

Using SAS® Macros to Analyze Lifetime Data with Left Truncation

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ABSTRACT

Like right censoring, left truncation is commonly observed in lifetime data, which requires proper technique to analyze in order to achieve unbiased results. This paper introduces how to analyze such left-truncated lifetime data using the native PHREG procedure, including generating survival estimates, testing homogeneity across samples, as well as generating survival plots. Alternatively, the paper demonstrates two new macro functions, namely %LT_LIFETEST and %LT_LOGRANKTEST, to conduct survival analysis with more flexibility for data with left truncation, such as enabling users to choose specific estimation time points and to perform weighted log-rank tests. The paper also provides updates on the previously presented %LIFETEST and %LIFETESTEXPORT macro functions for generating formatted survival analysis reports with added support for left-truncated data.

INTRODUCTION

In real life survival analyses, time-to-event or lifetime data are often incomplete due to either right censoring or left truncation, which requires special consideration and technique to properly analyze.

Right censoring occurs when there is only partial observation for lifetime up to certain time points [1]. In other words, the event time is unknown to the observers after certain time points. Such time points are often called the right censoring time and such data are considered right censored. For example, in a clinical trial, right censoring could occur when some participants become lost to follow-up or when the trial gets terminated at certain time point. Any events happen after the lost to follow-up time or the termination of the trial are not observable to the researchers.

On the other hand, left truncation occurs when certain individuals are completely unobservable if their event time does not exceed certain time points [1]. Such time points are called left truncation time or delayed entry time. Unlike right censoring, the lifetimes of left truncated individuals do not have any partial observation. In medical research, left truncation could occur when the researchers try to analyze individuals under certain selection criteria that are determined after the starting time. For example, when comparing overall survival since initial diagnosis for patients with chronic myeloid leukemia (CML) who have received hematopoietic stem cell transplantations (HCT) as treatment versus patients who have only received systemic therapies, left truncation would occur for the transplantation arm because patients who failed to survive long enough to be able to receive a transplantation were never being observed. Since such left truncation is often correlated with inferior survival, ignoring it could potentially yield biased results, as in the previous example, by giving the transplantation arm a survival advantage.

In SAS®, the LIFETEST procedure is commonly used to generate survival estimates based on the Kaplan Meier estimator [2] for lifetime data with only right censoring. However, as of version SAS/STAT® 14.3, it is not capable of adjusting left truncation. The PHREG procedure on the other hand can be used to analyze left truncated data by setting the ENTRYTIME= option of the MODEL statement. Although its main functionality is to fit Cox

proportional hazards model [3], it is possible to output crude survival estimates by leaving an empty covariate list in the MODEL statement. Combining with ODS GRAPHICS, it can also be used to generate empirical or unadjusted survival plots for left truncated data.

When comparing lifetime data across multiple samples, homogeneity tests for hazard rates such as the logrank test [4] and Fleming's weighted test [5] are commonly used for data with or without left truncation. The LIFETEST procedure can output p-values of the logrank test and Fleming's weighted test for data with no left truncation. When left truncation occurs, the PHREG procedure can be used instead to perform the score test as part of its global null hypothesis testing [6]. By fitting the group variable as the only covariate in the MODEL statement, the p-value of the score test is equivalent to that of an unweighted logrank test.

However, there are a few disadvantages of using the PHREG procedure to analyze left truncated lifetime data. First, since the main purpose of the PHREG procedure is for estimating hazard ratios based on the Cox regression model, it is not as intuitive to use as the LIFETEST procedure for producing survival estimates. For example, the PHREG procedure does not have the TIMELIST= option that allows users to output survival estimates at selected time points. Secondly, to get both the survival estimates and the score test p-value, two separate models need to be fit, one stratified, and one non-stratified. More importantly, unlike the LIFETEST procedure, currently the PHREG procedure is not capable of performing weighted homogeneity test such as Fleming's weighted logrank test for simultaneous comparison.

In this paper, the author will demonstrate the basic use of the PHREG procedure to analyze lifetime data with left truncation, and to generate survival plots. The author will then introduce two new macro functions, namely %LT_LIFETEST for more intuitive generation of survival probability estimates for left truncated data, and %LT_LOGRANKTEST for producing both the logrank test as well as Fleming's weighted test p-values for left truncated data. The author will also demonstrate the use of the updated %LIFETEST and %LIFETESTEXPORT macros, previously presented at the 2015 SAS Global Forum (Paper 2980-2015) [7], for generating publication ready survival analysis reports in Microsoft Word format with additional support for adjusting left truncation.

DATA SOURCE

Observational research data from the Center for International Blood and Marrow Transplant Research (CIBMTR) were used to demonstrate the use of the SAS codes and macros. Adult patients aged 18 years or above undergoing first allogeneic HCT for CML between 2007 and 2014 were selected (N = 572). The outcome of interest was overall survival where death was treated as the event of interest and lost to follow-up was treated as right censoring. Gender was used as the comparing variable. For the demonstration of analyzing right-censored and left-truncated data, time between the initial diagnosis of CML and death/lost to follow-up was used as the time variable. Since patients who did not have had a chance to receive transplantations were not observable through the registry, the data was left truncated at the time of transplantation.

The data set contains the following variables:

- DEAD 1 = Death, 0 = Lost to follow-up
- INTDXTX Time between diagnosis and transplantation, by months
- INTDXSURV Time between diagnosis and death/lost to follow-up, by months
- SEX 1 = Male, 2 = Female

USING THE NATIVE PHREG PROCEDURE

For left truncated lifetime data, a stratified Cox proportional hazards model without covariates can be fit using the PHREG procedure and the BASELINE statement can be used to generate the product limit survival estimates.

The basic code for such PHREG procedure is shown below:

```
proc phreg data = final;
  strata sex;
  model intdxsurv * dead(0) = / entrytime = intdxstx;
  baseline out = outsurv survival = survival stderr = stderr atrisk =
  atrisk / method = pl;
run;
proc sort data = outsurv;
  by sex intdxsurv;
proc print data = outsurv noobs;
  by sex;
  var intdxsurv survival stderr atrisk;
run;
```

The STRATA statement is used to tell the PHREG procedure to fit the model based on a stratified Cox regression, where the comparing group variable needs to be specified. The next MODEL statement is used to specify the time variable and the event variable. The covariate list of the MODEL statement after the equal sign needs to be left empty and the ENTRYTIME= option of the MODEL statement is used to specify the left truncation time. Under normal scenario, using these two statements combined will be meaningless as they give no hazard ratio estimates since there is no covariate being included in the model. However, by adding the BASELINE statement, they allow the PHREG procedure to generate survival estimates based on the stratified Cox regression model and returns the crude survival estimates for the left truncated data.

The output from the previous PHREG procedure is shown in Output 1, where event time, product limit survival estimates, standard errors of the survival estimates, as well as numbers at risk are listed:

----- Gender=1 Male -----			
intdxsurv	survival	stderr	atrisk
0.000	1.00000	.	23
5.296	0.95652	0.041588	23
7.039	0.93200	0.047043	39
8.454	0.89929	0.050580	57
8.520	0.88294	0.052191	55
9.342	0.86823	0.053322	60
9.375	0.85351	0.054378	59
9.408	0.83880	0.055362	58
...			
----- Gender=2 Female -----			
intdxsurv	survival	stderr	atrisk
0.000	1.00000	.	10
3.980	0.90000	0.09000	10

	5.099	0.84706	0.09827	17
	5.921	0.80248	0.10223	19
	6.053	0.76024	0.10479	19
	6.579	0.72404	0.10559	21
	9.276	0.70393	0.10450	36
	9.836	0.68676	0.10332	41
...				

Output 1. Output from PROC PHREG listing survival estimates for left truncated data

The PHREG procedure can also return the score test p-value as part of the global null hypothesis testing from the Cox regression, which is equivalent to the p-value of an unweighted logrank test and can be used for simultaneous comparison.

The code for fitting such a model is shown below:

```
proc phreg data = final;
  model intdxsurv * dead(0) = sex / entry = intdxtx;
run;
```

The output of the score test is shown as the following in Output 2:

Testing Global Null Hypothesis: BETA=0			
Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	0.9321	1	0.3343
Score	0.9270	1	0.3356
Wald	0.9260	1	0.3359

Output 2. Output from PROC PHREG for the score test

The PROC PHREG statement also provides the PLOTS= option. When combined with ODS GRAPHICS, it can be used to generate survival plots for left truncated data, as demonstrated below:

```
ods listing style = statistical;
ods graphics on / reset = all imagename = "ltphreg" imagefmt = png;
proc phreg data = final plots(overlay = row timerange = (0, 60)) =
survival;
  strata sex;
  model intdxsurv * dead(0) = / entry = intdxtx;
  baseline out = outsurv survival = survival / method = pl;
run;
ods graphics off;
```

The OVERLAY= option is needed here for the PROC PHREG statement to ensure that the survival plots across different strata are output in a single figure, or else it would generate plots in separate figures. The TIMERANGE= option allows the users to control the range of the time axis in the survival figure.

The empirical survival plots for overall survival stratified by sex from the previous code example is shown in Figure 1:

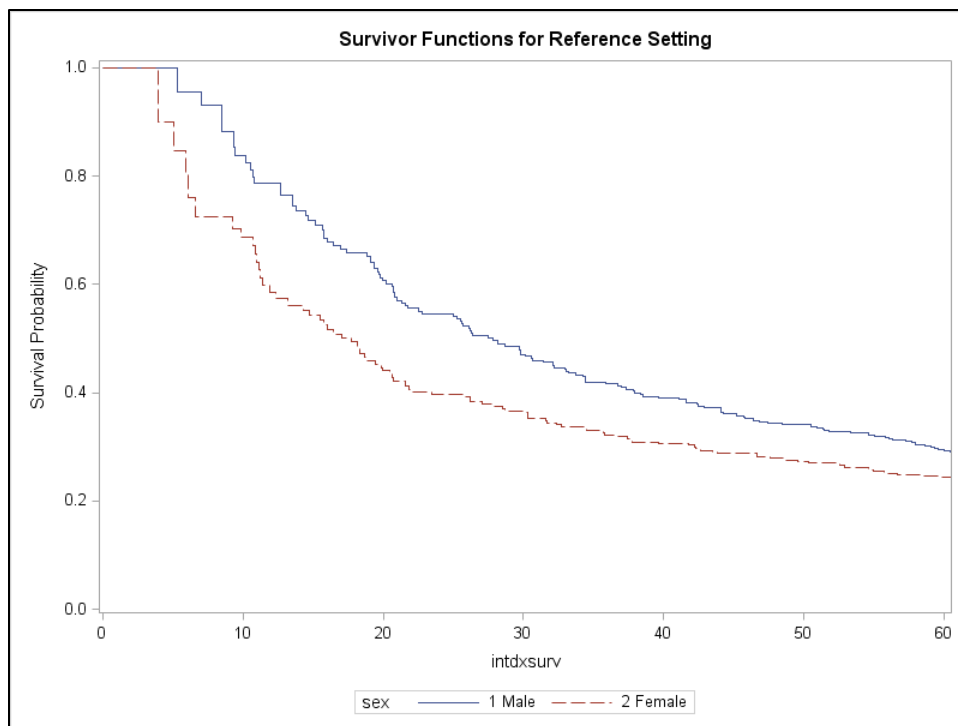


Figure 1. The survival plots for overall survival of left truncated data

USING THE %LT_LIFETEST AND %LT_LOGRANKTEST MACRO FUNCTIONS

The author developed the %LT_LIFETEST and %LT_LOGRANKTEST macro functions for more intuitive analysis of the left truncated lifetime data. The %LT_LIFETEST function is used to generate survival estimates based on the Kaplan-Meier estimator, while the %LT_LOGRANKTEST function is used to generate the logrank test p-value and the Fleming's weighted test p-values.

THE %LT_LIFETEST FUNCTION

The parameters for the %LT_LIFETEST function are:

- INDATA Name of the input data set
- OUTDATA Name of the output data set (optional)
- STRATA Comparing group
- EVENT Event of interest
- INTV Time to event
- LTIME Time to left truncation
- TIMELIST Select output time points (optional)
- NOPRINT Toggle whether print the results (default: 0)

The code for using %LT_LIFETEST is shown as follows:

```
%lt_lifetest(indata = final, strata = sex, event = dead, intv = intdxsurv,
ltime = intdxctx);
```

As shown in Output 3, the %LT_LIFETEST function lists event time, product limit survival estimates, failure rate estimates, standard errors of the survival estimates, numbers at risk, numbers of observed events, respectively:

Survival Probabilities					
----- SEX=1 Male -----					
INTDXSURV	SURVIVAL	FAILURE	STDERR	NUMBERATRISK	OBSERVEDEVENTS
5.296	0.95652	0.04348	0.042523	23	1
7.039	0.93200	0.06800	0.047987	39	1
8.454	0.89929	0.10071	0.051574	57	2
8.520	0.88294	0.11706	0.053165	55	1
9.342	0.86823	0.13177	0.054278	60	1
9.375	0.85351	0.14649	0.055317	59	1
9.408	0.83880	0.16120	0.056286	58	1
...					
----- SEX=2 Female -----					
INTDXSURV	SURVIVAL	FAILURE	STDERR	NUMBERATRISK	OBSERVEDEVENTS
3.980	0.90000	0.10000	0.09487	10	1
5.099	0.84706	0.15294	0.10301	17	1
5.921	0.80248	0.19752	0.10680	19	1
6.053	0.76024	0.23976	0.10921	19	1
6.579	0.72404	0.27596	0.10985	21	1
9.276	0.70393	0.29607	0.10862	36	1
9.408	0.70393	0.29607	0.10862	36	0
9.836	0.68676	0.31324	0.10732	41	1
...					

Output 3. Output from %LT_LIFETEST listing survival estimates across all event times

Additionally, the %LT_LIFETEST function also provides the TIMELIST parameter that allows the users to select specific time points for the survival estimates. Multiple time points can be specified separated by spaces:

```
%lt_lifetest(indata = final, strata = sex, event = dead, intv = intdxsurv,
ltime = intdxtx, timelist = 12 24 36);
```

As shown in Output 4, the output is shortened to only list the selected time points:

Survival Probabilities				
----- SEX=1 Male -----				
timelist	SURVIVAL	FAILURE	STDERR	NUMBERATRISK
12	0.78638	0.21362	0.058551	70
24	0.54596	0.45404	0.052774	116
36	0.41598	0.58402	0.044651	129
----- SEX=2 Female -----				

timelist	SURVIVAL	FAILURE	STDERR	NUMBERATRISK
12	0.58526	0.41474	0.098064	45
24	0.39599	0.60401	0.073074	85
36	0.32272	0.67728	0.061451	93

Output 4. Output from %LT_LIFETEST listing survival estimates at the selected time points

THE %LT_LOGRANKTEST FUNCTION

Similarly, the %LT_LOGRANKTEST function can be used for simultaneous comparison of left truncated lifetime data.

The parameters for the %LT_LOGRANKTEST function are:

- INDATA Name of the input data set
- OUTTEST Name of the output data set (optional)
- STRATA Comparing group
- EVENT Event of interest
- INTV Time to event
- LTIME Time to left truncation
- FLEMINGP Fleming's weight p (optional, default: 0)
- FLEMINGQ Fleming's weight q (optional, default: 0)
- NOPRINT Toggle whether print the results (default: 0)

The code for using %LT_LOGRANKTEST is shown below:

```
%lt_logranktest(indata = final, strata = sex, event = dead, intv =
intdxsurv, ltime = intdxtx);
```

As shown in Output 5, the output from %LT_LOGRANKTEST lists the chi-square statistic, degree of freedom, and p-value from the log-rank test, which is equivalent to a special case of Fleming's weighted test when both FLEMINGP and FLEMINGQ are 0:

Log-Rank Test for Survival Probabilities				
TEST	FLEMINGPQ	CHISQ	DF	PROBCHISQ
Log-Rank	Fleming(0,0)	0.9278049	1	0.335434

Output 5. Output from %LT_LOGRANKTEST for log-rank test

By altering the optional FLEMINGP and FLEMINGQ parameters, the users can also use the %LT_LOGRANKTEST function to perform logrank tests with different Fleming's weight, as demonstrated below:

```
* Model 1: Fleming's p = 1, q = 1;
%lt_logranktest(indata = final, strata = sex, event = dead, intv =
intdxsurv, ltime = intdxtx, flemingp = 0, flemingq = 1);
```

```
* Model 2: Fleming's p = 0, q = 1;
```

```

%lt_logranktest(indata = final, strata = sex, event = dead, intv =
intdxsurv, ltime = intdxtx, flemingp = 1, flemingq = 1);

* Model 3: Fleming's p = 1, q = 0;
%lt_logranktest(indata = final, strata = sex, event = dead, intv =
intdxsurv, ltime = intdxtx, flemingp = 1, flemingq = 0);

```

Based on the choosing of FLEMINGP and FLEMINGQ values, the first model gives more weight to the earlier time points, and the second model gives more weight to the middle time points, while the last model gives more weight to the later time points.

Output 6 shows the output from the above Fleming's weighted tests:

Log-Rank Test for Survival Probabilities				
TEST	FLEMINGPQ	CHISQ	DF	PROBCHISQ
Log-Rank	Fleming(0,1)	1.888162	1	0.1694094
Log-Rank Test for Survival Probabilities				
TEST	FLEMINGPQ	CHISQ	DF	PROBCHISQ
Log-Rank	Fleming(1,1)	1.2675601	1	0.2602249
Log-Rank Test for Survival Probabilities				
TEST	FLEMINGPQ	CHISQ	DF	PROBCHISQ
Log-Rank	Fleming(1,0)	0.0500754	1	0.8229321

Output 6. Output from %LT_LOGRANKTEST for Fleming's weighted tests

According to the results, the differences between the survival estimates are most significant during the early time points, less significant in the middle, and least significant during the later time points, which is consistent with the previous survival plots generated from the PHREG procedure.

UPDATED %LIFETEST AND %LIFETESTEXPORT MACRO

During the 2015 SAS Global Forum, the author presented the %LIFETEST and %LIFETESTEXPORT macros for generating publication ready survival analysis reports. Detailed information regarding the use of these two macro functions were provided in the 2015 paper. This paper only covers the newly implemented functionality for handling left truncation.

The major parameters for the %LIFETEST function:

- INDATA Name of the input data set
- STRATA Comparing group
- EVENT Event of interest
- COMPETERISK Event of competing risk
- INTV Time to event
- LTIME Time to left truncation
- TIMELIST Select output time points
- PWPVALUE Toggle point-wise p-values (default: 0)
- NATRISK Toggle numbers of risk (default: 0)
- CONFTYPE Type of transformation for confidence limits
- ALPHA Alpha level (default: 0.05)
- FLEMINGP Fleming's weight p (optional, default: 0)
- FLEMINGQ Fleming's weight q (optional, default: 0)

The parameters for the %LIFETESTEXPORT function:

- OUTDATA Name of the output report file
- RTFTITLE Title of the output report

The two functions are used along with each other to create survival analysis reports. The %LIFETEST function has been updated by adding the LTIME parameter to support analyzing of left truncated data, as well as adding the FLEMINGP and FLEMINGQ parameters for weighted logrank tests, as shown in the following example:

```
* Model 1: Unweighted logrank test;
%lifetest(indata = tmp, strata = sex, event = dead, intv = intdxsurv, ltime
= intdxtx, timelist = 12 24 36);

* Model 2: Fleming's p = 1, q = 1;
%lifetest(indata = tmp, strata = sex, event = dead, intv = intdxsurv, ltime
= intdxtx, timelist = 12 24 36, flemingp = 0, flemingq = 1);

* Model 3: Fleming's p = 0, q = 1;
%lifetest(indata = tmp, strata = sex, event = dead, intv = intdxsurv, ltime
= intdxtx, timelist = 12 24 36, flemingp = 1, flemingq = 1);

* Model 4: Fleming's p = 1, q = 0;
%lifetest(indata = tmp, strata = sex, event = dead, intv = intdxsurv, ltime
= intdxtx, timelist = 12 24 36, flemingp = 1, flemingq = 0);

%lifetestexport(outdata = test, rtftitle = "Univariate Analysis for Overall
Survival");
```

The macro automatically stacks multiple models in a single report and output it in a Microsoft Word document, as shown in Output 7:

Univariate Analysis for Overall Survival						
Outcomes Value	N	Male (N = 328)		Female (N = 244)		P
			Prob (95% CI)	N	Prob (95% CI)	
Overall survival	328			244		0.34
1-year		79	(66-89)%	59	(39-77)%	
2-year		55	(44-65)%	40	(26-54)%	
3-year		42	(33-50)%	32	(21-45)%	
Overall survival	328			244		0.17
1-year		79	(66-89)%	59	(39-77)%	
2-year		55	(44-65)%	40	(26-54)%	
3-year		42	(33-50)%	32	(21-45)%	
Overall survival	328			244		0.26
1-year		79	(66-89)%	59	(39-77)%	
2-year		55	(44-65)%	40	(26-54)%	
3-year		42	(33-50)%	32	(21-45)%	
Overall survival	328			244		0.82
1-year		79	(66-89)%	59	(39-77)%	
2-year		55	(44-65)%	40	(26-54)%	
3-year		42	(33-50)%	32	(21-45)%	

Output 7. Output from %LIFETESTEXPORT

An additional NATRISK parameter for the %LIFETEST function also allows users to control whether to list numbers at risk in the final report, as shown below:

```
%lifetest(indata = final, strata = sex, event = dead, intv = intdxsurv,
ltime = intdxtx, timelist = 12 24 36, natrisk = 1);

%lifetestexport(outdata = report, rtftitle = "Univariate Analysis");
```

The final report with numbers at risk looks like the following in Output 8:

Univariate Analysis						
Outcomes Value	N	Male (N = 328)		Female (N = 244)		P
			Prob (95% CI)	N	Prob (95% CI)	
Overall survival	328			244		0.34
1-year	70	79	(66-89)%	45	59 (39-77)%	
2-year	116	55	(44-65)%	85	40 (26-54)%	
3-year	129	42	(33-50)%	93	32 (21-45)%	

Output 8. Output from %LIFETESTEXPORT with NATRISK enabled

CONCLUSION

Like right censoring, left truncation often occurs in real world lifetime data and it requires proper adjustments in analyses to avoid biased results. Users can use the PHREG procedure in SAS or the %LT_LIFETEST and %LT_LOGRANGTEST macros to analyze lifetime data with left truncation. The macros provide a more intuitive approach for analyzing such data, as well as allow users to perform weighted homogeneity tests. Additionally, the updated

%LIFETEST and %LIFETESTEXPORT macros can be used to generate survival analysis reports for left truncated data.

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The data presented here are preliminary and were obtained from the Statistical Center of the CIBMTR. The CIBMTR is a research collaboration between the National Marrow Donor Program/Be The Match and the Medical College of Wisconsin. The analysis has not been reviewed or approved by the Advisory or Scientific Committees of the CIBMTR.