Epidemiology and risk factors associated with deaths from tuberculosis in older people who live in the capital of the Northeastern part of Brazil

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Abstract—Introduction: Tuberculosis (TB) is an extreme relevance pathology to the Public Health due to the morbidity and mortality high rates, with emphasis on the older population. The bacillus characteristic is intracellular, so a competent immune system must be needed to fight it through the cellular mechanisms.

Methods: Cross-sectional, documentary and analytical study based on the review of 128 medical records from the patients, who aged 60 years old or older at the time of the care due to TB or its complications from January 2006 to December 2016.

Results: The death prevalence was 44.5%. The bivariate analysis revealed that the men died 30% more than the women (PR = 1.3; CI 95% 0.81 - 2.07). In regard to the outcome (death and discharge), there was a statistical significance related to: a) clinical and epidemiological characteristics: Outpatient care (p = 0.002), ICU (p <0.001), Coma (p = 0.005), Hospitalization days (p <0.001 ), Treatment Adherence (p = 0.006), Treatment Abandonment (p = 0.036); b) risk and some associated factors: Malnutrition (p = 0.018), Hypertension (p = 0.024), HIV / AIDS (p = 0.010); The Poisson regression model for the outcome death / discharge shows ICU admission (p<001), Treatment adherence (p=002), Procedence origin (p=046).

Conclusion: The study showed different risk factors toward the death occurrence from the tuberculosis among the older people and illustrates the relevance of a continuous surveillance in order to monitor the TB.

Keywords—Tuberculosis, Epidemiology, immune system.

I. INTRODUCTION

Tuberculosis (TB) is an extreme relevance pathology to the public health due to the morbidity and mortality high rates with emphasis on the older population. Despite of presenting itself as a millenary disease, which is widely studied around the world, it is also offered an effective vaccination to avoid the contagion as well as effective treatments, there is still an enormous challenge to the global public health, especially in the underdeveloped countries without resources and diagnostic for the population treatment [1].

Its dissemination by the etiological agent Mycobacterium Tuberculosis occurs in an aerial way, by affecting a large number of people. Due to the bacillus characteristic that it is intracellular, a competent immune system must be needed in order to fight it through the cellular mechanism. In a healthy patient, the answer is given by the formation of the granulomas, which is the host's reaction to the bacillus invasion. In the older people, there is a weakness in the defense system and there is an increasingly frequent occurrence of TB cases in this age group [2].
As many developing countries, Brazil is in the process of demographic transition, by increasing significantly the number of older people in the recent decades. It is known that the older people’s organic condition, associated with other comorbidities, such as malnutrition and diabetes mellitus predispose the TB occurrence. In addition, the excessive consumption of the multiple medications and the lack of knowledge can result in the TB treatment abandonment, thus favoring the emergence of drug-resistant strains [3,4].

Drug-resistant tuberculosis (TBDR) is a priority concern from the World Health Organization (WHO). It is estimated that, in 2014, 480 thousand people developed TBDR and 190 thousand died [5].

Since 1997, WHO has published the global TB report to promote the epidemiological understanding from the disease, that is to be a facilitating tool in the strategy developments and goals for its treatment as well as the control. It has been emphasizing the problem scale with more than nine million cases registered in 2014, which were increased to 10.4 million in 2015.

Approximately six million cases of the disease were new in both periods. Four countries were responsible for 60% of its incidence, namely: India, Indonesia, China, Nigeria, Pakistan and South Africa. It also counts approximately one million and a half of deaths each year [6,7]. It is important to be mentioned that almost half of the global TB cases as well as two thirds of the TBDR cases come from Brazil, Russia, India, China and South Africa (BRICS) and some other emerging economies. These countries have a fundamental role toward the compliance with the global milestones defined by the “End TB Strategy” [6].

In Brazil, since 2003, TB has become a priority pathology for the Secretary of Health, because it is associated with social factors such as poverty and poor income distribution, precarious housing conditions, demographic pressure, disorderly growth of populations in cities, among some others.

Although there was a reduction in the incidence rate (41.5/100,000 inhabitants in 2005 to 32.4/100,000 inhabitants in 2016) and a mortality (2.9/100,000 inhabitants in 2003 to 2.2/100,000 inhabitants in 2015) TB in the country is a cause for a great concern due to the low treatment adherence, which it is one of the factors that can lead to the TBDR [8]. In addition, there was an increasing in the cases of Acquired Immuno Deficiency Syndrome (AIDS) among the older population and co-infection with the Human Immuno Deficiency Virus (HIV) further aggravating the TB and TBDR problem in the country [9].

In this context in order to characterize and analyse the risk factors for the TB development, it is necessary some epidemiological studies. The cross-sectional study has several advantages such as work easiness, execution low cost, and also presents quick results, by allowing the choice of the best strategy together with the most adequate public policy. Its greatest disadvantage is, that, it makes impossible the causality, since the exposure and the outcome factors are collected concomitantly [10]. For this disease, the correlations among explanatory and dependent variables can be made and the risk factors can be identified for the TB occurrence.

As it was shown above, this study aims to characterize the TB epidemiology, by associating possible risk factors to deaths from TB in older patients, who were admitted to a referral hospital in State of Ceará, Brazil.

II. METHODS

The study was conducted at São José Hospital (HSJ) for infectious diseases in Fortaleza, Northeastern part of Brazil. It is the fifth largest capital in the country with a population of 4,074,730 million inhabitants and a demographic density of 7,786.4 inhabitants / km².

HSJ is a large hospital with excellence in the patients’ care affected by the infectious diseases and a reference center in the treatment from TBDR in Ceará State. It is a public hospital linked to the Brazilian Unified Health System (SUS).

HSJ maintains all patients´ information on file through the medical records on the paper and they are daily stored at the Medical and Statistics Archive (SAME). The registration of each patient is carried out in the “Record from the Patients´ Discharge and Deaths” as well as the information such as: occurrence year, medical record number, age, origin and entry diagnosis.

Study Design and Data Collection

Cross-sectional, documentary and analytical study based on the review of patients´ medical records, who aged 60 years old or older at the time of the care due to TB or its complications. The information collection obtained from medical records was for the period from January 2006 to December 2016, and it occurred during the months of July 2016 to September 2017.

The initial data survey was carried out from the consultation in the “Records from the Patients´ Discharge and Deaths”, where each chart with the diagnosis of TB or TRDR was initially included in the study. The collection in the medical records was carried out in a census form in the SAME sector, by considering the older people assisted by
TB in the outpatient clinics, emergence, infirmary or intensive care unit (ICU) of HSJ.

TB or TBDR cases were diagnosed according to the medical criteria and they were performed only by the infectious professionals at HSJ. It was considered a lack of the treatment adherence, the patients whom the information was explicit in the medical record history. As this is a cross-sectional study, adherence to the treatment was not evaluated after hospitalization or consultation at the health service.

The information in the medical records was transcribed into forms that included the following data: a) sociodemographic and economic (number of medical records, age, origin, education, occupation, income and service sector; b) clinical (clinical disease form, risk factors and comorbidities that may follow the disease, immunosuppressed patient for any other reason); c) adherence to or abandonment from the treatment; d) outcome: discharge, death or moved to another hospital. All the information from each medical Record was filed year by year in the Microsoft Excel format spreadsheets.

Statistical Analysis

The spreadsheets made up an information bank, and they were analyzed by statistical software called "Statistical Package for Social Science"- SPSS version 20 (SPSS Co., Chicago, USA).

Bivariate analysis were performed, by using the Chi-square or Fisher's exact test. The measurement from the association used to measure the magnitude of the associations was the Prevalence Ratio (PR) and the respective confidence intervals (95% CI). For all statistical tests, it was considered a significance level of 5%.

In order to obtain PR estimates adjusted for confounding variables, multivariate analysis was performed, by using the Poisson regression model with some robust variance. The variables that were associated with the outcome in the bivariate analysis were selected for the multivariate analysis, with a value of p <0.25 and only those with a significant association at the level of p <0.05 were maintained in the final model.

III. RESULTS

From the total of 128 medical records included in the study, the prevalence of deaths was 44.5%. The age of the patients ranged from 60 to 93 years old, with a mean of 68.8 (SD ± 7.2). Prevailed: male gender (90; 70.3%), age group from 60 to 69 years old (80; 62.5%), income from a minimum wage (59; 46.1%) and low education (70; 54.7%). From the total participants, 94 (73.4%) were from Fortaleza. (Table 1)

| Variables          | Total n (%) | Death n (%) | Discharge n (%) | PR (IC 95%) | Value p |
|--------------------|-------------|-------------|----------------|-------------|---------|
| Gender             |             |             |                |             |         |
| Male               | 90 (70.3)   | 43 (47.8)   | 47 (52.2)      | 1.3 (0.81 - 2.07) | 0.255   |
| Female             | 38 (29.7)   | 14 (36.8)   | 24 (63.2)      |             |         |
| Age group          |             |             |                |             |         |
| 60 to 69 years old | 80 (62.5)   | 35 (43.8)   | 45 (56.3)      | 1.05 (0.51 - 2.14) | 0.921   |
| 70 to 79 years old | 36 (28.1)   | 17 (47.2)   | 19 (52.8)      | 1.13 (0.53 - 2.41) |         |
| 80 or more         | 12 (9.4)    | 5 (41.7)    | 7 (58.3)       |             |         |
| Occupation         |             |             |                |             | 0.383   |
| Unemployed         | 18 (14.5)   | 6 (33.3)    | 12 (66.7)      | 0.75 (0.38 - 1.49) |         |
| Employee / Retired | 106 (85.5)  | 47 (44.3)   | 59 (55.7)      |             |         |
| Income             |             |             |                |             | 0.605   |
| < 1 SM             | 33 (25.8)   | 17 (51.5)   | 16 (48.5)      | 1.16 (0.71 - 1.9) |         |
| ≥ 1 SM             | 59 (46.1)   | 24 (40.7)   | 35 (59.3)      | 0.92 (0.57 - 1.48) |         |
| > 1 SM             | 36 (28.1)   | 16 (44.4)   | 20 (55.6)      |             | 1       |
The bivariate analysis revealed that men died 30% more than women (PR = 1.3; CI 95% 0.81 - 2.07).

Table 2 highlights the study results, by showing the outcome related to the clinical and epidemiological characteristics with predominance of pulmonary TB as a clinical form (102; 79.7%). All the 128 patients were admitted to the hospital and 41 (32%) were undergoing outpatient’s treatment and had to be hospitalized, over the study period, 48 (37.5%) were admitted to the ICU due to some severe conditions or complications, 26 (22.6%) abandoned the treatment and only three cases were followed up at home by Directly Observed Treatment (ODD).

| Variables                       | Total n (%) | Death n (%) | Discharge n (%) | PR (IC 95%) | Value p |
|---------------------------------|-------------|-------------|-----------------|-------------|---------|
| **Clinical form**               |             |             |                 |             |         |
| Pulmonary                       | 102 (79.7)  | 45 (44.1)   | 57 (55.9)       | 1.32 (0.58 - 3.03) | 0.468¹ |
| Extrapulmonary                  | 12 (9.4)    | 4 (33.3)    | 8 (66.7)        | 0.71 (0.28 - 1.8)  | 1       |
| Pulmonary + extrapulmonary      | 14 (10.9)   | 8 (57.1)    | 6 (42.9)        | 1.71 (0.68 - 4.3)  |         |
| **Outpatient care**             |             |             |                 |             | 0.002¹  |
| Yes                             | 41 (32.0)   | 10 (24.4)   | 31 (75.6)       | 0.45 (0.25 - 0.8)  |         |
| No                              | 87 (68.0)   | 47 (54.0)   | 40 (46.0)       | 1           |         |
| **UTI**                         |             |             |                 |             | <0.001¹ |
| Yes                             | 48 (37.5)   | 42 (87.5)   | 6 (12.5)        | 4.67 (2.92 - 7.46) |         |
| No                              | 80 (62.5)   | 15 (18.8)   | 65 (81.3)       | 1           |         |
| **Coma**                        |             |             |                 |             | 0.005²  |
| Yes                             | 10 (7.8)    | 9 (90.0)    | 1 (10.0)        | 2.21 (1.64 - 2.99) |         |
| No                              | 118 (92.2)  | 48 (40.7)   | 70 (59.3)       | 1           |         |
| **Baar result (n=84)**          |             |             |                 |             | 0.922¹  |
| Positive                        | 47 (56.0)   | 17 (36.2)   | 30 (63.8)       | 1.03 (0.58 - 1.84) |         |
| Negative                        | 37 (44.0)   | 13 (35.1)   | 24 (64.9)       | 1           |         |
| **Culture result (n=65)**       |             |             |                 |             | 0.431¹  |
| Positive                        | 25 (38.5)   | 10 (40.0)   | 15 (60.0)       | 0.8 (0.45 - 1.42)  |         |
Risk Factors Related to TB Deaths

In the bivariate analysis, it was observed that in relation to the outcome (death and discharge), there was a statistical significance related to the outpatient’s care (p <0.002), ICU admission (p <0.001), patients in coma (p <0.005), treatment abandonment (p = 0.036). Meanwhile, the treatment adherence was a protective factor (p = 0.006).

From the 48 (37.5%) older people, who were admitted to the ICU, 42 (87.5) died, by representing 4.67 times higher RP, when it was compared to the outpatient’s care. Likewise, the older people in coma had a PR 2.21 times greater chance of dying, when they were compared to those who were not in coma. The smear test showed a positive result in 47 cases (36.7%) and the culture test was in only 25 (19.5%), however, without statistical significance.

Table 3 shows that among the risk factors related to the death outcome, the most prevalent are: smoking (63; 49.2%), followed by alcoholism (46; 35.9%), HIV / AIDS (39; 30.5), malnutrition (34; 26.6%), DM (28; 21.9%) and chronic obstructive pulmonary disease (COPD) (16; 12.5%). The other risk factors had a prevalence less than 10%. The factor associated with arterial hypertension was present in 45 cases (35.2%). There was a statistical association between risk factors for malnutrition (p = 0.018) and HIV / AIDS (p = 0.010) arterial hypertension (p = 0.024) and the occurrence of death from the disease.

Table 3. Outcome from the older patients diagnosed with tuberculosis according to the risk and associated factors.

| Variables        | Total n (%) | Death n (%) | Discharge n (%) | PR (IC 95%) | Value p  |
|------------------|-------------|-------------|-----------------|-------------|----------|
| Malnutrition     |             |             |                 |             | 0.018¹   |
| Yes              | 34 (26.6)   | 21 (61.8)   | 13 (38.2)       | 1.61 (1.12 - 2.33) |          |
| No               | 94 (73.4)   | 36 (38.3)   | 58 (61.7)       | 1           |          |
| Smoking          |             |             |                 |             | 0.737¹   |
| Yes              | 63 (49.2)   | 29 (46.0)   | 34 (54.0)       | 1.07 (0.73 - 1.57) |          |
| No               | 65 (50.8)   | 28 (43.1)   | 37 (56.9)       | 1           |          |
| Alcoholism       |             |             |                 |             | 0.574¹   |
| Yes              | 46 (35.9)   | 22 (47.8)   | 24 (52.2)       | 1.12 (0.76 - 1.66) |          |
| No               | 82 (64.1)   | 35 (42.7)   | 47 (57.3)       | 1           |          |
| Drugs using      |             |             |                 |             | 0.088²   |
| Yes              | 6 (4.7)     | 5 (83.3)    | 1 (16.7)        | 1.96 (1.29 - 2.95) |          |
| No               | 122 (95.3)  | 52 (42.6)   | 70 (57.4)       | 1           |          |
| Diabetes Mellitus|             |             |                 |             | 0.055¹   |

Chi-square test; ¹ Fisher's exact test
| Variables                  | PR adjusted | IC 95%     | Value p |
|----------------------------|-------------|------------|---------|
| **ICU admission**          |             |            |         |
| Yes                       | 5.72        | 3.32 - 9.87| <0.001  |
| No                        | 1           | -          |         |
| **Treatment adherence**    |             |            |         |
| Yes                       | 1           | -          | 0.002   |
| No                        | 1.68        | 1.22 - 2.32|         |
| **Origin**                 |             |            |         |
| Fortaleza                  | 1.52        | 1.01 - 2.96| 0.046   |

Table 4. Poisson regression model for the outcome (death) from older patients diagnosed with tuberculosis.
The study showed that the death occurrence from TB is associated with the identified risk factors, such as older people with HIV/AIDS co-infection, malnourished or with DM are more likely to develop severe forms and death than those who do not have these comorbidities. The high percentage of lethality demonstrates a weakness in the active search for the symptomatic respiratory cases in the older, who are followed up at the health service for some other causes. Therefore, our results point to the need of reassessing the program to combat tuberculosis in Ceará, with a higher qualification for monitoring the occurrence of the cases and standardized follow-up to the Secretariat of Health protocol.

The higher frequency from the disease in men corroborates with researchers, who point out a very strong correlation with the death in males, when they were compared to females, by including the fact that males are in a major risk factor in relation to the females [11-13].

Low income and education were marked in the studied population, by considering that 85.5% were retired and/or employees with an income of up one minimum wage. It is known that TB is related to some unfavorable economic situations. Studies concluded that TB is associated with the social context, the low level of education, in addition to some other socioeconomic factors. These factors make the patients, especially the older people, vulnerable to the maintenance of the basic supplies, which can affect access to the health service continuity and the treatment success, as well as the health condition itself that aggravates the clinical condition [14,15,16]. Likewise, other studies emphasize that, in general, the socioeconomic conditions from the population affected by the disease are always more precarious than the general population, thus favoring the emergence of more severe forms of the disease [11,15,17,18].

In the bivariate analysis, it was possible to demonstrate a moderate relationship from the DM in relation to death. The relationship between TB and DM follows the same line as the other factors, since the coexistence of both in the individuals leads to a clinical picture worsening. Studies report that blood hyperglycemia is related to the changings in immune responses, thus making diabetic older people more likely to contract the disease, in addition to the condition of the chronic hyperglycemia, as well as a lack of glycemic control, by having a negative impact on the TB treatment, thus suggesting a higher probability of death [19-21].

In the present study, arterial hypertension was associated with the older people’s outcome (p = 0.024). In a population-based cohort study on the increased risk of an acute coronary syndrome in patients with TB, was found a significant (p = 0.03) positive prevalence of arterial hypertension in the TB cohort (38.7 %) compared to the cohort without the disease (37.5%) [22]. Despite of this, it should be noted that there are contradictions in regard to the theoretical framework in the literature on this subject, since a systematic review, shows that there was no evidence in order to support an association between TB and hypertension [23]. For this reason, the authors from this review interpret the results with caution due to the lack of properly designed studies in relation to the methods.

Malnutrition and alcoholism were important risk factors for death. A percentage of 26.56% from patients had some level of malnutrition. In this context, authors emphasize that malnutrition has a high impact before the TB onset, as well as the frequent disease occurrence among the older people. This factor may be directly linked to the poor socioeconomic conditions from the population in this study. In addition, the malnutrition is also important in patients, who suffer from HIV / AIDS, since they often experience weight loss [24,25].

Although the alcoholism did not show statistical significance, it was decisive in the death outcome, since 47.8% from the alcoholics died. The association between alcohol consumption and tuberculosis is already known. However there have been inconclusive results related to several confounding factors and the complexity of combining the illicit drugs using with the tuberculosis, together with the profile from the affected population and the study scarcities that address this issue [26].

Smoking was a risk factor in the study population. Its high impact for the disease acquisition and death due to the complications in its treatment is a habit that is often associated with the bilateral pulmonary parenchyma, that often cause an advanced disease. In addition to be associated with lung injuries, it becomes an aggravating factor for TB, thus contributing to an unfavorable outcome.
and death. The same happens with the consumption of illicit drugs [27].

Another serious problem found in the study population concerns HIV/AIDS, that it is a complicated factor, by considering that through the bivariate analysis it was possible to observe statistical significance between HIV and death in this population (p = 0.010). HIV/AIDS co-infection with TB has become a problem worldwide, and also by considering that these two pathologies represent combinations with high mortality, especially in the most vulnerable population at the immune level [28].

This panorama is in a large part due to the antiretroviral treatment that contributes even more to the older people’s immune depression, by making TB treatment difficult and facilitating opportunistic infections, aggravating other comorbidities that the older people may present and, therefore, increasing the number of deaths [29,30]. In health services, the two diseases are investigated and treated together, through the rapid HIV test, since the virus investigation, when there is a demand for TB in the system, is a priority [31].

In regard to the outcome, TB is still one of the most lethal diseases on the planet, especially when it is associated with HIV / AIDS. In 2015, 1.2 million cases of co-infection occurred in the world (12% from the total cases), since the male gender was the most affected one. Likewise, people with the HIV virus are 26 times more likely to develop TB [32]. In this context, HIV / TB co-infection is at the top of the infectious diseases that kill the most in the world, as in the year of 2014, in which, one in three deaths from TB was associated with the virus [5].

The fact that ICU hospitalization, treatment adherence and the origin from the capital remained significant, when they were adjusted by the regression model, it is in line with the findings of some other studies that demonstrated associations from these factors for the patients’ outcome. Duro et al.[33] in a cohort study of TB patients, who need some intensive care had a high mortality rate. For the authors, most of the risk factors for mortality were related to the organ failure, however, other variables could be related, such as the delay in the diagnostic as well as therapeutic approach, which are important targets for the intervention.

It is important to mention that the treatment abandonment by 26 older people (22.6%) proved to be relevant, by considering that these older people, 15 (57.7%) died as an outcome. Therefore, abandoning treatment is a marker of a great importance, since it is inversely proportional to the increasing rate of cure, mortality and recurrence of the disease. In addition, it provides an increasing in resistant strains, difficulties in the healing process, an increasing in the treatment time and its cost [34].

The low financial condition results in displacement to the large centers in the search for survival, by implying people’s clusters in precarious health conditions. The county of Fortaleza has improved its Human Development Index (HDI) over the years, yet 75.21% (88 neighborhood) are classified as very low HDI, with only 6.83% (8 neighborhood) of the neighborhood classified high or very high HDI. As it was already mentioned, the hospital in which this study was carried out serves, for the most part, the population of most neighborhood with low HDI, with low education and income, and who are unable to have a private health service [35]. Meanwhile, Wang et al. [15] emphasize that to be older people is a risk factor for the development of extrapulmonary TB, as well as being retired and living in the urban areas.

Some limitations from the study can be highlighted, by emphasizing the deletion of records due to some information that is no longer explored, because there were incomplete medical records or because there was prospective information, such as the patient’s treatment adherence after being a patient from the Health Service. It is also noteworthy the fact that the prescription and formula were not evaluated in regard to the type of medication and treatment adherence. Although the study is limited to a large referral hospital, and cannot extrapolate its results to the general population, however, it is expected to reinforce the dimension of the TB problem in the older population and the need for further study of the topic in any other part of the world.

However, as important as the pathological aspects of the disease, are the psychosocial and economic nuances that present and feed an old disease, which has a vaccine and methods to reduce the likelihood of its development, emphasized, in this study, its large percentage death (44.5%) as an outcome.

V. CONCLUSION

The study showed a high occurrence of death from tuberculosis among older people. Risk factors for this outcome were co-infection with HIV/AIDS, malnutrition, hypertension, ICU admission, lack of adherence to the treatment and origin. An educational strategy is needed with a focus on detecting new cases with the assessment of close contacts with the patient diagnosed with TB. The study illustrates the relevance of continuous surveillance for TB monitoring in the city of Fortaleza. It is recommended to accompany the older people to reduce the number of patients that abandoning the treatment for the
disease. It is hoped that the risk factors identified can contribute as a tool to reduce cases among the older people through early identification and control.

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