Long-Term Case-Fatality Rate of Nontuberculous Mycobacterial Disease in People Living with HIV

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Research Article

Keywords: HIV/AIDS, nontuberculous mycobacteria, case-fatality rate, risk factors

Posted Date: December 10th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1144067/v1

Version of Record: A version of this preprint was published at Infectious Diseases of Poverty on February 7th, 2022. See the published version at https://doi.org/10.1186/s40249-022-00942-8.

Abstract

Background

Few data are available regarding the long-term case-fatality rate (CFR) among people living with HIV (PLWH) with nontuberculous mycobacteria (NTM) disease.

Objectives

To analyze the long-term CFR in patients with NTM disease and to identify risk factors for their death.

Methods

A retrospective cohort study of 379 cases of microbiologically confirmed NTM disease in PLWH was conducted during January 1, 2012 to December 31, 2020 in Shanghai, China. We used Kaplan-Meier survival analysis and log-rank test to compare long-term CFR in patients with disseminated NTM (DNTM) and localized NTM disease. Univariate Cox proportional hazards regression analysis and stepwise Cox proportional hazards regression model were used to estimate the predictors of long-term CFR.

Results

The cohort was follow-up for a median of 26 months. The total CFR was 15.7% by one year and increased to 22.6% at 5 years after the diagnosis of NTM disease. The 5-year CFR of PLWH with DNTM was significantly higher than that of localized NTM (26.7% vs. 19.6% for DNTM and localized NTM disease, respectively). Older age (hazard ratio [HR] = 1.04, 95% confidence interval [CI]: 1.02-1.06, $P <$ 0.001), comorbidity (HR = 2.05, 95% CI: 1.21-3.49, $P <$ 0.01), DNTM (HR = 2.08, 95% CI: 1.17-3.68, $P <$ 0.05), and HIV viral load (HR = 1.32, 95% CI: 1.12-1.55, $P <$ 0.001) were all independent risk factors of long-term CFR. In the subgroup analysis, time to culture positivity was negatively correlated with CFR in patients with DNTM (HR = 0.90, 95% CI: 0.82-0.98, $P <$ 0.05).

Conclusions

NTM was associated with significantly high long-term CFR in PLWH. Further approaches to prevent NTM disease in PLWH are urgently needed.

Introduction

Nontuberculous mycobacteria (NTM) disease is one of the leading opportunistic infections in people living with HIV (PLWH). Over the past decades, the number of cases of PLWH with NTM has increased

with advances in screening techniques, the AIDS epidemic and the increase in the number of immunocompromised patients. [1, 2] Recently, data from the United States showed that the overall prevalence of NTM (among PLWH admitted to hospital for pneumonia) was 49% (96/196). [3] In another study, 37 cases of disseminated NTM (DNTM) were identified in 7,349 patients with a median annual incidence of 110/100,000 HIV person-years, and the highest incidence in those with CD4+ T cell count <50 cells/mm^3 (5,300/100,000 person-years) between 2007 and 2012.[4]

In the pre-antiretroviral therapy (ART) era, case fatality rates (CFRs) were high for NTM and even more so for DNTM, with an annual CFR of 71%. [5] After the ART era, AIDS has become a chronic disease, which has led to a significant increase in life expectancy in PLWH, and the incidence of disseminated Mycobacterium avium complex (DMAC) has declined significantly from 65.3/1000 in 1992 to 2.0/1000 in 2015.[6] However, despite the availability of effective ART, the CFR for NTM remains high, with a CFR of 69% at 1 year and 27% at 3 years after diagnosis of DMAC.[7]

Modern population-based estimates of long-term survival of HIV-infected patients with NTM are lacking. Studies have indicated that the long-term survival of PLWH with tuberculosis (TB) was lower than that of non-TB patients.[8] We hypothesized that long-term CFR would also be elevated in PLWH with NTM. Therefore, we conducted this study.

Methods

Study subjects

A retrospective analysis was performed on the clinical data of PLWH with NTM in Shanghai Public Health Clinical Center (SPHCC) from January 1, 2012 to December 31, 2020. Inclusion criteria were as follows: 1.) HIV-1 infection confirmed by Western blotting. 2.) patients with at least one specimen were positive for mycobacterium culture and negative for MPB64, or mycobacterial sequencing results were NTM. 3). physicians deem that NTM was one of the etiologies of the diseases, but not colonization. Exclusion criteria were patients younger than 18 years.

Study design

The following characteristics were recorded: gender, age, behavioral risk factors (such as current or former smoking, alcohol abuse), comorbidities, opportunistic infections, CD4+ T cell count, HIV viral load, ART regimen, NTM treatment, symptoms and the time from the specimen culture initiation to positive report. Furthermore, we registered the high-resolution computed tomography (CT) scan. All abnormal CT scans were reported and divided into the seven categories: 1.) lymphadenopathy only; 2.) lymphadenopathy with nodules; 3.) lymphadenopathy with cavities; 4.) lymphadenopathy with cavities and nodules; 5.) nodules only; 6.) cavities only; 7.) consolidation only. We recorded the laboratory data of all patients, including T-SPOT result, blood cell count, hemoglobin, erythrocyte sedimentation rate, C-reactive protein and renal and liver function.

A diagnosis of DNTM was defined as a positive culture for mycobacterium from blood, cerebrospinal fluid, bone marrow, or biopsy of a sterile site or infection involving two or more noncontiguous body sites.

We defined comorbidities based on Charlson Comorbidity Index (CCI). [9, 10] It includes 19 major disease categories, including risk factors and potential prognostic factors for PLWH with NTM. Comorbidity data included diabetes, hypertension, cancer, chronic lung disease and other diseases. AIDS-defining opportunistic infections other than NTM infection were also recorded. Baseline CD4+ T cell count and HIV viral load were defined using the test results at admission or the closest record at admission. Anti-NTM medication use was defined as drug use at least more than 2 weeks.

For the prognosis analysis, survival time was defined as the time from the beginning of definitive diagnosis of NTM to death, loss to follow-up, or the end of follow-up (31 December 2020). Patients were followed up by telephone after discharge from the hospital. The outcome was all-cause mortality during the follow-up period.

The study was approved by the Ethics Committee of Shanghai Public Health Clinical Center. Informed consent was waived because of the retrospective design of the study.

Analysis

SPSS statistics 25.0 (IBM, Armonk, NY, USA) and Stata 16.0 (StataCorp LP, College Station, TX, USA) were used for statistical analysis. The Shapiro-Wilk test was used to test whether the data conformed to a normal distribution. Normally distributed data were reported as mean and standard deviation (mean ± s). Non-normally distributed data was presented as median and interquartile range (IQR). Categorical variables were summarized with frequency counts and presented as a rate (%). χ^2 test, t-test and Fisher's exact test were used to test for statistically significant differences. Kaplan-Meier survival analysis and log-rank test were used to compare long-term CFR in patients with DNTM and localized NTM disease. Univariate Cox proportional hazards regression analysis and stepwise Cox proportional hazards regression model were used to estimate the predictors of long-term CFR. $P < 0.05$ indicated statistical significance. In these analyses, hazard ratios were combined with 95% confidence intervals.

Results

Clinical characteristics of the study population

Three hundred and seventy-nine patients were included. Of these, 93.7% were male. The median age was 38.0 [IQR: (30.0-50.0)] years. 7.4% of the patients were current or former smokers and 2.6% consumed alcohol. One hundred and thirteen patients (29.8%) had comorbidities and 136 patients (35.9%) had opportunistic infections. In addition, the median CD4+ T cell count was 23.0 [IQR: (6.0-73.8)] cells/μL and the median of HIV viral load was 4.84 [IQR: (1.9-5.5)] log10 copies/mL. Two hundred and ninety-four patients (77.6%) received ART prior to anti-NTM therapy, and the median time from initiation of ART to initiation of anti-NTM therapy was 31.0 [IQR: (4.0-127.0)] months (**Table 1**).

Table1: Baseline characteristics of PLWH with NTM infection.

		N
General information		
	Total number of patients	379
	Male gender, N (%)	355(93.7%)
	Age [years], Median (IQR)	38.0(30.0-50.0)
	Smoking (current or former), N (%)	28(7.4%)
	Alcoholism, N (%)	10(2.6%)
	Comorbidity, N (%)	113(29.8%)
	Opportunistic infection, N (%)	136(35.9%)
Clinical manifestations		
	Fever, N (%)	236(63.4%)
	Cough, N (%)	164(44.1%)
	HIV wasting syndrome, N (%)	81(22.8%)
	Abdominal pain and diarrhea, N (%)	68(18.3%)
	Central nervous system symptoms, N (%)	48(12.9%)
	Rash, N (%)	43(11.6%)
HIV-related indicators		
	CD4+ T cell count [cells/μL], Median (IQR)	23(6.0-73.8)
	HIV viral load [log10 copies/mL], Median (IQR)	4.8(1.9-5.5)
	ART before NTM treatment, N (%)	294(77.6%)
NTM treatment	ART to anti-NTM time, Median (IQR)	31(4.0-127.0)
	Macrolides, N (%)	280(73.9%)
	Levofloxacin/Moxifloxacin, N (%)	248(65.4%)
	Ethambutol, N (%)	317(83.6%)
	Rifampicin/Rifabutin, N (%)	248(65.4%)
	Linezolid, N (%)	23(6.1%)

PLWH: people living with HIV

NTM: nontuberculous mycobacteria

IQR: interquartile range

HIV: human immunodeficiency virus

ART: antiretroviral therapy

The most frequently reported symptom was fever (63.4%). Cough was reported in 44.1% of all cases. 22.8% reported HIV wasting syndrome, 18.3% reported abdominal pain and/or diarrhea, 12.9% reported central nervous system symptoms such as headache and dizziness, and half of these patients had a combination of cryptococcal meningitis. The remaining 11.6% of patients had skin manifestations, such as rashes. (**Table 1**) For each year from 2013 to 2020, DNTM was account for almost half of the total number of NTM in PLWH (Fig. 1). Among the first reported positive specimens, sputum accounted for 60.7%, blood for 23.5%, stool for 6.9%, while the rest were puncture fluid (4.0%), bronchoalveolar lavage or bronchial lavage fluid (1.3%), pleural effusion (0.8%), cerebrospinal fluid (0.8%), bone marrow (0.8%), urine (0.5%), hydroperitoneum (0.3%), abdominal abscess (0.3%) and secretions from ruptured skin (0.3%). The median time to culture positivity was 13.9 [IQR: (9.5-23.5)] days.

Three hundred and twenty-six (86.0%) patients received CT scans. Lymphadenopathy, nodules, lymphadenopathy with nodules, cavities, lymphadenopathy with cavities, lymphadenopathy with cavities and nodules and consolidation account for 34.1%, 10.1%, 7.1%, 4.3%, 3.1%, 1.2% and 0.9%, respectively. The most common lymphadenopathy was mediastinal lymphadenopathy (128/148, 86.5%), followed by hilar lymphadenopathy (42/148, 28.4%) and retroperitoneal lymph (40/148, 27.0%) and lastly, axillary lymph nodes (20/148,13.5%), supraclavicular/infraclavicular lymph nodes (8/148, 5.4%), celiac lymph node (8/148, 5.4%), pelvic lymph nodes (1/148, 0.7%). In addition, 6.4% of them had no obvious abnormalities.

Treatment for NTM diseases consists of a multidrug regimen and a long course of therapy. Anti-NTM medication for patients included macrolides, levofloxacin/moxifloxacin, ethambutol, rifampicin/rifabutin, linezolid (**Table 1**), which lasted for 9 to 12 months. Almost all the enrolled patients received ART.

Survival Analysis

After a median of 26 months follow up, 69 patients (18.2%) died, and 48 (12.7%) lost follow-up. In 52.24% of all patients, the follow-up period exceeded 2 years. The life table method showed an overall CFR of 15.7% at 1 year, 19.0% at 2 years, 20.0% at 3 years, 22.6% at 5 years, and 27.9% at 7 years. Univariate Cox regression analysis indicated that the following parameters were statistically significant for survival: older age, HIV viral load, ART before NTM treatment, comorbidity, linezolid and DNTM. (Table 2). The probability of death in PLWH with NTM increased with time. (Fig. 2)

Table 2
Hazard ratio in univariate analysis and multivariate analysis. (Gender, age, smoking, alcoholism, comorbidity, opportunistic infection, CD4+ T cell count, HIV viral load, ART before NTM treatment, linezolid, DNTM and time to culture positivity will be added to the model using stepwise procedures.)

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95%CI	P	Hazard ratio	95%CI	P
Age	1.02	1.01-1.04	0.015	1.04	1.02-1.06	0.001
Comorbidity	2.01	1.24-3.23	0.005	2.05	1.21-3.49	0.008
DNTM	1.81	1.12-2.90	0.015	2.08	1.17-3.68	0.012
HIV viral load	1.25	1.07-1.46	0.006	1.32	1.12-1.55	0.001
Linezolid	3.64	1.85-7.15	0.001	4.71	2.25-9.83	0.001
Gender	1.59	0.50-5.04	0.435			0.697
Smoking	0.86	0.31-2.35	0.764			0.411
Alcoholism	1.30	0.32-5.29	0.719			0.592
Opportunistic infection	0.98	0.60-1.61	0.946			0.411
CD4+ T cell count	1.00	1.00-1.00[1]	0.243			0.795
ART before NTM treatment	0.53	0.32-0.89	0.015			0.221
Time to culture positivity	0.98	0.96-1.01	0.125			0.232
HIV: human immunodeficiency virus						
NTM: nontuberculous mycobacteria						
DNTM: disseminated nontuberculous mycobacteria						
ART: antiretroviral therapy						
[1] : 95% CI for hazard ratio of CD4+ T cell count: 0.996-1.001.						

Considering that gender, smoking, alcoholism, opportunistic infection, CD4+ T cell count, time to culture positivity were also important risk factors, these factors and all parameters that were statistically significant in the univariate analysis were included in a multivariate Cox proportional hazards model. The results showed a hazard ratio of 2.05 (95% confidence interval [CI]: 1.21-3.49, $P < 0.01$) for patients with comorbidities compared with those without comorbidities. The hazard ratio caused by older age was 1.04 (95% CI: 1.02-1.06, $P < 0.001$). High levels of HIV viral load were statistically significant, and had a hazard

ratio of 1.32 (95% CI: 1.12-1.55, $P < 0.001$). DNTM were significantly correlated with poor survival outcomes (HR = 2.08, 95% CI: 1.17-3.68, $P < 0.05$). (Table 2) Kaplan-Meier analysis also revealed that long-term CFR of DNTM group was significantly higher than that of the localized infection group (Fig. 3). Surprisingly, patients not treated with linezolid had a significantly longer survival time than those treated with linezolid (HR = 4.71, 95% CI: 2.25-9.83, $P < 0.001$).

In the subgroup analysis for patients with DNTM, time to culture positivity was negatively correlated with CFR (HR = 0.90, 95% CI: 0.84-0.96, $P < 0.01$). The longer time to a positive culture of the specimen, the lower the number of NTM, thus favoring survival. Older age (HR = 1.05, 95% CI: 1.02-1.08, $P < 0.01$), comorbidity (HR = 2.38, 95% CI: 1.14-4.96, $P < 0.05$) and linezolid usage (HR = 3.39, 95% CI: 1.43-8.02, $P < 0.01$) remained all independent risk factors for long-term CFR (Table 3).

Table 3
Hazard ratio in multivariate analysis of PLWH with DNTM. (Gender, age, smoking, alcoholism, comorbidity, opportunistic infection, CD4+ T cell count, HIV viral load, ART before NTM treatment, linezolid, DNTM and time to culture positivity will be added to the model using stepwise procedures.)

	Hazard ratio	95%CI	P
Age	1.05	1.02-1.08	0.004
Comorbidity	2.38	1.14-4.96	0.021
Linezolid	3.39	1.43-8.02	0.006
Time to culture positivity	0.90	0.84-0.96	0.002
HIV: human immunodeficiency virus.			
ART: antiretroviral therapy			
PLWH: people living with HIV.			
DNTM: disseminated nontuberculous mycobacteria.			

Discussion

To our knowledge, this is the largest study to date that evaluates the long-term CFR and associated prognostic factors for NTM in PLWH in modern ART era. Our study demonstrated that long-term CFR of PLWH with NTM remains high, even though patients have been treated or even recovered. Further analysis revealed that long-term CFR for disseminated infections was higher than those without disseminated infection. Older age, comorbidity, HIV viral load, DNTM and linezolid usage were all independent prognostic factors for PLWH with NTM. For patients with DNTM, the time to culture positivity was negatively correlated with CFR.

Lauren F. Collins et al. studied patients with HIV/AIDS from 1992-2015.[11] Despite of effective ART, they found that DMAC infection was associated with a significant increase in CFR in terms of the years following diagnosis. This was similar to the results in our study. Another Japanese study also showed that DNTM was significantly associated with CFR, and the median baseline CD4+T cell count was significantly lower in the non-survivors than in survivors.[12] However, their sample size of 24 is not very convincing and further studies are needed.

Data on the impact of NTM on long-term CFR in PLWH are limited, but studies in HIV-negative cohorts have also found high long-term CFR in NTM survivors. Typically, factors such as older age and comorbidities have been reported to be associated with poor prognosis. A systematic review gave an overall estimate of five-year CFR from NTM pulmonary disease studies. Despite of high heterogeneity of the enrolled studies, the pooled estimate of 5-year all-cause mortality of the 9035 patients was 27% (95% CI: 21.3-37.8).[13] Predictors of CFR that were consistent across studies included male, presence of comorbidities and older age of patients.[13]

Several studies have compared long-term CFR among PLWH after TB treatment completion, to those without TB.[8] The 5-year CFR for patients who completed TB treatment was 10.2% compared to patients without TB (5.6%).[8] In our study, the 5-year CFR for NTM was 22.6%, which appears to be more than twice as high as that of TB patients. Chiang, C-H. et al.[14] also reported that PLWH with DMAC (n = 58) had a three times higher 1-year CFR than those with TB (n = 98) (48.3% vs. 16.3%). This implies that we should be more concerned about long-term prognosis of NTM in PLWH.

Behavioral factors (such as smoking, alcoholism, etc.)[15, 16] and various respiratory or non-respiratory comorbidities[17] increase the risk of acquiring NTM and may partially account for the increase long-term CFR among NTM survivors. Multiple studies in largely HIV-negative populations have documented that structural lung defects and impaired pulmonary function after NTM infection, as well as many studies found a strong association with increased CFR between a history of NTM and COPD and bronchiectasis.[18–22] Recently, Ahmad Mourad et al. found that the expected survival was reduced by approximately 4 years for a diagnosis of NTM lung disease without comorbidity and 8.6 years for a diagnosis of NTM lung disease with comorbidity.[23] Among HIV-negative patients with NTM with and without comorbidities, the 5-years CFR after diagnosis was 44.9% and 25.0%, respectively.[23]

The high occurrence of disease relapse and increasing drug resistance may lead to an increased CFR. A multicenter study showed that 9.5% of patients with NTM pulmonary infection experienced multiple episodes, with 24.8% of them suffering from relapsing infections caused by the same NTM species.[24] An observational retrospective study from Italy revealed that 35.3% of patients had unsuccessful treatment outcomes, including discontinuation of therapy (13.5%), recurrence (11.2%), re-infection (5.3%), treatment failure (4.1%) and relapse (1.2%).[25] The treatment of treatment-refractory NTM cases or patients with drug-resistant NTM isolates remains challenging. This may indicate a poor prognosis and high CFR.

In addition, NTM may cause persistent inflammation and immune activation, which may increase susceptibility to HIV infection, promote HIV viral replication, and accelerate the progression of HIV disease.[26] As shown in a previous study, 79% (19/24) of the patients with DNTM in PLWH had the immune-reconstitution syndrome (IRS), suggesting difficulty in the management of DNTM.[27] Therefore, clinicians should pay high attention to DNTM in PLWH.

There are some limitations in our study. First, this study was conducted at a single center and due to its retrospective nature, our result may not be generalizable to other areas. Second, no further species identification was available for most patients. Several studies have found that different mycobacterium species were not significant for CFR analysis.[28, 29] However, a 15-year follow-up study of 1445 patients with NTM pulmonary disease showed that the accurate identification of the species or subspecies of the pathogen NTM is very important in the prognosis.[30] Data from Canada also showed that NTM disease were associated with higher rates of death for all species combined and for most individual species.[31] Therefore, further research is needed in species identification.

Conclusions

Long-term CFR for NTM in PLWH is high. Older age, comorbidity and DNTM are independent prognostic factors for NTM. These findings highlight the critical importance of PLWH with NTM, and suggest that PLWH with a history of NTM may require closer long-term follow-up.

Declarations

Ethical Approval and Consent to participate

The study was approved by the Ethics Committee of Shanghai Public Health Clinical Center. (Ethics approval number: 2020-Y112-01)

Informed consent was waived because of the retrospective design of the study.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Shanghai Commission of Science and Technology (20MC1920100 and 21Y11901200), Shanghai Municipal Health Commission (GWV-10.1-XK02), the development fund for Shanghai talents (2020089) and the Shanghai "Rising stars of Medical Talent" Youth Development Program [No. 2019-72].

Authors' contributions

LL, JC and HL conducted the study conception and design. JH and LG collected the data of patients. JH and JC analyzed and interpreted the data. JH wrote the manuscript. YS made grammatical revisions to the manuscript. JC critically revised and finally approved the manuscript. RZ, TQ, JS, ZW, WS, YT, JW, SX, JY and YS supervised the project. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

Authors' information

Not applicable.

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Figures

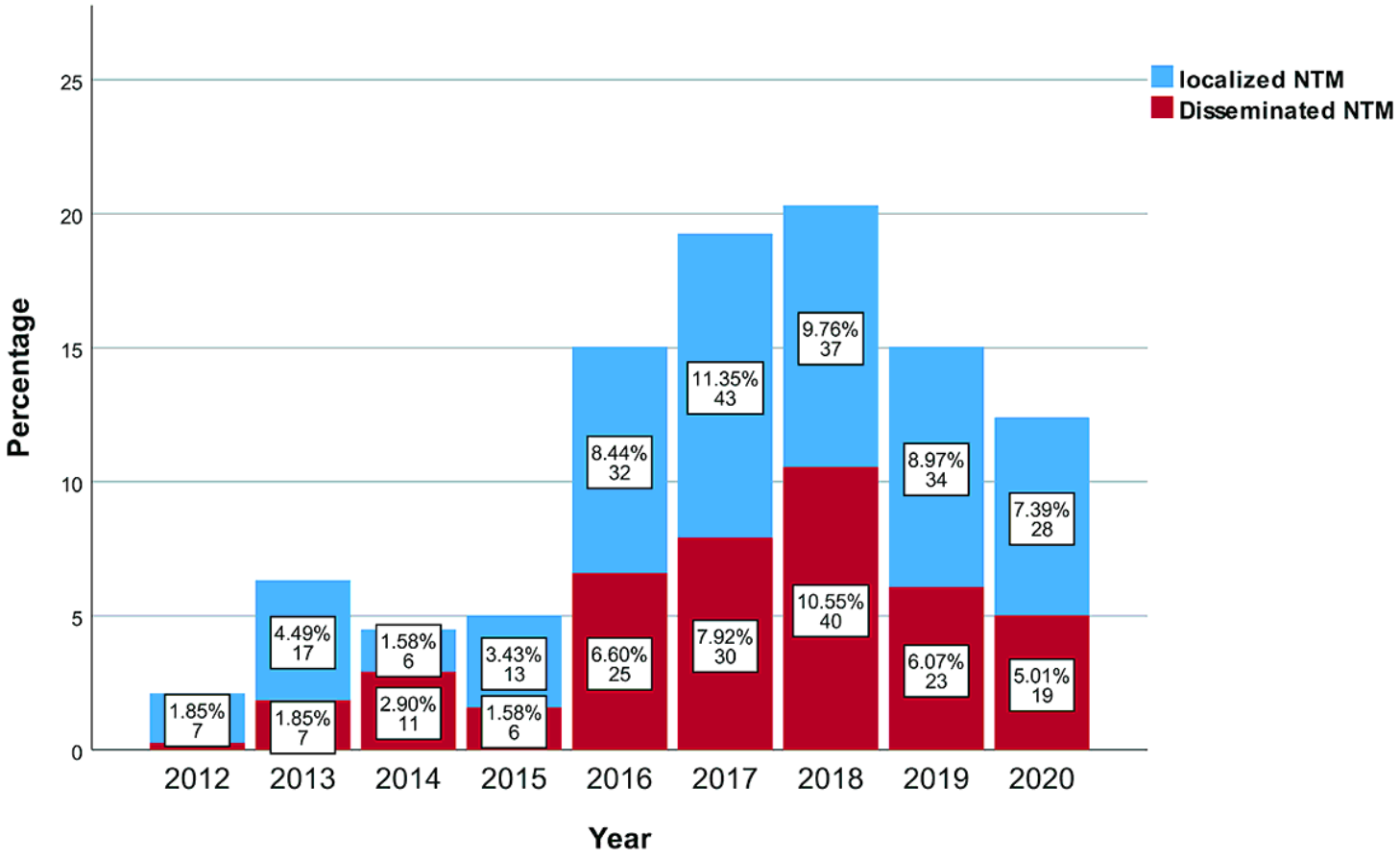

Figure 1

Stacked bar charts of PLWH with disseminated NTM and with localized NTM disease. Abbreviations: PLWH: people living with HIV NTM: nontuberculous mycobacteria

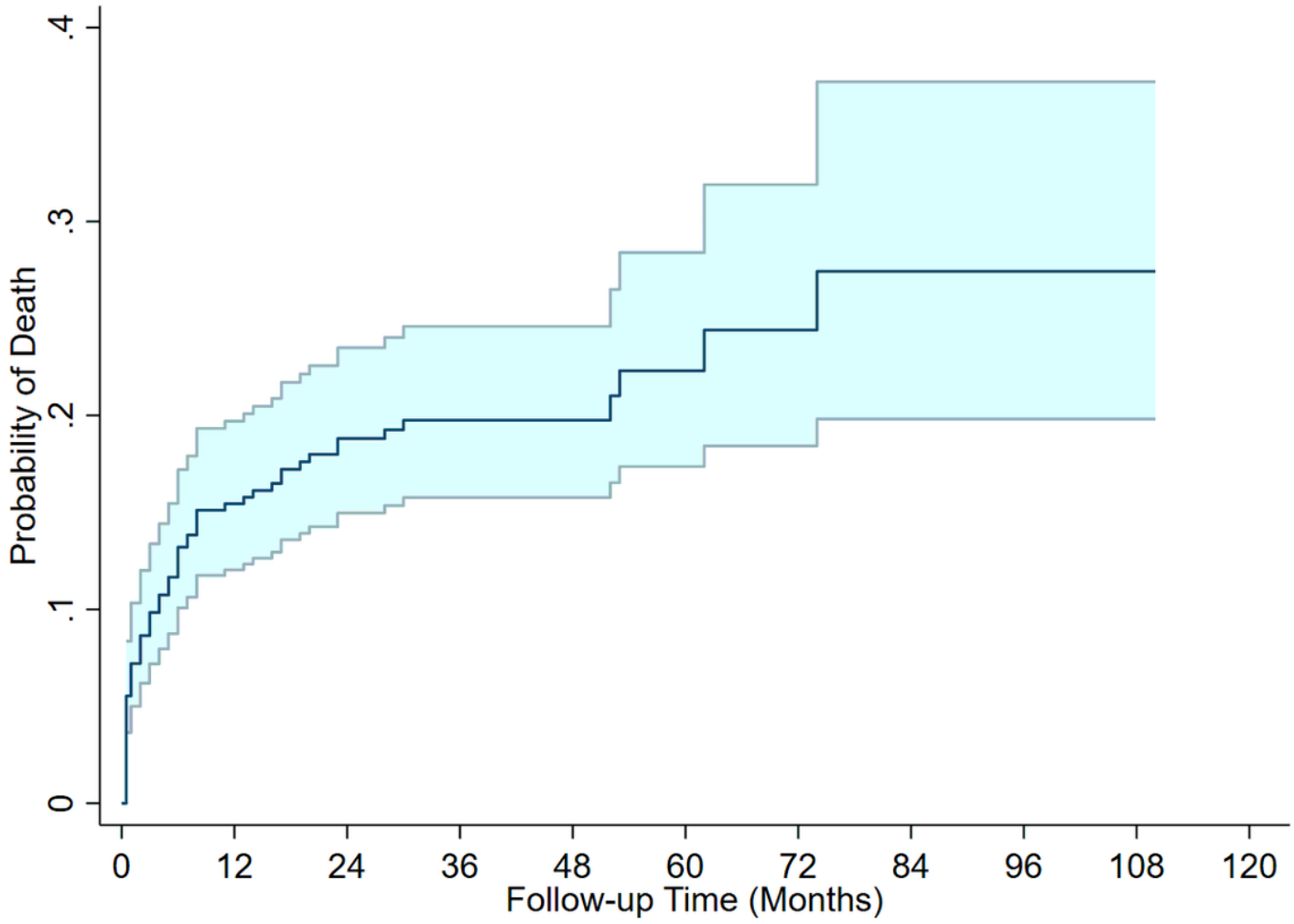

Figure 2

Probability of death (95% confidence interval) among PLWH with NTM. Abbreviations: PLWH: people living with HIV NTM: nontuberculous mycobacteria

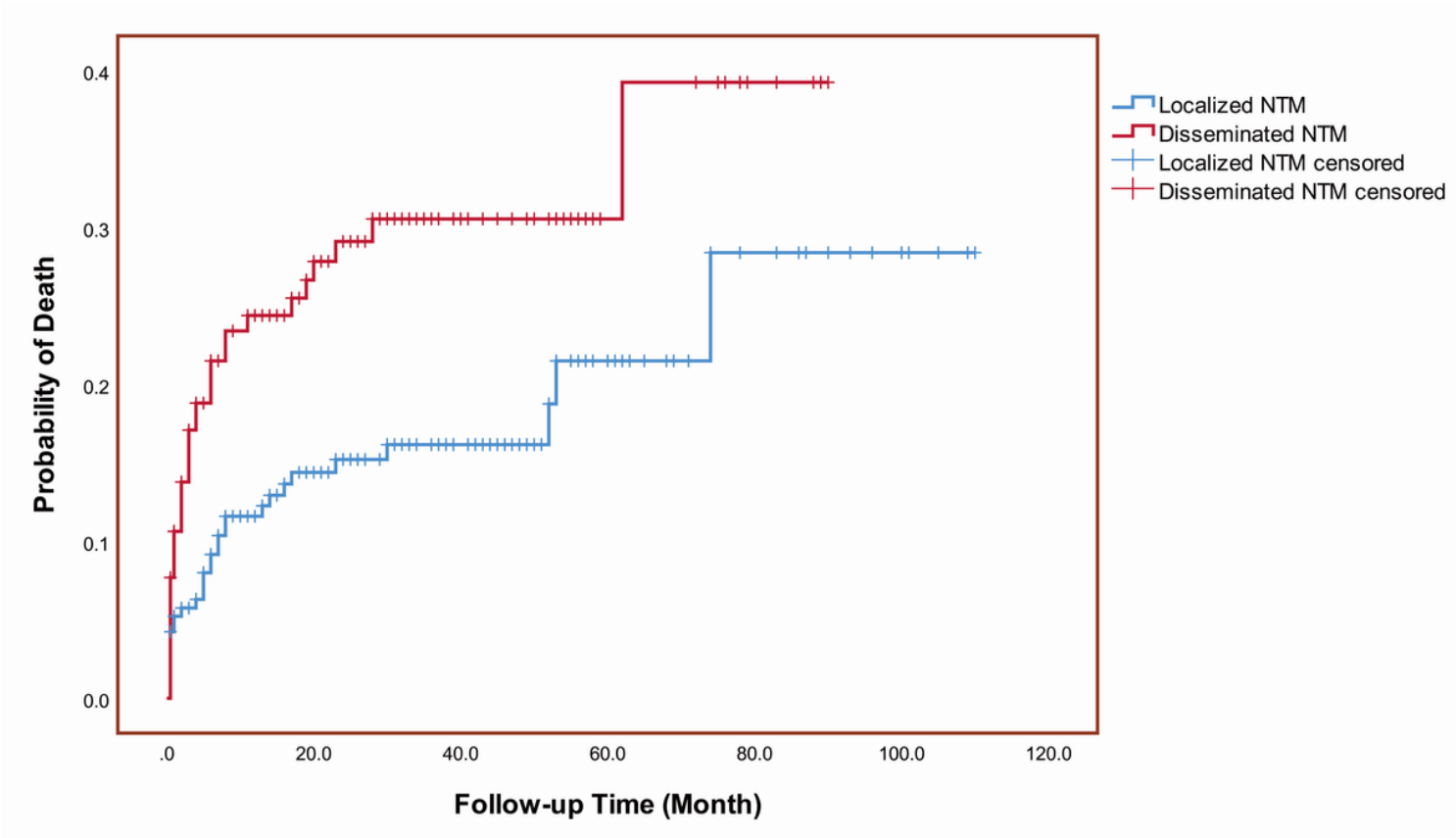

Figure 3

Probability of death among PLWH with disseminated NTM and localized NTM disease. Abbreviations: PLWH: people living with HIV NTM: nontuberculous mycobacteria