Survival Analysis of Chronic Active Hepatitis Patients with Prednisolone Treatment

Nick Wibert

Preface

In a clinical trial described by Kirk et al. (1980), 44 patients with chronic active hepatitis were randomized to the drug *prednisolone*, or to an untreated control group. The survival time of the patients, in months, following admission to the trial, was the response variable of interest.

Recall the four variables of interest from the random-right censorship model as outlined in the last project:

$$X_i, ..., X_n \overset{\text{iid}}{\sim} F$$
$$Y_i, ..., Y_n \overset{\text{iid}}{\sim} G$$
$$Z_i = \min\{X_i, Y_i\}$$
$$\delta = I(X_i \le Y_i)$$

where X_i is survival time, Y_i is censoring time, Z_i denotes which time was observed first, and δ_i is indicates whether observation i is censored (1 if uncensored, 0 otherwise).

Confidence intervals for median survival time (Exponential model)

Let's fit an Exponential model to each of the two groups separately. From these models we can calculate an estimate and 95% confidence interval for the median survival time within each group.

```
hep <- read.table("Chronic-active-hepatitis.dat", header=TRUE)
hep$treatment <- factor(hep$treatment, levels=1:2, labels=c("Pred","Ctrl"))

exp.pred <- survreg(Surv(time,status) ~ 1, data=hep, subset=treatment=="Pred",
                    dist="exponential")
exp.ctrl <- survreg(Surv(time,status) ~ 1, data=hep, subset=treatment=="Ctrl",
                    dist="exponential")
```

First, we must compute the MLE of λ using the formula

$$\hat{\lambda} = \frac{n_u}{\sum_{i=1}^{n} Z_i}$$

where $n_u = \sum_{i=1}^{n} \delta_i$ is the total number of uncensored observations.

Constructing median confidence intervals in R

```
# split data based on treatment; can now access groups using hep2$Pred and hep2$Ctrl
hep2 <- split(hep, hep$treatment)
```

```
## MEDIAN INTERVAL FOR CONTROL GROUP
# calculate MLE of lambda
n_u <- sum(hep2$Ctrl$status)
Z <- sum(hep2$Ctrl$time)
MLE <- n_u / Z; MLE
```

```
## [1] 0.01123596
```

```
# estimate median survival time
med <- log(2) / MLE; med
```

```
## [1] 61.6901
```

```
# log standard error of median estimate
SE <- 1 / sqrt(n_u); SE
```

```
## [1] 0.25
```

```
# create log confidence interval, and exponentiate to get true interval for median
z <- qnorm(1-(0.05/2))
lower <- log(med) - z*SE; upper <- log(med) + z*SE
ctrl.interval <- c(exp(lower), exp(upper))
```

```
## MEDIAN INTERVAL FOR TREATMENT GROUP
# calculate MLE of lambda
n_u <- sum(hep2$Pred$status)
Z <- sum(hep2$Pred$time)
MLE <- n_u / Z; MLE
```

```
## [1] 0.004564315
```

```
# estimate median survival time
med <- log(2) / MLE; med
```

```
## [1] 151.8622
```

```
# log standard error of median estimate
SE <- 1 / sqrt(n_u); SE
```

```
## [1] 0.3015113
```

```
# create log confidence interval, and exponentiate to get true interval for median
z <- qnorm(1-(0.05/2))
lower <- log(med) - z*SE; upper <- log(med) + z*SE
pred.interval <- c(exp(lower), exp(upper))

# print final intervals
ctrl.interval; pred.interval
```

```
## [1]   37.79332 100.69684
```

```
## [1]   84.10134 274.21849
```

We are 95% confident that the true median survival time lies on the interval $[37.8, 100.7]$ for the *control* group, and $[84.1, 274.2]$ for the *prednisolone* group.

Mantel-Haenszel test with a subset of the data

We wish to compare the survival distributions for the two groups in the study. A good way to do this is to perform the Mantel-Haenszel test for equality.

We will perform the Mantel-Haenszel test of equality in a chart format; but first, let's define a few variables that will be useful in the calculations. The deaths and risk sets at point t can be represented as a table:

	No. Dead	No. Alive
Prednisolone	D_1	$R_1 - D_1$
Control	D_2	$R_2 - D_2$

where D_i is the number of deaths in population i at time t, and R_i is the number alive in population i at the start of time t (the risk set). The null and alternative hypotheses are

$$H_0 : A_1(t) = A_2(t)$$
$$H_a : A_1(t) \neq A_2(t)$$

where $A_i(t)$ is the cumulative hazard function for population i.

Our test is concerned with D_1, which has a hypergeometric distribution if the null hypothesis is true. The mean and variance of this D_1 under the null hypothesis are defined as

$$E_{0,M}(D_1(t)) = (D_1 + D_2)\frac{R_1}{R_1 + R_2}$$

$$\text{Var}_{0,M}(D_1(t)) = (D_1 + D_2)\frac{R_1}{R_1 + R_2}\frac{R_2}{R_1 + R_2} = E_{0,M}(D_1(t))\frac{R_2}{R_1 + R_2}$$

and finally, we use these values to compute the Mantel-Haenszel test statistic,

$$MH = \frac{\sum_t [D_1(t) - E_{0,M}(D_1(t))]}{\sqrt{\sum_t \text{Var}_{0,M}(D_1(t))}}$$

though the statistic we will ultimately report is MH^2 due to the fact that it follows a chi-squared distribution under the null. All of the calculations are shown in the table below.

Time (t)	$D_1(t)$	$D_2(t)$	$R_1(t)$	$R_2(t)$	$E_{0,M}(D_1(t))$	$\text{Var}_{0,M}(D_1(t))$	$D_1(t) - E_{0,M}(D_1(t))$
54	1	0	5	5	$(1+0)\left(\frac{5}{5+5}\right) = \frac{1}{2}$	$\left(\frac{1}{2}\right)\left(\frac{5}{5+5}\right) = \frac{1}{4}$	$\frac{1}{2}$
55	0	1	4	5	$(0+1)\left(\frac{4}{4+5}\right) = \frac{4}{9}$	$\left(\frac{4}{9}\right)\left(\frac{5}{4+5}\right) = \frac{20}{81}$	$-\frac{4}{9}$
56	0	0	4	4	0	0	0
61	0	1	3	4	3/7	12/49	−3/7
63	0	1	3	3	1/2	1/4	−1/2
68	1	0	3	2	3/5	6/25	2/5
71	0	1	2	2	1/2	1/4	−1/2
125	0	0	2	1	0	0	0
140	0	0	1	1	0	0	0
143	1	0	1	0	1	0	0

$$MH^2 = \frac{\left(\sum_t [D_1(t) - E_{0,M}(D_1(t))]\right)^2}{\sum_t \text{Var}_{0,M}(D_1(t))} = \frac{(613/630)^2}{588131/396900} \approx \boxed{0.639}$$

The null distribution of MH^2 is a chi-squared distribution with 1 df. Therefore the p-value of our test is $P(\chi_1^2 > 0.639) \approx 0.42$ and we fail to reject the null hypothesis. There is *not* sufficient evidence to conclude that the survival distributions of the two groups are different.

Gehan test with a subset of the data

Form of Gehan test statistic is given by

$$U = \sum_{i=1}^{n_1} \sum_{j=1}^{n_2} \left[I\left(Z_j^{(2)} \geq Z_i^{(1)}\right) \delta_i^{(1)} - I\left(Z_j^{(2)} \leq Z_i^{(1)}\right) \delta_i^{(2)} \right]$$

where $Z_i^{(1)}$ denotes the observations from the first population and $Z_i^{(2)}$ denotes observations from the second.

Let the prednisolone group be population 1, and the control group be population 2 (as we did in the Mantel-Haenszel test).

```r
U <- 0   # initialize Gehan statistic
pred <- data.frame("time" = c(54,56,68,125,143),
                   "status" = c(1,0,1,0,1))

ctrl <- data.frame("time" = c(55,61,63,71,140),
                   "status" = c(1,1,1,1,0))

for (i in 1:5)
{
  for (j in 1:5)
  {
    # I1 and I2 represent the two indicator terms
    I1 <- ifelse(ctrl$time[j] >= pred$time[i], 1, 0)
    I2 <- ifelse(ctrl$time[j] <= pred$time[i], 1, 0)

    U <- U + (I1*pred$status[i] - I2*ctrl$status[j])
  }
}

U    # print Gehan statistic
```

```
## [1] -5
```

4

Two Procedures for Comparing Survival Distributions

In this section, we will carry out two hypothesis test procedures to compare the survival distributions for the Prednisolone group and the Control group (using the entire dataset this time). We will implement the `survdiff()` function from the R "survival" package to perform the tests.

We use the same hypotheses from earlier for both tests:

$$H_0 : A_1(t) = A_2(t)$$
$$H_a : A_1(t) \neq A_2(t)$$

where $A_i(t)$ is the cumulative hazard function for population i.

```
# log-rank (Mantel-Haenszel test)
survdiff(Surv(time,status) ~ treatment, data=hep, rho=0)
```

```
## Call:
## survdiff(formula = Surv(time, status) ~ treatment, data = hep,
##     rho = 0)
##
##                   N Observed Expected (O-E)^2/E (O-E)^2/V
## treatment=Pred 22       11     16.4      1.77      4.66
## treatment=Ctrl 22       16     10.6      2.73      4.66
##
##  Chisq= 4.7  on 1 degrees of freedom, p= 0.03
```

```
# Prentice/Peto-Peto modification of the Gehan test
survdiff(Surv(time,status) ~ treatment, data=hep, rho=1)
```

```
## Call:
## survdiff(formula = Surv(time, status) ~ treatment, data = hep,
##     rho = 1)
##
##                   N Observed Expected (O-E)^2/E (O-E)^2/V
## treatment=Pred 22     6.72    11.17      1.78      5.85
## treatment=Ctrl 22    12.29     7.84      2.53      5.85
##
##  Chisq= 5.8  on 1 degrees of freedom, p= 0.02
```

Observe that the MH test statistic is 4.7 while the P/P-P modification of the Gehan test statistic is 5.8. Under our standard confidence level of $\alpha = 0.05$, both test results would lead us to reject the null hypothesis, and conclude that prednisolone treatment has an effect on survival time. In other words, there is sufficient evidence to conclude that the survival distributions for the two groups (Prednisolone and Control) are different.

While both tests provided similar results in this case, we should use our "rough rule-of-thumb" for which test is better in this scenario. This rule of thumb states that if the survival curves *don't* cross, use the Mantel-Haenszel test; if they *do* cross, use the Gehan test.

Recall from our survival curve plot in Project 1 that the survival curves for these two groups *don't* cross; therefore, we would probably want to perform the MH test over the Gehan in this setting.