ABSTRACT
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1. Background

1.1. Tuberculosis: a public health problem

Tuberculosis remains a major public health problem with an annual burden of 9.0 million new cases and 1.5 million tuberculosis deaths globally. Amongst these cases, India accounts for 2.1 million new cases with an incidence of 171 (95% confidence interval, CI = 162 – 184) per 100 000 individuals. In 2013, the World Health Organization (WHO) estimated 0.24 million tuberculosis deaths in India in 2013 with a mortality rate of 19 (95% CI = 12 - 28) per 100 000 individuals. With this significant number of cases, India ranks first amongst the 22 high burden countries (HBCs) enlisted by WHO. Controlling tuberculosis morbidity and mortality is therefore one of the major public health priorities in India.

1.2. Tuberculosis in women

Despite a larger proportion of tuberculosis cases and deaths among men as compared to women, of Several studies conducted in developed countries at the end of the 19th and early 20th centuries have identified that the peak of tuberculosis mortality among women was in a lower age group than men in comparative ages, that is, younger women tuberculosis patients were at an increased mortality risk. That gender-specific risk factors contribute to lower treatment seeking amongst women as compared to men from developing countries has been reported. Studies have indicated that in developing country settings, a multiple step decision making process preceding access to care and the choice of sub optimally qualified health care provider as recognized contributor to increased risk of mortality amongst women. Studies conducted across various low and lower middle income countries suggest an underplay of social stigma and tuberculosis in women.

2. Research gap and study rationale

There are several studies reporting risk of mortality due to tuberculosis in India. There is however a paucity of age sex distributed tuberculosis mortality data in India, so that there is no data to determine whether there is an increased risk of mortality in young women tuberculosis patients. Few studies have examined gender specific risk factors of tuberculosis mortality through traditional epidemiological studies.
3. **Aim**

Thus the aim of the study was to determine survival and the risk factors for mortality in women patients who had been on directly observed treatment short course (DOTS) at various tuberculosis treatment centres in Pune city, India. During the study period, all participants had completed DOTS treatment.

4. **Objectives**

The objectives of the study were:

1. To determine survival probabilities of pulmonary tuberculosis patients at eighteen months after initiation of DOTS.
2. To determine whether there is a gender based difference in the survival probability of pulmonary tuberculosis patients at eighteen months after initiation of DOTS.
3. To determine the risk factors for mortality in women patients who were on DOTS.

5. **Method**

5.1 **Study design, setting and population:** The study was based on a retrospective cohort consisting of all registered patients initiating DOTS between January 2009 and December 2010.

5.2 **Brief description of the study:** Patients were traced to their respective addresses for determining their survival status at 18 months from initiation of treatment. Information on risk factor was collected through a face to face interview of families of expired patients. Every second surviving erstwhile patient was selected randomly for comparison. Data on clinical and treatment characteristics were collected from the treatment card.

5.3 **Ascertaining tuberculosis death:** Due to lack of medical certification of death as occurring due to tuberculosis, death due to tuberculosis was defined as a patient diagnosed with pulmonary tuberculosis, who had been on DOTS within 18 months of the date of interview, and were reported to have cough with or without haemoptysis, fever and weight loss prior to demise.

5.4 **Ethical consideration:** The study was approved by the Institutional Ethics Committee of Savitribai Phule Pune University.
5.5. **Statistical analysis:** Survival analysis was conducted using Kaplan Meier test followed by log rank test for testing significant difference in the survival probability. Univariate analysis was done using logistic regression test to determine odds ratio (OR at 95% CI) for each risk factor followed by multivariate analysis using multinomial logistic regression test.

6. **Results**

6.1. **Profile of the study cohort:** Between January 2009 to December 2010, 3802 patients had registered with the DOTS centres in the six Tuberculosis Units (TUs) in Pune city. The mean age of patients registered with the DOTS centres was years 37.34 (95% CI = 36.87 – 37.81). There were 66.0% (2511) males and 34.0% (1291) female patients. The mean age for male patients was significantly higher than that of female patients (39.39 years, 95% CI = 38.83 – 39.95 and 33.38 years, 95% CI = 32.58 – 34.18, P = 0.0001). More than half of women patients (56.3%) were aged below 30 years as compared to 32.2% of men in the cohort.

6.2. **Survival analysis of patients registered at the DOTS centres in Pune city in 2009 and 2010:** Eighteen months after initiation of DOTS, 2625 (69.0%) patients were surviving while 491 (14.9%) patients had expired due to tuberculosis. The mean survival was 16.72 months (95% CI = 16.60 – 16.84). Survival analysis showed a lower survival among male patients (P = 0.0001), patients aged more than 30 years (P = 0.0001), with history of tuberculosis (P = 0.0001), defaulting treatment (P = 0.0001) and those infected with HIV (P = 0.0001). The survival analysis revealed an overall higher survival amongst women patients (adjusted hazards ratio, AHR = 0.55, 95% CI = 0.44 – 0.68).

6.3. **Mortality estimates:** Mortality rate of the cohort was 111.43 per 1000 person years of observation (PYO). Overall case fatality rate (CFR) for the cohort was 15.20% (95% CI = 15.19 – 15.21). CFR was higher in men than women in all age groups. The cohort had a standardized mortality ratio (SMR) of 26.20 (95% CI = 23.88 – 28.52). Although CFR was higher in males in all age groups, SMR was higher in the women aged between 30 and 39 years as compared to men in the same age group.

6.4. **Risk factor analysis:** Risk factor data was collected for 475 relatives of expired cases and 879 randomly selected surviving individuals.
6.4.1. Risk factors for mortality among tuberculosis patients on DOTS: A higher risk of mortality due to tuberculosis was associated with monthly household income less than ₹2040 (OR = 3.36, 95% CI = 1.80 – 6.27), body mass index (BMI) less than 18.50 kg/m² (OR = 1.83, 95% CI = 1.16 – 2.89), treatment default (OR = 2.24, 95% CI = 1.13 – 4.46), interruption of treatment due to DOTS drugs related side effects (OR = 10.25, 95% CI = 5.88 – 17.88), alcohol consumption (OR = 6.08, 95% CI = 3.23 – 11.45) and single marital status (OR = 1.96, 95% CI = 1.21 – 3.18).

6.4.2. Gender difference in distribution of risk factors for tuberculosis mortality: As compared to men, women revealed association between risk of tuberculosis mortality and age less than or equal to 30 years (OR = 2.70, 95% CI = 1.41 – 2.17), residence in non slum areas in the city (OR = 2.68, 95% CI = 1.28 – 5.76), dependent status (OR = 31.88, 95% CI = 15.02 – 67.68), self medication for management of initial symptoms (OR = 8.48, 95% CI = 1.02 – 70.28) and reported as abused by family members perceived to be due to tuberculosis (OR = 10.19, 95% CI = 1.72 – 60.41).

6.4.3. Characterization of expired versus surviving women patients: As compared to surviving women, risk of mortality in deceased women was associated with no (OR = 5.63, 95% CI = 1.69 – 18.76) or less than five years of education (OR = 5.94, 95% CI = 1.79 – 19.78), irregular treatment (OR = 2.39, 95% CI = 1.08 – 5.31), complaints of side effects due to DOTS drugs (OR = 3.69, 95% CI = 1.85 – 7.36), single marital status (OR = 3.77, 95% CI = 1.41 – 10.08), alcohol consumption (OR = 12.77, 95% CI = 3.45 – 47.34), perception that problems while negotiating marital alliances of other members of the family arose due to the patient having tuberculosis (OR = 200.29, 95% CI = 16.82–2384.94) and reported as abused by family members perceived to be due to tuberculosis (OR = 14.04, 95% CI = 2.32 – 84.90).

7. Discussion
The major findings of this study are as follows. Women exhibited an overall higher survival than men at eighteen months from the initiation of DOTS. However the SMR was higher in women aged between 30 and 39 years compared to men, identifying the phenomenon that has been previously reported in the literature from developed countries.11–15,27 Women aged less than or equal to 30 years, residing in the non slum
areas, practising self medication and reportedly subjected to domestic abuse, perceived to be due to tuberculosis were at an increased risk of mortality than men. As compared to surviving women, risk of mortality was associated with women with no or education less than five years, single marital status, with perception of social stigma, suffering from DOTS drugs related side effects, irregular use of drugs while on treatment and consuming alcohol. The study identified that the increased mortality risk in younger female tuberculosis patients, were primarily due to risk factors related to social vulnerability.

8. Utility of the study: The study identifies that socially disadvantaged young women tuberculosis patients are at an increased mortality risk. Risk factor data from this study indicates that low cost, easily implementable additions can reduce mortality due to tuberculosis among women.

9. Limitations: Absence of information of 10% of the cohort due to incorrect contact information was addressed by analysing associated factors (i.e. registration at the peripheral TUs). These patients were excluded from subsequent analysis. Another limitation was absence of known HIV status among 34% amongst registered patients.