CODEN [USA] : IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

http://doi.org/10.5281/zenodo.4394648

Available online at: http://www.iajps.com *Research Article*

ALTERATION OF COAGULATION PROFILE IN MALARIA PATIENTS AND ITS CORRELATION WITH DEGREE OF PARASITEMIA.

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Article Received: June 2020 **Accepted:** July 2020 **Published:** August 2020

Abstract

Worldwide 3.2 million people are prone to malaria disease caused by Plasmodium species including Plasmodium falciparum and Plasmodium vivax while P. falciparum is the leading cause of deaths due to abrupt development of infection along with severe complications. It is known as the fifth leading cause of infectious diseases. The hold on the disease seemed to be difficult due to the ability of a parasite to create resistance in response to drugs and almost 85% reported cases of malaria were caused by falciparum species which is mostly found in the warmer and moist areas of the globe. This study considered the 100 patients and obtained repercussions of malarial patients indicate that 35.9% of cases of P. falciparum and 64.1 % cases of malaria were due to P.vivax. The mean values of age for patients and the control group was 25.35 ± 14.4 years. As the p-value for coagulation profile including APTT, PT, and d dimer was greater than 0.05. The platelet counts were measured both in P. vivax and P. falciparum malaria patients correlated with the degree of parasitemia as the P-value is less than 0.001 while the degree of correlation r = 0.894. Coagulation profile for P. vivax patients shows the normal PT and APTT while greater PT and APTT values in infected patients of P. falciparum were correlated with the degree of parasitemia as r = 0.0892. The percentage base on determining parasitic load was 53.3% of patients with a mild degree of parasitemia, 29.3% with moderate, and 17.4% suffered from severe parasitemia. Most coagulation abnormalities have risen because of liver involvement.

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Please cite this article in press Roman Abbas et al, ***Alteration Of Coagulation Profile In Malaria Patients And Its Correlation With Degree Of Parasitemia.,*** *Indo Am. J. P. Sci, 2020; 07(08).*

INTRODUCTION:

Worldwide 3.2 million people are prone to malaria disease caused by Plasmodium species including Plasmodium falciparum and Plasmodium vivax while P. falciparum is the leading cause of deaths due to abrupt development of infection along with severe complications. Approximately 350-500 million annually reported cases, 1.1-2.7 million deaths occur every year as a repercussion of several life-threatening issues of malaria. Therefore, globally it is known as the fifth leading cause of infectious diseases.[1] The hold on disease seemed to be difficult due to the ability of a parasite to create resistance in response to drugs and almost 85% reported cases of malaria were caused by falciparum species which is mostly found in the warmer and moist areas of the globe.[2] In malarial parasite, P. vivax considered the second most leading cause of health issues as it might be the reason of malaria relapses because of reactivation of hypnozoites.[4] In few cases enlarged spleen burst that could be lethal for the life of patients.[3] 90% of all the cases were found in Africa reported by WHO, where 1 million deaths occurred every year. A better management system can be helpful in the reduction of morbidity and mortality of malarial disease through earlier diagnosis with effectual treatment. Health clinics and hospital use the microscopic examination to diagnosis the parasite which is insufficient to ensure the good outcomes for maintenance of health. [9]

A well eminent characterization to determine the malarial infection is to observe the changes in blood count including the cell lining of red blood cells RBCs, leukocytes, and thrombocytes.[15] Malaria brought the hematological changes that are associated with several factors such as malarial immunity, degree of malaria-endemic, and along with the demographical factors, both adults and pediatric groups are equally affected by malaria concerning hematological alterations. A study demonstrated that less severe alteration was found in white blood cells than thrombocytopenia in a patient suffering from falciparum malarial infection.[5] The history of malaria patients shows more prominent changes in hemoglobin and platelet counts in comparison with WBC count.[6] The severity of disease determines the alteration of complications related to hemoglobin (Hb) level, red blood cells (RBCs) count, white blood cells (WBCs) count, lymphocyte, monocyte, and eosinophil counts.[7] Many other research findings exhibit the substantial differentiation in platelet, blood cell count and hemoglobin level amid the different complications with different severity of malarial patients.[8] Moreover, anemia, thrombocytopenia, splenomegaly, leukocytosis, and intravascular coagulation are the regular hematological abnormalities with malarial infection. The patients with chronic falciparum malaria having a lesser degree of parasitemia while such patients suffered from severe anemia, neutropenia, lymphocytosis, and thrombocytopenia in comprises acute diseased patients.[10] The degree of correlation was found among the infection severity and parasite density, fatality also had a correlation with the degree of parasitemia such as patients with a greater degree of parasite density shows climbing mortality rate.[11] In another condition where parasitemia was observed to very high because of Plasmodium falciparum infection may lead to anemia and immoderate hemolysis of RBCs during malarial infection takes a turn in anemia.[14] In malarial patients, the most common thrombocytopenia complication was documented and platelets count were observed to lowest in high parasitemia concentration.[13] Several studies attempted to identify that a high level of P. falciparum in patients brought the reduction in platelets count.[12] Severe malarial associated with alteration in blood coagulation profile which can use as a marker in the progress of disease pathogenicity. The blood coagulation system and platelets have an indispensable role in the removal of infected blood cells and boost the innate immunity to improve the response of the host defense mechanisms.[16] It was found to be interesting that platelets and the cellular portion of the coagulation system can kill the parasite like P. falciparum. Further, coagulation tests were studied including thrombin generation analysis. Multiple studies showed that this analysis has a correlation between thrombotic and bleeding complications in patients.[17]

MATERIALS AND METHODS:

This cross-sectional study was conducted at Department of Pathology Military Hospital Lahore from February 2020 to July 2020.

Sample size calculation:

The sample size of 100 was computed using the bio Math size calculator[18] considering 50 cases of known patients suffering from severe malaria irrespective of their gender and age (18 to 57 years) are included in this study. 50 cases of unknown patients might be suffering or not from mild malaria are considered as a control group. Patients with a medical history of certain diseases like hematological disorder, acute or chronic liver disease taking antimalarial drugs are excluded from the study.

Sample collection and evaluation of hematological parameters

The blood samples of patients 3ml to 5ml were drawn into vacutainer tubes of EDTA tubes and identification of malarial parasite was performed. The data analysis of hematological parameters

including hemoglobin (Hb %), platelet count, and total leukocyte count (TLC) were measured for all sample's groups auto Backmann Coulter analyzer. Coagulation profile including D-dimer and prothrombin time (PT) activated partial thromboplastin (APTT) were measured using the Coa Rad 2A.[19]

Statistical analysis

Data assay was completed using the spss version 23 the association of mean and standard deviation of different parameters within the groups were computed through descriptive analysis. The significant and non-signification relation of parameters with different conditions were determined through a one-way analysis of variance (ANOVA) while for the reason of significant difference post hoc test (Tukey's HSD test) was applied in comparison of groups. T-test applied to determine the 95% confidence interval.

RESULTS:

- The total of 100 patients were included in the study. The obtained results of malarial patients indicate that 35.9% of cases of P. falciparum and 64.1 % of cases of malaria were due to P.vivax. The mean values of age for patients and the control group was 25.35 ± 14.4 years. The mean values for hematological parameters and the coagulation profile along their confidence were mentioned in Table. 1. As the p-value for coagulation profile including APTT, PT, and d dimer was greater than 0.05. The platelet counts were measured both in P. vivax and P. falciparum malaria patients correlated with the degree of parasitemia as the P-value is less than 0.001 while the degree of correlation r = 0.894. Coagulation profile for P. vivax patients shows the normal PT and APTT while greater PT and APTT values in infected patients of P. falciparum were correlated with degree of parasitemia as r = 0.0892. The percentage of parasitema base on determining parasitic load was 53.3% of patients with a mild degree of parasitemia, 29.3% with moderate, and 17.4% suffered from severe parasitemia. Most coagulation abnormalities rose because of liver involvement.
- A study consist of 723 patients where 172 were diagnosis with malarial disease and more confirmation about the parasite was detected through smear analysis. The obtained results indicated that the 146 patients diagnosed with malaria due to Plasmodium viva and 18 had Plasmodium falciparum. The hematological observations show that significant ($p<0.005$) reduction was found in hemoglobin and statistical data for platelet count and total leukocytes shows $p<0.001$. The distribution of red cells was observed to be higher in malaria patient as compared to normal persons. Monocytes were small in numbers than control group $p<0.001$.[20]
- Another study attempted to identify the malarial disease complications considered the 159 acute patients including 32 with severe malaria and 17% females are the part of this study. The comparison of demographic history with the clinical features between the Plasmodium vivax and P. falciparum was also studied. The average duration of fever was 4 days before admittance to hospital and patients were recognized with different intervals of fever from inception. The level of hemoglobin in cohort falciparum was less than 10.5g/dL specifically in 3.5% males and 11.5% females while vivax cohort observation consists of 6.4% males and 11.6% females having hemoglobin concentration lower than 10.5g/dL. Particularly, no patient was showed anemia symptoms at the time of admission while during the stay of five days at the hospital they developed anemia. Patients with vivax malarial disorder had leukocytosis (WBC> 11,000 cells/mm^3) while falciparum was not seen with it. The variation was noticed in patients with thrombocytopenia as overall reading was 88.3% (143/158), 85.4% (33/36) of falciparum patients, and 89.3% (104/115) P. vivax patients were facing the same issue. However, another condition identified with both species of parasite, then patients 83.5% (5/6) diagnosed with thrombocytopenia. Although there was no specific association with duration of fever and platelet in both the circumstances including P. vivax and P. falciparum.[21]
- Another previous study reported 170 out of 340 people diagnosed with malaria during the cross-section study where hematological characteristics were detected through auto-analyzer and microscopic smear used to identify malaria. The red blood cells, white blood cells, hemoglobin, and lymphocytes reveal the lower mean values in comprises of normal people. The malarial patients were more prone to thrombocytopenia (85%) and (67%) anemia. The parasite density among the P. falciparum and P. vivax and lymphocyte with platelet count all shows the inverse correlation. The results of this study concluded that thrombocytopenia and anemia were the common complications of malaria cases.[22]

Table. 1. The comparison of hematological parameters with mean ± SD values

Parameters	With malaria		Without malaria		P-value
	Mean ± SD		Mean ± SD	95% Cl	
	P. falciparum	P. vivax			
Hb (g/dl)	9.29 ± 0.65	10.99 ± 0.56	11.9 ± 1.98	11.8	<0.05
TLC (×10^9/µL)	6.7 ± 0.02	5.12 ± 0.28	7.1 ± 2.9	6.9	<0.001
Lymphocytes (%)	21.4 ± 0.34	22.4 ± 0.09	28.3 ± 15.12	26.9	<0.001
Monocytes (%)	3.21 ± 0.03	2.4 ± 0.06	2.03 ± 0.31	0.97	<0.001
Platelets (×10^9/µL)	93.6 ± 3.99	94.7 ±4.54	1.42 ± 0.74	1.39	<0.05
PT (sec)	11.78 ± 0.05	10.09 ± 0.08	12.01± 0.01	10.02	>0.05
APTT(sec)	39.54 ± 3.58	37.02 ± 3.99	30.09 ± 0.05	31.5	>0.05
D dimer (ng/l)	263.31 ± 7.23	264.44 ± 7.34	250.04 ± 0.9	30.8	>0.05

Prothrombin time (PT), Activated partial thromboplastin time (APTT), Hemoglobin (Hb), Total leukocyte count (TLC)

Table. 2. Degree of parasitemia in coagulation and hematological parameters

Parameters	Parasitemia Mean ± SD			P-value
	Mild	Moderate	Severe	
Hb (g/dl)	10.29 ± 0.65	10.99 ± 0.56	11.99 ± 0.56	0.423
TLC (×10^3/µL)	6.7 ± 0.06	6.29 ± 0.17	6.52 ± 0.28	<0.001
Platelets (×10^3/µL)	98.6 ± 2.19	87.05 ± 0.9	90.7 ± 4.54	<0.001
PT (sec)	11.7 ± 0.05	12.78 ± 0.03	13.7 ± 0.57	0.001
APTT(sec)	38.67 ± 3.58	41.01 ± 2.05	44.56± 3.56	<0.001
D dimer (ng/l)	253.31 ± 5.23	264.7 ± 4.2	279.44 ± 3.34	0.001

Prothrombin time (PT), Activated partial thromboplastin time (APTT), Hemoglobin (Hb), Total leukocyte count (TLC)

DISCUSSION:

Malaria is a serious health issue especially in a hotter and humid area of the world and having a great contribution to enhanced health expenses. Amelioration in the malaria management system can bring accuracy in diagnosis to overcome the complications on time. Globally, many diagnostic strategies are underdeveloped not only for a specific area where the burden of malaria creating hurdles for society but also for developed countries where expertise lacking in the efficacious diagnosis of malaria.[23] In the current study, 35.9% of cases of P. falciparum and 64.1 % cases of malaria were due to P.vivax. Although, several studies demonstrated that 51.5% of cases of P. falciparum and vivax while 47.1% for both parasites exist in mixture form.[24] The average mean value of the age was 25.3 years and the majority of cases were noticed in the age group of 20-30 years. A highest percentage of malaria patients were 82 for adults. This study was about all age groups but notably, this disease found with high incidence in older age group it might be because of the majority of folks belongs to low socio-economic status including worker, and labors working without taking any precautionary measures.[25]

The malarial has a deep association with the coagulation system.[27] To estimate the potential of patients to produced thrombin that elucidates the whole hemostatic ability through the global coagulation test knows as thrombin generation

analysis.[26] thrombin is playing an indispensable role to determine the clotting time including the activated partial thromboplastin time (APTT) and prothrombin time (PT). Pathogenicity of malaria is associated with the impediment of blood vessels and adherence of parasitized blood cells to endothelial cells that lead to activation of endothelial and proceed coagulation cascade.[28] Many types of researches on malaria disease indicate the alteration in coagulation parameters.[29] The inhibitory effect of parasite driven protein (which is histidine-rich protein II) on anticoagulatory protein antithrombin it acts as an inhibitor of thrombin.[30] The diminution of endothelial protein C receptors (EPCR) because of infected erythrocytes with P. falciparum that convert the protein C to activated protein C (APC) (an anti-coagulatory protein) as a result of EPCR loss enhanced the level of thrombin.[31] The recombinant APC was also used in the treatment of infected person suffered severe P. falciparum malaria when standard treatment insufficient to responds.[32]

CONCLUSION:

The coagulation profile of patients shows that P.falciparum and P. vivax have the critical to develop advanced infection and complications. APTT, PT, and d-dimer were very helpful in determining the coagulation profile of infected patients which correlate with parasitemia. It is concluded that the laboratory assay such as platelet count, leukocytes, red blood cell all these parameters facilitate the diagnosis of malaria patients.

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