

1. (a) (4points) This is a randomized clinical trial. The patients were randomly assigned to the two drug treatments (two arms of the study) and followed to determine survival times.
- (b) (4 points) The experimental units are the patients. Patients are randomly assigned to the two treatment groups and the survival time responses are provided by the patients. The treatment factor is the type of drug used to treat patients with myelomatosis: drug A or drug B. There are no blocking or matching factors
- (c) (i) (6 points) Relative risk is defined as

$$RR = \frac{P(\text{die by 120 days} \mid \text{treated with drug A})}{P(\text{die by 120 days} \mid \text{treated with drug B})}$$

An estimate is $\hat{RR} = \frac{5/8}{1/8} = 5$

(ii) (6 points) Since the counts are small, it is best to use the exact randomization test which produces the following p-value:

$$p - \text{value} = 2 \left[\frac{\binom{10}{3} \binom{6}{5}}{\binom{16}{8}} + \frac{\binom{10}{2} \binom{6}{6}}{\binom{16}{8}} \right] = 2 \left[\frac{765}{12870} \right] = .118$$

In spite of the large estimate of relative risk, the evidence in the data is not sufficient to conclude that the two drug treatments provide different survival rates at 120 days.

You could have used the Pearson chi-square statistic (X^2) or the likelihood ratio test (G^2) for testing the equality of two binomial proportions. The estimated expected counts are

	Alive at 120 days	Dead before 120 days
Drug A	5	3
Drug B	5	3

$$\text{Then, } X^2 = \frac{(3-5)^2}{5} + \frac{(7-5)^2}{5} + \frac{(5-3)^2}{3} + \frac{(1-3)^2}{3} = 4.26$$

$$\text{and } G^2 = 2[3\log(3/5) + 7\log(7/5) + 5\log(5/3) + 1\log(1/3)] = 4.56.$$

Both values exceed $\chi_{1,.05}^2 = 3.84$. In this case the counts are too small for the large sample chi-square approximation to the null distributions of these statistics to be sufficiently accurate. The methods we used to construct approximate confidence intervals also relied on large sample normal approximations for distributions that are not sufficiently accurate in this case.

(d) (8 points) The Kaplan-Meier estimator is constructed as follows

Time	$(n_i - d_i)/n_i$	$\hat{S}(t)$
0	1	1
8	7/8	$(1)(7/8) = 7/8 = 0.875$
18	5/7	$(7/8)(5/7) = (5/8) = .625$
43	4/5	$(5/8)(4/5) = 1/2 = 0.500$
52	3/4	$(1/2)(3/4) = 3/8 = 0.375$
132	2/3	$(3/8)(2/3) = 1/4 = 0.250$
220	0/1	$(1/4)(0) = 0$

(e) (6 points) The null hypothesis is that the survivor curves are the same for the two drugs. The alternative is that the survivor functions are not the same. Since $3.92 > \chi_{1,.05}^2 = 3.84$, the observed difference in the survivor curves is significant at the .05 level. The underlying assumptions are that the survival time of any patient is independent of the survival time for any other patient, survival times are independent of any censoring mechanism (non-informative censoring), and failure precedes censoring if one patient is censored at the same time that another patient is observed to fail.

2. (a) (6 points) Compute the density

$$f(t) = -\frac{\partial S(t)}{\partial t} = \alpha\lambda(\lambda t)^{\alpha-1}e^{-(\lambda t)^\alpha}$$

Then, the hazard function is $h(t) = \frac{f(t)}{S(t)} = \alpha\lambda(\lambda t)^{\alpha-1}$

(b) (4 points) For these data the likelihood function is

$$\begin{aligned} L_{DrugA}(\alpha, \lambda) &= [\alpha\lambda(\lambda 8)^{\alpha-1}e^{-(\lambda 8)^\alpha}] [\alpha\lambda(\lambda 18)^{\alpha-1}e^{-(\lambda 18)^\alpha} \alpha]^2 [\lambda(\lambda 43)^{\alpha-1}e^{-(\lambda 43)^\alpha}] \\ &\times [\alpha\lambda(\lambda 52)^{\alpha-1}e^{-(\lambda 52)^\alpha}] [\alpha\lambda(\lambda 132)^{\alpha-1}e^{-(\lambda 132)^\alpha}] [e^{-(\lambda 132)^\alpha}] \\ &\times [\alpha\lambda(\lambda 220)^{\alpha-1}e^{-(\lambda 220)^\alpha}] \end{aligned}$$

(c) (6 points) Perform a likelihood ratio test. Let $(\hat{\alpha}_A, \hat{\lambda}_A)$ denote the mle's for the Weibull likelihood in part (b), obtained from the data for patients treated with Drug A, and let $L_{DrugA}(\hat{\alpha}_A, \hat{\lambda}_A)$ denote the value of likelihood function evaluated at $(\hat{\alpha}_A, \hat{\lambda}_A)$. Let $(\hat{\alpha}_B, \hat{\lambda}_B)$ denote the mle's for the parameters in the Weibull distribution computed from the data for the patients who were treated with Drug B, and let $L_{DrugB}(\hat{\alpha}_B, \hat{\lambda}_B)$ denote the value of the likelihood function evaluated at $(\hat{\alpha}_B, \hat{\lambda}_B)$. Under the null hypothesis the Weibull distributions for treatment with Drug A or Drug B would have the same parameter values. Let $(\hat{\alpha}, \hat{\lambda})$ denote the mle's for fitting a single Weibull distribution to the combined sample, and let $L(\hat{\alpha}, \hat{\lambda})$ denote the value of

likelihood function for the combined sample evaluated at $(\hat{\alpha}, \hat{\lambda})$. The likelihood ratio test rejects the null hypothesis that the Weibull distributions of the survival times are the same for treatment with Drug A or Drug B if

$$2\log\left(\frac{L_{DrugA}(\hat{\alpha}_A, \hat{\lambda}_A)L_{DrugB}(\hat{\alpha}_B, \hat{\lambda}_B)}{L(\hat{\alpha}, \hat{\lambda})}\right) > \chi_{(2),.05}^2 = 5.99$$

The chi-square approximation to the distribution of this test statistics is better for larger sample sizes.

You could do another test by constructing a proportional hazards model with a Weibull baseline distribution, and test the null hypothesis that the coefficient for the treatment variable is zero. This would be a slightly more powerful test if the proportional hazards assumption was correct, but the previous test is more general because it does not require a proportional hazards assumption.

You might consider the log-rank or Wilcoxon tests that do not require the specification of parameter models for the survival distributions for the two drugs, but those tests would have less power than the likelihood ratio test based on the Weibull distribution when the failure time distributions are Weibull. This problem instructed you to use the Weibull model.

3. (a) (8 points) To account for the pairing, use McNemar's test or the sign test or an exact test based on a binomial distribution with probability 0.5 for the off-diagonal counts in the 2×2 table. The value of McNemar's test is

$$X^2 = \frac{(28 - 9)^2}{28 + 9} = 9.76$$

Using a continuity correction, the value of McNemar's test is

$$X^2 = \frac{(|28 - 9| - 0.5)^2}{28 + 9} = 9.25$$

Both statistics exceed $\chi_{(1),.01}^2 = 9.21$, so the null hypothesis is rejected at the .01 level of significance. There is a higher incidence of smoking among women who gave birth to low birth weight babies.

Alternatively, you could describe how to obtain an exact p-value from a binomial test. This is a slightly better answer, because it does not use a large sample chi-square approximation.

Another large sample approach is to construct a 95% confidence interval for the natural logarithm of the conditional probability that the case smoked

and the control did not smoke divided by the conditional probability that the case did not smoke and the control smoked, i.e.,

$$\log(n_{11}/n_{21}) \pm (1.96)\sqrt{n_{12}^{-1} + n_{21}^{-1}} \Rightarrow (0.38, 1.86)$$

and note that the interval was shifted above zero.

Some people constructed an approximate 95% confidence interval for the marginal odds ratio. This was accepted if it was constructed properly.

Methods for comparing independent samples, such as the Pearson Chi-square test are inappropriate for paired data.

(b) (6 points) Use the basic result for conditional probabilities (Bayes Theorem):

$$P(A|B) = \frac{P(A \text{ and } B)}{P(B)} = \frac{P(B|A)P(A)}{P(B)}$$

Then,

$$\begin{aligned} e^\beta &= \frac{\frac{P(\text{smoker}|\text{case})}{P(\text{non-smoker}|\text{case})}}{\frac{P(\text{smoker}|\text{control})}{P(\text{non-smoker}|\text{control})}} \\ &= \frac{\frac{P(\text{case}|\text{smoker})P(\text{smoker})P(\text{case})}{P(\text{case}|\text{non-smoker})P(\text{non-smoker})P(\text{case})}}{\frac{P(\text{control}|\text{smoker})P(\text{smoker})P(\text{control})}{P(\text{control}|\text{non-smoker})P(\text{non-smoker})P(\text{control})}} \\ &= \frac{\frac{P(\text{case}|\text{smoker})}{P(\text{control}|\text{smoker})}}{\frac{P(\text{case}|\text{non-smoker})}{P(\text{control}|\text{non-smoker})}} \\ &= \frac{\text{odds that a smoker is a case}}{\text{odds that a non-smoker is a case}} \end{aligned}$$

(c) (6 points) The conditional likelihood function is

$$\begin{aligned} \prod_{i=1}^n \left(\frac{\frac{e^{\alpha_i+\beta} Y_{1i}}{1+e^{\alpha_i+\beta}} \frac{e^{\alpha_i} Y_{2i}}{1+e^{\alpha_i}}}{\frac{e^{\alpha_i+\beta} Y_{1i}}{1+e^{\alpha_i+\beta}} \frac{e^{\alpha_i} Y_{2i}}{1+e^{\alpha_i}} + \frac{e^{\alpha_i+\beta} Y_{2i}}{1+e^{\alpha_i+\beta}} \frac{e^{\alpha_i} Y_{1i}}{1+e^{\alpha_i}}} \right) \\ = \left(\frac{e^\beta}{1+e^\beta} \right)^{n_{12}} \left(\frac{1}{1+e^\beta} \right)^{n_{21}} \end{aligned}$$

where n_{12} is the number of pairs where the case is a smoker and the control is a non-smoker, and n_{21} is the number of pairs where the case is a non-smoker and the control is a smoker.

(d) (6 points) Using the large sample normal distribution for $\hat{\beta}$, compute $\hat{\beta} \pm (1.96)\hat{S}_{\hat{\beta}} \Rightarrow 1.135 \pm (1.96)(.383) \Rightarrow (.38432, 1.88568)$. Applying the exponential function the the endpoints of the interval yields (1.47, 6.59) as an approximate 95% confidence interval for $exp(\beta)$.

4. (a) (6 points) For two patients of the same age and having the same values for mismatch with the donor on the HLA-A2 antigen variable, e^{β_1} is the ratio of hazards of dying for a patient who had prior open-heart surgery to a patient who did not have prior open-heart surgery. Since the estimate is $exp(\hat{\beta}_1) = 0.463$, at any time point the risk of dying in the very near future is about 50% less for patients who previously had open heart surgery than for those who did not, given that the patients are the same age and have the same status for the HLA-A2 antigen mismatch variable.

(b) (8 points) The estimate is

$$[\hat{S}_0(t)]^{exp(-.770+0.620+(.049)(60)+(.032)(60))} = [0.8]^{111.05} = 1.73 \times 10^{-11}$$

The delta methos could be used to obtain an approximate standard error. Let $x^T = (1 \ 1 \ 60 \ 60)$ and let V denote the covariance matrix shown in the statement of the problem. Then the variance of $x^T\hat{\beta}$ is approximately $x^TVx = 2.67068$. Using the Delta methods, the variance of $(.8)^{exp(x^T\hat{\beta})}$ is approximatley

$$[\log(.8)e^{x^T\beta}(.8)^{exp(x^T\beta)}]^2 Var(x^T\hat{\beta})$$

Substituting $\hat{\beta}$ for β , the standard error of $(.8)^{exp(x^T\hat{\beta})}$ is approximately

$$[\log(.8)e^{x^T\hat{\beta}}(.8)^{exp(x^T\hat{\beta})}] \sqrt{2.67068} = 7.004 \times 10^{-10}$$

(c) (6 points) Compute the hazard ratio

$$exp(\hat{\beta}_3 + \hat{\beta}_4) = exp(.049 + .032) = 1.084$$

For patients who previously had open-heart surgery and who is a mismatch with the donor with respect to the HLA-A2 antigen, each one year increase in age increases the risk of dying in the near future by about 8.4%. An approximate 95% confidence interval is obtained by first computing an approximate 95% confidence interval for $\hat{\beta}_3 + \hat{\beta}_4$ as

$$\begin{aligned} (\hat{\beta}_3 + \hat{\beta}_4) \pm (1.96)\sqrt{(.00032 + .00014 + (2)(.00008))} &\Rightarrow (.081) \pm (1.96)\sqrt{.0062} \\ &\Rightarrow (0.032, 0.13) \end{aligned}$$

Apply the exponential function to the endpoints of the interval to obtain (1.03, 1.14) as an approximate 95% confidence interval.

(d) (4 points) Since the partial likelihood function depends only on the ordering of the observed survival and censoring times, this coding error wil have no effect on the parameter estimates or their estimated covariance amtrix and standard errors.

Stem-leaf Display of Exam Scores

9|5
9|2
8|55556788
8|12233
7|55677789
7|0223444
6|5556668
6|03
5|59
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