MATH 2625: Biostatistical Methods
Homework 3, due Thursday, February 27

Please submit a PDF or .doc version of your homework to Canvas by 3:30pm on the due date. Please type *all* responses. You are encouraged to use R for all calculations.

Theory

1. Let $y_1, \ldots, y_n$ be realizations from the RVs $Y_i \overset{iid}{\sim} Pois(\mu)$. Using each of the following test constructions, derive a test of the null and alternative hypotheses $H_0 : \mu = \mu_0$ vs $H_A : \mu \neq \mu_0$:

   (a) Score Test

   (b) Likelihood Ratio Test

   The Score Test

2. Suppose we have a sample, $x_1, \ldots, x_n$, from the RVs $X_i \overset{iid}{\sim} Bern(p)$. We wish to build a confidence interval for p but we know, a priori, that the event of interest is rare. For rare outcomes, it is common to use the complimentary log-log transformation: $g(p) = \log\left[-\log(1-p)\right]$. First find a $100(1-\alpha)\%$ CI for $g(p)$. Then, find a $100(1-\alpha)\%$ CI for p itself. State any necessary assumptions.

Case Studies

For the following case studies, create a structured abstract no longer than 4 pages in length (including figures, tables, and references). The Background section is provided for each and should be included in your write-up. You must write the Methods, Results, and Conclusion sections. Code should be included in an appendix as well.

1. Consider a study of a new treatment for multiple sclerosis. Code to construct the relevant tables is alongside this homework in the file `hw3Data.R`. Outcomes of interest are described below.

Background

An evolving understanding of the immunopathogenesis of multiple sclerosis suggests that depleting B cells, a type of white blood cell that produces antibodies, could be useful for treatment. We studied ocrelizumab, a humanized monoclonal antibody treatment that selectively depletes CD20-expressing B cells, in the primary progressive form of the disease. In this trial, we randomly assigned 732 patients with primary progressive multiple sclerosis in a 2:1 ratio to receive intravenous ocrelizumab (600 mg) or placebo every 24 weeks for at least 120 weeks and until a prespecified number of confirmed disability progression events had occurred. Disability progression was defined as an increase in the Expanded Disability Status Scale (EDSS). The primary outcome of interest was the percentage of patients with confirmed disability progression at 12 weeks. As secondary analyses, we are interested in 24-week percent confirmed disability progression as well as the 120-week percent worsened performance on the timed 25-foot walk—-a quantitative score of mobility and leg function.

2. Consider a study of determinants for small cell lung cancer. Code to construct the relevant tables is alongside this homework in the file `hw3Data.R`. Outcomes of interest are described below.

Background

Small cell lung carcinoma, or SCLC, is a highly malignant type of cancer that typically presents in the lungs. Given its tendency to metastasize early, the prognosis is poor with only 10 to 15% of patients surviving three years after diagnosis. Early diagnosis could potentially improve patient prognosis if treatment can be administered before the cancer metastasizes as SCLC does respond well to chemotherapy and radiotherapy in the early stages. The Harvard Lung Cancer Susceptibility Study was a case-control study conducted to identify possible risk factors associated with SCLC. In total, 1000 cases and 1000 controls were recruited, however after drop-out, there 984 cases and 969 controls available for analysis. While a large number of variables were selected, we are primarily interested in assessing the association between case status and two different genetic markers as well as smoking status. The genetic markers are the single nucleotide polymorphisms (SNPs) rs8034191_2 and rs1051730_1 which are found on Chromosome 15 in a region that had previously been identified to contain genes associated with SCLC. We're interested in seeing if either of the two SNPs are associated with SCLC using the appropriate measure of association. At each SNP, there are two possible alleles, A or B. The B allele is considered the risk allele. Subjects can have at most two risk alleles and it is thought that subjects with two risk alleles are at even more risk than those with just one (and those with one are at more risk than those with none). We might also want to see if the environmental factor, smoking status (levels: never, former, current), is associated with presence of SCLC.

Background

An evolving understanding of the immunopathogenesis of multiple sclerosis suggests that depleting B cells, a type of white blood cell that produces antibodies, could be useful for treatment. We studied ocrelizumab, a humanized monoclonal antibody treatment that selectively depletes CD20-expressing B cells, in the primary progressive form of the disease. In this trial, we randomly assigned 732 patients with primary progressive multiple sclerosis in a 2:1 ratio to receive intravenous ocrelizumab (600 mg) or placebo every 24 weeks for at least 120 weeks and until a prespecified number of confirmed disability progression events had occurred. Disability progression was defined as an increase in the Expanded Disability Status Scale (EDSS). The primary outcome of interest was the percentage of patients with confirmed disability progression at 12 weeks. As secondary analyses, we are interested in 24-week percent confirmed disability progression as well as the 120-week percent worsened performance on the timed 25-foot walk—-a quantitative score of mobility and leg function.

Methods

732 patients who were diagnosed with primary progressive multiple sclerosis were randomly selected for participation in this randomized clinical trial. The study was double-blind and placebo-controlled. Subjects were randomly assigned to the treatment or placebo group in a 2:1 ratio. Every 24 weeks, eligible participants were either administered 600 mg of intravenous ocrelizumab or a placebo drug. In total, 488 of the participants received the treatment while 244 received the placebo.

A check-in was conducted at the 12-week mark as well as the 24-week mark to determine whether subjects had undergone disability progression. As a secondary analysis, we also measured subjects' performance on the timed 25-foot walk at the end of the study (120 weeks). No subjects were lost during the 120 week-long trial.

To examine possible association between the ocrelizumab treatment and disability progression, we used a Pearson's Chi-Square test. We also examined the odds ratios to examine the magnitude of association. Progression results were collected at the 12 and 24-week mark, and at 120 weeks, subjects' performance on the 25-foot walk was also measured. All analyses were performed at the nominal level.

Results

12 weeks into the study, we observed that 33.0% of the 488 subjects who were administered the B cell depletion treatment underwent disability progression, while 39.3% of the 244 subjects who received the placebo also underwent disability progression. A more detailed summary of the findings is available in Table 1. At the 12-week mark, there was no significant difference in disability progression between those who received the ocrelizumab treatment and those who received the placebo ($p = 0.106, \chi^2 = 2.609, df = 1, N = 732$). While we observed within the trial that the odds of disability progression for patients who received ocrelizumab was 24.1% lower than patients who only received a placebo, these results were not statistically significant (OR = 0.76, 95% CI: [0.552, 1.044]).

Table 1: **Disability Progression After 12 Weeks by Treatment**

Treatment	Disability Progression	No Progression	Total
Ocrelizumab	161	327	488
Placebo	96	148	244
Totals	257	475	732

At the 24-week mark, we observed a disability progression in just 24.5% of the 488 subjects who received ocrelizumab. This is in comparison to 55.4% of the 157 receiving a placebo, as shown in Table 2. However, we did not find a significant association between receiving the ocrelizumab treatment and a lowered disability progression ($p = 0.109, \chi^2 = 2.569, df = 1, N = 732$). Despite the observed odds in the study of having a disability progression being 24.5% lower in patients receiving immunosuppression than in patients receiving the placebo, this observation was not statistically significant (OR = 0.755, 95% CI: [0.545, 1.047]).

Table 2: **Disability Progression After 24 Weeks by Treatment**

Treatment	Disability Progression	No Progression	Total
Ocrelizumab	144	344	488
Placebo	87	157	244
Totals	231	501	732

At the end of the study period, we found worsened 25-foot walk performance in 38.9% of the participants receiving ocrelizumab, while 55.3% of the control group had a worsened 25-foot walk. Further information is also available in Table 3. We found that in 120 weeks, patients who received ocrelizumab were significantly less likely to have worsened mobility. The subjects who were administered ocrelizumab were less likely to have a worsened 25-foot walk performance ($p < 0.0001, \chi^2 = 17.051, df = 1, N = 732$). Among the participants, the odds of having a worsened 25-foot walk performance were 48.5% lower among subjects receiving ocrelizumab than subjects receiving the placebo (OR = 0.515, 95% CI: [0.377, 0.703]).

Table 3: **Worsened Performance on 25-Foot Walk by Treatment**

Treatment	Worsened	Did not Worsen	Total
Ocrelizumab	190	298	488
Placebo	135	109	244
Totals	325	407	732