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Review Article

Hematological Changes in Malarial Patients from National Hospital, Lahore

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Author`s Contribution

[NJ, NA]Conception and design, Collection and assembly of data, Analysis and interpretation of the data, Statistical expertise,[JJ]Final approval and guarantor of the article

Article Info.

Received: Jan 25, 2022
Acceptance: 01 May, 2022

Conflict of Interest: None
Funding Sources: None

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DOI: 10.53389/RJAHS.2022010104

A B S T R A C T

Background: Malaria is well known worldwide parasitic disease with high rate of morbidity and mortality that usually found in tropics and subtropics areas. It is major health problem with regular and sometime long standing endemic disease caused by *Plasmodium* species.

Objective: The objective of this study was to observe malaria prevalence and malaria related hematological changes in individuals that visited National Hospital and Medical Centre Lahore, Pakistan.

Methodology: The retrospective study was conducted on malaria-suspected individuals that visited hospital from 1st August 2015 to 31st December 2017. Blood of suspected individuals were analyzed for the presence of Histidine-rich protein-II from *P.falciparum* and *Plasmodium Lactate dehydrogenase* from *Plasmodium* species through rapid chromatographic immunoassay. A Complete Blood Count (CBC) were also performed by Cell Dyn Ruby and Sysmex XE-2100 machines.

Results: Among the 5030 study population, 139 cases were diagnosed with malarial disease. Forty-nine out of total 139 patients were found anemic with 20 cases of microcytic blood picture. Marked thrombocytopenia was observed in 104 patients with varying degree of mild 92, moderate 07 and severe 05 thrombocytopenia. The present study showed majority of 102 cases with normal Hematocrit while 37 had low hematocrit. Normo-WBC count was observed in 107 patients, while 58 cases had elevated neutrophils with normal Eosinophils in 134 cases, Basophils 138 and monocyte count in 91 cases. Moreover, results also showed lymphopenia and lyphocytosis in 87 and 4 cases respectively.

Conclusion: The study reveals the presence of hematological abnormalities including anemia, mild to severe thrombocytopenia, lymphopenia and mild leukocytosis in malarial patients. Management of malarial patients can be coupled with general awareness among public and health care officials for the control of malarial vector in combating malaria and can be enhanced uncomplicated cases without the use of blood transfusion.

Keywords: Anemia, *Anopheles* mosquitoes, Thrombocytopenia, Plasmodium.

Introduction

The word malaria comes from the Italian words "mal" (bad) and "aria" (air). It stood for dirty or nasty air.[1] Giovanni Batista Grassi and Raimondo Filetti first introduced the names *Plasmodium vivax* and *P. malariae* for two of the malaria parasites in 1890.[2]

Malaria is caused by parasite of genus *Plasmodium* and there are 4 species *P. vivax*, *P. falciparum*, *P. malariae* and *P. ovale*.[3] Malaria is transmitted to humans through the bite of infected female Anopheles mosquitos, which carry infective sporozoites of the malaria parasite in their salivary gland. But others ways of malarial transmission are organ resettlement, blood transfusion, or by using blood contaminated needles or syringes.[4] The symptoms of malaria are associated with erythrocyte stage, because of the waste and toxins caused by destruction of the red blood cell by *Plasmodium.* [5]

There are two most commonly used diagnostic approaches used for the diagnosis of malaria, which are clinical and a microscopic examination.[4] First one is reliable and sufficient, and it should be confirmed by a lab tests. For the second one, thick and thin blood peripheral films preparation are done which is a gold standard method. The main goal of the malaria parasite are the red blood cells so peripheral blood

smears is the major diagnostic tool for the disease.[5] Others techniques may include; Immunological techniques which includes Antigen based Rapid Diagnostic Test (RDT) and Antibodies based Enzyme linked immunosorbent assay (ELISA), and Molecular technique is Polymerase Chain Reaction (PCR).[7]

The most essential measure to prevent malaria is a vaccination. Other ways are spraying, mosquitos' coils, wearing protective clothes, screening doors and windows and awareness by giving pamphlets or by conducting seminars.[8] In previous study , it was reported that 300-500 million cases and 1.5-2.7 million deaths caused by malaria parasite each year.[6] Globally, there were 212 million (range 148-304 million) new cases and 4429000 killings were estimated in 2015.[7] While 216 million cases were reported in 2016 which around 5 million cases were above average compared to 2015.[7] Despite a well-established malaria control programme 500,000 malaria infections and 50,000 malaria-attributable deaths occur each year in Pakistan.[11] Pakistan's climate ranges from tropical to temperate with dry conditions.[12] *P. vivax* (responsible for approximately 64% of infections) and *P. falciparum* (causing 36% of infections) are the two prevalent *Plasmodium* species in Pakistan.[13] The objective of current study was to observe the prevalence of malaria and investigate the hematological changes in malarial patients.

Methodology

This retrospective study was based on the data of malaria suspected individuals visiting Out Patient Department and In patient Department in a Chughtai lab at National Hospital from 1st August 2015 to 31st December 2017.

Individuals with chills, fever, headache, back pain, cough, chest pain, or gastrointestinal disturbance, regardless of gender or age, were chosen for the study. All the individuals presenting with known cause of fever or without (malaria smear negative) were excluded from this study. Blood samples were collected in a EDTA collecting tubes with a help of a tourniquet. No special preparation of the individuals is necessary prior to the specimen collection by approved technique.

All of the blood samples were taken by trained professionals who are familiar with working with all types of individuals. **S**uitable site for venipuncture was selected by putting the tourniquet 3 to 4 inches above the selected puncture site in patient. Non-latex gloves were used during the procedure. After choosing a vein, thoroughly clean the region in a circular motion. Then patient was requested to create a fist. Thumb was used to pull the skin while a strong hold was made on the patient's arm. The angle of the needle was 15-30 degree with the arm.

As soon as the collecting tube was full, the tourniquet was taken off. The puncture site was promptly covered in gauze. Pressure was applied to prevent the development of a hematoma. Supplies and materials that were contaminated were disposed of in the designated receptacles. The patient's name and lab number were written on each collection tube.

All blood samples were taken in EDTA collection tubes for CBC analysis. Blood samples were also analyzed through ICT. An automated Sysmex XE-2100 and Cell Dyn Ruby machine were used for CBC. The thick and thin blood peripheral smears stained with a Giemsa dye were used for conformational detection of the malarial parasite.

All the reagents were ready to use. Before opening the package it was ensured that all the test devices were brought to the room temperature. The test devices were stored at 2-30˚C and were stable through the expiration date printed on a sealed pouch. Each test device contain internally control which exhibited a burgundy colored band of the immunocomplex of a goat anti-mouse IgG/ mouse IgG (anti-Pan-LDH and anti-pHRP-II) gold conjugates regardless of the color development on any of the Test bands.

Prior to the testing device, the specimen and buffer were allowed to the room temperature (15-30˚C). Test cassettes were removed from the foil pouch. Test cassettes were placed on a clean and level surface and ensured that the devices were label with the specimen's ID number. With a 5ul mini plastic dropper provided the specimen of whole blood was pickup and then transfered it into the sample well (s1). Then 3 drops (120ul) of buffer were added into the buffer well (S) immediately. Results were read in 20-30 minutes.

For P.f or mixed malaria Positive: One line appeared in the control area, one line appeared in the Pan (T1) line area and one line appeared in Pf (T 2) Line area. P.f Positive: One line appeared in the control area, one line appeared in P.f (T 2) line area. For Negative Only one colored line appeared in the control area (Figure 5). For Invalid: Failure of the appearance of control lines either insufficient specimen volume or inaccurate procedural skills were likely reasons in the failure of control line. The procedure of the test was reviewed and new devices were used to repeat the test. The diagnosis of malaria was confirmed by thin and thick peripheral blood films stained with a Giemsa and Field stains for the malaria parasite. All the positive malaria smears were examined by the hematologist for the verification and also for the platelets count and others hematological changes.

Blood spreader was made from a slide which has ground glass polished sides. A small drop of a blood was placed at the center of the clean dry slide. By holding the spreader at 30 degree angle, the spreader was allowed to draw back to touch the drop of blood and hold it at 30 degree angle, and allowed the blood to spread into the edge of the spreader. Then spreader was pushed quickly forward to spread out the blood to covered one- half to two- thirds the slide. The slides were allowed to air dry. Then thin smears were fixed with absolute methanol for 30 seconds.

When the slides were completely air dried, placed them on the staining rack. After placing on the staining rack, slides were covered with the Giemsa stain (1:20 by adding 1 part of stain and 19 part of deionized water) for 15 - 20 minutes. Rinsed in a tap water and air dried it at the end.

Thick blood film was prepared by applying drop of blood to a clean microscope slide. By using the corner of a second slide, the film was spread in a circle about the size of a dime. Allowed it to air dry.

Staining results
Red Blood Cells …… Pink
Cytoplasm
Neutrophils ……..Light pink
Eosinophils …….. ..Light pink
Large Lymphocytes ……blue
Small Lymphocytes ……Darker blue
Monocytes …….. …Greyish-blue
Granules
Eosinophils …….. ..Orange to red
Neutrophils …….. ..pink to Purple
Basophils …… Dark blue
Platelets …….. ……Purplish-blue

When the thick smears were completely air dried, placed them on the staining rack. After placing on the staining rack, slides were covered with a reagent A for 3 secs and allowed to wash with a tap water. After washing slides were again covered with a reagent B for 3 secs and again allowed to wash with a tap water and Air dried.

Slides were focus at 10X objective where the red blood cells were in a one layer. Oil immersion was put into the slides and switched to the oil immersion lens. At least 200 fields were examined for the visualization of malaria parasites and cells counts.

Results

All of the 139 thin peripheral smears were showed a significant hematological changes while on a thick smears 83 (60%) cases were detected with P. falciparum and 56 (40%) cases were reported with a P. vivax. The study was conducted at National Hospital and Medical Center Lahore. Total 5030 samples were collected from the individuals for the presence of malaria parasite and in which 139 patients were diagnosed with a malarial disease as shown in (Table I). In this investigation, the range of individual's ages were between 2 years to 77 years (Table I). Most of the cases were diagnosed in the age group of 21-30 years where 42 (30%) cases were reported as a malarial disease. In this study the males were 87 (63%) and females were 52 (37%) (Table II). There were males predominance with a females.

Low platelets count was present in 104 (75% out of

Table I: Age wise distribution of confirmed malarial cases

No	Age (years)	No. of confirmed malarial cases No (%)
1	2-10	09 (6)
2	11-20	26 (19)
3	21-30	42 (30)
4	31-40	29 (21)
5	41-50	10 (07)
6	51-60	04 (03)
7	61-70	14 (10)
8	71-77	05 (04)
Total no. of confirmed malarial cases 139(100)		

Table II: Age and Gender wise distribution of malarial patients

Serial No	Age group (years)	Males (%)	Females No. (%)	No. of malarial patients
1	2-10	06 (4.3)	03 (2.1)	09 (6.4)
2	11-20	12 (8.6)	14 (10.0)	26 (18.7)
3	21-30	31 (22.3)	11 (7.9)	42 (30.2)
4	31-40	21 (15.1)	08 (5.7)	29 (20.8)
5	41-50	06 (4.3)	04 (2.8)	10 (7.1)
6	51-60	02 (1.4)	02 (1.4)	04 (2.8)
7	61-70	07 (5.0)	07 (5.0)	14 (10.0)
8	71-77	02 (1.4)	03 (2.1)	05 (3.5)
Total patients		87 (62.5)	52 (37.4)	139 (100)

Table III: Platelet count in the malarial patients

Platelet Count		Range (10^9/L)	N (%)
Normal		150-400	35 (25)
Thrombocytopenia	Mild	50-149	92 (66)
	Moderate	31-49	07 (05)
	Severe	≤30	05 (04)
	Total	05-149	104 (75)
Total			139 (100)

Table: IV: Distribution of hematological values of the malarial cases in males and females

Hematological parameters	Reference Range	Number of Patients (Total 139) with variable test values		
		Low No. (%)	Normal No. (%)	High No. (%)
Hemoglobin	11.5-16 g/dl (Female) 13-18 g/dl(Male)	49 (35)	90 (65)	0 (0)
Total Red Blood Cells	4.4-6.5×1012/L(Male) 4-6×1012/L(Female)	24 (17)	115 (83)	0 (0)
Hematocrit	36-46 %(Female) 38-52 %(Male)	37 (27)	102 (73)	0 (0)
Mean corpuscular Volume	75-95 fl	20 (14)	119 (86)	0 (0)
Mean Corpuscular Hemoglobin	26-32 pg	27 (19)	108 (78)	04(03)
Mean Corpuscular Hemoglobin Concentration	30-35 g/dl	11 (8)	127 (91)	01 (01)
Platelets count	150-400 ×109/L	104 (75)	35 (25)	0 (0)
White Blood Cells count	4-11 ×10^9/l	28 (20)	107 (77)	04 (03)
Neutrophils	40-75 %	06 (04)	75 (54)	58 (42)
Lymphocytes	20-50 %	87 (62)	48 (34)	04 (03)
Monocytes	2-10 %	05 (04)	91 (65)	43 (31)
Eosinophils	1-6 %	0 (0)	134 (96)	05 (04)
Basophils	0-2%	0 (0)	138 (99)	01 (01)

Table V: Distribution of hematological values of the malarial cases in males

Hematological parameters	Reference Range	Number of Patients (Total 87) with variable test values		
		Low	Normal	High
Hemoglobin	13-18g/dl	30 (21.5)	57 (41.0)	0 (0)
Total Red Blood Cells	4.4 6.5×1012/L (Male)	15 (10.7)	72 (51.7)	0 (0)
Hematocrit	38-52 %	23 (16.5)	64 (46.0)	0 (0)
Mean corpuscular Volume	75-95 fl	12 (8.6)	75 (53.9)	0 (0)
Mean Corpuscular Hemoglobin	26-32 pg	17 (12.2)	68 (48.9)	02 (1.4)
Mean Corpuscular Hemoglobin Concentration	30-35 g/dl	07 (5.0)	79 (56.8)	01 (0.7)
Platelets count	150-400 ×10^9/L	65 (46.7)	22 (15.8)	0 (0)
White Blood Cells count	4-11 ×10^9/l	17 (12.2)	67 (48.2)	02 (1.4)
Neutrophils	40-75 %	04 (2.9)	47 (33.8)	36 (25.8)
Lymphocytes	20-50 %	55 (39.5)	30 (21.5)	02 (1.4)
Monocytes	2-10 %	03 (2.1)	56 (40.2)	28 (20.1)
Eosinophils	1-6 %	00 (0)	83 (59.7)	04 (2.8)
Basophils	0-2%	00 (0)	86 (61.8)	01 (0.7)

139) cases, in which mild thrombocytopenia patients with a range of 50-149 ×109/L were 92 (66% of 139 or 88% of 104). 07(05% of 139 or 7% of 104) patients had a moderate thrombocytopenia with a range between 31-49 ×109/L. and severe thrombocytopenic cases were 05 (4% of 139 or 5% of 104) with a range of 5.5-30. While 34 (24% of 139) patients had a normal platelets count (Table III).

Out of 139 malarial diagnosed cases, there were 49 (35%) patients were anemic at the time of presentation, from which normocytic normochromic anemic were 29 patients (21% of 139 or 59 % of 49) and microcytic were 20 cases (14% of 139 or 41% of 49) (Table IV). Low red cell count was seen in this current study in 24 patients (17% of 139) cases while 37 cases (27% of 139) had low hematocrit and 102 patients (73% of 139) had normal hematocrit (Table IV). Normal MCV was seen in 119 (86%) malarial diagnosed patients, low in 20 (14%) cases. MCH was typically normal in 108 patients (78% out of 139) and in 27 patients (19% out of 139) had low MCH whereas 04 (03% out of 139) had high levels. Normal MCHC was seen in 127 (91%), high in 01 (01%) and low in 11 (8%) (Table IV). Total leukocytes findings showed 107 (77%) to be in normal range.

Differential leukocytes count showed neutrophils count in the normal range in 75 (53%) cases. 87 (62%) had a low lymphocyte counts (lymphopenia), 48 (34%) had a lymphocyte count in a normal range. In this investigation many

Table VI: Distribution of hematological values of the malarial cases in females

Hematological parameters	Reference Range	Low	Normal	High
Hemoglobin	13-18g/dl	19 (13.6)	33 (23.7)	00 (0)
Total Red Blood Cells	4-6×10^{12}/L Females	09 (6.4)	43 (30.9)	00 (0)
Hematocrit	38-52 %	14 (10.0)	38 (27.3)	00 (0)
Mean corpuscular Volume	75-95 fl	07 (5.0)	45 (32.3)	00 (0)
Mean Corpuscular Hemoglobin	26-32 pg	10 (7.1)	40 (28.7)	02 (1.4)
Mean Corpuscular Hemoglobin Concentration	30-35 g/dl	04 (2.8)	48 (34.5)	00 (0)
Platelets count	150-400 ×10^9/L	39 (28.0)	13 (9.3)	00(1.4)
White Blood ells count	4-11 ×10^9/l	11 (7.9)	40 (28.7)	02 (1.4)
Neutrophils	40-75 %	02 (1.4)	28 (20.1)	22 (15.8)
Lymphocytes	20-50 %	32 (23.0)	18 (12.9)	02 (1.4)
Monocytes	2-10 %	02 (1.4)	35 (25.1)	15 (10.7)
Eosinophils	1-6 %	00 (0)	51 (36.6)	01(0.7)
Basophils	0-2%	00 (0)	52 (37.4)	00 (0)

of the malarial diagnose patients (65%) found normal monocyte count but the previous studies has also show increase monocyte count as well as Eosinophils and Basophils were also found normal in the ,many of the cases 134 (96%) and 138 (99%) (Table IV).

Table VII: Hematological changes in a *P. falciparum and P. vivax*

Hematological changes	*P. falciparum* No. (%)	*P. vivax* No. (%)
Low Haemoglobin	32 (38)	17 (30)
Low platelets count	64 (77)	40 (71)
Normal WBC count	62 (75)	45 (80)
Low WBC count	12 (14)	16 (28)
High WBC count	3 (4)	1 (2)
Normal Neutrophils count	43 (53)	32 (57)
Low Neutrophils count	4 (5)	2 (4)
High Neutrophils count	37 (44)	21 (36)
Normal Lymphocytes count	31 (37)	17 (30)
Normal Monocytes count	56 (67)	35 (63)
Normal Eosinophils count	82 (99)	52 (93)

In present study total 87 (62.5%) males were diagnosed with a malaria. In current study 52 (37.4%) females were diagnosed with malaria.

According to our there with 83 (60%) and 56 (40%) cases were diagnosed with a P. falciparum and P. vivax respectively. In the patients with a P. falciparum 62 (75%) had a normal WBC count and in the P. vivax there were 45 (80%) cases with a normal WBC count (Table VII).

Discussion

In this study, 139 confirmed cases of malarial diagnosed patients in both males and females. In which males 87 (63%) were more commonly affected than the females 52 (37%) as a better dressed so they are relatively protected against mosquito bite. These results were very similar to the previous studies.[14] It was noticed in a study that were remarkable changes occurred with hemoglobin, platelets and white cells and lymphocytes in the patients diagnosed with malaria. The results indicated that PCV was slightly less in 37 (27%) in the malaria infected patients, in which 23 (16.5%) patients were males and 14 (10%) were females. This finding are slight changed from a study performed in 2014, showed significant decrease PCV level among the malarial infected patients.[15] These results were also slightly different from the work held by Garba[16] This PCV level slightly lower due to the some degrees of hemolysis in malaria infected patients. It may also be seen due to normocytic normochromic anemia seen in malaria infected subjects.

In this organized study, there were 35% of the patients had anemic which is different and lower from the results reported in 2012[17] but in our study majority of these cases were normocytic and normochromic which is familiar with Facer and Beales reports.[8,9] There were 49 patients with anemia in which males were 30 (21.5%) and a 19 (13.6%) were females. In our study 32 (38%) cases were diagnosed with a P. falciparum and 17 (30%) with a P. vivax, which is lower than the previous report in 2008.[4] In malarial patients' pathogenesis of anemia is particularly complicated and incompletely understood. Other factors that involved to anemia are decreased the ability of red blood cell to change shape under a stress, splenic phagocytosis and as well as high level of removal occurs from the circulation.[10]

The inconsistent degree of a reduction in circulating platelets are consistently report in the different types of malaria.[21] This study indicated that 104 (75%) individuals diagnosed with malarial having a thrombocytopenia which is consistent with the results of Robinson studied in 2001[22] and is higher than other studies. investigators Rodriguez which was studied in 2005.[23] Ninety-two 92 (66%) patients had a mild low platelets count, 07 (05%) had moderate and 05 (04%) had severe thrombocytopenia, while the patients with normal

platelet count were 35 (25%). According to the study organized in Pakistan indicated that there were 87.27% patients had thrombocytopenia.[11] This was similar to our results. According to the other study which indicated 58% of the patients with low a platelet counts that is lower than our study. In the present organized studied there were 66% mild, 05% moderate and 04% severe cases were occurred which was closed to the results in previous study conducted by Shaikh MA.[24]

In Contrast to other reports, leukopenia was observed as a common finding in both non-immune and semi immune patients.[25] According to our study 62 (77%) patients with a normal WBC count were reported with a P. falciparum while 45 (80%) with a P. vivax which is near to the previous reports.[17] There were 28 (20%) cases with a low leukocyte count in which 17 (12.2%) cases were reported in males and 11 (7.9%) were females and 12 (14%) and 16 (28%) due to P. falciparum and P. vivax respectively which is quite different with a report in a 2008.[4] In present organized study lymphocyte count was low in 87 (62%) patients in which 55 (39%) were males and 32 (23%) patients were females which is different to the report conducted in 2014.[26] Neutrophils count was normal in 75 (54%), in which males were 47 (33.8%) and females were 22 (15.8%) diagnosed with a malaria parasite, these findings which were slightly lower from earlier reports of among malaria cases.[12] In this study 06 (04%) of males and 02 (1.4%) cases of females had a low neutrophils count. Eosinophils and Basophils count were present in 96% and 99% of the patients in which males and females were 83 (59.7%) and 51 (36.6%) respectively, which assists previous investigators.[9] These results were also nearly to the study held in Karachi, Pakistan.[28]

In the present study all of the positive cases on malaria rapid diagnostic test were also confirmed by the blood peripheral smears for the presence of a plasmodium parasites, and in which 83 (60%) cases were diagnosed with a P. falciparum while 56 (40%) cases were diagnosed with a P. vivax which is quite similar to the previous study[29] but unfortunately different from study conducted in 2011.[30] In the last study malaria prevalence in Lahore was 2%.[29] Environmental changes resulting in water-logging may have reduced suitable habitats for the more efficient vector, female Anopheles mosquitoes.[31] Additionally although, overall socioeconomic conditions and the public health infra-structure are comparatively better in Lahore especially in defense area than in the rest of the others sites in Lahore, but the patients from the others sites that visited National Hospital and difference in climate from the previous few years may play a role in a results and controlling malaria. [32]

Conclusion

This study was concluded significant abnormalities in hematological parameters of malarial patients with occurrence of leukocytosis and lymphopenia along with a decrease in hemoglobin both in children and adults. Mild to severe presences of thrombocytopenia. Microscopy remains the gold standard to confirm MP in suspected patients and RDTs have also acceptable sensitivity. It is also very necessary to conduct seminars throughout the year for the prevention of malaria in a city.

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