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Let's Flip: An Approach to Understand Median Follow-up by the Reverse Kaplan-Meier Estimator from a Statistical Programmer's Perspective

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ABSTRACT

In time-to-event analysis, sufficient follow-up time to capture enough events is the key element to have adequate statistical power. Achieving an adequate follow-up time may depend on the severity and prognosis of the disease. The median follow-up is the median observation time to the event of interest, which is an indicator to see the length of follow-up. There are several methods to calculate median follow-up, and we have chosen to use the more robust and code-efficient reverse Kaplan-Meier (KM) estimator in our paper.

Median follow-up is a less commonly presented descriptive statistic in reporting survival analysis result, which could pose some challenges to understand. This paper aims to provide the concept of median follow-up, the statistical interpretation of median follow-up both numerically and visually, and the SAS® LIFETEST procedure to delineate survival plots and compute survival function using the reverse KM estimator. We present a simple and robust approach of calculating median follow-up using the reverse Kaplan-Meier estimator by flipping the meaning of event and censor (Schemper and Smith, 1996), i.e., event becomes censor while censor becomes the endpoint.

INTRODUCTION

In oncology studies, we use a lot of time-to-event analysis, which is to assess the time up to the event of interest, like from treatment to death, disease relapse or progression. Time and event are two major components of survival analysis. Whether or not a subject experiences the event of interest during the study period is depicted using an indicator variable often coded as 1=event occurred or 0=event did not occur during the study observation period. Censoring these components provides the basis for the analysis. Observations are called censored when the information about a subject's survival time is incomplete; the most commonly encountered form is right censoring. Right censoring occurs when a subject leaves the study before an event occurs, or the study ends before the event has occurred. Completeness of follow-up is important, especially in clinical trials, since unequal follow-up in the treatment groups can bias the analysis of results. In survival studies, information on participants who do not complete the study is often ignored as their data can be included up to the time at which they were lost to follow-up. Accuracy to quantify follow-up is very important to a study.

Time to event studies must have sufficient time to follow-up to capture enough events and thereby ensure there is sufficient power to perform appropriate statistical tests. The follow-up time of the subject is affected by the severity of the disease and its prognosis. For example, a 5-year follow-up may be sufficient for a lung cancer trial to capture enough events of interest, but this follow-up duration will only give a short-to-medium-term indication among breast cancer patients as a result of the better prognosis of breast cancer (Clark, Bradburn, Love & Altman, 2003). So, the length of follow-up is important to report because the findings of a study should be extracted from the time frame in which most of the subjects have had the event or remained under observation. This time frame is where the Kaplan-Meier estimate is most stable (Betensky, 2015). The median follow-up time is to understand the median time to censoring, the median observation time for subjects who are event-free at the end of study.

EXISTING STATISTICAL METHODS

Based on Schemper and Smith (1996), there are several methods used to estimate median follow-up time. Time to follow up can be quantified using the methods below. We would like to briefly introduce the pros and cons of each.

Observation time (T-OBS): Observe the follow-up time based on all subjects in the study. The time of follow-up is the time from study start to the time the last subject has an event or is censored. The pro is that it includes all subjects in the study. However, it may underestimate the median follow-up time when the study has a higher risk of early events, as it is directly affected by the observed time of event.

Censoring time (T-CENS): Observe the follow-up time based on the censoring of subjects in the study. The time of follow-up is from the study start to the time the last subject is censored. This method may systematically underestimate median follow-up time because it only takes into account the censoring data. It may not be stable or available for median follow-up time if the number of survivors is small.

Time to end-of-study (T-END): The time of follow-up is from study entry to the end of study. Subjects who die or leave the study will not affect the analysis in this method. Though it would not suffer from the loss-to-follow-up, it obviously would overestimate the follow-up time.

Known function time (KFT): This method is a mixture of methods 1 and 3.It uses the known observation time of event and censor, which is event time for the event subjects and study end time for censored subjects. It tends to overestimate follow-up time.

Reverse Kaplan-Meier (Reverse KM): This method is calculated in the same way as the Kaplan-Meier estimate of the survival function, but with the meaning of the status indicator reversed so that our event of interest becomes the censor. So here the censor becomes event (S=0) data and the event of interest becomes subjects censored (S=1) on the study. For example, death of a subject will be censored with unknown observation time. This way the unobservable follow-up time of that subject is interpreted as the follow-up time.

Korn's potential follow-up (KORN): This method takes the risk of loss-to-follow-up, and combines it with the reverse Kaplan-Meier method. It has been cited as taking much computation effort.

REVERSE KAPLAN-MEIER APPROACH

Our focus is on the reverse KM method for median follow-up for which we will use sashelp.*BMT* data as an example to demonstrate the program snippet and output. At the time of transplant, each patient is classified into one of three risk categories: ALL (acute lymphoblastic leukemia), AML-Low Risk (acute myelocytic leukemia, low risk), and AML-High Risk, which are defined in the GROUP variable. The endpoint of interest is the disease-free survival time, which is the time in days to death, relapse, or the end of the study. It is defined in the STATUS variable (1 is an event and 0 is censored).

The reverse KM method weighs in more advantages over other methods. It combines the advantage of Korn's potential follow-up to overcome the underestimate follow-up time bias. From the Schemper and Smith (1996) article, the reverse KM method was approximately as robust as Korn's method, irrespective of increasing survival hazard or subject-loss hazard. However, with the available computer program for KM, reverse KM is comparatively easy from a computational perspective. Therefore we would like to choose reverse KM as our method to estimate time of median follow-up in this paper.

For this purpose, we use the reverse Kaplan–Meier estimator to use all subjects in the analysis. It is done by just reversing the censoring status indicator for the endpoint. Below is the program snippet where "STATUS" is the censoring variable with values of 0 or 1. The program aims to calculate median follow-up time for the population set with overall survival as the endpoint. The censored subjects are reverted back to uncensored while quantifying follow-up time here in this method, STATUS=1 from STATUS=0.

```
proc lifetest data=bmt method=pl alpha=.05 outsurv=ci95 plots=survival;
    time T_M*STATUS(1);
    strata GROUP;
run;
```

We would like to see the follow-up time among ALL, AML-High Risk and AML-Low Risk groups, so in the reverse of the normal KM method, we used disease progression (STATUS=1) as censored here, as those subjects are censored with unknown follow-up time. The rest of parameters are used as in KM, which uses follow-up time in months (T_M) as the time variable, analyzed by disease (GROUP).

Figure 1 presents the median follow-up time of each group in a tabular format. Overall, the follow-up time is 49.5 months (95% CI 45.1, 55.3) for subjects in the study. For the ALL group, median follow time is 44.0 months (95% CI 36.7, 48.3), AML Low is 51.8 months (95% CI 45.8, 60.9), and AML High is 66.9 months (95% CI 37.6, 74.4).

In Figure 2. The KM Plot with Median Follow-up Time for Disease Groupswe used the Wu (2018) mKMplot macro to generate the KM plot in follow-up time. It is done by just reversing the censoring status indicator for the endpoint. Here, the event is subjects censored at disease progression, median is the median follow-up time, and the number of subjects is still the subjects in the study (at risk).

Table: Follow-Up Time for Disease Free Survival

	ALL (N=38)	AML-Low Risk (N=54)	AML-High Risk (N=45)
Median duration of follow-up for Disease Free Survival (months) (95% CI)	44.0 (36.7, 48.3)	51.8 (45.8, 60.9)	66.9 (37.6, 74.4)

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Figure 1. The Table of Follow-up Time for Disease Progression.

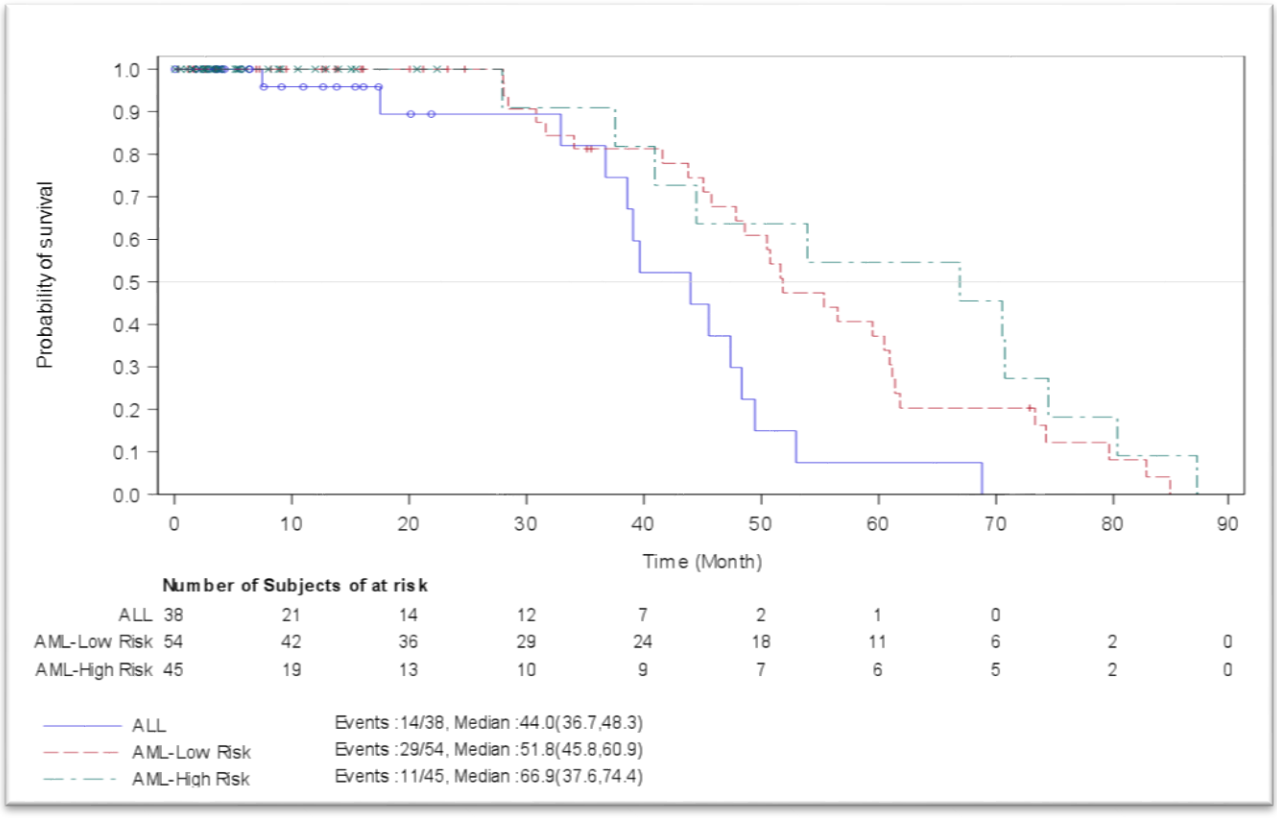

Figure 2. The KM Plot with Median Follow-up Time for Disease Groups

```
%mKMplot ( _indata= BMT
           ,_timevar= T_M
           ,_censorvar= STATUS(1)
           ,_stratavar= GROUP
           ,_tinterval= 10
           ,_ref= 0
           ,_stratalis=
           ,_datafl=
           ,_header= "Figure 1: Kaplan-Meier Plot of Median Follow-up"
           ,_Xlabel= "Time (Month)"
           ,_Ylabel= "Probability of follow-up"
           ,_ARtitle="Number of Subjects of at risk"
           ,_Refline= Y
           ,_fnmed= Y
           ,_fnhr= N
           ,_fnp= N
           ,_outtype=rtf);
```

CONCLUSION

Combining the advantages of robust modeling and computational ease, reverse KM is the approach we would like to recommend for calculating follow-up time in oncology clinical trials.

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