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"Epidemiological Profile of Multidrug-Resistant Tuberculosis (MDR-TB) and Risk Factors Associated with Mortality in the Prefecture of Meknes, Morocco"

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Abstract

Background and objectives: Tuberculosis is a ubiquitous, contagious infectious disease caused by the Mycobacterium Tuberculosis Complex (MTC), it constitutes a major public health problem both nationally and internationally. Unfortunately, what has made the disease even more challenging to manage is the development of resistance to various first-line antitubercular drugs, The main objective of this study is to describe the epidemiological profile of (MDR-TB) in the Meknes prefecture, Fes-Meknes region.

Material and Methods: This is a cross-sectional study of MDR-TB cases monitored at the Tuberculosis and Respiratory Disease Diagnostic Center (CDTMR) in the city of Meknes, Fez-Meknes region. Data collection was conducted over a period spanning from January 2017 to December 2022 (6 years).

Results: The study analyzed 28 cases of MDR-TB in Meknes Prefecture, revealing a predominantly young (mean age: 17.32 years) and male population (85.7%), with most patients residing in urban areas (85.7%). Nearly all cases (99%) were smear-positive. Treatment durations varied: 50% underwent 24 months, 46.4% completed 11 months, and 3.6% received six months. The mortality rate was 10.7%, with three deaths, while 89.3% of patients survived. Relapse occurred in 32.1% of cases. Risk factors were prevalent, with 75% of patients having at least one; smoking was reported in 53.6% of cases, suggesting its role in disease progression. The bivariate analysis explored factors associated with mor-

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tality in individuals with MDR-TB. The overall mortality rate was 10.7%. Gender, residence, relapse history, diabetes, and HIV were not associated with mortality (all p>0.05). Notably, sensory side effects showed a significant association with mortality (p=0.008).

Conclusion: Managing MDR-TB requires addressing comorbidities, mitigating side effects, and improving adherence through equitable healthcare interventions. Future efforts should focus on bridging rural access gaps and targeting behavioral health determinants.

Introduction

Tuberculosis is a ubiquitous, contagious infectious disease caused by the Mycobacterium tuberculosis complex (MTC), characterized by slow multiplication and resistance to acid and alcohol decolorizing agents, hence their designation as Acid-Fast Bacilli (AFB) [1].

This disease affects all age groups, and any organ can be affected. It constitutes a major public health problem both nationally and internationally. However, it remains a disease that can be prevented and treated. Unfortunately, what has made the disease even more challenging to manage is the development of resistance to various first-line antitubercular drugs, which is due to different mutations in the MTC genome. In recent years, the emergence of resistance to Tuberculosis (TB) treatments, particularly multidrug-resistant TB (MDR-TB), characterized by resistance to at least rifampicin and isoniazid, has become a major public health challenge in many countries and a barrier to successful global TB control efforts [2]. Some strains have developed resistance to second-line antitubercular drugs, leading to what is known as extensively Drug-Resistant (XDR) tuberculosis. XDR-TB occurs when tuberculosis-causing bacteria become resistant not only to isoniazid and rifampicin (the drugs that define multidrug-resistant TB) but also to all fluoroquinolones and at least one of the second-line injectable drugs, such as amikacin, kanamycin, or capreomycin. This form of TB can emerge when second-line treatments are misused or poorly managed, ultimately rendering them ineffective [3].

According to 2022 international epidemiological data, tuberculosis is one of the leading causes of death worldwide. The number of people affected by tuberculosis disease was estimated at 10.6 million, equivalent to 133 cases per 100,000 inhabitants. Among bacteriologically confirmed pulmonary tuberculosis cases, 175,650 cases of Multidrug-Resistant Tuberculosis (MDR-TB) were diagnosed and treated [1]. In Morocco according to the ministerial report from 2021, a total of 29,327 TB cases were recorded., translating to an incidence of 80 per 100,000 inhabitants. Of these, 51% were pulmonary forms. Among these cases, 295 developed multidrug-resistant tuberculosis, representing 1% of the cases [4,5].

The main objective of this study is to describe the epidemiological profile of multidrug-resistant pulmonary tuberculosis in the Meknes prefecture, Fes-Meknes region.

Materials and methods

Study design

This is a cross-sectional study of pulmonary tuberculosis cases monitored at the Tuberculosis and Respiratory Disease Diagnostic Center (CDTMR) in the city of Meknes, Fez-Meknes region. Data collection was conducted over a period spanning from January 2017 to December 2022 (6 years).

Study population

Inclusion criteria: All cases diagnosed and treated as pulmonary tuberculosis (including all forms of resistance) at the CDTMR in the city of Meknes during the study period were included.

Exclusion criteria: All cases of extrapulmonary tuberculosis (including all forms of resistance) and pulmonary tuberculosis cases diagnosed outside the study period were excluded.

Ethical considerations

Authorization from the provincial delegation and the head physician of the CDTMR was obtained, along with strict adherence to patient anonymity and confidentiality of their information.

Data collection

Data collection was carried out through the computerized database of the CDTMR in the city of Meknes, with additional data gathered from medical records for certain variables. The main variables collected and analyzed include: sociodemographic data (age, gender, origin, and occupation), bacteriological and therapeutic data, culture results and antibiogram or molecular biology results at the time of multidrug-resistant tuberculosis diagnosis, the prescribed treatment regimen, recorded adverse effects, and patient outcomes during treatment.

Outcome's definitions:

Based on the results of the microscopic examination, we have two categories of cases: Pulmonary tuberculosis with negative microscopy TPM (0) and pulmonary tuberculosis with positive microscopy TPM (+). In our study, the confirmation of drug-resistant tuberculosis is carried out using molecular biology methods: the gene amplification technique coupled with automated extraction (Xpert MTB/RIF). If resistance to rifampicin is detected, it is further confirmed with the reverse hybridization technique on a strip (the Genotype MTBDR Plus test and the Genotype MTBDR sl test). Based on the results of these techniques, we classify cases into five categories: Isoniazid-resistant Tuberculosis (TB-Hr): tuberculosis caused by MTC strains that are resistant to isoniazid but remain sensitive to rifampicin, Rifampicin-Resistant Tuberculosis (TB-RR): tuberculosis caused by MTC strains that are resistant to rifampicin. These strains may be either sensitive to isoniazid or resistant to it (in which case it is classified as MDR-TB), or they may be resistant to other first- or second-line antitubercular drugs. Multidrug-resistant tuberculosis (MDR-TB): tuberculosis caused by MTC strains resistant to at least isoniazid and rifampicin. Extensively drug-resistant tuberculosis (XDR-TB): tuberculosis resistant to rifampicin, a fluoroquinolone, and at least one of the group A drugs, bedaquiline or linezolid et Pre-extensively drug-resistant tuberculosis (pre-XDR TB): multidrug-resistant tuberculosis with additional resistance to fluoroquinolones [6].

Data analysis

Statistical analysis was performed using SPSS software version 26.0. A descriptive analysis was conducted for all variables, with the results presented as percentages for qualitative variables and as mean ± Standard Deviation for quantitative variables. We used a Chi-square test (or Fisher's exact test when

conditions were not met) for the comparison of percentages, and Student's t-test for the comparison of means, to identify potential associations between antitubercular drug resistance and various factors.

Results

The study included 28 cases of Multidrug-Resistant Tuberculosis (MDR-TB) in Meknes Prefecture. The mean age of the participants was 17.32 years (±6.86 years), indicating a predominantly young population. The majority of the cases were male (85.7%), and most resided in urban areas (85.7%), with only 14.3% coming from rural settings. Regarding diagnostic status, nearly all patients (99%) were smear-positive (TPM+), with only one smear-negative (TPM−) case. The duration of treatment varied, with 50% of the cases undergoing a 24-month regimen, 46.4% completing 11 months, and only 3.6% treated for six months. The study observed a mortality rate of 10.7%, with three deaths recorded, while 89.3% of the patients survived. Relapse was reported in 32.1% of cases, whereas 67.9% did not experience a recurrence of the disease. Risk factors were prevalent in the sample, with 75% of the participants presenting at least one risk factor and 25% reporting none. Smoking was identified in more than half of the cases (53.6%), highlighting its potential role in disease progression, while 46.4% were non-smokers. Table 1 represent the results.

Adverse events related to treatment were documented in a minority of cases. Neurological and sensory side effects each occurred in 7.1% of patients, while digestive complications were also observed in 7.1%. Hematological effects were slightly more common, affecting 10.7% of cases, whereas renal complications were rare, appearing in only 3.6% of patients. Despite these challenges, treatment adherence was generally good, with 82.1% of patients demonstrating proper compliance, though 17.9% were classified as having poor adherence. The results are represented in Table 1.

The bivariate analysis explored factors associated with mortality in individuals with multidrug-resistant tuberculosis (MDR-TB). The overall mortality rate was 10.7%, with three deaths recorded among the 28 cases. Gender did not show a significant association with mortality (p=1.000). Residence also did not show a significant relationship with mortality, although a higher proportion of deaths occurred among urban residents (66.7%) compared to rural residents (33.3%) (p=0.382). Regarding smear status, all deaths occurred in smear-positive (TPM+) patients, with no mortality recorded among smear-negative (TPM−) cases (p=1.000). Relapse history also did not significantly affect mortality; the proportion of deaths among those without relapse (33.3%) was similar to the proportion of non-deaths without relapse (p=1.000). Risk factors were present in all patients who died (100%), compared to 72% in the non-mortality group (p=0.551) (Table 2).

Diabetes and HIV status were assessed, with mortality observed in 33.3% of those with diabetes or HIV, compared to 4% among those without these conditions. However, these differences were not statistically significant (p = 0.206 for both factors). The presence of treatment side effects showed a higher, though not statistically significant, proportion of deaths (66.7%) compared to those without side effects (33.3%) (p=0.188) (Table 2).

Table 1: Socio-demographic, clinical and epidemiological characteristics of individuals (N=28).

Variables		N	Mean +/- SD
Age (years)		28	17.32 +/- 6.86
Variables		**N**	**(%)**
Gender	 Men women	28 24 4	 85.7 14.3
Résidence	 Rural Urbain	28 4 24	 14.3 85.7
Smear status	 TPM+ TPM-	28 27 1	 99 1
Treatment period (months)	 6 months 11 months 24 months	28 1 13 14	 3.6 46.4 50
Death	 Yes No	28 3 25	 10.7 89.3
Relapse	 Yes No	28 9 19	 32.1 67.9
Risk factors	 Yes No	28 21 7	 75 25
Tobacco smoking	 Yes No	28 15 13	 53.6 46.4
Alcoholism	 Yes No	28 4 24	 14.3 85.7
Cannabis use	 Yes No	28 4 24	 14.3 85.7
Diabetes	 Yes No	28 2 26	 7.1 92.9
HIV	 Yes No	28 2 26	 7.1 92.9
Drogue use	 Yes No	28 1 27	 3.6 96.4
Therapeutic adherence	 Good Bad	28 23 5	 82.1 5
Side effects	 Yes No	28 8 20	 28.6 71.4
Neurologique SE	 Yes No	28 2 26	 7.1 92.9
Sensory SE	 Yes No	28 2 26	 7.1 92.9
Digestive SE	 Yes No	28 2 26	 7.1 92.9
Hematological SE	 Yes No	28 3 25	 10.7 89.3
Renal SE	 Yes No	28 1 27	 3.6 96.4
Total		28	100%

Abbreviations: SD: Standard deviation; TPM: Tuberculin positive Mantoux; HIV: Human immunodeficiency virus; SE: Side effects.

Table 1: Bivariate analysis researching factors associated with the mortality in individuals with TBK-MR.

Variables	Mortality N (%)		P-value
	No	Yes	
	89.3	10.7	
Gender Men Women	 21 (84%) 4 (16%)	 3 (100%) 0 (0%)	1.000
Residency Rural Urbain	 3 (12%) 22 (88%)	 1 (33.3%) 2 (66.7%)	0.382
Smear statues TPM+ TPM-	 24 (96%) 1 (4%)	 3 (100%) 0 (0.00%)	1.000
Relapse No Yes	 17 (68%) 8 (32%)	 2 (66.7%) 1 (33.3%)	1.000
Risk factors No Yes	7 (28%) 18 (72%)	0 (0.00%) 3 (100%)	0.551
Diabetes No Yes	 24 (96%) 1 (4%)	 2 (66.7%) 1 (33.3%)	0.206
HIV No Yes	 24 (96%) 1 (4%)	 2 (66.7%) 1 (33.3%)	0.206
Side effects No Yes	 19 (76%) 6 (24%)	 1 (33.3%) 2 (66.7%)	0.188
Sensory SE No Yes	 25 (100%) 0 (0.00%)	 1 (33.3%) 2 (66.7%)	0.008
Hematological SE No Yes	 23 (92%) 2 (8%)	 2 (66.7%) 1 (33.3%)	0.298
Renal SE No Yes	 25 (100%) 0 (0.00%)	 2 (66.7%) 1 (33.3%)	0.107

Abbreviations: TPM: Tuberculin positive mantoux; HIV: Human immunodeficiency virus, SE: Side effects.

Notably, sensory side effects were significantly associated with mortality (p=0.008). All deaths occurred in patients who experienced sensory side effects (66.7%), whereas no deaths were recorded among those without these side effects. Hematological and renal side effects also showed higher mortality proportions (33.3%) compared to those without these complications but were not statistically significant (p=0.298 and p=0.107, respectively) (Table 2).

Discussion

The aim of this study is the define the epidemiological characteristics and factors associated with mortality in Multidrug-Resistant Tuberculosis (MDR-TB) which can provide critical insights for improving management and outcomes.

As observed in our study, MDR-TB is predominantly associated with younger populations, with a mean age of 17.32 ± 6.86 years. This finding aligns with those of other studies conducted in Brazil and South Africa, which reported a median age of 38 years in Brazil and a mean age of 37.7 years in South Africa, respectively [7,8]. Men often represent a larger proportion of cases, with a proportion of 85.7% in our study and 64.4% in Brazil [7]; which may be attributed to higher exposure in occupational settings or behavioral risk factors like smoking and substance abuse [9].

The presence of comorbid conditions and risk factors is clearly noticed in several studies [7,10], ours showed that risk factors were prevalent with 75% of the participants presenting at least one risk factor and 25% reporting none and smoking was identified in more than half of the cases (53.6%).

In the present study, 10.7% of MDR-TB cases resulted in death. This outcome aligns with the results of several studies conducted in various countries, such as Brazil, Peru, and Malaysia, which reported mortality rates of 14.3%, 18.6%, and 19.2%, respectively [7,9,11]. Factors associated with mortality in MDR-TB were assessed, with key findings highlighting smear status, diabetes, and HIV status. All deaths occurred in smear-positive (TPM+) patients, while no mortality was recorded among smear-negative (TPM−) cases (p = 1.000). Additionally, mortality was observed in 33.3% of patients with diabetes or HIV, compared to 4% among those without these conditions (p=0.206). Another study conducted in South Africa found that MDR-TB/HIV co-infected patients had a 50% higher mortality rate compared to non-HIV patients [12].

Diabetes has been independently associated with increased mortality in MDR-TB patients. Research indicates that individuals with both diabetes and MDR-TB have a higher risk of death compared to non-diabetic MDR-TB patients [7]. Diabetes can impair the immune response, making it more difficult for the body to fight TB infections. Moreover, diabetes may affect the pharmacokinetics of TB medications, potentially reducing their effectiveness [11].

For HIV, it compromises the immune system by depleting CD4+ T cells, which play a critical role in fighting TB infections. This immunosuppression makes it harder for the body to control MDR-TB, leading to faster disease progression and a higher risk of mortality that's why studies have shown that MDR-TB patients with HIV co-infection have a mortality rate up to 4-10 times higher than those without HIV [13].

Adverse events, such as medication side effects, have been linked to higher mortality. Our study showed that sensory side effects were associated with a higher mortality rate (p=0.008). These side effects often reduce treatment adherence and worsen patient outcomes.

It is true that our study provides new insights and perspectives that can inform policy and practice. However, it also has some limitations, such as the small sample size, which reduces statistical power and generalizability. This limitation was beyond our control, as only 28 well-documented cases of MDR-TB were available over a six-year period, The study was conducted in a single institution that represents only the prefecture of Meknes city, which limits its external validity.

Conclusion

The interplay of demographic, clinical, and behavioral factors highlight the complexity of managing MDR-TB. Addressing comorbidities, mitigating side effects, and improving adherence through comprehensive and equitable healthcare interventions are essential for reducing mortality. Future studies should explore tailored strategies to bridge gaps in rural access and address behavioral determinants of health.

These findings reinforce the need for targeted interventions, such as early detection and management of comorbidities and

exposures, robust patient support systems to ensure adherence, and mitigation of adverse effects through personalized treatment approaches. Strengthening public health infrastructure, especially in high-burden urban areas, and addressing behavioral risk factors are crucial for reducing mortality.

Author declarations

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