Who were the tuberculosis patients who died precociously due to the disease in Southern Brazil? A retrospective cohort study

Danielle Talita dos Santos (✉ danielletalita@hotmail.com)
Universidade de Sao Paulo  https://orcid.org/0000-0001-9817-7979

Luana Seles Alves
Universidade de Sao Paulo

Juliane Almeida Crispim
Universidade de Sao Paulo

Josilene Dália Alves
Universidade de Sao Paulo

Denisse Andrea Cartagena Ramos
Universidade de Sao Paulo

Jonas Bodini Alonso
Universidade de Sao Paulo

Ivaneliza Simionato de Assis
Universidade de Sao Paulo

Antonio Vieira Ramos
Universidade de Sao Paulo

Elma Mathias Dessunti
Universidade Estadual de Londrina Centro de Ciencias da Saude

Ione Carvalho Pinto
Universidade de Sao Paulo

Pedro Fredemir Palha
Universidade de Sao Paulo

Ricardo Alexandre Arcêncio
Universidade de Sao Paulo

Carla Nunes
Universidade Nova de Lisboa

Research article

Keywords: survival analysis, tuberculosis, HIV, mortality, risk factors
Abstract

BACKGROUND A diagnosis of tuberculosis (TB) is no sign that the disease will be treated successfully, as death still occurs among those who are diagnosed by health services. The study aimed to identify the TB patients who died precociously due to the disease and associated factors in Southern Brazil. METHODS We conducted a retrospective cohort study, where all deaths from TB were gathered, including cases of TB/HIV joint infection (ICD A15.0–A15.9 and ICD B20.0), which occurred between 2008 and 2015 in Southern Brazil. Techniques for survival analysis were applied, including the Kaplan-Meier test and Cox’s regression, from which the mean, median and IC 95 of survival (in days) were estimated; the hazard ratio (HR) obtained and the associated causative factors identified. RESULTS A total of 205 were found: 131 of these resulted from TB alone, while 74 had origins in joint infection of TB/HIV and only 179 deaths were included in the survival analysis. The first group had a median survival of 19 days, and the second group had a median survival of 28 days; however, the difference was not statistically significant. The median survival for the whole sample was 22 days, with 59.1% of these individuals dying within 30 days and 72.5% passing away within 60 days after diagnosis (minimum = 1, maximum = 349, SD = 68.8 and mean = 50 days). The use of alcohol (HR 1.9, IC 95 1.2–3.1) was associated with precocious death in the studied patients. CONCLUSION Most of the deaths occurred prematurely (within 2 months), which evidenced that the diagnoses have been made too late, when the disease was already in its advanced stages. The use of alcohol was associated with the precocious deaths. Although the diagnostic and treatment are free in Brazil and the patients have gotten the diagnosis, they died. Early, sensitive diagnosis, with social support and a comprehensive care might reduce the early mortality among with patients with addiction problems.

Background

Even though the treatment of tuberculosis (TB) has been established since the late 1940s, the illness is still one of the top 10 causes of death by disease globally [1]. In 2017, a total of 1.3 million HIV-negative people, in addition to some 300 000 people living with HIV/AIDS (PLWHA), died as a result of TB [1]. At present, a group of 30 countries accounts for 84% of TB cases worldwide, and Brazil is currently in 19th place in this world ranking [1]. In Brazil, the mortality rate as a result of TB was 2.2 deaths for every 100,000 people in 2017, and the prevalence of the disease was 32.4/100,000 inhabitants [2].

TB is the main cause of death among PLWHA [1,3], and the risk of dying from TB is up to 10.6-fold higher in this group, when compared with the general population under study [3]. Mortality from TB is also higher among people with comorbidities such as diabetes mellitus and risk factors such as alcohol consumption and tobacco smoking [4,5,6]. Other factors have also been identified as possible causes, such as age, being male, having a lower educational level, as well as socio-economic factors such as the location of one’s abode and social conditions [4,7].

Studies using the technique of survival analysis have found that death from TB was most common in the first 3 months after diagnosis among patients with coinfection with human immunodeficiency virus and
TB (TB/HIV) [8], while another study observed that the majority of deaths took place within 2 months after the start of treatment for TB [3]. A study with an HIV-negative population found that the median survival was 12 days, considering those who died of TB [9].

Some studies that evaluated survival in relation to TB focused mainly on people with TB/HIV coinfection [3,8,10,11] and on the delay in commencement of treatment for TB, considering the period from diagnosis to the start of antituberculosis activities [8,12]. Some studies have addressed the issue of premature deaths from TB [9,11,13], considering those deaths which occurred in the intensive stage of treatment, which comprises the first 2 months of treatment [9,14].

Analysis of premature death from the moment of diagnosis up to the moment of death from TB, as well as the associated factors, will serve to advance existing knowledge on the topic and improve the control of this disease in Brazil[15,16]. It is also relevant to establish the factors related to premature mortality among TB patients. In the light of the points here raised, this study aimed to identify the TB patients who died precociously due to the disease and associated factors in Southern Brazil.

**Methods**

*Study design and population*

This is a retrospective cohort study, consisting of survival analysis. The population was made up of cases of death from a basic cause registered under CID 10 codes: A 15.0 to 19.0 (tuberculosis) and B 20.0 (HIV disease resulting in tuberculosis—TB/HIV) which occurred between 2008 and 2015.

*Place of study*

The region of the study was the south of Brazil, and the cohort studied corresponded to the municipality of Curitiba, the capital of the State of Paraná, with an estimated population of 1,971,185 people and a demographic density of 4,027.04 people per square kilometre [17]. This is a Brazilian state capital with a Human Development Index (HDI) of 0.823, placing Curitiba in tenth place on the national ranking. The percentage of people considered poor stood at 1.73%, while 7.93% of the population was vulnerable to poverty, and the GINI Index stood at 0.55 [18]. Within the municipality of Curitiba, the municipality had the following coefficients: prevalence of 14 cases per 100,000 people, and mortality of 1.2 per 100,000 people [19]. The deaths were clustered in the southern region of the municipality and were associated with low HDIs in the respective regions [20].

*Data source and procedures*

The data were obtained from the Mortality Information System (MIS) and from the Disease Notification Information System (DNIS), from the Secretariat of Health of the State of Paraná (SESA), and information from the latter source completed the clinical and operational picture regarding TB.

*Variables under study*
The main variable under analysis was the total time (in days) which elapsed between the date on which the diagnosis of TB was confirmed and the date of death as a result of TB. Deaths which occurred within the first 60 days after diagnosis were considered as premature [9,14]. The independent variables are described in Table 1 and include social and demographic dimensions, as well as clinical and operational variables.

**Linkage of databases**

We established linkage between the MIS and DNIS databases, so as to obtain the clinical and operational variables in addition to the date of diagnosis of TB as obtained from SINAN. In this procedure, we considered the keys, which are the elements of information that identify the registration number, date of birth, and identification of the mother, in a unique manner. For the application of this technique, we used the SPSS software, version 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.).

**Data analysis**

We applied descriptive statistics in order to obtain the absolute values and percentage frequencies of the categorical variables. In the case of continuous variables (time in days and age) we obtained the minimum and maximum values, arithmetic mean, median and standard deviation (SD).

The Kaplan-Meier method was used to estimate the probability of survival, thereby allowing a comparison of the groups through application of the non-parametric log-rank test, when we obtained the median and mean values of survival (in days), distributed according to the independent variables[21,22].

We carried out bivariate analysis to estimate the effect of the independent variables and also to obtain the hazard ratio (HR). After this stage was completed, we performed Cox's multiple regression [23], including in the model the clinically relevant variables and those with p < 0.2. The results were shown as hazard ratios (HR), with confidence intervals of 95% (CI). A type I error rate of 5% was also established, considering results with p < 0.05 as statistically significant. The analysis was carried out using the SPSS software, version 24.0 (IBM).

The study was approved by the Research Ethics Committee of São Paulo University (USP), under number CAAE No. 64515717.9.0000.5393.

**Results**

We studied a total of 205 cases, of which 131 (63.9%) had a diagnosis of TB (ICD A15–A19) and 74 (36.1%) were diagnosed with TB and HIV coinfection (ICD B20.0) as the main cause of death in the files. Linkage was also established between MIS and DNIS for 179 (87.3%) of the cases. In the descriptive analysis, we considered the 179 cases of death (Table 1), while in the survival analysis, we considered 149 deaths which contained information regarding dates within the criteria as established. In Figure 1, we show the Flow Chart presenting the cases of the death analysed in the study.
Out of the 179 deaths which occurred and were analysed in the period studied, 105 (58.6%) of them had a diagnosis of TB (ICD A15.0 to A19) and 74 were diagnosed with TB and HIV coinfection (ICD B20.0). The descriptive results are shown in Table 2, where one can see that most cases, 138 (77.1% of the total), occurred in males. The White race prevailed among the deaths, with 120 cases (67%), while the mean age was 47 (minimum 20, maximum 94, median 44 and SD = 14).

The most common clinical presentation was pulmonary TB, with 132 cases (73.7%). There was a total of 139 new cases (77.7%), and in 144 of the cases (80.4%), the diagnosis was confirmed by radiographic examination.

The results of survival analysis are shown in Table 3. The median survival from diagnosis up to death, among those who died from a basic cause of either TB alone or coinfection of TB and HIV, was 22 days; it was also observed that 88 of the patients (59.1% of the total) died within 30 days after diagnosis, and 107 (72.5%) died within 60 days after diagnosis (minimum survival 1 day; maximum 349 days; standard deviation (SD) = 68.8 and mean = 50 days).

In Table 3 we can see that the survival of the group with TB/HIV was higher than that of the group with only TB; however, the log-rank test showed no statistical significance. The variables gender, age bracket, educational level and marital status, as well as the other clinical and operational variables did not show statistically significant correlations with survival. The sole exception was the variable alcohol use, which showed statistical significance (p < 0.05) in the Kaplan-Meier log-rank test, being associated with lower survival. The clinical variables, especially TB/HIV coinfection, type of entry, use of other drugs, and use of alcohol, all had p < 0.20. These variables were then subjected to bivariate analysis (Table 3), while only two variables, namely use of alcohol and use of other drugs, were inserted in Cox's regression analysis. Cox's regression analysis produced a hazard ratio (HR) of 1.0, IC95% = 1.2 to 3.0 and a P value of 0.004 for the use of alcohol variable, which continued to be the only statistically significant variable within the model (see Figure 2).

**Discussion**

The study identified that precocious deaths due to tuberculosis were associated with alcohol consumption. Most of the deaths occurred within 2 months, which evidenced that the diagnoses have
been made too late, when the disease was already in its advanced stages. Some studies[9,13,14] investigated the phenomenon of premature death among patients with TB, one such study observing similar results with a median survival time of 21 days in Korea[13]; another study found that 19% of the patients died within 7 days and 41% died within the first month after the start of treatment for TB[14]. Another study, this time developed in Africa, found a mean survival span of 2 months in 53.3% of the people who started their TB treatment, and in this case, mortality among HIV-positive people was higher than for those who were HIV-negative or whose HIV status was unknown[3].

The short survival period found (less than a month) points to the severity of the disease at the moment of diagnosis, suggesting that the diagnosis was very tardy[9,10], which makes us wonder whether the control measures used, such as the directly observed treatment strategy (DOTS), as well as others such as active search, are effectively being implemented in order to achieve effective control of this disease. Another study found a higher percentage of treatment abandonment and a lower rate of cure in those Brazilian municipalities where the DOTS strategy was more widely applied; in contrast, those municipalities that made less use of the strategy obtained poorer results [24].

The difficulty in accessing services at the moment of symptom onset [13], especially in vulnerable groups or when health service providers are not qualified to recognize a cough as being a clinical sign of TB should be borne in mind; one study showed that only 42.2% of all TB patients were diagnosed correctly at their first visit to the health services [25]. This result suggests the need for an attention model that gives higher value to the active search for patients within the territories, and the tracking of TB among the population at large, and in regular appointments for patients living with HIV, not to mention the search for latent TB infection (ITLB) [15,16,24].

Other factors may also be related to the progression and worsening of TB, and these may involve issues that are more specifically related to any one individual patient, such as the decision to seek health advice, which is arrived at through a decision-making process based on prior knowledge and on the ability to judge their own state of health. A study found that 68% of patients living with TB in Zambia took a long time to seek health care, even if they recognised the symptoms of the disease and suspected that they were ill [26]. Health education helps to improve knowledge and also build awareness in the population about their own state of health; in this regard, a randomised study[27] found that after an educational session, the group that had received advice and guidance about TB showed better knowledge, attitudes and practices.

Brazil has a special protocol in place for monitoring the deaths that occur with some mention of TB as one of the causes, a protocol which, among other aims, seeks to investigate these patients’ individual health conditions and their access to health services, as well as analysing and correcting the information that appears in the different information systems used, namely SIM, SINAN and the TB Site [16]. This is a strategic initiative to improve the qualification of the data; however, according to evidence from the study itself, it is important to verify the phase at which the patient passed away, in stratified fashion, whether the case was being monitored by the service and if this happened in the early or the later phase of
treatment. This is important because, depending on the phase at which the patient met his or her demise, actions also need to be modulated, as premature death makes us think about whether measures and protocols have been effectively implemented so as to impact on mortality from TB [28].

The difference in survival between people with TB and those with TB/HIV did not show any statistical significance, even though the median of the group with coinfection was higher, meaning that they survived longer than the group that only had TB. One point that could justify this result is the fact that people living with HIV/AIDS often receive ongoing medical monitoring from a multiprofessional team, including medical appointments, examinations and regular administration of medication, which leads to intermittent contact with health professionals and also increases opportunities for recognition of signs and symptoms of TV, which is, in fact, recommended as part of the protocol of caring for these patients: the investigation of TB in every medical appointment [15].

Most people who met their end through TB and coinfection from TB and HIV were male and had a low education level, which agrees with the findings of other studies [13,29]. The most common clinical manifestation was the pulmonary variety, even though there was no association with survival in this particular study. As well as being the most common clinical form, it is also the most relevant, as this is a transmittable form of the disease. A study found that individuals with the pulmonary form had a longer survival period than those with the extrapulmonary form of the disease [30].

The present study found that the use of alcohol increased the chances of premature death from TB. The evidence pointing to the effects of alcohol, within specialised literature, has shown harmful effects with regard to over 200 illnesses and diseases [31] (WHO, 2013), and a metanalysis [32] also found that the use of alcohol was linked to a greater risk (RR 1.35, IC 95% 1.09–1.68) of getting full-blown TB when compared with those who abstained from alcohol. In addition, the risk of the disease developing increased together with an increase in the consumption of ethanol (in grams per day).

There are also other factors which could be linked to the use of alcohol, such as malnutrition, overcrowded housing, and use of other substances [33,34]. Low immunity has already been documented as an explanation which assigns an increased risk for development of TB and of dying of this disease [35]. A study found that patients who died from TB, or who showed an important clinical worsening, also showed low levels of the alpha tumoral necrosis factor (TNF-α), this being a cytokine present in the inflammatory response, which would suggest a low immune response [9], thus showing a progression and worsening of the disease.

The use of drugs other than top-of-the-range drugs for the treatment of TB showed an inverse relationship, i.e. patients using other drugs as supportive therapy survived longer. A study carried out in Brazil showed that the deaths from TB that occurred were in fact associated with other bacterial infections in PLWGA, which could be addressed with the use of complementary therapies, apart from TB itself [11]. Due to monitoring in health services and antiretroviral therapy, PLWHA could be afforded some protection when compared with groups that did not receive any monitoring, which would justify the longer survival within this group, in the present report [15].
In Brazil, there was an increase in primary resistance to isoniazid, from 4.4% to 6.0%, and there were 583 cases of MDRTB (II National Investigation into Resistance to Antituberculosis Medications), which indicates the need to use other medications for the treatment of TB [36]. Treatment of MDRTB is a current challenge that requires the development of other safe and efficient medications.

Regarding the use of top-line drugs, rifampicin (R), isoniazid (H) Pyrazinamide (Z) (scheme: RHZ) and Ethambutol (E) were present in most cases, and only Ethambutol seems to have been used less often, which could be due to the fact that this medication was only included in the initial treatment scheme as of 2009 [36,37] (first 2 months), which would justify the lower occurrence of this drug within the study when compared to the frequency of use of RHZ.

One of the limitations of this study refers to the use of secondary data that were entered into the form in advance, as there were gaps in form-filling or missing information. Only recently (2017) the protocol launched for monitoring deaths with a mention of TB, one of the purposes of this being that of correcting, both quantitatively and qualitatively, the information that appeared in the different information systems, DNIS and MIS.

**Conclusion**

The study found deaths from TB occurring prematurely, which points to a possibility of tardy diagnosis of the disease, then in a more advanced phase. The consumption of alcohol also increased the risk of premature death from TB. These deaths should be avoided through adoption of the actions mentioned in the programmes for control of TB, such as application of the DOTS supervised treatment, the intensification of active screening, and the tracking of possible cases that could lead to worsening and premature death. The identification of possible patients prone to this worsening process and eventually death could be a way of improving this outcome. TB is an old disease, yet one that is still present; at one time it was a synonym for death, and it is not acceptable that this disease should continue to end lives in this day and age, especially considering patients who have already been diagnosed and who could have received the necessary intervention, so that the outcome of death could be avoided.

**Declarations**

**Ethics approval and consent to participate:**

The study was approved by the Institutional Review Board at the University of Sao Paulo (USP) under CAAE No. 64515717.9.0000.5393. Informed consent was not required, as data were based on official data sets and were previously anonymous.

**Consent for publication:** Not Applicable

**Availability of data and material:**
The database is carried out by the Epidemiological Surveillance Division and Secretary of Health of the State of Parana, Brazil and restrictions apply to the availability of these data, which were used under license for the current study, so are not publicly available. The first author had registered with details as well as contact data in case of interest in collaborative work or further information.

**Competing interests:**

The authors declare that they have no competing interests.

**Funding:**

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) (Processo: Programa de Doutorado Sanduíche no Exterior –88881.132524/2016–01) and CNPQ (Bolsa produtividade em pesquisa - Grant 305236/2015–6); Fundação de Amparo a Pesquisa do Estado de São Paulo -FAPESP (process 2015/17586–3) support for collection data.

**Authors’ contributions:**

Nunes C and Santos DT conceived the study. Santos DT, Alves LS, collected and initially computed the data. Santos, DT, Nunes C, Alonso JB and Arcencio RA analyzed and constructed the results from the data. Santos DT, Nunes C, Arcencio RA and Cartagena D writing the manuscript. Crispim, J, Alves JD, Ramos AV, Dessunti EM, Pinto IC, Palha PF reviewed and edited the manuscript. All authors read and approved the final manuscript.

**Acknowledgements**

The authors would like to thank the Epidemiological Surveillance Division and Secretary of Health of the State of Parana for making the data available, mainly for Betina M. Alcantara Gabardo and Viviane Serra Melanda for the support.

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Tables

Table 1 Source of data and independent variables under study
|                          | Independent Variables | Classes                                      |
|--------------------------|------------------------|----------------------------------------------|
| Date of Death            | Date                   |                                              |
| Gender                   | Female                 | Male                                         |
| Age                      | Continuous             |                                              |
| Ethnicity                | White / Oriental       | Afrodescendant                               |
| Educational Level        | 8 years of schooling or more | 7 years of schooling or less                |
| Marital Status           | Married / Common-Law Marriage | Single / Widowed / Separated or Divorced     |
| Type of Entry            | New case               | Re-entry or Retreatment                      |
| Institutionalised        | No                     | Yes                                          |
| Examination: X-ray       | Normal                 | Yes, suspicious results                      |
| Clinical category        | Pulmonary              | Extrapulmonary                               |
| Aggravation – Use of alcohol | No                  | Yes                                          |
| Aggravation - *Diabetes Mellitus* (DM) | No | Yes                                          |
| Examination: Bacilloscopy | Negative               | Positive                                     |
| Culture                  | Negative               | Positive                                     |
| Medication used: Rifampicin | Yes                 | No                                           |
| Medication used: Isoniazid | Yes                 | No                                           |
| Medication used: Pyrazinamide | Yes                | No                                           |
| Medication used: Ethambutol | Yes                 | No                                           |
| Medication used: Streptomycin | Yes                | No                                           |
| Medication used: Other drugs | Yes                | No                                           |
| Supervised treatment -DOTS | Yes                  | No                                           |

*Source: Mortality Information System – MIS

**Source: Disease Notification Information System – DNIS
Table 2: Distribution of social, clinical and operational characteristics of the patients who died as a result of TB and TB/HIV in Curitiba (2008-2015).
| Variables (n=179) | Categories                                              | n  | (%)  |
|------------------|---------------------------------------------------------|----|------|
| Coinfection (Basic cause) | Yes TB/HIV                                              | 74 | 41,3 |
|                  | No (TB)                                                 | 105| 58,7 |
| Sex              | Female                                                  | 41 | 22,9 |
|                  | Male                                                    | 138| 77,1 |
| Ethnicity        | White or Oriental                                       | 120| 67,0 |
|                  | Afrodescendant                                          | 45 | 25,1 |
|                  | Not informed                                            | 14 | 7,9  |
| Educational Level| 0-7 years of schooling                                  | 104| 58,1 |
|                  | 8 or more years of schooling                            | 50 | 27,9 |
|                  | Not informed                                            | 25 | 14,0 |
| Marital Status   | Married / Common-Law Marriage                           | 50 | 27,9 |
|                  | Single / Widowed / Separated or Divorced                | 113| 63,1 |
|                  | Not informed                                            | 16 | 9,0  |
| Type of entry    | New case                                                | 139| 77,7 |
|                  | Re-entry or Retreatment                                 | 29 | 16,2 |
|                  | Not informed                                            | 11 | 6,1  |
| Institutionalised| No                                                      | 141| 78,8 |
|                  | Yes                                                     | 17 | 9,5  |
|                  | Not informed                                            | 17 | 9,5  |
| X-Ray confirmation of diagnosis | Normal                                           | 35 | 19,6 |
|                  | Yes/suspicious                                          | 144| 80,4 |
| Clinical Form    | Pulmonary                                               | 132| 73,7 |
|                  | Extrapulmonary                                          | 47 | 26,3 |
| Use alcohol      | No                                                      | 108| 60,3 |
|                  | Yes                                                     | 63 | 35,2 |
|                  | Not informed                                            | 8  | 5,0  |
| Diabetes Mellitus (DM) | No                                                | 167| 93,3 |
|                  | Yes                                                     | 3  | 1,7  |
|                  | Not informed                                            | 9  | 5,0  |
| Bacilloscopy     | Negative                                                | 46 | 25,7 |
|                  | Positive                                                | 96 | 53,6 |
|                  | Not informed                                            | 37 | 20,7 |
| Sputum culture   | Negative                                                | 23 | 12,8 |
|                  | Positive                                                | 25 | 14,0 |
|                  | Not informed                                            | 131| 73,2 |
| Rifampicin       | No                                                      | 14 | 7,8  |
|                  | Yes                                                     | 149| 83,2 |
|                  | Not informed                                            | 16 | 8,9  |
| Isoniazid        | No                                                      | 14 | 7,8  |
|                  | Yes                                                     | 149| 83,2 |
|                  | Not informed                                            | 16 | 8,9  |
| Pyrazinamide     | No                                                      | 14 | 7,8  |
|                  | Yes                                                     | 149| 83,2 |
|                  | Not informed                                            | 16 | 8,9  |
| Ethambutol       | No                                                      | 51 | 28,4 |
|                          | Yes     | 112    | 62,6  |
|--------------------------|---------|--------|-------|
|                          | Not informed | 16    | 9,0   |
| Streptomycin             | No      | 159    | 88,8  |
|                          | Yes     | 4      | 2,2   |
|                          | Not informed | 16    | 9,0   |
| Etionamida               | No      | 161    | 89,9  |
|                          | Yes     | 1      | 0,6   |
|                          | Not informed | 17    | 9,5   |
| Medication used: Other drugs | No  | 148    | 82,7  |
|                          | Yes     | 9      | 5,0   |
|                          | Not informed | 22    | 12,3  |
| Supervised treatment     | No      | 28     | 15,6  |
|                          | Yes     | 133    | 74,3  |
|                          | Not informed | 18    | 10,1  |

**Table 3** – Survival: Kaplan-Meier and bivariate Cox analysis of patients who died of TB and TB/HIV and social, clinical and operational variables, Curitiba (2008-2016).
| Variables            | Categories                          | n | Median | SD | CI95%      | p-value ** | HR     | CI95%   | p-value |
|----------------------|-------------------------------------|---|--------|----|------------|------------|--------|--------|---------|
| Basic Cause          | TB*                                 | 86| 19     | 4.6| 9.9-28.1  | 0.11       | 0.1    | 0.4-1.1| 0.12    |
|                      | TB/HIV                              | 63| 28     | 10.7| 6.8-49.1  |            |        |        |         |
| Sex                  | Female*                             | 33| 16     | 6.6| 2.8-29.1  | 0.34       |        |        |         |
|                      | Male                                | 116| 23     | 4.1| 15.1-30.9 |            |        |        |         |
| Ethnicity            | White or Oriental                   | 98| 20     | 4.5| 11.2-28.8 | 0.28       |        |        |         |
|                      | Afrodescendant                      | 41| 33     | 8.9| 15.4-50.5 |            |        |        |         |
| Educational Level    | 8 or more years of schooling *       | 42| 23     | 6.4| 10.2-35.7 |            |        |        |         |
|                      | 0-7 years of schooling               | 86| 17     | 4.6| 7.9-26.1  | 0.67       |        |        |         |
| Marital Status       | Married / Common-Law Marriage*       | 45| 26     | 6.7| 12.8-39.1 | 0.45       |        |        |         |
|                      | Single / Widowed / Separated or Divorced | 88| 16     | 3.7| 8.6-23.3  |            |        |        |         |
| Type of entry        | New case*                           | 117| 19     | 3.8| 11.4-26.5 | 0.08       | 0.6    | 0.3-1.1| 0.97    |
|                      | Re-entry or Retreatment              | 26| 46     | 20.3| 6.1-85.9  |            |        |        |         |
| Institutionalised    | No*                                 | 119| 22     | 4.6| 12.8-31.1 | 0.35       |        |        |         |
|                      | Yes                                 | 16 | 23     | 9.9| 3.5-42.4  |            |        |        |         |
| X-Ray confirmation of diagnosis | Normal*                           | 11| 22     | 6.1| 10.1-33.8 |            |        |        |         |
|                      | Yes/suspicious                      | 113| 23     | 4.6| 13.8-32.1 | 0.95       |        |        |         |
| Clinical Form        | Pulmonary*                          | 103| 21     | 7.8| 6.5-37.4  | 0.68       |        |        |         |
|                      | Extrapulmonary                      | 43 | 22     | 4.4| 12.3-29.6 |            |        |        |         |
| Alcohol use          | No*                                 | 93 | 23     | 6.5| 10.1-35.8 | 1.5        | 1.1-2.2| 0.04    |         |
|                      | Yes                                 | 50 | 20     | 7.1| 6.1-33.8  | 0.03       |        |        |         |
| DM                   | No*                                 | 139| 23     | 3.6| 15.7-30.2 | 0.83       |        |        |         |
|                      | Yes                                 | 3  | 7      | 1.6| 3.7-10.2  |            |        |        |         |
| Bacilloscopy         | Negative*                           | 12 | 58     | -  | -          | 0.94       |        |        |         |
|                      | Positive                            | 24 | -      | -  |            |            |        |        |         |
|              | Negative | 41  | 46  | -   | -    | 0,69 |
|--------------|----------|-----|-----|-----|------|------|
| Sputum culture | Positive | 79  | 35  | 20,1| 0-74,4|      |
|              | Negative | 5   | 17  | 10,9| 0-38,4|      |
| Rifampicin   | Não*     | 5   | 17  | 10,9| 0-38,5|      |
|              | Sim      | 132 | 23  | 4,5 | 14,1-31,8| 0,78 |
| Isoniazid    | Não*     | 5   | 17  | 10,9| 0-38,5|      |
|              | Sim      | 132 | 23  | 4,5 | 14,2-31,8| 0,78 |
| Pyrazinamide | Não*     | 6   | 7   | 7,8 | 0-22,6|      |
|              | Sim      | 131 | 23  | 4,6 | 14,0-31,9| 0,30 |
| Ethambutol   | Não*     | 36  | 25  | 6,8 | 11,8-38,2| 0,76 |
|              | Sim      | 101 | 22  | 5,4 | 11,3-32,7|      |
| Streptomycin | Não*     | 134 | 22  | 4,6 | 12,9-31,1| 0,21 |
|              | Sim      | 3   | -   | -   | -     |      |
| Medication used: Other drugs | Não*     | 123 | 23  | 3,9 | 12,2-30,8| 0,4  |
|              | Sim      | 8   | -   | -   | -     | 0,09 |
| Supervised treatment -DOTS | Não * | 18  | 24  | 12,7| 0-48,9|      |
|              | Sim      | 117 | 22  | 4,6 | 12,9-31,1| 0,48 |

**Figures**
**Figure 1**

Flow chart of deaths as analysed in the study
Figure 2

Curves obtained by Kaplan-Meier survival analysis, with regard to aggravation by alcohol consumption in patients who died of TB and TB-HIV. Curitiba (2008-2016).