Dose-Response Study: A Categorical Data Analysis

Ruoxi Li

rl3401

Table of Contents

1. Abstract

This study investigates the dose-response relationship of a test drug compared to a placebo in a sample of 217 participants distributed across nine different centers. Participants were divided into four groups based on the dosage received. The objective is to assess the drug's efficacy across different dosages and its consistency across genders. Our findings reveal a statistically significant increasing dose-response relationship, demonstrating efficacy across all three dosage levels. Furthermore, the treatment effect is consistent across sexes, suggesting the drug's broad applicability. However, the study has its limitations, such as depending on the assumption that efficacy increases monotonically and the potential variability in conclusions drawn from using different multiple comparison procedures.

2. Introduction

The exploration of dose-response relationships is crucial in the development and approval of new drugs, providing insight into the effective dosage range and potential gender differences in drug efficacy. This study aims to analyze the efficacy of a test drug across 3 dosage levels in comparison to a placebo. Utilizing a dataset of 217 individuals, the research employs association tests, trend test, and interaction tests to investigate the presence of a dose-response relationship and assess the consistency of treatment effects across different sexes. By addressing these aims, the study seeks to offer comprehensive insights into the drug's efficacy, thereby informing dosage recommendations and ensuring its broad applicability.

3. Data Summary

This study's dataset evaluates the dose response of an test drug compared to a placebo, incorporating 217 individuals across 9 different centers, each identified by a unique patient ID. Treatments are classified into four levels: placebo with 56 participants, low dose with 54 participants, medium dose with 54 participants, and high dose with 53 participants. Treatment efficacy is assessed through binary response outcomes, where 'resp=1' denotes a positive reaction, indicating efficacy, and 'resp=0' signifies a lack of response. The dataset encompasses demographic data, capturing gender with 121 females and 96 males, alongside age, which varies from 28 to 80 years.

Table1.Summary Statistics of Treatment Response and Proportions

	Response [b]			
Treatment [a]	**1**	**0**	**Total**	**Proportion** [c]
0	11	45	56	19.64%
1	21	33	54	38.89%
2	24	30	54	44.44%
3	28	25	53	52.83%
Total	84	133	217	38.71%

[a] Treatment: 0=Placebo, 1=low dose, 2 =medium dose, 3=high dose.

[b] Response: 1=response, 0=lack of response.

[c] Proportion: the proportion of response in each treatment group.

4. Methods

4.1. Association Tests

In our analysis, we evaluate the effectiveness of various dosages of a test drug compared to a placebo. We use the Cochran–Mantel–Haenszel (CMH) test for this purpose, setting our significance threshold at 0.05. To manage the Type I error rate across pairwise comparisons, we employ the Gatekeeping procedure. This is a predefined step-down method that operates on the assumption that there is a monotonic increase in drug response with increasing dosage.

For the Gatekeeping procedure, we begin by testing the efficacy difference between the high dose and the placebo, at a significance level of $\alpha = 0.05$. If the p-value exceeds 0.05, we fail to reject the null and claim that there is no significant efficacy difference between the high dose and the placebo, implying no dosage level elicits a response under the assumption of monotonic efficacy. If the p-value is less than 0.05, we reject the null and proceed to compare the medium dose against the placebo with similar hypotheses and significance level. If the p-value is greater than 0.05, we fail to reject the null and conclude that only the high dose is effective. If the p-value is less than 0.05, we reject the null and proceed to compare the low dose against the placebo with similar hypotheses and significance level. A p-value greater than 0.05 would indicate that no significant efficacy difference between the low dose and the placebo, which means only medium and high doses show efficacy. Conversely, If the p-value is less than 0.05, we reject the null and confirm the efficacy of the low dose, implying all three dosage level shows efficacy.

4.2. Interaction Test

To investigate potential interactions between sex and treatment efficacy, we apply the Breslow-Day test for each pairwise comparison. This analysis is conducted with a significance threshold set at $\alpha = 0.05$. This approach facilitated the examination of the homogeneity of the odds ratios across different treatment groups, thereby assessing if the interaction between sex and treatment efficacy was statistically significant.

4.3. Trend Test

A CMH test at a significance level of 0.05 is conducted for trend analysis. We articulate the null hypothesis as there exists no correlation between treatment dose and response and the alternative hypothesis that there is a nonzero correlation between treatment dose and response. A p-value less than 0.05 will lead to the rejection of the null hypothesis, demonstrating a significant dose-response relationship. After establishing statistical significance, we will analyze the data further to ascertain whether the observed relationship exhibits an increasing or decreasing trend.

5. Results

5.1. Association Tests

In our association tests, we evaluated the efficacy of three dosage levels using a Gatekeeping procedure and tested the following hypotheses in sequence:

The initial hypothesis: $H_{0H}: \mu_H = \mu_P$ vs. $H_{1H}: \mu_H \neq \mu_P$
The second hypothesis: $H_{0M}: \mu_M = \mu_P$ vs. $H_{1M}: \mu_M \neq \mu_P$
The third hypothesis: $H_{0L}: \mu_L = \mu_P$ vs. $H_{1L}: \mu_L \neq \mu_P$

Table2. Efficacy Evaluation of Three Dosage Levels Using Gatekeeping Procedure

Test Group	**X^2**	**DF**	**Pr > X^2**	**OR (95%CI)** [a]
High vs Placebo	12.93	1	0.0003	4.58 (1.96,10.74)
Medium vs Placebo	7.72	1	0.0054	3.27 (1.40, 7.66)
Low vs Placebo	4.89	1	0.0270	2.60 (1.11,6.13)

[a] OR denotes the odds ratio, 95% CI refers to the 95% confidence interval.

Given that all p-values are less than 0.05, we reject the null hypothesis in the third hypothesis and assert that all three dosage levels show efficacy. Furthermore, the OR and their 95% CI are greater than 1, indicating that each dosage level is effective.

The use of MCP is necessary. In our analysis, we employed a Gatekeeping procedure, which enables us to manage the risk of Type I error inflation that could arise from conducting multiple pairwise comparisons.

5.2. Interaction Test

Hypothesis for high dose is H_0: No interaction between sex and the effect of the high dose vs. H_1: An interaction exists between sex and the effect of the high dose. Hypothesis for medium dose is H_0: No interaction between sex and the effect of the medium dose vs. H_1: An interaction exists between sex and the effect of the medium dose. Hypothesis for low dose: is H_0: No interaction between sex and the effect of the low dose vs. H_1: An interaction exists between sex and the effect of the low dose.

Table3. Interaction Test for Sex and Treatment Efficacy on Varying Dose Levels

Test Group	**X^2**	**DF**	**Pr > X^2**
High vs Placebo	0.19	1	0.6614
Medium vs Placebo	0.07	1	0.7952
Low vs Placebo	0.15	1	0.6966

The outcomes from the Breslow-Day test for high, medium, and low doses all produced p-values exceeding 0.05. Consequently, we do not reject the null hypotheses for these tests, leading to the conclusion that there is no statistically significant interaction between sex and the effects of treatment at any dosage level.

The application of MCP is unnecessary. The reason is that the interaction tests are exploratory and conducted independently for each treatment level. The primary aim is to explore potential interactions rather than confirm hypothesis-driven predictions.

5.3. Trend test

H_0: there is no correlation between dose and response.

H_1: There is a nonzero correlation between dose and response.

Table4.1. Trend Test for Dose and Response

X^2	DF	$Pr > X^2$
12.73	1	0.0004

Table4.2. Summary Statistics of Treatment Response and Proportions

	Response [b]			
Treatment [a]	**1**	**0**	**Total**	**Proportion [c]**
0	11	45	56	19.64%
1	21	33	54	38.89%
2	24	30	54	44.44%
3	28	25	53	52.83%
Total	84	133	217	38.71%

[a] Treatment: 0=Placebo, 1=low dose, 2 =medium dose, 3=high dose.

[b] Response: 1=response, 0=lack of response.

[c] Proportion: the proportion of response in each treatment group.

The p-value is smaller than 0.05, therefore we reject the null and claim that there is a nonzero correlation between dose and response. By checking table1, we can observe that it is a increasing dose response relationship.

6. Discussion and Conclusion

In our analysis, association tests have demonstrated efficacy across all three dosage levels. The trend test further substantiates an increasing dose-response relationship, indicating a positive correlation between the dosage administered and the effect observed. Additionally, interaction tests reveal that the treatment's efficacy is uniformly observed across different sexes, affirming the treatment's broad applicability.

However, our study has some limitations. The foundational assumption of monotonic efficacy, while supported by our findings, remains a hypothesis that may not universally apply to all treatment contexts or patient demographics. Moreover, our employment of a Gatekeeping procedure to control the family-wise error rate. While Gatekeeping is a powerful MCP, it is also worth noting that alternative methods such as the Bonferroni correction, could lead to different conclusions. This observation highlights the importance of selecting an appropriate MCP that aligns with the study's design and objectives.

In conclusion, our findings contribute insights into the dose-response relationship of the investigated treatment, with demonstrated efficacy across all tested doses and consistent effects across genders. Future research should explore the potential for non-monotonic dose-response relationships in with diverse patient demographics to validate the universality of our findings.

7. Appendix

7.1. SAS Code

```
data dta41;
    input Obs CTR PID TRT SEX $ AGE RESP;
    datalines;
```

1	501	1	2	M	46	0
2	501	2	1	M	64	1
3	501	3	3	M	43	1
4	501	4	0	F	48	1
5	501	5	2	M	49	0
6	501	6	0	M	56	0
7	501	7	3	F	53	0
8	501	8	1	M	58	0
9	501	9	1	F	70	0
10	501	10	0	M	53	0
11	501	11	2	F	54	1
12	501	12	3	M	61	1
13	501	13	0	F	44	0
14	501	14	2	F	65	1
15	501	15	1	M	44	1
16	501	16	3	M	55	1
17	501	17	2	F	67	1
18	501	18	3	M	48	0
19	501	19	1	F	58	0
20	501	20	0	M	61	0
21	501	21	2	M	73	0
22	502	1	1	M	41	0
23	502	2	2	M	62	1
24	502	3	3	M	47	0
25	502	4	0	F	48	0
26	502	5	3	M	65	0
27	502	6	2	F	60	0
28	502	7	1	F	38	0
29	502	8	0	F	51	0
30	502	9	3	M	46	0
31	502	10	1	M	47	0
32	502	11	2	F	51	1
33	502	12	0	M	40	0
34	502	13	1	M	54	1
35	502	14	2	M	68	0
36	502	15	3	F	28	1
37	502	16	0	F	59	0
38	502	17	2	F	50	0

39	502	18	3	F	75	0
40	502	19	0	F	57	1
41	502	20	1	M	62	1
42	502	21	1	F	60	0
43	502	22	3	M	64	1
44	502	23	2	M	57	0
45	502	24	0	F	47	1
46	502	25	1	F	66	0
47	502	26	3	M	55	0
48	502	27	2	F	42	1
49	502	28	0	F	55	0
50	502	29	2	M	44	0
51	502	30	0	F	44	0
52	502	31	1	F	56	1
53	502	32	3	M	58	0
54	502	33	1	M	58	1
55	502	34	0	F	44	0
56	502	35	3	M	54	0
57	503	1	0	M	50	0
58	503	2	1	F	74	0
59	503	3	2	F	55	1
60	503	4	3	M	55	0
61	503	5	1	F	51	0
62	503	6	3	F	39	1
63	503	7	0	F	59	0
64	503	8	2	M	57	0
65	503	9	1	F	59	0
66	503	10	2	F	52	0
67	503	11	0	F	54	0
68	503	12	3	M	55	0
69	503	13	3	F	70	0
70	503	14	1	M	78	0
71	503	15	2	M	52	1
72	503	16	0	F	66	0
73	503	17	1	M	37	0
74	503	18	3	M	41	1
75	503	19	2	F	51	0
76	503	20	0	M	58	0
77	503	21	3	M	55	1
78	503	22	0	F	65	1
79	504	1	2	M	49	1
80	504	2	1	F	35	1
81	504	3	3	F	53	1
82	504	4	0	F	43	0

83	504	5	2	M	37	0
84	504	6	1	F	44	0
85	504	7	3	M	61	1
86	504	8	0	F	60	1
87	504	9	0	F	53	0
88	504	10	2	M	55	0
89	504	11	3	F	43	1
90	504	12	1	M	58	1
91	504	13	1	M	55	0
92	504	14	0	F	54	0
93	504	15	3	M	45	0
94	504	16	2	F	54	1
95	504	17	1	F	50	0
96	504	18	0	M	60	0
97	504	19	2	F	47	1
98	504	20	3	F	64	0
99	504	21	2	F	57	0
100	504	22	0	M	50	0
101	504	23	1	M	48	0
102	504	24	3	M	54	1
103	504	25	3	M	72	0
104	504	26	0	F	80	0
105	504	27	1	F	57	1
106	504	28	2	M	58	0
107	504	29	3	M	50	1
108	504	30	2	M	49	1
109	504	31	1	F	59	0
110	504	32	0	F	69	1
111	504	33	0	M	56	1
112	504	34	2	M	73	1
113	505	1	0	F	57	0
114	505	2	3	M	49	0
115	505	3	1	F	60	1
116	505	4	2	F	54	0
117	505	5	1	F	54	0
118	505	6	3	F	79	1
119	505	7	2	F	32	1
120	505	8	0	M	41	0
121	505	9	1	M	61	0
122	505	10	2	M	47	0
123	505	11	0	M	57	0
124	505	12	3	M	44	1
125	505	13	1	F	67	0
126	505	14	3	F	51	1

127	505	15	0	F	56	0
128	505	16	2	M	53	1
129	505	17	1	M	56	1
130	505	18	0	M	61	1
131	505	19	2	F	71	0
132	505	20	3	F	48	0
133	505	21	1	F	40	1
134	505	22	0	M	59	0
135	505	23	3	F	35	1
136	506	1	0	F	74	0
137	506	2	2	F	66	1
138	506	3	3	F	74	0
139	506	4	1	M	52	0
140	506	5	3	F	50	1
141	506	6	0	M	46	0
142	506	7	1	M	53	0
143	506	8	2	F	51	0
144	506	9	3	F	54	0
145	506	10	2	F	73	0
146	506	11	0	M	56	0
147	506	12	1	M	54	0
148	506	13	3	M	57	1
149	506	14	2	F	33	0
150	506	15	0	M	34	0
151	506	16	1	F	61	1
152	507	1	1	F	49	1
153	507	2	0	F	58	0
154	507	3	3	M	53	0
155	507	4	2	M	52	1
156	507	5	0	F	63	0
157	507	6	1	F	60	0
158	507	7	2	F	70	0
159	507	8	3	M	53	1
160	507	9	0	M	60	0
161	507	10	3	F	31	1
162	507	11	2	M	38	0
163	507	12	1	F	60	1
164	507	13	1	F	47	0
165	507	14	0	M	59	0
166	507	15	3	M	69	0
167	507	16	2	M	61	0
168	507	17	3	F	49	0
169	507	18	2	F	66	1
170	507	19	1	F	72	1

171	507	20	0	F	69	0
172	507	21	1	F	56	1
173	507	22	2	F	43	0
174	508	1	1	F	48	0
175	508	2	3	F	38	1
176	508	3	0	M	47	0
177	508	4	2	F	66	1
178	508	5	2	F	29	0
179	508	6	0	M	58	0
180	508	7	1	M	58	1
181	508	8	3	F	50	0
182	508	9	3	F	47	1
183	508	10	2	F	56	0
184	508	11	0	F	69	0
185	508	12	1	F	44	0
186	508	13	2	F	52	1
187	508	14	3	M	65	1
188	508	15	0	F	41	1
189	508	16	1	F	46	1
190	508	17	2	F	46	0
191	508	18	1	M	73	0
192	508	19	0	F	56	0
193	508	20	3	F	41	1
194	508	21	3	M	59	1
195	508	22	1	F	45	0
196	508	23	2	F	67	1
197	508	24	0	F	71	0
198	508	25	1	F	49	1
199	508	26	0	M	62	1
200	509	1	1	M	43	0
201	509	2	3	F	61	1
202	509	3	0	F	48	0
203	509	4	2	F	58	1
204	509	5	1	F	53	1
205	509	6	0	M	52	0
206	509	7	2	M	54	1
207	509	8	3	M	63	1
208	509	9	0	F	55	0
209	509	10	1	M	52	0
210	509	11	2	F	52	1
211	509	12	3	F	58	0
212	509	13	0	F	53	0
213	509	14	2	F	54	0
214	509	15	3	M	67	0

```
215    509     16     1      M      57      0
216    509     17     2      F      49      0
217    509     18     0      F      46      1
run;

/* Data Summary Table */
proc freq data=dta41; tables trt*resp;

/* Pairwise test of each dose vs placebo */
proc freq data=dta41; tables trt*resp/cmh; where trt in (0,1) ;
proc freq data=dta41; tables trt*resp/cmh; where trt in (0,2) ;
proc freq data=dta41; tables trt*resp/cmh; where trt in (0,3) ;

/* Treatment by sex interaction, using pairwise test of each dose vs placebo
*/
proc freq data=dta41; tables sex*trt*resp/cmh; where trt in (0,1) ;
proc freq data=dta41; tables sex*trt*resp/cmh; where trt in (0,2) ;
proc freq data=dta41; tables sex*trt*resp/cmh; where trt in (0,3) ;

/* Overall trend test */
proc freq data=dta41; tables trt*resp/cmh ;
```