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STATISTICAL ANALYSIS OF RISK FACTORS OF MALARIA RELATED IN-HOSPITAL MORTALITY: A CASE STUDY AT TEPI GENERAL HOSPITAL, SOUTH WESTERN ETHIOPIA

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AUTHOR'S CONTRIBUTION

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Malaria is a major challenge to public health and socio-economic development worldwide and in sub –Saharan Africa in particular. It causes an estimated 300 to 500 million cases and 1.5 to 2.7 million deaths worldwide each year, of which 80% of the cases and 90% of the deaths occur in Sub-Saharan Africa. The main objective of this study was to identify the risk factors of malaria related in-hospital mortality. The data were taken from hospital records at Tepi General Hospital, South Western Ethiopia. A sample of 535 patients were used for the study. The data were analyzed using the classical logistic regression. The results of the study showed that 78.5% of malaria patients were found to be discharged while the rest 21.5% died of malaria in the health center. The classical logistic regression analysis were identified significant predictors. The results from multivariable analysis revealed that age of patient, residence of patient, type of malaria species diagnosed, time from symptom onset to diagnoses, malaria complication, pregnancy and total length of stay in hospital were factors associated with health status of malaria patients. Governmental and non-governmental organizations should focus on continuous awareness creation of early diagnoses and treatment to the societies in rural part of South Western Ethiopia.

Keywords: Logistic regression; malaria; risk factors; in-hospital mortality; Tepi General Hospital.

ABBREVIATIONS

FMOH : Federal Ministry of Health

MOH : Ministry Of Health

OR : Odd Ratio

SNNPR : South Nations Nationalities People Region

WHO : World Health Organization

WMR : World Malaria Report

1. BACKGROUND

Malaria is a vector-borne disease caused by Plasmodium parasites. The parasites are spread to people through the bites of infected Anopheles mosquitoes, called "malaria vectors". It remains to be a major challenge to public health and socio-economic development worldwide and in sub – Saharan Africa in particular [1,2]. It causes an estimated 300 to500 million cases and 1.5 to 2.7 million deaths worldwide each year, of which 80% of

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the cases and 90% of the deaths occur in Sub-Saharan Africa (WHO, 2016).

In Ethiopia, it is also a leading public health problem, where 75 % of the country's land surface is malarias and 68% of the populations are at risk of malaria infection. Thus, malaria is a public health concern and all age groups of the population are vulnerable. Children under five years of age and pregnant women are generally considered to be at a higher risk [3].

There are over 120 species of the parasite genus Plasmodium in the world (Ribeiro, 2006). However, only four of these infect humans to cause malaria. These four species of Plasmodium parasites are *Plasmodium falciparum*, Plasmodium vivax, Plasmodium ovale and Plasmodium malaria. Among the four species, *Plasmodium falciparum* is by far the most aggressive species, distributed globally especially common in Africa (WHO, 2016).

Malaria death was defined as a death from fever with microscopically confirmed Plasmodium species. Despite considerable progress in malaria control over the past decade, malaria remains a serious problem particularly in Sub Saharan Africa. An estimated 300 million to 500 million cases and 1.5 to 2.7 million deaths occur worldwide each year due to malaria, and over 2400 million remain at risk (WHO, 2009) Africa. One of four childhood deaths in Africa is caused by malaria.

In Ethiopia, *Plasmodium falciparum* is the dominant species followed by *P. vivax* and these two species accounts for 60% and 40% of all malaria cases respectively. *P. malariae* accounts only for less than 1% of cases and is restricted in distribution. But, *P. ovale* is rarely reported [4]. However, the relative frequency of the species varies from place to place and from season to season. For instance, in SNNPR *plasmodium falciparum* accounts for 59% of confirmed malaria cases, *P. vivax* were 27% and 13% mixed infection. However, *P. falciparum* is responsible for most hospital and health center admissions, morbidity and mortality [5].

In SNNPR, the high transmission season of malaria cases usually goes from August through December [6]. Even though, there is a little reduction of death cases, the results of the survey as well as the routine surveillance data demonstrated that malaria continues to be a significant public health challenge and a major public health problem in the region [7]. However, measuring malaria burden in a population is a challenge in most developing countries, because most disease incidences and deaths occur outside of the formal health care, particularly at home [8].

In 2007, there were 3,763,136 people at risk and 1,128,941 cases in the SNNPR [5]. Still now, malaria ranks first among the leading ten top diseases in the areas. *Plasmodium falciparum* and Plasmodium vivax are the two dominant parasite species with relative frequency of 60 % and 40 % respectively [4], MOH, 2014. Even though, this proportion varies from zone to zone and from season to season. In malaria epidemic situations, falciparum is the dominant parasite species that causes severe manifestations and majority of malaria deaths happen due to infection by this parasite [11,12]. Determining the major factors that may affect malaria related in-hospital mortality is important to design better strategy and ultimately improve the care provided or treatment condition at all levels of health care [8]. The general objective of this study was to identify the risk factors of malaria related in-hospital mortality in Tepi General Hospital, South Western Ethiopia.

2. METHODS

2.1 Study Area and Design

The current study was conducted in Tepi General Hospital, South Nation Nationalities and Peoples of Region, Southwestern Ethiopia. The study is retrospective, which was retrieved from the patients' cards of malaria positive cases.

2.2 The Study Variables

The response variable in this study is the binary response variable which is named as "Discharged/Death status" of patients leveled as whether persons died of malaria in hospital or not. This status of patient is coded as 1, if the patient died in hospital and 0, if the patient discharged of malaria positive under laboratory confirmed.

The explanatory variables that are included in the study are sex of patient, Age of patient, Residence of patient; Season when patient diagnosed: dry season (Oct.-March) wet season (April-September); type of malaria species diagnosed, time from symptom onset to diagnoses (days); Body temperature in the first diagnosis (°C); Body temperature in the last diagnosis (°C); Malaria complication; Malaria in pregnancy cases; and Total length of stay in hospitalization.

2.3 Data

The data were obtained from record reviews of all inpatient malaria cases of laboratory confirmed malaria positive admitted to the pediatric ward from

June 2017 to June 2020 in Tepi General Hospital, South Western Ethiopia. The recorded patient card contains all information on a patient from admission to discharge or death status recorded by nurses, laboratory staff, attendants, and clinicians.

2.4 Method of Statistical Analysis

Logistic regression analysis extends the techniques of multiple regression analysis in which the outcome variable is categorical. Logistic regression allows one to predict a discrete outcome, such as group membership, from a set of predictor variables that may be continuous, discrete, dichotomous, or a mix of any of these (Gellman and Hill, 2007, Stephenson [9]).

The maximum likelihood estimation technique was applied to estimate parameters of the model. The logistic model $P_i = \frac{e^{X_i'\beta}}{1+e^{X_i'\beta}}$, since observed values of Y say, Y_i's (i=1, 2,…,n) are independently distributed as binomial and, the maximum likelihood function of Y is given by:

$$L(Y;\beta) = \prod_{i=1}^{n} P(y_i \mid X_{i1}, X_{i2},...,X_{ik}) = \prod_{i=1}^{n} \left[\frac{e^{X_i\beta}}{1+e^{X_i\beta}}\right]^{y_i} \left[\frac{1}{1+e^{X_i\beta}}\right]^{(1-y_i)}$$

The objective of stating the likelihood function is to get an estimator $\hat{\beta} = \left(\hat{\beta}_0, \hat{\beta}_1, ..., \hat{\beta}_k\right)$ of β which maximizes the likelihood function of the above equation. Since the likelihood equations are non-linear in the parameters, the Newton-Raphson iterative maximum likelihood estimation method that expresses $\hat{\beta}$ at the $(u+1)^{th}$ cycle of the iteration is expressed as $\hat{\beta}_{u+1} = \hat{\beta}_u + (X'\hat{V}_u X)^{-1} XR_u$, where u=0,1,2,3, … and $\hat{V}_u$ is a diagonal matrix. Finally, $\hat{\beta}$ is the resultant maximum likelihood estimator of β [10, 13,14,15].

3. RESULTS AND DISCUSSION

The data were obtained from records of 535 patients who were laboratory confirmed malaria positive in-patients during June 2017 to June 2020. The result displayed in Table 1 shows percentages and counts of discharged/death status of patient with respect to the explanatory variables. Out of the 535 patients considered, 420 (78.5%) patients were discharged while 115 (21.5%) patients were died.

Accordingly, 46.8% of laboratory confirmed malaria patients were male and the rest 53.2% were female. From the residence of patient diagnosed in the health center, 52.7% patients were urban resident and 47.3% were from rural residents. Out of 535 malaria patients, 26.3% were referred to the health center.

Table 1. Test of Association between Discharged/Death Status and Explanatory Variables

Variable	Category	Status				Total		Chi-Square Value	
		Discharge		Death					
		Count	%	Count	%	Count	%	Df	P-value
Sex of patient	Male	205	82.1	44	17.9	249	46.8	1	
	Female	216	75.3	70	24.7	286	53.2		0.151
Age of patient	<5	120	62.5	48	37.5	168	31.4	3	0.000
	5 -14	176	82.1	14	17.9	190	35.4		
	15 -44	69	71.6	42	28.4	111	20.8		
	≥45	54	92.7	12	7.3	666	12.4		
Residence of patient	Urban	249	88.7	32	11.3	281	52.7	1	0.000
	Rural	170	67.1	84	32.9	254	47.3		
Season when patient diagnosed (wet or dry)	Dry	185	83.9	39	16.1	224	42.1	1	0.015
	Wet	234	70.3	77	29.7	311	57.9		
Type of malaria species diagnosed	P. Falciprum	212	63.4	76	36.6	288	53.8	1	0.000
	P. Vivax	170	84.2	25	15.8	195	36.4		
	Mixtured	37	76.1	14	23.9	51	9.6		

Time from symptom onset to diagnoses (days)	< 3 days	252	93.4	18	6.6	270	50.6	2	0.000
	3- 5 days	115	75.3	38	24.7	153	28.6		
	> 5 days	51	56.4	60	43.6	111	20.8		
Body temperature in the first diagnoses (°C)	38-40 (°C)	252	80.2	59	19.8	311	58.1	1	1.476
	≥ 41 (°C)	167	74.8	57	25.2	224	41.9		
Body temperature in the last diagnoses (°C)	35-37 (°C)	409	96.7	13	3.3	422	78.7	2	0.000
	38-40 (°C)	12	13.1	85	86.9	97	18.4		
	≥ 41 (°C)	0	0.0	16	100.0	16	3.0		
Malaria complication	No	294	87.2	22	12.8	316	59.4	1	
	Yes	128	58.4	91	41.6	219	40.6		0.000
Pregnancy cases	No	180	81.5	17	18.5	197	37.1	1	0.000
	Yes	33	47.9	53	52.1	86	16.1		
Total length of stay in hospital (days)	< 3 days	125	61.7	79	38.3	204	38.2	2	0.000
	3-5 days	196	84.3	12	15.7	208	39.0		
	> 5 days	98	89.7	25	10.3	123	22.8		
Treatment given (drugs)	Quinine	250	73.5	90	26.5	340	63.6	1	0.045
	Chloroquine	170	87.2	25	12.8	195	36.4		

Moreover, significant association was found between malaria patient health status and the explanatory variables: age of patient, residence of patient, season when patient diagnosed, type of malaria species diagnosed, time from symptom onset to diagnosis, body temperature in the last diagnoses (°C), malaria complication, pregnancy cases, total length of stay in hospitalization and treatment given. However, no association was found between patients' health status and the explanatory variable: sex of patient and body temperature of patients in the first diagnosis (°C), because the asymptotical significance value of p-value exceeds level of significance.

The proportion of death due to malaria within the age categories <5 years, 5-14 years, 15-44 years and ≥ 45 years were 37.5%, 17.9%, 28.4% and 7.3%, respectively. This shows that the probability of that a patient dying was high in children age group < 5 years old and drops in the age group 5-14 years, then increases in 15-44 years age group and decline in the last age group. This suggests a curvature in the age group and the probability of in-hospital mortality. The proportions of death for time from symptom onset to diagnoses (days) from categories < 3 days, 3-5 days and > 5 days were 6.6%, 24.7% and 43.6% respectively. This indicates that the probability of that a patient dies increases with time from symptom onset to diagnoses and it tells as patients with late diagnosis after symptom appearance are more likely to die than those diagnosed at early stage.

The proportion of total length of stay in hospitalization in the category of < 3 days, 3-5 days, and > 5 days were 38.3%, 15.7% and 10.3% respectively. This shows as length of stay in hospitalization increases the risk of dying from malaria in the health center decreases. The proportion of malaria patient dying with type of malaria species diagnosed accounts for P. falciprum, P.vivax and mixture were 36.6%, 15.8% and 23.9% respectively. The proportion of death were high for patients who have complicated malaria cases which shows that 41.6% and 12.8% were the proportion of death on account of un complicated malaria cases.

The result also revealed that the proportion of malaria patient death that was diagnosed during wet season is 29.7% and for patients diagnosed during dry season is 16.1% in the health center. This implies that probability of death was high for patients diagnosed during wet season.

The difference between –2 log likelihood for the best-fitted model and –2 log likelihood for the null model (in which all the coefficient values are set to zero in block 0) has a chi square distribution with degrees of freedom equal to the number of predictors; this difference is the model chi-square that SPSS refers to. The difference between -2 log likelihood values for models with successive terms added also has chi-squared distribution. In Table 2 the -2 log likelihood value for the null model or the restricted model and final model are 560.918 and 102.102, respectively. In our case model chi-square has 13 degrees of freedom, a value of 458.816 and a probability of p-value (0.000) < 5% level of significance. This shows that the model in final model has a good fit which indicating that the predictor variables do have a significant effect. In addition, the result of a chi-square value shows statistically significant at 5% level of significance, and the independent variables predict the dependent variable well and model is good fit model [16].

Table 2. Summary statistics of the likelihood ratio test

Model	Model Fitting Criteria	Likelihood Ratio Tests		
	-2 Log Likelihood	Chi-Square	Df	Sig.
Null model (Intercept only)	560.918			
Final model	102.102	458.816	8	0.000

Table 3. Model Summary of Cox & Snell R^2 and Nagelkerke R^2

Model Summary		
-2Log likelihood	Cox & Snell R^2	Nagelkerke R^2
102.102	0.574	0.886

Table 4. Parameter estimates of binary logistic regression using forward stepwise variable selection Method

Variables	Category	$\hat{\beta}$	S.E.($\hat{\beta}$)	Wald	Df	Sig.	Exp (B)	95.0% C.I. for Exp (B)	
								Lower	Upper
Age of patient	<5(ref)			7.594	3	0.034			
	5 -14	-1.840	0.826	4.959	1	0.026	0.159	0.031	0.802
	15 -44	-1.533	0.778	3.880	1	0.039	0.216	0.047	0.992
	≥45	-2.079	0.787	6.983	1	0.008	0.125	0.027	0.585
Residence of patient	Urban	1.607	0.521	9.526	1	0.001	4.989	1.798	11.843
Type of malaria species diagnosed	*P. falciprum*			14.518	2	0.000			
	P. vivax	-3.329	0.945	12.402	1	0.000	0.036	0.016	0.229
	Mixtured	-2.984	0.984	9.195	1	0.043	0.051	0.019	0.348
Time from symptom onset to diagnoses	< 3 days			9.528	2	0.009			
	3- 5 days	0.897	0.693	1.674	1	0.044	2.452	0.630	9.536
	> 5 days	1.204	0.731	2.712	1	0.025	3.334	0.795	11.977
Malaria complication	Yes	1.213	0.516	5.522	1	0.020	3.364	1.223	9.254
Pregnancy	Yes	0.733	0.534	1.887	1	0.038	2.082	0.731	5.930
Total length of stay in hospital	< 3 days (Ref)			5.979	2	0.019			
	3-5 days	-1.364	0.658	4.292	1	0.045	0.256	0.070	0.929
	> 5 days	-0.415	0.323	1.648	1	0.038	0.661	0.351	1.244
Constant		-6.207	1.602	15.019	1	0.000	0.012	0.002	0.873

** Ref; in the brackets indicates the reference category for each predictors.*

Nagelkerke's R^2 in Model Summary Table 3 is 0.886, which indicates that 88.6% of the variability in the malaria patient status was explained by the explanatory variables.

The results in Table 4 shown that the values of the odds ratio interpretation of age categorized as < 5, 5-14, 15-44 and ≥ 45 years. The patient of 5-14 age group was 0.159 times less likely to die by malaria than the reference category. Also for individuals in the age group 15-44 years and ≥ 45 years the odds of dying of malaria is 0.216 and 0.125 times less likely than for under five children age (the reference category) respectively. This implies that, death by malaria is high for those in the age group of less than five years. The odds ratio of resident of patient, it is categorized as urban and rural. Apparently, the result shown that the odds of death due to malaria for rural resident is 4.989 times more likely than for patients from urban areas.

The relationship between time from symptom onset to diagnose and malaria patient status is also statistically significant. The risk of malaria patient death increases

with time from symptom onset to diagnoses increases at 5% level of significance [17,18]. The odds ratio shows that patients with 3-5 days from symptom onset to clinical diagnosis is 2.452 times more likely to die by malaria than patient with < 3 days earlier to diagnoses. Patients with > 5 days of symptom onset to diagnosis is 3.334 more likely to die by malaria than the reference category (< 3 days).

Malaria complication cases indicates that the odds of an individual having complicated malaria or severe malaria is 3.364 times more likely than for those uncomplicated malaria. Pregnant women cases are 2.082 times more likely to die of malaria than those who were not pregnant (the reference category). The odds of dying of malaria with total length of stay in hospitalization 3-5 days and > 5 days were found to be 0.256 and 0.661 times less likely than for the reference category (whose length of stay in hospitalization is < 5 days) respectively.

3.1 Discussion

The study attempted to identify the risk factors of malaria related in-hospital mortality at Tepi General Hospital, South Western Ethiopia. The results of the study shown that, out of a sample of 535 patients hospitalized for malaria from June 2017 to June 2020, 78.5% patient were discharged while 21.5% patients were died by malaria.

In the logistic regression model with forward stepwise method, seven variables were identified as risk factors of malaria related in-hospital mortality. These are age of patient, residence of patient, type of malaria species diagnosed, time from symptom onset to diagnosis (days), malaria complication, pregnancy cases and total length of stay in hospitalization.

The results for time from symptom onset to diagnoses, were also similar with the study reported in Ethiopia by Wakgari [19]; Mesganaw et al. [20] and in Uganda by Bachou et al. [21] and also for pregnancy cases the result confirms with the study by Newman et al. (2008) in Ethiopia. Similar results were also reported in earlier studies in South Africa in St. Augustines Hospital, were found that body temperature of patient in the last diagnoses were significant to the risk of malaria patient death [22].

4. CONCLUSION

Among the samples considered for the study, the death rate due to malaria estimated to be 21.5%. The health status of malaria patients at the center was found to be significantly associated with age of patient, residence of patient, season when patient diagnosed, type of malaria species diagnosed, referral status, time from symptom onset to diagnosis, malaria complication, pregnancy cases, total length of stay in hospitalization or days and treatment given. The results from multivariable analysis revealed that age of patient, residence of patient, type of malaria species diagnosed, time from symptom onset to diagnoses, malaria complication, pregnancy and total length of stay in hospital were factors associated with health status of malaria patients. Governmental and non-governmental organizations should focus on continuous awareness creation of early diagnoses and treatment to the societies in rural part of South Western Ethiopia.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Author has declared that no competing interests exist.

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