Chapter 13: Categorized Time-to-Event Data

13.1 Introduction

- *Time-to-event-data:* generated from studies that have time from treatment or exposure until some event as their outcome

Event: Death

Recurrence of some condition

Emergence of a developmental characteristic

Outcome: Actual lifetime (or waiting time)

- Grouped survival data (*categorized survival data):* when only the interval of time during which an event occurs can be determined

→ Examining dental patients for caries at 6 mo. periods

→ Evaluating animals every 4 hours after exposure to bacteria

→ Examining patients every 6 weeks for recurrence of a medical condition for which they have been treated

- Since study is conducted over a period of time, subjects may leave before study ends ⇒ *withdrawal*:

→ Protocol violations, may join study in progress, may drop out for other reasons

→ Number of withdrawals per interval can be determined

→ Assume withdrawal is independent of condition being studied and that multiple withdrawals occur uniformly throughout interval

Section 13.2: Discusses life table methods for computing survival rates

Section 13.3: Discusses Mantel-Cox test as one strategy to compare survival rates among treatments

Section 13.4: Discusses piecewise exponential model used to model grouped survival data

13.2 Life Table Estimation of Survival Rates

- Data to compare active and control treatment to prevent recurrence of a medical condition that had been healed

	Withdrawals			Recurrences			No	
Trt	Yr 1	Yr 2	Yr 3	Yr 1	Yr 2	Yr 3	Recur	Total
Control	9	7	6	15	13	7	17	74
Active	9	3	4	12	7	10	45	90

- Survival rate (waiting time rate): $S(y) = 1 - F(y)$ $= \Pr\{Y \geq y\}$, where Y denotes continuous lifetime of a subject, and $F(y) = \Pr\{Y \leq y\}$ is cumulative probability distribution function. Weibull distribution and exponential distribution are commonly used

- Estimation of survival rates can be done by *life table* (*actuarial*) method. Determine number of subjects at risk for each interval (no recurrence + recurrence + withdraw)

	Controls			
Interval	No Recur.	Recur.	Withdrawals	At Risk
0-1 Year	50	15	9	74
1-2 Years	30	13	7	50
2-3 Years	17	7	6	30
	Active			
Interval	No Recur.	Recur.	Withdrawal	At Risk
0-1 Year	69	12	9	90
1-2 Years	59	7	3	69
2-3 Years	45	10	4	59

- Define n_{ijk} to be number of patients in ith group with jth status for kth time interval, where

$i = 1, 2$	for control and active groups
$j = 0$	corresponds to no recurrence during time interval,
$j = 1,2$	corresponds to those with recurrence and those withdrawn during kth interval, respectively
$k = 1, \ldots, t$	time intervals

- The n_{i0k} are determined from:

$$n_{i0k} = \sum_{j=1}^{2} \sum_{g=k+1}^{t} n_{ijg} + n_{i0t}$$

- Probability of surviving at least k intervals computed as:

$$G_{ik} = \prod_{g=1}^{k} \frac{n_{i0g} + 0.5n_{i2g}}{n_{i0g} + n_{i1g} + 0.5n_{i2g}} = \prod_{g=1}^{k} p_{ig}$$

where p_{ig} denotes estimated conditional probability for surviving gth interval given that subject has survived all preceding intervals

- Standard error of G_{ik} is estimated as

$$s.e.(G_{ik}) = G_{ik}\sqrt{\sum_{g=1}^{k}\frac{(1-p_{ig})}{(n_{i0g}+n_{i1g}+0.5n_{i2g})p_{ig}}}$$

$$= G_{ik}\sqrt{\sum_{g=1}^{k}\frac{(1-p_{ig})}{(n_{i0g}+0.5n_{i2g})}}$$

where $(n_{i0g}+n_{i1g}+0.5n_{i2g})$ is effective number at risk during gth interval

- $0.5 \times n_{i2g}$ is used in numerator and denominator of p_{ig} since average exposure to risk for withdrawing subjects is assumed to be one-half the interval

- Using data on recurrences of medical condition, life table estimates of surviving kth interval for active treatment are:

$$G_{21} = \frac{69+0.5(9)}{69+12+0.5(9)} = 0.8596$$

$$G_{22} = 0.8596 \times \frac{59+0.5(3)}{59+7+0.5(3)} = 0.7705$$

$$G_{23} = 0.7705 \times \frac{45+0.5(4)}{45+10+0.5(4)} = 0.6353$$

- Standard errors of the G_{ik} are computed as follows:

$$s.e.(G_{21}) = 0.8596 \times \sqrt{\frac{12/85.5}{69+0.5(9)}} = 0.038$$

$$s.e.(G_{22}) = 0.7705 \times \sqrt{\frac{12/85.5}{69+0.5(9)} + \frac{7/67.5}{59+0.5(3)}} = 0.046$$

$$s.e.(G_{23}) = 0.6353 \times \sqrt{\frac{12/85.5}{69+0.5(9)} + \frac{7/67.5}{59+0.5(3)} + \frac{10/57}{45+0.5(4)}} = 0.055$$

- Results of *life table method* for Medical Condition Data

Controls	Estimated Survival Rates	Standard Errors
0-1 Year	0.7842	0.0493
1-2 Years	0.5649	0.0627
2-3 Years	0.4185	0.0665
Active		
0-1 Year	0.8596	0.0376
1-2 Years	0.7705	0.0464
2-3 Years	0.6353	0.0545

- The next section will discuss a test to compare survival rates between treatment groups

13.2.1 Computing Survival Estimates with the LIFETEST Procedure

The life table analysis method for categorized time-to-event data may also be performed with PROC LIFETEST in SAS

- By default, PROC LIFETEST uses the Kaplan-Meier method to calculate survival estimates. However, using METHOD=LT in the PROC statement results in estimates using the lifetable method

- Case-record datasets should include variables for any stratification (e.g., treatment), survival time periods (e.g., 0-1 Years), and an indicator for whether or not the subject was censored.

- For example, a patient who withdrew partway through a study would be censored at the interval during which they withdrew, since there is no way of knowing how much longer they continued before experiencing the event of interest.

- Subjects who completed the study with no event are also considered to be censored at the end of the study (using the current example, this occurs at 3 years).

- All patients who actually experienced the event are not censored.

- Frequency data sets should be set up with two observations per interval and per stratification variable.

- The first observation for each interval/stratification level will include subjects who withdrew (censored), and the second level will include subjects who had the event.

- After all levels are input, one final observation for each interval/stratification group is included for patients who ended the study with no event.

- Each observation in the data set should include the interval, any stratification variables, a censoring indicator, and a count variable.

- SAS code for creating dataset:

```
data medical;
  input interval treatment $ censor count @@;
  datalines;
   0 control   1   9       0 control    0  15
   1 control   1   7       1 control    0  13
   2 control   1   6       2 control    0  7
   3 control   1   17
   0 active    1   9       0 active     0  12
   1 active    1   3       1 active     0  7
   2 active    1   4       2 active     0  10
   3 active    1   45
   ;
   run;
```

- SAS code for LIFETEST Life Table Method:

```
ods graphics on;
proc lifetest data=medical method=lt plots=(s,ls)
          intervals=0 to 3 by 1;
   freq count;
   strata treatment;
   time interval*censor(1);
   ods output  Lifetest.Stratum1.LifeTableEstimates=my
        (keep=STRATUM treatment LowerTime UpperTime
           Survival StdErr);
   ods output
        Lifetest.Stratum2.LifeTableEstimates=my2
        (keep=STRATUM treatment LowerTime UpperTime
           Survival StdErr);
run;
ods graphics off;

data all;
  set my my2;
run;
proc print; data=all noobs; run;
```

where

• METHOD=LT specifies the life table method

• the TIME statement indicates
[survival time variable]*[censoring indicator]
(the latter is the value indicating censoring)

• the STRATA statement indicates any stratification variables (e.g. TREATMENT, if multiple treatment groups)

• PLOTS=(S,LS) requests plots of estimated survival and the negative log of estimated survival. ODS GRAPHICS ON/OFF statements are required for plots to be displayed.

•ODS OUTPUT statements store quantities from LIFETEST in a data set for later use.

Output 13.1 Censoring Information

Summary of Censored Subjects

Summary of the Number of Censored and Uncensored Values

Stratum	treatment	Total	Failed	Censored	Percent Censored
1	active	90	29	61	67.78
2	control	74	35	39	52.70
Total		164	64	100	60.98

Active: 29 recurrences, 61 censored

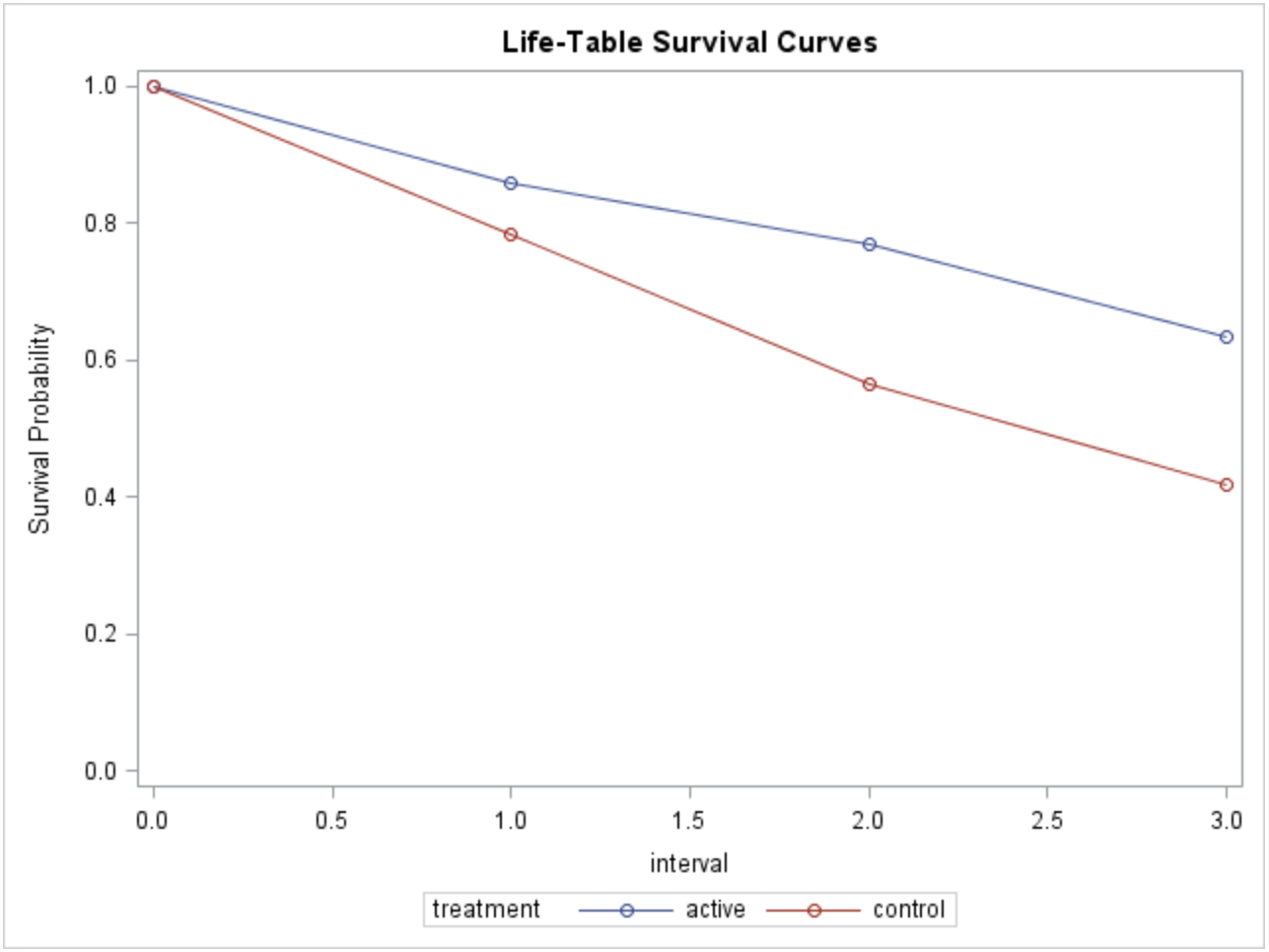
Control: 35 recurrences, 39 censored

Output 13.2 Survival Estimates

STRATUM	treatment	Lower Time	Upper Time	Survival	StdErr
1	active	0	1	1.0000	0
1	active	1	2	0.8596	0.0376
1	active	2	3	0.7705	0.0464
1	active	3	.	0.6353	0.0545
2	control	0	1	1.0000	0
2	control	1	2	0.7842	0.0493
2	control	2	3	0.5649	0.0627
2	control	3	.	0.4185	0.0665

Survival estimates and standard errors are the same as the hand calculations previously presented.

Output 13.3 Survival Plot



Active

Control

Output 13.4 Homogeneity of Survival Curves

Test of Equality over Strata

Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	5.8836	1	0.0153
Wilcoxon	5.3880	1	0.0203
-2Log(LR)	9.3178	1	0.0023

The p-values for all three tests provide evidence of differences in the survival curves between treatment groups. Note that the p-value for the Log-Rank test is smaller than Wilcoxon. Likelihood Ratio is smallest for these data.

• The logrank and Wilcoxon tests are non-parametric tests and require no assumptions for the event time distribution.

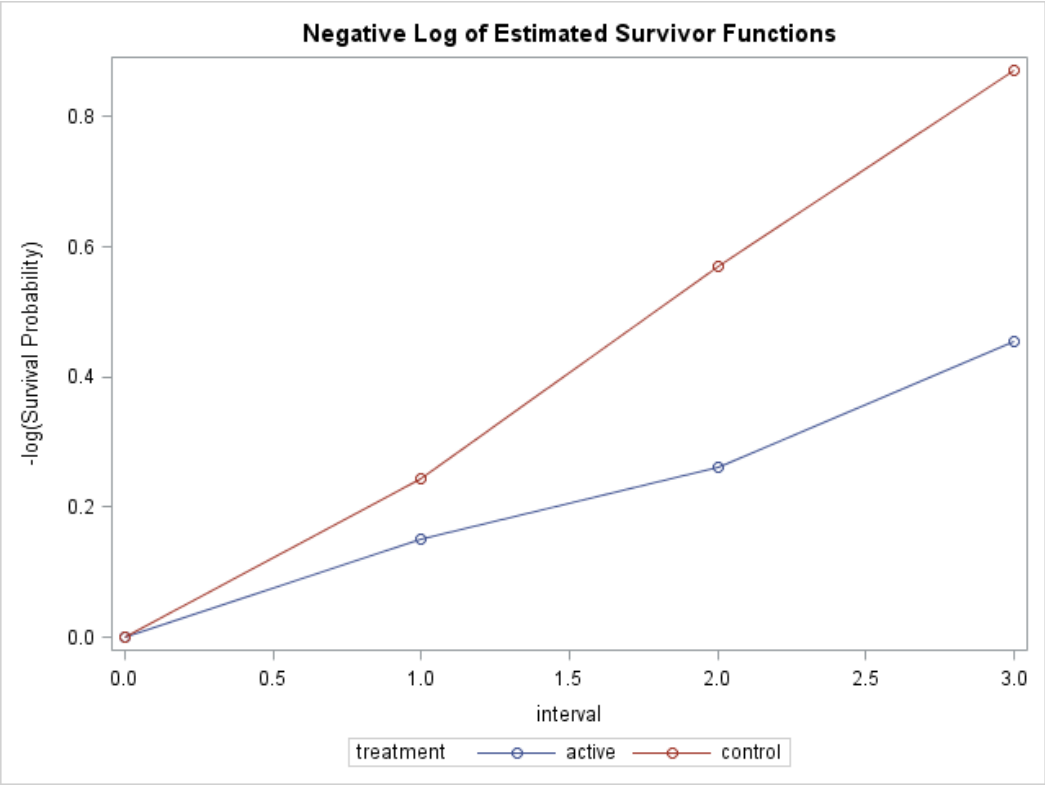
• The Wilcoxon test is more powerful than the logrank test when there is a tendency for one group to have fewer early events than the other as well as longer survival

• The logrank test is more powerful when the two groups have similar rates of early events with one having more long-term survivors than the other

• If we can assume the event time distribution is exponential, the likelihood ratio test is a more powerful test than the logrank test

The assumption of an exponential event time distribution can be evaluated through examining linearity in a plot of the negative log of survival.

Output 13.5 Negative Log of Survival Plot



Control

Active

Linearity may be reasonable, but uncertainty as to whether exponential distribution applies.

13.3 Mantel-Cox Test

- Interested in comparing survival curves to determine which treatment had more favorable outcome
- Mantel (1966) and Cox (1972) suggested an extension of Mantel-Haenszel methodology for survival data:

→ restructure usual frequency table to a set of 2×2 tables in the above life table format

→ perform Mantel-Haenszel computations on set of tables

- Row variable: treatment

  Column variable: numbers recurred and not recurred

  Strata variable: time intervals

- Mantel-Cox test for grouped data is equivalent to log rank test for comparing survival curves for ungrouped data

- Withdrawals are handled by either grouping them with no recurrences or eliminating them entirely (more conservative approach)

- Life table format for study of medical condition recurrence with data grouped together by intervals and with withdrawals excluded

Interval	Treatment	Recurrences	No Recurrences
0-1	Control	15	50
	Active	12	69
1-2	Control	13	30
	Active	7	59
2-3	Control	7	17
	Active	10	45

```
data clinical;
   input time $ treatmnt $ status $ count @@;
   datalines;
 0-1    control  recur   15   0-1  control   not   50
 0-1    active   recur   12   0-1  active    not   69
 1-2    control  recur   13   1-2  control   not   30
 1-2    active   recur    7   1-2  active    not   59
 2-3    control  recur    7   2-3  control   not   17
 2-3    active   recur   10   2-3  active    not   45
 ;

 proc freq order=data;
        weight count;
        tables time*treatmnt*status / cmh;
 run;
```

- $Q_{MC} = 8.029$ with $p = 0.0046$

- Can also apply Mantel-Cox test to situation with additional explanatory variables

  Following data is from a study on gastrointestinal patients being treated for ulcers:

Center	Trt	Healed at 2 Weeks	Healed at 4 Weeks	Not Healed 4 Weeks	Total
1	A	15	17	2	34
1	P	15	17	7	39
2	A	17	17	10	44
2	P	12	13	15	40
3	A	7	17	16	40
3	P	3	17	18	38

Restructure data into life table format:

```
data duodenal;
input center time $ treatment $ status $ count @@;
datalines;
1 0-2 A healed 15 1 0-2 A not 19
1 0-2 P healed 15 1 0-2 P not 24
1 2-4 A healed 17 1 2-4 A not  2
1 2-4 P healed 17 1 2-4 P not  7
2 0-2 A healed 17 2 0-2 A not 27
2 0-2 P healed 12 2 0-2 P not 28
2 2-4 A healed 17 2 2-4 A not 10
2 2-4 P healed 13 2 2-4 P not 15
3 0-2 A healed  7 3 0-2 A not 33
3 0-2 P healed  3 3 0-2 P not 35
3 2-4 A healed 17 3 2-4 A not 16
3 2-4 P healed 17 3 2-4 P not 18
;
run;
```

- PROC FREQ statement for Mantel-Cox test:

```
proc freq data=duodenal;
        weight count;
        tables center*time*treat*status / cmh;
run;
```

- H_0: Within each center, the distribution of time to healing is the same for placebo and active treatment
- $Q_{MC} = 4.253$ with $p = 0.039$
- Conclude difference in survival between placebo and active treatment, adjusted for center.

- PROC LIFETEST in SAS can also be used to compare survival curves to determine which treatment had a more favorable outcome

- Using the PROC LIFETEST example from Section 13.2, the output will contain the test of equality over strata without adding any addition statements to the SAS code

- LIFETEST handles withdrawals by grouping them with the no recurrences. The Mantel-Cox test using PROC FREQ for the example in this section removed the withdrawals entirely. The two approaches produced different results.

13.4 Piecewise Exponential Models

- Statistical models can extend analysis of grouped survival data by providing a description of pattern of event rates
- They can describe pattern over time as well as describe variation due to influence of treatment and explanatory variables: one useful model is piecewise exponential

- Following data pertain to experience of patients undergoing treatment for ulcers. Two types of surgeries were randomly assigned, and patients were evaluated at 6 months, 24 months, 60 months

Operation	Time (months)	Death or Recurrence	Re-op or Lost	Satisfactory	Exposure (months)
V + D/A	0 – 6	23	15	630	3894
	7 – 24	32	20	578	10872
	25 – 60	45	71	462	18720
V + H	0 – 6	9	5	329	2016
	7 – 24	5	17	307	5724
	25 – 60	10	24	273	10440

- $i = 1$ for V + D/A, $i = 2$ for V + H
  $k = 1$ for 0 – 6 mo, $k = 2$ for 7 – 24 mo, $k = 3$ for 25 – 60 mo

The total person-months of exposure, $N_{ik,}$ is calculated for each treatment *i* during each interval *k* using the following formula:

$$N_{ik} = a_k (n_{i0k} + 0.5n_{i1k} + 0.5n_{i2k})$$

where

a_k = 6, 18, 36 is the length (months) of the *k*th interval

n_{i0k} = number completing *k*th interval without failure or withdrawal

n_{i1k} = number of failures during *k*th interval

n_{i2k} = number of withdrawals during *k*th interval

e.g. for V + D/A, 7 – 24 months:

$N_{12} = 18\times(578 + 0.5\times32 + 0.5\times20) = 10872$

- Make the following assumptions to fit piecewise exponential model:

  →Withdrawals are uniformly distributed during time intervals in which they occur and are unrelated to treatment failures

  →Within-interval probabilities of treatment failures are small. Time-to-failure events have independent exponential distributions

- Piecewise exponential model assumes independent exponential distributions with hazard parameters λ_{ik} for respective time periods

- Relationship of failure events to explanatory variables is specified through models for λ_{ik}:

$$\lambda_{ik} = \exp(\alpha + \eta_k + \boldsymbol{x}_i'\boldsymbol{\beta})$$

Model has proportional hazards structure, where $\{\eta_k\}$ is constant value of hazard function within kth interval when $\boldsymbol{x}_i = 0$

Parameter vector $\boldsymbol{\beta}$ relates hazard function for ith population to explanatory variables $\boldsymbol{x}_i$

13.4.1 An Application of the Proportional Hazards Piecewise Exponential Model

- Can also use GENMOD to fit piecewise exponential models:

```
proc genmod data=vda;
       class treatment time;
       model failure = time treat
             / dist=poisson  link=log  offset=nmonths;
run;
```

TIME and TREATMENT defined as class variables, LINK=LOG specified so that model is in loglinear form, OFFSET = NMONTHS specified since quantity n_{ik}/N_{ik} is being modeled

- Parameter interpretations:

GENMOD Parameter	Model Parameter	Value	Interpretation
INTERCEPT	α	-5.8164	Log incidence density for V + H, 0 – 6 mo.
TIME 7 – 24	η_1	-0.8847	Increment for 7 – 24 interval
TIME 25 – 60	η_2	-1.0429	Increment for 25 – 60 interval
TREAT vda	β	0.8071	Increment for treatment V + D/A

Output 13.6 Model Information

Model Information

Description	Value
Data Set	WORK.VDA
Distribution	POISSON
Link Function	LOG
Dependent Variable	FAILURE
Offset Variable	NMONTHS
Observations Used	6

Class Level Information

Class	Levels	Values
TREATMENT	2	vda vh
TIME	3	25-60 7-24 _0-6

Output 13.7 Goodness-of-Fit Criteria

Criteria For Assessing Goodness of Fit

Criterion	DF	Value	Value/DF
Deviance	2	2.5529	1.2764
Scaled Deviance	2	2.5529	1.2764
Pearson Chi-Square	2	2.6730	1.3365
Scaled Pearson X2	2	2.6730	1.3365
Log Likelihood	.	279.8914	.

Output 13.8 Parameter Estimates

Analysis of Parameter Estimates

Parameter		DF	Estimate	Std Err	ChiSquare	Pr>Chi
INTERCEPT		1	-5.8164	0.2556	517.6601	0.0001
TIME	25-60	1	-1.0429	0.2223	22.0015	0.0001
TIME	7-24	1	-0.8847	0.2414	13.4319	0.0002
TIME	_0-6	0	0.0000	0.0000	.	.
TREATMENT	vda	1	0.8071	0.2273	12.6067	0.0004
TREATMENT	vh	0	0.0000	0.0000	.	.
SCALE		0	1.0000	0.0000	.	.

- $\Pr\{\text{survival for } k \text{ intervals}\} =$

  $\Pr\{\text{survival for } k-1 \text{ intervals}\} \times e^{-\lambda_{ik} a_k}$

  where $\lambda_{ik} = \exp(\alpha + \eta_k + \boldsymbol{x}_i'\boldsymbol{\beta})$, and a_k is length of kth interval, $k = 1, 2, \ldots, t$.

- Model-Estimated Failure / Survival Rates

Group	Interval	Failure Rate Formula (λ)	Estimated Within Interval Failure Rate ($\hat{\lambda}$)	Estimated Survival Rate
V + H	0 – 6	$e^{\hat{\alpha}}$	$e^{-5.8164} = 0.002978$	$1e^{-0.002978 \times 6} = 0.9823$
V + H	7 – 24	$e^{\hat{\alpha}+\hat{\eta}_1}$	$e^{-5.8164-0.8847} = 0.001230$	$0.9823e^{-0.001230 \times 18} = 0.9608$
V + H	25 – 60	$e^{\hat{\alpha}+\hat{\eta}_2}$	$e^{-5.8164-1.0429} = 0.001050$	$0.9608e^{-0.001050 \times 36} = 0.9252$
V + D/A	0 – 6	$e^{\hat{\alpha}+\hat{\beta}}$	$e^{-5.8164+0.8071} = 0.006676$	$1e^{-0.006676 \times 6} = 0.9607$
V + D/A	7 – 24	$e^{\hat{\alpha}+\hat{\beta}+\hat{\eta}_1}$	$e^{-5.8164+0.8071-0.8847} = 0.002756$	$0.9607e^{-0.002756 \times 18} = 0.9142$
V + D/A	25 – 60	$e^{\hat{\alpha}+\hat{\beta}+\hat{\eta}_2}$	$e^{-5.8164+0.8071-1.0429} = 0.002353$	$0.9142e^{-0.002353 \times 36} = 0.8399$

- Within interval failure rate is highest for first interval and lower for other two intervals; failure rate is higher for V + D/A than for V + H

13.4.2 Using PROC LOGISTIC to Fit the Piecewise Exponential Model

- When incidence rates $\{\lambda_{ik}\}$ are small (less than 0.05) and exposures N_{ik} are very large, logistic regression can be used to approximate Poisson regression
- Can facilitate approximation by rescaling exposure factor by multiplying it by a number such as 10,000; **the only adjustment needed after parameter estimation is to add to resulting intercept estimate the log of multiplier chosen**
- The following SAS statements fit piecewise exponential model to duodenal ulcer data using LOGISTIC: (SMONTHS is the exposure in months multiplied by 100,000)

```
data vda;
        input treatment time $ failure months;
        smonths=100000*months;
        datalines;

1     _0-6    23      3894
1     7-24    32     10872
1    25-60    45     18720
0     _0-6    9       2016
0     7-24    5       5724
0    25-60    10     10440

;
proc logistic;
        class time / param ref;
        model failure/smonths=time treatment time*treatment /
                scale=none  include=2  selection=forward;
run;
```

Output 13.9 Score Statistic

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	34.7700	3	< .0001
Score	39.0554	3	< .0001
Wald	36.2836	3	< .0001

Residual Chi-Square Test

Chi-Square	DF	Pr > ChiSq
2.6730	2	0.2628

Output 13.10 Goodness-of-Fit Statistics

Deviance and Pearson Goodness-of-Fit Statistics

Criterion	DF	Value	Value/DF	Pr > Chi-Square
Deviance	2	2.5529	1.2764	0.2790
Pearson	2	2.6730	1.3365	0.2628

Number of events/trials observations: 6

Output 13.11 Parameter Estimates

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-17.3293	0.2556	4595.1888	< .0001
time	25-60	1	-1.0430	0.2223	22.0023	< .0001
time	7-24	1	-0.8848	0.2414	13.4324	0.0002
treatment		1	0.8071	0.2273	12.6068	0.0004

$$L_{PE} = \prod_{i=1}^{6} \prod_{j=1}^{2} \lambda_{ij}^{n_{ij}} [\exp(-\lambda_{ij} N_{ij})]$$

$$N_{ij} = \left\{ \tfrac{1}{2} \begin{bmatrix} \text{number} \\ \text{healed} \end{bmatrix} + \tfrac{1}{2} \begin{bmatrix} \text{number} \\ \text{withdrawn} \end{bmatrix} + \begin{bmatrix} \text{number} \\ \text{not healed} \end{bmatrix} \right\} \times \left\{ \begin{matrix} \text{Length of} \\ j\text{th interval} \end{matrix} \right\}$$

healed: $\lambda_{ij} e^{-(\lambda_{ij} a_j / 2)}$

not healed: $e^{-(\lambda_{ij} a_j)}$

withdrawal: $e^{-(\lambda_{ij} a_j / 2)}$

Loglinear model $\lambda_{ij} = \exp(\boldsymbol{x}'_{ij}\boldsymbol{\beta})$

Proportional hazards $\lambda_{ij} = \exp(\alpha_j + \boldsymbol{x}'_i\boldsymbol{\beta})$

$$= \lambda_j \exp(\boldsymbol{x}'_i\boldsymbol{\beta})$$

$$\frac{\lambda_{ij}}{\lambda_{i'j}} = \exp[(\boldsymbol{x}_i - \boldsymbol{x}_{i'})'\boldsymbol{\beta}]$$

$$\mathrm{L}_{PO} = \prod_{i=1}^{6}\prod_{j=1}^{2} \frac{(N_{ij}\lambda_{ij})^{n_{ij}}[\exp(-N_{ij}\lambda_{ij})]}{n_{ij}!}$$

$$= \mathrm{L}_{PE}\left[\prod_{i=1}^{6}\prod_{j=1}^{2} \frac{N_{ij}^{n_{ij}}}{n_{ij}!}\right]$$

Maximize L_{PE} by same $\hat{\boldsymbol{\beta}}$ that maximizes L_{PO}

MLE equations $\boldsymbol{X}'\boldsymbol{n} = \boldsymbol{X}'\hat{\boldsymbol{\mu}} = \boldsymbol{X}'\boldsymbol{D}_{\boldsymbol{N}}[\exp(\boldsymbol{X}\hat{\boldsymbol{\beta}})]$

$$\boldsymbol{V}_{\hat{\beta}} = (\boldsymbol{X}'\boldsymbol{D}_{\hat{\mu}}\boldsymbol{X})^{-1}$$

$$Q_P = \sum_{i=1}^{6}\sum_{j=1}^{2}(n_{ij} - \hat{\mu}_{ij})^2 / \hat{\mu}_{ij}$$

$$Q_L = \sum_{i=1}^{6}\sum_{j=1}^{2} 2n_{ij}\log(n_{ij}/\hat{\mu}_{ij})$$

$$Q_{RS} = (\boldsymbol{n}-\hat{\boldsymbol{\mu}})'\boldsymbol{W}\left[\boldsymbol{V}_{\boldsymbol{W}'(\boldsymbol{n}-\hat{\boldsymbol{\mu}})}\right]^{-1}\boldsymbol{W}'(\boldsymbol{n}-\hat{\boldsymbol{\mu}})$$

Relative to model $[\boldsymbol{X},\boldsymbol{W}]$, d.f. = rank($\boldsymbol{W}$)