Project-Final-Report

December 8, 2023

1 Analyzing the Impact of Ascites and D-Penicillamine on Mortality in Primary Biliary Cirrhosis Patients: A Statistical Inference Study

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1.1 1. Introduction

Primary biliary cirrhosis (PBC) is a chronic condition characterized by gradual damage and deterioration of the liver's bile ducts, leading to substantial liver-related health challenges. PBC stands as a prominent contributor to liver-related illnesses and fatalities. The prognosis of PBC is influenced by multiple factors critical to effective treatment (Prince et al., 2002). Notably, advanced PBC often manifests the complication of ascites, characterized by an accumulation of fluid in the abdominal cavity (Purohit, 2015). This project endeavors to examine how ascites impacts the prognosis of patients receiving D-penicillamine. It's worth noting that the effectiveness of D-penicillamine remains uncertain (Purohit, 2015). We chose to analyze this to improve patient treatment insights. Thus, we are asking the following question:

For Primary Biliary Cirrhosis patients administered with D-Penicillamine, does the presence of Ascites determine their mortality? To investigate this, we shall analyze the difference in mortality rate based on the following categorical variables and the scale parameter will be a standard error of proportions.

- Type of treatment (D-penicillamine or Placebo)
- Presence of Ascites

The analysis will focus on comparing proportions, as both "Drug" type and "Ascites" presence have only two discrete outcomes. Standard error will be used to quantify the statistic's variation from the population proportion. This project seeks to provide insights into the impact of "Ascites" on the prognosis of PBC patients treated with "D-penicillamine," using a comprehensive dataset for a thorough investigation.

The dataset used is the Cirrhosis Patient Survival Prediction dataset from the UCI Machine Learning Repository, containing information on 418 PBC patients. Each patient's data includes patient status ("Status"), drug type ("Drug"), age, sex, and various clinical parameters.

1.2 2. Methods & Results

1.2.1 Loading Necessary Libraries

```
[1]: install.packages("infer")
     install.packages("gridExtra")
     library(tidyverse)
     library(broom)
     library(repr)
     library(digest)
     library(infer)
     library(gridExtra)
    The downloaded binary packages are in
    /var/folders/p5/hwwszq5n2kv_18jljl_3nq1h0000gn/T//RtmpeSYQgs/downloaded_packages
    The downloaded binary packages are in
    /var/folders/p5/hwwszq5n2kv_18jljl_3nq1h0000gn/T//RtmpeSYQgs/downloaded_packages
      Attaching packages
                                     tidyverse 1.3.2
     ggplot2 3.4.4
                                  1.0.1
                          purrr
     tibble 3.1.8
                          dplyr
                                  1.0.10
     tidyr 1.3.0
                          stringr 1.5.1
     readr 2.1.4
                          forcats 1.0.0
    Warning message:
    "package 'stringr' was built under R version 4.2.3"
      Conflicts
    tidyverse_conflicts()
     dplyr::filter() masks stats::filter()
     dplyr::lag()
                    masks stats::lag()
    Attaching package: 'gridExtra'
    The following object is masked from 'package:dplyr':
        combine
```

1.2.2 Downloading Dataset from the Web

• Downloading the dataset that is stored in a public repository.

```
[2]: # URL containing the dataset
url <- "https://raw.githubusercontent.com/Rithika-Nair/STAT-201-Final_Project/
→main/cirrhosis.csv"

# Download cirrhosis.csv from the url
download.file(url, "cirrhosis.csv")

# Store the dataset into variable
cirr_data <- read.csv("cirrhosis.csv")

# Display the first few rows of the dataset
head(cirr_data)
```

		ID	N_Days	Status	Drug	Age	Sex	Ascites	Hepatomega
		<int></int>	<int $>$	<chr $>$	<chr $>$	<int $>$	<chr $>$	<chr $>$	<chr $>$
A data.frame: 6×20	1	1	400	D	D-penicillamine	21464	F	Y	Y
	2	2	4500	\mathbf{C}	D-penicillamine	20617	F	N	Y
	3	3	1012	D	D-penicillamine	25594	M	N	N
	4	4	1925	D	D-penicillamine	19994	F	N	Y
	5	5	1504	CL	Placebo	13918	F	N	Y
	6	6	2503	D	Placebo	24201	F	N	Y

Table 1: Cirrhosis Dataset

1.2.3 Data Cleaning and Preprocessing

• Selecting columns relevant to our analysis: Status, Drug, Ascites.

```
Status Drug
                                                   Ascites
                         <chr>
                                  <chr>
                                                   <chr>
                         D
                                  D-penicillamine
                                                   Y
                         \mathbf{C}
                                 D-penicillamine
                                                   Ν
A data.frame: 6 \times 3
                         D
                                                   Ν
                                 D-penicillamine
                         D
                                  D-penicillamine
                                                   Ν
                         CL
                                 Placebo
                                                   Ν
                        D
                                 Placebo
                                                   Ν
```

Table 2: Cirrhosis Dataset with Variables of Interest

• Checking for missing values in each of the columns and removing the rows that contain missing values.

```
[4]: # Printing the number of missing values in each column
print(sum(is.na(cirrhosis$Status)))
print(sum(is.na(cirrhosis$Drug)))
```

```
print(sum(is.na(cirrhosis$Ascites)))
```

- [1] 0
- [1] 106
- [1] 106

```
Ascites
                         Status
                                Drug
                         <chr>
                                 <chr>
                                                   <chr>
                        D
                                 D-penicillamine
                                                   Y
                        D
                                 D-penicillamine
                                                  N
A data.frame: 6 \times 3
                        D
                                 D-penicillamine
                                                  Ν
                        CL
                                 Placebo
                                                   Ν
                     4
                     5
                                 Placebo
                                                   Ν
                        D
                     6 \mid D
                                 Placebo
                                                   Ν
```

144

Table 3: Refined Cirrhosis Dataset with Variables of Interest

1.2.4 Exploratory data analysis

- We shall conduct our analysis by grouping the patients into 2 different groups.
 - Group 1: Patients administered with D-penicillamine and have Ascites
 - Group 2: Patients administered with D-penicillamine but don't have Ascites.

```
Status
                                 Drug
                                                   Ascites
                         <chr>
                                 <chr>
                                                   <chr>
                                                   Y
                        D
                                 D-penicillamine
                        D
                                 D-penicillamine
                                                  Ν
A data.frame: 6 \times 3
                        D
                                 D-penicillamine
                                                  Ν
                        D
                                 D-penicillamine
                                                  Ν
                        D
                                 D-penicillamine
                                                  Ν
                        D
                                 D-penicillamine
```

Table 4: Patients Administered D-pencillamine in Filtered Cirrhosis Dataset

Now, we will perform bootstrapping to estimate confidence intervals for the proportions of patients with and without Ascites ("Y" and "N"). With a seed for reproducibility, we will conduct 1,000 bootstrap replicates for each category. The resulting confidence intervals will help assess the precision of our estimates, providing a range within which the true population proportion likely lies.

```
A tibble: 1 \times 2 \begin{array}{c} lower\_ci & upper\_ci \\ <dbl> & <dbl> \\ \hline 0.09333333 & 0.2666667 \end{array}
```

Table 5: 95% Confidence Interval for Patients Exhibiting Ascites

```
A tibble: 1 \times 2 \begin{array}{c} lower\_ci & upper\_ci \\ <dbl> & <dbl> \\ \hline 0.7333333 & 0.9066667 \end{array}
```

Table 6: 95% Confidence Interval for Patients Not Exhibiting Ascites

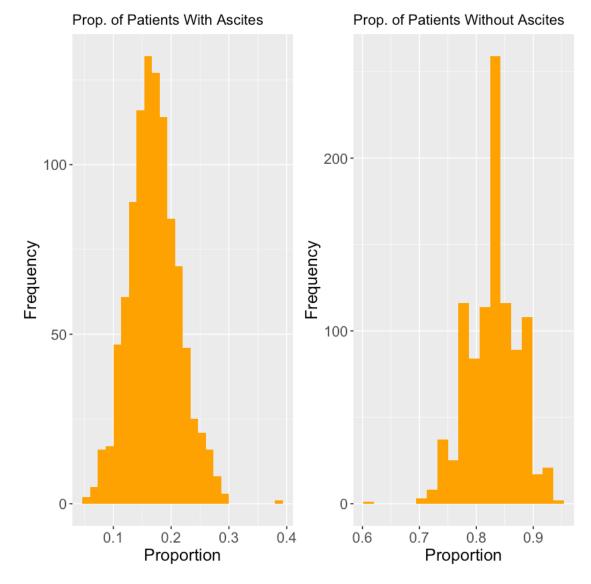


Figure 1: Distribution of Patients with Ascites vs without Ascites.

Now, we examine the mortality rates within each group to understand the proportion of individuals who have unfortunately passed away.

A tibble:
$$2 \times 2 \frac{\text{Ascites prop}}{\text{Chr}>} \frac{\text{Abl}>}{\text{V}}$$

A tibble: $2 \times 2 \frac{\text{Ascites prop}}{\text{N}} = 0.8$

Table 7: Proportion of Patients with Ascites Status who have Deceased

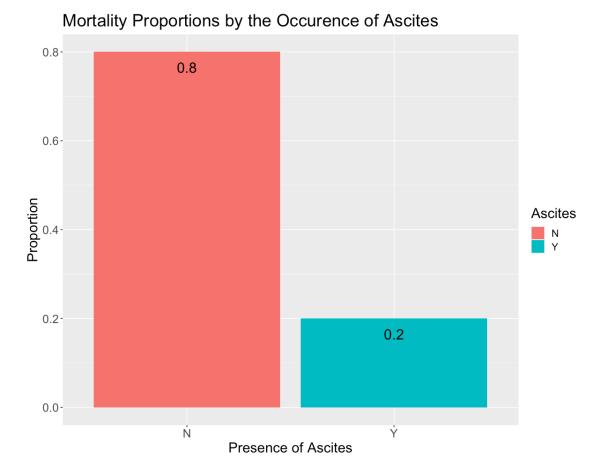


Figure 2: Mortality Rates Based on the Presence of Ascites.

Figure 2 indicates a noteworthy contrast in the mortality rates of the two groups of patients, thus suggesting a significant difference.

1.2.5 Hypothesis Testing

The estimates produced in the previous section are insufficient as there is no mention of the statistical significance of the evidence. Therefore, we will need to perform hypothesis testing to determine the reliability of our conclusion. We plan to support our data by testing the following hypothesis:

• \$ H_0 : p_1 - p_2 = 0\$ • \$ H_1 : p_1 - p_2 0\$

Here, p_1 denotes the proportion of patients administered with D-penicillamine and have Ascites who died, while p_2 represents the proportion of patients administered with D-penicillamine and do not have ascites but still died. The objective is to assess the statistical evidence supporting our conclusions. The null hypothesis states that there is no difference in mortality rates between patients administered with D-penicillamine and have Ascites (p_1) and those administered with D-penicillamine without ascites (p_2) who died whereas the alternative hypothesis states that there is a difference between mortality rates between the two groups.

We have chosen a significance level of $\alpha=0.05$ for our hypothesis testing, striking a balance between the probabilities of type 1 and type 2 errors. Opting for a lower significance level would elevate the risk of committing a type 2 error, which, here, is more consequential than a type 1 error. A type 2 error would imply the erroneous conclusion that there is no difference in mortality rates when, in fact, there is. Conversely, increasing the significance level would necessitate stronger evidence to reach a statistically significant conclusion. Hence, our selected significance level aligns with the objective of minimizing both types of errors while maintaining a practical balance.

Using a two-tailed test to assess mortality rate differences in D-penicillamine patients with and without Ascites ensures a comprehensive analysis, detecting significance in either direction. This approach minimizes the risks of type 1 and type 2 errors, aligning with a thorough evaluation of the research hypothesis while maintaining practicality.

1.2.6 Creating the null model

 Now, we shall calculate the summary statistic and make a null distribution using the infer package.

	replicate	stat
	<int $>$	<dbl $>$
A infer: 6×2	-0.02481390	
A inform 6 × 2	2	0.06823821
A filler: 0×2	3	0.16129032
	4	0.06823821
	5	-0.11786600
	6	0.16129032

Table 8: 1000 samples taken from the Null Model using Infer Package

1.2.7 Calculating test statistic

• Now, we shall calculate the observed difference in mortality rates using infer package.

```
A infer: 1 \times 1 \frac{\text{stat}}{\text{<dbl>}} 0.1612903
```

Table 9: Observed Difference In Proportions

1.2.8 Visualizing the p-value

- The final step is to visualize the p-value on the null distribution
- This means that, if the null hypothesis holds true, how surprised would we be to see a difference in mortality rates of 16.13%?
- We accomplish this by first visualizing the null distribution using the function visualize() function of infer package, and then we shall use shade_p_value function and set obs_stat to obs_diff_prop and we will set the direction = "right" because our alternative hypothesis is "more extreme" than the hypothesized world.

Simulation-Based Null Distribution

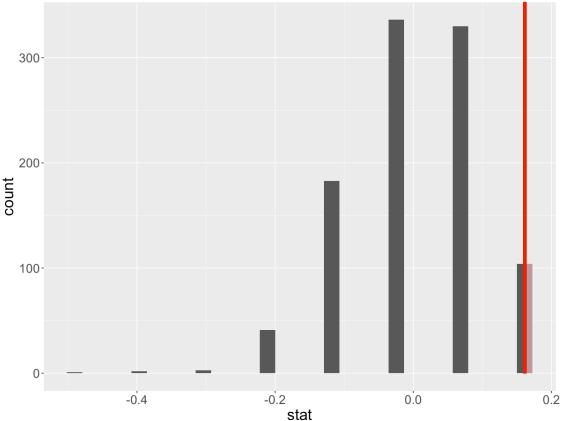


Figure 3: Simulation Based Null Distribution

- After visualizing the p-value (Figure 3), we can tell that there are chances that we will see a difference in the survival rates of 16.13% in a hypothesized world of no difference in the mortality rates between the two groups.
- Therefore, we would fail to reject the null hypothesis, in statistical terminology "Do not reject H_0 ".

1.2.9 Computing the p-value

• We shall compute the p-value using get_p_value function with obs_stat = obs_diff_prop and direction = "right".

A tibble:
$$1 \times 1 = \frac{\text{p_value}}{\text{}}$$

$$0.104$$

Table 10: P-Value calculated from Null Distribution

- This information indicates that there is a 10.4% probability of observing a mortality rate difference as substantial as 16.13% between individuals treated with D-penicillamine, distinguishing between those with and without ascites, solely due to random sampling fluctuations in a null distribution.
- Since the p-value is larger than our 5% significance level, we fail to reject the null hypothesis.

1.2.10 Bootstrap method for difference in proportions

• We shall now use boostrapping methods to test our hypothesis.

```
replicate
                           stat
                <int>
                            <dbl>
                1
                           0.1774194
                2
                           0.1940299
A infer: 6 \times 2
                           0.1896552
                4
                           0.1093750
                5
                           0.1639344
                6
                           0.1641791
```

Table 11: 1000 samples taken using Bootstraping with Infer Package

Table 12: Upper and Lower Bounds of 95% Confidence Interval from Bootstrapping

```
axis.title=element_text(size=20),
plot.title = element_text(size=22))
percentile_ci_plot
```

Simulation-Based Bootstrap Distribution

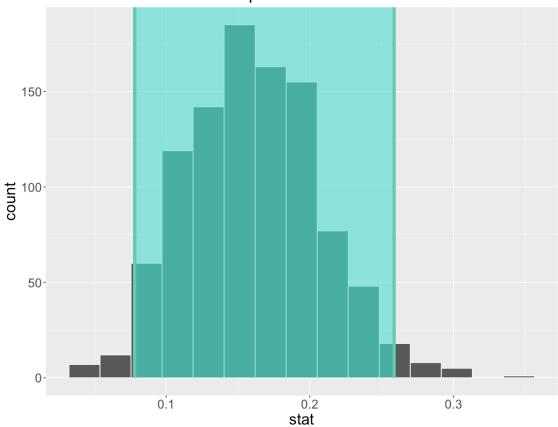


Figure 4: Simulation-based Bootstrap Distribution with 95% confidence interval

- From Figure 4, we are 95% confident that the true difference in the population proportions p_1-p_2 lies between 7.81% and 25.86%
- We can also deduce that our calculated p-value of 0.104 falls within the 95% confidence interval (0.0781, 0.2586), indicating that the disparity between p_1 and p_2 lacks statistical significance.

1.2.11 Standard Error Method

- Since the bootstrap distribution is roughly normally distributed, we can also compare it with the confidence interval generated from the standard error method.
- Here, we would use the get_ci function and set level = 0.95, type = se and point_estimate = obs_diff_prop.

Table 13: Upper and Lower Bounds of 95% Confidence Interval from standard error method

1.2.12 Visualize using Standard Error Method

• Now, we'll visualize the bootstrap distribution again using the confidence interval we calculated using the standard error method.

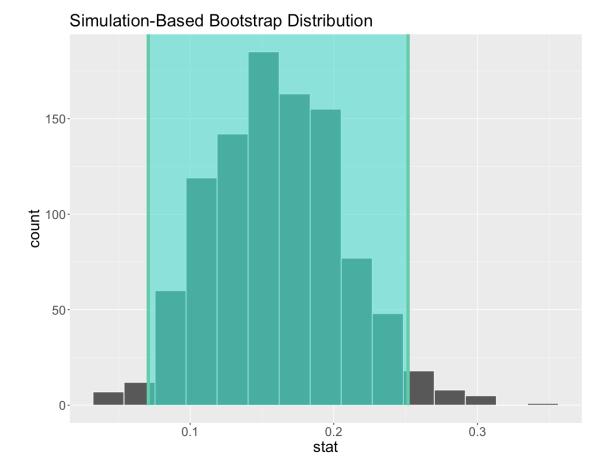


Figure 5: Simulation-Based Bootstrap Distribution using standard error method

• Again, here we notice that the p-value of 0.104 is included in the confidence interval which shows that difference between p_1 and p_2 is not statistically significant.

1.2.13 Two Sample Z-test: Comparing the proportions of two independent populations using asymptotics

Here, we'll consider the following case:

•
$$H_0: p_1 - p_2 = 0$$
 vs $H_1: p_1 - p_2 \neq 0$

to test H_0 , we will use the following test statistic:

$$Z = \frac{\hat{p_1} - \hat{p_2}}{\sqrt{\hat{p}(1-\hat{p})(\frac{1}{n_1} + \frac{1}{n_2})}}$$

Pooled proportion is given by,

$$\hat{p} = \frac{n_1 \hat{p_1} + n_2 \hat{p_2}}{n_1 + n_2}$$

```
Warning message in prop.test(x = c(sum(sample_1$Status == "D"),
sum(sample_2$Status == :
"Chi-squared approximation may be incorrect"
```

```
estimate1 estimate2
                                        statistic
                                                                                                     method
                                                   p.value
                                                                parameter
                                                                            conf.low
                                                                                         conf.high
A tibble: 1 \times 9 <dbl>
                            <dbl>
                                        < dbl >
                                                   <dbl>
                                                                <dbl>
                                                                             <dbl>
                                                                                         <dbl>
                                                                                                     < chr >
                            0.8387097
                                        2.419355
                                                   0.1198443
                                                                            0.0697395
                                                                                         0.2528411
                                                                                                     2-sample tes
```

Table 14: Results using prop.test() from 2 sample Z-test

- In the above code snippet, we calculated the p.value, conf.low and conf.high using prop.test() function in R. We used a 2-sample Z-test for comparing the proportions.
- We found the p.value of 0.1198, which is higher than our significance level of 0.05.
- Due to this, we shall not reject the null hypothesis at a 5% significance level.

1.2.14 Bootstrapping vs Asymptotic Methods

	Lower CI	Upper CI	P-value
Bootstrapping	0.0781	0.2597	0.104
Asymtotic	0.0697	0.2528	0.1198

Table 15: Comparison table between Bootstrapping and Asymptotic methods

From the preliminary analysis, we expected to see a significant difference between the mortality of patients who were administered with D-penicillamine and had Ascites and mortality of patients who were administed with D-penicillamine and did not have Ascites. This hypothesis was tested using both bootstrapping and asymptotic methods. For asymptotic method, we chose to do the two-sample Z test because the population is not normally distributed due to the discrete random variables and we have a large enough sample size under the assumption: $n\hat{p} \geq 10$ and $n(1-\hat{p}) \geq 10$. Therefore, the null model is a fairly good approximation here.

Examining results from Bootstrapping and the Z-test reveals similar p-values (Table 15) and under our 0.05 significance level, both methods fail to produce significant results. Moreover, the confidence intervals presented by both tests are also similar (Table 15).

Bootstrapping holds advantages over asymptotic methods, as it doesn't depend on distribution assumptions and is useful in deriving sampling distributions of unknown sample statistics which is a limitation of asymptotic methods.

1.3 3. Discussion

Our study focused on a critical aspect of Primary Biliary Cirrhosis (PBC) treatment, investigating the impact of ascites on mortality rates in patients undergoing D-Penicillamine treatment. Initial examination of raw data revealed that patients without ascites had higher survival rates than those with ascites (Figure 2), suggesting a potential link between ascites and increased mortality risk.

To strengthen our findings, we performed hypothesis testing on the difference in mortality rates between the two groups. The resulting p-value of 0.104 (Table 10), exceeding the 5% significance level, led us to accept the null hypothesis, indicating that observed differences could be attributed to chance.

Further analysis, utilizing both bootstrap and standard error methods at a 95% confidence level (Table 12 & 13), produced non-significant intervals. Consequently, there is insufficient evidence to assert that ascites directly influence mortality rates in PBC patients treated with D-penicillamine. Despite initial expectations based on preliminary analysis, the unexpected results suggest the presence of other factors influencing mortality rates alongside ascites. Notably, consistent confidence intervals from both methods affirm the reliability of our testing.

1.3.1 Conclusion

To summarize, while our study found numerical differences in mortality rates between PBC patients with and without ascites, the lack of statistical significance suggests that ascites should not be viewed as the only determinant of mortality in patients undergoing D-Penicillamine therapy. This finding has certain clinical practice implications. It emphasizes the complexity of managing PBC and the requirement for a comprehensive treatment plan that takes into account a range of possible risk factors. Understanding the complex and numerous aspects of PBC mortality may result in customized medical approaches, thereby enhancing the chance of survival for individuals struggling with this chronic illness.

1.3.2 Future Direction

Future research paths, firstly, may explore the interaction between Ascites and comorbid conditions like diabetes, cardiovascular diseases, or conditions noted in the dataset, yielding valuable insights for more effective treatments. Secondly, investigating the response to D-Penicillamine treatment at early, middle, and late stages of PBC in the presence of Ascites could enhance intervention strategies and treatment efficacy. Lastly, to overcome the limitations of the current study's sample size and diversity, subsequent research should encompass a more diverse patient population, including various ethnicities, age groups, and geographic regions, for a comprehensive understanding of PBC treatment outcomes.

1.4 4. References

Prince, M., Chetwynd, A., Newman, W., Metcalf, J. V., & James, O. F. W. (2002). Survival and symptom progression in a geographically based cohort of patients with primary biliary cirrhosis: Follow-up for up to 28 years. Gastroenterology, 123(4), 1044–1051. https://doi.org/10.1053/gast.2002.36027

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Dickson, E., Grambsch, P., Fleming, T., Fisher, L., and Langworthy, A.. (2023). Cirrhosis Patient Survival Prediction. UCI Machine Learning Repository. https://doi.org/10.24432/C5R02G.