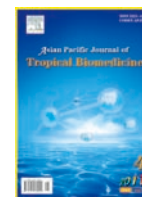




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Association of ABO blood group and *Plasmodium falciparum* malaria in Dore Bafeno Area, Southern Ethiopia

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ABSTRACT

Objective: To assess the distribution of ABO blood group and their relationship with *Plasmodium falciparum* (*P. falciparum*) malaria among febrile outpatients who sought medical attention at Dore Bafeno Health Center, Southern Ethiopia. **Methods:** A total of 269 febrile outpatients who visited Dore Bafeno Health Center, Southern Ethiopia, were examined for malaria and also tested for ABO blood groups in January 2010. The blood specimens were collected by finger pricking, stained with Geimsa, and examined microscopically. Positive cases of the parasitemia were counted. CareStart™ Malaria Pf/Pv Combo was also used to test the blood specimens for malaria. ABO blood groups were determined by agglutination test using ERYCLONE® antisera. Data on socio-demographic characteristics and treatment status of the participants were also collected. Chi-square and ANOVA tests were used to assess the difference between frequencies and means, respectively. **Results:** Out of a total of 269 participants, 178 (66.2%) febrile patients were found to be infected with *Plasmodium* parasites, among which 146 (54.3%), 28 (10.4%), and 4 (1.5%) belonged to *P. falciparum*, *P. vivax*, and mixed infections, respectively. All febrile patients were also tested for ABO blood groups and 51.3%, 23.5%, 21.9% and 3.3% were found to be blood types of O, A, B and AB, respectively. Both total malaria infection and *P. falciparum* infection showed significant association with blood types ($P < 0.05$). The proportion of A or B but not O phenotypes was higher ($P < 0.05$) in individuals with *P. falciparum* as compared with non-infected individuals. The chance of having *P. falciparum* infection in patients with blood groups A, B and AB was 2.5, 2.5 and 3.3 times more than individuals showing blood O phenotypes, respectively. The mean *P. falciparum* malaria parasitaemia for blood groups A, B, AB, and O were $3\ 744/\mu\text{L}$, $1\ 805/\mu\text{L}$, $5\ 331/\mu\text{L}$, and $1\ 515/\mu\text{L}$, respectively ($P < 0.01$). **Conclusions:** The present findings indicate that individuals of blood groups A, B and AB are more susceptible to *P. falciparum* infection as compared with individuals of blood group O. Nevertheless, further in depth studies are required to clearly establish the role that ABO blood group plays in *P. falciparum* malaria.

1. Introduction

The ABO blood groups consist of A, B and H carbohydrate antigens which can regulate protein activities during infection and antibodies against these antigens [1,2]. A number of studies were conducted to investigate the association between ABO blood group system and some disease conditions [3–8]. Some of these studies reported significant associations, suggesting that ABO blood groups

have an impact on infection status of the individuals possessing a particular ABO blood group [5–8].

In view of a heavy burden placed on human health due to malaria, a good many investigations have been conducted to find out whether or not ABO blood groups antigens are associated with susceptibility, resistance, or severity of *P. falciparum* malaria. Nonetheless, these studies have reported contradictory results. Some studies reported the absence of significant association between *P. falciparum* (prevalence, parasitaemia or antibody titer) and ABO antigens [4,9–14]. On the other hand, other studies have shown that high frequency of malaria episodes has been observed among blood group 'A' individuals as compared with other blood groups individuals [15]. Large numbers of severe malaria cases were also reported among blood group 'A'

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individuals^[16,17]. Furthermore, Migot–Nabias and Pathirana *et al*^[18,19] observed low parasitaemia and uncomplicated malaria cases among blood group ‘O’ individuals, respectively.

Variations in reports on the association of ABO blood groups and disease progression of *P. falciparum* malaria show the complexity of the interaction between the parasite and host immune responses. In addition, studies have shown the impact of other red blood cells (RBC) polymorphisms including haemoglobin (Hb) abnormalities such as HbS, HbC, thalassemia and deficiency in erythrocyte complement receptor (CR) or glucose–6–phosphate dehydrogenase on *P. falciparum* malaria susceptibility and severity^[18,20–23]. This makes it difficult to make a clear analysis on the association of ABO blood groups and *P. falciparum* because so far most of the study designs have been conducted *in vivo*. Therefore, this study aims to assess the distribution of ABO blood groups and their relationship with *P. falciparum* malaria among febrile outpatients who sought medical attention at Dore Bafeno Health Center, Southern Ethiopia.

2. Materials and methods

2.1. Study area and population

A cross–sectional study was conducted at Dore Bafeno Health Center, Southern Ethiopia, to assess the association of ABO blood groups antigens with malaria in January 2010. Dore Bafeno is located at about 23 km to the southwest of Hawassa town. The area has an elevation of about 1 708 m above sea level. It has an estimated total population of 139 891, consisting of 70 503 males and 69 388 females.

The study population was composed of febrile outpatients who sought medical attention at Dore Bafeno Health Center in January 2010. A total of 269 febrile outpatients were selected as study participants, excluding individuals who took antimalarial drugs within two weeks before blood test and who refused to participate in the study. The target populations were almost from the same ethnic (Sidama) group.

2.2. Ethical approval

The study obtained ethical clearance from the Institutional Research Board (IRB) of the Akililu Lemma Institute of Pathobiology, Addis Ababa University, and from the Health Bureau of South Nations Nationalities and Peoples Region (SNNPR). Malaria positive cases were treated with antimalarial drugs based on the current national treatment guideline of Ethiopia.

2.3. Clinical and laboratory diagnosis

Before collecting blood sample, explanation about the

study was given and a written informed consent was obtained from every study participant including the guardians of children. Capillary blood was collected by finger pricking using 70% isopropanol and sterile disposable lancet. Heel puncture was used for infants. Immediately, thin film was spread on grease free, frosted end, labeled slide using a smooth edged slide spreader. Thick film was also prepared on the same slide. Thin film was then fixed with methanol. The blood film was stained with 10% Giemsa for 10 minutes. Finally, the films were examined under an oil immersion microscope objective (100×). Parasitemia was determined for febrile patients who tested positive for *P. falciparum* by counting the number of parasites (asexual forms only) against 200 white blood cells (WBC). This counting was done by using hand tally counters. Then, the number of parasites per microliter of blood was calculated^[24]. CareStart™ Malaria PflPv Combo test was also performed parallel with blood film examination using the same blood sample following manufacturer’s instruction (Access Bio, Inc. NJ USA). Similarly, the blood group of the study participants was determined by direct slide method, using agglutinating A and B Monoclonal ERYCLONE® anti–sera alongside with the former procedures.

2.4. Data analysis

Data were entered in Microsoft Excel, checked for its correctness, and exported to and analyzed using SPSS version 13 (SPSS Inc, Chicago, IL). *Chi*–square test was used to assess the difference between frequencies (the associations between blood groups and *P. falciparum* malaria cases). ANOVA was used to test the difference between parasitemia means. Observed difference was considered to be significant for $P < 0.05$.

3. Result

3.1. Malaria infection

Out of a total of 269 febrile patients who visited Dore Bafeno Health Center for medical attention, 178 (66.2%) were found to be infected with *Plasmodium* parasites as determined by microscopy. The prevalence of malaria was found to be the highest among under–five children as compared with older age groups but the difference was not significant ($P > 0.05$). Similarly, the prevalence was higher among females (67.2%) than males (65.3%) and this difference was not statistically significant (Table 1).

3.2. ABO blood groups and malaria infection

All febrile patients examined for malaria were also tested for ABO blood groups. Accordingly, 51.3%, 23.5%, 21.9% and 3.3% were found to be blood types of O, A, B and AB,

Table 1Prevalence of malaria by age and sex among the study participants at Dore Bafeno Health Center, Southern Ethiopia, January 2010 [*n* (%)].

Age	Number examined	<i>P. falciparum</i>	<i>P. vivax</i>	Mixed*	Total
≤5	67	43 (64.2)	7 (10.4)	0 (0.0)	50 (74.6)
6–15	112	61 (54.5)	11 (9.8)	4 (3.6)	76 (67.8)
>15	90	42 (46.7)	10 (11.1)	0 (0.0)	52 (57.8)
Total	269	146 (54.3)	28 (10.4)	4 (1.5)	178 (66.2)
χ^2, P		4.75, 0.09	0.89, 0.96	5.69, 0.06	5.11, 0.08
Sex					
Male	144	80 (55.5)	11 (7.6)	3 (2.0)	94 (65.3)
Female	125	66 (52.8)	17 (13.6)	1 (0.8)	84 (67.2)
χ^2, P		0.21, 0.65	2.55, 0.11	0.75, 0.39	0.11, 0.74

*Mixed infection of *P. falciparum* and *P. vivax*.**Table 2**Frequency of ABO blood groups among *Plasmodium*-infected cases at Dore Bafeno Health Center, Southern Ethiopia, January 2010 [*n* (%)].

Blood group	Number examined	Infection type				Total	χ^2, P
		<i>P. falciparum</i>	<i>P. vivax</i>	Mixed*	Non-infected		
A	63	41 (65.1)	5 (7.9)	1 (1.6)	16 (25.4)	63 (23.5)	61.6, <0.0100
B	59	38 (64.4)	7 (11.9)	0 (0.0)	14 (23.7)	59 (21.9)	55.5, <0.0100
AB	9	7 (77.8)	0 (0.0)	0 (0.0)	2 (22.2)	9 (3.3)	14.6, <0.0100
O	138	60 (43.5)	16 (11.6)	3 (2.2)	59 (42.8)	138 (51.3)	74.9, <0.0100
Total	269	146 (54.3)	28 (10.4)	4 (1.5)	91 (33.8)	269 (100)	183.0, <0.0001
χ^2, P		13.9, 0.0030	1.8, 0.6150	1.5, 0.6880	10.4, 0.0150	126.2, 0.0001	

Table 3Comparison of frequency of ABO blood groups among *P. falciparum*-infected individuals with that of non-*Plasmodium*-infected individuals at Dore Bafeno Health Center, Southern Ethiopia, January 2010 [*n* (%)].

Blood group	Age group	Numbers with blood type	<i>P. falciparum</i> infected	Non- <i>Plasmodium</i> -infected	χ^2, P	χ^2, P
A	≤5	16	13 (81.2)	1 (6.3)	8.64, 0.003	5.99, 0.050
	6–15	21	16 (76.2)	5 (23.8)		
	>15	26	13 (50.0)	10 (38.5)		
	Total	63	42 (66.7)	16 (25.4)		
B	≤5	14	10 (71.4)	3 (21.4)	2.76, 0.090	1.17, 0.556
	6–15	28	20 (71.4)	6 (21.4)		
	>15	17	8 (47.1)	5 (29.4)		
	Total	59	38 (64.4)	14 (23.7)		
AB	≤5	1	1 (100.0)	0 (0.0)	0.00, 1.000	0.32, 0.852
	6–15	4	3 (75.0)	1 (25.0)		
	>15	4	3 (75.0)	1 (25.0)		
	Total	9	7 (77.8)	2 (22.2)		
O	≤5	36	19 (52.8)	13 (36.1)	0.78, 0.370	0.08, 0.777
	6–15	59	26 (44.1)	14 (23.7)		
	>15	43	18 (41.9)	22 (51.2)		
	Total	138	63 (45.7)	59 (42.8)		

respectively ($\chi^2=126.2, P<0.01$). The highest proportion of individuals in all blood groups were infected with *P. falciparum* as compared with other groups (*P. vivax*, mixed and non-infected), and this difference was statistically significant ($P<0.01$). In general, malaria infection showed significant association with blood group ($\chi^2=10.4, P=0.015$) with the highest proportion (77.8%) observed among individuals with AB blood group, followed by those with

blood group B (64.4%). Prevalence of *P. falciparum* infection also showed similar pattern ($\chi^2=13.9, P<0.01$) with the highest proportion (77.8%) observed among individuals with AB blood group, followed by those with blood group A (65.1%) (Table 2).

65.1%, 64.4%, 77.8% and 43.5% of individuals with A, B, AB and O blood types, respectively had *P. falciparum* infections. The proportion of A or B but not O phenotypes was higher

($P < 0.05$) in individuals with *P. falciparum* compared with non-infected individuals. *P. falciparum* infection do not show association ($P > 0.05$) with age in all the 4 blood groups (Table 3).

The chance of having *P. falciparum* infection in patients with blood groups A, B and AB was 2.5 ($\chi^2 = 6.941$, $P = 0.008$, $OR = 2.46$, 95% confidence interval $CI = 1.256-4.804$), 2.5 ($\chi^2 = 6.841$, $P = 0.009$, $OR = 2.54$, 95% $CI = 1.260-5.119$) and 3.3 ($\chi^2 = 2.284$, $P = 0.131$, $OR = 3.28$, 95% $CI = 0.737-14.380$) times higher than individuals showing blood O phenotypes, respectively. Also, this probability of *P. falciparum* infection for patients with blood group A, B and AB was found higher ($OR > 1.5$) when compared with blood group O individuals for each age groups.

3.3. ABO blood type and *P. falciparum* parasitaemia

About 38.1% (16/42), 47.4% (18/38), 22.2% (2/9) and 66.7% (42/63) *P. falciparum* infected individuals of blood group A, B, AB and O, respectively had parasite density of less than 1000 parasites/ μ L of blood. In contrast, 59.5% (25/42), 52.6% (20/38), 77.8% (7/9) and 33.3% (21/63) *P. falciparum* infected individuals of blood group A, B, AB and O, respectively had parasite density of greater than 1000 parasites/ μ L of blood. Only 2.4% (1/42) individuals of *P. falciparum* infected patients with blood group A had a parasite density of greater than 100 000 parasites/ μ L of blood. Mean *P. falciparum* malaria parasitaemia for blood groups A, B, AB and O were 3 744/ μ L, 1 805/ μ L, 5 331/ μ L, and 1 515/ μ L respectively. This difference was statistically significant ($P < 0.01$, $F = 11.510$).

4. Discussion

In this study, high percentage of O blood group (51.3%) phenotype was observed among the study participants followed by A (23.5%), B (21.6%), and AB (3.3%). This agrees with some previous studies that also reported high frequency of group 'O' and low frequency of group 'A' phenotypes in tropical regions where malaria is rampant [14,25,26]. On the other hand, other studies reported high prevalence of blood group 'A' and low prevalence of blood group 'O' phenotypes in colder regions where malaria has not been endemic [14,27]. Hence, the present finding seems to substantiate the hypothesis about a selective (survival) evolutionary advantage of *P. falciparum* infection on blood group O cells compared with other blood group types (A, B or AB) in areas where malaria is endemic [28].

In this study, significantly higher proportions of individuals with blood group A, B and AB but not O were found to be infected with *P. falciparum* as compared with non-*P. falciparum* infected individuals. This is also consistent with previous reports [29,30], suggesting that individuals with blood groups A, B and AB are more susceptible to *P. falciparum* infection than those with O group. Beiguelman and Santos *et*

al [15,31] similarly observed significant association between the presence of A or B antigen and the number of malarial episodes in Brazil. Several mechanisms relate to these associations, including affinity for *Anopheles* species, shared ABO antigens with *P. falciparum*, impairment of merozoite penetration of RBCs, as well as cytoadherence, endothelial activation and rosetting [32]. On the other hand, absence of association between ABO system and malaria infection was also observed in other populations [10,13,29,33,34]. Also, in contrast to our observation, Rowe and Tekeste *et al* [35,36] documented absence of difference in the frequency of ABO blood groups between healthy controls and those with uncomplicated malaria, suggesting insignificant effect of the ABO blood groups on uncomplicated clinical malaria disease. However, in accordance with our findings, Rowe *et al* [35] observed the absence of significance difference in the frequency of group O between uncomplicated malaria cases and the healthy controls.

The lowest mean parasitaemia was also observed among individuals with blood group O as compared to blood groups A, B and AB. Similarly, Migot-Nabias *et al* [18] observed lower *P. falciparum* parasitaemia in those with blood group O as compared to non-O subjects. In addition, other studies also reported a high chance of severe malaria or high parasitaemia cases in individuals possessing blood group A or AB cells than among individuals with blood group 'O' [16, 17,19,29].

The mechanism by which 'A' promotes susceptibility and 'O' confers a relative protective effect against high *P. falciparum* parasitaemia is not well understood. Nevertheless, different studies have come up with their reasonable explanations on the basis of rosette formation. Several reports support the hypothesis that blood group A represents a risk factor for high chance of rosette, which is usually characterized by high *P. falciparum* parasitaemia during malaria infection and a reducing effect of blood group 'O' on rosette [37–45]. The presence of several glycosylated adhesion molecules such as intracellular adhesion molecule 1 [38], complement receptor 1 [37], heparin sulfate-like glycosaminoglycan [40,41], platelet glycoprotein CD36 [46–54], high level von Willebrand factor [43], low arginine and nitrate levels [42], presence of cellular micro-particles [44] and the nature of sugar molecules (trisaccharides) [55] in blood group 'A' cells promote a high chance of binding with the rosette-forming surface molecules of the *P. falciparum* such as Duffy binding-like domain 1 alpha of *P. falciparum* erythrocyte membrane protein-1 [21,56], rifs [57,58]. On the other hand, blood group 'O' cells show deficiency of most of the above adhesive molecules and contain disaccharides sugar molecules which reduce the rate, size and stability of rosette formed during *P. falciparum* infection [44,55].

The present study only employed parasitaemia as a laboratory marker to determine the association of ABO blood groups and *P. falciparum* malaria. The study also did not consider factors like HbS, HbC, CR, iron status of the host,

place of residence of the study population which could affect the nature of *P. falciparum* infection among the study population. Had more laboratory markers or clinical features (e.g. cerebral malaria) been used, more information would have been generated on the associations. Nevertheless, the findings indicate that individuals of blood group A, B and AB are more susceptible to *P. falciparum* infection as compared with individuals with the blood type O. Further in-depth studies are required to clearly establish the role of ABO blood groups in the *P. falciparum* malaria.

Conflict of interest statement

We declare that we have no conflict of interest.

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