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Nationwide evaluation of treatment outcomes and survival of patients with nontuberculous mycobacterial pulmonary disease

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Running head: Treatment outcomes in NTM-PD

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SUMMARY

Background: The impact of treatment on nontuberculous mycobacterial pulmonary disease (NTM-PD) is difficult to assess in a real-world setting. We aimed to determine the nationwide treatment outcomes and long-term survival of NTM-PD patients.

Methods: retrospective cohort study on all Croatian residents with respiratory NTM isolates from 2006 to 2015 with follow up to 2020. ATS/IDSA guidelines and the NTM-NET consensus statement were used to establish NTM-PD diagnosis and score the adequacy of treatment.

Results: Guideline based treatment (GBT) was started in 50/98 (51%) of treated patients, but the recommended duration was followed in only 35.7% (35/98). GBT treated patients had higher chance of being cured (OR 3.79, 95% CI 1.29 to 11.1, p=0.012) compared to inadequately treated/untreated patients. Patients with MX-PD achieved high cure rates (>80%) with both GBT and TB treatment (p=0.57). Five-year all-cause mortality in inadequately treated (37.1%) or untreated (46.2%) patients was higher compared to GBT treated (27.8%) patients (p = 0.29).

Conclusion: Only one third of patients treated for NTM-PD received GBT which resulted in a four-time higher chance of being cured. This was mostly driven by improved rates in MAC-PD, FC, and smear positive patients, with no clear impact of GBT on MX-PD.

Key words: NTM-PD, treatment outcomes, long term survival

ABREVIATIONS

AFB acid fast bacilli

ATS American Thoracic Society

BMI body mass index

CIPH Croatian Institute of Public Health

FC fibro cavitary

GBT guideline based treatment

IDSA Infectious Diseases Society of America

MAC *Mycobacterium avium* complex

MAC-PD *Mycobacterium avium* complex pulmonary disease

MX-PD *Mycobacterium xenopi* pulmonary disease

NB nodular bronchiectatic

NRML National Reference Mycobacteria Laboratory

NTM non-tuberculous mycobacteria

NTM-PD non-tuberculous mycobacterial pulmonary disease

SCC spontaneous culture conversion

TB tuberculosis

TTP time to positivity

INTRODUCTION

Nontuberculous mycobacteria (NTM) are ubiquitous in our environment.[1,2] NTM pulmonary disease (NTM-PD), the most common disease form, is an important entity in humans which mostly affects the elderly population with underlying lung disease. [2-5] Diagnosis of NTM-PD is complex, while treatment requires long-term administration of species-specific multidrug regimens.

In 2020, new international guidelines for the management of NTM-PD were published.[2] They offer recommendations on management of NTM-PD caused by the most common NTM species. A recent document added recommendations for 7 rarer NTM species.[6] Additionally, outcome definitions have now been proposed for NTM-PD.[7] However, despite these new clear recommendations on the treatment and outcomes of NTM-PD, real world data from two recent retrospective studies showed heterogeneous practice in NTM-PD management, relatively low cure rates and high rates of unsuccessful outcomes.[8,9]

Our previous studies showed increasing prevalence of NTM isolation and NTM-PD in Croatia (with significant geographical differences within the country), established *M. xenopi* and MAC as the most frequent causative agents of NTM-PD, and explored the characteristics and possible risk factors for NTM-PD in our setting.[10-13] In this retrospective cohort study, we aimed to evaluate the treatment outcomes and long-term survival after therapy completion in a real-life setting using nationwide data from the Croatian national registry of patients with NTM isolates.

METHODS

We conducted a retrospective cohort study on all Croatian residents with NTM isolated from respiratory samples in the period from January 1st 2006 to December 31st 2015 with follow-up up to December 31st 2020. The study was approved by the Ethics Committee of the Croatian Institute of Public Health (CIPH; file number 001-487/1-10 and 381-15-21-2). All NTM isolates were identified at the National Reference Mycobacteria Laboratory (NRML) at CIPH as previously described. [10,11]

Clinical, radiological, treatment and outcome data were extracted from the national NTM registry which includes all Croatian residents with NTM isolates from 2005 onwards.

An NTM isolation episode was defined as one or more NTM isolates from a single person. In cases of multiple species found within the same episode, the species considered to be underlying the disease was the one with more isolates and/or associated with more clinical importance in our setting.[11] In case of a similar number of different NTM species isolates and/or species of equal importance, the episode was classified as co-infection.

Definite NTM-PD and "no disease" were defined according to the ATS/IDSA guidelines.[14] "Probable disease" was used if the likelihood of NTM-PD was high, but one part of the criteria was not met.

Adequate NTM treatment was defined as guideline-based treatment (GBT) for at least 12 months after culture conversion; shorter duration adequate treatment as a regimen based on the guidelines but for a total duration of <12 months; TB protocol as a standard first-line regimen usually given for tuberculosis, while inadequate NTM protocol included patients given single drug regimens or unusual drug combinations.

Treatment outcomes, recurrence, and reinfection were defined according to the NTM-NET consensus statement.[7] Microbiological cure was assessed at the end of the adequate NTM treatment or at 12 months after NTM identification in case of shorter regimens or in untreated patients. Death as an outcome was defined as death due to any reason within 12 months from NTM identification point. Deaths occurring outside this period were assessed in long-term survival calculations. Given the possibility that some untreated patients died prior to establishing NTM-PD diagnosis, curve analysis was also done after exclusion of all patients dying within 4 months of NTM isolation. Microsoft Excel (Microsoft, Redmond, WA, USA) was used to tabulate data, calculate frequencies, percentages, and median ages. The $\chi 2$, Odds ratio and Kaplan-Meier survival analysis were performed using MedCalc (v 20.111, MedCalc Software, Ostend, Belgium). P values less than 0.05 were considered significant.

RESULTS

The NRML identified 2221 pulmonary NTM episodes. After excluding concomitant active tuberculosis, 1928 episodes remained. Isolation frequency, clinical relevance of different NTM species and stratification of NTM-PD cases is shown in **Table 1**.

Complete medical records were available for 29.1% of all NTM isolation episodes, but the percentage of evaluated records reached >55% in the case of MAC, *M. xenopi*, and *M. kansasii*, the NTM species known to be of higher clinical interest in our setting.[10,11]

Criteria for definite, probable, and no disease were met by 137 (29.1%), 31 (6.6%) and 303 (64.3%) of the 471 episodes with full medical information, respectively. The mean age of NTM-PD patients was 64.1 years, 47.4% were female and COPD was the most common comorbidity (45.9%). The detailed characteristics of our cohort have been previously published (13). Out of 98 (71.5%) patients that started therapy, GBT was given in 50 (50/98=51.0%), but the recommended treatment duration was followed in only 28 (28.6%) patients.

Unsuccessful treatment outcomes were recorded in 39/98 (39.8%) patients (14/98 (14.3%) deaths and 25/98 (25.5%) treatment failures). Cure was achieved in 55/98 (56.1%), while four patients were lost to follow-up. In 80 patients with available follow-up data, microbiological cure was achieved in 82.8% (24/29), 64.7% (22/34), and 69.2% (9/13) finishing adequate NTM treatment, TB treatment, or short NTM treatment, respectively (**Table 2**). Spontaneous culture conversion occurred (SCC) in 41.2% (7/17) untreated patients.

Patients with definite NTM-PD treated according to the guidelines had a higher chance of being cured (OR 3.79, 95% CI 1.29 to 11.1, z statistics =2.427, p=0.0152) compared to inadequately treated/untreated patients, regardless of radiological NTM-PD form.

None of the 62 patients achieving cure on treatment or SCC experienced a recurrence within the first 12 months of follow-up, but 8/62 died due to causes other than NTM-PD within the next 12 months. Nine of the 54 long-term surviving patients (16.7%) experienced a recurrence of NTM-PD within the study period, but several years (mean 32.2 months) after initial treatment completion. Four had a recurrence with the same NTM species while five had a reinfection with different NTM.

Median follow up was 69.9 months (range 0.1-181.6). One-year and 5-year all-cause mortality amounted to 18.2% and 37.6%. We noticed a trend towards a higher 5-year all-cause mortality in inadequately treated (37.1%) or untreated (46.2%) patients compared to adequately treated (27.8%) patients (log-rank test p= 0.29) (**Figure 1A**). Median survival was 142.4 (95%CI 60.7-142.4), 94.4 (57.8-120) and 67 (16.1.-101.4) months for adequately, inadequately, and untreated patients, respectively. The differences in survival were less pronounced when patients dying within 4 months of NTM isolation were excluded (log-rank test p=0.63, **Figure 1B**).

In fifteen patients receiving "short NTM treatment", treatment was mostly intentionally ceased after reaching initial culture conversion, while two patients stopped early due to side effects. One patient soon died of another cause, one was lost to follow-up, while three experienced fast recurrence.

Death occurred in 28.2% (11/39) of untreated patients. Seven died before establishing NTM-PD, one refused treatment, and in three cases NTM was dismissed as the cause of clinical worsening. Of the remaining 28 patients, four refused offered therapy, while in 18 cases physicians opted for watchful waiting. For the remaining 6 patients (2 MAC, 4 *M. xenopi*), the reasons remain unknown.

Cure results stratified according to the species and treatment protocol are shown in **Table 2.** In contrast to MAC-PD, for *M. xenopi* PD (MX-PD) high cure rates (>80%) were achieved both with adequate NTM treatment and TB treatment (chi square p=0.579), and irrespective of radiological manifestation (**Table 2**). Treatment was started in 35/39 (89.7%) of patients with FC radiological manifestation. Six patients (15.8%) died, while microbiological cure was achieved in 63.6% (7/11) and 83.3% (10/12) completing TB and adequate NTM treatment, respectively. Four patients not receiving therapy were all alive at 12 months follow-up, but microbiological data (remained culture positive) was available in one case. Compared to FC, treatment was started in 57/85 (67%) of NB NTM-PD cases (chi square p=0.009). While six (10.5%) died, adequate NTM treatment, short NTM treatment, and TB treatment achieved microbiological cure in 82.4% (14/17), 63.6 (7/11) and 63.2% (12/19) cases, respectively. Out of 114 NTM-PD with available microscopy finding, 47 (41.2%) were acid-fast bacilli (AFB) smear positive. Both FC and NB manifestations were equally represented within this subgroup. Treatment was administered in 91.5% (n=43) of AFB+ and 61.2% (n=41) of AFB- cases (chi-square p=0.0003). In adequately treated patients, cure was achieved more often in AFB- than AFB+ patients (78.6% vs. 60%, chi square p=0.28), and the same signal was observed for both MAC-PD and MX-PD (**Table 3**). In MX-PD treated with TB protocol, the cure rate was doubled (8/9 vs. 4/9) in smear negative patients (**Table 3**).

DISCUSSION

Our population-based study provides a "real-world" assessment of NTM-PD management with a long-term follow-up. Most (77.85%) of NTM-PD patients in our cohort received antibiotic treatment, and smear positivity and FC disease likely influenced treatment initiation decision. GBT was administered in one third of the treated cases and resulted in a four-time higher chance of being cured. Interestingly, while GBT was important for the outcomes of patients with MAC-PD, FC and AFB+, we observed no clear impact of treatment regimens on cure rates of MX-PD patients and in AFB- patients. NTM-PD was mostly caused by *M. xenopi* and MAC, and the overall 5-year mortality amounted to 37.6%.

NTM-PD does not necessarily require treatment and understanding the nature of the disease is important for patient management.[2,15] It has been shown for MAC-PD that 40-60% of patients (especially with NB manifestation) remain stable for several years after diagnosis even without treatment.[16-19] In our cohort, SCC amounted to 41% but this may be influenced by the diversity of causative NTM species and the loss to follow up rate in untreated patients. In line with some other studied cohorts, SSC was 30% in the MAC-PD subgroup.[19,20] Important prognostic factors related to MAC-PD progression were low BMI,[16,19, 21-23] FC disease,[16-19,23] extensive disease[19,22] and AFB positive smears.[18, 21] A study from England identified FC disease manifestation and systemic symptoms as factors associated with treatment initiation.[24]

Poor guidelines adherence (less than a third of treated patients received GBT) is concordant with the results from the literature.[25-27] This non-adherence is undesirable as patients on GBT had almost a 4 times higher chance of being cured compared to patients receiving any other form of therapy or no therapy, which was also shown by Abate et al.[8] No difference was observed between the cure rates of FC and NB disease, which contrasts with previous observations of lower microbiological cure rates in MAC PD patients with FC disease,[28, 29] but our cohort included different NTM species and not just MAC. Although not significant, cure rates were higher in adequately treated smear negative patients, and this was observed for both MAC and MX-PD. Even MX-PD patients treated with a TB protocol achieved high cure rates if smear negative (88.9 vs 44.5%, Table 4). This may be explained by differences in the bacterial load as it has been previously shown that MAC-PD patients with longer liquid culture time-to-positivity (TTP; likely due to lower bacterial load) have higher chance of culture conversion.[30,31]

Unsuccessful outcome was observed in 39.8% of treated patients. Overall, this is in concordance with the recently published study from Italy,[9] but there were more deaths and treatment failures in our cohort. This is probably attributable to a greater variety in disease management (patients managed in different centers across the whole country), as compared to a cohort treated in a single, regional reference center.[9] Reoccurrence rate of 16.7% is like the study from Italy[9] but in contrast to a high rate (48%) of microbiological recurrence shown by Wallace et al.[32] However, their cohort encompassed only NB MAC disease in a predominantly female population managed in a large single center.

All these findings reveal the complexity of NTM-PD management. It is not surprising that the more severe the disease (i.e. smear positive, FC disease), the more important it is to administer adequate treatment. On the other hand, it is rather unexpected that TB treatment achieved high cure rates in MX-PD, or that different treatment protocols achieve equal cure rates in smear negative patients regardless of radiological manifestation. Based on these observations, one could argue that a portion of patients was likely over treated and would not progress or achieve culture conversion if left untreated. Still, the cure rates in all the treated subgroups were doubled in comparison to the cure

rates observed in untreated patients. Thus, one might also advocate starting with treatment earlier, when bacterial loads are still low as manifested in smear negativity, as it appears to be beneficial in terms of short-term outcomes. The lack of difference between therapy regimens' success in the treatment of "lighter" forms of NTM-PD is hard to elucidate. It could partly be explained by the heterogeneity of our cohort and differences in NTM species' pathogenicity, while the used guidelines mostly relied on the data derived from the studies done in MAC-PD.

Also, it is surprising that *M. xenopi*, the second most frequently NTM species and the most common cause of NTM-PD in Croatia, seemingly has a lover clinical significance and pathogenicity in comparison to data from other countries.[33,34] Only about a third of all evaluated *M. xenopi* isolates truly represented disease. Furthermore, compared to MAC-PD, microbiological cure seemed to be easier to achieve in MX-PD, regardless of the treatment protocol. This observation warrants further investigations, both into bacterial virulence factors as well as into bacterial factors underlying the different response to treatment.

NTM-PD is associated with high morbidity and mortality.[35-38] Although we didn't find a significant difference between treated and untreated patients, similarly to the study by Abate et al,[8] we observed a trend towards higher mortality in untreated/inadequately treated patients.

The major strengths of our study include its real-life approach, nationwide cohort of different NTM-PD patients and 5-year follow up. It gives insight into the treatment outcomes of patients managed according to the guidelines but also those receiving inadequate treatment or no treatment. The major limitations of our study are its retrospective design, small number of patients in each subgroup, and the lack of antimicrobial susceptibility testing (since it is not performed routinely in Croatia).

CONCLUSION

This nationwide retrospective cohort study confirms the heterogeneity and complexity of NTM-PD management in a real-world setting. GBT was administered in only one third of the treated cases but resulted in a four-time higher chance of being cured, mostly being driven by improved cure rates in MAC-PD, AFB+ patients and patients with FC disease. We observed no clear impact of GBT on cure rates of patients with MX-PD or in AFB- patients. Continuation of our registry, increasing the number of patients included and prolongation of follow-up could potentially shed some light at the observed differences regarding the impact of NTM species, disease severity and GBT on the outcomes and long-term survival of NTM-PD patients in Croatia.

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Table 1. Nontuberculous mycobacteria isolation frequency, clinical relevance (according to the percentage of isolates meeting the diagnostic criteria for NTM pulmonary disease) in Croatia, and stratification of NTM pulmonary disease cases according to gender and radiological manifestation

NTM	Medical records evaluated / total isolation episodes (%)	Definite NTM-PD (according to the ATS/IDSA criteria); n (%)	Definite NTM-PD cases				
			Gender		Radiological manifestation		
			M (%)	F (%)	FC (%)	NB (%)	Other (%)
M. gordonae	91/822 (11.1)	2 (2.2)	1 (50)	1 (50)	1 (49)	1 (51)	0 (0)
M. xenopi	166/296 (56.1)	55 (33.1)	33 (60)	22 (40)	17 (30.3)	35 (66)	3 (3.7)
M. fortuitum	57/220 (25.9)	2 (3.5)	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)
M. terrae	7/128 (5.5)	0 (0)	-	-	-	-	-
MAC	81/127 (63.8)	54 (66.7)	24 (44.4)	30 (55.6)	13 (23.4)	37 (66.7)	4 (9.9)
M. avium	45/70 (64.3)	32 (71.1)	14 (43.8)	18 (56.3)	6 (17.9)	24 (76.1)	2 (6)
M. intracellulare	30/47 (63.8)	20 (66.7)	8 (40)	12 (60)	7 (37.2)	11 (44.5)	2 (18.3)
*M. chimaera***	6/7 (85.7)	2 (33.3)	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)
MAC-undetermined	0/3 (0)	0 (0)	-	-	-	-	-
M. chelonae	15/95 (15.8)	0 (0)	-	-	-	-	-
M. abscessus	14/43 (32.6)	6 (42.9)	1 (16.7)	5 (83.3)	1 (9.2)	4 (87.5)	1 (3.3)
M. kansasii	14/24 (58.3)	8 (57.1)	6 (75)	2 (25)	2 (20.7)	5 (64)	1 (15.3)
Other*	26/173 (15)	10 (38.5)	5 (50)	5 (50)	5 (65.7)	5 (34.3)	0 (0)
Total	471/1928 (24.4)	137 (29.1)	72 (52.6)	65 (47.4)	39 (28.9)	89 (64.8)	9 (6.4)

ATS/IDSA – American Thoracic Society/Infectious Diseases Society of America, MAC – *Mycobacterium avium* complex; NTM – nontuberculous mycobacteria; NTM-PD - nontuberculous mycobacterial pulmonary disease

* Two patients had co-infection with two different NTM species – one with *M. avium* and *M. xenopi* and other with *M. xenopi* + *M. kansasii*

** Identification of *M. chimaera* was available only for 23 *M. intracellulare* isolates from the year 2013 till the end of study period.

Table 2. Treatment outcomes of nontuberculous mycobacterial pulmonary disease (NTM-PD) cases, stratified according to the causative species and administered treatment

NTM species		***M. xenopi* (n=55)**	*M. xenopi (by radiological manifestation)*			**MAC (n=54)**	MAC (by radiological manifestation)			***M. kansasii* (n=8)**	Other (n=20)	**Total (n=137)**
Administered treatment	Outcome		FC (n=17)	NB (n=35)	Other (n=3)		FC (n=13)	NB (n=37)	Other (n=4)			
TB treatment	Treated (n)	20	7	12	1	10	4	5	1	5	8	43
	Death <12 months (n)	5	3	2	0	3	2	0	1	0	1	9
	Lost to follow-up	0	0	0	0	0	0	0	0	0	0	0
	Microbiological cure*	12/15	4/4	7/10	1/1	2/7	1/2	1/5	0/0	4/5	4/7	22/34
Adequate NTM treatment	Treated (n)	11	6	5	0	17	6	11	0	1	6	35
	Death <12 months (n)	1	1	0	0	2	0	2	0	0	1	4
	Lost to follow-up	1	0	1	0	0	0	0	0	0	1	2
	Microbiological cure*	8/9	5/5	3/4	0/0	12/15	4/6	8/9	0/0	1/1	3/4	24/29
Short NTM treatment	Treated (n)	4	1	3	0	10	2	8	0	0	1	15
	Death <12 months (n)	0	0	0	0	1	0	1	0	0	0	1
	Lost to follow-up	0	0	0	0	1	0	1	0	0	0	1
	Microbiological cure*	3/4	1/1	2/3	0/0	6/8	1/2	5/6	0/0	0/0	0/1	9/13
Inadequate NTM treatment	Treated (n)	0	0	0	0	2	0	2	0	0	3	5
	Death <12 months (n)	0	0	0	0	0	0	0	0	0	0	0
	Lost to follow-up	0	0	0	0	1	0	1	0	0	0	1
	Microbiological cure*	0/0	0/0	0/0	0/0	0/1	0/0	0/1	0/0	0/0	0/3	0/4
No treatment	Total (n)	20	3	15	2	15	1	11	3	2	2	39
	Death <12 months(n)	8	0	7	1	3	0	1	2	0	0	11
	Lost to follow-up	7	3	3	1	2	0	1	1	1	1	11
	Culture conversion**	3/5	0/0	3/5	0/0	3/10	0/1	3/9	0/0	1/1	0/1	7/17

FC – fibro-cavitary; MAC – *Mycobacterium avium* complex; NB – nodular-bronchiectatic; NTM – nontuberculous mycobacteria; NTM-PD – NTM pulmonary disease; TB treatment – regimen usually administered for drug-sensitive tuberculosis; NTM treatment – guidelines based treatment in the duration of > 12 months after culture conversion; short NTM treatment - guidelines based treatment in the duration of < 12 months after culture conversion; death – death within the 12 months of NTM identification; * - finding multiple consecutive negative cultures from respiratory samples after culture conversion and until the end of treatment; **- multiple negative cultures from respiratory samples in untreated patients with available microbiological follow-up at 12 months after initial NTM identification;

Table 3 Treatment outcomes according to the causative NTM species, administered treatment, and smear result.

	Smear status	Cure	Treatment failure	Death
All adequately treated NTM-PD (n=35; 29/35 have known smear status)	AFB + (15)	9/15 (60%)	3/15 (20%)	3/15 (20%)
	AFB – (n=14)	11/14 (78.6%)	2/14 (14.3%)	1/14 (7.1%)
Adequately treated MAC-PD (n=17; 16/17 have known smear status)	AFB + (n=7)	4/7 (57.1%)	2/7 (28.6%)	1/7 (14.3%)
	AFB - (n=9)	7/9 (77.8%)	1/9 (11.1%)	1/9 (11.1%)
Adequately treated MX-PD (n=11; 9/11 have known smear status	AFB + (n=5)	3/5 (60%)	1/5 (20%)	1/5 (20%)
	AFB – (n=4)	4/4 (100%)	n.a.	n.a.
MX-PD treated with TB protocol (n=20, 18/20 have known smear status)	AFB + (n=9)	4/9 (44.5%)	3/9 (33.3%)	2/9 (22.2%)
	AFB – (n=9)	8/9 (88.9%)	0	1/9 (11.1%)

AFB – acid fast bacilli; MAC-PD – pulmonary disease caused by Mycobacterium avium complex; MX-PD – pulmonary disease caused by *Mycobacterium xenopi*; NTM – nontuberculous mycobacteria; TB - tuberculosis

FIGURE LEGENDS

Figure 1. All-cause mortality in patients with definite NTM-PD stratified according to the administered therapy.

A) all NTM-PD patients with follow-up information included (n=134); B) patients who died within 4 months of NTM identification are excluded from all three groups (included n=118); Adequate arm includes all patients that received adequate NTM treatment in duration >12 months after becoming culture negative, as well as those that died within the first 12 months of NTM therapy. Inadequate arm consists of patients receiving short adequate NTM regimen (<12 months), TB regimen or inadequate NTM regimen (i.e. monotherapy)

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Author contributions: MJM conceptualized and designed the study, collected and analyzed the data, drafted and revised the manuscript, and provided final approval of the version to be published. GG, IS, LZ, MS, AS, AM, IM, LKB, LC, MO and JvI made substantial contributions to the collection and interpretation of data and critical revision of the manuscript and provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are investigated appropriately and resolved.

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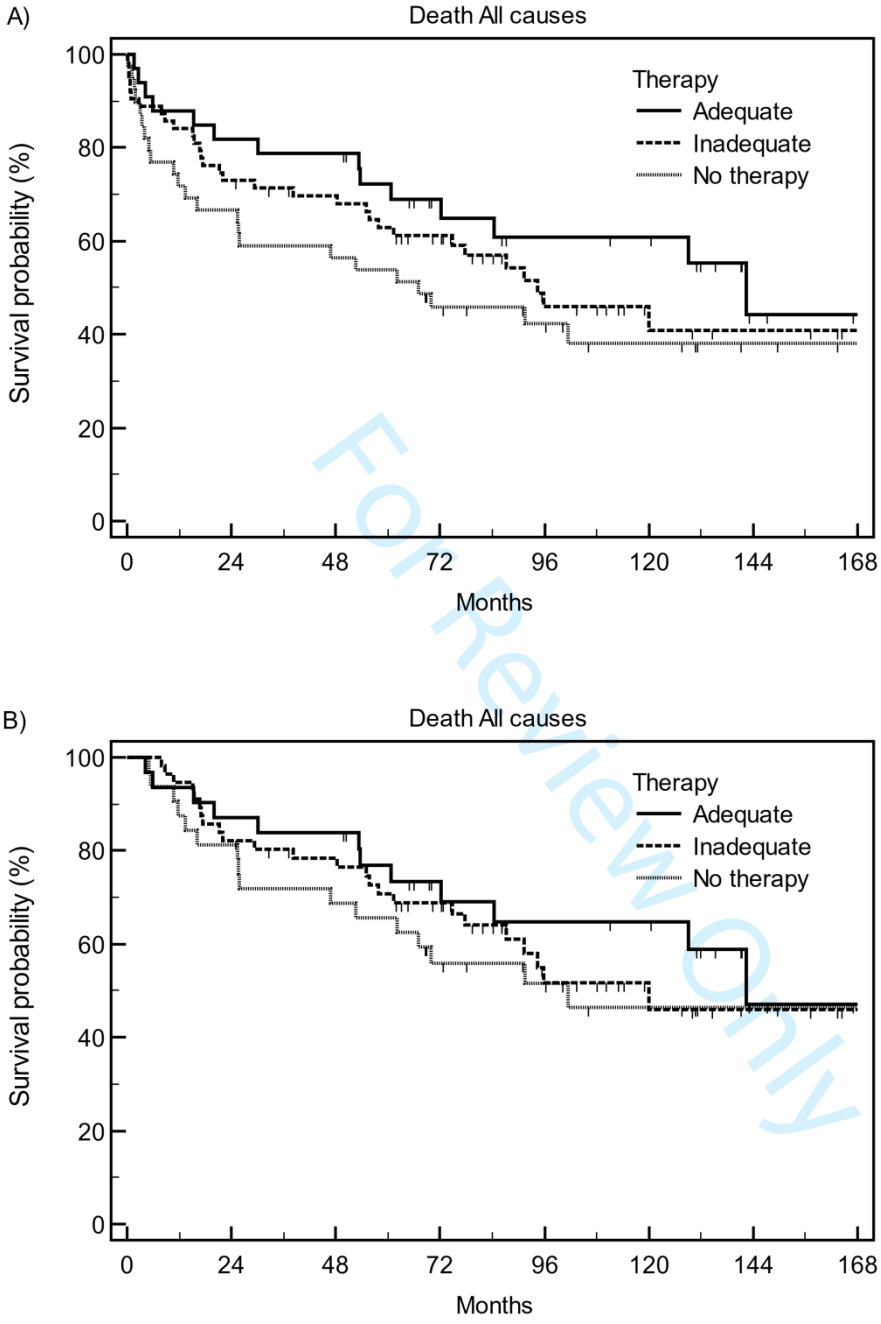
Figure 1. All-cause mortality in patients with definite NTM-PD stratified according to the administered therapy.



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