Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 26 (2022) 100294

Contents lists available at ScienceDirect

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

journal homepage: www.elsevier.com/locate/jctube

Clinical characteristics and imaging features of patients with nontuberculous mycobacteria in a tertiary care center

Talal Almutairi [a,b,c,*], Abdulellah Musaid Almohaya [d], Abdulah Alqahtani [a,b,e], Ohud Alkinani [c], Faisal Alasmari [c,f], Khalifa Binkhamis [a,b]

[a] Microbiology Unit, Department of Pathology, College of Medicine, King Saud University, Riyadh, Saudi Arabia
[b] King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia
[c] King Fahad Medical City, Riyadh, Saudi Arabia
[d] Internal Medicine Department, Al-Diriyah Hospital, Ministry of Health, Riyadh, Saudi Arabia
[e] Department of Microbiology and Immunology, College of Medicine, King Khalid University, Abha, Saudi Arabia
[f] Alfaisal University, Saudi Arabia

ARTICLE INFO

Keywords:
Nontuberculous Mycobacteri
Tuberculosis mycobacterium
Immunocompromised
Pseudoinfection

ABSTRACT

Background: Non-tuberculous mycobacteria (NTM) are ubiquitous organisms that occasionally causes invasive diseases in humans, but they are under-reported in Saudi Arabia. We aimed to describe NTM infections and apply the American Thoracic Society/Infectious Diseases Society of America ATS/IDSA criteria.
Method: Positive laboratory reports for NTM between January 2006 and December 2017 were retrospectively reviewed, and then classified into respiratory and non-respiratory specimens. ATS/IDSA criteria were applied to all respiratory specimens. Host status, clinical presentation, species identification, imaging, treatment, and outcome data were collected using a standardized form and analyzed. Cases with duplication or incomplete data were excluded.
Results: 183 unique patients with positive NTM culture were included. Median age was 52 years and males represented 59%. Majority of cases were in the respiratory specimens group (n = 146), of which only 15 cases have met the ATS/IDSA criteria. Overall, cases were primarily known to have non-immunocompromising condition but 27% had either an active malignancy (n = 35), HIV (n = 13), or primary immunodeficiency (n = 8). 68.3% of cases presented with respiratory symptoms with or without fever. Among the identified NTM species (51.9%), slowly growing NTM were predominant. Anti-NTM therapy was provided in only 22.4% of this cohort. Death was documented only in 5 cases; all were in the respiratory group and were not treated.
Conclusion: Though uncommon to isolate, only one in every ten respiratory NTM isolates was found potentially true pathogen in a single center in Saudi Arabia. Future studies on NTM prevalence in Saudi Arabia are recommended.

1. Introduction

Mycobacterium, a genus of Actinobacteria and one of the oldest and largest genera of bacteria, are described as opportunistic organisms [1]. The genus of Mycobacterium share 94.3% of the 16S rRNA gene within the genus and each has the potential to cause a wide variety of diseases. In the recent years, the rapid development in technology of identification, such as polymerase chain reaction (PCR), has identified more than 170 species of mycobacteria [2]. Mycobacterium tuberculosis complex (MTC), the most famous among mycobacterium genus, are the pathogens causing human tuberculosis (TB) disease. [3]. Outside the MTC, mycobacterial organisms are referred to as atypical mycobacteria, mycobacteria other than TB (MOTT), or more recently given the name: nontuberculous mycobacteria (NTM).

The NTMs are considered environmental bacteria that can be ubiquitous in water, soil, and plants[4]. Although the mode of transmission to human is not completely understood, direct or indirect human-to-human transmission of certain strains of M. abscessus has been confirmed by whole genome sequencing in the literature[5]. The battle between the NTM species against the host immunity play a significant role in the spectrum of the NTM disease. Nevertheless, they can infect immunocompetent and, more profoundly, immunosuppressed

* Corresponding author.

https://doi.org/10.1016/j.jctube.2021.100294

Available online 27 December 2021

individuals [6]. According to the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) guidelines, evaluation of a pulmonary NTM infection depends on specific microbiological, radiological, and clinical findings, as well as the exclusion of other diseases, such as tuberculosis.

It is observed that there is a geographic variation in NTM prevalence [7,8]. Amongst Mycobacterium, the prevalence of NTM was widely variable, being low in a country like Belgium (2.1%) and high in India (34%). More importantly, an increasing trend of NTM disease is observed in North America (3–6% per year) [9] and Chine [10], but not in Europe [11]. The prevalence of NTM infection in Saudi Arabia is not known yet, likely because they are not among the list of reportable diseases in the country.

In the view of scarce data on NTM infections in our region, we aim to review cases with NTM in a single tertiary care center in Riyadh, Saudi Arabia.

2. Methods

2.1. Study population and study design:

After approval by the Institutional Review Board (IRB) at the institute, a retrospective review was performed at KFMC, a 1200-bed tertiary health care center in Riyadh, Saudi Arabia, between January 2006 and December 2017 for patients who had at least single nontuberculosis mycobacterium culture from any specimen type. We reviewed their medical records and collected the demographic, clinical presentation, medical history, microbiological results, imaging findings, the decision of treatment, and survival outcome. Patients with incomplete data were excluded.

We classified patients' specimens into a pulmonary and extrapulmonary specimens, or both. We evaluated those with respiratory specimens using the 2020 American Thoracic Society/Infectious Diseases Society of America (IDSA), which combines clinical, radiological, and microbiological criteria after excluding other etiologies. At the same time, the non-respiratory specimens are stratified by physician decision on treatment. For cases with multiple isolates of NTM species, only the first isolate of species is included in the analysis.

2.2. Culture and identification

NTM isolates cultured on Lowenstein Jensen (LJ) medium and Mycobacterium Growth Indicator Tube liquid media (Becton Dickinson (BD) BACTEC MGIT 960 System) the MGIT system. It is nonradiometric which uses advanced fluorometric technology that detects O2 consumption. All specimens have been processed according to the microbiological standard procedures. After excluding the MTB complex, we recognize NTM by positive AFB and negative real-time PCR (GeneXpert MTB/RIF assay Cepheid USA) MTB complex Kit). On request, the specimen is sent to a reference laboratory for species level identification, as it is not available in-house in our institute.

2.3. Data analysis:

We performed descriptive and comparative analysis among patients who fit our study criteria. We compared patients with slowly growing mycobacteria against rapidly growing mycobacteria using the chi-square test to obtain predictors among study variables. Data were presented in frequencies, percentages, average using IBM/SPSS V.23 (Armonk, New York, USA) software.

3. Results

Annually, our laboratory department receive requests for mycobacterial culture at a rate of 1,000 per year, where it yielded positive culture 5–10% for all types of mycobacteria. We found a total of 183 positive cultures of NTM between 2006 and 2017 that fit our study criteria. The highest case number was found during the years of 2008 (n = 25), 2013 (n = 24), and 2016 (n = 23). While there was an increasing trend of unidentified species over the years toward 2017, there was a decreasing trend to isolate the group of slowly growing mycobacteria. We also observed that annual NTM isolated from non-respiratory specimens were less than 5 isolates per year, except the year of 2016 when it doubled to 11 specimens per year, the majority of which were unidentified 6/11 (Fig. 1).

The median age among all patients was 52 years; however, patients with respiratory specimens were slightly older (median 54 years), while those with non-respiratory specimens were significantly younger (median 38 years). Furthermore, more than 60% of the cases were between the ages 19–65 years, with a similar percentage across respiratory and non-respiratory groups. Keeping in mind that the pediatric age group was the minority in this cohort (10.9%), a higher proportion of this age group was observed in the non-respiratory specimen group (21.6%). Male predominance was observed in the whole cohort and in the respiratory specimens group (59 and 58.2%, respectively), while it was even higher among the non-respiratory specimens group (62.2%). Medical comorbidities were found in the vast majority of patients with positive NTM culture (85.8%). Cardiovascular disease (32.4–34.2%) and diabetes mellitus (25.3–29.7%) were the most common comorbidities among the whole cohort, the respiratory specimens, and non-respiratory specimens group. However, after we applied the ATS/IDSA criteria, pulmonary disease (40%), and diabetes mellitus (40%) were the most common among the respiratory specimens group. Active malignancy was found in 19.1% of all patients, with the highest proportion among those who met ATS/IDSA pulmonary NTM criteria (26.7%). Surprisingly, none of the 12 patients with HIV or the 6 patients with other types of immunodeficiencies who had respiratory specimens had met ATS/IDSA pulmonary NTM criteria (Table 1).

In the current analysis, 94.5% of patients were symptomatic prior to NTM culture. Respiratory symptoms (dry or wet cough, dyspnea, and chest pain) with or without fever were the presenting symptoms in at least 68.3% of all cases and 79.5% of cases with positive NTM respiratory specimens, while fever with constitutional symptoms (weight loss, night sweats, anorexia, fatigue) was present in 16.4% of all cases. As expected, non-respiratory symptoms were the most common among non-respiratory specimens group (45.9%). Lung imaging was requested in 141/146 (96.6%) of cases with respiratory specimens. The findings were compatible with ATS/IDSA pulmonary criteria in 41/141 cases (29.1%) cases, including nodules (n = 18), bronchiectasis (n = 12), or cavity (n = 11), while the majority of the rest were either normal (n = 25) or other unrelated findings (n = 75) (Table 1).

Culture specimens were mostly from pulmonary category (n = 146, 79.8%), including sputum (n = 114), deep respiratory sample (n = 27), or other respiratory specimens (n = 5), while the remaining extrapulmonary specimens (n = 37, 20.2%) were mostly from non-sterile sites (n = 21), sterile sites (n = 13), or multiple sites (n = 3). Species of NTM were identified in 51.9% of the isolates (n = 95), and there was no difference in the likelihood of identification between respiratory versus non-respiratory specimens (51.4 vs. 54.1%). Furthermore, the slowly growing mycobacteria (SGM) was the predominant group compared to rapidly growing mycobacteria (RGM) (40.4 vs. 11.5%), with variable distribution when comparing respiratory (SGM, 33.9 vs. RGM, 7.1%) versus non-respiratory specimens (SGM, 6.6 vs. RGM, 4.4%). Overall, the most common SGMs were *M. Simiae* (n = 21), *M. gordonae* (n = 14), *M. riyadhense* (n = 11), and *M. szulgai* (n = 10), while the most common RGMs were *M. chelonae* (n = 8), *M. abscessus* (n = 5), and *M. fortuitum* (n = 5). However, species that were isolated from patients who met ATS/IDSA pulmonary criteria were *M. Simiae* (n = 2), *M. riyadhense* (n = 2), *M. chelonae* (n = 2), *M. avium* (n = 1), and *M. scrofulaceum* (n = 1) (Table 2).

Treatment of NTM positive culture was attempted in 33/146 (22.6%) and 8/33 (21.6%) of cases with respiratory and non-respiratory

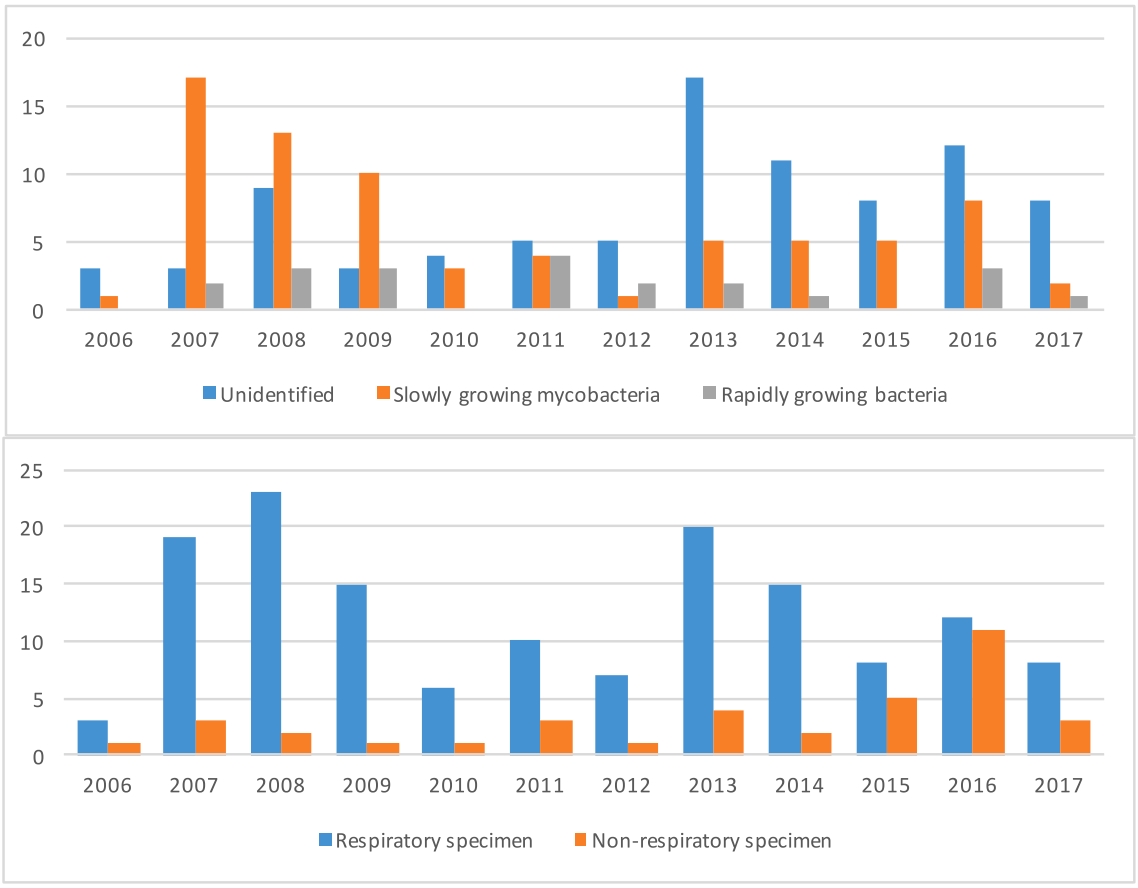

Fig. 1. Species group and specimens types over the study period. RGM: Rapidly growing mycobacteria. SGM: Slowly growing bacteria. ATS/IDSA criteria: including all 2020 infectious diseases society of America.

specimens, respectively. Although this percentage was slightly higher among those who met ATS/IDSA pulmonary criteria (26.7%), the majority of them did not receive treatment due to the following reasons: early discharge before culture results (n = 3), patients were already recovered at the time culture result (n = 3), the patient died before culture result (n = 1), or no clear reason and infectious disease team were not involved (n = 4). Despite those patients with no treatment was the majority, only five patients died within one year of culture date. (Table 2) Detailed exploration on these five cases is presented in Table 3.

ATS/IDSA criteria for NTM pulmonary disease were applied to all respiratory specimens (n = 146) in this cohort, and 95.9% (n = 140) have met the symptoms criteria, 28.8% (n = 42) met the imaging criteria, 23.3% (n = 34) met the microbiologic criteria, and only 21.9% (n = 32) had the three criteria altogether. (Table 4).

Then we compared those with SGM and RGM against the study variables (Table 5). We found male gender (OR = 3) or the presence of symptoms were predictors for SGM. The age, preexisting medical conditions, specimen type, or outcome were not significantly different between the two species group.

4. Discussion

In this study, we describe the clinical, radiological, and microbiological features of non-tuberculous mycobacterium (NTM) that were isolated from pulmonary and extrapulmonary sites over 11 years, with an insight on their association with comorbidities and prognosis. We have found that only the minority had been considered pathogenic and very rarely resulted in a poor outcome. Although most of the NTM were pulmonary in origin, only 10.3% have met all requirements in ATS/IDSA criteria.

Since humans are in contact with NTM in the environment, colonization and infection can be transient, intermittent, prolonged. Although NTM and MTB are two different pathogens, they share epidemiological and clinical similarities, which is challenging for laboratories to identify and for physicians to treat especially in resources-limited settings. Also, the standard medication regimens used for MTB complex not appropriate for NTM [12]. It is essential to improve diagnostic tools for diagnosing NTM and MTB infections to initiate the appropriate therapy. The treatment of NTM and method of susceptibility testing depend on the type of species and individual strains. Therefore, early identification is critical for the treatment of the disease. In recent times, chemical testing has been replaced by molecular methods, and MALDI-TOF MS for the identify species and NTM, which is extensively helpful in facilitating treatment [12,13].

Smear positivity and similar respiratory presentation can challenge differentiating NTM from MTB which results in underestimation of the true incidence of NTM in different countries [14]. The more confusing part of NTM is the likelihood of being a colonizer, which is not a big concern in MTB. Although ATS/IDSA criteria is designed to overcome this, but given that the criteria was based only on M. *kansasii*, and M. *abscessus* this could overestimate the rate of true infection due to other NTM species [15]. While NTM incidence increases and TB incidence decreases, even in TB endemic countries, TB continue to receive larger global public health attention due to higher mortality risk. In Saudi Arabia, a steady decrease of TB incidence was achieved in 2020 by half the rate in 2010 [16], however we still lack national surveillance data on NTM.

Older age matters in increasing risk of various types of infections [17]. While previous studies from western countries have found NTM infected patients had a median age of 68 years [18], we observed

Table 1
Demographic, comorbidities, clinical presentations, radiological features, treatment, and outcome of all patients with positive culture for nontuberculous Mycobacterium in a tertiary care center, Riyadh, Saudi Arabia, between 2006 and 2017, (n = 183).

Parameter		Total n = 183 (%)	Respiratory specimens n = 146 (79.8)		Non-respiratory specimens n = 37 (20.2)
			Total	met ATS/IDSA criteria n = 15 (10.3%)	
Age	*Median*	*52 years*	*54 years*	*48 years*	*38 years*
	≤18 years	20 (10.9)	12 (8.2)	0 (0)	8 (21.6)
	19–65 years	116 (63.4)	93 (63.7)	11 (73.3)	23 (62.2)
	>65 years	47 (25.7)	41 (28.1)	4 (26.7)	6 (16.2)
Sex	Male	108 (59)	85 (58.2)	8 (53.3)	23 (62.2)
	Female	75 (41)	61 (41.8)	7 (46.7)	14 (37.8)
Preexisting medical condition	Cardiovascular disease (HTN, CVA, IHD, CHD, VHD).	62 (33.9)	50 (34.2)	4 (26.7)	12 (32.4)
	Diabetes mellitus	48 (26.2)	37 (25.3)	6 (40)	11 (29.7)
	Pulmonary diseases (BA, bronchiectasis, COPD, ILD)	42 (23)	39 (26.7)	6 (40)	3 (8.1)
	Malignancy (Solid or hematologic)	35 (19.1)	30 (20.5)	4 (26.7)	5 (13.5)
	Medically free	26 (14.2)	19 (13)	2 (13.3)	7 (18.9)
	Autoimmune disease (PCD, IBD, SLE, MS)	17 (9.3)	8 (5.5)	1 (6.7)	9 (24.3)
	Renal or liver disease	15 (8.2)	14 (9.6)	1 (6.7)	1 (2.7)
	History of mycobacterium tuberculosis infection	16 (8.7)	15 (10.3)	2 (13.3)	1 (2.7)
	Human immunodeficiency virus (HIV)	13 (7.1)	12 (8.2)	0 (0)	1 (2.7)
	Smoker or ex-smoker	9 (4.9)	9 (6.2)	2 (13.3)	0 (0)
	Primary immunodeficiency	8 (4.4)	6 (4.1)	0 (0)	2 (5.4)
Presentation	Respiratory symptoms	66 (36.1)	62 (42.5)	7 (46.7)	4 (10.8)
	Respiratory symptoms + fever	59 (32.2)	54 (37)	4 (26.7)	5 (13.5)
	Fever and/or B symptoms	30 (16.4)	23 (15.8)	4 (26.7)	7 (18.9)
	Other symptoms	18 (9.8)	1 (0.7)	0 (0)	17 (45.9)
	Asymptomatic	10 (5.5)	6 (4.1)	0 (0)	4 (10.8)
Chest X-ray or CT scan findings, (not done in 5 cases)	Normal	–	25 (17.1)	0	–
	Cavity	–	11 (7.5)	6 (40)	–
	Nodules	–	18 (12.3)	7 (46.7)	–
	Bronchiectasis	–	12 (8.2)	2 (13.3)	–
	Other findings	–	75 (51.4)	0	–

- Respiratory specimens include: expectorated sputum, induced sputum, bronchoalveolar lavage, tracheal aspirate, gastric aspirate (for pediatric age group), and lung biopsy. Lung imaging include: Chest X-ray and computed tomography (CT).

younger age in this cohort including respiratory group, those who met ATS/IDSA criteria, and non-respiratory group (median age 54–38 years). This difference should be interpreted with caution given the difference in older population between the Saudi and western countries (3 vs 16%). (ref: World Bank staff estimates based on age/sex distributions of United Nations Population Division's World Population Prospects: 2019 Revision). The predominance of the male gender found in this study was in concordance with previous studies, which depicts that the gender of patients are potential risk factors for NTM infections [18-20].

While the minority in this study were with no pre-existing comorbidities (14.2%), we found that preexisting pulmonary diseases was associated with NTM infection, especially COPD and bronchial asthma (BA). Historically, medication in this group of patients, COPD and BA, showed a dramatic relationship between immunosuppression and increased risk of pulmonary NTM diseases [21]. Furthermore, NTM is recognized as an important cause of chronic lung infection in many countries. Nevertheless, pulmonary NTM can still occur in patients with no underlying lung disease [27,28].

Susceptibility to extra-pulmonary NTM is more in patients with TB disease, diabetes mellitus and chronic kidney disease [22-24]. Additionally, the increase in the use of immune-modulating drugs might explain the world-wide rise in NTM infection prevalence [25,26]. In contrast, immunocompromised individuals were not the majority in this paper, potentially because the study was performed in a single center. However, the increasing number of immunocompromised patients, including those with solid organ transplantation, malignancies, diabetes mellitus, renal failure, as well as the increasing prevalence of primary immunodeficiencies puts Saudi population at risk and more susceptible to NTM infections [27-30].

Similar to the rest of the world, a progressive rise in reporting NTM species is observed in the literature, likely due to increase in identification and increase in use of immunosuppressive agents. [31] Recent studies have noted that the increase in middle eastern and Asian countries was seen mainly with the rapidly growing NTM, as opposed to Europe and North America in which the slowly growing NTM predominated [10], However, in the current study, we noted a predominance of SGM over RGM especially among respiratory isolates, even if we adjust per AST/IDSA criteria. Previous studies from Saudi Arabia have mostly reported NTM species with M. fortuitum and M. abscessus with clinical relevance of 28–34% [20,32] Nevertheless, these species were much less reported in the current report and were mostly regarded as colonizers. Clearly, the species distribution in this study is different from the previous reports. However, they may not reflect the reality of species distribution because 48.1% of the samples were not yet identified. This may hint toward the challenges in the species identification in our center.

M. Simiae is a rare environmental species of NTM that was the first reported from a monkey's lymph node [33,34]. True infection due to M. Simiae is relatively rare, and estimated to be as low as 10% [35,36] and most of them were associated with immunocompromised patients, including HIV patients [37-39]. In our cohort, 3/23 (13%) were considered pathogenic and were treated with Anti-NTM therapy, one was a renal transplant patient and the other two had a non-immunocompromised state. We had 3 cases of M. Simiae isolated from the respiratory system of HIV patients, but none of them were considered pathogenic. All the 23 cases have survived at one year post culture date.

M. riyadhense was identified in 2009 and reported from many countries. It is a slow-growing Mycobacterium, and it is very close to M. szulgai phylogenetically [40]. Furthermore, by using biochemical

Table 2
Specimens type, results of identifications, and radiological findings, stratified by specimens types and ATS/IDSA criteria for pulmonary disease, among all patients with nontuberculous Mycobacterium in a tertiary care center, Riyadh, Saudi Arabia, between 2006 and 2017, (n = 183).

Parameter			Total n = 183 (%)	Respiratory specimens n = 146 (79.8%)		Non-respiratory specimens n = 37 (20.2%)
				Total	met ATS/IDSA criteria n = 15 (10.3%)	
Category of Specimens site	Pulmonary	Sputum	114 (62.3)	114 (62.3)	4 (26.7)	–
		Deep respiratory specimens	27 (14.8)	27 (14.8)	11 (73.3)	–
		Other respiratory specimens	5 (2.7)	5 (2.7)	–	0 (0)
	Extrapulmonary	Non-Sterile sites	21 (11.5)	–	–	21 (11.5)
		Sterile sites	13 (7.1)	–	–	13 (7.1)
		Multiple sites	3 (1.6)	–	–	3 (1.6)
Species identification	Species not identified		88 (48.1)	88 (48.1)	7 (46.7)	71 (38.8)
	SGM	Total	74 (40.4)	62 (33.9)	6 (40)	12 (6.6)
	(n = 74)	*M. Simiae*	21 (11.5)	17 (9.3)	2 (13.3)	4 (2.2)
		M. gordonae	14 (7.7)	12 (6.6)	0 (0)	2 (1.1)
		M. riyadhense	11 (6)	8 (4.4)	2 (13.3)	3 (1.6)
		M. szulgai	10 (5.5)	10 (5.5)	0 (0)	0 (0)
		M. xenopi	7 (3.8)	6 (3.3)	0 (0)	1 (0.5)
		M. avium	5 (2.7)	3 (1.6)	1 (6.7)	2 (1.1)
		M. scrofulaceum	2 (1.1)	2 (1.1)	1 (6.7)	0 (0)
		M. kansasii	2 (1.1)	2 (1.1)	0 (0)	0 (0)
		M. kubicae	1 (0.5)	1 (0.5)	0 (0)	0 (0)
		M. parascrofulaceum	1 (0.5)	1 (0.5)	0 (0)	0 (0)
	RGM	Total	21 (11.5)	13 (7.1)	2 (13.3)	8 (4.4)
	(n = 21)	*M. chelonae*	8 (4.4)	5 (2.7)	2 (13.3)	3 (1.6)
		M. abscessus	5 (2.7)	2 (1.1)	0 (0)	3 (1.6)
		M. fortuitum	5 (2.7)	5 (2.7)	0 (0)	0 (0)
		M. conceptionense	2 (1.1)	1 (0.5)	0 (0)	1 (0.5)
		M. mageritense	1 (0.5)	0 (0)	0 (0)	1 (0.5)
Treatment	Treated		41 (22.4)	33 (22.6)	4 (26.7)	8 (21.6)
	Not treated		142 (77.6)	113 (77.4)	11* (73.3)	29 (78.4)
Outcome	Survived		178 (97.3)	141 (96.6)	14 (93.3)	37 (100)
	Died		5 (2.7)	5 (3.4)	1 (6.7)	0 (0)

Lung imaging include: Chest X-ray and computed tomography (CT).
* Reasons of not treating those who fit ATS/IDSA criteria (n = 11): culture results came after patient sent home (n = 3), patients were already recovered at the time culture result (n = 3), patient died before culture result (n = 1), or no clear reason and infectious disease team was not involved (n = 4).

Table 3
Details on the patients who died at 1 year of positive NTM culture (n = 5).

No.	Year	Age, sex	Specimen	Species	Medical History	Presentation	Lung Imaging	Met all ATS/IDSA criteria	Treatment	Culture date to death interval (days)
2	2007	39, F	Single sputum	M. gordonae	Hypopharyngeal cancer	Fever and dry cough,	CXR: normal.	No	No	60
3	2007	76, M	Single sputum	M. Simiae	Diabetes Mellitus, Ischemic heart disease.	Dyspnea.	CT: right lower lobe consolidation	No	No	299
4	2012	62, M	Single sputum	Unidentified	Renal cell cancer, Ischemic heart disease	Dry cough.	CT: left upper lobe interlobular septal thickening.	No	No	53
5	2013	76, M	BAL	Unidentified	Acute myelocytic leukemia, Diabetes Mellitus, Hypertension	Febrile neutropenia, dry cough, and dyspnea.	CXR: normal	No	No	7
1	2016	48, F	BAL	Unidentified	Diabetes Mellitus	Weight loss	CT: peripheral bilateral nodules.	Yes	No	66

testing, it is close to M. szulgai and M. malmoense [41]. M. riyadhense can cause pulmonary and extrapulmonary disease [41-43]

Until now, no commercial methods can recognize M. riyadhense species, and it needed advanced molecular diagnostics. From this study, 11 patients of M. riyadhense infection, 9 of them were from respiratory specimen, five out of 11 were known cases of HIV, and 2 patients were medically free. Although treatment was provided in 9 of the 11 cases, only 6 cases had ATS/IDSA criteria of true infection, and no death was documented at one year.

In our center, M. gordonae was found in 14 patients, where 12 of them had it from a single sputum sample, therefore none of these 14 cases were treated and all survived at one year. This is expected as M. gordonae is one of the weakest pathogens among all the NTMs, and its isolation is typically considered as a contaminant. The organism is ubiquitous, and it is the most common isolated from the environment especially the water. Nosocomial transmission has also been reported from tap water used for the washing of medical items [44]. Although M. gordonae is typically believed as a contaminant, there are numerous reports showed the organism could cause disease in immunocompetent and immunosuppressed patients. M. gordonae infections mainly

Table 4
Application of ATS/IDSA criteria among patients with positive respiratory specimens for nontuberculous Mycobacterium in a tertiary care center, Riyadh, Saudi Arabia, between 2006 and 2017 (n = 146).

ATS/IDSA criteria		n (%)
Symptom criteria:	Yes	140 (95.9)
	No	6 (4.1)
- Pulmonary or Systemic Symptoms.		
Imaging criteria:	Yes	42 (28.8)
	No	104 (71.2)
- CXR: nodular or cavitary, or,		
- HRCT: bronchiectasis with multiple small nodules		
Microbiology criteria:	Yes	34 (23.3)
	No	112 (76.7)
- At least two separate expectorated sputum samples or,		
- At least one bronchial wash or lavage, or,		
- Lung biopsy with histologic and positive culture, or,		
- Lung biopsy with histologic and one positive sputum.		
Meeting all criteria	Yes	15 (10.3)
	No	131 (89.7)

associated with corticosteroid treatment, HIV infection, malignancy, organ transplant recipients, and those in the extreme of age groups [45]. All cultures should be interpreted with caution since these cultures potentially represent contamination in the absence of pathological evidence. A study conducted in Roma proves the importance of the environmental survey for M. gordonae isolates and compare it to clinical isolates by using molecular tools as it is crucial to differentiate pseudo-outbreak from actual clinical infection [46].

All cases infected by M. Simiae, M. riyadhense, and M. szulgai presented with at least one symptom, where dry cough, fever, dyspnea, weight loss, hemoptysis, chest pain, and productive cough among their presentation. We could not appreciate significant differences between specific presentations within the species. Lung radiology findings in NTM infection are typically categorized into nodular, cavitary, or bronchiectasis changes [47].These changes were found only in 41/141 patients with respiratory specimens. Unfortunately, majority of cases that had these changes were not identified to species level. We could not find a radiological pattern toward specific species in this cohort, in contrast to previous studies were Mycobacterium avium-intracellulare complex and Mycobacterium M. kansasii showed significant differences in presenting symptoms and remarkable radiological finding from other NTMs [23,48].

Mortality due to NTM is variable between species. Early reports on rapidly growing mycobacterium estimated fatality around 15% [49]. However, such mortality risk is largely affected by underlying patient condition [50]. Recently, any respiratory isolation of NTM species was found an independent risk for death at five years irrespective to the status according to ATS/IDSA criteria [51]. We believe that the very low fatality in our cohort (2.7%) was largely affected by three variables, that we had younger population age, we used a relatively short-term outcome, and we have higher percentage of untrue NTM infections encountered in our center.

5. Limitations

In this study, there are multiple limitations. One is being a retrospective study. Second, the study was conducted in a single referral center. Also, about 50% of total NTM collected samples were not identified to the species level. Finally, susceptibility testing and treatment details were not completely available.

Ethical approval

Approval for this study was obtained in Novamber 2019 from King Fahd Medical City institutional review board: 19–256.

Table 5
Comparison with SGM and RGM against the study variables of identified species in a tertiary care center, Riyadh, Saudi Arabia, between 2006 and 2017 (n = 95).

Parameter		SGM n = 74 (77.9)	RGM n = 21 (22.1)	P-value	Odds ratio (95% confidence interval) For SGM
Age	≤18 years	8 (10.8)	2 (9.5)	0.92	
	19–65 years	48 (64.9)	13 (61.9)		
	>65 years	18 (24.3)	6 (28.6)		
Sex	Male	48 (64.9)	8 (38.1)	0.028	3.0 (1.1–8.17)
	Female	26 (35.1)	13 (61.9)		ref
Medical history*	Pulmonary Disease	17 (23)	6 (28.6)	0.61	
	Diabetes Mellitus	20 (27)	8 (38)		
	Malignancy	16 (21.6)	2 (9.5)		
	HIV	10 (13.5)	0		
	Non-HIV Immunodefidency	2 (2.7)	1 (4.8)		
	Renal/Liver disease	5 (6.8)	2 (9.5)		
	Autoimmune	5 (6.8)	0 (0)		
	Cardiovascular diseases	24 (32.4)	8 (38.1)		
	Medically Free	11 (14.9)	5 (23.8)		
History of MTB		5 (6.8)	3 (14.3)	–	
Symptoms	Fever + Respiratory symptoms	26 (35.1)	6 (28.6)	0.013	13 (1.1–147.8)
	Respiratory symptoms	28 (37.8)	7 (33.3)		12 (1.1–133.6)
	Fever and/or B symptoms	15 (20.3)	1 (4.8)		45 (2.2–937.3)
	Other symptoms	4 (5.4)	4 (19)		3 (0.2–42.6)
	Asymptomatic	1 (1.4)	3 (14.3)		ref
Specimen	Sputum	50 (67.6)	11 (52.4)	–	
	• *Adjusted by ATS/IDSA microbiology criteria*	*0 (0)*	*1 (4.8)*		
	Deep respiratory specimens	12 (16.2)	1 (4.8)		
	• *Adjusted by ATS/IDSA microbiology criteria*	*6 (8.1)*	*1 (4.8)*		
	Other respiratory specimens	0	1 (4.8)		
	• *Adjusted by ATS/IDSA microbiology criteria*	*0*	*0*		
	Non-pulmonary, Non-Sterile sites	6 (8.1)	3 (14.3)		
	Non-pulmonary, Sterile sites	3 (4.1)	5 (23.8)		
	Non-pulmonary, Multiple sites	3 (4.1)	0		
Treatment	Treated	21 (28.4)	5 (23.8)	0.68	
	Not treated	53 (71.6)	16 (76.2)		
Outcome	Survived	72 (97.3)	21 (100)	0.446	
	Died	2 (2.7)	0 (0)		

*Patients could have more than one category.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Ventura M, Canchaya C, Tauch A, Chandra G, Fitzgerald GF, Chater KF, et al. Genomics of Actinobacteria: Tracing the Evolutionary History of an Ancient Phylum. Microbiol Mol Biol Rev 2007 Sep 5,;71(3):495–48.

[2] McNabb A, Eisler D, Adie K, Amos M, Rodrigues M, Stephens G, et al. Assessment of partial sequencing of the 65-kilodalton heat shock protein gene (hsp65) for routine identification of Mycobacterium species isolated from clinical sources. J Clin Microbiol 2004;42(7):3000–11.

[3] https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type=%22country%22&lan=%22EN%22&iso2=%22SA%22.

[4] Falkinham JO. Surrounded by mycobacteria: nontuberculous mycobacteria in the human environment. J Appl Microbiol 2009 -08;107(2):356–67.

[5] Bryant JM, Grogono DM, Greaves D, Foweraker J, Roddick I, Inns T, et al. Whole-genome sequencing to identify transmission of Mycobacterium abscessus between patients with cystic fibrosis: a retrospective cohort study. The Lancet 2013;381 (9877):1551–60.

[6] Ungaro R, Mikulska M. The skin and soft tissue infections in hematological patients. Curr Opin Infect Dis 2020;33(2):101–9.

[7] Jesudason MV, Gladstone P. Non tuberculous mycobacteria isolated from clinical specimens at a tertiary care hospital in South India. Indian J Med Microbiol 2005; 23(3):172–5.

[8] Ding LW, Lai CC, Lee LN, Hsueh PR. Disease caused by non-tuberculous mycobacteria in a university hospital in Taiwan, 1997–2003. Epidemiol Infect 2006;134(5):1060–7.

[9] Prevots DR, Marras TK. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: a review. Clin Chest Med 2015;36(1):13–34.

[10] Al-Ghafli H, Al-Hajoj S. Nontuberculous mycobacteria in Saudi Arabia and gulf countries: a review. Can Respir J 2017;2017.

[11] Maurya AK, Nag VL, Kant S, Sharma A, Gadepalli RS, Kushwaha RS. Recent methods for diagnosis of nontuberculous mycobacteria infections: Relevance in clinical practice. Biomed Biotechnol Res J 2017;1(1):14.

[12] Raju RM, Raju SM, Zhao Y, Rubin EJ. Leveraging advances in tuberculosis diagnosis and treatment to address nontuberculous mycobacterial disease. Emerg Infect Dis 2016;22(3):365–9.

[13] Genc GE, Demir M, Yaman G, Kayar B, Koksal F, Satana D. Evaluation of MALDI-TOF MS for identification of nontuberculous mycobacteria isolated from clinical specimens in mycobacteria growth indicator tube medium. New Microbiol 2018;41 (3):214–9.

[14] Gopalaswamy R, Shanmugam S, Mondal R, Subbian S. Of tuberculosis and non-tuberculous mycobacterial infections–a comparative analysis of epidemiology, diagnosis and treatment. J Biomed Sci 2020;27(1):1–17.

[15] Chien J-Y, Lai C-C, Sheng W-H, Yu C-J, Hsueh P-R. Pulmonary infection and colonization with nontuberculous mycobacteria, Taiwan, 2000–2012. Emerg Infect Dis 2014;20(8):1382–5.

[16] Lin C, Yang Y, Lu M, Tsai Y, Hsieh M, Lee Y, et al. Incidence of nontuberculous mycobacterial disease and coinfection with tuberculosis in a tuberculosis-endemic region: A population-based retrospective cohort study. Medicine 2020;99(52).

[17] Castle SC. Clinical relevance of age-related immune dysfunction. Clin Infect Dis 2000;31(2):578–85.

[18] Cassidy PM, Hedberg K, Saulson A, McNelly E, Winthrop K. Nontuberculous mycobacterial disease prevalence and risk factors: a changing epidemiology. Clin Infect Dis 2009;49(12):e124–9.

[19] Mokaddas E, Ahmad S. Species spectrum of nontuberculous mycobacteria isolated from clinical specimens in Kuwait. Curr Microbiol 2008;56(5):413–7.

[20] Varghese B, Memish Z, Abuljadayel N, Al-Hakeem R, Alrabiah F, Al-Hajoj SA, et al. Emergence of clinically relevant non-tuberculous mycobacterial infections in Saudi Arabia. PLoS Negl Trop Dis 2013;7(5):e2234.

[21] Hojo M, Iikura M, Hirano S, Sugiyama H, Kobayashi N, Kudo K. Increased risk of nontuberculous mycobacterial infection in asthmatic patients using long-term inhaled corticosteroid therapy. Respirology 2012;17(1):185–90.

[22] Marušić A, Katalinić-Janković V, Popović-Grle S, Janković M, Mažuranić I, Puljić I, et al. Mycobacterium xenopi pulmonary disease–epidemiology and clinical features in non-immunocompromised patients. J Infect 2009;58(2):108–12.

[23] Matveychuk A, Fuks L, Priess R, Hahim I, Shitrit D. Clinical and radiological features of Mycobacterium kansasii and other NTM infections. Respir Med 2012; 106(10):1472–7.

[24] Youmbissi JT, Malik QT, Ajit SK, Al Khursany IA, Rafi A, Karkar A. Non tuberculous mycobacterium peritonitis in continuous ambulatory peritoneal dialysis. J Nephrol 2001;14(2):132–5.

[25] Winthrop KL. Pulmonary disease due to nontuberculous mycobacteria: an epidemiologist's view. Fut Microbiol 2010;5(3):343–5.

[26] Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007;175(4): 367–416.

[27] Alqurashi KA, Aljabri KS, Bokhari SA. Prevalence of diabetes mellitus in a Saudi community. Ann Saudi Med 2011;31(1):19–23.

[28] Al-Sayyari AA, Shaheen FA. End stage chronic kidney disease in Saudi Arabia. Saudi Med J 2011;32(4):339–46.

[29] El Mouzan MI, Al Salloum AA, Al Herbish AS, Qurachi MM, Al Omar AA. Consanguinity and major genetic disorders in Saudi children: a community-based cross-sectional study. Ann Saudi Med 2008;28(3):169–73.

[30] Bouchbika Z, Haddad H, Benchakroun N, Eddakaoui H, Kotbi S, Megrini A, et al. Cancer incidence in Morocco: report from Casablanca registry 2005–2007. Pan African Med J 2014;16. https://doi.org/10.11604/pamj.2013.16.31.2791.

[31] Rindi L, Garzelli C. Increase in non-tuberculous mycobacteria isolated from humans in Tuscany, Italy, from 2004 to 2014. BMC Infect Dis 2015;16(1):1–5.

[32] AL-Harbi A, AL-Jahdali H, AL-Johani S, Baharoon S, Bin Salih S, Khan M. Frequency and clinical significance of respiratory isolates of non-tuberculous mycobacteria in Riyadh, Saudi Arabia. Clin Respir J 2016;10(2):198–203.

[33] El Sahly HM, Septimus E, Soini H, Septimus J, Wallace RJ, Pan X, et al. Mycobacterium simiae pseudo-outbreak resulting from a contaminated hospital water supply in Houston, Texas. Clin Infect Dise 2002 October 1;35(7):802–807.

[34] Karasseva V. Occurrence of atypical mycobacteria in Macacus rhesus. Acta Microbiol Acad Sci Hung 1965;12:275–82.

[35] Rynkiewicz DL, Cage GD, Butler WR, Ampel NM. Clinical and microbiological assessment of Mycobacterium simiae isolates from a single laboratory in southern Arizona. Clin Infect Dis 1998;26(3):625–30.

[36] Valero G, Peters J, Jorgensen JH, Graybill JR. Clinical isolates of Mycobacterium simiae in San Antonio, Texas. An 11-yr review. Am J Respir Crit Care Med 1995; 152(5 Pt 1):1555–57.

[37] B B, J E, S J, Jm C, Ml F. Mycobacterium simiae Infection in an Immunocompromised Patient without Acquired Immunodeficiency Syndrome. Clin Infect Dis 2002 /01/24;34(5):26.

[38] Legrand E, Devallois A, Horgen L, Rastogi N. A molecular epidemiological study of Mycobacterium simiae isolated from AIDS patients in Guadeloupe. J Clin Microbiol 2000;38(8):3080–4.

[39] Sampaio JL, Artiles N, Pereira RM, Souza JR, Leite JP. Mycobacterium simiae infection in a patient with acquired immunodeficiency syndrome. Braz J Infect Dis 2001;5(6):352–55.

[40] Al-Hajoj S, Varghese B, Van Ingen J, Van Soolingen D. Mycobacterium riyadhense overlooked: we can only find what we are looking for. J Infect Dev Ctries 2013;7 (3):293–94.

[41] van Ingen J, Al-Hajoj SAM, Boeree M, Al-Rabiah F, Enaimi M, de Zwaan R, et al. Mycobacterium riyadhense sp. nov., a non-tuberculous species identified as Mycobacterium tuberculosis complex by a commercial line-probe assay. Int J Syst Evol Microbiol 2009;59(5):1049–53.

[42] Tortoli E, Pecorari M, Fabio G, Messinò M, Fabio A. Commercial DNA probes for mycobacteria incorrectly identify a number of less frequently encountered species. J Clin Microbiol 2010;48(1):307–10.

[43] Godreuil S, Marchandin H, Michon A, Ponsada M, Chyderiotis G, Brisou P, et al. Mycobacterium riyadhense pulmonary infection, France and Bahrain. Emerg Infect Dis 2012;18(1):176–78.

[44] Wallace RJ, Brown BA, Griffith DE. Nosocomial outbreaks/pseudo-outbreaks caused by nontuberculous mycobacteria. Annu Rev Microbiol 1998;52(1):453–90.

[45] Weinberger M, Berg SL, Feuerstein IM, Pizzo PA, Witebsky FG. Disseminated infection with Mycobacterium gordonae: report of a case and critical review of the literature. Clin Infect Dis 1992;14(6):1229–39.

[46] Scorzoli ni L, Mengoni F, Mastroianni CM, Baldan R, Cirillo DM, De Giusti M, et al. Pseudo-outbreak of Mycobacterium gordonae in a teaching hospital: importance of strictly following decontamination procedures and emerging issues concerning sterilization. New Microbiol 2016;39(1):25–34.

[47] Woodring JH, Vandiviere HM. Pulmonary disease caused by nontuberculous mycobacteria. J Thorac Imaging 1990;5(2):64–76.

[48] Simons S, van Ingen J, Hsueh P-R, Van Hung N, Dekhuijzen PNR, Boeree MJ, et al. Nontuberculous mycobacteria in respiratory tract infections, eastern Asia. Emerg Infect Dis 2011;17(3):343–9.

[49] Griffith DE, Girard WM, Wallace RJ. Clinical features of pulmonary disease caused by rapidly growing mycobacteria. An analysis of 154 patients. Am Rev Respir Dis 1993;147(5):1271–8.

[50] Park SC, Kang MJ, Han CH, Lee SM, Kim CJ, Lee JM, et al. Prevalence, incidence, and mortality of nontuberculous mycobacterial infection in Korea: a nationwide population-based study. BMC Pulm Med 2019;19(1). https://doi.org/10.1186/s12890-019-0901-z.

[51] Novosad SA, Henkle E, Schafer S, Hedberg K, Ku J, Siegel SAR, et al. Mortality after Respiratory Isolation of Nontuberculous Mycobacteria. A Comparison of Patients Who Did and Did Not Meet Disease Criteria. Ann ATS 2017;14(7):1112–119.