BIOS 662

Homework 8 Solution

December, 2018

Question 1

As mentioned in the question, the "sample" is the number of operations. These occur at a distinct point in time (and the outcome is vital status at 6 weeks after the operation). The rate of interest is deaths per 100,000 operations. We could think of it as "if 100,000 operations were performed in a year, how many people would die within 6 weeks of the operation". Our estimate would be the same if the 100,000 operations occurred over a longer or shorter period than a year. In the example on page 6 of the "Rates and Proportions" overheads, a person without diabetes is at risk of diabetes as long as he/she is being followed in the study. There the incidence of 0.033 can be thought of as the probability of a person becoming diabetic if followed for a year. But in the current problem it is just the short time immediately after the operation that is considered. It does not make sense to try to express this as risk over a year — the risk of death related to the operation decreases with time since the operation, so the risk in the first 6 weeks is unlikely to be representative of the risk over a longer period (such as a year) or even over a shorter period (such as in the first week).

(a) Let $I_{H,10^5}$ and $I_{C,10^5}$ denote the death rates per 100,0000 (per year) for halothane and cyclopropane, respectively.

$$\hat{I}_{H,10^5} = c \cdot \frac{\text{number of deaths}}{\text{number of operations using halothane}}$$

where $c = 100,000$. A corresponding formula holds for $I_{C,10^5}$.

So,

$$\hat{I}_{H,10^5} = 100,000 \cdot \frac{2,375}{146,200} = 1,624.5 \text{ deaths per 100,000 operations per year}$$

and

$$\hat{I}_{H,10^5} = 100,000 \cdot \frac{2,109}{68,169} = 3,093.8 \text{ deaths per 100,000 operations per year.}$$

To test whether the rates differ significantly, that is, $H_0 : I_{H,10^5} = I_{C,10^5}$ versus $H_0 : I_{H,10^5} \neq I_{C,10^5}$, the c terms drop out and we can use a two-sample test of proportions. The sample sizes are large and under H_0,

$$\frac{p_1 - p_2}{\sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}} \sim N(0,1).$$

Using $\alpha = 0.05$, the critical region is $C_{0.05} = \{|z| > 1.96\}$. Here

$$\frac{p_1 - p_2}{\sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}} = \frac{0.0162 - 0.0309}{\sqrt{\frac{0.0162(1-0.0162)}{146200} + \frac{0.0309(1-0.0309)}{68169}}} = -19.8 < -1.96.$$

So we reject H_0 and conclude that the death rate when cyclopropane is used is significantly higher than when halothane is used.

(b) Using all the operations, the weights are given in Table 1, with w_i being the number of operations in physical status category i divided by the total number of operations.

Status	Operations	Weight
Unknown	69,239	0.162
1	185,919	0.435
2	104,286	0.244
3	29,491	0.069
4	3,419	0.008
5	21,797	0.051
6	11,112	0.026
7	2,137	0.005
Total	427,400	1.000

Table 1: Weights for direct standardization

Denote the standardized incidence rates by $I_{H_{adj},10^5}$ and $I_{C_{adj},10^5}$, where for $j \in \{\text{C,H}\}$,

$$\hat{I}_{j_{adj},10^5} = c \cdot \hat{p}_{j_{\text{adj}}} = c \cdot \frac{\sum_{k=1}^{K} w_k \hat{p}_{jk}}{\sum_{k=1}^{K} w_k}.$$

The values of $\hat{p}_{jk}$ are given in Tables 2 and 3 for halothane and cyclopropane, respectively. Using these, $\hat{I}_{H_{adj},10^5} = 100,000 \times 0.018091 = 1,809.1$ deaths per 100,000 operations per year and $\hat{I}_{C_{adj},10^5} = 100,000 \times 0.026843 = 2,684.3$ deaths per 100,000 operations per year.

To test $H_0 : I_{H_{adj},10^5} = I_{C_{adj},10^5}$ versus $H_A : I_{H_{adj},10^5} \neq I_{C_{adj},10^5}$, note that the constant c cancels out again and we have

$$Z = \frac{\hat{I}_{H_{adj},10^5} - \hat{I}_{C_{adj},10^5}}{\sqrt{\widehat{\text{Var}}(\hat{I}_{H_{adj},10^5} - \hat{I}_{H_{adj},10^5})}} \sim N(0,1).$$

Here

$$\widehat{\text{Var}}(\hat{I}_{H_{adj},10^5} - \hat{I}_{H_{adj},10^5}) = \frac{\sum_{k=1}^{K} w_k^2 \left(\widehat{\text{Var}}(\hat{p}_{Hk}) + \widehat{\text{Var}}(\hat{p}_{Ck})\right)}{\left(\sum_{k=1}^{K} w_k\right)^2}$$

with $\widehat{\text{Var}}(\hat{p}_{Hk})$ and $\widehat{\text{Var}}(\hat{p}_{Ck})$ given in Tables 2 and 3 for halothane and cyclopropane, respectively.

So $Z = (0.0181 - 0.0268)/\sqrt{4.95954 \times 10^{-7}} = -12.4 < -1.96$, and as in part (a) we reject H_0.

SAS code for direct standardization plus edited output:

```
proc stdrate data=hw7q2b refdata=hw7q2c method=direct
          effect stat=rate(mult=100000);
    population group=group event=deaths total=ops;
reference total=ops_total;
strata status / stats effect;
```

```
            Directly Standardized Rate Estimates
                   Rate Multiplier = 100000

         --------Study Population-------  -Reference Population-
         Observed  Population-     Crude  Expected   Population-
group      Events          Time      Rate    Events          Time
cyclo        2109         68169    3093.8   11472.6        427400
halo         2375        146200    1624.5    7731.9        427400

     Directly Standardized Rate Estimates
           Rate Multiplier = 100000

         -----------Standardized Rate----------
                    Standard      95% Normal
group    Estimate     Error   Confidence Limits
cyclo      2684.3   62.7938    2561.2    2807.4
halo       1809.1   37.6699    1735.2    1882.9


              Rate Effect Estimates (Rate Multiplier = 100000)

                                      Log
-------group------      Rate         Rate    Standard
   cyclo      halo     Ratio        Ratio       Error          Z    Pr > |Z|

  2684.3    1809.1    1.4838       0.3946      0.0313      12.60      <.0001
```

(c) In calculating the standardized incidence ratio the constant c again cancels out, so we can work with the proportions.

To test $H_0 : \pi_{\text{halothane}}/\pi_{\text{overall}} = 1$ versus $H_A : \pi_{\text{halothane}}/\pi_{\text{overall}} \neq 1$ we first calculate

$$s = \frac{\hat{p}_{\text{halothane}}}{\hat{p}_{\text{overall}}} = \frac{\sum_{k=1}^{K} n_k}{\sum_{k=1}^{K} N_k m_k / M_k} = \frac{O}{E}.$$

If $\widehat{\text{Var}}(O) = \sum_k n_k$ and $\widehat{\text{Var}}(E) = \sum_k \left(\frac{N_k}{M_k}\right)^2 m_k$, then $\widehat{\text{Var}}(s) = \frac{\widehat{\text{Var}}(O) + s^2 \widehat{\text{Var}}(E)}{E^2}$,

Status (k)	Weight (w_k)	Operations	Deaths	$\hat{p}_{Hk}$	$\widehat{\text{Var}}(\hat{p}_{Hk})$
Unknown	0.16200	23684	419	0.01769	0.000000734
1	0.43500	65936	125	0.00190	0.000000029
2	0.24400	36842	560	0.01520	0.000000406
3	0.06900	8918	617	0.06919	0.000007221
4	0.00800	1170	182	0.15556	0.000112272
5	0.05100	6579	74	0.01125	0.000001690
6	0.02600	2632	287	0.10904	0.000036912
7	0.00500	439	111	0.25285	0.000430332
Total	1.00000	146200	2375	—	—

Table 2: Halothane estimates for direct standardization

Status (k)	Weight (w_k)	Operations	Deaths	$\hat{p}_{Ck}$	$\widehat{\text{Var}}(\hat{p}_{Ck})$
Unknown	0.16200	10147	297	0.02927	0.000002800
1	0.43500	27444	91	0.00332	0.000000120
2	0.24400	14097	361	0.02561	0.000001770
3	0.06900	3814	403	0.10566	0.000024777
4	0.00800	681	127	0.18649	0.000222778
5	0.05100	7423	101	0.01361	0.000001808
6	0.02600	3814	476	0.12480	0.000028639
7	0.00500	749	253	0.33778	0.000298646
Total	1.00000	68169	2109	—	—

Table 3: Cyclopropane estimates for direct standardization

and under H_0, $Z = (s-1)/\sqrt{\widehat{\text{Var}}(s)} \sim N(0,1)$.

Using the data in Table 4, $O = 2,375$, $E = 2,695.12$, $s = 2,375/2,695.12 = 0.88$, $\widehat{\text{Var}}(O) = 2,375$ and $\widehat{\text{Var}}(E) = 848.27$.

So $\widehat{\text{Var}}(s) = \dfrac{2375 + 0.88^2 \cdot 848.27}{2695.12^2} = 0.00043$ and $Z = \dfrac{0.88-1}{\sqrt{0.00043}} = -5.73 < -1.96$.

Thus we reject H_0 and we conclude that the mortality rate for halothane is significantly less than the overall death rate.

SAS uses a somewhat different estimator for the variance. It uses

$$\widehat{\text{Var}}(s) = \frac{O}{E^2} = \frac{2375}{2695.12^2} = 0.00033$$

and this yields

$$Z = \frac{0.88-1}{\sqrt{0.00033}} = -6.57.$$

```
proc stdrate data=hw7q2 refdata=hw7q2 method=indirect stat=rate;
    population event=dth_halo total=ops_halo;
reference event=dth_total total=ops_total;
strata status / stats smr;
```

Standardized Morbidity/Mortality Ratio

Observed Events	Expected Events	SMR	Standard Error	95% Normal Confidence Limits		Z	Pr > |Z|
2375	2695.12	0.8812	0.0181	0.8458	0.9167	-6.57	<.0001

	Reference		Halothane			
Status (k)	m_k	M_k	n_k	N_k	$N_k m_k / M_k$	$\left(\frac{N_k}{M_k}\right)^2 m_k$
Unknown	1,378	69,239	419	23,684	471.36	161.23
1	445	185,919	125	65,936	157.82	55.97
2	1,856	104,286	560	36,842	655.68	231.64
3	2,135	29,491	617	8,918	645.62	195.23
4	590	3,419	182	1,170	201.90	69.09
5	314	21,797	74	6,579	94.77	28.61
6	1,392	11,112	287	2,632	329.71	78.10
7	673	2,137	111	439	138.25	28.40
Total	8,783	427,400	2,375	146,200	2695.12	848.27

Table 4: Counts for indirect standardization

Question 2

(a) Tables 5 and 6 give the calculations for the Kaplan-Meier curves for group 1 and group 2, respectively.

Figure 1 has the Kaplan-Meier survival function estimates for the two groups, plotted using the R code:

```
library("survival")

fit <- survfit(Surv(timedeath, death)~group,conf.type="none")

pdf("HW8_Surv.pdf",width=11,height=8.5)

plot(fit,xlab="Time (days)",ylab="S(t)",lwd=c(1,3),cex.axis=1.6,
   main="Kaplan-Meier estimates for the two groups",cex.lab=1.6,
 cex.main=1.6,cex.sub=1.6)

legend(425,1.0,c("New treatment","Placebo"),lwd=c(3,1),cex=1.6)

dev.off()
```

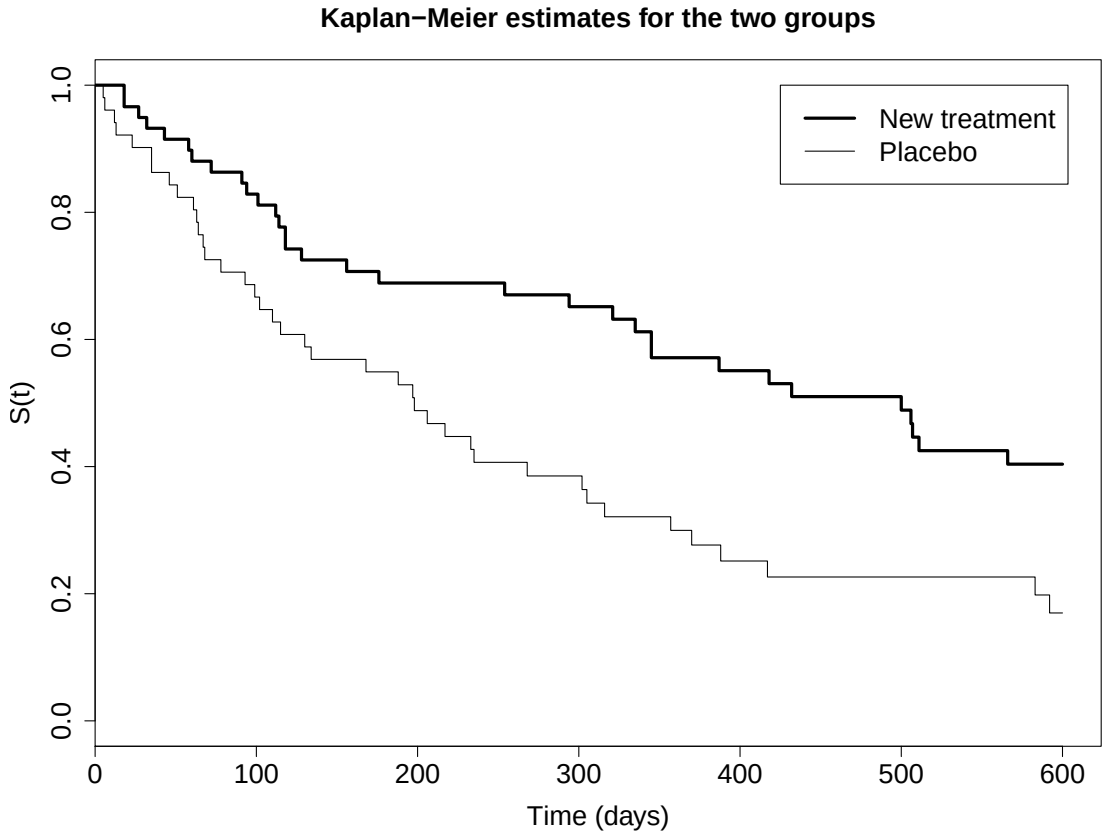

Figure 1: Calculation of Kaplan-Meier estimate for group 1

$t_{(j)}$	m_j	q_j	$R(t_{(j)})$	$\hat{S}(t_{(j)})$
5	1	0	51	0.98039
6	1	0	50	0.96078
12	1	0	49	0.94118
13	1	0	48	0.92157
23	1	0	47	0.90196
35	2	0	46	0.86275
46	1	0	44	0.84314
51	1	0	43	0.82353
61	1	0	42	0.80392
63	1	0	41	0.78431
64	1	0	40	0.76471
67	1	0	39	0.74510
68	1	0	38	0.72549
78	1	0	37	0.70588
93	1	0	36	0.68627
99	1	0	35	0.66667
102	1	0	34	0.64706
110	1	0	33	0.62745
115	1	0	32	0.60784
130	1	0	31	0.58824
134	1	0	30	0.56863
168	1	1	29	0.54902
188	1	0	27	0.52869
197	1	0	26	0.50835
198	1	0	25	0.48802
206	1	0	24	0.46768
217	1	0	23	0.44735
233	1	0	22	0.42702
235	1	1	21	0.40668
268	1	0	19	0.38528
302	1	0	18	0.36387
305	1	0	17	0.34247
316	1	0	16	0.32106
357	1	1	15	0.29966
370	1	1	13	0.27661
388	1	0	11	0.25146
417	1	1	10	0.22632
583	1	0	8	0.19803
592	1	6	7	0.16974

Table 5: Calculation of Kaplan-Meier estimate for group 1

$t_{(j)}$	m_j	q_j	$R(t_{(j)})$	$\hat{S}(t_{(j)})$
18	2	0	59	0.96610
27	1	0	57	0.94915
32	1	0	56	0.93220
43	1	1	54	0.91494
58	1	0	53	0.89768
60	1	0	52	0.88041
72	1	0	51	0.86315
91	1	0	50	0.84589
94	1	0	49	0.82863
101	1	0	48	0.81136
112	1	0	47	0.79410
114	1	0	46	0.77684
118	2	0	45	0.74231
128	1	2	43	0.72505
156	1	0	40	0.70692
176	1	1	39	0.68879
254	1	0	37	0.67018
294	1	2	36	0.65156
321	1	0	33	0.63182
335	1	0	32	0.61207
345	2	0	30	0.57127
387	1	0	28	0.55087
418	1	0	27	0.53046
432	1	1	26	0.51006
500	1	0	24	0.48881
506	1	0	23	0.46756
507	1	0	22	0.44630
511	1	0	21	0.42505
566	1	19	20	0.40380

Table 6: Calculation of Kaplan-Meier estimate for group 2

(b) Tables 7 and 8 have data for doing the log-rank test "by hand". We want to test $H_0 : S_1(t) = S_2(t)$ for all t against $H_A : S_1(t) \neq S_2(t)$ for at least one t. Under H_0, $X = (O_1 - E_1)^2/V_1 \sim \chi^2_1$. So the critical region is $C_{0.05} = \{X : X > \chi^2_{1,0.95} = 3.84\}$.

Using the data in Tables 7 and 8:

$$X = (O_1 - E_1)^2/V_1 = (40 - 27.8195)^2/16.7682 = 8.85 > 3.84.$$

So we reject H_0 and conclude that the new treatment tends to increase survival time in comparison with placebo. We confirm the result using SAS:

```
proc lifetest;
   time timedeath*death(0);
   strata group;

       Test of Equality over Strata
                                    Pr >
Test      Chi-Square      DF    Chi-Square

Log-Rank      8.8468       1      0.0029
```

Note that if one does the calculations using group 2 in X one obtains the same value for the statistic. In that case $O_2 = 32$ and $E_2 = 44.1805$.

(c) Let X be an indicator of being in group 2, that is $X = 0$ if in group 1 and $X = 1$ if in group 2. The model is

$$\log \lambda(t) = \log \lambda_0(t) + \beta X$$

We want to test $H_0 : \beta = 0$ versus $H_A : \beta \neq 0$. We have not covered details of how the test is conducted and so will use just the output from SAS or R. Using SAS with the option "rl" in the "model" statement to obtain the "risk limits", that is, a 95% confidence interval for the hazard ratio, needed in part (d):

```
proc phreg;
   model timedeath*death(0) = group01 / ties=exact rl;


The PHREG Procedure

               Analysis of Maximum Likelihood Estimates

                    Parameter      Standard
Parameter    DF      Estimate         Error    Chi-Square    Pr > ChiSq

group01       1      -0.69719       0.23939        8.4820        0.0036

  Analysis of Maximum Likelihood Estimates

               Hazard      95% Hazard Ratio
Parameter       Ratio      Confidence Limits

group01         0.498       0.311       0.796
```

$t_{(k)}$	m_{1k}	$R_1(t_{(k)})$	m_{2k}	$R_2(t_{(k)})$	m_k	$R(t_{(k)})$	E_{1k}	V_{1k}
5	1	51	0	59	1	110	0.46364	0.24868
6	1	50	0	59	1	109	0.45872	0.24830
12	1	49	0	59	1	108	0.45370	0.24786
13	1	48	0	59	1	107	0.44860	0.24736
18	0	47	2	59	2	106	0.88679	0.48889
23	1	47	0	57	1	104	0.45192	0.24769
27	0	46	1	57	1	103	0.44660	0.24715
32	0	46	1	56	1	102	0.45098	0.24760
35	2	46	0	55	2	101	0.91089	0.49107
43	0	44	1	54	1	98	0.44898	0.24740
46	1	44	0	53	1	97	0.45361	0.24785
51	1	43	0	53	1	96	0.44792	0.24729
58	0	42	1	53	1	95	0.44211	0.24665
60	0	42	1	52	1	94	0.44681	0.24717
61	1	42	0	51	1	93	0.45161	0.24766
63	1	41	0	51	1	92	0.44565	0.24705
64	1	40	0	51	1	91	0.43956	0.24635
67	1	39	0	51	1	90	0.43333	0.24556
68	1	38	0	51	1	89	0.42697	0.24467
72	0	37	1	51	1	88	0.42045	0.24367
78	1	37	0	50	1	87	0.42529	0.24442
91	0	36	1	50	1	86	0.41860	0.24337
93	1	36	0	49	1	85	0.42353	0.24415
94	0	35	1	49	1	84	0.41667	0.24306
99	1	35	0	48	1	83	0.42169	0.24387
101	0	34	1	48	1	82	0.41463	0.24271
102	1	34	0	47	1	81	0.41975	0.24356
110	1	33	0	47	1	80	0.41250	0.24234
112	0	32	1	47	1	79	0.40506	0.24099
114	0	32	1	46	1	78	0.41026	0.24195
115	1	32	0	45	1	77	0.41558	0.24287
118	0	31	2	45	2	76	0.81579	0.47659
128	0	31	1	43	1	74	0.41892	0.24343
130	1	31	0	42	1	73	0.42466	0.24432
134	1	30	0	42	1	72	0.41667	0.24306
156	0	29	1	40	1	69	0.42029	0.24365
168	1	29	0	39	1	68	0.42647	0.24459
176	0	28	1	39	1	67	0.41791	0.24326
188	1	27	0	38	1	65	0.41538	0.24284

Table 7: First part of table for log-rank test

$t_{(k)}$	m_{1k}	$R_1(t_{(k)})$	m_{2k}	$R_2(t_{(k)})$	m_k	$R(t_{(k)})$	E_{1k}	V_{1k}
197	1	26	0	38	1	64	0.40625	0.24121
198	1	25	0	38	1	63	0.39683	0.23936
206	1	24	0	38	1	62	0.38710	0.23725
217	1	23	0	38	1	61	0.37705	0.23488
233	1	22	0	38	1	60	0.36667	0.23222
235	1	21	0	38	1	59	0.35593	0.22924
254	0	20	1	37	1	57	0.35088	0.22776
268	1	19	0	36	1	55	0.34545	0.22612
294	0	18	1	36	1	54	0.33333	0.22222
302	1	18	0	35	1	53	0.33962	0.22428
305	1	17	0	35	1	52	0.32692	0.22004
316	1	16	0	35	1	51	0.31373	0.21530
321	0	15	1	33	1	48	0.31250	0.21484
335	0	15	1	32	1	47	0.31915	0.21729
345	0	15	2	30	2	45	0.66667	0.43434
357	1	15	0	28	1	43	0.34884	0.22715
370	1	13	0	28	1	41	0.31707	0.21654
387	0	12	1	28	1	40	0.30000	0.21000
388	1	11	0	27	1	38	0.28947	0.20568
417	1	10	0	27	1	37	0.27027	0.19722
418	0	9	1	27	1	36	0.25000	0.18750
432	0	9	1	26	1	35	0.25714	0.19102
500	0	9	1	24	1	33	0.27273	0.19835
506	0	9	1	23	1	32	0.28125	0.20215
507	0	9	1	22	1	31	0.29032	0.20604
511	0	9	1	21	1	30	0.30000	0.21000
566	0	9	1	20	1	29	0.31034	0.21403
583	1	8	0	19	1	27	0.29630	0.20850
592	1	7	0	19	1	26	0.26923	0.19675
	40		32				27.8195	16.7682

Table 8: Second part of table for log-rank test

Equivalently, in R:

```
> coxph(Surv(timedeath, death)~group01)
> summary(coxph(Surv(timedeath, death)~group01))

Call:
coxph(formula = Surv(timedeath, death) ~ group)

  n= 110, number of events= 72

         coef exp(coef) se(coef)      z Pr(>|z|)
group -0.6972    0.4980   0.2394 -2.913  0.00358 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

      exp(coef) exp(-coef) lower .95 upper .95
group     0.498      2.008    0.3115    0.7961
```

In either case the p-value associated with the test of $\beta = 0$ is 0.0036. So we reject H_0 and we conclude that the time to death differs significantly between the two treatment groups, with the new treatment being better than placebo.

(d) The hazard ratio estimate is $\exp(\hat{\beta}) = \exp(-0.6972) = 0.498$. The 95% CI can be obtained from SAS or R output. Alternatively, as in Table 16.7 of the text, a 95% CI for β is given by $\hat{\beta} \pm 1.96 \cdot \text{SE}(\hat{\beta}) = -0.6972 \pm 1.96 \cdot 0.2394 = (-1.166, -0.228)$. Taking antilogs gives the 95% CI for the hazard ratio as $(0.311, 0.796)$.

(e) The model is now

$$\log \lambda(t) = \log \lambda_0(t) + \beta_{group} X_{group} + \beta_{age} X_{age}$$

and the SAS code and output as below. The p-value for age is 0.0339, so age has a significant efect on survival. The associated hazard ratio is greater than one, so the hazard increases with age, that is, older age is associated with poorer survival probability. The hazard ratio for the treatment group variable has not changed substantially.

```
proc phreg;
   model timedeath*death(0) = group01 age / ties=exact rl;

The PHREG Procedure

                  Analysis of Maximum Likelihood Estimates

                Parameter   Standard                              Hazard
Parameter  DF    Estimate      Error   Chi-Square   Pr > ChiSq     Ratio

group01     1    -0.72071    0.24017       9.0047       0.0027     0.486
age         1     0.04922    0.02320       4.5012       0.0339     1.050
```

(f) Looking at Table 5, the time at which $\widehat{S}(t)$ is first ≤ 0.5 is at $t = 198$.