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Research article

COMPARISON OF HEMATOLOGICAL PARAMETERS BETWEEN PLASMODIUM FALCIPARUM, PLASMODIUM VIVAX AND CONTROL GROUP

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ABSTRACT

Aims: Malaria, a morbid disease of Tropical countries, may harmful if it cannot be diagnosed at its early phase, by observing the changes in hematological parameters. Our aim was to compare the hematological parameters between Plasmodium falciparum and vivax in relation to control healthy group in West Bengal. **Methods and materials:** In total 238 slide or dual antigen positive patients (120= Plasmodium vivax, 118=plasmodium falciparum) clinical hematological, renal parameters were compared. **Results:** In Plasmodium vivax and falciparum, male to female ratio was 3:1 and 1.3:1 respectively. Significant elevation in erythrocyte sedimentation rate (ESR),differential lymphocyte count, creatinine and significant lowering of platelet count, fasting blood sugar (FBS) were observed in plasmodium vivax group, whereas, significant elevation of hemoglobin, differential monocyte count, mean corpuscular hemoglobin concentration were seen in plasmodium falciparum group. Haemoglobin and FBS were significantly lower, whereas, ESR, creatinine, differential monocyte count were high in vivax group, total white blood cell and platelet count, hematocrit were low in both Plasmodium infection and mean corpuscular hemoglobin, differential lymphocyte count were significantly low in falciparum group as compared to control group. **Conclusion:** Combination of low hemoglobin, fasting blood sugar and significantly raised ESR is highly significant in predicting severity of Plasmodium infection in patients of malaria endemic areas, which was evidenced in our present study. P. falciparum and vivax suffered from lymphopenia and thrombocytopenia respectively.

Keywords: Hematological parameters, Plasmodium falciparum, Plasmodium vivax, West Bengal

INTRODUCTION

Malaria, a morbid disease of Tropical countries, like, India, Pakistan, Bangladesh, is now of global importance; because, it is responsible for 1.5 to 2 million of deaths yearly in the world[1], and three fourth of cases were suffered in India amongst 2.48 million of malarial cases of South-East Asia.[2] In Tropical countries, where malaria is endemic, it is very essential to differentiate malaria from other viral or bacterial infections by symptoms and signs[3] to prevent future fatal complications, like, cerebral, renal, and gastrointestinal. Hence in these areas, unnecessary antimalarial treatment to treat the possible cases before diagnosis is one of the causes of drug resistance. [4] In India, Plasmodium falciparum (p. falciparum) and Plasmodium vivax (p. vivax) are responsible for malaria. This disease is transmitted by the bite of the anopheles mosquito. Incubation period in malaria is ten to fifteen days. After entry, the sporozoites in the circulation in the human body, attach to the hepatocytes through the receptors for thrombospondin and properdin.[5] In the hepatocytes, sporozoites are transformed to schizonts. Each schizont produces a large number of merozoites in the hepatocyte. Most of

the merozoites are released into circulation. In the circulation, each merozoite is entered in the red blood cell (RBC) and produces 24 to 32 merozoites during the asexual stage of the life cycle. As p. falciparum enters the RBC, following thing things may occur. Firstly, increased secretion of inflammatory cytokines (tumor necrosis factor α, interleukin 1, 10 and interferon γ), secondly, due to over expression of cell adhesion molecule, endothelial cell become activated, thirdly, coagulation cascade activation as a result of platelet activation and endothelial damage, fourthly**,** sequestration of parasitized RBC due to over expression of cell adhesion molecule, iNOS.[6-10] As a result, there are changes in the morphology and number in different cell lines. Now-a-days, in case of p. vivax malaria, biochemical and hematological parameters occur. Hematological changes include hemoglobin, packed cell volume (Hct), total white blood cell count (WBC), platelet count, blood glucose, Creatinine. These changes may vary with the nutritional status, demographic factors, individual and environmental immunity.[11] Our aim was to compare the hematological and renal parameters between p. falciparum and p. vivax affected patients in relation to healthy group in West Bengal.

MATERIALS AND METHODS

Inclusion criteria: Total 238 patients [120 plasmodium vivax (males 90 and females 30) and 118 plasmodium falciparum (males 68 and females 50)] between the ages of 2 to 80 years who were admitted in our hospital from 2011 to 2013 years with symptoms and signs suggestive of malaria, like, fever with chill and rigor, headache, nausea with or without vomiting, arthralgia, diarrhea, weakness, drowsiness, confusion, stupor, anemia, jaundice, signs of dehydration, hepatomegaly, and slpenomegaly, whose blood were positive for malaria parasite in thick or thin blood film stained by Giemsa stain and/or dual antigen positive for plasmodium vivax or plasmodium falciparum. They were subdivided into 2 groups according their antigen positive type (Group A: Plasmodium vivax (N=120), Group B: Plasmodium falciparum (N=118)

Exclusion criteria: We excluded the patients suffering from different infection producing sepsis, dengue infection, viral hepatitis, Leptospirosis during this period.

Ethical clearance: This three years study was conducted only after getting permission from the ethics committee of our hospital and informed consent obtained from our patients' parties.

Detailed clinical history was taken from the patient, followed by, thorough clinical examination. Then blood was used for thick and thin blood film, stained with Gimsa stain, for detection of malaria parasite under microscope and for detection of malarial antigen of both p. falciparum and p. vivax. If at least, one asexual form of parasite was detected in 100 microscopic fields of thick blood film examined under microscope using oil - immersion lens (100xmagnification) – it is considered as positive.

After confirmation of the diagnosis, 5 ml. of blood was collected from each patient aseptically in a vial containing ethylene diamine tetra acetic acid (EDTA) and was promptly analyzed for routine hematological parameters, which included, the following, like, total WBC count, hemoglobin (Hb) estimation, hematocrit (Hct), Mean Corpuscular Hemoglobin (MCV), Mean Corpuscular Hemoglobin (MCH), mean corpuscular hemoglobin (MCHC), erythrocyte sedimentation rate (ESR), platelet count.

Another 2 ml. of blood was collected in a vial and serum was separated and estimated Creatinine, blood sugar. Hemoglobin was estimated by the acid hematin method, PCV by Wintrobe's method, blood sugar by enzymatic method, Creatinine by the alkaline picrate method. These are all conventional methods. Similarly, blood from 100 patients in the healthy group (Group C: n=100), which consist of patient's party, lab technicians having no history of disease in the recent past or present were done of same parameters. Data were collected and analyzed statistically.

Statistical analysis : The data were expressed in terms of means±SD (standard deviation). Then, all the means were compared between p. vivax and p. falciparum group and control group separately at 95% confidence interval using student 't'test and, 'p' value were extracted. 'p' value of less than 0.05 was considered as statistically significant. In statistics, a confidence interval (CI) is a type of interval estimate of a population parameter and is used to indicate the reliability of an estimate. It is an observed interval. In applied practice, confidence intervals are typically stated at the 95% confidence level.

RESULTS

Table:1 Comparison between p. vivax and p. falciparum affected patients as compared to control group

Parameters	P. vivax (Group A)	P. falciparum (Group B)	Control Group C(100)	95% CI$	P value$	95% CI@	P value@	95% CI^	P value^
Age (years)	42.82±88.4	27.2±14.2	32.49±4.15	-0.61 — 31.85	0.059	-7.11 – 27.77	0.24	-8.18 -2.39	0.00**
Temperatures (ºF)	101.72±0.20	100.9±0.19	98.1±0.31	0.75 – 0.84	0.00**	3.55 – 3.68	0.00**	2.73 –2.86	0.00**
Hemoglobin (gm%)	11.785±2.1	12.32±1.52	12.51±0.45	-1.008 – -0.07	0.02*	-1.14-- -0.30	0.00**	-0.50 – 0.12	0.22
ESR mm/1st hour	75.18±6.42	68.78±7.79	15.75±5.56	4.57 – 8.22	0.000***	43.01— 77.20	0.00**	51.87— 55.54	0.00**
MCV (fl)	82.74±8.41	83.14±7.85	84.62±8.56	-2.47 – 1.67	0.704	-4.14 – 0.38	0.10	-3.67 – 0.71	0.18
MCH (pg)	27.72±8.21	28.94±6.45	32.64±4.52	-3.10 – 0.66	0.204	-6.73 -- -3.10	0.00**	-5.21 – -2.18	0.00**
MCHC (g/dl)	34.18±1.62	35.47±1.48	35.10±1.98	-1.58 – -0.79	0.000***	-1.14 – 0.70	0.64	-0.09 – 0.83	0.11
Hematocrit	34.88±4.346	33.179±3.136	41.45±5.2	0.73— 2.669	0.000***	-7.84 -- -5.29	0.00**	-9.39 – -7.14	0.00**
Total WBC count /cc	6653.16±1999.0	6008.92±1393.5	8096.21±35.4	203.50— 1084.98	0.00**	-1837.23 -1048.86	0.00**	-2362.13 – -1812.44	0.00**
Differential count									
lymphocyte count (%)	42.14±12.42	36.39±15.45	44.13±15.87	2.17 – 9.32	0.00**	-5.75 – 1.77	0.29	- 11.93 – - 3.54	0.000***
Monocyte count (%)	10.10±2.17	13.59±6.80	8.68±4.95	-4.77 – -2.205	0.00**	-0.57 – 1.77	0.01*	2.29 – 5.52	0.00**
Neutrophil count (%)	42.67±21.02	46.39±18.18	43.77±21.31	-8.74 – 1.302	0.145	- 6.14 – 5.14	0.86	-2.65– 7.89	0.32
Eosinophil count (%)	3.01±4.19	4.12±4.79	2.92±7.1	-2.25 – 0.04	0.58	- 1.43 – 1.61	0.90	-0.39– 2.79	0.14
Basophil count (%)	1.45±2.12	1.72±1.64	0.57±0.12	-0.75 – 0.21	0.27	-0.01 – 1.07	0.055	0.82 – 1.47	0.00**
Platelet count Lack/ cc	1.61.±0.61	1.81.±0.91	2.51.±0.81	-293.95— 39410.8	0.053	-1.851241--- 70602.88	0.00**	-93244 -- -46753.37	0.00**
Creatinine mg/dl	0.94±0.57	0.71±0.45	0.71±0.25	0.098— 0.361	0.00**	0.109—0.35	0.00**	0.09-0.09	1.0
Fasting blood sugar mg/dl	93.8±18.67	100.35±10.89	98.25±11.92	-10.46— -2.63	0.00**	-8.70—0.19	0.04*	-0.94 – 5.14	0.17

$= Comparison with P.Vivax vs P. Falciparum, @= Comparison with P. Vivax vs Control, ^= Comparison with P. Falciparum vs Control, *Significant, **Very significant, ***extremely significant

A. Characteristics of the studied population –In case of p. vivax, affected male (n=90) to female (n=30) ration was 3:1, whereas, in case of falciparum (male=68, female=50), it was 1.36:1. Temperature in both p. vivax and p. falciparum groups were significantly raised as compared to control group.

B. Comparison of hematological parameters between p. vivax (120) and p. falciparum (n=118) group – P. vivax showed a significant elevation in ESR (75.18±6.42 vs. 68.78±7.79 mm / 1st hour, p=0.00), differential lymphocyte count [(42.14±12.42) % vs. (36.39±15.45) %, p=0. 00], creatinine (0.94±0.57 vs. 0.71±0.45 mg/dl, p=0. 00) and significant lowering of platelet count (161792.45±61165.62 vs. 181350.87±91122.45/cc, p=0. 05) Fasting blood sugar level (93.8±18.67 vs. 100.35±10.89 mg/dl, p=0. 00) as compared to p. falciparum group. Whereas, p. falciparum group showed a significant elevation in hemoglobin (12.32±1.52 vs. 11.78±2.1 gm/dl, p=0.02), differential monocyte count [(13.59±6.80) % vs. (10.10±2.17) %], and MCHC (35.47±1.48 vs. 34.18±1.62 g/dl, p=0.00), and significant lowering of WBC count (6653.16±1999.01 vs. 6008.92±1393.56 /cc, p=0.00), as compared to p. vivax group.

C. Comparison of hematological parameters between p. vivax group (n=120) and control group (n=100) – In p. vivax group, hemoglobin (11.78±2.1 vs. 12.51±0.45 gm/dl, p=00), MCH (27.72±8.21 vs.

32.64± 4.52 pg, p=0.00), Hct (34.88±4.34 vs. 41.45±5.2, p=0.00), total WBC count (6653.16±1999.01 vs. 8096.21±35.41 /cc, p=0.00), total platelet count (161792.45±1165.62 vs. 251350.10±81315.62 / cc, p=0.00), fasting blood sugar level (93.8±18.67 vs. 98.25±11.92 gm/dl, p=0.04) were significantly low as compared to healthy control group. Whereas, in former group showed significantly raised ESR (75.18±6.42 vs. 15.75±5.56 mm / 1st hour, p=0.00), differential monocyte count [(10.10±2.17) % vs. (8.68±4.95) %, p=0.01] and serum creatinine (0.94±0.57 vs. 0.71±0.25 mg/dl, p=0.00) as compared to later group.

D. Comparison of hematological parameters between p. falciparum group (n=118) and control group (n=100) -- MCH (28.94±6.45 vs. 32.64±4.52 pg), Hct (33.17±3.13 vs. 41.45±5.2, p=0.00), total WBC count (6008.92±1393.56 vs. 8096.21±1035.41), differential lymphocyte count [(36.39±15.45) % vs. (44.13±15.87) %, p=0.00] total platelet count (181350.87±91122.45 vs. 251350.10±81315.62 /cc, p=0.00) were reduced significantly in p. falciparum group, whereas, ESR (68.78±7.79 vs. 15.75±5.56 mm /1st hour), differential monocyte count[(13.59±6.80) % vs. (8.68±4.95) %, p=0.00], basophil count [(1.72±1.64) % vs. (0.57±0.12) %, p=0.00] were raised significantly as compared to control group.

DISCUSSION

After the development of the microscope by Antonie Van Leeuwenhoek in the 15th century, diagnosis of many parasitic diseases including malaria was possible. Moreover, in the last three decades, many more investigation methods have come into action, thus refine and modify our diagnosis. Due to huge cost for development Newer tests based on serology (Falkon assay screening test ELISA (FAST-ELISA, Rapid antigen detection systems (RDTs), real-time polymerase chain reaction, loop-mediated isothermal amplification (Lamp and Luminex), mass spectrometry[12] to diagnose accurately the malaria infection at its earliest phase, direct microscopy and sociological methods and hematological parameters for supporting diagnosis are still the gold standard for the diagnosis of malaria infection.

In our present study, male to female ratio were 3:1, 1.36:1 in p. vivax and p. falciparum respectively. But, when we considered the total number of affected patients, the ratio was 1.97:1, whereas, in the study done by Muwonge H et al. The ratio was 2.5:1.[13] In a study done by Hussain M M et al[14]. The ratios were 1.73:1 and 2:1 at p. vivax and p. falciparum respectively. Our study showed the extreme male preponderance over female in case of p. vivax infection than p. falciparum infection.

Mean age of incidence of malaria in our study in p. vivax, p. falciparum and control group were 42.88±88.4 years, 27.2±14.2 years and 32.49±4.15 years respectively, which showed an age incidence in p. falciparum was close to the control group. But in a study done by Hussain M M et al[14] age incidence were 29.25±1.9 years, 27.98±2.4 years and 29.48±2.6 years in p. vivax, P. falciparum and control group respectively, which showed an age incidence in the case of p. falciparum group was nearer to the our value (, 27.2±14.2 years), whereas, in the case of p. vivax group, age incidence was much higher in our study than the study of Hussain M M et al[14] (42.88±88.4 years vs. 29.25±1.9 years).

P. vivax, p. falciparum and control groups in our study showed mean axillary temperature of 101.7±0.01^{o} F, 100.9±0.1^{o} F and 98.1±0.31^{o} F respectively, which was higher as compared to the study done by Hussain M M et al (99.65±0.1^{o} F, 98.91±0.3^{o} F and 97.68±0.1^{o} F in p. vivax, p. falciparum and the control group respectively). [14]

In malaria, anemia is multifactorial in origin—like, hemolysis of parasitized and non-parasitized RBC, depressed or ineffective erythropoiesis[15], nutritional deficiency, especially in case of females, blood due to hook worm infestation (which is most common in West Bengal), decreased erythrocyte production. [16] Present study demoed significantly low hemoglobin in p. vivax group (11.785±2.1 gm/dl) as compared to the p. falciparum group (12.32±1.52 gm/dl, p=0.02) and control group (12.51±0.45 gm/dl, p=0.00). This observation is not consistent with previous reports of Plasmodium infection, in which, hemoglobin degradation resulting anemia had a good correlation with severity of infection due to p. falciparum.[17] In present study, low hemoglobin may be due to nutritional deficiency or increased blood loss in association with hemolysis of parasitized or non-parasitized RBCs.

In our present study, ESR was significantly raised in p. vivax than in p. falciparum (75.18±6.42 mm/1st hour vs. 68.78±7.79 mm/1st hour) as shown in other study done by Hussain M M et al (82.19±5.1 mm/1st hour vs. 77.79±4.5 mm/1st hour).[14] Again, combination of low hemoglobin and raised ESR, as shown in our study, was highly significant hematological parameters in predicting p. vivax malaria infection in endemic areas in patients who are symptomatic, but false smear negative or serologically negative due to very low parasitemia, as shown in other studies done by Erhart et al[18] and Gerardin et al.[19]

Mean value of total WBC count was significantly low in p. falciparum group as compared to p. vivax group (6008.92±1393.56/cc vs. 6653.16±1999.01, p=0.00). Commonly, the total WBC count is within normal range[20, 21], except, in a few studies, where there was evidence of leucopenia. [21, 22] In our present study, in p. falciparum group, there was also leucopenia, which was also consistent with other Indian study done in malaria endemic area, where there was also evidence of leucopenia.[23] In Panama[22] and Turkey[24], also there were evidences of leucopenia in cases of p. vivax, p. falciparum and dual infection.

In our present study, there was significant reduction differential lymphocyte count in p. falciparum ((36.39±15.45) %, p=0.00) as compared to p. vivax (42.14±12.42) % and control group (44.13±15.87) %. Usually, differential lymphocyte count in acute malaria, varies with the increase or decrease in differential WBC lines. Hence, in respect to differential lymphocyte count, varying reports (increase, decrease or normal) were observed in different studies in case of acute malaria infection[21]. According to recent literature, lymphopenia may occur in non-immune adult[21, 25] and in children in endemic areas. [17, 21] In the present study, though, the differential lymphocyte count was within normal range, but, it was in the low range of normal in p. falciparum group. The factors responsible for transient lymphopenia are: **firstly**, tissue distribution of lymphocytes[26] from freely flowing blood stream to the endothelial lining of the blood vessels to adhere[27], **secondly**, lymphocyte destruction due to Fas-induced apoptosis. [28] Owing to the high rate of lymphocyte destruction in p. falciparum affected patients, both absolute and differential count will be low.[29] This may explain why mean total lymphocyte counts was in lower range of normal in p. falciparum group.

Usually, phagocytes (Neutrophil and macrophages) and/or natural killer [NK] cells are the effector cells, been activated as a result of an immune response to blood borne pathogens. So, obviously, an early pathological hall-mark in acute malaria is reticulo-endothelial cell hyperplasia involving macrophages.[21] Monocytosis was the constant hematological finding in different studies of acute malaria[17, 30-32] as well as, in our present study, where significant monocytosis were observed in both p. vivax and p. falciparum groups [(10.10±2.17)%, vs. (13.59±6.80)%,], as compared to control group[(8.68±4.95)% p =0.01].

In our study, mean neutrophil count was within normal range as compared to control group [p. vivax= (42.67±21.02) %, p. falciparum= (46.39±18.18) %, control group = (43.77±21.31) %], which was consistent with the other study in India[31], where 85% of patients had normal Neutrophil count, as well as, study done in Singapore.[33] Though, few studies demonstrated neutropenia[27], which may be the result of increased margination and sequestration of neutrophils due to increased expression of cell adhesion molecules [ICAM—1 and VCAM—1] occurred in acute malaria. Some earlier studies demonstrated neutrophilia also.[17]

Though our study showed no difference in eosinophil count in p. vivax and p. falciparum [(3.01±4.19) %, (4.12±4.79) %] as compared to control (2.92±7.1) %, but few studies in the world[34], showed evidence of eosinopenia, whose significance was not explained. But, during recovery, these patients showed rebound neutrophilia[34], which was explained as the result of enhanced T-helper—2 cell response, which occurred during this period.

Now-a-days, lots of work have been going on regarding the platelet hemostasis in acute malaria, because of the fact that, complexes of platelet and coagulation factors surround the flowing and sequestrated parasitized RBCs and enclose vascular endothelium.[21] The different studies on acute malaria in the world[17,23, 31, 35, 36] showed that the magnitude of thrombocytopenia varied according to species and severity of infection. It was also shown that p. vivax group was associated with severe thrombocytopenia than p. falciparum group. Similarly, our present study showed thrombocytopenia in p. vivax group was more severe than that in p. falciparum group (161792.45±61165.62 /cc. vs. 181350.87±91122.45/cc), though the count was within

normal limit, as compared to control group (251350.10±81315.62/cc). This thrombocytopenia stimulates bone marrow to produce an increased number of megakaryocytes, which ultimately produce megaplatelets and leave the bone marrow to enter the circulation; the stimulating factor being thrombopoietin, a key platelet growth factor, which was described in the study done by Cyril et al[37]. As a result of increased number of megaplatelets, mean platelet volume will be increased during acute malaria infection.[17, 23].

The pathophysiology of thrombocytopenia is multifactorial. Firstly, splenic sequestration of RBC, secondly, antibody mediated platelet dysfunction, thirdly, release of adenosine diphosphate (ADP) as a result of hemolysis of parasitized RBCs, fourthly, abnormal megakaryocytosis, fifthly, invasion of platelets by parasites, sixthly, phagocytosis of platelets, seventhly, oxidative stress.[21, 38]

In our present study, MCHC was significantly reduced in p. vivax group as compared to p. falciparum group (34.18±1.62 g/dl. Vs. 35.47±1.48 g/dl, p=0.00), but, only MCH were reduced in both groups as compared to control group (p. vivax = 27.72±8.21 pg., p. falciparum = 28.94±6.45 pg., control = 32.64±4.52 pg.). But, all the RBC indices were within normal limits, which may be due to the following factors: firstly, low production of cytokines, secondly, less endothelial cell activation; thirdly, milder changes in coagulation profile, fourthly, diminished sequestration, fifthly, decreased hemolysis in less severe malaria.

Our present study demoed significantly raised serum creatinine level in p. vivax group as compared to p. falciparum (0.94±0.57 mg/dl, vs. 0.71±0.45 mg/dl., p=0.00) and control group (0.71±0.25 mg/dl.). This study was consistent with the study done by Ogdaboyl E O et al[39] and Delanghe J et al[40], in which, raised creatinine was seen in the Nigerian population. The elevated serum creatinine is probably due to ineffective filtration ability as a result of renal functional impairment.

In our study, plasma glucose level was lower in p. vivax group (93.8±18.67 mg/dl) as compared to p. falciparum group (100.35±10.89 mg/dl) and control group (98.25±11.92 mg/dl). This low blood glucose levels as well as low hemoglobin level are the two most reliable indicators and hematological parameters in predicting the presence of p. vivax malaria as shown in other studies also[18, 19].

CONCLUSION

Malaria infection was twice more common in males than females. Younger age group was the victim of plasmodium falciparum, whereas, plasmodium vivax affected higher age group. Plasmodium vivax affected patients were more anemic. The combination of low hemoglobin, low fasting blood sugar and significantly raised ESR is highly significant in predicting severity of Plasmodium infection in patients of malaria endemic areas, which was evidenced in our present study. Lymphopenia was observed in Plasmodium falciparum affected patients, whereas, thrombocytopenia in Plasmodium vivax affected patients, but, significant monocytosis was observed in both groups. Significantly reduced MCHC was observed in Plasmodium vivax groups, whereas, MCH was reduced in both groups.

Conflict of interest: Nil.

REFERENCES

1. Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI. The global distribution of clinical episodes of Plasmodium falciparum malaria. Nature. 2005;434: 214-17
2. Yadav D, Chandra J, Dutta AK. Benign tertian malaria: how benign is it today? Indian J. Pediatr. 2012;79(4): 525-27
3. Lathia TB, Joshi R. Can hematological parameters discriminate malaria from non malarious acute febrile illness in the tropics? Indian J. Med. Sci. 2004;58: 239-44
4. Barnish G, Bates I, Iboro J. Newer drug combinations for malaria. BMJ. 2004;328: 1511-12
5. Nadeem M, Ali N, Qamar MA. Hematological findings in acute malarial infection list of authors along with highest qualification and institute. Biomedica. 2002;18: 62-65
6. Costa E T M, Avril M, Nogueira A, Gysin J. Cytoadhesion of Plasmodium falciparum-infected erythrocytes and the infected placenta: a two-way pathway. Brazilian Journal of Medical and Biological Research. 2006;39(12): 1525-36
7. Francisschetti I M B. Does activation of blood coagulation cascade have a role in malaria pathogenesis? Trends in Parasitology. 2008;24(6): 258-63

8. Ghosh K, Shetty S. Blood coagulation in falciparum malaria—a review. Parasitology Research. 2008;102(4): 571-76
9. Clark LA, Budd AC, Alleva LM, Cowden WB. Human malarial disease: a consequence of inflammatory cytokine release. Malaria Journal. 2006;5:85
10. Haldar K, Mohandas N. Malaria, eryrhrocytic infection, and anemia. Hematology/The Education Programme of the American Society of Hematology. 2009;10:87-93
11. Price R N, Simpson J A, Nosten F. Factors contributing to anemia after uncomplicated falciparum malaria. Am. J. Trop. Med. Hyg. 2001;65: 614-22.
12. Ndao M. Diagnosis of parasitic diseases: old and new approaches. Interdisciplinary Perspectives on Infectious Diseases. 2009; Article ID 278246.
13. Muwonge H, Kikomeko S, Sembajjwe LF, Seguya A, Namugwanya C. How reliable are Hematological Parameters in predicting Uncomplicated Plasmodium falciparum Malaria in an Endemic region? ISRN Tropical Medicine. 2013; Article ID 673798.
14. Hussian MM, Sohali M, Abhishek K, Raziuddin M. Investigation on Plasmodium vivax infection influencing the host factors in tribal dominant and malaria endemic population of Jharkhand. Saudi J Biol Sci. 2013;20(2): 195-203
15. Weatherall DJ, Miller LH, Baruch DI, Marsh K, Doumbo OK, Casals-Pascual C. et al. Malaria and the red cell. Hematology Am. Soc. Hematol. Educ. Program. 2002;35-57
16. Philips RE, Pasvol G. Anemia in Plasmodium falciparum malaria. Baillieres Clin. Hematol. 1992;5: 315-30.
17. Maina RN, Walsh D, Gaddy C, Nongo G, Waitumbi J, Otieno L. Impact of Plasmodium falciparum infection on hematological parameters in children living in Western Kenya. Malar. J. 2010;9(suppl 3):S_4
18. Erhart LM, Yingyuen K, Chuanak N, Buathong N, Laoboonchai A, Miller RS. et al. Hematological and clinical indices of malaria in a semi-immune population of Western Thailand. Am. J. Trop. Med. Hyg. 2004;70: 8-14.
19. Gerardin P, Rogier C, Ka AS, Jouvencel P, Brousse V, Imbert P. Prognostic value of thrombocytopenia in African children with falciparum malaria. Am. J. Trop. Med. Hyg. 2002;66: 686-91
20. Haroon H, Fazel PA, Naeem A, Mobin A, Naqvi A, Makki K. Hide and seek hematological aspects of malaria—a developing country perspective. Journal of Infection in Developing Countries. 2013;7(3): 273-79
21. Abdalla S H, Pasvol G. malaria: A Hematological Perspective.2004; Imperial College Press, London. www.uptodate.com/contents/anemia-in-malaria
22. Reiley C G, Barrett Jr O. Leukocyte response in acute malaria. Am. J. of the Med. Sciences. 1971;262(3): 153-58
23. Chandra S, Chandra H. Role of hematological parameters as an indicator of acute malarial infection in uttarakhand state of India. Mediterranean Journal of Hematology and infectious Diseases. 2013;5(1): Article ID e2013009.
24. Koltas LS, DEmirhindi S, Hazar S, Ozcan K. Supportive presumptive diagnosis of plasmodium vivax malaria: thrombocytopenia and red cell distribution width. Saudi Medical Journal. 2007;28(4): 535-39
25. Richards M W, Behrens RH, Doherty JE. Short report: Hematological changes in acute, imported Plasmodium falciparum malaria. Am. J. of Trop. Med. And Hyg. 1998;59(6): 859
26. Hviid L, Kemp K, Kern P. What is the cause of lymphopenia in malaria? Infection and Immunity. 2000;68(10): 6087-89
27. Dale DC, Wolff SM. Studies of the Neutropenia of acute malaria. Blood. 1973;41(2): 197-206
28. Kern P, Dietrich M, Hemmer C, Wellinghausen N. Increased levels of soluble Fas ligand in serum in Plasmodium falciparum malaria. Infection and Immunity. 2000;68(5): 3061-63
29. Balde AT, Sarthou J, Roussilhon C. Acute Plasmodium falciparum infection is associated with increased percentage of apoptotic cells. Immunology Letters. 1995;46(1-2): 59-62
30. Abdalla SH. Peripheral blood and bone marrow leucocytes in Gambian children with malaria: numerical changes and evaluation of phagocytosis. Annals of Tropical Paediatrics. 1988;8(4):250-58
31. Akhtar S, Gumashta R, Mahore S, Maimoon S. Hematogical changes in malaria: a comparative study. Journal of Pharmacy and Biological Sciences. 2012;2(4):15-19

32. El-Shoura SM. Falciparum malaria in naturally infected human patients: IV-Ultra structural changes in peripheral white blood cells. Annales de Parasitologie Humaine et Comparee. 1993;68(4):169-75
33. Kueh YK, Yeo KL. Hematological alterations in acute malaria. Scandinavian Journal of Hematology. 1982;29(2):147-52
34. Davis TME, Ho M, Supanaranond W, Looareesuwan S, Pukrittayakamee S, White N J. Changes in the peripheral blood eosinophil count in falciparum maqlaria. Acta Tropica. 1991;48(3): 243-46
35. Taylor W RJ, Widjaja H, Basri H. Changes in the total leukocyte and platelet counts in Papuan and non Papuan adults from Northeast Papua infected with acute Plasmodium vivax or uncomplicated Plasmodium falciparum malaria. Malaria Journal; 2008;7: article 259.
36. Khan SJ, Abbas Y, Marwat MA. Thrombocytopenia as an indicator of malaria in adult population. Malaria research and treatment. 2012;Article ID 405981.
37. Kreil A, Wenisch G, Brittenham S, Looareesuwan S, Peck-Radosavljevic M. Thrombopoietin in Plasmodium falciparum malaria. British Journal of Haematology. 2000;109(3):534-36
38. Lacerda MVG, Maurao MPG, Coelho H C, Santos JB. Thrombocytopenia in malaria: who cares? Memorias do Instituto Oswaldo Cruz. 2011;106910: 52-63.
39. Ogdaboyl EO, Tsado RD. Renal and hepatic dysfunction in malaria patient in Minna, North Central Nigeria. Online J. Health Allied Sci. 2009; 8(3):8
40. Delanghe J, De Slypere JP, De Buyzere M, Robbrecht J, Wieme R, Vermeulen A. Normal reference values for creatine, creatinine and carnitine are lower in vegetarians. Clin. Chem. 1989;35(8):1802-03