An Overview of Survival Analysis

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WHAT IS SURVIVAL ANALYSIS?

In logistic regression, we are interested in studying how risk factors were associated with presence or absence of disease. Sometimes we are interested in how a risk factor or treatment affects time to disease or some other event. Or we may have study dropout, and therefore subjects who we are not sure if they had disease or not.

In these cases, logistic regression is not appropriate.

Survival analysis is used to analyze data in which the Time until the Event is of interest. The response is often referred to as a Failure Time, Survival Time, or Event time.

Survival analysis is a class of Statistical Methods for studying the Occurrence and Timing of events.

Most often these methods are applied to the study of deaths, i.e. where the outcome of interest is death, hence the name Survival Analysis.

WHAT IS SURVIVAL ANALYSIS? Continue…

Examples includes:

- ✓ Time until tumor recurrence
- ✓ Time until cardiovascular death after some treatment intervention
- ✓ Time until AIDS for HIV patients
- ✓ Time until a machine part fails

In general it consists of techniques for positive-Valued variables as it deals with Time variable.

In survival analysis, subjects are usually followed over a specified time period and focus is on time at which Event of interest occurs.

Survival Time response is usually:

- ✓ Continuous
- ✓ May be incompletely determined for some Subjects
- ✓ Always >= 0

Incompletely Observed Responses are Censored.

WHY USE SURVIVAL ANALYSIS?

Survival data have two features that are difficult to handle with conventional statistical methods like:

- ✓ Censoring and
- ✓ Time-dependent variable

Censoring: Censoring is present when we have some information about a subject's event time, but we don't know the exact event time. Subjects are said to be censored if they:

- ✓ A subject does not experience the event before the study ends
- ✓ A person is lost to follow-up during the study period
- ✓ A person withdraws from the study

Observations are called censored when the information about their survival time is incomplete.

Time-dependent variable:
It is the time of first occurrence of the event of interest

WHY USE SURVIVAL ANALYSIS? Continue…

Consider below examples:

1. The risk of dying in Intensive Care Unit (ICU) within 30 days from the admission.
2. Survival rate of advanced breast cancer patients at 5 years from the diagnosis date.

In first example we can describe the endpoint results simply by

“n” and % Rate (events/totals).

Comparison can be feasible in this case due to below main reasons:

- ✓ Limited length of required observation period (30 days), hence low risk for loosing patient which means low risk of lost to follow-up; Hence data will be complete.
- ✓ At end of the 30 days time, patient can be either dead or alive (discharged or not).

WHY USE SURVIVAL ANALYSIS? Continue…

In Second example more appropriate is to use a survival analysis method due to below reasons:

- ✓ Considering higher length of follow-up period (5 years), there is an high risk to loose patient (lost to follow-up). Hence required data may be incomplete.
- ✓ Usually such study requires longer period (sometimes varying from 2 to 5 years), therefore if we perform an interim analysis, not all the patients had enough time to reach the 5 years survival endpoint.
- ✓ The time when the event has been observed (e.g. 1 year Vs 3 years) with this “chronic” disease, make a substantial difference as time to event is a objet of interest. Hence simply checking how many patients died in the 0-5 years period and removing lost to follow-up patients is not sufficient.

Objectives & Approaches

Usually the Objectives of Survival Analysis are:

- ✓ Estimate Time-to-Event for a group of individuals, such as Time until Disease Progression or Time until Death.
- ✓ To compare Time-to-Event between two or more groups, such as Study Treatment vs. Placebo in a randomized controlled trial.

There are numerous methods in Survival Analysis, such as:

- ➢ Life Tables
- ➢ Kaplan-Meier Estimators
- ➢ Exponential Regression
- ➢ Log-Normal Regression
- ➢ Proportional Hazards Regression
- ➢ Competing Risks Models

In Biomedicine, Kaplan-Meier (KM) Estimator is the most widely used method for Estimating Survival functions.

This method is also known as Product-Limit Estimator

Survival Analysis (K-M Estimator): SAS Procedure

In most of the Oncology studies one of the important objective is Time to Event of interest like:

- ✓ Progression-Free Survival Time - PFS
- ✓ Overall Survival Time – OS, etc.

To produce K-M estimates, LIFETEST procedure is used.

It is primarily designed for univariate analysis of the timing of events.

It produces survival estimates and graphs of survival curves.

This procedure tests whether survival curves are the same in two or more groups.

It also tests for associations between event times and time-constant covariates.

Survival Analysis (K-M Estimator): SAS Procedure

General syntax of LIFETEST (K-M method):

```
proc lifetest data = event  timelist = 3 6 9 method = km;

    time etime*ecensflg(1);

    strata  treatment;

    ods output  censoredsummary = summary  quartiles =qt
    productLimitEstimates = est  homtests=ht;

run;
```

Where, event = Time to Event data set

etime = Time to Event (in month)

ecensflg = Censor Flag

ecensflg =1 if had an event, ecensflg =0 if no event by time etime

Survival Analysis (Log-rank Test)

Survival data are generally described in terms of two related probabilities; Survival S(t) and Hazard h(t).

- ✓ Survival is the probability that an individual survives from the Time of Origin to a specified Time “t”.
- ✓ Hazard is the probability that an individual who is under observation at Time “t” has an Event at that Time.

Log-rank Test :

It is the most widely used method of comparing two or more groups for survival estimates. As it’s a non-parametric test, it compares the Median Survival Time –to-event for two or more groups.

We use log-rank test to test the null hypothesis of no difference between survival estimates of two or more groups.

By using “homtests” option in lifetest procedure, we can obtain p-value for log-rank test.

Survival Analysis (Cox Regression)

Cox Regression (Proportional Hazards model) :

To approach survival analysis in a multivariate way, the Cox model is used. The Cox model a semi-parametric regression model used to test the effect of a set of covariates.

It's a survival analysis method which describes the relation between event incidence and covariates.

Hazard Function & Hazard Ratio:

- ✓ The Hazard is a function of Time and represents the instantaneous probability that the event of interest will occur at a specified time "t" given that it has not occurred prior to "t".
- ✓ Hazard ratio is a ratio of probability of event occurrence in one group to the probability of event occurrence in other group.
- ✓ It's the ratio of probabilities.

Survival Analysis (Cox Regression) Continues…

Using PHREG procedure we can produce estimate of Hazard Ratio.

General syntax of PHREG (Cox Regression):

```
proc phreg data = event;
    model etime*ecensflg(1) = trtsort / ties=breslow rl;
    ods output parameterestimates=hr;
run;
```

Where,

event = Time to Event data set

etime = Time to Event (in month)

ecensflg = Censor Flag

ecensflg =1 if had an event, ecensflg =0 if no event by time etime

Survival Analysis (Cox Regression) Continues…

Interpretation of Hazard Ratio:

- ✓ A positive parameter estimate indicates that the hazard increases with increasing values of the covariate, while a negative estimate shows that the hazard decreases with increasing values of the covariate.

- ✓ The magnitude of the effect of a specific covariate on the event time is expressed as hazard ratio. This is an estimate of the relative survival experience of two groups.

- ✓ If the value of Hazard Ratio is greater than 1 then the estimate of time to event in first group (numerator group) is more than the estimate of time to event in second group (denominator group) and vice versa.

Thank you!!!