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# Predictive Identification of Individuals At Risk for Nontuberculous Mycobacterial Lung Disease From a Non–Cystic Fibrosis Bronchiectasis Cohort

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M. Mirsaeidi[1], Q. Zhang[2], E.D. Chan[3], C. Vinnard[4], E. Chou[2], G. Eagle[2], M. Leuchars[2], R. Zhang[5], T.K. Marras[6]

[1]Miller School of Medicine, University of Miami, Miami, FL, United States; [2]Insmed Incorporated, Bridgewater, NJ, United States; [3]National Jewish Health, Denver, CO, United States; [4]Rutgers, The State University of New Jersey, Newark, NJ, United States; [5]Orbis Data Solutions, Woburn, MA, United States; [6]University of Toronto and Toronto Western Hospital, Toronto, ON, Canada

## BACKGROUND

- Nontuberculous mycobacterial lung disease (NTMLD) is associated with a substantial clinical burden, including structural lung damage, decreased lung function,[1] increased risk of respiratory failure,[2] and increased mortality[3]
- Structural lung damage manifested by bronchiectasis may render patients more susceptible to NTMLD and can complicate the evaluation of NTMLD[4]
  - Delay in diagnosis or misdiagnosis of NTMLD may lead to disease progression and structural lung damage, which could increase its associated mortality risk and economic burden
- Proactive identification of patients with bronchiectasis who have an increased risk for NTMLD could facilitate timely management of this disease
  - Beyond well-known risk factors such cystic fibrosis (CF) and emphysema, both of which are associated with bronchiectasis, other risk factors for NTMLD in the bronchiectasis population are not as well established

## OBJECTIVE

- To develop a predictive algorithm for individuals at risk for NTMLD from an incident cohort of patients with non-CF bronchiectasis.

## METHODS

### Incident bronchiectasis cohort

- A non-CF, HIV-negative bronchiectasis incident cohort was identified from a large United States national managed care database
  - Baseline patient characteristics were extracted from medical and pharmacy insurance claims during the year prior to first bronchiectasis diagnosis
  - NTMLD risk was assessed based on patient demographics, comorbidities, and use of immunosuppressants using a Cox regression model

### Training, testing, and application cohorts

- Three individual cohorts were randomly selected to develop, test, and apply a predictive algorithm for NTMLD risk identification (**Box 1**)

### Box 1

**Training cohort:** 176 NTMLD patients out of 5264 people with bronchiectasis

**Testing cohort:** 174 NTMLD patients out of 5265 people with bronchiectasis

**Application cohort:** 4462 people with bronchiectasis without known NTMLD diagnosis

- The training cohort was used to develop the NTMLD risk algorithm using logistic regression with Firth correction to adapt for rare diseases
- This algorithm was then validated in the testing cohort and a receiver operating characteristic (ROC) curve was generated to allow selection of an optimal cut-off point for risk prediction based on the following:
  - The balance of sensitivity and specificity to enable a greater proportion of correct identification of true NTMLD patients while avoiding false positives
  - Cost consequences of each potential cut-off point (**Box 2**)
  - Potential cut-off points were defined according to predicted probability of NTMLD estimated from the training model and validated using the testing model

### Box 2

**Hypothetical Cost Scenario*†**

Total cost = (false negatives x $25,000) + (true positives x $14,000) + (false positives x $500)

**False negatives** (undiagnosed NTMLD): hypothetical yearly cost assumed to be $25,000 including the cost of disease, but not treatment

**True positives** (correctly diagnosed with NTMLD): hypothetical yearly cost assumed to be $14,000 including disease, treatment, and potential improvement in outcomes

**False positives** (incorrectly diagnosed with NTMLD): hypothetical cost associated with diagnosis assumed to be $500, including follow-up testing and office visits

**True negatives** (correctly diagnosed with no NTMLD): assumed to have no cost consequences (not included in the formula)

*Constructed to illustrate the plausibility of cost implications being factored into the decision-making process to identify at-risk individuals (Cost implications refer to potential healthcare cost by the payer and patients as a result of true-positives, true-negative, false-positive, and false-negative identification of an individual).

†All costs in formula are nominal.

### Risk identification

- The validated predictive algorithm was applied to the application cohort to estimate the number of at-risk non-CF bronchiectasis patients who have not been diagnosed with NTMLD

## RESULTS

- The overall non-CF bronchiectasis sample (N=14,886) had a mean age of 65±18.5 years; 63% were women, 37% were using an immunosuppressive agent, and the mean Charlson Comorbidity Index (CCI) score was 1.5 (**Table 1**)

### Table 1. Baseline Characteristics of 14,886 HIV-negative Non-CF Bronchiectasis Patients

| Baseline Variables | NTMLD n=350 | Non-NTMLD n=14,536 |
|---|---|---|
| Age, years; mean (SD) | 68 (12.8) | 65 (17.7) |
| Female | 83 (292) | 63 (9126) |
| CCI; mean (SD) | 1.0 (1.8) | 1.5 (2.2) |
| Asthma | 15.7 (56) | 18.3 (2663) |
| Atherosclerosis | 3.4 (12) | 6.0 (873) |
| Arrhythmia | 15.7 (56) | 17.2 (2498) |
| Coronary artery disease | 10.3 (36) | 15.0 (2187) |
| Cancer | 12.0 (42) | 18.0 (2611) |
| Congestive heart failure | 3.1 (12) | 9.0 (1309) |
| Diabetes | 10.6 (38) | 20.2 (2943) |
| Gastroesophageal reflux disease | 18.0 (63) | 21.5 (3130) |
| Heart valve disease | 9.7 (35) | 12.5 (1824) |
| Hyperlipidemia | 41.1 (145) | 50.0 (7256) |
| Hypertension | 40.9 (143) | 51.9 (7544) |
| Immunosuppressive drug use* | 43.1 (152) | 41.2 (5991) |
| Inhaled corticosteroids | 17.1 (61) | 17.3 (2516) |
| Systemic corticosteroids | 36.3 (127) | 34.5 (5011) |
| Mental disorders† | 14.6 (52) | 16.4 (2379) |
| Metastatic carcinoma | 2.0 (7) | 4.3 (628) |
| Moderate or severe liver disease | 1.4 (5) | 0.50 (73) |
| Myocardial infarction | 1.4 (5) | 3.7 (533) |
| Obesity | 1.1 (5) | 6.9 (1011) |
| Organ transplant (solid) | 0.29 (1) | 0.62 (90) |
| Pectus excavatum | 0 (0) | 0.12 (18) |
| Pneumonia | 25.7 (91) | 19.5 (2834) |
| Rheumatological disease | 5.4 (19) | 4.8 (702) |
| Tuberculosis | 1.4 (5) | 0.34 (50) |

Data presented as % (n) unless otherwise noted.
CCI, Charlson Comorbidity Index; SD, standard deviation.
*Beyond corticosteroids, other immunosuppressants in the NTMLD and non-NTMLD patients included methotrexate (2.6% and 1.8%, respectively), tumor necrosis factor-alpha blockers (0.29% and 0.77%, respectively), and miscellaneous immunosuppressants (3.7% and 3.4%, respectively).
†Encompasses International Classification of Diseases, 9th revision (ICD9) codes 290-299 and 310-319.

### Table 2. Risk Factors for NTMLD (Cox Model Based on Overall Sample)*

| Risk Factor | Hazard Ratio | 95% CI | *P*-value |
|---|---|---|---|
| Age | 1.2 | 1.1, 1.2 | <0.001 |
| Female gender | 2.6 | 2.0, 3.5 | <0.001 |
| CCI | 0.90 | 0.83, 0.97 | 0.037 |
| Congestive heart failure | 0.46 | 0.25, 0.87 | 0.016 |
| Diabetes | 0.65 | 0.46, 0.93 | 0.019 |
| Hypertension | 0.69 | 0.54, 0.87 | 0.002 |
| Moderate or severe liver disease | 7.0 | 2.7, 18.1 | <0.001 |
| Obesity | 0.23 | 0.08, 0.61 | 0.003 |
| Pneumonia | 1.6 | 1.3, 2.0 | <0.001 |

CCI, Charlson Comorbidity Index.
*In the overall bronchiectasis sample, increasing age, female gender, moderate or severe liver disease, and pneumonia were associated with increased NTMLD risk, while CCI, congestive heart failure, diabetes, hypertension, and obesity were associated with decreased NTMLD risk.

### Table 3. Baseline Characteristics of Training, Testing, and Application Cohorts

| Baseline Variables | Training Cohort n=5264 | Testing Cohort n=5265 | Application Cohort n=4462 |
|---|---|---|---|
| Age, years; mean (SD) | 66 (17.7) | 65 (17.9) | 64 (18.1) |
| Female | 62% (3263) | 64% (3362) | 64% (2836) |
| CCI; mean (SD) | 1.5 (2.2) | 1.5 (2.2) | 1.5 (2.2) |
| Asthma | 18.4 (967) | 18.3 (961) | 18.3 (816) |
| Atherosclerosis | 5.8 (307) | 6.1 (323) | 5.7 (257) |
| Arrhythmia | 17.1 (903) | 16.8 (883) | 17.3 (774) |
| Coronary artery disease | 14.4 (759) | 14.5 (761) | 15.8 (706) |
| Cancer | 17.5 (921) | 17.6 (926) | 18.2 (812) |
| Congestive heart failure | 8.8 (465) | 8.4 (445) | 9.3 (414) |
| Diabetes | 21.0 (1108) | 19.1 (1008) | 20.0 (895) |
| GERD | 21.2 (1117) | 21.2 (1119) | 22.0 (981) |
| Heart valve disease | 12.1 (636) | 12.8 (675) | 12.4 (552) |
| Hyperlipidemia | 49.2 (2591) | 49.8 (2622) | 49.2 (2198) |
| Hypertension | 51.2 (2697) | 51.4 (2707) | 51.5 (2299) |
| Immune system diseases | 3.3 (174) | 3.0 (156) | 3.2 (144) |
| Immunosuppressive drug use* | 41.3 (2176) | 41.4 (2178) | 41.3 (1844) |
| Inhaled corticosteroids | 17.5 (923) | 17.5 (919) | 17.4 (779) |
| Systemic corticosteroids | 34.6 (1822) | 34.5 (1817) | 34.6 (1547) |
| Mental disorder† | 16.3 (858) | 16.5 (871) | 16.2 (722) |
| Metastatic carcinoma | 4.3 (227) | 4.3 (230) | 4.0 (178) |
| Moderate or severe liver disease | 0.51 (28) | 0.47 (25) | 0.58 (27) |
| Myocardial infarction | 3.6 (190) | 3.4 (179) | 3.8 (171) |
| Obesity | 6.7 (354) | 7.0 (370) | 6.6 (293) |
| Organ transplant (solid) | 0.47 (25) | 0.72 (39) | 0.69 (32) |
| Pectus excavatum | 0.15 (9) | 0.13 (7) | 0.07 (3) |
| Pneumonia | 19.7 (1039) | 20.0 (1053) | 19.4 (866) |
| Rheumatological disease | 4.9 (259) | 4.9 (257) | 4.7 (209) |
| Tuberculosis | 0.38 (21) | 0.40 (21) | 0.34 (15) |

Data presented as n (%) unless otherwise noted.
CCI, Charlson Comorbidity Index; ~~CI, confidence interval;~~ GERD, gastroesophageal reflux disease; SD, standard deviation.
*Beyond corticosteroids, other immunosuppressants in the training, testing, and application cohorts included methotrexate (1.7%, 1.9% and 2.0%, respectively), TNF blockers (0.78%, 0.76%, and 0.74%, respectively), and miscellaneous immunosuppressants (3.6%, 3.2%, and 3.3%, respectively).
†Encompasses International Classification of Diseases, 9th revision (ICD9) codes 290-299 and 310-319.

### Table 4. Predictive Results from the Final Training Model

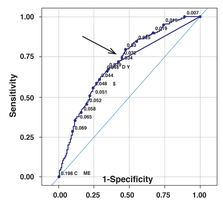
| Odds Ratio Estimates | | | |
|---|---|---|---|
| Effect | Point Estimate | 95% CI | *P*-value |
| Age | 1.03 | 1.01, 1.04 | <0.001 |
| Female gender | 2.26 | 1.55, 3.29 | <0.001 |
| CCI | 0.92 | 0.84, 1.01 | 0.08 |
| Pneumonia | 1.35 | 0.94, 1.93 | 0.10 |
| Aspergillosis | 1.28 | 0.23, 6.98 | 0.78 |
| Diabetes | 0.50 | 0.29, 0.85 | 0.01 |
| Hypertension | 0.55 | 0.39, 0.77 | <0.001 |
| Immune system diseases | 1.65 | 0.80, 3.41 | 0.18 |
| Systemic corticosteroids | 1.52 | 1.1, 2.07 | 0.009 |
| Obesity | 0.06 | 0.004, 0.96 | 0.05 |

CCI, Charlson Comorbidity Index; CI, confidence interval.

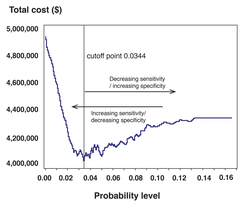
- **Figure 1A** presents the ROC curve generated from the testing cohort
  - Individuals with a predicted probability greater than the cut-off of 0.034 were classified as at risk for NTMLD; this risk classification cut-off corresponded to 70% sensitivity and 58% specificity (**Figure 2**)
  - Using the predictive algorithm and cutoff probability, 1808 potential NTMLD patients were predicted from the application cohort (n=4462) (**Figure 3**)
  - Positive predictive value (PPV) – percentage of positives that are true positives
    - Out of 1808 predicted NTMLD patients, we anticipated a PPV of 5.4%
  - Negative predictive value (NPV) – percentage of negatives that are true negatives
    - Out of 2654 predicted non-NTMLD patients, we anticipated an NPV of 98.3%
  - Cost consequences were calculated based on the classification of patients according to the algorithm with a cut-off of 0.034
- **Figure 1B** shows cost consequences associated with each potential cut-off point
  - The hypothetical cost implications given the selected cut-off of 0.034 for the application cohort was >$4,000,000 annually
  - Based on the cost curve, the predictive model is likely associated with the minimal healthcare cost consequence, attributable to the combination of true and false identification rates

### Figure 1. ROC and cost curves

**A. ROC Curve of Testing Model**




**B. Curve of Cost Consequences**




ROC, receiver operating characteristic.

### Figure 2. False-positive and false-negative calculations in the testing cohort

| Predicted | Observed: NTMLD | Observed: No NTMLD | |
|---|---|---|---|
| Positive | True positive N=122 | False positive N=2138 | N=2260 PPV=5.4% |
| Negative | False negative N=52 | True negative N=2953 | N=3005 NPV=98.3% |
| | N=174 Sensitivity=70% | N=5091 Specificity=58% | |

### Figure 3. Hypothetical false positives and false negatives in the application cohort

| Predicted | NTMLD | No NTMLD | |
|---|---|---|---|
| Positive | True positive (5.4%) N=98 | False positive (94.6%) N=1710 | N=1808 PPV=5.4% |
| Negative | False negative (1.7%) N=45 | True negative (98.3%) N=2609 | N=2654 NPV=98.3% |
| | N=143 | N=4319 | |

## CONCLUSIONS

- A simple predictive algorithm was constructed to identify individuals with non-CF, HIV-negative bronchiectasis potentially at risk for NTMLD
  - Increasing age (odds ratio [OR]=1.03), female gender (OR=2.3), and systemic corticosteroid use (OR=1.5) were associated with an increased risk of NTMLD
  - Diabetes (OR=0.5), hypertension (OR=0.55), and obesity (OR=0.06) were associated with a decreased predicted risk for NTMLD (C-statistic=0.72)
- The algorithm has a 70% chance to detect a true NTMLD patient, but has a relatively low specificity
- This model appears over-predictive of the NTMLD positive while holding a very high NPV; the low PPV may not be unexpected when predicting a rare disease
- Hypothetical cost analysis suggests the feasibility of identifying incident non-CF bronchiectasis patients at risk for NTMLD while taking healthcare cost implications into consideration

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