Lost to Follow – Up During Diagnosis (LTFU) of Tuberculosis Patients: A Mixed Method Study on Determinant’s and Potential Solutions.

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Abstract: Background: Loss to follow up of tuberculosis patient during diagnosis is an important barrier to achieve elimination of TB by 2025 in India. This study estimated the burden and trend of loss to follow up of TB patient during diagnosis, explored tuberculosis patient’s perspective for becoming Loss To Follow Up during diagnostic period (LTFU) and stakeholders’ initiatives and suggested solutions for the same. Methods: Mixed Method study was used - Quantitative (Record based cohort study) and Qualitative (In – depth interview with LTFU patients on their challenges faced and barriers for not giving 2nd sputum sample and free list with stakeholders). Data were extracted from RNTCP Laboratory Register for the cohort of patients registered between January 2014 and December 2018 in a DMC of tertiary care teaching hospital. Qualitative interviews were carried out using interview guide. Results: Of the total 1678 positive cases, 90 (5.3%) were LTFU. On adjusted analysis distance >75km from medical college (Relative risk 2.3; 95%CI: 1.2–6.0) and year of diagnosis were identified as significant risk factors. In Manual content analysis showed five categories of challenges faced by LTFU cases namely 1) lack of awareness; 2) addictions; 3) stigma; 4) Employment related barriers and 5) perception on drug side effects. Free listing conducted between staffs of hospital and from stakeholders the main suggested solutions identified were 1) context-based counselling; 2) friendly patient tracking; and 3) proactive in-service. Conclusion: There was significantly decreasing trend in LTFU patients over the years (in 2014 – 6% to 0.5% in 2018). Co-ordinated context-specific pro-active interventions are required to achieve End TB strategy of the nation

Key Words: LTFU, Mixed methods research, Suggested solutions, Stakeholder’s perspective

Introduction:
Tuberculosis (TB) has existed for millennia and remains a major global health problem.[1] India with the largest number of patients with tuberculosis, runs the largest TB control program in the world, TB patients who are lost to follow-up before starting therapy are infectious and have high mortality rates and can spread infection to other people in the community. Loss to follow up (LTFU) can occur at multiple stages of care pathway, those includes patient who received a diagnosis of tuberculosis on the basis of only one positive sputum smear drop out of care during diagnostic process, who fail to provide second sample (lost to follow-up during diagnostic period or diagnostic default)[2] and before initiating tuberculosis treatment are defined as Pre – treatment loss to follow up, formerly known as initial defaulter[2,3] which is a barrier to tuberculosis (TB) control in India’s Revised National TB Control Programme (RNTCP). People with active TB can infect 10–15 other people through close contact over the course of a year (WHO).[4] LTFU should be one of the primary concerns in the battle against TB. In India, RNTCP’s annual report suggests that more than 135,000 (14.6%) smear-positive patients were lost to follow-up prior to starting on TB treatment (PTLFU) in 2013.[5] World Health Organization (WHO) estimates that India has nearly one million “missing” TB patients, these “missing” patients are either undiagnosed or are diagnosed but not reported. We should prioritize finding these patients and linking them to effective treatment.[6,7] The Medical College’s involvement and contribution in RNTCP through task force mechanism is well appreciated and highly helpful. The unique problem of Pondicherry is that the majority of patients utilizing the services of medical colleges are from the border districts of Tamil Nadu. Most of these patients after receiving the results from the laboratory fail to report to the DOTS centre for referral slip and contribute to burden of Initial defaulters. As these patients are from border district the mechanism to track these patients was difficult. Hence, the present study aims to find out the various factors that influences the Loss to Follow Up during Diagnostic period among TB patients under DOTS in RNTCP. Further, help us to take corrective measures to prevent the patient from initial defaulting. With this backdrop this study was taken up to
explore the facilitating factors, barriers for LTFU cases and interventions implemented to reduce LTFU cases.

**Materials and Methods:**

**Study setting:** This study was undertaken by the Department of Community Medicine, Sri Manakula Vinayagar Medical College and Hospital (SMVMCH), located in Rural of Pondicherry union territory. SMVMCH is situated in the border of Puducherry sharing with Villupuram district and provide comprehensive service to the people residing around the border of UT and Tamil Nadu (Villupuram district). Quarterly 215 - 397 patients are screened for pulmonary TB using sputum microscopy. About 95 % of these patients are from Villupuram district. The study was held at Designated Microscopy Centre (DMC), under the supervision of RNTCP STF (State Task Force).

**Design and Sampling:**

Sequential explanatory mixed methods study was used. Record based cohort design was adopted to extract the determinants of LTFU as a part of quantitative method. Descriptive qualitative methods (In – depth interview with LTFU cases and free listing with stakeholders) were then carried out between February and June 2019. The data of all patients (N=1678) registered during the study period of five years (2014 to 2018) were extracted from RNTCP lab register. From the notification register 90 LTFU cases were line listed. Then four free listing activity were done with TB Health Visitor, laboratory technician, Senior Treatment Supervisor and Core-committee coordinator from SMVMCH to find out the measures implemented to reduce the proportion of single sputum. In – depth interview was conducted with purposively selected six LTFU cases to know the barrier for not giving 2nd sputum sample.

**Definitions and Patient Selection:** This study included the smear positive patients diagnosed in our DMC who did not return to health care facility to give 2nd sputum sample and collect their report and were therefore defaulters for initiation of anti-tuberculosis treatment. These patients were traced with available contact details and interviewed.

**Presumptive pulmonary TB** is defined as a person with any of the signs and symptoms suggestive of TB including cough >2 weeks, significant weight loss, haemoptysis, and any abnormality in chest radiograph.[2,8] 

Presumptive TB patients who received a diagnosis of tuberculosis on the basis of only one positive sputum smear drop out of care during diagnostic process, who fail to provide a second smear (loss to follow-up during diagnostic period or diagnostic default). [2]

**Data Source, Collection and Analysis:**

The smear positive Pulmonary TB patients diagnosed using sputum microscopy in DMC, SMVMCH and referred for treatment was extracted from RNTCP Laboratory Register and TB Notification register (From 2014-2018) using extraction sheet. The following details were extracted socio-demographic details – namely age, gender, date of diagnosis, address of the patient, distance from DMC(SMVMCH), IP/OP, name of referring health facility, reason for diagnosis, result of smear-1, result of smear-2, whether chest x ray taken, HIV status of the patient, diabetes status of the patient and whether Aadhaar liked. The extracted data was analyzed to find out the trend of the cases reported. Free listing was conducted with the stakeholders and were asked to list the measures taken to reduce the proportion of single sputum patients at SMVMCH. The list was noted by the Principal Investigator (PI) and the similar contents were deleted. The reasons (facilitating factors and barriers) for the loss to follow up during diagnosis in TB care pathway was explored by conducting IDI interview with the LTFU patients. The verbal consent for IDI was obtained through phone calls and home visits were made by the PI. IDIs were conducted after obtaining informed consent and it was conducted in local language Tamil. Interview was conducted using interview guide with open ended questions, IDI was conducted by principal investigator trained in qualitative research methods (QRM). Interview was audio recorded with patient’s permission and each IDI lasted for 23 – 40 minutes. To ensure participant validation debriefing was done before closing the interview and was asked if they wanted to add extra information. Prior permission was booked with all participants in order to ensure that the interviews took place at their own chosen convenient times and sites.

**Data Analysis:**

The Quantitative data was entered in Epi Info (version 7.2.2.6 developed by Centre of Disease Control, Atlanta, USA and WHO) software package. The entered data were transferred to SPSS 24 software (SPSS Inc., Chicago, Illinois, USA) package for analysis. Statistical measures like frequency and percentage were used to analyse categorical variables. Continuous variables which followed a normal distribution like age of the respondents were expressed in mean and standard deviation.

Audio recorded transcripts were transcribed into English. Transcriptions were proof-read and edited and manually analysed thematically. Category code was reviewed by another author trained in qualitative research for better interpretation and to increase the validity of the study.

Statements in italic indicate direct statement from participants. Consolidation criteria for reporting qualitative research guidelines were used for reporting the findings.[9]

**Ethical Consideration:**

The study protocol was approved by the SMVMCH - Institutional Ethics Committee No.EC/04/2019. Participant information sheet was provided to the study participants. Written informed consent was obtained. Confidentiality and privacy of the data was maintained.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N(1678)</th>
<th>LT FU(90)</th>
<th>Unadjusted odds OR 95% CI</th>
<th>P value</th>
<th>Adjusted odds OR 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatric</td>
<td>58</td>
<td>1(1.71)</td>
<td>1(Ref)</td>
<td>NA</td>
<td>2.60(3.3 - 19.8)</td>
<td>0.3</td>
</tr>
<tr>
<td>Adult</td>
<td>1140</td>
<td>60(5.31)</td>
<td>3.20(4 - 23)</td>
<td>0.25</td>
<td>3.10(4.3 - 23)</td>
<td>0.27</td>
</tr>
<tr>
<td>Geriatric</td>
<td>480</td>
<td>29(6.1)</td>
<td>3.70(5.0 - 27)</td>
<td>0.20</td>
<td>3.10(4.1 - 23.8)</td>
<td>0.27</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1283</td>
<td>75(5.5)</td>
<td>1.2(0.6 - 2.1)</td>
<td>0.55</td>
<td>1(Ref)</td>
<td>0.71</td>
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<tr>
<td>Female</td>
<td>305</td>
<td>10(3.3)</td>
<td>10(Ref)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Distance From SMVMCH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nearby (&lt;25 km)</td>
<td>1067</td>
<td>48(4.5)</td>
<td>1(Ref)</td>
<td>NA</td>
<td>1(Ref)</td>
<td>0.10</td>
</tr>
<tr>
<td>Moderate (&gt;25 &lt;50kms)</td>
<td>330</td>
<td>23(7)</td>
<td>1.60(95% CI: 2.6)</td>
<td>0.07</td>
<td>1.59(9 - 2.6)</td>
<td></td>
</tr>
<tr>
<td>Far (&gt;50kms)</td>
<td>156</td>
<td>11(7)</td>
<td>1.10(0.6 - 3)</td>
<td>0.72</td>
<td>1.20(0.6 - 3)</td>
<td>0.59</td>
</tr>
<tr>
<td>Year wise distribution of cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>397</td>
<td>24(6)</td>
<td>1.132 (0.667 - 1.922)</td>
<td>0.10</td>
<td>14.1(1.9 - 105)</td>
<td>0.01</td>
</tr>
<tr>
<td>2015</td>
<td>327</td>
<td>29(8.9)</td>
<td>20.8(2.8 - 134)</td>
<td>0.03</td>
<td>22.5(165 - 0.002)</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>369</td>
<td>18(4.9)</td>
<td>10.91(5.8 - 82)</td>
<td>0.02</td>
<td>11.8(1.6 - 90)</td>
<td>0.02</td>
</tr>
<tr>
<td>2017</td>
<td>370</td>
<td>18(4.9)</td>
<td>10.91(5.8 - 82)</td>
<td>0.02</td>
<td>11.8(1.6 - 93)</td>
<td>0.02</td>
</tr>
<tr>
<td>2018</td>
<td>215</td>
<td>10(5)</td>
<td>1 Ref)</td>
<td>NA</td>
<td>NA</td>
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</tr>
</tbody>
</table>

**Results:**

Quantitative: Among the 1678 bacteriologically confirmed TB patients diagnosed in our DMC; the proportion of LTFU...
cases was 90 (5.3%); 95% CI: 4.3 – 6.5). Majority of LTFU cases were found to be adults, 6.1% (29) patients were found to be geriatric age group. Most of LTFU cases [83% (75)] were males. Around 8.8%(11) were residing more than 75kms from DMC, SMVMCH respectively, There were more number of LTFU cases in 2015 – 29(8.9%) when compared to 2018 - 1 (0.5%). (Table 1)On adjusted analysis, when compared to pediatric age group, adult and geriatric population and male gender were found to be at risk of becoming diagnostic default and also presumptive TB patients, who were residing far from DMC. (Table 1)

On adjusted analysis, distance >75km from medical college and year of diagnosis (2014) were identified as significant risk factors for positive pulmonary TB patients to become LTFU during diagnosis. (Table 1)

Qualitative: The free listing expressed by stakeholders about the initiatives taken to reduce LTFU cases are 1) context-based counselling; 2) friendly patient tracking; and 3) proactive in-service. (Table 2). It was found that patient had been re-examined and diagnosed positive (using sputum examination) elsewhere in different centre and hence it was possible to collect information regarding their TB treatment history.

Table 2: Stakeholders responses evolved from free listing:

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Counselling was given to TB suspects/presumptive TB patients by LT/TBHV/MO about</td>
</tr>
<tr>
<td>• the importance of second sputum sample and treatment</td>
</tr>
<tr>
<td>• Counseling was given to caregivers about the importance of second sputum sample</td>
</tr>
<tr>
<td>• Phone calls were made</td>
</tr>
<tr>
<td>• Collected alternate phone numbers</td>
</tr>
<tr>
<td>• Home visits were made by TBHV for Puducherry patients</td>
</tr>
<tr>
<td>• Training of interns and staff nurse</td>
</tr>
<tr>
<td>• Was also informed to respective DTO</td>
</tr>
<tr>
<td>• Active follow with ward sisters</td>
</tr>
<tr>
<td>• Disclosing the results only after receiving second sputum</td>
</tr>
<tr>
<td>• Reinforcing during core – committee meeting</td>
</tr>
<tr>
<td>• Not discharging patients without referral slip</td>
</tr>
<tr>
<td>• Second sputum was received with gap of 2 hours from the patients coming from distance places</td>
</tr>
</tbody>
</table>

The five categories emerged from IDIs conducted among traceable LTFU patients are mentioned below:

**Category 1: Lack of awareness about TB** – among the 6 participants, 4 stated that lack of awareness, low education was main reason for not giving 2nd sputum sample and for delaying TB treatment. A 45 year old woman stated “I have never stepped into school and I got married at 17 years itself, I had no knowledge about TB”.

Motivating factor for giving 2nd sample and starting TB treatment was – active follow up of staff nurse and TBHV who visited her house and gave awareness about TB and motivated which made her to visit health centre, start treatment and complete the course.

**Category 2: Addictions (alcohol and smoking)**– Two participants stated that alcohol and smoking were the main barriers for not returning to health care facility for giving 2nd sputum sample and for not initiating TB treatment. A 37 years old gentleman stated “I used to drink alcohol morning, afternoon and night. I had cough for almost a month and one day they took me to nearby PHC, after 2 days they told I had TB. I cannot drink if I should take TB treatment”, hence he refused to give 2nd sputum sample.

Motivating factor for returning to health facility for giving 2nd sputum sample and for initiating TB treatment - patient stated “I developed blood in sputum and constant fever and cough persisted - I had fear of dying. My wife’s and daughter’s continuous support motivated me to start return to health facility for further management.” So, both fear of dying and family support played a major role to bring back the patient to TB care pathway.

**Category 3: Stigma towards TB**

All the LTFU cases reported to be feared and associated with discrimination. In this case lack of family support and negligence were the barriers for LTFU during diagnosis. Another female participant reported that “when I had TB, my own son whom I raised did not come and see me and I had no one to take me to hospital and support me”. Another 40-year-old male participant stated that “I had awareness on TB but I didn’t accept that I had TB. I started to isolate myself in a room, used separate plate and didn’t go to any relative’s marriage and meet anyone. I was scared that when people come to know they will not respect me, but my wife took good care of me and made me to visit PHC correctly. Staff nurse, TBHV, Medical officer also supported and encouraged me. A 45-year-old female stated that “I was worried that I will die because I had TB and I didn’t know treatment will cure TB, but counselling given by health worker helped me to overcome the fear and encouraged me to return to health facility for further management.”

The motivating factor which helped to break the barrier of LTFU of TB patients - proper counselling of the health visitors and intense family support.

**Category 4: Employment related barrier**

A 37-year-old male stated that “I am working as daily labour; I was scared that if I start on treatment I cannot go for work and people will avoid me. I was also scared that I will not be able to lift heavy weight”. Loss of wage and work related constrains are the main barriers for not returning to health facility and treatment delay.

**Category 5: Perception on drugs side effects**

A 40-year-old male participant stated that “Because the size of the tablet was big and I was scared of the side effects, I did not want to start treatment, hence I didn’t return to health care facility and went for homeopathy treatment. But even homeopathy doctor told me to initiate TB treatment. My friend constantly supported me and guided me to diagnose and helped in initiating treatment.

**Discussion:**

In this study the proportion of presumptive TB patients who had given only one sputum sample and did not return to health care facility for 2nd sputum sample further resulting in treatment delay were found to be 5.3% which is less when compared to other studies that had 12.9% to 18.6% [10 11]. Study conducted by Gopi et al [3] reported initial defaulters at 9% and 8.3% by Buu TN et al [12].
In our study major risk factors identified were found to be male when compared to female, which is in contrast with study conducted by Balasubramanian et al.[13], which had equal rates of defaulters among males and females. In our study majority of the loss to follow up cases were adults belonging to age group of 34 – 54 which is productive age group. Muhammed G et al [14] reported that initial defaulters were found to be in the age group of 45 – 54 years. The identified reason for diagnostic LTFU were lack of awareness about TB, lack of family support and illiteracy. Other factors - addictions like alcohol and smoking, work related constrains, loss of wages and stigma were found to be barriers for LTFU cases. Similar findings were reported in the study conducted by Gopi et al [3], who found lack of awareness regarding TB, alcoholism, lack of adequate support, stigma associated with TB were the main reasons for not initiating treatment among TB patients. Similarly, study conducted by Sophia V et al [15] found males and alcoholics being predictive factors for defaults. Alcohol use has been found been barrier to TB care in India.[16]

In our study the motivating factors which made them to return to health care facility and treatment initiation were counselling by the health staff (staff nurse, TBHV), intense family support, fear of dying and government support to compensate loss of wages.

In the present study we found long distance from DMC >75 kms from home and lack of motivation to be the reasons for not giving 2nd sputum sample, which is similar to the study conducted by Rawat et al.[17]

The measures taken by stakeholders were identified through free listing. They suggested context-based counselling. Counselling was given to TB suspects/presumptive TB patients by LT/TBH/MO about the importance of second sputum sample and treatment. Counselling was given to caregivers about the importance of second sputum sample. Friendly patient tracking was done using alternate phone numbers that were collected. Home visits were made by TBHV for Puducherry patients. Proactive in-service training of interns [18] and staff nurses were also conducted. Missing cases was also informed to respective District Tuberculosis Officer(DTO). Active follow-up with ward sisters, disclosing the results only after receiving second sputum, reinforcing during core – committee meeting, not discharging patients without referral slip were implemented. Second sputum samples that were received with gap of 2 hours from the patients coming from distance places were also recommended to collect same day samples.[19] Similar initiative was reported in study done in Rajahmundry where same day diagnosis with two spot samples, one hour apart, was followed.[20] Best approach is to use “onion” model, which considers drop – offs along several points in the patient care. This model helps us to identify different points of intervention to keep TB patient engaged in diagnosis and treatment.[21]

The main strength is robust mixed method design adopted and analysis of data pertaining to larger sample. Since it is retrospective in nature, we could only trace six TB patients over phone for the interview.

Conclusion:
The proportion of LTFU of TB patient were less 5.3% when compared to previous studies. Identified risk factors were male gender, higher age group, and people coming from far distance. Intensive active measures taken by stakeholders could have been the reason for decline of LTFU cases. Hence, proper counselling at multiple levels at Tertiary Care Centre by Medical Officer, Laboratory Technician and TBHV during diagnosis and treatment will ensure treatment adherence and help us to move towards ending TB by 2035.

References: