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PAPERS

What do the clinical features of positive nontuberculous mycobacteria isolates from patients with HIV/AIDS in China reveal? A systematic review and meta-analysis

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Background China has a high burden of nontuberculous mycobacterial (NTM) infections. Immunocompromised populations, such as those with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), are at a higher risk of being infected with NTM than immunocompetent individuals. Yet, there is a paucity of information on the clinical features of positive NTM isolates from patients with HIV/AIDS in China. To address this gap, we conducted a systematic review and meta-analysis of existing studies, comparing them against current expert consensus to provide guidance for clinical practice.

Methods Two researchers independently searched eight databases (SinoMed, China National Knowledge Infrastructure, Wanfang, VIP, Cochrane Library, PubMed, Embase, and Web of Science) from inception to 26 December 2022 to retrieve published Chinese- and English-language studies reporting clinical features of NTM-positive isolates among patients with HIV/AIDS in China.

Results We included 28 studies with 1861 patients. The rate of positive NTM isolates detected from men among all patients was 87.3%. NTM species distribution was mainly *Mycobacterium avium* complex (64.3%), which was predominant in different regions. The five most common clinical symptoms were fever (68.5%), cough or expectoration (67.0%), appetite loss (49.4%), weight loss (45.5%), and superficial lymphadenectasis (41.1%). The prevalence of laboratory tests were as follows: albumin <35 g/L (55.6%), erythrocyte sedimentation rate >20 mm/h (91.4%), anaemia (59.0%), predominantly mild, CD4+ T cell count ≤50 pieces/μL (70.3%), and CD4+ T cell count 51-200 pieces/μL (22.1%). Lesion manifestations in thoracic imaging mainly included bilateral lung involvement (83.8%), showed stripe shadows (60.3%), patchy shadows (42.9%), nodules (40.6%), and bronchiectasis (38.6%). Accompanied signs included thoracic lymph node enlargement (49.5%). Seventy per cent of symptoms improved after treatment.

Conclusions Focusing on clinical symptoms, laboratory tests, and thoracic imaging helps with initial screening for NTM infections. Physicians should raise awareness of the diagnosis and treatment of *Mycobacterium avium* complex, providing guidance for experimental treatment, screening of priority populations for NTM infections, and prophylactic treatment of NTM disease.

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Human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) is a major contributor to the global burden of disease, accounting for the second highest number of disability-adjusted life years among 10-24, and 25-49-year-olds [1]. At least one million people are currently living with HIV/AIDS in China, with a growing number

of reported cases across all age groups [2]. Simultaneously, antiretroviral therapy (ART) has led to a reduction in morbidity and mortality, a gradual increase in average life expectancy, and a decrease in associated opportunistic infections (OIs) in patients with HIV/AIDS [3].

However, the rapid increase in CD6+ T-cell counts during the first three to four months of ART treatment may promote the development of OIs [4]. In high-income countries, including the USA and Canada, disseminated *Mycobacterium avium* complex or *Mycobacterium kansasii* infection of the species nontuberculous mycobacterial (NTM) is the third most common OI, after *pneumocystis jirovecii* pneumonia and oesophageal candidiasis [5]. Moreover, people living with HIV with NTM disease were associated with a long-term case-fatality rate (CFR), with overall CFR increasing from 15.7% at one year to 22.6% at five years [6].

In low- and middle-income countries (LMICs), NTM infections are largely overlooked due to limitations in medical resources and technology, with the first case of NTM lung disease in Ecuador being diagnosed in 2017 [7]. There is also a significant delay in the diagnosis of NTM diseases, especially in rural areas [8], and a high risk of misdiagnosis of *Mycobacterium tuberculosis* (MTB) infections, with a misdiagnosis rate of 92.81% and a maximum misdiagnosis time of 21 years [9]. NTM infections are not a notifiable infectious disease in most countries, and these factors combine to make NTM infections uncommon in studies of OIs in patients with HIV/AIDS in LMICs [10,11].

In fact, the number of NTM infections in LMICs is grossly underestimated. A national survey of tuberculosis (TB) prevalence among participants aged ≥15 years in Gambia showed an NTM separation rate of 39.8% [12] and 29.0% in India [13]. The National TB Epidemiological Sample Survey in China showed that the prevalence rate of NTM isolation increased from 11.1% in 2001 to 22.9% in 2010 [14,15]. The rate of NTM isolation of patients with HIV/AIDS in Shanghai was much higher than suggested by the National TB Epidemiological Sample Survey [16]. Some MTB infections have co-infection with NTM, particularly among patients with HIV [17-19]. NTM infections are also one of the common opportunistic infections in Chinese patients with HIV/AIDS [20-22].

NTM refers to mycobacterial species other than MTB complex and *Mycobacterium leprae* [23], which are commonly found in the natural environment (eg, water and soil) [24,25] and cause infection in susceptible individuals with underlying diseases, including chronic obstructive pulmonary disease, immunodeficiency, and HIV infection [26]. Various NTM infections, which do not have a specific clinical presentation [27], are less susceptible to standard anti-tuberculous drug regimens and require longer treatment durations than MTB infections [28,29].

Currently, there is little information on the clinical features of NTM isolates from patients with HIV/AIDS, which can easily lead to misdiagnosis, underdiagnosis, and even delay in clinical treatment. An expert consensus on diagnosis and treatment of patients with HIV/AIDS combined with NTM infections was published in China only in 2019 [30] and has not been updated since. Moreover, it was based on small sample studies and was unsupported by a systematic review and meta-analysis, the highest level of evidence in evidence-based medicine. Therefore, studying NTM isolates from patients with HIV/AIDS is of great significance not only for China, but for LMICs at large. Accordingly, we conducted a systematic review and meta-analysis of positive NTM isolates from patients with HIV/AIDS in China in terms of gender distribution, species distribution, clinical symptoms, laboratory tests, thoracic imaging manifestations, and treatment outcome.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines in conducting this study [31-33].

Search strategy

We systematically searched Chinese (SinoMed, China National Knowledge Infrastructure (CNKI), Wanfang, and VIP) and English databases (Cochrane Library, PubMed, Embase, and Web of Science). To capture all relevant literature, we used a combination of subject terms and free terms such as "HIV", "AIDS", and "NTM", adjusted for each database (Table S2 in the **Online Supplementary Document**). We set no restrictions on the type of published literature and limited the time span from inception to 26 December 2022. We searched the included studies' references for potentially relevant information.

Inclusion and exclusion criteria

We included cross-sectional, case-control, cohort, or case series studies on Chinese patients with HIV/AIDS associated with positive NTM isolates. The observed indicators were clinical symptoms, laboratory tests, thoracic imaging manifestations, species distribution and treatment outcome. If multiple articles examined a clinical indicators, but were based on the same sample data (e.g. data from the same institution or from the same study period), we only included the article with the most descriptive statistics of the data in question. All articles had to meet the diagnostic criteria for NTM isolated from culture [23].

The exclusion criteria were as follows: non-Chinese and -English literature; duplicate publications; unavailability of the required data; case studies, reviews, book chapters, expert opinions, comments, and so on; and basic studies, such as cellular and animal studies.

Study selection

Two researchers (L Wang and HX Wang) independently searched the literature, conducted deduplication, and performed the initial title/abstract screening, followed by a full-text screening of the retrieved studies. Subsequently, they collected the relevant data and cross-checked for the appropriateness of inclusion. Disagreements were resolved through discussion or negotiation with a third researcher (Y Ren).

Quality assessment

As we included studies with varying designs, we used a different risk of bias tools to assess possible sources of bias, depending on the design in question. We used the scales recommended by the Agency for Healthcare Research and Quality (AHRQ) [34] to assess the quality of cross-sectional studies, the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies [35], and the Joanna Briggs Institute (JBI) Critical Appraisal Checklist [36] for case-series studies (Table S3-S6 in the **Online Supplementary Document**). Two investigators (L Wang and HX Wang) independently evaluated the risk of bias in the included studies and cross-checked the results with a third investigator (Y Ren), resolving disagreements through discussion. We tabulated data from the included studies to identify bias in the quality evaluation phase.

Data extraction

We extracted the following information: first author, publication date, region of study subjects, sample size, study type, and gender distribution, observation indicators (clinical symptoms, laboratory tests, thoracic imaging manifestations, species distribution, and treatment outcome), and key elements of risk of bias evaluation.

Statistical analysis

Based on clinical considerations, we pooled similar and appropriate characteristics. We performed meta-analyses using Stata, version 17.0 (StataCorp, College Station, Texas, USA) for observations with three or more included studies. We conducted Freeman-Tukey double inverse sine transformation for dichotomous variables with extreme rates (r) of 0 or 1 [37]. We converted continuous variables from medians and quartiles to means and standard deviations according to Luo et al. (online calculator: https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html) [38], with effect scale mean deviation values/event rates (R values) and 95% confidence intervals (CIs) as effect size indicators. We performed meta-analyses using a fixed-effects model when I^2 was <50% and P was ≥0.10 (indicating no statistical heterogeneity in the literature); if I^2 was ≥50% or P was ≤0.10 (indicating statistical heterogeneity), we used a random-effects model. Additionally, we performed subgroup analyses of regions and sample sizes to explore the sources of heterogeneity. We considered differences statistically significant at $P<0.05$.

RESULTS

Search results

We retrieved 709 studies from the preliminary search, including 140 studies in English and 569 in Chinese. After the screening process, we included 28 studies (**Figure 1**).

Characteristics and quality assessment of included studies

Twenty-eight studies involved 1861 patients with HIV/AIDS-positive NTM isolates, including 23 cross-sectional studies, three case-control studies, one cohort study, and one case series. They were published between

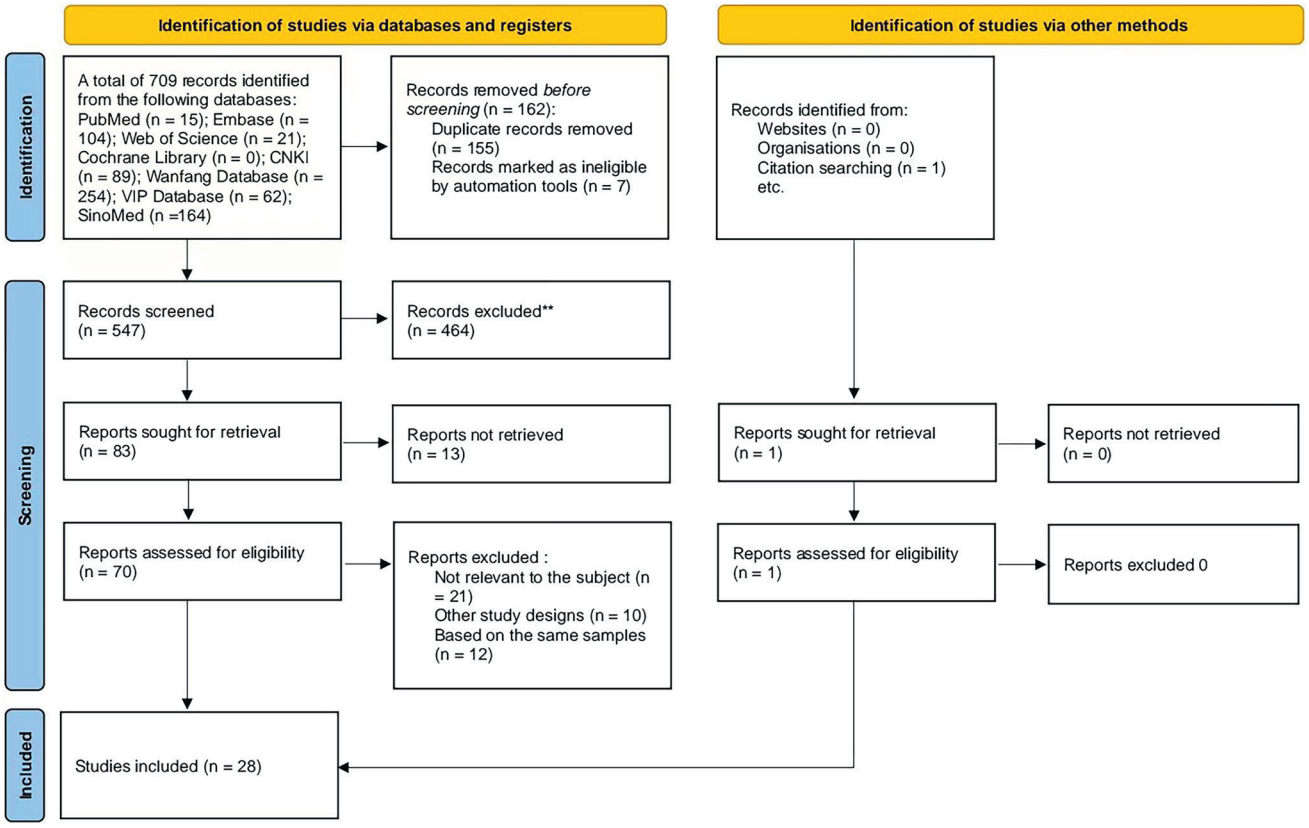

Figure 1. Flowchart of positive NTM in patients with HIV/AIDS systematic review study selection.

2008 and 2022, with 15 (53.6%) being published between 2018 and 2022. The studies were conducted in 13 regions (provinces, municipalities directly under the central government, and autonomous regions), mostly in the southern region, chiefly Guangxi (**Figure 2**, **Table 1**, and Table S7 in the **Online Supplementary Document**). Most of the patients were men (87.3%; 95% CI=83.2-91.0) (**Figure 3**).

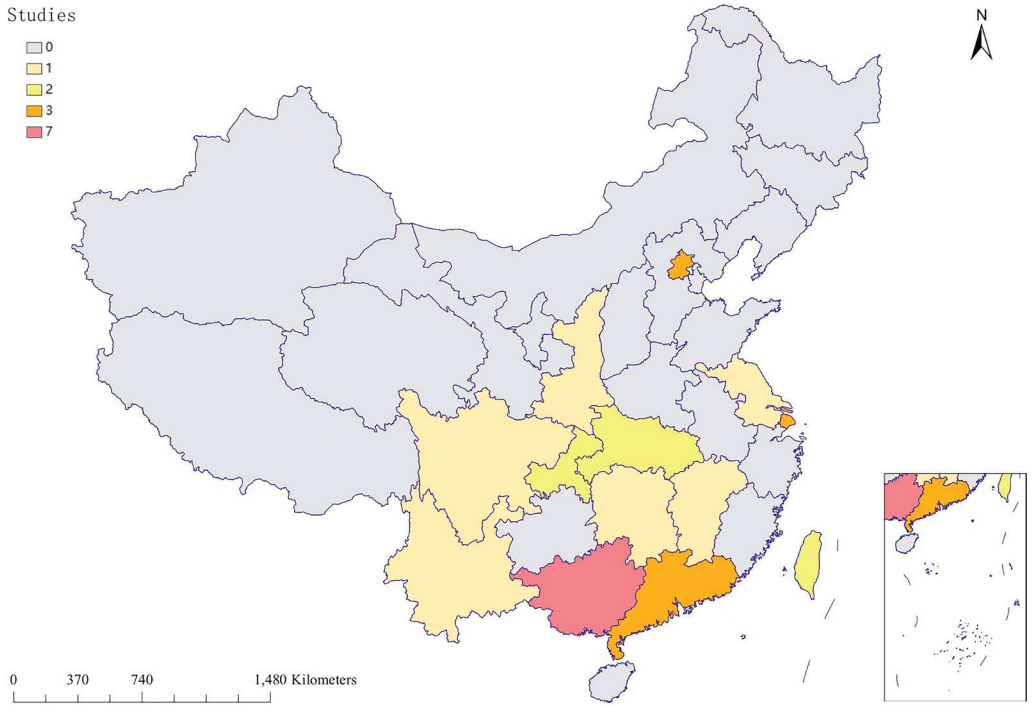

Figure 2. China maps for distribution of included studies.

Table 1. Essential information and quality assessment of included literature in systematic review of positive NTM from patients with HIV/AIDS in China

Study	Study design	Location (W/E/N/S/C)	Survey date	Total sample size	Men, n (%)	Observed indicators				
						Clinical symptoms	Laboratory tests	Thoracic imaging manifestations	Species distribution	Treatment outcome
Song et al., 2011 [39]	Case-series study	Beijing (N)	2009-2010	5	4 (80)	No	Yes	Yes	Yes	No
Ding et al., 2022 [40]	Cross-sectional study	Beijing (N)	2016-2021	71	62 (87.3)	Yes	Yes	Yes	Yes	Yes
Wang et al., 2017 [41]	Cross-sectional study	Beijing (N)	2009-2015	33	28 (84.8)	No	Yes	Yes	No	Yes
Wu et al., 2017 [42]	Cross-sectional study	Guangdong (S)	2008-2015	31	28 (90.3)	Yes	Yes	Yes	Yes	No
Cao et al., 2021 [43]	Cross-sectional study	Guangdong (S)	2014-2019	43	38 (88.4)	Yes	Yes	No	Yes	No
Jiang et al., 2014 [44]	Cross-sectional study	Guangdong (S)	2006-2010	13	13 (100)	Yes	No	Yes	No	No
Meng et al., 2008 [45]	Cross-sectional study	Guangxi (S)	2006-2007	36	NA	Yes	Yes	Yes	No	Yes
Meng et al., 2018 [46]	Cross-sectional study	Guangxi (S)	2012-2015	29	19 (65.5)	Yes	Yes	Yes	No	Yes
R. Lan et al., 2011 [47]	Case-control study	Guangxi (S)	2005-2008	102	82 (80.4)	No	Yes	No	Yes	No
Zhang et al., 2011 [48]	Case-control study	Guangxi (S)	2006-2008	82	NA	Yes	No	No	No	No
Yin et al., 2015 [49]	Cross-sectional study	Guangxi (S)	2009-2012	97	77 (79.4)	Yes	No	Yes	No	Yes
Huang et al., 2022 [50]	Cross-sectional study	Guangxi (S)	2018-2019	11	NA	No	Yes	No	Yes	No
Zhou et al., 2013 [51]	Cross-sectional study	Guangxi (S)	2006-2010	135	106 (78.5)	No	No	No	Yes	No
Wang et al., 2022 [52]	Cross-sectional study	Hubei (C)	2019-2021	9	8 (88.9)	Yes	Yes	No	No	Yes
Li et al., 2016 [53]	Cross-sectional study	Hubei (C)	2012-2015	27	24 (88.9)	Yes	Yes	Yes	No	No
Deng et al., 2013 [54]	Cross-sectional study	Hunan (C)	2008-2011	63	NA	Yes	Yes	Yes	No	No
Wang et al., 2021 [55]	Cross-sectional study	Jiangsu (E)	2017-2020	97	NA	No	Yes	No	Yes	No
Huang et al., 2021 [56]	Cross-sectional study	Jiangxi (E)	2017-2020	22	16 (72.7)	No	Yes	Yes	Yes	No
Li, 2018 [57]	Cross-sectional study	Shaanxi (W)	2016-2017	50	50 (100)	Yes	Yes	Yes	No	No
Zhu et al., 2013 [58]	Cross-sectional study	Shanghai (E)	2007-2012	27	27 (100)	Yes	Yes	Yes	No	No
Sun et al., 2019 [59]	Cross-sectional study	Shanghai (E)	2006-2015	377	329 (87.3)	No	No	No	Yes	No
Tian at al., 2022 [60]	Case-control study	Shanghai (E)	2015-2021	169	161 (95.3)	No	Yes	No	No	No
Wang et al., 2019 [61]	Cross-sectional study	Sichuan (W)	2014-2018	59	50 (84.7)	Yes	Yes	Yes	Yes	No
Zhang et al., 2021 [62]	Cross-sectional study	Yunnan (W)	2012-2019	90	69 (76.7)	No	Yes	No	Yes	No
Li et al., 2018 [63]	Cross-sectional study	Chongqing (W)	2013-2015	23	16 (69.6)	Yes	Yes	Yes	No	No
Liu et al., 2021 [64]	Cross-sectional study	Chongqing (W)	2019-2020	44	34 (77.3)	Yes	Yes	No	Yes	No
Chou et al., 2011 [65]	Cross-sectional study	Taiwan (E)	2004-2008	22	21 (95.5)	Yes	No	No	Yes	No
Chiang et al., 2020 [66]	Retrospective cohort study	Taiwan (E)	1996-2016	94	86 (91.5)	Yes	No	Yes	No	No

NA – not available, W – western region, E – eastern region, N – northern region, S – southern region, C – central region

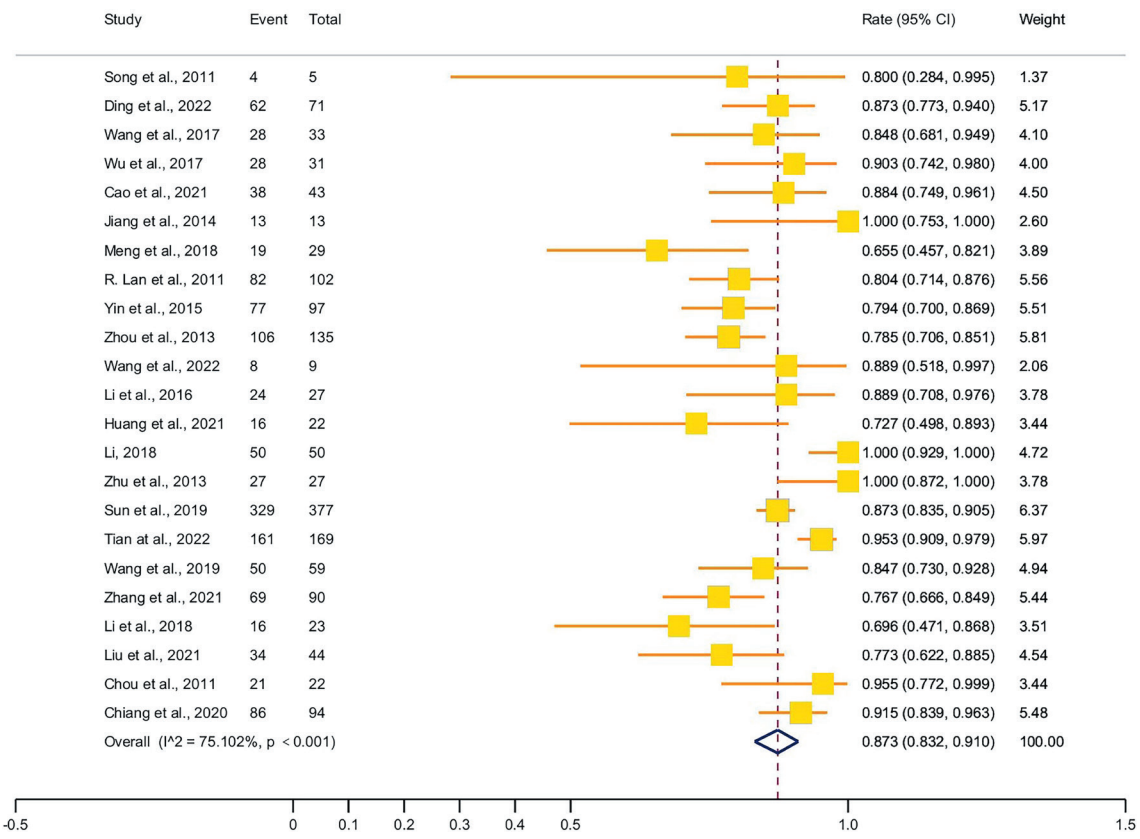

Figure 3. Forest plot of the proportion of men among positive NTM isolates from patients with HIV/AIDS.

Species distribution

The species distribution of NTM isolates positive was mainly *Mycobacterium avium* complex (MAC) (64.3%; 95% CI = 51.8-76.7), *Mycobacterium kansasii* (9.4%; 95% CI = 5.4-14.2), *Mycobacterium gordonae* (8.7%; 95% CI = 4.4-13.0), *Mycobacterium abscessus* complex (4.0%), and other mycobacterial species (16.0%) (**Table 2**).

Table 2. Results of a meta-analysis of species distribution among positive NTM isolates from patients with HIV/AIDS

NTM species distribution	Pooled estimate (95% CI)	Number of studies	Heterogeneity		Event/total
			P-value	I^2	
Mycobacterium avium complex	64.3 (51.8-76.7)	14	<0.001	95.0	522/834
Mycobacterium abscessus complex	4.0 (1.9-6.7)	10	0.049	46.9	29/645
Mycobacterium kansasii	9.4 (5.4-14.2)	11	<0.001	75.4	86/796
Mycobacterium gordonae	8.7 (4.4-13.0)	9	<0.001	79.3	68/666
Other NTM species*	16.0 (10.6-21.4)	13	<0.001	78.6	129/763

CI – confidence interval, NTM – nontuberculous mycobacterial
*All other NTM species accounted for less than the above four species.

Clinical symptoms

The more common clinical symptoms included fever (68.5%; 95% CI = 61.8-75.1), cough or expectoration (67.0%; 95% CI = 54.5-79.5), appetite loss (49.4%; 95% CI = 1.7-97.1), weight loss (45.5%; 95% CI = 28.9-62.2), superficial lymphadenectasis (41.1%; 95% CI = 30.5-51.6), fatigue (38.2%; 95% CI = 18.1-58.3), dyspnoea (34.9%; 95% CI = 17.0-52.8), erythra (30.6%), abdominal pain or diarrhoea (27.4%), chest pain (24.3%), night sweats (17.4%), and haemoptysis (4.3%) (**Table 3**).

Laboratory tests

In the laboratory tests, the haemoglobin count was 93.907 g/L (95% CI = 82.988-104.827 g/L) and CD4+ T cell count was 33.772 pieces/μL (95% CI = 15.289-52.255). Albumin (ALB) levels <35 g/L were observed

Table 3. Results of meta-analysis of clinical symptoms in positive NTM isolates from patients with HIV/AIDS

Clinical symptoms	Pooled estimate (95% CI)	Number of studies	Heterogeneity		Event/total, n/N
			P-value	I^2, %	
Fever	68.5 (61.8-75.1)	16	<0.001	74.7	495/743
Cough or expectoration	67.0 (54.5-79.5)	14	<0.001	95.2	477/721
Dyspnoea	34.9 (17.0-52.8)	8	<0.001	95.2	163/433
Chest pain	24.3 (3.8-54.0)	3	<0.001	94.1	59/195
Abdominal pain or diarrhoea	27.4 (23.2-31.7)	7	0.164	34.6	118/415
Night sweats	17.4 (10.8-23.9)	6	0.032	59.1	59/342
Fatigue	38.2 (18.1-58.3)	10	<0.001	97.4	217/596
Erythra	30.6 (5.6-55.6)	3	<0.001	88.9	24/94
Weight loss	45.5 (28.9-62.2)	12	<0.001	96.1	280/623
Haemoptysis	4.3 (1.6-7.0)	4	0.845	0.0	10/215
Appetite loss	49.4 (1.7-97.1)	3	<0.001	98.5	62/166
Superficial lymphadenectasis	41.1 (30.5-51.6)	10	<0.001	78.7	143/381

CI – confidence interval

in 55.6% (95% CI = 19.1-92.2) of studies, erythrocyte sedimentation rate (ESR)>20 mm/h in 91.4% (95% CI = 69.8-100.0), C-reactive protein (CRP)>6 mg/L in 82.5% (95% CI = 71.1-93.8), anaemia in 59.0% (95% CI = 38.1-79.8), CD4+ T cell count ≤50 pieces/μL in 70.3% (95% CI = 57.5-81.7), CD4+ T cell count 51-200 pieces/μL in 22.1% (95% CI = 14.8-30.3), and CD4+ T cell count >200 pieces/μL in 4.6% (95% CI = 0.8-10.3) (**Table 4** and **Table 5**).

Table 4. Results of meta-analysis of laboratory tests on positive NTM isolates from patients with HIV/AIDS

Laboratory tests*	MD	95% CI	Number of studies	Heterogeneity	
				P-value	I^2, %
Haemoglobin count (g/L)	93.907	82.988-104.827	5	<0.001	92.7
$CD4^+$ T cell count (pieces/μL)	33.772	15.289-52.255	6	<0.001	99.3

CI – confidence interval, MD – mean deviation
*Continuous variables, mean deviation (95% CI).

Table 5. Results of meta-analysis of laboratory tests on positive NTM isolates from patients with HIV/AIDS

Laboratory tests*	Pooled estimate (95% CI)	Number of studies	Heterogeneity		Event/total
			P-value	I^2, %	
ALB<35 (g/L)	55.6 (19.1-92.2)	4	<0.001	95.8	90/146
ESR>20 (mm/h)	91.4 (69.8-100.0)	3	0.001	84.7	117/135
CRP>6 (mg/L)	82.5 (71.1-93.8)	3	0.013	76.9	144/174
Anemia	59.0 (38.1-79.8)	7	<0.001	93.0	146/238
$CD4^+$ T cell count ≤50 (pieces/μL)	70.3 (57.5-81.7)	13	<0.001	89.9	417/630
CD4+ cell count 51-200 (pieces/μL)	22.1 (14.8-30.3)	13	<0.001	78.6	153/630
CD4+ cell count >200 (pieces/μL)	4.6 (0.8-10.3)	13	<0.001	82.2	60/630

MD – mean deviation, CI – confidence interval, ALB – albumin, ESR – erythrocyte sedimentation rate, CRP – C-reactive protein
*Dichotomous variables, prevalence rate (95% CI).

Thoracic imaging manifestations

Thoracic imaging manifestations (**Table 6**) show that the distribution of lesions was mainly bilateral lung involvement (83.8%; 95% CI = 70.7-93.9), followed by single lung involvement (12.8%; 95% CI = 5.1-22.8) and with no rare abnormalities (8.7%; 95% CI = 0.0-26.0). Furthermore, changes in lesion morphology and density mostly manifested as stripe shadow (60.3%; 95% CI = 41.9-77.4), patchy shadows (42.9%; 95% CI = 26.8-58.9), nodules (40.6%; 95% CI = 27.7-53.5), bronchiectasis (38.6%; 95% CI = 27.7-49.5), ground glass opacity (33.4%; 95% CI = 15.8-51.0), and some as cavitary lesions (13.0%), while millet shadows (4.6%) were rare. The accompanying signs were thoracic lymph node enlargement (49.5%; 95% CI = 25.8-73.3), abdominal lymph node enlargement (26.4%, 95% CI = 9.1-43.7), pleural thickening (14.9%; 95% CI = 8.1-21.7), hydrothorax (12.2%), and hydropericardium (11.2%).

Table 6. Results of meta-analysis of thoracic imaging manifestations in positive NTM isolates from patients with HIV/AIDS

Thoracic imaging manifestations	Pooled estimate (95%CI)	Number of studies	Heterogeneity		Event/total
			P-value	I^2, %	
Distribution of lesions					
Single lung involvement	12.8 (5.1-22.8)	7	<0.001	75.2	45/297
Bilateral lung involvement	83.8 (70.7-93.9)	7	<0.001	83.4	240/297
No abnormalities	8.7 (0.0-26.0)	10	<0.001	95.3	85/446
Changes in lesion morphology and density					
Patchy shadows	42.9 (26.8-58.9)	8	<0.001	91.8	155/371
Nodules	40.6 (27.7-53.5)	10	<0.001	89.6	157/470
Millet shadow	4.6 (0.4-11.9)	8	<0.001	83.5	23/387
Cavitary lesion	13.0 (5.0-23.4)	14	<0.001	89.5	110/602
Stripe shadow	60.3 (41.9-77.4)	6	<0.001	88.7	144/291
Ground glass opacity	33.4 (15.8-51.0)	4	0.001	81.9	46/161
Bronchiectasis	38.6 (27.7-49.5)	6	0.034	58.6	84/219
Accompanying signs					
Thoracic lymph node enlargement	49.5 (25.8-73.3)	9	<0.001	94.5	148/346
Abdominal lymph node enlargement	26.4 (9.1-43.7)	3	0.002	84.2	45/150
Hydropericardium	11.2 (7.0-15.4)	5	0.357	8.7	27/213
Hydrothorax	12.2 (4.7-22.2)	10	<0.001	86.1	59/441
Pleural thickening	14.9 (8.1-21.7)	7	0.022	59.4	48/290

CI – confidence interval

Treatment outcome

Analysis of treatment outcome showed that symptoms improved (70.0%; 95% CI = 56.9-83.0) in most patients after treatment, with death and other outcomes accounting for 6.2% (95% CI = 3.2-9.9) and 22.6% of total outcomes (**Table 7**).

Table 7. Results of meta-analysis of treatment outcome with positive NTM isolates from patients with HIV/AIDS

Treatment outcome	Pooled estimate (95% CI)	Number of studies	Heterogeneity		Event/total
			P-value	I^2, %	
Symptoms improve*	70.0 (56.9-83.0)	6	<0.001	83.2	184/275
Death	6.2 (3.2-9.9)	6	0.377	6.2	20/275
Others†	22.6 (9.9-35.3)	6	<0.001	86.8	71/275

CI – confidence interval

*Symptom improvement is defined as getting better after treatment during hospitalisation.

†Others include automatic discharge, transfer to another hospital, and no apparent improvement.

Subgroup analyses

We found differences between regions and some disease characteristics in the subgroup analyses (Table S8 and S9 in the **Online Supplementary Document**). For example, cough or expectoration was more frequent in the western (88.4%; 95% CI = 79.4-97.4) than the northern region (33.8%; 95% CI = 23.9-45.4, $P < 0.001$). We found no significant association between sample size (per study) and disease characteristics; however, fever (74.6%; 95% CI = 68.3-80.8 vs 61.6%; 95% CI = 50.6-72.7 ($P = 0.045$)), night sweats (33.2%; 95% CI = 17.1-49.3 vs 14.8%; 95% CI = 9.2-20.4 ($P = 0.034$)), and manifestations of stripe shadows on thoracic imaging (78.3%; 95% CI = 49.9-97.5 vs 44.0%; 95% CI = 27.6-61.1 ($P = 0.042$)) were more common in sample sizes of with <50 than those with ≥50 patients, while anaemia was less frequent in sample sizes with <50 than in ones with ≥50 patients (53.9%; 95% CI = 32.8-75.0 vs 86.4%; 95% CI = 75.5-93.0 ($P = 0.005$)).

Both subgroup analyses showed a high degree of heterogeneity and an $I^2 \geq 50\%$. We hypothesise that the above-mentioned differences were caused by confounding factors outside the selected subgroup criteria, including data collection era, clinical typing (pulmonary NTM disease, extrapulmonary NTM disease, or disseminated NTM disease) and infection strain species.

DISCUSSION

Clinical significance of positive NTM isolates

Positive NTM isolation from clinical specimens at different sites has different implications: NTM isolated from non-sterile sites, such as sputum and bronchial lavage fluid, should exclude the possibility of specimen contamination or respiratory colonisation, while that from sterile sites, such as blood, cerebrospinal fluid, and puncture fluid, is more likely to be infectious or pathogenic [67,68]. When contamination of the specimen is excluded, positive NTM isolates include NTM colonisation, NTM infections, and NTM disease. As the immune status of the body changes, NTM colonisation or infections may progress to NTM disease, resulting in systemic tissue and organ damage.

Initial screening strategies for NTM infections from patients with HIV/AIDS in China

Both TB infections and NTM infections can cause the same clinical symptoms, with the four clinical symptoms recommended by the World Health Organization for screening for TB infections including cough, fever, night sweats, and weight loss [69]. Moreover, a recent systematic review of patients co-infected with HIV and TB shows that C-reactive protein testing and chest imaging can be useful for screening TB infections [70]. There is no recommended screening strategy for NTM infections from patients with HIV/AIDS in China. We found that fever, cough or expectoration, appetite loss, weight loss, and superficial lymphadenectasis were the five most common clinical symptoms, while the incidence of haemoptysis was 4.3%, unlike TB, which is the leading cause of haemoptysis worldwide [71]. Therefore, these clinical symptoms can be used for the initial screening of NTM infections.

In our study, 55.6% of patients had an ALB<35 g/L, 91.4% had an ESR>20 mm/h, and 59% had anaemia, which was predominantly mild. Moreover, most patients had thoracic imaging involvement, and only 8.7% of patients had no thoracic imaging changes, mainly showing stripe shadows, patchy shadows, nodules, bronchiectasis, and signs of thoracic lymph node enlargement. However, some studies have found that acute infections of HIV/AIDS combined with MTB, with the thoracic imaging manifestations being mainly pneumonia-like exudates or solid shadow and nodules are rare [72]. Thus, thoracic imaging (x-ray or computed tomography) should be used as a routine and necessary means to diagnose NTM infections, regardless of whether they present with clinical symptoms, which is important for the early detection of the disease.

In summary, we consider that clinical symptoms, including fever, cough or expectoration, appetite loss, weight loss, and superficial lymphadenectasis without haemoptysis, laboratory tests, including ALB, erythrocyte sedimentation rate, and haemoglobin, and thoracic imaging are helpful in the initial screening for NTM infections.

Priority population for screening for NTM infections from patients with HIV/AIDS in China

We found the CD4+ T cell count to be 33.772 pieces/μL (95% CI = 15.289-52.255 pieces/μL) in the included studies, with 70.3% of patients having a CD4+ T cell count ≤50 pieces/μL (95% CI = 57.5-81.7). Men comprised 87.3% of the total population. Water and soil are important transmission routes for NTM infections [24,25], and some species such as *Mycobacterium abscessus* can be transmitted interpersonally [73]. Therefore, we propose that patients with HIV/AIDS who are severely immunosuppressed (CD4+ T cell count <50 pieces/μL), especially men and patients with HIV/AIDS who are chronically exposed to unclean water sources in occupations related to exposure to soil (eg, farmers, gardeners) and have been or are being exposed to repeated NTM infections or NTM disease may be a priority population for screening for NTM infections.

Principles of treatment for NTM disease from patients with HIV/AIDS in China

There is a lack of studies on the distribution of the NTM species over large areas of China. We found that the distribution of NTM species in China was dominated by *Mycobacterium avium* complex, which accounted for 64.3% of the species, while being predominant in different regions. *Mycobacterium avium* complex is a slow-growing mycobacterium. Therefore, when the results of the NTM species identification are unclear, experimental treatment for *Mycobacterium avium* complex infections may be feasible for critically ill patients or in cases when the disease is progressing rapidly. Physicians should also raise awareness of the diagnosis and treatment of *Mycobacterium avium* complex.

Prophylactic treatment of NTM disease for patients with HIV/AIDS in China

Current Chinese expert consensus recommends prophylactic treatment for patients with HIV/AIDS with a CD4+ T cell count <50 pieces/μL [30], mainly based on guidelines and literature from high-income countries in Europe and North America that do not correspond to the circumstances in LMICs with scarce medical resources and weak economies. We found that approximately 30.0% of hospitalised patients failed to improve after treatment, making prophylactic treatment particularly important. Patients with HIV/AIDS should receive prophylactic anti-tuberculosis treatment with isoniazid, rifampicin, and rifapentine after active TB has been ruled out, regardless of the degree of immunosuppression or being tested for MTB infections [69]. Prophylactic treatment for NTM disease includes azithromycin, clarithromycin, and rifabutin [67,68]. We found that 22.1% of patients had a CD4+ T cell count of 51-200 pieces/μL, and the Food and Drug Administration showed weak drug interactions between clarithromycin, rifabutin, and the three prophylactic anti-tuberculosis drugs [74]. Therefore, it may be more appropriate to up-regulate CD4+ T cell count to ≤200 pieces/μL for the prophylactic treatment of NTM disease in patients with HIV/AIDS in China.

Strengths and weakness

This is the first systematic review of positive NTM isolates from patients with HIV/AIDS in China. We followed PRISMA guidelines [31-33] in reporting and conducting the review, ensuring that all relevant studies are included. Consequently, it not only provides theoretical support for existing expert consensus in China, but also fills a relevant gap and provides information for future clinical research directions.

This study had certain limitations. Most of the included studies did not specify the type of clinical infection, and the selected control groups varied (eg, HIV/AIDS co-infection with NTM vs MTB and HIV/AIDS vs non-HIV/AIDS co-infection with NTM). Therefore, we were unable to make a definitive analysis of HIV/AIDS co-infection with NTM/MTB and HIV/AIDS co-infection with pulmonary NTM disease/extrapulmonary NTM disease/disseminated NTM disease. Additionally, the sample size of the included studies was too small, and the findings cannot be applied to all regions. Moreover, some of our recommendations are based on hypothetical reasoning inferred from our findings, and their specific clinical value and feasibility require further confirmation through cohort studies, clinical trials, and cost-benefit analyses.

CONCLUSIONS

Focusing on clinical symptoms, laboratory tests, and thoracic imaging helps with initial screening for NTM infections. Physicians should raise awareness of the diagnosis and treatment of *Mycobacterium avium* complex, providing guidance for experimental treatment, screening of priority populations for NTM infections, and prophylactic treatment of NTM disease

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Additional material
Online Supplementary Document

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