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Research paper

Statistical analysis of the symptoms contributing to the diagnosis of malaria: a case study of federal medical Centre Ilara, Ogun state, Nigeria

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Abstract

Malaria in humans is an acute or sub-acute infectious disease caused by one of six protozoan species of the genus Plasmodium: P. falciparum, P. vivax, P. ovale wallikeri, P. ovale curtisi, P. malariae and P. knowlesi, transmitted by Anopheles mosquitoes. Malaria remains one of the most serious global health problems with the World Health Organization (WHO) reporting hundreds of millions of cases and hundreds of thousands of deaths annually, predominantly in sub-Saharan Africa. The study aimed at carrying out statistical analysis on patients who presented themselves to the physician on their claim of having malaria, a case study of Federal Polytechnic Ilaro Medical Centre, Ogun state, Nigeria. The participants were 337 patients of which 180 are Female and 157 are Male within the age range of 3-77 years of age. The statistical analysis of symptoms contributing to the diagnosis of malaria highlighted several key findings. Logistic regression was used for the basic analysis of the dataset and it was discovered that people in the age range 38–47 years are mostly affected with malaria and that females are the most infected gender species with headache being the most significant symptom based on its Wald statistic value.

Keywords: *Diagnosis; Logistic regression; Malaria parasite; Odd ratio; Symptoms JEL Classification: C15.*

1. Introduction

Malaria remains one of the most serious global health problems, with the World Health Organization (WHO) reporting hundreds of millions of cases and hundreds of thousands of deaths annually, predominantly in sub-Saharan Africa (World Health Organization, 2023). Malaria is caused by Plasmodium parasites, transmitted through the bites of infected female Anopheles mosquitoes. The lifecycle of Plasmodium involves several stages both in the mosquito and within the human host, complicating efforts at control and eradication (Carter & Mendis, 2002). Malaria is a major public health problem in Nigeria, causing significant morbidity and mortality, particularly among young children and pregnant women (Nigeria Malaria Indicator Survey, 2015). The country has made some progress in reducing the burden of the disease through the implementation of various control measures, but the problem persists (Oladimeji et al., 2019).

The most severe form of malaria is caused by Plasmodium falciparum, but other species such as P. vivax, P. ovale, and P. malariae also affect humans (Collins & Jeffery, 2005). Transmission occurs through the bite of an infected mosquito, which introduces the parasites from its saliva into a person's bloodstream. The parasites travel to the liver, where they mature and reproduce. After several days, the mature parasites enter the bloodstream and begin to infect red blood cells, leading to the symptoms of the disease (White, 2018).

Malaria is an acute febrile illness with an incubation period of 7 days or longer. Thus, malaria should always be considered when a febrile illness develops one week or more after the first possible exposure (WHO, 2023). The most severe form is caused by P. falciparum, with variable clinical features including fever, chills, headache, muscular aching and weakness, vomiting, cough, diarrhea, and abdominal pain. Other symptoms related to organ failure may supervene, such as acute renal failure, pulmonary edema, generalized convulsions, and circulatory collapse, followed by coma and death (Gomes et al., 2002). The initial symptoms are nonspecific and cannot be distinguished from those of other common febrile illnesses in the locality, such as acute respiratory infections, dengue fever, and septicemia. It is important that the possibility of falciparum malaria is considered in all cases of unexplained fever starting at any time between 7 days after the first possible exposure to malaria and 3 months (or, rarely, later) after the last possible exposure (White et al., 2014). Any person who experiences a fever during this period should immediately seek diagnosis and effective treatment, and should inform medical personnel of the possible exposure to malaria infection. Falciparum malaria may be fatal if treatment is delayed beyond 24 hours after the onset of clinical symptoms (Trampuz et al., 2003).

Early diagnosis and treatment of malaria reduce disease and prevent deaths. It also contributes to reducing malaria transmission. The best available treatment, particularly for P. falciparum malaria, is artemisinin-based combination therapy (ACT) (Dondorp et al., 2010). WHO recommends that all cases of suspected malaria be confirmed using parasite-based diagnostic testing (either microscopy or rapid diagnostic

test) before administering treatment. Results of parasitological confirmation can be available in 15 minutes or less. Treatment solely based on symptoms should only be considered when a parasitological diagnosis is not possible (WHO, 2023).
Vector control is the main way to reduce malaria transmission at the community level. It is the only intervention that can reduce malaria transmission from very high levels to close to zero (Lengeler, 2004). For individuals, personal protection against mosquito bites represents the first line of defense for malaria prevention. The two forms of vector control are the use of insecticide-treated mosquito nets (ITNs) and indoor spraying with residual insecticides (WHO, 2015).
The clinical presentation of malaria can vary, but common symptoms include fever, headache, chills (rigor), and sweating, which typically appear a few weeks after being bitten (Caraballo, 2014). If not treated promptly, malaria can progress to more severe forms and cause more serious symptoms, which can be fatal (White, 2018). Some of the symptoms of malaria include fever & hyperpyrexia, rigor & chills, headache & diarrhea, Coca-Cola urine, cold & convulsion, prostration, jaundice, bitter tongue, anemia, hyperglycemia & vomiting & fatigue (CDC, 2022). The study therefore aimed at identifying the key symptoms that significantly contribute to the accurate diagnosis of malaria.

2. Empirical literature

Malaria is the fifth leading cause of death from infectious disease worldwide, and the second leading cause of death in Africa. The World Health Organization (WHO) estimated that about 3.3 billion people in 97 countries are at risk of infection with malaria and 1.2 billion are at high risk; 1 or more in 1000 chance of getting malaria in a year (WHO, 2014). About 214 million cases of malaria occurred globally in 2014 and the disease led to 438,000 deaths, representing a decrease in malaria case incidence and mortality rates of 37% and 60% since 2000, respectively (WHO, 2015). Malaria kills one child every 30 seconds and it's the third leading cause of death for children under five years worldwide, after pneumonia and diarrheal disease (CDC, 2014). In 2010, there were an estimated 219 million malaria episodes, of which approximately 81% were recorded in Africa, and an estimated 660 000 malaria deaths, of which 91% were in Africa. The burden is heaviest in the African Region, where an estimated 90% of all malaria deaths occur, and in children aged under 5 years, who account for 78% of all deaths (WHO, 2015). Thirty countries in Sub-saharan Africa account for 90% of global malaria deaths. Nigeria, Democratic Republic of Congo (DRC), Ethiopia and Uganda account for nearly 50% of the global deaths. Malaria is the second leading cause of death from infectious diseases in Africa after HIV/AIDS. About one out of five deaths of children under 5 years in Africa is due to malaria (Breman et al., 2004).
The malaria parasite is transmitted to human by mosquitoes belonging to the genus Anopheles. Malaria parasite can also be transmitted through blood transfusion, organ transplant, or the shared use of needles or syringes (CDC, 2014), and from mother to child (congenital malaria). The nature of morbidity can also be affected by the stability of transmission. As transmission intensity decreases, the cumulative risk for experiencing a severe disease episode during childhood increases (Snow et al., 1998). Severe malaria becomes less likely as children grow older, but when severe malaria does occur, 8-15 years old children (60.6%) are more likely to develop life-threatening cerebral manifestations than those who are 4-7 years old (28.2%) or younger (11.3%) (Imbert et al., 1997). Thus, cerebral malaria is more likely to develop from malaria infections in epidemic-prone regions, which may in part account for the high case fatality rates noted during epidemics. Many biological and environmental factors shape the character of malaria in a given location. Nearly all the people who live in endemic areas are exposed to infection repeatedly. Those who survive malaria in childhood gradually build up some immunity. They may carry the infection, serving as reservoirs for transmission by mosquitoes without developing severe disease (Sullivan et al., 1999). In other areas, where the infection rate is low, people do not develop immunity because they rarely are exposed to the disease. This makes them more susceptible to the ravages of an epidemic.
Malaria can be categorized in two categories: uncomplicated or complicated (severe). Uncomplicated malaria has three stages: a cold stage, a hot stage, and a sweating stage. The cycle lasts between 6-10 hours. The cold stage consists of shivering. A patient in the hot stage suffers from fever, headaches, vomiting, and seizures (frequently in young children). The sweating stage consists of sweats and tiredness (CDC, 2014). Tertian and quartan periodicities are associated classical attacks. In tertian attacks the symptomatic stages occur every second day. These attacks are caused by P. falciparum, P. vivax, and P. ovale. In quartan attacks, the symptomatic stages occur every third day. P. malariaeis the cause of quartan periodicity (Bloland, 2001). Uncomplicated malaria can be misdiagnosed as influenza or the common cold. This occurs in countries where malaria is not common; therefore, the patient is not expected to have malaria. In endemic areas, malaria symptoms are recognized (CDC, 2014). Severe malaria occurs when a patient suffers from organ failure or abnormalities in the blood or metabolism. Severe malaria is associated with cerebral malaria, severe anemia, hemoglobinuria, acute respiratory distress syndrome, abnormal blood coagulation, low blood pressure, acute renal failure, hyperparasitemia, metabolic acidosis and hypoglycemia. Severe malaria requires urgent and aggressive treatment (CDC, 2014). Severe falciparum malaria is caused mainly by extensive 22 parasitized erythrocyte sequestration and consequent dysfunction of vital organs. Direct visualization of the microcirculation and measurement of individual vessel flows in the retinal, buccal, and rectal circulations show reversible heterogeneous microvascular obstruction with patterns matching exactly those noted in tissues from fatal cases (WHO, 2000). The extent of microvascular obstruction parallels clinical severity and established prognostic measures, such as plasma lactate and base deficit (WHO, 2000). Patients with severe malaria usually have low concentrations of L-arginine, a precursor of nitric oxide, and increase in those of asymmetric dimethylarginine (Tan et al., 2011). Endothelial activation causes exocytosis of intracellular Weibel-Palade bodies, which contain bioactive molecules such as von Willebrand factor and angiopoietin 2. Ultra-long multimers of von Willebrand factor can bind activated platelets expressing CD36 (the receptor for PfEMP1), and thereby mediate cytoadherence (Wells, 2009).

3. Methodology

3.1. Binary logistic regression

Binary logistic regression is a statistical method used for modeling binary outcome variables based on one or more predictor variables. In the context of malaria, researchers and healthcare professionals often use binary logistic regression to analyze the relationship between various symptoms and the likelihood of a malaria diagnosis. This method is particularly useful in medical research as it can handle various types of independent variables and provide insights into the probability of disease presence given certain symptoms. Logistic regression will be a valuable statistical method in the context of analyzing the spread of malaria in Nigeria for several reasons: it suitability of modelling a binary outcome; estimation of probability of specific outcome; it allows inclusion of multiple independent variables; and assess significance of each independent variables.

3.2. Data collection

The data used in this study was obtained as a secondary data from the health record office of Federal Medical Centre, Ilaro, Ogun state, Nigeria, for the period of 4 weeks. The test results of 337 patients as compared to their claims of malaria infection were extracted. The record include patients' age, sex and fifteen (15) malaria symptoms.
For the purpose of this study and the nature of logistic model, the data is coded as follows: The outcome of the diagnosis is coded as 1 if the patient is diagnosed of malaria, and 0 if otherwise, Age is between 3 and 77 years which are of continuous data type. Sex is codes as 1 if female and 0 for male, Symptoms which are encoded as 1 for the presence and 0 if otherwise.

3.3. Model specification

In multiple linear regression, the main activity is to draw least square line around which the value of Y (i.e. the outcome variable) are distributed. In contradiction to that, the logistic regression estimates the probability that a certain individual will have malaria or not in the case of this study.
If p is the probability of having malaria given the symptoms, then (1-p) is the probability of not having malaria. Since the study considered several symptoms in deciding the eventual outcome (Presence or Non-presence) of malaria in patients, the odds ratio of each patient is calculated as the joint effect of all the predictors (malaria symptoms) and it is expressed mathematically as follows;

$$\text{Odd} = \frac{\text{p}}{1-\text{P}} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 \ldots + \beta_n X_n \quad (1)$$

The log odds, also known as the logit, is a transformation of probability that is commonly used in logistic regression. The log odds of an event is defined as the natural logarithm of the odds of that event occurring. Mathematically, it can be represented as:

$$\text{Log odds} = \log\left(\frac{\text{p}}{1-\text{P}}\right) \quad (2)$$

In the context of this study, the log odds can help quantify the relationship between various symptoms (predictor variables) and the likelihood of severe malaria (response variable). By estimating the coefficient in the logistic regression model, the effect of each symptom on the log odds of severe malaria can be determined. For example, a positive coefficient indicates that presence a particular symptom is associated with higher log odds (or higher probability) of severe malaria, while a negative coefficient indicates the opposite.
By exponentiation of the coefficients, the odds ratios can be obtained, which provide a measure of the effect size of each predictor variable on the likelihood of severe malaria. The odds of an event denoted as OR = $\frac{\text{p}}{1-\text{P}}$
The odds ratio (OR) is a key measure in logistic regression, particularly in the fields of medical and public health research, to describe the strength and direction of the association between predictors (like symptoms) and a binary outcome (such as the presence or absence of a disease). In the context of malaria, understanding odds ratios can help identify which symptoms significantly increase (or decrease) the likelihood of having the disease.
The odds ratio in the context of logistic regression compares the odds of the outcome occurring (e.g., having malaria) in the presence of a particular predictor (e.g., a symptom like fever), to the odds of the same outcome occurring without that predictor. Mathematically, if we consider a binary predictor variable X (e.g., fever present = 1, fever absent = 0), the odds ratio for having malaria given the presence of fever can be expressed as:

$$\text{OR} = \frac{\text{odds of having malaria}|\text{fever is present}}{\text{odds of having malaria}|\text{fever is absent}} \quad (3)$$

In logistic regression, the odds of the outcome (having malaria) when the predictor X is present is modeled by the logistic function:

$$\text{Odds}(Y=1|X=1) = e^{\beta 0+\beta 1} \quad (4)$$

Where:
β_0 is the intercept of the model,
β_1 is the coefficient for the predictor X
Similarly, when the predictor X is absent:
Odds $(Y=1|X=0) = e^{\beta 0}$
Thus, the odds ratio (OR) associated with the predictor X, which in this example could represent a symptom like fever, is given by:

$$\text{OR}=\frac{e^{\beta 0+\beta 1}}{e^{\beta 0}}=e^{\beta 1}$$

$$\text{Logit P}(Y_i) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 \ldots + \beta_k X_k \quad (5)$$

i = 1 (Presence of malaria) or 0 (Non-presence of Malaria)
Where;
p is the probability that a patient has malaria given the symptoms
β_0 is the overall malaria risk
β_j is the fraction by which the risk of being diagnosed of malaria having fever is increased or decreased per unit change in x_j; j = 1, 2, , , k
X_1 = Fever X_2 = Cold X_3 = Rigor X_4 = Fatigue
X_5 = Headache X_6 =Bitter-Tongue X_7 = Vomiting
X_8 = Diarrhea X_9 = Convulsion X_{10} = Anemia X_{11} = Jaundice X_{12} = Cocacola-Urine X_{13} = Hypoglycemia X_{14} = Prostration
X_{15} = Hyperpyrexia

The coefficients (β) in logistic regression are estimates obtained from maximum likelihood estimation (MLE), which differs from the ordinary least squares method used in linear regression. The likelihood function L for binary logistic regression, given parameters β and data X, is given by:

$$(\beta|X) = \prod_{i=1}^{n} P(1 - P_i)^{1-y_i} \quad (6)$$

Where Y_i is the observed outcome (0 or 1), and Pi is the predicted probability of the outcome being 1 for the i-th observation. Some of the assumptions of logistic regression include; binary outcome of the response variable, independence of observations, linearity in log odds of response and predictor variables; and independence of predictor variables.

4. Results and discussion

4.1. Descriptive analysis

The frequency distributions of the dependent and independent variables are given in Table 1.

Table 1: Frequency Distribution of the Symptoms of Malaria

Symptoms	Non-Presence	Presence	Total Patients
Fever	84	253	337
Cold	146	191	337
Rigor	222	115	337
Fatigue	174	163	337
Headache	101	236	337
Bitter Tongue	201	136	337
Vomiting	312	25	337
Diarrhea	223	114	337
Convulsion	221	116	337
Anemia	219	118	337
Jaundice	115	222	337
Cocacola-Urine	155	182	337
Hypoglycemia	48	289	337
Prostration	263	74	337
Hyperpyrexia	290	47	337

Table 2: Cross Tabulation of Gender & Severe Malaria

Malaria Sex	Non-Presence	Presence	Total
Male	103 (46.55%)	54 (46.61%)	157
Female	118 (53.45%)	62 (53.39%)	180
Total	221	116	337

Table 2 shows the cross-tabulation of severe malaria and gender and it can be seen that female patients were more male and there were 62 (18.39%) of the total population which are females and truly diagnosed of malaria.

Table 3: Model Summary

	Odds Ratio	Estimate	Std. Error	Pr(>|z|)	Z value
Intercept	0.09817	-2.32104	0.60033	0.000111 ***	-3.866
Fever	0.98066	-0.01953	0.28413	0.945189	-0.069
Cold	1.45017	0.37168	0.25175	0.139849	1.476
Rigor	1.16895	0.15610	0.25583	0.541733	0.610
Fatigue	1.26072	0.23168	0.24515	0.344638	0.945
Headache	2.14723	0.76418	0.28221	0.006773 **	2.708
Bitter Tongue	0.83518	-0.18011	0.24857	0.468715	-0.725
Vomiting	1.05922	0.05753	0.47893	0.904384	0.120
Diarrhea	1.59590	0.46744	0.25138	0.062961	1.859
Convulsion	0.65672	-0.42050	0.25902	0.104498	-1.623
Anemia	0.95291	-0.04823	0.25599	0.850549	-0.188
Jaundice	1.11861	0.11209	0.25801	0.663980	0.434
Cocacola-Urine	1.39749	0.33468	0.24570	0.173155	1.362
Hypoglycemia	2.13815	0.75994	0.39249	0.052841*	1.936
Prostration	0.55504	-0.58871	0.31220	0.059337*	-1.886
Hyperpyrexia	1.07106	0.06865	0.35884	0.848282	0.191

The results of fitted binary logistic regression model are presented in Table 3. From the Table it can be seen that only Headache with p-value of 0.006773 indicating a significant impact on the odds of being diagnosed of malaria (p-value < 0.05). The two symptoms, Hypo-glycemia and Prostration with p-values of 0.052841 and 0.059337 respectively were significant at 10% level of significance (p-value < 0.10) indicating a possible association with having severe malaria. However, all other symptoms included in the analysis have p-values greater than 0.05, therefore, they are not associated with having severe malaria.

The logistic regression modelled the odds of being diagnosed with malaria based on various symptoms and it revealed several important associations. The odds ratios indicate that certain symptoms significantly increase the likelihood of a malaria diagnosis. For example, patients with headache (OR = 2.14723) and hypoglycemia (OR = 2.13815) are more than twice as likely to be diagnosed with malaria compared to those without these symptoms. Other symptoms that increase the odds include cold (OR = 1.45017), diarrhea (OR = 1.59590), and cocacola-urine (OR = 1.39749).

Conversely, some symptoms are associated with a decreased likelihood of malaria diagnosis. For instance, prostration (OR = 0.55504), convulsion (OR = 0.65672), and bitter tongue (OR = 0.83518) reduce the odds of malaria diagnosis. The intercept (OR = 0.09817)

represents the baseline odds of malaria in the absence of any of these symptoms. Overall, the analysis highlights specific symptoms as strong predictors of malaria, with some increasing and others decreasing the probability of diagnosis.
To give more clarity to the p-value, the z-value was used. The z-value obtained from the logistic regression model summary provides information about the significance of each coefficient estimate in the model. The z-value in logistic regression is calculated using the following formula

$$\text{z-value} = \frac{\text{Coefficient Estimate}}{\text{Standard Eroor of the coefficient estimate}}$$

The z-value represents the number of standard deviations the coefficient estimate is from zero. It indicates how significant the coefficient estimate is relative to its standard error. Larger absolute z-values indicate stronger evidence against the null hypothesis and greater significance of the coefficient estimate in predicting the outcome variable.
Fitted Model:

Logit (Severe malaria) = -2.32104 - 0.01953(Fever) + 0.37168(Cold) - 0.15610(Rigor) +0.23168(Fatigue) + 0.76418(Headache) - 0.18011(Bitter Tongue) + 0.05753(vomiting) + 0.46744(Diarrhea) – 0.42050(Convulsion) - 0.04823(Anemia) + 0.11209(Jaundice) +0.33468(Cocacola Urine) + 0.75994(Hypoglycemia) – 0.58871(Postraction) + 0.06865(Hyperpyrexia)

From the above model:
The statistical analysis reveals varying impacts of symptoms on the odds of being diagnosed with malaria. Notably, an increase in the presence of fever, rigor, bitter tongue, convulsion, anemia, and prostration urine significantly decreases the odds of malaria diagnosis, with fever showing the most substantial reduction (odds ratio of 2.32104). Conversely, symptoms like cold, fatigue, vomiting, diarrhea, jaundice, cocacola urine, hypoglycemia, and hyperpyrexia increase the odds of a malaria diagnosis, although these increases are generally smaller, with the odds ratio for cold being the highest at 0.37168. These findings suggest that certain symptoms are more strongly associated with reducing or increasing the likelihood of a malaria diagnosis, highlighting the importance of a nuanced approach to clinical assessments.

5. Summary and conclusion

The study presented statistical analysis of symptoms that contribute to the diagnosis of malaria among children and adults based on the data collected from the Federal Medical Centre, Ilaro, Ogun state Nigeria. The study covered a period of four (4) weeks monitoring of patients attendance, their consultation with physician and malaria test results as compared to their claims of malaria infection.
The statistical analysis of symptoms contributing to the diagnosis of malaria highlighted several key findings. The findings from the study revealed that people in the age bracket 38–47 years are mostly affected with malaria and that females are the most infected gender species with headache being the most significant symptom based on its Wald statistic value. These results provide valuable insights into the epidemiology of malaria and underscore the importance of early detection and treatment. By understanding the symptomatology of malaria, healthcare professionals can improve diagnostic accuracy and implement timely interventions, ultimately reducing the burden of the disease.
The study therefore concluded that headache is a significant symptom associated with the diagnosis of malaria while diarrhea, hyperglycemia and prostration also have impact on diagnosis of malaria. Although, female is the most gender affected by malaria, the study concluded that sex and age do not have effect on the diagnosis of malaria

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