SAS® GLOBAL FORUM 2018

USERS PROGRAM

April 8 – 11 | Denver, CO
Colorado Convention Center

#SASGF
Presenter
Colleen McGahan, Biostatistical Lead, Cancer Surveillance & Outcomes, BC Cancer, Canada

Colleen has been a Biostatistician for 20 years and started using SAS when she moved from the UK to Vancouver, British Columbia, Canada over 15 years ago.

Colleen currently leads a team of Biostatisticians at BC Cancer providing a statistical consulting service to researchers and policy makers across the agency.

Colleen enjoys her involvement in the SAS user community and has been the President of the Vancouver SAS User Group (VanSUG) for over 10 years.
Competing Risk Survival Analysis

A Novel Way to Look at Wait Time Data
About the presentation

• Aimed at analysts:
  – Familiar with survival analysis
  – Seeking to learn how to implement survival analysis with competing risks.
• Provides an overview of the method
• Walks through an example using a novel way to look at healthcare treatment wait time data
Introduction

When do we use survival analysis?

• The response of interest is the time until the occurrence of a well-defined event

• For some subject/units the event of interest has not been observed
Introduction
What are censored observations?

• For subjects that have not experienced the event of interest we do not know whether or when they will experience it

• Only know they have not done so by the time the data are analyzed
Introduction

Censored Observations

- Assumed to be:
  - Random
  - Non-informative

- The reason for censoring is independent of the event of interest.

- Have the same future risk of the event of interest as subjects who have not been censored and have not had the event of interest
Introduction
Survivor Function

• $S(t)$

• The probability that the event of interest has not occurred by time $t$ given still being at risk of having the event of interest.

• Bound by 0 and $\infty$ where $S(0)=1$ and $S(\infty)=0$

• Given enough time, the event of interest is bound to occur in each subject
Introduction
Competing risk events

• A subject may experience an event or events other than the one of interest which either hinders the event of interest from happening or alters the probability of experiencing the event of interest.
Introduction

Competing risk events - Example

• Time to colonoscopy for clients on a wait list for receipt of a colonoscopy

• Event of interest = receipt of colonoscopy

• Censored = still on wait list at time of analysis
Introduction

Competing risk events - Example

• What if the client:
  • Dies
  • Opt out from having colonoscopy
  • Is assessed by a nurse who determines colonoscopy is not required

• The ‘risk’ has changed

• Event of interest will not occur

• Therefore, these events are competing risk events
Key Concepts

Hazard Function

- \( h(t) \)
- The instantaneous risk of experiencing the event at time \( t \), given being event free until that time

Cumulative Hazard Function

- \( H(t) \)
- The hazard function added over time from time 0 to time \( t \).
Key Concepts

Survivor Function

• $S(t)$

• Has a one-to-one link to the cumulative hazard function for that event by:

\[ S(t) = e^{-H(t)} \]
Key Concepts
Cumulative Incidence Function (CIF)

• Is one minus the survivor function

• Also a direct relationship between the CIF and the hazard function.

\[ F(t) = 1 - e^{-H(t)} \]

• Often obtained using the non-parametric Kaplan-Meier (KM) method.
Key Concepts

Cause Specific Hazard of an event of interest

• The instantaneous risk of experiencing event $k$ at time $t$, given not having experienced any other type of events up until that time.

• If we assume independence of all events then KM estimator could be used to obtain the cause-specific hazard function of the $k$th event.

• Computed for the $k$th event by treating all the other events as censored.
Key Concepts
Cause Specific Hazard of an event of interest

• Example: 2 events;

<table>
<thead>
<tr>
<th>Event of interest</th>
<th>Censor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt of colonoscopy</td>
<td>Nurse assessment with outcome of not proceeding to colonoscopy</td>
</tr>
<tr>
<td>Nurse assessment with outcome of not proceeding to colonoscopy</td>
<td>Receipt of colonoscopy</td>
</tr>
</tbody>
</table>
Key Concepts

Cause Specific Hazard of an event of interest

- Cox proportional hazards model is also based on the cause-specific hazard function.

- So, assuming independence of all events the cause-specific hazard function of the \( kth \) event can be obtained using KM and Cox proportional hazards model.

- In reality, in a competing risk setting, we are unable to explicitly test this independence.
Key Concepts

Cause Specific Hazard of an event of interest

Example,

Had a client not been assessed by a nurse with the outcome of not proceeding to colonoscopy we would never know whether they would have continued on to have the colonoscopy since receipt of colonoscopy is now unobservable for these clients.
Key Concepts

Cause Specific Hazard of an event of interest

Given this lack of independence;

Cause-specific hazard is really a mix of the hazards of:

- a nurse assessment resulting in not proceeding to colonoscopy
  AND
- the receipt of colonoscopy

The effect of a covariate on one type of event alone is likely to be very different from the effect of a covariate on both types of events combined.
Key Concepts

Cause Specific Hazard of an event of interest

• The true cause-specific hazard of an event of interest in the presence of competing risks needs to be derived from the joint and marginal survivor functions

• However, due to this unobservable phenomenon, the joint distribution of the competing risk events is unidentifiable
Key Concepts
Cumulative Incidence Function in presence of competing events

• In a competing risk setting, the CIF for event \( k \) can no longer be directly linked to its hazard function

• As seen in the equation below:

\[
\text{CIF}_k = F_k(t) = \int_0^t S(u) h_k(u) du,
\]

Where,

\[
S(u) = e^{-H_1(u) - H_2(u) \ldots - H_k(u)} = \text{overall survival function which is determined by all events}
\]

\( h_k(u) \) is the cause-specific hazard for event \( k \).
Key Concepts
Cumulative Incidence Function in presence of competing events

• Denotes the probability of experiencing the kth event before time \( t \) and before the occurrence of a different type of event.

• The sum of the CIF estimates for each type of event equals the CIF estimates of the incidence of the composite outcome consisting of all the events.

• It does not rely on some joint function of the multiple events which is unidentifiable.
Key Concepts
Cumulative Incidence Function in presence of competing events

• **Gray (1988)** proposed a non-parametric test to compare two or more CIFs.

• Fine and Gray (1999) proposed a proportional hazards model aimed at modeling the CIF with covariates, by treating the CIF curve as a subdistribution function.


Key Concepts
Cumulative Incidence Function in presence of competing events

• The risk set:

• For competing risk event analysis includes:
  subjects who are currently event free as well as those who have previously experienced a competing event.

• For standard survival analysis includes:
  subjects who experience a competing event would be censored and therefore exit the risk set.
Implementing Gray (1988) CIF method

• Requires no new SAS procedures in SAS/STAT® 13.1 and later versions

• LIFETEST procedure is used with minor changes in the SAS statements

• Detailed example looking at time to colonoscopy for clients participating in the British Columbia (BC) Colon Screening program.
Implementing Gray (1988) CIF method

Example - Wait times in a healthcare setting

- Rely on large administrative datasets
- Often report the median and 90th percentile wait times only for clients that have received the procedure
- Tells us nothing about the clients that are on the wait list and still waiting for the procedures
Implementing Gray (1988) CIF method

Example - Wait times in a healthcare setting

• It can underestimate the time to procedure because it systematically excludes those clients that could have longer wait times

• It does not recognize time spent in queue by individuals who for some reason are no longer proceeding to have the procedure
Implementing Gray (1988) CIF method

Example - Wait times in a healthcare setting

• Propose the application of survival analysis to look at wait times in the healthcare setting

• Time to colonoscopy in the BC Colon Screening program is a particular scenario where competing risk survival analysis should be implemented.

• This utilizes the experience of all participants, including those who have not yet had their procedure or will not receive the procedure because of competing events.
Example – Time to Colonoscopy

Start of Wait: Positive FIT result

Yes
Waiting for Assessment

No
Discharged/Death

Yes

No

Waiting for Colonoscopy

Yes
Proceeding to Colonoscopy

No

No
Discharged/Death

No

Had Colonoscopy

No

Event

Competing event

Censored
Example – Time to Colonoscopy

• The Canadian national target: Clients should receive their colonoscopy within 60 days of their positive FIT result.

• The BCCSP has the responsibility of monitoring colonoscopy wait times across British Columbia and for 4 different health regions who participate in the screening program.
Example – Time to Colonoscopy

PROC LIFETEST

• Can be used to obtain the probability that a client on the wait list will receive a colonoscopy within 60 days

• Provides insight into the patterns of care once patients are on the waitlist.

• We will look at the difference it makes if the competing events are ignored and treated as censored observations.
Example – Time to Colonoscopy

The Data

<table>
<thead>
<tr>
<th>client_id</th>
<th>fit_to_cscope</th>
<th>status</th>
<th>surv_censor</th>
<th>crisk_censor</th>
<th>ha</th>
</tr>
</thead>
<tbody>
<tr>
<td>361</td>
<td>14525</td>
<td>27 not proceeding</td>
<td>0</td>
<td>1</td>
<td>2 3</td>
</tr>
<tr>
<td>362</td>
<td>14553</td>
<td>53 had cscope</td>
<td>1</td>
<td>1</td>
<td>1 3</td>
</tr>
<tr>
<td>363</td>
<td>14585</td>
<td>51 had cscope</td>
<td>1</td>
<td>1</td>
<td>1 3</td>
</tr>
<tr>
<td>364</td>
<td>14653</td>
<td>110 had cscope</td>
<td>1</td>
<td>1</td>
<td>1 1</td>
</tr>
<tr>
<td>365</td>
<td>14684</td>
<td>74 had cscope</td>
<td>1</td>
<td>1</td>
<td>1 3</td>
</tr>
<tr>
<td>366</td>
<td>14685</td>
<td>211 still waiting</td>
<td>0</td>
<td>0</td>
<td>0 1</td>
</tr>
<tr>
<td>367</td>
<td>14715</td>
<td>134 had cscope</td>
<td>1</td>
<td>1</td>
<td>1 1</td>
</tr>
<tr>
<td>368</td>
<td>14833</td>
<td>60 had cscope</td>
<td>1</td>
<td>1</td>
<td>1 3</td>
</tr>
<tr>
<td>369</td>
<td>14907</td>
<td>47 not proceeding</td>
<td>0</td>
<td>0</td>
<td>2 3</td>
</tr>
<tr>
<td>370</td>
<td>14935</td>
<td>112 still waiting</td>
<td>0</td>
<td>0</td>
<td>0 1</td>
</tr>
<tr>
<td>371</td>
<td>14940</td>
<td>81 not proceeding</td>
<td>0</td>
<td>0</td>
<td>2 1</td>
</tr>
<tr>
<td>372</td>
<td>14985</td>
<td>80 discharged</td>
<td>0</td>
<td>0</td>
<td>3 3</td>
</tr>
<tr>
<td>373</td>
<td>15115</td>
<td>145 had cscope</td>
<td>1</td>
<td>1</td>
<td>1 1</td>
</tr>
<tr>
<td>374</td>
<td>15183</td>
<td>53 had cscope</td>
<td>1</td>
<td>1</td>
<td>1 3</td>
</tr>
<tr>
<td>375</td>
<td>15191</td>
<td>20 not proceeding</td>
<td>0</td>
<td>0</td>
<td>2 3</td>
</tr>
</tbody>
</table>
Example – Time to Colonoscopy

The Data

- Number and percentage of clients in the different states

<table>
<thead>
<tr>
<th>Status</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>discharged</td>
<td>40</td>
<td>0.12</td>
<td>40</td>
</tr>
<tr>
<td>had cscope</td>
<td>23311</td>
<td>69.00</td>
<td>23351</td>
</tr>
<tr>
<td>not proceeding</td>
<td>8444</td>
<td>24.99</td>
<td>31795</td>
</tr>
<tr>
<td>still waiting</td>
<td>1989</td>
<td>5.89</td>
<td>33784</td>
</tr>
</tbody>
</table>
Example – Time to Colonoscopy
Standard Kaplan-Meier Method

```
ODS GRAPHICS ON;
PROC LIFETEST DATA=wait OUTSURV=km_output
   PLOTS=SURVIVAL(FAILURE NOCENSOR STRATA=PANEL) TIMELIST=60;
   TIME fit_to_cscope*surv_censor (0);
   STRATA ha;
RUN;
```
Example – Time to Colonoscopy

Standard Kaplan-Meier Method

Panel plot of failure curves using standard KM method, censoring competing event observations.
### Example – Time to Colonoscopy

**Standard Kaplan-Meier Method**

<table>
<thead>
<tr>
<th>Stratum: ha fit_to_cscope</th>
<th>Survival 60.000</th>
<th>Failure</th>
<th>Survival Standard Error</th>
<th>Number Failed</th>
<th>Number Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8075</td>
<td>0.1925</td>
<td>0.0102</td>
<td>287</td>
<td>1154</td>
</tr>
<tr>
<td>2</td>
<td>0.6279</td>
<td>0.3721</td>
<td>0.0103</td>
<td>830</td>
<td>1344</td>
</tr>
<tr>
<td>3</td>
<td>0.5898</td>
<td>0.4102</td>
<td>0.0132</td>
<td>573</td>
<td>781</td>
</tr>
<tr>
<td>4</td>
<td>0.5585</td>
<td>0.4415</td>
<td>0.0129</td>
<td>666</td>
<td>799</td>
</tr>
</tbody>
</table>
Example – Time to Colonoscopy

Competing Risk Non-parametric Method

```
PROC LIFETEST DATA=wait OUTSURV=km_output
   PLOTS=SURVIVAL(FAILURE NOPRINT NOCCENSOR STRATA=PANEL) TIMELIST=60;
   TIME fit_to_cscope*surv_censor (0);
   STRATA ha;
RUN;
```

For reference: Standard KM code

```
PROC LIFETEST DATA=wait OUTCIF=cr_cif_output
   PLOTS=CIF(TEST) TIMELIST=60;
   TIME fit_to_cscope*crisk_censor (0) / EVENTCODE=1;
   STRATA ha;
RUN;
```

Competing risk code
Example – Time to Colonoscopy
Competing Risk Non-parametric Method

PROC LIFETEST DATA=wait OUTSURV=km_output
   PLOTS=SURVIVAL(FAILURE NOCENSOR STRATA=PANEL) TIMELIST=60;
   TIME fit_to_cscope*surv_censor (0);
   STRATA ha;
RUN;

PROC LIFETEST DATA=wait OUTCIF=cr_cif_output
   PLOTS=CIF(TEST) TIMELIST=60;
   TIME fit_to_cscope*crisk_censor (0) / FAILCODE=1;
   STRATA ha;
RUN;

For reference: Standard KM code

Competing risk code
Example – Time to Colonoscopy

Competing Risk Non-parametric Method

Cumulative Incidence Functions

Gray's Test p < .0001

CIF for each health region overlaid on one plot.
## Example – Time to Colonoscopy

### Competing Risk Non-parametric Method

#### Summary of Failure Outcomes

<table>
<thead>
<tr>
<th>Stratum</th>
<th>ha</th>
<th>Failed Events</th>
<th>Competing Events</th>
<th>Censored</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>737</td>
<td>306</td>
<td>635</td>
<td>1678</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1699</td>
<td>520</td>
<td>292</td>
<td>2511</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>1081</td>
<td>580</td>
<td>155</td>
<td>1816</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>1283</td>
<td>408</td>
<td>113</td>
<td>1804</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>4800</strong></td>
<td><strong>1814</strong></td>
<td><strong>1195</strong></td>
<td><strong>7809</strong></td>
</tr>
</tbody>
</table>

#### Competing risk:
Summary of failure outcomes

#### Kaplan Meier:
Censor summary
Example – Time to Colonoscopy
Competing Risk Non-parametric Method

<table>
<thead>
<tr>
<th>Stratum: ha fit_to_cscope</th>
<th>Cumulative Incidence</th>
<th>Standard Error</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60.000</td>
<td>0.1710</td>
<td>0.00919</td>
</tr>
<tr>
<td>2</td>
<td>60.000</td>
<td>0.3305</td>
<td>0.00939</td>
</tr>
<tr>
<td>3</td>
<td>60.000</td>
<td>0.3155</td>
<td>0.0109</td>
</tr>
<tr>
<td>4</td>
<td>60.000</td>
<td>0.3692</td>
<td>0.0114</td>
</tr>
</tbody>
</table>

Competing Risk estimates:
The probability of receiving a colonoscopy as the first event prior to, or on, 60 days.
Example – Time to Colonoscopy
Competing Risk Non-parametric Method

PROC LIFETEST DATA=wait OUTCIF=cr_cif_output
   PLOTS=CIF(TEST) TIMELIST=60;
   TIME fit_to_cscope*crisk_censor (0) / EVENTCODE=1;
   STRATA ha;
RUN;
Example – Time to Colonoscopy
Competing Risk Non-parametric Method

PROC LIFETEST DATA=wait OUTCIF=cr_cif_output
   PLOTS=CIF(TEST) TIMELIST=60;
   TIME fit_to_cscope*crisk_censor (0) / EVENTCODE=1;
   STRATA ha / GROUP=ha;
RUN;

STRATA ha / GROUP=sex;

Gray’s test tests the homogeneity of the CIFs between males and females stratified by health region.
Since, this code specifies the same GROUP variable as the STRATA variable it is not feasible to perform the Gray’s test. It is simply used to produce the plot.
Example – Time to Colonoscopy
Competing Risk Non-parametric Method

Panel plot of cumulative incidence curves
Example – Time to Colonoscopy

Competing Risk Non-parametric Method

```
PROC LIFETEST DATA=wait OUTCIF=cr_cif_output
   PLOTS=CIF(TEST) TIMELIST=60;
   TIME fit_to_cscope*crisk_censor (0) / EVENTCODE=1;
   STRATA ha;
RUN;
```
Example – Time to Colonoscopy

Competing Risk Non-parametric Method

Output dataset:
Example – Time to Colonoscopy
Competing Risk Non-parametric Method

• When EVENTCODE= is used, the OUTCIF= dataset will only produce data for the event of interest

• If EVENTCODE without the equal sign is used it includes the estimate for all event types.

• Although TIMELIST=60 was specified the OUTCIF= dataset provides the CIF estimates at all time points unless the REDUCEOUT option is specified in the PROC LIFETEST statement

• The data are ordered by event type i.e. first the CIF estimates at each time point for event type 1, then the CIF estimates at each time point for event type 2 etc.
Example – Time to Colonoscopy
Competing Risk Non-parametric Method

• The output from the OUTCIF= data can be manipulated to obtain the CIF for all events.

• The code following produces a panel plot by health region showing the CIF for:
  • receipt of colonoscopy,
  • having a nurse assessment resulting in an outcome of not proceeding to colonoscopy,
  • being discharged from the screening program
  • the composite of all these types of events for each health region whereby health region constitutes the panel
Example – Time to Colonoscopy
Competing Risk Non-parametric Method
Example – Time to Colonoscopy

Competing Risk Non-parametric Method

PROC SORT DATA=cr_cif_output
   OUT=cr_cif_output2;
   BY ha fit_to_cscope failcode;
RUN;

DATA cif;
   SET cr_cif_output2;
   BY ha fit_to_cscope failcode;
   IF FIRST.fit_to_cscope THEN cum_cif=0;
   cum_cif + cif;
   failcode='4';
   IF LAST.fit_to_cscope THEN OUTPUT;
   DROP cif;
   RENAME cum_cif=cif;
RUN;

PROC FORMAT;
   VALUE event 1='Had Cscope'
       2='Not Proceeding'
       3='Discharged'
       4='All events';
RUN;

PROC SGPANEL DATA=cr_cif_output3;
   FORMAT failcode event.;
   PANELBY failcode event.;
   SERIES X=fit_to_cscope Y=cif /
       GROUP=failcode;
RUN;
Example – Time to Colonoscopy
Competing Risk Non-parametric Method
### Example – Time to Colonoscopy

**Competing Risk Non-parametric Method**

<table>
<thead>
<tr>
<th>Health Region</th>
<th>Colonoscopy clients only – receipt in 60 days</th>
<th>KM method – receipt of colonoscopy</th>
<th>Competing risk – receipt of colonoscopy</th>
<th>Competing risk – composite of all events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.23</td>
<td>0.19</td>
<td>0.17</td>
<td>0.31</td>
</tr>
<tr>
<td>2</td>
<td>0.52</td>
<td>0.37</td>
<td>0.33</td>
<td>0.46</td>
</tr>
<tr>
<td>3</td>
<td>0.60</td>
<td>0.41</td>
<td>0.32</td>
<td>0.57</td>
</tr>
<tr>
<td>4</td>
<td>0.47</td>
<td>0.44</td>
<td>0.37</td>
<td>0.56</td>
</tr>
</tbody>
</table>
Conclusion

• The implementation of competing risk analysis requires only a few minor edits to the options in PROC LIFETEST compared to what would be used in standard survival analysis.

• In order to gain a greater understanding of the system at hand and to more accurately measure the outcome of interest, it is important to incorporate all events in survival analysis in a competing risk event setting, not just the event of interest.

• Looking at the effect of the composite of all events provides further insight into interpretation.
Competing Risk Survival Analysis
A Novel Way to Look at Wait Time Data

Questions?
Your feedback counts!

Don't forget to complete the session survey in your conference mobile app.

1. Go to the Agenda icon in the conference app.
2. Find this session title and select it.
3. On the sessions page, scroll down to Surveys and select the name of the survey.
4. Complete the survey and click Finish.
SAS®
GLOBAL FORUM
2018

April 8 - 11 | Denver, CO
Colorado Convention Center