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A compression of Kaplan Meier vs. Weighted Kaplan-Meier in Comparing Estimation of Heavy Censoring Data

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Abstract

This study aimed to compare estimations of Kaplan-Meier (K-M) and Weighted Kaplan-Meier (W-K-M) as an alternative method to deal with the problem of heavy-censoring data for Children under-five years, whom do not reach the event of interest during the end period of the study. Usually, this kind of biostatistics study has been estimated based on K-M. In such situations survival probabilities, can be estimated for censored observation by K-M estimator. However, in case of heavy censoring these estimates are biased and overestimate the survival probabilities. For heavy censoring a new method was proposed (Bahrawar Jan, 2005) to estimate the survival probabilities by weighting the censored observations by non-censoring rate. But the main defect in this weighted method is that it gives zero weight to the last censored observation. The survival rates of the patients with standard error estimation based on K-M vs. W-K-M for 5 years shown in **Table 3**. In cases where censoring assumption is not made, and the study has many censored observations, estimations obtained from the K-M are biased and are estimated higher than its real amount. But W-K-M decreases bias of survival probabilities by providing appropriate weights and presents more accurate understanding. Weighted Kaplan-Meier was the suitable method to estimate the Survival Time of these patients, have determined after surgery at Jafar ibn Oaf Hospital for Children in Sudan form January 2012 to December 2016. The five years' survival rate for these patients were evaluated based on K-M and W-K-M. A total of 245(22%) Children<5 years passed away by the end of the study and 853(78%) Children<5 years were censored. The median of survival time for these patients was 16 days.

Keywords: Survival Analysis; Duration; Kaplan-Meier; Weighted Kaplan-Meier; Censored Data.

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1. Introduction

10 diseases have been more prevalent in Sudanese Children, however, could lead to the significant morbidity and mortality. Understanding that children with these diseases present differently than adults and often present with unique risk factors will optimize outcomes in Children. Despite an increased incidence of pediatric, there is often a delay in diagnosis, and cases may remain under or misdiagnosed. Clinical presentation will vary based on the child's age, and children will have risk factors that are less common than in adults [28].

One of the most important prognostic indicators which are considered after diagnosis and treatment for patients is an increase in patients' survival rate particularly in the Sickle cell disease survival rate. Different methods have been designed to estimate the survival rate among which the most common one is the non-parametric Kaplan-Meier method. This method is severely affected by censoring assumption, so that if the patients under study were followed the time in which they were censored, the rate of occurrence of the event among them will be the same as those subjects who were not censored at that time, in other words, it can be said that the censoring has occurred randomly and is independent of the event [9]. The reliability of Kaplan Meier estimations is affected by censoring assumption [11-35]. For example, a study may be terminated with a large number of censoring, which could be due to loss to follow up, withdrawal and alternative outcome than the focused event.

The large number of censored observations results in reducing the number of patients at risk in the following time-points, and the estimations produced by Kaplan Meier of the survival function would not be reliable anymore. High levels of censoring can suggest several problems in the study.

The Quick end (by which most patients do not have an outcome at the end of the study) and a pattern of censoring that makes a lot of subjects be excluded from the study in a specific time, are among these problems. Hence, large number of censored observations make the survival estimations contain error and be estimated higher than their real amounts. Unfortunately, no suitable test determines the validity of the censoring assumption, and this is just a judgment made by researchers. To modify Kaplan-Meier estimations, *Jan* and his colleagues presented a method named Weighted Kaplan-Meier [24-25].

Their study revealed that if there is high censorship (27% in their study), Kaplan Meier estimations will contain an error, and their amounts will be estimated more than actual. Other methods were also presented by *Shafiq* and his colleagues and *Huang* to resolve the problem of Kaplan-Meier unreliable estimations [28-29]. *(Ramadurai* and his colleagues), investigated and reported in the paper all methods and procedures which had been proposed to estimate the survival function up to the time of their study.

Their results showed that Weighted Kaplan-Meier is a suitable method to estimate the survival probability [34]. Thus, this study aimed to determine the survival rate of patients with above 5 types of disease undergone surgery at the most important the researcher used the standard Kaplan-Meier method and Weighted Kaplan-Meier as an alternative method to deal with the problem of high level of censorship.

2. Materials and Methods

The methodology used for in this study to estimate the heavy censoring was, the samples for survival rate with a good prognostic indicator for 1098 Sudanese Children<5 years affected by 5 of the highest 10 types of diseases at Jafar ibn Oaf Hospital for Children in Sudan from January 2012 to December 2016, **Table 1**. 1098 patients with the following data were studied: 1) the patients had been hospitalized and had undergone surgery from 2012-2016 in surgical wards of Sudan at Jafar ibn Oaf Hospital for Children, 2) they had records in the archives of the hospital, and in their files, their addresses and phone numbers were available for subsequent follow-ups. The survival time of patients was determined after surgery and those patients who were still alive at the end of study period or the ones whose data were not available after a specific time-period were censored. Data analyzed by statistical packages "NCSS or XLSTAT" that K-M and W-K-M were used to estimate the survival rate of patients after surgery, however, the Weighted Kaplan Meier was significant statically in dealing with heavy-censoring data.

3. Survival Analysis

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 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. 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 and his colleagues (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 K-M (1958) method for estimating the survival function. 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) 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 and his colleagues 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* and his colleagues *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 those 5 diseases Meningitis data, by comparing the estimated survival probabilities obtained through the above-mentioned methods.

Survival data means the time observed for any individual who are undergoing in an experimental study from a well-defined time origin until the occurrence of some 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 a disease prevalent among children<5 years.

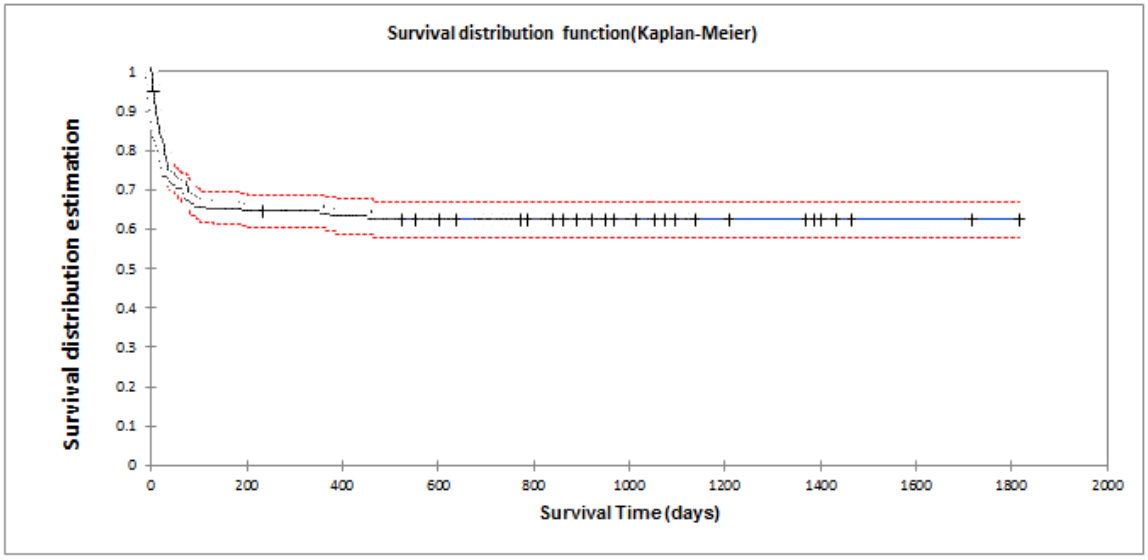

Figure 1: Kaplan-Meier curve for the time probability of 5 samples of diseases during 5 Yrs.

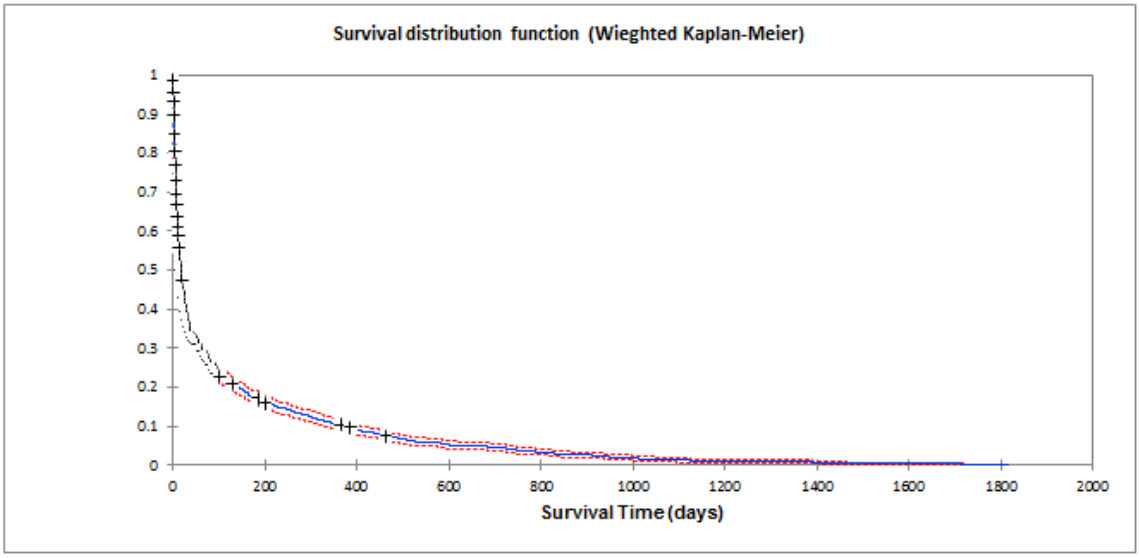

Figure 2: Weighted Kaplan-Meier curve for the time probability of 5 samples of diseases during 5 Yrs.

3.1 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 affected Children.

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 withdraw 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 whereas 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".

3.2 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 □ *t); t>0, if F(t)*

is the cumulative distribution function of *t*, then

F(t)=P (T □ *t)* □ *1* □ *S(t).* (1)

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*. Then 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

$$h(t) = lim_{\Delta t \to 0} \frac{P(t \le T < t+\Delta t)/T \ge t)}{\Delta t} = \frac{f(t)}{S(t)} \quad (2)$$

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)* ≥ *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)* population indicates the type of risk to which the under study is exposed as a function of time. The cumulative hazard function is denoted by *h(t)* and is defined as *t.*

$$H(t) = \int h(x)dx = -\log S(t) \quad (3)$$

3.3 Kaplan-Meier vs. Weighted Kaplan-Meier

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 n is the total number of monitored participants in the study and $t_1, t_2, ..., t_n$ are the observed times. The survival time of some of these patients may have been censored. So, we assumed that the number of focused outcomes is r in which $r \le n$ and $t_{(1)} \le t_{(2)} \le \cdots \le t_{(r)}$ will be patients' ordered event times. Now, the number of patients who have survived before $t_{(j)}$ (including those who have died at this time) is $n_{(j)}$, and the number of those who have focused outcome at $t_{(j)}$, is d_j, $(1 \le j \le r)$ Therefore, in the time interval less than t which is shown in $\widehat{S}(t)$, the Kaplan-Meier estimator is as follows:

$$\widehat{S}(t) = \prod_{j:t_{(j)}<t} \left\{ \frac{n_j - d_j}{n_j} \right\} \quad (4)$$

If $t \le t_{(1)}$ in which $t_{(1)}$ is the smallest survival time observed, so $\widehat{S}(t) = 0$.

To calculate the Weighted Kaplan-Meier method in this study, a method provided by Jan and his colleagues was used (12-13). They showed that when a considerable proportion of observations were censored, Kaplan-Meier estimation would be unreliable and inefficient. As in Kaplan-Meier we assumed, C_J is number of censored patients at $t_{(j)}$ and W_J is the weights of censored observations. As the rate of un-censoring will be as follows:

$$W_J = \left\{\frac{n_j - c_j}{n_j}\right\}$$

If $t_{(j)}$ is one event-time, $W_J = 1$ and if $t_{(j)}$ is a cencored time, $0<W_J<1$. Now, the Weighted Kaplan Meier estimation is defined as follows:

$$S^*(t) = \prod_{j:t_{(j)}<t} W_J \left\{\frac{n_j - d_j}{n_j}\right\} \qquad (6)$$

In this formula, $S^*(t)$ solves the problem of overestimation (that existed in the Kaplan-Meier estimations) by proper weighing.

4. Type of Diseases

Acute renal failure (ARF) is defined as an acute decline in renal function characterized by an increase in blood urea nitrogen (BUN) and serum creatinine values, often accompanied by hyperkalemia, metabolic acidosis, and hypertension. Significant morbidity and mortality can accompany ARF. Children<5 years who have ARF recover their renal function either partially or completely or they develop end-stage renal disease. They also may develop associated multiorgan disease. ARF is divided into three forms: prerenal failure (most common), intrinsic renal failure, and post renal failure. Treatment ranges from conservative medical management to dialysis or renal transplantation, depending on the severity of kidney disease and degree of renal function recovery. Worldwide, most cases of ARF in children are due to hemolytic-uremic syndrome or volume depletion [22,23].

A congenital heart defect (CHD)1, also known as a congenital heart anomaly or congenital heart disease, is a problem in the structure of the heart that is present at birth. Signs and symptoms depend on the specific type of problem. Congenital heart defects are divided into two main groups: cyanotic heart defects and non-cyanotic heart defects, depending on whether the child has the potential to turn bluish in color. The problems may involve the interior walls of the heart, the heart valves, or the large blood vessels that lead to and from the heart.

Leukemia “Leukemia is the most common cancer in children and teens, accounting for almost 1 out of 3 cancers. Most childhood leukemia’s are acute lymphocytic leukemia (ALL). Most of the remaining cases are acute myeloid leukemia (AML). Chronic leukemia’s are rare in children.”; Septicemia “*Septicemia* is an infection of the blood,

[1] "Factors Contributing to Congenital Heart Disease". *Lucile Packard Children’s Hospital at Stanford.* Archived *from the original on 4 July 2010*. Retrieved 30 July 2010.”

also known as bacteremia or blood poisoning. ... *Septicemia* is a serious bloodstream infection. ... *Septicemia* occurs when a bacterial infection elsewhere in the body, such as in the lungs or skin, enters the bloodstream"; Sickle cell disease" Sickle cell disease is an inherited blood disorder characterized by defective hemoglobin (a protein in red blood cells that carries oxygen to the tissues of the body)."

Table 1: Kaplan-Meier for estimating the survival function (Events)

Stratum	Total observed	Total failed	Total censored	Time steps(days)
Acute Renal Failure	100	22	78	51
Congenital Deformity Heart	104	34	70	53
Leukemia	98	19	79	70
Septicemia	483	155	328	75
Sickle cell disease	313	15	298	195
Overall	1098	245	853	444

Table 2: The total of Children<5 yrs. Death and censored during the study period

Total observed	Event 1	Total Censored
1098	245	853

5. Results

This study was conducted on 1098 patients of Children<5 years undergone surgery, 100 with Acute Renal Failure (22 died, 78 censored and median of survival time was16 days); 104 with Congenital Deformity Heart (34 died and 70 censored and median of survival time was 16 days); 98 with Leukemia (19 died and 79 censored and median of survival time was 16 days); 483 with Septicemia (155 died and 328 censored and median of survival time was 6 days) and 313 with Sickle cell disease (15 died and 298 censored and median of survival time was 16 days)). Totally status of these patients was 245(22%) died by the end of the study and 853 (78%) were censored **Table 1**. The general survival median time of Children patients was 16-day survival rates per disease, as well as standard error and a 95% confidence interval for both methods. The result based on Kaplan Meier method these estimations and the estimations calculated a according to Weighted Kaplan-Meier were presented in **Table 3**, respectively. The results showed that Weighted Kaplan-Meier presents better estimations (lower standard errors and shorter confidence intervals). Survival probabilities derived from both methods are shown in **Figure 3**.

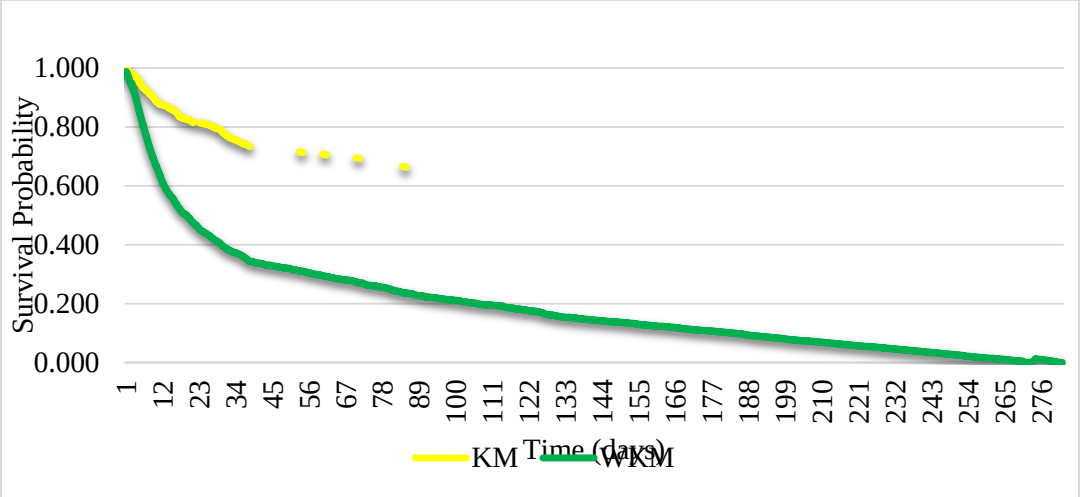

Figure 3: The Survival Curves for Children<5 years for 5 diseases using K-M) and W-K-M

Methods as **Figure 3** illustrates, the estimations derived from both methods are approximately close to each other at the beginning of the study where the rate of censoring was low. But as time passes and the rate of censoring increases, Kaplan-Meier estimations always estimate the survival probabilities more than their real amounts whereas Weighted Kaplan-Meier presents more accurate estimations for patients' survival by placing appropriate weights for censored observations.

6. Conclusion

The Five years survival rate for all 5 diseases affected Children<years were estimated 0.98% based on Weighted Kaplan Meier which was lower than Kaplan-Meier estimation (0.99%) as in Table 3. The high survival rate estimated by Kaplan-Meier during study period was not unexpected because Kaplan-Meier-known as a standard method for estimating such probabilities was severely affected by the censoring assumption. In cases where this assumption was violated (high levels of censoring), it causes biased estimations in the results of the study. Therefore, high levels of censoring affect the reliability of Kaplan-Meier estimations. Unfortunately, no good test is available to check the censoring assumption except this judgment made.

Generalization of Kaplan-Meier method with proper weights causes unbiased estimations of survival probability at any time. As shown in **Figure 3**, at the beginning of the study the rate of censoring is low and the estimations of both methods are nearly identical, but as time goes by the end of the study and as the censored observations increase, the discrepancy between the estimations of two methods arises. **Table 3** also showed that Weighted Kaplan-Meier estimations had lower standard errors and shorter confidence intervals and revealed that a more accurate statistical analysis can be made based on them. Moreover, one of the problems existing in Kaplan-Meier survival curve with the last censored observation is the fact that the survival function for observations after that time is indefinable (10). But the survival curve of Weighted Kaplan-Meier using proper weighing reaches the horizontal

axis even if the last observation is censored.

Table 3: The Five years survival rate estimation and 95% confidence interval by K-M and W-K-M for 5 diseases

Disease Type	Kaplan-Meier Estimation (SE)	Weighted Kaplan-Meier Estimation (SE)	95% CI K-M	95% CI W-K-M
Acute Renal Failure	0.99 (0.0153)	0.98 (0.0077)	0.7576-0.8045	0.1470-0.1515
Congenital Deformity Heart	0.99 (0.0157)	0.98 (0.0077)	0.7469-0.7944	0.1472-0.1518
Leukemia	0.99 (0.0152)	0.98 (0.0077)	0.7619-0.8089	0.1475-0.1521
Septicemia	0.99 (0.0147)	0.98 (0.0078)	0.7832-0.8290	0.1487-0.1534
Sickle cell disease	0.99 (0.0147)	0.98 (0.0079)	0.7791-0.8257	0.1482-0.1528

Large amounts of censoring in Kaplan-Meier method causes survival probability to be constant at these time-points whereas the number of subjects at risk decreases markedly. The constancy of survival probabilities leads in overestimation but Weighted Kaplan-Meier-using appropriate weights-reduces bias in survival probabilities in censored time-points and resolves the problem of overestimation. Censoring assumption is necessary to estimate survival probabilities; moreover, it is indispensable for common tests in survival analysis. Furthermore, the need for more research has been much felt on alternative methods in cases where the study is teemed with censored observations.

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