

SAS® Macros for Time – Dependent Effects and Risk Factors on Survival

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ABSTRACT

In traditional Kaplan-Meier or Cox regression analysis, typically a risk factor measured at baseline is examined for its association with survival thereafter. During follow-up however, things may change, such that either the effect of a fixed baseline risk factor may vary over time, resulting in a weakening or strengthening of associations over time, or the risk factor itself may vary over time. In the former case, such as effect is often seen in what appears to be significant differences in survival not necessarily overall, among all survival times, but early on or at later survival times. We address such time-dependent effects on survival by creating two SAS® macros, one for landmark and another for quantile survival regression. As opposed to the currently available SAS® procedure for quantile survival regression, our quantile survival analysis macro includes a test for significant differences among the levels of a categorical covariate within quantiles of survival time by constructing a plot of the estimated difference in survival time between levels of a categorical covariate that are shown along with 95% confidence intervals (CI). Using these plots, the significant quantiles are readily identified based on whether or not the 95% CI includes zero or not and the corresponding survival times are also displayed. For addressing a baseline risk factor known to vary at a single fixed a priori specified time (a.k.a., landmark time), we developed a SAS® macro for landmark survival analysis that constructs Kaplan–Meier plots in two parts: pre- and post-landmark, along with log-rank p-values.

INTRODUCTION

The traditional Kaplan-Meier or Cox regression analysis summarizes the mean or median on the lifetime distribution. While lifetime distributions are more often of skewness, extreme survival times (short and long survival time) can be of special interest [1]. Also, the association of some covariates, especially for time dependent covariates, may change over time. Quantile survival analysis can implement the distribution of quantiles of the lifetime on its covariates, such as 10th, 20th, 90th percentiles [1]. The SAS® macro %QuantLife_PLOT creates a plot on quantile regression along with a Kaplan–Meier (KM) plot, in which the estimates of differences of survival time between levels of a categorical covariates with their 95% confidence intervals (%95 CI) are shown. Using these plots, the significant quantiles are readily identified based on if the 95% CI include zero and the corresponding survival times are also displayed.

When studying survival, it is not advisable to determine groups at baseline based on something that will happen in the future. Landmark analysis is one of most commonly used approaches for the analysis of these kinds of time-dependent covariates in time-to-event data. It considers response at a fixed landmark time-point, and then removes patients with event or censored before that landmark time-point from analysis. This macro (%Landmark_PLOT) creates a Kaplan–Meier plot in two parts, i.e., pre-landmark and post landmark along with the respective log-rank p-values.

DEFINING MACRO PARAMETERS AND EXAMPLES

1 THE MACRO %QUANTLIFE_PLOT

The macro has 6 parameters in which 5 parameters must be provided by the users when the macro is called: The parameters are listed in Table 1.

Macro Variable	Description	required
DATASET	The name of the data set to be analyzed.	Yes
EVENT	Name of time to event outcome variable.	Yes
CENSOR	Name of censoring indicator variable. Values of 0 indicate censored.	Yes
CLIST	The list of categorical variables. The proc quantile treats higher level as reference. It permits list multiple variables.	Yes
FILENAME	File name for output table.	Yes
OUTPATH	File path for output table to be stored.	Yes
DEBUG	Set to T if running in debug mode. Work datasets will not be deleted in debug mode. This is useful if you are editing the code or want to further manipulate the resulting data sets. The default value is F.	Optional

Table 1. Parameters and the description for %QuantLife_PLOT macro.

DRUG ABUSE STUDY EXAMPLE

The example dataset uses drug abuse data from Hosmer and Lemeshow [2]. This study focuses on the treatment effect on reducing drug abuse. We use the macro to perform quantile regression to analyze survival times and create plots. The main variables of the dataset are as below.

Time: time to return to drug use (days)
 Status: event indicator, 1= return to drug use, 0= censored time
 Age: age at enrollment (years)
 Race: 1= White 0= non-White
 Treatment: 1= six-month treatment 0= three-month treatment

The following SAS® program is used to conduct the quantile survival analysis:

```
Title "Figure 1 Plot of Quantile Survival for Different Treatment";
%QuantLife_PLOT (DATASET=UIS,
                  EVENT=TIME,
                  CENSOR=CENSOR,
                  CLIST =treat,
                  OUTPATH= C:\Users\Chao\Documents\,
                  DEBUG=t);
Title;
```

So far, there are no additional options in PROC QUANTLIFE for controlling the reference level of a categorical variable. This coding scheme creates underlying binary dummy variables in the model where the last sorted level of the CLASS variable is the reference level. If formats are applied then the sorted order of the formatted values determines the "last" level. The only way to manipulate the reference level is to change the values of the CLASS variable in a prior DATA set and/or apply a format. The order of format should be consistent with data values, for example, race: 0=AA, 1=White, but not:

1=AA, 0=While [3, 4] (Figure 1).

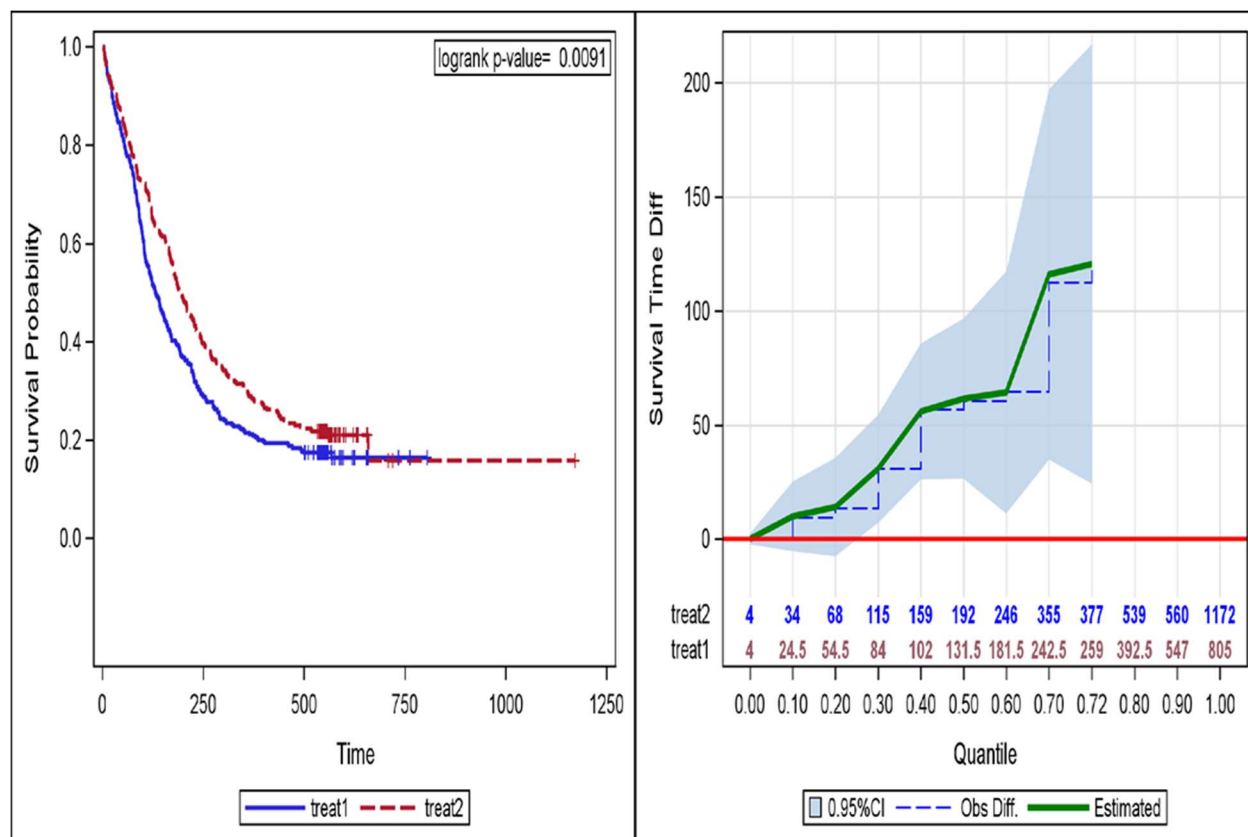


Figure 1. Plot of Quantile Survival for Different Treatment

As seen in Figure 1, the KM plot (left) shows significant differences between the two treatments (the log rank test $p = 0.009$). The plot of quantile survival analysis (right) shows that the treatments are significantly different after the 25th percent quantile time. The plot does not show the estimated difference curve, the observed difference line and the 95% CI band after the 72nd percent quantile time as there are no events at or after that time-point.

2 THE MACRO %LANDMARK_PLOT

The landmark method was introduced by Anderson *et al.* in the journal of Clinical Oncology in 1983 [5]. This paper addressed the issue of bias in the analysis of survival of “responders” and “non-responders”, since the response status was not determined at the start of the study. In another words, “responders” versus “non-responders” is something that is not known at baseline as it is a time-dependent covariate. So it is unreasonable to make groups based on something that will happen in the future. To understand the idea of landmark approach, we take the Stanford heart transplant data as an example [6]. Patients are permitted to be on a waiting list and the time to event is calculated as the time from admittance to the waiting list until death, which may be subject to censoring. We are interested in the effect of heart transplant on survival. Heart transplant, a time-dependent covariate, is initially assigned as 0, and gets the value 1 when patient receives a heart transplant. At the landmark time, patients who have an event or are censored before this time point are removed and the two groups compared, i.e., the group with a heart transplant

received before or at landmark, the other group without, using a traditional Kaplan-Meier or Cox regression model.

This macro has 9 parameters and first 8 parameters must be provided by the users when the macro is called. The parameters are presented in Table 2.

Macro Variable	Description	required
DATASET	The name of the data set to be analyzed.	Yes
EVENT	Name of time to event outcome variable.	Yes
CENSOR	Name of censoring indicator variable. Values of 0 indicate censored.	Yes
LANDMARK	The value of fixed time point, for example 200 days after treatment.	Yes
T_DEPENDENT	Variable of waiting time, such as waiting time for transplant.	Yes
VAR_DEPENDENT	Time-dependent variable (category variable)	Yes
FNAME	File name for output table.	Yes
OUTPATH	File path for output table to be stored.	Yes
DEBUG	Set to T if running in debug mode. Work datasets will not be deleted in debug mode. This is useful if you are editing the code or want to further manipulate the resulting data sets. The default value is F.	Optional

Table 2 Parameters and the description of %Landmark_PLOT macro.

HEART TRANSPLANT EXAMPLE

The dataset consists of 103 cardiac patients who were enrolled in the transplantation program between 1967 and 1974 [6, 7]. After enrollment, patients waited different lengths of time until a suitable donor heart was found. Patients were followed until death or until the termination date of April 1, 1974. Of the 69 transplant recipients, only 24 patients were still alive at termination. The data set contains the following variables which will be used in the macro.

SURV: is the survival time (or censoring time) in days.

DEAD: 1=dead 0=alive

Wait: waiting time before transplant

Trans: transplant indicator 1= transplant 0=non-transplant

The following code was used to generate landmark plot for time-dependent covariate, 'Trans':

```
Title 'Figure 2 landmark plot for transplant';
%Landmark_PLOT (DATASET=wk,
                EVENT=SURV1,
                CENSOR=dead,
```

```

LANDMARK=200,
T_Dependent=wait,
Var_Dependent =trans,
OUTPATH= C:\Users\Chao\Documents\,
FILENAME=landmark plot for transplant,
DEBUG=t);

Title ;

```

Figure 2 shows the output of the landmark plot. As seen in the figure, survival is significantly different between transplant and non-transplant group ($p < 0.0001$), whereas, the conclusion is inverse if we consider transplant to be a time-dependent covariate ($p = 0.975$).

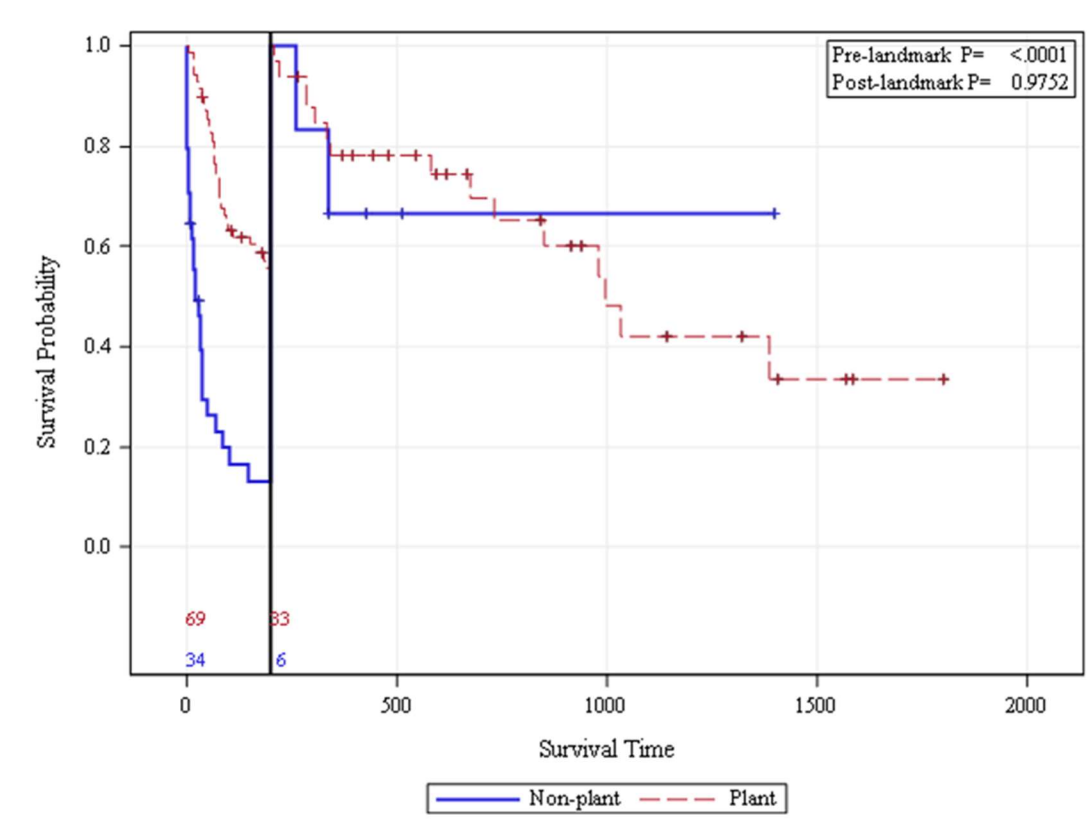


Figure 2 Output Produced by %Landmark_PLOT macro

CONCLUSION

When the effects of covariates on the lifetime distribution differ with the covariate level, quantile regression is especially useful. The plot created by the quantile survival analysis macro includes a test for significant differences among the levels of a categorical covariate within quantiles of survival time. Using these plots, the significant quantiles are readily identified based on if the 95% CI includes zero or not and the corresponding survival times are also displayed.

In case of time to event data, the effect of the time - dependent covariates is not the same as that of a time-independent covariate and thus it is unadvisable to define groups at the beginning of the study based on something that will happen later. Landmark analysis considers response at fixed point in landmark time and calculates the effect of the covariate pre- and post-landmark time point in two separate KM plots. The output from these two macros can be directly used for presentations and publications.

The syntax of the macros is too detailed to be provided in appendix of this paper. Please free contact the author directly to get the two macros.

REFERENCES

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