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Factors Associated with Mortality from Multidrug-Resistant Tuberculosis in Kinshasa (2011-2018)

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Abstract

Introduction: Multidrug-resistant tuberculosis (MDR-TB) represents a serious threat to global tuberculosis control. In the Democratic Republic of Congo, few studies have been conducted to identify the factors associated with mortality. **Methodology:** This study examined the factors associated with mortality during the management of MDR-TB in Kinshasa, DRC. It was a cross-sectional analytical study of patients undergoing anti-tuberculosis treatment from January 1, 2011, to December 31, 2018, whose treatment outcomes were known. The study included 1806 MDR-TB cases, of which 233 resulted in death, through an exhaustive sampling method. Data were analyzed using SPSS 26, and multivariate analysis using multiple logistic regression identified the factors associated with mortality. **Results:** Among the 1806 cases included in the study, 233 (12.9%) died. The average age was 33.87 years (±13.06), ranging from 1 to 84 years, with a median age of 32 years. Among the deceased, 58.3% were male, with a sex ratio of 1.4; 12% were HIV co-infected, and 65% were on antiretroviral therapy, of whom 70.1% received the 9-month short regimen. The median time to treatment initiation was 13 days (IQR 22). Factors associated with mortality included HIV-positive status (p = 0.001), the 20-month long treatment regimen (p = 0.025), and the absence of antiretroviral therapy administration (p = 0.016). **Conclusion:** The mortality rate for MDR-TB remains high. The HIV-positive status, the 20-month long treatment regimen, and the lack of antiretroviral therapy were the key factors associated with MDR-TB mortality in Kinshasa. Timely treatment initiation and continuous

patient monitoring are crucial strategies to reduce MDR-TB deaths. The emergence of multidrug-resistant pulmonary tuberculosis reflects deficiencies in the tuberculosis control program in Kinshasa.

Subject Areas

Infectious Diseases

Keywords

Multidrug-Resistant Tuberculosis, Factors, Mortality, Kinshasa, DRC

1. Introduction

Tuberculosis (TB) is an infectious disease caused by the bacilli of the *Mycobacterium tuberculosis* complex, also known as *Koch's Bacillus* (B.K.), which appears as thin, filamentous rods that are straight or slightly curved and acid-fast [1].

This disease remains widespread in sub-Saharan Africa due to, on one hand, the weakness of the healthcare system and, on the other hand, the low standard of living of the population [1].

TB can be cured if effective treatment (lasting at least six months) is properly followed until completion. However, poorly followed or mismanaged treatment leads to drug resistance in anti-tuberculosis medications.

When untreated, TB progresses and can cause death. TB is among the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ahead of HIV/AIDS) [2]. Multidrug resistance (MDR) occurs when *Mycobacterium tuberculosis* becomes resistant to at least rifampicin and isoniazid [3] [4]. Multidrug-resistant tuberculosis (MDR-TB) is considered a severe form of TB and represents a major global public health threat [4]-[8].

The WHO Global Tuberculosis Report, published in 2022, states that MDR-TB incidence increased by 3% from 2020 to 2021, with 450,000 new cases of rifampicin-resistant TB (RR-TB) recorded in 2021 [5] [9]. 214,000 deaths were reported, of which 90% were adults, 65% were men, and 10% were living with HIV [5] [9]. The mortality rate of MDR-TB varies between 4% and 18% in sub-Saharan Africa, where most countries are endemic. Drug-resistant TB undermines the progress achieved in tuberculosis control [10]. Africa, despite accounting for 11% of the world's population, bears 27% of the global burden of MDR-TB, mainly due to the high prevalence of HIV [11].

The persistence of MDR-TB is primarily attributed to poverty, population growth, exacerbated by migration, and war, which has significantly increased mortality in HIV-endemic areas [12].

Despite progress in TB control over recent decades, MDR-TB has emerged as a new epidemic characteristic that could jeopardize these advancements [13] [14]. Comorbidities, such as HIV co-infection, are among the key determinants of high

mortality, particularly in patients not receiving antiretroviral therapy (ART) [15].

In Tanzania (2017), Mollet *et al.* concluded that being HIV-positive, with low CD4 counts and delayed ART initiation, were risk factors for mortality among MDR-TB patients [16].

Similarly, Bajehsonl M in Nigeria found that HIV infection was linked to mortality among MDR-TB patients, and late initiation of ART increased the risk of death eightfold [17].

The Democratic Republic of the Congo (DRC) is one of the 30 countries that account for over 87% of global TB cases [2]. It ranks 5th in Africa and 11th worldwide among countries with the highest burden of MDR-TB [12].

In Kinshasa, a 2018 study recorded 221 MDR-TB cases, including 34 deaths, representing a mortality rate of 15.38% [18].

2. Patients and Methods

Study Framework: The study was conducted from January 1, 2011, to December 31, 2018, at the Provincial Coordination for Tuberculosis Control (CPLT) in Kinshasa, Democratic Republic of the Congo (DRC).

Regarding TB control, activities are coordinated by CPLT, in collaboration with the Core Health Zone Team, across 143 Screening and Treatment Health Centers (CSDT), distributed among 35 health zones.

Among these CSDTs, 40 had a package for MDR-TB management, and 17 GeneXpert machines contributed to rifampicin resistance screening.

Study Type: This was a cross-sectional analytical study, focusing on patients followed from January 1, 2011, to December 31, 2018.

Patients were treated for MDR-TB at CSDT centers.

Two standardized therapeutic regimens are used in the DRC for MDR-TB:

1) Short regimen (9 months):

- 4 Km-Mfx-Pto-H-Cfz-E-Z/5 Mfx-Cfz-E-Z

2) Long regimen (20 months):

- 6 - 8 Km/Cm-Lfx-Pto-Cs-E-Z/14-12 Lfx-Pto-Cs-E-Z

However, regular patient monitoring is recommended throughout the administration period. This monitoring is performed in three dimensions:

- Bacteriological monitoring: Smears and cultures are performed monthly during the intensive phase and every two months during the continuation phase of the long regimen or monthly for the short regimen.
- Non-bacteriological biological monitoring: This includes renal, hepatic, thyroid functions, and electrolytes, which are assessed at specific intervals.
- Clinical monitoring: Includes radiography and audiometry [2].

An exhaustive sampling method was chosen (n individuals selected once without replacement in the given population). Data were collected from the CPLT database, which included reported MDR-TB cases.

The secondary database of reported MDR-TB cases during the study period at the provincial tuberculosis coordination in Kinshasa was reviewed to select cases

that received treatment after MDR-TB confirmation via GeneXpert MTB/RIF, with known outcomes such as deaths, treatment failures, completed treatments, and recoveries.

Patients with unclear outcomes were excluded from the study.

A data triangulation process was conducted to ensure quality control between coordination data and records found in treatment center registries.

Inclusion Criteria: All cases of MDR-TB confirmed by GeneXpert MTB/RIF during the study period in the city-province of Kinshasa, placed under treatment, and with a known outcome were included.

Exclusion Criteria: Any case of MDR-TB declared lost to follow-up during the study period in the city-province of Kinshasa after being placed under treatment was excluded from the study.

Sample size: The total of 1,806 patients present in the database who met the inclusion criteria constituted our sample.

Data Collection Technique

The database of MDR-TB cases reported annually at the CPLT in the city-province of Kinshasa contained the following information: year, quarter, health zone (ZS), CSDT/treatment site, age, sex, tuberculosis location, registration group, HIV serology, antiretroviral therapy (ART), treatment regimen, tuberculosis confirmation date, outcomes, side effects, initial treatment weight, and height.

Data Processing and Analysis

After sorting the data based on variables of interest, a verification process was conducted to ensure completeness and consistency.

Data were analyzed using SPSS 26 (Statistical Package for Social Sciences), following these approaches:

- Proportions were calculated for sex, registration group, tuberculosis site, HIV infection, antiretroviral therapy (ART), and treatment type.
- Mean and standard deviation were calculated for age.
- Median and interquartile range were computed for time to treatment initiation.
- A significance threshold of 0.05 was set, and bivariate analyses were conducted to examine the association between mortality and each independent variable.
- Multivariate analysis using logistic regression identified factors associated with MDR-TB mortality. Adjusted odds ratios (ORa) with a 95% confidence interval were used to verify the relationship between mortality and identified factors

3. Results

The age distribution was not normal (Kolmogorov-Smirnov normality test = 0.088, with $p = 0.000$ ($p < 0.05$)). The average age was 33.87 years (±13.06), and the median age was 32 years (IQR 18). Regarding sex, more than half of the cases were male, with a sex ratio of 1.4 (See Table 1).

From Table 2, it appears that almost all MDR-TB cases had a pulmonary localization of the disease. Regarding patient categories, nearly one-third of MDR-TB

Table 1. Demographic characteristics of MDR-TB cases.

Variable	N	%	Average (±DS)	Min-Max
Age (in years)	1806		33.87 (±13.06)	1 - 84
0 - 14 years old	35	1.94		
15 - 29 years old	753	41.69		
30 - 44 years old	649	35.94		
45 - 59 years old	280	15.50		
≥60 years old	89	4.93		
Sex				
Male	1053	58.31		
Female	753	41.69		

Table 2. Clinical and therapeutic characteristics of MDR-TB cases.

Variables	Effective (n = 1806)	Percentage (%)
Tuberculosis affected area		
TP+	1794	99.34
TEP	12	0.66
Patient categories		
New patient	560	31.01
Relapse	263	14.56
Retreatment	84	4.65
Failure of first-line treatment	334	18.49
Failure of retreatment	528	29.24
Other	37	2.05
HIV serology		
Positive	217	12.02
Negative	1589	87.98
Traitement antirétroviral		
No	1665	92.19
Yes	141	7.81
Types of treatment		
Long treatment (20 months)	540	29.90
Short treatment (9 months)	1266	70.10
Delay before treatment initiation		
Long delay (>14 days)	665	36.8
Short delay (≤14 days)	1141	63.2

cases had never previously received anti-tuberculosis treatment or had undergone treatment for less than one month.

Concerning HIV serological status, approximately one in ten cases was co-infected with HIV. Regarding the treatment regimen, seven out of ten cases benefited from the short 9-month treatment. More than half of the cases were placed under treatment within less than two weeks after diagnosis.

Table 3. Treatment outcomes of managed MDR-TB cases.

	Outcome | Count (n = 1806) | percentage (%)	Outcome | (n = 1806) | percentage (%)
Cured	162	8.97
Treatment completed	1352	74.86
Death	233	12.90
Failure	59	3.27

From **Table 3**, it appears that nearly one in ten cases (12.90%) died after being placed under anti-tuberculosis treatment. The majority of cases experienced therapeutic success (Cured and Treatment Completed).

Evolution of MDR-TB Fatality in Kinshasa (2011-2018).

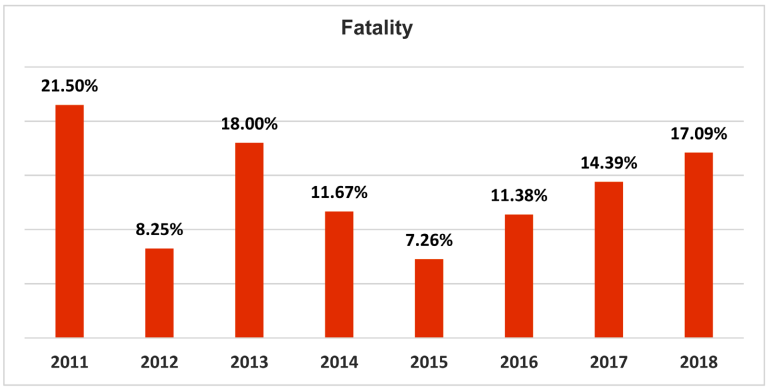

Figure 1. MDR-TB fatality in Kinshasa from 2011 to 2018.

Based on **Figure 1**, three peaks were observed in 2011, 2013, and 2018, with an upward trend in fatality rates starting in 2015.

Findings from **Table 4**.

In bivariate analysis, mortality was significantly associated with age, sex, treatment type, antiretroviral therapy, and time to treatment initiation. Specifically, the mortality odds were 1.37 times higher in male patients; Mortality was 0.68 times lower in patients receiving long treatment. The odds of mortality were 2.18 times higher in patients with a long delay before treatment initiation. Mortality was 1.59 times higher in patients who did not receive antiretroviral therapy (ART).

Table 4. Factors associated with death after bivariate and multivariate analyses.

		Bivariate analyses		Multivariate analyses	
Variables	% death	ORb (IC95%)	P	ORa (IC95%)	p
Age group (in years)			0.006		
0 - 14	1.3	1			
15 - 29	33.0	0.82 (0.24 - 2.75)			
30 - 44	37.8	0.60 (0.18 - 1.99)			
45 - 59	19.7	0.48 (0.14 - 1.63)			
≥60	8.2	0.48 (0.14 - 1.62)			
Sex			0.024*		0.017*
Male	51.5	1.37 (1.04 - 1.81)		0.54 (0.34 - 0.89)	
Female	48.5	1		1	
TB affected area			0.696		
TP+	99.1	1.35 (0.29 - 6.21)			
TEP	0.9	1			
Patients categories			0.085		
Relapse	29.2	1			
Retreatment	17.2	0.77 (0.51 - 1.17)			
Failure of first-line treatment	5.6	0.78 (0.39 - 1.44)			
Failure of retreatment	12.4	1.40 (0.89 - 2.20)			
Failure of retreatment	31.8	0.848 (0.59 - 1.21)			
Other	3.4	0.50 (0.22 - 1.14)			
Types of treatment			0.008*		0.025*
Long treatment	37.3	0.68 (0.51 - 0.90)		2.09 (1.09 - 3.98)	
Short treatment	62.7	1		1	
HIV infection	0.195				0.001*
Positive	14.6	0.77 (0.52 - 1.14)		2.94 (1.58 - 5.46)	
Negative	85.4	1		1	
Antiretroviral traitement			0.041*		0.016*
No	88.8	1.59 (1.01 - 2.97)		2.53 (1.19 - 5.37)	
Yes	11.2	1		1	
Time to treatment initiation			0.022*	0.932	
Long time (>14 days)	30	2.18 (1.62 - 2.94)		1.02 (0.60 - 1.73)	
Short time (≤14 days)	70	1		1	

*Value $p < 0.05$.

In multivariate analysis (after adjusting for all independent variables), four variables remained significantly associated with mortality: Sex (Male) was found to be a protective factor, with 0.54 times lower odds of mortality in male patients. Patients undergoing the long 20-month regimen were 2.09 times more likely to experience mortality than those on the short 9-month regimen. Mortality was 2.94 times higher among HIV co-infected patients. Patients who did not receive ART had 2.53 times higher odds of mortality than those who received it.

4. Discussions

This study was initiated to determine the factors associated with mortality from multidrug-resistant tuberculosis (MDR-TB) in Kinshasa.

Key Findings: Individual Characteristics: Age: No significant association was found between age and mortality. This result differs from findings by Gayoso in Brazil [19] and Chingonzoh *et al.* in South Africa [14], where age over 60 years was associated with mortality. This discrepancy may be due to comorbidities prevalent in older age groups. Sex: More than half of the cases (58.31%) were male. This proportion differs from Shamsa K *et al.*'s findings in Pakistan (51.3%) [20]. However, sex was not a risk factor for MDR-TB mortality, similar to studies conducted by Samuel OM *et al.* in South Africa [21].

MDR-TB Fatality Rate: The fatality rate of MDR-TB in Kinshasa was 12.9%, similar to the findings of Salomon M and collaborators in Ethiopia [22].

An upward trend in mortality was observed starting in 2015 in Kinshasa. The years 2014-2015 corresponded to a period when healthcare providers received support through a study on short treatment regimens, improving patient monitoring.

Over time, patient monitoring and district health service support weakened, contributing to rising mortality.

These findings diverged from studies by multiple other researchers [23]-[26].

4 Factors Associated with MDR-TB Mortality in Kinshasa: Male patients were more protected than female patients. This could be due to higher treatment adherence among men, unlike women, who may face greater barriers to consistent treatment. Differences in sample size and regional context could explain these variations. Regarding the treatment Type factors, Patients on the long regimen (20 months) had twice the mortality risk compared to those on the short 9-month regimen. Longer treatments often compromise adherence, as patients tire of daily medication intake.

Regarding Clinical Factors: HIV infection was significantly associated with mortality, aligning with findings by Edson W Mollel *et al.* in Tanzania [25].

When it comes to Antiretroviral Therapy (ART): Mortality was higher among patients who did not receive ART. This result was similar to Gayoso *et al.*'s findings in Brazil [13] [19] and Chingonzoh *et al.* in South Africa [27]. HIV-positive patients without ART often have extremely low CD4 counts (<50 cells/μL), increasing their risk of death despite MDR-TB treatment [26]. HIV co-infection and

lack of ART contribute to severe immunosuppression, making them major mortality risk factors in MDR-TB patients in Kinshasa.

5. Study Limitations

This study had certain limitations. The use of a secondary database restricted the analysis to only the variables included within it, which did not allow for the examination of other factors such as patients' medical history; other socio-demographic characteristics such as occupation, education level, and lifestyle habits that could influence treatment outcomes.

Regarding patient outcomes, cases of lost-to-follow-up and those with unclear outcomes were excluded from the study, as it was difficult to determine whether they were alive or deceased.

To prevent confounding factors, these lost-to-follow-up cases and patients with uncertain outcomes were excluded from the study.

6. Conclusion

The findings of this study indicate that MDR-TB fatality remains high in Kinshasa. The treatment regimen, HIV co-infection, and lack of antiretroviral therapy (ART) were identified as key factors associated with mortality. It is crucial to initiate treatment promptly for MDR-TB patients once the diagnosis is confirmed to improve survival rates. The emergence of multidrug-resistant pulmonary tuberculosis reflects shortcomings in the implementation of the tuberculosis control program in Kinshasa.

7. Recommendations

- To the National Tuberculosis Control Program:
  - Ensure regular supply of medications and medical inputs to CPLTs for MDR-TB and HIV management.
  - Strengthen collaboration with the HIV/AIDS control program to implement joint prevention and treatment activities.
- To For CPLT Kinshasa:
  - Conduct formative supervision of tuberculosis control activities.
  - Organize audits of all MDR-TB-related deaths to improve response strategies.
- For CSDTs (TB Diagnosis and Treatment Centers):
  - Initiate timely treatment for MDR-TB patients upon diagnosis.
  - Implement systematic HIV screening for all patients undergoing MDR-TB treatment.
  - Ensure comprehensive care for HIV/MDR-TB co-infected patients by providing ART and conducting bacteriological, biological, and clinical follow-ups.
- For Community Health Workers:
  - Conduct home visits for all patients under treatment to monitor adherence

and ensure they correctly take medications.

Authors Contributions

Trésor Kashinde Mosomo, Blaise Musubaho Keukeu and Claude Ngona Mandro have designed and analysed this study's statistical data.

Roland Vangu Vangu and Blaise Blaise Makoso Nimi have contributed to data collection.

Emmanuel Kasereka Wanzuwite: manuscrit proofreading.

Géorges Kubuya Katundi: manuscrit proofreading.

Antoinette Tshefu Kitoto oversaw the study. All the authors read and approved the final and reviewed version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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