Factors associated with mortality or survival of patients with tuberculosis: an integrative review

Fatores associados à mortalidade ou sobrevivência de pacientes com tuberculose: uma revisão integrativa

Factores asociados con la mortalidad o supervivencia de pacientes con tuberculosis: una revisión integradora

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ABSTRACT

Objective: To identify factors associated with mortality or survival of patients with isolated Tuberculosis (TB) or TB/HIV co-infection. **Methods:** A literature review was performed in the following databases: PubMed, Web of Science, Scopus, Health Virtual Library, and SciELO sing the following search terms: "Survival" OR "Mortality" AND "Epidemiological factors" OR "Epidemiological determinants" OR "Associated factors". Recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyzes methodology were used. **Results:** The factors associated with mortality or reduced survival were male sex, age >30 years in TB/HIV co-infection cases, advanced age in isolated TB cases, low schooling or up to 8 years of schooling, unemployment, TB/HIV co-infection, recent diagnosis of HIV, CD4 <50 cells, other immunosuppressive diseases, diabetes, renal disease, smoking, alcoholism, weight loss, and recently treatment started. **Final considerations:** Factors associated with TB mortality or survival did not differ from those associated with TB morbidity. However, excluding TB/HIV co-infection, the socioeconomic factors are evidenced.

Keywords: Tuberculosis, Associated factors, Survival, Mortality.

RESUMO

Objetivo: Identificar os fatores associados à mortalidade ou sobrevida de pacientes com tuberculose (TB) isolada ou coinfecção TB / HIV. **Métodos:** Foi realizada uma revisão da literatura nas seguintes bases de dados: PubMed, Web of Science, Scopus, Health Virtual Library e SciELO.org, utilizando os seguintes termos de busca: "Sobrevida" OR "Mortalidade" AND "Fatores Epidemiológicos" OR "Determinantes Epidemiológicos" OR "Fatores Associados". Utilizou-se as recomendações de Principais itens para relatar Revisões sistemáticas e Meta-análises (PRISMA). **Resultados:** Os fatores associados à mortalidade ou redução da sobrevida foram sexo masculino, idade> 30 anos nos casos de coinfecção TB/HIV, idade avançada em casos isolados de TB, baixa escolaridade ou até 8 anos de estudo, desemprego, coinfecção por TB / HIV, diagnóstico recente de HIV, contagem de células CD4 <50, outras doenças imunossupressoras, diabetes, doença renal, tabagismo, alcoolismo, perda de peso e tratamento iniciado recentemente. **Considerações finais:** Os fatores associados à mortalidade ou sobrevida por TB não diferiram daqueles associados à morbidade por TB. Porém, excluindo a coinfecção TB/HIV, os fatores socioeconômicos são evidenciados.

Palavras-chave: Tuberculose, Fatores associados, Sobrevivência, Mortalidade.

RESUMEN

Objetivo: Identificar factores asociados a la mortalidad o supervivencia de pacientes con tuberculosis (TB) aislada o coinfección TB/VIH. **Métodos:** Se realizó una revisión de la literatura en las siguientes bases de datos: PubMed, Web of Science, Scopus, Health Virtual Library y SciELO.org utilizando los siguientes términos de búsqueda: "Supervivencia" OR "Mortalidad" AND "Factores epidemiológicos" OR "Determinantes epidemiológicos" OR "Factores asociados". Se utilizaron las recomendaciones de los elementos clave preferidos para informar las revisiones sistemáticas y la metodología de metaanálisis (PRISMA). **Resultados:** Los factores asociados a la mortalidad o supervivencia reducida fueron sexo masculino, edad> 30 años en casos de coinfección TB/VIH, edad avanzada en casos aislados de TB, baja escolaridad o hasta 8 años de escolaridad, desempleo, coinfección TB/VIH, diagnóstico reciente de VIH, células CD4 <50, otras enfermedades inmunosupresoras, diabetes, enfermedad renal, tabaquismo, alcoholismo, adelgazamiento, tratamiento iniciado recientemente. **Consideraciones finales:** Los factores asociados con la mortalidad o supervivencia por TB no fueron diferentes de los asociados con la morbilidad por TB. Sin embargo, excluyendo la coinfección TB/VIH, se evidencian los factores socioeconómicos.

Palabras clave: Tuberculosis, Factores asociados, Supervivencia, Mortalidad.

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INTRODUCTION

The morbidity and mortality rates of Tuberculosis (TB) remain high, especially in countries with high disease burden, even with multiple efforts to control it World Health Organization (WHO) (2018). Mortality is a critical event considering that TB is a treatable and curable disease. Some factors associated with TB that lead to the death, include human immunodeficiency virus (HIV) infection or the development of acquired immunodeficiency syndrome (AIDS) and other comorbidities along with multidrug resistance, lifestyle, and socioeconomic factors (SAN PEDRO A e OLIVEIRA RM, 2013; RONALD LA, et al., 2016). Therefore, understanding these factors can help contribute to a comprehensive approach for treating the disease. Similarly, quantifying the strength of the identified associations will allow health professionals to emphasize the most relevant factors according to the patient profile (ADAMU AL, et al., 2017).

The term survival refers to the continuation of life beyond what is supposed or expected, an extension of life, an increase in time. However, for epidemiology, analyzing the survival of individuals is a widely used method when one intends to study events related to time until the occurrence of a certain factor of interest, and therefore, it cannot be interpreted as the opposite of mortality (PECEGO AC, et al., 2016).

The survival and clinical evolution of TB patients improved after the disease was considered a priority by the WHO, despite this fact, the lack of access to health services, lack of early diagnosis, problems with treatment adherence, HIV/AIDS co-infection, multidrug resistance and the socioeconomic situation negatively impact the evolution of cases (ABEDI S, et al., 2019). Besides, the use of alcohol and gender are associated with death, revealing inequality between men and women. This way, the vulnerability associated with mortality must be considered when analyzing TB evolution. Another precious action in the TB control program is the properly follow-up of the cases, mainly if it is by means of directly observed treatment, since it is a way to guarantee the treatment was effectively administered (SANTOS DT, et al., 2021).

Studies of factors exclusively associated with survival of patients with TB are scarce. The term survival is often misinterpreted as the opposite of mortality. With the advent of AIDS, studies have been focused only on this disease (ZENNER D, et al., 2015), which often shortens the survival of patients with TB; some studies have analyzed TB as an AIDS-associated factor of mortality or survival but only a few have analyzed only TB (MELO MC, et al., 2017; CUNHA R, et al., 2017; BALABANOVA Y, et al., 2011; MOOSAZADEH M, et al., 2014). One example is one study conducted in the Southern Brazil, where it was found that the chances of precocious death within 60 days was about 10 times greater than the chance of early death within 30 days (SANTOS DT, et al., 2021). Hence, this study aimed to identify factors associated with mortality or survival of patients with isolated TB or TB/HIV co-infection.

METHODS

This integrative review was conducted to answer the question “What are the factors associated with the mortality or survival of patients with TB?”

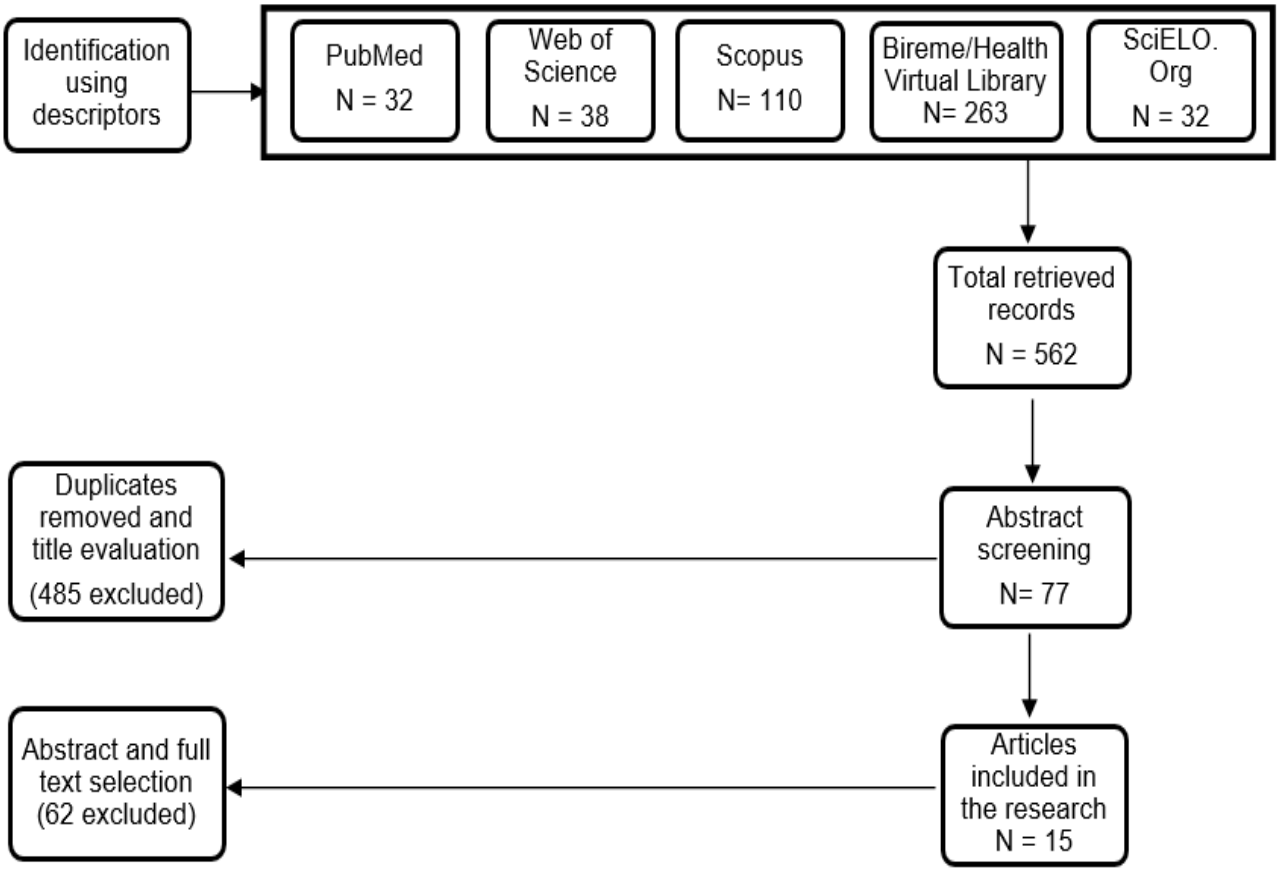
For the web search, we used a strategy called PVO (patients or population, variables, and outcomes), adapted to each bibliographic database using the following terms: “Survival” OR “Mortality” AND “Epidemiological factors” OR “Epidemiological determinants” OR “Associated factors” (FRAM D, et al., 2014). The final search was conducted on June 2019 with no date or language restrictions, because it was expected to include all of the manuscripts on survival or mortality related to TB. The following databases were searched: PubMed, Web of Science, Scopus, Bireme/Health Virtual Library and Scientific Electronic Library Online (SciELO). These database were selected because they are relevant for the theme, since previous assays retrieved repeated articles.

The inclusion criteria were: Publications from 1970 to 2019, the year of the retrieval data; research results of primary data collection; studies on survival or mortality TB, even if approached AIDS. Exclusion criteria were the factors that made a study ineligible to be included in this review, that is, those that not approached the theme of associated factors to TB survival or mortality.

In all phases of this review, the articles were selected by two independent researchers. In case of disagreement among the reviewers, the article was included and analyzed in the next step.

Using the Preferred Reporting Items for Systematic Reviews protocol (PRISMA) and checklist, the search and articles selection was done step by step - title and abstract analysis, followed by full text critical reading with data extraction (**Figure 1**). The inclusion criteria were articles that could answer the research question of this review.

Figure 1 - Summary of the results of the systematic review on mortality and survival of patients with tuberculosis.



Source: Rocha AC, et al., 2021.

The level of scientific evidence of the studies was assessed according to Oxford Centre Evidence-Based Medicine (OCEBM) (2009). Per this criterion, evidence was classified into scores 1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, and 5 depending on the type of study. Thus, according to the interpretation of these categories, a score was assigned to each study (OCEBM, 2009).

A spreadsheet was created to record data extracted from the articles, by bibliography database, with the following information: title, author's name, country of origin, journal, year and language of publication, type of study, population sample, period in months of the study, initial and final sample size, factors associated with mortality or survival, inclusion and exclusion criteria, objectives, type of data analysis, minimum and maximum confidence interval, main statistical estimators, and main conclusions. Additionally, it was included the judged level of evidence using Oxford Center Evidence Based Medicine criterion.

RESULTS

Because there was no limit of the publication year, the selected studies were published between 2004 and 2019, of which eight (53.3%) from Brazil. Most of the cohort studies were performed in a hospital setting. Primary and secondary data sources were used in the articles, such as information systems for notifiable diseases or mortality data, questionnaires or interviews of the patients, and data from medical records. These studies included adults or children with TB or TB/HIV co-infection (**Frame 1**).

Frame 1 - Characterization of the studies about (TB) by author, year, country of origin, language, objectives, population and level of evidence

Author (year)	Country of origin	Language	Objective	Population (sample)	SEL*
ROSSETO M, et al. (2019)	Brazil	Portuguese	To analyze the occurrence of TB/HIV/AIDS co-infection, hospitalization and mortality outcomes and their risk factors in cases reported for TB/HIV/AIDS	Cases of pulmonary TB infection (2419)	2B
MOOSAZADEH M, et al. (2014)	Islamic Republic of Iran	English	To determine predictive factors of mortality in TB patients	TB patients who died (752)	3B
GESESEW H, et al. (2016)	Ethiopia	English	To determine incidence and predictors of TB/HIV mortality	Patients with TB/HIV co-infection. (272)	2B
PECEGO AC, et al. (2016)	Brazil	English	To analyze factors associated with mortality in critically ill patients with TB/HIV co-infection	TB/HIV co-infected patients (44)	2B
CHUQUIYAURI HARO R, et al. (2004)	Peru	Spanish	To describe the clinical and epidemiological characteristics and mortality of hospitalized TB patients	Inpatients with TB (1248)	2B
KOLAPPAN C, et al. (2006)	India	English	To measure mortality and excess of mortality rate and risk groups	TB patients (2422)	2B
LIMA MS, et al. (2016)	Brazil	English	To describe epidemiological patterns and mortality time related to TB/HIV co-infection	Patients who died with TB/HIV co-infection (19,815)	2B
PELAQUIN MHH, et al. (2007)	Brazil	Portuguese	To identify factors associated with death and cure of TB patients	TB patients (96)	2B
ABEDI S, et al.(2019)	Will	English	To check mortality determinants in TB patients	Patients enrolled in the TB Control Program (2493)	2B
ALBUQUERQUE MFPM, et al. (2009)	Brazil	English	To analyze the probability of survival in people living with HIV and to identify risk factors for TB death.	TB patients (1459)	2B
REBOUÇAS MC, et al. (2017)	Brazil	English	To evaluate TB incidence and its consequences among individuals diagnosed with virological failure of HIV	People living with HIV (146)	2B
BIRLIE A, et al. (2015)	Ethiopia	English	To assess the time of reported deaths and its associated factors	TB cases under directly observed treatment (750)	2B
SILVA ESCADA RO, et al. (2017)	Brazil	English	To assess mortality of patients who started HIV treatment after tuberculosis treatment	Patients with TB/HIV co-infection (246)	2B
ADAMU AL, et al. (2017)	Nigeria	English	To assess child mortality during TB treatment	TB patients under 15 years old (299)	2B
SILVA DR, et al. (2010)	Brazil	English	To identify clinical and epidemiological factors associated with death in patients with an in-hospital diagnosis of tuberculosis	Patients who started TB treatment after hospitalization (311)	2B

Subtitle: *Scientific Evidence Level (SEL) using Oxford Centre Evidence-Based Medicine (OCEBM) (2009) TB = tuberculosis; HIV = Human Immunodeficiency Virus; AIDS = Acquired Immune Deficiency Syndrome.
Source: Rocha AC, et al., 2021.

The factors associated with TB mortality or survival were identified in several studies. Although the studies had different designs and were conducted in various regions of the world, they revealed some common elements among the main demographic and socioeconomic factors, such as male gender, older age of patients with TB and the younger age group of those with TB/HIV co-infection, low schooling, and poor housing conditions. Common lifestyle factors such as smoking, alcoholism, and comorbidities such as diabetes, kidney disease, immunosuppressive diseases and cancer were found. In the clinical aspects of the disease, factors such as treatment <60 days, previous TB treatment, extra-pulmonary disease, and pulmonary and extra-pulmonary disease together contributed to the shorter life span or increased mortality (**Frame 2**).

The presence of HIV/AIDS and its association with patient mortality was significant. It influences the lifespan of patients with TB after diagnosis. In most studies and in these cases, there was an association between TB and HIV co-infection. Further, some peculiarities that were important for the increase of unsuccessful outcomes were observed in cases with low count of CD4 cells (**Frame 2**).

Frame 2 - Factors associated with tuberculosis mortality or survival, estimators adopted, and main conclusions.

Author (year)	Associated Factors	Adopted Estimators (CI)	Key Findings
ROSSETO M, et al. (2019)	Up to 7 years of education Health Districts Center (CEN) Gloria/Cruzeiro/Cristal (GCC) East/Northeast (LENO) North/ Baltazar axis (NEB) Northwest/Humaita/Navegantes/ Ilhas (NHNI) Restinga/ Extreme South (RES) Southern/Center-Southern (SCS) Type of entry Relapse Return after default	 RR 3.9 (2.3-7.1) RR 1.5 (1.2-2.0) RR 1.6 (1.2-2.2) RR 1.4 (1.03-2.2) RR 2.0 (1.5-2.9) RR 1.5 (1.04-2.3) RR 1.4 (0.96-2.0) RR 2.0 (1.4-3.0) RR 1.3 (1.03-1.7) RR 1.5 (1.2-1.9)	Lower education, type of entry (relapse and return after default), and the most vulnerable health districts of living have the highest TB mortality.
MOOSAZADEH M, et al. (2014)	Immunosuppressive drug use HIV infection Renal complications	OR 3.9 (1.4-10.6) OR 19.1 (3.1-115.0) OR 6.8 (1.8-25.5)	HIV-positive serology, history of kidney disease, and immunosuppressive drug use increase the risk of death.
GESESEW H, et al. (2016)	Age (35-44 years) female sex worker Bedridden WHO HIV stage 2 WHO HIV stage 3 WHO HIV stage 4	AHR 2.9 (1.0-7.6) AHR 9.1 (2.7-30.7) AHR 3.2 (1.2-8.7) AHR 0.2 (0.06-0.5) AHR 0.3 (0.1-0.8) AHR 0.2 (0.04-0.5)	Predictors of mortality: age between 35 and 44 years, female sex worker, bedridden as functional status, WHO HIV clinical disease stage 1 patients compared to patients in stages 2, 3 and 4
PECEGO AC, et al. (2016)	CD4 cell count <50 cells/mm³ Recent HIV diagnosis at admission	HR 4.5 (1.6-12.4) HR 0.3 (0.1-0.7)	Six-month mortality in critically ill patients with TB/HIV co-infection is high and strongly associated with a CD4 cell count below 50 cells/mm3.
CHUQUIYAURI HARO R, et al. (2004)	Age over 30 years TB/HIV co-infection	OR 1.6 (1.2-2.1) OR 5.4 (3.9-7.3)	Age over 30 years and being HIV infected are independently associated with death during hospitalization for TB
KOLAPPAN C, et al. (2006)	Age over 60 years smoking and alcoholism Default Failure	AHR 3.0 (1.7- 5.3) AHR 2.9 (1.8-4.7) AHR 3.3 (1.9–5.5) AHR 7.7 (3.4–17.5)	Older age, treatment default, treatment failure and the combination of smoking and alcoholism are risk factors for TB mortality.
LIMA MS, et al. (2016)	Male sex Region of Residence Southeast South	RR 2.4 (2.2; 2.7) RR 2.4 (1.8- 3.0) RR 3.2 (2.5- 4.1)	The highest mortality rates are found among males, those in economically productive age groups, and residents of the Southeast and South regions.

Author (year)	Associated Factors	Adopted Estimators (CI)	Key Findings
PELAQUIN MHH, et al. (2007)	Age over 50 years Alcoholism Be employed	OR 8.6 (2.5-29.3) OR 30.8 (9.5-100.2) OR 0.3 (0.1-0.9)	The combination of suffering from alcoholism, being unemployed, and being over 50 years increase the chance of mortality by 25 times
ABEDI S, et al.(2019)	Male Diabetes TB-HIV co-infection Cancer development	HR 1.8 (1.2-2.6) HR 1.7 (1.2-2.6) HR 22.1 (7.3-66.4) HR 4.8 (2.6-8.8)	Male gender, TB/HIV co-infection and concurrent development of TB and cancer are determinant factors of death.
ALBUQUERQUE MFPM, et al. (2009)	HIV positive co-infection Late initial treatment (>60 days) Weight loss Previous TB treatment	HR 6.5 (1.7-24.9) HR 2.7 (1.4-5.4) HR 2.5 (1.3-5.0) HR 2.0 (1.1-3.5)	In the first year of follow-up, the factors associated with death are older ages, HIV-positive serology, and late initial treatment for TB Considering the entire study period, the predictive factors associated with death are age, HIV positive serology, late initial treatment, weight loss, and previous TB treatment.
REBOUÇAS MC, et al. (2017)	Less than 8 years of study Last CD4 count < 200 mm3	RR 3.3 (1.1-10.1) RR 6.1 (1.8-20.9)	Low education and low CD4 cell count in the diagnosis of virological failure are risk factors associated with TB and early mortality.
BIRLIE A, et al. (2015)	Weight < 35kg HIV positive	OR 3.9 (1.6-9.3) OR 2.3 (1.2-4.2)	Most deaths occur in the first two months of TB treatment. TB/HIV co-infection and a baseline body weight of <35 kg increase the mortality rate during TB treatment.
SILVA ESCADA RO, et al. (2017)	CD4 T cell count at TB diagnosis (≤ 50 cells/mm3) Mechanical ventilation Disseminated TB	HR 3.1 (1.7-5.6) HR 2.8 (1.2-6.8) HR 3.7 (1.3-10.6)	Mortality is higher in the first three months of the TB treatment. CD4 T cell count ≤50 cells/mm3, requirement of mechanical ventilation, and presence of disseminated clinical presentation of TB are independently associated with higher mortality risk.
ADAMU AL, et al. (2017)	Extra-pulmonary disease Both pulmonary and extra-pulmonary disease Previous TB treatment	AHR 2.2 (1.3-3.9) AHR 3.0 (1.7-5.4) AHR 2.0 (1.1-2.8)	It occurred high and early mortality of children. Risk factors for mortality include previous treatment for TB, HIV infection, extra-pulmonary disease, and both pulmonary and extra-pulmonary disease.
SILVA DR, et al. (2010)	In-hospital deaths Mechanical ventilation Consolidation in chest X-ray Negative sputum smear Predictors after discharge Duration of hospitalization Current smoker	OR 30.2 (13.3-68.5) OR 3.9 (1.6-9.7) OR 7.4 (1.9-28.5) OR 1.0 (1.01-1.03) OR 2.1 (1.0-4.3)	Mechanical ventilation, consolidation in chest x-ray, and negative sputum smear are predictors of in-hospital deaths. Predictors of mortality after discharge include total duration of hospitalization and being a current smoker.

Subtitles: TB = Tuberculosis; HIV = Human Immunodeficiency Virus; AIDS = Acquired Immune Deficiency Syndrome; WHO = World Health Organization; OR = Odds Ratio; AHR = Adjusted Hazard Ratio; HR = Hazard Ratio; CI = Confidence Interval
Source: Rocha AC, et al., 2021.

A summary of the main factors associated with TB patient mortality or survival described in the studies is presented in **Frame 3**.

Frame 3 - Summary of main factors associated with tuberculosis mortality or survival

Associated Factors	References
Age	CHUQUIYAURI HARO R, et al. (2004) KOLAPPAN C, et al. (2006) PELAQUIN MHH, et al. (2007) GESESEW H, et al. (2016)
Sex	CHUQUIYAURI HARO R, et al. (2004) ABEDI S, et al. (2019)
Years of schooling	ROSSETTO M, et al. (2019) PELAQUIN MHH, et al. (2007)
Place or state of residence	ROSSETTO M, et al. (2019) LIMA MS, et al. (2016)
Weight loss	BIRLIE A, et al. (2015) ALBUQUERQUE MFPM, et al. (2009)
Occupation	PELAQUIN MHH, et al. (2007) GESESEW H, et al. (2016)
Clinical Form	PELAQUIN MHH, et al. (2007) SILVA ESCADA RO, et al. (2017)
Smoking	KOLAPPAN C, et al. (2006); SILVA DR, et al. (2010)
Alcoholism	KOLAPPAN C, et al. (2006)
Use of drugs	SILVA DR, et al. (2010)
Late treatment	ALBUQUERQUE MFPM, et al. (2009)
HIV positive	MOOSAZADEH M, et al. (2014) CHUQUIYAURI HARO R, et al. (2004) ABEDI S, et al. (2019) GESESEW H, et al. (2016) PECEGO AC, et al. (2016)
CD4 smaller than 200mm^3	REBOUÇAS MC, et al. (2017)
CD4 smaller than 50mm^3	SILVA ESCADA RO, et al. (2017) PECEGO AC, et al. (2016)

Subtitle: HIV = Human Immunodeficiency Virus
Source: Rocha AC, et al., 2021.

DISCUSSION

The analysis of this review brought the possibility of understanding factors associated with survival and death of TB patients. Even in different countries with different approaches and populations, the factors described were similar.

The associated factors are related to the socioeconomic characteristics of the population of patients with TB. Male gender, found in several studies throughout this review, is described in the literature to be associated with high TB incidence and mortality rates (ROSSETTO M, et al., 2019; CHUQUIYAURI HARO R, et al., 2004; KOLAPPAN C, et al., 2006; ABEDI S, et al., 2019; BIRLIE A, et al., 2015; HORTON KC, et al., 2016). This corroborates the understanding that when males fall ill with TB, they need differentiated attention that meets their needs, avoiding the most severe outcome, which is death (ABEDI S, et al., 2019).

Another condition referred to was ethnicity or race/skin color, like: Black, Yellow, White, Mixed Ethnicity (Black and White) and Indigenous. Blacks, due to their poor social condition, manifest more episodes of TB when compared to other races (NAHID P, et al., 2011). The greatest vulnerability to TB occurs among those who live with poor nutrition and poor housing conditions. It is noteworthy that black population has a higher risk of death due to TB than the white population (LIMA MS, et al., 2016).

The presence of social inequalities is a determining factor for hospitalization and death of TB patients (ROSSETTO M, et al., 2019). Mortality among patients with TB/HIV co-infection, when analyzed by regions of Brazil, is still high in places with greater social vulnerability (LIMA MS, et al., 2016). It is emphasized that social inequalities make it possible to spread various diseases, especially infectious diseases (BASTA PC, et al., 2013). This fact has great relevance, which led the (WHO) to propose the reduction of social inequalities as one of the most important goals to be achieved by 2015, to reduce the incidence and mortality from TB (WHO, 2018).

Low education, unemployment and living conditions were observed as factors associated with TB mortality and survival, which in addition to reaffirming the existence of social inequalities, contribute to lower adherence of individuals to TB treatment, leading to treatment default (PELAQUIN MHH, et al., 2007; REBOUÇAS MC, et al., 2017). TB plans should consider not only actions in the health sector but also actions in other socioeconomic and political sectors, which favor health education strategies toward these patients (M'IMUNYA JM, et al., 2012).

TB bacilli infection can occur at any age. Mortality in patients with TB/HIV co-infection is predominant in the ages >30 years or a little later in the age group of 35-44 years. This fact shows how much co-infection affects adult young individuals of economically active age and therefore can impact society and how these two diseases deserve attention due to their potential to cause early mortality (LIMA MS, et al., 2016; LIN CH, et al., 2014; GESESEW H, et al., 2016).

The age for mortality is higher in patients with TB than in those with TB/HIV co-infection. This is often attributed to the delayed diagnosis due to atypical clinical conditions. Older age and the onset of other health problems may reactivate the dormant infectious focus, and people become ill because the body's defense system is not functioning satisfactorily (ROSSETTO M, et al., 2019; CHUQUIYAURI HARO R, et al., 2004; KOLAPPAN C, et al., 2006; ABEDI S, et al., 2019; REBOUÇAS MC, et al., 2017; GESESEW H, et al., 2016; ALBUQUERQUE MFPM, et al., 2009).

Among the lifestyle habits that contribute to mortality or survival, alcoholism, smoking and illicit drug use stood out (KOLAPPAN C, et al., 2006; SILVA DR, et al., 2010). Alcohol use is known to cause difficulties in treatment adherence, treatment default, cases of multidrug-resistant TB, and hepatotoxicity (SILVA DR, et al., 2018). Smoking causes active disease progression and delay in converting the sputum smear to negative (NOVOTNY, et al., 2017). The use of illicit drugs contributes to the high transmission of TB because these patients often have more damaging lifestyle habits and difficulty adhering to treatment (SILVA DR, et al., 2010). Factors such as alcoholism, smoking and illicit drug abuse contribute to treatment failure and more severe cases that may shorten survival or lead to patient death (KOLAPPAN C, et al., 2006; SILVA DR, et al., 2010)

Associated comorbidities may influence outcomes unfavorably for patients with TB, such as diabetes mellitus and kidney diseases (REBOUÇAS MC, et al., 2017). Diabetes mellitus leads to multi-resistance in patients with TB, leading to a higher risk of treatment failure (SILVA DR, et al., 2018). Kidney disease is also associated with unfavorable TB outcomes (MOOSAZADEH M, et al., 2014). The use of immunosuppressive drugs and cancer also contributes to lower survival and higher mortality (MOOSAZADEH M, et al., 2014; ABEDI S, et al., 2019).

Most studies in this review were conducted with patients with TB/HIV co-infection, yet they were included to gain a broader picture of TB mortality. It is undeniable that TB/HIV co-infection is an important factor related to mortality of patients with TB. Undoubtedly, the AIDS epidemic contributes a lot to increased TB mortality (MOOSAZADEH M, et al., 2014; CHUQUIYAURI HARO R, et al., 2004; ABEDI S, et al., 2019; GESESEW H, et al., 2016; PECEGO AC, et al., 2016).

In patients with AIDS, TB is the most common infectious disease present and has an impact on the quality of life and mortality. In several studies, HIV infection was significant in increase mortality rate (ROSSETTO M, et al., 2019; ABEDI S, et al., 2019; BIRLIE A, et al., 2015; HORTON KC, et al., 2016; NAHID P, et al., 2011; LIMA MS, et al., 2016; BASTA PC, et al., 2013; PELAQUIN MHH, et al., 2007; REBOUÇAS MC, et al., 2017; SILVA ESCADA RO, et al., 2017; ADAMU AL, et al., 2017; PECEGO AC, et al., 2016).

Mortality due to TB even among HIV-infected patients was ten times higher than HIV-free patients (BIRLIE A, et al., 2015). However, it should be noted that no-TB patients, in other words HIV positive patients are also hospitalized and may often have the death as outcome (SILVA ESCADA RO, et al., 2017).

Other factors related to HIV status, such as the stage of infection, were checked for mortality and survival. The WHO determines four stages of infection depending on the timing and changes that have already occurred and states that stage 1 of HIV is important for mortality from the disease because this stage is when infection with the virus causing AIDS occurs, until the first signs of the disease appear. However, one of the studies found that stage 2 was more important for mortality, which often goes unnoticed by the individual (MOOSAZADEH M, et al., 2014; MINISTÉRIO DA SAÚDE, 2018).

In addition, it verifies the early death of these individuals hospitalized with TB/AIDS comorbidity, when followed up after discharge, more than half died in six months. Most of these patients were diagnosed with HIV infection 30 days before critical care admission. This shows the severity of the two epidemics given that these patients could have been co-infected for some time and their clinical conditions were aggravated by the untreated disease evolution (GESESEW H, et al., 2016).

Another important fact in TB/HIV co-infection is the defense cells of the human body. The CD4 cells, which defend against the body's aggressors. When the virus enters the cell, it gradually leads to difficulty in fighting infections. Thus, using antiretroviral medication as early as possible decreases viral replication. The lesser the CD4 lymphocytes, the greater the vulnerability of the immune system and the greater the risk of complications and infections. In some selected studies, CD4 <50 cells was a factor associated with mortality (SILVA ESCADA RO, et al., 2017; PECEGO AC, et al., 2016).

It is relevant to emphasize that clinical comorbidities, the use of immunosuppressive drugs, and low weight are conditions that contribute to shorter survival of patients, and among them, having a history of kidney disease, cancer, diabetes, and early initial treatment were statistically associated with TB death (ABEDI S, et al., 2019; BIRLIE A, et al., 2015; REBOUÇAS MC, et al., 2017; ALBUQUERQUE MFPM, et al., 2009; MOOSAZADEH M, et al., 2015).

Alcoholism and smoking were also considered risk factors for mortality and decreased survival as they cause decreased immunity and social problems, increasing the incidence of the disease and making it difficult for the affected to recover (KOLAPPAN C, et al., 2006; SILVA ESCADA RO, et al., 2017).

TB death, which should be a rare event, occurred precocious in some studies; approximately 21% died within 48 hours of hospitalization and more deaths occurred in the first months of treatment. In addition, the length of hospital stay was relevant in these deaths (BIRLIE A, et al., 2015; SILVA ESCADA RO, et al., 2017).

TB/HIV co-infection is undoubtedly a risk factor for death, but it is relevant that the most severe problem is the lack of timely diagnosis and early treatment of both diseases. This delay in diagnosis decreases the chances of defense of the patient's body, generating complications and often death. However, the complications that cause the death of the TB patient are not just co-infection. This fact occurs due to the worsening of their condition, often caused by diagnostic difficulties and non-adherence to treatment. It is noteworthy that the diagnosis of the disease is often made in the hospital environment and the delay contributes to the poor outcome (ALBUQUERQUE MFPM, et al., 2009).

Other important factors are the patient's conditions of vulnerability because TB has a close relationship with poor socioeconomic conditions, so there is a need for improvement in some social factors, such as poverty reduction, encouraging education, as well as the use of appropriate tools to enable the individual to understand their disease, thus creating conditions that favour adherence to treatment. It is also necessary not only to invest in TB control program, moreover reinforce the offering of an effective program with easy access to all (ROSSETO M, et al., 2019).

Another problem is the lack of effective monitoring of patients with comorbidities because those infected with TB can hinder the efficiency of treatment for pathologies and death may occur (ADAMU AL, et al., 2017).

FINAL CONSIDERATIONS

This systematic review provides the possibility to better understand the survival and mortality in patients with TB. Although the selected studies were performed with different methodologies and heterogeneous populations, it is clear that some factors related to death and survival are repeated in the most diverse places and countries. It is observed that there are several factors that can be associated with mortality and survival in patients with TB. Through this study, it was possible to identify the main risk factors according to the populations of the studies found. It is suggested that further studies related to these factors may quantify the strength of association of each factor with TB as these should be considered for effective functioning of the TB control program.

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