The Magic of Pretest/Posttest & Longitudinal Data Analysis 6 Week Webinar Class

CLASS 5:

SPECIAL CONSIDERATIONS IN PRETEST/POSTTEST & LONGITUDINAL DATA ANALYSIS

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Welcome to **Week 5 Special Considerations in Pretest/Posttest & Longitudinal Data Analysis** of our 6-week webinar class *The Magic of Pretest/Posttest & Longitudinal Data Analysis*.

Introduction

Up to this point in our webinar, we have examined and discussed how *Longitudinal data analysis* (including Pretest/Posttest design) examines how outcomes change over time. However, what if you desired to implement a study that examined how a factor such as *relapse* (e.g., smoking, drinking, illness) occurred over a period of time. Within such an analysis the traditional forms of analysis we have examined at this point, such as multiple linear regression and other types of procedures employing analysis of variance (ANOVA) would not be appropriate. *Relapse* is what is known as an *event occurrence*. In such an analysis, the researcher would be examining whether and/or when an outcome, such as relapse, happens. Thus, the question becomes, which **test** would be appropriate when a researcher is examining *Whether* or *When* an outcome occurs over a period of time.

The Special Consideration of *Whether* and *When*: The Use of Survival Analysis

Survival Analysis represents a popular family of statistical tests that are appropriate for use when a researcher must describe, whether events occur (such as marriage) and/or when events occur (such as mortality) over a period on time. The procedures can describe when an outcome occurs one time, such as high school graduation or multiple times, such as the number of times a study participant leaves a job. However, all *Survival Analysis* studies must have 3 features:

- There must be a well defined "**event**" (you clearly know when the event has happened)
- There must be a clearly defined "**beginning**" of time for observation
- There must be a meaningful "**metric**" for measuring time (minutes, hours, months)

Many times, the research question for a *Survival Analysis* study might mention these features, for example the RQ might state:

After a smoking intervention (beginning of observation), in how many days (time metric/when) does the average person relapse into smoking (event)

The time metric should be measured in units as precise as needed. Thin smaller units are called *continuous*, while thick units (categorical types) are called *discrete*.

Censoring

Consider that the research question above includes the term "*does the average person relapse into smoking.*" This statement seems to have overlooked the fact that many study participants will not relapse in the study period. Furthermore, these is likely, to be attrition in the study (i.e., dropout) that will preclude a researcher from knowing if the event occurred among a certain number of cases. Thus, the question becomes how would a researcher treat such cases when conducting a survival analysis.

The answer is a technique known as *censoring*. A case is censored when a researcher is unaware if the study participant did or did not experience the event due to dropout or if the study participant did not experience the event during the study period.

Types of Censoring:
Informative Censoring vs. *Informative Censoring*

Censoring can be divided into several categories. For example, censoring can be *Non-informative Censoring*, where the investigator understands the reason a case must be censored in an analysis and does so. These reasons may include the aforementioned dropout (due to natural circumstances such as study participant relocation) or the event did not occur over the study period. Here the researcher has a degree of control over the process of censoring. Most survival analysis studies assume this is the primary type of censoring present in analysis.

Censoring may also be classified as *Informative Censoring*, in which case the *dropout of a study participant might occur for a reason related to the study event*. For example, in a study of relapse, a participant might dropout because he or she did relapse and did not want to inform the investigator. This type of censoring creates bias in the findings and is to be avoided whenever possible.

Types of Censoring:
Right Censoring vs. *Left Censoring*

Censoring can also be classified as *Right Censoring*, in which the event time is unknown because *event occurrence* is not observed during the study period.

Censoring can also be classified as *Left Censoring*, which is more problematic. Left censoring involves an event time rendered unknown because the *beginning of time* is not observed effectively. For example, a survival analysis might begin to observe when a condition is developed (event occurrence). However, a study participant might have already started to develop this condition before the observation period. Such as instance would be an example of left censoring.

The Kaplan-Meier Method

One of the most common types of survival analysis is the **Kaplan-Meier** (a.k.a., product-limit) method. The Kaplan-Meier method is a nonparametric (ranked order analysis) method that estimates the probability of an event (dichotomous) past given time points (calculates distribution curve). The survival distributions of two or more groups (between-subjects) can be compared for equality.

Sample Study to Illustrate the Kaplan-Meier Method

We will now design a sample study toward illustrating how to perform and interpret the Kaplan-Meier method. Suppose all 100 people in our Happiness intervention study smoke cigarettes and desire to quit. Likewise, suppose we have an additional group of 50 study participants that attended a hypnosis intervention designed to help them quit or at least curtail smoking. Subsequently, we would want to determine the relative effectiveness of these interventions (the *Happiness* intervention and *hypnosis* intervention) on 3 groups:

- Our experimental intervention group (n=50)
- Our control intervention group (n=50)
- A hypnotherapy group (n=50)

Specifically, we would want to determine if/when smokers that quit after the intervention smoke again (Yes/No).

Let's assume participants were observed for 2 years (104 weeks) after the interventions concluded. Also, let's state that a successful result would be where smokers did not start smoking again or there is a longer length of time before smoking again. For example, if participants in the experimental intervention group started to smoke again towards the end of the second year, but participants in the control intervention group started smoking again in the middle of the first year, then the experimental intervention group would be more effective.

Goals of Kaplan-Meier Study

Our Kaplan-Meier study will encompass two main goals. First, we must determine if there is a *statistically significant* difference between the survival distributions of the three interventions. Second, we must identify *which intervention group* is significantly different the other (known as *all pairwise comparisons*).

6 Test Assumptions of the Kaplan-Meier Method

We will review 6 test assumptions that must be met in order for us to appropriately employ the Kaplan-Meier method of survival analysis, which are:

Assumption 1: The **event status** should be *mutually exclusive* (either Yes or No, no crossover) and *collectively exhaustive* (where all cases are either "censored" or "event"). Our data will meet these criteria as we will be clearly be able to identify if/when a study participant begins to smoke again (Yes/No) after their respective intervention.

Assumption 2: The **survival time**, i.e., the time to an event or censorship, must be **clearly defined and precisely measured**. This is our **time metric**, such as days, weeks, months, years, etc. Our survival time/time metric is in weeks from 0 weeks to a cut-off of 104 weeks.

Assumption 3: Where possible, **left-censoring** should be **minimized or avoided**. Recall, left-censoring occurs when the starting point of an experiment is not easily identifiable effectively. Our study is clear regarding the beginning of the observation period. This would be more relevant if examining smoking (Y/N) after developing a lung disease if it was unclear when the disease was developed.

Assumption 4: There should be **independence of censoring and the event**. In other words, there should be *No Informative Censoring* where the reason why cases are censored does not relate to the event. As for as we know, this assumption has been met within out study.

Assumption 5: There should be **no secular trends** (a.k.a., **secular changes**) that impact the study occurrence. For example, a factor might develop, such as a new drug or treatment that might change outcomes for part of the sample, such as a treatment to curtail smoking. These secular trends would bias the results. As for as we know, this assumption has been met within out study.

Assumption 6: There should be a **similar amount and pattern of censorship per group**. Failure to meet the assumption can lead to false conclusions being drawn about differences in group survival distributions. This will be checked as we analyze our data.

Kaplan-Meier: Needed Variables

To perform the Kaplan-Meier survival analysis, we need at least the four following variables:

1) Case identifier (Variable: ID)
2) Survival time variable (Variable: Time)
3) Event status variable (Variable: Status)
4) Intervention groups (Variable: Group)

Performing Kaplan-Meier

To perform the Kaplan-Meier survival analysis in SPSS go to:

- **Analyze, Survival, Kaplan-Meier**
- Enter *Time* (var.) into the box **Time**
- Enter *Group* (var.) into the box **Factor**
- Enter *ID* (var.) into the box **Label Cases By**

- Enter *Status* (var.) into the box **Status**
  - **Define Event**: Click *Single Value*, enter *1*, click *Continue*
- Click the *Options* box
- Check *Survival table(s)* and *Mean and median survival* (should be checked by default)
- Check *Survival*
- Click *Continue*
- Click the *Compare Factor* box
- Check *Log rank, Breslow* and *Tarone-Ware*
- Check *Pooled over strata*
- Click *Continue*
- Click OK or Paste

Output for the Performing Kaplan-Meier

The first box within the output of the Kaplan Meier procedure will be the **Care Processing Summary** presented below.

Case Processing Summary

Study Group	Total N	N of Events	Censored	
			N	Percent
Control	50	43	7	14.0%
Experimental	50	43	7	14.0%
Hypnosis	50	43	7	14.0%
Overall	150	129	21	14.0%

The Number and % of Censored Cases is Similar By Group

Here the **Care Processing Summary** describes the number and percentage of censored cases by study group (recall these should be similar across study groups to avoid bias). IN our analysis we see that each of the study groups have the same number and percentage (*n*=7; 14%) of cases censored.

The output of the Kaplan Meier procedure will also include the **Overall Comparisons** table presented below, which will indicate if this overall survival curve model is statistically significant. We can see for example in the first line, that the Log Rank (Mantel-Cox) is statistically significant ($p<.001$).

Overall Comparisons

	Chi-Square	df	Sig
Log Rank (Mantel-Cox)	69.757	2	.000
Breslow (Generalized Wilcoxon)	63.387	2	.000
Tarone-Ware	67.962	2	.000

There is a Statistically Significant Difference Between Curves

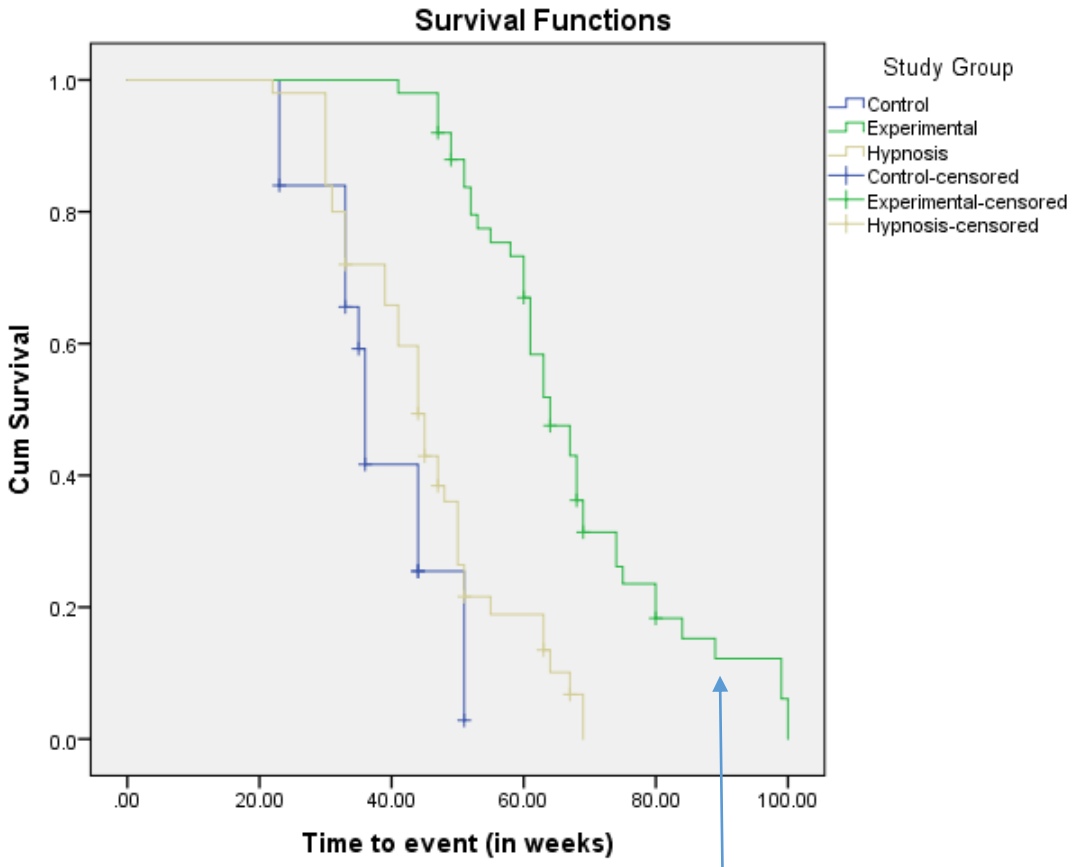
The output of the Kaplan Meier procedure will also include the **Means and Medians for Survival Time** table presented below. This box will indicate the mean length of time to event for each study group. , which will indicate if this overall survival curve model is statistically significant. We can see for example in the first line, that the Log Rank (Mantel-Cox) is statistically significant ($p<.001$).

Means and Medians for Survival Time

Group	Mean				Median			
	Estimate	SE	95% CI		Estimate	SE	95% CI	
			Lower	Upper			Lower	Upper
Control	38.42	1.4	35.7	41.1	36.0	0.4	35.2	36.8
Hypnosis	45.38	1.8	41.8	49.0	44.0	1.7	40.7	47.3
Experimental	67.74	2.4	63.1	72.4	64.0	2.8	58.4	69.6
Overall	51.45	1.6	42.3	54.6	50.0	1.4	47.3	52.7

The Experimental Group has the highest mean to event

Finally, the output of the Kaplan Meier procedure will also include the image below that presents the **Survival Functions** for each study group. Here we can see the trajectory of each survival curve, including the tendency for the experimental group to extend far to the right, reflecting exaggerated periods to the event of smoking relapse in comparison to the other two study groups.



The (Green) Experimental Group has a trajectory in the Higher Rate and Ends in a Higher Area!

Note

Please note that the Kaplan Meier provides an analysis of time to event by group, but covariate variables cannot be included in the analysis. Subsequently, we may wonder how can we perform a survival analysis while considering the impact of covariate variables? For example, what if we know relapse into smoking is linked to *Age* and *Education Level*. In such a case, we would want to control for these variables in analysis to better observe intervention effects. In other words, we want to examine that the observed smoking relapse is not just a function of *Age* and *Education Level*.

Cox proportional-hazards

The Cox's proportional hazards model is an appropriate tool toward examining the survival-time (time-to-event) for groups while considering the effect of predictor/explanatory variables. The procedure is analogous to regression rather than non-parametric KM ranked test. One assumption of Cox Regression is that the covariate variables have the same level of influence on the event over time. If this is not the case you may want to consider using the *Cox Regression with time varying covariates* when this is compromised (available in SPSS)

Performing Cox proportional-hazards

To perform the Cox's proportional hazards model in SPSS go to:

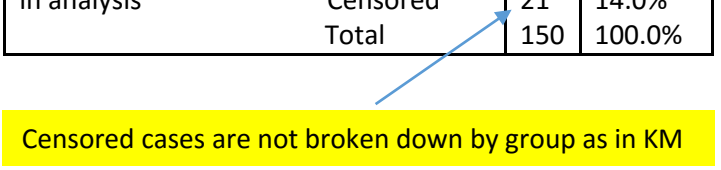
- **Analyze, Survival, Cox Regression**
- Enter *Time* (var.) into the box Time
- Enter *Status* (var.) into the box Status
  - Define Event: Click *Single Value*, enter *1*, click *Continue*
- Enter Covariates vars. (group, age, education) into the Covariates box
  - Click *Categorical*: Bring over group & education into the right hand column

- Click *Categorical*: Bring *group* & *education* into the right hand column, click *Continue*
  - Note: Reference category is highest (Last) value
- Click *Plots*, check *Survival*, put *group* var. in the box *Separate Lines for*, Click *Continue*
- Click *Options*, check *CI for Exp(B) 95% CI*, Click *Continue*
- Click *OK* or *Paste*

Output for the Performing Cox proportional-hazards

The first box within the output of the Cox proportional-hazards procedure will be the **Care Processing Summary** presented below. Notice while the table displays the number and percentage of cases censored the values are not separated by study group. This information may be gleaned from our KM analysis.

Case Processing Summary			
		N	Percent
Cases available in analysis	Event	129	86.0%
	Censored	21	14.0%
	Total	150	100.0%



The output of will also include the **Omnibus Test of Model Coefficients** table presented below, which will indicate if this overall survival curve model is statistically significant. We can see for example in the highlighted box reflecting the overall score that the test is statistically significant ($p<.001$).

Omnibus Test of Model Coefficients

-2 Log Likelihood	Overall Score			Changes from Prev. Step			Changes from Prev. Block		
	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
952.17	98.26	85	.000	104.24	5	.000	104.24	5	.000

The overall model is statistically significant

The output of will also include the **Variables in the Equation** table presented below. Notice the highlighted column describes that all of the predictors are statistically significant ($p<.05$).

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Group			30.16	2	.000			
Group (1)	1.56	.32	24.31	1	.000	4.76	2.56	8.86
Group(2)	1.41	.27	26.41	1	.000	4.09	2.39	7.01
Age	-.05	.01	30.39	1	.000	.95	.94	.97
Education Level			12.64	2	.002			
Education Level (1)	.81	.27	9.29	1	.002	2.24	1.33	3.77
Education Level (2)	.13	.29	.19	1	.667	1.13	.64	2.00

All 3 predictors have statistically significant findings

Next, refer to the highlighted column below labeled Exp(B), which presents the **Hazard Ratio (HR)**. The HR is the ratio of the hazard rates by levels of a predictor variable as per units of time. For example, consider an experimental/control drug treatment study, with an HR of 2.0. This might indicate the control group die at a rate 2 x the experimental group per unit of time observed (e.g., per year).

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Group			30.16	2	.000			
Group (1)	1.56	.32	24.31	1	.000	4.76	2.56	8.86
Group(2)	1.41	.27	26.41	1	.000	4.09	2.39	7.01
Age	-.05	.01	30.39	1	.000	.95	.94	.97
Education Level			12.64	2	.002			
Education Level (1)	.81	.27	9.29	1	.002	2.24	1.33	3.77
Education Level (2)	.13	.29	.19	1	.667	1.13	.64	2.00

Note the Hazzard Ratios (HR)

As we interpret the HR for the study groups included in our analysis, let's keep in mind that in the sectioned piece of the table below, Group reflects the Experimental group, which is the reference group, while Group (1) is the Control group and Group (2) is the Hypnosis group.

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Group			30.16	2	.000			
Group (1)	1.56	.32	24.31	1	.000	4.76	2.56	8.86
Group(2)	1.41	.27	26.41	1	.000	4.09	2.39	7.01

Group: Experimental (Reference group)
Group (1): Control Group
Group (2): Hypnosis Group

Special Considerations

As we interpret the HR in the sectioned table below, we see Group (1): Control Group is almost 5 times (HR=4.76) more likely to experience the event *Smoking Relapse* in reference to the Experimental Group (Reference group), while controlling for the effects of *Age* and *Education Level*.

Variables in the Equation								
	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Group			30.16	2	.000			
Group (1)	1.56	.32	24.31	1	.000	4.76	2.56	8.86
Group(2)	1.41	.27	26.41	1	.000	4.09	2.39	7.01

Group (1): Control Group is almost 5 times (HR=4.76) more likely to experience the event *Smoking Relapse* in reference to the Experimental Group (Reference group)

(While controlling for the effects of *Age* and *Education Level*)

Furthermore, in the sectioned table below, we see Group (2): Hypnosis Group is over 4 times (HR=4.09) more likely to experience the event *Smoking Relapse* in reference to the Experimental Group (Reference group), while controlling for the effects of *Age* and *Education Level*.

Variables in the Equation								
	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Group			30.16	2	.000			
Group (1)	1.56	.32	24.31	1	.000	4.76	2.56	8.86
Group(2)	1.41	.27	26.41	1	.000	4.09	2.39	7.01

Group (2): Hypnosis Group is over 4 times (HR=4.09) more likely to experience the event *Smoking Relapse* in reference to the Experimental Group (Reference group)

(While controlling for the effects of *Age* and *Education Level*)

As we observe the other HRs, keep in mind that *Age* is a continuous variable, so the HR is not interpreted like a categorical variable. However, we do see that EL (1): HS/GED Group is over 2 times (HR=2.24) more likely to experience the event *Smoking Relapse* in reference to EL Graduate School, while EL (2) is not statistically significant (*p*=.667).

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Group			30.16	2	.000			
Group (1)	1.56	.32	24.31	1	.000	4.76	2.56	8.86
Group(2)	1.41	.27	26.41	1	.000	4.09	2.39	7.01
Age	-.05	.01	30.39	1	.000	.95	.94	.97
Education Level			12.64	2	.002			
Education Level (1)	.81	.27	9.29	1	.002	2.24	1.33	3.77
Education Level (2)	.13	.29	.19	1	.667	1.13	.64	2.00

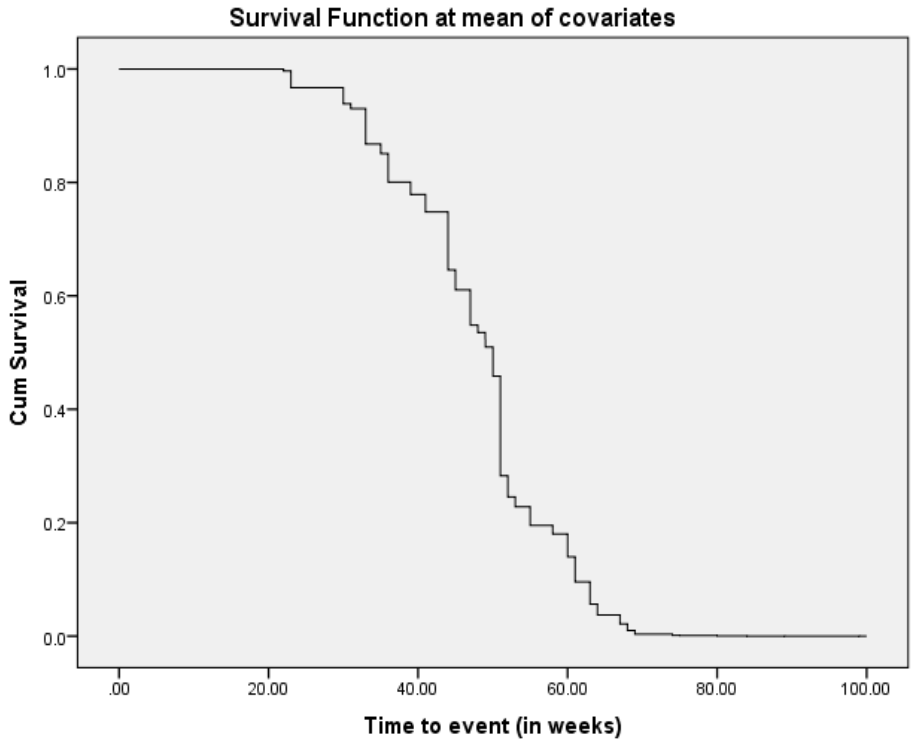
HR of continuous var. *Age*
not interpreted like the categorical

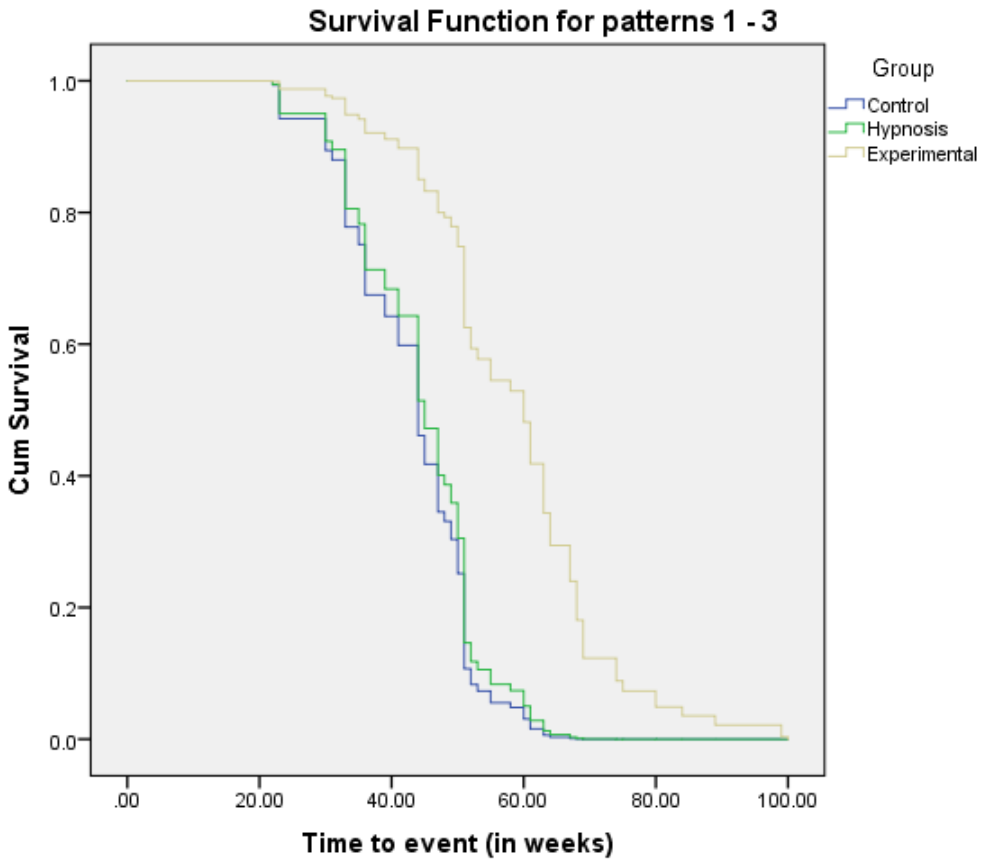
But, EL (1): HS/GED Group is over 2 times (HR=2.24) more likely to experience the event *Smoking Relapse* in reference to EL Graduate School

EL (2) is not statistically significant (*p*=.667)

Lastly, the output also includes the two images below. The first presents the Survival Function at the Mean of Covariates. The second reflects the individuals event curves similarly as was done in the KM procedure.

Special Considerations




Survival Function for patterns 1 - 3
Group
Control
Hypnosis
Experimental
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
20.00
40.00
60.00
80.00
100.00
Time to event (in weeks)

Special Considerations