Survival Analysis HW4

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Problem 1

a) Construct the 17 2x2 tables for the log-rank test.

i	Group	Events at $t_{(i)}$	Survival at $t^+_{(i)}$	Expected	At risk at $t^-_{(i)}$
1	0	0	21	1	21
-	1	2	19	1	21
-	-	2	40	-	42
—	—	—	—	—	—
2	0	0	21	1.05	21
-	1	2	17	0.95	19
-	-	2	38	-	40
—	—	—	—	—	—
3	0	0	21	0.55	21
-	1	1	16	0.45	17
-	-	1	37	-	38
—	—	—	—	—	—
4	0	0	21	1.14	21
-	1	2	14	0.86	16
-	-	2	35	-	37
—	—	—	—	—	—
5	0	0	21	1.2	21
-	1	2	12	0.8	14
-	-	2	33	-	35
—	—	—	—	—	—
6	0	3	18	1.91	21
-	1	0	12	1.09	12
-	-	3	30	-	33
—	—	—	—	—	—
7	0	1	16	0.59	17
-	1	0	12	0.41	12
-	-	1	28	-	29
—	—	—	—	—	—
8	0	0	16	2.29	16
-	1	4	8	1.71	12
-	-	4	24	-	28
—	—	—	—	—	—
10	0	1	14	0.65	15
-	1	0	8	0.35	8

i	Group	Events at $t_{(i)}$	Survival at $t^{+}_{(i)}$	Expected	At risk at $t^{-}_{(i)}$
-	-	1	22	-	27
—	—	—	—	—	—
11	0	0	13	1.24	13
-	1	2	6	0.76	8
-	-	2	19	-	21
—	—	—	—	—	—
12	0	0	12	1.33	12
-	1	2	4	0.67	6
-	-	2	16	-	18
—	—	—	—	—	—
13	0	1	11	0.75	12
-	1	0	4	0.25	4
-	-	1	15	-	16
—	—	—	—	—	—
15	0	0	11	0.73	11
-	1	1	3	0.27	4
-	-	1	14	-	15
—	—	—	—	—	—
16	0	1	10	0.79	11
-	1	0	3	0.21	3
-	-	1	13	-	14
—	—	—	—	—	—
17	0	0	10	0.77	10
-	1	1	2	0.23	3
-	-	1	12	-	13
—	—	—	—	—	—
22	0	1	6	1.56	7
-	1	1	1	0.44	2
-	-	2	7	-	9
—	—	—	—	—	—
23	0	1	5	1.71	6
-	1	1	0	0.29	1
-	-	2	5	-	7
—	—	—	—	—	—

b) Verify the rank statistics by calculating the difference of the observed and expected in each 2x2 tables

```
d0_e0<-c(0-1,0-1.05,0-0.55,0-1.14,0-1.2,3-1.91,1-0.59,
         0-2.29,1-0.65,0-1.24,0-1.33,1-0.75,0-0.73,1-0.79,0-0.77,1-1.56,1-1.71)
```

The series is -1, -1.05, -0.55, -1.14, -1.2, 1.09, 0.41, -2.29, 0.35, -1.24, -1.33, 0.25, -0.73, 0.21, -0.77, -0.56, -0.71. The sum of each difference of the observed and expected is -10.26. The calculation result differs slightly from the actual result due to the retention of decimals.

The result is same as the following rank statistics:

$$L = \sum_{i=1}^{k} (d_{0i} - e_{0i}) = -10.25$$

c) Include the variance calculation for each of the 2x2 tables as well and verify that

$$var(L) = \sum_{i=1}^{k} \frac{n_{0i} n_{1i} d_i (n_i - d_i)}{n_i^2 (n_i - 1)} = 6.26$$

```
n0 <- c(21,21,21,21,21,21,17,16,15,13,12,12,11,11,10,7,6)
n1 <- c(21,19,17,16,14,12,12,12,8,8,6,4,4,3,3,2,1)
n <- c(42,40,38,37,35,33,29,28,23,21,18,16,15,14,13,9,7)
d <- c(2,2,1,2,2,3,1,4,1,2,2,1,1,1,1,2,2)

L=sum(n0*n1*d*(n-d)/(n^2*(n-1)))
L
```

```
## [1] 6.256961
```

Problem 2

Step 1: Prepare a table shell or figure shell to compare the simulation results For example:

Group 1		Group 2		Power			
Mean	SD	Mean	SD	Logrank	Wilcoxon	Tarone-Ware	Peto-Prentice
1.5	1	2.5	1				
1.8	2	3.0	2				

Step 2: Choose parameters – parameters may need to be adjusted to obtain adequate power for comparisons

- Sample size n1 and n2 for Groups 1 and 2, respectively;
- Create two survival datasets, given that both of the failure times are log-normally distributed, with equal variance but different means.
- Choose maximum follow-up time
- Choose simulation trials, for power trials=2000

Step 3: For each trial

- Generate data for two independent groups based on normal distributions, with sample size n1 and n2 for Groups 1 and 2, respectively
- Transform normally distributed data to log-normal
- Generate independent random censoring data using exponential distribution
- Obtain observed survival data
- Test between group difference in survival time and obtain the p-values for log-rank, Wilcoxon, Tarone-Ware, and Peto-Prentice

Step 4: Repeat Step 3 for 2000 times

Step 5: Calculate the proportion of p-values that are significant at the level of 2-sided 0.05 (or 1-sided 0.025). Especially compare the powers of Wilcoxon test with other tests, to see whether the Wilcoxon test has the optimal power or not.

Problem 3

Please discuss how to perform the analysis: stratified or non-stratified analyses? Different methods of analysis can be used for a trial, depending on its goals. A non-stratified analysis is suitable if the trial aims to evaluate the new treatment in the whole population, without considering the biomarker status. However, a stratified analysis is a more proper choice if the trial aims to evaluate the new treatment in different subgroups based on the biomarker status.

How would you recommend the analysis? To avoid as-treated analysis, which may generate bias, I would first devide patients into 2 groups by biomarker status before the new treatment. Then, I would recommend a stratified analysis, because the true outcomes may be covered up without stratification. This would allow me to estimate the treatment effect and its confidence interval for each subgroup separately, and test for statistical significance.

Besides, I would perform a subgroup analysis by biomarker status, using a Cox proportional hazards model to adjust for potential confounding factors. This would allow me to control for other variables that may affect the survival outcome, such as age, gender, disease stage, etc.

Do you think if FDA should approve this drug? I think FDA should get more information before they make a decision, so I don't think they would approve this drug after a single trial.

First, the magnitude and significance of the treatment effect in the biomarker+ subgroup are not reported. Besides, we are still not sure about the safety and tolerability of the new treatment in both subgroups. Last but not the least, the expense of producing the new treatment should be taken into consideration.

To sum up, the FDA would need to weigh all these factors carefully and balance the benefits and risks of the new treatment for both subgroups. The FDA would also need to review the quality and rigor of the trial design, conduct, analysis, and reporting, as well as any other relevant data from preclinical or clinical studies.

Homework link: https://github.com/zk2275/Survival_Analysis_HW4