Survival Analysis Assignment Solutions

David M. Rocke

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A clinical trial is intended to test a new treatment for malignant melanoma vs. current standard of care. The main outcome is disease-free survival. Each patient has a time t in days after start of therapy that either represents the time of recurrence or death (if status $= 1$) or the end of the study (if status $= 0$). Each patient has two covariates we can use: Tx $= 1$ if they are on the new therapy or Tx $= 0$ if they are on standard of care. There are four subtypes of melanoma, which we will characterize as Type $=$ A, B, C, or D. The effect of the new therapy may differ among the four subtypes.

1. We can estimate the survival curve for patients on the new and standard therapy including all four subtypes using the Kaplan-Meier product limit estimator. Suppose at a given time t (in days after starting therapy), and for a particular subset of the patients, that there are 194 patients whose survival or censoring time is at least t. Suppose that 3 patients died or relapsed on day t and 2 patients had a censoring time of t. By what fraction does the estimated survival curve drop at time t? How many patients are in the risk set just before t and just after t?

- By what fraction does the estimated survival curve drop at time t?
- It drops to 191/194 of the previous value, which is a fractional drop of 3/194.
- How many patients are in the risk set just before t and just after t?
- 194 before 189 after.

2. Write down the Cox model for predicting survival from Tx, Type, and the Tx by Type interaction including a definition of the coefficients and their relationship to survival. State the important assumptions.

The hazard function is

$$\begin{aligned} \eta &= \beta_{Tx} Tx + \beta_B Type_B + \beta_C Type_C + \beta_D Type_D \\ &\quad + \beta_{TxB} Type_B Tx + \beta_{TxC} Type_C Tx + \beta_{TxD} Type_D Tx \\ h(t|Tx, Type) &= h_0(t) e^{\eta} \end{aligned}$$

We assume that the the hazard functions are proportional (written into the model) and that censoring is non-informative.

3. If there are 20 patients at risk at a given time and 1 of them fails, write down the contribution (factor) to the partial likelihood from that failure time in terms of the model specification. Does it depend on the base hazard?

$$
\begin{aligned}
\eta_i &= \beta_{Tx} Tx_i + \beta_B Type_{Bi} + \beta_C Type_{Ci} \\
&\quad + \beta_D Type_{Di} + \beta_{TxB} Type_{Bi} Tx_i \\
&\quad + \beta_{TxC} Type_{Ci} Tx_i + \beta_{TxD} Type_{Di} Tx_i \\
\theta_i &= \exp(\eta_i) \\
\text{PL Contrib.} &= \frac{\theta_1}{\sum_{i=1}^{20} \theta_i}
\end{aligned}
$$

It does not depend on the base hazard.

4. Which will generate more accurate coefficient estimates, a study with 1000 patients of whom 900 survive to the end of the study without recurrence, or a study with 500 patients 300 of whom survive? Why?

In general, the "n" in a survival analysis is the number of failures, which is 100 in the first case and 200 in the second, so the second analysis would in general be more accurate.

5. Describe the most appropriate hypothesis test for whether the interaction term is required in the model. How the test statistic be calculated? To what specific statistical distribution would the test statistic be compared?

The best procedure is to compare the main-effects-only model to the interaction model. Since there is one Tx variable and 3 Type variables, the interaction also has three coefficients. The likelihood ratio test is generally the best. Minus twice the log likelihood ratio should be compared to a chi-squared distribution on three df. Other possibilities are the score test and the Wald test.

6. Suppose that the reference levels of the covariates are Tx = 0 and Type = A. List all the coefficients in the model (symbolically). In terms of those coefficients, what would be the estimated log hazard ratio of a patient with Type B melanoma on Tx =1 to a patient with Type C melanoma on Tx = 0? What would be the estimated hazard ratio?

$$
\begin{aligned}
\text{Coefs} &= \beta_{Tx}, \beta_B, \beta_C, \beta_D, \beta_{TxB}, \beta_{TxC}, \beta_{TxD} \\
\text{Patient 1} &= \beta_{Tx} + \beta_B + \beta_{TxB} \\
\text{Patient 2} &= \beta_C \\
\text{log hazard ratio} &= \beta_{Tx} + \beta_B + \beta_{TxB} - \beta_C \\
\text{hazard ratio} &= \exp(\beta_{Tx} + \beta_B + \beta_{TxB} - \beta_C) \\
\text{est. hazard ratio} &= \exp(\hat{\beta}_{Tx} + \hat{\beta}_B + \hat{\beta}_{TxB} - \hat{\beta}_C)
\end{aligned}
$$

7. How would you examine the proportionality assumption, graphically and/or with a statistical test?

- Correlation of Shoenfeld residuals with time (`cox.zph`).
- Plot of complementary log-log hazards for groups. Look for parallel.
- Plot of hazards for groups from Cox model vs. hazards from Kaplan-Meier curves.
- Many other possibilities.

8. If it appears that the different subtypes have non-proportional hazards, how would you change the model so that this could be accommodated?

One way would be to use a strata term for a grouping variable that was non-proportional. One could also use a time-dependent covariate.