Factors Associated With Treatment Outcome in Patients With Nontuberculous Mycobacterial Pulmonary Disease: a Large Population-based Retrospective Cohort Study in Shanghai

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Research

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Abstract

Background: Investigate factors associated with treatment outcome in patients with nontuberculous mycobacterial pulmonary disease (NTMPD).

Methods: This retrospective cohort study examined NTMPD patients in Shanghai from January 2014 to December 2018. The distribution and incidence of the different causative species were determined. The outcomes of patients infected with different NTM species were compared. Univariate and multivariate binary logistic regression analyses were used to determine the odds ratios (ORs) and 95% confidence intervals (CIs) for the association of different factors with treatment failure.

Results: The most common species were *Mycobacterium avium* complex (MAC) (50%), *M. abscessus* (28%), and *M. kansasii* (15%). Over five years, the proportions of *M. kansasii* and *M. abscessus* increased, and that of MAC decreased. The treatment success rate was significantly greater for patients infected with *M. kansasii* (89.9%) than MAC (65.0%, *P*<0.001) and *M. abscessus* (36.1%, *P*<0.001). Multivariate analysis indicated the risk factors for treatment failure were pathogenic NTM species (*M. abscessus*: aOR=9.355, *P*<0.001; MAC: aOR=2.970, *P*=0.021), having an elevated ESR (>60mm/h: aOR=2.658, *P*<0.001), receipt of retreatment (aOR=2.074, *P*<0.001), middle-aged and elderly (>60 years-old: aOR=1.739, P=0.021; 45–60 years-old: aOR=1.661, P=0.034).

Conclusions: The main bacterial species responsible for NTMPD infections in Shanghai were MAC, *M. abscessus*, and *M. kansasii*. Patients with *M. kansasii* infections had a higher rate of treatment success. Multiple factors including infection by *M. abscessu* or MAC, an elevated ESR, receiving retreatment, middle-aged and elderly were associated with treatment failure.

Background

Infection by nontuberculous mycobacteria(NTM) has become a major public health problem in many geographical regions[1–3]. The detection of NTM has increased because of the increased prevalence of diseases that cause immunodeficiency, such as HIV/AIDS; the increased use of immunosuppressive agents or hormones; and improvements in bacterial identification, such as genetic sequencing. Data from previous epidemiological surveys of tuberculosis(TB) in China showed that the rate of NTM isolation was 4.3% in 1979, 11.1% in 2000, and 22.9% in 2010. There are more than 200 known NTM species worldwide, most of which are parasitic bacteria, although only a few are pathogenic to humans. The common pathogenic NTM species include *Mycobacterium avium* complex(MAC), *M.abscessus*, *M.kansasii*, and *M.malmoense* [4]. Different NTM species have different geographical distributions[5, 6]. For example, MAC, *M.abscessus*, *M.fortuitum*, and *M.kansasii* are very commonly reported in the Pacific region[7]. China is a country with heavy burden of NTM diseases. However, current epidemiological data on NTM pulmonary disease (NTMPD), such as the distribution and incidence of different causative species are very limited.

Most NTM are naturally resistant to commonly used anti-mycobacterial drugs[4], and treatment with multiple drugs is often necessary. The treatment course for NTM is typically very long and the cost is high[8]. Moreover, the side effects of antibiotics are often substantial[9], and the development of new drugs has been slow. As a result, the clinical efficacies of available treatments are unsatisfactory and the recurrence rate is very high. Screening patients for risk factors associated with treatment failure is important because it may help predict disease prognosis, prevent disease progression, and improve therapeutic outcome. Very few previous studies examined the risk factors for NTMPD treatment failure.

We conducted a large retrospective cohort study from 2014 to 2018 to examine treatment outcome in patients with NTMPD in Shanghai. We systematically investigated the incidence, causative bacterial species, drug susceptibility tests, treatment outcomes, sputum culture conversion rate, and risk factors associated with treatment failure in these patients. Our findings may help improve the clinical management of patients with NTMPD.

Methods

Patient selection

Data of 1263 NTMPD patients who were treated at Shanghai Pulmonary Hospital between January 2014 and December 2018 were retrospectively collected. This study was approved by the Ethics Committees of Shanghai Pulmonary Hospital. The flow diagram is presented in Fig. 1. All included patients were: (*i*) 18 to 80 years-old and met the diagnostic criteria of NTMPD according to the Experts Consensus of Chinese Medical Association; (*ii*) provided sputum or bronchoalveolar lavage fluid (BALF) specimens that were subjected to polymerase chain reaction(PCR) reverse dot blot hybridization for bacterial species identification, with confirmation of results; and (*iii*) received regular treatment under the guidance of physicians and had complete clinical data available. Patients were excluded if they: (*i*) were pregnant and lactating women; (*ii*) had an HIV infection; (*iii*) had co-infection with two *Mycobacterium* species.

Culture methods, species identification, and drug susceptibility testing

Sputum or BALF specimens from patients were cultured and identified as NTM at least twice using the BACTEC MGIT 960 method in accordance with the *Chinese Tuberculosis Bacteriological Examination Procedure.* Drug susceptibility tests for isoniazid, rifampicin, ethambutol, amikacin and ofloxacin were performed. Molecular biological detection of NTM species in sputum or BALF specimens was performed using PCR-reverse dot blot hybridization in accordance with the instructions of a *Mycobacterium* identification gene detection kit(Yaneng BIOscience Co., Shenzhen)

Study design and follow-up

This was a retrospective cohort study that examined patients from January 2014 to December 2018. For each patient, the onset of anti-NTM treatment was used as the start-point, and death, loss to follow-up, or

end of follow-up(December 2020) was used as the end-point. All enrolled patients were inpatients and were followed up through the outpatient department of the hospital after discharge. All data were recorded in detail, including demographic data, clinical manifestations, laboratory test results, imaging findings, and treatment outcomes. All the enrolled patients received anti-NTM therapy. The selection of anti-NTM drugs were based on the results of drug susceptibility tests and the Experts Consensus of Chinese Medical Association. Briefly, patients with *M.kansasii* infection were treated with a regimen containing at least 3 of the following drugs: isoniazid(5mg/kg), rifampicin(10mg/kg), ethambutol(15mg/kg), clarithromycin (1000mg/d) or azithromycin (500mg/d), and moxifloxacin (400mg/d). Patients infected with MAC were treated at least 3 of the following drugs: rifampicin or rifabutin (300mg/d), ethambutol, clarithromycin or azithromycin, amikacin(400mg/d) and moxifloxacin. Patients with *M.abscessus* infection were treated at least 4 of the following drugs: clarithromycin or azithromycin, amikacin, cefoxitin(200mg/kg), faopenem(300mg/d), moxifloxacin, linezolid(600mg/d) and clofazimine (100-200mg/d).

The results of sputum smears, NTM cultures, drug susceptibility tests, and chest computed tomography(CT) within 1 month before onset of anti-NTM treatment were used as baseline. Routine blood indexes, indicators of liver and kidney function, and electrolytes were assessed once per month after treatment onset. Sputum smears, NTM cultures, drug susceptibility tests, and chest CT examinations were performed every 3 months after treatment onset. Chest CT examinations were also performed every 6 months during the first year after treatment cessation, and then every year until the end of the study. Sputum examinations were performed if lesions increased, if new pulmonary cavities appeared, or if pulmonary cavities worsened.

Treatment outcome and prognosis

Recurrence within 1 year was defined as chest CT indicating increased pulmonary lesions, new pulmonary cavities or worsened pulmonary cavities, and the same pathogenic NTM species(detected in at least two cultures and/or by molecular techniques) after the end of treatment.

There were 6 categories of outcome: (*i*) cure; no lung lesion activity, gradual closure of pulmonary cavities, and negative sputum smears and cultures; (*ii*) markedly effective; negative sputum smears, lesions significantly absorbed, and pulmonary cavities closed or significantly reduced; (*iii*) effective; negative sputum smears, pulmonary lesions significantly absorbed or not significantly absorbed, and pulmonary cavities reduced; (*iv*) ineffective (stable disease); no changes in clinical condition before and after treatment, and no significant change in sputum smear results or imaging examinations; (*v*) deterioration; positive sputum smears, or new lesions, or increased pulmonary cavities, or appearance of new pulmonary cavities; and (*vi*) death. For some statistical analyses, efficacy was classified as “success” (*i* + *ii* + *iii*) or “failure” (*iv* + *v* + *vi*).

Statistical analysis

SPSS version 20.0(SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The χ^2 test was used to compare the treatment outcomes and prognoses of patients with the three most common NTM species

and a *p* value below 0.05 in a two-sided test indicated statistical significance. The Bonferroni method was used for pairwise comparisons. The sputum culture conversion rate of patients over time in three groups was plotted using the Kaplan-Meier method, and statistical significance of differences was determined by Log-Rank test. Unconditional binary logistic regression was used for univariate and multivariate analyses to identify risk factors for treatment failure. The unadjusted odds ratio(OR) and 95% confidence interval(CI) for each variable were first calculated using univariate regression. Multivariate regression was then performed using the forward conditional method. The test level(α) for including a variable was 0.05, and the test level(α) for excluding a variable was 0.10. The adjusted OR(aOR) and 95% CI was calculated for each included variable.

Results

Abundances of different NTM species in NTMPD patients

From January 2014 to December 2018, there were 1263 patients who were diagnosed as NTMPD with confirmation by species identification at Shanghai Pulmonary Hospital. We identified *M.intracellulare*(542, 43%), *M.abscessus*(357, 28%), *M.kansasii*(185, 15%), *M.avium*(86, 7%), other NTM species(56, 4%), and mixed infections(37, 3%). The 56 other species were *M.szulgai*(8), *M.scrofulaceum*(11), *M.chelonae*(12), *M.xenopi*(8), *M.gordonae*(4), *M.fortuitum*(5), unidentified NTM species(6) and *M.malmoense*(2). The 37 cases of mixed infections were *M.tuberculosis* with NTM(8), *M.abscessus* with *M.intracellulare*(22), *M.abscessus* with *M.avium*(4), *M.scrofulaceum* with *M.intracellulare*(3). (Fig. 2)

Among all positive mycobacterial cultures in samples of sputum and BALF, the overall NTM detection rate increased steadily over time(2014: 9.1%; 2015: 10.9%; 2016: 12.1%; 2017: 13.7%; 2018: 15.5%). We further analysed the three most common NTM species (MAC, *M.abscessus*, *M.kansasii*). From 2014 to 2018, there were steadily increasing percentages of patients with *M.kansasii* and *M.abscessus*. However, the percentages of patients with MAC decreased over time. (Fig. 3)

The results of drug susceptibility test of the three major NTM species

Among the 802 patients, the drug resistance rates of *M.kansasii* to amikacin, isoniazid, rifampicin, ethambutol and ofloxacin were 2.5%, 25.3%, 13.9%, 19.0% and 12.7%, respectively. The drug resistance rates of MAC and *M.abscessus* to the five drugs were 21.6%, 85.4%, 39.6%, 27.8%, 54.0% and 25.1%, 100%, 99.1%, 98.2%, 99.1%, respectively. (Table 1)

Table 1
Drug resistance rates of the three major NTM species.

Drug	*M. kansasii* (n = 158) (n, %)	MAC (n = 417) (n, %)	*M. abscessus* (n = 227) (n, %)
Am	4(2.5)	90(21.6)	57(25.1)
INH	40(25.3)	356(85.4)	227(100)
RFP	22(13.9)	165(39.6)	225(99.1)
EMB	30(19.0)	106(27.8)	223(98.2)
Ofx	20(12.7)	225(54.0)	225(99.1)

Am: amikacin, INH:isoniazid, RFP: rifampicin, EMB: ethambutol, Ofx: ofloxacin.

Outcomes and sputum culture conversion rate of NTMPD patients infected with the three major NTM species

We analysed the records of 802 patients with NTMPD and classified 495 patients (61.7%) in a “treatment success” group and 307 patients (38.3%) in a “treatment failure” group. Among the 495 patients who had successful treatment, 70(8.7%) were cured, 206(25.7%) had markedly effective treatment, and 219(27.3%) had effective treatment. Among the other 307 patients who experienced treatment failure, 276(34.4%) had ineffective treatment, 25(3.1%) had deterioration, and 6(0.7%) died. There were 21 cases (2.6%) of recurrence within 1 year, 1 involving *M.kansasii* (0.6%), 9 involving MAC (2.1%), and 11 involving *M.abscessus* (4.8%).

We also compared the treatment outcomes and the sputum culture conversion rate of patients infected with the three major NTM species. The treatment success rate was 89.9% for patients with *M.kansasii*, 65.0% for patients with MAC, and 36.1% for patients with *M.abscessus*. Pairwise comparisons indicated that the success rate was significantly higher for patients with *M.kansasii* than for patients in the other two groups(both $P < 0.001$, Table 2). However, the three groups had no statistically significant differences in recurrence within one year. The median time to sputum culture conversion of *M.Kansasii*, MAC and *M.abscess* was 4 months (95%CI: 3.472–4.528), 10 months (95%CI: 7.107–12.893) and 24 months(no sputum culture conversion after treatment), respectively. The sputum negative conversion rate of *M.Kansasii* were 89.9%, significantly higher than those of the other two groups which were 65.0% and 36.1%, Log rank $P < 0.001$, as shown in Fig. 4.

Table 2
Outcomes of NTMPD patients infected with the three major NTM species.

Outcome	M. *Kansasii* (n = 158) (n, %)	MAC (n = 417) (n, %)	*M. abscessus* (n = 227) (n, %)	χ^2	*P*[a]
Success	142(89.9)	271(65.0)	82(36.1)	117.841	**< 0.001**
Cure	32(20.3)	21(5.0)	17(7.5)	33.917	**< 0.001**
Markedly effective	79(50.0)	96(23.1)	31(13.6)	67.694	**< 0.001**
Effective	31(19.6)	154(36.9)	34(15.0)	41.541	**< 0.001**
Failure	16(10.1)	146(35.0)	145(63.9)	117.841	**< 0.001**
Ineffective	14(8.9)	133(31.9)	129(56.8)	88.074	**< 0.001**
Deterioration	2(1.2)	11(2.6)	12(5.3)	–	0.059[a]
Death	0(0.0)	2(0.5)	4(1.8)	–	0.094[a]
Recurrence (within 1 year)	1(0.6)	9(2.1)	11(4.8)	–	0.027[a]

[a] *P*-value corrected using Fisher's exact method when the expectation was below 5, –: no statistical value.

Univariate analysis of factors associated with treatment failure in NTMPD patients

We performed a univariate analysis to identify factors significantly associated with treatment failure(Table 3). The results indicated that treatment failure was more common in patients who were middle-aged and elderly(45 ~ 60 years-old and > 60 years-old), were female, received retreatment, complicated with Chronic Obstructive Pulmonary Disease, had bronchiectasis, had pulmonary cavities, had involvement of multiple lung fields(3 ~ 4 lung fields and 5 ~ 6 lung fields), had elevated ESR(> 60 mm/h), were infected by different NTM species(MAC, *M.abscessus*), had gastrointestinal reactions(all $P < 0.05$). (Table 3).

Table 3
Univariate analysis of factors associated with treatment failure in NTMPD patients.

Factor	Success (n = 495) (n, %)	Failure (n = 307) (n, %)	OR	95% CI	*P* value
Age, years					
18 ~ 44	145(29.3)	46(15.0)	1(ref)		
45 ~ 60	161(32.5)	104(33.9)	2.036	1.347, 3.078	**0.001**
> 60	189(38.2)	157(51.1)	2.618	1.767, 3.881	**< 0.001**
Female	244(49.3)	186(60.6)	1.581	1.185, 2.111	**0.002**
Retreatment NTMPD	131(26.5)	155(50.5)	2.881	2.121, 3.912	**< 0.001**
Smoking history	50(10.1)	22(7.2)	0.571	0.369, 1.732	0.800
Rural residence	215(43.4)	141(45.9)	1.112	0.831, 1.488	0.476
History of pulmonary TB	137(27.7)	94(30.6)	1.145	0.836, 1.568	0.399
COPD	27(5.4)	32(10.4)	2.167	1.279, 3.670	**0.004**
Pneumoconiosis	17(3.4)	10(3.3)	1.193	0.728, 2.095	0.893
Long-term use of corticosteroid/ immunosuppressant	13(2.6)	12(3.9)	1.508	0.679, 3.349	0.313
Diabetes Mellitus	34(6.9)	16(5.2)	0.746	0.404, 1.375	0.347
BMI (kg/m^2)					
≥ 18.5	322(65.1)	180(58.6)	1(ref)		
<18.5	173(34.9)	127(41.4)	1.313	0.980, 1.760	0.068

95% CI: 95% confidence interval, OR: unadjusted odds ratio, TB: tuberculous, COPD: chronic obstructive pulmonary disease, BMI: body mass index, ESR: erythrocyte sedimentation rate, MAC: *Mycobacterium avium* complex.

Factor	Success (n = 495) (n, %)	Failure (n = 307) (n, %)	OR	95% CI	*P* value
Pulmonary cavities	249(50.3)	180(58.6)	1.404	1.056, 1.873	**0.020**
Bronchiectasis	306(61.8)	218(71.0)	1.513	1.114, 2.055	**0.008**
Involvement of lung fields					
1 ~ 2	146(29.5)	51(16.6)	1(ref)		
3 ~ 4	115(23.2)	73(23.8)	1.817	1.178, 2.802	**0.007**
5 ~ 6	234(47.3)	183(59.6)	2.239	1.542, 3.251	**< 0.001**
ESR(mm/l)					
<15	168(33.9)	73(23.8)	1(ref)		
15 ~ 60	272(54.9)	164(53.4)	1.388	0.991, 1.942	0.056
>60	55(11.2)	70(22.8)	2.929	1.872, 4.582	**< 0.001**
Anemia	417(84.2)	256(83.4)	0.927	0.630, 1.364	0.700
Albumin (g/L)					
> 34	430(86.9)	247(80.5)	1(ref)		
25 ~ 34	53(10.7)	51(16.6)	1.304	0.784, 2.171	0.306
< 25	12(2.4)	9(2.9)	2.036	1.169, 3.522	0.813
Bacterial species					
M. kansasii	142(28.7)	16(5.2)	1(ref)		
MAC	271(54.7)	146(47.6)	4.781	2.746, 8.326	**< 0.001**
M. abscessus	82(16.6)	145(47.2)	15.694	8.756, 28.128	**< 0.001**

95% CI: 95% confidence interval, OR: unadjusted odds ratio, TB: tuberculous, COPD: chronic obstructive pulmonary disease, BMI: body mass index, ESR: erythrocyte sedimentation rate, MAC: *Mycobacterium avium* complex.

Factor	Success (n = 495) (n, %)	Failure (n = 307) (n, %)	OR	95% CI	*P* value
Treatment regimen changes	143(28.9)	108(21.8)	1.336	0.985, 1.811	0.062
Adverse drug reactions					
Hepatotoxicity	43(8.7)	24(4.8)	0.891	0.529, 1.501	0.666
Cytopenia	43(8.7)	21(6.8)	0.618	0.255, 1.498	0.287
Hypersensitivity	17(3.4)	14(4.6)	1.344	0.653, 2.766	0.423
Gastrointestinal	21(4.2)	26(8.5)	2.088	1.153, 3.781	**0.015**

95% CI: 95% confidence interval, OR: unadjusted odds ratio, TB: tuberculous, COPD: chronic obstructive pulmonary disease, BMI: body mass index, ESR: erythrocyte sedimentation rate, MAC: *Mycobacterium avium* complex.

Multivariate analysis of factors associated with treatment failure in NTMPD patients

We then performed a multivariate binary logistic regression analysis to identify factors significantly and independently associated with treatment failure(Table 4). The results indicated that four risk factors were significantly and independently associated with treatment failure. In order of risk, these factors were: pathogenic NTM species (*M. abscessus*: aOR = 9.355, $P < 0.001$; MAC: aOR = 2.970, $P < 0.001$), having an elevated ESR (> 60mm/h: aOR = 2.658, $P < 0.001$), receipt of retreatment (aOR = 2.074, $P < 0.001$), middle-aged and elderly (> 60 years-old: aOR = 1.739, $P = 0.021$; 45 ~ 60 years-old: aOR = 1.661, $P = 0.034$).

Table 4
Multivariate analysis of factors associated with treatment failure in NTMPD patients.

Factor	aOR	95% CI	*P value*
Retreatment NTMPD	2.074	1.470, 2.926	**< 0.001**
Age, years			
18 ~ 44	1(ref)		
45 ~ 60	1.661	1.038, 2.659	**0.034**
> 60	1.739	1.088, 2.778	**0.021**
ESR(mm/h)			
< 15	1(ref)		
15 ~ 60	1.185	0.800,1.755	0.398
> 60	2.658	1.560, 4.529	**< 0.001**
Bacterial species			
M. kansasii	1(ref)		
MAC	2.970	1.620, 5.443	**< 0.001**
M. abscessus	9.355	4.977, 17.584	**< 0.001**

95% CI: 95% confidence interval, aOR: adjusted odds ratio, ESR: erythrocyte sedimentation rate, MAC: *Mycobacterium avium* complex

Discussion

The present study was a large retrospective cohort study of 1263 patients diagnosed with NTMPD in Shanghai from 2014 to 2018 that investigated the incidence, bacterial species distribution, drug susceptibility tests, treatment outcome, and risk factors associated with treatment outcome. We found that the major causative species were MAC, *M.abscessus*, and *M.kansasii*. The treatment success rate and sputum culture conversion rate were much higher in patients with *M.kansasii* infections than in those with infections by the other two species. Among these patients, infection by *M.abscessus*, infection by MAC, having an elevated ESR, receipt of retreatment, middle-aged and elderly had significant and positive associations with treatment failure. These findings thus provide important additional information regarding the clinical prediction of prognosis in patients with NTMPD and may help to improve treatment outcomes in these patients.

The most common NTM species in the world are MAC, *M.abscessus*, and *M.kansasii*[10], identical to our findings in NTMPD patients in Shanghai from 2014 to 2018, although we also identified changing percentages of these species over time. In particular, we found that the percentages of *M.kansasii* and

M.abscessus increased, and that the percentage of MAC decreased. We also found that multi-NTM infections were common, similar to a 2020 study that was conducted in Chongqing, China[11]. However, the distribution of different NTM species varies in different countries. In Europe and North America, MAC, *M.gordonae*, *M.xenopi*, and *M.fortuitum* are the most common, but in South America, MAC, *M.kansasii*, *M.gordonae*, and *M.fortuitum* are the most common[12]. These geographic differences may be due to various factors, such as temperature, humidity and living habit of local residents.

Previous studies reported that many NTM species had natural drug resistance, especially to conventional first-line anti-TB drugs[13, 14]. Our study has come to the same conclusion. Drug resistance is particularly notable in *M.abscessus.* This drug resistance may be due to the cell wall acting as a natural barrier, drug efflux systems, drug inactivation, mutation or deletion of drug target sites, plasmids[15], or a combination of factors. Therefore, in clinical practice, NTMPD patients require a long treatment course, but treatment efficacy is often low and the recurrence rate is often high. This present study showed that there were significant differences in the treatment success rates and sputum culture conversion rates of patients infected with different NTM species. In particular, patients infected with *M.kansasii* had significantly better outcomes than patients infected with MAC or *M.abscessus*.

Our large retrospective cohort study also analysed the risk factors for treatment failure in NTMPD patients from Shanghai. We found that the risk of treatment failure was greater for patients infected with *M.abscessus*(aOR = 9.355) and MAC(aOR = 2.970) compared to those with *M.kansasii* infections, consistent with previous studies[16, 17]. Among our three most common NTM species, *M.kansasii* was the most sensitive to common anti-TB drugs. Macrolides, quinolones, aminoglycosides and sulfonamides are also effective against *M.kansasii*; so it is easier to develop a regimen that includes more than three effective drugs. Relative to *M.kansasii*, MAC has much greater rates of resistance to amikacin, isoniazid, rifampicin, ethambutol, doxycycline, clarithromycin, linezolid, and moxifloxacin[18]. *M.abscessus* is the most problematic species, because of its high rates of resistance to rifamycin, macrolides (including clarithromycin and azithromycin), and other key therapeutic drugs[19, 20], potentially due to induced drug resistance or drug resistance caused by mutations[21]. Our results showed that *M.abscessus* had an extremely high drug resistance rate to all the first-line anti-TB drugs, only sensitive to amikacin (74.9%). The 2020 American Thoracic Society Guidelines recommended linezolid and clofazimine as suitable for treatment of *M.abscessus* infections[4]. In this study, there were only 21(9.3%) patients with *M.abscessus* infection were treated with linezolid and 19(8.4%) patients were treated with clofazimine because these two drugs were not widely used for NTMPD treatment in Shanghai from 2014 to 2018. We believe this might be part of the reason for the low treatment success rate in patients infected with *M.abscessus*.

Previous studies of MAC lung disease (MAC-LD) found that female sex correlated with poor prognosis[22, 23]. Studies in the United States and Denmark showed that the mortality rate was significantly greater for elderly women with NTMPD[24, 25]. Our multivariate results indicated that treatment failure correlated with age, but not with female sex. Relative to patients younger than 45 years, the aOR for treatment failure was 1.661 for patients aged 45 to 60 years and 1.739 for patients older than 60 years.

A recent study suggested that a history of previous NTMPD might be related to unfavorable treatment outcomes in patients with lung disease due to *M.abscessus* infection[26]. We found that the aOR for treatment failure was 2.074 for those who previously received NTMPD treatment. This may be because the initial structural damage of lung tissue caused by the sequelae of NTMPD and by low local drug bioavailability. In addition, during NTMPD retreatment, an increased drug resistance, high treatment cost, long treatment course, and psychological factors of the patient may contribute to poor patient compliance and increased treatment difficulties.

Gochi et al.[27] found that patients who were older and had lower BMI values were more likely to experience aggravation of MAC-LD, and increased levels of serum inflammatory indicators. We found no effect of BMI on outcome, but patients with an elevated ESR had an notable risk for poor outcome(> 60mm/h: aOR = 2.658). ESR and C-reactive protein are common inflammatory markers, and increased levels may reflect the systemic inflammatory response caused by NTMPD infection, and often indicate disease progression. ESR > 50 mm/h was found to be a negative prognostic factor of radiologic deterioration in NTMPD complicated with rheumatoid arthritis[28]. A previous animal study of MAC-LD found that the level of certain proinflammatory and anti-inflammatory cytokines, such as TNF-α and gamma interferon, were greater in mice with severe or advanced MAC infections[29].

An increasing number of studies have confirmed that chest imaging features are related to the prognosis of patients with NTMPD[23, 30, 31], such as bronchiectasis and pulmonary cavity. Patients with NTMPD often present with bronchiectasis[32–34]. There is also evidence that the occurrence of NTM may correlate with alpha-1-antitrypsin deficiency in patients with bronchiectasis[35] and that bronchiectasis is a predisposing factor for reinfection with NTM species[36]. Our univariate analysis identified bronchiectasis as a significant risk factor for treatment failure, but it was no longer significant in the multivariate analysis. Our results also showed infection by *M.abscessus* was significantly correlated with treatment failure. Because a high proportion of patients infected by *M.abscessus* have bronchiectasis, we consider bronchiectasis as a confounding factor for treatment failure.

This study found that the major species causing NTMPD in Shanghai during 2014 to 2018 were MAC, *M.abscessus*, and *M.kansasii*. The treatment success rate in patients with *M.kansasii* infections was much higher than in those infected by the other two species. Patients who were infected by *M.*abscessus or by MAC, had an elevated ESR, received retreatment and those were middle-aged or elderly had significant increased risk of treatment failure. We therefore recommend that when clinicians encounter a patient with any of these conditions, they should carefully evaluate disease status and perform drug susceptibility tests, and then implement the most appropriate treatment regimen. The Directly Observed Treatment Strategy which is applied in TB management should be considered for patients with NTMPD, and patients should be closely monitored for adverse drug reactions and compliance to minimize the risk of treatment failure. Our results provide valuable insights for the prediction of prognosis and improvement of treatment outcome in patients with NTMPD. The current study also has a few limitations. It had a retrospective cohort design, and complete clinical data, especially the drug susceptibility results

such as clarithromycin, azithromycin, cefoxitin, doxycycline, clarithromycin, and linezolid were not available. We therefore suggest that the results of this study need verification by large, multi-center, prospective cohort studies.

Conclusions

The major causative species causing NTMPD in Shanghai during 2014 to 2018 were MAC, *M.abscessus*, and *M.kansasii*. The treatment success rate and sputum culture conversion rate were much higher in patients with *M.kansasii* infections than in those with infections by the other two species. Among these patients, infection by *M.abscessus*, infection by MAC, having an elevated ESR, receipt of retreatment, middle-aged and elderly had significant and positive associations with treatment failure.

Abbreviations

NTMPD: nontuberculous mycobacterial pulmonary disease; NTM: nontuberculous mycobacterial; MAC: Mycobacterium avium complex; TB: tuberculous; PCR: polymerase chain reaction; BALF: bronchoalveolar lavage fluid; CT: computed tomography; 95% CI: 95% confidence interval; OR: odds ratio; aOR: adjusted odds ratio; MAC-LD: Mycobacterium avium complex lung disease; COPD: chronic obstructive pulmonary disease; BMI: body mass index; ESR: erythrocyte sedimentation rate

Declarations

Authors' contributions

(I) Conception and design: QS, WS, LPC, SHC, HL, XWG; (II) Administrative support: QS, WS; (III) Provision of study materials or patients: LPC, SHC, HL, XWG, XNS, JC, WS; (IV) Collection and assembly of data: LPC, SHC, HL, XWG, XNS, JC, WS, QS; (V) Data analysis and interpretation: LPC, SHC, QS; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Availability of data and materials

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

Ethics approval and consent to participate

This study was approved by the Ethics Committees of Shanghai Pulmonary Hospital.

Consent for publication

Not applicable.

Competing interests

All authors declare no conflicts of interest.

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Figures

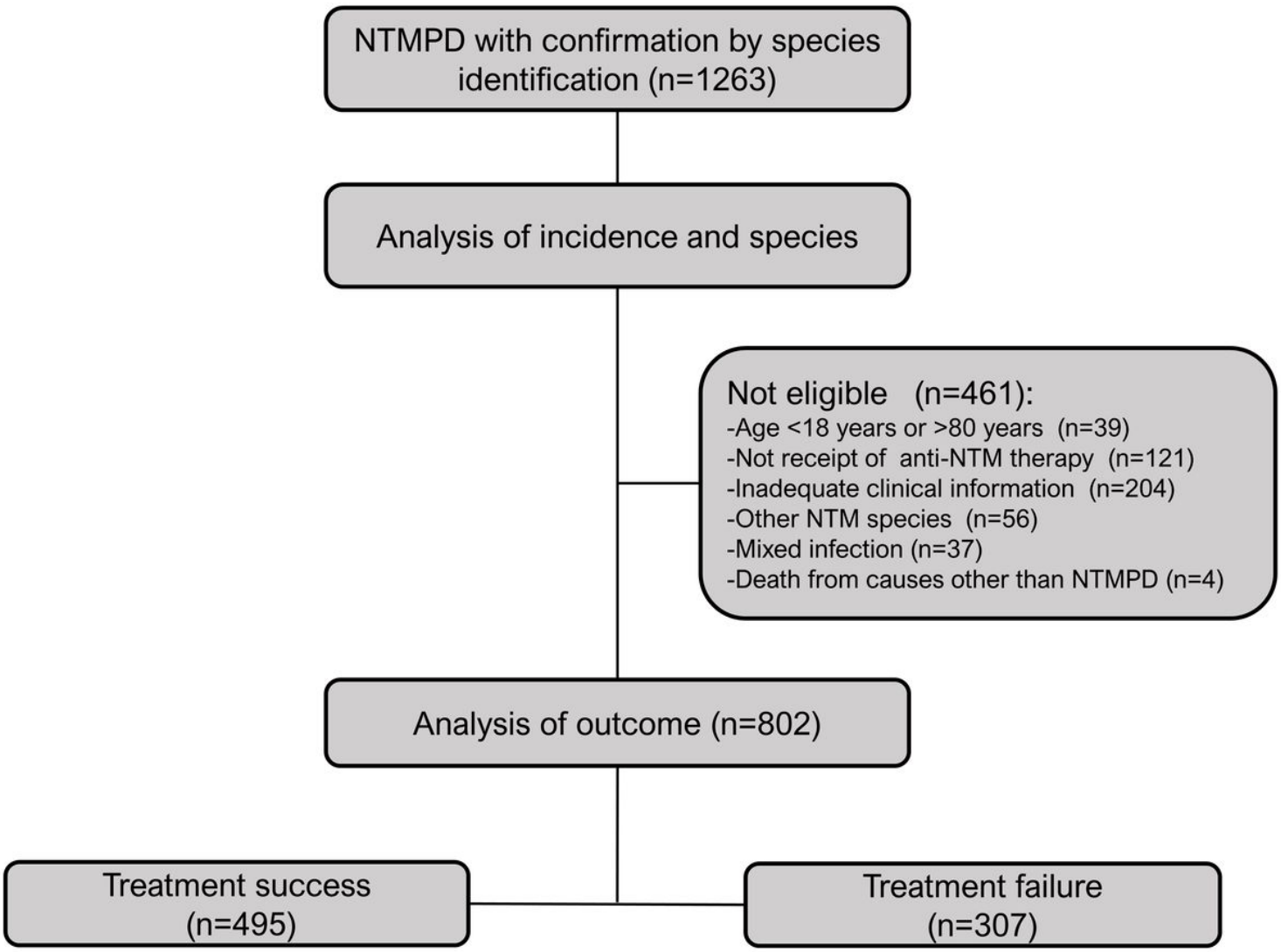

Figure 1

Identification and disposition of patients with NTMPD.

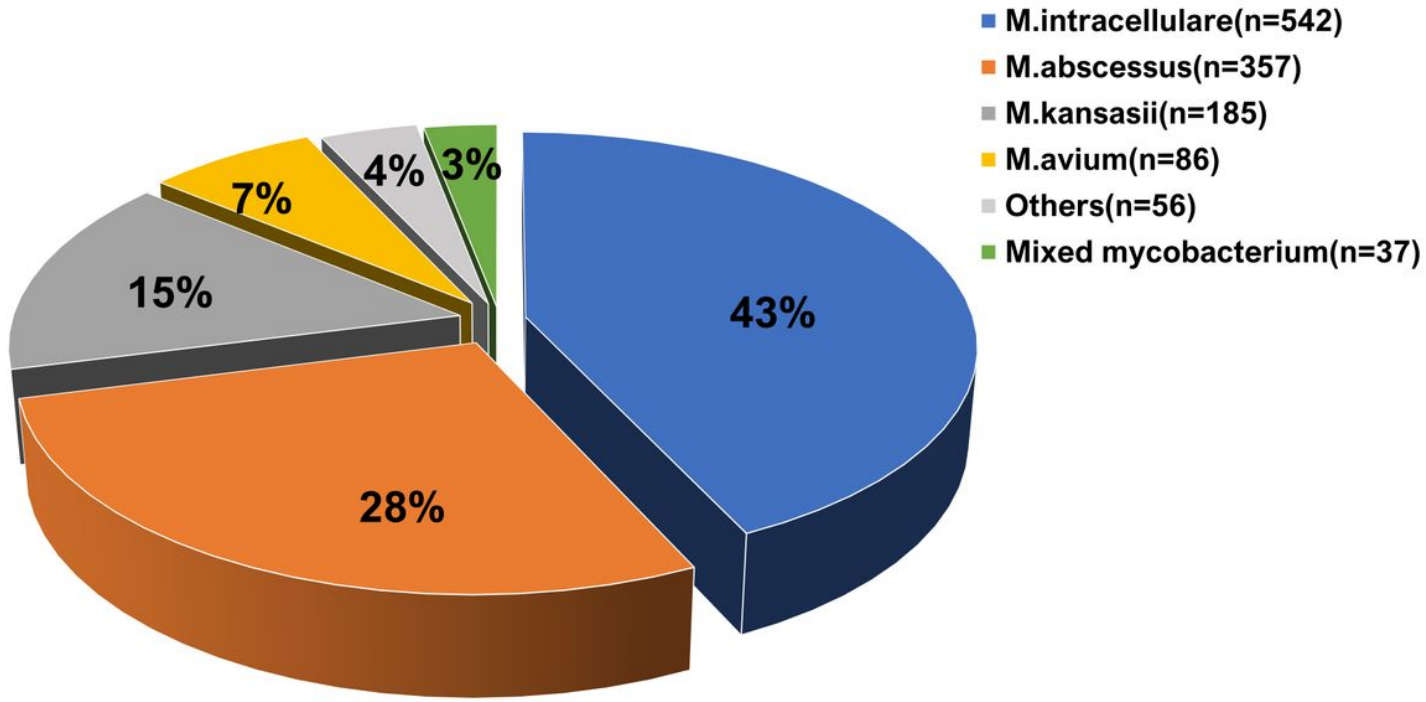

Figure 2

Abundances of different NTM species in NTMPD patients.

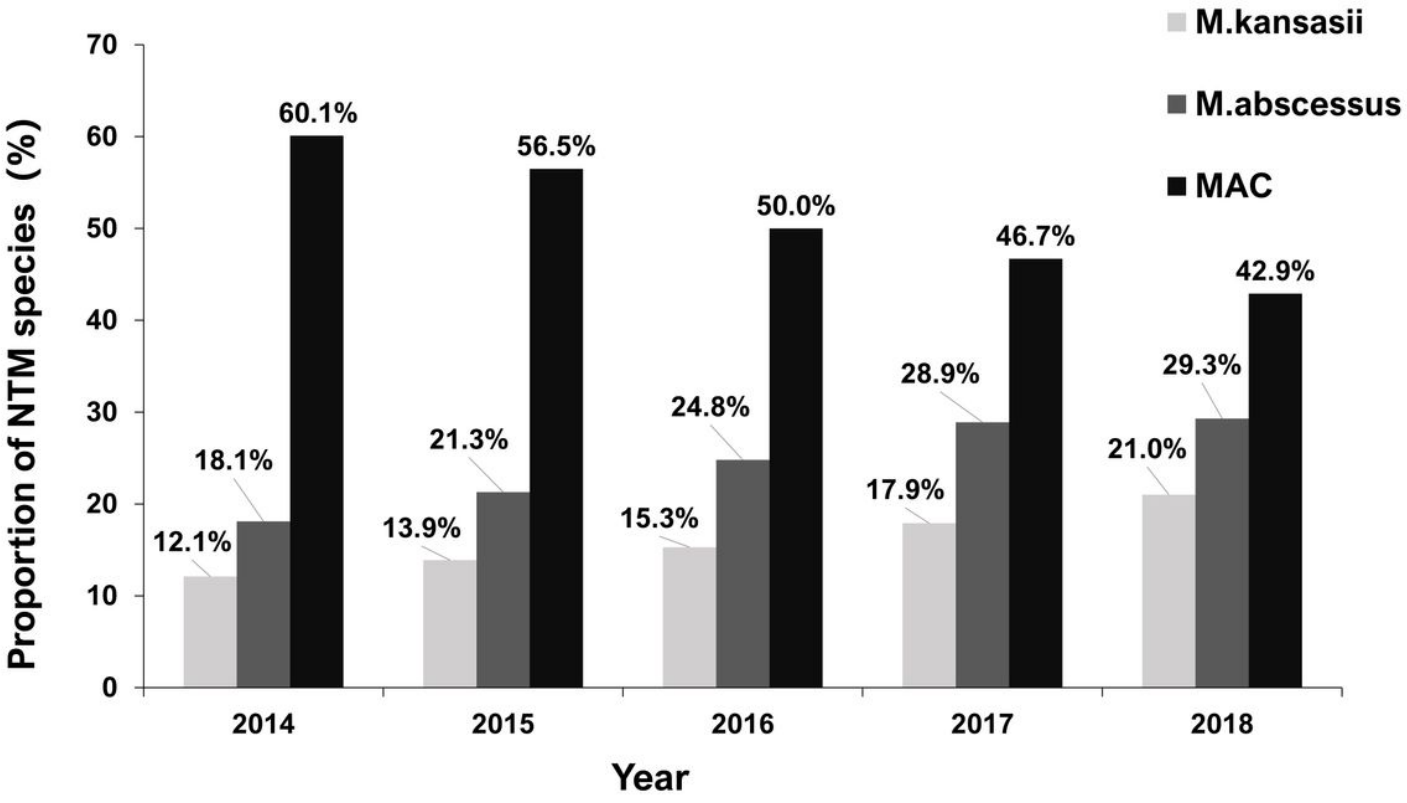

Figure 3

Changes in the abundances of major NTM species in NTMPD patients from 2014 to 2018.

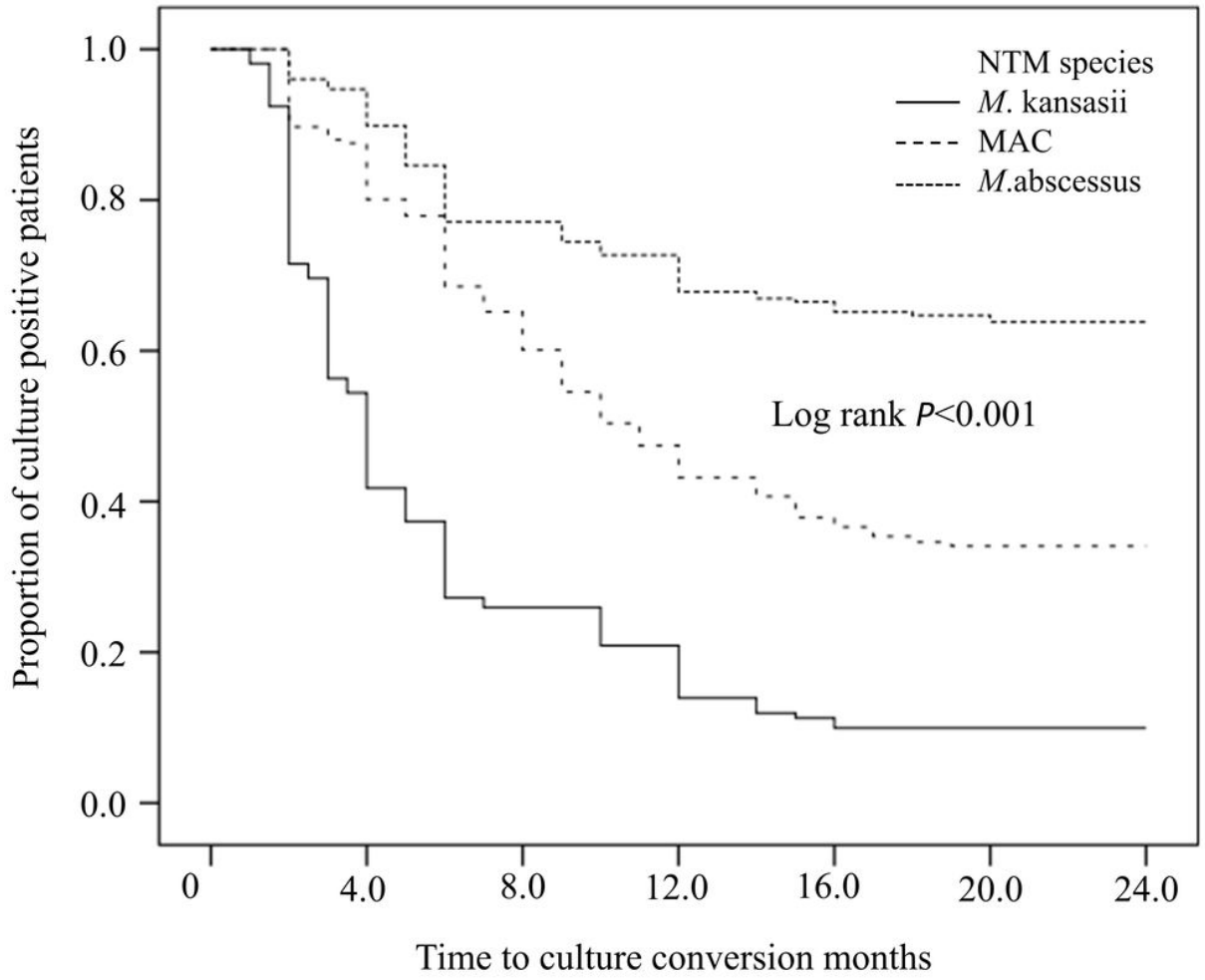

Figure 4

Comparison of sputum culture conversion rate of patients with M. Kansasii, MAC and M. abscess infection.