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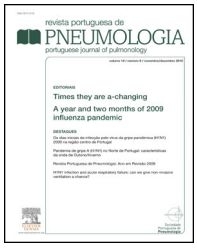

ORIGINAL ARTICLE

Tuberculosis deaths in Northern Portugal. Predictors of mortality during TB treatment – A five-year analysis (2008–2012)

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Abstract The burden of tuberculosis in the Northern Region of Portugal remains high despite the implementation of risk group oriented strategies. Therefore characterization of the factors that relate to mortality among tuberculosis patients in this geographical region is relevant and explains the purpose of this study.

Records in the national surveillance system for tuberculosis characteristics for patients living in the North of Portugal and who completed tuberculosis treatment between 2008 and 2012 were studied by means of a retrospective case–control study design. Simple and multiple regressions were performed in order to assess the relationship between patient demographic, clinical and social history data with patient survival.

Male individuals over 45 years old with prior cancer (OR 4.63, 90% CI 2.66–8.04) and disseminated tuberculosis (OR 1.96, 90% CI 0.48–0.99) were identified as being those with the highest risk of death throughout tuberculosis treatment.

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Introduction

Despite the general trend of decreasing tuberculosis rates, Portugal remains one of the countries with the highest burden of tuberculosis in Europe, with intermediate incidence rates, close to those of the East European countries. According to the World Health Organization (WHO), in 2012 in Portugal the estimated prevalence of tuberculosis was of 34 cases per 100,000 population (including infection by the Human Immunodeficiency Virus (HIV)). Since 2010 the mortality rate has remained nearly constant with 1.2 deaths per 100,000 population reported in 2010, 1.3 deaths per 100,000 population in 2012 and 1.3 deaths per 100,000 population reported in 2013.[1,2]

In Portugal, all cases of TB are managed in outpatient TB centers. These centers are responsible for the management of TB and screening of all people at risk. Notification of tuberculosis cases to the General Directorate of Health (GDH) by clinicians is mandatory, i.e., notification happens the moment the treatment begins, whenever there is a change (adverse event, knowledge of resistance, interruption, continuation phase) and at the end of treatment (completion, death, interruption, abandon, unsustained diagnosis). Incidence notifications are collected by the Sistema de Vigilância da Tuberculose em Portugal (SVIG-TB), the specific National Tuberculosis Central Program (PNT) information system managed by the PNT coordination team at the GDH. In 2012 the case detection rate was 89%,[1] with 88.3% of the case detections made through passive screening, 5.1% through contacts and 1.9% from vulnerable or risk groups screening.[3]

Like most countries of the European Union, the distribution of the Portuguese tuberculosis incidence varies considerably throughout Portugal.[4,5] The Northern Region of the country has the highest tuberculosis incidence rate, with 37.4 cases per 100,000 population reported in Porto Metropolitan Area in 2012 and 26.7 cases per 100,000 population reported in Viana do Castelo in the same year.[3] The risk factors contributing to tuberculosis also have a different distribution within the country. Between 2004 and 2006, HIV/Acquired Immune Deficiency Syndrome (AIDS), overcrowding, unemployment and imprisonment were identified as risk factors specially affecting the dynamic of tuberculosis in Porto Metropolitan Area.[4]

The current economic crisis has had an impact at a social level on the Portuguese population, leading to rising unemployment rates, wealth inequality, poverty, increasing stress and deteriorating the living conditions. With this new socio-economic context, high incidences of HIV coinfection and the risk of multidrug-resistant and extremely resistant tuberculosis, there are new challenges for the control of the disease in Portugal. A better understanding of the demographic, behavioral risk factors, disease progression, treatment practices and clinical indicators associated with death among tuberculosis patients is therefore necessary in order to adapt tuberculosis strategies to the reality of the Northern Region of Portugal.

This study aims to identify the factors related to mortality among tuberculosis patients in the North of Portugal.

Materials and methods

Study subjects

The data was obtained from the national surveillance system for tuberculosis, SVIG-TB. This database records information on the cases that have started tuberculosis treatment in Portugal, both new cases and re-treatments throughout the period of tuberculosis treatment, up to its termination. It gathers information on patient demographic, clinical characteristics and social history.

No prior approval from a data protection agency is required as per Portuguese law no. 67/98 of 26 October regarding this type of study and the type of data collected (http://www.cnpd.pt/bin/legis/nacional/lei_6798.htm).

Patients undergoing tuberculosis treatment, living in the Northern Region of Portugal at the time of tuberculosis detection and having completed tuberculosis treatment between 2008-01-01 and 2012-12-31 were considered eligible for this study.

Residence in the Northern Region of Portugal was defined according with the Nomenclature of Territorial Units for Statistics II (NUTS II) of Portugal, as per criteria sourced from Instituto Nacional de Estatística (http://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_base_dados).

Study design

A retrospective case–control study was conducted to compare the characteristics of the patients diagnosed with tuberculosis who died between January 2008 and December 2012 while undergoing tuberculosis treatment (cases) with those of the patients that completed the treatment in the same observation period (controls).

During the period studied 5003 tuberculosis cases were notified in the North region of Portugal, 3.87% (194 patients) of which did not have complete information on treatment regimen or follow up.

Each case was first identified in the database and the patients that immediately preceded and that immediately followed him or her in the database were defined as controls. No particular pairing was performed as the order of the individuals in the dataset was arbitrary.

Methods

The characteristics reported in SVIG-TB were used to identify which patient features predicted death. Demographic, clinical and social history data were based on the information recorded in SVIG-TB database only. Patients' nationalities were grouped according to the epidemiological regions criterion used by WHO.[1] Based on literature review, risk factors were selected according[1] to their relevance in predicting tuberculosis mortality.[4,6,8]

Definitions

Nursing home residency, homelessness, incarceration and other risk factors were grouped into the category ''other risk factors'' due to the small number of individuals observed

within each individual category. Diseases prior to tuberculosis diagnosis were analyzed according to their clinical relevance. The variable ''cancer'' encompassed lung cancer, linfoma or mielodisplasic disease and cancers in other organs. Diabetes, silicose, other interstitial disease, sarcoidose, articular inflammatory disease and other diagnosed diseases were grouped into the ''other diseases'' variable due to the small number of individuals within each category.

Analysis

Demographic, clinical and socio history descriptive data are presented in this paper.

Simple and multiple logistic regressions were performed to assess the relationship between patient's characteristics and patient's binary outcome (death/success). Odds-ratio (OR) and associated 95% confidence intervals (CI) were reported. The initial set of covariates was selected a priori based on the epidemiological mechanism or relevant previously published literature. From a bivariate analysis of each covariate with the outcome, only those factors with a p-value less than 0.2 were selected to be included in the multiple model. Then a backward selection procedure was used to generate a parsimonious model as the final model.

The model presented a deviance of >0.05. Its asymptotic chi-squared distribution did not allow the rejection of the null hypothesis that the model exhibited an adequate goodness-of-fit ($p < 0.05$).

The significance level was set at 0.05. Statistical analyses were performed with R: A Language and Environment for Statistical Computing, version 3.0.0.[7]

Results

In the Northern Region of Portugal, between January 2008 and December 2012, a total of 366 cases were recorded in SVIG-TB database as deaths from tuberculosis patients who had initiated tuberculosis treatment. These cases were analyzed across with 732 tuberculosis patients that completed the treatment in the same period, in a 1:2 case–control ratio, in a total of 1098 individuals.

Frequencies of demographic, behavioral and clinical characteristics of the study population are presented in Table 1.

The male female ratio was 4.30 and 2.05 among cases and controls. An overall mean age of 52.23 ± 18.73 years for cases and 50.03 ± 21.81 years for controls was determined. Fifty-one percent of the reported deaths occurred in the >65 years group. The majority of the patients were Portuguese living in Porto Metropolitan Area at the time of tuberculosis diagnosis ($n = 193$ cases, 53% and $n = 384$ controls, 52%). Deaths were reported mainly in retired individuals ($n = 199$, 54%) whereas controls worked in the industry ($n = 174$, 24%) and service sectors ($n = 172$, 23%) or were retired at the time of tuberculosis diagnosis ($n = 159$, 22%). Unknown professional status accounted for 93 (26%) and 164 (22%) of the notifications in the case and control groups, respectively.

Thirty-six cases (9.8%) and 61 controls (8.3%) had a past history of tuberculosis (6 cases had two prior tuberculosis treatments, 2 cases had three and 1 case had five previous

Table 1 Frequencies and bivariate logistic regression of demographic, behavioral and clinical characteristics of cases ($N = 366$) and controls ($N = 732$).

	Cases *N* (%)	Controls *N* (%)
Sex		
Male	297 (81)	492 (67)
Female	69 (19)	240 (33)
Age group (years)		
<45	67 (18)	373 (51)
45–64	112 (31)	234 (32)
>65	187 (51)	125 (17)
Mean ± standard deviation		
Female	68.70 ± 17.95	44.66 ± 19.79
Male	51.54 ± 17.32	46.61 ± 17.26
Country of origin		
Portugal-born	364 (99)	706 (96)
Foreign-born	2 (1)	26 (4)
Central Europe	0 (0)	1 (4)
High income countries	0 (0)	7 (27)
Africa-countries with low HIV prevalence	1 (50)	6 (23)
Latin America	0 (0)	1 (4)
Africa-countries with high HIV prevalence	0 (0)	2 (8)
East Europe	0 (0)	6 (23)
South-East Asia	0 (0)	3 (11)
Unknown	1 (50)	0 (0)
Residence (Municipalities)		
Porto Metropolitan Area	193 (53)	384 (52)
Outside Porto Metropolitan Area		
Minho-Lima	24 (7)	49 (7)
Cavado	19 (5)	40 (6)
Ave	38 (10)	81 (11)
Tamega	55 (15)	104 (14)
Douro	17 (5)	36 (5)
Alto Tras-os-Montes	20 (5)	38 (5)
Professional activity		
Agriculture sector	5 (1)	15 (2)
Industry sector	40 (11)	174 (24)
Services sector*	26 (7)	172 (23)
Children/Students	0 (0)	42 (6)
Unemployed	3 (1)	6 (1)
Retired	199 (54)	159 (22)
Unknown	93 (26)	164 (22)
Number of prior treatments		
One	27 (75)	55 (90)
More than one	9 (25)	6 (10)
Prior treatment status		
Completed	27 (75)	46 (75)
Failure due to insuccess	5 (14)	8 (13)
Failure due to interruption	2 (6)	0 (0)
Chronic	1 (3)	7 (12)
Unknown	1 (3)	0 (0)
MDR TB		
Isoniazide (S | R | U)*	7 | 0 | 1	20 | 1 | 1
Rifampicin (S | R | U)*	8 | 0 | 0	22 | 0 | 0

Table 1 (*Continued*)

	Cases *N* (%)	Controls *N* (%)
Site of current TB		
Pulmonary	240 (66)	490 (66)
Disseminated		
Disseminated	30 (8)	28 (4)
Meningea	18 (5)	34 (5)4
CNS	4 (1)	5 (1)
Extra pulmonary		
Lymphatic extra | intrathoracic	15 (4) | 3 (1)	53 (7) | 5 (1)
Pleural	36 (10)	72 (10)
Bone/Joint	3 (1)	8 (1)
Other	16 (4)	37 (5)
Missing	1 (0)	0 (0)
Previous diseases to TB		
HIV	65 (18)	88 (12)
Diabetes	36 (10)	41 (6)
Lung cancer	27 (7)	6 (1)
Linfoma or Mielodisplasia	8 (2)	3 (0)
Other organs cancer	26 (7)	12 (2)
COPD	32 (9)	15 (2)
Hepatic disease	24 (7)	26 (4)
Silicose	9 (3)	12 (2)
Articular inflamatory disease	1 (0)	4 (1)
Other interstitial disease	1 (0)	5 (1)
Sarcoidose	0 (0)	1 (0)
Other	56 (16)	65 (10)
Radiological findings		
Normal	40 (11)	116 (16)
Cavitated	98 (27)	264 (36)
Non-cavitated	187 (51)	328 (45)
Missing	41 (11)	24 (3)
Sarcoidose	0 (0)	1 (0)

* S, sensible; R, resistente; U, unknown.

treatments). Seventy-five percent of the patients completed the previous treatments and the main cause of treatment failure was unsuccessful treatment, which occurred in 5 of the cases (14%) and in 8 of the controls (13%).

The primary presentation site of tuberculosis was pulmonary, documented in 275 cases (75%) and in 540 of the controls (74%). Non-cavitated imaging was documented in 187 cases (51%) and in 328 controls (45%). Radiological information was missing in 41 of the cases (11%) and in 24 of the controls (3%).

Sixteen percent of the cases ($n = 57$) and 3% of the controls ($n = 21$) had cancer at the time of tuberculosis diagnosis and the lung cancer was the most frequent among the cases ($n = 27$, 7%), while cancer in other organs was the most frequent amongst the control group ($n = 12$, 2%).

Regarding the analysis of the crude effects, Table 2, disseminated tuberculosis (including meningeal and central nervous system (CNS) forms) emerged as significant factor in predicting tuberculosis mortality, with an OR of 1.58 (95% CI 1.07–2.35). Non-cavitated imaging yield an OR of 1.65 (95% CI 1.11–2.47) when compared with normal radiological pattern results.

Cancer emerged as a significant factor in predicting tuberculosis mortality, with an OR of 6.25 (95% CI 3.72–10.48). Chronic obstructive pulmonary disease (COPD) and hepatic disease also yield as independent factors of death from tuberculosis, with an increased odds of 4.58 (95% CI 2.45–8.57) and 1.91 (95% CI 1.08–3.37), respectively.

HIV infection was shown to positively contribute to tuberculosis mortality OR of 1.58 (95% CI 1.12–2.24). Other risk factors such as drug or alcohol addiction also led to an increased risk of death with an OR of 1.67 (95% CI 1.11–2.51) and 1.49 (95% CI 1.07–2.07), respectively. Records of alcohol consumption patterns were missing in 38 of the cases (10%) and in 27 of the controls (4%).

Regarding the multiple analysis, gender was a significant contributor to tuberculosis mortality. Female sex presented an OR of 0.44 (95% CI 0.31–0.63). Individuals aged between 45 and 64 years old and more than 64 years old showed a significant difference in tuberculosis mortality, with an OR of 2.21 (95% CI 1.53–3.18) and 8.76 (95% CI 6.07–12.64), respectively. Cancer contributed with an increased odds of 4.63 (95% CI 2.66–8.04) to tuberculosis related mortality. Also tuberculosis primary location yield as predictor of mortality. Disseminated tuberculosis yield an OR of 1.96 (95% CI 1.25–3.07) and extra-pulmonary tuberculosis an OR of 0.68 (95% CI 0.48–0.99).

Discussion

In the Northern Region of Portugal, between 2008 and 2012, male patients over 45 years old with prior cancer and disseminated tuberculosis were found to be at higher risk of death throughout tuberculosis treatment.

The Northern Region of Portugal has been identified as a critical area of tuberculosis over recent years. In 2012 Porto Metropolitan Area reported the highest tuberculosis incidence rate.[3] In this city, between 2004 and 2006, HIV/AIDS had the highest incidence of the country, along with a high prevalence of overcrowded accommodation and the second greatest number of prisoners in Portugal, all being reported as major risk factors for tuberculosis in this specific geographic location.[4] When looking into our study, the prevalence of these risk factors was consistent with the data previously published for this population, i.e. a high prevalence of HIV infected patients was found in our data and 1% of our patients were in prison at the time of tuberculosis diagnosis.[3] Regardless of these facts, living in Porto Metropolitan Area did not have a significant relationship with increased tuberculosis mortality.

Our data have also shown that after the Porto Metropolitan Area, Tâmega, Ave and Minho-Lima were the regions with the highest number of deaths.

Age has been described as an independent predictor of tuberculosis mortality.[6] Likewise, in our study, patients older than 45 years old were more at risk than younger patients. In the multiple analysis, being aged between 45 and 64 years-old yield an increase odds of 2.21 (95% CI 1.53–3.18) and patients aged more than 64 years old yield an increased odds of 8.76 (95% CI 6.07–12.64). Older patients presented poorer functional status. In our data a higher prevalence of

Table 2 Frequencies and bivariate logistic regression of demographic, behavioral and clinical characteristics of cases (*N* = 366) and controls (*N* = 732).

	Cases *N* (%)	Controls *N* (%)	Bivariate logistic regression OR (CI 95%)	Multivariate logistic regression OR (CI 95%)
Sex				
Male	297 (81)	492 (67)	1	
Female	69 (19)	240 (33)	0.48 (0.35–0.65)	0.44 (0.31–0.63)
Age group (years)				
<45	67 (18)	373 (51)	1	
45–64	112 (31)	234 (32)	2.66 (1.89–3.76)	2.21 (1.53–3.18)
>64	187 (51)	125 (17)	8.33 (5.9–11.76)	8.76 (6.07–12.64)
Residence				
Porto	193 (53)	384 (52)	1	
Outside Porto	173 (47)	348 (48)	0.99 (0.77–1.27)	
Risk group				
Drug user				
Yes	45 (12)	62 (8)	1.67 (1.11–2.51)	
No	284 (78)	652 (89)	1	
Missing	37 (10)	18 (2)		
Excess alcohol use				
Yes	72 (20)	112 (15)	1.49 (1.07–2.07)	
No	256 (70)	593 (81)	1	
Missing	38 (10)	27 (4)		
Other				
Yes	62 (17)	78 (11)	1.83 (1.27–2.62)	
No	283 (77)	650 (89)	1	
Missing	21 (6)	4 (1)		
Diseases prior to diagnosis				
HIV infection				
Positive	65 (18)	88 (12)	1.58 (1.12–2.24)	
Negative	301 (82)	644 (88)	1	
COPD				
Yes	32 (9)	15 (2)	4.58 (2.45–8.57)	
No	334 (91)	717 (98)	1	
Cancer				
Yes	57 (16)	21 (3)	6.25 (3.72–10.48)	4.63 (2.66–8.04)
No	309 (84)	711 (97)	1	1
Hepatic disease				
Yes	24 (7)	26 (4)	1.91 (1.08–3.37)	
No	342 (93)	706 (96)	1	
Other				
Yes	107 (29)	132 (18)	1.88 (1.4–2.52)	
No	259 (71)	600 (82)	1	
TB primary location				
Pulmonary	240 (66)	490 (67)	1	
Disseminated	52 (14)	67 (9)	1.58 (1.07–2.35)	1.96 (1.25–3.07)
Extra-pulmonary	73 (20)	175 (24)	0.85 (0.62–1.17)	0.68 (0.48–0.99)
Missing	1 (0)	0 (0)		
Radiology				
Normal	40 (11)	116 (16)	1	
Cavitated	98 (27)	264 (36)	1.08 (0.7–1.65)	
Non-cavitated	187 (51)	328 (45)	1.65 (1.11–2.47)	
Missing	41 (11)	24 (3)	–	
Treatment				
First line	296 (81)	632 (86)	1	
Other than first line	70 (19)	100 (14)	1.49 (1.07–2.09)	

HIV, human immunodeficiency virus; COPD, chronic obstructive pulmonary disease; TB, tuberculosis;

COPD ($n = 32$, 68%) and higher overall comorbilities ($n = 108$, 45%), along with a higher prevalence of cancer and hepatic disease (with similar prevalence found in both groups aged more than 45 years old) was found. Additionally, in patients aged more than 64, extra-pulmonary forms of tuberculosis, more difficult to diagnose, were also more frequent ($n = 98$, 40%).[8]

Immune system dysfunctions like those occurring in HIV infected patients and in cirrhotic individuals, have been described as factor for increased tuberculosis susceptibility and are related to tuberculosis mortality.[9] Consistently, the crude effects of hepatic disease at the time of tuberculosis diagnosis, HIV infection, drug use and alcohol excessive consumption on mortality by tuberculosis were also shown to be statistically significant in the present study.

Cancer was identified as an independent predictor of tuberculosis mortality in the adjusted multiple analysis, with an OR of 4.63 (95% CI 2.66–8.04). In our study 57 of the cases (16%) had cancer at the time of tuberculosis diagnosis. The most prevalent cancer in our study, was lung cancer ($n = 27$, 7%). Cancer is a known risk factor for TB (REF) and is related with high mortality – particularly lung cancer, as stated in previous studies in the region, where it was found that 80% of the lung cancer diagnoses were performed at the later phases of the disease making potentially curative treatment impractical and explaining the high fatality rate observed in this form of cancer.[10,11] In the Northern Region of Portugal, lung cancer is reported as the second most frequent primary cancer, mostly afflicting individuals aged more than 60.[11]

Disseminated and extra-pulmonary tuberculosis relate with immune suppression, with a significantly higher prevalence among immune-compromised patients. In late HIV infection these forms of tuberculosis account for more than 50% of all tuberculosis cases.[8,12] In our study, a high prevalence of risk factors and comorbidities were found, some of them directly impacting on patient immune status, such as HIV infection, alcoholism, hepatic disease and diabetes.[3,8,13] Not surprisingly disseminated disease (primary diagnosis of tuberculosis in the CNS, meningitis or disseminated forms) came up as a significant contributor to tuberculosis mortality when compared with pulmonary tuberculosis.

Extra-pulmonary location, a less severe presentation form of tuberculosis, yield an OR of 0.68, 95% CI 0.48–0.99.

Our study has several limitations, most of which related to the fact that it is based on a retrospective database. As we worked with a predefined database, we could not include data that could have been considered important to us, such as CD4 counts, viral load, highly active antiretroviral therapy on e.g. HIV patients.

A strength of this study is based on the fact that notification is mandatory, and all tuberculosis cases are managed in a defined structure, i.e. outpatient tuberculosis centers. Notification is made by the medical doctor and all data is reviewed 3 times a year with the regional coordinators of the tuberculosis national program. We analyzed data from 1098 patients that could give us a good perspective of the characteristics.

Vital records were not accessed for this study due to country legislation constraints. Clinical records could not be easily accessed due to the geographic dispersion of the cases. For these reasons the vital status reported in SVIG-TB database was the one prevailing and taken into consideration for the purpose of this study and selection of study subjects.

Our study is the first to highlight the most important predictors of death from tuberculosis in the Northern Region of Portugal, between 2008 and 2012. It also consolidates geographic-specific information and identifies patient's characteristics that relate to a higher risk of death.

Conclusion

Age, cancer and disseminated TB were predictors of death during TB treatment in our population. This highlights the need for special care in these patients, and increase awareness for TB particularly among oncologists.

Conflict of interests

The authors declare that there is no conflict of interest and that this research received no grant from any funding agency in the public, commercial or not-for-profit sectors.

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Author's contributions

Ana Cristina Franco Spínola and Raquel Duarte were involved in the data collection, validation, study design, statistical analysis, data and results analysis and paper writing and review. Mariana Campos and Ana Rita Gaio were involved in the statistical analysis. Ana Maria Correia and Marta Campos were involved in data collection and validation.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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