The Cavity as a Lasting Abode for Tuberculous Bacilli

An Observational Study

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Abstract

The aim of this study was to determine the factors associated with persistent sputum positivity at the end of 2 months of treatment in patients presenting with (drug-susceptible) pulmonary tuberculosis at a tertiary care hospital in Karachi. A cross-sectional study was conducted at the Department of Chest Medicine (Ward 12), Jinnah Postgraduate Medical Center (JPMC), Karachi, over 6 months. 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, 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 pro-forma. Patients were followed up at 2 months of treatment with a sputum smear. Data analysis was done on SPSS (Statistical Package for Social Sciences-version 20.0). Rate of sputum positivity after 2 months of anti-tubercular drug treatment was 17.8%. None of the above-mentioned demographic and clinical factors was associated with persistence of sputum positivity except for the presence of CXR cavities, which made it 5.5 times more likely that the patient would remain smear-positive at 2 months (p = 0.035). The finding of chest radiograph cavities makes it highly likely that a pulmonary tuberculosis patient may remain infectious or have an unfavorable outcome despite taking treatment for 2 months. Clinicians and national policymakers should thus bear in mind the implications this can have with regard to disease control and therefore pay particular attention to such patients in terms of stringent monitoring and directly observed treatment short-course (DOTS) provision.

Keywords Clinical factors · Drug-sensitive tuberculosis · Persistent positivity · Pulmonary tuberculosis · Smear-positive · Sputum smear

Abbreviations

AFB Acid-fast bacilli
BMI Body mass index
CI Confidence interval
COVID-19 Coronavirus disease due to SARS CoV-2
CXR Chest radiograph
DM Diabetes mellitus
ESR Erythrocyte sedimentation rate
HIV Human immunodeficiency virus
IFN Interferon
MDR Multidrug resistant
OR Odds ratio
PTB Pulmonary tuberculosis
SPSS Social Package for Social Sciences
TB Tuberculosis
TTD Time to detection
WHO World Health Organization
XDR Extensively drug resistant

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 correlate 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, erythrocyte sedimentation rate (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 2 months of treatment in patients with drug-sensitive pulmonary tuberculosis presenting to a tertiary care hospital in the metropolitan city of Karachi.

In the COVID era, co-infection with COVID-19 raises concerns about the interactions between the two diseases with respect to immune responses, morbidity, and mortality. SARS CoV-2 activates the adaptive immune response, with the CD4+ T cell response providing protective immunity [13]. In a patient with latent/active TB, co-infection may alter the course of COVID-19 disease. Though little is known about the exact immune responses at play in co-infected patients, evidence provided by a study performed on whole blood and bronchoalveolar lavage fluid suggest that active TB increases the risk of severe COVID-19 disease, due to increased abundance of circulating myeloid subpopulations and increased interferon (IFN) production [14].

The first ever global cohort of COVID-19 and active/former tuberculosis patients constituted 49 patients (42 had active TB and 7 had TB sequelae) recruited by the Global Tuberculosis Network (GTN) in 8 countries on 3 continents [15]. This observational study concluded that COVID-19 could occur before, after, or simultaneously with TB. No causal associations were established due to the small number of patients. Also, authors agreed that larger, longitudinal studies were required to definitively ascertain the role of COVID-19 in accelerating progression from latent to active TB and the impact of TB sequelae on COVID-19 outcomes.

The global TB and COVID-19 study by the GTN/WHO on nearly 700 patients in 40 countries is expected to clarify many ambiguities on the interactions of the two diseases, including the risk of progression to active TB in those with latent TB [16].

TB/COVID-19 co-infection may spell poor outcomes, including higher mortality. Combined data from the 8 countries and Sondalo Hospital study show an 11.6% case fatality rate (8/69) [17]. The study shows that mortality may be more related to occurrence of comorbidities and older age than TB alone. However, higher death rates may occur in cases with resistant or severe forms of TB even in the young.

The COVID-19 pandemic has given rise to new fears about the fate of undiagnosed/unreported TB patients as access to TB care services has become limited. This is evidenced by a drop in TB notification rates [18]. High burden countries like Pakistan need to step up policies and invest in active case-finding strategies so that the success gained in terms TB mortality is not reversed.

Since our study was predominantly conducted before the pandemic took hold in Pakistan, we did not consider or test for COVID-19 among our enrolled patients.

Through this study, we sought to determine the factors associated with persistent sputum positivity at the end of 2 months of treatment in patients with drug-sensitive pulmonary tuberculosis presenting to a tertiary care hospital in the metropolitan city of Karachi.

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 (randomly selected among out-patients) 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 acid-fast bacilli (AFB) were included and labeled as having pulmonary tuberculosis. Patients who did not give consent and had history of hepatitis C and B or human immunodeficiency virus (HIV) infection, malignancy, sarcoidosis, TB treatment failure, TB treatment interruption, retreatment, or multi/extensively drug-resistant (MDR/XDR) TB were excluded. Patients with malignancy, HIV, and hepatitis B or C were
excluded as the occurrence of the above conditions may alter the presentation of TB disease due to immunosuppression.

Sampling

Assuming the proportion of smear grade +1, 19.6% [6], based on 95% two-sided significance level (1-alpha), 80% power, and 9% margin of error, the representative sample size calculated (considering the local study by D’Souza et al.) was 73 patients using non-probability consecutive sampling.

Board Approval

This study was conducted after approval (No. F.2–81/2019-GENL/21153/JPMC) 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, comorbidities, and smoking habits was taken and recorded in a form. A person who smoked at least 100 cigarettes in his/her lifetime was labelled a smoker (according to Centers for Disease Control and Prevention https://www.cdc.gov/nchs/tobacco/tobacco_glossary.htm). All those who were known diabetics and on anti-diabetic treatment were considered as diabetics.

Chest X-ray 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-tuberculosis drug regimens (comprising isoniazid, rifampicin, ethambutol, and pyrazinamide) as recommended by the National TB Control Programme of Pakistan [19] (based on WHO Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update [20]). 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 Xpert MTB/RIF (to rule out rifampicin resistance) before initiating treatment and with microscopy at 2 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 acid-fast bacilli (AFB) observed per high power field (HPF) as follows [21]:

- > 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 (Statistical Package for Social Sciences) 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, and 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 73 patients (n = 43, 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, which reflects the socioeconomic status of most, if not all, patients who visit public sector hospitals. 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 2 months of initiation of antituberculosis 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 socio-economic 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. Similarly, the differences with regard to diabetes and the extent of radiologic involvement between both groups were 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 chest radiograph (CXR) \(( p = 0.031 \)), while half the patients who converted had cavities. 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 \(( \text{OR} = 5.5 \) as shown in Table 3.

### Table 1 Association of sputum positivity with demographic characteristics

| Factors               | Total | Sputum converted (\( n = 60 \)) | Sputum non-converted (\( n = 13 \)) | Sig.\(^1\) |
|-----------------------|-------|---------------------------------|-------------------------------------|-----------|
| Gender                |       |                                 |                                     |           |
| Male                  | 43 (58.9) | 36 (60.0)                  | 7 (53.8)                             | 0.683     |
| Female                | 30 (41.1) | 24 (40.0)                  | 6 (46.2)                             |           |
| Age (years)           |       |                                 |                                     |           |
| Below 40              | 38 (52.1) | 32 (53.3)                  | 6 (46.2)                             | 0.639     |
| 40 or above           | 35 (47.9) | 28 (46.7)                  | 7 (53.8)                             |           |
| BMI (kg/m²)^2         |       |                                 |                                     |           |
| < 18.5 (underweight)  | 27 (37.0) | 22 (37.3)                  | 5 (38.5)                             | 0.989     |
| 18.5–24.9 (normal)    | 30 (41.1) | 24 (40.7)                  | 5 (38.5)                             |           |
| ≥ 25 (overweight)     | 16 (21.9) | 13 (22.0)                  | 3 (23.0)                             |           |
| Occupation            |       |                                 |                                     |           |
| Student               | 26 (35.6) | 22 (36.7)                  | 4 (30.8)                             | 0.410     |
| Employed              | 28 (38.4) | 21 (35.0)                  | 7 (53.8)                             |           |
| Unemployed            | 19 (26.0) | 17 (28.3)                  | 2 (15.4)                             |           |
| Education             |       |                                 |                                     |           |
| Illiterate            | 30 (41.1) | 24 (40.0)                  | 6 (46.2)                             | 0.411     |
| Primary               | 14 (19.2) | 12 (20.0)                  | 2 (15.4)                             |           |
| Secondary             | 20 (27.4) | 15 (25.0)                  | 5 (38.5)                             |           |
| Higher                | 9 (12.3)  | 9 (15.0)                   | 0 (0)                                |           |
| Marital status        |       |                                 |                                     |           |
| Single                | 23 (31.5) | 20 (33.3)                  | 3 (23.1)                             | 0.743     |
| Married               | 50 (68.5) | 40 (66.7)                  | 10 (76.9)                            |           |
| Socio-economic status |       |                                 |                                     |           |
| Lower class           | 32 (43.8) | 26 (43.3)                  | 6 (46.2)                             | 0.885     |
| Lower middle class    | 32 (43.8) | 27 (45.0)                  | 5 (38.5)                             |           |
| Middle class          | 9 (12.3)  | 7 (11.7)                   | 2 (15.4)                             |           |

Values given in parentheses are percentages

\(^1\)Sig significance

\(^2\)BMI body mass index

### 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 et al [22], 18% by Sheetal et al [5], 19.5% by D’Souza et al [6]). A few studies have shown relatively higher rates of non-conversion (25.3% by Diktanas et al [23], 33.2% by Yellappa et al [24], 25.4% by Motao et al [25]).

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 et al [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 [3, 6, 11, 23–25].

The presence of diabetes or smoking did not impact the rate of conversion at 2 months in the present study, a finding alike to many studies [10, 11, 23]. However, works by Babalik et al [12] and Sheetal et al [5] have shown that smokers are more likely to have delayed sputum conversion.

A multitude of studies [3, 6, 10, 22–26] have demonstrated the relationship between a high initial bacillary
### Table 2 Association of sputum positivity with environmental and clinical factors

| Factors                        | Total           | Sputum converted (n = 60) | Sputum non-converted (n = 13) | Sig.¹ |
|-------------------------------|-----------------|---------------------------|------------------------------|-------|
| House                         |                 |                           |                              |       |
| Own                           | 43 (58.9)       | 35 (58.3)                 | 8 (61.5)                     | 0.831 |
| Rented                        | 30 (41.1)       | 25 (41.7)                 | 5 (38.5)                     |       |
| Smoker                        |                 |                           |                              |       |
| Yes                           | 45 (61.6)       | 24 (40.0)                 | 4 (30.8)                     | 0.754 |
| No                            | 28 (38.4)       | 36 (60.0)                 | 9 (69.2)                     |       |
| Diabetic                       |                 |                           |                              |       |
| Yes                           | 56 (76.7)       | 14 (23.3)                 | 3 (23.1)                     | 0.984 |
| No                            | 17 (23.3)       | 46 (76.7)                 | 10 (76.9)                    |       |
| Initial smear                 |                 |                           |                              |       |
| Scanty                        | 15 (20.5)       | 14 (23.3)                 | 1 (7.7)                      | 0.460 |
| 1+                            | 9 (12.3)        | 8 (13.3)                  | 1 (7.7)                      |       |
| 2+                            | 19 (26.0)       | 14 (23.3)                 | 5 (38.5)                     |       |
| 3+                            | 30 (41.1)       | 24 (40.0)                 | 6 (46.2)                     |       |
| Initial gen expert            |                 |                           |                              |       |
| Very low/trace                | 1 (1.4)         | 1 (1.7)                   | 0 (0)                        | 0.566 |
| Low                           | 15 (20.5)       | 14 (23.3)                 | 1 (7.7)                      |       |
| Medium                        | 26 (35.6)       | 20 (33.3)                 | 6 (46.2)                     |       |
| High                          | 31 (42.5)       | 25 (41.7)                 | 6 (46.2)                     |       |
| CXR extension side            |                 |                           |                              |       |
| Unilateral                    | 45 (61.6)       | 37 (61.7)                 | 8 (61.5)                     | 0.993 |
| Bilateral                     | 28 (38.4)       | 23 (38.3)                 | 5 (38.5)                     |       |
| CXR extension lobes           |                 |                           |                              |       |
| Localized                     | 29 (39.7)       | 24 (40.0)                 | 5 (38.5)                     | 0.918 |
| Multi-lobar                   | 44 (60.3)       | 36 (60.0)                 | 8 (61.5)                     |       |
| CXR cavity                    |                 |                           |                              |       |
| Present                       | 41 (56.2)       | 30 (50.0)                 | 11 (84.6) *                 | 0.031 |
| Absent                        | 32 (43.8)       | 30 (50.0)                 | 2 (15.4)                     |       |

*Shows significantly higher proportion at 5% level of significance by using chi-square test

Values given in parentheses are percentages

¹Sig significance

### Table 3 Predicting factors of sputum smear positivity

| Factors                        | Sputum converted (n = 60) | Sputum non-converted (n = 13) | OR¹ (95% CI²)          | p-value |
|-------------------------------|---------------------------|------------------------------|------------------------|---------|
| Male patients                 | 36 (60.0)                 | 7 (53.8)                     | 0.78 (0.23–2.60)       | 0.683   |
| Age > 40 years                | 32 (53.3)                 | 6 (46.2)                     | 1.33 (0.40–4.44)       | 0.639   |
| BMI< 18.5 kg/m²               | 22 (37.3)                 | 5 (38.5)                     | 1.09 (0.28–4.28)       | 0.901   |
| Employed                      | 21 (35.0)                 | 7 (53.8)                     | 1.83 (0.47–7.19)       | 0.385   |
| Illiterate                    | 24 (40.0)                 | 6 (46.2)                     | 1.29 (0.38–4.30)       | 0.683   |
| Married                       | 40 (66.7)                 | 10 (76.9)                    | 1.67 (0.41–6.74)       | 0.474   |
| Lower economic class          | 26 (43.3)                 | 6 (46.2)                     | 1.12 (0.34–3.74)       | 0.853   |
| Own house                     | 35 (58.3)                 | 8 (61.5)                     | 1.14 (0.33–3.91)       | 0.831   |
| Smoking                       | 24 (40.0)                 | 4 (30.8)                     | 0.67 (0.18–2.41)       | 0.537   |
| Diabetes                      | 14 (23.3)                 | 3 (23.1)                     | 0.99 (0.24–4.09)       | 0.984   |
| 3+ smear                      | 24 (40.0)                 | 6 (46.2)                     | 1.29 (0.38–4.30)       | 0.683   |
| CXR bilateral sides           | 23 (38.3)                 | 5 (38.5)                     | 0.73 (0.21–2.56)       | 0.627   |
| CXR multi-lobe extension      | 36 (60.0)                 | 8 (61.5)                     | 1.07 (0.31–3.65)       | 0.918   |
| CXR cavity                    | 30 (50.0)                 | 11 (84.6) *                 | 5.50 (1.12–27.0)       | 0.035   |

*Shows significantly higher proportion at 5% level of significance

¹OR odds ratio

²CI confidence interval

³BMI body mass index

⁴CXR chest radiograph
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 [10, 12, 23]. 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 [3, 11, 22, 23] that have also documented cavitation as a predictor of persistent sputum positivity. Interestingly, half of our patients who did convert also had one or more cavities on the CXR.

A limitation of the present study is the use of smear microscopy for follow-up (albeit in accordance with WHO guidelines [20] and the local TB Control Programme [19]) at 2 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, its correlation with culture (which is the gold standard) is debatable; a German study [27] has reported a strong correlation between smear microscopy and time to culture positivity within the first 2 months of treatment. The same holds true for Xpert MTB/RIF, a rapid, easily available nucleic acid amplification test; its ability to detect non-viable bacilli with greater sensitivity precludes its use as a follow-up tool.

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. The current study sets a precedent for future much 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 [26–28].

**Conclusion**

Our study shows that the presence of one or more cavities can strongly predict ($p = 0.035$) sputum non-conversion at 2 months and thus flag patients who may be at risk for poor outcomes. 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 centers, even in low-income countries) would help national TB control programs focus their resources (strict monitoring and DOT) towards care for these particular patients.

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**Author Contribution** Nadia Jawad: Acquisition and analysis of data and drafting the work.

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

Nausheen Saifullah: Final approval of the version to be published.

Naseem Ahmed: Revising the work critically and supervision.

**Availability of Data and Material** N/A.

**Code Availability** N/A.

**Declarations**

**Ethics Approval** Taken from JPMC Institutional Review Board Committee on June 10, 2019.

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

**Consent for Publication** N/A.

**Conflict of Interest** The authors declare no competing interests.

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