C.9 Cox Proportional Hazards Model

In a study of peritonitis disease, survival duration (in years) was compared between two regimens (control and experimental). The survival has been taken to be affected by severity of disease at admission (assessed by APACHE score), sex and age in the two groups. These are the covariates in this example. The uncensored values denote death within the follow-up period whereas censored denotes both lost-to follow-up and alive subjects at the end of the study.

Basic assumption of survival analysis is that censoring should have nothing to do with the survival pattern—both censored and uncensored person should have similar characteristics. To test this, first unpaired *t*-tests should be applied to compare the mean APACHE score in censored and uncensored subjects.

Command to run unpaired *t*-test to compare the APACHE score in censored and uncensored group:

```
T-TEST GROUPS=Censored(0 1)
/VARIABLES=APACHEatadmission
/CRITERIA=CI(.95).
```

This commands run the unpaired t-test to compare the mean APACHE score in censored (coded as 0) and uncensored (coded as 1), CRITERIA= CI(.95) calculates the 95% confidence interval for mean difference. The following table displays the mean, SD, standard error of mean of APACHE score in censored and uncensored subjects and the next table results of *t*-test.

Group Statistics

	Censored	N	Mean	Std. Deviation	Std. Error Mean
APACHE at admission	uncensored	63	23.84	9.185	1.157
	censored	17	25.65	7.689	1.865

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
APACHE at admission	Equal variances assumed	.981	.325	-.743	78	.460	-1.806	2.432	-6.648	3.036
	Equal variances not assumed			-.823	29.563	.417	-1.806	2.195	-6.291	2.679

Levene test for equality of variances is applied to check the equality of variances in APPACHE score in censored and uncensored groups before deciding which *t*-test result is applicable. Levene test not significant ($P = 0.325$) represents no violation of homogeneity of variance assumption. The *P*-value of *t*-test for equal of variances can be used. This found no significance difference in mean APACHE score in censored and uncensored values.

Chi-square test is applied to compare proportion of males and females in censored and uncensored subjects.

Command to run the chi-square test:
```
CROSSTABS
/TABLES=Censored BY Sex
/FORMAT=AVALUE TABLES
/STATISTICS=CHISQ
/CELLS=COUNT
/COUNT ROUND CELL
/METHOD=EXACT TIMER(5).
```

This command displays the following contingency tables between sex and censoring and runs the chi-square and other similar tests. Cell frequencies are not small and chi-square results can be believed. No chi-square is significant.

Censored * Sex Crosstabulation

Count

		Sex		
		0	1	Total
Censored	uncensored	28	35	63
	censored	9	8	17
Total		37	43	80

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
Pearson Chi-Square	.389[a]	1	.533	.591	.362	
Continuity Correction[b]	.122	1	.727			
Likelihood Ratio	.388	1	.533	.591	.362	
Fisher's Exact Test				.591	.362	
Linear-by-Linear Association	.384[c]	1	.536	.591	.362	.178
N of Valid Cases	80					

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 7.86.

b. Computed only for a 2x2 table

c. The standardized statistic is -.620.

Similar comparison is required for age at onset also.

Command to run unpaired t-test to compare the age at onset:
```
T-TEST GROUPS=Censored(0 1)
/MISSING=ANALYSIS
/VARIABLES=AgeatonsetYears
/CRITERIA=CI(.95).
```

Group Statistics

	Censored	N	Mean	Std. Deviation	Std. Error Mean
Age at onset (Years)	uncensored	63	50.00	10.526	1.326
	censored	17	49.53	13.816	3.351

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means							
										95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Age at onset (Years)	Equal variances assumed	2.063	.155	.153	78	.879	.471	3.083	-5.667	6.608
	Equal variances not assumed			.131	21.270	.897	.471	3.604	-7.018	7.959

Levene test is not significant – thus equal variances can be assumed. Average age at onset in censored observations is 49.53 years and in uncensored is 50.00 years and the difference is not statistically significant ($P = 0.879$). All the three covariates are similar in subjects with censored and uncensored survival. Thus this basic assumption is fulfilled.

As an additional enquiry, you can test whether APACHE score at admission differed between males and females. For this the command is as follows:

Command for t-test for difference in mean APACHE score in males and females:
```
T-TEST GROUPS=Sex(0 1)
/MISSING=ANALYSIS
/VARIABLES=APACHEatadmission
/CRITERIA=CI(.95).
```

Group Statistics

	Sex	N	Mean	Std. Deviation	Std. Error Mean
APACHE at admission	Female	37	23.54	9.197	1.512
	Male	43	24.81	8.650	1.319

Independent Samples Test

	Levene's Test for Equality of Variances	t-test for Equality of Means	t-test for Equality of Means

		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
APACHE at admission	Equal variances assumed	.062	.803	-.638	78	.526	-1.273	1.997	-5.250	2.703
	Equal variances not assumed			-.635	74.609	.528	-1.273	2.007	-5.271	2.724

Although APACHE score is higher in males but not statistical significant. Just to explore the data further, find correlation between APACHE score and age at onset of the disease. This is not needed for this problem.

Command to run the Pearson correlation between the APACHE score and age:
```
CORRELATIONS
/VARIABLES=APACHEatadmission AgeatonsetYears
/PRINT=TWOTAIL NOSIG
/MISSING=PAIRWISE.
```

This command displays the correlation with two-tailed *P*-value and the number of subjects after excluding pair values if either APACHE score or age has missing. Nothing is missing in this example. The correlation is 0.132, which is not high.

		APACHE at admission	Age at onset (Years)
APACHE at admission	Pearson Correlation	1	.132
	Sig. (2-tailed)		.243
	N	80	80
Age at onset (Years)	Pearson Correlation	.132	1
	Sig. (2-tailed)	.243	
	N	80	80

Now, it is a good idea to explore whether the two groups are similar with respect to the baseline characteristics. The following is the test for age at onset.

Command for unpaired t-test for group differences in age at onset:
```
T-TEST GROUPS=Group(0 1)
/MISSING=ANALYSIS
/VARIABLES=AgeatonsetYears
/CRITERIA=CI(.95).
```

Following table gives means, SDs and SEs.

Group Statistics

	Group	N	Mean	Std. Deviation	Std. Error Mean
Age at onset (Years)	0	40	48.90	10.068	1.592
	1	40	50.90	12.293	1.944

Following tables displays the results of *t*-test. In this case, Levene test for equality of variances is significant and tells that homogeneity of variance assumption is violated by these data. The

P-value (*P* = 0.429) of *t*-test for unequal variances found no significant difference in mean age at onset in the two groups.

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Age at onset (Years)	Equal variances assumed	4.066	.047	-.796	78	.428	-2.000	2.512	-7.002	3.002
	Equal variances not assumed			-.796	75.086	.429	-2.000	2.512	-7.005	3.005

Command for unpaired t-test to compare the APACHE score in the two groups:

```
T-TEST GROUPS=Group(0 1)
/MISSING=ANALYSIS
/VARIABLES=APACHEatadmission
/CRITERIA=CI(.95).
```

Group Statistics

	Group	N	Mean	Std. Deviation	Std. Error Mean
APACHE at admission	0	40	24.48	9.021	1.426
	1	40	23.98	8.830	1.396

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
APACHE at admission	Equal variances assumed	.030	.863	.251	78	.803	.500	1.996	-3.474	4.474
	Equal variances not assumed			.251	77.964	.803	.500	1.996	-3.474	4.474

APACHE score at admission in the two groups also is not significantly different (*P* = 0.803). A chi-square test for equality of sex distribution should also be done but that is not shown here. These tests establish that the two groups were not different to begin with. Assuming that all other factors not in the model are also same in the two groups, any difference in survival can be attributed to the difference in regimens.

After this exploration, ground is set for **Cox proportional hazard model**. First is to confirm that the hazards are proportional or not.

Command to run whether the hazard is proportional between the two groups:

```
COXREG DurationofsurvivalYears
/STATUS=Censored(0)
/STRATA=Group
/PLOT HAZARDS LML.
```

This command tests the proportionality of hazard assumption between the two groups. The option STATUS = Censored(0) represents event has happened (death) in this command. Many would like it to be coded as 1 but that does not matter so long as we know. The variable Group was declared as STRATA instead of covariate so that this comparison can be done. PLOT command displays log minus log (LML) hazard for each group to visually check the proportionality assumption.

The following table gives the data summary. Seventeen out of 80 observations are censored and these are nearly equally divided in the two groups.

Stratum Status[a]

Stratum	Event	Censored	Censored Percent
0	31	9	22.5%
1	32	8	20.0%
Total	63	17	21.3%

a. The strata variable is : Group

Figure C.9(a) displays the cumulative hazard for both the groups. Cumulative hazard at 5 years is much more than at 1 year. The difference between the two hazard curves remains proportional over the time. This proportionality is easily seen in the Figure C.9(b) on LML hazard. These plots are almost parallel for the groups.

Hazard Function at mean of covariates
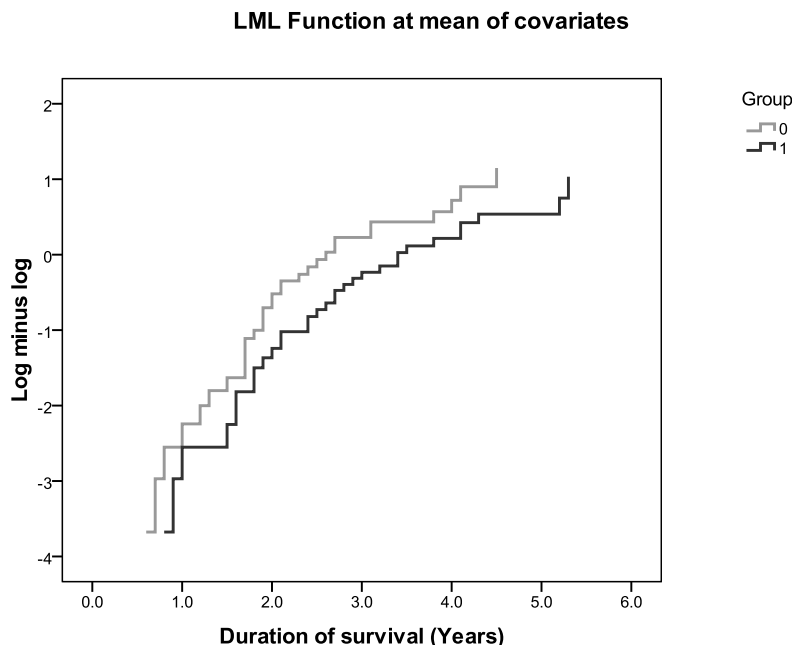
LML Function at mean of covariates
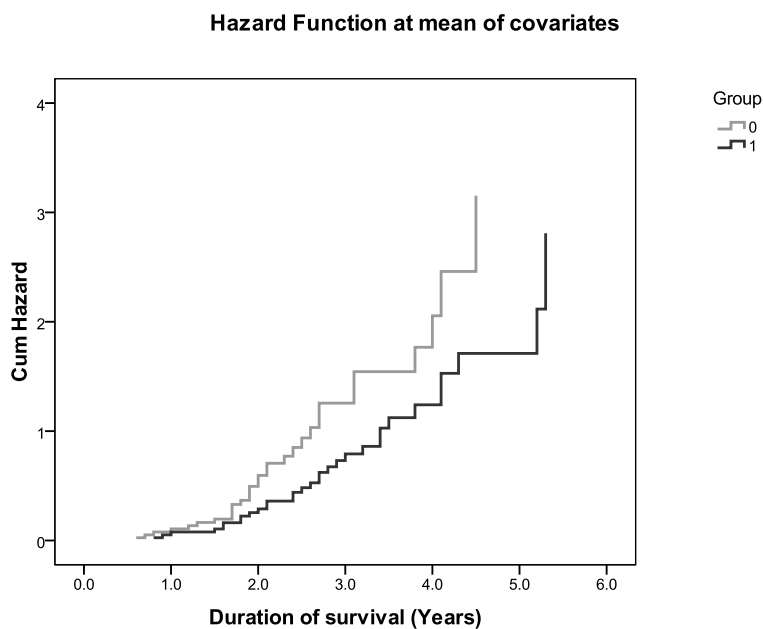
FIGURE C.9 (a) Cumulative hazards for group and sex (b) Log minus log hazard for group and sex

Thus, Cox proportional hazard model is suitable for these data.

Command to run the Cox-regression model:
```
COXREG DurationofsurvivalYears
/STATUS=Censored(0)
/PATTERN BY Group
/CONTRAST (Sex)=Indicator(1)
/CONTRAST (Group)=Indicator
/METHOD=ENTER AgeatonsetYears APACHEatadmission Sex Group
/PLOT SURVIVAL
/PRINT=BASELINE.
```

This command runs Cox-regression for survival considering survival duration as the dependent time variable. STATUS defines censoring with zero for death. PATTERN By Group option plots the survival curve for both the regimens separately. CONTRAST options are for binary variables Sex and Group. By default last category is considered as the reference category but for sex first category (female) was selected as reference category and for Group 1 is automatically selected as reference category. Age at onset and APACHE score are entered as continuous variable in the model. METHOD option is for the method of selecting the variable – here ENTER method is used that forced all the four independents in to the model. PLOT option displays the survival curve. The PRINT = BASELINE option displays the table for baseline hazard $h_0(t)$ at different time points and $h_1(t)$ value at same time points at the mean level of the covariates.

The following table displays the frequencies and coding scheme of the categorical variables. Test regimen was taken as reference (which is code for control in this case) and for sex female was taken as reference.

Categorical Variable Codings[c,d]

	Frequency	(1)[b]
Group[a] Test	40	1
Control	40	0
Sex[a] Female	37	0
Male	43	1

a. Indicator Parameter Coding

b. The (0,1) variable has been recoded, so its coefficients will not be the same as for indicator (0,1) coding.

c. Category variable: Group

d. Category variable: Sex

The following is value of $-2\ln L$ at the beginning without any covariate.

Block 0: Beginning Block
Omnibus Tests of
Model Coefficients

-2 Log Likelihood
439.542

The following table shows that when all the four covariates are entered, $-2\ln L$ reduces by 15.038 and this is statistically significant ($P = 0.005$) at 4 df.

Block 1: Method = Enter
Omnibus Tests of Model Coefficients[a,b]

	Overall (score)			Change From Previous Step			Change From Previous Block		
-2 Log Likelihood	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
424.137	15.038	4	.005	15.404	4	.004	15.404	4	.004

a. Beginning Block Number 0, initial Log Likelihood function: -2 Log likelihood: 439.542

b. Beginning Block Number 1. Method = Enter

The following table displays the coefficients, their SE, relative risk exp(B) and its 95% confidence interval.

Variables in the Equation

							95.0% CI for Exp(B)	
	B	SE	Wald	df	Sig.	Exp(B)	Lower	Upper
AgeatonsetYears	.000035	.011	.000	1	.997	1.000	.979	1.021
APACHEatadmission	.051	.016	9.929	1	.002	1.052	1.019	1.086
Sex	.207	.262	.622	1	.430	1.230	.735	2.057
Group	-.672	.273	6.036	1	.014	.511	.873	.299

The APACHE score and Group are significant predictor for mortality. exp(B) is the relative risk and represents the change in risk with each unit change in the value of the covariate. For example

each unit increase in the APACHE score is expected to increase the risk of mortality by 5.2% relative to control because exp(B)=1.052. Similarly test regimen decreases the risk of mortality by nearly one-half compared with control since exp(B)=0.511. The regression equation can be written as:

$$h_1(t) = h_0(t) \times exp^{[0.000035 \times Age + 0.051 \times APACHE + 0.207 \times sex - 0.672 \times group]}$$

The regression equation for control (Group=0) is

$h_1(t) = h_0(t) \times exp^{[0.000035 \times Age + 0.051 \times APACHE + 0.207 \times sex - 0.672 \times 0]}$.

The regression equation for test regimen (Group=1) is

$h_1(t) = h_0(t) \times exp^{[0.000035 \times Age + 0.051 \times APACHE + 0.207 \times sex - 0.672 \times 1]}$.

The following table displays the baseline cumulative hazard rate at different time (t), survival probability, its SE, and cumulative hazard rate $h_1(t)$ at mean values of the covariates.

Survival Table

Time	Baseline Cum Hazard	At mean of covariates		
Years		Survival	SE	Cum Hazard
.6	.002	.989	.010	.011
.7	.004	.979	.015	.022
.8	.008	.956	.021	.044
.9	.011	.945	.024	.056
1.0	.015	.922	.028	.081
1.2	.018	.911	.030	.094
1.3	.020	.899	.032	.107
1.5	.025	.874	.036	.134
1.6	.030	.850	.039	.162
1.7	.041	.802	.044	.221
1.8	.051	.763	.047	.271
1.9	.064	.709	.051	.343
2.0	.076	.667	.053	.406
2.1	.093	.607	.055	.499
2.3	.098	.591	.056	.525
2.4	.116	.539	.058	.618
2.5	.128	.504	.059	.684
2.6	.142	.469	.059	.757
2.7	.172	.398	.059	.920
2.8	.181	.381	.058	.966
2.9	.190	.362	.058	1.016
3.0	.200	.343	.058	1.069
3.1	.222	.306	.057	1.184
3.2	.234	.287	.056	1.250
3.4	.265	.242	.055	1.417
3.5	.282	.221	.054	1.509
3.8	.325	.176	.050	1.736
4.0	.349	.155	.048	1.866
4.1	.436	.097	.038	2.331
4.3	.471	.081	.035	2.518

4.5	.514	.064	.031	2.747
5.2	.717	.022	.024	3.831
5.3	1.065	.003	.006	5.692
6.1	.	.000	.	.

For example at survival duration 4 years, the baseline cumulative hazard rate $h_0(t) = 0.349$ and cumulative hazard rate at mean values of covariates is

$h_1(4\ years) = 0.349 \times exp[0.000035 \times 49.90 + 0.051 \times 24.225 + 0.207 \times 0.538 + 0.672 \times 0.5] = 0.349 \times exp(1.684) = 0.349 \times 5.387 = 1.88$. The value of h_1 at 4 years from the table is 1.866 that is close to the 1.88. The difference is due to rounding off in calculations.

You can calculate the cumulative hazard for each regimen separately and for various combinations of values of the covariates by substituting the values in the regression equation.

Covariate Means and Pattern Values

		Pattern	
	Mean	1	2
AgeatonsetYears	49.900	49.900	49.900
APACHEatadmission	24.225	24.225	24.225
Sex	.538	.538	.538
Group	.500	1.000	.000

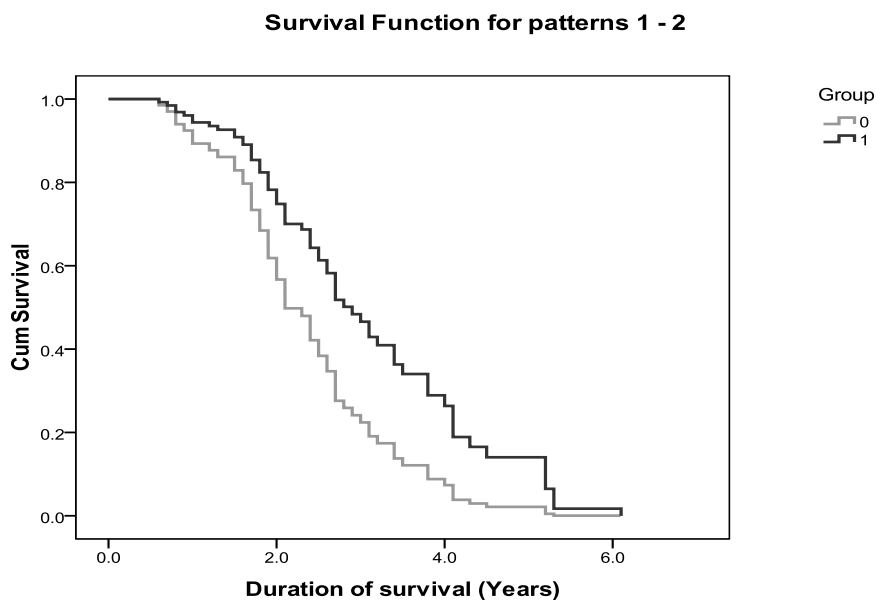Figure C.9(c) gives the survival curve for the two groups.

FIGURE C.9(c) Survival curve in the two groups

Now we need to test whether the difference between the two survival curves is statistically significant or not. This is done by log-rank test.

Command to run the log rank test:
```
KM DurationofsurvivalYears BY Group
/STATUS=Censored(0)
/PRINT MEAN
/PLOT SURVIVAL
/TEST LOGRANK.
```

This command runs the Kaplan-Meier method to obtain the two survival curves and test the significance of difference between the two groups using log-rank method. PRINT option displays the mean and median of each group. PLOT option displays the survival curve for both the groups.

Case Processing Summary

Group	Total N	N of Events	Censored N	Percent
0	40	31	9	22.5%
1	40	32	8	20.0%
Overall	80	63	17	21.3%

The following table displays the mean and median duration of survival in two regimen groups, and their SEs and CIs. The median survival duration for test regimen (group = 1) is 2.9 years which is higher than 2.1 years for control group. Note that mean is much higher than median in this case.

Means and Medians for Survival Time

	Mean[a]		95% Confidence Interval		Median		95% Confidence Interval	
Group	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
0	2.469	.195	2.086	2.852	2.100	.266	1.580	2.620
1	3.156	.242	2.681	3.631	2.900	.291	2.330	3.470
Overall	2.839	.166	2.514	3.165	2.600	.142	2.321	2.879

a. Estimation is limited to the largest survival time if it is censored.

The following table displays the results of log-rank test. The difference between the survival patterns in the two groups is statistically significant ($P = 0.032$).

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	4.584	1	.032

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

Figure C.9(d) gives the two survival curves again, this time with + sign for censored values. These are slightly different from the curves obtained earlier by Cox method.
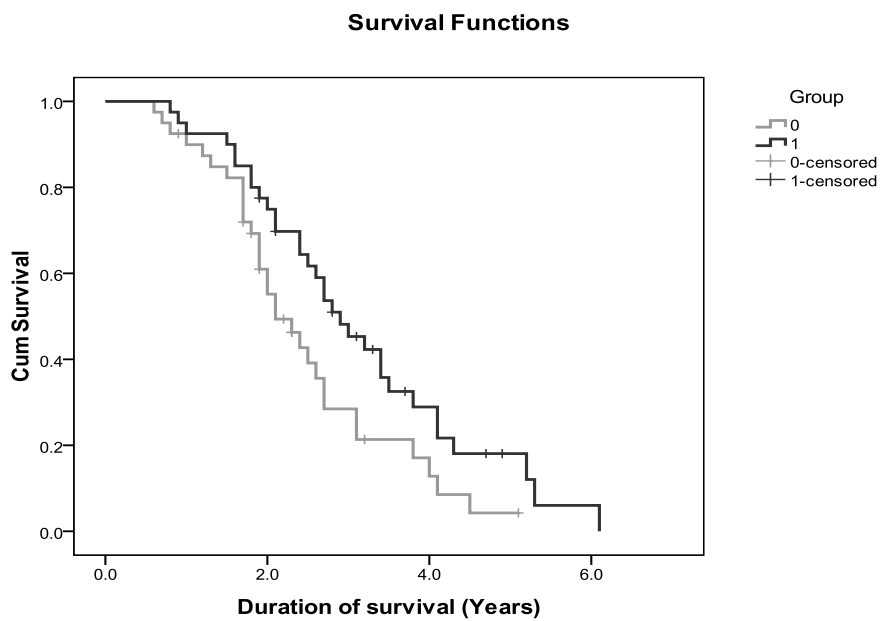
Survival Functions

FIGURE C.9 (d) Survival curves in the two groups by the Kaplan-Meier method

The survival function of test group descends more slowly than the survival function of control group.