

ESTIMATION OF SURVIVAL TIME OF PATIENTS WITH UTERINE FIBROID

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Abstract : Survival Analysis, also known as failure time analysis or time to event analysis is one of the most significant advancement of mathematical statistics in the last quarter of 20th century. It has become the de facto standard in bio medical data analysis. This paper in particular studies the survival of patients with uterine fibroids, a non-cancerous growth that occur in the womb. Complete clinical and follow up data of selected patients with uterine fibroid were retrospectively analyzed. Survival analysis was performed using Kaplan Meier analysis and comparisons among groups were analyzed using logrank rank test. Independent factors were deduced and risk functions are to be established.

Key Words: Fibroid, Kaplan Meier Analysis, Log rank test, Survival time.

Introduction : Uterine fibroids, also known as leiomyomas, are the most common pelvic mass found in women. Fibroids are benign tumors that arise from the uterine muscular tissue (myometrium). They occur in 20-50% of women, with increasing incidence as women get older. They are found more commonly, tend to occur at younger age, and present with greater number and size in women.

Fibroids can be found on the outer surface of the uterus (subserosal), embedded within the myometrial wall (intramural), within the inner cavity of the uterus (submucosal), or a combination of the 3 locations. As will be discussed below, the location of the fibroid is an important determinant of the clinical significance for a particular woman. Their presence can vary in size and number from woman to woman.

Oftentimes they are asymptomatic. If symptomatic, the most common problems are excessive or irregular vaginal bleeding, pelvic pain, and pressure on surrounding organs such as the bladder and intestines. The likelihood and severity of the symptoms often, but not always, correlate with an increasing number and size of the tumors. Fibroids are also associated with an increased risk of infertility and miscarriage.

Treatment : Medications that decrease estrogen production, such as GnRH agonists (for example, Lupron), lead to a marked shrinkage in the size of uterine fibroids and diminution of symptoms. The effect however is temporary.

Myomectomy, or the surgical removal of fibroids, is the accepted treatment for women with symptomatic fibroids who wish to maintain their ability to conceive. It is well documented that the uterus heals well and can support a pregnancy after a myomectomy.

Fibroids that are entirely submucous, or with a very small intramural component, are best removed vaginally with a hysteroscope.

For intramural fibroids, the decision to perform a myomectomy by either laparoscopy or laparotomy depends on the expertise of the surgeon, as well as the number and size of the fibroids. If multiple

incisions on the uterus are required to remove the fibroids or if the fibroid is large, the abdominal approach is preferable. However, the decision to choose one method over the other depends on the size and location of the fibroid, and the skill and experience of the surgeon.

Research subjects were treated in "Maruti fertility Clinic" during the period "Jan 2007 to Dec 2012". They were all diagnosed as patients with Uterine fibroid. Thus, study includes patients with uterine fibroid each possessing different characters of factors which includes age of patients, Blood group, diagnosis period, waiting time, position of fibroid, Symptoms, Type of treatment taken etc., Of these the primary factor of consideration is the waiting time of the patient from the time of diagnosis to the time of occurrence of event. Event of interest of the study is the time when treatment is taken.

Clinical data: The age of 29 patients under study were between 16 and 56 with the median age 35.6. Eating habit of patients include 13 vegetarians and 16 non vegetarians. Of 29 patients 17 had intramural fibroid, 10 submucosal and 2 subserosal fibroid. The symptoms of fibroid include 6 patients with inconception, 10 with abdominal pain as symptom, 12 with heavy bleeding and 1 miscarriage. Present study attempts to answer the fraction of patients who will survive a past certain time, Of those who survive the rate at which the event is met, rate of increase or decrease in the odds of survival due to particular factor influencing the occurrence of the event.

Treatment: The treatment for Uterine fibroid include GnRH (injection), myomectomy (Laparoscopic or open surgery or/and Hysterectomy (Laparoscopic or open surgery)). In this study 5 patients were cases of hysterectomy, 14 cases of myomectomy, 1 received GnRH and 9 yet to receive a treatment.

Univariate Analysis: Estimation of the three survival functions (survivorship, density and hazard) functions for censored data is found. The observation period of the patients is taken for 5 years and patients whose waiting time is more than 60 months are considered to be censored data. (Right censored).

Statistical Analysis :SPSS 18.o software was used for statistical analysis. Chi square test was used for nominal data.The Kaplan Meier method and log rank test were respectively used for survival rate and single

factorial analysis. Cox regression analysis was performed for multi variance analysis. Statistical significance was indicated by $p < 0.05$.

Plot of Survival function and Hazard function of patients with respect to the waiting time.

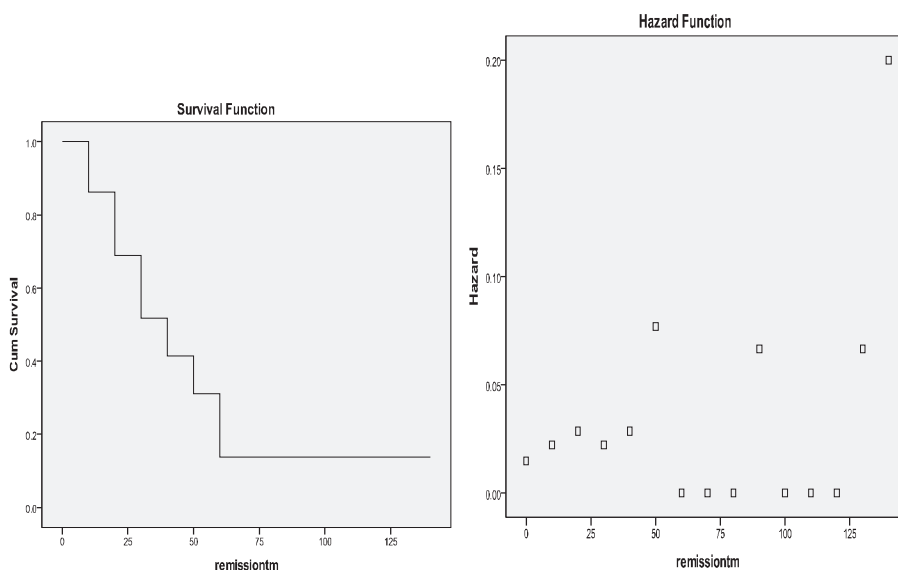


Fig 1(a)&1(b) representing the survival curve and hazard function of 29 patients with uterine Fibroid

Fig 1(a) & 1(b) represents respectively the survival and hazard pattern of 29 patients with Uterine Fibroid with respect to their waiting time (i.e) time from diagnosis to time of treatment (in month and Year).The Median Survival time is found to be approximately 39.5 months. The peak of high frequency occurrence of event(treatment undertaken) occurs in 50 to 60 months. In addition,the hazard function shows a fluctuating pattern in the first 125 months and then reaches its peak at approximately 143.75 months.

Table I Comparison of PL Estimates of patients with Fibroid in different positions in Uterus

Survival rate of patients with fibroid in different positions in Uterus.

Position	Intramural	Submucal	Subserol
0-10	0.88	0.80	1.00
10-20	0.71	0.60	1.00
20-30	0.47	0.60	0.50
30-40	0.35	0.50	0.50
40-50	0.18	0.50	0.50
50-60	0.06	0.20	0.50
60-70	0.06	0.20	0.50
>70	0.06	0.20	0.50

Table I gives the PL estimate of the survival function $\hat{S}(t)$ for the different positions of Fibroid in the Uterus. The Median Survival time can be estimated by linear interpolation. For patients with fibroid in the intramural position median survival time was about 29 months. Median Survival time of patients with fibroid in submucal and subserosal positions were respectively 39 months and 26 months respectively. These results indicates that

patients with fibroid in submucal position had slightly better survival experience than intramural and subserosal positions. For example 50% of the patients with Fibroid in submucal position survival atleast 39 months

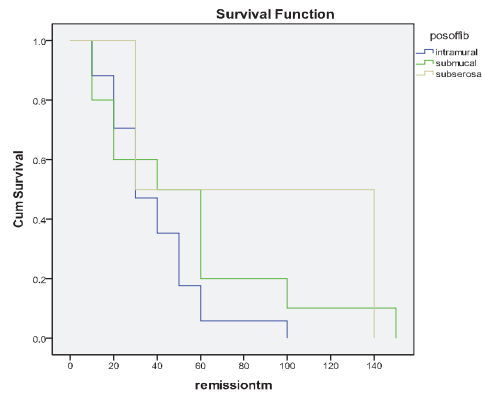


Fig.2 Overall Survival curve of patients with fibroids in different positions.

In Fig 2 the estimated survival functions $\hat{S}(t)$ for patients with fibroid in different positions. The Median survival time (50 percentile point for the three groups can also be determined graphically. The survival curves clearly show that the patients with fibroid in subserosal position had better survival experience than the other two groups.

Examining The Prognostic Homogeneity Of The Patients With Respect To The Position Of Fibroid In Uterus.

At this stage it is tested whether the difference between the three treatment groups with respect to position of fibroid is statistically significant. A Statistical test of significance is needed but before that the homogeneity of groups of patients with respect to the prognostic factors are tested. Apart from the influence of position of fibroid on the survival time there are many other sub factors like symptoms, age of patients, treatment taken, number of children etc., which may also influences the survival time of the patients.^[2]

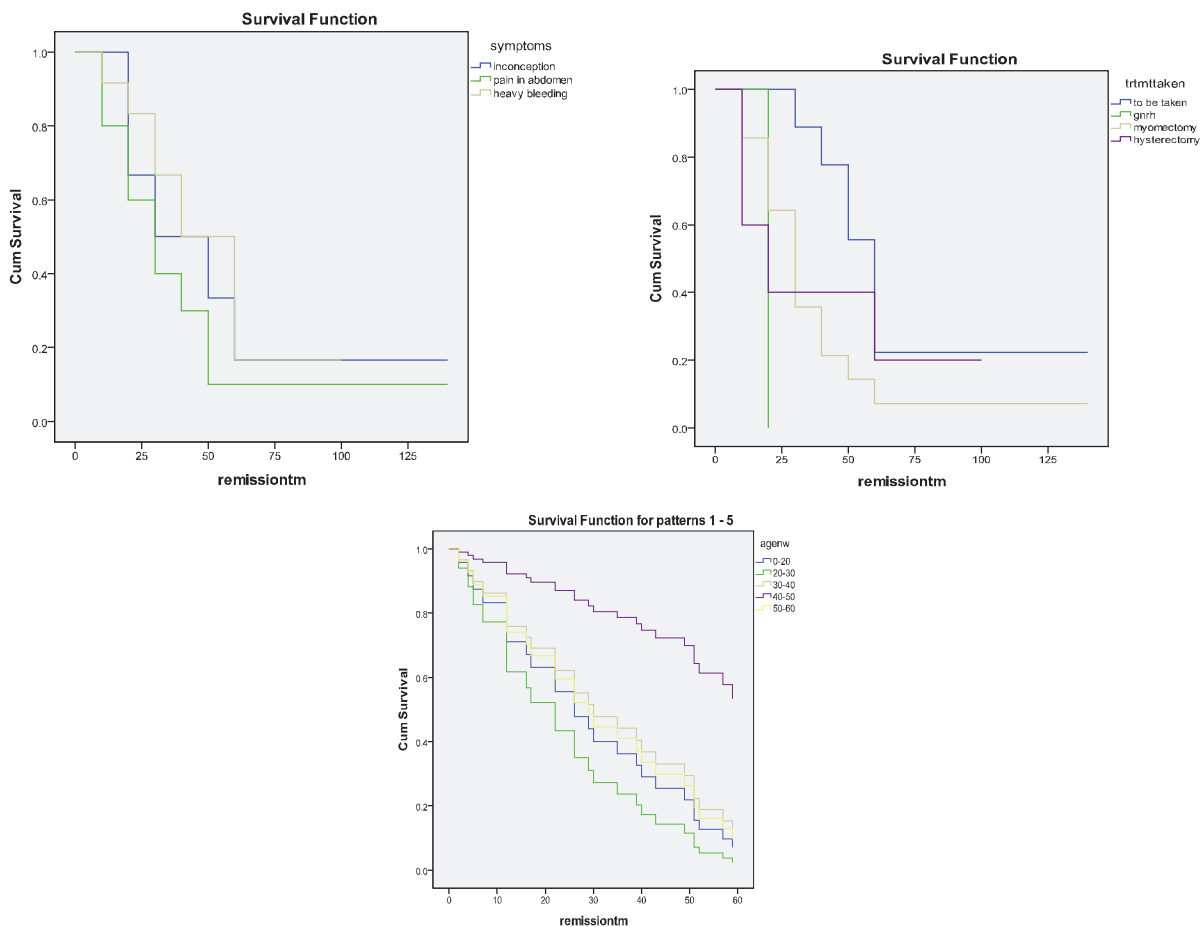


Figure 3(a),3(b),3(c)- Overall Survival curves of patients with different factors.

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Table II Univariate analysis of 29 patients with Uterine Fibroid				
Variable	No.,of patients event	No., of attaining Survival time	Survival time (log rank)	P value
Age				
0-20	3	3	29.66	0.689
20-30	1	1	26.00	
30-40	20	17	43.95	
40-50	2	1	95.00	
50-60	3	3	33.00	
Treatment taken				
To be taken	9	7	65.66	0.103
Gnrh	1	1	12.00	
Myomectomy	14	13	32.92	
Hysterectomy	5	4	44.34	
Position of fibroid				
Intramural	17	16	31.41	0.264
Submucal	10	8	53.20	
Subserosal	2	1	82.50	
Symptoms				
Inconception	6	5	48.66	0.025
Pain in abdomen	10	9	35.10	
Heavy Bleeding	12	10	45.42	
Misconception	1	1	5.00	
No of children				
Unmarried	4			
0	14	13	40.42	0.910
1	10	8	49.20	
2	5	4	35.40	
Food habit				
Veg	13	10	56.53	0.178
Non Veg.,	16	15	31.62	

Table II and Fig 3(a),3(b) &3(c) shows the complete detailed result of single factorial analysis.

One way to analyze the data is first to determine which of the 5 variables could be considered of significant prognostic importance. Patients are grouped into sub groups in a meaningful ways.

It is found the Median survival time increases as the age increases and is maximum in the age group 40-50. Patients in the age group 20-30, intramural position of fibroid; miscarriage and pain in abdomen as symptom have significantly shorter survival duration than those without these characteristics.

Based on the p value (<0.05) symptoms due to fibroid is identified as the next factor influencing the survival time of the patients.

It is found that the differences in survival time of patients with respect to position of fibroid and Symptoms are not significant, ($\chi^2=2.663$, and $\chi^2=4.1$ resp.,). However there exists significant difference in

the survival time with respect to treatment given, number of children of the respondents, Food habit and age of patients ($\chi^2 =6.191, \chi^2 =0.189, \chi^2 =1.8, \chi^2 = 2.181$ resp.,).

Thus we can see that the data do not show heterogeneity between the treatment groups for factors like position of fibroid and symptoms. However, heterogeneity is found in the age of patients, treatment given, number of children of patients and their food habit.

Multi Variance Analysis: [3] Using variable factors with statistical ignificance obtained from single factorial analysis and other possible clinically influencing actors, all were included in the Multi variance analysis-Cox regression .From table 3 the p-values for the factors age, position, treatment taken and number of children are 0.747, 0.119, 0.128 and 0.50 respectively. Also the p values of symptom and food habit are 0.013 and 0.07 which are closer 0.05 [4].

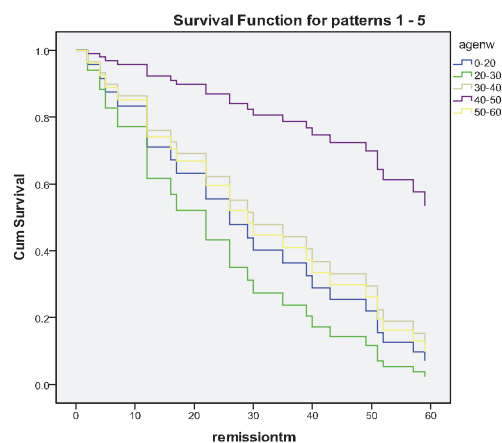
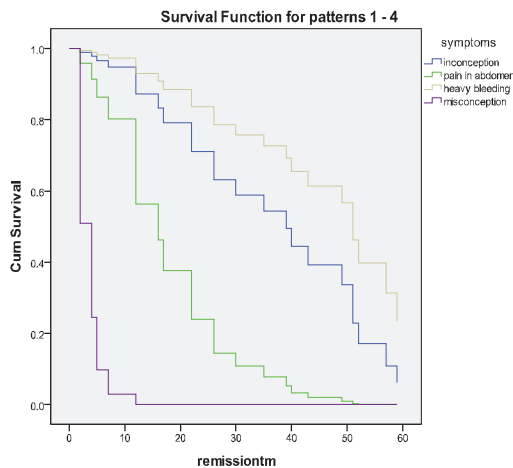
The Prognostic risk predictive function: The predictive model of survival in case of patient in age group 0-20 with fibroid in intramural position, over bleeding symptom with one child was established as,

$S(I)=0.127X_1+7.433X_2-3.008X_3+1.058X_4-1.327X_5$, Thus for each patient based on their characteristics regarding their age, position of fibroid, Symptoms, treatment taken and number of children S(I) can be calculated.^[5]

Identification of Risk factors

Table III Cox regression analysis of patients with Uterine Fibroid

Variable	B	SE	Wald	Df	P	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
age			1.940	4	.747			
agenw(1)	.127	.822	.024	1	.878	1.135	.227	5.680
agenw(2)	.477	1.180	.163	1	.686	1.611	.159	16.288
agenw(3)	-.088	.632	.020	1	.889	.915	.265	3.159
agenw(4)	-1.315	1.159	1.289	1	.256	.268	.028	2.600
Position			4.258	2	.119			
Position(1)	7.433	106.868	.005	1	.945	1690.424	0.00	1.964E94
Position(2)	5.442	106.881	.003	1	.959	230.825	0.00	2.190E93
Symptoms			10.79	3	0.013			
symptoms(1)	-4.282	1.587	7.278	1	.007	.014	.001	.310
symptoms(2)	-3.008	1.574	3.652	1	.056	.049	.002	1.080
symptoms(3)	-5.206	1.745	8.903	1	.003	.005	.000	.168
trtmtaken			5.684	3	.128			
trtmtaken(1)	-1.955	.936	4.359	1	.037	.142	.023	.887
trtmtaken(2)	-1.274	1.601	.633	1	.426	.280	.012	6.450
trtmtaken(3)	-.945	.933	1.026	1	.311	.389	.062	2.419
noofchild			1.387	2	.500			
noofchild(1)	1.058	.903	1.374	1	.241	2.882	.491	16.916
noofchild(2)	.892	.993	.807	1	.369	2.440	.348	17.094
foodhab	-1.327	.735	3.256	1	.071	.265	.063	1.121



Discussion

In this study the overall average survival time for patients with Uterine fibroid was 31.67months. For survival status of these 29 patients with different position of Uterine fibroid such as intramural, submucal and subserosal (from figure 2) are 64%,

32% and 4% respectively. However, the survival rate of patients with different symptoms like inconception, abdominal pain, Heavy bleeding are 20%, 36% and 40% respectively. Survival rates of patients who have taken different treatment like GnRh, Myomectomy, Hysterectomy are 40%, 52% and 16% respectively

From the Univariate analysis of various factors affecting the survival time of the patients the position of fibroid and the symptoms acts as major factors influencing the survival time.

The regression coefficient and the significance level for the variables based on Wald's test is calculated. The sign of coefficients indicates whether the

variables are positively or negatively related to the event of interest. It is inferred that two variables symptoms and number of children of the respondent are negatively related to the survival time.

Also number of children of the patient, age and food habit plays as factor of importance in influencing the survival time.

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