International Journal of Academic and Applied Research (IJAAR)
ISSN: 2643-9603
Vol. 6 Issue 4, April - 2022, Pages:123-131

Determining the Factors Affecting the Recurrence of Mycetoma (Eumycetoma) using Kaplan-Meier method

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Abstract*: In survival analysis, Recurrent events approaches has become a useful approach to account for covariate effects on the distribution of an event time of interest The main objectives of this paper is Determining the factors affecting the recurrence of mycetoma using Kaplan-Meier method. Mycetoma (eumycetoma) is a dangerous and takes patient to the late stages of the disease as it is painless in the beginning. Furthermore, has a high recurrence rate. In our study, we conducted estimates of survivor and hazard functions with non-parametric methods, Analyze Mycetoma data and identify factors affecting recurrence. Methodology for our study includes descriptive statistics and Kaplan Meier. 171 patients with Madurella mycetomatis were included in the study at the Mycetoma Research Centre, Khartoum, Sudan between 1991 and 2021. According to the results we found from Kaplan-Meier analysis, eight factors are significant (age, duration of disease, veins, periosteal reaction, Organism, Ultra sound, treatment and Duration of treatment).*

Keywords: Nonparametric, survival analysis, Log Rank (Mantel-Cox) peto, Breslow (Generalized Wilcoxon) and Tarone-Ware

1. Introduction:

Mycetoma is a chronic granulomatous neglected tropical disease that affect individuals of poor socio-economic status. The disease is caused either by bacteria (actinomycetoma) or fungal (eumycetoma); with the fungal type been the most prevalent and chronic form especially in Africa [1]. Different species of fungi and bacteria cause mycetoma, which occur as saprophytes in soil and on plants. Eumycetoma is associated with a variety of fungi Leptosphaeria senegalensis, Curvularia lunata, Neotestidina rosatii, acreamonium spp, Fusarium spp and the most commonly Madurella mycetomatis. Actinomycetoma is caused by aerobic species of actinomycetes belonging to the genera Nocardia, Streptomyces and Actinomadura with Nocardia brasiliensis, Actinomadura madurae, Actinomadura pelletieri, and Streptomyces somaliensis being most common. Mycetoma has been reported all around the world. Tropic and subtropical regions are host to this disease, particularly between latitudes of 15° S and 30° N (Sudan, Somalia, Senegal, India, Yemen, Mexico, Venezuela, Colombia, and Argentina); however, the disease extends well beyond this belt. Among the reported cases, the majority are in Sudan and Mexico, with Sudan being the most endemic country [2]. The disease severity varies from one individual to other and it depend on may factors including; causative organism; host; immunological status however in general the disease severity ranges from a mild swelling lesion to death. Despite improvements in the field of Mycetoma diagnosis and treatment however the complication and recurrence rate is still very high specially in eumycetoma [3]. Proper treatment of mycetoma requires an adequate and accurate diagnosis of the causative organisms. Eumycetoma and actinomycetoma are two types of mycetoma caused by microorganisms of both fungal and bacterial origin, respectively. Various diagnostic tools and techniques have been developed over the years to determine and identify the causative agents. These include direct microscopy and cytological, histopathological, and immunohistochemically techniques in addition to the classical grain culture **[**4**].** Mycetoma therapy differs depending on its etiology. Medications are effective against actinomycetoma, such as Septrin and vancomycin. Antifungal agents and surgical excision are used to treat Eumycetoma. it does not respond well to medication (anti-fungal such as azoles). A dose of 100–200 mg of Iitraconazole per day has been used with/without surgical management for 6–12 months [5]. The role of surgery is limited, and it is mostly used to treat cases that are no longer responding to medical treatment or to aid in the healing process [6]. Therefore, due to the high rate of recurrence associated with Mycetoma (eumycetoma) there is much interest in preventive and treatment measures. Recurrent events data analysis is quite common in biomedicine. It arises from survival analysis when each study subject experiences two or more events (failures), and the failures should be the same kind of event. Survival analysis is most common use in medical research, although, there has been a vast literature on recurrent events data analysis. Several studies have been conducted on recurrent event models and mycetoma such as Marie et. Al (2020), proposed a method for estimating a joint frailty model based on such interval counts and observed or independently censored terminal events. [7]. Jimmy T. Efird and Charulata Jindal (2018), described a method to impute censored follow-up times using a counting process method [8]. Wei Yang et.al (2017), reviewed a number of statistical methods for analyzing ordered recurrent events of the same type, including Poisson regression and three commonly used survival models that are extensions of Cox proportional hazards regression [9]. Xiaoyan Sun et.al (2016), discussed how quantile regression can be extended to model counting processes, and thus lead to a broader regression framework for survival data [10]. AHMED, Elhadi Abdalla et al. (2022) isolated and assessed the DNA of mycetoma fungi using black-grains and to apply amplification of ITS region and nucleotide sequences [11]. R. J. Hay (2021), traced the first contributions to the description of the disease and its pathogenesis [12]. Mohamed D. A. Gismalla et.al (2019), reviewed the surgical treatment of eumycetoma patients [13]. Wilson Lim et.al (2018), proposed Addressing the most neglected diseases through an open research

model [14]. Ahmed Hassan Fahal, Amel Altayeb Ahmed and Wendy van de Sande (2017), provided an update on the laboratory investigations used in the diagnosis of mycetoma [15].

2. Research problem:

Outcome event that may occur more than once over follow up time for a given subject. Such events are called recurrent events. there are a lot of researches done in field of the recurrence event on the endemic disease but yet it still poor statistical research done for Mycetoma (eumycetoma) disease specifically on recurrent event, therefore the current study aims to use modern statistical techniques to determine the factors that are affected the recurrences.

3. Research Importance:

Mycetoma is a dangerous disease that takes the patient to late stages because it is painless at the beginning, and is old but unknown to most individuals, which indicates that it is a neglected disease. Despite the severity of Mycetoma clinical, medical and community, in addition Mycetoma has a highly rate of recurrence specially eumycetoma due to the patient can relapse after recovery for reasons unknown to researchers.

4. Research methodology

In this research we use descriptive statistics and Kaplan Meier to determine which variable effects the recurrence of Mycetoma. this process will be applied using Stata version (17) and SPSS version (28) software.

4.1 Research data:

This retrospective study was carried out at Mycetoma Research Center(MRC). There are 10000 patients in the Mycetoma center from 1991 to 2021, for which 171 patients with eumycetoma who had disease recurrence one or more times from initial treatment till they are fully recovered and then developed the disease again. The clinical records of these patients were carefully collected by doctors using sheets carefully designed by the MRC and reviewed by us. During our revision we have found missing files that we have personally corrected by referring back to the main files or contacting patients in person, this considers as secondary data.

4.2. Explanatory factors:

age, gender, residence, occupation, disease site, size, and duration in years, family history, previous surgery and type of surgery, Sinuses, grains, discharge, X-ray, US, Histology, Cytology, treatment, cure.

4.3. Target variable:

The target variable is the Outcome variable (which includes Recurrence, Cured, currently on treatment or loss of follow-up).

5. Study Limitations:

Mycetoma Research Centre (MRC), University of Khartoum, Khartoum, Sudan, Soba hospital. Sudan University of Science and Technology Faculty of Sciences, Department of Statistic, Khartoum, Sudan. All patients with Mycetoma recurrence after fully recovered and patient had no recurrence disease in the period 1991 and 2021.

6. Ethical statement:

Ethical clearance was obtained from Soba Hospital Ethical Committee. Patients' informed consents proved to be unnecessary in this study.

7. The Kaplan Meier method:

Kaplan-Meier estimate of survivor and hazard functions Given n individuals with observed survival times, some of the observations may be censored and there may also be more than one individual who fails at the same observed time Therneau and Grambsch (2000). We suppose that there are n individuals with observed survival times$t_1, t_2, \dots, t_n$ some of these observation may be right-censored, and there may also be more than one individual with the same observed survival times. We therefore suppose that there are r death times amongst the individuals where $(r \leq n)$. After arranging these death times in ascending order the j^{th} is denoted $(t_{(j)})$ for j = 1,2,…..,r, and so the r ordered death times are $t_{(1)} < t_{(2)} < t_{(3)} < t_{(4)} < \cdots < t_{(r)}$. The number of individuals who are alive just before time $t_{(j)}$, including those who are about to die at this time, will be denoted $n_{(j)}; j = 1,2, \dots \dots, r$ and d_j will denote the number who die at this time Collett (2003). We count the total number of individuals alive at the start of the interval $n_{(j)}; j = 1,2, \dots \dots, r$ and the number of individuals who died (d_j) in the time interval [16]. The Kaplan-Meier estimate of the survival function is given by

$$\widehat{S(t)} = \prod_{j=1}^{k} \left(\frac{n_j - d_j}{n_j} \right)$$

8. Result and discussion:

8.1 Descriptive analysis for the study variable:

This part contains descriptive for our study variable by frequency and percentage.

Table (1): Demographic profile of study participants:

Factors	**Categories**	**N (%)**
Age	less than 15	11 (6.4%)
	15 - 30	101 (59.1%)
	30 - 45	38 (22.2%)
	45 - 60	13 (7.6%)
	more than 60	8 (4.7%)
Sex	Male	116 (67.8%)
	Female	55 (32.2%)
Occupation	house wife	29 (17%)
	Worker	27 (15.8%)
	Farmer	44 (25.7%)
	Student	51 (29.8%)
	Others	20 (11.7%)
State	Khartoum	20 (11.7%)
	AL Jazeera	70 (40.9%)
	Sennar	15 (8.8%)
	White Nile	25 (14.6%)
	West Sudan	26 (15.2%)
	East Sudan	6 (3.5%)
	North Sudan	9 (5.3%)

Source: prepared by the researcher by using IBM SPSS28, 2022

Table (1) showed most of patients are male (116(67.8%)) and (55(32.2%)) are female. Their age classified into groups between less than 15 years and more than 60 years the age between 15 – 30 represent most of the study patient 101 with (59.1%) and the least affected group their age is more than 60 with (8 (4.7%)). Most of the patients in this study reside in AL Jazeera state (70(80.8%)). Farmers (44 (24.7%)) and (51 (29.8%)) students were the commonest jobs among patients in the study.

Table (2): Clinical history

Factors	**Categories**	N (%)
Duration of disease	<= 5	110 (64.3%)
	6 – 15	52 (30.4%)
	16 – 25	7 (4.1%)
	25+	2 (1.2%)
Discharge Type	Pus	2 (1.2%)
	Black	147 (86%)
	None	22 (12.9%)
Pain	Yes	42 (24.6%)
	No	129 (75.4%)
Trauma	Yes	39 (22.8%)
	No	121 (70.8%)
	Not sure	11 (6.4%)
Previous Surgery	None	59 (34.5%)
	Once	70 (40.9%)
	Twice	20 (11.7%)
	3Times	12 (7%)
	More	10 (5.8%)
Anesthesia	General	52 (30.4%)

	Spinal	17 (9.9%)
	Local	32 (18.7%)
	None	70 (41%)
Recurrence	Yes	68 (39.8%)
	No	103 (60.2%)
Family History	Yes	23 (13.5%)
	No	148 (86.5%)

Source: prepared by the researcher by using IBM SPSS28, 2022

Table (2) showed Most of the study patient underwent to an operation or surgery outside the center once time (70(40.9%)). Patients who had recurrent after surgery outside the mycetoma in this study are (68(39.8 %)). most of the study patient Discharging black grains were found in (147 (78.9%)) patients. Most patient said there is no pain (129(75.4%)) and (42(24.6%)) feeling pain. Not sure trauma is (11(6.4%)) while patient not exposed to trauma are (121(70.8%)). (148(86.5%) patient have no family history and (23(13.5%) patient with family history.

Table (3): clinical examination

Factors	**Categories**	**N (%)**
Site	left foot	73 (42.7%)
	right foot	77 (45%)
	right hand	8 (4.7%)
	left hand	2 (1.2%)
	Others	11 (6.4%)
Size	less than 5cm	41 (24%)
	5-10cm	49 (28.7%)
	more > 10cm	75 (43.9%)
	Operated	6 (3.5%)
Sinuses	None	31 (18.1%)
	Active	65 (38%)
	Healed	71 (41.5%)
	Multiple	4 (2.34%)
Grains	None	92 (53.8%)
	Present	79 (46.2%)
Glands	No	148 (86.5%)
	Yes	23 (13.5%)
Veins	None	163 (95.3%)
	Present	8 (4.7%)
Sweating	No	162 (94.7%)
	Yes	9 (5.3%)
Medical Problem	Yes	8 (4.7%)
	No	163 (95.3%)

Source: prepared by the researcher by using IBM SPSS28, 2022

Table (3) showed Commonest size more >10cm (75(43.9%)). Left hand (2(1.2%)), most site is right foot and left foot respectively (77(45%)) (73(42.7%)). sinuses healed (71(41.5%)). (79(46.2%) of patient they have grains and (92(53.8%)) have no grain. most of the study patient said they have no medical problem (163(95.3%)), no glands (148(86.5%)), no veins (163(95.3%)) and no sweating (162(94.7%)).

Table (4): Radiological diagnosis

Factors	**Categories**	N (%)
X- rays		
Normal	No	136 (79.5%)
	Yes	35 (20.5%)
Soft Tissue	No	101 (59.1%)
	Yes	70 (49.9%)
bone destruction	No	144 (84.2%)
	Yes	27 (15.8%)
periosteal reaction	No	155 (90.6%)
	Yes	16 (9.4%)
Not done	No	125 (73.1%)
	Yes	46 (26.9%)
Ultra Sound	EM	61 (35.7%)
	No grains	7 (4.1%)
	Mycetoma	2 (1.2%)
	Normal	1 (0.6%)
	not done	99 (57.9%)
	Not significant	1 (0.6%)

Source: prepared by the researcher by using IBM SPSS28, 2022

Table (4) showed radiological evaluations X-ray revealed not normal (136(79.5%)) and normal (35(20.5%)), (70(49.9%)) affected soft tissue mass and (101(59.1%)) not affected, (27(15.8%)) they have bone destruction and (144(84.2%)) have not. Radiological evaluations US revealed (61(35.7%)) EM and (99(57.9%)) not done ultra sound.

Table (5): Clinical characteristic

Factors	**Categories**	N (%)
Organism	no organism	7 (4.1%)
	MM	133 (77.8%)
	not done	22 (12.9%)
	Other	9 (5.3%)
Treatment	Iitraconazole + Folic Acid	31 (18.1%)
	Ketoconazole + Folic Acid	134 (78.4%)
	Penicillin + gresufution	6 (3.5%)
Duration of treatment	<= 2	56 (32.7%)
	2 – 6	56 (32.7%)
	6 – 10	31 (18.1%)
	10 – 14	16 (9.4%)
	14 – 18	8 (4.7%)
	18+	4 (2.3%)
Amputation	Amputated	29 (16.9%)
	not amputated	142 (83.1%)
Surgery	Yes	161 (94.2%)
	No	10 (5.8%)
Surgery Type	Amputation	29 (16.9%)
	WLE	129 (75.4%)
	excision biopsy	3 (1.8%)

	None	9 (5.3%)
	DE bulking	1 (0.6%)
Cure	Yes	82 (48%)
	No	89 (52%)
Recurrence	recurrence after cure	82 (48%)
	recurrence after surgery	89 (52%)
Compliance	Regular	103 (60.2%)
	Irregular	68 (39.8%)
Outcome	Cured	33 (19.3%)
	Lost to follow up	97 (56.7%)
	until now on treatment	41 (24%)

Source: prepared by the researcher by using IBM SPSS28, 2022

Table (5) showed the patient whom recurrence after surgery (89(52%)) and recurrence after cure (82(48%)). (68(39.8%)) irregular in follow_ up and (103(60.2%)) they are regularly following. (134(78.4%)) of the patient take treatment Ketoconazole + Folic Acid and Iitraconazole + Folic Acid with (31(18.1%)). Patient underwent to surgery (161(94.2)) and (10(5.8%)) they are not. Most of the study patient did surgery (142(83%)). WLE surgical type is commonest operation done in the center (129(75.4%)) in comparison with amputation (29(16.7%)). Patient cured and recurrent after cured (82(48%)). Cured in outcome variable (33(19.3%)), (97(56.7%)) lost to follow up and (41(24%)) until now on treatment.

8.2 Test the significance factors:

We used Log Rank (Mantel-Cox) peto, Breslow (Generalized Wilcoxon) and Tarone-Ware tests to determine the factor affected on recurrence.

Table (6): The result of Log Rank (Mantel-Cox) peto, Breslow (Generalized Wilcoxon) and Tarone-Ware tests:

Factors		Log Rank (Mantel-Cox)peto		Breslow (Generalized Wilcoxon)		Tarone-Ware	
		Chi	p-value	Chi	p-value	Chi	p-value
Demographic profile	Age	74.11	0.002**	74.22	0.0022**	79.32	0.000**
	Sex	0.03	0.862	0.03	0.8641	0.02	0.895
	Occupation	2.79	0.593	2.77	0.5971	4.6	0.331
	State	4.22	0.647	4.16	0.6545	3.61	0.729
clinical history	Dise. Dur	71.08	0.000**	71.56	0.0008**	76.47	0.000**
	Discharge type	0.07	0.964	0.05	0.976	0.9164	0.17
	Pain	0.28	0.596	0.27	0.602	0.52	0.472
	Trauma	0.12	0.940	0.13	0.937	0.16	0.923
	family history	0.02	0.882	0.03	0.873	0	0.948
clinical examination	Site	0.67	0.956	0.61	0.962	1.15	0.886
	Size	1.32	0.724	1.3	0.729	1.02	0.797
	Sinuses	4.45	0.217	4.59	0.363	3.55	0.315
	Grains	0.63	0.429	0.83	0.363	0.63	0.429
	Glands	0	0.959	0.06	0.814	0	0.959
	Veins	3.49	0.062	5.12	0.024*	3.49	0.062
	Sweating	0.05	0.826	0.01	0.908	0.05	0.826
	Medical Problem	0	0.998	0	0.968	0.02	0.896
images investigation	x-ray	9	0.334	9.17	0.328	6.34	0.609
	Normal	0.6	0.439	0.52	0.470	0.22	0.648
	soft tissue	0.21	0.645	0.19	0.659	0	0.984
	bone destruction	0.06	0.800	0.07	0.793	0.07	0.792
	Periosteal. re	7.07	0.008**	7.13	0.008**	5.23	0.022*

	not done	0.02	0.894	0.01	0.903	0.1	0.749
	Ultrasound	10.31	0.067	10.26	0.069	11.44	0.043*
laboratory diagnosis	Cytology	4.71	0.195	4.87	0.182	6.25	0.100
	Histology	4.19	0.242	4.2	0.241	4.03	0.259
clinical characteristic	Organism	7.64	0.05*	7.57	0.056	8.73	0.033*
	Treatment	9.61	0.008**	9.5	0.009**	9.67	0.008**
	Rx-dur	261.87	0.000**	262.95	0.000**	279.78	0.000**
	Amputation	1.39	0.238	1.42	0.233	0.69	0.405
	Surgery	0.01	0.937	0.01	0.930	0.14	0.713
	Outcome	2.16	0.339	2.12	0.346	1.04	0.593

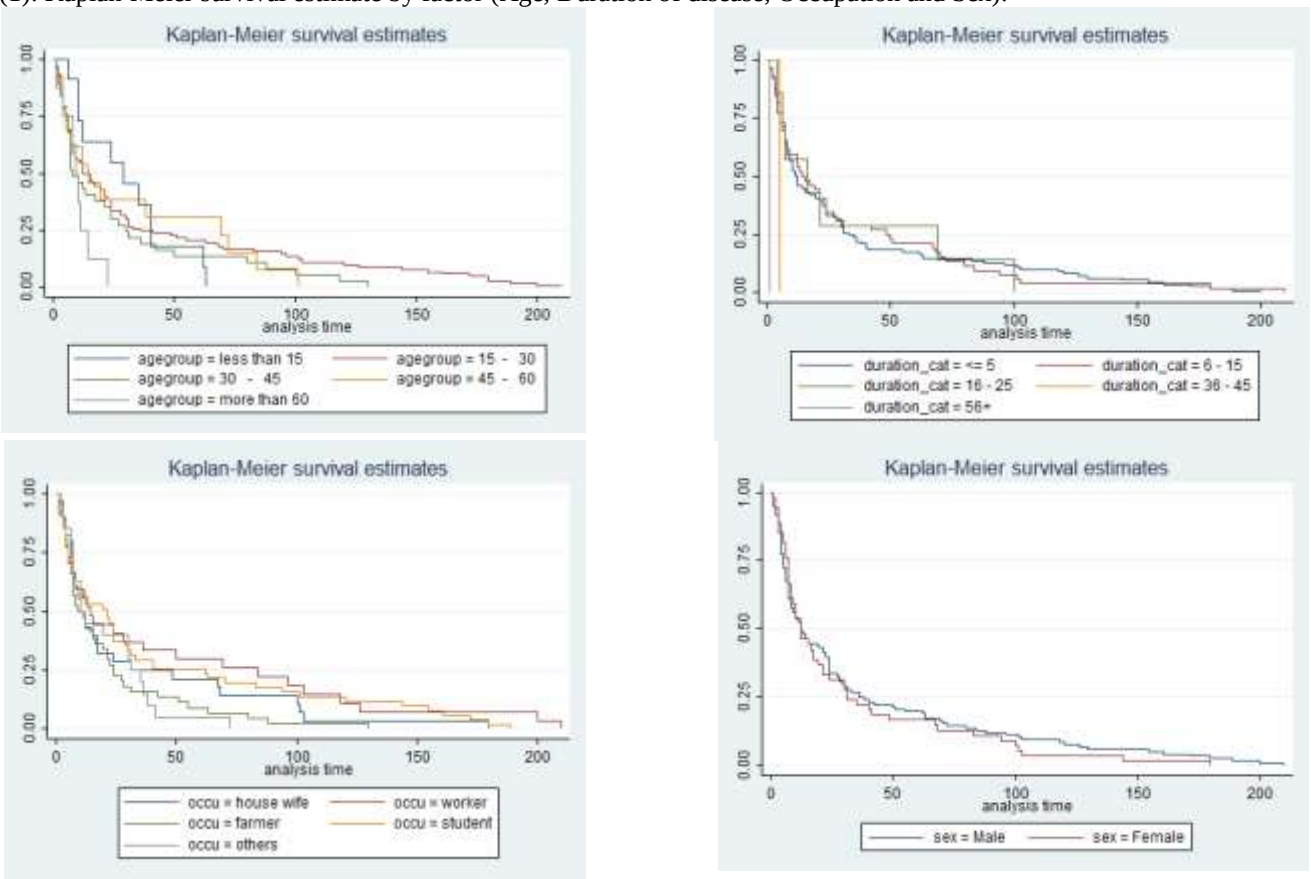
** high significance (<0.001), * significance (<0.05)
Source: prepared by the researcher by using IBM SPSS28, 2022

Table (6) show that the value of chi-square test (Log Rank (Mantel-Cox) peto, Breslow (Generalized Wilcoxon) and Tarone-Ware tests) is (74.11, 74.22 ,79.32 respectively), with (P-value = 0.00<0.05), and this showed there is significant difference between the estimated survival functions for the Age. Thus, the probability of survival is varying according to age. there are other variables are significance (duration of disease, veins, periosteal reaction, Organism, Ultra sound, treatment and Duration of treatment) as we showed on above table by *, **.

8.3: Kaplan Meier graphs

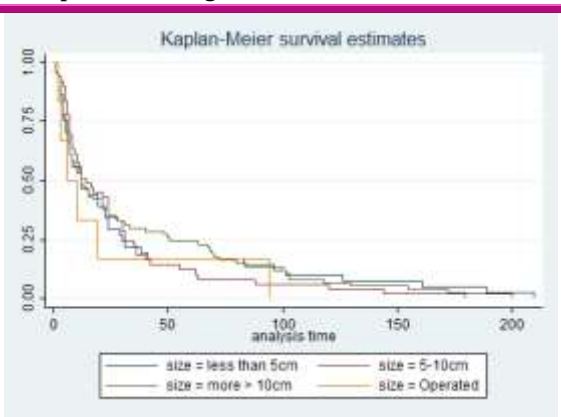
Survival and hazard function with recurrence time were plotted depending on the study's significant factors. Hazard function draft on appendix.

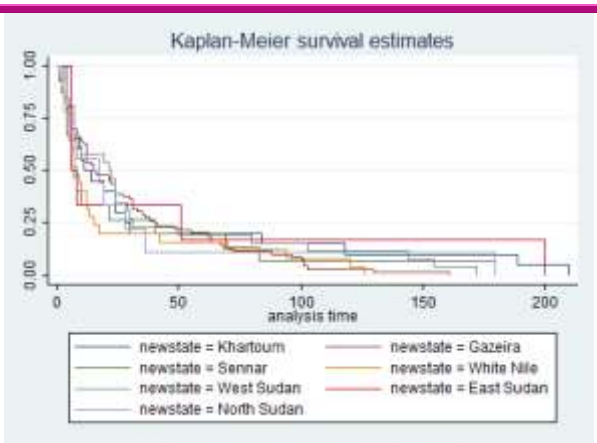
Figure (1): Kaplan-Meier survival estimate by factor (Age, Duration of disease, Occupation and Sex):

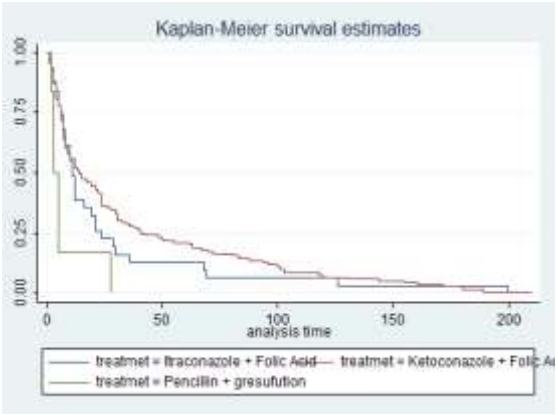


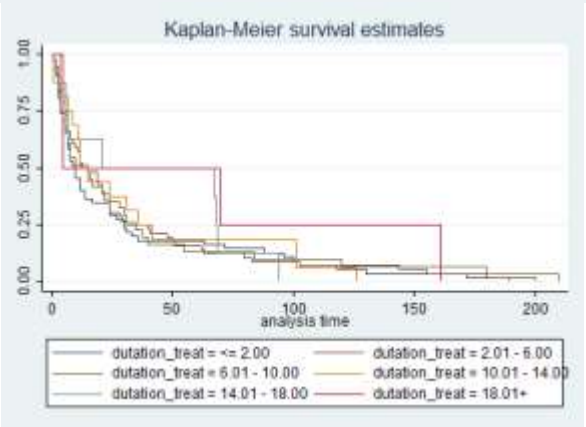
Source: prepared by the researcher by using STATA 17, 2022

Figure (2): Kaplan-Meier survival estimate by factor (Size, State, treatment and duration of treatment):









Source: prepared by the researcher by using STATA 17, 2022

9. Conclusions:

The general conclusions we can draw from modeling recurrent event for an endemic disease mycetoma are:

1- The majority of the study patients were male (67.8%) and (32.2%) female. Their age classified into groups between less than 15 years and more than 60 years. the age between 15 – 30 represent most of the study patient with (59.1%) and the least affected group their age is more than 60 with (4.7%). In this study most of patients in this study live in the Al Jazeera state (80.8%). Farmers were the most affected (24.7%) followed by students (29.8%). Past history of surgical was reported once time (70(40.9%)). Patients who had recurrent after surgery outside the mycetoma in this study are (68(39.8 %)). The majority of the study patient Discharging black grains (147 (78.9%)). Most patient said there is no pain (129(75.4%)) and (42(24.6%)) feeling pain. Not sure trauma is (11(6.4%)) while patient not exposed to trauma are (121(70.8%)). (148(86.5%) patient have no family history and (23(13.5%) patient with family history. The most common size more >10cm (75(43.9%)). The right foot and left foot (77(45%)) (73(42.7%)) respectively are most affective site with healed sinuses (71(41.5%)). most of the study patient said they have no grain (92(53.8%)), no medical problem (163(95.3%)), no glands (148(86.5%)), no veins (163(95.3%)) and no sweating (162(94.7%)). An evaluation of the X-rays revealed not normal (138(79.5%)) and normal (35(20.5%)), (70(49.9%)) affected soft tissue mass and (101(59.1%)) not affected, (27(15.8%)) have bone destruction and (144(84.2%)) do not. majority of the patient recurrence after surgery (89(52%)) followed by recurrence after cure (82(48%)). (68(39.8%)) irregular in follow-up and (103(60.2%)) they are regularly following. Most of the patient take treatment Ketoconazole + Folic Acid (134(78.4%)) followed by Iitraconazole + Folic Acid with (31(18.1%)). Most of the Patient underwent to surgery (161(94.2)) and (10(5.8%)) they are not. Most of the study patient underwent to surgery (142(83%)). WLE surgical type is most common operation done in the center (129(75.4%)) in comparison with amputation (29(16.7%)). Patient cured and recurrent after cured (82(48%)). Cured in outcome variable (33(19.3%)), (97(56.7%)) lost to follow up and (41(24%)) until now on treatment

2- Depending on the result we obtained from Kaplan Meier method we find there are eight significant factors (age, duration of disease, veins, periosteal reaction, Organism, Ultra sound, treatment and Duration of treatment) with (P-value <0.05) according to Log Rank (Mantel-Cox) peto, Breslow (Generalized Wilcoxon) and Tarone-Ware tests used for evaluation the significant.

Acknowledgement:

Thanks to Mycetoma research center for providing me with the opportunity to work in accommodating environment. My special thanks and appreciation to prof. Ahmed Hassan ALfahal which was be the best guide to me. Thanks to all those who helped me complete this study and stood beside me.

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