

# Predictors of Tuberculosis Treatment Default in Pulmonary and Extrapulmonary Tuberculosis

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## Abstract

**Background :** To detect the predictors of treatment defaults in Pulmonary Tuberculosis (PTB) and Extra Pulmonary Tuberculosis (EPTB).

**Methods:** In this cross sectional study 140 adults, with diagnosis of pulmonary tuberculosis (PTB) and extra pulmonary tuberculosis (EPTB), with treatment defaults, were included. The study protocol incorporated demographic, clinical characteristics of patients, structured questionnaire, physical examinations, radiological, laboratory investigations and relevant predictors for TB treatment defaults. The statistical analysis was performed using SPSS 20.

**Results:** Mean age of study group was 42.3±20.3. Majority (67.1%) were male. Ninety four (67.1%) had PTB and 46 (32.9%) had EPTB. Factors identified to be associated with TB treatment default were male gender, distance from the health post, displacement, financial constraints, no body at home to bring medicine or take patients to hospital, routes closed in winters, subjective improvement of symptoms and travelling/shifting to other place.

**Conclusions:** Treatment default is seen in pulmonary and extra pulmonary tuberculosis. Due to lack of uniform diagnostic and therapeutic strategy in EPTB treatment, most physicians treat on clinical symptoms for a prolonged duration of 12 to 24 months.

**Key Words:** Tuberculosis (TB), Multidrug resistance (MDR), pulmonary tuberculosis (PTB), extrapulmonary tuberculosis (EPTB), Treatment default.

## Introduction

World Health Organization (WHO) declared TB a globally prevalent and leading cause of death in

almost all countries of the world.<sup>1-3</sup> About 0.5 million MDR-TB cases were reported worldwide. Poverty, emergence of HIV and MDR-TB are the important factors to re-emergence of tuberculosis in developing countries. In 2007 there were an estimated 181/100,000 new cases and 223/100,000 prevalent cases in our country. WHO ranked Pakistan as fifth amongst TB high burden 22 countries of the world, and is also estimated fourth one in the highest prevalence of MDR-TB, globally.<sup>4</sup> Although PTB is the most common presentation of TB cases but EPTB is not altogether rare. EPTB involves any part of the body other than lungs. Mycobacterium tuberculosis (MTB) may spread through blood, lymphatics, and lie dormant for years in any organ.<sup>5-6</sup> As EPTB presents non specifically, therefore diagnosis becomes difficult with extraordinary delay. WHO estimated that 34,000 (15%) of newly reported cases in 2007 were EPTB category in Pakistan.<sup>7-8</sup>

EPTB is also a common problem all over the world. In 2011, 14% of all cases of TB in Brazil reported belonged to EPTB. Patients co-infected with human immunodeficiency virus (HIV) also reported in this category. EPTB is favored by AIDS epidemic infection. Such and other conditions that suppress immune function have not been studied in our country.<sup>9-10</sup>

## Patients and Methods

All adults with clinical diagnosis of TB, based on history, clinical examination and laboratory investigations were admitted to hospital. The data was obtained on standardized forms and entered in SPSS 20. TB defaulters were patients who interrupted treatment for two consecutive months or more as defined by WHO.<sup>11-12</sup> Variables studied were age, gender, treatment performed, type of treatment, clinical form, sputum smear microscopy, diabetes mellitus and other co-morbidities. The association of potential risk factors with defaulting was initially

studied. The ethical committee approved the study. PTB was defined as TB affecting the lung parenchyma. EPTB was defined as TB affecting organs and tissues outside of the lungs (e.g. skin, bones and joints, meninges, etc.). Miliary TB was also classified as EPTB. Pearson's chi-square test was used to compare the rates of PTB and EPTB. Variables with a P value < 0.05 were included

## Results

Total 140 TB patients were enrolled in the study. From the total study population 67.1% (94/140) were males and 32.9% (46/140) were females. The mean age of the study population was 42.3± 20.3 (Mean± SD) (Table 1). The statistical analysis of gender showed a statistical significant risk of default in male with EPTB as compared to females with PTB.

**Table 1: Risk factors for PTB and EPTB in TB treatment default cases**

Main reasons for default	Total	PTB	P-Value	EPTB	P Value
N (%)	140 (%)	94 (67.1%)	.004**	46 (32.9%)	.022**
Age (mean ± SD)	42.3 ± 20.3		.669		.011
Male	94 (67.1)	69 (49.2)	.125	25 (17.9)	.001
Female	46 (32.9)	25 (17.9)	.001*	21 (15.0)	.323
Distance	18 (12.9)	14 (10)	.001*	4 (12.9)	.007*
Displacement	12 (8.6)	4 (2.9)	.001*	8 (5.7)	.024*
Financial Constraint	8 (5.7)	4 (2.9)	.558*	4 (2.9)	.001*
Nobody at home to bring medicine or take patient to hospital	13 (9.3)	11 (7.97)	.399*	2 (1.4)	.001*
Route closed in winters	21 (15)	15 (10.7)	.001	6 (4'3)	.001
Side effect for drugs	28 (20)	20 (14.3)	.001	8 (5.7)	.001
Improvement	39 (27.9)	25 (17.8)	.525	14 (10)	.003*
Went abroad	1 (.7)	1 (.7)	.002		
Type of TB first time	140 (100)	87 (62.1)	.001	53 (37.9)	.001
Contact of relation	99 (70.71)	58 (41.4)	.720	41 (29.2)	.998
Duration of treatment default (weeks), mean ± SD)	8.44 ± 4.52		.398		.992
Duration of treatment default (months), mean ± SD)	9.01 ± 7.6		.005		.110
Associated condition	55 (39.3)	29 (20.7)	.001	26 (18.6)	.070
Default relative TB	20 (14.2)	10 (7.1)	.635	10 (7.1)	.992
Reporting back	85(60.7)	55(39.3)	.001	30(21.4)	.001
Default Numbers (Each type Treatment defaults during study)	118 (84.2)	118 (84.2)	.224	118 (84.2)	.257
Condition of arrival (sick, bed bound & moribund)	104 (74.2)	57 (40.7)	.011	47 (33.5)	.039
Mortality	14 (10)	5 (3.6)	.001	9 (6.4)	.001

The age has the statistical significant association with EPTB treatment default in adults. There was statistically significant association between treatment defaults receiving treatment for first time with PTB & EPTB (p=0.001).TB treatment default had been observed in both PTB and EPTB patients. Out of these pulmonary TB cases were 94 (67.1%) including pulmonary parenchymal TB (58.6%), pleural effusion

(2.11%), pneumothorax (0.7%) and extensive PTB (5.69%). Amongst 46 (32.9%) EPTB, abdominal TB 8 (5.8%), TB lymph-adenopathy 14 (10%), TBM 14 (10%) skin TB 2 (2.1%), disseminated TB 2 (1.4%) and bone TB 1 (.7%) , Miliary TB 3 (2.2%) and breast TB 1 (0.7) cases were reported. The PLUM-Ordinal analysis revealed that clinical TB forms PTB (p=004\*\*) EPTB (p=0.002\*\*) to its TB treatment defaults was of high significance .There was significant association between improvement to treatment and TB treatment default as well as co-infection of TB in diabetes mellitus and corticosteroid therapy. Duration of treatment in weeks, number of defaults and treatments default in relative had no significant association with treatment default in contrary to treatment default in months (p=0.05).

## Discussion

Both PTB & EPTB are common in TB treatment defaults. High TB treatment default rate is most significant factor for the development of multi drug resistance (MDR-TB), high morbidity and mortality in PTB and EPTB. The thick population in city, distant periphery, traveling from far away, poverty and road closed during winter makes difficult for treatment follow-up. In addition, special diagnostic difficulty in EPTB further complicates the situation. The factors leading to treatment default should be considered before making effective strategies for TB control programs. TB patient groups having DOT'S coverage were higher in city than in the remote district. In south east Asia gender as well as non-compliance are risk factors for treatment default<sup>13</sup>. We observed that the adult's population, gender, non-compliance and poor socio economic class were at risk of abandoning treatment. TB/ HIV coinfection and alcoholism has been identified as risk factor for treatment default worldwide.<sup>1,14</sup> Alcoholism and anti tuberculosis drugs have been associated with increase in the risk of liver damage.<sup>14-15</sup> Diabetes mellitus (DM) being the disease of old had no increased risk of treatment default.<sup>16</sup> The double burden of TB and DM is a significant public health problem in low and middle income countries.<sup>17</sup> The poor quality of TB service, large population, sub-optimal implementation of public health facilities, inadequate knowledge, insufficient explanation of disease to the patients were also important risk factors for low adherence to treatment. The statistically similarity of the results with and without DOTs in Asia, raises questions about quality anti TB programs. The uniform strategy should be investigated to deal with issues like relationship

between patient and health professional, positive attitude of the patient and service provider. The easy accessibility of patients to healthcare units can improve treatment adherence. Others significant factors associated with treatment default are poor education, the occurrence of default in the previous treatment, TB/ HIV coinfection, alcoholism and other comorbidities. Patients with these conditions should be considered as target populations, for individualized attention and priority by health professionals, with main emphasis on contemplating DOTS.

The limitation of the our study was non evaluation of TB/ HIV coinfection, alcoholism, negative attitudes of health professionals and patient, sub-optimal implementation of public health facilities and other comorbidities and under reporting of EPTB. We found that the most frequent sites of EPTB were meninges, lymph nodes followed by the abdomen, skin and bone involvement. The lymph node was the most common site of extrapulmonary involvement in USA in the past. TB pleurisy occurs frequently in association with PTB. Evidence suggests that pleural TB represents an early manifestation of primary infection by MTB and may serve as a sentinel event in recent transmission studies.<sup>18</sup>

The proportion of EPTB as TB clinical forms seems to be higher in countries with a low incidence of TB, such as in Australia, Japan, and USA. The reasons for these differences are unknown but could be related to different epidemiological patterns of persons with TB as a consequence of recent infection. Conversely in countries with a high incidence of TB, EPTB usually represents a smaller fraction of all cases. In 2011 EPTB was 19% in India, 4% in Indonesia and 18% in Pakistan. EPTB was 12.6% in our study which is similar to high TB burden countries<sup>19</sup>. The higher ratio females in PTB cases compared with EPTB cases was statistically significant in our study. Western investigators have reported that EPTB is more prevalent as racial distribution in Asian as compared to the Caucasians and ethnicity has relevancy in other region.<sup>19-27</sup>

Clinical parameters in our study have significant relevance with earlier reports<sup>22</sup>. EPTB prevalent and occurred in 26.2% of HIV-infected patients.<sup>23</sup> Mycobacterial cultures are not usually performed during evaluation of TB suspects and are indicated only in specific instances, such as in cases of suspected EPTB or drug resistant TB and in vulnerable populations. DOTS is strongly recommended to enhance treatment completion and cure of the patient. EPTB is also hazardous health problem due to its high

mortality and morbidity rates in world<sup>24-26</sup>. EPTB is less contagious, less frequent, and difficult to diagnose than PTB, hence less well addressed in Pakistan and in Azad Kashmir.

## Conclusions

1. Both PTB & EPTB are an important clinical problem in TB treatment defaults in our country.
2. High TB treatment default rate is most significant factor for the development of MDR-TB and high morbidity and mortality in TB treatment defaults.
3. Improved diagnostic and therapeutic modalities in PTB & EPTB in TB treatment defaults and supervised treatment programmes are essential prerequisites for optimizing care and better treatment outcomes.
4. Easy accessibility of patients to health care facilities and direct observational treatment (DOT) can improve treatment adherence

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