NON-PARAMETRIC ESTIMATION OF THE SURVIVAL PROBABILITY OF CHILDREN AFFECTED BY TB MENINGITIS

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ABSTRACT

In life threatening diseases, majority of the patients do not experience the event of interest during the follow-up period resulting in heavy censoring. The traditional Kaplan-Meier estimator over estimates the survival function. The TB Meningitis disease which is prevalent among children carries high mortality and morbidity. In this paper the two methods namely Weighted Kaplan-Meier estimator and Modified Weighted Kaplan-Meier estimators are applied to study the survival probability of children affected by TB Meningitis. The results are compared with the celebrated Kaplan-Meier, Nelson-Aalen and Huang's methods of estimation. The data used for the study have been collected from the Tuberculosis Research Center, ICMR, Chennai

Keywords: Censored data, Survival Function, Kaplan-Meier estimate, TB Meningitis.

1. INTRODUCTION

Survival analysis refers to the collection of statistical procedures used to study the time between entry into the observation and to the occurrence of some event of interest for the study population, which is often called as time-to-event analysis. Time to occurrence of a particular event carries a great significance in reliability, medical or biological studies. The time indicates any unit of time from the beginning of follow-up of an individual until an event of interest occurs. The outcome variable of interest is the elapsed time between a well-defined starting and ending points. In medical research the outcome variable (or) event of interest may be the death of a patient, relief from pain, the recurrence of symptoms, disease incidence, relapse from remission, remission duration of certain disease in clinical trials, incubation time of certain diseases, such as AIDS, Hepatitis B etc., and in industry, the failure time of certain manufactured products (Cox and Snell 1968; Crowley and Hu, 1977; Kalbfleisch and Prentice, 1980; Miller, 1981; Cox and Oakes, 1984; Clayton, 1978; Jenkins, 1997; Andersen ,1992).

An initial step in the analysis of survival data is to provide numerical or graphical summaries of the survival times of the population under study. These summaries will describe in detail about the nature of the data under study and will be helpful to carrying out the detailed analysis for the survival data. The development of methods has been particularly motivated by the need to analyze medical and health sciences data, in particular survival data. Survival data are summarized through the estimates of the survival function and hazard function. Several non-parametric methods, which do not require any specific assumptions about the underlying distribution of the survival time, have been discussed by the several authors during past six decades or so.

Many researchers had written reports about life table (Berkson and Gage, 1950; and Gehan, 1969). Peto et al. (1976) have published an outstanding review of some statistical methods related to clinical trials. The developments in the field that have had the most thoughtful impact on clinical trials are the Kaplan-Meier (1958) method for estimating the survival function.

The Kaplan-Meier (1958), which will be explained later and also known as product limit estimator, has become an important attractive estimator in the analysis of survival data. Because of its simplicity and easy to understand, this estimator has been in the continued attention of several authors.

In the case of heavy censoring, the Kaplan-Meier (1958) estimate is not reliable and over estimating the survival probabilities (Susan, 2001) and also the Kaplan-Meier survival curve fails to give reliable estimates at the end points. To have a reliable estimate, in the case of heavy censoring, an improved method of Kaplan-Meier estimate, namely Weighted Kaplan-Meier method of estimation (Jan et al. 2005) were applied and proved for reliable estimate, by introducing the weights based on the non-censored rate. Then, followed by the Weighted Kaplan-Meier method, a modified form of this, namely Modified Weighted Kaplan-Meier method (Shafiq et al. 2007) were introduced by assigning a new weight in the case of the last observation is censored. Then, a Weighted Empirical Survival Function (WESF) was used by Huang (2008), in which choices of weights were introduced for obtaining the survival function. Later, the well known Nelson-Aalen estimate is also used for obtaining the survival function by using its interrelationship between the survival function and the cumulative hazard function. Finally, in this paper, some conclusions are drawn for the TB Meningitis data, by comparing the estimated survival probabilities obtained through the above mentioned methods.

SURVIVAL DATA:

Survival data means the time observed for each individuals who are undergoing in an experimental study from a well defined time origin until the occurrence of some particular event of interest (or) end-point (Collett, 2003). A common feature of the survival data is the presence of censoring and truncated observations. Another characteristic of survival data is that the survival time cannot be negative. The event of interest in this study is the death of a patient due to TB Meningitis, a disease prevalent among children.

CENSORING:

The survival time of an individual is said to be censored, when the event of interest could not be recorded for that individual. In this study the event of interest is the death of a patient.

The reasons for the censored survival time could be the termination of the experiment as in a clinical study it may not be feasible to continue or follow-up the experiment until all the subjects under study have failed or experienced the event of interest or subjects may withdrawn willfully or may getting dropped from the study. In this case it may not be possible to have complete information for all the subjects,Censoring is broadly classified into two categories: Informative and non-informative.In this study we consider informative censoring only. Some of the important types of censoring are Type I censoring (or fixed time censoring), Type II censoring (or fixed number censoring), random censoring and Interval censoring (Cox and Oakes, 1984; Kalbfleisch and Prentice, 1980; Miller, 1981). Type I and Type II are singly censored data where as Type III is random censored data (Cohen, 1965). Type I, Type II and random censoring data are right censored. It is to be noted that when there are no censored observations, the set of survival times is said to be "complete".

BASIC QUANTITIES IN SURVIVAL ANALYSIS:

Let T be the positive random variable denoting the time to occurrence of the event of interest. In summarizing the survival data the two functions namely survival function and the hazard function are of central interest. The survival function usually denoted by $S(t)$ which estimates the probability that a subject survives greater than or equal to some specified time t. Therefore, the survival function is,

$$S(t) = P(T \geq t)\,;\, t > 0$$

If $F(t)$ is the cumulative distribution function of t, then,

$$F(t) = P(T \leq t) = 1 - S(t)\,.$$

The properties of the survival function are monotonically non-increasing; at time $t = 0$, $S(t) = 1$ and at infinite time $t, S(t) = 0$. The function $S(t)$ is also known as the cumulative survival rate. The graph of $S(t)$ on time is called as the survival curve.

The hazard function at time t is defined as

$$h(t) = \lim_{\Delta t \to 0} \frac{P((t \leq T < t + \Delta t)/T \geq t)}{\Delta t} = \frac{f(t)}{S(t)}$$

The hazard function is also known as instantaneous death rate, or the conditional mortality rate. Some of the characteristics of the hazard function are, $h(t)$ may increase, decrease or remain constant or follow any other pattern, $h(t) \geq 0$ and has no upper limit and it is not a probability and depends on time units. The shape of the hazard function $h(t)$ indicates the type of risk to which the population under study is exposed as a function of time.

The cumulative hazard function is denoted by $H(t)$ and is defined as

$$H(t) = \int_0^t h(x)\,dx = -\log S(t)\,.$$

The function $H(t)$ is also known as the integrated hazard function (Collett, 2003). For the present work the analysis has been carried out using SPSS 13.0 software.

2. NON-PARAMETRIC ESTIMATION OF THE SURVIVAL PROBABILITY:

2.1 KAPLAN-MEIER ESTIMATION OF THE SURVIVAL FUNCTION:

The Kaplan-Meier (product limit) method is a special case of the life table technique, in which the series of time intervals are formed in such a way that only one death occurs in each time interval and the death occurs at the beginning of the interval (Collett, 2003).

Suppose that there are n individuals with observed survival times $t_1, t_2, ..., t_n$ and r death times amongst the individuals, where $r \leq n$. The ordered death times $t_{(j)}, j = 1,2,...,r.$ are $t_{(1)} < t_{(2)} < ... < t_{(r)}$. Let $n_j, j = 1,2,...,r$ be the number of individuals who are alive just before the time $t_{(j)}$ and let $d_{(j)}$ be the number of individuals who die at time $t_{(j)}$. The probability for an individual dies during the interval $t_{(j+1)}$ to $t_{(j)}$ is estimated by $\frac{d_j}{n_j}$. Therefore the corresponding estimated survival probability in that interval is $\frac{(n_j - d_j)}{n_j}$. If the censored survival times and one or more death times are same, then in this case it is assumed that the censored survival time(s) is taken to occur immediately after the death time. So, the estimated survival function for any time t in the j^{th} constructed time interval from $t_{(j)}$ to $t_{(j+1)}$, $j = 1,2,...,r$, and all preceding time intervals is leads to the following Kaplan-Meier estimate of the survivor function,

$$\hat{S}(t) = \prod_{t \leq t_j} \left(\frac{n_j - d_j}{n_j} \right)$$

for $t_{(j)} \leq t < t_{(j+1)}, j = 1,2,...,r,$ with $\hat{S}(t) = 1$ for $t < t_{(1)}$ and $\hat{S}(t) = 0$ for $t > t_{(r)}$ if $t_{(r)}$ is the last observation. It is noted that the Kaplan-Meier estimate is unspecified for the largest censored survival time. The plot of the Kaplan-Meier estimate of the survivor function is a step-function, where the estimated survival probabilities are constant between adjacent death times and decreases at each death time. Also, it is to be noted that the Kaplan-Meier estimate is a generalization of the empirical survival function, which includes both censored and complete observations. It is pertinent to note the following points about the Kaplan-Meier estimator in spite of its simplicity and wide applicability. Miller (1981) in a path breaking research paper "what price Kaplan-Meier?" has stated the following.

The asymptotic efficiency of the Kaplan-Meier estimator is low when compared to the efficiency obtained under the parametric setup. He has examined this aspect by taking two parametric models namely exponential and Weibull.

2.2 NELSON-AALEN ESTIMATOR:

The Nelson-Aalen Estimator, an alternative estimate of the survival function which is based on the individual event times and of cumulative hazard at time t is defined as:

$$\hat{H}(t) = \sum_{:t_j \le t} \frac{d_j}{n_j}, \text{ for } t > 0$$

Using this integrated function the estimate of the $S(t)$ is given by $\hat{S}(t) = \exp(-\hat{H}(t))$. The Kaplan-Meier estimate of the survivor function is given by

$$\hat{S}(t) = \prod_{t \le t_j} \left(\frac{n_j - d_j}{n_j} \right) = \prod_{t \le t_j} \left(1 - \hat{\lambda}_j \right)$$

Now, instead of using KM estimate, we adopt the method proposed by Nelson-Aalen through the integrated hazard function $H(t)$ to estimate the survivor function.

2.3 Modified Forms of Kaplan-Meier Method of Estimation:

Weighted Kaplan-Meier Estimator of Survival Function

Jan et al. (2005) claims that in life threatening diseases when some portion of the data is censored, the Kaplan Meier estimator becomes unreliable and inefficient. To deal with the situation they define a weight W_j at time $t_{(j)}$ as

$$W_j = \frac{n_j - d_j}{n_j}, \text{ which is known as non-censored rate.}$$

where $W_j = 1$ if there is no censoring and $W_j < 1$ in case of censoring at time t_j. Then, the Weighted Kaplan-Meier estimator is defined as

$$S^{**}(t) = \begin{cases} 1; \text{ for } t = 0 \\ \prod_{j:t_{(j)} \le t} W_j \left(\frac{n_j - d_j}{n_j} \right); \text{ for } t_{(j)} \le t \text{ ; } j = 1,2,\ldots,n. \\ 0; \text{ for } t > t_n \end{cases}$$

In this case $S^{**}(t)$ will reach zero, if the last observed survival time is censored. In the case of no censoring, $n_j - d_j = n_{j+1}$ as there are no censoring times then $W_j = 1$. This leads to

$$S^{**}(t) = \begin{cases} 0 & ;\text{for } t < t_{(1)} \\ \dfrac{n_k}{n_{k+1}} & ; \quad \text{for } t_{(k)} \le t < t_{(k+1)} \text{ and } k = 1,2,\ldots,n-1. \\ 1; \text{for } t \ge t_n & \end{cases}$$

MODIFIED WEIGHTED KAPLAN-MEIER ESTIMATOR:

The main defect in the above Weighted Kaplan-Meier method is that it gives zero weight to the last censored observation and probability is equal to zero. To overcome this difficulty, Shafiq et al. (2007) proposed a new weight which gives a non-zero weight to the last censored observation. The proposed Modified Weighted Kaplan-Meier estimator is then,

$$S^{**}(t) = \Pi_{T \le t} W_j \left[1 - \frac{d_j}{n_j} \right]$$

Where, the weight functions $W_j = \left[1 - \text{Sin}\left(\dfrac{c_j * P_j}{n_j} \right) \right]$ is known as a non-censoring rate.

Both the Modified Weighted Kaplan-Meier and the Weighted Kaplan-Meier estimators give same weight to all censored observations. They also give same probability of survival, but the important point is that Weighted Kaplan-Meier estimator gives zero weight to the last censored observation while the modified weighted estimator gives it some non zero weight and has a small probability of survival.

Huang's Estimator of Survivor Function

Huang (2008) studied a Weighted Empirical Survivor Function (WESF). It has been shown that by choosing appropriate weights the estimator proposed by him is more efficient than the Kaplan-Meier estimate in both censored and uncensored data.

For the censoring case, the idea of the above WESF for the uncensored case has been applied to obtain a weighted KME as given below:

$$\hat{S}_{KMW}(t) = \begin{cases} 1, & t < \tau_1 \\ \prod_{i=1}^{j} \left(1 - \dfrac{d_i}{n_i} \right) \left(1 - p_{k,i} \right), & \tau_j \le t \le \tau_{j+1}, \; j = 1,\ldots,k-1. \end{cases}$$

The weights suggested by Huang are,

$$w \equiv p_{n,i} = \frac{1}{\sqrt{n(n-1)}}; \; i = 2,\ldots,n-1.$$

$$w_{1,n} = p_{n,1} = p_{n,n} = \frac{1}{2}\left(1 - \frac{n-2}{\sqrt{n(n-1)}} \right)$$

3. APPLICATION TO THE TB MENINGITIS DATA

DATABASE DESCRIPTION:

Tuberculosis (TB) meningitis occurs when tuberculosis bacteria (Myobacterium tuberculosis) invade the membranes and fluid surrounding the brain and spinal cord. The infection usually begins elsewhere in the body, usually in the lungs, and then travels through the bloodstream to the meninges where small abscesses (called microtubercles) are formed. When these abscesses burst, TB meningitis is the result.Of all form of TB , TM Meningitis carries a high mortality and morbidity. In areas where TB prevalence is high, TB meningitis is most common in children aged 0 - 6 years, and in areas where TB prevalence is low, most cases of TB meningitis are in adults. This data have been collected from the Tuberculosis Research Centre (ICMR), Govt. of India, Chennai (Ramachandran et al. 1997).

The data presented here is obtained from randomized clinical trial and it consists of 225 cases of TB meningitis among children. The event of interest is occurrence of death over a period of five years. The following are the covariates were also considered including time and status (event-1, censored-0):The treatment (treatment1, treatment2), Mantoux (mm), History of contact TB (yes-1, no-0), Clinical stages(conscious-1,semi-conscious-2 and un-conscious-3), Weight at baseline (in kg), Chest X-ray (normal-0, abnormal-1), Sputum Smear (positive-1,negative-0), Sputum Culture (positive-1,negative-0), Protein level(normal-0, abnormal-1), gender(male-1, female-0) and Age (in months).The covariates are not used in the analysis for this paper.

4. RESULTS AND DISCUSSION

The computation of survival probabilities for the TB Meningitis data using the Kaplan Meier, Nelson-Aalen, Weighed Kaplan Meier, Modified Kaplan Meier and Huang methods have been presented in tables 4.1 and 4.2.The survival probabilities computed using the above methods have been plotted in figures 4.1 and 4.2.

Table 4.1: Survival Probabilities on the TB Meningitis data, obtained through the K-M estimate and the Nelson-Aalen method:

Survival Time	n_j	d_j	c_j	K-M Estimate	Nelson-Aalen Estimate
0	225	0	0	1.00000	1.00000
1	225	3	36	0.98667	0.98676
30	186	2	4	0.97606	0.97620
36	180	1	7	0.97063	0.97079
60	172	3	10	0.95371	0.95401
90	159	3	11	0.93571	0.93618
120	145	1	2	0.92926	0.92974
150	142	2	5	0.91617	0.91674
180	135	1	2	0.90938	0.90997
260	132	3	0	0.88872	0.88953
261	129	3	0	0.86805	0.86908
262	126	3	0	0.84738	0.84863
263	123	3	0	0.82671	0.82818
264	120	3	0	0.80604	0.80773
265	117	3	0	0.78538	0.78729
266	114	3	0	0.76471	0.76684
267	111	3	0	0.74404	0.74639

268	108	3	0	0.72337	0.72594
269	105	3	0	0.70271	0.70549
270	102	11	0	0.62692	0.63337
271	91	3	0	0.60626	0.61283
272	88	3	1	0.58559	0.59229
273	84	3	0	0.56467	0.57151
274	81	3	0	0.54376	0.55073
275	78	3	0	0.52285	0.52995
276	75	3	0	0.50193	0.50917
277	72	3	0	0.48102	0.48839
278	69	3	0	0.46010	0.46761
279	66	3	0	0.43919	0.44683
280	63	3	0	0.41828	0.42605
281	60	3	0	0.39736	0.40528
282	57	3	0	0.37645	0.38450
283	54	3	1	0.35554	0.36372
284	50	3	0	0.33420	0.34254
285	47	3	0	0.31287	0.32136
286	44	3	0	0.29154	0.30018
287	41	3	0	0.27021	0.27900
288	38	3	0	0.24887	0.25782
289	35	3	0	0.22754	0.23664
290	32	3	2	0.20621	0.21546
330	27	1	9	0.19857	0.20763
630	17	1	0	0.18689	0.19577
720	16	8	2	0.09345	0.11874
1079	6	1	0	0.07787	0.10051
1080	5	4	0	0.01557	0.04516
1081	1	0	1	0.01557	0.04516

Table 4.2: Survival Probabilities on the TB Meningitis data obtained through the K-M estimate, WKME, MWKME and Huang's methods:

Surv-ival Time	n_j	d_j	c_j	K-M Estimate	Weights for WKME	WKME	Weights for MWKME	MWKME	Huang's estimate
0	225	0	0	1.00000	1.00000	1.00000	1.00000	1.00000	1.00000
1	225	3	36	0.98667	0.84000	0.82880	0.84279	0.83155	0.97007
30	186	2	4	0.97606	0.97849	0.80226	0.97873	0.80511	0.95412
36	180	1	7	0.97063	0.96111	0.76677	0.96134	0.76968	0.9488

									2
60	172	3	10	0.95371	0.94186	0.70960	0.94291	0.71308	0.93227
90	159	3	11	0.93571	0.93082	0.64804	0.93218	0.65217	0.91468
120	145	1	2	0.92926	0.98621	0.63470	0.98630	0.63880	0.90837
150	142	2	5	0.91617	0.96479	0.60372	0.96529	0.60795	0.89558
180	135	1	2	0.90938	0.98519	0.59037	0.98530	0.59457	0.88895
260	132	3	0	0.88872	1.00000	0.57696	1.00000	0.58106	0.86874
261	129	3	0	0.86805	1.00000	0.56354	1.00000	0.56754	0.84854
262	126	3	0	0.84738	1.00000	0.55012	1.00000	0.55403	0.82834
263	123	3	0	0.82671	1.00000	0.53670	1.00000	0.54052	0.80813
264	120	3	0	0.80604	1.00000	0.52329	1.00000	0.52701	0.78793
265	117	3	0	0.78538	1.00000	0.50987	1.00000	0.51349	0.76773
266	114	3	0	0.76471	1.00000	0.49645	1.00000	0.49998	0.74752
267	111	3	0	0.74404	1.00000	0.48303	1.00000	0.48647	0.72732
268	108	3	0	0.72337	1.00000	0.46962	1.00000	0.47295	0.70712
269	105	3	0	0.70271	1.00000	0.45620	1.00000	0.45944	0.68691
270	102	11	0	0.62692	1.00000	0.40700	1.00000	0.40989	0.61283
271	91	3	0	0.60626	1.00000	0.39358	1.00000	0.39638	0.59263
272	88	3	1	0.58559	0.98864	0.37585	0.98902	0.37867	0.57243
273	84	3	0	0.56467	1.00000	0.36242	1.00000	0.36514	0.55198
274	81	3	0	0.54376	1.00000	0.34900	1.00000	0.35162	0.53154
275	78	3	0	0.52285	1.00000	0.33558	1.00000	0.33809	0.51110
276	75	3	0	0.50193	1.00000	0.32215	1.00000	0.32457	0.49065
277	72	3	0	0.48102	1.00000	0.30873	1.00000	0.31105	0.47021

278	69	3	0	0.46010	1.00000	0.29531	1.00000	0.29752	0.44976
279	66	3	0	0.43919	1.00000	0.28188	1.00000	0.28400	0.42932
280	63	3	0	0.41828	1.00000	0.26846	1.00000	0.27048	0.40888
281	60	3	0	0.39736	1.00000	0.25504	1.00000	0.25695	0.38843
282	57	3	0	0.37645	1.00000	0.24161	1.00000	0.24343	0.36799
283	54	3	1	0.35554	0.98148	0.22397	0.98251	0.22588	0.34755
284	50	3	0	0.33420	1.00000	0.21053	1.00000	0.21233	0.32669
285	47	3	0	0.31287	1.00000	0.19709	1.00000	0.19878	0.30584
286	44	3	0	0.29154	1.00000	0.18365	1.00000	0.18522	0.28499
287	41	3	0	0.27021	1.00000	0.17021	1.00000	0.17167	0.26413
288	38	3	0	0.24887	1.00000	0.15678	1.00000	0.15812	0.24328
289	35	3	0	0.22754	1.00000	0.14334	1.00000	0.14457	0.22243
290	32	3	2	0.20621	0.93750	0.12178	0.94339	0.12360	0.20158
330	27	1	9	0.19857	0.66667	0.07818	0.68450	0.08147	0.19411
630	17	1	0	0.18689	1.00000	0.07358	1.00000	0.07668	0.18269
720	16	8	2	0.09345	0.87500	0.03219	0.93754	0.03594	0.09135
1079	6	1	0	0.07787	1.00000	0.02683	1.00000	0.02995	0.07612
1080	5	4	0	0.01557	1.00000	0.00537	1.00000	0.00599	0.01531
1081	1	0	1	0.01557	0.00000	0.00000	0.15853	0.00095	0.01531

Figure 4.1: The Survival Curves for the TB Meningitis data obtained by K-M estimator and Nelson-Aalen estimator

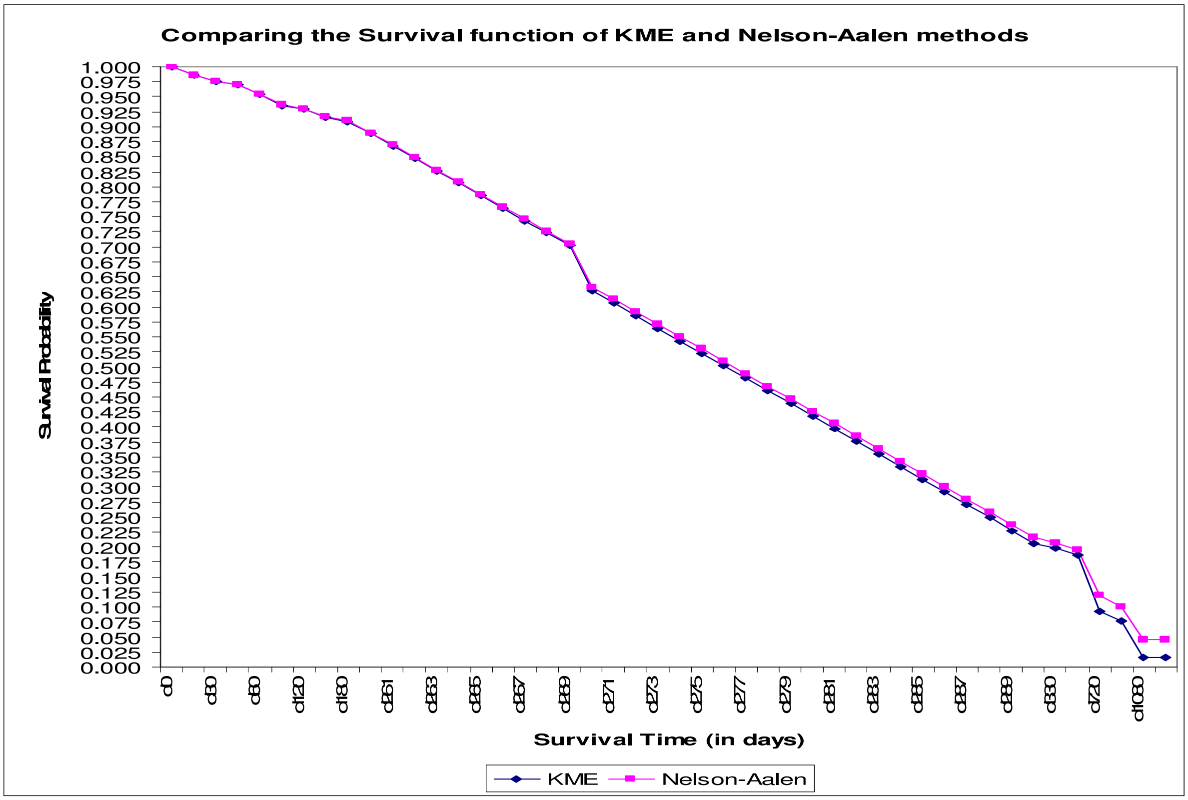

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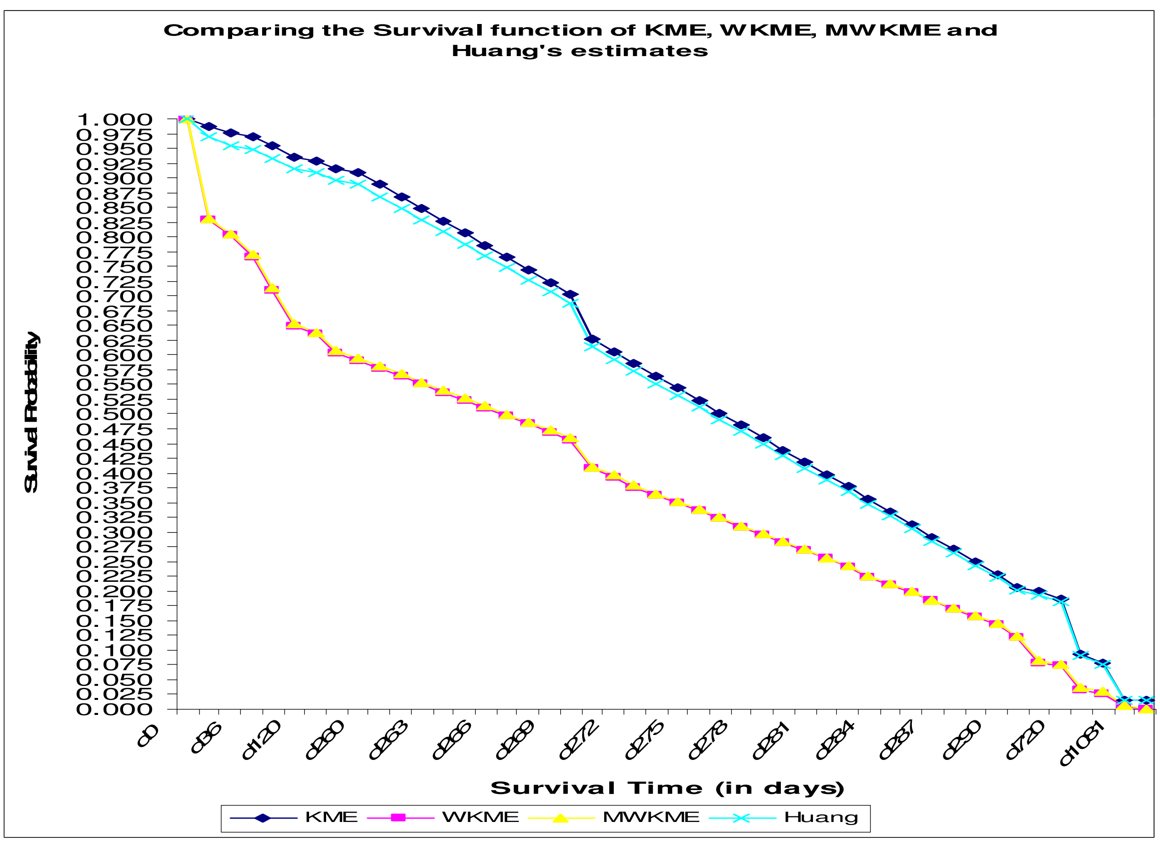
Figure 4.2: The Survival Curves for the TB Meningitis data by Kaplan-Meier, Weighted KME, and Modified Weighted KME and Huang's Estimate.



It is observed from table (Table 4.1) and the associated figure (Figure 4.1) that the Nelson-Aalen method gives slightly a higher probability of Survival than the traditional Kaplan-Meier method at all the time points as expected (Collett, 2003) and in the tail part of the survival times the survival probability is higher than the traditional Kaplan-Meier estimator compared to the initial stages.

As far as the other estimators are concerned the results are presented in Table 4.2 and Figure 4.2. As expected the Kaplan –Meier estimator and the Huang estimator in estimating the survival probabilities perform equally well at different time points. In view of the heavy censoring (49%) the Kaplan Meier estimator is biased and over estimates thr survival probability. Further, as observed by Jan et al.(2005), the Weighted Kaplan-Meier method gives better estimates in the case of heavy censoring. It is further noticed that the Modified Weighted Kaplan-Meier estimator is also in agreement with the Weighted Kaplan-Meier method. By assigning a non-zero weight in the Modified Weighted Kaplan-Meier method the survival probability is also defined for the last censored observation whereas the survival probability is zero in the case of Weighted Kaplan-Meier method, since the weight assigner is zero. Therefore it is concluded that the both the WKME and MWKME address the problem of heavy censoring by removing the bias of overestimating the survival function in the celebrated Kaplan-Meier estimator.

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