Eight year survey of tuberculosis in-hospital mortality in the South Eastern part of Romania

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Abstract: Romania remains a high burden TB European country, with an incidence of 70.2‰ in 2014 although the incidence, mortality, and morbidity are constantly decreasing.

Objectives. To determine the level of TB-associated mortality in the deaths cohort of inpatients from Clinical Pneumophtisiology Hospital and identifying the risk factors of TB death-related.

Material and method. A retrospective study was done recording demographic characteristics, comorbidities, duration of the hospitalization since death, chest Xray pattern, HIV, and drug-resistant status, and TB category were recorded.

Results. From a total of 4,609 TB patients 247 deaths due to all causes were registered from 2010 to 2017, from witch 126 deaths were caused by tuberculosis disease (51%) with an overall fatality rate of 2.7%. Most cases with TB deaths (n=7 26.5%), were declared new cases of TB. Death occurred in the first 7 days (55.5%). The mean interval of surviving after admission in hospital was 13.09 days +/- 14.355 std dev; F=17.698; p=0.000). Comorbidities associated with TB were alcoholism (32%), COPD (14%), malignancies (3.6%), diabetes (7%), heart disease (5%), hepatitis and liver cirrhosis (4%), AIDS (0.8%). Risk factors consisted in delayed diagnosis of extensive fibro-cavitary pulmonary tuberculosis active disease (74.6%), male gender, age under 60 year-old, low income or homelessness (15%), unemployment and the absence of medical insurance (35%), cachexia (58%), MDR (n=1; 0.8%) were identified. 12 patients died due to massive hemoptysis. Delayed anti TB therapy was noticed in 21% with negative smears.

Conclusion. Tuberculosis remains an important cause of mortality in a Tertiary Care Pneumophtisiology hospital.

Key Words: tuberculosis, in-hospital mortality, comorbidities.

INTRODUCTION

Tuberculosis is still having a high morbidity and mortality worldwide [1]. In our era, despite the discovery and availability of preventive and curative chemotherapy, Pulmonary Tuberculosis (PTB) is still a fatal air borne transmitted disease. In Romania, a developing and high burden TB European country, with several lower income regions, mortality is monitored in tandem with TB morbidity and, in the last decade, both indicators are decreasing. The impact of implementing directly observed therapy was noticed, in Romania, by a descendend trend of TB global incidence from 142.2‰ in 2002 to 70.2‰ in 2014 [2]. Considering the availability of appropriate antiTB drugs, in-hospital mortality can be considered a new epidemiological indicator of the delayed diagnosis and severity of TB disease.

OBJECTIVES

A 8 year retrospective study was performed in order to determine in hospital TB-associated mortality in the deaths cohort of inpatients, registered in an administrative electronic database of a Tertiary Care...
Clinical Pneumophtisiology Hospital, and to determine the risk factors TB death-related.

MATERIALS AND METHODS

A retrospective cohort study of TB died cases was assessed at Clinical Pneumophtisiology Hospital of Constanta, Romania, a 185-bed regional hospital. There were 25,741 patients admitted for hospitalization, from 01 January 2010 to 31 December 2017. The diagnosis of active TB disease was provided by bacteriological exams (positive smears, liquid culture using BACTEC™ MGIT™ (automated mycobacterial detection system; Becton Dickinson, Sparks, MD, USA) and/or solid culture on Lowenstein Jensen medium), with detecting Mycobacterium tuberculosis (MTB) and drug sensitivity testing (DST), histology and/or typical clinical and radiological features of tuberculosis. Eligible cases were considered all registered in-hospital PTB deaths. Electronic hospital admissions source and written medical records of all 247 died inpatients were analyzed, collecting demographic characteristics, spectrum of comorbidities, duration of the hospitalization measured in days, symptoms, sputum smear, culture, and drug-sensitivity test results, chest radiological lesions pattern and extension, HIV and drug resistant (DR) status, and TB category of every notified case (new case, relapse, failure, abandon) data. According to the localization, TB disease was considered as pulmonary (P), extrapulmonary (TB) or both (P+EP). Chest Xray lung lesions were classified as infiltrative, nodular, cazeous ulcerated, cavitary lung lesions, and micronodular pattern of miliary TB and the extension as unilateral or bilateral was noticed. Cases with isolated MTB strains with primary or secondary resistant pattern to both isoniazid and rifampicine were reported as multidrug resistant (MDR) TB disease. Deaths were reviewed respecting the previous obtained informed consents and anonymity of patients. The primary outcome consisted to determine annually in-hospital mortality rate TB related. According to the 2002 edition of McGraw-Hill Concise Dictionary of Modern Medicine, in-hospital mortality rate was calculated annually by the ratio: "the death rate/1000 admissions at a particular hospital". The second outcome referred to the impact of TB risk factors related to in-hospital deaths. Comorbidities were isolated or multiple requiring categorized group of obstructive lung diseases (OLD) as bronchial asthma and COPD, chronic lung disease, malignity, metabolic syndrome, cardiovascular diseases, immunosuppressive conditions.

Statistical analysis including Anova analysis, Kaplan Meier method of survival, cox regression, log rank (Mantel Cox) was done using SPPS 19 version and EPI INFO version 7, considering a p value below 0.05 as significant.

The study was approved to be performed and published by the local ethics committee of Clinical Pneumophtisiology Hospital Constanta.

RESULTS

A total of 4,609 TB patients were reported among all 25,741 admitted cases from 2010 to 2017. There were reported 247 deaths during hospitalization (0.95%) in patients with a mean and median age of 59 years (Fig. 1). Death outcome was observed predominantly among males (n=213; 86.2%), mean aged 59 years +/- 11.511 dev std. without differences comparative with females (F=0.003; p=0.954).

A half of all deaths were caused by tuberculosis disease (n=126; 51%) with an overall fatality rate of 2.7% and an in-hospital mortality, by any cause of death, of 9.6‰ (n=247/25,741)(Table 1). The trend of TB admitted cases declined from 2010 to 2017, but mortality increased in the last three years (Fig. 2). TB in-hospital mortality rate among admitted TB cases during this interval was 4.9‰ (Table 1).

Death caused by active TB disease was registered mostly among new cases of tuberculosis (n=72; 57%) than relapses (n=21; 26.5%), failures (n=12; 9.5%) or chronics (2.5%). The mean interval of survival after admission in hospital was two times more decreased in nonTB cases versus TB ones (7.07 days +/- 6.595 versus 13.09 days +/- 14.355 std dev; F=17.698; p=0.000). The fatal events produced sooner, in the first 7 days, in 55.5% of all cases (Fig. 3), were more frequently among nonTB

![Figure 1. Distribution of cases by the group of age according to the cause of death.](image)

![Figure 2. The trend of TB admitted cases in hospital and deaths reported within hospitalization; 2010-2017.](image)
patients (58/126; 46% versus 79/121; 65%; OR=0.4535; RR=0.705; chi2=9.2295; p=0.0023). Comorbidities were more frequently diagnosed in nonTB group (82/121; 67.7% versus 48/126; 38%; OR=0.2927; RR=0.5621; chi2=21.7118; p=0.000), with predominance of cardiovascular and metabolic diseases, having no significant impact on reducing the mean time of survival among TB cases (OR=1.38; RR=1.15; chi2=1.568; p=0.21) (Fig. 3). Illness associated TB consisted in alcoholism (32%), COPD (14%), malignancies (3.6%), diabetes (7%), heart disease (5%), hepatitis and liver cirrhosis (4%), AIDS (0.8%). The mean age for dead TB patients was significantly lower (55.38 years +/-11.518 dev std) comparative with nonTB ones (62.92 years +/- 11.75 std dev) according to Anova analysis (F= 26.193; p= 0.000). The group of age 50-59 years is the most vulnerable decade to the occurrence of severe forms of TB followed by consequent death (Fig. 3).

Survival analysis by Kaplan Meier method reveals significant decreased values of mean and median time of survival in nonTB cases than TB ones (p=0.000) (Tabel 2; Fig. 4) but, calculating the risk of death among all inpatients, the values of odds ratio (OR) and risk ratio (RR) are statistically higher among TB cases (n=126/4609) than nonTB (n=121/21,132) [OR= 4.8805 (3.750- 6.2764), RR= 4.7744 (3.279- 6.1147); chi2= 185.9546; p=0.000].

Identified risk factors consisted in delayed diagnosis of extensive fibrocavitary pulmonary tuberculosis active disease (n=94/126: 74.6%), especially new cases than relapses (65/72 versus 13/21; OR= 5.7143; RR= 1.4583; chi2=9.571; p=0.0019), a high rate of admissions through the emergency units (78%), male gender, age under 60 year-old (mean age 55.91 years +/-12.071 std dev; limits from 26 to 84 yrs), poverty combined with homelessness (n=18; 15%), unemployment and the absence of medical insurance (n= 28; 35%), cachexia (n=73; 58%), MDR (n=1; 0.8%). Deaths was related with AIDS in only one case of all disseminated TB disease forms (n=15; 12%). Masive hemoptysis was recorded.
TABLE 2. Means and Medians for Survival Time among cases (TB and non TB)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>95% Confidence Interval</th>
<th>Median</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>Estimate</td>
<td>Std. Error</td>
<td>Lower Bound</td>
<td>Upper Bound</td>
</tr>
<tr>
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<td>7.066</td>
<td>0.600</td>
<td>5.891</td>
<td>8.241</td>
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<td>1=Yes</td>
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<td>1.279</td>
<td>10.581</td>
<td>15.594</td>
</tr>
<tr>
<td>Overall</td>
<td>10.138</td>
<td>0.739</td>
<td>8.688</td>
<td>11.587</td>
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Overall Comparisons

- Log Rank (Mantel-Cox) 13.768 1 0.000

as cause of death in 12 TB patients. Regimens of antiTB drugs were started in the first 2 days after admissions in hospital in 82% of cases. Delayed anti TB therapy was noticed in a few cases with negative smears (21%). Most of the TB cases with reported death were delayed diagnosis. Symptoms like prolonged cough, breathlessness, sweats, loss of appetite and weight were noticed in the majority of admitted patients (n=106; 84%). Cachexia was mostly associated with poverty (34/46 versus 39/80; OR=2.9786; RR=1.5162; chi2=7.5281; p=0.006).

DISCUSSIONS

Tuberculosis has been a mandatory notifiable disease in Romania since 1965. According to the most recent epidemiological report presented by the head of the National Romanian Programme of TB Surveillance and Control, in the IVth Romanian National Conference of Tuberculosis in April 2018, in Romania, in the last 12 years, the trend of TB decreased by 43% in prevalence, 50% in global morbidity, 56% mortality and 56% the pediatric morbidity [3]. Despite these figures, the burden of TB in Romania is underestimated because of the immigration phenomenon. Migrant TB is a new form of TB with imprecise evolution and impact on general population health [4]. The in-hospital mortality is higher than mortality reported in general outpatient population, ambulatory or primary care services as CBP de Almeida et al. showed in their meta-analysis [5]. It is a paradox of coexisting severe extensive forms of PTB and a continuous decreasing of annual TB notifications in Constanta county in the last years. A rising population of advanced and fatal pulmonary TB disease cases is observed among inpatients [6-7]. Despite the availability of DOT, the delayed TB diagnosis is a risk to higher rates of mortality [8-10] and the most severe forms are associated with death within a week of admission [11] as our study evidenced. One of the limit of our study can be the assessment of the subgroup of TB cases with negative smears. These cases received later therapy than cases with positive smears and difficult diagnosis of underlying malignancies could be an issue [12].

TB represents a major cause of hospitalization and death among HIV individuals worldwide even in high-income settings [13]. In the last decade of XXth century, in Romania, and most of all Constanta county, there was an input of paediatric TB HIV related morbidity and mortality [14,15]. Long term survivors become adults and there are several studies revealing TB - HIV/AIDS related is more likely to have a reserved prognosis because of severe immunosupression, disseminated forms of TB, severe complications, tendency to relapse, failure of antiTB treatment, including MDR [16]. Both HIV and MDR are considered important predictors of in-hospital mortality [5] but they were not identified in our study. Although other studies revealed the burden of HIV/AIDS in Constanta, Romania [15], or a high association of HIV with disseminated TB in adults [17], our study showed that deaths caused by disseminated TB were not HIV related and the impact of HIV infection/AIDS on in-hospital TB mortality was insignificant, as well as MDR. Drug addiction related or not with TB, TB-HIV was not identified but it could be underestimated among cases in Romania.

This is the first study of in-hospital TB morbidity performed in Romania revealing a low rate (4.9‰) but a substantial risk of mortality (RR=4.7744; p=0.000) among hospitalized TB adult patients. A systemic review and meta-analysis of in-hospital TB mortality, published in 2016, mentioned the huge impact of HIV infection and reported an attributable TB deaths rate of 24.9% [4]. Despite Constanta County is considered an intermediate TB burden with a low HIV prevalence, the trend of TB in-hospital mortality is rising in the last years as a similar retrospective cohort study of 349 hospitalized patients mean aged 62 years showed [5]. Reserved prognosis and death of hospitalized TB patients related with poverty and comorbidities as cachexia, anemia, cardiovascular diseases and older age over 65% was revealed even in countries with a low burden TB like Israel [6]. Studies revealed that nutritional deficit can represent a cause of increased mortality in patients [18,19], especially in those hospitalized with PTB secondary [20] as our study revealed cachexia and poverty association. More effective combat of TB morbidity and mortality rates requires a reconfiguration of adequate funding especially for preventing the spreading of poverty, TB and the most dangerous MDR and XDR TB forms [21].
CONCLUSIONS

In hospital mortality caused by TB active disease increased slowly but the risk of fatal TB prognosis in non HIV hospitalized adults is critically high especially and represents a red flag for the Romanian National Programm of TB Control. There were identified host risk factors as male gender, age up to 60 year-old, alcoholism, unemployment and poverty related with delayed diagnosis and treatment of severe PTB. Most patients with PTB that do not survive the disease diagnosis are new cases at first treatment, with extended fibrocavitary lung disease and intense contagiosity and they die in the first 7 days after admission.

Conflict of interest. The authors declare that there is no conflict of interest.

References