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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.

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.

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. Although ground-glass opacities was assigned a binary score, it exhibited sparseness in the “2” and “3” categories. To facilitate stable model estimation, this feature was dichotomized into a binary variable, with 0 representing no involvement in the given lobe, and 1 indicating involvement in the lobe (i.e. the “1”, “2”, and “3” categories were collapsed into the “1” binary score). 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.

For the features with ordinal outcomes (tree-in-bud 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 i=1,…,166 be subject, j=RUL,…,LLL be lobe, k=JW,VH be rater, and l=1,2,3 be the cut-points between the ordinal categories. Our statistical model can thus be expressed as:

λ\_ijkl= logit(P(Score\_ijk≤l))=α\_l+β\_1 (lobe\_j )+β\_2 (rater\_k )+b\_i+b\_k(i) ,

where α\_l is the cut-point-dependent intercept, b\_i is the random intercept for subject with b\_i∼N(0,σ\_subject^2), and b\_k(i) is the nested random effect for rater within subject with b\_k(i) ∼N(0,σ\_rater^2).

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 i=1,…,166 be subject, j=RUL,…,LLL be lobe, k=JW,VH be rater, and l=1,2,3 be the cut-points between the ordinal categories. Our statistical model can thus be expressed as:

λ\_ijkl= logit(P(Score\_ijk≤l))=α\_l+β\_1 (lobe\_j )+β\_2 (rater\_k )+b\_i,

where α\_l is the cut-point-dependent intercept and b\_i is the random intercept for subject with b\_i∼N(0,σ\_subject^2). 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 i=1,…,166 be subject, j=RUL,…,LLL be lobe, k=JW,VH be rater, and l=1,2,3 be the cut-points between the ordinal categories. Our statistical model can thus be expressed as:

λ\_ijkl= logit(P(Score\_ijk≤l))=α\_l+β\_1l (lobe\_j )+β\_2l (rater\_k )+b\_i,

where α\_l is the cut-point-dependent intercept, β\_1l is the cut-point-dependent coefficient vector for lobe, β\_2l is the cut-point-dependent coefficient vector for rater, and b\_i is the random intercept for subject with b\_i∼N(0,σ\_subject^2).

For the features with binary outcomes (ground-glass opacities, 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 i=1,…,166 be subject, j=RUL,…,LLL be lobe, and k=JW,VH be rater. Our statistical model can thus be expressed as:

λ\_ijk= logit(P(Score\_ijk=1))=β\_0+β\_1 (lobe\_j )+β\_2 (rater\_k )+b\_i+b\_k(i) ,

where b\_i is the random intercept for subject with b\_i∼N(0,σ\_subject^2), and b\_k(i) is the nested random effect for rater within subject with b\_k(i) ∼N(0,σ\_rater^2).

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 i=1,…,166 be subject, j=RUL,…,LLL be lobe, k=JW,VH be rater, and l=1,2,3 be the cut-points between the ordinal categories. Our statistical model can thus be expressed as:

λ\_ijk= logit(P(Score\_ijk=1))=β\_0+β\_1 (lobe\_j )+β\_2 (rater\_k )+b\_i+b\_k(i) ,

where α\_l is the cut-point-dependent intercept and b\_i is the random intercept for subject with b\_i∼N(0,σ\_subject^2). 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.

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 proportional odds models fit in SAS. 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.

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 the lobes within each cut-point, again by subtracting the corresponding log-odds estimates. Standard errors were determined through the model’s variance-covariance matrix, Wald 95% confidence intervals were formed, and resulting estimates were exponentiated to yield values on the odds scale.

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