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Survival analysis for recurrence of mycetoma using life tables and Kaplan Meier methods

Shima Abdalgader[1], Afra Hashim[2] and Al Taiyb Ahmed[3]

[1]Sudan international university, Faculty of computing
[2,3]Sudan University of Science and Technology-College of Science-Statistics Department, Khartoum11111, Sudan
[1]Email: shimaabdo991@gmail.com

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 to study the behavior of the recurrence of mycetoma using lifetable and 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. In our study, we conducted estimates of survivor and hazard functions with non-parametric methods, the result that obtained from Kaplan Meier quartiles for all study factors the probability of occurrence the recurrence 1 in Q1 is (0.23 to 0.62), Q2 is (0.40 to 0.75) and Q3 is (0.70 to 0.87) and the probability of recurrence 2 for Q1 is (0.085 to 0.90), Q2 is (0.24 to 0.93) and Q3 is (0.49 to 0.96). The h(t) result that we found from life table, the minimum value for patients at risk during the time interval from [40 100) is 0.01 The maximum value for patients at risk during the period from [200 220] and the results from time interval [20-40) are four patients getting the event, there is no recurrence in patients during the time intervals [120 140), [140 160), [180 200) and [220). the maximum S(t) during the time interval from [0 20).*

Keyword: quartiles, survivor function, hazard function, nonparametric method.

1. Introduction:

A mycetoma is a chronic granulomatous inflammatory disease that affects the skin and subcutaneous tissue, through both fungi and bacteria, and is classified as either an eumycetoma or an actinomycetoma. [1] [2]. Mycetoma is characterized by a painless subcutaneous mass, numerous sinuses, and a discharge that contains grains of different colors, sizes, and consistency [2]. In fact, late presentation is the norm in most patients, which is explained by several factors, including the painless nature of the disease, the low socioeconomic status and health education of patients, and the absence of health facilities in endemic areas [3] [4] [5] [6]. Puncture wounds caused by thorns or other sharp objects are the most common cause of foot infections. 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. Sudan being the most endemic country [7]. The most cases reported in males than females (3:1), probably attributable to men being more commonly involved in agricultural work. [8] [9] The condition is most common in young adults (16–40 years old) [10] and is uncommon in children. 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 **[**11**].** The recurrence of symptoms occurs after at least 3 consecutive ultra sound tests either after surgery or after treatment. The risk of recurrence is high; a higher recurrence rate was seen among patients who missed their treatments. but many patients have a relapse following remission. Identifying prognostic factors in patients at high risk of recurrence provides a window of opportunity for specific secondary prevention as well as initiation of long-term maintenance treatment [12]. 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. [12]. Jimmy T. Efird and Charulata Jindal (2018), described a method to impute censored follow-up times using a counting process method [13]. 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 [14]. 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 [15]. 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 [16]. R. J. Hay (2021), traced the first contributions to the description of the disease and its pathogenesis [17]. Mohamed D. A. Gismalla et.al (2019), reviewed the surgical treatment of eumycetoma patients [18]. Wilson Lim et.al (2018), proposed Addressing the most neglected diseases through an open research model [19]. 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 [20].

2. Research problem:

Mycetoma management is the key for eradication of the infection from patients; however, certain patients even with the good management plans suffer from recurrence that causes a big burden on the medical field and a lot of suffering in the patient's life science it highly coasty and very time consuming. Therefore, using this statistical study to help identify the problem will drastically help the medical field and significantly improved patient's life.

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 due to the patient can relapse after recovery for reasons unknown to researchers.

4. Research methodology:

In this research we use descriptive statistics, Kaplan Meier and lifetable to study the behavior of the recurrence of Mycetoma. this process will be applied using Stata version (17) and SPSS version (28) software.

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. Material and method:

7.1. Survival and Hazard Function:

The basic quantity employed to describe time-to-event phenomenon is the Survival Function S(t), and it is defined as [21]:

$$S(t) = P(\mathrm{T} > \mathrm{t}) \tag{1}$$

where, $S(t)$ the probability an individual survives beyond time t.

Since a unit either fails, or survives, and one of these two mutually exclusive alternatives must occur, we have

$$S(t) = 1 - F(t). \qquad F(t) = 1 - S(t)$$

$$F(t) = P(T \leq t) = \int_0^t f(u)\, du \tag{2}$$

where, F(t) is the cumulative distribution function (CDF). If T is a continuous random variable, then S(t) is a continuous, strictly decreasing function. The survival function is the integral of the probability density function (pdf), f (t), that is

$$S(t) = \int_{\infty}^{t} f(x)\, dx \tag{3}$$

Thus,

$$f(t) = -\frac{dS(t)}{dt} \tag{4}$$

A hazard function is a measure of the probability that an individual who survived until time t will continue to survive at that time. the probability that an individual will be alive in the interval t to $t + \delta t$ given that the survived until time t is:

$$P(t \leq T < t + \delta(t) | T \geq t)$$

To get the probability per units times we divide by the interval $\delta(t)$ to get:

$$\frac{P(t \leq T < t + \delta t | T \geq t)}{\delta t}$$

$$h(t) = \lim_{\delta t \to 0} \frac{P(t \leq T < t + \delta t | T \geq t)}{\delta t}$$

where, h(t) is called the hazard rate, instantaneous death rate, the interesting rate and the force of mortality and can be looked at as an approximation the probability that an individual's survivor in the interval S(t) [22].

7.2. Estimation of survivor and hazard function:

Given a set of survival data the next step is to summarize it, this can be done through the survival function and hazard function. Once the survival and hazard function are estimated, other summary measures like the median survivor time and variance percentiles can be estimated [22].

There are two methods for estimate S(t) and h(t)

1. Nonparametric method.
2. parametric method.

7.3. Nonparametric method:

These methods don't assume knowledge of the distribution of survival time among these are: [22].

1. the life table estimate
2. the Kaplan Meier estimate

7.3.1 The life table estimate of $S(t)$:

This estimate when there is censored and if the data are grouped. Suppose survival times are determined in study that continued for a certain period. If the period of the study is divided into a number of interval usually between 5 and 15, that are not necessarily equal. The life table displays the various results obtained from the analysis, including: Interval Start: time interval. Number Entering Interval (n_j): The number of individuals who alive at the start of the interval. Number Withdrawing during Interval (C_j): the number of censored cases in this interval assuming censoring occur uniformly through the interval . the average number of censoring is $\frac{C_j}{2}$ and the average number of individuals who are alive is $n_j' = n_j - \frac{C_j}{2}$. The probability of death in the interval is $(\frac{d_j}{n_j'})$ and the probability of surviving is $(\frac{n_j'-d_j}{n_j'})$. The probability that an individual survivor up to time t' and after is (assuming) death in the interval are independent is the probability of survivor probability in the K^{th} interval and the $K-1$ previous interval $\widehat{S(t)} = \prod_{i=1}^{n} \frac{n_j'-d_j}{n_j'}$ $t_k' \leq t \leq t_{k+1}'$ this is called the life table estimated of survival function. Suppose the interval $(j, j+1)$ censoring occurs uniformly if the number censored in this interval is t_j , the average number of individuals at rate in the interval $n_j' = n_j - \frac{C_j}{2}$ where, n_j is number alive j before the start of the interval also if d_j individuals die in the interval and death occurs uniformly in the interval. the average number surviving the interval is $(n_j' - \frac{d_j}{2})$. The length of the interval is t_j time units (i.e. $t_j = t_{j+1} - t_j$) the average rate of death per units time is $\frac{d_j}{(n_j' - \frac{d_j}{2})t_j}$ this is life table estimated of the hazard function. i.e. $h(t) = \frac{d_j}{(n_j' - \frac{d_j}{2})t_j}$ $t_{(j)} \leq t \leq t_{(j+1)}$ it is given the hazard of risk of death for time in the J^{th} interval [22].

7.3.2 The Kaplan Meier estimate of the survivor function:

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 [23]. The Kaplan-Meier estimate of the survival function is given by

$$\widehat{S(t)} = \prod_{j=1}^{k} \left(\frac{n_j - d_j}{n_j} \right) \quad (5)$$

8. Result and discussion:

Data were collected from the Mycetoma Research Center(MRC) in Khartoum, Sudan. A sample of 171 patients who had disease recurrence one or more times from initial treatment till they are fully recovered and then developed the disease again. This final data after our revision as we mentioned in chapter one. This data is nonprobability sample (purposive sample) we used this type of data to achieve our main objectives for this research. The study variables included age by groups, gender (male and female), address contain 7 states, occupation, pain, trauma, disease site, size of affected area, and duration of the disease in years, family history, previous surgery and type of surgery, Sinuses, grains, discharge, X-ray (Normal, periosteal reaction, soft tissue and bone destruction), Ultra Sound, Histology, Cytology, treatment, duration of treatment, cure (recovery of patients) and Recurrence.

8.1. Estimation of the survival and hazard function:

In this part we used life table approach to estimate the probability of patients to get recurrence or not and the probability of hazard for recurrence.

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Table (1): life table to estimate survival and hazard function, standard error and probability density function:

Recurrence		n_j	C_j	n_j'	d_j	$\frac{d_j}{n_j'}$	$\frac{n_j' - d_j}{n_j'}$	$\widehat{S(t)}$	Std. $(\widehat{S(t)})$	P.d.f	Std. (P.d.f)	h(t)	Std. Error(h(t))
1	0	171	0	171.0	100	.58	.42	.42	.04	.029	.002	.04	.00
	20	71	0	71.0	31	.44	.56	.23	.03	.009	.001	.03	.00
	40	40	0	40.0	8	.20	.80	.19	.03	.002	.001	.01	.00
	60	32	0	32.0	8	.25	.75	.14	.03	.002	.001	.01	.00
	80	24	0	24.0	5	.21	.79	.11	.02	.001	.001	.01	.01
	100	19	0	19.0	6	.32	.68	.08	.02	.002	.001	.02	.01
	120	13	0	13.0	3	.23	.77	.06	.02	.001	.001	.01	.01
	140	10	0	10.0	2	.20	.80	.05	.02	.001	.000	.01	.01
	160	8	0	8.0	3	.38	.63	.03	.01	.001	.001	.02	.01
	180	5	0	5.0	3	.60	.40	.01	.01	.001	.001	.04	.02
	200	2	0	2.0	2	1.00	0.00	0.00	0.00	.001	.000	.10	0.00
2	0	171	47	147.5	3	.02	.98	.98	.01	.001	.001	.00	.00
	20	121	24	109.0	4	.04	.96	.94	.02	.002	.001	.00	.00
	40	93	21	82.5	3	.04	.96	.91	.03	.002	.001	.00	.00
	60	69	12	63.0	3	.05	.95	.87	.04	.002	.001	.00	.00
	80	54	15	46.5	1	.02	.98	.85	.04	.001	.001	.00	.00
	100	38	7	34.5	1	.03	.97	.82	.05	.001	.001	.00	.00
	120	30	6	27.0	0	0.00	1.00	.82	.05	0.000	0.000	0.00	0.00
	140	24	6	21.0	0	0.00	1.00	.82	.05	0.000	0.000	0.00	0.00
	160	18	7	14.5	2	.14	.86	.71	.08	.006	.004	.01	.01
	180	9	3	7.5	0	0.00	1.00	.71	.08	0.000	0.000	0.00	0.00
	200	6	2	5.0	1	.20	.80	.57	.14	.007	.006	.01	.01
	220	3	3	1.5	0	0.00	1.00	.57	.14	0.000	0.000	0.00	0.00

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

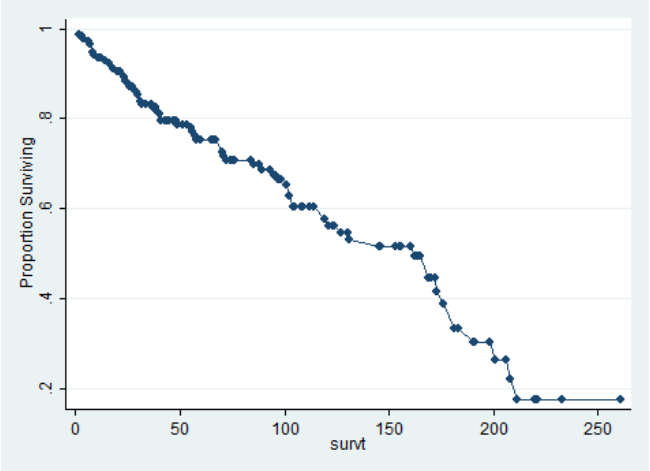
Table (1) show the following:

- **Interval Start**: Which we divided into periods as we previously chose, which are 12 periods and two stratum recurrence 1 and recurrence 2.
- **Number Entering Interval** (n_j): This column is gradually decreasing according to recurrence. To clarify this, we note that its first value was 171, which is the number of study cases, then the second value was 71, which is the result of subtracting the first value Censoring 171 from the number of those who got recurrence in the period from 0 to 20 and their number 100 patients, which is the result of (171-100-0=71) and so on for the third value was 40 and it results from (71-31-0=40) and so on for the rest of the periods.
- Number Withdrawing during Interval (C_j): the number of censored cases in this interval. It is the number of censored cases who dropped out or withdrew from the study in a certain period. In our example above, we find that in the category from 0 to 20, we find that there are no censored values, and this can also be known from looking at the data.
- Number Exposed to Risk (n_j') :The number of surviving cases minus one half the censored cases. This is intended to account for the effect of the censored cases. For the first interval $n_j' = n_j - \frac{C_j}{2}$=171-0=171. And so on for others value.
- Number of Terminal Events (d_j): The number of patient that experience the Recurrence event in this interval. They are the number of people who reached the event and the event in our example here is the recurrence, as the number of people who recurrent during the period 0 to 20 is 100 and the number of patients got recurrence in the period from 20 to 40 is 31 and so on for the rest of the periods
- Proportion Terminating ($\frac{d_j}{n_j'}$) : The probability of recurrence, which is the result of dividing the fifth column Number of Terminal Events (d_j) by the fourth column Number Exposed to Risk (n_j') , and we will take the first case for clarification (100/171=0.58). and so on for the rest of the periods.

- Proportion Surviving ($\frac{n_j' - d_j}{n_j'}$): One minus the proportion terminating.

  1-0.58=0.42
- Cumulative Proportion Surviving at End of Interval ($\widehat{S(t)} = \prod_{i=1}^{n} \frac{n_j' - d_j}{n_j'}$): The proportion of recurrence case from the start of the table to the end of the interval.
- Standard error of cumulative (Std. ($\widehat{S(t)}$)= $\widehat{S(t)} \pm Z_{1-\alpha/2}\widehat{S(t)}\sqrt{\frac{\sum d_j}{n_j(n_j - d_j)}}$
- Probability Density (P.d.f): An estimate of the probability of experiencing the terminal event during the interval.
- Hazard Rate ($h(t) = \frac{d_j}{(n_j' - \frac{d_j}{2})t_j}$). An estimate of experiencing the terminal event during the interval, conditional upon surviving to the start of the interval. (t_j :length of interval)
- The greatest number and proportion of terminal events occur within two years, which suggests that patients should be monitored more closely during their first year to be sure of their cure or not recurrent of disease.

Figure (1): life table to estimate survival and hazard function



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

8.2 Estimate the survival function and hazard function of recurrence

We used Kaplan Meier to estimate survival and hazard probabilities for recurrent events for study factors. quartiles calculated for the values which estimated (survival and hazard function) to represent all recurrence interval (period) by stratum. Q1: 25%, Q2: 50% (median) and Q3: 75% OF recurrence time.

Table (2): Quartile Statistics for survival functions of Demographic data:

Factors		Recurrence 1				Recurrence 2			
		N	Q1	Q2	Q3	N	Q1	Q2	Q3
Age	less than 15	11	0.520	0.694	0.857	.	.	.	.
	15 - 30	101	0.557	0.721	0.863	9	0.344	0.525	0.649
	30 - 45	38	0.560	0.731	0.846	6	0.404	0.431	0.520
	45 - 60	13	0.547	0.727	0.865	.	.	.	.
	more than 60	8	0.483	0.670	0.847	2	0.123	0.245	.
Sex	Male	116	0.561	0.735	0.858	13	0.320	0.508	0.622
	Female	55	0.553	0.708	0.818	5	0.423	0.449	0.823
occupation	house wife	29	0.544	0.724	0.855	3	0.413	0.443	.
	Worker	26	0.545	0.743	0.858	3	0.086	0.322	.
	Farmer	44	0.545	0.730	0.859	4	0.415	0.544	0.657
	Student	51	0.511	0.718	0.859	7	0.263	0.526	0.644

	Others	20	0.569	0.726	0.818	1	.	.	.
State	Khartoum	20	0.511	0.706	0.836	1	.	.	.
	AL Jazeera	70	0.539	0.723	0.860	7	0.484	0.551	0.711
	Sennar	14	0.594	0.724	0.828	2	0.394	0.486	.
	White Nile	25	0.599	0.737	0.820	3	0.437	0.504	.
	West Sudan	26	0.533	0.699	0.821	5	0.159	0.383	0.622
	East Sudan	6	0.467	0.708	0.750	.	.	.	.
	North Sudan	9	0.495	0.688	0.851	.	.	.	.

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

Table (2) shows quartiles of the survival function for recurrent events to each stratum. In stratum 1 the age (more than 60) has minimum value (8) their probability of recurrence1 is (0.483) in Q1, (0.670) in Q2 and (0.847) in Q3 and their probability of got recurrence is 0 for recurrence2 whereas (15-30) has maximum value (101) their probability of recurrence is (0.557) in Q1, (0.721) in Q2 and (0.863) in Q3 and their probability of got recurrence is (0.344) in Q1, (0.525) in Q2 and (0.649) in Q3 for recurrence2 and so on for the rest of the factors.

Table (3): Quartile Statistics for survival functions of clinical history:

Factors		Recurrence 1				Recurrence 2			
		N	Q1	Q2	Q3	N	Q1	Q2	Q3
duration of disease	<= 5	109	0.25	0.5	0.7	10	0.901	0.933	
	6 – 15	51	0.25	0.5	0.75	7	0.815	0.892	0.959
	16 – 25	6	0.25	0.5	0.75	1	.	.	.
	25+	.	.	.	.	.	.	.	.
Discharge type	Pus	1	.	.	.	.	.	.	.
	Black	145	0.556	0.72	0.848	16	0.392	0.512	0.647
	Yellow	1	.	.	.	.	.	.	.
	None	22	0.546	0.713	0.863	2	0.366	0.409	.
Pain	Yes	42	0.543	0.706	0.844	5	0.343	0.514	0.78
	No	129	0.564	0.725	0.849	13	0.368	0.513	0.632
Trauma	Yes	39	0.56	0.731	0.856	3	0.402	0.449	.
	No	121	0.57	0.721	0.849	12	0.3	0.491	0.6
	Not sure	11	0.367	0.55	0.773	3	0.612	0.673	.
family history	Yes	23	0.516	0.693	0.865	1	0.393	0.497	0.638
	No	148	0.559	0.731	0.843	17	0.45	0.7	0.939

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

Table (3) shows quartiles of the survival function for recurrent events to each recurrence. the duration of disease (<=5) has maximum value (109) in recurrence 1 their probability of recurrence is (0.25) in Q1, (0.5) in Q2 and (0.7) in Q3 and (10) patients in recurrence 2 with probability distribution (0.901) in Q1, (0.933) in Q2 and (0) in Q3 , whereas (16-25) has minimum value (6) and there are no patients his disease duration more than 25 years their probability of recurrence is (0.901) in Q1, (0.933) in Q2 and (0) in Q3 for recurrence 2 for the two durations consequently and so on for the rest of the factors.

Table (4): Quartile Statistics for survival functions of Demographic data:

Factors		Recurrence 1				Recurrence 2			
		N	Q1	Q2	Q3	N	Q1	Q2	Q3
Site	left foot	73	0.559	0.715	0.824	10	0.426	0.5	0.683
	right foot	77	0.546	0.721	0.868	7	0.2	0.458	0.597
	right hand	8	0.55	0.7	0.85	1	.	.	.
	left hand	2	0.5	0.625	.	.	.	.	.
	Others	11	0.57	0.727	0.864	.	.	.	.
Size	less than 5cm	41	0.51	0.705	0.844	7	0.396	0.468	0.69
	5-10cm	49	0.577	0.74	0.845	4	0.39	0.456	0.607
	more > 10cm	75	0.555	0.726	0.848	6	0.188	0.518	0.642
	Operated	5	0.602	0.75	0.875	1	.	.	.
Sinuses	None	30	0.53	0.703	0.851	4	0.384	0.455	0.858
	Active	65	0.531	0.714	0.847	5	0.429	0.593	0.665
	Healed	70	0.585	0.736	0.855	9	0.293	0.48	0.538
	Multiple	4	0.438	0.656	0.839	.	.	.	.
	Operated	1	.	.	.	.	.	.	.
Grains	None	92	0.551	0.716	0.854	11	0.403	0.485	0.67
	Present	79	0.566	0.73	0.869	7	0.254	0.518	0.59
Glands	No	148	0.557	0.73	0.85	17	0.431	0.491	0.638
	Yes	23	0.565	0.727	0.864	1	.	.	.
Veins	None	163	0.557	0.728	0.857	18	0.402	0.498	0.634
	Present	8	0.578	0.688	0.844	.	.	.	.
Sweating	No	162	0.559	0.724	0.85	18	0.404	0.499	0.628
	Yes	8	0.57	0.748	0.875	.	.	.	.
Medical Problem	Yes	8	0.541	0.719	0.844	.	.	.	.
	No	163	0.554	0.729	0.867	18	0.403	0.496	0.631

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

Table (4) shows quartiles of the survival function for recurrent events to each recurrence. the size (operated) has minimum value (5) with probability of occurrence the recurrence (0.602) in Q1, (0.75) in Q2 and (0.875) in Q3 in recurrence 1 and value (1) in recurrence 2 with probability of occurrence the recurrence (0) in Q1, Q2 and Q3, size (more >10cm) has maximum value (75) with probability of occurrence the recurrence (0.555) in Q1, (0.726) in Q2 and (0.848) in Q3 for recurrence 1 and in recurrence 2 value (6) with probability of occurrence the recurrence (0.188) in Q1, (0.518) in Q2 and (0.642) in Q3. and so on for the rest of the factors.

Table (5): Quartile Statistics for survival functions of imaging and laboratory investigation:

Factors		Recurrence 1				Recurrence 2			
		N	Q1	Q2	Q3	N	Q1	Q2	Q3
Normal	No	136	0.567	0.723	0.864	14	0.414	0.508	0.621
	Yes	35	0.526	0.705	0.864	4	0.206	0.530	0.701
soft tissue	No	101	0.550	0.720	0.816	10	0.439	0.543	0.660

	Yes	70	0.555	0.733	0.867	8	0.304	0.486	0.565
	No	144	0.562	0.726	0.849	16	0.369	0.471	0.624
bone destruction	Yes	27	0.536	0.731	0.849	2	0.582	0.592	.
	No	155	0.556	0.727	0.856	18	0.405	0.504	0.638
periosteal reaction	Yes	15	0.622	0.750	0.875	.	.	.	.
	No	125	0.550	0.735	0.859	14	0.342	0.511	0.635
not done	Yes	46	0.566	0.707	0.833	4	0.444	0.477	0.856
	EM	61	0.582	0.719	0.864	8	0.277	0.459	0.561
	No grains	6	0.575	0.740	0.875	.	.	.	.
	Mycetoma	2	0.333	0.500	.	.	.	.	.
Ultrasound	Normal	1	.	.	.	.	.	.	.
	not done	99	0.514	0.704	0.854	10	0.423	0.541	0.677
	Not significant	1	.	.	.	.	.	.	.
	MM	75	0.589	0.740	0.871	10	0.338	0.449	0.533
	no grain	6	0.500	0.682	0.841	1	.	.	.
Cytology	non specific	3	0.500	0.667	.	.	.	.	.
	Not Done	87	0.497	0.688	0.857	6	0.520	0.653	0.812
	not done	69	0.579	0.740	0.868	7	0.251	0.390	0.538
	MM	85	0.534	0.719	0.860	10	0.423	0.536	0.707
Histology	NO GRAIN	6	0.410	0.688	0.854	.	.	.	.
	Non Specific	11	0.493	0.676	0.844	1	.	.	.
	no organism	7	0.485	0.707	0.857	1	.	.	.
	MM	133	0.563	0.709	0.857	15	0.411	0.474	0.634
Organism	not done	22	0.430	0.713	0.860	1	.	.	.
	Other	9	0.437	0.680	0.847	1	.	.	.

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

Table (5) shows quartiles of the survival function for recurrent events to each recurrence. the patients whose periosteal reaction (yes) has minimum value (15) with probability of occurrence the recurrence (0.62) in Q1, (0.75) in Q2 and (0.875) in Q3 for recurrence 1 and no patients in recurrence 2, the patient whose periosteal reaction(No) has maximum value (155) with probability of occurrence the recurrence (0.556) in Q1, (0.727) in Q2 and (0.856) in Q3 for recurrence 1 and the patients in recurrence 2 their periosteal reaction(No) are (18) with probability of occurrence the recurrence (0.405) in Q1, (0.504) in Q2 and (0.638) in Q3. and so on for the rest of the factors.

Table (6): Quartile Statistics for survival functions of clinical characteristic:

Factors		Recurrence 1				Recurrence 2			
		N	Q1	Q2	Q3	N	Q1	Q2	Q3
	Iitraconazole + Folic Acid	30	0.608	0.736	0.873	4	0.233	0.408	0.495
	Ketoconazole + Folic Acid	134	0.552	0.722	0.853	12	0.387	0.504	0.694
Treatment	Penicillin + gresufution	6	0.491	0.636	0.773	1	.	.	.
	<= 2.00	55	0.232	0.500	0.750	7	0.647	0.897	0.952
	2.00 - 9.00	80	0.247	0.494	0.704	9	0.778	0.875	0.953
duration of treatment	9.00 - 16.00	26	0.250	0.500	0.704	2	0.855	0.908	.
	16.00+	6	0.250	0.500	0.714	0	.	.	.
	Yes	161	0.245	0.491	0.702	17	0.841	0.912	0.965
Surgery	No	10	0.250	0.400	0.750	1	.	.	.

amputation	Yes	28	0.250	0.483	0.750	2	0.901	0.933	
	No	141	0.250	0.493	0.732	16	0.815	0.892	0.959
Outcome	Cured	33	0.580	0.734	0.860	1	.	.	.
	Lost to follow up	96	0.522	0.720	0.860	11	0.421	0.583	0.670
	until now on treatment	41	0.591	0.716	0.858	6	0.300	0.507	0.589

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

Table (6) shows quartiles of the survival function for recurrent events to each recurrence. the patients whose takes the treatment (Penicillin + gresufution) are (6) with probability of occurrence the recurrence (0.491) in Q1, (0.636) in Q2 and (0.773) in Q3 for recurrence 1 and there is only one patient in recurrence 2, with probability of occurrence the recurrence (0) in Q1, Q2 and Q3 and the patients whose takes the treatment (Ketoconazole + Folic Acid) are (134) in recurrence 1 with probability of occurrence the recurrence (0.552) in Q1, (0.722) in Q2 and (0.853) in Q3 the treatment (Ketoconazole + Folic Acid) are (12) with probability of occurrence the recurrence (0.387) in Q1, (0.504) in Q2 and (0.694) in Q3 for recurrence 2. and so on for the rest of the factors.

9. Conclusion:

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- According to the life table, the maximum number of patients who had the event during the time interval between 0 and less than 20 is 100, and the minimum number of patients who had the event during the time interval between 140 and less than 160 is 2, As a contrast, the maximum value of S(t) during the time interval from 0 to less than 20 and the minimum value of S(t) during the time interval from 140 to less than 160. For the h(t), the minimum value for patients at risk during the time interval from [40 100) is 0.01 The maximum value for patients at risk during the period from [200 220] and the results from time interval [20-40) are four patients getting the event, There is no recurrence in patients during the time intervals [120 140), [140 160), [180 200) and [220). the maximum S(t) during the time interval from [0 20).

3- from Kaplan Meier quartiles result for all study factors we found the probability of occurrence the recurrence 1 in Q1 is (0.23 to 0.62), Q2 is (0.40 to 0.75) and Q3 is (0.70 to 0.87) and the probability of recurrence 2 for Q1 is (0.085 to 0.90), Q2 is (0.24 to 0.93) and Q3 is (0.49 to 0.96).

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References:

[1] Fahal A, Mahgoub ES, Hassan AME, Abdel-Rahman ME. (2015). Mycetoma in the Sudan: An Update from the Mycetoma Research Centre, University of Khartoum, Sudan. PLoS Negl Trop Dis 9(3): e0003679. https://doi.org/10.1371/journal.pntd.0003679 PMID: 25816316.

[2] Bonifaz A, Tirado-SaÂnchez A, CalderoÂn L, SauÂ l A, Araiza J, HernaÂndez M. (2014). Mycetoma: Experience of 482 Cases in a Single Center in Mexico. PLoS Negl Trop Dis 8(8): e3102. https://doi.org/10.1371/journal.pntd.0003102 PMID: 25144462.

[3] Fahal A, Mahgoub ES, EL Hassan AM, Jacoub AO, Hassan D. (2015) Head and Neck Mycetoma: The Mycetoma Research Centre Experience. PLoS Negl Trop Dis 9(3): e0003587. https://doi.org/10.1371/ journal.pntd.0003587 PMID: 25768090.
[29] Fahal AH. (2004). Mycetoma: a thorn in the flesh. Trans R Soc Trop Med Hyg. 98(1):3±11. PMID: 14702833.
[4] Suleiman SH, Wadaella ES, Fahal AH. (2016). The Surgical Treatment of Mycetoma. PLoS Negl Trop Dis 10(6): e0004690. https://doi.org/10.1371/journal.pntd.0004690 PMID: 27336736.
[5] Hay RJ, Fahal AH. (2015). Mycetoma: an old and still neglected tropical disease. Trans R Soc Trop Med Hyg. 109(3):169±70. https://doi.org/10.1093/trstmh/trv003 PMID: 25667234.
[6] Gemeinhardt H. Zum Begriff und zur diagnostischen Bedeutung der "Pilzdruse". Path Microbiol 1969; 33: 77–94.
[7] Balabanoff VA. Mycetomas originated from South-East Bulgaria. Ann Parasitol Hum Comp 1980; 55: 605–613.
[8] Avram A, Cojocaru I, Dul_amit__a L. Le pied de Madura _a Monosporium apiospermum. A propos de 3 cas roumains. Dermatologica 1968; 136: 176–186.
[9] Avram A, Porojan I, Cojocaru I. Trois nouveaux cas roumains de pied de Madura. Agents incrimin_es: Nocardia asteroids, Cephalosporium falciformeet Madurella mycetomi. Dermatologica 1968; 136: 311–320.
[10] van de Sande WWJ, Fahal AH, Goodfellow M, Maghoub ES, Welsh O, Zijlstra EE. (2014). The merits and pitfalls of the currently used diagnostic tools in mycetoma. PLoS Negl Trop Dis 8(7): e2918. https://doi.org/10.1371/journal.pntd.0002918 PMID: 24992636
[11] Paulon, G., De Iorio, M., Guglielmi, A., & Ieva, F. (2020). Joint modeling of recurrent events and survival: A Bayesian non-parametric approach. Biostatistics, 21(1), 1-14.
[12] Efird, J. T., & Jindal, C. (2018). Using a Counting Process Method to Impute Censored Follow-Up Time Data. International Journal of Environmental Research and Public Health, 15(4), 690.
[13] Yang, W., Jepson, C., Xie, D., Roy, J. A., Shou, H., Hsu, J. Y., ... & Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. (2017). Statistical methods for recurrent event analysis in cohort studies of CKD. Clinical Journal of the American Society of Nephrology, 12(12), 2066-2073.
[14] Sun, X., Peng, L., Huang, Y., & Lai, H. J. (2016). Generalizing quantile regression for counting processes with applications to recurrent events. Journal of the American Statistical Association, 111(513), 145-156.
[15] Ahmed, E. A., Nour, B. Y., Abakar, A. D., Ahmed, G. M., & Ahmed, A. E. (2022). Direct Extraction and Assessment of Genomic DNA of Mycetoma Fungi from Black-grains Specimen. Gezira Journal of Health Sciences, 17(1), 24-36.
[16] Hay, R. J. (2021). Mycetoma–a history of the first contributions to the description of the disease and its pathogenesis. Transactions of The Royal Society of Tropical Medicine and Hygiene, 115(4), 283-286.
[17] Gismalla, M. D., Ahmed, G., MohamedAli, M. M., Taha, S. M., Mohamed, T. A., Ahmed, A. E., & Hamed, L. S. (2019). Surgical management of eumycetoma: experience from Gezira Mycetoma Center, Sudan. Tropical Medicine and Health, 47(1), 1-6.
[18] Lim, W., Melse, Y., Konings, M., Phat Duong, H., Eadie, K., Laleu, B., ... & van de Sande, W. W. (2018). Addressing the most neglected diseases through an open research model: The discovery of fenarimols as novel drug candidates for eumycetoma. PLoS neglected tropical diseases, 12(4), e0006437.
[19] Ahmed, A. A., van de Sande, W., & Fahal, A. H. (2017). Mycetoma laboratory diagnosis. PLoS neglected tropical diseases, 11(8), e0005638.
[20] Hanagal, D. D. (2019). Modeling survival data using frailty models (2nd ed.). Boca Raton: Chapman & Hall/CRC.
[21] Collett, D. (2015). Modelling survival data in medical research (3rd ed.). Taylor & Francis Group, LLC.
[22] Mamour, E. M. K. (2019). A Comparative Study of Parametric and Non-Parametric Survival Analysis Models for Breast Cancer Patients (Doctoral dissertation, Sudan University of Science and Technology).