Risk factors associated with death in patients who initiate treatment for tuberculosis after two different follow-up periods

Fatores de risco associados com o óbito em pacientes que iniciam o tratamento para a tuberculose após dois diferentes períodos de seguimento

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Abstract

Introduction: Mortality from tuberculosis, which should be a rare event, still affects a large portion of the population of developing countries. In this context, Recife, a city in the northeast of Brazil where this study was developed, has the highest tuberculosis mortality rates of the Brazilian capitals. **Objective**: To analyze survival probability and identify risk factors for death from tuberculosis in a cohort of patients living in Recife who started treatment for tuberculosis. **Methodology**: A cohort of newly diagnosed TB cases was followed up from the beginning of treatment (in 2001-2003) until June 2007. Survival probability was estimated by Kaplan-Meier method; and Cox Regression analysis was used to identify risk factors. **Results**: At the end of the follow-up period, the survival probability after beginning TB treatment was 95.9%. Older ages, positivity for HIV and late initial treatment were statistically associated with death from TB in one year follow-up. When the analysis was done considering the total period of follow-up, older ages, positivity serology for HIV, late initial treatment, weight loss, and history of previous treatment remained in the multivariate Cox regression model. **Conclusion**: A more comprehensive analysis, specifically for deaths from tuberculosis as the underlying and non-underlying cause, allowed identification of a greater number of predictive factors that would otherwise not be detected if follow-up had lasted only until the end of treatment. These results can guide feasible interventions for health services aiming to reduce case-fatality from tuberculosis.

Keywords: Tuberculosis. Death. Cohort study. Survival analysis.

Resumo

Introdução: A mortalidade por tuberculose, que deveria ser um evento raro, ainda acomete uma grande parcela da população dos países em desenvolvimento. Nesse contexto, Recife, situada no Nordeste do Brasil, tem uma das mais altas taxas de mortalidade das capitais brasileiras. **Objetivo:** Analisar a probabilidade de sobrevida e identificar os fatores de risco para o óbito por tuberculose numa coorte de pacientes que iniciaram o tratamento na cidade do Recife. **Metodologia**: Uma coorte de pacientes com tuberculose recém-diagnosticada foi acompanhada a partir do início do tratamento (2001-2003) até junho de 2007. A probabilidade de sobrevida foi calculada através do Kaplan-Meier e realizou-se a análise de regressão de Cox para a identificação dos fatores de risco para o óbito. **Resultados**: A probabilidade de sobrevida após o início do tratamento ao final do período de seguimento foi de 95,9%. Idade mais avançada, sorologia positiva para HIV e demora em iniciar o tratamento estiveram estatisticamente associadas com o óbito por tuberculose em um ano de acompanhamento. Quando a análise foi realizada considerando o tempo total de acompanhamento, além das variáveis anteriores, encontramos também perda de peso no inicio do tratamento e história de tratamento prévio. **Conclusão**: A análise com maior período de seguimento e mais específica para mortes por tuberculose possibilitou a identificação de um maior número de fatores de risco, que não seriam detectados caso o seguimento tivesse ocorrido apenas até a alta do tratamento. Esses resultados podem guiar intervenções factíveis para os serviços de saúde visando reduzir a mortalidade por tuberculose.

Palavras-chave: Tuberculose. Óbito. Coorte. Análise de sobrevida.

Introduction

Tuberculosis (TB) is one of the most important causes of death worldwide, with estimated 1.7 million deaths due to TB in 2006. The burden of the disease is higher in 22 developing countries, among which Brazil holds 16th position[1]. Even in regions where Directly Observed Therapy strategy (DOTS) is implemented, mortality rates are high after discharge from TB treatment[2].

One of the commitments made by countries members of the United Nations at the Millennium Assembly (and reaffirmed by the Stop TB initiative) is the goal of reducing by half the prevalence of tuberculosis and mortality rates from tuberculosis by 2015, taking as reference 1990's rates[1].

In Brazil, in spite of marked improvement of some epidemiological tuberculosis control indicators[3], TB remains a major challenge for health services and for society[4]. The number of deaths due to tuberculosis is still considerable, especially among individuals living with AIDS[3]. In 2006, the country reported a mortality rate from all forms of tuberculosis of 4.0/100,000 inhabitants[1]. However, Bierrenbach and colleagues[5] describe a consistent reduction in mortality rates from tuberculosis, as the underlying and non-underlying cause, between 1980 and 2004. In the same paper, Recife, where the study reported here is located, appears as the Brazilian state capital with the highest tuberculosis mortality rate: 9.1/100,000 inhabitants.

Mortality due to tuberculosis in cohorts of patients during or after the end of treatment has been shown to increase with age[6-10], male sex[7,8], late initial treatment[10], smoking[11-13], cases of mixed pulmonary and extra-pulmonary forms[6,7], resistance to drugs[2,14], co-infection with HIV/AIDS[7], and low family income[10].

However, the diversity of methodologies used for analysis precludes the possibility of comparing the risk factors found. Some studies have analyzed the death from any cause during the course of treatment for tuberculosis, while others followed patients

after discharge. Besides, "death during the course of treatment" is a limited indicator of tuberculosis mortality[15]. In treatment cohorts only a small subset of all estimated TB deaths is registered, as well as deaths due to cases never diagnosed or never treated. Some deaths occur after the end of treatment; others, although recorded during treatment, are not due to TB[16]. Moreover, in studies based on death certificates or on results from autopsies, dealing with tuberculosis when it is not the underlying (primary) cause is a problem too. Recent studies that considered tuberculosis as an associated cause and not just as the main cause reported a considerable increase in the mortality rate[17,18].

Another issue that hinders the comparability of studies is the fact the majority analyze risk factors with information on exposures collected after death in retrospective study designs (which may be incomplete) or from secondary data, and therefore limited to study exposures which were adequately collected in regular information systems.

Also, information is lacking on risk factors for death at different periods after completion of treatment in patients who underwent treatment for tuberculosis. As the path from illness to death is complex, it is reasonable to expect different risk factors according to the length of time during and after treatment.

The purpose of this paper is to estimate the survival probability and associated risk factors for deaths related to tuberculosis either as main or associated cause in a cohort of patients who started tuberculosis treatment at primary health care units. To examine potentially different risk factors, we considered two follow-up periods: one year and at the end of follow-up study (six and a half years). The results could contribute to identify opportunities for public health intervention with the potential to reduce mortality from TB.

Methods

The location of the study, Recife, is a city in the northeast of Brazil with 1,515,050 inhabitants. The city comprises 94 districts divided into six political-administrative regions, called Health Districts (DS)[19]. The tuberculosis control program has been decentralized as of 2000, with gradual transfer of activities from reference centers to primary health care units as part of the Family Health Program (FHP)[20].

The study population consisted of a cohort of individuals residing in Recife who began treatment for tuberculosis (new patients and patients with history of previous treatment) during the period from May 2001 to July 2003 at primary health care units. Patients were invited to participate in the study after being diagnosed with tuberculosis. Those who agreed to participate signed a consent form, were interviewed by trained professionals using a standard questionnaire, and had sputum and blood collected for analysis.

Data on deaths was obtained through systematic search in the Mortality Information System (SIM/MS) for the period from 1st May 2001 (the first day of the study) until the end of patient follow-up on 30th June 2007. SIM/MS is a national and sub-national electronic system with all routine mortality data coded to International Coding Disease (ICD). Registration of deaths is managed by the Ministry of Health (MS) in Brazil. Three patients were excluded because they did not have a record of being treated in the Disease Notification System (SINAN). SINAN/MS is an electronic system with notifications of infectious diseases managed by the Ministry of Health (MS) in Brazil.

Information on risk factors was obtained from a standardized questionnaire applied when patients started treatment. Risk factors studied included sex and clinical factors: late initial treatment, defined as time elapsed since the onset of symptoms to initiation of treatment (the cut-off point of 60 days was adopted according to Santos et al.[21]), clinical form of TB (pulmonary or extra pulmonary), report of recent weight loss, HIV co-infection, positive bacteriological test (smear and/or culture), and history of previous treatment for tuberculosis. We also investigated the role

of the following socio-economic variables on time to death from tuberculosis: density of people living in the house of the patient, patient's employment status, illiteracy, alcohol use (does not drink, drinks socially, and excessive use of alcohol as drinks every day or after starting to drink has difficulty to stop) and smoking (defined as smokers, former smokers or non-smokers) and variables related to the health service: number of health units visited because of symptoms before starting treatment, and visits from staff of the Family Health Program (FHP). The place of residence of the patient in relation to the Health Unit where treatment was delivered: in the same Health District and in the same neighborhood.

Survival time was defined as the time in days from the beginning of treatment to death from tuberculosis as the main or associated cause. Censoring occurred either at the end of the study or death from other causes. Kaplan-Meier method and log rank test were used to estimate survival probability and statistical significance for categorical covariates. Two periods of time were considered for analysis: at one year and at the end of follow up.

Cox proportional hazards model was applied to estimate the effect of risk factors. Variables selected in the univariate analysis ($p < 0.25$) and those considered clinically relevant were included in a multivariate model. The assumption of proportional of hazards was checked using Shoenfeld residuals.

Results were reported using hazard ratios (HR) and corresponding 95% confidence interval (CI). A two-tailed $p < 0.05$ was considered statistically significant. All models were fitted using the statistical package R version 2.9[22] and library survival[23].

Results

During the period from May 2001 to July 2003, a total of 1,459 patients started tuberculosis treatment. Among them, 165 (11.3%) deaths were registered between May 2001 and 30th June 2007, 54 (3.7%) due to tuberculosis as the underlying or associated cause.

The mean follow-up time was 1,753.7 days (range 4 – 2,371). Among the total deaths from tuberculosis, 42.6% occurred during the first year of follow up. The cumulative risk of death from tuberculosis (basic or associated cause) by the end of the study was 4.1% (95%CI: 3.0-5.3). The frequency of death from tuberculosis was similar between those who have left treatment (3.8%) and those who did not quit (3.7%).

Among the 54 deaths reported by SIM, only 30 deaths had records in SINAN (TB surveillance system) during the study period (from May 2001 to June 2007). The other 24 deaths (19 from tuberculosis as the underlying cause and 05 from tuberculosis as the non-underlying cause) were recorded in SINAN with other outcomes: cure (13), abandonment (8), and patients transferred to other services (3).

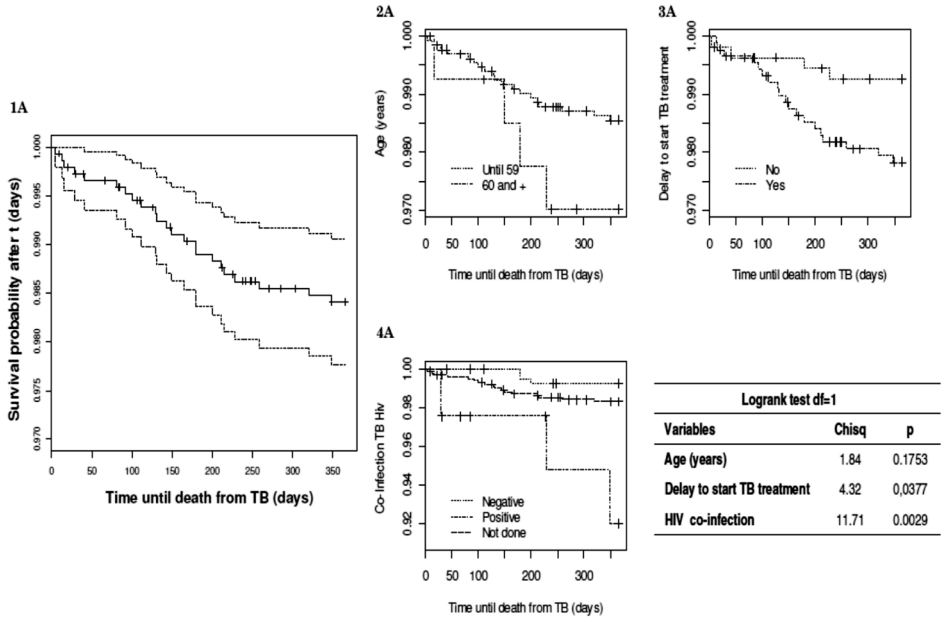
Time until death due to tuberculosis ranged from four days to 1,966 days. The case-fatality from tuberculosis rate on cohort was 7.7/1000 person-years. The probability of survival after TB treatment at the end of follow up was 95.9% (95%CI: 94.8 – 97.0) (Figure 2).

Table 1 displays the results of the univariate analysis for risk factors for death from tuberculosis in cases studied at two different periods after the beginning of treatment. Table 2 shows the final multivariate Cox model considering different time spans. The variables age, late treatment, and HIV serology remained in the two final models. At one year of follow up, weight loss (HR 2.77 $p = 0.06$) was border line significant, while previous treatment for tuberculosis (HR 1.30; $p = 0.58$) presented no effect.

Considering survival until the end of the study (six and a half years), the following variables were kept in Cox multivariate model: age, HIV serology, late initial treatment, weight loss, and previous treatment for tuberculosis.

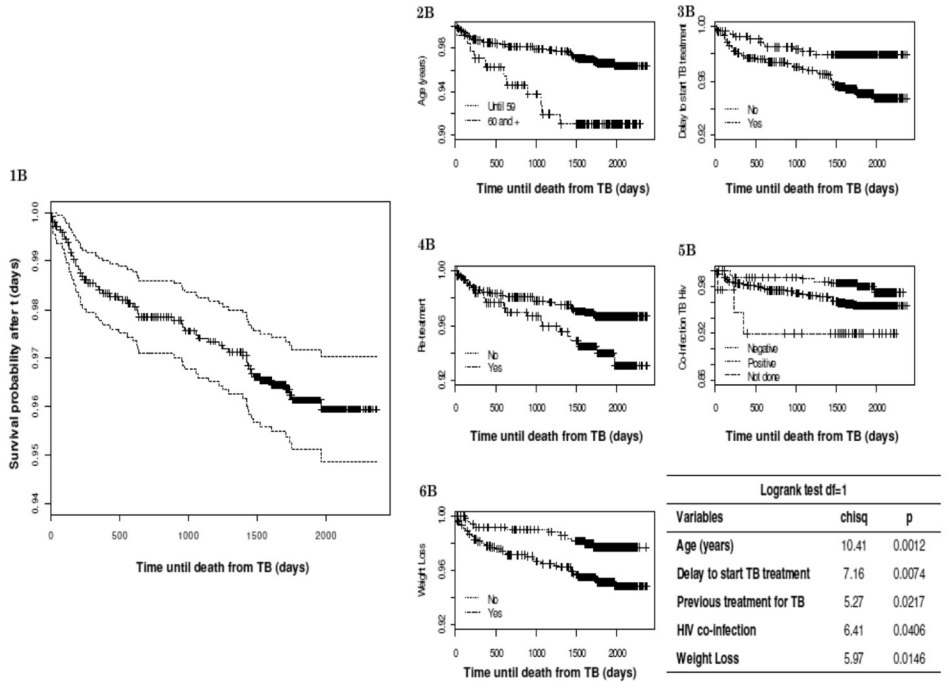
Discussion

At the end of the follow-up period, the probability of survival after beginning tre-



Logrank test df=1		
Variables	**Chisq**	**p**
Age (years)	1.84	0.1753
Delay to start TB treatment	4.32	0,0377
HIV co-infection	11.71	0.0029

Figure 1 – Kaplan Meier estimate for survival probability and Logrank test, global with 95% CI and stratified for age, late initial TB treatment and HIV co-infection for 1 year of follow-up.
Figura 1 *– Estimativa da probabilidade de sobrevida por Kaplan Meier e teste de Logrank, global com IC95% e estratificado por idade, atraso no início do tratamento para TB e co-infecção por HIV após um ano de seguimento.*



Logrank test df=1		
Variables	**chisq**	**p**
Age (years)	10.41	0.0012
Delay to start TB treatment	7.16	0.0074
Previous treatment for TB	5.27	0.0217
HIV co-infection	6.41	0.0406
Weight Loss	5.97	0.0146

Figure 2 – Kaplan Meier estimate for survival probability and Logrank test, global with 95% CI and stratified for age, previous treatment for TB, late initial TB treatment, HIV co-infection and weight loss for total time of follow up.
Figura 2 *– Estimativa da probabilidade de sobrevida por Kaplan Meier e teste de Logrank, global com IC95% e estratificado por idade, tratamento anterior para TB, atraso no início do tratamento para TB, co-infecção por HIV e perda de peso no tempo total de seguimento.*

Table 1 - Univariate analysis of factors associated with death from tuberculosis - underlying and associated cause - during treatment and after discharge from tuberculosis treatment in tuberculosis (TB) patients treated in Recife, Pernambuco, Brazil, 2001-2007.

Tabela 1 *– Análise univariada dos fatores associados ao óbito por tuberculose - causa básica e causa associada - durante o tratamento e após a alta do tratamento para tuberculose (TB) em pacientes tratados em Recife, Pernambuco, Brasil, 2001-2007.*

	One year follow up		Untill the end of follow up (79 months)	
	HR (CI)	*p*	HR (CI)	*p*
Sex				
Female	1.0		1.0	
Male	1.27 (0.52 – 3.08)	**0.600**	1.35 (0.75 – 2.41)	**0.320**
Age (years)				
Continuous variable	1.03 (1.01 – 1.06)	**0.008**	1.04 (1.03 – 1.06)	**<0.001**
Cigarette smoking				
Never smoking or given up smoking	1.0		1.0	
Ever smoking	1.27 (0.49 – 3.21)	**0.620**	1.56 (0.87 – 2.79)	**0.140**
Alcohol consumption				
None or light drinker	1.0		1.0	
Heavy drinker	2.47 (0.91 – 6.7)	**0.075**	2.38 (1.22 – 4.65)	**0.011**
Literacy				
Yes	1.0		1.0	
No	1.31 (0.48 – 3.52)	**0.600**	1.86 (1.03 – 3.38)	**0.041**
Employment				
Yes	1.0		1.0	
No	0.94 (0.41 – 2.14)	**0.880**	1.15 (0.66 - 1.99)	**0.610**
Number of individuals per household				
1–4	1.0		1.0	
≥ 5	0.77 (0.32 – 1.83)	**0.550**	0.68 (0.38 – 1.21)	**0.190**
Previous treatment for tuberculosis				
No	1.0		1.0	
Yes	1.36 (0.56 – 3.32)	**0.490**	1.73 (0.98 – 3.02)	**0.055**
Weight loss				
No	1.0		1,0	
Yes	2.65 (0.9 – 7.78)	**0.077**	2.23 (1.15 – 4.33)	**0.0170**
HIV co-infection				
No	1.0		1.0	
Yes	10.8 (2.17 – 53.5)	**0.004**	4.47 (1.19 – 16.9)	**0.027**
Not known	2.23 (0.65 – 7.63)	**0.200**	2.14 (1.00 – 4.54)	**0.049**
Clinical form of tuberculosis				
Pulmonary	1.0		1.0	
Extra pulmonary	0.63 (0.15 – 2.70)	**0.540**	0.25 (0.06 – 1.03)	**0.056**
Late initial treatment				
≤ 60 days	1.0		1,0	
> 60 days	2.97(1.01-8.73)	**0,048**	2.41(1.24-4.67)	**0.009**
Bacteriology (acid-fast bacillus staining and/or mycobacterial culture)				
Negative	1.0		1.0	
At least one positive	0.71 (0.23 – 2.23)	**0.560**	0.96 (0.46 – 2.01)	**0.920**
Not done	0.96 (0.29 – 3.19)	**0.950**	0.57 (0.23 – 1.37)	**0.210**
Number of health units				
Only 1	1.0		1.0	
≥ 2	0.88 (0.35 – 2.25)	**0.800**	1.05 (0.55 – 2.0)	**0.880**
HS in neighborhood of residence				
Yes	1.0		1,0	
No	1.6 (0.37 – 6.81)	**0.530**	1.46 (0.58 – 3.67)	**0.420**
HS in same district of residence				
Yes	1.0		1,0	
No	1.2 (0.53 – 2.74)	**0.660**	1.15 (0.67 – 1.97)	**0.610**
Residence in areas of FHP visits				
Yes	1.0		1,0	
No	1.91 (0.75 – 4.88)	**0.180**	1.14 (0.65 – 2.0)	**0.640**

Table 2 - Multivariate analysis of factors associated with death from tuberculosis - underlying and associated cause - during treatment and after discharge from tuberculosis treatment in tuberculosis (TB) patients treated in Recife, Pernambuco, Brazil, 2001-2007.

Tabela 2 *– Análise multivariada dos fatores associados ao óbito por tuberculose - causa básica e causa associada - durante o tratamento e após a alta do tratamento para tuberculose (TB) em pacientes tratados em Recife, Pernambuco, Brasil, 2001-2007.*

	One year follow up		Untill the end of follow up (79 months)	
	HR (CI)	*p*	HR (CI)	*p*
Age (years)				
Continuous variable	1.03 (1.01 – 1.06)	**0.005**	1.04 (1.02 – 1.06)	**<0.001**
Late initial treatment				
≤ 60 days	1.0		1.0	
> 60 days	2.98 (1.014 – 8.77)	**0.047**	2.77 (1.42 – 5.42)	**0.003**
Weight loss				
No			1.0	
Yes			2.53 (1.26 – 5.07)	**0.008**
Previous treatment for tuberculosis				
No			1.0	
Yes			1.98 (1.12 – 3.52)	**0.018**
HIV co-infection				
No	1.0		1.0	
Yes	13.2 (2.6 – 65.8)	**0.002**	6.55 (1.72 – 24.9)	**0.006**
Not known	2.36 (0.69 – 8.07)	**0.170**	2.54 (1.19 – 5.45)	**0.016**

atment for TB was 95.9%, corresponding to a cumulative risk of dying from tuberculosis as the underlying or associated (non-underlying) cause of 4.1% (95%CI: 3.0-5.3). TB case-fatality rate in this cohort was 7.7/1000 person-years.

The present study provides a more specific analysis of TB mortality as it did not consider deaths from all causes among patients during or after tuberculosis treatment. The existence of a national mortality information system (SIM) allowed identifying deaths from TB, both as an underlying or associated cause, making the study more comprehensive[5,18,24]. At the same time, the use of SIM could also identify 24 tuberculosis deaths not reported to SINAN. In Brazil, some authors found a considerable percentage of deaths from tuberculosis that had not been notified to the tuberculosis surveillance system[25-27].

Factors associated with death from TB changed over time in the present cohort study. In the first year of follow-up, factors associated with death were age, positive serology for HIV, and late initial treatment for tuberculosis. Considering the whole study period, predictive factors associated with death from tuberculosis were age, positive serology for HIV, late initial treatment, history of weight loss, and previous tuberculosis treatment. It is important to emphasize that weight loss and previous treatment for tuberculosis were already associated with death at one-year follow-up, but with no statistically significance. Considering that these risk factors are time-independent variables, as was verified by Schoenfeld residuals test, we can conclude that at one year of follow-up, the study did not have the power to show that because of the small numbers of deaths at the time.

The risk of death from TB increased with the increase in age as has been shown by other studies[6-10]. Among elderly patients, time from the onset of symptoms to diagnosis of TB is higher due to complicated TB

diagnosis[28]. The association became increasingly more significant as the follow-up time got longer, as would be expected (Table 2).

The role of tuberculosis as the leading cause of death among patients infected with HIV is already recognized[29,30]. Moreover, TB patients co-infected with HIV have a higher risk of death registered by verbal autopsy[31]. When studying factors associated with death from TB as primary cause in Recife, Domingos et al.[7] found HIV/AIDS co-infection was one of the most important predictive factors. The authors also reported that besides HIV/AIDS, age, abandonment of previous tuberculosis treatment, gender, and clinical presentation remained statistically significant in the final model.

The delay to start TB treatment was identified as a predictor of death at the one year follow-up analysis. In a previous analysis of data from the same cohort of patients, following them only until the end of the treatment and considering all causes of death, we found that late initial treatment was predictive factor for death[10]. Late initial treatment increases the severity of the disease. Most deaths occurred during the first year after beginning treatment (39/54), which indicates the importance of early diagnosis at primary health services.

Alcohol consumption (defined as heavy drinking) was not a predictive factor for death from tuberculosis in the two periods considered. Alcohol consumption was not associated with recurrence of tuberculosis in the same study population[32].

The history of weight loss reported by patients at the beginning of treatment was also one of the predictors for death from tuberculosis. Low BMI has been reported as a risk factor for death from TB and is associated with survival of patients who begin treatment for tuberculosis[33]. Weight loss is a sign of malnutrition and is associated with greater severity of disease.

The history of previous treatment for tuberculosis is also a sign of poor prognosis and was associated with death from TB considering the total time of follow-up of the cohort. Some authors have shown the importance of abandonment as a risk factor for death from tuberculosis[7,34], and abandonment has been reported as the main reason for retreatment in Recife[35].

No socio-economic variables proved to be predictors of death from tuberculosis in the present study variable, not even those related to health services. The variables gender, smoking, clinical form of tuberculosis, bacteriology, and treatment outcome were not associated with death from TB, either.

In relation to smoking, although there are evidences of its association with *M. tuberculosis* infection, progression from infection to disease[36,37], and recurrence of the diasease[32], it has not yet been clearly identified as a predictor of death from tuberculosis. A systematic review conducted by Bates et al.[38] on the association between smoking and mortality from tuberculosis produced a summarized RR of 2.15 (95%CI: 1.38-3.35). However, the authors did not consider this result valid because there was a significant heterogeneity of the studies included.

This study has some limitations. Culture for *Mycobacterium tuberculosis* and susceptibility tests are not done routinely in primary health care units in Recife. Consequently, it was not possible to study drug resistance as a risk factor for death from TB. Another issue concerns the small proportion of patients who had HIV serology (although HIV tests were ordered for all patients, only 30.2% were tested).

Finally, including tuberculosis as an associated cause of death and performing analysis in two different periods of follow-up allowed us to identify a greater number of deaths from TB and their predictive factors. Other outcomes registered for these patients by the TB surveillance system did not provide any further hints on the deaths that occurred after the end of treatment. These results can guide feasible interventions for health services aimed at reducing mortality from tuberculosis.

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