



SAS[®] GLOBAL FORUM 2018

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Presenter

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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 ∞ 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
 - Opts 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;

Event of interest	Censor
Receipt of colonoscopy	Nurse assessment with outcome of not proceeding to colonoscopy
Nurse assessment with outcome of not proceeding to colonoscopy	Receipt of colonoscopy

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 k th 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,

$S(u) = e^{-H_1(u)-H_2(u)\dots-H_k(u)}$ = 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 k th 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.

[Gray 1988] RJ Gray. A class of K-sample tests for comparing the cumulative incidence of a competing risk. The Annals of statistics (1988): 1141-1154

[Fine and Gray 1999] JP Fine and RJ Gray. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association 1999; 94.446: 496-509



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

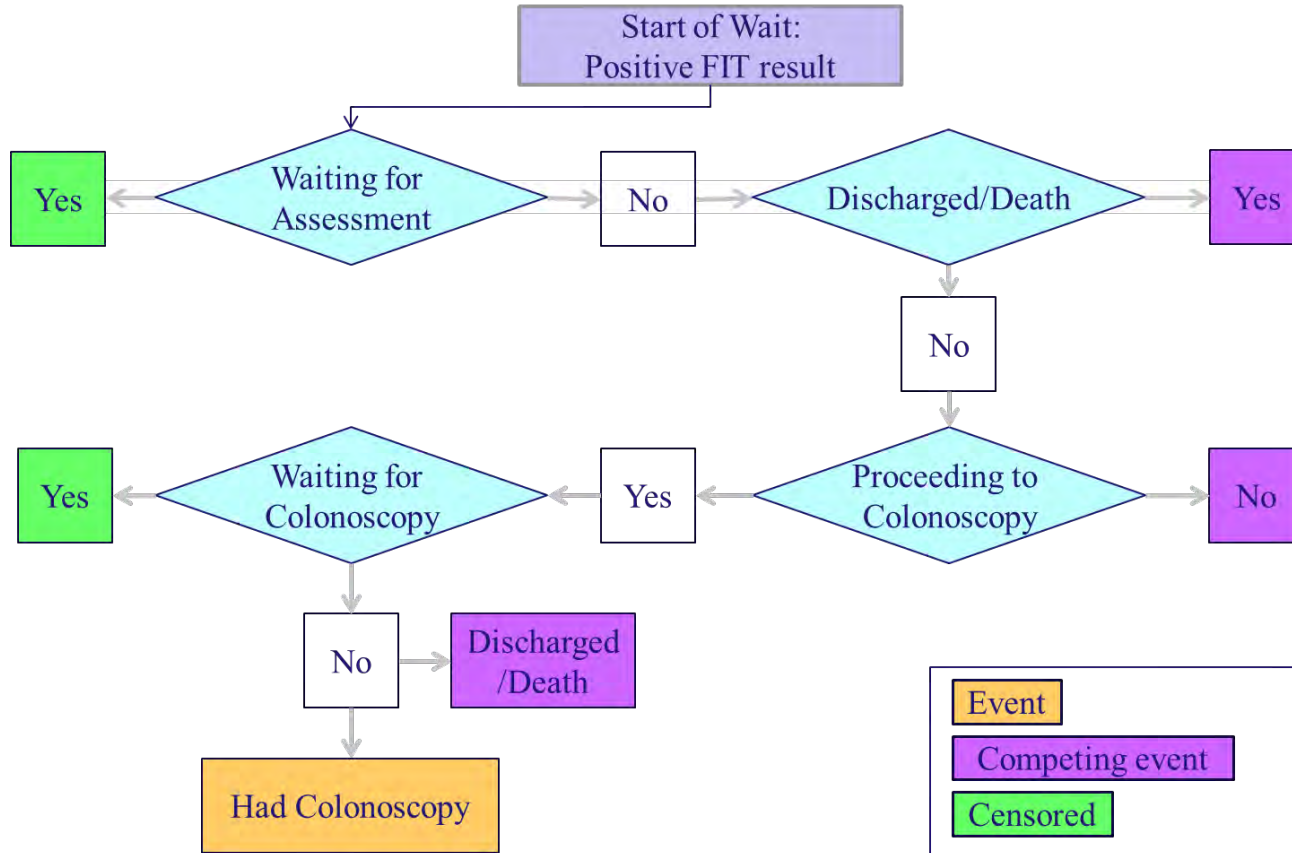
- It can underestimate the time to procedure because it systematically excludes those clients that could have longer wait times
- It does not recognize time spent in queue by individuals who for some reason are no longer proceeding to have the procedure

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



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

VIEWTABLE: Work.Wait1

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

Example – Time to Colonoscopy

The Data

- Number and percentage of clients in the different states

The FREQ Procedure

	Frequency	Percent	Cumulative Frequency
discharged	40	0.12	40
had cscope	23311	69.00	23351
not proceeding	8444	24.99	31795
still waiting	1989	5.89	33784

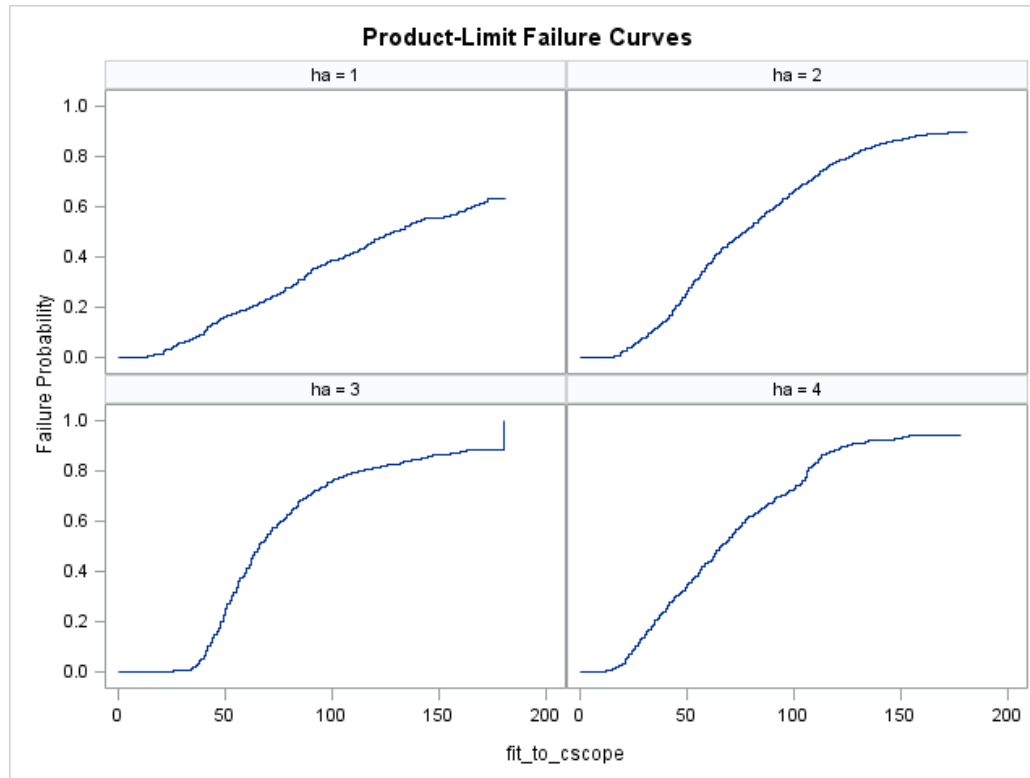
Example – Time to Colonoscopy

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

Stratum: ha	fit_to_cscope	Survival	Failure	Survival Standard Error	Number Failed	Number Left
1	60.000	0.8075	0.1925	0.0102	287	1154
2	60.000	0.6279	0.3721	0.0103	830	1344
3	60.000	0.5898	0.4102	0.0132	573	781
4	60.000	0.5585	0.4415	0.0129	666	799

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;
```

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;
```

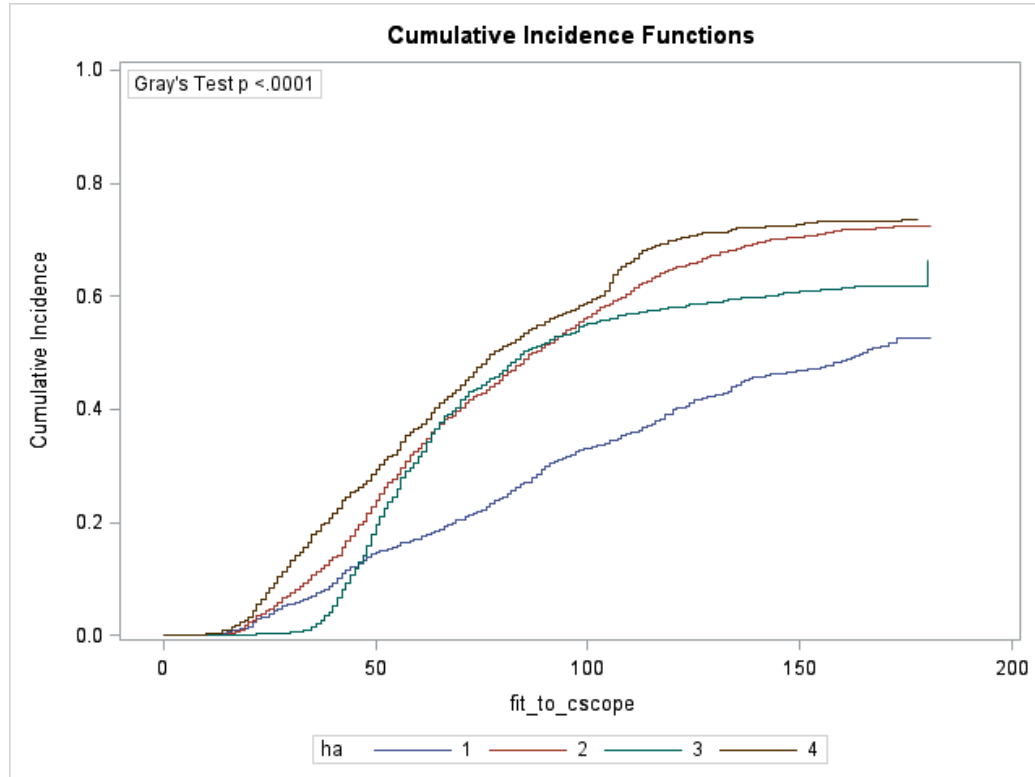
For reference: Standard KM code

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

Competing risk code

Example – Time to Colonoscopy

Competing Risk Non-parametric Method



CIF for each health region overlaid on one plot.

Gray's Test for Equality of Cumulative Incidence Functions		
Chi-Square	DF	Pr > Chi-Square
342.0487	3	<.0001

Example – Time to Colonoscopy

Competing Risk Non-parametric Method

Competing risk:
Summary of failure outcomes

Summary of Failure Outcomes					
Stratum	ha	Failed Events	Competing Events	Censored	Total
1	1	737	306	635	1678
2	2	1699	520	292	2511
3	3	1081	580	155	1816
4	4	1283	408	113	1804
Total		4800	1814	1195	7809

Kaplan Meier:
Censor summary

Summary of the Number of Censored and Uncensored Values					
Stratum	ha	Total	Failed	Censored	Percent Censored
1	1	1678	737	941	56.08
2	2	2511	1699	812	32.34
3	3	1816	1081	735	40.47
4	4	1804	1283	521	28.88
Total		7809	4800	3009	38.53

Example – Time to Colonoscopy

Competing Risk Non-parametric Method

ha	fit_to_cscope	Cumulative Incidence	Standard Error	95% Confidence Interval	
1	60.000	0.1710	0.00919	0.1534	0.1895
2	60.000	0.3305	0.00939	0.3122	0.3490
3	60.000	0.3155	0.0109	0.2943	0.3370
4	60.000	0.3692	0.0114	0.3469	0.3914

Competing Risk estimates:
The probability of receiving a colonoscopy as the first event prior to, or on, 60 days.

Stratum: ha	fit_to_cscope	Survival	Failure	Survival Standard Error	Number Failed	Number Left
1	60.000	0.8075	0.1925	0.0102	287	1154
2	60.000	0.6279	0.3721	0.0103	830	1344
3	60.000	0.5898	0.4102	0.0132	573	781
4	60.000	0.5585	0.4415	0.0129	666	799

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;
```

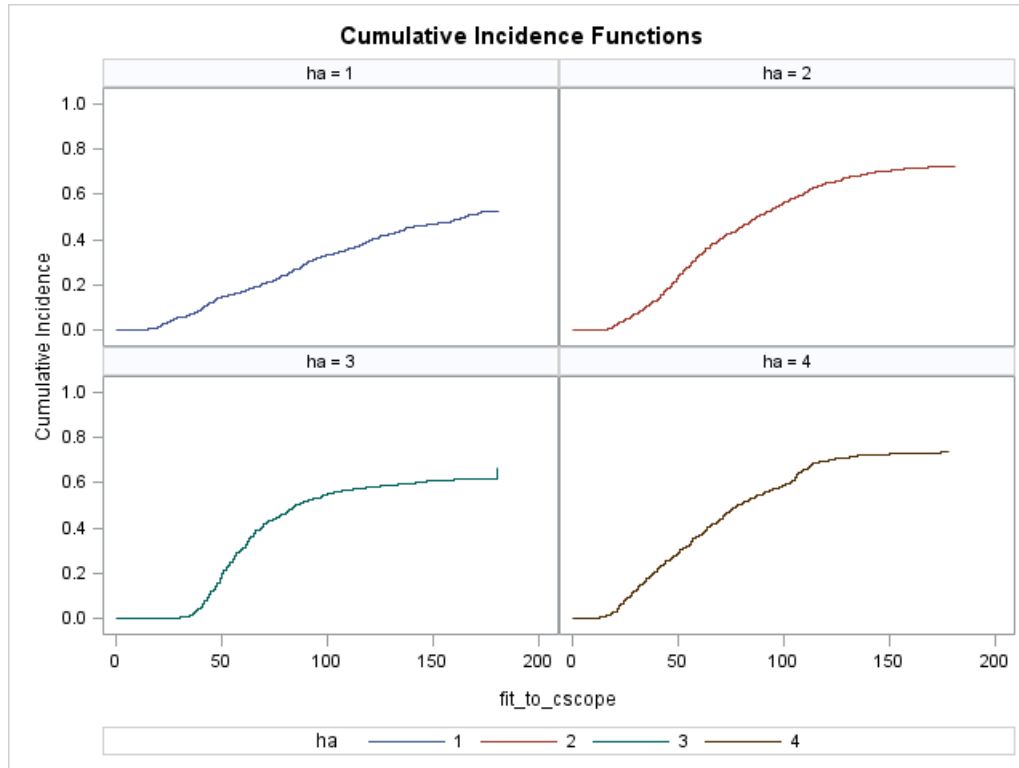
```
STRATA ha / GROUP=sex;
```

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:

VIEWTABLE: Work.Cr_cif_output (Cumulative Incidence Estimates)

	Event of Interest	ha	fit_to_cscope	Number At Risk	Number of Failed Events	Number of Events of All Types	Number Censored	Cumulative Incidence Function Estimate	Standard Error for CIF by Aalen method	ALPHA	Transform for CIF Confidence Limits	Lower 95% Confidence Limit for CIF	Upper 95% Confidence Limit for CIF	Stratum Number
1	1	1	0	1678	0	0	0	0	0	0.05		.	.	1
2	1	1	0	1678	0	3	0	0	0	0.05	LOGLOG	.	.	1
3	1	1	1	1675	0	19	0	0	0	0.05	LOGLOG	.	.	1
4	1	1	2	1656	0	8	0	0	0	0.05	LOGLOG	.	.	1
5	1	1	3	1648	0	11	0	0	0	0.05	LOGLOG	.	.	1
6	1	1	4	1637	0	5	0	0	0	0.05	LOGLOG	.	.	1
7	1	1	5	1632	0	9	0	0	0	0.05	LOGLOG	.	.	1
8	1	1	6	1623	0	6	0	0	0	0.05	LOGLOG	.	.	1
9	1	1	7	1617	0	3	0	0	0	0.05	LOGLOG	.	.	1
10	1	1	8	1614	0	2	0	0	0	0.05	LOGLOG	.	.	1
11	1	1	0	1612	0	0	0	0	0	0.05	LOGLOG	.	.	1

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.

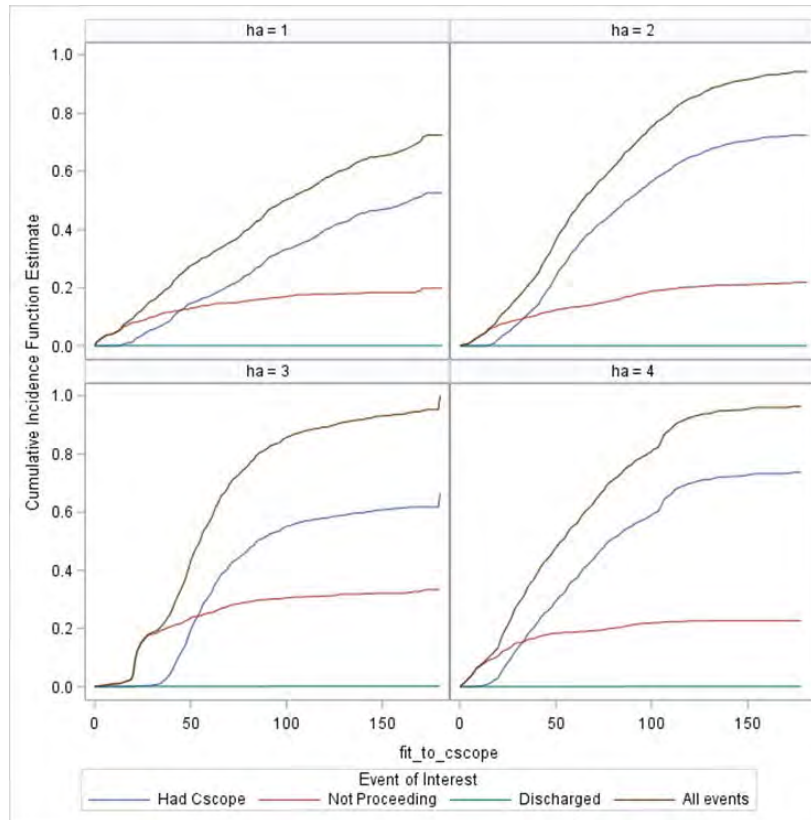
Example – Time to Colonoscopy

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;
```

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```
DATA cr_cif_output3;
  SET cr_cif_output cif;
RUN;
```

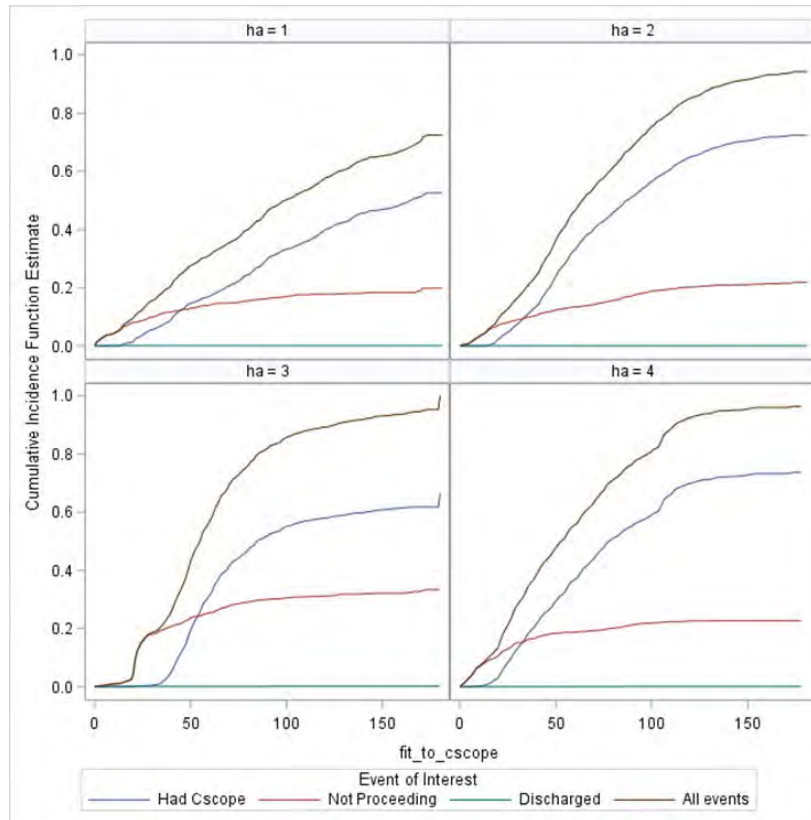
```
PROC FORMAT;
  VALUE event 1='Had Cscope'
  2='Not Proceeding'
  3='Discharged'
  4='All events';
RUN;
```

```
PROC SGPANEL DATA=cr_cif_output3;
  FORMAT failcode event.;
  PANELBY ha;
  SERIES X=fit_to_cscope Y=cif
  / GROUP=failcode;
RUN;
```

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Example – Time to Colonoscopy

Competing Risk Non-parametric Method



Example – Time to Colonoscopy

Competing Risk Non-parametric Method

Health Region	Colonoscopy clients only – receipt in 60 days	KM method – receipt of colonoscopy	Competing risk – receipt of colonoscopy	Competing risk – composite of all events
1	0.23	0.19	0.17	0.31
2	0.52	0.37	0.33	0.46
3	0.60	0.41	0.32	0.57
4	0.47	0.44	0.37	0.56



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?

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