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Surviving the Cox Proportional Hazards Model with the POWER Procedure

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ABSTRACT

Prior to the release of SAS/STAT® 14.2, power analyses for survival methods were immured to a single option—TWOSAMPLESURVIVAL—within the POWER procedure. The weakness of TWOSAMPLESURVIVAL is its inability to address the aspects of survival analysis like the Cox proportional hazards model. Modeling is a key tool toward understanding this association of a given number of covariates with an outcome and thus requires a high level of statistical power. Statistical power informs researchers of the probability of their study predicting a conclusion to be true when in fact it should be false, which is called a type II error. The appropriate sample size ensures a low probability of a type II error equating to a high level of statistical power. With the new features in SAS/STAT 14.2, researchers are now able to conduct power analyses for the Cox proportional hazards model in survival statistics by using the COXREG option in PROC POWER. Researchers can now prospectively power survival models to maintain a high level of confidence that the association between the covariates and survival time is reliable and robust.

INTRODUCTION

Survival analysis is a statistical method for analyzing data where the response is measured from time, beginning of the study, until occurrence of a specific event of interest (Kleinbaum and Klein 2012). For this specific statistical method, the study includes information collected from each observation (patient, participant, etc.) regardless of whether the observation left the study or had the event. Those observations that left or did not have the event are denoted as right censored. These are still included because they provide valuable information from the time they were in the study. There are a variety of analytics that are similar to other types of statistical analyses (i.e. comparison, modeling, etc.), yet in survival analysis those right censored observations are used in the analyses.

One regression model used in survival analysis is the Cox Proportional Hazards Model. The model is commonly used for investigating the association between the survival time of the observations and one or more predictor variables. Understanding how different covariates impact an observation's length of survival can be essential when determining what components to use together in either lengthening or decreasing a survival time of an observation. To develop an accurate model that can be used to generalize to a larger population, the model needs to have the correct sample size. Determining the correct sample size for the model building process is done through the analytical process known as power analysis.

For performing power analysis on the Cox Proportional Hazard Model with PROC POWER COXREG, there are three key functions that are necessary to understand: survival probability, hazard rate, and hazard ratio. Survival probability is the probability that a random individual survives (does not experience the event of interest) past a certain time (t). The hazard rate is the rate per unit of time that an individual experiences the event of interest in the next unit of time given they have survived up until that specified time. The

hazard ratio is the ratio of hazard rates corresponding to conditions described by two levels of a chosen explanatory variable.

POWER ANALYSIS

When conducting research with the goal of publishing, a priority should be ensuring the analysis has a high power. Power analysis stems from the idea of statistical power, which is the probability of making a type II error. A type II error is when a researcher predicts a conclusion to be true when in fact it should be false—a false negative. Through power analysis, the resource usage and design of the study can be optimized, which improves the chances of conclusive results with maximum efficiency. Power can be affected by four primary factors: significance level, sample size, magnitude of the effect of the variable, and variance in the measured response variable. Various power analyses have been developed to accommodate those factors for specific statistical methods (i.e. regression, comparison, predictive, etc.). Within survival statistics there are two methods to determine power in SAS®: TWOSAMPLESURVIVAL and COXREG.

COXREG VS. TWOSAMPLE SURVIVAL

The COXREG and TWOSAMPLESURVIVAL perform the same type of analysis but are meant to be used in different circumstances. An incorrect test leads to inaccurate sample size or power calculations. Just like performing power analyses for other statistical methods that are not survival related, you choose the specific power option that was developed for that specified statistical method. Different power analyses require unique criteria based on the specific statistical method.

The TWOSAMPLESURVIVAL option with PROC POWER was developed by SAS to be used for calculating desired power and sample size for three survival techniques: Log-Rank test, Gehan test, and the Tarone-Ware test. The COXREG option was developed by SAS to be used for those same calculations for the Cox Proportional Hazards Model. For the survival techniques being powered in TWOSAMPLESURVIVAL, the survival probability is being compared between two groups which is different than looking at the predictive ability of covariates or modeling. Using TWOSAMPLESURVIVAL to calculate power or sample size for a Cox Proportional Hazards Model would produce incorrect values due to the option not using the appropriate information for the calculations. The option does not take into consideration the r-square value or the standard deviation yet instead uses other unnecessary information such as accrual time and follow-up time. Not using the correct information is the precise reason why this new option within the POWER procedure is so crucial. A *post-hoc* demonstration of what happens to your power when you use the wrong option is shown below.

HOW TO PERFORM SURVIVAL POWER ANALYSIS IN SAS

TWOSAMPLESURVIVAL

Below is the shell code for performing a TWOSAMPLESURVIVAL test on a balanced design. Table 1 describes what needs to be inputted on each statement line. If the statement has an asterisk (*) attached, then there are certain instances when those statements need to be used. If this procedure is being used prospectively to determine the needed sample size or number of events of interest to achieve a certain power, the `npergroup` line will be filled in as a missing value (.). Otherwise, if the sample size or total number of events is already known, the `power` line will be filled in as missing (.) to determine its value.

```

proc power;
  twosamplesurvival test=
    curve("Control") =
    curve("Treatment") =
    groupsurvival =
    accrualtime =
    followuptime =
    npergroup =
    power = ;
run;

```

SAS Statement Line	Description
twosamplesurvival test	Specific statistical analysis being Conducted: Log-Rank Gehan, or Tarone-ware is supported
curve("Control")	Survival curve for control group
curve("Treatment")	Survival curve for treatment
groupsurvival	Survival curve within each group
accrualtime	Length of time used to recruit participants into the study
followuptime	Length of time in the study past the accrual time
npergroup*	The number of participants within each group
power*	The desired power

Table 1. Statement line descriptions for a TWOSAMPLESURVIVAL balanced design POWER procedure.

Below is the shell code for performing a TWOSAMPLESURVIVAL test on an unbalanced design. Table 2 describes what needs to be inputted on each statement line. If the statement has an asterisk (*) attached, then there are certain instances when those statements need to be used. If this procedure is being used prospectively to determine the needed sample size or number of events of interest to achieve a certain power, then either ntotal or eventstotal line will be filled in as a missing value (.). Only one of those statements can be used in this procedure for a single run. Otherwise, if the sample size or total number of events is already known, the power line will be filled in as missing (.) to determine its value.

```

proc power;
  twosamplesurvival test=
    curve("Control") =
    refsurvival =
    hazardratio =
    accrualtime =
    followuptime =
    groupweights =
    ntotal =
    eventstotal=
    power = ;
run;

```

SAS Statement Line	Description
twosamplesurvival test	Specific statistical analysis being Conducted: Log-Rank Gehan, or Tarone-ware is supported
curve("Control")	Survival curve for control group
refsurvival	Survival curve for the reference group
hazardratio	Hazard ratio or direction of the effect
accrualtime	Length of time used to recruit participants into the study
followuptime	Length of time in the study past the accrual time

SAS Statement Line	Description
groupweights	How the sample size is divide between the two groups
ntotal*	Sample size
eventstotal*	Total number of events of interest
power*	The desired power

Table 2. Statement line description for a TWOSAMPLESURVIVAL unbalanced design POWER procedure.

COXREG

Below is the shell code for performing a COXREG test. Table 3 describes what needs to be inputted on each statement line. If the statement has an asterisk (*) attached, then there are certain instances when those statements need to be used. If this procedure is being used prospectively to determine the needed sample size or number of events of interest to achieve a certain power, then either ntotal or eventstotal line will be filled in as a missing value (.). Only one of those statements can be used in this procedure for a single run. Otherwise, if the sample size or total number of events is already known, the power line will be filled in as missing (.) to determine its value. The statement line eventprob only is needed when computing the initial sample size not number of events of interest.

```
proc power;
  coxreg
    sides =
    hazardratio =
    rsquare =
    stddev =
    power =
    ntotal =
    eventstotal =
    eventprob =;
run;
```

SAS Statement Line	Description
sides	Insert whether doing a one-side test (1) or a two-sided (2)
hazardratio	Hazard ratio or direction of the effect
rsquare	Specifies two scenarios for multiple correlation with the covariates
stddev	Variability
power*	The desired power
ntotal*	Sample size
eventstotal*	Total number of events of interest
Eventprob *	Overall event probability

Table 3. Statement line description for a COXREG POWER procedure.

POWER ANALYSIS DEMONSTRATION

For the demonstration, *post-hoc* power analyses were done using data from a study completed at Spectrum Health in Grand Rapids, Michigan. The study was a comparison between two different heart valve implants to determine what makes one better than the other. To model what makes a better implant, a Cox Proportional Hazards Model was used. Table 1 shows how using the incorrect power options provides a faulty power value.

	COXREG	TWOSAMPLESURVIVAL																																																		
SAS Code	<pre>proc power; coxreg sides = 1 hazardratio = 0.428 rsquare = 0.0171 stddev = 0.5088 power = . eventstotal = 54; run;</pre>	<pre>proc power; twosamplesurvival test=LOGRANK curve("Control")=(5 10 13):(0.99 0.98 0.90) curve("Treatment")=(5 10 12):(0.98 0.88 0.85) groupsurvival="Control" "Treatment" accrualtime=2 followuptime =1 npergroup=401 power=.; run;</pre>																																																		
SAS Output	<table border="1"> <thead> <tr> <th colspan="2">Fixed Scenario Elements</th> </tr> </thead> <tbody> <tr> <td>Method</td> <td>Hsieh-Lavori normal approximation</td> </tr> <tr> <td>Number of Sides</td> <td>1</td> </tr> <tr> <td>R-square of Predictors</td> <td>0.0171</td> </tr> <tr> <td>Test Hazard Ratio</td> <td>0.428</td> </tr> <tr> <td>Test Standard Deviation</td> <td>0.50088</td> </tr> <tr> <td>Total Expected Events</td> <td>54</td> </tr> <tr> <td>Alpha</td> <td>0.05</td> </tr> </tbody> </table> <table border="1"> <thead> <tr> <th>Computed Power</th> </tr> </thead> <tbody> <tr> <td>Power</td> </tr> <tr> <td>0.927</td> </tr> </tbody> </table>	Fixed Scenario Elements		Method	Hsieh-Lavori normal approximation	Number of Sides	1	R-square of Predictors	0.0171	Test Hazard Ratio	0.428	Test Standard Deviation	0.50088	Total Expected Events	54	Alpha	0.05	Computed Power	Power	0.927	<table border="1"> <thead> <tr> <th colspan="2">Fixed Scenario Elements</th> </tr> </thead> <tbody> <tr> <td>Method</td> <td>Lakatos normal approximation</td> </tr> <tr> <td>Accrual Time</td> <td>2</td> </tr> <tr> <td>Follow-up Time</td> <td>1</td> </tr> <tr> <td>Group 1 Survival Curve</td> <td>Control</td> </tr> <tr> <td>Form of Survival Curve 1</td> <td>Piecewise Linear</td> </tr> <tr> <td>Group 2 Survival Curve</td> <td>Treatment</td> </tr> <tr> <td>Form of Survival Curve 2</td> <td>Piecewise Linear</td> </tr> <tr> <td>Sample Size per Group</td> <td>401</td> </tr> <tr> <td>Number of Sides</td> <td>2</td> </tr> <tr> <td>Number of Time Sub-Intervals</td> <td>12</td> </tr> <tr> <td>Group 1 Loss Exponential Hazard</td> <td>0</td> </tr> <tr> <td>Group 2 Loss Exponential Hazard</td> <td>0</td> </tr> <tr> <td>Alpha</td> <td>0.05</td> </tr> </tbody> </table> <table border="1"> <thead> <tr> <th>Computed Power</th> </tr> </thead> <tbody> <tr> <td>Power</td> </tr> <tr> <td>0.116</td> </tr> </tbody> </table>	Fixed Scenario Elements		Method	Lakatos normal approximation	Accrual Time	2	Follow-up Time	1	Group 1 Survival Curve	Control	Form of Survival Curve 1	Piecewise Linear	Group 2 Survival Curve	Treatment	Form of Survival Curve 2	Piecewise Linear	Sample Size per Group	401	Number of Sides	2	Number of Time Sub-Intervals	12	Group 1 Loss Exponential Hazard	0	Group 2 Loss Exponential Hazard	0	Alpha	0.05	Computed Power	Power	0.116
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Table 4. PROC POWER Comparison: COXREG vs. TWOSAMPLESURVIVAL.

CONCLUSION

Having the correct sample size or power is an important piece of doing research, so an investigator needs to ensure they are using the appropriate option. Prior to SAS/STAT 14.2, TWOSAMPLESURVIVAL was only one option within PROC POWER for survival analysis. However, TWOSAMPLESURVIVAL was not designed to accurately calculate the appropriate sample size or power for the Cox Proportional Hazard Model. SAS has now developed an option called COXREG within the POWER procedure to perform those calculations. With this new option, investigators can perform survival modeling with the appropriate sample size for a desired power or perform an accurate *post-hoc* power analysis on their model.

REFERENCES

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