PREDICTORS OF MORTALITY IN PATIENTS WITH TUBERCULOSIS DISEASE: RESTROSPECTIVE STUDY

FATORES PREDITORES DE MORTALIDADE EM DOENTES COM TUBERCULOSE: ESTUDO RETROSPETIVO

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TABLE OF CONTENTS

ABSTRACT

Background: Tuberculosis is a human infectious disease caused by the pathogenic strains of *Mycobacterium Tuberculosis complex*. Although effective antibiotics are available it continues to be a major global health problem with considerable mortality. The risk factors for this outcome are not completely known. The human immunodeficiency virus (HIV) co-infection and the development of resistant strains to the actual treatment are pointed as important factors. The aim of this study is the evaluation of the significant predictors of mortality in tuberculosis patients.

Methods: We performed a retrospective observational study in a University Hospital in Portugal, during a three-year period (2011-2013). We included all patients with a coded diagnosis of tuberculosis from the Department of adult Pulmonary Medicine and Infectious Disease. Clinical variables and data of test results were collected trough the hospital patients' database and patients' electronic clinical files.

Results: A total of 90 patients were identified and 14 patients died during the follow-up. We found a total mortality of 14% at 12 months and 19% at 24 months of follow-up. Smoking, HIV, HIV with low CD4 count, anemia, high red cell distribution width (RDW) value, neurologic disease, clinical diagnosis and treatment side effects showed significance in the unadjusted analysis, but only anemia, HIV with low CD4 count and clinical diagnosis were significant ($p<0.05$) with upon adjustment for confounders.

Conclusion: The significant predictors of mortality in our population of TB patients were anemia, low CD4+ count in HIV patients and clinical diagnosis. These findings help to identify patient groups with high risk of mortality, needing a careful approach.

Keywords: Tuberculosis, mortality, predictors, HIV, low CD4+ number, clinical diagnosis, anemia

RESUMO

A Tuberculose é uma doença infeciosa causada pelas estirpes patogénicas do complexo *Mycobacterium Tuberculosis*. Apesar da existência de tratamento antibiótico eficaz continua a ser um problema de saúde major à escala global, com uma mortalidade considerável. Os fatores de risco para a sua mortalidade não são completamente conhecidos. A coinfecção com o vírus da imunodeficiência humana (VIH) e o desenvolvimento de estirpes resistentes ao tratamento atual são apontados como fatores importantes. O objetivo deste estudo é a avaliação de fatores preditores de mortalidade em doentes com tuberculose.

Métodos: Foi realizado um estudo retrospetivo observacional, num Hospital Universitário em Portugal, durante um período de estudo de 3 anos (2011-2013). Foram incluídos todos os doentes com diagnóstico codificado de tuberculose, internados no Serviço de Pneumologia e Infeciologia. As variáveis clínicas e os resultados dos testes realizados foram recolhidos através da base de dados do hospital e do processo clínico electrónico do doente.

Resultados: Um total de 90 doentes com diagnóstico codificado de tuberculose foram identificados, tendo 14 falecido no período de seguimento. Encontrámos uma mortalidade global de 14% aos 12 meses e 19% aos 24 meses. O tabagismo, VIH, VIH com contagem baixa de CD4, anemia, coeficiente de variação eritrocitário (RDW) alto, doença neurológica, diagnóstico clínico e efeitos adversos ao tratamento demonstraram significância no estudo não ajustado, mas apenas a anemia, o VIH com contagem de CD4

baixa e o diagnóstico clínico foram significativos ($p<0.05$) após ajuste para os confundidores.

Conclusão: Concluímos que os preditores significativos de mortalidade em tuberculose, no nosso estudo, foram anemia, contagem de CD4 baixa em doentes VIH positivos e diagnóstico clínico. Estes achados ajudam a identificar grupos de doentes com elevado risco de mortalidade que necessitam de uma abordagem mais cuidada.

Palavras chave: Tuberculose, mortalidade, preditores, VIH, baixa contagem de CD4, diagnóstico clínico, anemia

INTRODUCTION

Tuberculosis (TB) is the human infectious disease caused by the pathogenic strains of *Mycobacterium tuberculosis complex* (MBT). The disease affects mostly the lungs (pulmonary TB) but every organ can be affected (extra-pulmonary TB). It's estimated that one third of world's population is infected with Mycobacterium tuberculosis and only a minority of them will develop active disease (10%). An early progression is considered when active disease is developed during the first year of infection (*primary tuberculosis*). This type of response is uncommon (5% of all cases), but more frequent among immunocompromised individuals and children. [1, 2] Most of those infected develop a latent TB infection (LTBI), remaining asymptomatic during long periods of time. The majority of LTBI cases will not develop active disease in a lifetime, however a small part of them show late disease progression with development of active disease after decades (*postprimary* or *TB reactivation*). This risk of conversion to active disease is increased when a patient is immunocompromised. TB affects usually more men than women and typically in the productive age groups. [1, 2]

The cause of TB was identified by Robert Koch in 1882 and effective antibiotics have been available for decades now. However the disease remains a major global health problem, affecting millions of people worldwide (9.0 million estimated in 2013). [1] Although TB is primarily associated with poverty and developing countries, it is a significant concern in Europe, especially among vulnerable groups. Portugal has an intermediate incidence rate (21.1/100.000 in 2013), higher than the European Union (EU)/ European Economic Area (EEA) average (13.5/100.000 in 2012).[3, 4] Most of the

reported cases in Portugal come from urban areas and the typical patient is a drug user, alcoholic, migrant, homeless and/or prisoner.[4]

The co-infection with the immunodeficiency virus (HIV) and the emergence of multidrug-resistant (MDR, drug-resistance to isoniazid and rifampicin) and extensively drug-resistant (XDR, drug-resistance to isoniazid and rifampicin, a fluoroquinolone and one injectable drug) strains of *Mycobacterium tuberculosis* are the main current challenges to disease control.[1, 5, 6] Globally in 2013, an estimated 13% of all TB cases were HIV-positive (1.1 millions). [1] Portugal has one of the highest prevalence rates of co-infection in the European Region (ER) – 14.5% versus an average of 8% in 2013, and the HIV-test coverage in TB patients has been decreasing (76.67% in 2013 vs 85% in 2010). [1, 3, 4]

Although the mortality rate from tuberculosis has been diminishing (45% since 1990), this is still the second worldwide leading cause of death from an infectious disease. In 2013, 1.5 million people died from TB, including 360.000 HIV-positive (25% of all TB deaths). These numbers are unacceptable given that most TB deaths are preventable. [1] The risk factors for this outcome are not completely known. The co-infection with HIV and resistant strains (MDR-TB and XDR-TB) have been well described.[1, 7] In HIV patients, the $CD4^+$ lymphocyte count was an important predictor, underlining the importance of the immune system function. [8-10] Advancing age, male gender, alcohol and/or drug abuse, smoking and comorbidities (including malignancy, chronic obstructive pulmonary disease |COPD|, diabetes, liver cirrhosis, anemia, neurologic disease and renal disease) were also identified in previous studies [7, 11-13]. Clinical and delayed diagnosis, disease severity, treatment side effects, extra-pulmonary

TB and previous TB or treatment were also found to be important.[1, 13] Recently, the red blood cell distribution width (RDW) emerged as a possible important signal of TB severity.[14] Some studies however, suggest that most of TB deaths are due to non-TB related causes. [12]

A better understanding of the determinants/risk factors to TB mortality could help in its prevention through aggressive identification and treating high risk individuals. Another clear benefit would be improved allocation of public health resources. [7]

The aim of this study is the evaluation of the significant predictors of mortality in tuberculosis patients.

METHODS

Study design and oversight

We conducted a retrospective observational study in a University Hospital in Portugal. The study was approved by the Medical School Scientific Board, and the requirement for informed consent was waived due to the retrospective nature of the study.

Study patients

The study included all patients with a coded diagnosis of tuberculosis from the Departments of adult Pulmonary Medicine and Infectious Diseases during a three year period (2011-2013). The patients were identified through a search of the hospital patient's database. This database contains clinical data from all patients treated at this center, including the primary diagnosis, all the coded secondary diagnosis and the main performed tests for each patient.

Data collection

The relevant variables were collected from the hospital patients' database and the patients' electronic clinical files. Clinical variables included epidemiological characteristics (sex, age and job), habits (drug, alcohol abuse and smoking), comorbidities, previous TB diagnosis and treatment, organ involvement and duration of symptoms before diagnosis. Smoking, alcohol and drug abuse were considered if they were present at TB diagnosis. Late diagnosis was considered when achieved more than 30 days after admission. The patients' comorbidities were organized in different groups, including hepatic disease, history of malignancy, renal disease, neurologic disease, HIV infection and anemia. TB type was organized in two groups: pulmonary and extra-

pulmonary TB. Severe disease was considered when central nervous system or miliary forms occurred.

The data on the test results (at time of diagnosis) included the method of diagnosis (culture or pathology vs clinical probability) and results of drug susceptibility testing (DST), anemia, RDW value, HIV status and blood CD4+ count (for HIV positive patients). Anemia was considered when hemoglobin value was inferior to 11 g/dl and RDW alterations when the RDW value was above 14.0%. Low number of CD4+ cells was considered less than 500 cells/mm^3. DST results were separated as sensible, resistant (any resistance), MDR and XDR. Clinical diagnosis was attributed when no confirmation (laboratorial/pathological anatomy) of tuberculosis infection was found but treatment was started, due to clinical and/or radiological indicators. The data on treatment and evolution included the number of admissions, complications and side effects. The date of last contact with the Health System (until July 28, 2014) or the date and cause of death (when available) were recorded for the survival analysis.

Statistical Analysis

The statistical analysis was performed using the STATA software package version 13.1 (StataCorp, USA). The continuous variables were characterized using measures of central tendency (mean) and distribution (standard deviation), and the categorical variables were characterized using proportions. The differences in quantitative variables between two groups were tested with Students t test for independent variables or Wilcoxon rank-sum test, according to normality, as tested by Shapiro Wilk. The relationships between categorical variables were tested using chi-square. A p-value under 0.05 was considered statistically significant.

For the survival analysis, the estimated median survival at 12 and 24 months was calculated over full data. A univariate analysis was carried on using Log-Rank for sex, young age (under 50 years), alcohol abuse, drug abuse, smoking, DST results, extra-pulmonary TB, prior TB, clinical diagnosis, severe disease, late diagnosis, treatment side effects, anemia, high RDW, hepatic disease, history of malignancy, neurologic disease, renal disease, HIV status and in HIV group, low CD4+ count. For the multifactorial analysis, the factors achieving a 0.2 significance level in the Log-Rank test were used to construct an initial Cox Proportional Hazard Model. A step-down procedure was then used to select the significant predictors at a 0.05 level.

RESULTS

During the study period, a total 90 TB patients were recorded, including 62 (69%) males and 28 (31%) females. The patients' epidemiological and clinical data are detailed in table 1. The mean age was 52.5 ± 17.9 years (range: 20 to 88), with no significant differences between genders (53.2 for females and 52.2 to males, $p>0.05$, t test). Most cases had pulmonary forms of TB (74; 82%), and no previous TB history (83; 92%). Alcohol abuse was present in 6 (7%) patients, smoking in 17 (19%) and drug abuse in 4 (4%) (Figure 1).

Table 1: Patients' Epidemiological and Clinical Characteristics

Variable	Global (n=90), n (%)
Gender	62M (69)/28F (31)
Age	
mean (years)	52.5±17.9
range (years)	20-88
Alcohol abuse	6 (7)
Smoking	17 (19)
Drug abuse	4 (4)
Extra-pulmonary TB	16 (18)
Clinical diagnosis	11 (12)
Previous TB	7 (8)
Hepatic disease	14 (16)
History of malignancy	12 (14)
Renal disease	5 (5)
Neurologic disease	6 (6)
Anemia	29 (32)
HIV	20 (22)
Gender	17M (85)/ 3F (15)
Age	
mean (years)	44.3±10.6
range (years)	30-77
CD4+ count	18
mean (cells/mm^3)	200.8±212.5
range (cells/mm^3)	1- 629
< 500 cells/mm^3	14 (70)

* Values are expressed as mean ± standard deviation.
TB, tuberculosis, HIV, human immunodeficiency virus.

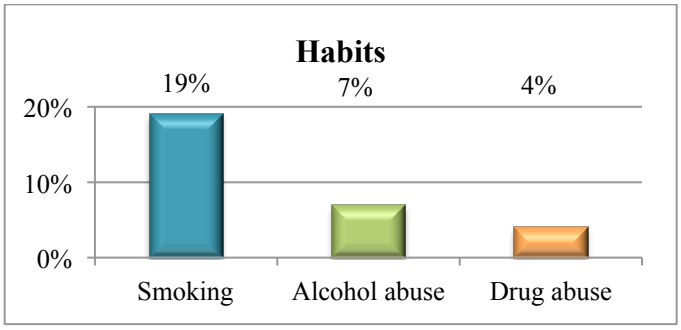

Figure 1: Patients' habits

Considering comorbidities, hepatic disease was found in 14 (16%) patients, neurologic disease in 6 (7%) and renal disease in 5 (6%). History of malignancy was present in 12 (13%) patients, anemia in 29 (32%) and HIV infection in 20 (22%). (Figure 2).

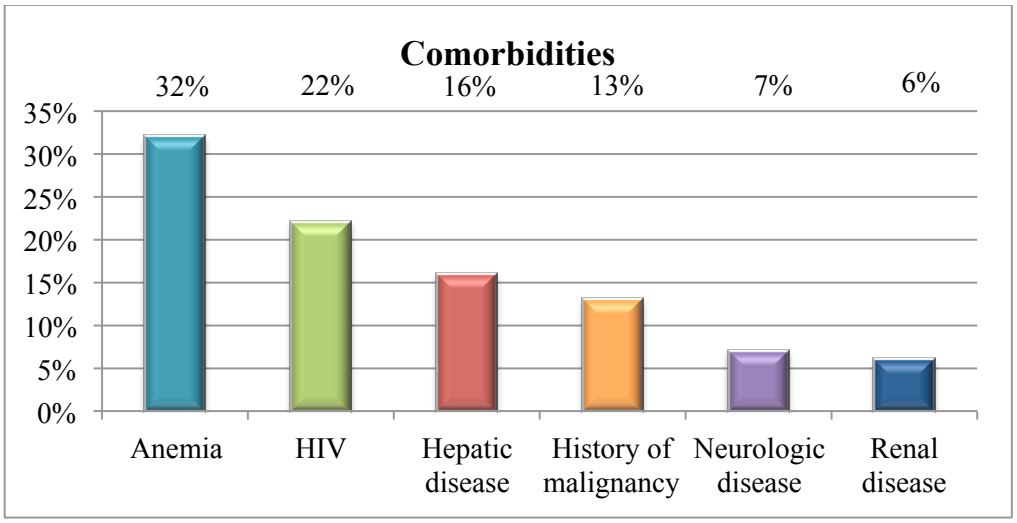

Figure 2: Patients' comorbidities

Eleven patients (12%) were treated after presumptive clinical diagnosis, four with extra-pulmonary and seven with pulmonary TB, versus 79 (88%) that had laboratory confirmation of TB.

Regarding the HIV group the mean age was 44.3 ± 10.6 years, significantly different from the non-HIV group 54.8 ± 18.9 years ($p<0.05$, t test) (Table 2.) There were no significant differences in gender distribution between the HIV and non-HIV group

(p=0.078, chi-square). The mean CD4+ count was 200.8 ± 212.5 (range: 1 to 629), and 14 patients (70%) had a count below 500 cells/mm^3.

Table 2: Comparison between age in HIV and non-HIV group

Group	n	Mean	St. Dev.	p-value*
HIV +	20	44.3	10.57	0.0189
HIV-	70	54.84	18.84	

*The p-value was obtained from a Student t test.
HIV, human immunodeficiency vírus, St. Dev, standard deviation.

Considering mortality, a total of 14 patients (3 females and 11 males) died during a median follow-up of 15.9 months. The estimated survival for the whole population was 86.0% (95% CI: 76.12 to 92.05%) at 12 months and 81.1% (95% CI: 69.92 to 88.43%) at 24 months. For the HIV patients, estimated survival was 84.1% (95% CI: 58.3 to 94.6) at 12 months and 61.2% (95% CI: 32.1 to 80.9) at 24 months. For non-HIV patients, estimated survival was 86.4% (95% CI: 75.3 to 92.7) at both 12 and 24 months.

The results from the univariate (Log-Rank) and multivariate (Cox Proportional Hazards) mortality analysis are detailed in table 3. Upon building a Cox Proportional Hazards model the significant predictors were anemia, HIV with low CD4 count and a clinical diagnosis. Survival curves, built from the unadjusted analysis, for the whole population, for anemia, low number of CD4 count in HIV patients and for diagnosis form are shown in the figures 3, 4, 5 and 6, respectively.

Table 3: Tuberculosis Mortality Predictors analysis

Unadjusted analysis*

Variable	p-value
Gender	0.4587
Young	0.2307
Alcohol abuse	0.3670
Drug abuse	0.6809
Smoking	**0.1030**
TB type	0.9476
Severe	0.9004
Clinical Diagnosis	**0.0589**
Previous TB	0.7902
HIV	**0.0909**
Hepatic Disease	0.6345
History of malignancy	0.3249
Renal Disease	0.2881
Anemia	**0.0001**
RDW alterations	**0.0198**
Neurologic disease	**0.033**
DST	0.4996
Late Diagnosis	0.3084
Low CD4	**0.0526**
Side effects	**0.0694**

Adjusted Analysis**

Variable	p-value
Clinical Diagnosis	0.037
Anemia	0.000
Low CD4	0.030

* Unadjusted results are not adjusted for any confounders. The p-value was obtained from a univariate mortality analysis using Log-Rank Test.

** Adjusted results are mutually adjusted for all variables in the table. The p-value was obtained from a multivariate mortality analysis using Cox proportional hazards model.

TB, tuberculosis, HIV, human immunodeficiency virus, RDW, red blood cell distribution width, DST, drug susceptibility testing

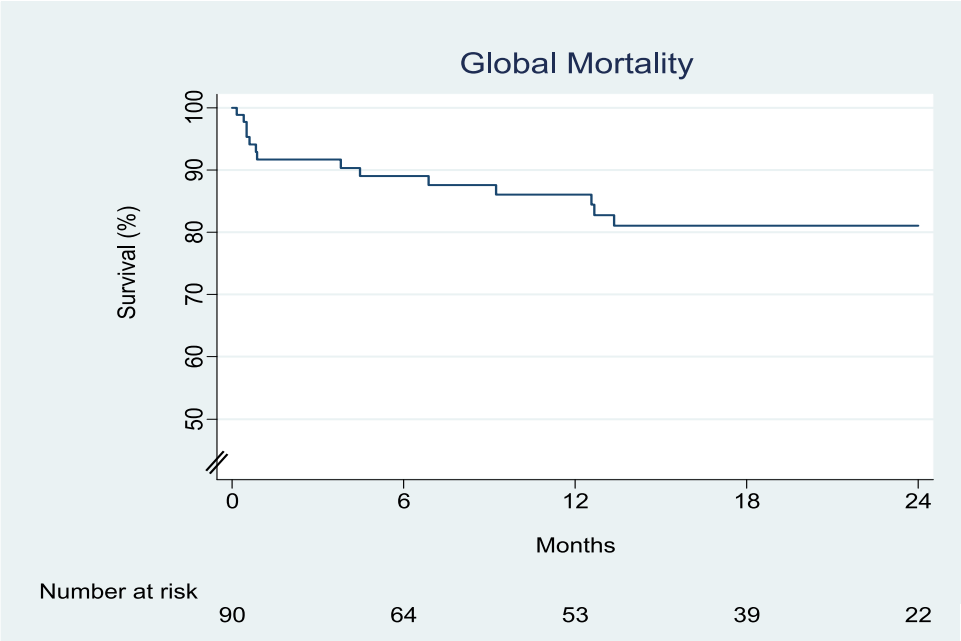

Figure 3: Survival curve for whole TB cases. (y-axis starts at 50% for visual effects).

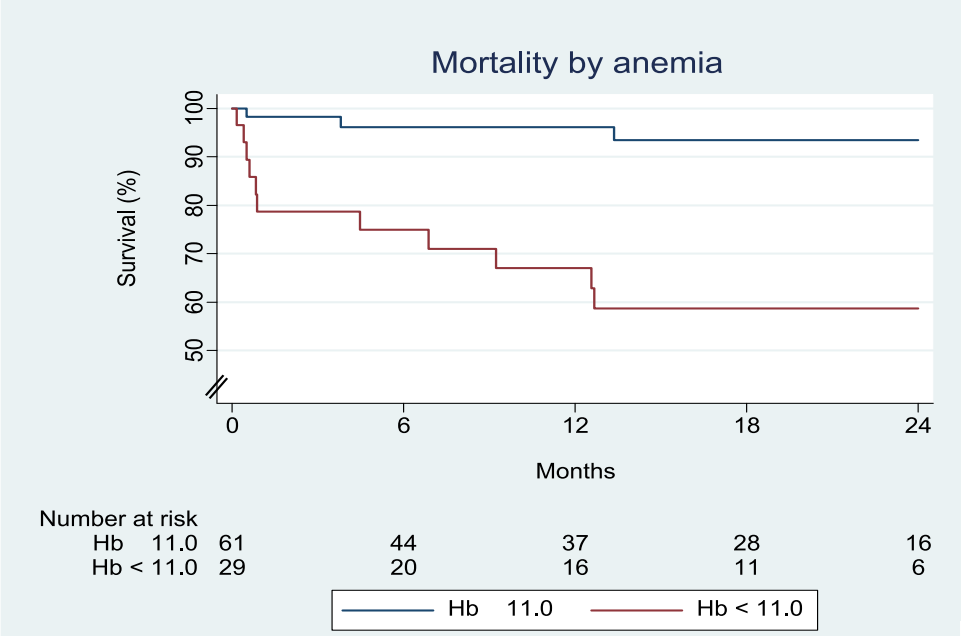

Figure 4: Survival curves for patients with and without anemia. (y-axis starts at 50% for visual effects).

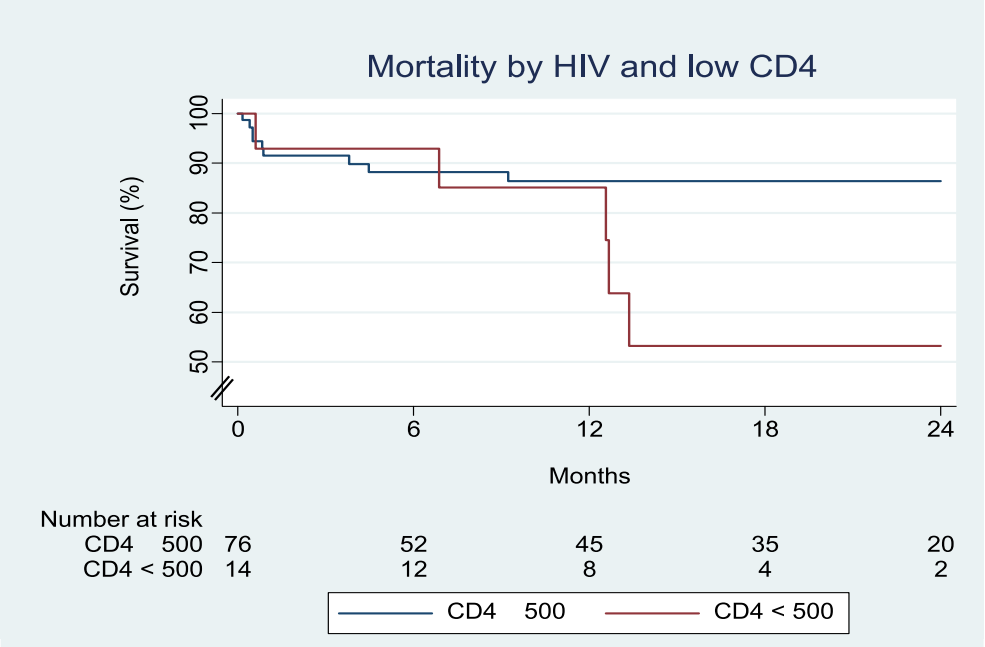

Figure 5: Survival curves for HIV patients with and without low number of CD4 count. (y-axis starts at 50% for visual effects).

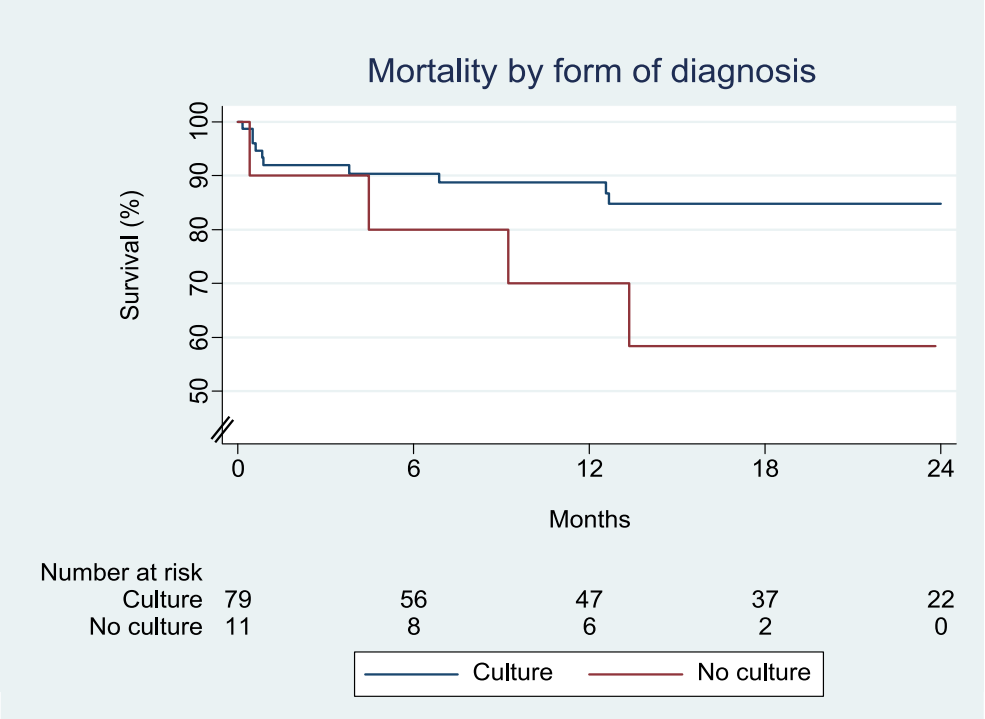

Figure 6: Survival curves for patients with or without diagnosis by culture or pathology. (y-axis starts at 50% for visual effects).

DISCUSSION

We evaluated a hospital based Portuguese cohort of tuberculosis patients and found that anemia, HIV with low CD4 count and a clinical diagnosis were significant mortality predictors. Smoking, high RDW value, neurologic disease and treatment side effects showed significance in the univariate analysis, but did not hold upon adjustment for confounders.

We found a total mortality of 14% at 12 months and 19% at 24 months, which is higher than reported for Portugal. This mortality may be due to the hospital base of this cohort, since hospitals tend to care for more severe patients. A high number of HIV patients were also included, possibly explaining higher mortality.

Anemia was present in 32% of our TB patients, similar to previous studies (32%-94%).[15, 16] One possible explanation is the condition called anemia of chronic diseases, due to the chronic status of TB and HIV infections. In addition, co-infected patients (TB and HIV) tend to have lower haemoglobin levels than those with only one condition. [17] Iron-deficiency may also be a cause. The presence of anemia at the time of TB diagnosis, has been related with higher mortality. [15] This risk is higher when other conditions like poor health status, nutritional deficiencies/malnutrition, iron deficiency or severe disease are also present. [15, 17] Patients with anemia are also at higher risk for TB infection, recurrence and progression, HIV disease progression and poor clinical outcomes. [15, 17]

HIV, and especially HIV with low CD4+ count is associated with severe immune suppression, higher probability of TB disease and reactivation of LTBI. These patients frequently display disseminated primary and extra-pulmonary TB and have an increased

mortality from the disease. In fact, tuberculosis is the leading cause of death in HIV patients.[1, 9] The CD4+ T cells have an important role in immunity against tuberculosis. Their functions in active TB include the maintenance of the granulomas' organization, with enclosure of mycobacteria and producing INF-y, which is important for macrophage activation and infection control. When CD4+ T cells are compromised a deficient containment occurs. [18, 19] In addition the diagnosis of TB becomes more challenging due to the disease's atypical presentations. An increased risk of drug interactions (antiretroviral therapy and anti-TB drugs), overlapping toxicity and the immune reconstitution inflammatory syndrome hinders our capacity for disease control, underpinning the higher risk of death. [8]

Eleven patients from this cohort were treated after presumptive clinical diagnosis, four with extra-pulmonary and seven with pulmonary TB. While this may be useful in severe disease requiring prompt and aggressive treatment and lead to disease control and cure in a number of patients, others may be harmed by such strategy. Importantly, severe disease usually occurs in debilitated patients with a higher risk of death or severe consequences from inadequate treatment. The World Health Organization (WHO) recommends that treatment may be initiated in cases of smear-negative pulmonary tuberculosis after two negative sputum smears are collected, chest x-ray findings are consistent and the patient has not responded to a trial of broad-spectrum antibiotics. In very-ill patients or patients with proven or suspected HIV, if there is a strong clinical suspicion, anti-TB treatment may be started.[20] In our study, the lack of a smear, culture, or tissue consistent with tuberculosis was associated with a worse prognosis. This is probably associated with increased severity in these patients, although inadequate

treatment cannot be excluded. These results underline the need for careful clinical evaluation of a patient before the start of anti-TB treatment in the absence of microbiological proof of infection.

Approximating 20% of the worldwide population smokes tobacco. An increased number of alveolar macrophages has been found in smokers, but they have an impaired function, reducing their immune response to MBT.[21] Smoking has been associated with a higher risk for TB infection, progression of LTBI to active disease, relapses, poor treatment outcomes and higher risk of death. Measures to avoid and control smoking are important to reduce TB mortality and reach the other targets of TB control.[11, 21]

The RDW is part of laboratorial blood routine analysis, measuring the variation of red blood cell volume and is an important tool in the evaluation of anemia. Recent studies have shown that RDW elevation is related to the prognosis of several diseases (congestive heart failure, acute myocardial infection, pulmonary embolism, pneumonia, COPD, obstructive sleep apnea syndrome and sepsis). The cause of RDW elevation isn't known but some studies point to the inflammatory status as the main reason. Severe pulmonary TB had been associated with higher levels of RDW, when compared to mild and moderate cases.[14]

Adverse reactions to TB treatment are common even with first-line anti-tuberculosis drugs, leading to patient morbidity and even mortality. When a severe adverse reaction is recognized, the responsible drug must be stopped and switched to second-line drugs. Second-line drugs are associated with lower effectiveness, more side effects and longer treatment which decreases adherence and increases treatment failures,

relapses of infection and hospitalizations. Mortality is especially important with drug-induced hepatitis. [22]

Neurological disorders, either acute or chronic, have an increased risk of pulmonary infections development.[23] Muscle weakness (more frequent in neuromuscular disorders), loss of mobility, disability in airway protection with deficiency in secretions' clearance and more need of intubation can possible justify this higher risk.[23] Excluding the genetic neurologic diseases, neurological disorders, like dementia or stroke, are more frequent in advanced age, leading to a higher risk of infection and mortality due to impaired immune function and comorbidities.

Our data showed that TB was more common among men than women, was more prevalent in the economically productive ages groups and HIV patients had TB earlier when compared to non-HIV patients, what is in accordance with other studies.[1] Generally most of TB deaths occur among men, as in this study, but recent reports from the WHO show that deaths in women are rising. [1]

Advancing age is considered one of the strongest independent risk factors to TB death. Late diagnosis, delayed treatment, reduced immune response, frequent underlying comorbidities and higher risk of developing adverse drug effects are possible explanations. [7, 12, 24] MDR is also a strong independent risk factor due to the use of less efficiency drugs, longer treatment, higher risk of adverse drug reactions and treatment failure. [7] Male gender, alcohol and/or drug abuse and some comorbidities (malignancy, COPD, diabetes, renal failure, liver cirrhosis) were relevant in other studies. [7, 12] However we did not find this in our study. The sample size and the observed low frequency of these comorbidities and MDR forms in our population are probable

explanations. Our study did not show late diagnosis and consequent delayed treatment to be important factors to mortality. However a quick diagnosis and treatment remains an important factor for success in TB treatment. [12]

This study has some limitations. As a retrospective study, the data is dependent on the quality of the clinical recordings. For most subjects, only the culture collection date and not the results date were available, changing the data on the time of diagnosis. Finally, this study did not include an analysis of the cause of death, and part of the recorded mortality may have been unrelated to TB.

In conclusion, we analysed the mortality from a Portuguese hospital-based cohort of tuberculosis patients and found that the significant predictors of mortality after adjustment were the level of haemoglobin, a low CD4 count in HIV patients and treatment administration without confirmation of TB infection. Although these findings are limited by the retrospective nature of the study and the sample size, they help to identify patient groups with high mortality, needing a careful approach. This could also help in an improved allocation of TB resources. Smoking prevention campaigns and a better HIV test coverage for TB patients are needed for achieving the Millennium Development Goal (MDG) and Stop TB Partnership targets.

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