

Observation Study among Cured Cases of Pulmonary Tuberculosis: A Long-Term Study under the Revised National Tuberculosis Control Program

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ABSTRACT

Background: Tuberculosis is one of the leading causes of mortality in India. The Revised National Tuberculosis Control Program (RNTCP) is a robust public health system to deal with Tuberculosis (TB) in India. Unless the treated patient comes back to the system with signs and symptoms of TB due to relapse or re-infection, there is no mechanism of follow-up or any method to know the relapse rate in the population. This study aimed to analysed trends in relapse tuberculosis cases and describe their associations with socio-demographic and clinical factors.

Subjects dan Method: In this prospective cohort study, 750 selected sample size who were declared “Cured” in four randomly selected TB units of Gwalior district were followed up for 1–5 years through home visits by trained staff with structured data collection forms. Data Collection was done between January 2022 to June 2022 and afterwards analyzed using Microsoft excel spreadsheet.

Results: The mean age of the index cases was Mean= 30.53; SD= 14.24 years, and there were 39 females and 64 males. At early stage (1-to-2-year posttreatment follow-up of 248 index cases) 199 (80.2%) were healthy and working without any symptoms of TB. Symptoms of TB were present in 49 (19.8%) cases. The after 2-year posttreatment TB Symptoms were present in 54 (19.3%) cases.

Conclusion: Long-term follow-up of cured, new smear-positive TB cases reinforce the effectiveness of anti-TB treatment under the RNTCP as assessed by improved health outcomes in more than two-thirds of cases and posttreatment survival of 80.72% of index cases. Further investigation needed to continue such follow-up for all TB cases treated under the RNTCP for effective end-TB strategy.

Keywords: tuberculosis treatment, follow-up, relapses, RNTCP

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BACKGROUND

Despite the significant achievements of The Revised National Tuberculosis Control Program (RNTCP), the burden of Tuberculosis (TB) continues to be India's severest health crisis and kills an estimated 480,000 Indians every year and more than 1400 every day (Central TB Division, 2017). Treat-

ment success under the DOTS concerns two outcomes-cured and treatment completed. Despite assessed as cured, patients can develop recurrent disease sometime after completing treatment either due to relapse of the same infection or reinfection with a different strain of Mycobacterium tuberculosis (MTB)(Chiang and Riley, 2005;

Verver et al., 2005). A relapse of the disease is an outbreak of the TB process in people who have previously had TB and successfully completed its treatment. Many researchers confuse Reinfection and Superinfection. In the case of reinfection, a person becomes infected again after the pathogen has been eliminated from the body, and in the case of superinfection, the patient is infected with another type (strain) of the pathogen until complete recovery. Exogenous or true reinfection can cause a recurrence of the disease only in cases of complete recovery with sanitation of the body, which in practice is extremely rare. With an incomplete cure, the entry of new mycobacteria is also possible, while layering with a new superinfection occurs. With endogenous reinfection, mycobacteria multiply from old foci, which is clinically manifested by exacerbation and progression of the disease (Bobokhojaev et al., 2018).

Recurrent disease is still considered to be an important measure of the efficacy of TB treatment, and it also has a major impact on patients. Recurrence rate is high in countries of high TB incidence (Sadacharam et al., 2007; Thomas et al., 2005) and reinfection is the principal cause, especially in the presence of high prevalence of coexisting human immunodeficiency virus (HIV) (Sonnenberg et al., 2001; Palmieri et al., 2002) There are recommendations according to which patients with residual post tuberculosis changes in the lungs (RPTCL), especially with large RPTCL, are at high risk of disease recurrence and therefore should be observed in the general medical Network (Bobokhojaev et al., 2018). Social factors in the patient also contribute to the development of relapses (Shao et al., 2021). Patients with recurrent tuberculosis in epidemiological terms are a "hidden reservoir of infection" since most of them are dominated by bacterial excretion (Azhar, 2012). Tuberculosis

recurrences tend to be more severe and often give a positive drug-susceptibility test to anti-tuberculosis drugs (Zong et al., 2018).

In the India, unfortunately, cases of relapse are not uncommon. However, a differentiated account of exogenous and endogenous reactivation of the tuberculous process has not been established to date, and the incidence of TB relapses has not been studied (Mathur et al., 2019) According to the Standards of TB Care in India, after completion of TB treatment, the patients should be followed up with clinical and/or sputum examination at the end of 6 months and twelve months. Long-term follow-up of cured TB patients will be useful for assessing health outcomes, which enables early detection of recurrence and mortality among these patients. MoHFW India 2014) .This study followed patients whose declared as "Cured" as per the RNTCP guidelines to study the frequency of relapses of pulmonary tuberculosis and factors contributing to their development in the Gwalior district of North Madhya Pradesh India. This study aimed to analyzed trends in relapse tuberculosis cases and describe their associations with socio-demographic and clinical factors.

SUBJECTS AND METHOD

1. Study Design

This was a study of community-based with prospective cohort design, an outcome-centric tracking of adult cured CAT I PTB cases as per the RNTCP definition and are referred to as index cases, using a structured, designed questionnaire, containing both close-ended and open-ended questions. As per the protocol, adult cured CAT I PTB patients (Sadacharam et al., 2007) who completed their treatment till June 30, 2021 (minimum 1 years after completing treatment) but not before January 1, 2017 to (maximum 5 years after completing treat-

ment) constituted the reference population. Thus, the post treatment duration for the study participants was between 1 years and 5 years. Under Gwalior Municipal Corporation, there were nine TB units (TUs) until 2021. For feasibility, this study took four TUs nearby to the institute, namely, District TU, Medical College TU, Morar and Hazira TU; treatment cards (TB card) and the patient records were obtained, and all the eligible participants were enlisted. Number of participants from each TU was calculated as per probability proportional to size. Contact details of all selected patients were obtained from their treatment cards, and efforts were made through visits/ repeat visits to contact them for the personal interview. Of the 750 patients were able to track the health status in 527 patients (281 men and 246 women, age groups 19 to 44 years old (271 peoples), age groups 45 to 69 years old (256 peoples). Out of total 527 tracking cases 103 cases of relapse TB (Index cases) were finally studied. The rest for various reasons were lost from further observation. Data Collection was done between January 2022 to June 2022 with simultaneous data entry and analysis. Data collection was done with the support from District TB Control Officer was obtained to facilitate home visits to the index cases which were conducted at the beginning of the data collection, followed by monthly visits until the end of the study. During the home visits, the following symptoms of TB were explored through interactions with the index cases: chronic cough of >2 weeks' duration, production of sputum and blood-streaked sputum, unexplained weight loss, fever, fatigue /tiredness, night sweats, breathlessness, and chest pain. An index case or a family member of an index case was noted even with any one of the above symptoms either alone or in combination.

2. Inclusion Criteria

All eligible and willing to participate were included in the study and for the non-survivors; available relative was interviewed to ascertain probable cause of death.

3. Exclusion Criteria

Participants not fulfilling any one of the above criteria or unwilling to participate were excluded from the study

4. Operational Definition of Variables

Data variables included: TB registration number, socio-demographic characteristics at the time of TB relapse diagnosis (age, sex, place of residence, occupation etc.), clinical characteristics of index TB cases (TB type, category of TB recurrent, and comorbidities) and treatment outcomes. Microbiological and treatment variables included smear test results, history of TB treat.

5. Study Instruments

A pre-designed, pre-tested, structured interview-based questionnaire was used for data collection from all the study participants. A face-to-face interview was conducted to collect patient information.

6. Data Analysis

A descriptive analysis of the index cases was performed. Frequency tables were used for categorical variables. Non-parametric continuous variables were analyzed using the percentage proportion. The rate ratio was calculated to compare the recurrence rate with socio-demographical and clinical variables.

7. Research Ethics

Ethical endorsement was taken from Institutional Ethical Committee of Gajra Raja Medical College, Gwalior (M.P.) before starting the investigation by the approval certificate no 839/IEC-GRMC/2020. Permission to include TB units and DMC was obtained from the Chief Medical Health Officer (CMHO) of Gwalior district, who is responsible for overseeing health centres in the

study district. Examination didn't need any intrusive or non-obtrusive diagnostic strategy or with holding of any medication recommended by treating specialist or beginning any new medication. Study participants were informed about the objective of the study before data collection and asked for consent. All data was treated in a strictly confidential manner according to the ethical principles.

RESULTS

A total of 103 index cases were contacted from four selected TUs of Gwalior district in Madhya Pradesh State, India. In the observed cohort of patients during a 5-year follow-up, relapses of pulmonary tuberculosis were not observed in 424 patients out of 527, which is 80.42% of cases (Table 1). At the same time, out of 103 (19.73%) cases of recurrences, 49 or 9.32% of cases were classified as early and 54 or 10.24% of cases as late relapses.

The mean and SD age of the index cases was (Mean= 32.62; SD= 15.13) years; it was (Mean= 30.53; SD= 14.21) years and

(Meam= 34.62; SD= 15.22) years among males and females, respectively. There were 64 (62.1%) males and 39 (47.87%) females among a total of 103 index cases. There were 24 (23.3%) of unmarried index cases, which was little higher among women than men. Alcoholism and smoking were prevalent at around more than 25% among male index cases, whereas some cases also reported among women index cases. Significantly majority of index cases 89 (86.4%) were found in lower class p=0.010). Sputum smear (SS) grading was not statistically significantly different among men and women index cases (p=0.203). HIV as a comorbidity was present in seven (3.7%) cases. Proportion of Muslim women index cases was observed to be higher but was not found to be statistically significant (p=0.193). Nuclear family setup was observed among the index cases but was not statistically significant with respect to the gender of patients (p= 0.460). Index cases according to Terms of development of relapses (Early vs Late) were more or less same.

Table1. Socio-demographic characteristic of relapse TB patients (N=103)

| Characteristics | Category | Male | | Female | | Total | |
|---|--------------------------|------|------|--------|------|-------|------|
| | | n | % | n | % | n | % |
| Marital Status | Married | 51 | 79.7 | 28 | 71.8 | 79 | 76.7 |
| | Unmarried | 13 | 20.3 | 11 | 28.2 | 24 | 23.3 |
| Alcohol | Yes | 23 | 35.9 | 4 | 10.2 | 27 | 26.2 |
| | No | 41 | 64.1 | 35 | 89.8 | 76 | 73.8 |
| Smoking | Yes | 22 | 34.3 | 6 | 15.4 | 28 | 27.2 |
| | No | 42 | 65.7 | 33 | 84.6 | 75 | 72.8 |
| Type of Family | Single/Nuclear | 35 | 54.7 | 23 | 58.9 | 58 | 56.3 |
| | Joint | 29 | 45.3 | 16 | 41.1 | 45 | 53.7 |
| Socio Economic status | Upper class (I) | 0 | 0 | 0 | 0 | 0 | 0 |
| | Upper Middle (II) | 1 | 1.6 | 0 | 0 | 1 | 0.09 |
| | Lower Middle (III) | 9 | 14.1 | 5 | 12.8 | 14 | 13.6 |
| | Lower (IV) | 54 | 84.3 | 34 | 87.2 | 88 | 85.4 |
| Sputum Smear (SS) grade at the time of diagnosis | Negative | 217 | 41.2 | 205 | 38.9 | 422 | 80.1 |
| | Positive Scanty | 5 | 7.8 | 4 | 10.2 | 9 | 8.7 |
| | Positive 1+ | 23 | 5.9 | 19 | 48.7 | 42 | 40.8 |
| | Positive 2+ | 15 | 23.4 | 8 | 20.5 | 23 | 22.3 |
| Terms of Development of relapses | Positive 3+ | 21 | 32.8 | 8 | 20.5 | 29 | 28.1 |
| | Early [12 to <24 months] | 31 | 48.4 | 18 | 46.1 | 49 | 47.6 |
| | Late [24 to 60 Months] | 33 | 51.6 | 21 | 53.8 | 54 | 52.4 |

An analysis of the age and sex characteristics of patients showed in Table 2. that most of the cases of pulmonary tuberculosis recurrence occurred in men aged 19 to 44 years. Thus, among 103 patients with a de-

veloped recurrent process, there were 39 men (37.9%) and 23 women (22.3%) aged 19 to 44, as well as 25 men (24.3%) and 16 women (15.5%) at the age of 45 to 69 years.

Table 2. Gender and age characteristics of patients and the timing of the development of relapses

| Category | 19-44 Years. (N=62) | | | | 45-69 Years. (N=41) | | | |
|----------|---------------------|----------------|-----------|----------------|---------------------|----------------|-----------|----------------|
| | Men | | Women | | Men | | Women | |
| | Frequency | Percentage (%) | Frequency | Percentage (%) | Frequency | Percentage (%) | Frequency | Percentage (%) |
| Early | 19 | 38.8 | 11 | 22.4 | 12 | 24.5 | 7 | 14.3 |
| Late | 20 | 37.0 | 12 | 22.2 | 13 | 24.1 | 9 | 16.7 |

A retrospective as well as prospective analysis of the initial forms of the disease showed that relapses of pulmonary tuberculosis occurred more often in patients who had undergone fibrous-cavernous pulmonary tuberculosis (67.3% early and 77.7%

late relapses), then in patients with disseminated pulmonary TB (28.6% and 14.8%, respectively) and fewer after infiltrative pulmonary TB (4.1% and 7.4% respectively) (Table 3).

Table3. Retrospective analysis of relapses depending on initial forms of pulmonary tuberculosis

| Category | Fibrous cavernous | | Disseminated | | Infiltrative | |
|----------|-------------------|----------------|--------------|----------------|--------------|----------------|
| | Frequency | Percentage (%) | Frequency | Percentage (%) | Frequency | Percentage (%) |
| Early | 33 | 67.3 | 14 | 28.6 | 2 | 4.1 |
| Late | 42 | 77.7 | 8 | 14.8 | 4 | 7.4 |

The next step in our study was to analyse the causes of relapses depending on concomitant diseases (Table 4). It should be noted that all three HIV-infected individuals (100%) and 8 patients with diabetes mellitus (100%) developed relapses of tuberculosis in the early stages. Out of 79 patients with chronic nonspecific lung diseases, TB recurrence developed in 48

(61%) patients, while early recurrence developed in 36 (73.5%) and late recurrence in 12 (22.2%) patients; 12 patients with concomitant liver diseases and 6 with gastric and duodenal ulcers did not develop relapses of the disease. Out of 272 cases without comorbidities, only 46 (16.9%) had relapses of the disease and almost all of them were in the late stages of follow-up

Table 4. Retrospective analysis of the development of relapses depending on the presence of concomitant diseases

| Category | HIV-inf. | | Diabetes mellitus | | COPD | | No comorbidities | |
|----------|----------|-----|-------------------|------|------|------|------------------|------|
| | n | % | n | % | n | % | n | % |
| Early | 3 | 6.1 | 8 | 16.3 | 36 | 73.5 | 2 | 4.1 |
| Late | 0 | 0 | 0 | 0 | 12 | 22.2 | 44 | 81.5 |

DISCUSSION

Despite the significant achievements of modern science, the burden of tuberculosis

(TB) in India is still high, which is mainly due to the high level of reactivation of the tuberculosis process in patients who re-

covered from pulmonary TB (WHO, 2019). In previous studies (Mathur et al., 2019; Sharma et al., 2019) revealed the main definitions associated with the reactivation of the tuberculosis process, according to which the reactivation of the pulmonary process after TB implies both exacerbation and relapse of the disease. A relapse of the disease is an outbreak of the TB process in people who have previously had TB and successfully completed its treatment.

Often in clinical practice it is difficult to differentiate in reinfection and relapse conditions from another, sometimes this requires sequencing of the genome of Mycobacterium TB. Practitioners also often can't verify the fact of re-infection with Tuberculosis, because it is not known whether the patient's body was completely eliminated (eradication) from Tuberculosis. In previous studies (Mathur et al., 2019; Sharma et al., 2019; Basu et al., 2021), pointed to factors contributing to the reactivation of the tuberculosis process, which may be facilitated by labour migration with the likelihood of superinfection with another strain of mycobacterium TB. Despite the repeated visits, this study could not track more than one-fourth (213) of cases mainly due to the incomplete or wrong address, migration or death due to some unknown diagnosis. Our loss in FU was higher than in a study from Lucknow (Prasad et al., 2008) which followed cases after 1 year of completion of the treatment.

Majority of cases (68%) in this study belonged to 18 to 45 years age group which constitutes the most productive segment of the society. It was similar reported by another study (66.2%) (Piparva, 2017; Sharma et al., 2019) but higher than other studies (27.5%) (Bareilly et al., 2015; Dave et al., 2013; Sharma et al., 2019). also reported prevalence of younger age group among MDRTB patients with the mean age of their

study groups being 29.7 years and 33.25 years respectively. The occupational profile of patients revealed that a majority of them labourer followed by household workers and skilled workers. Mukherjee et al. (2015) observed a higher prevalence of pulmonary TB in household workers followed by labourer and skilled workers. The most common form of substance use was smoking 2 (27%), followed by alcohol 27 (26%), with duration of more than 5 years was most common among study participants. Similar findings were observed by Mukherjee et al. (2015) and Basu et al. (2021) found that history of smoking (28%), and alcohol intake (28%) were present. Out of 527 cases tracking in this study, 103 (19.5%) developed the symptoms suggestive of TB. It was higher than 12.3% relapse reported from Kolkata (Saha, 2013), during the 18-month period and also from another study Prasad et al. (2008) where up to 90% remained asymptomatic after a 1 year of completion of treatment. This study has relapse rate close to study from Gujarat (Dave et al., 2013) followed a cured cohort of 657 cases 2 years after completion and reported 15.3% of them either as dead or relapse. In the absence of any other explanation, relapse rates could be attributed to reappearance /recurrence of TB. In this study, the coexisting illnesses such as HIV, diabetes, and chronic obstructive pulmonary diseases (COPD) which could contribute to relapse COPD were observed in majority of cases 48 (46%). However, addictions such as tobacco chewing/smoking and alcohol were observed in 26% & 27% respectively. These findings are similar to A hospital-based audit (Hooi and Goh, 1995).

In the present study, relapse cases were not found to be associated significantly with age, gender, smoking status, alcohol consumption, SS at diagnosis, and marital status, but was found significantly (P

<0.056) associated with socioeconomic status probably due to the inclusion of only cured new sputum smear positive (NSP) patients. Datiko and Lindtjørn (2009) and Mathur et al. (2019) have reported similar findings; however, other studies have reported significant associations of relapses in cases during follow-up with the above mentioned factors and Lower socio-economic status was also an independent factor in predicting recurrent TB (Joseph et al., 2015; Hung et al., 2015). Consistent with these study results, this study also found that male gender and lower economic status were predictors of TB recurrence, implying that smoking and poor nutrition could be potentially triggers. Among the factors associated with the relapse of TB, there were statistically significant differences between males and females in regard to addiction ($p= 0.014$), employment ($p < 0.012$). This Study found that DM and COPD were independently associated with recurrent TB. These findings, together with the identification of possible risk factors associated with recurrent TB, raise a number of important issues and highlight various areas where India needs to focus its TB control efforts.

This study indicated a number of factors that seem to be associated with recurrent TB, although in view of the substantial size of the study and the need to balance clinical and statistical significance, this study had been selective in teasing out the factors that deem to be important clinically and from a public health perspective. First, the risk of recurrent TB was highest among older adults (36 to 55 years). Unaware of any previous studies that have identified particular age groups as being more at risk of recurrent TB, this study postulate that this finding is likely linked to other co-determinants such as poor treatment adherence, that in this study were unable to assess and control for in this study (Cox et al., 2006).

Further investigation would be needed to establish these reasons so that more targeted measures aimed at mitigating these factors could be implemented. Certain co-morbidities were found to be associated with an increased risk of recurrent TB, including HIV and COPD, those are well known to increase the risk of recurrent TB both in high and low TB burden settings (Millet et al., 2013; Didilescu et al., 2000). COPD was associated with recurrent TB, corroborating the findings from other studies (Hung et al., 2015). COPD may increase the risk of recurrent TB because of fibrotic changes in the lung and reduced anti-TB drug penetration into the lung tissue (Yusupova et al., 2016).

Thus, the results of this observation revealed the occurrence of relapses within 5 years in 19.3% of cases. A retrospective and prospective analysis of the initial forms of the disease showed that relapses of pulmonary tuberculosis occurred more often in patients who had fibrous-cavernous pulmonary tuberculosis, then in patients who had disseminated pulmonary TB, and less often after suffering infiltrative pulmonary TB. Relapses of the disease occurred more often in men aged 19 to 44 years. The development of relapses of pulmonary tuberculosis has a statistically significant dependence on the form of the initial disease, the presence of comorbid diseases such as HIV, diabetes mellitus, and COPD. At the same time, it turned out that the social status of all patients with relapses corresponds to the level of poverty, which should also be taken into account.

These findings, together with the identification of possible risk factors associated with incidence of TB relapses has need of continuous studied, particularly in light of the country's rapidly emerging MDR-TB epidemic. This study has limited importance because findings are based on the data of

only four TUs from urban area selected purposively, hence findings cannot be generalised and another limitation of the study is that the SS examination and X-ray were done only in symptomatic cases and household contacts only and not in the entire study cohort.

AUTHOR CONTRIBUTION

Dr Anil K Agarwal, Dr Divyani Aharwal, Dr Rani Verma raised the initial research question, managed data collection, ran statistical analysis, drew tables and graphs. Dr Anil K Agarwal, Dr Divyani Aharwal, Dr Ramniwas Mahore refined research questions, planned study design, planned and ran statistical analysis, interpreted results, and wrote up manuscript. Dr Anil K Agarwal, Dr Divyani Aharwal, Dr Rani Verma, Dr Priyanka Kushwaha suggested issues in discussion.

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CONFLICT OF INTEREST

The authors whose names are listed have certified that have NO affiliations with or involvement in any organization or entity with any financial interest, non-financial in the subject matter or materials discussed in this manuscript.

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