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A comparative study on hematological changes in malaria: A Rewa District

Akhilesh Kumar Suman

Research Scholar, School of Environmental Biology, A.P.S. University, Rewa, Madhya Pradesh, India

Abstract
The hematological changes usually associated with malaria are well known. This study was conducted to estimate and compare the predominance & severity of hematological changes in common types of malaria. This study included 200 patients, out of which 37 (18.5%) patients were found to harbor malaria parasite by either of the techniques (Table: 1). *P. falciparum* malaria was commoner than *P. vivax* having 19 cases (51.35%) versus 14 cases (37.84%) respectively, while Mixed infection represented only 4 cases (10.81%). Monocyte as well as neutrophils were increased respectively in 7 (18.92%) and 5 (13.51%) cases. However, lymphopenia was present in 9 (24.32%) cases. Commonly 26 (70.27%) had thrombocytopenia and 10 (27.03%) had normal platelets. The Peripheral smear examination showed 8 (21.62%) of the patients were anemic with normocytic normochromic except in 4 (10.81%), where it was Normocytic hypochromic. *P. falciparum* as well as *P. vivax* can cause significant hematological changes with high incidence of thromboctopenia, anemia, lymphopenia and monocytosis.

Keywords: Hematology, Malaria, *Plasmodium falciparum*, *Plasmodium vivax.*

1. Introduction
Malaria continues to be a major health problem in some of the most populated areas of the world. It is one of the important causes of febrile illnesses in our part of the world. Malaria is well-known to human being since centuries; it is a disease of tropical and subtropical countries particularly Africa and Asia. In spite of advances information, malaria continues to cause significant morbidity and mortality worldwide. Malaria is one of the most prevailing human infections in the world. More than 40% of the world population reside in malaria-endemic area and it is predictable that 300-500 million cases and 1.5-2.7 million deaths occur each year [1]. Mortality rate is usually elevated (20%) in severe malaria (parasitemia >5%) [2]. Hematological changes, which are the most common complications, play a significant role in these serious complications. The hematological abnormalities that have been reported to consistently companion which comprise anemia, thrombocytopenia, atypical lymphocytosis and infrequently disseminated intravascular coagulation [3]. Leucopenia, leucocytosis, Neutopenia, Neutrophilia, Eosinophilia and monocytosis also have been reported [2, 4]. The aim of this study was to assess the hematological changes which occurs in different types of malaria. In tropical countries like India, malaria remains an essential health problem. The infection rate of the world population was 250 million per year, and the mortality rate was 1-2 million per year [1]. In the present day, the most vital difficulty in the management of malaria is drug resistance of *P. falciparum* to the various anti-malarial drugs. The majorities of the shared complications commencing due to malarial consequences is from hyperparasiteamia. Mortality is very high (10-30%) in complicated *P. falciparum* infection. Hematological changes play key role in these lethal complications.
In the Indian subcontinent, distribution is heterogenous and governed by many climatic and physiological risk factors. It is caused by protozoa parasite of the genus plasmodium which infects and destroys red blood cells. Four species of plasmodia (*P. falciparum, P. malariae, P. ovale* and *P. vivax*) cause malaria in humans of which *P. falciparum* is the cause of morbidity and mortality [12, 13] However, *Plasmodium vivax* is the major malarial parasite in India, contributing towards the majority of cases [14, 15].
The clinical diagnosis of malaria is challenging because of the non-specific nature of the signs and symptoms, which overlap considerably with other febrile illnesses common in tropical regions. This impairs diagnostic specificity and often promotes the indiscriminate use of antimalarials. As parasites of the blood for the majority of their complex life cycle, they expectedly induce hematological alterations. Hematological abnormalities are considered a hallmark of malaria and statistical analyses have shown that many of these hematological values may lead to an increased clinical suspicion for malaria, thus initiating a prompt institution of specific therapy even in the absence of a positive smear report for malaria.

2. Materials and Methods
The present comparative cross sectional study was conducted in central hospital laboratory of GMH & Sanjay Gandhi Hospital, Rewa over two years period from April 2014 to March 2015. The clinically suspected cases of malaria were included in the study. The diagnosis of malaria was confirmed by thin and thick blood films stained with Leishman's stain for malaria parasite and Antigen Histadine Release Protein 2 (HRP2) test. The study was premeditated to include clinically suspected cases of malaria and patients were excluded on the basis of history and finding suggestive of Dengue, chronic liver disease, bleeding disorder, thrombocytopenia, drug intake or conditions which might have contributed in blood changes. Complete Blood Count was performed using an automated SYSMEX machine and WBC differential was also done for all patients. All malaria positive smears were studied for confirmation, identification of species and review of smear for platelets count and other hematological changes. Data was analyzed by Epi. Info

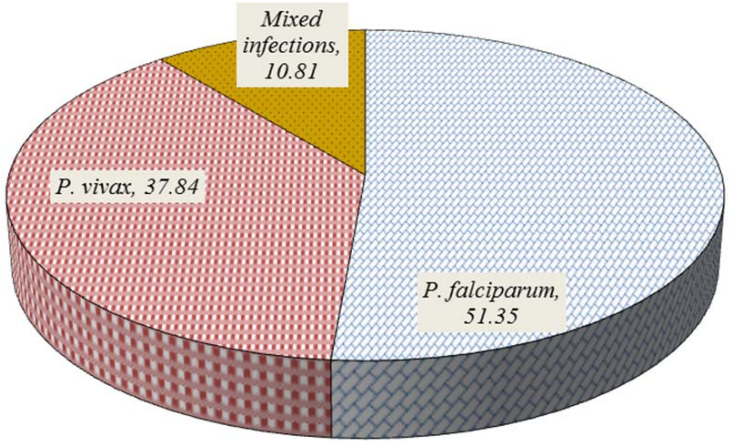
Statistical Software. p value of < 0.05 was taken as significant for all statistical analysis.

3. Results and Discussion

This study included 200 patients, out of which 37 (18.5%) patients were found to harbor malaria parasite by either of the techniques (Table: 1). *P. falciparum* malaria was commoner than *P.vivax* having 19 cases (51.35%) versus 14 cases (37.84%) respectively, while Mixed infection represented only 4 cases (10.81%). Out of all the malaria positive cases, majority of cases i.e. 64 cases (86.48%) showed subnormal haemoglobin. However, significant difference in the incidence of anaemia in *P. falciparum* 35(89.7%) and *P.vivax* 23(85.18%) cases with p value (> 0.05) was found, which is in contrast to the observation by Murphy GS, Old feild EC [2].

Table 1: Distribution of species in Malaria Positive Cases (n=37)

S. No.	Species	Number	Percentage
1.	*P. falciparum*	19	51.35
2.	*P. vivax*	14	37.84
3.	*Mixed infections*	4	10.81
	Total	37	100.00



Graph 1 : Distribution of species in Malaria Positive Cases

Differential leukocyte count showed normal neutrophil count in 32(86.49%), normal lymphocytes in 25(67.57%), normal monocytes in 29(78.38%), normal basophil in 36(97.30%) and normal eosinophils in 31(83.78%) patients. Monocyte as well as neutrophils were increased respectively in 7 (18.92%) and 5(13.51%) cases. However, lymphopenia was present in 9(24.32%) cases. Commonly 26(70.27%) had thrombocytopenia and 10 (27.03%) had normal platelets. (Table-2).

Table 2: Hematological profile of malaria positive cases (n=37)

Parameter → Species↓	HB	TLC	Neu	Lymph	Mono	Eosin	Baso	Platelets
P. falciparum	32	04	2	09	01	01	01	26
	86.49	10.81	5.41	24.32	2.70	2.70	2.70	70.27
P. vivax	05	30	32	25	29	31	36	10
	13.51	81.08	86.49	67.57	78.38	83.78	97.30	27.03
Mixed infections	00	03	04	03	07	05	0	01
	0.00	8.11	10.81	8.11	18.92	13.51	0.00	2.70

The Peripheral smear examination showed 8(21.62%) of the patients were anemic with normocytic normochromic except in 4(10.81%), where it was Normocytic hypochromic. It was observed that 2 cases (5.41%) had Macrocytic Microcytic peripheral smear. Nucleated Red Blood Corpuscles (NRBCs) /100 White Blood Corpuscles (WBCs) were seen in 8(21.62%) cases. *Hypersegmented nuetrophils* in 1(2.7%) cases and toxic changes in 4(10.81%) cases were also seen. Atypical lymphocytes were observed in 3(8.11%) cases with their predominance in *P. falciparum* 2(10.53%) and *P.vivax* 1(7.69%) cases. Reticulocytes count was found to be raised in 7(18.92%) cases (Table: 3).

Table 3: Distribution of peripheral smear changes species wise in malaria positive cases (n=37)

S. No.	Variables	Pv (n=13)	Pf (n=19)	Mix (n=5)	Total (n=37)
1.	Normocytic normochromic	5	3	00	8
		38.46	15.79	00	21.62
2.	Normocytic hypoochromic	2	2	00	4
		15.38	10.53	00	10.81
3.	Macrocytic microcytic	1	1	00	2
		7.69	5.26	00	5.41
4.	NRBCs*	2	5	1	8
		15.38	26.32	20.00	21.62
5.	Reticulocytes	1	3	3	7
		7.69	15.79	60.00	18.92
6.	Toxic granules	1	2	1	4
		7.69	10.53	20.00	10.81
7.	Atypical lymphocytes	1	2		3
		7.69	10.53	00	8.11
8.	Hypersegmented polymorphs	0	1		1
		00	5.26	00	2.70

*Nucleated Red Blood Corpuscles.

The hematological changes related with malaria infection are familiar, but precise changes may vary with category of malaria, with the background of hemoglobinopathy, nutritional status, demographic factors and malaria immunity [5]. We observed in our study several significant changes concerning with hemoglobin, platelets and white cells. Anemia was present in 86.48% and in majority of these cases was normocytic normochromic type, a finding which is parallel with the reports of Facer and Beals [3, 6]. The pathogenesis of anemia in malaria is particularly complex, multi factorial and incompletely understood. It is thought to result from a combination of hemolysis of parasitized red blood cells; accelerated removal of both parasitized and innocently un-parasitized red blood cell, depressed as well as ineffective erythropoiesis with dys-erythropoietic changes and anemia of chronic disease [7, 8]. Other factors causative to anemia in malaria include decreased red blood cell deformability, splenic phagocytosis and/or pooling, so they have an increased rate of clearance from the circulation [9]. Tumour necrosis factor alpha (TNF-α) has also been implicated and may cause ineffective erythropoiesis [8].

Anemia develops because of direct parasitization of erythrocytes by plasmodium resulting in lysis of infected cells. Certain immunological factors also play a major role in development of anemia [9]. Nonrmocytic normochromic pattern was observed as the predominant type of anaemia and it correlate with the degree of parasitemia [10]. Reticulocytes reflects the increase erythroid activity in the marrow which is due to compensatory erythroid hyperplasia [11].

The ultimate mechanism of thrombocytopenia in malaria has been not described but researchers have recommended the following mechanism which might be a causative factor for thrombocytopenia in *P. falciparum* and *P. vivax* infection:

(i) Decreased thrombopoiesis, but bone marrow examination usually shows normal or increased megakaryocytes [4];

(ii) Peripheral destruction, induced by *P. falciparum,* in which immune complexes generated by malarial antigens lead to sequestration of the injured platelets by macrophages in the spleen, although this mechanism has not been properly evaluated in *P. vivax* malaria [17];

(iii) Some workers have suggested Disseminated Intravascular Coagulation (DIC) as a major mechanism, but others have found no evidence or have hardly ever seen DIC in any of their patients, including those with severe thrombocytopenia [18];

(iv) The spleen has been implicated as a site of excess sequestration. Splenomegaly alone, however, cannot be the mechanism as most patients who develop thrombocytopenia do so early in the course of the infection before splenic enlargement has developed;

(v) In acute malaria infection platelets are found to be hypersensitive and there is increased concentrations of platelet-specific proteins such as beta thromboglobulin (ßTG), platelet factor 4 (PF4). Production of thromboxane A2 and prostacyclin also increased [18]. It has also been postulated that these hypersensitive (hyperactive) platelets will enhance haemostatic responses, and may be this is why bleeding episodes are rare in acute malarial infections, despite the significant thrombocytopenia [16].

In our study thrombocytopenia was observed in 71.6% as shown in previous studies [10]. An immune mechanism contributes to destruction of platelets [19]. The platelets survival is reduced in severe P. *falciparum* malaria. Enhanced splenic uptake or sequestration may contribute to thrombocytopenia. In patients with disseminated intravascular coagulation (DIC) platelets may removed from the circulation at sites of fibrin deposition. Thrombocytopenia in common findings in *P. falciparum* and *P. vivax* malaria and it does not correlate with severity, unless it is profound i.e. <20,000/cmm [7].

Contrasting to some studies which showed leukopenia a common finding in both non-immune and semi immune patients [3], we observed normal WBC count in 81.1% of the patients. Neutrophil count was normal in 85.1% of cases, a finding which differs from earlier reports of either neutropenia or neutrophilia among malaria cases [20]. Yet, lymphopenia and monocytosis was noticed in 24.32% and 18.90% patients respectively which is consistent with the previous studies [20, 21]. Normal eosinophil and basophil count was found in 82.4% and 98.99 %, which support former studies [3].

The present study showed total and differential count was normal in few number of cases. Stages of infection detection is important and also the drugs effect since antimalarial drugs

affect the leucocytes count. Because majority of cells are in expanded marginal pool, Neutrophil count usually remain normal. Neutrophils leucocytosis occurs due to associated bacterial infection [17].

Dhungat *et al.* concluded that although a reliable diagnostic marker, there is no prognostic significance of thrombocytopenia in malarial fevers [22]. The suggested mechanism of thrombocytopenia may be through peripheral destruction [23], the relative thrombocytopenia may also be due to a shortened life span of the platelets [24]. Antiplatelet antibodies have also been implicated in the pathogenesis of thrombocytopenia [25].

4. Conclusions

The study concludes that *P. falciparum* as well as *P.vivax* can cause significant hematological changes with high occurrence of thrombocytopenia, anemia and lymphopenia. We observed that hematological changes such as anemia, thrombocytopenia and leucopenia showed a statistically significant correlation with malarial infection. The blood changes are so distinguishing that the diagnosis of malaria should be considered in the existence of above findings [17]. It would be interesting to further evaluate a larger sample size and detect, as well as compare differences between malaria infected and non-infected febrile cases.

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