

Practical "Univariable survival analysis"

P8

M. Hauptmann

Exercise 1 Dataset `bromo.sav` is an example of an animal tumorigenicity study. In those studies, animals (rats, mice) are exposed at different doses and followed until death or end of study. Subjects alive at the end of the study are terminally sacrificed. All subjects are necropsied at death. This dataset includes the data of the US National Toxicology Program (NTP) long-term study on 1-bromopropane (1-BP), a new solvent effective in dissolving fats, waxes and resins. It is used in the furniture and the dry cleaning industry, and is considered as possible replacement for other organic solvents that damage the ozone layer in the upper atmosphere. Case reports demonstrate neurotoxic, reproductive, development and other health effects in workers who use or make 1-BP. The dataset includes 50 mice of each gender exposed to four levels of 1-BP (0, 125, 250, 500 ppm) and followed until death over two years (with no interim sacrifices). Variables are

- **sex:** gender (0=female, 1=male)
 - **dose:** dose of 1-bromopropane in ppm
 - **event:** event indicator (1=death, 0=censored)
 - **time:** time to death or end of study (730 days for males, 729 for females)
 - **count:** frequency of observation
- (a) How many events occur in each dose group, by gender.
SPSS tip: Tell SPSS about the frequency with which each record occurred by clicking Data – Weight Cases and selecting the appropriate variable. Then click Analyze – Descriptive Statistics - Crosstabs and fill in the form.
- (b) Determine the range of follow-up time.
SPSS tip: Click Analyze – Descriptive Statistics – Descriptives and fill in the form.
- (c) Prepare Kaplan-Meier curves for survival and one minus survival by gender and compare gender-specific survival times. Do male mice have a longer survival than female mice?
SPSS tip: Click Analyze – Survival – Kaplan-Meier and fill in the form. Under Compare Factors, request a logrank test. Under Options, request a survival plot.
- (d) Evaluate whether survival times differ by dose group and whether the association is confounded by gender.
SPSS tip: Click Analyze – Survival – Kaplan-Meier and fill in the form. Under Compare Factors, request a logrank test. Under Options, request a survival plot. Do this again and add gender as stratification variable.
- (e) Is demonstrating heterogeneity of survival among dose groups sufficient for a causal interpretation? How can the ordinal scale of the dose categories be used to make the statistical analysis more efficient? What is the conclusion from such an analysis?
SPSS tip: As before, but request a linear trend test under Compare Factors. Use sensible scores to represent each category such as 0, 1, 2, 3 or 0, 125, 250, 500.

Exercise 1 – Suggested answer

(a) Prepare a cross-tabulation.

```
CROSSTABS
  /TABLES=dose BY event BY sex
  /FORMAT=AVALUE TABLES
  /CELLS=COUNT
  /COUNT ROUND CELL.
```

			event		Total
			0	1	
0	dose	0	34	16	50
		125	33	17	50
		250	30	20	50
		500	26	24	50
		Total	123	77	200
1	dose	0	23	27	50
		125	26	24	50
		250	18	32	50
		500	13	37	50
		Total	80	120	200

There are consistently more events among male mice compared with female mice.

(b) Calculate descriptive statistics on follow-up time.

```
DESCRIPTIVES VARIABLES=time
  /STATISTICS=MEAN STDDEV MIN MAX.
```

	N	Minimum	Maximum	Mean	Std. Deviation
time	400	38	730	669.65	91.656
Valid N (listwise)	400				

Follow-up time ranges from 38 to 730 days.

(c) Make KM curves by sex and compare them based on a logrank test.

```
KM time BY sex
  /STATUS=event(1)
  /PRINT NONE
  /PLOT SURVIVAL OMS
  /TEST LOGRANK.
```

Case Processing Summary

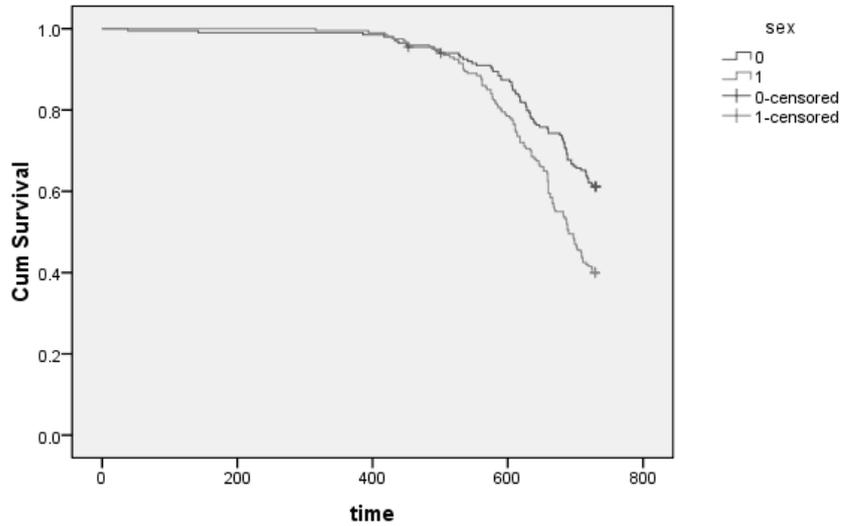
sex	Total N	N of Events	Censored	
			N	Percent
0	200	77	123	61.5%
1	200	120	80	40.0%
Overall	400	197	203	50.8%

Overall Comparisons

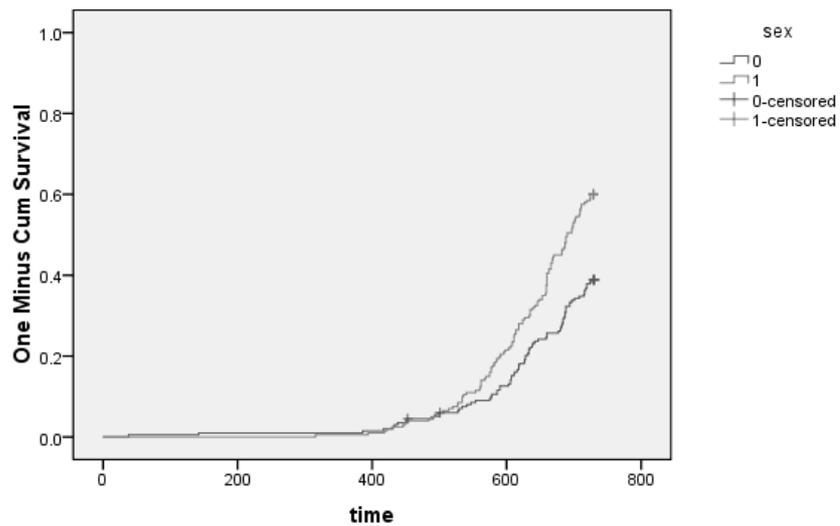
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	17.248	1	.000

Test of equality of survival distributions for the different levels of sex.

Survival Functions



One Minus Survival Functions



There are few events until around 400 days. After around 500 days, sex-specific KM curves start to separate, with poorer survival among male mice. The difference is highly statistically significant ($p < .001$).

(d) Request KM curves by dose groups with the logrank test.

```
KM time BY dose
/STATUS=event(1)
/PRINT NONE
/PLOT SURVIVAL
/TEST LOGRANK.
```

Case Processing Summary

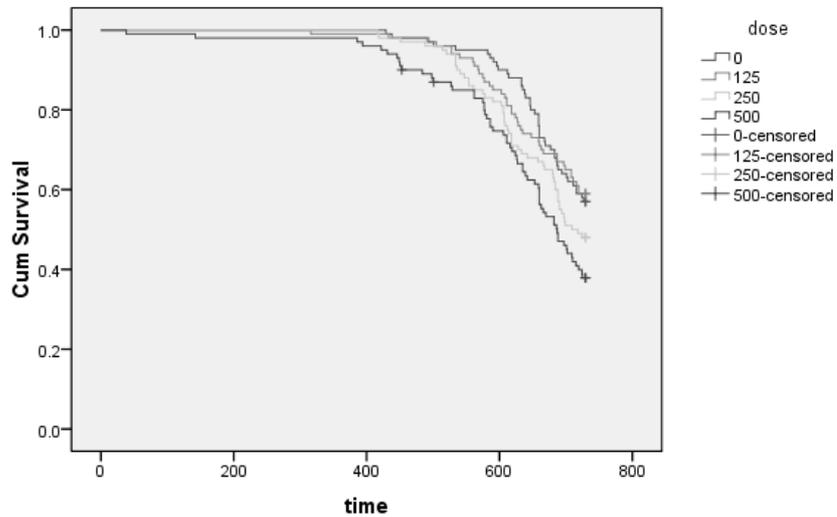
dose	Total N	N of Events	Censored	
			N	Percent
0	100	43	57	57.0%
125	100	41	59	59.0%
250	100	52	48	48.0%
500	100	61	39	39.0%
Overall	400	197	203	50.8%

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	13.128	3	.004

Test of equality of survival distributions for the different levels of dose.

Survival Functions



The 3-degree of freedom logrank test of homogeneity of survival across dose categories rejects the null hypothesis at $p=.004$, i.e., there is strong evidence that survival differs across dose groups. The KM plot shows that mice in the highest dose group have poorest survival, those in the unexposed group have the best survival, and the rest is intermediate.

Because gender is strongly associated with survival, we evaluate whether it confounds the dose-survival association using a logrank test of dose stratified by sex.

```
KM time BY dose
/STRATA=sex
/STATUS=event(1)
/PRINT NONE
/TEST LOGRANK.
```

Overall Comparisons^a

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	13.351	3	.004

Test of equality of survival distributions for the different levels of dose.

a. Adjusted for sex.

The stratified logrank test gives the same result as the unstratified ($p=.004$), i.e., gender is not a confounder. This is expected since gender is by design not related to dose (equal number of female and male mice per dose group), which is a requirement for a confounder.

(e) The logrank test for trend is appropriate.

```
KM time BY dose
  /STATUS=event(1)
  /PRINT NONE
  /TREND
  /TEST LOGRANK.
```

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	11.348	1	.001

The vector of trend weights is -3, -1, 1, 3. This is the default.

It is not possible to use alternative (non-default) scores by clicking in SPSS. It is, however, possible to include alternative scores in the syntax: copy and paste it into the syntax window and submit it.

```
KM time BY dose
  /STATUS=event(1)
  /PRINT NONE
  /TREND(0,1,2,3) [or /TREND(0,125,250,500)]
  /TEST LOGRANK.
```

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	11.348	1	.001

The vector of trend weights is 0, 1, 2, 3.

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	12.189	1	.000

The vector of trend weights is 0, 125, 250, 500.

The p-values using scores 0, 1, 2, 3 are the same as with the default scores -3, -1, 1, 3 because they are also equidistant. Scores 0, 125, 250, and 500 appear to be most appropriate since they reflect the actual dose levels given. Those scores yield a slightly smaller p-value ($p<.001$).