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Two Shades of Gray: Implementing Gray's Test
for Equivalence of CIF in SAS 9.4

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Abstract

Prior to SAS 9.4, the only way to test for equivalence over CIFs for competing risks in survival analysis was to use the %cif macro. With the implementation of SAS 9.4 this test can be easily achieved using PROC LIFETEST. This paper will highlight, using a dataset of survival data, the two methods of completing this task in SAS with emphasis on the differing output and how the calculations vary slightly. The goal will be for the user to save time by switching from the macro and to begin using the standardized method through PROC LIFETEST.

Introduction

Survival Analysis is typically defined as the group of statistical methods used to analyse data that can occur over a period of time, with the outcome normally being a binary variable of occurrence vs. nonoccurrence (Kleinbaum and Klein, 2012). This technique most often is used in situations where death is an outcome, hence the "survival" aspect.

This type of data is often sensitive, and can have additional bias introduced if standard statistical methodology is applied to it. One such hurdle is the concept of competing risks. This is the idea that a risk that is not the main matter of interest can interfere with the event. For example, if you're studying the time to death for disease X, and disease Y also happens to frequently afflict the population of interest, then disease X and Y are said to be competing risks. Normal Kaplan-Meier (KM) curves and estimates may not sufficiently account for both of these risks as the KM curves may become over inflated, especially when compared to each other. The way this is handled is by looking at the Cumulative incidence functions (CIF) which can be modeled by a cumulative incidence curve (CIC).

A CIC is an alternative to KM graphs in that they estimate the probability that an individual will experience an event of a particular type by time t . This changes in that it doesn't just give an overall probability of having an event but instead breaks it down between all the events of interest (competing risks).

Cumulative incidence functions for each event are calculated. These curves begin at 0 and calculate the probability of that event happening. Gray's Test is used for checking if cumulative incidence curves are the same at all time points t . A significant p-value indicates that we have strong enough evidence to suggest the cumulative incidence curves are not the same at all time points t .

The dataset used is taken from bone marrow transplant patients. This dataset is described in Klein and Moeschberger (2003) and contains data from 137 patients that received a bone marrow transplant grouped into three categories: acute lymphoblastic leukemia (ALL), acute myelocytic leukemia (AML) low-risk, and acute myelocytic leukemia (AML) high-risk. This dataset is extensive with many possible predictors ranging from sex of patient to platelet recovery indicator. For simplicity the authors have chosen to focus only on the groups as the only predictor. The variable “status” was added to the dataset where 0 indicates a censored patient, 1 indicates a patient who relapsed, and 2 where patients died before relapsing. The competing risks in this dataset are relapsing and death.

SAS® Analysis Techniques

Prior to the introduction of SAS 9.4 the most accepted way to conduct Gray’s Test for equivalence of CIFs was to use the %cif macro. Since the introduction of SAS 9.4, the %cif macro has been made a part of the LIFETEST procedure. This implementation of the %cif macro in PROC LIFETEST has made it easier (and slightly quicker) to apply Gray’s Test to competing risks survival data. In addition to the enabling of PROC LIFETEST to use the %cif macro a SAS user can also call upon PHREG procedure to find additional features that will allow them to plot the CIF curves for use in Gray’s Test. This allows for a cleaner, easier output and allows the potential saving of time from having to edit the %cif macro output. The online SAS help documentation for the %cif macro specifies that the functionalities of the macro have been implemented in PROC LIFETEST with SAS 9.4.

PROC PHREG

The first implementation of cumulative incidence curves in a procedure in SAS was done through the PROC PHREG procedure starting in SAS/STAT 13.1 (So, Lin, Johnson, 2014). The authors go into detail (using the same dataset) about how to produce CIC’s using the PROC PHREG procedure. This can be done by building a dataset to be used with the baseline covariates argument. It can further be seen that options for the plot have been specified on the proc line. This is calling for the CIF to be plotted and the overlay command calls for the three groups to be plotted on the same graph. Without the overlay command a user would receive three separate graphs. The following code will produce Figure 1:

```
proc format;
    value DiseaseGroup 1='ALL'
    2='AML-Low Risk'
    3='AML-High Risk';
data risk;
    group=1;output;
    group=2;output;
    group=3;output;
    format group DiseaseGroup.;
run;
```

```

proc phreg data=bone plots(overlay=bystratum)=cif;
  class group;
  model t*status(0)=group/eventcode=1;
  baseline covariates=risk out=_null_/rowid=group;
run;

```

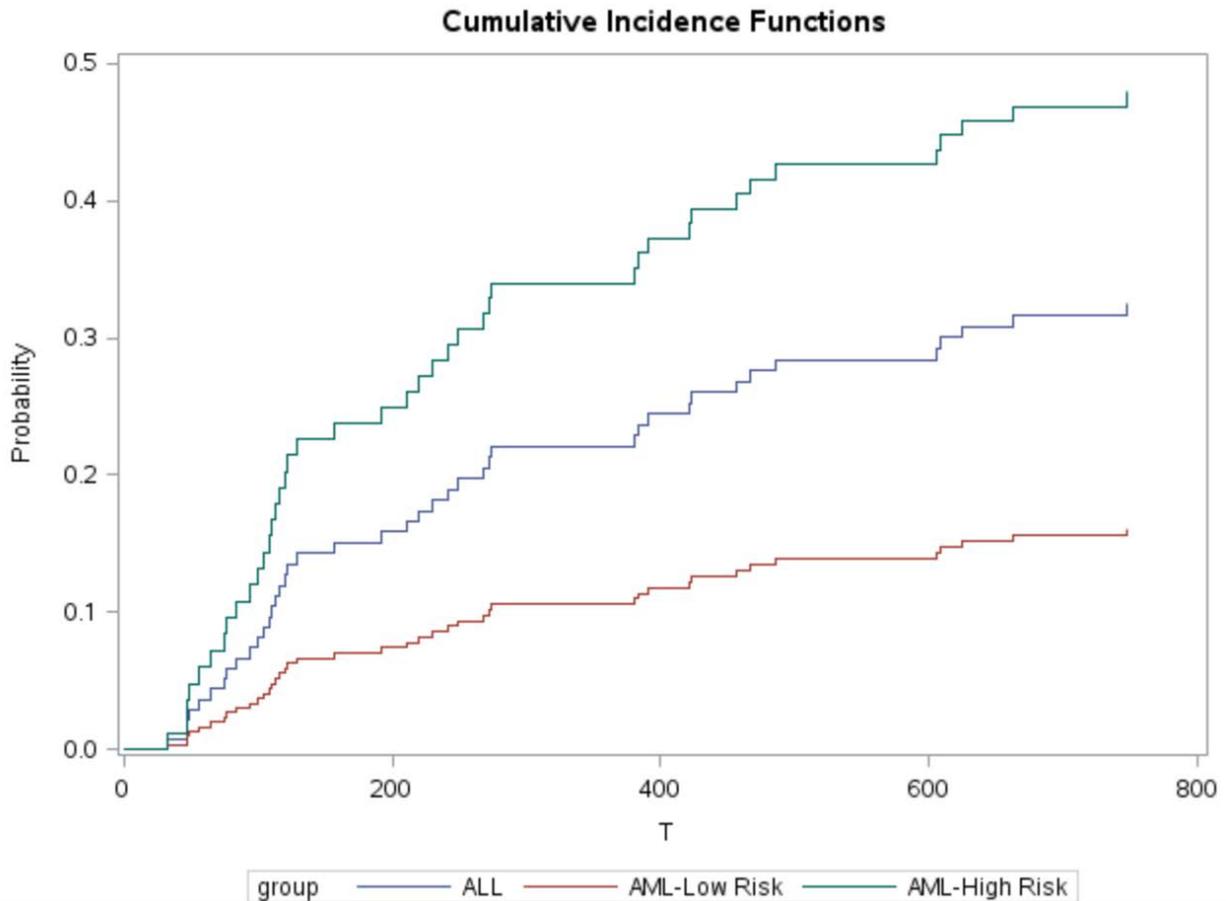


Figure 1. Cumulative Incidence Curves for the groups produced by PROC PHREG

There is a higher risk that a patient diagnosed with AML-High Risk will relapse when compared to those diagnosed with ALL or AML-Low Risk.

%cif Macro

Prior to SAS 9.4 the most utilized way to implement Gray's Test in SAS would be to use the %cif macro. More specifically, one would need to use the SAS/IML package. The macro is preloaded into SAS via the autocall library, so there is no need to run any code to load the macro, one can just call upon the macro at any time.

When calling the macro, a user only need to use the inputs of data, time variable, censoring code, and status code (in any order). But to generate a more specific or desirable output a user

can use other parameters such as title, group, etc. From that point it is rather straightforward using the %cif macro.

The following input will have SAS compute the CIF for event=1 (relapse). The required input is the dataset which is entitled bmt. The time covariate, which in this case is t. The status covariate, which is entitled status. The event code of interest, which is 1 since we will be focusing on relapse. The censoring indicator and whether or not there is any groupings. This code produces a lengthy output:

```
%CIF(data=bone,time=t,status=status,event=1,censored=0,group=group);
```

First a user will see a breakdown of every data point in the dataset. This will give CIF values as well as standard errors. With small datasets this is menial but as datasets become larger and larger this output becomes quite lengthy.

Following this output of the dataset the user will next see the actual CIF curves for the groups in Figure 2.

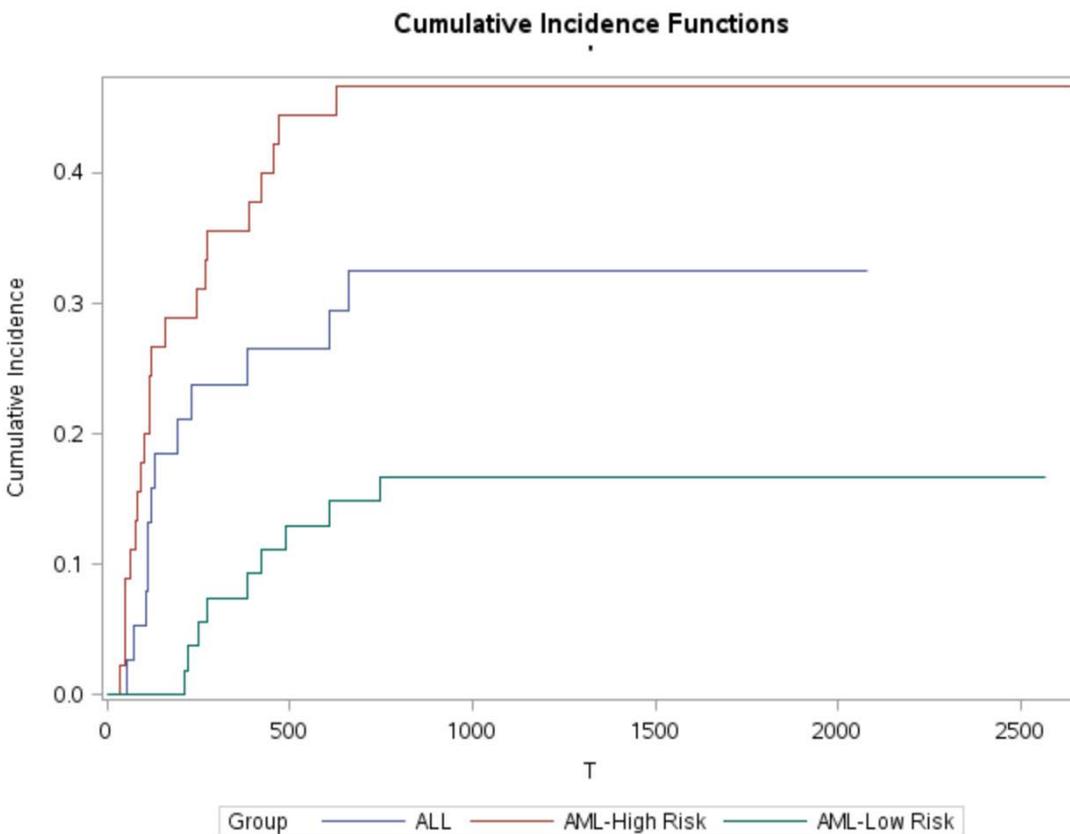


Figure 2. Cumulative Incidence Curves for the groups produced by PROC PHREG

As can be seen above in Figure 2 and as seen earlier using PROC PHREG, there seems to be a notable separation in the CIF curves for the three groups where the ALL group seems to have

a much higher incidence of relapse than the other groups. This would leave us to believe that the chi-square statistic associated with Gray's Test would be significant, meaning there is a significant difference in the CIF for relapse between the groups. And the last part of the output supports that notion with a significant p-value of 0.0026, as shown in Figure 3.

| Chi-Square | DF | Pr > Chi-Square |
|------------|----|-----------------|
| 11.9229 | 2 | 0.0026 |

Figure 3. Chi-Square output for Gray's Test using %CIF macro

PROC LIFETEST

PROC LIFETEST was recently revamped in SAS 9.4 to actually include all of the functionality found in the %cif macro above. The following code is used to produce this output, assuming that the most recent version of SAS/STAT is installed, currently 14.1:

```
proc lifetest data=bone plots=cif(test);  
    time t*status(0) / eventcode=1;  
    strata group;  
run;
```

Running this code invokes calculations similar to the %cif macro and will actually produce almost the same output as above, but within the specified parameters in the PROC LIFETEST statement. The plots option will produce plots of the CIF as well as produce a test statistic and p-value. Once eventcode is specified in the time statement then PROC LIFETEST will perform a CIF analysis and not Kaplan-Meier graphs. You can specify the exact eventcode using the eventcode= option (as above) or you can just type in just "eventcode". If just eventcode is requested, without a specific event, then PROC LIFETEST will calculate the test statistic for all of the competing risks in the given dataset.

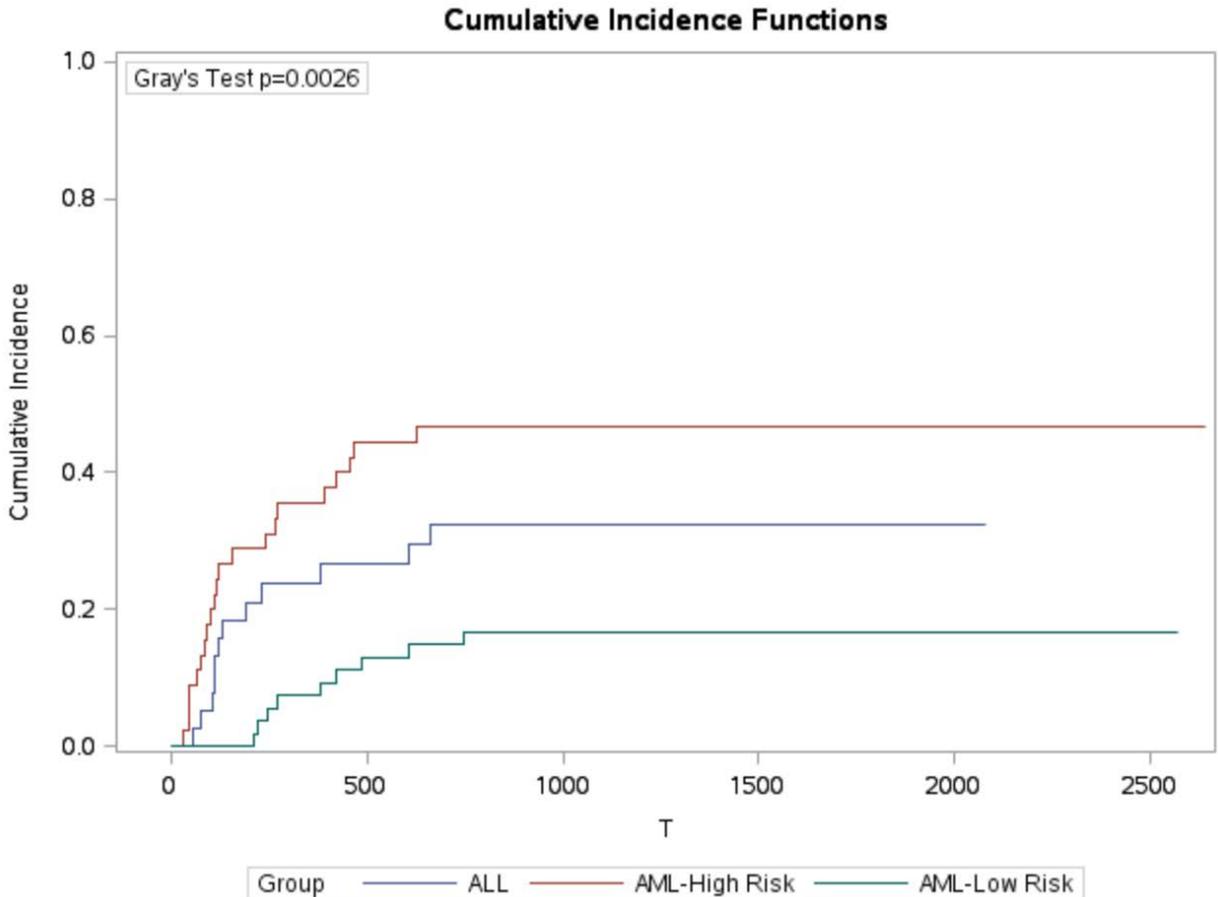


Figure 4. Cumulative Incidence Curves for the groups produced using PROC LIFETEST

Nearly the same graph as above is produced, with some edits in the scaling of the axes and now included in the graph is the Gray's Test p-value. Whether this saves time or space it could be helpful for any presentation or project. Also, the chi-square test statistic is identical to that of the %cif macro. With the new formatting in PROC LIFETEST, the output, shown in Figure 5, is more conveniently titled "Gray's Test for Equality of Cumulative Incidence Functions" compared to just stating "Chi-Square" in Figure 3. This may help to alleviate any confusion about the statistic being used.

| Gray's Test for Equality of Cumulative Incidence Functions | | |
|--|----|-----------------|
| Chi-Square | DF | Pr > Chi-Square |
| 11.9229 | 2 | 0.0026 |

Figure 5. Chi-Square output for Gray's Test using PROC LIFETEST

Conclusion

With the new functionality, the results obtained from the %cif macro are actually built right into PROC LIFETEST, allowing for additional customization. The old method still works, however, so if the only output of concern is for the CIF curves and implementing Gray's test, then the macro may be better suited for that task. However, simplifying and combining macros and procedures is a benefit to the community. The CIF curves are produced in %cif, PROC LIFETEST, and PROC PHREG, but PROC PHREG fails to produce Gray's test statistic or p-value. While most statisticians would rely on more than just a p-value, the CIF curves are helpful in determining significance in differences between CIF curves. Because of this the authors feel that when doing a competing risks analysis one should use either the %cif macro or PROC LIFETEST to truly gather as much information as possible.

References

Klein, J. P., & Moeschberger, M. L. 2003. *Survival Analysis Techniques for Censored and Truncated Data*. New York, NY: Springer-Verlag New York, Inc.

Kleinbaum, D. G., & Klein, M. 2012. *Survival Analysis A Self Learning Text*. New York, NY: Springer Science+Business Media, LLC.

So, Y., Lin, G., & Johnston, G. "Using the PHREG Procedure to Analyze Competing-Risks Data". <<https://support.sas.com/rnd/app/stat/papers/2014/competingrisk2014.pdf>>

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