BIOST 544: Homework 1

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Background

There is a belief that the effectiveness of the anti-angiogenesis agent TFD725 (evaluated in the **nsclc** dataset) may be different for older vs younger patients. We will use the nsclc dataset to attempt to evaluate this.

Analysis

1) As a first pass, we will consider a few subgroups of patients: Those 50 and older (50+), 55+, 60+, 65+, and 70+. Please estimate/evaluate the probability a patient on TFD725+docetaxel will survive past 400 days in each of those subgroups. Please also give an interval estimate for each of those probabilities.

For a patient in a subpopulation of the TFD725+docetaxel treatment arm, the probability of surviving past 400 days is estimated by the proportion of survivors in that subpopulation. Assuming a Binomial distribution, we can simulate outcomes using the sample size and observed proportion, then define a 90% confidence interval based on these simulations.

Table 1 shows the observed 400-day survival proportions and their confidence intervals for each age subgroup (note: subgroups are overlapping and share members).

Table 1: Estimated probability of 400-day survival within overlapping subsets of the treatment arm

Age	N	Estimate	90% CI
50 +	186	0.49	0.44 - 0.55
55 +	165	0.49	0.43 - 0.55
60 +	104	0.48	0.4 - 0.56
65 +	39	0.64	0.51 - 0.77
70 +	7	0.86	0.57 - 1

Table 1 and histograms of the simulated sampling distribution of P(Survived|Age) within the treatment group (see Supplementary), suggest treated patients aged under 65 years have roughly equal chance of survival, while treated patients aged over 65 years have comparatively higher rates of survival. We see as well that older, smaller samples have wider confidence intervals.

We can split these age groups into non-overlapping subgroups to more closely inspect how each age contributes to the overall survival proportion. The table below displays the 400-day survival proportions and confidence intervals for each non-overlapping age subgroup.

Table 2: Estimated probability of 400-day survival within subsets of the treatment arm

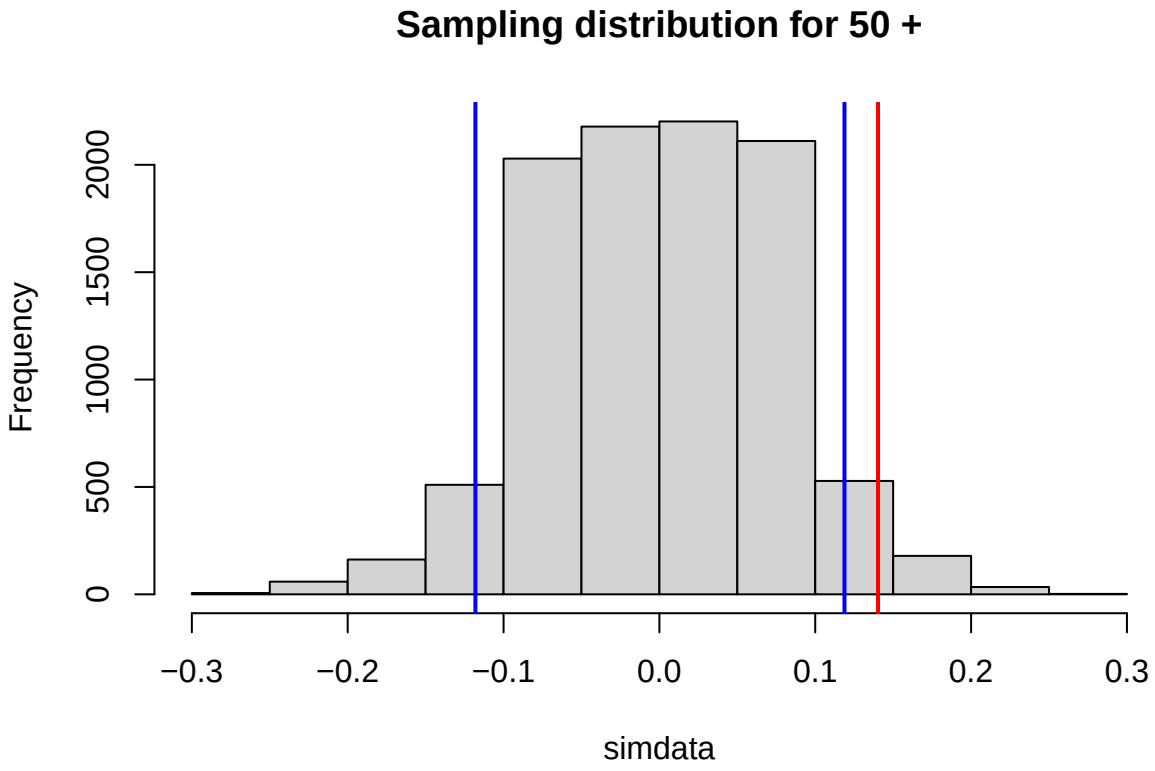
Age	N	Estimate	90% CI
[50,55)	9	0.78	0.56-1
[55,60)	36	0.47	0.33-0.61
[60,65)	28	0.46	0.32-0.61
[65,70)	18	0.72	0.56-0.89
[70,75]	5	0.80	0.4-1

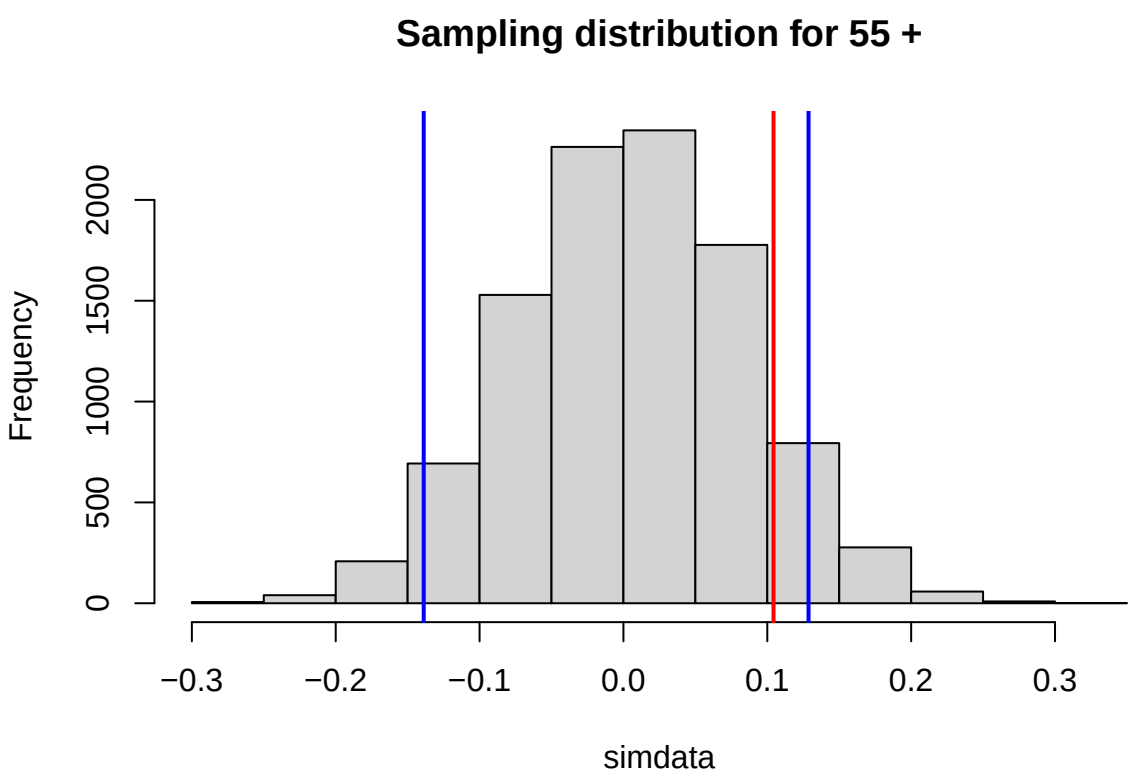
Age	N	Estimate	90% CI
Table 2 and histograms of the simulated sampling distribution of P(Survived	Age) within the treatment group (again, see Supplementary), suggest treated patients aged 55-64 years have roughly equal chance of survival, while treated patients aged over 65 and under 55 years have comparatively higher rates of survival. Although, the subgroups with higher estimates of survival have very few members and higher uncertainty.		

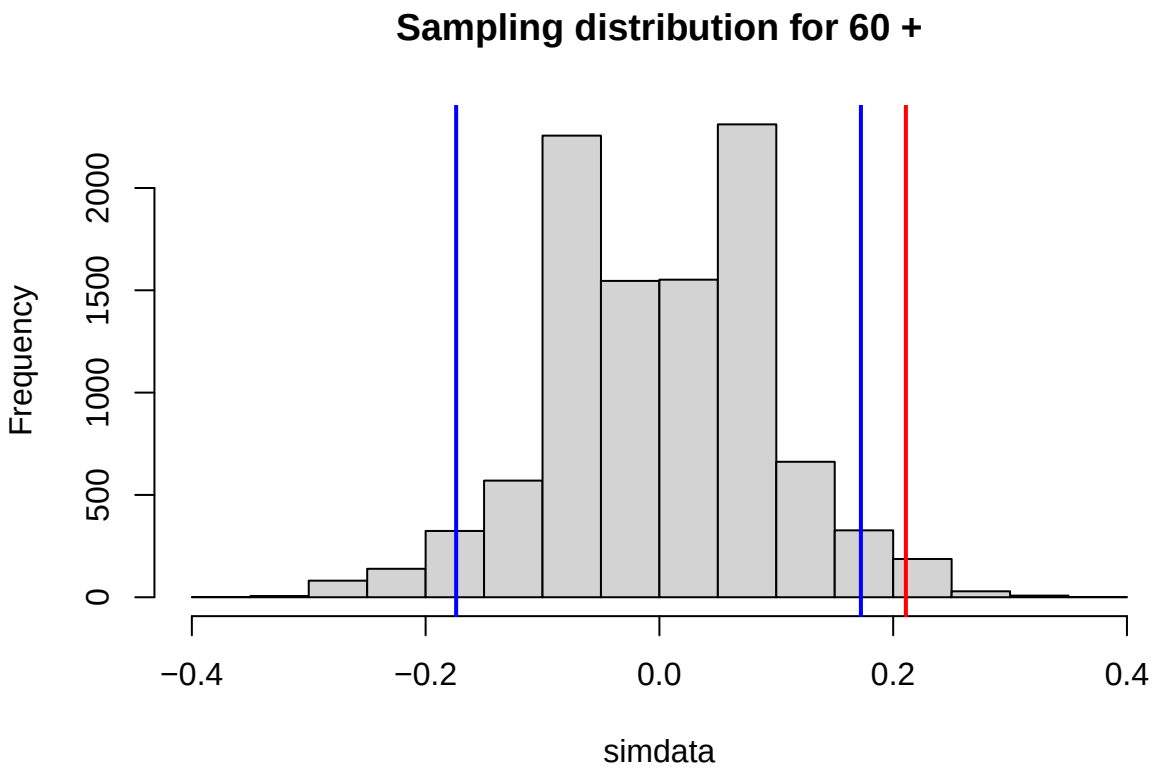
2) Now, in each of those subgroups evaluate whether TFD725+docetaxel is more effective than docetaxel alone (and the magnitude of any potential treatment effect). In addition, evaluate if the treatment

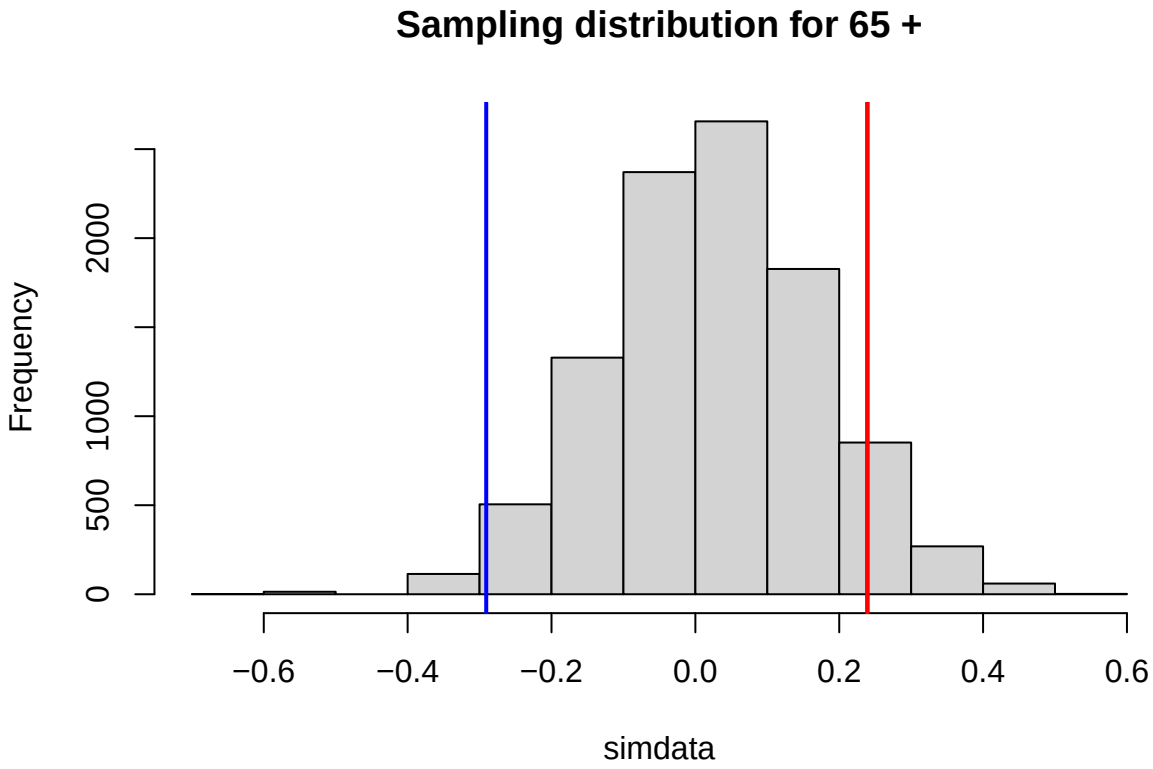
effect appears to substantively and/or systematically differ across age (or if the data doesn't give a clear answer to this).

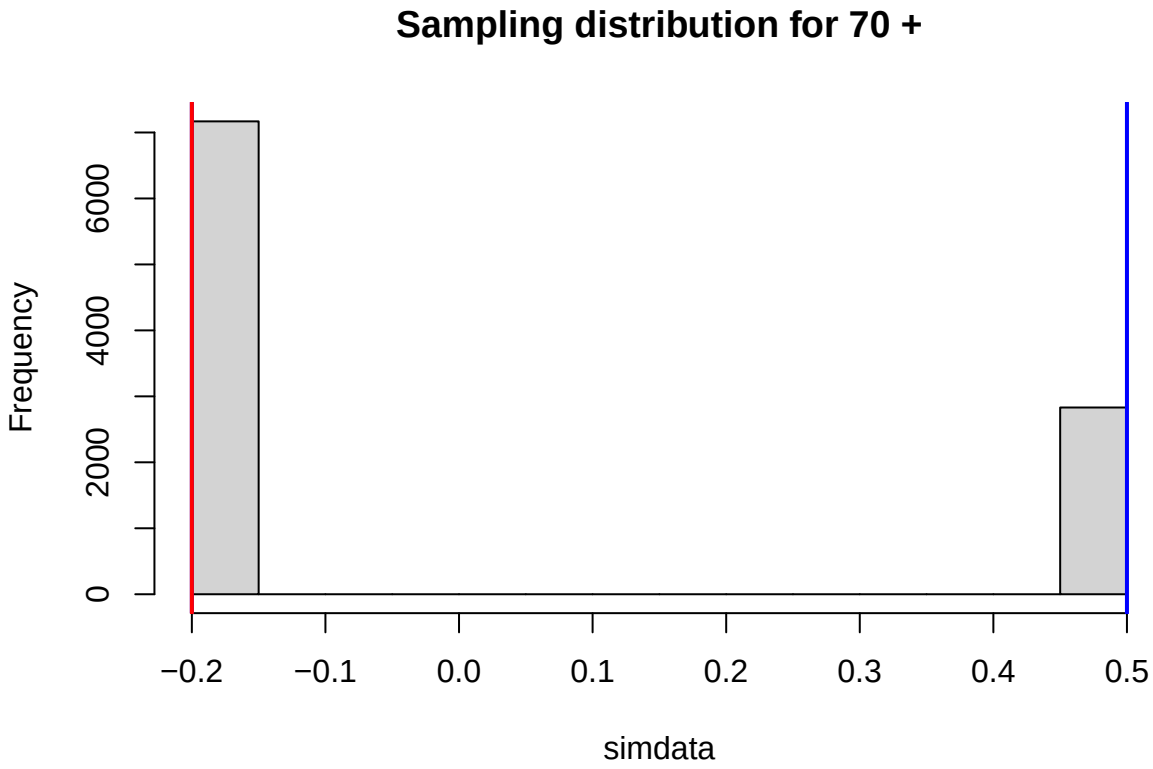
For a patient in a subpopulation of the TFD725+docetaxel treatment arm, the probability of surviving past 400 days is estimated by the proportion of survivors in that subpopulation. Assuming a Binomial distribution, we can simulate outcomes using the sample size and observed proportion, then define a 90% confidence interval based on these simulations.



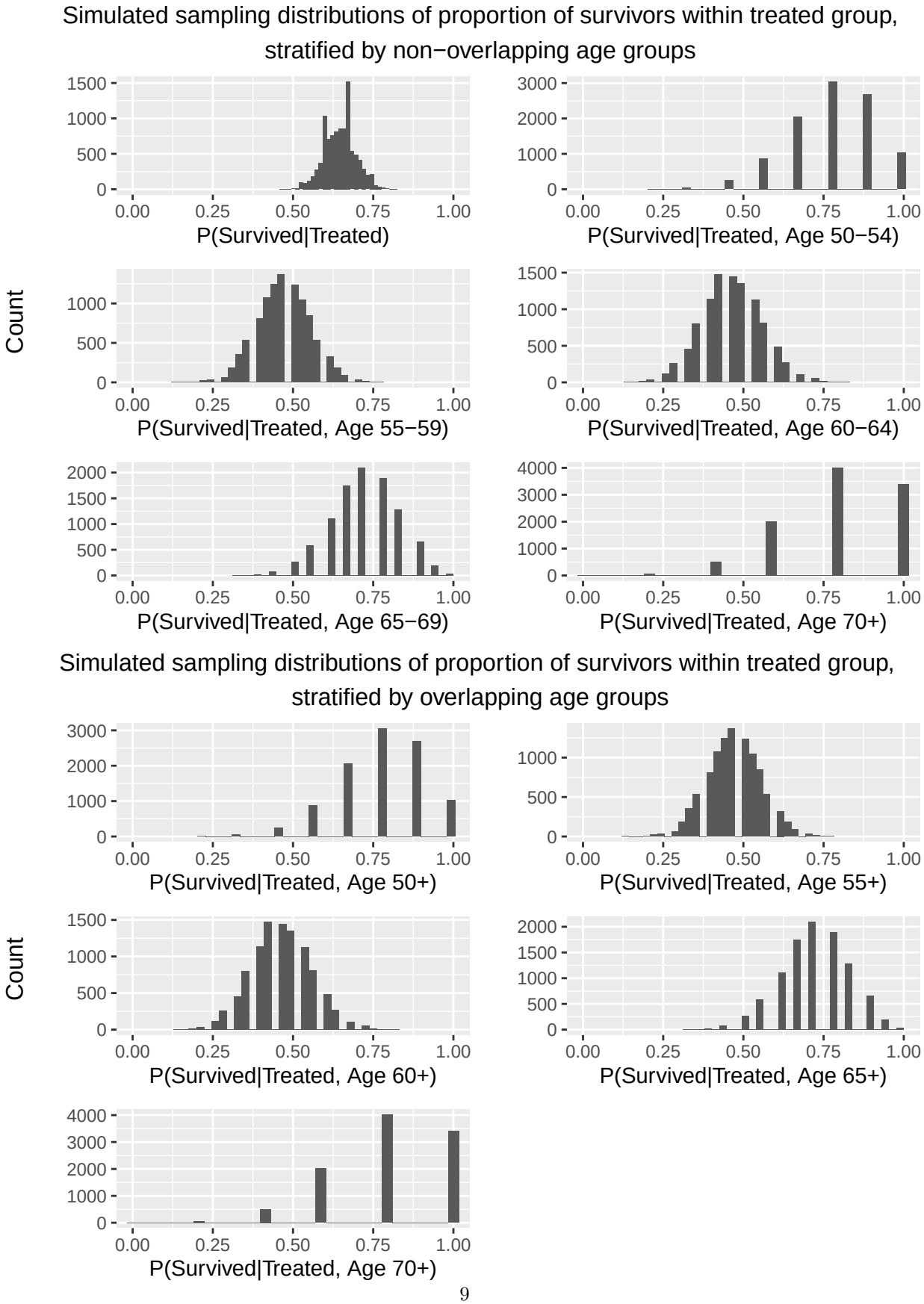

Sampling distribution for 55 +
Frequency
0
500
1000
1500
2000
−0.3
−0.2
−0.1
0.0
0.1
0.2
0.3
simdata


Sampling distribution for 60 +
Frequency
0
500
1000
1500
2000
−0.4
−0.2
0.0
0.2
0.4
simdata


Sampling distribution for 65 +
Frequency
0
500
1000
2000
−0.6
−0.4
−0.2
0.0
0.2
0.4
0.6
simdata


Sampling distribution for 70 +
Frequency
0
2000
4000
6000
−0.2
−0.1
0.0
0.1
0.2
0.3
0.4
0.5
simdata

Supplementary



End of report. Code appendix begins on the next page.

Code Appendix

```
# setup options
knitr::opts_chunk$set(echo = FALSE, message = FALSE)
options(knitr.kable.NA = '-')
options(digits = 3)
labs = knitr::all_labels()
labs = labs[!labs %in% c("setup", "llm_appendix", "allcode")]
# clear environment
rm(list=ls())

# load relevant packages
library(dplyr)      # data frame manipulation
library(knitr)      # table formatting
library(ggplot2)    # plotting
library(gridExtra)  # assembling multiply plots on the same page

# load data
nsclc <- read.table("../data/nsclc-modified.txt")

## ===============
## Question 1
## ===============
simulate_sample_dist <- function(n, p){
  nsamp <- 10000
  sample_means <- rbinom(nsamp, n, p) / n
  return(list(
    simdata = sample_means,
    estimate = p,
    ci = quantile(sample_means, c(0.05, 0.95))))
}

## ============================
## Overlapping age groups
## ============================
# calculate and store proportion of success within treatment group
means.treated <- data.frame()
age_cutoffs <- seq(50, 70, 5)
for (c in age_cutoffs) {
  subset <- subset(nsclc, age >= c, select = survival.past.400)
  new_row <- data.frame(age = paste(c,"+"),
                        n = nrow(subset),
                        mean = mean(subset$survival.past.400))
  means.treated <- rbind(means.treated, new_row)
}

# simulate sampling distributions for each subpopulation of the treated group
res50 <- simulate_sample_dist(means.treated$n[1], means.treated$mean[1])
res55 <- simulate_sample_dist(means.treated$n[2], means.treated$mean[2])
res60 <- simulate_sample_dist(means.treated$n[3], means.treated$mean[3])
res65 <- simulate_sample_dist(means.treated$n[4], means.treated$mean[4])
res70 <- simulate_sample_dist(means.treated$n[5], means.treated$mean[5])
```

```r
# add 5% and 95% simulated percentiles to means table
means.treated$perc5 <-
  c(res50$ci[1], res55$ci[1], res60$ci[1], res65$ci[1], res70$ci[1])
means.treated$perc95 <-
  c(res50$ci[2], res55$ci[2], res60$ci[2], res65$ci[2], res70$ci[2])
# inspect estimates and 90% CIs
means.treated %>%
  mutate(CI = paste(round(perc5,2), "-", round(perc95,2))) %>%
  select(-c(perc5, perc95)) %>%
  knitr::kable(digits = 2,
               col.names = c("Age", "N", "Estimate", "90% CI"),
               caption = "Estimated probability of 400-day survival within overlapping subsets of the ti

# plot each simulated sampling distribution
gg50.2 <- ggplot(mapping=aes(res50$simdata)) + geom_histogram() +
  xlab("P(Survived|Treated, Age 50+)") + ylab("") +
  coord_cartesian(xlim = c(0,1))

gg55.2 <- ggplot(mapping=aes(res55$simdata)) + geom_histogram() +
  xlab("P(Survived|Treated, Age 55+)") + ylab("") +
  coord_cartesian(xlim = c(0,1))

gg60.2 <- ggplot(mapping=aes(res60$simdata)) + geom_histogram() +
  xlab("P(Survived|Treated, Age 60+)") + ylab("") +
  coord_cartesian(xlim = c(0,1))

gg65.2 <- ggplot(mapping=aes(res65$simdata)) + geom_histogram() +
  xlab("P(Survived|Treated, Age 65+)") + ylab("") +
  coord_cartesian(xlim = c(0,1))

gg70.2 <- ggplot(mapping=aes(res70$simdata)) + geom_histogram() +
  xlab("P(Survived|Treated, Age 70+)") + ylab("") +
  coord_cartesian(xlim = c(0,1))

## ============================
## Non-overlapping age groups
## ============================
# create a factor variable from patient age
nsclc$age2 <- cut(nsclc$age,
                  seq(50,75,5),
                  include.lowest = TRUE, right = FALSE)
                  # labels = c("50+","55+","60+","65+","70+")
# inspect subgroup sizes
# table(nsclc$age2)
# remove the few observations whose age was below 50 (their age2 is NA)
nsclc <- subset(nsclc, !is.na(age2))

# calculate and store proportion of success within treatment group
means.treated <- nsclc %>%
  filter(tx == 1) %>%
  group_by(age = age2) %>%
  summarize(n = n(), mean = mean(survival.past.400))
```

```r
# simulate sampling distributions for each subpopulation of the treated group
res <- simulate_sample_dist(sum(means.treated$n), mean(means.treated$mean))
res50 <- simulate_sample_dist(means.treated$n[1], means.treated$mean[1])
res55 <- simulate_sample_dist(means.treated$n[2], means.treated$mean[2])
res60 <- simulate_sample_dist(means.treated$n[3], means.treated$mean[3])
res65 <- simulate_sample_dist(means.treated$n[4], means.treated$mean[4])
res70 <- simulate_sample_dist(means.treated$n[5], means.treated$mean[5])

# add 5% and 95% simulated percentiles to means table
means.treated$perc5 <-
  c(res50$ci[1], res55$ci[1], res60$ci[1], res65$ci[1], res70$ci[1])
means.treated$perc95 <-
  c(res50$ci[2], res55$ci[2], res60$ci[2], res65$ci[2], res70$ci[2])
# inspect estimates and 95% CIs
means.treated %>%
  mutate(CI = paste(round(perc5,2), "-", round(perc95,2), sep="")) %>%
  select(-c(perc5, perc95)) %>%
  knitr::kable(digits = 2,
               col.names = c("Age", "N", "Estimate", "90% CI"),
               caption = "Estimated probability of 400-day survival within subsets of the treatment arm

# plot each simulated sampling distribution
gg <- ggplot(mapping=aes(res$simdata)) + geom_histogram() +
  xlab("P(Survived|Treated)") + ylab("") + coord_cartesian(xlim = c(0,1))

gg50 <- ggplot(mapping=aes(res50$simdata)) + geom_histogram() +
  xlab("P(Survived|Treated, Age 50-54)") + ylab("") +
  coord_cartesian(xlim = c(0,1))

gg55 <- ggplot(mapping=aes(res55$simdata)) + geom_histogram() +
  xlab("P(Survived|Treated, Age 55-59)") + ylab("") +
  coord_cartesian(xlim = c(0,1))

gg60 <- ggplot(mapping=aes(res60$simdata)) + geom_histogram() +
  xlab("P(Survived|Treated, Age 60-64)") + ylab("") +
  coord_cartesian(xlim = c(0,1))

gg65 <- ggplot(mapping=aes(res65$simdata)) + geom_histogram() +
  xlab("P(Survived|Treated, Age 65-69)") + ylab("") +
  coord_cartesian(xlim = c(0,1))

gg70 <- ggplot(mapping=aes(res70$simdata)) + geom_histogram() +
  xlab("P(Survived|Treated, Age 70+)") + ylab("") +
  coord_cartesian(xlim = c(0,1))
calc_stat <- function (data) {
  diff.means <- with(data,
    mean(survival.past.400[tx==1]) - mean(survival.past.400[tx==0]))
  return(diff.means)
}

simulate_perm_trial <- function(data){
  # permute exposure status
  perm.data = data
```

```r
  perm.data$tx = perm.data$tx[sample(1:nrow(perm.data), replace=FALSE)]

  ## return the difference in means from permuted data
  return(calc_stat(perm.data))
}

nsims <- 10000
age_cutoffs <- seq(50, 70, 5)
for (c in age_cutoffs) {
  nsclc_subset <- subset(nsclc, age >= c)
  simdata <- replicate(nsims, simulate_perm_trial(nsclc_subset))
  # simulated sampling distribution
  hist(simdata, main = paste("Sampling distribution for", c, "+"))
  # inner 95% percentiles
  abline(v = quantile(simdata, probs=c(0.05, 0.95), names = FALSE),
         col = "blue", lwd = 2)
  # observed value
  abline(v = calc_stat(nsclc_subset), col = "red", lwd = 2)
}


# ggplot(mapping = aes(simdata)) + geom_histogram()
# plot each simulated sampling distribution
gridExtra::grid.arrange(gg, gg50, gg55, gg60, gg65, gg70,
                        top = "Simulated sampling distributions of proportion of survivors within treat
                        left = "Count")

# plot each simulated sampling distribution
gridExtra::grid.arrange(gg50.2, gg55.2, gg60.2, gg65.2, gg70.2,
                        top = "Simulated sampling distributions of proportion of survivors within treat
                        left = "Count")
```

End of document.