PhUSE 2013

Paper SP06

Computing the 'Competing Risks'

Modeling Survival Data with Competing Risk Events using SAS Macros

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ABSTRACT

Competing Risk (CR) event is one that a patient may experience (other than the event of interest) which can prevent the event of interest from occurring. A naive use of classical survival analysis methods in the presence of CR leads to a bias by overestimating the probability of disease incidence. Hence it is important to account for CR events when estimating disease incidence. This can be done using a cumulative incidence function (CIF) calculated by appropriately accounting for the presence of CR events. A nonparametric approach to implement above is possible using SAS in-built macro '%CIF'. This approach however, cannot directly model the effect of covariates or prognostic factors on CIF. A model-based approach proposed by Gray and Fine (1999) can overcome this problem. Present paper demonstrates both the approaches to deal with survival data in presence of CR through examples using SAS® macros.

Key words: Competing risk, Cumulative incidence, %CIF, survival analysis.

INTRODUCTION

Survival analysis encompasses investigation of time- to- event data; where time from some defined origin to an event of interest is measured. Event of interest are events like cancer relapse, myocardial infarction, discharge from hospital or death due to a specific cause. The feature that makes survival data analysis special is 'censoring'; i.e. not all subjects in the study will have experienced the event of interest at the end of the follow-up period. The main assumption of censoring is that any subject whose survival time is censored will experience the event of interest if followed up long enough.

Time to event is described by the survival function, presenting the probability of an individual surviving up to time t and the hazard function, representing the rate of occurrence of the event at time t. Kaplan–Meier estimation of survival probabilities, log-rank test for comparing survival distributions and Cox's proportional-hazards model for assessing the effect of predictors on survival are widely used analysis tools. These tools are based on the premises of the assumption of non-informative censoring; i.e. participants who drop out of the study do so due to the reasons unrelated to the study. Violation of this assumption can invalidate any sort of survival analysis, from Kaplan-Meier estimation to the Cox model.

COMPETING RISK

Some times, a patient can experience more than one type of event. If the event other than the event of interest occurs, and if it alters the probability of experiencing the event of interest then these events are known as 'Competing Risk events' (CR). For example, in the study of incidence of mortality due to breast cancer (BC), among the BC patients, a patient may die due to causes unrelated to the disease. Hence, 'death due to other cause' is a competing risk event for breast cancer specific mortality. Competing risks prevent an event of interest from occurring rather than just preventing the researcher from seeing it happen (censoring). Assumption of censoring does not hold true here as competing risks (death due to other cause) make the event of interest (BC death) impossible to observe.

Examples

- Researcher is interested in estimating incidence of ovarian cancer among BC patients.
  - A BC patient dies due to breast cancer prior to development of ovarian cancer is a CR,
  - A BC patient undergoes a prophylactic treatment for breast cancer, which makes the possibility of developing ovarian cancer to almost nil and hence it is a CR for development of ovarian cancer.

- In the study of local relapse, time to local relapse is of interest. Relapse at other locations or death without local relapse are competing risk events.

CUMULATIVE INCIDENCE FUNCTION

Classical survival analysis methods, used in presence of CR, lead to a bias as they ignore the information in censoring due to CR event. Kalbfleisch and Prentice (1980) introduced 'Cumulative Incidence Function' approach to analyze survival data when CRs exist. Cumulative incidence function (CIF) is the cumulative probability of an event of

interest (failure from a specific cause) over time. If there are two or more treatment groups in data, it is often of interest to estimate the cumulative incidence of an event, and also to determine whether there is a difference in the cumulative incidence rates among treatment groups. In standard survival analysis this is dealt using Log Rank test. In presence of CR, use of log-rank test is not appropriate. Gray (1988) identified this issue and proposed a non parametric approach for comparing cumulative incidence functions among different groups in the presence of competing risks.
Nonparametric approach, however cannot directly model the effect of covariates or prognostic factors on CIFs. A model-based approach proposed by Gray and Fine (1999) can overcome this problem. It is a direct regression modeling of the effect of covariates on the cumulative incidence function for competing risks data.

Present paper is divided into two major parts

I. Theoretical concepts of survival analysis data in presence of competing risk events
II. Programming aspects using SAS with the help of an example
   - '%CIF' macro: It implements non parametric method for estimating cumulative incidence functions. This macro also enables user to test for the equality of cumulative incidence functions across treatment groups.
   - '%PSHREG' macro: Developed by researchers from Medical University of Vienna. It enables us to implement model proposed by Gray and Fine (1999).

Part I- CUMULATIVE INCIDENCE FUNCTION ESTIMATION IN THE PRESENCE OF COMPETING RISK EVENTS

Cumulative Incidence function (CIF) is also referred as 'subdistribution function' in literature. CIF, hazard of CIF and cause specific hazard function are some of the important mathematical functions in the setting of competing risks.

Consider a data of n observations with k different possible competing risk events. Some subjects do not experience any of the k events and therefore are 'censored observations'. Let d_{ji} be the number of events of type j that occur at time t_i and j =1, 2,..... k .The number at risk at time t_i is denoted by n_i .The CIF can be calculated as the sum over all t_i of the probabilities of observing event j at time t_i , given that the individual did not experience any event prior to t_i .The survival probability of remaining event-free prior to t_i is $\hat{S}(t_{i-1})$. Therefore cumulative probability of being event-free immediately prior to t_i and experiencing an event of type j at t_i is

$\hat{F}_j(t) = \sum_{t_i \le t} \hat{h}_{ji}\, \hat{S}(t_{i-1})$, where h_{ji} is the 'cause specific hazard' for event j at time t_i. It can be estimated as $\frac{d_{ji}}{n_i}$.

Thus CIF can be estimated as $\boxed{\hat{F}_j(t) = \sum_{t} \frac{d_{ji}}{n_i} \hat{S}(t_{i-1})}$ .....(1)

CIF estimator for an event of type j depends not only on the number of individuals who have experienced this type of event (j[th] event), but also on the number of individuals who have not experienced any other type of event.

THE KAPLAN–MEIER ESTIMATE APPLIED TO SURVIVAL DATA SUBJECT TO COMPETING RISK OVERESTIMATES THE EVENT RATE

It is common practice to apply the KM method to estimate the probability of an event when there is a single event of interest and no competing risks. The typical formula for the KM estimate is

$$\hat{S}(t) = \prod_{t_i \le t} \frac{n_i - d_i}{n_i} \quad \text{..... .... (2)}$$

where $t_1 < t_2 < t_3 < .....$ are the ordered time points at which an event was observed, n_i and d_i represent the number of patients at risk and the number of events at time t_i . This also can be expressed as the probability of event

$$P(t) = 1 - S_i(t) = \sum_{t_i \le t} \frac{d_i}{n_i} \hat{S}(t_{i-1}) \text{ .... (3)}$$

In the presence of CR above formula gets modified depending on the number of events a cohort may experience. Without loss of generality, suppose there are at least 2 types of events: event of interest, identified with the subscript 'e', and the competing risk event, identified with the subscript 'cr'. Kalbfleisch and Prentice (1980) introduced the formula for the probability of an event of interest in the presence of CR:

$$\hat{P}_e(t) = \sum_{t_i \le t} \frac{d_{e_i}}{n_i} \hat{S}(t_{i-1}) \quad \text{..... (4)}$$

It is interesting to note the relationship between (3) and (4)

Since d_i is the number of all events at t_i, it comprises of the sum of the number of events of interest d_{ei} and the number of CR events d_{cri} at time t_i.

$$d_i = d_{e_i} + d_{cr_i} \quad \text{..... (5)}$$

Therefore, probability of total no. of events d_i at time t_i can be presented as

$$\hat{p}(t) = \hat{p}_e(t) + \hat{p}_{cr}(t)$$

Thus the probability of all events (estimated by 1-KM) can be decomposed in the probabilities for each type of event. Thus cumulative probability of event based on KM estimator overestimates the probability of event of interest if CRs are present and get ignored in the analysis. The magnitude of overestimation depends on the incidence of competing events.

COMPARISON OF CUMULATIVE INCIDENCE FUNCTIONS AMONG GROUPS

If two or more treatment groups exist among the subjects then usually interest lies in testing whether there is any group effect on survival. For example if there are two treatments or doses of the drugs then one may would be keen to know how the incidence of an event of interest vary among these groups. The log-rank test or Gehan-Wilcoxon test are popularly used options in standard survival analysis settings. We can not use it in presence of competing risk events since cumulative incidence function of an event is not defined solely by its corresponding cause-specific hazard. (Gray 1988; Pepe 1991; Fine and Gray 1999).
When treatment effects on the cumulative incidence function are compared, the null hypothesis H_0 is that the cumulative incidence functions are identical across treatment groups pertaining to CR setting. To test this hypothesis, Gray (1988) proposed a nonparametric test (modified chi-square test) for testing equality of the cumulative incidence functions.
Researcher may be further interested in observing probability of a specific endpoint say cumulative incidence of an event of interest for individuals with a given set of covariate or diagnostic factors in competing risk settings. Non parametric approach discussed earlier, cannot directly model the effect of covariates or prognostic factors on CIFs and therefore one has to look beyond theory of Gray proposed for nonparametric settings.

MODELING APPROACH TO TEST THE EFFECT OF COVARIATES IN COMPETING RISK SETTING

Fine and Gray in 1999 introduced an approach to directly model the effect covariates on CIF. Fine and Gray (F&G) modified the Cox PH model to allow for presence of CR. The technical modification consists of keeping the CR observations in the risk set with a diminishing weight. This way F&G model the subdistribution hazards. The effects estimated using F&G model shows the differences between the treatment groups in terms of subdistribution hazard ratios. Interested readers are recommended to refer to the paper by Fine and Gray (1999) for methodological details.

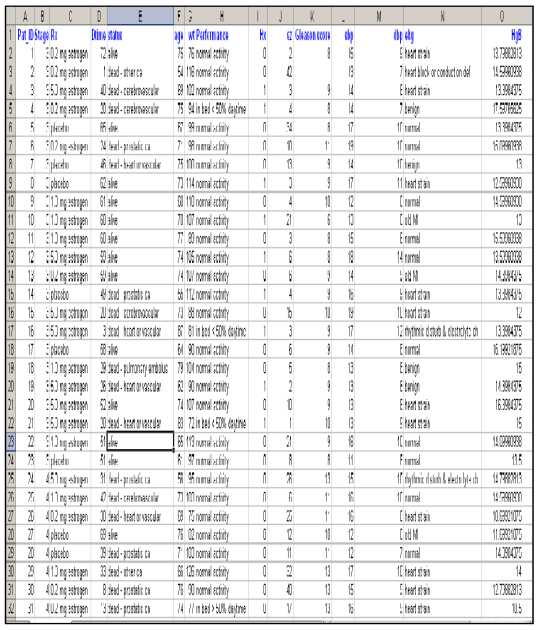
A SAS macro %PSHREG is developed by researchers from Medical University of Vienna. It enables us to implement model proposed by F&G (1999). The macro modifies an input data set by separating follow-up periods of patients with competing events into several sub-periods as suggested by F&G.

In PSHREG macro, proc PHREG has been modified to compute the proportional subdistribution hazards model. Therefore %PSHREG macro facilitates to make full use of the various options offered by PROC PHREG for modeling. %PSHREG macro can also verify the assumptions for proportional hazards modeling by allowing the analysis of residuals and can be extended to model the time-dependent effects of covariates. However, discussion of these methods is outside the scope of this paper.

BYAR STUDY

To understand the concept of CIF and illustrate the application of %CIF and % PSHREG macro, this paper uses part of data from a randomized clinical trial (Byar study by Byar and Green) comparing treatments for prostate cancer. Primary interest was to assess the effect of treatment (Rx) on primary outcome namely prostate cancer related death. Five hundred and two prostate cancer patients with clinical stages III or IV were randomized to receive either a low or high doses of the active treatment diethylstilbestrol (DES).

BYAR Data



Understanding the data

1. **Pat_ID:** Identification of subject
2. **Staging:** Disease staging (Stage III and IV)
3. **Treatment (Rx):** binary variable
   - 0 - Subjects receiving placebo or 0.2 mg of DES – lower dose
   - 1 - Subjects receiving 1.0 or 5.0 mg of DES – higher dose
4. **Dtime:** follow-up time in months
5. **Stat:** Outcome as Alive, cancer deaths, CVD related deaths, deaths due to other reasons.
   - 0- Censored
   - 1- Event of Interest (Cancer deaths)
   - 2- Competing Events (Deaths due to other reasons)
6. **Performance:**
   - 0 – Normal and
   - 1- Limitation of activity
7. **Lesion:** Size of primary lesion categorized as
   - 0- <30 cm2
   - 1- >=30 cm2
8. **Gleason :** Gleason score
   - 0<=10
   - 1>10
9. **Age, weight:** Age and weight of subjects

Data interpretation: Patient Id 001 with prostate cancer stage III is randomized to lower DES arm with primary response as 'Alive' at 72 months of study entry.

DATA MANAGEMENT (BYAR STUDY)

ID	Follow-up (months)	Status	Scenario (I)		Scenario (II)	
001	72	Alive	C	0	C	0
002	1	Dead other cause	C	0	E-CR	2
[illegible]		Alive	C	0	C	[illegible]
004	40	Alive	C	0	C	0
005	65	Dead Prostate Can	E	1	E	1
006	24	Dead Prostate Can	E	1	E	1
----	-----	----	----	----	-----	----
----	-----	-------	----	-----	-----	-----
----	-----	-----	----	-----	-----	-----
501	34	Dead cerebrovascu	C	0	E-CR	2
502	25	Dead heart disease	C	0	E-CR	2

Non cancer deaths are censored

NON CANCER DEATHS grouped as 'Competing Risk

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

CUMULATIVE INCIDENCE OF CANCER DEATHS IGNORING CR EVENTS

Event of interest is 'cancer death'. In 1st scenario all other events like alive and death due to cerebrovascular disease or other causes experienced by the subjects apart from cancer deaths are considered as 'censored'. Incidence of an event of interest is estimated using product limit or (1-KM) method in this scenario.

CUMULATIVE INCIDENCE OF CANCER DEATHS ACCOUNTING FOR CR EVENTS

In II[nd] Scenario, cancer deaths are 'event of interest'. Deaths due to cerebrovascular disease or due to other causes experienced by the subjects are grouped under the umbrella of Competing Risk events. And those have not yet experienced the event of interest or left the study or loss to follow-up are 'censored'. Incidence of an event is estimated using % CIF macro.

ESTIMATION OF CUMULATIVE INCIDENCE FUNCTION USING %CIF MACRO

Requirement of Macro: The %CIF macro requires Base SAS and SAS/IML in SAS 9.2 or later releases. SAS/GRAPH is also required in SAS 9.2.

Website: http://support.sas.com/kb/45/997.html
Description of macro: The %CIF macro computes the crude cumulative incidence function estimates for survival data whose endpoints are subjected to competing risks (Klein and Moeschberger, 2003).

Statement: %CIF (Data=, out=, Time=, Status=, Event=, Censored=, Group=, options=)

```
%CIF(DATA=BYAR,TIME=DTIME,STATUS=Stat,EVENT=1,CENSORED=0,GROUP=DOSE, TITLE= CUMULATIVE
INCEDENCE FUNCTION IN LOWER DES VS. HIGHER DES DOSE);
```

Parameters

- DATA=Byar data set to analyze.
- TIME= 'dtime' variable specifies follow-up time collected in months.
- STATUS = 'Stat' specifies the variable that contains response at the time of follow-up.
- EVENT =1 specifies the value for the event of interest. In this example, the event of interest is cancer death.
- CENSORED=0 specifies the value used to indicate censoring. Values that are specified with the STATUS Parameter other than those specified with the EVENT= and CENSORED= parameters are for competing risks.
- GROUP= 'Dose' (Rx) requests a cumulative incidence curve for group (lower and higher dose of DES).

Figure 1: Cumulative Incidence Estimates with 95% Confidence Limits (for dose 0 and Dose 1)

DOSE	dtime	CIF	StdErr	Lower 95% Limits	Upper 95% Limits
0	0	0.00000	0.000000	0.00000	0.00000
0	0	0.01594	0.007920	0.00531	0.03796
0	1	0.02789	0.010413	0.01238	0.05406
0	2	0.04781	0.013493	0.02606	0.07928
0	4	0.05578	0.014513	0.03193	0.08902
.	.	.	.	.	.
.	.	.	.	.	.
0	71	0.46501	0.036988	0.39117	0.53545
0	74	0.49077	0.043131	0.40387	0.57190
1	0	0.00000	0.000000	0.00000	0.00000
1	0	0.01594	0.007920	0.00531	0.03796
1	2	0.01992	0.008837	0.00753	0.04344
1	4	0.02390	0.009660	0.00989	0.04880
.	.	.	.	.	.
.	.	.	.	.	.
.	.	.	.	.	.
.	.	.	.	.	.
1	65	0.30038	0.030932	0.24112	0.36171
1	66	0.30976	0.031879	0.24856	0.37282
1	70	0.32490	0.034574	0.25836	0.39303

For Low dose, CIF estimated as 0.49 (95% CI 0.40, 0.57)

Figure 1 displays %CIF output of estimates of the cumulative incidence functions of cancer death for each of the Rx group, the standard errors, and the 95% confidence intervals for Scenario II.

COMPARISON OF INCIDENCE OF CANCER IN SCENARIO I AND SCENARIO II

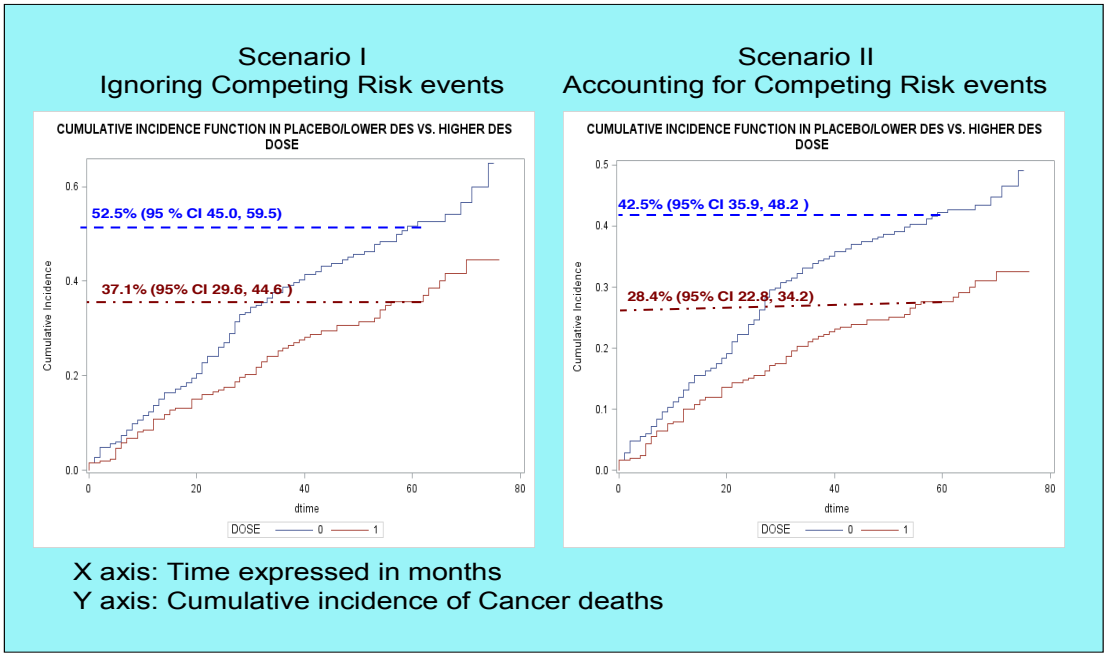


Figure II Incidence of Cancer Deaths without accounting for competing risk (Using 1-KM approach) and Incidence of Cancer Deaths accounting for competing risk (using %CIF macro) at same time point i.e. at 60 month of follow-up.

Cumulative incidence of cancer deaths is [42.5% (95% CI 35.9, 48.2)] in scenario II is lesser than that of cumulative incidence [52.5% (95 % CI 45.0, 59.5)] in scenario I at 60 month time point in higher dose of DES. Similar is true with lower dose of DES. It is [28.4% (95% CI 22.8, 34.2)] vs. [37.1% (95% CI 29.6, 44.6)] in scenario II and scenario I respectively.
Thus, we observe that, cumulative incidence of event of interest gets overestimated if CR events are present and are ignored during estimation of incidence of event of interest.

TESTING THE EQUALITY OF CUMULATIVE INCIDENCE FUNCTIONS OF CANCER DEATHS BETWEEN TREATMENT GROUPS

Next step is to test the effect of lower and higher doses of DES on incidence of cancer related deaths. %CIF macro uses Gray's approach to answer the question. Results of the test are presented in the output. This result is presented by default using %CIF macro.

Gray's Test for Equality of Cumulative Incidence Functions

Chi-Square	DF	Probability
10.885	1	0.0010

Figure III presents p value using Gray test to test the equality of Incidence functions

Cumulative incidence of cancer deaths is significantly different (p=0.0010) between the low and high DES treatment groups.

Let's check stratified cancer death incidence in two treatments, where stratum is 'disease staging' defined as stage III and IV using % CIF macro. It is enabled using 'STRATA= parameter option'.

```
%CIF(DATA=byar,TIME=DTIME,STATUS=Stat,EVENT=1,CENSORED=0,GROUP=DOSE, STRATA=stage);
```

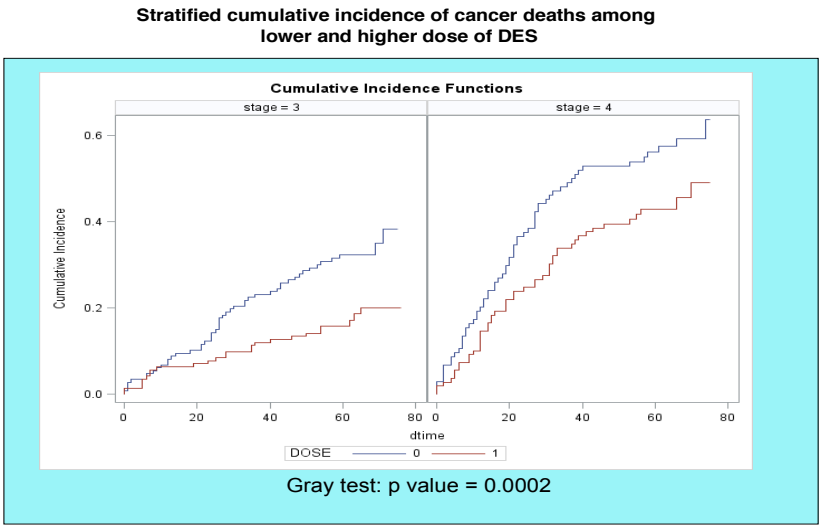


Figure IV Stratified test of cumulative incidence between treatment groups

Thus, p value 0.0002 is estimated based on Gray's test. It presents p value testing difference between lower and higher dose of DES stratified on staging of patients.

%PSHREG MACRO TO ESTIMATE THE DIFFRENCE IN CIF BETWEEN GROUPS WITH SET OF COVARIATES

In Byar Study data, a set of covariates such as age, weight, performance, gleason score category and lesion are present. % PSHREG macro directly models the difference in CIF of an event interest in presence of covariates.

Requirement of Macro: The %PSHREG macro requires SAS in SAS 9.2 or later releases. SAS/GRAPH is also required in SAS 9.2.

Website: http://cemsiis.meduniwien.ac.at/en/kb/science-research/software/statistical-software/pshreg/

Description: The %PSHREG macro prepares data to fit a proportional subdistribution hazards model as proposed by F&G

Statement: %PSHREG (Data=, TIME=, CENS=, FAILCODE=, CENCODE=, VARLIST=, CENGROUP=, OPTIONS=);

```
%pshreg(data=Byar, time=dtime, cens=stat, failcode=1, cencode=0,  varlist=dose age wt
hx performance gleason lesion, cuminc=1, options=rl);
```

Parameters

- DATA=Byar data set to analyze.
- TIME= 'dtime' variable specifies follow-up time collected in months.
- CENS = 'Stat' specifies the variable that contains response at the time of follow-up.
- FAILCODE ='1' is the indicator value to indicate event of interest. Default value is 1.
- CENCODE = '0' is the indicator value to indicate censoring status. Default value is 0.
- VARLIST= dose, age, wt, hx, performance, gleason and lesion is a list of covariates.
- CUMINC= 1 specifies that it plots the cumulative incidence curves. It is stratified based on the levels of the first variable specified in the variable list. Now, it plots the cumulative incidence curves based on the levels of dose (i.e. higher and lower dose of DES).
- OPTIONS='rl' specifies ratio limits for hazard ratio calculated. Many options those are available with proc phreg can be used here.

Output: The PSHREG macro: Fine-Gray model

The PHREG Procedure

Model Information

Data Set	WORK.DAT_CRR
Dependent Variable	_start_
Dependent Variable	_stop_
Censoring Variable	_censcrr_
Censoring Value(s)	0
Weight Variable	_weight_
Ties Handling	BRESLOW

Number of Observations Read	5150
Number of Observations Used	4938

Summary of the Number of Event and Censored Values

Total	Event	Censored	% Censored
4938	175	4763	96.46

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	2072.889	1979.077
AIC	2072.889	1993.077
SBC	2072.889	2015.231

Cumulative Incidence Functions

The PSHREG macro: Fine-Gray model

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	StdErr Ratio	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits		Label
DOSE	1	-0.60268	0.15523	0.994	15.0742	**0.0001**	**0.547**	0.404	0.742	
age	1	-0.02084	0.00992	0.952	4.4138	0.0356	0.979	0.961	0.999	age
wt	1	-0.00848	0.00569	0.989	2.2147	0.1367	0.992	0.981	1.003	wt
hx	1	-0.20670	0.16291	1.009	1.6098	0.2045	0.813	0.591	1.119	hx
performance	1	0.28631	0.24062	1.052	1.4159	0.2341	1.332	0.831	2.134	
gleason	1	0.89924	0.16689	1.001	29.0348	**<.0001**	**2.458**	1.772	3.409	
lesion	1	0.97633	0.18373	0.984	28.2364	**<.0001**	**2.655**	1.852	3.805	

Figure V indicates the output of running %PSHREG macro

Results of %PSHREG are presented above. When %PSHREG is run, by default, Proc phreg is invoked using modified dataset to estimate Fine-Gray model and its output is directly shown in the output destination. Three model fit statistics are calculated: -2log L, AIC and SBC. Output also displays a summary of the number of events and censored values. It is important to note that the quantity displayed in the summary of events or censored does not indicate the real number of patients.

In analysis of Maximum Likelihood Estimate table, results are presented with the parameter estimate, standard error, standard error ratio, chi-square value, p-value and hazard ratio (subdistribution hazard ratios denoted by Hazard ratios). They have similar interpretation as hazard ratios. From the results shown above,

- Dose has significant impact on cancer deaths (HR=0.547, p<0.0001), indicating higher dose is protective against cancer deaths in comparison to the lower dose of DES.
- Two more variables have significant influence on the outcome. High Gleason score and higher lesion size have higher risk for cancer related deaths (HR =2.45 and 2.65 with p<0.0001 respectively).

COMPARISON OF RESULTS OF % PSHREG MACRO WITH R PACKAGE 'cmprsk'

Interested users can cross check the results obtained using % PSHREG by using crr function of open source R software package 'cmprsk'.

LIMITATIONS OF PAPER

This paper discusses scenario of one competing risk event. In reality, complex trials mainly in elder population where multimorbidity is more prevalent may come across more than one competing risk scenario. There, we need to extend same method for analyzing the data. Secondly, it is also possible to compute analysis of time dependent effect of covariates on CIF using % PSHREG but this paper introduces few features of %PSHREG and reader is suggested to refer to the report of macro for further insight.

CONCLUSION

For any disease specific drug development program, estimating disease incidence accurately is a key factor. Presence of competing risks may hamper the estimation of true disease incidence. Therefore, it is crucial to recognize the presence of competing risks if any. As illustrated through the BYAR study; if competing risks are ignored, cancer death incidence gets overestimated when computed using KM approach. %CIF macro facilitates estimation of disease incidence and treatment comparison in competing risk setting. %PSHREG macro enables to assess the effect of covariates.

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ACKNOWLEDGMENTS

Thanks to the group from Medical University of Vienna for providing the free %PSHREG Macro program. I also thank colleagues at Cytel who took the time to review the paper and provide their valuable feedback.

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