

Survival Analysis in Clinical Trials

We've already covered survival analysis in great detail [here](#). This will be review, application to clinical trials, and SAS implementation.

Survival analysis uses classic methods of studying occurrence and time of events; it was traditionally designed to study death, but can be used with any type of time to event outcome. These are special cases when a t-test is not appropriate; as the data is skewed and there are values that need to be censored before the end of study.

Participants enter the study event-free and the outcome is to assess **if and when** the event occurred. We can then investigate if the event occurs differently in other groups. Patients are typically randomized at different dates in the recruitment period and time is measured on a continuous scale. We measure time in the study as the time between randomization and either the patient:

- Has the event (**Failure time**)
- Is last measured in the study and does not have the event (**Censoring time**)

Right Censoring

Most common form of censoring and the ideal scenario; Participants are followed for a time but the event of interest does not occur. All we know is that the time of the event is greater than a certain value but it is unknown by how much.

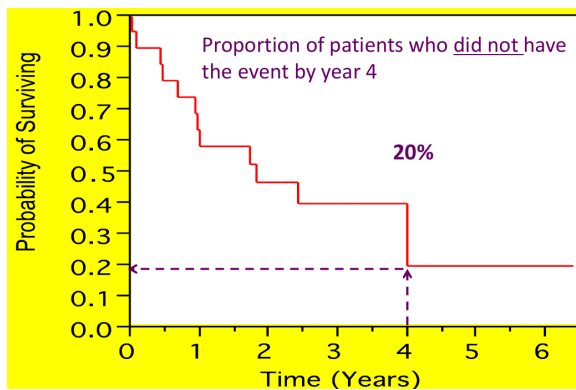
- End of study
- Loss to follow-up (withdrawal or dis-enrollment)
- A competing risk - A different event that occurs and makes it impossible to determine when the event of interest occurs

Interval Censoring

The time for an event occurs between two time points in the study but the investigators do not know the exact date. This could occur when the outcome is self-reported at 3 month intervals, for example. There are special methods for interval censoring in SAS we will not cover here (PROC ICLIFETEST)

The Survival Function

The survival function $S(t)$ is a mathematical function that represents the probability of surviving beyond a particular time t . We can plot the % surviving (without event) on the Y-axis and time on the X-axis to see when most of the events occurred.



Each step is an "event", but censored events are often marked as an 'X' (no step)

The most commonly used method for estimation of the survival function is the **Kaplan-Meier (or product-limit estimator)**. Suppose there are k distinct event times and n subjects at risk of event, with d_j subjects with outcome at time t_j :

$$S(t) = \prod_{j:t_j \leq t} \left[1 - \frac{d_j}{n_j}\right]$$

We can visualize this in a chart:

$$n_j = n_{j-1} - d_{j-1} - c_{j-1}$$

$$S_j = S_{j-1} * (1 - d_j/n_j)$$

Time interval	N at risk	N Failed	N Censored	Interval survival probability	KM survival probability
(Days)	(n_j)	(d_j)	(c_j)	($1 - d_j/n_j$)	$\prod(1 - d_j/n_j)$
0 -14.99	4	0	0	$1 - 0/4 = 1$	1
15-24.99	4	0	1	$1 - 0/4 = 1$	1
25-36.99					
37-39.99					
40					

Kaplan-Meier estimates are calculated from the conditional probability of experiencing the event

$$P(A, B, C) = P(C | A, B) * P(B|A) * P(A)$$

Ex. $S(37)$ -> Survival estimate at day 37 = $P(T > 37 \ \& \ T > 25 \ \& \ T > 15)$ -> Probability of surviving past day 37, 25 and 15

* Computes tables of survival estimates, KM survival curves and log-rank test;

```
proc lifetest data=mysurv;
```

```
time time*cvd_death(0);
```

```
strata treat;
```

```
run;
```

Above `cvd_death` is the name of the event/censoring variable, and the `strata` is what we want to compare survival.

Product-Limit Survival Estimates					
time	Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.00	1.0000	0	0	0	12
8.00	0.9167	0.0833	0.0798	1	11
8.00 *	.	.	.	1	10
52.00 *	.	.	.	1	9
63.00	0.8148	0.1852	0.1194	2	8

In the above sample output:

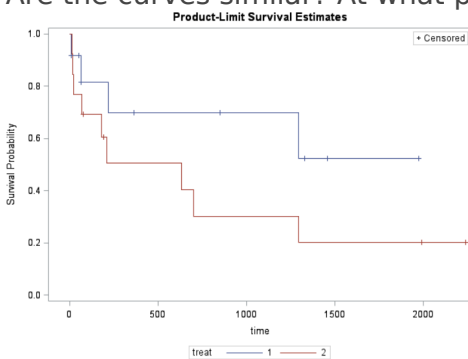
- "Survival" Represents the KM survival estimate
- "Failure" is the cumulative probability of the event (1 - KM probability).

Summary Statistics for Time Variable time				
Quartile Estimates				
Percent	Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)
75	1296.00	LOGLOG	210.00	.
50	632.00	LOGLOG	23.00	1296.00
25	70.00	LOGLOG	13.00	210.00

The quartile estimates Point Estimate gives the smallest event time such that the probability of event is greater than [.25/.5/.75]. There may not be a point estimate if the number of observed events/Failure never reached the percent.

Comparing Survival Curves

Are the curves similar? At what point do they diverge? When do most events occur?



H_0 : No difference in survival between treatments (KM survival curves are the same)

H_A : Difference in survival between treatments (KM survival curves are the different)

Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	2.0256	1	0.1547
Wilcoxon	1.3227	1	0.2501
-2Log(LR)	2.0050	1	0.1568

Log-rank test:

$$\sum_{j=1}^r (d_{1j} - e_{1j})$$

$$e_{1j} = n_{1j} * d_j / n_j$$

Where r is the number of event times d_{1j} is the number of events in group 1 at time j and e_{1j} is the expected number of events in group 1 at time j .

Wilcoxon test:

$$\sum_{j=1}^r n_j(d_{1j} - e_{1j})$$

Where n_j is number of individuals at risk at each time point (Weighted sum); Gives more weight to early times than later times

Both log-rank and Wilcoxon test follow a chi-square distribution with 1 df (if G treatments then df = G - 1)

Assumption: Non-Informative Censoring

We assume all individuals who are censored have the same risk of the event (or prognosis) as those who remain in the study (conditional on explanatory variables). There is no statistical test for informative censoring, we just need to adjust estimates for variables that are likely to affect the rate of censoring (need regression models).

Ex. The outcome is death and very sick subjects are less likely to attend study visits.

Comparing Treatments

Outcome	Test	Regression model	Measure of effect
Continuous	T-test	ANOVA/linear regression	Mean difference
Binary	Chi-square test	Logistic regression	Odds ratio
Time to event	Log-rank test	Cox regression	Hazard ratio

The **Hazard (or hazard rate)** is the instantaneous risk/rate of experiencing the event at time t. It is not a risk.

Hazard function

Numerator: Probability of the event occurring in interval $[t, t+\Delta t]$ CONDITIONAL on being event-free at time t

$$h(t) = \lim_{\Delta t \rightarrow 0} \frac{P(t \leq T \leq t + \Delta t | T \geq t)}{\Delta t}$$

Limit: we make the interval very small

Denominator: length of interval

Interpretation: "The hazard of event for the new treatment is 44% of the hazard of the active control group. The 95% CI contains 1 so it is not significant."

In the Cox Proportional Hazards Regression we create dummy variables fro the treatment group:

$$h(t|X) = h_0(t) * e^{\beta_1 X}$$

Which can be expressed as:

$$\log(h(t|X)) = \log(h_0(t)) + \beta_1 X$$

HR<1 (or $\beta < 0$): lower hazard of the event compared to reference group

HR>1 (or $\beta > 0$): larger hazard of the event compared to reference group

Proportional Hazards assumption must be met for a Cox model. That is the separate treatment plots of $\ln(-\ln(S(t)))$ vs t should be parallel.

Also we can adjust for covariates just like in proc glm ANOVA where we assess interaction and factors.

```
*Cox Model;
proc phreg data=mysurv;
class treat (param=ref ref='2');
model time*cvd_death(0)=
treat/risklimits;
run;

*Log-log survival plot;
proc lifetest data=mysurv plots=(loglogs);
time time*cvd_mort(0);
strata treat;
run;
```

Partial Likelihood

The LR function for Cox models can be factored into

- One part that depends on $h_0(t)$ and β
- The other part that depends on β alone (partial likelihood)
- We treat the partial likelihood as an ordinary likelihood:
 - Estimate values of β that maximize partial likelihood
 - Asymptotically consistent and normally distributed
 - Estimates are (only slightly) less efficient

Revision #4

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