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by

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**ABSTRACT**

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**CHAPTER I**

**INTRODUCTION**

**Research Objectives**

Our project aims to apply logistic regression mixed models with ordinal and binary outcomes to non-tuberculous mycobacterial lung disease (NTM-LD) data. The modeling approaches take inspiration from a previous study done on a preliminary NTM-LD data set but incorporates more complex modeling choices and methods for handling different aspects of the data. The primary research question we will explore is “are there differences in the frequencies and severities for each of the specific CT features among the lung lobes in NTM-LD?” Answering this question will pave the way to more targeted treatment of NTM-LD and serve as evidence for lifestyle and treatment choices that those with NTM-LD and their healthcare providers should consider in the treatment of this disease.

**Introduction to Non-Tuberculous Mycobacterial Lung Disease**

Non-tuberculous mycobacteria (NTM) are a group of microbial organisms with about 200 species that are related to Mycobacterium tuberculosis and Mycobacterium leprae, the etiologic agents of tuberculosis and leprosy (Matsumoto et al., 2019). NTM lung disease (NTM-LD) is a chronic infection of the lungs and is the most common of the NTM infections. It is most often caused by Mycobacterium avium complex, Mycobacterium abscessus group, and Mycobacterium kansasii (Gopalaswamy et al., 2020). Infection most often occurs through the inhalation or aspiration of aerosolized soil, water, or biofilms that harbor NTM (Miller, 1994). Although NTM organisms are ubiquitous in the environment, most individuals do not develop NTM-LD through exposure. NTM-LD primarily develops in those with predisposing lung conditions or compromised immune function, such as the elderly (Miller, 1994; Erasmus et al., 1999). Individuals with severe immunocompromised states often develop disseminated NTM disease rather than isolated NTM-LD (Liu et al., 2021).

There are two main radiographic manifestations of NTM-LD: a fibrocavitary form characterized by opacification and cavitation of the upper lobes seen mostly in men with underlying emphysema and a nodular bronchiectasis form characterized by nodules and bronchiectasis that commonly affects the right middle lobe and lingula. Depending on the cohort studied, this form may be more frequently seen in women (Miller, 1994).

Erasmus et al. (1999) noted that the disease manifests in a number of radiologic patterns, including consolidation, cavitation, nodules, and bronchiectasis. In the existing literature, the severity and frequency of the disease tends to favor some parts of the lung more than others for some studies, while this was not observed in others.

For example, Reich and Johnson (1992) studied a group of 29 patients with Mycobacterium avium complex pulmonary disease and identified 6 elderly women from this group without predisposing pulmonary conditions with previously unexplained patterns of with a greater predisposition in the lingula and right middle lobe. They hypothesized that suppression of cough in these women may have led to the development of disease in these regions, using the term “Lady Windermere syndrome” to describe the pattern (Reich & Johnson, 1992). Moore et al. (1993) examined 40 culture-positive NTM patients and scored ten lung zones on a 3-point scale (mild, moderate, severe) for bronchiectasis, air-space disease, and nodules. Bronchiectasis was most pronounced in the right middle lobe and lingula, whereas nodules were evenly distributed. Hazelton et al. (2000) reported CT findings in 14 patients with Mycobacterium chelonae. Two radiologists used consensus scoring; bronchiectasis and nodules were present in 13/14 cases but were diffusely distributed across lobes for the most part. Two of these patients, however, did present with more severe bronchiectasis in the right middle lobe and lingula. Lee et al. (2013) compared 369 immunocompromised versus immunocompetent patients. Three radiologists rated each lobe on a 5-point severity scale for lesions with lobar scores summed per patient, and scored bronchiectasis by determining its severity and extent and multiplying these values. Group differences were tested with paired t-tests to compare the groups and found that immunocompromised patients had significantly more nodules and cavities. For bronchiectasis, the top three most affected lobes for immunocompromised patients were the right middle lobe, left upper lobe, and lingula, while the top three most affected lobes for immunocompetent patients were the right upper lobe, right middle lobe, and lingula.

**Statistical Background**

**Ordinal Logistic Regression**

Ordinal logistic regression allows for the analysis of ordinal outcomes, which are responses that fall into ordered categories (e.g., “no disease”, “mild disease”, “moderate disease”, and “severe disease”). A seminal example of an ordinal logistic regression model is the proportional odds model described by McCullagh (1980). Let be our ordinal variable of interest with ordered categories labeled , and let be the cumulative probability of falling in category or below, given covariates . The proportional odds assumption says that the cumulative odds follow:

where is a category-specific intercept or threshold and is a vector of regression coefficients common across categories. The model ensures through using the same for all cut points that comparing with depends only on and not on , the main idea of the proportional-odds framework. Put more simply, under the proportional odds assumption, the regression coefficients corresponding to our covariates is assumed to be equal across category thresholds. This means that the effect of the covariates on the odds of being at or below a particular category is constant, regardless of the threshold considered.

McCullagh’s model can be further extended to include random effects to account for within-cluster or within-subject correlation. Hedeker and Gibbons (1994) provide a multilevel formulation of an ordinal logistic regression model, where repeated observations are nested within higher-level units ; e.g. subjects or clusters). The repeated, individual observations are referred to as level-1, while the subjects are referred to as level-2. The representation of this ordinal logistic regression model is as follows:

where is the unobserved latent response strength for the observation in level-2 unit , are predictors whose effects vary by subject or cluster (i.e. the random effects), are predictors whose effects are constant across subjects (i.e. fixed effects), and is the residual error. We assume that follows a multivariate normal distribution with mean vector and covariance . This mapping of onto ordinal categories through multiple thresholds allows the model to extend the standard ordinal logistic regression framework while accounting for correlation in repeated measures per subject. This modeling approach reflects the expected heterogeneity across units and allows for more accurate inference to be made with data containing repeated measures or nested structures present in the data.

Agresti (2010) gives another interpretation of a random-intercept ordinal model with cluster-specific (i.e. subject specific) random effects, given by:

where is the ordinal response for observation in cluster , is the random effect for cluster , is the category-specific threshold, are the values of explanatory variables for observation in cluster , with corresponding beta coefficients . Here follows a normal distribution with variance , which describes how individual intercepts scatter around the population-average intercept. Including in the model addresses the fact that responses within the same cluster (e.g. repeated measures within the same subject) tend to be more similar than responses from different clusters. Agresti (2010) further notes that subjects with large positive tend to be more likely to fall into the upper categories of the ordinal scale, where the converse (subjects with negative tend to be in lower ordinal categories) also tends to be the case. The above approach outlined by Agresti aligns with the multilevel framework outlined by Hedeker and Gibbons (1994), where the random intercepts provide a subject-level shift of the ordinal cut points, which accounts for within-cluster correlation.

In a given proportional-odds model, a positive coefficient for a categorical predictor (e.g., a specific lung lobe compared to a reference lobe) indicates that observations in this category have higher odds of belonging to the more severe ordinal outcome category compared to the reference category. We also have that represents the odds ratio for being in outcome category or above. As an example, if we have that , then , meaning the odds of being in a higher ordinal outcome category multiply by 1.65 when an observation falls in that category of . The converse is also true; a negative implies that the category has lower probability of being in the higher-severity ordinal outcome levels. As the proportional-odds assumption uses one slope across all category cut points, the odds-ratio interpretation is the same across each cumulative split of the ordinal scale.

For our study’s ordinal outcomes, subjects’ disease severity is grouped into four ordered categories: “0” indicating no presence of the specified CT feature of interest in the given lobe, “1” indicating less than 25% involvement of the given lobe with the CT feature of interest, “2” indicating between 25 and 50% involvement of the given lobe with the CT feature of interest, and “3” indicating more than 50% involvement of the given lobe with the CT feature of interest. Fitting a proportional-odds model to our data allows us to capture how predictor variables (in our case, which lobe of the lung and which rater is assessing it) affect the likelihood of moving into more severe disease categories. For example, a significant positive coefficient on a specific lobe would indicate that this lobe is associated with a higher probability of falling into more severe disease categories relative to other lobes.

**Logistic Regression**

In contrast with ordinal logistic regression, which involves the analysis of ordinal outcomes, standard logistic regression is concerned with the analysis of dichotomous, or two-level, outcomes (e.g. “Yes or No” or “0 or 1”). Logistic regression models can be understood and expressed in the form laid out by Hosmer et al. (2013): Let be a binary outcome taking values 0 or 1, and let be the probability , where x is a vector of predictor variables. For logistic regression, we let:

which constrains to remain in the interval (0,1) for all values of . Through taking the logit transformation, given by:

we get a linear relationship with the parameters . This is conceptually like standard linear regression, but the outcome now follows a Bernoulli, rather than a normal, distribution.

Also by Hosmer et al. (2013), we know that follows a binomial process with mean , and as we stated before that , we also have that . Since for , we thus have that that which depends on , unlike with linear regression. We typically estimate parameters through maximum likelihood methods, providing coefficient estimates … which maximize the probability of the observed data under the logistic model.

Similar to our random-effects extensions to ordinal logistic models, binary logistic regression can also include random effects to account for unobserved heterogeneity or within-cluster correlation. As outlined by Larsen et al. (2000), let be our binary outcome and . A logistic regression model that incorporates random effects would thus be of the form:

with representing the fixed-effect parameters, the row of the design matrix for the fixed effects, the random effects that are normally distributed with mean 0 and variance matrix , and the row of the design matrix for the random effects. Through incorporating these random effects into our logistic regression model, we can account for correlation among observations that share the same higher-level grouping structure, like repeated measures within individuals or subjects nested within clusters. The random effects capture unobserved heterogeneity across these groups, allowing the model to adjust the log-odds of the outcome based on group-specific deviations from the population-average relationship defined by the fixed effects .

**CHAPTER II**

**METHODS**

**Data**

Our dataset is comprised of data from lung CT images from 166 patients with NTM-LD. These patients were referred to this study conducted by National Jewish Health by their primary care physicians. Each subject’s lung CT images were assessed by two radiologists who were blind to each other’s ratings. Lung CT images were rated according to the presence of 8 radiologic features associated with NTM-LD in the CT images. These 8 features include tree-in-bud opacities, large nodules, ground-glass opacities, consolidation, bronchiectasis, atelectasis, and thin and thick wall cavities.

The following are definitions for each of these features provided by Hansell et al. (2008). Tree-in-bud opacities are small branching nodular opacities that look like a budding tree in lung CT images and are a result of mucous impaction and inflammation. Nodules are round opacities measuring up to 3 centimeters in diameter. For the purposes of our study, we consider large nodules to be nodules greater than 1 centimeter in diameter. Ground-glass opacities appear as hazy opacities in CT images of the lung and are caused by fluid in the airspaces of the lungs or thickening of lung tissue. Consolidation, which appears opaquer than ground-glass opacities on CT images, refers to the condition of the lung being rendered solid because of fluid or other disease byproduct replacing the alveolar air of the lungs. Bronchiectasis refers to permanent dilation of the bronchi, or airways, resulting from infection, obstruction, or congenital abnormalities. This can be identified in CT scans from the widening and lack of tapering of bronchi. Atelectasis is the collapse or reduction in inflation of all or part of the lung and is identified in scans through a reduction in volume and increase in opacity. Cavities are gas-filled spaces within areas of consolidation, masses, or nodules. Example CT images for each of these features can be found in Appendix A Figures (Hansell et al., 2008).

For each subject, 6 regions of the lungs were assessed for these features: the right upper lobe (RUL), right middle lobe (RML), right lower lobe (RLL), left upper segment (LUS), left lingular segment (LLS), and left lower lobe (LLL), with the left upper lobe divided into the LUS and LLS per what is standard in the literature for the study of NTM-LD (Hazelton et al., 2000; Lee et al., 2013). We refer to these 6 regions as “lobes” for the remainder of the paper. The raters scored each of the subject’s 6 lobes separately according to the involvement of the feature present in the given lobe. 5 of the features (tree-in-bud opacities, ground-glass opacities, consolidation, bronchiectasis, and atelectasis) were assigned an ordinal score of 0 through 3 for each lobe, with 0 indicating no involvement of the feature in the given lobe, 1 indicating involvement of less than 25% of the given lobe with the feature, 2 indicating involvement of between 25 and 50% of the given lobe with the feature, and 3 indicating more than half of the lobe’s involvement with the feature. The other 3 features (large nodules, thin wall cavities, and thick wall cavities) were assigned a binary score of 0 or 1, with 0 indicating the absence of the feature in the given lobe, and 1 indicating its presence. With 6 lobes scored for each subject and 2 different raters performing the scoring, there are 12 repeated measures per subject for each feature.

The data was provided by the lead pulmonologist of the study in the form of an Excel document, with separate sheets for each of the two radiologist’s scores. Data was arranged in wide format, with each subject’s scores provided in a single row and lobes as columns, with every group of 6 columns representing the scores for a new feature. Minimal data cleaning was performed, including steps to assign each subject with a new ID to deidentify the data and convert the data to long format (making a new row within each subject for each of the 6 lobes) for ease of modeling purposes.

**Modeling**

Our approach to modeling the data for this study was inspired by statistical analyses performed in a pilot study of this data with 71 subjects. In this pilot study, features with ordinal outcomes were modeled using ordinal logistic regression mixed models with a cumulative logit link and random intercepts for subjects. Similarly, features with binary outcomes were modeled using logistic regression mixed models with a logit link and random intercepts for subjects. In the pilot study, a consensus score was achieved between the two raters, meaning only one set of scores was analyzed. In our study, however, we include rater as a variable for our modeling and retain both sets of raters’ scores for our analysis.

**Features with Ordinal Outcomes**

For the features with ordinal outcomes (tree-in-bud opacities, ground-glass opacities, consolidation, bronchiectasis, and atelectasis), we modeled using three approaches. The first approach, which we refer to as our full model, used an ordinal logistic regression mixed modeling approach, with ordinal score as the outcome, lobe and rater as fixed effects, a random intercept for subject, a nested random effect for rater within subject, and a cumulative logit link function. In a similar way to Hedeker and Gibbons (1994), we can express this model using statistical modeling notation as follows. Let be subject, be lobe, be rater, and be the cut-points between the ordinal categories. Our statistical model can thus be expressed as:

,

where is the cut-point-dependent intercept, is the random intercept for subject with , and is the nested random effect for rater within subject with .

Our second modeling approach, which we refer to as our reduced model, again used an ordinal logistic regression mixed modeling approach, with ordinal score as the outcome, lobe and rater as fixed effects, a random intercept for subject, with a cumulative logit link function, but without a nested random effect for rater within subject. In a similar way to Agresti (2010), we can express this model using statistical modeling notation as follows. Let be subject, be lobe, be rater, and be the cut-points between the ordinal categories. Our statistical model can thus be expressed as:

,

where is the cut-point-dependent intercept and is the random intercept for subject with . This reduced approach was taken primarily for the features where the full model did not converge due to the complex random effects structure. We also fit this reduced model for the features where the full model did converge as a means of sensitivity analysis to check if the simpler random effects structure changes the model estimate for the effect of lobe, which is our main estimate of interest in addressing the research question.

Our third modeling approach sought to relax the proportional odds assumption outlined by McCullagh (1980) that the other two modeling approaches abide by, thereby allowing the effect of lobe to differ across the category thresholds. We again modeled this using an ordinal logistic regression mixed modeling approach, with ordinal score as the outcome, lobe and rater as fixed effects that we allowed to differ across the category thresholds, a random intercept for subject, and a cumulative logit link function. We can express this model using statistical notation similar to that outlined by Lin et al. (2021). Let be subject, be lobe, be rater, and be the cut-points between the ordinal categories. Our statistical model can thus be expressed as:

,

where is the cut-point-dependent intercept, is the cut-point-dependent coefficient vector for lobe, is the cut-point-dependent coefficient vector for rater, and is the random intercept for subject with .

**Features with Binary Outcomes**

For the features with binary outcomes (large nodules, thin wall cavities, and thick wall cavities), we modeled using two approaches. The first approach, which we refer to as our full model, used a logistic regression mixed modeling approach, with binary score as the outcome, lobe and rater as fixed effects, a random intercept for subject, a nested random effect for rater within subject, and a logit link function. In a similar way to Larsen et al. (2000), we can express this model using statistical modeling notation as follows. Let be subject, be lobe, and be rater. Our statistical model can thus be expressed as:

,

where is the random intercept for subject with , and is the nested random effect for rater within subject with .

Our second modeling approach, which we refer to as our reduced model, again used a logistic regression mixed modeling approach, with binary score as the outcome, lobe and rater as fixed effects, a random intercept for subject, with a logit link function, but without a nested random effect for rater within subject. Again by Larsen et al. (2000), we can express this model using statistical modeling notation as follows. Let be subject, be lobe, be rater, and be the cut-points between the ordinal categories. Our statistical model can thus be expressed as:

,

where is the cut-point-dependent intercept and is the random intercept for subject with . This reduced approach, like in the ordinal features case, was taken primarily for the binary features where the full model did not converge due to the complex random effects structure. We also fit this reduced model for the features where the full model did converge as a means of sensitivity analysis to check if the simpler random effects structure changes the model estimate for the effect of lobe, which is our main estimate of interest in addressing the research question.

**Estimation Method**

Estimation of the model parameters in all our above generalized linear mixed models was performed through the adaptive Gaussian quadrature method. In the case of generalized linear mixed models, the likelihood function cannot be expressed in closed form due to the presence of random effects. These random effects must be integrated out to achieve the marginal likelihood, since the random effects are non-observable values, and this integral with respect to the random effect is what makes the likelihood estimation an intractable problem. Adaptive Gaussian quadrature is a method of numerical integration that approximates this marginal likelihood by evaluating the integrand at a set of abscissas (quadrature points) and summing weighted values of the integrand at these points (Pinheiro & Chao, 2006). This approximation can be expressed as follows:

where is a probability density function, is a function integrated against it, is the number of quadrature points, are the weights, and are the abscissas. In standard Gaussian quadrature, the integrand, and thus the placement of abscissas, is assumed to be centered at zero and symmetric. Adaptive Gaussian quadrature improves upon this by centering and scaling the placement of abscissas depending on the density function of the random effects (Capanu et al., 2013).

**Comparison of Model Fit**

To assess how well each of the modeling approaches fits our data, we calculated the Akaike Information Criterion (AIC), given by:

,

where is the maximum likelihood of the model given the data evaluated at the estimated parameters, and is the total number of estimated parameters. AIC offers a balanced view of the model between goodness of fit and model complexity, as the term penalizes models with more parameters to avoid overfitting (Burnham & Anderson, 2004).

**Software Used**

The non-proportional odds model for our ordinal features were fit and all analyses for this model was performed in R Version 4.4.2 using the clmm2 function. All other full and reduced models were fit in SAS Version 9.4 using the GLIMMIX procedure, along with all analysis performed for these models.

**Comparisons Between Lobes**

**Features with Ordinal Outcomes**

To address the research question of if there are differences in the frequencies and severities for each of the specific CT features among the lung lobes in NTM-LD, we constructed pairwise contrasts of the fixed-effect estimates for the lobe variable in our models using “estimate” statements for our models fit in SAS and the emmeans function for our R model. As our ordinal logistic regression models compare lower levels to higher levels by default (in other words, lower disease severity to higher disease severity), we first flipped the signs on these estimates before calculating the contrasts to get the comparisons in the other direction. We then exponentiated the results of these contrasts to get the odds ratios of being in a higher disease severity category between the lobes. Confidence intervals for these odds ratios were calculated by exponentiating the Wald 95% confidence limits produced by GLIMMIX. Need to include how we did it for the R model as well

For the non-proportional odds model, which produces three fixed-effect estimates for the 5 non-reference lobes (one for each severity cut-point), pairwise contrasts were constructed between each of these estimates.

**Features with Binary Outcomes**

Similar to the features with ordinal outcomes, we performed lobe-specific analyses for those with binary outcomes. Pairwise contrasts were constructed for each of the estimates for the lobe variable in our models. Unlike with our ordinal logistic regression models, we did not flip the signs on these estimates before constructing the contrasts. Confidence intervals for these odds ratios were again calculated by exponentiating the Wald 95% confidence limits produced by GLIMMIX.

**Multiple Testing Correction**

As there are 6 lobes we are performing pairwise contrasts for, there are 15 unique pairwise contrasts performed in total for the models with a single fixed-effect estimate for the lobe variable and 45 (need to verify this number) unique pairwise contrasts performed in total for the non-proportional odds model with 3 fixed-effect estimates for the lobe variable. In order to correct for these multiple tests, we used the False Discovery Rate (FDR) multiple testing correction approach outlined by Benjamini and Hochberg and provided below.

Suppose we test hypotheses based on corresponding p-values , let be the ordered p-values, and let be the null hypothesis corresponding to . For independent test statistics, the following procedure controls the FDR at : let be the largest for which , then reject all (Benjamini & Hochberg, 1995).

As we are evaluating these tests at a nominal significance threshold of , our FDR-corrected p-values are thus , and hypotheses with were determined to be significant.