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Survival Analysis
Biostatistics 140.641

Problem Set 3
Due date: Monday, 10/17/2022

1. The following data are the time to maintain remission for 42 patients with acute leukemia in two groups: 6MP (mercaptopurine) vs placebo. Time is measured by weeks. Reference: Freireich et al. (1963) Blood, p699.

   Placebo: 1, 1, 2, 2, 3, 4, 4, 5, 5, 8, 8, 8, 8, 11, 11, 12, 12, 15, 17, 22, 23

   6MP: 6, 6, 6, 7, 10, 13, 16, 22, 23, 6^+, 9^+, 10^+, 11^+, 17^+, 19^+, 20^+, 25^+, 32^+, 32^+, 34^+, 35^+.

   (a) Assume that the remission times from the above two groups are associated through the proportional hazards model. Describe the 2-sample proportional hazards model and state your interpretation of the model. Describe the constraint of the model if there is any.

   (b) Confirm the validity of the proportional hazards model by an exploratory method.

2. In the following questions (a)$\sim$(d), assume that the failure time T_0 has the exponential density $f_0(t) = \lambda e^{-\lambda t}$, $\lambda > 0$.

   (a) Derive the hazard function of T_0.

   (b) Verify that for a positive constant c, the random variable cT_0 has the hazard function λ/c. Please interpret this result.

   (c) Let $h(\cdot)$ denote a hazard function, and let T denote a failure time variable. Consider <u>model I</u>: $h(t; x) = \lambda e^{\beta x}$, and <u>model II</u>: $T = T_0 e^{\alpha x}$, where x is the covariate, and β and α are parameters. Find the relationship between α and β.

(d) Interpret Models I and II.

3. Suppose T is a continuous survival time and $x = 0, 1$ indicates control/treatment assignment. Consider the following proportional hazards models: For $t \geq 0$,

   (1) $\lambda(t;x) = \lambda_0(t)e^{\beta x}$, $-\infty < \beta < \infty$.
   (2) $\lambda(t;x) = \lambda_0(t)e^{\beta x}$, $-\infty < \beta < 0$.
   (3) $\lambda(t;x) = \lambda_0(t)e^{(\beta t)x}$, $-\infty < \beta < 0$.
   (4)$\lambda(t;x) = \lambda_0(t)e^{\beta x+\gamma(1-x)}$, $-\infty < \beta < \infty, -\infty < \gamma < \infty$.
   (5) $\lambda(t;x) = \lambda_0(t)e^{\beta x+\gamma x I(t\geq 5)}$, $-\infty < \beta < \infty, -\infty < \gamma < \infty$.
   (6) $\lambda(t;x) = \lambda_0(t)e^{(\beta_0+\beta_1 t)x}$, $-\infty < \beta_0 < \infty,\ \beta_1 > 0$,
   (7) $\lambda(t;x) = \lambda_0(t)e^{(\beta_0+\beta_1 t+\beta_2 t^2)x}$, $-\infty < \beta_0 < \infty,\ -\infty < \beta_1 < \infty$,
   $-\infty < \beta_2 < \infty$
   (8) $\lambda(t;x) = \lambda_0(t)e^{(\beta_1 t+\beta_2 t^2)x}$, $-\infty < \beta_1 < \infty, -\infty < \beta_2 < \infty$

   (a) Which models imply constant relative hazard between the treatment and control groups? Please provide explanations.

   (b) Which models allow for possible cross-over(s) in hazard functions for $t > 0$ from the two groups? Please provide explanations.

   (c) Suppose the hazard functions of treatment and control groups could be different. Which models enforce that the hazard functions of the two groups start with the same value at t=0? Please provide explanations.

   (d) Suppose the hazard functions of treatment and control groups could be different. Which models allow for the possibility that the hazard functions of the two groups start with the same value at t=0 and gradually become different? Please provide explanations.

4. Consider the following hypothetical clinical trial data.

   Treatment A: 2, 3, 4+, 6, 12+, 18+, 20

   Treatment B: 7+, 12, 17+, 25, 29+, 30+

(a) Compute the log-rank test and the (2-sided) p-value. Do you reject the hypothesis that there is no difference between treatment A and treatment B? Explain.

(b) Compute the Gehan test and the (2-sided) p-value. Interpret your results based on the p-value.

(c) Compute the Taron-Ware test and the (2-sided) p-value. Interpret your results based on the p-value.

(d) Comment on the use of the three tests above.

5. Choose correct answers (multiple choices):

   Let $h_0(t)$ and $h_1(t)$ respectively be the hazard function for continuous failure times T_0 and T_1. If two hazard functions do not cross-over at any time $t > 0$, it implies that their respective survival functions

   (a) definitely cross-over at certain $t > 0$
   (b) definitely do not cross-over for $t > 0$
   (c) could cross-over at certain $t > 0$, depending on their specific probability structures.

   Please provide an analytical explanation to verify your answer.