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Tuberculosis in southern Morocco: Retrospective analysis from 2006 to 2012

La tuberculose au sud du Maroc: Analyse rétrospective (2006-2012)

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Abstract

Introduction: Tuberculosis, a global major concern, causes millions of deaths annually despite WHO strategies. A persistent gap in detection and treatment facilitates rapid spread in high-burden countries.
Aims: Analyze the clinical-epidemiological profile of tuberculosis patients in Laayoune and Tarfaya, Morocco, emphasizing risk factors and evolution of the tuberculosis
Methods: Retrospective analysis of 1332 tuberculosis cases at the Respiratory Diseases Diagnosis and Treatment Center in Laayoune (2006-2012). Variables with P < 0.10 in univariate analysis were included in multivariate analysis using multiple logistic regression to define the risk factors for tuberculosis, expressed as odds ratios (OR) with a 95% confidence interval (CI).
Results: The analysis revealed a pulmonary predominance (≈61%), with pleural (41.3%) and lymph node (31.5%) tuberculosis prevalent among extrapulmonary cases. Among 515 extrapulmonary tuberculosis cases, intestinal tuberculosis (14 cases) showed the highest mortality rate at 14.29%. The 15 to 64 age groups had a significantly higher risk of contracting pulmonary tuberculosis to children, and the 65 and over age group also had the highest risk of developing pulmonary tuberculosis (aOR=5.83 [2.43, 14.00]). Other risk factors included rural origin, personal history of tuberculosis, and smoking, all significantly associated with pulmonary tuberculosis (aOR=2.40 [1.001, 5.76]; aOR=2.00 [1.11, 3.61]; aOR=2.38 [1.40, 4.06]). Conversely, female gender was a protective factor (aOR=0.53 [0.40, 0.70]). Regarding recovery and loss to follow-up rates, they were higher in those with pulmonary tuberculosis (39.0% vs 2.1%; aOR=33.41 [17, 66.52]; 16.9% vs 10.3%; aOR=1.57 [1.02, 2.41], respectively).
Conclusion: Holistic initiatives across various sectors will be essential to eliminate tuberculosis by 2030.

Key words: tuberculosis, epidemiology, risk factors, Morocco, mortality, Laayoune.

Résumé

Introduction: La tuberculose, préoccupation mondiale majeure, génère des millions de décès annuels malgré les stratégies de l'OMS. Une lacune persiste dans la détection et le traitement, favorisant la propagation rapide dans les pays à forte charge.
Objectifs: Analyser le profil clinico-épidémiologique des patients tuberculeux à Laayoune et Tarfaya, Maroc, en mettant en avant facteurs de risque et évolution de la tuberculose.
Méthodes: Analyse rétrospective de 1332 cas de tuberculose, au Centre de Diagnostic et de Traitement des Maladies Respiratoires de Laayoune (2006-2012). Les variables avec P < 0,10 en analyse univariée ont été incluses dans une analyse multivariée par régression logistique multiple pour définir les facteurs de risque de la tuberculose, exprimée en rapports de cotes (OR) avec un IC à 95%.
Résultats: L'analyse a révélé une prédominance pulmonaire (≈61%), avec tuberculose pleurale (41.3%) et ganglionnaire (31.5%) prévalentes parmi les cas extrapulmonaires. Parmi les 515 cas de tuberculose extrapulmonaire, la forme intestinale (14 cas) affiche le taux de mortalité le plus élevé à 14,29%, étant significativement associée au décès. Les groupes de 15 à 64 ans ont présenté un risque significativement plus élevé par rapport à ceux des enfants de contracter la tuberculose, et le groupe de 65 ans et plus a affiché le risque le plus élevé également de développer une tuberculose pulmonaire (aOR=5.83 [2.43, 14.00]). D'autres facteurs de risque incluent l'origine rurale, les antécédents personnels de la tuberculose, et le tabagisme, tous présentant une association significative avec la tuberculose pulmonaire (aOR=2.40 [1.001, 5.76] ; aOR=2.00 [1.11, 3.61] ; aOR=2.38 [1.40, 4.06]). En revanche, le sexe féminin s'est révélé être un facteur protecteur (aOR=0.53 [0.40, 0.70]). Pour ce qui est de la guérison et des taux de perdus de vue, ils étaient plus élevés chez ceux atteints de tuberculose pulmonaire (39,0% vs 2,1%; aOR=33,41 [17, 66,52]; 16,9% vs 10,3%; aOR=1,57 [1,02, 2,41], respectivement).
Conclusion: Pour éliminer la tuberculose d'ici 2030, des initiatives holistiques soutenues dans divers secteurs seront essentielles.

Mots clés: tuberculose, épidémiologie, facteurs de risque, Maroc, mortalité, Laâyoune

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Introduction

Tuberculosis (TB), caused by Mycobacterium tuberculosis (MTB) complex, remains a significant global public health challenge. It can be diagnosed based on clinical and radiological data, but confirmation remains exclusively bacteriological and/or histological [1]. Despite improved living conditions and effective treatments, TB persists as a leading global cause of mortality, ranking among the top ten. The World Health Organization (WHO) has set the ambitious goal of eradicating TB by 2035 [2]. The Global Tuberculosis Report 2021 revealed a concerning surge in TB cases, reaching around 10.6 million, marking a 4.5% rise from 2020. Disturbingly, TB-related deaths totaled 1.6 million, with 187,000 occurring among HIV-positive individuals. Furthermore, there was a troubling 3% rise in drug-resistant TB cases from 2020 to 2021. Notably, 450,000 new instances of rifampicin-resistant TB were documented in 2021, signifying the first increase in several years [3]. In 2019, TB's impact on Morocco included around 35,000 new cases and roughly 2,900 deaths, resulting in a mortality rate of 8.1 per 100,000 inhabitants as per WHO data. In 2020, recorded cases decreased slightly to 29,018, encompassing all TB forms. During the same period, 240 cases of TB–HIV co-infection were reported [4]. An anti-TB program provides free diagnosis and care through health establishments and TB diagnostic centers. The 2018–2021 national plan aims to decrease TB-related deaths by 40% compared to 2015. This study analyzes the clinical-epidemiological profile of tuberculosis patients in Morocco's Laayoune and Tarfaya Provinces, highlighting risk factors and disease evolution.

Methods

Characteristics and Research Context

This retrospective study, spanning seven years from 2006 to 2012, analyzed a cohort of 1332 tuberculosis patients. Data were gathered from medical records, and the patient registry at the Center for the Diagnosis and Treatment of Respiratory Diseases (CDTRD) in Laayoune, Morocco, covering a population of around 260,000 inhabitants.

Case selection and exclusion criteria

To avoid potential selection bias, we included all diagnosed and reported tuberculosis (TB) cases throughout the study period.

Operational definitions

New Case: A patient who has never undergone treatment for tuberculosis (TB) or has previously received anti-TB treatment for less than four weeks.
Relapse: A new episode of TB in a patient previously considered "cured" after completing a prior treatment.
Cured: A patient declared free of pulmonary tuberculosis (PTB) with bacteriological confirmation. This includes a negative test result in the last month and at least one more before that.
Treatment Completed: A patient who has successfully completed treatment, although test results may be unavailable.
Treatment Failure: A patient who still tests positive after five months of treatment.
Death: A patient who dies during or before treatment.
• *Lost to follow-up*: Patient did not start treatment or interrupted it for two months or more, indicating irregular follow-up.
• *TB patient with unknown HIV status*: A TB case that was not screened for HIV or lacks proof of HIV treatment. Reclassification is needed in case of a subsequent HIV status.

Statistical analysis

We conducted our statistical analysis using Stata version 14. Categorical variables underwent the chi-square test and Fisher's exact tests. Variables with a P value < 0.10 in the univariate analysis were included into a multivariate analysis using the multiple logistic regression method. The primary objective was to identify variables associated with pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB), and to compare the evolution of cases. Variables with a P value < 0.05 were considered independent risk factors, and the outcomes were expressed as odds ratios (OR) with a 95% confidence interval (95% CI).

Ethical considerations

This retrospective analysis of de-identified medical records adhered to the ethical principles outlined in the Declaration of Helsinki for medical research involving human subjects. Authorization for data usage was obtained from the Regional Directorate of the Ministry of Health in Laayoune and the CDTRD, Laayoune, for the period from January 2006 to December 2012. Access to the records was limited to health professionals to ensure confidentiality, and individual informed consent was not obtained, as this study involved retrospective analysis of existing data. Additionally, to safeguard confidentiality, the names or identification numbers of TB patients were not included in the checklist.

Results

The sociodemographic profile of the patients

During the study period, 1332 patients were enrolled, and all of them were included in our sample. About 63.3% of patients were male, resulting in a male/female ratio of approximately 1.72. The majority of patients (97.3%) resided in urban areas, with over half of them (52.6%) falling in the age range of 15 to 34 years (Figure 1).

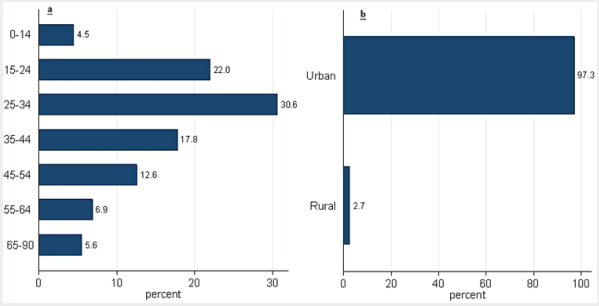

Figure 1. Distribution of patients according to age (a) and origin (b) (N = 1332).

Forms, diagnostic aspects, and anatomical sites affected by TB

During the study period, PTB constituted over half (61.3%) of TB cases, with EPTB accounting for a little over a third (38.7%), primarily manifesting as pleural involvement (41.3%) or lymph node affliction (31.5%). Regarding treatment outcomes, less than a quarter (24.7%) were declared cured, although treatment was successfully completed by more than a third of them (36.4%). Additionally, 14.3% of patients were lost to follow-up, and 21.1% were transferred. Death was recorded in 3.2% of cases. The Acquired Immune Deficiency Syndrome related (AIDS-related) status was unknown for the majority of patients, with only 0.2% of TB patients diagnosed as HIV positive (Table 1).

Table 1. TB forms, affected sites, outcomes, and HIV status (N= 1332).

Forms of TB	Variables	
	Number (N)	Percentage (%)
PTB	817	61.3
EPTB	515	38.7
Location of TB		
Cerebral	15	3.0
Dermal	6	1.2
Ganglionary	159	31.5
Intestinal	14	2.8
Bone	35	6.9
Peritoneal	36	7.1
Pleural	208	41.3
Urogenital	20	4.0
Others	10	2.0
Status and outcomes		
Cured	330	24.7
Treatment completed	486	36.4
Patient transferred	281	21.1
Lost to follow-up	191	14.3
Death	43	3.2
HIV status		
Status unknown	1329	99.77
HIV-positive	3	0.2

Our study focused on a total of 515 cases of extrapulmonary tuberculosis, and the findings were analyzed. Among these cases, 163 were related to lymph node tuberculosis, with a mortality rate of 2.45%. Pleural tuberculosis cases (212 cases) showed a mortality rate of 4.25%. For bone tuberculosis (37 cases), the mortality rate was 8.11%, while for peritoneal tuberculosis (36 cases), it was 8.33%. Finally, among the 14 cases of intestinal tuberculosis, the mortality rate was 14.29%. No deaths were recorded in other forms of extrapulmonary tuberculosis (Figure 2,3).

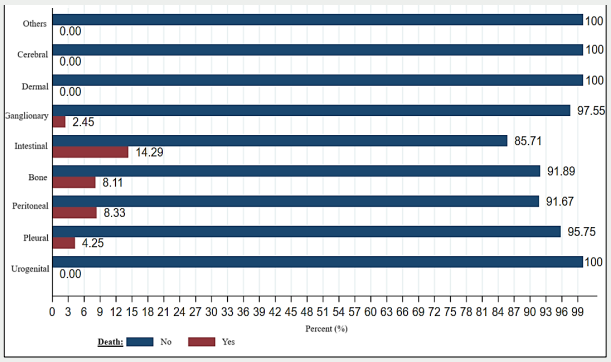

Figure 2. Analysis of mortality percentages in extrapulmonary tuberculosis based on affected anatomical sites.

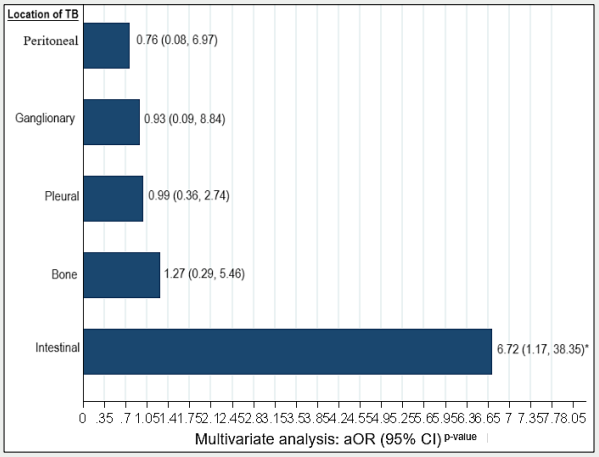

Figure 3. Anatomical Site-Specific Adjusted Logistic Model for Mortality in Extrapulmonary Tuberculosis Patients. The model was adjusted for gender, origin, age, personal history, and diabetes.

Factors related to the various forms of TB

Age is a significant determinant of specific TB forms, with children facing a substantially higher risk of EPTB (7.9% vs. 2.3%; $p < 0.001$). In contrast, those aged 15-44 exhibit an elevated risk for both TB forms ($p < 0.001$), along with a significantly increased risk of PTB compared to childrens. With regards to gender, PTB affects males much more than females (70.7% vs. 29.3%; aOR = 0.53 [0.40, 0.70]; $p < 0.001$).

Both forms of TB were considerably more common in patients who lived in urban areas than those who lived in rural areas (96.6% vs. 3.4% and 98.5% vs 1.5%; $p < 0.001$). However, patients who lived in rural areas were more likely to develop PTB rather than EPTB (3.4% vs. 1.5%; aOR=2.40 [1.001, 5.76]).

A personal history of TB was also linked to the risk of PTB (8.8% vs. 5.0%; aOR=2.00 [1.11, 3.61]), and smoking significantly increases the likelihood of PTB (13.0% vs. 4.5%; aOR=2.38 [1.40, 4.06]; $p < 0.01$) (Table 2).

Table 2. Logistic modeling of the factors linked to different forms of TB (N= 1332).

	Forms of TB		p-value	Univariate analysis c OR (95% CI) p-value	Multivariate analysis a OR (95% CI) p-value
	EPTB N (%)	PTB N (%)			
Age (years)					
<15	41 (7.9)	19 (2.3)	***	Ref	Ref
15-24	115 (22.2)	178 (21.8)		3.34(1.84, 6.03) ***	3.29(1.65, 6.57) **
25-34	153 (29.6)	255 (31.2)		3.59(2.01, 6.42) ***	2.89(1.47, 5.69) **
35-44	86 (16.6)	151 (18.5)		3.78(2.06, 6.93) ***	3.36(1.65, 6.83) **
45-54	55 (10.6)	113 (13.8)		4.43(2.35, 8.34) ***	3.59(1.71, 7.54) **
55-64	39 (7.5)	53 (6.5)		2.93(1.48, 5.80) **	2.85(1.29, 6.30) *
≥65	28 (5.4)	48 (5.9)		3.69(1.80, 7.57) ***	5.83(2.43, 14.00) ***
Gender					
Male	266 (51.7)	578 (70.7)	***	Ref	Ref
Female	249 (48.3)	239 (29.3)		0.44(0.35, 0.55) ***	0.53(0.40, 0.70) ***
Origin					
Urban	475 (98.5)	733 (96.6)	*	Ref	Ref
Rural	7 (1.5)	26 (3.4)		2.40(1.03, 5.58) *	2.40(1.001, 5.76) *
Personal history of TB					
No	398 (95.0)	620 (91.2)	*	Ref	Ref
Yes	21 (5.0)	60 (8.8)		1.83(1.09, 3.06) *	2.00(1.11, 3.61) *
Smoking					
No	399 (95.5)	591 (87.0)	***	Ref	Ref
Yes	19 (4.5)	88 (13.0)		3.12(1.87, 5.21) ***	2.38(1.40, 4.06) **

* p<0.05; ** p<0.01; *** p<0.001

Association between patient outcomes and different forms of TB

After adjusting for covariates—including gender, geographic origin, age and personal history of TB we obtained some significant findings about the clinical outcomes of patients with different forms of TB. It was observed that patients suffering from PTB had a higher rate of cases lost to follow-up (16.9% vs. 10.3%; aOR=1.57 [1.02, 2.41]; p < 0.05). Similarly, patients with PTB were more prone to relapse (8.3% vs. 2.3%; aOR=5.18 [1.80, 14.89]; p < 0.01).

Nevertheless, patients affected by PTB had a significantly higher cure rate than those with EPTB (39.0% vs. 2.1%, aOR=33.41 [17, 66.52]; p < 0.001) (Table 3). However, there was no difference in the proportion of deaths between patients with PTB and EPTB (p > 0.05) (Table 3).

Table 3. Univariate and multivariate logistic analysis of the association between patient prognosis and the different forms of TB (N= 1332).

Variables	Number of patients		p-value	Univariate analysis c OR (95% CI) p-value	Multivariate analysis a OR (95% CI) p-value
	Yes N (%)	No N (%)			
Lost to follow-up					
Form of TB ϕ					
EPTB	53 (10.3)	462 (89.7)	**	1	1
PTB	183 (16.9)	679 (83.1)		1.77 (1.26, 2.48) **	1.57 (1.02, 2.41) *
Relapse					
EPTB	12 (2.3)	503 (97.7)	***	1	1
PTB	68 (8.3)	749 (91.7)		3.80 (2.03, 7.10) ***	5.18 (1.80, 14.89) **
Healing					
EPTB	11 (2.1)	504 (97.9)	***	1	1
PTB	319 (39.0)	498 (61.0)		29.34(15.9, 54.2) ***	33.41 (17, 66.52) ***
Death					
EPTB	21 (4.1)	494 (95.9)	**NS**	1	1
PTB	22 (2.7)	795 (97.3)		0.65 (0.35, 1.19)	0.49 (0.24, 1.00)

ϕ : All models were adjusted for gender, provenance, age, and personal history of TB; NS: not significant.

* p<0.05; ** p<0.01; *** p<0.001

Discussion

From 2006 to 2012, 1,332 cases of TB were recorded. Our analysis revealed a higher prevalence among men than women, with a male/female ratio of 1.72. This aligns with WHO's global observations (2016), indicating a higher frequency among men with a male-to-female ratio of 1.6 [5]. The gender gap in TB prevalence has prompted various explanatory hypotheses, including biological differences in disease development and disparities in care access, particularly in developing countries. [6,7]. Men are more likely to face risk factors related to potential TB exposure, contributing to increased prevalence, as suggested by studies [6–8]. These complex factors underscore the importance of a holistic approach to understanding gender disparity in TB. Contrastingly, women were more likely to be affected by EPTB, consistent with trends observed in several studies [9,10]. While over half of all TB cases occurred in the 15 to 34 age group, all age groups were affected, highlighting the indiscriminate nature of the disease. EPTB cases were most frequent in children, aligning with findings by Ossalé Abacka et al. [10] and Chahboune et al. [11]. The high prevalence of EPTB in children and adolescents could be explained by their relatively immature immune systems, making them more likely to manifest the discrete clinical symptoms of TB, mostly in the form of extrapulmonary cases.

Regarding extrapulmonary manifestations, the study revealed a notable prevalence of pleural involvement, closely followed by lymph node involvement. These findings confirm the existing literature, emphasizing lymph nodes and pleura as the most frequent extrapulmonary locations for the disease [12–14]. The recent increase in pleural TB cases in Morocco, suggests possible recent transmission. Previous studies, such as one in San Francisco, have highlighted pleural TB's distinct nature, potentially indicating recent transmission [15]. These findings demonstrate the importance of deepening our understanding of pleural TB to strengthen disease control in regions like Morocco. Further research is imperative regions the role of different immune responses associated with to MTB infection in various anatomical locations.

The prevalence of PTB is 2.40 times higher in rural areas than in urban areas. This disparity suggests potential diagnostic delays in rural areas due to factors like restricted access to health-care facilities, absence of diagnostic services close to villages, long travel distance to the nearest health center, and limited monitoring by health workers [16]. The risk of PTB recurrence in individuals with a personal history of the disease may be influenced by several factors in our study, including potential MTB persistence despite completing anti-TB treatment, comorbidities, drug resistance, and unfavorable socioeconomic conditions.

Smoking, confirmed as a risk factor by several studies, significantly increases the risk of MTB infection by weakening pulmonary defenses [17,18]. Such as mucociliary clearance and the immune response [19]. Previous studies have also noted higher mycobacterial loads in smokers [20]. Our results further highlight the importance of quitting smoking to strengthen immunity, reduce vulnerability to TB, and improve lung health.

Our study also revealed that 93.2% of the cases were new, while 6% were relapses. In 2020, another study carried out by Eddabra and Neffa in the same province indicated a similar prevalence of 93.40% for new cases and 6.60% for retreatments [20]. The lack of evolution in the results shows that there had been a certain stability in the prevalence of TB for the region over several years, indicating a degree of constancy in the disease's epidemiological situation.

On the other hand, this study revealed that 14.3% of cases were lost to follow-up, while 3.2% died. The rate of loss to follow-up far exceeded the national rate of 7.6% [21], and was higher than rates observed in other regions, such as southern Ethiopia (11.2%) [22], China (6.8%) [23], and Georgia (12.5%) [24], although it is lower than the rates recorded in Norway (17%) [25], India (29.6%) [26], and Mozambique (44.9%) [27]. However, such variations may be attributed to differences in study design, sample size, patient monitoring systems, study parameters, sociodemographic factors, lifestyle, and access to health care. Compared with patients with EPTB, the rate of loss to follow-up was significantly higher for the patients with PTB. This finding is particularly concerning because loss to follow-up among patients with PTB risks further spreading the pathogen.

The overall goal of anti-TB treatment is to ensure a relapse-free cure for all patients, thus stopping the onward transmission of MTB and preventing the bacteria from acquiring further drug resistance. A cure was declared in less than a third of TB patients, and this rate is well below the 74.6% reported by Assao Neino et al. for Niamey, Niger, [28] and the 35.12% reported by Chahboune et al. for Settat, Morocco [11] . The observed low proportion of cures in our study may be due to a considerable number of patients who completed their treatment but lacked sufficient data to be declared cured. Notably, the cure rate was significantly higher in patients with PTB when compared to those with EPTB, with this difference being statistically significant. Therapeutic failure was observed in 0.7% of cases, which is similar to the proportion reported by Chahboune et al. (0.63%) [11], although markedly lower than the rate of 7% reported by Boushab et al. for Mauritania [29].

The present study documented 35 deaths, which corresponds to a TB-specific mortality rate of 16.53 per 100,000 inhabitants based on a total population for the two provinces of 260,000 inhabitants. This is much higher than the national average rate of 8.1 per 100,000 people [29]. Deaths were distributed relatively equally between patients with pulmonary and EPTB (i.e., 2.7% vs. 4.1%), with this difference not being statistically significant. However, the overall mortality reported in this study was higher than the 2.76% death rate noted in the study conducted by Chahboune et al. for Settat, Morocco [29]. In our study, 2.8% of patients exhibited intestinal tuberculosis, aligning with the prevalence of gastrointestinal tuberculosis, which typically accounts for 1% to 3% of all tuberculosis cases globally [31]. Our analysis of extrapulmonary anatomical sites

revealed a noteworthy association between intestinal tuberculosis and the risk of mortality, consistent with findings from previous research [32,33].. Intestinal tuberculosis can manifest either concurrently with active pulmonary disease or as a primary infection without pulmonary involvement. However, the diagnosis of intestinal tuberculosis is frequently delayed, leading to inappropriate treatment and increased mortality [32]. A high level of diagnostic suspicion is crucial when patients present with unexplained abdominal symptoms. Diagnostic tools include considerations of coexistence with pulmonary tuberculosis, utilization of CT imaging, colonoscopies, assessment of pathological features, acid-fast bacilli examination, and evaluation of the response to antituberculosis therapy [32].

In this study, the HIV status was only known for three patients who were declared HIV positive, while it remained unknown for the remainder of patients throughout the study period. In 2020, within the same region, HIV-status was reported for only 45 out of 211 patients (21.32%), of whom 36 were HIV seronegative and nine were seropositive in the PTB and TB groups. Simultaneously, 63.99% of patients had not been tested for HIV, while 1.42% had refused the test [30]. These results do not align with the specific objective established by the National Strategic Plan for TB Prevention and Control 2018–2021, which aimed to test 95% of TB patients in 2021 and provide antiretroviral treatment to 100% of patients co-infected with TB/HIV. Consequently, further efforts are necessary to establish routine HIV testing for all TB patients, considering that TB become an opportunistic disease when associated with AIDS. Moreover, TB exacerbates viral replication in HIV-infected individuals, thereby accelerating disease progression [31].

Conclusion

During the seven years of study period, the CDTRD in Laayoune recorded 1,332 cases of TB, with the pulmonary form being predominant. Extrapulmonary forms, however, were more prevalent in women and those aged under 15, with pleural and lymph node involvement being most common. Risk factors for PTB in our study included a rural origin, a personal history of TB, and smoking, with these being significantly associated with this disease. Recovery was a more common outcome in patients with the pulmonary form of the disease, with the treatment failure rate of 0.7%. Notably, our findings reveal that intestinal tuberculosis was significantly linked to mortality. The mortality rate exceeded the national average rate, and it was distributed relatively evenly between pulmonary and extrapulmonary forms. Overall, an integrated approach to fighting the disease is crucial for eliminating it by 2030 in Morocco.

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Abbreviations list
AIDS: Acquired Immune Deficiency Syndrome
CDTRD: Center for the Diagnosis and Treatment of Respiratory Diseases
EPTB: Extrapulmonary Tuberculosis
HIV: Human Immunodeficiency Virus
MTB: Mycobacterium Tuberculosis
PTB: Pulmonary Tuberculosis
TB: Tuberculosis
WHO: World Health Organization

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