# P8108 Homework 4

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## Problem 1

Table 1: Log-rank test $2 \times 2$ tables

| $t_{(i)}$ | Group | Events at $t_{(i)}$ | Survival at $t_{(i)}$ | Expected | At risk $t_{(i)}^-$ | $d_{0i} - e_{0i}$ | $\frac{n_{0i}n_{1i}d_i(n_i-d_i)}{n_i^2(n_i-1)}$ |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 21 | 1.00 | 21 | -1.00 | 0.49 |
| | 1 | 2 | 19 | 1.00 | 21 | | |
| | Total | 2 | 40 | | 42 | | |
| 2 | 0 | 0 | 21 | 1.05 | 21 | -1.05 | 0.49 |
| | 1 | 2 | 17 | 0.95 | 19 | | |
| | Total | 2 | 38 | | 40 | | |
| 3 | 0 | 0 | 21 | 0.55 | 21 | -0.55 | 0.25 |
| | 1 | 1 | 16 | 0.45 | 17 | | |
| | Total | 1 | 37 | | 38 | | |
| 4 | 0 | 0 | 21 | 1.14 | 21 | -1.14 | 0.48 |
| | 1 | 2 | 14 | 0.86 | 16 | | |
| | Total | 2 | 35 | | 37 | | |
| 5 | 0 | 0 | 21 | 1.20 | 21 | -1.20 | 0.47 |
| | 1 | 2 | 12 | 0.80 | 14 | | |
| | Total | 2 | 33 | | 35 | | |
| 6 | 0 | 3 | 18 | 1.91 | 21 | 1.09 | 0.65 |
| | 1 | 0 | 12 | 1.09 | 12 | | |
| | Total | 3 | 30 | | 33 | | |
| 7 | 0 | 1 | 16 | 0.59 | 17 | 0.41 | 0.24 |
| | 1 | 0 | 12 | 0.41 | 12 | | |
| | Total | 1 | 28 | | 29 | | |
| 8 | 0 | 0 | 16 | 2.29 | 16 | -2.29 | 0.87 |
| | 1 | 4 | 8 | 1.71 | 12 | | |
| | Total | 4 | 24 | | 18 | | |
| | 0 | 1 | 14 | 0.65 | 15 | 0.35 | 0.23 |

Table 1: Log-rank test $2 \times 2$ tables *(continued)*

| $t_{(i)}$ | Group | Events at $t_{(i)}$ | Survival at $t_{(i)}$ | Expected | At risk $t_{(i)}^{-}$ | $d_{0i} - e_{0i}$ | $\frac{n_{0i} n_{1i} d_i (n_i - d_i)}{n_i^2 (n_i - 1)}$ |
|---|---|---|---|---|---|---|---|
| 10 | 1 | 0 | 8 | 0.35 | 8 | | |
| | Total | 1 | 22 | | 23 | | |
| 11 | 0 | 0 | 13 | 1.24 | 13 | -1.24 | 0.45 |
| | 1 | 2 | 6 | 0.76 | 8 | | |
| | Total | 2 | 19 | | 21 | | |
| 12 | 0 | 0 | 12 | 1.33 | 12 | -1.33 | 0.42 |
| | 1 | 2 | 4 | 0.67 | 6 | | |
| | Total | 2 | 16 | | 18 | | |
| 13 | 0 | 1 | 11 | 0.75 | 12 | 0.25 | 0.19 |
| | 1 | 0 | 4 | 0.25 | 4 | | |
| | Total | 1 | 15 | | 16 | | |
| 15 | 0 | 0 | 11 | 0.73 | 11 | -0.73 | 0.20 |
| | 1 | 1 | 3 | 0.27 | 4 | | |
| | Total | 1 | 14 | | 15 | | |
| 16 | 0 | 1 | 10 | 0.79 | 11 | 0.21 | 0.17 |
| | 1 | 0 | 3 | 0.21 | 3 | | |
| | Total | 1 | 13 | | 14 | | |
| 17 | 0 | 0 | 10 | 0.77 | 10 | -0.77 | 0.18 |
| | 1 | 1 | 2 | 0.23 | 3 | | |
| | Total | 1 | 12 | | 13 | | |
| 22 | 0 | 1 | 6 | 1.56 | 7 | -0.56 | 0.30 |
| | 1 | 1 | 1 | 0.44 | 2 | | |
| | Total | 2 | 7 | | 9 | | |
| 23 | 0 | 1 | 5 | 1.71 | 6 | -0.71 | 0.20 |
| | 1 | 1 | 0 | 0.29 | 1 | | |
| | Total | 2 | 5 | | 7 | | |

## Problem 2

**a**

- Step 1: Prepare a table shell or figure shell to compare the simulation results as below:

| Group 1 | | Group 2 | | Tests | | | |
|---|---|---|---|---|---|---|---|
| $\mu_1$ | $\sigma_1$ | $\mu_2$ | $\sigma_2$ | Log-rank | Wilcoxon | Tarone-Ware | Peto-Prentice |
| 2.0 | 3.0 | 3.0 | 3.0 | | | | |
| 0.5 | 0.2 | 0.8 | 0.2 | | | | |
| 2.0 | 3.0 | 3.0 | 4.0 | | | | |
| 0.5 | 0.2 | 0.8 | 0.4 | | | | |

- Step 2: Choose parameters-parameters may need to be adjusted to obtain adequate power for comparisons
  - Determine sample size $n_1$, $n_2$ for Group 1 and 2, respectively.
  - Choose censoring distributions for Groups 1 and 2, we can use the same distribution. For example, assume that individuals entered the study at a constant rate in the interval 0 to $T$ and failed according to an exponential distribution. Censoring proportions used are 10% (we can also try different censoring rate).
  - Choose maximum follow-up time.
  - Choose the number of simulation trials, for example, $n_{\text{trial}} = 2000$
- Step 3: For each simulation trial:
  - Generate data for two independent groups based on normal distributions with different $\mu$ and $\sigma$ as shown in the table above, with sample size $n_1$ and $n_2$ for Groups 1 and 2, respectively. Then transform the normally distributed data to log-normal.
  - $\mu$ and $\sigma$ are chosed considering the nature of log-normal distribution. Since the hazard rate from log-normal distribution at region $0 < \mu \leq 1$ and $0 < \sigma \leq 1$ with $t > 0$ will increase and up to the maximum point then will decrease depend on the value of $\mu$ and $\sigma$, either for the value $\mu > \sigma$ or $\mu < \sigma$. Hazard rate from log-normal distribution at region $\mu > 1$ and $\mu > 1$ with $t > 0$ has a pattern decreasing.
  - Generate independent random censoring data using exponential distribution.
  - Obtain the observed survival data.
  - Conduct test between group difference in survival time and obtain the p-values for log-rank, Wilcoxon, Tarone-Ware, and Peto-Prentice.
- Step 4: Repeat the 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).

**b**

In this case, we are actually testing the power of Peto-Prentice test.

- Step 1: Prepare a table shell or figure shell to compare the simulation results as below:

| Group 1 | | Group 2 | | Tests | | | |
|---|---|---|---|---|---|---|---|
| $\alpha_1$ | $\beta_1$ | $\alpha_2$ | $\beta_2$ | Log-rank | Wilcoxon | Tarone-Ware | Peto-Prentice |
| 2.0 | 2.0 | 3.0 | 3.0 | | | | |
| 0.5 | 0.2 | 0.8 | 0.5 | | | | |
| 2.0 | 3.0 | 3.0 | 2.0 | | | | |
| 0.5 | 0.2 | 0.8 | 0.4 | | | | |

- Step 2: Choose parameters-parameters may need to be adjusted to obtain adequate power for comparisons
  - Determine sample size $n_1$, $n_2$ for Group 1 and 2, respectively.
  - Choose censoring distributions for Groups 1 and 2, we can use the same distribution. For example, assume that individuals entered the study at a constant rate in the interval 0 to $T$ and failed according to an exponential distribution. Censoring proportions used are 10% (we can also try different censoring rate).
  - Choose maximum follow-up time.
  - Choose the number of simulation trials, for example, $n_{\text{trial}} = 2000$
- Step 3: For each simulation trial:
  - Generate data for two independent groups based on normal distributions with different $\mu$ and $\sigma$ as shown in the table above, with sample size $n_1$ and $n_2$ for Groups 1 and 2, respectively. Then transform the normally distributed data to log-normal.
  - Parameters for the log-logistic distribution is choosed based on the fact that it can have a non-monotonic hazard function when $\beta > 1$, the hazard function is unimodal (when $\beta \leq 1$, the hazard decreases monotonically).
  - Generate independent random censoring data using exponential distribution.
  - Obtain the observed survival data.
  - Conduct test between group difference in survival time and obtain the p-values for log-rank, Wilcoxon, Tarone-Ware, and Peto-Prentice.
- Step 4: Repeat the 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).

## Problem 3

**a**

> Please discuss what you think of an analysis by including all subject? Overall analyses including all subjects can be stratified or non-stratified analyses.

There are clear qualitative interaction between treatment groups and biomarker groups. The overall analyses will result in average treatment effects of the two biomarker groups.

- The overall analysis without stratification is equivalent to use mixture distribution within each treatment group, which results in an averaged risk between the two biomarker strata. The averaged risk in each treatment group will depend upon the proportion of subjects distributed in each biomarker stratum in the group. The averaged risk will then be tested for the difference between treatments.
- The overall analysis with stratification is to test the difference between the treatment groups first.The group differences for each stratum will then be averaged.
- How similar the results of the two overall tests may depend upon the distribution of the biomarkers within each treatment group.If the distribution is balanced between the two treatment groups, the results of the two overall tests should be close to each other.

**b**

> How would you recommend the analysis?

As mentioned before, it might not appropriate to use one overall non-stratified analyses under this circumstance, irrespective of stratified or non-stratified. The overall analysis is not helpful in interpreting the results. There should be separate analyses for each biomarker group.

**c**

> Do you think if FDA should approve this drug?

From an ethical perspective, I don't think FDA should approve the drug. Since the treatment actually harms the subjects in the biomarker - subgroup, we shouldn't treat patients with biomarker - in this way. We should consider a safer drug.

The drug could be approved if their is an unmet need for the treatment of this disease.

## Reference


1. Edmunson, J.H., Fleming, T.R., Decker, D.G., Malkasian, G.D., Jefferies, J.A., Webb, M.J., and Kvols, L.K., Different Chemotherapeutic Sensitivities and Host Factors Affecting Prognosis in Advanced Ovarian Carcinoma vs. Minimal Residual Disease. Cancer Treatment Reports, 63:241-47, 1979.

2. Kurniasari, Dian & Widyarini, R & Warsono, & Antonio, Yeftanus. (2019). Characteristics of Hazard Rate Functions of Log-Normal Distributions. Journal of Physics: Conference Series. 1338. 012036. 10.1088/1742-6596/1338/1/012036.

3. Bennett, S. (1983). Log-Logistic Regression Models for Survival Data. Journal of the Royal Statistical Society. Series C (Applied Statistics), 32(2), 165–171. https://doi.org/10.2307/2347295


## Appendix: Code for this report

```
knitr::opts_chunk$set(echo = FALSE, message = FALSE, warning = FALSE)
library(tidyverse)
library(knitr)
library(kableExtra)
opts <- options(knitr.kable.NA = "")
event_time = c(1,2,3,4,5,6,7,8,10,11,12,13,15,16,17,22,23)
log_rank_tab <- tibble(
  ti = rep(event_time, each = 3),
  Group = rep(c(0, 1, "Total"), length(event_time)),
  event_ti = c(0,2,2, 0,2,2, 0,1,1, 0,2,2, 0,2,2, 3,0,3, 1,0,1, 0,4,4, 1,0,1, 0,2,2, 0,2,2, 1,0,1, 0,1,
  survival_ti = c(21,19,40, 21,17,38, 21,16,37, 21,14,35, 21,12,33, 18,12,30, 16,12,28, 16,8,24, 14,8,2
  risk_ti = c(21,21,42, 21,19,40, 21,17,38, 21,16,37, 21,14,35, 21,12,33, 17,12,29, 16,12,18, 15,8,23,
  event_ti_tol = rep(c(2,2,1,2,2,3,1,4,1,2,2,1,1,1,1,2,2), each=3),
  event_ti0 = rep(c(0,0,0,0,0,3,1,0,1,0,0,1,0,1,0,1,1), each = 3),
  risk_ti_tol = rep(c(42,40,38,37,35,33,29,28,23,21,18,16,15,14,13,9,7), each = 3),
  risk_ti0_tol = rep(c(21,21,21,21,21,21,17,16,15,13,12,12,11,11,10,7,6), each = 3),
  risk_ti1_tol = risk_ti_tol - risk_ti0_tol,
  expect_0 = risk_ti0_tol/risk_ti_tol * event_ti_tol,
  expect_1 = risk_ti1_tol/risk_ti_tol * event_ti_tol,
  expect_na = rep(-1, length(expect_0)),
  d_e = event_ti0 - expect_0,
  var_comp = risk_ti1_tol*risk_ti0_tol*event_ti_tol*(risk_ti_tol - event_ti_tol)/(risk_ti_tol^2*(risk_t
)

#test_merge_list = list(c(1,4,7),c(2,5,8),c(3,6,9),c(-1,-1,-1))

merge_by_order <- function(vector_list){
  n_vec = length(vector_list)
  unique_vec_list = list()
  unique_len = 0
  for(vec in vector_list){
    vec_unique = unique(vec)
    unique_len_old = unique_len
    unique_len = length(vec_unique)
    if(unique_len >= unique_len_old){
      unique_vec_list = append(unique_vec_list, as.list(vec_unique))
    }else{
      unique_len = unique_len_old
```

```
      vec_unique = rep(vec_unique, length.out = unique_len_old)
      unique_vec_list = append(unique_vec_list, as.list(vec_unique))
    }

  }
  #print(unique_vec_list %>% unlist())
  t(matrix(unique_vec_list %>% unlist(),unique_len, n_vec)) %>% as.vector()
}

#merge_by_order(test_merge_list)

log_rank_tab$Expected = merge_by_order(list(log_rank_tab$expect_0, log_rank_tab$expect_1, log_rank_tab$
log_rank_tab$d0i_e0i = merge_by_order(list(log_rank_tab$d_e, log_rank_tab$expect_na +1, log_rank_tab$exp
log_rank_tab$var = merge_by_order(list(log_rank_tab$var_comp, log_rank_tab$expect_na, log_rank_tab$expe

log_rank_tab %>% select(c("ti","Group","event_ti", "survival_ti", "Expected", "risk_ti","d0i_e0i", "var
  mutate(Expected = ifelse(Expected == -1, NA, Expected),
         d0i_e0i = ifelse(d0i_e0i == 0, NA, d0i_e0i),
         var = ifelse(var == -1, NA, var)) %>%
  kable(col.names = c("$t_{(i)}$","Group", "Events at $t_{(i)}$", "Survival at $t_{(i)}$", "Expected",

d_e_sum = sum(log_rank_tab$d0i_e0i, na.rm = T)
var_sum = sum(ifelse(log_rank_tab$var == -1, NA, log_rank_tab$var), na.rm = T)
res_tab_log_norm = tibble(
  mu1 = c(2, 0.5, 2, 0.5),
  s1 = c(3, 0.2, 3, 0.2),
  mu2 = c(3, 0.8, 3, 0.8),
  s2 = c(3, 0.2, 4, 0.4),
  logrank = rep(NA, 4),
  wilcoxon = rep(NA, 4),
  tw = rep(NA, 4),
  pp = rep(NA, 4),
)

res_tab_log_norm %>% kable(col.names = c("$\\mu_1$", "$\\sigma_1$", "$\\mu_2$", "$\\sigma_2$", "Log-ran
res_tab_pp = tibble(
  a1 = c(2, 0.5, 2, 0.5),
  b1 = c(2, 0.2, 3, 0.2),
  a2 = c(3, 0.8, 3, 0.8),
  b2 = c(3, 0.5, 2, 0.4),
  logrank = rep(NA, 4),
  wilcoxon = rep(NA, 4),
  tw = rep(NA, 4),
  pp = rep(NA, 4),
)

res_tab_pp %>% kable(col.names = c("$\\alpha_1$", "$\\beta_1$", "$\\alpha_2$", "$\\beta_2$", "Log-rank"
```