

Comorbidities associated with nontuberculous mycobacterial disease in Japanese adults: A claims-data analysis

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Abstract

Background

Nontuberculous mycobacterial (NTM) lung disease is one of a growing number of chronic health problems that is difficult to cure in aging societies. While it is important to be vigilant about associated comorbidities in order to provide better patient care, data on the prevalence of comorbidities stratified by country or region are scarce. We aimed to elucidate the comorbidities associated with NTM disease based on Japanese health insurance claims data.

Methods

Cross-sectional analyses were performed using the claims data for 2014 provided by the Japan Medical Data Center Co., Ltd. Patients aged 20–75 years with ≥ 3 claims associated with NTM disease were identified and matched to 10 sex-and-age-matched controls that had never made a claim for NTM disease. Thirty-one comorbidities previously suspected to be associated with NTM disease were selected, and the prevalence of these comorbidities compared between cases and controls.

Result

Overall, 419 NTM patients (134 males and 285 females) and 4190 non-NTM controls were selected from the JMDC database. Aspergillosis, asthma, bronchiectasis, chronic heart failure, diffuse panbronchiolitis, gastroesophageal reflux, interstitial pneumonia, lung cancer, cancer other than breast, lung, ovary, or prostate cancer, and rheumatic arthritis were associated with NTM disease in both males and females. Chronic obstructive pulmonary disease was associated with NTM in males while chronic kidney disease, osteoporosis, and Sjögren syndrome were associated with NTM in females.

Conclusion

NTM disease was associated with multiple comorbidities that should be considered when providing medical care to individuals with NTM disease.

1. Introduction

Nontuberculous mycobacterial (NTM) lung disease is one of a growing number of chronic health problems that is difficult to cure. Some patients remain stable without treatment, but others die despite being treated with multidrug combination antimycobacterial chemotherapy. The incidence of NTM lung disease is rapidly increasing worldwide [1], and lifelong antimycobacterial chemotherapy is often required to control the disease.

Patients with chronic NTM disease, regardless of whether they are on treatment or not, are getting older and their quality of life may be lowered [2]. In the Japanese aging society, patients with NTM disease have become older, and prevalence of the NTM disease is higher in older people. Individuals with NTM disease often suffer from other health problems such as malignancies or cardiovascular diseases, and these comorbidities are often the cause of death [3]. It is important to pay attention to comorbidities in the management of NTM disease in order to provide optimal patient care.

Previous retrospective studies have shown that diffuse panbronchiolitis, lung cancer, and rheumatoid arthritis may be associated with NTM disease [4–6]. Population-based studies have also identified comorbidities such as chronic obstructive pulmonary diseases (COPD), osteoporosis, gastroesophageal reflux (GERD), cystic fibrosis to be associated with NTM disease [7, 8]. Marras et al. [9] analyzed the comorbidities associated with NTM disease using claims data of the United States managed-care population, which included both NTM and non-NTM patients. However, disease prevalence should be analyzed on the basis of the data of each country or region because differences in environmental and genetic factors lead to different comorbidities (e.g., the prevalence of atherosclerosis or cardiovascular disease differs in each country or region) [10, 11]. In addition, the pathogenic species of *Mycobacterium* vary by country and region [8, 12] and the prevalence of different species may lead to the different clinical picture. Therefore, we conducted claims-data-based analyses to determine the comorbidities associated with NTM disease in Japan.

2. Methods

2.1 Data source

Analyses were conducted using claims data provided by the Japan Medical Data Center Co., Ltd. (JMDC). JMDC has contracts with multiple Japanese health insurance societies and has accumulated reimbursement data from more than 3,000,000 individuals. The JMDC database includes only individuals aged < 75 years because individuals aged ≥ 75 years are covered by National Health Insurance and membership of the original health insurance society is terminated on reaching the age of 75 years. Personal information is encrypted and claims data are recorded chronologically for each individual under a unique encrypted identifier. The database records information on all medical consultations from all medical institutions and medical care providers.

2.2 Study design, Patient identification, and matching

A case-control study was conducted using JMDC data. Individuals with NTM disease were included from 1,440,973 individuals who were registered in JMDC in 2014. Individuals aged ≥ 20 years with ≥ 3 claims associated with NTM disease (International Classification of Diseases, tenth revision [ICD-10] A31.0 or A31.9) on separate occasions ≥ 1 month apart from January 2014 to December 2014 were identified from the JMDC data. The prevalence of NTM disease in 2014 was calculated. Controls that never had a claim associated with NTM disease were randomly extracted from patients who visited a medical facility at least once in 2014. A total of ten controls were matched by sex and age for each case.

Other comorbidities were identified utilizing ICD-10 codes from medical claims based on ≥ 3 claims separate occasions ≥ 1 month apart in 2014 as well (Table 1). Only confirmed diagnoses were included in the analysis. The 31 comorbidity complexes that had previously been suspected as associated with NTM disease were selected and compared [4–9, 13, 14].

Table 1
ICD-10 codes for definition of comorbidity complexes

Comorbidity complexes	ICD-10 codes
Arrhythmia	I44.x, I45.x, I47.x, I48.x, I49.x
Aspergillosis	B44.x
Asthma	J45.x
Bone fracture	M80.x, M84.0, M84.3, M84.4, M96.6, S02.x, S22.x, S32.x, S42.x, S52.x, S62.x, S72.x, S82.x, S92.x, T02.x, T08, T14.2, T91.1, T93.2, T94.1
Breast cancer	C50.x
Bronchiectasis	J47
Chronic heart failure	I11.x, I42.x, I50.x
Chronic kidney disease	N18.x, N28.9
COPD	J43.x, J44.9
Crohn's disease	K50.x
Depression	F32.x, F33.x
Diabetes mellitus	E10.x-E14.x, R73.0
Diffuse panbronchiolitis	J44.8
Dyslipidemia	E78.x
GERD	K21.0, K21.9
Heart valve disease	I05.x-I08.x, I34.x-I37.x, I38
HIV infection	B24
Hypertension	I10, I11.x, I12.x, I15.x
Ischemic heart disease	I20.x, I21.x, I24.x, I25.1, I25.2, I25.5, I25.6, I25.9
Interstitial pneumonia	J84.1, J84.9, J70.4
Liver cirrhosis	B18.1, B18.2, K70.3, K74.6

COPD: chronic obstructive pulmonary diseases, GERD: gastroesophageal reflux, HIV: human immunodeficiency virus, PM/DM: polymyositis/dermatomyositis, SLE: systemic lupus erythematosus

Comorbidity complexes	ICD-10 codes
Lung cancer	C34.x
Osteoporosis	M80.x, M81.x
Other cancer	C00.x-C26.x, C30.x-C33.x, C37.x-C41.x, C43.x-C49.x, C51.x-C55.x, C57.x, C58.x, C60.x, C62.x-C85.x, C88.x, C90.x-C97.x
Ovary cancer	C56
PM/DM	M33.x
Prostate cancer	C61
Rheumatic arthritis	M06.9
Sjogren syndrome	M35.0
SLE	M32.1, M32.9
Systemic sclerosis	M34.x
COPD: chronic obstructive pulmonary diseases, GERD: gastroesophageal reflux, HIV: human immunodeficiency virus, PM/DM: polymyositis/dermatomyositis, SLE: systemic lupus erythematosus	

Ethics approval was not applicable to this study based on Ethical Guidelines for Medical and Health Research Involving Human Subject issued by the Japanese Ministry of Health, Labour and Welfare since only completely encrypted data were used.

2.3 Statistical analysis

The proportion of comorbidities among NTM group and non-NTM group was compared by chi-square test. We addressed multiple testing by setting a Bonferroni-adjusted significance level of P -value < 0.000806 ($0.05/62$) as we tested 31 comorbidity complexes separating sex. All statistical analyses and matching were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 419 NTM patients (134 males and 285 females) were selected from the JMDC database, and 4190 non-NTM controls (1340 males and 2850 females) were identified. The sex and age distribution of the patients is shown in Fig. 1. The median age was 59 years (males 58, females 60); 68% (285/419) were female. Overall, 1,440,973 people were registered in JMDC in the year 2014, and the prevalence of NTM diseases in the patients aged 20–75 years old was calculated as 29.0 /100,000 population.

The prevalence of comorbidities is shown in Tables 2 and 3. Of the respiratory diseases considered, aspergillosis, asthma, bronchiectasis, diffuse panbronchiolitis (DPB), interstitial pneumonia, and lung cancer were significantly associated with NTM disease in both sex groups. In addition, GERD, other cancer, and rheumatic arthritis were significantly associated with NTM disease in both sex groups. COPD was also significantly associated with NTM disease in males, while chronic kidney disease (CKD), osteoporosis, and Sjögren syndrome were significantly associated with NTM disease in females. The prevalence of chronic heart failure was significantly associated with NTM disease in the unstratified analysis, but not in the sex-stratified analysis.

Table 2
NTM disease and Comorbidity complexes

Comorbidity complexes	NTM(N = 419) n (%)	non-NTM (N = 4190) n (%)	P value
Arrhythmia	28 (6.68)	176 (4.20)	0.0243
Aspergillosis	8 (1.90)	0 (0)	< 0.0001*
Asthma	77 (18.3)	194 (4.63)	< 0.0001*
Bone fracture	13 (3.10)	64 (1.52)	0.0255
Breast cancer	4 (0.954)	43 (1.02)	> 0.99
Bronchiectasis	74 (17.6)	6 (0.143)	< 0.0001*
Chronic heart failure	31 (7.39)	130 (3.10)	< 0.0001*
Chronic kidney disease	16 (3.81)	54 (1.28)	0.000403*
COPD	13 (3.10)	22 (0.525)	< 0.0001*
Crohn's disease	2 (0.477)	0 (0)	0.00825
Depression	16 (3.81)	107 (2.55)	0.149
Diabetes mellitus	62 (14.7)	608 (14.5)	0.884
Diffuse panbronchiolitis	8 (1.90)	0 (0)	< 0.0001*
Dyslipidemia	105 (25.0)	1110 (26.4)	0.561
GERD	83 (19.8)	355 (8.47)	< 0.0001*
Heart valve disease	11 (2.62)	54 (1.28)	0.0455
HIV infection	0 (0)	0 (0)	NA
Hypertension	110 (26.2)	1166 (27.8)	0.529
Ischemic heart disease	29 (6.92)	191 (4.55)	0.04
Interstitial pneumonia	25 (5.96)	14 (0.334)	< 0.0001*
Liver cirrhosis	4 (0.954)	25 (0.596)	0.33
Lung cancer	19 (4.53)	13 (0.310)	< 0.0001*
Osteoporosis	46 (10.9)	220 (5.25)	< 0.0001*
Other cancer	41 (9.78)	117 (2.79)	< 0.0001*

COPD: chronic obstructive pulmonary diseases, GERD: gastroesophageal reflux, HIV: human immunodeficiency virus, PM/DM: polymyositis/dermatomyositis, SLE: systemic lupus erythematosus, *statistically different, NA not applicable

Comorbidity complexes	NTM(N = 419) n (%)	non-NTM (N = 4190) n (%)	P value
Ovary cancer	1 (0.238)	8 (0.190)	0.576
PM/DM	1 (0.238)	2 (0.0477)	0.249
Prostate cancer	0 (0)	15 (0.357)	0.389
Rheumatic arthritis	23 (5.48)	66 (1.57)	< 0.0001*
Sjögren syndrome	10 (2.38)	13 (0.310)	< 0.0001*
SLE	3 (0.715)	7 (0.167)	0.0552
Systemic sclerosis	4 (0.954)	3 (0.0715)	0.00189
COPD: chronic obstructive pulmonary diseases, GERD: gastroesophageal reflux, HIV: human immunodeficiency virus, PM/DM: polymyositis/dermatomyositis, SLE: systemic lupus erythematosus, *statistically different, NA not applicable			

Table 3
NTM disease and Comorbidity complexes analyzed separating sexes

Comorbidity complexes	Male N = 1474			Female N = 3135		
	NTM, N = 134	non-NTM, N = 1340	P value	NTM, N = 285	non-NTM, N = 2850	P value
Arrhythmia	15 (11.19)	71 (5.29)	0.0105	13 (4.56)	105 (3.68)	0.417
Aspergillosis	5 (3.73)	0 (0)	< 0.0001*	3 (1.05)	0 (0)	0.000744*
Asthma	30 (22.3)	60 (4.47)	< 0.0001*	47 (16.4)	134 (4.70)	< 0.0001*
Bone fracture	3 (2.23)	8 (0.597)	0.0705	10 (3.50)	56 (1.96)	0.0854
Breast cancer	0 (0)	1 (0.0746)	> 0.99	4 (1.40)	42 (1.47)	> 0.99
Bronchiectasis	13 (9.70)	1 (0.0746)	< 0.0001*	61 (21.4)	5 (0.175)	< 0.0001*
Chronic heart failure	11 (8.20)	43 (3.20)	0.00731	20 (7.01)	87 (3.05)	0.00158
Chronic kidney disease	5 (3.73)	25 (1.86)	0.185	11 (3.85)	29 (1.01)	0.000605*
COPD	9 (6.71)	11 (0.820)	< 0.0001*	4 (1.40)	11 (0.385)	0.0408
Crohn's disease	2 (1.49)	0 (0)	0.0821	0 (0)	0 (0)	NA
Depression	2 (1.49)	32 (2.38)	0.763	14 (4.91)	75 (2.63)	0.0374
Diabetes mellitus	28 (20.89)	241 (17.98)	0.412	34 (11.9)	367 (12.8)	0.71
Diffuse panbronchiolitis	5 (3.73)	0 (0)	< 0.0001*	3 (1.05)	0 (0)	0.000744*
Dyslipidemia	26 (19.4)	345 (25.7)	0.118	79 (27.7)	765 (26.8)	0.779
GERD	35 (26.1)	118 (8.80)	< 0.0001*	48 (16.8)	237 (8.31)	< 0.0001*
Heart valve disease	6 (4.47)	17 (1.26)	0.0139	5 (1.75)	37 (1.29)	0.427

COPD: chronic obstructive pulmonary diseases, GERD: gastroesophageal reflux, HIV: human immunodeficiency virus, PM/DM: polymyositis/dermatomyositis, SLE: systemic lupus erythematosus, *statistically different, NA not applicable

	Male N = 1474			Female N = 3135		
HIV infection	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Hypertension	40 (29.8)	432 (32.2)	0.628	70 (24.5)	734 (25.7)	0.722
Ischemic heart disease	14 (10.4)	75 (5.59)	0.0344	15 (5.26)	116 (4.07)	0.35
Interstitial pneumonia	12 (8.95)	4 (0.298)	< 0.0001*	13 (4.56)	10 (0.350)	< 0.0001*
Liver cirrhosis	3 (2.23)	3 (0.223)	0.012	1 (0.350)	22 (0.771)	0.716
Lung cancer	10 (7.46)	8 (0.597)	< 0.0001*	9 (3.15)	5 (0.175)	< 0.0001*
Osteoporosis	4 (2.98)	10 (7.46)	0.0318	42 (14.7)	210 (7.36)	< 0.0001*
Other cancer	18 (13.4)	45 (3.35)	< 0.0001*	23 (8.07)	72 (2.52)	< 0.0001*
Ovary cancer	0 (0)	0 (0)	NA	1 (0.35)	8 (0.280)	0.576
PM/DM	0 (0)	0 (0)	NA	1 (0.35)	2 (0.0701)	0.249
Prostate cancer	0 (0)	15 (1.11)	0.387	0 (0)	0 (0)	NA
Rheumatic arthritis	6 (4.47)	5 (0.373)	0.00016*	17 (5.96)	61 (2.14)	0.000458*
Sjögren syndrome	0 (0)	0 (0)	NA	10 (3.50)	13 (0.456)	< 0.0001*
SLE	0 (0)	1 (0.0746)	> 0.99	3 (1.05)	6 (0.210)	0.0413
Systemic sclerosis	1 (0.746)	1 (0.0746)	0.174	3 (1.05)	2 (0.0701)	0.0647
COPD: chronic obstructive pulmonary diseases, GERD: gastroesophageal reflux, HIV: human immunodeficiency virus, PM/DM: polymyositis/dermatomyositis, SLE: systemic lupus erythematosus, *statistically different, NA not applicable						

4. Discussion

We conducted a case-control study using JMDC data and investigated the coexistence of NTM disease and comorbid conditions in Japanese adults. JMDC has collected reimbursement data since 2005 and the size of the database makes it valuable resource for estimating the prevalence of diseases. This is the first study evaluating comorbidities associated with NTM disease in Japanese adults based on a case-control analysis using Japanese health insurance claims database. human immunodeficiency virus (HIV)

and cystic fibrosis are well-known risk factors of NTM disease [15]. However, our data did not contain individuals with these diseases because of their low prevalence in Japan. The calculated prevalence and the proportion of females with NTM disease were similar to those reported in a previous Japanese study [14] of NTM lung disease (NTM-LD). It is likely that the majority of cases in our study had NTM-LD. A strength of this study is that it included 10 sex-and-age-matched non-NTM controls per case. In addition, we performed Bonferroni-adjustment to resolve the problem of multiple hypothesis testing.

Respiratory diseases and a variety of systemic conditions are comorbid with NTM disease. In terms of respiratory diseases, Marras et al. [9, 16] found an association between NTM disease and aspergillosis, asthma, bronchiectasis, COPD, lung cancer, and tuberculosis in the United States (US) claims-data analysis. Our data showed that interstitial lung disease and asthma were comorbid with NTM disease in addition to the classical risk factors such as COPD. A Korean study with 810 NTM-LD patients revealed that 42 patients (5.2%) had interstitial lung disease, which is a similar proportion to that found in our study [17]. Asthma and COPD, especially if treated with inhaled corticosteroid therapy, and the use of systemic immunosuppressive agents have previously been identified as strongly associated with NTM-LD [8, 9, 18, 19], which might also contribute to the development of NTM-LD in individuals with interstitial lung disease.

Bronchiectasis is a leading comorbidity associated with NTM disease, and chronic NTM pulmonary infection can lead to bronchiectasis [20]. A large registry in US showed a close link between NTM-LD and bronchiectasis [21], while a European study did not find a strong association between the two conditions [22]. These different findings might have arisen because NTM-LD development can be affected by microbiological, environmental, and host factors [12]. In our study, 17.6% of the cases had bronchiectasis, but the prevalence of bronchiectasis may have been underestimated. Previous Japanese studies using high-resolution computed tomography (CT) showed most patients with lung disease caused by *Mycobacterium avium* complex had bronchiectasis [23, 24]. Bronchiectasis may have been underdiagnosed in the claims data because it is caused by various underlying diseases and physicians may have diagnosed only the primary diseases.

Tsuji et al. [4] conducted a retrospective study of 33 patients with diffuse panbronchiolitis (DPB) and found that 7 (21.2%) of the patients also had pulmonary NTM disease. In our analysis, 1.9% of patients with NTM disease also had DPB. This fact is more characteristic in Japanese or Asian patients than it is among individuals in the US or Europe because DPB mainly affects East Asian people [25]. We speculated that DPB is a risk factor for NTM disease, but does not occur due to NTM disease. *Mycobacterium* spp. also easily colonize the respiratory tract of DPB patients because DPB is accompanied mucociliary dysfunction and various bacteria colonize the respiratory epithelium [4]. NTM is a well-recognized pathogen in cystic fibrosis patients [26, 27]. However, the prevalence of cystic fibrosis in Japan is very limited, and there were no patients with cystic fibrosis in our data.

Kusumoto et al. [5] pointed out the high incidence of lung cancer in patients with NTM-LD, with an estimated incidence rate of 124.6 per 100,000 patient-years. This incidence is much higher than that

reported in Japan. NTM diseases might be a risk factor for lung cancer, as patients with NTM-LD have chest CT scans more frequently than healthy individuals and are therefore more likely to have other lung nodules discovered incidentally. Kusumoto et al. also speculated that chronic lung inflammation might cause lung cancer, however, the pathogenesis of lung cancer in relation to NTM disease is unknown [5].

In terms of systemic complications, patients with NTM had a significantly higher prevalence of chronic heart failure, GERD, cancer other than breast, lung, ovary, or prostate cancer, and rheumatic arthritis than controls in both males and females. Females with NTM disease also had a significantly higher prevalence of CKD, osteoporosis, and Sjögren syndrome than controls. The coexistence between NTM disease and chronic heart failure, GERD, other cancer, and rheumatic arthritis has been reported previously [8, 9, 16]. Chao et al. [28] reported an increased risk of NTM disease in patients with Sjögren syndrome based on an analysis of Taiwan's National Health Insurance Research Database analysis. Pulmonary abnormalities have been described as an extra-glandular involvement of Sjögren syndrome [29]. NTM-LD may be an underlying condition in patients with Sjögren syndrome because some patients with Sjögren syndrome have been reported to develop bronchiectasis [30, 31], and pulmonary involvement in patients with Sjögren syndrome can be difficult to distinguish from NTM-LD using CT.

Menopause is a well-known risk factor for NTM disease [32], and osteoporosis also frequently occur in those population. Low serum estradiol had been related to development of NTM-LD [33], and it might be a confounding factor between osteoporosis and NTM diseases. In addition, Jeon et al. [13] reported the association between severe vitamin D deficiency and development of NTM disease; thus, vitamin D deficiency may also be a confounding factor of these diseases. Measurement of serum vitamin D level was not supported by the health insurance system in Japan in 2014, so we were unable to assess whether there was an association between vitamin D deficiency and NTM disease. COPD, a common chronic pulmonary disease, has been reported to be an independent risk factor of osteoporosis [34] and so there is a need to investigate the mechanism of development of osteoporosis in patients with NTM disease.

This study should be interpreted in light of several limitations. First, the analysis was based on data from a claims database. Since we did not have access to the clinical or microbiological information of the participants, the prevalence of some disease complexes might differ from that based on a true diagnosis. Researchers have defined their targeted diseases by ≥ 2 claims in several previous claims-data analyses [9, 16, 35–38]; however, we defined by ≥ 3 claims to increase the specificity. The calculated prevalence and proportion of women were similar to that reported in the previous study [14]; thus, the accuracy of our diagnosis of NTM disease is likely to be comparable to that of previous studies. Second, we were unable to differentiate the *Mycobacterium* species due to unavailability of microbiological information. Third, JMDC database did not include patients aged ≥ 75 years belonging to National Health Insurance. It would be ideal to have included patients aged ≥ 75 years as comorbidities increases with advanced age.

In conclusion, we elucidated the comorbidities complex associated with NTM disease in Japanese adults based on a claims-data analysis. Clinicians should be aware of these specific comorbidities when

providing medical care for patients with NTM disease.

Abbreviations

CKD

chronic kidney disease

COPD

chronic obstructive pulmonary diseases

CT

computed tomography

DPB

diffuse panbronchiolitis

GERD

gastroesophageal reflux

HIV

human immunodeficiency virus

ICD-10

International Classification of Diseases, tenth revision

JMDC

Japan Medical Data Center Co., Ltd.

NTM

non-tuberculous *Mycobacterium*

NTM-LD

non-tuberculous *Mycobacterium* lung disease

PM/DM

polymyositis/dermatomyositis

SLE

systemic lupus erythematosus

US

United States

Declarations

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Conflict of Interest: none

Ethics approval: Ethics approval was not applicable to this study based on Ethical Guidelines for Medical and Health Research Involving Human Subject issued by the Japanese Ministry of Health, Labour and

Welfare since only completely encrypted data were used.

Author contribution

SU designed the study, analyzed, and drafted the manuscript; TA and KM designed the study and participated in editing the manuscript; KY confirmed the analyses, and revised the article for intellectual content; YU and TN conceptualized the study and revised the article for intellectual content; YH conceptualized the study, supervised, and acquired funding; NH participated in editing the manuscript, acquired funding, and revised the article for intellectual content. All authors read and critically revised the first as well as the subsequent and final drafts of this manuscript.

Availability of data

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

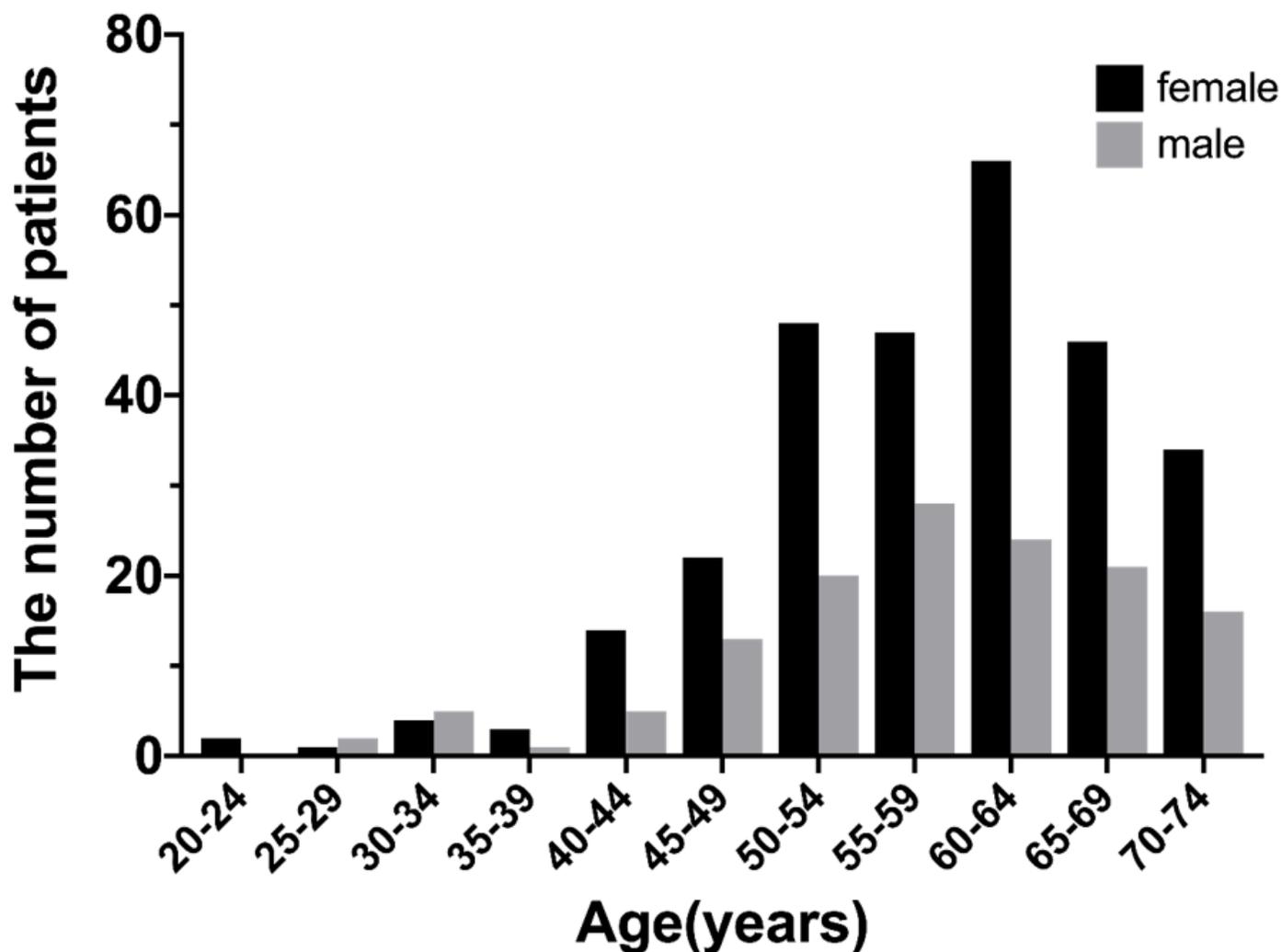


Figure 1

The distribution of the patients with NTM disease by sex and age