) expired. Out of these 4 (4.38%) were of *Plasmodium vivax*, 3 (14.28%) were *Plasmodium falciparum* and 3 (27.27%) were mixed malaria. 8/10 patients who expired had four or more organ dysfunction. ARDS had the most significant correlation with mortality [Table:3]

Table-1: Distribution of subjects according to OPTIMAL and MP Smear test results.

Results	OptiMAL test	Percentage	MP Smear Positive	Percentage
PV positive	92	74.19	74(88)	62.7
PF positive	21	16.94	10(19)	8.47
Mixed malaria	11	8.87	7(11)	7.63
Total	124	100.00	91(118)	77.1

Table-2: Laboratory Parameters.

Parameter	PF positive		PV positive		Mixed malaria		p value
	No.	Percentage	No	Percentage	No.	Percentage	
Hb							
> 12g%	6	28.57	27	29.35	0		0.049
10-12%	6	28.57	32	34.78	4	36.36	
7-10%	5	23.81	27	29.35	7	63.63	
< 7%	4	19.04	6	6.52	0	0	
Mean ± SD	10.06 ± 3.38		10.89 ± 2.42		9.41 ± 1.25		
Leucocyte count							
<4000	4	19.04	20	21.74	3	27.29	0.977
4,000-11,000	13	61.9	68	73.91	7	63.63	
>11,000	4	19.04	4	4.35	1	9.09	
Mean ± SD	7319.04 ± 4931.7		7014.13 ± 7918.36		7254.55 ± 4159.41		
Platelet count							
>1,50,000	1	4.76	4	4.35	0	0.00	0.196
1,00,00- 1,50,000	3	14.29	11	11.96	1	9.09	
50,000-1,00,000	6	28.57	20	21.74	3	27.27	
20,000-50,000	8	38.09	39	42.39	5	45.45	
<20,000	3	14.29	18	19.56	2	18.18	
Mean ± SD	42352.94 ± 22433.07		37592.11 ± 23545.8		38300 ± 20155.23		

Parameter	PF positive		PV positive		Mixed malaria		p value
	No.	Percentage	No	Percentage	No.	Percentage	
Bilirubin							
< 1.1 mg%	4(17)	23.52	19(56)	33.92	2(8)	25.00	0.17072
1.1-3.00 mg%	7(17)	41.17	23(56)	41.07	2(8)	25.00	
>3.00 mg%	7(17)	41.17	14(56)	25.00	4(8)	50.00	
Mean ± SD	5.02 ± 6.79		3.17 ± 4.28		3.89 ± 3.48		
SGOT(10-40 U)							
<40 U	8	38.09	49(82)	59.75	3(9)	33.33	0.04891
40-120 U	9	42.86	30(82)	36.58	6(9)	66.67	
>120 U	4	19.04	03(82)	3.66	0	0	
Mean ± SD	86.43 ± 99.15		51.89 ± 42.26		81.00 ± 90.03		
SGPT(10-40 U)							
<40 U	8	38.09	53(82)	64.63	6(9)	66.67	0.03245
40-120 U	10	47.62	24(82)	29.27	3(9)	33.33	
>120 U	3	14.28	05(82)	6.09	0	0	
Mean ± SD	73.14 ± 74.68		43.53 ± 36.30		39.20 ± 16.66		

Parameter	PF positive		PV positive		Mixed malaria		p value
	No.	Percentage	No	Percentage	No.	Percentage	
<45	6	28.57	52(91)	57.14	3	27.27	0.041
45-100	13	61.9	31(91)	34.06	4	36.36	
>100	2	9.52	7(91)	7.69	4	36.36	
Mean ± SD	64.48 ± 37.35		48.58 ± 33.34		75.64 ± 48.38		
Crt(0.3-1.1mg%)							
<1.2mg%	14	66.67	72	78.26	5	45.45	0.01697
1.2-3.0	6	28.57	17	18.48	6	54.54	
>3.0	1	4.76	3	3.36	0	0	
Mean ± SD	1.46 ± 1.11		1.08 ± 1.01		1.20 ± 0.58		

ABG pO2						
<60%	1(10)*		5(20)		1(5)	0.56743
60-90%	4(10)		11(20)		1(5)	
>90%	5(10)		4(20)		3(5)	

Table-3 Frequency of various complications in severe malaria.

Criteria	P. vivax No (%) of patients 25 (27.1)	P. falciparum No (%) of patients 9 (42.86)	Mixed No (%) of patients 5 (45.45)	Total No (%) of patients 39 (31.45)
Severe anemia < 7 mg%	5	4	2	11
Encephalopathy	3	3	4	10
Hypotension	10	2	3	15
Jaundice > 3 mg%	16	7	4	27
Creatinine > 3 mg%	3	3	0	6
Thrombocytopenia < 80,000	23	9	5	37
ARDS	7	4	2	13
Hypoglycemia	1	0	0	1
Acidosis	3	4	1	8
Expired	4	3	3	10
Upto 2 organ failure	15	2	1	18
3 or more organ failure	10	7	4	21

Discussion

In our study, laboratory findings in malaria caused by various plasmodium species were being described. The prevalence of different types of malaria varies in different regions and states of India. In our study majority of the patients belonged to the state of Punjab where Plasmodium vivax is the predominant type. [13]. Among clinical features fever was the leading presentation in our study. In our study, pallor, jaundice and hepatosplenomegaly were the most common signs observed. Jaundice was noticed in 42.8% of

Plasmodium falciparum and 36.3% of mixed malaria. In Plasmodium vivax only 22.83 % of cases had jaundice. In a study done at Rohtak by Nityanand and Agarwal jaundice was described in 100% of the Plasmodium falciparum patients as compared to 42.8% in this study [14].

Laboratory Profile of Patients- Among hematological profile, thrombocytopenia is a common feature of acute malaria and occurs in both P. falciparum and P.vivax

regardless of the severity of infection. Severe thrombocytopenia has been reported most commonly with *P. falciparum* [15]. In our study, 95.24% of *falciparum*, 95.65% of *vivax* and 100% cases of mixed malaria had thrombocytopenia. This hematological alteration is a result of peripheral destruction and consumption. A few postulated mechanisms for thrombocytopenia in malaria include macrophage activation, increased levels of cytokines and antiplatelet immunoglobulin which cause platelet destruction. Other mechanisms include oxidative stress, sequestration in non-splenic areas and pseudothrombocytopenia due to clumping of platelets [16]. Another common hematological complication seen in malaria is Anemia. The two common causes of anemia are increased hemolysis and decreased rate of erythrocyte production from bone marrow [17]. Cytokine-related dyserythropoiesis also probably contributes to anemia [18]. Severe anemia is a common feature of *P. falciparum* malaria. In *vivax*-endemic areas, *P. vivax* is a major risk factor for severe anemia, particularly in young children [19]. Malnutrition and intestinal parasitic infections aggravate this problem in highly endemic areas. In our study, 42.8% of *falciparum*, 35.8% *vivax* and 63.6% of mixed malaria had anemia ($Hb < 10\text{mg}\%$). In a study from Bikaner, anemia was reported in 54% of *falciparum* malaria [20]. In yet another study conducted in Indore, anemia was reported in 56.06% of *Plasmodium falciparum* and 31.8% *Plasmodium vivax* infection respectively [21].

Renal involvement has been reported commonly with *P. falciparum* and occasionally with *P. vivax* infections. It can occur as an isolated complication or as a component of multiorgan involvement [22]. The precise mechanism of ARF in malaria is not clearly known. Several hypotheses including mechanical obstruction caused by cytoadherence and sequestration of infected erythrocytes, immune-mediated glomerular pathology, alterations in the renal and systemic hemodynamics, release of cytokines, reactive oxygen intermediates, and nitric oxide have been proposed.

The hemolysis, disseminated intravascular coagulation, and rhabdomyolysis in malaria also contribute to the pathogenesis of ischemic tubular necrosis and ARF [23]. Various histological pictures including acute tubular necrosis (the commonest), interstitial nephritis, and proliferative glomerulonephritis have been described in malarial ARF either alone or in combination [22,24,25].

Glomerular injury associated with malaria is commonly seen in the pediatric population. Mild proteinuria, microhematuria, and casts are reported in 20% – 50% of cases [26]. Both nephrotic and acute nephritic syndromes have been described with *falciparum* and *vivax* malaria [27,28].

Renal impairment is known to occur with *falciparum* malaria but is rare in patients of *vivax* malaria. However there have been reports of ARF, electrolyte abnormality, abnormal proteinuria and urinary sediments in *vivax* malaria. In our study, 33.3% of *Plasmodium falciparum*, 54.5% of mixed malaria and 21.7% of *Plasmodium vivax* had renal dysfunction. In our study there were statistically more number of patients with renal dysfunction in *Plasmodium falciparum* and mixed malaria. In a study from Rajasthan in *falciparum* malaria 21.7% of patients had uremia [29]. In another study from Bikaner on severe *Plasmodium vivax* malaria 45% had renal dysfunction [30].

Hepatic dysfunction in malaria is common, but hepatic encephalopathy is unusual, and most of the patients described have had either isolated infection with *P. falciparum* or a mixed infection with *P. vivax* [31]. In endemic areas, severe malaria should feature in the differential diagnosis of fulminant hepatic failure (FHF). In this study 26 patients had hyperbilirubinemia (Total Bilirubin $>3\text{ gm}\%$). Hyperbilirubinemia observed in cases of *vivax* malaria can be attributed to increased hemolysis of both parasitized and non-parasitized erythrocytes as well as to hepatic injury, as has been observed in cases with *P. falciparum* malaria [32]. Similar to *falciparum* malaria, dilated hepatic sinusoids containing hypertrophied kupffer cells and parasitized red cells may also be contributory to hepatic injury in *Plasmodium vivax* infection [33].

Alterations in pulmonary physiology in malaria include airflow obstruction, impaired ventilation, reduced gas transfer, and increased pulmonary phagocytic activity [34]. Acute respiratory distress syndrome (ARDS) in malaria is likely to be a continuous spectrum from subclinical lung involvement in uncomplicated malaria to frank ARDS in severe malaria [35]. ARDS is considered to be the most severe form of acute lung injury in malaria and has been reported most commonly with *P. falciparum* malaria. The prevalence of ARDS in patients with malaria as documented in various studies ranges from 2.1% to 29.1% [36].

Pulmonary edema has been reported by several investigators to be one of the fatal complications of *P. falciparum* malaria often in association with disseminated intravascular coagulation, renal failure, cerebral malaria, and shock. Fein et al emphasized that pulmonary edema in patients with *P. falciparum* malaria is noncardiogenic resulting from increased permeability of the alveolar–capillary membrane [37].

In this study, cough was present in 24/124 (19.4 %) of the patients, while 14/124 (11.3%) of the patients had breathing difficulty. ARDS/ALI was present in 13 cases, of which 7 were *Plasmodium vivax* and 4 cases were of *Plasmodium falciparum*, 2 were cases of mixed malaria. Six patients required mechanical ventilation. There are only a few well-documented reports of ARDS in *Plasmodium vivax* infected cases. Tanios et al; 2001, had reported a case of *Plasmodium vivax* complicated by ARDS [38]. In a study from Rajasthan, 11 cases of severe *vivax* malaria were reported 3 of which had ARDS [2].

Complications in severe malaria are either sequestration related, such as cerebral malaria, renal dysfunction, hepatic dysfunction, and ARDS, or non-sequestration related, such as anemia and thrombocytopenia. Non-sequestration–related complications are known to occur in *Plasmodium vivax* infection quite frequently. However, for sequestration-related complications, it was always presumed that coexisting *Plasmodium falciparum* infection may evade appearance in blood film because of heavy sequestration.

Previously, it was thought that the severe disease with *vivax* infection is actually caused by co-infection of *vivax* and *falciparum* species. However, with application of the recently developed tests of malarial antigen it has become evident that *vivax* mono-infection can be a cause of severe malaria. The mechanisms of organ involvement in *vivax* malaria are controversial. In this study 39 (31.45%) patients had severe malaria, diagnosed as per WHO criteria. The most common complication observed was thrombocytopenia. The other complications observed were jaundice and hepatic dysfunction, which is similar to the reported observations in severe *Plasmodium falciparum* malaria and *Plasmodium vivax* malaria in this region [2,7,8,30]. For predicting the outcome of severe *falciparum* malaria scoring system have been devised [39]. This scoring system have taken into consideration various organ dysfunction for the prediction of the outcome.

Mohapatra and Das have suggested another scoring system called MSS (Malaria Severity Score) [40]. Here 7 organ dysfunction were taken into consideration namely Neurologic, Renal, hematological, cardiovascular, respiratory, hepatic and metabolic dysfunction.

General awareness of the presentations of complicated malaria such as hepatic dysfunction jaundice and renal failure is needed among primary care physicians so as to treat these patients in more appropriate way. Routinely, jaundiced patients with altered consciousness and a short history are considered to have viral hepatitis rather than malarial hepatitis. This can sometimes leads to disaster in terms of prompt institution of appropriate therapy. There was a significant association of ARF with rising bilirubin levels. This elevation of bilirubin was typically an increase in conjugated bilirubin. The concomitant renal failure may contribute to the elevated conjugated hyperbilirubinemia by virtue of decreased excretion of conjugated bilirubin. Once the complications develop removal of parasites could not reverse the organ damage and hence the mortality. Therefore, in addition to antimalarial drugs, organ support is mandatory in the management of severe malaria.

Although *P. vivax* malaria is widely considered benign, recent studies have demonstrated that it accounts for a substantial proportion of hospitalized malaria patients in agreement with our study. The observation that a significant proportion of severe malaria morbidity is also caused by *P. vivax* would have tremendous implications for control of the infection especially as *P. vivax* invariably increases relative to *P. falciparum* under effective transmission reduction [41,42]. Thus, every effort to reduce or eliminate malaria burden must also target *P. vivax* along with *P. falciparum* in regions where both of these species coexist.

Conclusions

Plasmodium vivax malaria was the commonest type of malaria observed. Severe *plasmodium vivax* was associated with all the complications described in *falciparum* malaria. Mixed malaria was associated with the largest proportion of severe malaria and the mortality was the highest in this group. Laboratory parameters play a very vital role in predicting the outcome for these patients. ARDS had the most significant correlation with mortality. Other significant factors contributing to death were jaundice, severe

anemia and renal failure. Age and platelet counts had no significant correlation to mortality. Patients of malaria should be monitored for occurrence of different complications as their early detection and the appropriate treatment or referral to higher center can be life-saving.

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