Cavities Herald Persistent Sputum Positivity

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An Observational Study

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ABSTRACT

Aim: To determine the factors associated with persistent sputum positivity at the end of two months of treatment in patients presenting with (drug-susceptible) pulmonary tuberculosis at a tertiary care hospital in Karachi.

Setting: A cross-sectional study was conducted at the Department of Chest Medicine (Ward 12), Jinnah Postgraduate Medical Center (JPMC), Karachi over six months.

Methods:
A sample of 73 consenting, newly diagnosed, smear positive drug-susceptible pulmonary tuberculosis patients was studied. Demographic (age, gender, height, weight and duration of tuberculosis, body mass index (BMI), socioeconomic, occupational, marital, educational and residential statuses) and clinical factors (chest X-ray extent and cavities, initial smear results, diabetic and smoking statuses) which may be associated with sputum non-conversion were entered in a proforma. Patients were followed up at two months of treatment with a sputum smear. Data analysis was done on SPSS-20.0.

Results:
Rate of sputum positivity after two months of treatment was 17.8%. None of the factors was associated with persistence of sputum positivity except for the presence of chest radiograph (CXR) cavities; which made it 5.5 times more likely that the patient would remain smear-positive at two months (p=0.035).

Conclusion:
The finding of CXR cavities makes it highly likely that a pulmonary tuberculosis patient may remain infectious or have an unfavourable outcome despite taking treatment for 2 months. Clinicians and national policy-makers should thus bear in mind the implications this can have with regard to disease control and pay particular attention in terms of stringent monitoring and Directly Observed Treatment Short-course (DOTS) provision.
**Keywords:** Pulmonary, Tuberculosis, Sputum, Pulmonary inflammation

**INTRODUCTION:**

Tuberculosis (TB) continues to be a colossal public health challenge globally and remains one of the world's deadliest diseases; killing about 1.5 million and infecting about 10 million people worldwide in 2018\(^1\). An untreated patient has the potential to infect another 10-15 people each year, depending upon bacillary load, duration of close contact and duration of antitubercular treatment\(^2,3\). On starting effective antitubercular treatment, bacillary load decreases rapidly, which correlates with reduced infectivity\(^4\). Therefore, infection control measures are recommended for all sputum smear-positive patients until serial smears convert to negative\(^5,6\).

Sputum microscopy for acid-fast bacilli serves as a well-validated and cost-effective means of measuring treatment response\(^7\). Non-conversion of sputum smear at the end of the second month of treatment has been documented to be associated with unfavorable outcomes such as failure and relapse within 2 years of follow up\(^8,9\). Several factors that correlate with heavy initial bacillary load (higher sputum smear and culture grading at diagnosis, shorter time to detection (TTD) of *Mycobacterium tuberculosis* on liquid cultures) and radiologically extensive disease have been linked with sputum smear/culture non-conversion at the end of the second month of TB treatment\(^10\). Additionally, increasing age, ESR, male sex, smoking, diabetes mellitus (DM), malnutrition, anemia, and thrombocytosis have also been associated with persistent sputum positivity\(^11,12\).

Through this study, we sought to determine the factors associated with persistent sputum positivity at the end of two months of treatment in patients with drug-sensitive pulmonary tuberculosis presenting to a tertiary care hospital in the metropolitan city of Karachi.

An understanding of the relevance of these factors pertaining to persistent sputum positivity can help clinicians foresee which patients will remain infectious for a longer period of time and may have worse outcomes. This stratification may also improve large-scale TB control activities.

**MATERIAL AND METHODS:**
Study design, setting and duration: This cross-sectional study was conducted after an ethical approval (NO.F.2-81/2019-GENL/21153/JPMC) at the Department of Chest Medicine (Ward 12), Jinnah Postgraduate Medical Center (JPMC), Karachi over a period of about 6 months from September 14, 2019 to March 16, 2020.

Patients: Consenting adult patients aged 20-60 years of either gender presenting with pulmonary infiltrate (opacity with or without air bronchogram) or cavity on chest radiograph along with persistent productive cough and fever (body temperature ≥ 37.8 °C) and confirmed by positive sputum smear on sputum microscopy for AFB were included and labelled as having pulmonary tuberculosis. Patients who did not give consent, had history of hepatitis C, B or HIV infection, malignancy, sarcoidosis, TB treatment failure, TB treatment interruption, retreatment or multi/extensively drug-resistant [MDR/XDR] TB were excluded.

Sampling: Assuming the proportion of smear grade +1, 19.6%, based on 95% two-sided significance level (1-alpha), 80% power and 9% margin of error, the representative sample size calculated was 73 patients using non-probability consecutive sampling.

Board approval: This study was conducted after approval from the institutional ethical review board. Informed consent was obtained from all the patients for assigning them to the study and using their data in research.

Procedures and investigations: A brief history of demographic data, duration of disease, co-morbidities, smoking habits was taken and recorded in a form. A person who smoked at least a 100 cigarettes in his/her lifetime was labelled a smoker. All those who were known diabetics and on anti-diabetic treatment were considered as diabetics.

Chest Xray findings (with regard to extent and cavitation) were also noted at diagnosis. Each participant’s height (in meters) and weight (to the nearest kilogram) were measured. Every patient received weight-based anti-tubercular drug regimens (comprising isoniazid, rifampicin, ethambutol and pyrazinamide) as recommended by the National TB Control Programme of Pakistan (based on WHO Guidelines for treatment of drug-susceptible tuberculosis and patient care- 2017 update). Drug compliance was
evaluated (on compliance form) by confirmation from close relative of patient and retrieval of empty blister packs of prescribed drugs.

Patients’ sputum was examined with microscopy and XpertMTB/RIF (to rule out rifampicin resistance) before initiating treatment and with microscopy at two months of treatment. Sputum induction was done by means of 3% saline nebulization for patients who were unable to spontaneously produce sputum. The smears were prepared by the Ziehl–Neelsen method, examined for AFB by microscopy and graded according to the number of AFB observed per high power field (HPF) as follows:

- > 10 AFB per oil immersion field in 20 fields as 3+ positive.
- 1–10 AFB per oil immersion field in 50 fields as 2+ positive.
- 10–99 AFB per 100 oil immersion fields in 100 fields as 1+ positive.
- 1–9 AFB per 100 oil immersion fields in 100 fields as sputum positive scanty.

Data analysis: Data were analyzed on SPSS Version 20.0. Mean and standard deviations were calculated for the quantitative variables like age, height, weight and duration of tuberculosis. Frequencies and percentages were calculated for the qualitative variables like gender, BMI, socioeconomic status, occupational status, marital status, educational status, residential status and clinical factors such as results of initial smear, chest x-ray extension, presence of chest x-ray cavities, smoking and diabetes mellitus. Effect modifiers were controlled through stratification of age, gender, BMI, socioeconomic status, occupational status, marital status, educational status to see the effect of these on outcome (smear positivity). Post stratification chi square test was applied on stratified variables as well as the above-mentioned clinical factors associated with the persistent sputum positivity by taking p-value of ≤ 0.050 as statistically significant. Odds ratio was also calculated and OR >1 was considered significant.

RESULTS:
Males comprised the majority of the patients (58.9%). Overall mean age of the patients was 38.6±15.6 years. Less than half the participants (n=30, 41.1%) had a normal BMI, with more than a third being
underweight (37%). Most (58.9%) patients were literate to some extent and all 73 patients belonged to lower to middle socioeconomic strata. Smokers constituted 61.6% (n=45) of the study participants whereas diabetics made up three-quarters (n=56, 76.9%).

On initial sputum analysis, smear grade 3+ was the most common (n=30, 41.1%), followed by 2+ (n=19), scanty (n=15) and 1+ (n=9). A substantial number of patients had unilateral (61.6%), multilobar (60.3%) involvement on chest X ray while more than half (n=41, 56.2%) had one or more cavities.

After two months of initiation of antitubercular drugs, 60 (82.2%) had negative follow-up sputum smears whereas 13 (17.8%) were found to be sputum smear positive, of which 5 (6.8%) were scanty, 6 (8.2%) were 1+ and 2 (2.7) were 2+.

None of the demographic features (gender, age, BMI, occupation, education, marital status and socioeconomic status) was found to be significantly associated with persistent sputum positivity (Table-1). The proportion of smokers was less among non-converted as compared with converted group (30.8% vs. 40.0%, p=0.754), though not statistically significant (Table-2). Similarly, the differences with regard to diabetes and the extent of radiologic involvement between both groups was statistically unremarkable. Initial bacillary load as indicated by smear grade and Xpert burden did not predict sputum non-conversion (p=0.460 and 0.566 respectively).

However, 84.6% of the non-converted patients had one or more cavities on CXR (p=0.031). CXR cavitation was found in most patients with high initial smear grades; precisely 68.4% of those with grade 2+ and 60% of those with grade 3+, but this was statistically insignificant (p=0.330)

Further analysis by logistic regression revealed that CXR cavities were 5.5 times more likely to be associated with persistence of AFB on follow-up smears (OR=5.5) as shown in table-3.

**DISCUSSION:**

The proportion of patients whose sputum did not convert in our study was 17.8%, similar to other studies from the region (11.1% by Wang JY et al, 18% by Sheetal et al, 19.5% by D'Souza et al). A few
studies have shown relatively higher rates of non-conversion (25.3% by Diktanas et al\textsuperscript{17}, 33.2% by Yellapa et al\textsuperscript{18}, 25.4% by Caetano et al\textsuperscript{19})

All of the demographic variables including age, gender and body mass index (BMI) were found to be non-significant in relation to smear positivity which is similar to the study by Bouti K et al\textsuperscript{10}, who reported no association of age, sex, weight, alcoholism, addictions and previous TB disease. In contrast, some studies have cited increasing age and/or male gender as predictors of sputum non-conversion\textsuperscript{3,6,11-19}.

The presence of diabetes or smoking did not impact the rate of conversion at two months in the present study; a finding alike to many studies\textsuperscript{10,11,17}. However, works by Babalik A et al\textsuperscript{12} and Sheetal et al\textsuperscript{5} have shown that smokers are more likely to have delayed sputum conversion.

A multitude of studies\textsuperscript{3,6,10,16-20} have demonstrated the relationship between a high initial bacillary load (smear grade 3+) and likelihood of persistent sputum positivity, though our study has shown no such association (p=0.683, OR 1.29, 95% CI 0.38-4.30).

Radiologic extent of disease has been reported by several studies as being a predictor of sputum non-conversion\textsuperscript{10,12,17}. This includes the involvement of a greater number of lobes, cavitation and/or military disease. We investigated the extent (unilateral/bilateral and multilobar) of disease but found no association with persistent sputum positivity. However, the presence of one or more cavities (OR=5.50, CI 1.12-27.0; p=0.035) strongly predicted non-conversion of sputum at 2 months. Our finding is corroborated by similar reports from other studies\textsuperscript{3,11,16,17} that have also documented cavitation as a predictor of persistent sputum positivity.

A limitation of the present study is the use of smear microscopy for follow-up (albeit in accordance with WHO guidelines\textsuperscript{14} and the local TB Control Programme\textsuperscript{13}) at two months. Ideally, it is the negative cultures that truly reflect sputum conversion but getting cultures is less cost-effective and more time-consuming and therefore not feasible. Since the microscopy also reports non-viable bacteria, it’s correlation with culture (which is the gold standard) is debatable; though a German study\textsuperscript{21} has reported a
strong correlation between smear microcopy and time to culture positivity within the first two months of treatment.

The current study sets a precedent for future larger studies at national level that could also draw conclusions about outcomes at the end of treatment and occurrence of relapse. Previous studies have highlighted the association between high smear grades and treatment failure/relapse.\textsuperscript{20,22}

**CONCLUSION:**

One of the key measures in making TB treatment and control activities a success is identifying patients at high risk of transmission and poor outcomes. The recognition of individuals at high-risk of non-conversion through the use of chest radiograph (which is done across all TB centres, even in low-income countries) would help national TB control programs focus their resources (strict monitoring and DOT) towards care for these particular patients.

**DECLARATIONS:**

i. Funding: N/A

ii. Conflicts of interest: All authors have no conflicts of interest or disclosures

iii. Ethics approval: Taken from JPMC Institutional Review Board Committee on 10th June 2019

iv. Consent to participate: An informed consent for participation was taken from either the patient themselves or the attendant, whichever was possible

v. Consent for publication: N/A

vi. Availability of data and material (data transparency): N/A

vii. Code availability (software application or custom code): N/A

viii. Authors' contributions

Nadia Jawad: Acquisition and analysis of data, drafting the work

Nausheen Saifullah: Final approval of the version to be published

Naseem Ahmed: Revising the work critically, supervision

Saira Jafri: Analysis and interpretation of data, revising the manuscript critically for important intellectual content
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