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ABSTARCT

Objective:

Malaria is a fatalinfective disease, related to dreadful complications in severe cases. It is generallyestablished by hematological variations such as anemia and thrombocytopenia that are considered as prognostic indicators for malaria fever.Therefore, this study was intended to assess the incidence of hematological abnormalities associated with patients suffering from malaria.

Methodology:

This cross sectional study was conducted in the medical wards of Khyber Teaching Hospital, Peshawar using non-probability convenient sampling technique. The duration of the study was about 4 months from September 2021 to December 2021. A total of 100 patients who possessed positive malarial parasite on peripheral smears of both genders having age between 10 to 70 years were included in the study. Variables such as age was documented as Mean±SD. Frequencies and percentages were reported for gender, hematocrit and platelet count.

Results: Thestudy findings revealed that 61(61%) patients were males and 39(39%) were females with their observed mean age being28.29±13.70 years. Most of thepatients aged between 10-20 years followed by 30(30%) cases who were aged 21-30 years. Furthermore, overall distribution of thrombocytopenia revealed that most of the patients 23(23%) had platelet count in the range of 71000-90000, 21(21.0%) patients had platelet count in the range of 51000-70000. Additionally, hematocrit distribution revealed that 41(41%) patients had hematocrit in the range of 36-45% followed by 34(34.0%), who had it in the range of 26-35%. Frequency of hematocrit with respect to gender revealed that 32(52.4%) males reported 36-45% hematocrit.

Conclusion: This study concluded that thrombocytopenia and anemia were commonly observed hematological abnormalities detected in patients with malaria infection caused by Plasmodium vivax. It is suggested that thrombocytopenia and anemia in a febrile patient indicate malaria fever therefore additional particular tests can be employed forconfirmation.

Keywords: Anemia, thrombocytopenia, malaria fever, Plasmodium vivax.

INTRODUCTION

Malaria is animportantworldwide health dilemma with a significant disease encumbranceall over the world [1]. In the year 2019, approximately 4,09000 deaths were occurred by 229 million cases of malaria, most of which were from African continent (WHO World Malaria Report 2020) [1]. Malaria is caused by single-celled parasites that belong to the Plasmodium genus. In humans, five species of Plasmodium cause malaria: P. vivax, P. ovale, P.falciparum,P. knowlesi and P. malariae[2].

The most prevalent malaria species is P. vivax. P. vivax malaria can infect approximately 2.5 billion individuals worldwide [3]. P. vivax can stay alive in coolerenvironment only owing to its latent liver phase rather than other species of malaria that possess extensiveenvironmental range and can survive in tropics, subtropics and moderateenvironments. World Malaria Report in 2018 stated that P. vivax caused malaria in 74.1% of cases in the United States of America in 2017. Apart from P. vivax endemicity overlaps considerably with that of P. falciparum in many parts of the world, malaria infections are caused by P. vivax exclusively in many places of Southeast Asia for instance South Korea [3].

Usually, the incubation period for vivax malaria is 12 - 17 days, however relapse canhappen up to 2 years later from inactivehypnozoites [4]. Typical clinical manifestations of malaria are pyrexia, headache, vomiting, nausea, body pains, anemia, and jaundice. Occasionally, clinical diagnosis of malaria becomesperplexingdue to the nonspecific symptoms and similarity of signs and symptoms with other pyreticinfections. Because of the parasitic life cycle, patients with P. vivax malaria have a tendency ofintermittent fevers at about every 42 to 56 hours [5]. Therefore the fever of P. vivax is occasionally regarded as "tertian fever." Besides the classicclinical manifestations, malaria is oftenrelatedtohematological changes such as hemolytic anemia, leukopenia, leukocytosis, neutropenia, neutrophilia, hemoglobinuria, and variation of thrombocytopenia [6-8]. Clinically, anemia is the most frequent symptom observed in adults and

children infected with P. vivax malarial parasite. In contrast to falciparum malaria, vivax malaria does not cause sequestration; consequently the failure of organ systems tooisinfrequent [4, 5, 9, 10].

In case of unavailability of findings of parasitological examination, variations of the hematological profile in malaria helps physician to establish an effectual and timely therapeutic management to prevent death that may result from main complications.[11]

World Health Organizationin 2010 proposed guidelines that all cases of malaria should experience testing before commencing treatment. Clinically, two leading diagnostic modalities are applicable: Light microscopy and rapid diagnostic tests (RDTs).[12] Visualization of P. vivax parasites directly on Giemsa-stained blood smears using light microscopy is recognized as gold standard for the identification of vivax malaria.[13]Subsequently, RDTs have become progressivelywidely used diagnostic tool, particularly in situation oflimited resources.[13] RDTs identify one or more Plasmodium antigens in the blood. They are considered as a fast diagnostic tool with no need of a proficient laboratory technician to read blood smears.[14]

As far as therapeutic management is concerned, Chloroquineis the main treatment for uncomplicated vivax malaria. Hypnozoite phase of P. vivax can be treated by addition of primaquine to the treatment regimens. However, primaquine is contraindicated in patients with G6PD deficiency and pregnant women. Hematological changes such as severe hemolytic anemia is caused by primaquine in case of G6PD deficiency [15]. Furthermore, primaquine is not recommended in pregnancy due to the risk of fetal hemolysis.[16] Consequently, primaquine treatment is delayed till after delivery [17]. Globally, WHO suggested administration of intravenous artesunate (2.4mg/kg IV or IM at 0, 12hr, and 24hr then daily basis) for the management of severe malaria. Numerousresearches have endorsed the effectiveness and safety of artesunate in the management of severe malaria against formerly administered IV quinidine [18,19].A case report published has revealed that P. vivax causes cerebral malaria, renal insufficiency, acute respiratory distress, and shock.[4,5] Moreover, splenic rupture is anotherinfrequent complication that possesses higher mortality rate of up to 80% [20].

Even though,many researches have shown thrombocytopenia in association with malaria as a frequent outcome[21,22], its relationship withthe type of malaria and numerous hematological factors has not been assessedcomprehensively in largeresearches. In Pakistan, there is scarce data

available regarding hematological variations associated with malaria. Therefore, this study was intended to assess the hematological variations in patients suffering from malaria fever by P. vivax.

METHODOLOGY

This cross sectional study was conducted in the medical wards of Khyber Teaching Hospital, Peshawar using non-probability convenient sampling technique. The duration of the study was about 4 months from September 2021 to December 2021. A total of 100 patients who werediagnosed with positivemalarial parasite on peripheral smears of both genders having age between 10 to 70 years were included in the study whereas patients diagnosed with dengue, congo, chikungunya and platelets less than 150,000 were excluded from the study.

Samples of blood were drawn into a 3 ml tube with ethylenediaminetetraacetic acid (EDTA) through venipuncture by skilled staff for peripheral blood smear and wereexamined for malarial parasites usingconventional microscopy. Hemoglobin (Hb), hematocrit (Hct) and platelet count were evaluated by using a hematology analyzer, HumaReader Plus (HUMAN Diagnostic Worldwide, Wiesbaden, Germany).Clinically, patients were examined for identification of malarial fever. Blood peripheral smear was performed to investigate viral parasite. Examination of complete blood count, LFTs, RFTs, HbA1c, U/S abdomen and Pelvis, Hepatitis B/C status was performed. Malaria was detected withthe help of clinical checkup and lab examination test.
Data was analyzed by using Statistical packages for social sciences (SPSS) Version 20.0.Variables such as age was documented as Mean±SD. Frequencies and percentages were reported for gender, hematocrit and platelet count.

RESULT

A total of 100 patients diagnosed with Malarial Parasite plasmodium vivax on peripheral smear were included. Out of these, 61(61%) patients were males and 39(39%) were females with their observed mean age was 28.29±13.70 years. Age distribution among 100 patients revealed that 42(42%) patients were in the age between 10-20 years, 30(30%) were in between 21-30 years, 09(09%) patients were in between 31-40 years, 10(10%) were in between 41-50 years, 06(06%) were in between 51-60 yearsand 03(03%) were in 61-70 years. Furthermore, overall distribution of thrombocytopenia revealed that most of the patients 23(23%) had platelet count in the range of 71000-90000 while 21(21.0%) patients had platelet count in the range of 51000-70000.

Additionally, hematocrit distribution revealed that 41(41%) patients had hematocrit values in the range of 36-45% followed by 34(34.0%) cases whose hematocrit values were in the range of 26-35%, as depicted in Table I.

Frequency of hematocrit with respect to gender revealed that 3(4.9%)males reported <15% hematocrit, 12(19.6%) reported 15-25% range of hematocrit, 13(21.3%) reported 26-35% range of hematocrit, 32(52.4%) males reported 36-45% range of hematocrit and only 1(1.63%) case of male reported 38.00% hematocrit. Furthermore, 9(23.0%) females had 15-25% hematocrit, 21(53.8%) females had 26-35% hematocrit, and 9(23.0%) females had 36-45% hematocrit, as depicted in Table II.

Distribution of thrombocytopenia with respect to age groups revealed that 10000-30000platelets were observed in 5(5.0%) cases between 10-20 years and 3(3.0%) cases between 21-30 years of age. Furthermore, 31000-50000platelets were observed in 13(13.0%)cases between 10-20 years and 3(3.0%) cases between 31-40 years of age. Moreover, 51000-70000platelets were observed in 9(9.0%) cases between 21-30 years while equally distributed 3(3.0%) in all age groups except between 31-40 years of age. Additionally, 71000-90000platelets were observed in 9(9.0%) cases between 21-30 years, as depicted in Table III.

Table I: Demographic characteristics of patients with malaria fever (n=100).

Variable		**Mean±SD n(%)**
Age (years)		28.29±13.70
Age (years)	**10-20**	42(42.0%)
	21-30	30(30.0%)
	31-40	9(9.0%)
	41-50	10(10.0%)
	51-60	6(6.0%)
	61-70	3(3.0%)
Gender	**Male**	61(61%)
	Female	39(39%)
Distribution of	**Less than 15%**	3(3.0%)

hematocrit (%)	**15-25%**	21(21.0%)
	26-35%	34(34.0%)
	36-45%	41(41.0%)
	38.00%	1(1.0%)
Distribution of Platelets count (Platelets/µl)	**10000-30000**	9(9.0%)
	31000-50000	16(16.0%)
	51000-70000	21(21.0%)
	71000-90000	23(23.0%)
	91000-110000	12(12.0%)
	111000-130000	9(9.0%)
	131000-150000	3(3.0%)
	171000-190000	4(4.0%)
	2,00000	3(3.0%)

Table II: Frequency of Hematocrit with gender distribution

Variables		**Male (n=61)**	**Female (n=39)**
Distribution of hematocrit (%)	**Less than 15%**	3(3.0%)	0(0.0%)
	15-25%	12(12.0%)	9(9.0%)
	26-35%	13(13.0%)	21(21.0%)
	36-45%	32(32.0%)	9(9.0%)
	38.00%	1(1.0%)	0(0.0%)

Table III: Distribution of thrombocytopenia with respect to age groups.

Variables		10-20 years	21-30 years	31-40 years	41-50 years	51-60 years	61-70 years
Distribution of Platelets count (Platelets/µl of blood)	10000-30000	5(5.0 %)	3(3.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
	31000-50000	13(13.0 %)	0(0.0%)	3(3.0%)	0(0.0%)	0(0.0%)	0(0.0%)
	51000-70000	3(3.0%)	9(9.0%)	0(0.0%)	3(3.0%)	3(50.0%)	3(3.0%)
	71000-90000	6(6.0%)	9(9.0%)	2(2.0%)	3(3.0%)	3(3.0%)	0(0.0%)
	91000-110000	9(9.0%)	3(3.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
	111000-130000	3(3.0%)	3(3.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
	131000-150000	0(0.0%)	3(3.0%)	0(0.0%)	1(1.0%)	0(0.0%)	0(0.0%)
	171000-190000	3(3.0%)	0(0.0%)	1(1.0%)	3(3.0%)	0(0.0%)	0(0.0%)
	2,00000	0(0.0%)	0(0.0%)	3(3.0%)	0(0.0%)	0(0.0%)	0(0.0%)

DISCUSSION

Malaria usually affects hematologicalprofile such asanemia and thrombocytopenia. Researches have revealed that low platelet count is considered as a sensitive indicatorfor malaria detection in the incidence of acute feverdisease [23]. Even though the particular mechanism of thrombocytopenia in malaria is ambiguous, researches have demonstrated that invasion of the parasite causes abnormalities in platelets' structure, developsoxidative stress, sequestration in the spleen, and platelet devastation mediated by immunoglobulin G (IgG) [24,25]. Likewise, researches have revealed the peripheral deterioration of RBCs, unproductive hematopoiesis, and sequestration in the spleen as probable causes of anemia induced by malaria[22]. The present study demonstrated the clinical outcomes associated with malarial parasite infection by P. vivax.

The present study showed the male predilection 61(61%) in patients suffering from malaria fever. These findings were supported by another research wherein mostly patients were male (64.9%).[26]Likewise, one research by Manas et. al corroborated these findings and showed male predisposition (64,1%). This can be elucidated asmales are more probable to work in malaria prevalentregionsfor instancemineworkers, fishermen and forest workers [27].

The most observed complication of P. vivax malarial infection is manifested as mild to severe thrombocytopenia. The present study revealed that thrombocytopenia was found in most of the patients infected with P. vivax malarial parasite. These findings wereconsistent with the research by Kochar et al. who showed the significant relationship of thrombocytopenia with P. vivax as compared to low platelet counts withP. falciparuminfection ($p < 0.0001$) [25]. Similarly, another research reported total, 54.4% of patients with malaria fever revealed thrombocytopenia. Their study revealed that thrombocytopenia associated with P. vivax was found in 71.4% patients.[28] These facts were supported by additionalresearches presenting thrombocytopenia associated with P. vivax was observed in 63% cases by Khan et al. [29],82% cases in research by Srivastava et al. [30], and 93.3% patients in research by George and Alexander[31]. In contrast, few studies have revealed that P. vivax-associated thrombocytopenia was seen in less than 60.0% cases [32,33].

Notably, another research demonstrated that the second most prevalent hematological variation associated with malaria fever is anemia that was more pronounced in P. falciparum infections in comparison with *P. vivax*indicating that anemia has reportedly more association with P. falciparum infection [7]. These findings were similar to studies directed by Jain and Kaur

[34] and Shah et al,[35] howevercontrasted from researches performed in Dubai that showed an insignificant association of anemia between P. vivax (63%) and P. falciparum (67%) infections [36]. Multiple factors and mechanisms are suggested to be involved in development of anemia in malaria fever for example mechanical devastation of the parasitized red blood cells, decreased production of RBC in bone marrow, and phagocytosis of RBCs infected by parasites [37]. Furthermore, tumor necrosis factor and IL-10 have also been associated with development of anemia by P. falciparum malaria[38].The present study showed consistency with the above reported research and revealed that mostly patients 41(41%) reported 36-45% hematocrit indicating that the incidence of anemia was high.

Remarkably, thrombocytopenia was the most prevalent hematological variation in malaria patients. One of the studies revealed high incidence of thrombocytopenia in malaria fever [11]that was endorsed by an Indian study, [23].Another research by Bhandary et al[39] showed that prevalence of thrombocytopeniadifferentiatesmalaria fever from other acute febrile illnesses. Consequently, it is suggested that thrombocytopenia can be utilized as a helpful diagnostic standard for malariaalong with clinical manifestationsparticularly in those situations where microscopic diagnosis is insufficient. The present study was in agreement with the above mentioned studies and revealed that thrombocytopenia was observed in most of the patients that can be considered as supportive investigative criterion for malaria fever.

This study had few limitations that the platelet counts were not serially observed and therefore, its association to severity or consequencecannot be evaluated. Also, complications associated with malaria fever were not assessed.

To keep in vision, the hematological alterations according to age and gender, it is imperative to use precautionary measures in population. The present study reveals greater incidence and hematological variations observed in younger people than other age groups. Therefore, it is advised to cover body properlyalong with restrictingoutside activities in younger people duringmalaria season. Make sure to use proper mosquito nets together withmosquito repellent. Timely recommendation by a health professional with the existence of symptoms may lessenmore complications and its extent.

CONCLUSION

This study concluded that thrombocytopenia and anemia were commonly observed hematological abnormalities detected in patients with malaria infection by Plasmodium vivax.It is suggested that thrombocytopenia and anemia in a febrile patient indicate malaria fever therefore additional particular tests can be employed for confirmation. Hence, thrombocytopenia can be used as helpful diagnostic standard for malariabesides clinical manifestations and additional laboratory investigations.

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