Journal of Applied Sciences

ISSN 1812-5654

science alert

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OPEN ACCESS Journal of Applied Sciences

ISSN 1812-5654
DOI: 10.3923/jas.2023.105.110

Research Article
Evaluation of Differential Analytic Model as a Tool for the Diagnosis of Malaria Infection

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Abstract

Background and Objective: Malaria is a life-threatening parasitic disease that is entirely preventable and curable but considered as one of the main diagnoses of acute febrile illness in the tropics. Alteration of various haematological parameters has been observed among patients with malaria parasite infection. Analytic models are used to provide an explicit framework for understanding accurate malaria diagnosis in the human population. It is therefore necessary to make a critical assessment of the predictive differential model for accurate diagnosis. **Materials and Methods:** Blood samples were collected from volunteer subjects using the standard method. These were analyzed and evaluated using an automated haematology analyzer. **Results:** The Fisher's linear discriminant function for gender classification of haematological properties of malaria patients obtained by subtraction is presented as: z = -0.0030PCV-0.0315WBC-0.0557NEUT-0.0367LYMP-0.2227MONO+0.0018PLT. The sample mean of the discriminant function scores was obtained by the constant coefficients as, $\bar{z}$ = 6.354. The threshold against which a paediatric patient discriminating score is evaluated as 0.0000, this is obtained by taking the average of the centroid function. This implies that any new patient with discriminant scores greater than 0.0000 would be diagnosed to be a male, otherwise, a female. These data analysis hypotheses efficiently the categorization of the genders with 59.3% accuracy based on the retribution estimate method and 53.6% accuracy based on the leave one out method. **Conclusion:** This model could be useful as preliminary data to adopt better strategies for precise diagnosis of Malaria infection.

Key words: Predictive, diagnosis, malaria infection, gender, paediatrics, differential modelling, retribution estimates

Citation: Ndako, J.A., S.A. Junaid, O.Y. Ozoadibe, V. Dojumo and A.O. Owolabi, 2023. Evaluation of differential analytic model as a tool for the diagnosis of malaria infection. J. Appl. Sci., 23: 105-110.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Malaria is one of the most widespread and life-threatening parasitic infections in the world and still constitutes a major public health problem that has had a profound effect on human lives remains one of the most serious, life-threatening infectious diseases[1,2]. Malaria infection is much more frequent and more intense in children and pregnant women than in any other age group. However, the burden of malaria in terms of detectable parasitaemia, asymptomatic and submicroscopic infections in school-aged children (5-14 years) remain underappreciated[3]. Reports show its leading cause of both morbidity and deaths in regions that are endemic[4]. A significant portion of the population in endemic areas, particularly in Sub-Saharan Africa, continues to die due to malaria[5]. Malaria poses to be one of the most serious challenges to contemporary society. It is a major problem for both human and economic development in areas where it is endemic, such as Nigeria. The fundamental to efficient illness care in malaria patients in a timely and accurate clinical diagnosis. The most extensively adopted method for diagnosing malaria in the tropics is unreliable because the clinical features of malaria are varied and it might be difficult to differentiate it from most infections in a tropical nation[6]. In hyper-endemic regions, where, subtle symptoms of chronic malaria might lead to misdiagnosis, malaria cases are frequently under-diagnosed. On the other hand, there is a risk of over diagnosis. Furthermore, in these locations, febrile diseases caused by a variety of reasons may be misinterpreted as malaria. Technical skill and repetitive smear tests are required for microscopic diagnosis which is the recognized approach for laboratory detection of malaria[7]. The malaria parasite, *Plasmodium*, is a bloodstream parasite that induces hematologic problems. Anaemia, thrombocytopenia, leucopenia, lymphocytosis and less commonly, disseminated intravascular coagulation are some of the changes that have been seen[8]. However, in severe malaria, several haematological changes differ from the problems encountered[9]. The biochemical changes that take place during the asexual stage of the malaria parasite's life cycle in the human host are linked to the hematologic changes that characterize the disease. When a merozoite enters the erythrocytes, the secretion of inflammatory cytokines (IL-1, IL-10), activation of the coagulation cascade (attributable to platelet consumption and endothelial damage) and sequestration of parasitized red blood cells (due to increased expression of cell adhesion molecules) all occur[10]. These as well as other processes, set in motion the events that lead to structural and quantitative alterations in the different blood cells[11]. Malaria therapy must be precise, necessitating the use of additional diagnostic markers. This study, therefore, evaluates the haematological profile of subjects infected with the malaria parasite using the differential analytic model. The presence of such indicator may heighten the suspicion for malaria parasite infection thereby guiding accuracy in diagnosis and prompting a more diligent search for specific therapy.

MATERIALS AND METHOD

Study area: The study was carried out at the Department of Medical Laboratory Section of the LMU Medical Centre from January to August, 2019. Omuran- is a city located in North Central Nigeria precisely Located in Kwara-South Senatorial Zone in Kwara State-Nigeria.

Study design and population: The study population was made up of individuals who were chosen at random from the clinic's outpatient department. The test and control groups were both male and female and ranged in age from 0-15 years. To collect demographic data and other relevant information, a well-structured questionnaire was employed. A total of 200 samples were used in this investigation, with 80 samples showing evidence of falciparum malaria on a peripheral blood film, 60 samples showing evidence of vivax malaria and 60 samples from healthy people serving as controls.

Ethical permit and consent to participate: The ethical committee of the Landmark University Medical Center approved the protocol of this study with the ethical approval reference: LMC/2019/03/36. Consents to participate were obtained from recruited subjects before sample collection.

Inclusion and exclusion criteria: Subjects confirmed for Malaria infection were recruited for the study. Person who showed no interest in the study and are negative for malaria infection were excluded.

Sample collection and processing: Blood samples were collected from the subjects using the standard method. Malaria parasite infection was screened using a rapid test kit (Bio line)Abbot Bioline™ USA Malaria Ag *Plasmodium falciparum* test is a rapid, qualitative test for the detection of histidine-rich protein 2 (HRP-2) antigen of *Plasmodium falciparum* in human whole blood. This is further confirmed microscopically using capillary blood specimens aseptically collected from a finger prick of volunteer subjects using

sterile blood lancet. Thick and thin blood film smears were prepared based on standard procedure. The full blood count to determine the haematological parameters were analyzed and evaluated using an automated haematology analyzer the Sysmex® KX-21N.-Sysmex Europe GmbH. Calibration of the instrument and processing of the samples was done according to the manufactures instruction. Standard procedures are strictly adhered to during the assay process.

Data analysis: We used the t-test for continuous variables and the x^2 Test for categorical variables to determine the univariate association of gender and haematological indices predictive of malaria. Diagnostic accuracy was measured by computing sensitivity, specificity, predictive values and likelihood ratios. The precision of these estimates was evaluated using 95% confidence intervals.

Hypothesis: It was hypothesized that the presence of asymptomatic malaria infections, the inability to accurately diagnose the level of parasitemia and gametocytemic infectious stage, coupled with the difficulty in achieving adequate diagnosis in low malaria prevalence communities have serious implications for malaria elimination campaigns. In addition, some haematological parameters among subjects living in malaria-endemic communities have not been consistently described as a standard for accurate malaria diagnosis.

RESULTS AND DISCUSSION

Evaluating the predictive differential model: The presented data showed predictive differential modelling for the diagnosis of malaria infection with a focus on gender and haematological properties. The analysis was carried out using the TOST package in the R statistical software. Results are reported for gender tests at effect size, d = 0.7, p = 0.01 and n = 70.3418 at 93.2% statistical power. The data used are described in Table 1 (a and b mean observation from Table 1 shows that the mean haematological properties of the male are a bit higher than the females except for the case of lymphocytes. The observed effect of the monocytes between the genders of the patients was observed to be statistically equivalent to zero and statistically not different from zero based on the null hypothesis test at $p<0.05$. This also implies that the observed effect does not differ from zero and it is too small to be considered. Fisher's linear discriminant method was successfully applied to categorize malaria patient's gender based on haematological characteristics. The result in Table 2 Similarly showed the gender-based description for the haematological properties, this analytical model was able to efficiently categorize the genders based on the retribution estimate method as further indicated in Fig. 1 and as described by Bbosa *et al.*[12] and Everitt and Palmer[13]. This shows that the model is better at predicting malaria infection than diagnosis based only on clinical signs and symptoms. Based on the equivalent and two samples independence testing (Table 3), the observed effect of the packed cell volume, total white blood cells, neutrophils, lymphocytes and platelets between the genders of the patients were observed to be statistically not equivalent to zero and statistically different from zero based on the null hypothesis test at $p<0.05$. This implies that the observed effect is very much different from zero and it is large enough to care about. However, it has been reported that low haemoglobin and platelet levels have also been associated with malaria infection[14,15].

The Fisher's linear discriminant function for gender classification of haematological properties of malaria patients obtained by subtraction (Table 3) is presented as z = -0.0030 PCV-0.0315WBC-0.0557NEUT-0.0367LYMP-0.2227 MONO+0.0018PLT. The sample mean of the discriminant function scores was obtained by the constant coefficients as, $\bar{z} = 6.354$.

The threshold against which a patient discriminating score is evaluated as 0.0000, is obtained by taking the average of the centroid function. This implies that any new patient with discriminant scores greater than 0.0000 would be diagnosed to be a male, otherwise, a female.

Table 1: Gender base descriptive statistics for the haematological properties

	PCV		WBC		NEUT	
Statistic	Female	Male	Female	Male	Female	Male
Mean	34.057	34.471	8.084	8.587	63.557	65.700
Std. Err.	0.493	0.413	0.453	0.420	1.973	1.514
Std. Dev.	4.121	3.459	3.791	3.514	16.504	12.668
Median	33.500	34.500	7.500	7.750	66.000	67.500
Range	26.000	18.000	19.600	18.300	68.000	57.000
Min	24.000	27.000	2.400	2.700	23.000	29.000
Max	50.000	45.000	22.000	21.000	91.000	86.000

PCV: Packed cell volume, WBC: White blood cell and NEUT: Neutrophil

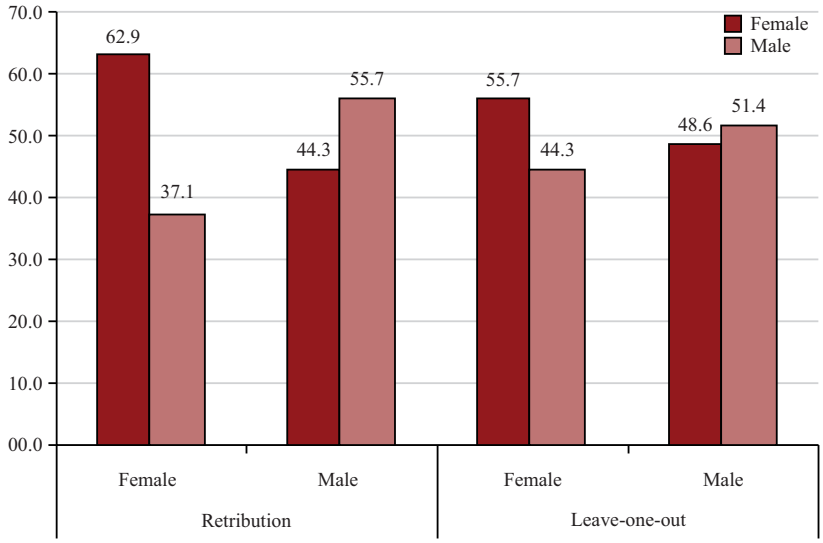

Fig. 1: Retribution estimate analysis based on gender

Table 2: Gender base descriptive statistics for the haematological properties

	LYMP		MONO		PLT	
Statistic	Female	Male	Female	Male	Female	Male
Mean	28.600	25.443	7.743	9.086	269.043	257.929
Std. Err.	1.912	1.340	0.361	0.366	10.796	12.351
Std. Dev.	15.997	11.209	3.020	3.059	90.324	103.334
Median	23.500	24.500	8.000	9.000	250.500	241.500
Range	63.000	48.000	16.000	16.000	392.000	383.000
Min	5.000	9.000	0.000	3.000	120.000	88.000
Max	68.000	57.000	16.000	19.000	512.000	471.000

LYMP: Lymphocytes, MONO: Monocytes and PLT: Platelet count

Table 3: Gender-based equivalence testing between their haematological properties

	Equivalence test result		Null hypothesis test result	
Measures	t-statistics	p-value	t-statistics	p-value
PCV	3.497	0.0003	-0.644	0.5210
WBC	3.327	0.0006	-0.814	0.4170
NEUT	3.280	0.0007	-0.862	0.3900
LYMP	-2.789	0.0031	1.352	0.1790
MONO	1.527	0.0645	-2.614	0.0100
PLT	-3.464	0.0004	0.678	0.4990

PCV: Packed Cell Volume, WBC: White blood cell, NEUT: Neutrophil, LYMP: Lymphocytes, MONO: Monocytes and PLT: Platelet count

Hypothetic significance: The retribution estimate and the leave-one-out method were used to check the performance of the classification methodology used based on previous studies[12,13]. The retribution estimate approach shows that 62.9 and 44.3% of the gender were correctly classified while 37.1 and 55.7% were wrongly classified to be female and male respectively (Fig. 1).

Generally, the retribution estimate method was 59.3% accurate while the leave one out method was 53.6% accurate. However, classification efficiency dropped by 5.7%.

Although, Box's test for equality of the covariance matrices concluded that the matrices of each gender are not the same at $p<0.05$, a linear discriminant is preferable over a quadratic function[14]. The canonical correlation was observed to be very low and 92.07% (lambda value = 0.9207) of the total variance in the discriminant scores was not explained by the gender differences. The Chi-square test confirms that the haematology properties do not differ between genders at $p<0.05$ (Table 4) which shows the classification function coefficient, this defines the discriminant function analysis of

Table 4: Classification function coefficients

Status	PCV	WBC	NEUT	LYMP	MONO	PLT	Constant
Female	0.8123	-3.3480	73.6434	73.8455	63.0504	0.1622	-3663.182
Male	0.8153	-3.3165	73.6991	73.8822	63.2731	0.1604	-3669.536

Function at gender centroid for the females = -0.2913 and function at gender centroid for the males = 0. 2913

Table 5: Statistics check for good classification

Box's M	Eigenvalue	Wilk's lambda
Value = 96.4161	Value = 0.086	value = 0.9207
Approximate = 4.3784	Variance (%) = 100	Chi-square = 11.1477
df1 = 21, df2 = 70043801	Cumulative (%) = 100	df = 6
p-value = 7.5788×10^{-11}	Canonical correlation = 0.2815	p-value = 0.0839

the variables discriminate between naturally occurring groups in this data analysis. The result of these tests nullifies the conducted discriminant analysis in Table 5 and Fig. 1. The differential analytic model in this study observed the gender difference between the haematological properties of malaria patients. Recent studies equally showed that these variables are significant while gender and nationality also played a significant role in predicting malaria[16]. This study validates the usefulness of the model in the accurate diagnosis and tracking treatment regimen of malaria infection among the gender studied.

CONCLUSION

The predictive differential model would be useful in adopting better strategies at precise diagnosis of Malaria infection by health care practitioners and would further halt the transmission and prevention of malaria infection in malaria-endemic communities. While, a discriminating model among the sexes based on the haematological parameters as established in this study can be further explored.

SIGNIFICANCE STATEMENT

Finally, the sensitivity and specificity of this predictive model were 59.3% accuracy based on the retribution estimate method and 53.6% accuracy based on the leave one out method, this predictive model when used will reduce the waiting time and improve the diagnosis of malaria and efficiently. Categorize the genders, further adopt better strategies and precision at screening for malaria infection among the population.

ACKNOWLEDGMENTS

The authors acknowledge the efforts of all the Medical Laboratory scientists at the LMU-Medical centre on their various contributions during the assay of the samples. Miss Oludolapo Olatinsu and Mr. Segun-Light Jegede are appreciated for the layout of this work and for interpreting the statistical data, respectively.

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