

## Title

**Relative Risk of All-Cause Mortality in Patients  
With Nontuberculous Mycobacterial Lung  
Disease in a Large US Managed Care Population**

Relative Risk of  
All-Cause  
Mortality in  
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Large US  
Managed Care  
Population

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Disclosure:

Quan Zhang is an employee of Insmmed Incorporated.

# Introduction

- Reports on the risk of all-cause mortality in patients with nontuberculous mycobacterial lung disease (NTMLD) have shown reasonable convergence:
  - Novosad et al. (2017) reported a 5-year mortality rate of 35.1% (2005-06) from an NTMLD patient cohort in Oregon State (N=316)
  - Marras et al. (2017) reported a 5-year mortality rate of 34.4% (2001-2013) from an NTMLD patient cohort in Ontario, Canada (N=8,469)
  - Hayashi et al. (2012) reported a 5-year mortality rate of 23.9% from a MAC specific NTMLD clinical study cohort in Japan (N=634)
  - Andre´jak et al (2010) reported a 5-year mortality rate of 40.1% (1997-2008) from an NTMLD patient cohort in Denmark (N=1282)
  - Fleshner et al. (2016) reported a mortality rate of 4.2 deaths per 100 patient-years from an NIH NTMLD clinical study cohort (N=106)

## Rationale and Objective

- The studies suggest that all-cause mortality ranged between about 4-8% per year
- Despite this knowledge, the relative mortality impact of NTMLD in society is not yet well understood
- This study aimed to assess the relative risk of all-cause mortality in patients with a clinical diagnosis of NTMLD compared with an age-gender matched individual cohort from a large US national managed care insurance claims database

## Methods: Study Sample

- Patient cohort with NTMLD:
  - Patients from a US national managed care insurance plan with physician claims (ICD-9 0.031; ICD-10 A31.0) for NTMLD on  $\geq 2$  separate occasions  $\geq 30$  days apart (n=2005) were identified between 2007 and 2016
  - A control group without NTMLD (n=6014) was randomly selected and matched 3:1 to the NTMLD sample according to age at the NTMLD diagnosis, gender, and insurance coverage period
  - The date of NTMLD diagnosis in the patient cohort was assigned to the matched controls as the index date

## Methods: Mortality Measure

- Mortality data originated from the Social Security Death Master File in the US
- The number of mortality records after 2011 were reduced about 30% owing to discontinued local death reporting to the master file
- While the change in reporting practice could lead to underestimation of mortality rates, the relative risk of mortality is unlikely to be affected unless reporting differed over disease groups or was disease-dependent within a locality such as a particular US state

## Baseline Patient Characteristics (1/2)

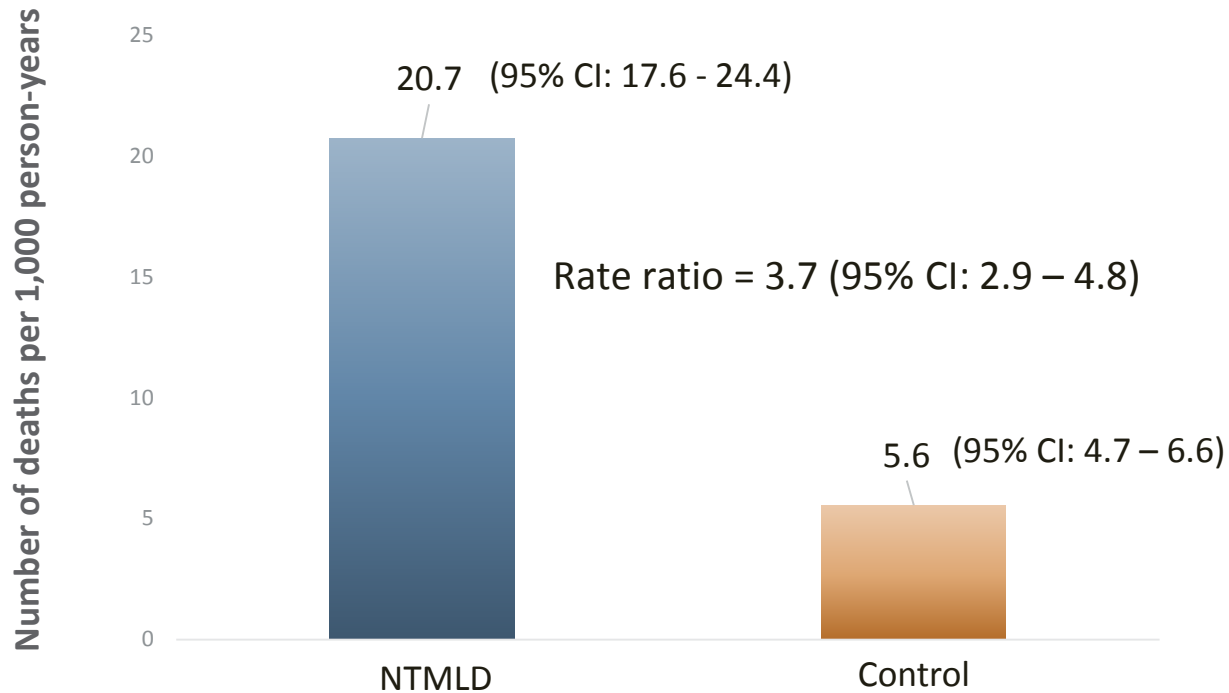
Baseline Variables	NTM group (n=2005)	Control group (n=6014)
Age at Index Date (Mean, SD)	67 (15)	67 (15)
Female	65.7% (1318)	65.7% (3953)
Charlson Comorbidity Index (Mean, SD)	2.2 (2.4)	0.5 (1.3)
Asthma	23.3% (468)	3.5% (211)
Bronchiectasis	36.5% (731)	0.1% (9)
CAD	18.5% (370)	6.6% (397)
Cancer	18.9% (378)	5.0% (303)
CHF	11.9% (238)	4.1% (247)
COPD	52.0% (1043)	5.9% (353)
Cystic fibrosis	2.1% (43)	0.0% (0)
Depression	9.9% (199)	3.8% (228)
Diabetes	15.4% (308)	12.4% (743)



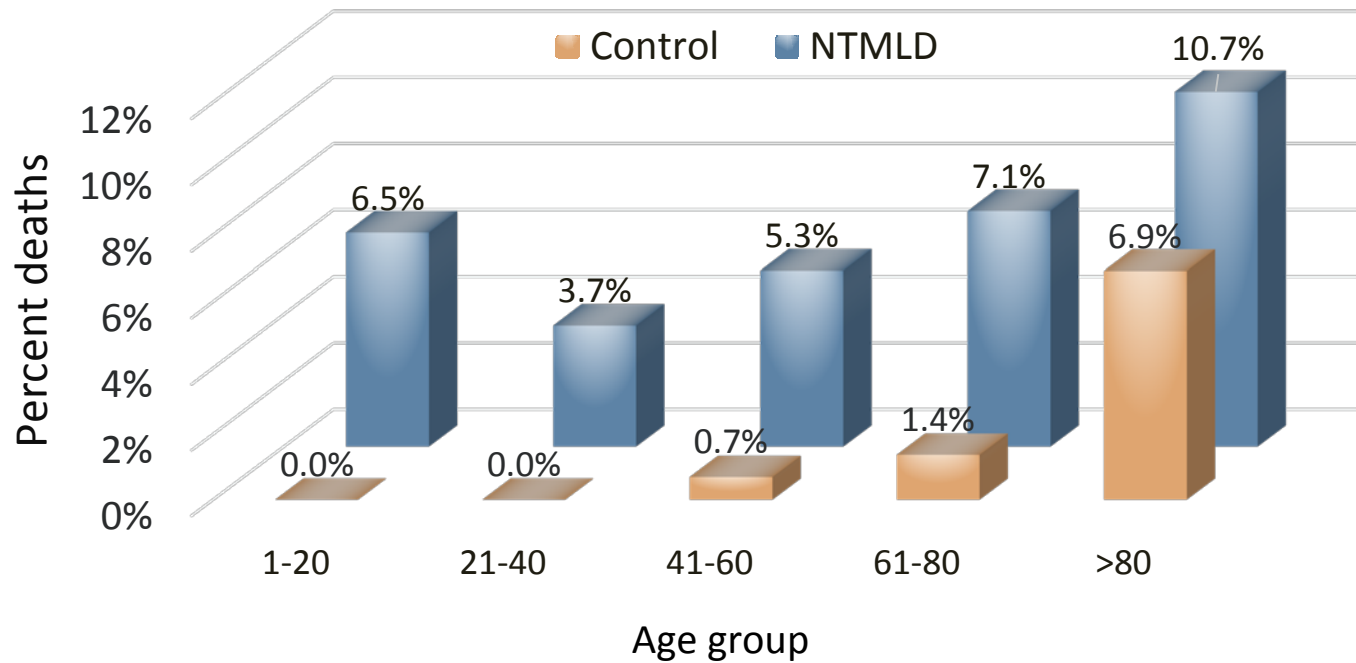
## Baseline Patient Characteristics (2/2)

Baseline Variables	NTM group (n=2005)	Control group (n=6014)
GERD	25.9% (519)	7.5% (451)
Immune deficiency	7.7% (154)	0.3% (17)
Immunosuppressant drug use	55.1% (1104)	14.6% (877)
Lung cancer	6.1% (122)	0.6% (35)
Metastatic Carcinoma	3.4% (68)	0.7% (44)
Myocardial Infarction	4.6% (93)	1.4% (87)
Obesity	3.8% (76)	4.0% (241)
Pneumonia	44.5% (892)	1.7% (103)
Rheumatoid disease	6.0% (120)	1.2% (74)
Tobacco use	23.0% (462)	4.0% (241)
Tuberculosis	8.0% (161)	0.1% (4)

## Unadjusted Death Rate Per 1,000 Person-years with NTMLD vs. Matched Control Group



## All-cause mortality over age groups between NTMLD and Control



## Risk Factors for All-Cause Mortality from Cox Regression with Multivariable Adjustment

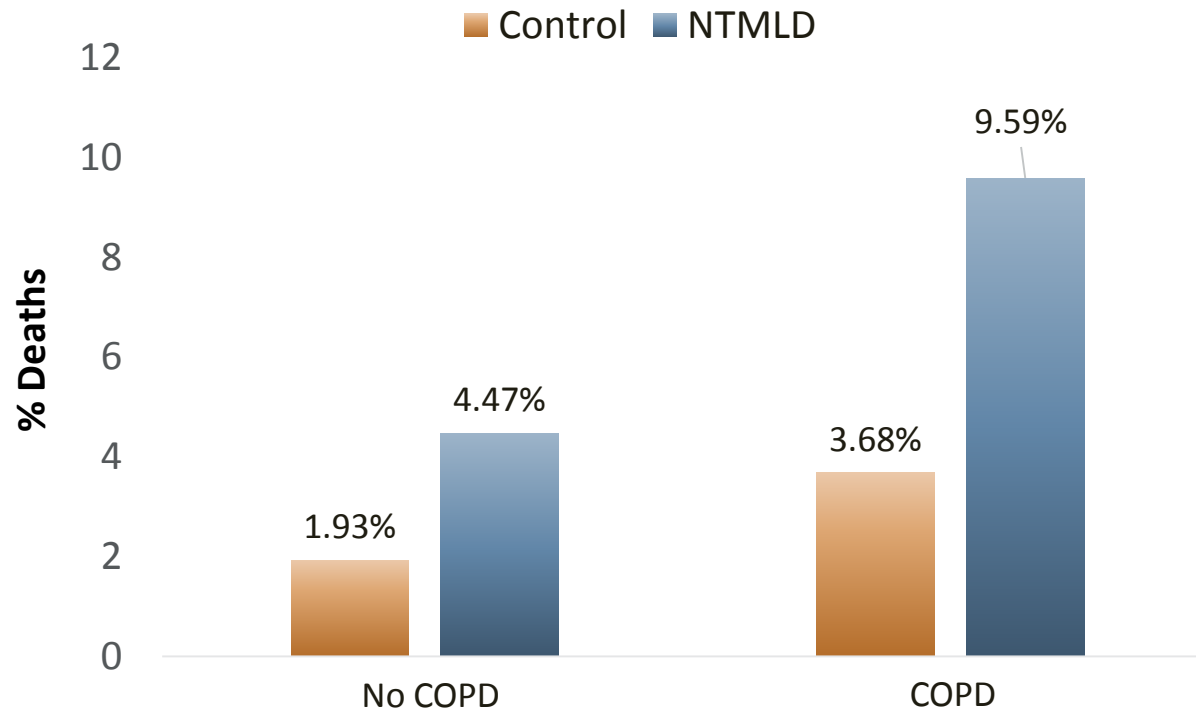
Parameter	Hazard Ratio	95% Hazard Ratio CI	P > $\chi^2$
NTMLD vs. Control	2.11	1.56 2.85	<.0001
Age Group (in 20 years)	2.35	1.94 2.84	<.0001
Male vs. Female	1.48	1.15 1.90	0.002
Atherosclerosis	0.57	0.34 0.96	0.0351
CHF	2.37	1.73 3.25	<.0001
COPD	1.44	1.05 1.98	0.0231
Immune deficiency	2.00	1.23 3.27	0.0056
Inhaled corticosteroids	1.44	1.05 1.97	0.0224
Mental disorder	1.65	1.21 2.25	0.0017
Metastatic carcinoma	2.23	1.25 4.00	0.0069
Moderate or severe liver disease	6.40	2.90 14.14	<.0001
Obesity	0.31	0.11 0.83	0.0198
Lung Cancer	1.87	1.14 3.09	0.0139

CCI was removed (p-value=0.055) due to collinearity: (NTMLD vs. Control HR=2.04 [95%CI: 1.51, 2.77])

In sensitivity analyses:

- CF had a wide CI (0.245-13.72, p=0.5542), hence removed. Removing cystic fibrosis patients (n=43), the hazard ratio of NTMLD vs. Control remained the same (HR=2.15, 95% CI: 1.59, 2.91)
- controlling for M. abscessus (n=20), the hazard ratio of NTMLD vs. Control was 2.17 (95% CI: 1.61, 2.94)

## Incremental Risk of Mortality in Patients with NTMLD with or Without COPD



## Summary

- Study limitation
  - Change of reporting patterns to the social security death master file since 2011 would lead to sizable under-estimation of absolute mortality rate in the study population
  - Baseline patient illness burden largely differed between the NTMLD patient group and matched controls, potentially attenuating the effectiveness of statistical adjustment
- Takeaways
  - Patients with NTMLD had a nearly quadrupled observed risk for all-cause mortality relative to the matched controls and doubled risk after multivariable adjustment
  - it is conceivable that with substantially higher comorbidity, NTMLD magnifies mortality risk in these patients who experience compounded illness burden



Thank you!