Computing the ‘Competing Risks’
Modeling Survival Data with Competing Risk Events
using SAS Macros

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SP06
Why Competing Risk?

Frequency of studies published on the subject of competing risks within the last 10 years steadily increased over time.


Summary of FDA Public Workshop

The interpretation of overall survival may be confounded by competing risk of mortality, salvage treatments, and crossover.
Outline

- Standard Survival Analysis Techniques
- Concept of Competing Risk (CR) Events
- Analysis techniques in CR setup
  - Estimation of incidence of an event of interest using % CIF (ignoring and accounting for CR)
  - Comparison of incidence among treatment groups using % CIF
  - Assessing effect of covariates on incidence using % PSHREG
Survival Analysis

- Survival Analysis - Time to event analysis

- Event of interest:
  - Cancer relapse
  - Myocardial infarction
  - Discharge from hospital
  - Death due to a specific cause

- Survival Function

- Hazard Function
Censoring

- What is censoring?

- Assumed to have the same probability of experiencing the event of interest (non-informative censoring)

- Standard survival analysis techniques: Assumption of non-informative censoring

Not all subjects enrolled in the study will have experienced the event of interest
# Standard Survival Analysis Techniques

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Method</th>
<th>SAS Proc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimating Survival Function</td>
<td>Kaplan Meier method</td>
<td>Proc lifetest</td>
</tr>
<tr>
<td>Comparison of Survival Functions</td>
<td>Log Rank Test</td>
<td>Proc lifetest</td>
</tr>
<tr>
<td>Assessing effect of covariates</td>
<td>Cox Regression Model</td>
<td>Proc phreg</td>
</tr>
</tbody>
</table>
Concept of Competing Risk

- A cohort of Breast Cancer (BC) patients
- Event of Interest is ‘death of a patient due to breast cancer’
- Some deaths due to causes unrelated to the disease.
- Researcher: Is it an event of interest? – No
- Cases to be treated as censored ????
Competing Risk Event

Group of Breast Cancer patients

Follow-up

Alive

Death due to other reasons

Death due to Breast cancer

Censored

Competing Risk

Event of Interest

End of study
Competing Risk (CR)

- Either precludes the occurrence of another event or
- Alters the probability of occurrence of other event
- Use of classical survival analysis methods lead to a bias

Gooley, TA; Leisenring, W; Crowley, J; Storer, BE, "Estimation of failure probabilities in the presence of competing risks: new representations of old estimators" Statistics in Medicine 1999 pp. 695-706
Here we are…

- Standard Survival Analysis Techniques
- Concept of Competing Risk (CR) Events

**Analysis Techniques in CR setup**

- Estimation of incidence of an event of interest using % CIF (ignoring and accounting for CR)
- Comparison of incidence among treatment groups using % CIF
- Assessing effect of covariates using % PSHREG
Cumulative Incidence Function (CIF)

- Kalbfleisch and Prentice (1980) introduced ‘Cumulative Incidence Function’ approach to analyze survival data when CRs exist.

- Cumulative probability of an event of interest over time.

- Also referred as ‘subdistribution function’
Gray’s Test

- Two or more groups: To test the difference in the cumulative incidence rates among treatment groups.

- Gray (1988) proposed a modified Chi-square test approach.

%CIF Macro

- SAS inbuilt macro ‘%CIF’
- Estimates crude cumulative incidence function.
- Also compares cumulative incidence functions across treatment groups.
- Statement:
  \texttt{\%CIF (Data=, Out=, Time=, Status=, Event=, Censored=, Group=, options=)}
Test the Effect of Covariates

- Probability of cumulative incidence for subjects with a given set of covariate

- Fine and Gray (1999) and Klein and Andersen (2005) proposed approaches to directly model the effect covariates on CIF.

- Fine and Gray (F&G) method will be discussed.

- Based on proportional hazards model.
% PSHREG

- Developed by researchers from Medical University of Vienna.
- Available in Public Domain
- Implements model proposed by F&G (1999).
- Facilitates to use various options offered by proc phreg.
- Statement:
  \[
  \%pshreg (Data=, Time=, Cens=, Failcode=, Cencode=, Varlist=, Cengroup=, Options=);
  \]

Example
BYAR Study

- Randomized Clinical Trial (Byar study by Byar and Green, 1980)

- Primary interest - To assess the effect of treatment (Rx) on prostate cancer related deaths.

- 502 prostate cancer patients with clinical stage III or IV.

- Randomized to either low or high doses of diethylstilbestrol (DES).
<table>
<thead>
<tr>
<th>Pat_ID</th>
<th>Stage</th>
<th>Rx</th>
<th>Dtime</th>
<th>status</th>
<th>age</th>
<th>wt</th>
<th>Performance</th>
<th>Lesion</th>
<th>Gleason</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>0.2 mg estrogen</td>
<td>72</td>
<td>alive</td>
<td>75</td>
<td>76</td>
<td>normal activity</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>0.2 mg estrogen</td>
<td>1</td>
<td>dead - other ca</td>
<td>54</td>
<td>116</td>
<td>normal activity</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>5.0 mg estrogen</td>
<td>40</td>
<td>dead - cerebrovascular</td>
<td>69</td>
<td>102</td>
<td>normal activity</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>0.2 mg estrogen</td>
<td>20</td>
<td>dead - cerebrovascular</td>
<td>75</td>
<td>94</td>
<td>in bed &lt; 50% daytime</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>placebo</td>
<td>65</td>
<td>alive</td>
<td>67</td>
<td>99</td>
<td>normal activity</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>0.2 mg estrogen</td>
<td>24</td>
<td>dead - prostate ca</td>
<td>71</td>
<td>98</td>
<td>normal activity</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>placebo</td>
<td>46</td>
<td>dead - heart or vascular</td>
<td>75</td>
<td>100</td>
<td>normal activity</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>placebo</td>
<td>62</td>
<td>alive</td>
<td>73</td>
<td>114</td>
<td>normal activity</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>501</td>
<td>4</td>
<td>placebo</td>
<td>49</td>
<td>dead - prostate cancer</td>
<td>55</td>
<td>112</td>
<td>normal activity</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>502</td>
<td>3</td>
<td>5.0 mg estrogen</td>
<td>20</td>
<td>dead - cerebrovascular</td>
<td>73</td>
<td>88</td>
<td>normal activity</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>
# CR Analysis Dataset

<table>
<thead>
<tr>
<th>ID</th>
<th>Follow-up (months)</th>
<th>Status</th>
<th>Scenario (I)</th>
<th>Scenario (II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>001</td>
<td>72</td>
<td>Alive</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>002</td>
<td>1</td>
<td>Dead other cause</td>
<td>C</td>
<td>E-CR</td>
</tr>
<tr>
<td>003</td>
<td>20</td>
<td>Alive</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>004</td>
<td>40</td>
<td>Alive</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>005</td>
<td>65</td>
<td>Dead Prostate Cancer</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td>006</td>
<td>24</td>
<td>Dead Prostate Cancer</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td>----</td>
<td>--------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>--------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>501</td>
<td>34</td>
<td>Dead cerebrovascular</td>
<td>C</td>
<td>E-CR</td>
</tr>
<tr>
<td>502</td>
<td>25</td>
<td>Dead heart disease</td>
<td>C</td>
<td>E-CR</td>
</tr>
</tbody>
</table>

Event of Interest (E): death due to cancer,
Event of competing risk (E-CR): death due to heart disease, cerebrovascular, other causes etc.
Scenario I: Event and censored without accounting for CR, Scenario II: Event and censored accounting for CR
C : Censored
## Incidence of Cancer Deaths

<table>
<thead>
<tr>
<th>Scenario I</th>
<th>Scenario II</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ignores CR</td>
<td>• Accounting for CR</td>
</tr>
<tr>
<td>• Subjects alive / Loss to FUP /</td>
<td>• Subjects alive / Loss to FUP /</td>
</tr>
<tr>
<td>died due to other causes</td>
<td>withdrew ‘censored’</td>
</tr>
<tr>
<td>‘censored’</td>
<td>• Death due to other causes grouped</td>
</tr>
<tr>
<td></td>
<td>as ‘CR’.</td>
</tr>
<tr>
<td>• KM method</td>
<td>• % CIF macro</td>
</tr>
</tbody>
</table>
% CIF Macro

%CIF (DATA=BYAR,
    TIME= dtime,
    STATUS=stat,
    EVENT=1,
    CENSORED=0,
    GROUP=dose,
    TITLE= Cumulative Incidence Function in lower vs. higher DES arms);

/*** DATA=Byar data set to analyze ***********/
/*** dtime: follow-up time in months ***********/
/*** Stat: Response at the time of follow-up******/
/*** EVENT =1: Code for event of interest********/
/***CENSORED=0: code to indicate censoring***/
/***dose’ (Rx) requests a CI curve for DES arms***/
Cumulative incidence of event of interest gets overestimated if CR events are present and ignored during estimation.
Testing the Equality of Cumulative Incidence

- Gray’s approach to assess the equality between treatment groups in competing risk setting.

<table>
<thead>
<tr>
<th>Gray's Test for Equality of Cumulative Incidence Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-Square</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>10.885</td>
</tr>
</tbody>
</table>

- Incidence of cancer deaths is significantly different ($p=0.0010$) between two treatment groups.

- By default using %CIF
To Estimate the difference in CIF between Groups with Covariates

- A set of covariates as age, weight, performance, Gleason score and lesion.
- % pshreg macro directly models the difference in CIF in presence of covariates.
% PSHREG Macro

% pshreg (DATA=BYAR, /*** DATA=Byar data set to analyze ***/)
TIME= dtime, /*** dtime: follow-up time in months ***/)
CENS=stat, /*** Stat: Response at the time of follow-up*/
FAILCODE=1, /*** 1: code for event of interest***/
CENCODE=0, /*** 0 : code to indicate censoring***/
VARLIST = dose age wt performance gleason lesion /*covariates*/
CUMINC=1 , /** 1:Plots the cumulative incidence curves **/
OPTIONS =rl); /*** rl: limits for hazards ratio***/
Output of % pshreg macro

The PSHREG macro: Fine-Gray model

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>StdErr</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOSE</td>
<td>1</td>
<td>-0.60268</td>
<td>0.15523</td>
<td>0.994</td>
<td>15.0742</td>
<td>0.0001</td>
</tr>
<tr>
<td>age</td>
<td>1</td>
<td>-0.02084</td>
<td>0.00992</td>
<td>0.952</td>
<td>4.4138</td>
<td>0.0356</td>
</tr>
<tr>
<td>wt</td>
<td>1</td>
<td>-0.00848</td>
<td>0.00569</td>
<td>0.989</td>
<td>2.2147</td>
<td>0.1367</td>
</tr>
<tr>
<td>hx</td>
<td>1</td>
<td>-0.20670</td>
<td>0.16291</td>
<td>1.009</td>
<td>1.6098</td>
<td>0.2045</td>
</tr>
<tr>
<td>performance</td>
<td>1</td>
<td>0.28631</td>
<td>0.24062</td>
<td>1.052</td>
<td>1.4159</td>
<td>0.2341</td>
</tr>
<tr>
<td>gleason</td>
<td>1</td>
<td>0.89924</td>
<td>0.16689</td>
<td>1.001</td>
<td>29.0348</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>lesion</td>
<td>1</td>
<td>0.97633</td>
<td>0.18373</td>
<td>0.984</td>
<td>28.2364</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

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## Quick Recap

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Method</th>
<th>SAS Tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence estimation</td>
<td>CIF</td>
<td>% CIF</td>
</tr>
<tr>
<td>Comparison Incidence</td>
<td>Gray Test</td>
<td>% CIF</td>
</tr>
<tr>
<td>Assessing effect of covariates</td>
<td>Fine and Gray method</td>
<td>% PSHREG</td>
</tr>
</tbody>
</table>
Conclusion

Estimating disease incidence accurately is a key factor for successful drug development programme.

Presence of competing risks may hamper the estimation of true disease incidence.

**Disease incidence gets overestimated if presence of competing risks is ignored during analysis.**
References


Thank-You

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