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Extrapulmonary tuberculosis in Coimbra: a cross-sectional study

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Extrapulmonary tuberculosis in Coimbra: a cross-sectional study

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LIST OF ABBREVIATIONS

CI: Confidence interval

EPTB: Extrapulmonary tuberculosis

HIV: Human immunodeficiency virus

OR: Odds ratio

PTB: Pulmonary tuberculosis

SD: Standard deviation

SVIG-TB: Portuguese National Tuberculosis Surveillance System

TB: Tuberculosis

WHO: World Health Organization

ABSTRACT

Introduction: Tuberculosis (TB) is the main cause of death from a single infectious agent. It most frequently affects the pulmonary parenchyma, causing pulmonary tuberculosis (PTB). However, it can spread to any organ or tissue, causing extrapulmonary tuberculosis (EPTB). Taking into account that PTB patients are largely responsible for the transmission of the disease, reports from official entities highly focus on this form of TB. Therefore, there hasn't been much effort in studying the evolution and characteristics of EPTB worldwide. **Objective:** This study aims to analyse EPTB's evolution and characteristics in Coimbra, Portugal.

Methodology: We carried out a cross-sectional study of all EPTB patients followed at the Pulmonology Diagnostic Centre of Coimbra, Portugal, between January of 2009 and December of 2018. Incidence, sociodemographic and clinical data were analysed. Binominal logistic regression was conducted to determine the risk factors associated with EPTB and the risk factors for mortality during anti-TB treatment. Multinominal logistic regression was performed to assess the risk factors for each EPTB location.

Results: The study included 590 patients with TB. Of these, 401 (68%) had PTB and 189 (32%) had EPTB. The most frequent EPTB sites observed were lymph nodes (36%) and pleura (27.5%). Of the 189 cases, 164 completed the treatment (86.8%) and 12 died (6.3%). The overall incidence of TB in Coimbra had a 4.3% medium annual decline rate from 2009 to 2018. The incidence of EPTB remained relatively stable during the 10-year period, fluctuating around 4 cases per 100 000 habitants. Age's increase, females and unknown HIV status were risk factors for EPTB. Females were at a significantly elevated risk for lymph nodes TB, genitourinary TB and skin TB. Patients with unknown HIV status were at a significantly higher risk for pleural TB and tuberculosis in other sites. Patients with positive HIV status or with an increased age were at a significantly elevated risk for miliary TB. Risk factors for mortality during anti-TB treatment were age, positive and unknown HIV status.

Conclusion: The incidence of TB in Coimbra is decreasing, but EPTB's incidence remained relatively stable during the 10-year period. Coimbra had a higher burden of EPTB than the observed in Portugal, Europe and world. We identified risk factors for EPTB, EPTB sites and for mortality during anti-TB treatment. It is fundamental to develop EPTB guidelines worldwide, so that diagnostic and treatment procedures could be standardized.

Keywords: Extrapulmonary tuberculosis; Risk factors; Evolution.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*. It is the main cause of death from a single infectious agent and belongs to the top 10 causes of death worldwide.[1]

The bacillus is transmitted mainly through droplet infection.[2] It most frequently affects the pulmonary parenchyma, causing pulmonary tuberculosis (PTB). However, it can spread to any organ or tissue through lymphatic or hematogenous pathways or direct extension. When this occurs, it is called extrapulmonary tuberculosis (EPTB).[1] Still, in 10-50% of cases there is a concurrent pulmonary involvement.[3]

The diagnosis of EPTB requires a high clinical suspicion. Patients with active infection present the typical constitutional symptoms. However, the manifestations also vary according to the affected body site.[3] For instance, lymph node tuberculosis manifests itself frequently through cervical lymphadenopathy.[4] Pleural tuberculosis has a more acute presentation: pleural effusion accompanied by pleuritic chest pain and dyspnea.[5, 6] Osteoarticular tuberculosis manifests mainly through spondylitis or Pott's disease, but can affect any bone.[4] Gastrointestinal tuberculosis affects mainly the ileocecal region.[4] Tuberculosis meningitis is the most common form of the central nervous system tuberculosis.[4] Genitourinary tuberculosis can manifest through pyelonephritis syndrome.[3]

To reach definite diagnosis, the bacillus must be detected from a specimen through mycobacterial stain and culture, nucleic acid amplification test (Xpert® MTB/RIF assay), immunological tests and histology. Depending on the body site of the EPTB, different diagnostic procedures can be selected.[3, 7, 8]

The treatment regimen of an active infection of EPTB is the same as the PTB's. It requires a scheme of rifampicin, isoniazid, pyrazinamide and ethambutol for two months, followed by rifampicin and isoniazid for four months. However, it is recommended to extend the therapy for twelve months, in cases of tuberculous meningitis, and for nine months, in cases of tuberculous spondylitis with neurological involvement.[4, 9] Corticosteroids are recommended as an adjuvant in the treatment of tuberculous pericarditis and tuberculous meningitis.[4, 7, 9] Surgical interventions are often needed, most frequently to establish diagnosis by obtaining specimens, but also to treat complications of EPTB.[3, 7]

Taking into account that PTB patients are largely responsible for the transmission of the disease[1], reports from official entities highly focus on this form of TB. Therefore, there hasn't been much effort in studying the evolution and characteristics of EPTB worldwide. Given its

wide variety and nonspecific manifestations, it is fundamental to better understand this form of disease. Particularly, in Portugal, since this country was responsible for 5% of all EPTB notified cases in the European Union/European Economic Area between 2003 and 2014.[10] This study aims to analyse EPTB's evolution and characteristics in Coimbra, Portugal, according to the data base of Coimbra's Pulmonology Diagnostic Centre.

MATERIAL AND METHODS

Study design and data source

A cross-sectional study of EPTB patients followed at the Pulmonology Diagnostic Centre of Coimbra, Portugal, between January of 2009 and December of 2018. The data was collected from the Portuguese National Tuberculosis Surveillance System (SVIG-TB), a notification and follow-up program of all tuberculosis cases in Portugal.

Ethical approval

Patient's consent and ethics committee approval were not required, since all patient data was obtained fully anonymized from the SVIG-TB database.

Study data

This study included all patients diagnosed with TB and followed at the Pulmonology Diagnostic Centre of Coimbra, Portugal, between January of 2009 and December of 2018. No cases were excluded.

The sociodemographic and clinical data analysed were age, gender, HIV status, site of disease, treatment outcome and year of diagnosis. The age was studied through the exact age at time of diagnosis and its corresponding class (0-19; 20-44; 45-64; 65-84 or ≥85). Gender was categorized in male or female and HIV status in negative, positive or unknown. Site of disease was classified as EPTB or PTB. EPTB cases were divided in sites, according to the diseases' location: lymph nodes, pleura, bones, gastrointestinal, genitourinary, miliary, skin and others. The latter included all cases in other body sites that are not the previous. Treatment outcome was classified as completed, died (during anti-TB treatment), default (patients that interrupted the treatment) and transferred (patients that were transferred to other medical centres). At last, year of diagnosis was divided in 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017 and 2018.

Data of the resident population in Coimbra was used to calculate the incidence of TB. It was collected from PORDATA, an official and certified statistical data base of Portugal.

Statistical analysis

Descriptive analysis was conducted for categorical variables (absolute and relative frequencies) and numerical variables (mean, standard deviation, minimum and maximum).

Statistically significant associations for the depend variables EPTB, EPTB sites and treatment outcome were examined through the chi-square test, Mann-Whitney test and Kruskal-Wallis test, as appropriate. Binominal logistic regression was conducted to determine the risk factors associated with EPTB and the risk factors for mortality during anti-TB treatment, with calculation of odds ratios (OR) and 95% confidence intervals (95%CI). Multinominal logistic regression was performed to assess the risk factors for each EPTB location, with calculation of OR and 95%CI.

Statistical analyses were carried out using IBM® SPSS® Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). Significance level was set for p-values <0.05.

RESULTS

Study population and its characteristics

From 2009 to 2018, there were 590 patients with TB followed at the Pulmonology Diagnostic Centre of Coimbra. Of these, 401 (68%) had PTB and 189 (32%) had EPTB.

The EPTB patients' sociodemographic and clinical characteristics are shown in Table I, Figure 1 and Figure 2. The mean age was approximately 58 years (± 21), ranging from 1 to 100 years. A higher proportion of EPTB cases were between 65 and 84 years old (40.2%). Most of the patients were male (53.4%) and had a negative HIV status (56.6%). The proportion of unscreened patients for HIV was 37.6% (Table I). The most frequent EPTB sites observed were lymph nodes (36%) and pleura (27.5%), representing 63.5% of the different locations across the body. (Figure 1). Of the 189 cases, 164 completed the treatment (86.8%) and 12 died (6.3%) (Figure2).

Table I Characteristics of EPTB's patients in Coimbra, Portugal, 2009-2018.

Patient characteristics	**Number of Patients 189 (100%)**
Age (years)	
Mean	57.6
SD	21
Minimum	1
Maximum	100
Age classes, n(%)	
0-19	5 (2.6%)
20-44	50 (26.5%)
45-64	49 (25.9%)
65-84	76 (40.2%)
≥85	9 (4.8%)
Gender, n(%)	
Male	101 (53.4%)
Female	88 (46.6%)
HIV status, n(%)	
Negative	107 (56.6%)
Positive	11 (5.8%)
Unknown	71 (37.6%)

SD, standard deviation; HIV, human immunodeficiency virus.

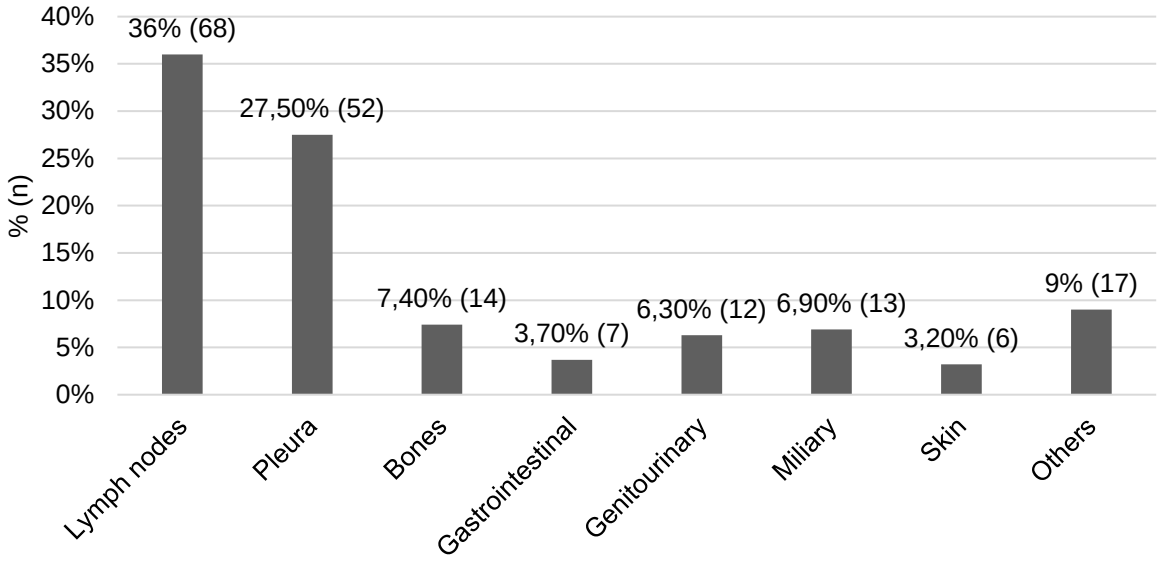

Figure 1 Distribution of EPTB sites in Coimbra, Portugal, 2009-2018.

Figure 2 Treatment outcome of EPTB patients in Coimbra, Portugal, 2009-2018.

Evolution of TB incidence from 2009 to 2018 (Figure 3)

The overall incidence of TB in Coimbra had a 4.3% medium annual decline rate from 2009 to 2018. The cumulative reduction between 2015 and 2018 was 23.2%, reaching its lowest incidence in 2018 (8.5 cases per 100 000 habitants).

The absolute incidence of EPTB remained relatively stable during the 10-year period, fluctuating around 4 cases per 100 000 habitants. The PTB incidence decreased from 9.7 to 4.1 cases per 100 000 habitants, which corresponds to a 6% annual decline rate.

From 2016 to 2018, there was an increase of 92% of EPTB cases and a 41% decrease of PTB cases, which lead to an inversion of tendency in 2018 with 51.4% of all cases being EPTB.

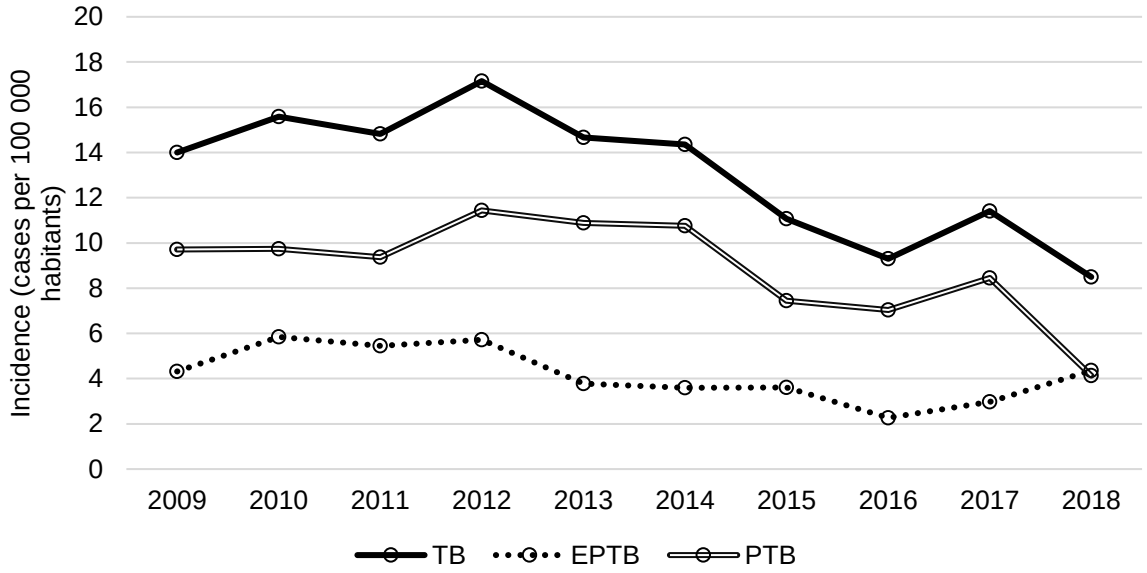

Figure 3 Evolution of TB, EPTB and PTB incidence in Coimbra, Portugal, 2009-2018.

Risk factors associated with EPTB

The Mann-Whitney test found statistically significant difference between EPTB and PTB ages (p=0.001). The chi-square test found statistically significant associations between location of TB and age classes (p<0.001), gender (p=0.001) and HIV status (p=0.021).

Binominal logistic regression was performed to identify risk factors associated with EPTB, compared to PTB. Age, gender and HIV status were the statistically significant factors associated with a higher probability of EPTB (Table II). For every increase in one year of age, the adjusted odds of having EPTB increases by a factor of 1.014 (95%CI 1.005-1.023). The adjusted odds of having EPTB is 1.874 (95%CI 1.301-2.700) times higher for females than males. The adjusted odds of having EPTB is 1.537 (95%CI 1.048-2.257) times higher for patients with unknown HIV status than negative HIV status. (Table II).

In summary, age's increase, females and unknown HIV status were risk factors for EPTB (Table II).

Table II Risk factors associated with EPTB compared to PTB in Coimbra, Portugal, 2009-2018.

Variable	EPTB n=189 (32%)	PTB n=401 (68%)	OR (95%CI)	p-Value
Age (mean±SD)				
	57.6 ±21	51.6 ±20	1.014 (1.005-1.023)	**0.003**
Age classes, n (%)				
0-19	5 (2.6%)	5 (1.2%)		
20-44	50 (26.5%)	152 (37.9%)		
45-64	49 (25.9%)	134 (33.4%)		
65-84	76 (40.2%)	88 (21.9%)		
≥85	9 (4.8%)	22 (5.5%)		
Gender, n (%)				
Male	101 (53.4%)	272 (67.8%)	Reference	
Female	88 (46.6%)	129 (32.2%)	1.874 (1.301-2.700)	**0.001**
HIV status, n (%)				
Negative	107 (56.6%)	274 (68.3%)	Reference	
Positive	11 (5.8%)	18 (4.5%)	2.155 (0.964-4.817)	0.061
Unknown	71 (37.6%)	109 (27.2%)	1.538 (1.048-2.257)	**0.028**

EPTB, extrapulmonary tuberculosis; PTB, pulmonary tuberculosis; OR, odds ratio; CI, confidence interval; SD, standard deviation; HIV, human immunodeficiency virus.

Risk factors associated with EPTB sites

The Kruskal-Wallis test found no statistically significant differences in age across the various EPTB sites (Table III). The chi-square test found statistically significant associations between EPTB sites and age classes, gender and HIV status (Table III).

Multinominal logistic regression was performed to identify risk factors associated with EPTB sites, compared to PTB. Age, gender and HIV status were the statistically significant factors associated with a higher probability of some of the EPTB sites (Table IV). The adjusted relative risk of lymph node TB would be expected to increase by a factor of 4.13 (95%CI 2.38-7.18) for females, comparatively to males. The adjusted relative risk of pleural TB would be expected to increase by a factor of 2.1 (95%CI 1.13-3.88) for unknown HIV status, comparatively to negative HIV status. For genitourinary TB, the adjusted relative risk would be expected to increase by a factor of 3.93 (95%CI 1.16-13.33) for females, comparatively to males. For every year increase in the patient's age, the adjusted relative risk of miliary TB would be 1.05 (95%CI 1.01-1.1) times higher than PTB. The adjusted relative risk of having miliary TB would be expected to increase by a factor of 31.88 (95%CI 6.8-149.39) for positive HIV status, comparatively to negative HIV status. The adjusted relative risk of skin TB would be expected to increase by a factor of 9.73 (95%CI 1.12-84.85) for females, comparatively to males. For TB in other sites, the adjusted relative risk would be expected to increase by a factor of 2.9 (95%CI 1.04-8.09) for unknown HIV status, comparatively to negative HIV status. (Table IV)

In summary, females were at a significantly elevated risk for lymph nodes TB, genitourinary TB and skin TB. Patients with unknown HIV status were at a significantly higher risk for pleural TB and tuberculosis in other sites. Patients with positive HIV status or with an increased age were at a significantly elevated risk for miliary TB (Table IV).

Table III Association between EPTB sites and sociodemographic and clinical variables in Coimbra, Portugal, 2009-2018.

Variable	Lymph nodes (n=68)	Pleura (n=52)	Bones (n=14)	Gastrointestinal (n=7)	Genitourinary (n=12)	Miliary (n=13)	Skin (n=6)	Others (n=17)	p-Value
Age (mean±SD)									0.644
	58.3±19.7	53.3±24.4	62±23.6	54.1±17	58.3±16,3	60.2±17.8	68.2±26.2	59.5±17.8	
Age classes									**0.022**
0-19	1 (1.5%)	1 (1.9%)	2 (14.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)	
20-44	16 (23.5%)	22 (42.3%)	1 (7.1%)	3 (42.9%)	2 (16.7%)	2 (15.4%)	2 (33.3%)	2 (11.8%)	
45-64	21 (30.9%)	7 (13.5%)	2 (14.3%)	2 (28.6%)	6 (50%)	5 (38.5%)	0 (0%)	6 (35.3%)	
65-84	27 (39.7%)	21 (40.4%)	8 (57.1%)	2 (28.6%)	3 (25%)	5 (38.5%)	2 (33.3%)	8 (47.1%)	
≥85	3 (4.4%)	1 (1.9%)	1 (7.1%)	0 (0%)	1 (8.3%)	1 (7.7%)	2 (33.3%)	0 (0%)	
Gender									**<0.001**
Male	22 (32.4%)	37 (71.2%)	12 (85.7%)	6 (85.7%)	4 (33.3%)	10 (76.9%)	1 (16.7%)	9 (52.9%)	
Female	46 (67.6%)	15 (28.8%)	2 (14.3%)	1 (14.3%)	8 (66.7%)	3 (23.1%)	5 (83.3%)	8 (47.1%)	
HIV status									**<0.001**
Negative	43 (63.2%)	26 (50%)	8 (57.1%)	5 (71.4%)	7 (58.3%)	6 (46.2%)	5 (83.3%)	7 (41.2%)	
Positive	0 (0%)	4 (7.7%)	0 (0%)	0 (0%)	0 (0%)	6 (46.2%)	0 (0%)	1 (5.9%)	
Unknown	25 (36.8%)	22 (42.3%)	6 (42.9%)	2 (28.6%)	5 (41.7%)	1 (7.7%)	1 (16.7%)	9 (52.9%)	
Treatment outcome									0.703
Completed	60 (88.2%)	44 (84.6%)	14 (100%)	5 (71.4%)	12 (100%)	10 (76.9%)	4 (66.7%)	15 (88.2%)	
Transferred	3 (4.4%)	3 (5.8%)	0 (0%)	1 (14.3%)	0 (0%)	1 (7.7%)	0 (0%)	1 (5.9%)	
Default	1 (1.5%)	1 (1.9%)	0 (0%)	0 (0%)	0 (0%)	1 (7.7%)	1 (16.7%)	0 (0%)	
Died	4 (5.9%)	4 (7.7%)	0 (0%)	1 (14.3%)	0 (0%)	1 (7.7%)	1 (16.7%)	1 (5.9%)	

OR, odds ratio; CI, confidence interval; HIV, human immunodeficiency virus.

Table IV Risk factors for EPTB sites compared to PTB in Coimbra, Portugal, 2009-2018.

Variable	Lymph nodes (n=68) OR (95%CI)	Pleura (n=52) OR (95%CI)	Bones (n=14) OR (95%CI)	Gastrointestinal (n=7) OR (95%CI)	Genitourinary (n=12) OR (95%CI)	Miliary (n=13) OR (95%CI)	Skin (n=6) OR (95%CI)	Others (n=17) OR (95%CI)
Age								
	1.01 (1.0-1.03)	1.00 (0.99-1.02)	1.02 (0.99-1.05)	1.01 (0.97-1.04)	1.01 (0.99-1.04)	**1.05 (1.01-1.1)**	1.04 (0.99-1.09)	1.02 (0.99-1.04)
Gender								
Male	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Female	**4.13 (2.38-7.18)**	0.88 (0.46-1.68)	0.32 (0.71-1.47)	0.33 (0.04-2.79)	**3.93 (1.16-13.33)**	0.96 (0.23-4.05)	**9.73 (1.12-84.85)**	1.87 (0.69-5.07)
HIV status								
Negative	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Positive	1.31 (0.74-2.3)	2.31 (0.72-7.46)	2.4E-8 (2.4E-8-2.4E-8)	1.5E-8 (1.5E-8-1.5E-8)	4.2E-8 (4.2E-8-4.2E-8)	**31.88 (6.8-149.39)**	7.01E-8 (7.01E-8-7.01E-8)	3.1 (0.34-27.46)
Unknown	4.01E-8 (4.01E-8-4.01E-8)	**2.1 (1.13-3.88)**	1.68 (0.56-5.04)	0.99 (0.19-5.25)	1.61 (0.49-5.32)	0.32 (0.04-2.7)	0.36 (0.04-3.26)	**2.9 (1.04-8.09)**

OR, odds ratio; CI, confidence interval; HIV, human immunodeficiency virus.

Risk factors for mortality during anti-TB treatment in patients with EPTB

The Mann-Whitney test found statistically significant differences in age for treatment outcome ($p<0.001$). The chi-square test found a statistically significant association between treatment outcome and HIV status ($p=0.012$). There were no statistically significant associations between treatment outcome and age classes ($p=0.05$), gender ($p=0.754$) and EPTB sites ($p=0.722$). Default and transferred cases were excluded from the analysis.

Binominal logistic regression was performed to identify risk factors associated with mortality during anti-TB treatment, compared to completing the treatment. Age and HIV status were the statistically significant factors associated with a higher probability of death (Table V). Default and transferred cases were excluded from the analysis.

The odds of dying during anti-TB treatment increases by a factor of 1.110 (95%CI 1.029-1.197) for every year increase in patient's age, given the other variables in the model are held constant. The odds of dying during anti-TB treatment is 32.980 (95%CI 1.447-751.863) times higher for patients with positive HIV status and 7.704 (95%CI 1.467-40.460) times higher for patients with unknown HIV status than patients with negative HIV status, given the other variables in the model are held constant. (Table V)

In summary, age's increase, positive and unknown HIV status were risk factors for TB mortality (Table V).

Table V Risk factors for mortality during anti-TB treatment for EPTB patients, in Coimbra, Portugal, 2009-2018.

Variable	Died n=12 (6.8%)	Completed n=164 (93.2%)	OR (95%CI)	p-Value
Age (mean±SD)				
	76.1±12.8	56.6±20.6	1.110 (1.029-1.197)	**0.007**
Age classes, n (%)				
0-19	0 (0%)	5 (3%)		
20-44	1 (8.3%)	43 (26.2%)		
45-64	1 (8.3%)	45 (27.4%)		
65-84	8 (66.7%)	65 (39.6%)		
≥85	2 (16.7%)	6 (3.7%)		
Gender, n (%)				
Male	7 (58.3%)	88 (53.7%)	Reference	
Female	5 (41.7%)	76 (46.3%)	0.443 (0.112-1.762)	0.248
HIV status, n (%)				
Negative	2 (16.7%)	99 (60.4%)	Reference	
Positive	1 (8.3%)	8 (4.9%)	32.980 (1.447-751.863)	**0.028**
Unknown	9 (75%)	57 (34.8%)	7.704 (1.467-40.460)	**0.016**

Default and transferred cases were excluded from the analysis.

OR, odds ratio; CI, confidence interval; SD, standard deviation; HIV, human immunodeficiency virus.

DISCUSSION

The Sustainable Development Goals and the World Health Organization's (WHO) Global End Tuberculosis Strategy are the leading worldwide strategies to control TB. The first sets a target to end the global TB epidemic by 2030. The second sets milestones and targets to reduce by 90% the absolute number of TB deaths and by 80% the TB incidence between 2015 and 2030. They have been responsible for the steady reduction of the global burden of tuberculosis.[1]

Indeed, Portugal has reported an average of 5% annual decline rate in the TB incidence from 2013 to 2017, falling below 20 cases per 100 000 habitants since 2015.[11] The WHO European Region has stated a 5.1% annual reduction rate between 2009 and 2018, with an average of 30 cases per 100 000 habitants in 2017.[12, 13] Globally, 1.6% rate of decline per year has been reported, with an average of 130 cases per 100 000 habitants.[1] Likewise, this study demonstrates that Coimbra too follows this trend, with an average of 4.3% annual decline rate in the TB incidence from 2009 to 2018, reaching 8.5 cases per 100 000 habitants in 2018.

The cumulative reduction of TB cases in our study between 2015 and 2018 was 23.2%. This means that Coimbra has already achieved the 2020 End TB Strategy milestone to reduce the TB incidence rate in 2020 by 20% against the 2015 baseline. In comparison, the WHO European Region is on track to achieve this milestone, but only decreased 15.2% for the period 2015-2018.[12] Globally, most WHO regions are not on track to reach this milestone.[1]

In Coimbra, EPTB represented 32% of all TB burden from 2009 to 2018, fluctuating around 4 cases per 100 000 habitants. It is similar to a study conducted in Vila Nova de Gaia, Portugal, that reported a 32.6% EPTB burden between 2008 and 2012.[14] However, it is higher than most reports. Indeed, in Portugal, it represented 28.5% of all cases in 2017.[11] In the European Union and European Economic Area, it has remained stable between 2003 and 2014, with 20% of all cases.[10] Globally, its total burden was 15% in 2018.[1] The observed inversion of tendency in 2018, with 51.4% of EPTB cases and 48.6% of PTB, is an isolated event limited to the region of Coimbra. No similar occurrence was reported in Portugal, Europe or globally, as the tendency remained the same as described before. These variances result from differences in epidemiological factors, such as cultural customs and migration patterns, and different diagnostic practices across countries and continents.[15]

The most common EPTB sites observed, lymph nodes and pleura, are in accordance with previous Portuguese studies[11, 14] and worldwide publications.[4, 10] However, the less common sites distribution is not as well-established, as it varies according to geographic location.[4] Differences in epidemiological factors, such as cultural customs and migration patterns, have a role on site distribution. Additionally, the lack of evidence-based guidelines for the diagnosis of EPTB leads to disparities on diagnostic practices.[15] Experts in India have already developed EPTB guidelines for their country, to homogenize the diagnosis and management of the various forms of EPTB.[16] The same should be done worldwide, so that diagnostic and treatment procedures could be standardized.

There are several well-established risk factors for EPTB.[4, 10, 17] Age and female gender are two of them that are also identified in our study. Specifically, female gender for lymph nodes, genitourinary and skin TB and age for miliary TB. A study has suggested that hormonal factors have a role in the development of EPTB in females, particularly in women in menopause.[18] Furthermore, it is known that increasing age is probably associated with some immunosuppression that confers a higher susceptibility to the disease and its dissemination.[18] We also identified patients with HIV co-infection at a higher risk for miliary TB, in accordance with previous reports.[19] The advanced immunosuppression typical of these patients is the responsible for the enhanced dissemination and more severe forms of EPTB.[19] However, individuals with unknown HIV status were the ones at a higher risk of EPTB. There are two possible explanations for this event. In one hand, we have a higher proportion of unscreened patients for HIV infection (37.6%) than in the rest of the country (6% in 2018)[12] and the WHO European Region (8.5% in 2018),[12] despite the recommendations for HIV screening in TB patients and the availability of HIV tests and treatment in Portugal.[20] In the other hand, EPTB is linked to HIV positive individuals that have advanced immune suppression.[19] So, it would be necessary for the HIV positive patients in our study to have advanced immune suppression to be identified as risk factors for EPTB. Therefore, it would be interesting to include the CD4 cells count in the surveillance program, so that further studies could take this parameter into account.

Our EPTB's treatment completion rate (86.8%) was higher than the 77.6% accomplished in Portugal in 2016,[11] with 12 in 189 of our EPTB patients (6.3%) dying during treatment from 2009 to 2018. Patients co-infected with HIV were the ones with the higher risk of dying, a well-established risk factor. It is known that the mortality rate rises with the decrease of the CD4 cells, being higher when there are less than 200 cells/µl.[19] An

unknown HIV status was also identified as a risk factor, again in consequence of a higher proportion of unscreened patients for HIV infection. Age was also identified as a risk factor for mortality, as the majority of this patients (66.7%) had between 65 and 84 years old. This is in accordance with previous studies and may be related to the higher prevalence of comorbidities and progressive immunosuppression in this age group.[18, 21]

There are some limitations in our study. First, the unavailability of data regarding patient's comorbidities (diabetes, end-stage renal disease, immunosuppressive therapy), addictions (alcohol consumption, injecting drug use) and country of origin. These are known risk factors that influence the progression and form of TB disease. The existence of concurrent PTB wasn't also available, which didn't allow us to distinguish it from exclusive EPTB and analyse their differences. Second, we don't analyse the impact of the drug resistance in treatment in Coimbra, an increasing concern worldwide. Lastly, the scarcity of studies dedicated to the EPTB's evolution in Portugal, Europe and worldwide difficulted the comparison with our study.

CONCLUSION

The incidence of TB in Coimbra is decreasing, leading to the important achievement of the 2020 End TB Strategy milestone. However, EPTB's incidence remained relatively stable during the 10-year period, fluctuating around 4 cases per 100 000 habitants.

EPTB represented 32% of all TB burden in Coimbra from 2009 to 2018, higher than the reported in Portugal, Europe and world. The most common body sites were lymph nodes and pleura, representing 63.5% of the different locations across the body. Female gender and increased age were risks factors for this form of disease and positive HIV status specially for miliary TB, in agreement with previous reports. Our EPTB's treatment completion rate was high (86.8%), with 6.3% of our patients dying during treatment. Risk factors for mortality were increasing age and positive HIV status. The considerable proportion of unscreened patients for HIV in Coimbra suggests that we should reinforce this screening, given the strong association between TB and HIV infection.

The scarcity of studies dedicated to EPTB and of evidence-based guidelines for its diagnosis leads to disparities on diagnostic practices. Therefore, it is important to elaborate EPTB guidelines worldwide, so that diagnostic and treatment procedures could be standardized.

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