

A Clinical Study on Risk Factors for Recurrent Pulmonary Tuberculosis – a Hospital-Based Study

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Abstract

Aim of the Study: The aim of this study was to understand and identify risk factors in recurrent cases of pulmonary tuberculosis (TB).

Materials and Methods: A total of 54 patients attending tertiary teaching hospital with recurrent pulmonary TB were included in this study. Patients who were earlier cured using a four-drug treatment regimen of rifampicin, isoniazid, and pyrazinamide (RHZ) were included in this study. The risk factors studied were age, gender, race, duration of symptoms, lesion cavitation, extent of disease, diabetes mellitus (DM), alcoholism, HIV infection, delayed negative sputum conversion, treatment compliance, and medication doses. To detect recurrence, the patients were monitored for 7.7 ± 2.0 years after cure. Data were analyzed using the student's t-test and the Chi-square test.

Observations and Results: A total of 54 patients with symptoms of recurrence of pulmonary TB were included in this study. The mean age was 38.12 ± 4.60 years. There were 34 (62.96%) males and 21 (38.88%) females. The male-to-female ratio was 1.61:1. The mean age among the males was 40.09 ± 5.62 , and it was 34.12 ± 3.75 years. The mean duration of the symptoms was 82.45 ± 7.15 (12–238) days. There were 19 (35.18%) patients who were chronic alcoholics. The number of patients who showed cavity in their X-ray lung investigation was 46/54 (85.18%). The noncompliance among the diabetic patients was 2/54 (3.70%) with the total number of patients with DM was 20/54 (37.03%). Among the 54 patients, 31/54 (57.40%) patients were tested for HIV screening; among them, 07/31 (22.58%) tested positive for HIV. There were 07/31 (22.58%) positive HIV test patients in the recurrence group, and 09.01% HIV positive incidence in the nonrecurrence group which was statistically significant ($P < 0.05$).

Conclusions: Recurrence of TB was more common in HIV-positive patients, and in patients, who did not comply with the self-administered treatment (RHZ regimen). Patients presenting at least one of these risk factors can benefit from the implementation of a posttreatment surveillance system for early detection of recurrence. An alternative to prevent noncompliance with TB treatment would be the use of supervised treatment.

Key words: Isoniazid, Recurrence, Rifampicin, Risk factors, Tuberculosis

INTRODUCTION

An ideal antituberculosis (TB) treatments should provide high cure rates, few adverse effects, and low disease recurrence rates. The treatment protocols should be acceptable to the patients with minimal side effects. The three-drug regimen consisting of the combined use

of rifampin (RIF), isoniazid (INH), ethambutol, and pyrazinamide (PZA), meets the parameters as long as the medications are administered in the right doses and for the prescribed duration.^[1] The importance of the duration of the treatment protocol may not be appreciated by the naïve patients and there always tendency to stop the treatment with the improvement of symptoms initially. However, if the treatment protocols are followed strictly, the cure rates reach near to 100%, as well as rates of regimen change due to toxicity and rates of recurrence lower than 5%, can be obtained. Certain factors, such as duration of treatment, bactericidal/bacteriostatic activity of the medications, mode of administration (daily or intermittent), and noncompliance have been identified as being associated

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with recurrence of TB. With the outbreak of the HIV infection epidemic, some studies have shown higher recurrence rates in infected (HIV-positive) patients,^[2-8] whereas others show similar values.^[9-11] The treating physicians should always be aware of the risk factors for recurrence of pulmonary TB after achieving a cure, to take measures to ensure treatment success. In this context, a clinical study was conducted to observe and identify risk factors associated with the recurrence of cured pulmonary TB in patients treated with the short-course regimen used in Brazil (RIF+ INH+ ethambutol+ PZA regimen).

Period of Study

June 2015–May 2017.

Institution of Study

Kannur Medical College, Anjarakandy, Kannur, Kerala.

Type of Study

A retrospective, cross-sectional and controlled observational study.

MATERIALS AND METHODS

In the present study, 54 patients were included as per the inclusion criteria from among a total number of 3832 patients who were treated for pulmonary TB over 10 years. This required information was collected from the medical records department of the hospital. A total of 54 patients attending tertiary teaching hospital with recurrent pulmonary TB were included in the study. Patients who were earlier cured using a three-drug treatment regimen of Rifampicin, INH, Ethambutol, and PZA (RHZ) were included in the study. The risk factors studied were age, gender, race, duration of symptoms, lesion cavitation, extent of disease, diabetes mellitus (DM), alcoholism, HIV infection, delayed negative sputum conversion, treatment compliance, and medication doses. Institutional ethical clearance was obtained for the study.

Inclusion criteria

1. Patients aged above 20 years were included.
2. Patients of both genders were included.
3. Patients who were diagnosed as pulmonary TB and treated with four-drug regimen were included.
4. Patients with the risk factors such as mellitus, alcoholism, and HIV infection were included.
5. Patients with negative sputum conversion, treatment compliance, and medication doses were included in this study.

Exclusion criteria

1. Patients with age below 20 years were excluded.
2. Patients with three-drug regimen and other regimens were excluded from the study.

This was a controlled observational study comparing the incidence of recurrence in a group of individuals who had cured pulmonary TB and were exposed to a series of potential risk factors with the incidence of recurrence in another group of individuals who also had cured pulmonary TB but were not exposed to such risk factors. Initially, exposure was measured, and at a later time, it was determined whether or not recurrence had occurred. Therefore, we attempted to identify patient characteristics or attributes that could be associated with a greater likelihood of recurrence of pulmonary TB. The risk factors studied were age, gender, race, duration of symptoms, extent of disease, cavitation on chest X-ray, noncompliance, delayed negative sputum conversion (after the 4th month of treatment), DM, alcoholism, medication doses, and HIV infection. The treatment was self-administered, delivered to the patient every 30 days, and consisted of RIF+ INH + ethambutol+ PZA for 2 months and RIF+INH for another 4 months. Patients with HIV-positive screening and DM were administered additional RIF+INH for 7 months in the second phase of treatment. Patients with delayed negative sputum conversion received RIF+INH until they had three consecutive negative sputum samples. The dosage of medicines used in this study was adjusted according to the norms established by the Indian TB Association, i.e., weight < 45 kg, R: 300 mg, H: 200 mg, ethambutol 450 mg, and Z: 1000 mg; weight from 45 to 55 kg, R: 450 mg, H: 300 mg, ethambutol 600 mg, and Z: 1500 mg; and weight >55 kg, R: 600 mg, H: 400 mg, and Z: 2000 mg). The duration of symptoms was defined as the interval between the onset of the respiratory symptoms and the diagnosis of TB. Pulmonary lesions on chest X-rays were classified as “cavitary” or “noncavitary” and as “extensive” (affecting an area greater than that of one lung) or “nonextensive.” Treatment compliance was evaluated by pill counts, regularity in attending medical appointments, and information obtained from the patient or family members. All patients with a history of excessive alcohol consumption to the point of causing harm to their personal or professional relationships were considered alcoholics. All the data were analyzed using standard statistical methods.

OBSERVATIONS AND RESULTS

A total of 54 patients with symptoms of recurrence of pulmonary TB were included in this study. The mean age was 38.12 ± 4.60 years. There were 34 (62.96%) males and 21 (38.88%) females. The male-to-female ratio was 1.61: 1. The mean age among the males was 40.09 ± 5.62 , and it was 34.12 ± 3.75 years. The mean duration of the symptoms was 82.45 ± 7.15 (12–238) days. There were 19 (35.18%) patients who were chronic alcoholics. Among these only two patients (10.52%) accepted another

regimen of antituberculous treatment after diagnosed with recurrent TB. It showed that the rate of noncompliance was higher in alcoholics than in nonalcoholics ($P = 0.021$; where P significant at < 0.05). The number of patients who showed cavity in their X-ray lung investigation was 46/54 (85.18%). 11/54 (20.37%) patients declined again antituberculous treatment. The noncompliance among the diabetic patients was 2/54 (3.70%) with the total number of patients with DM was 20/54 (37.03%). Among the 54 patients, 31/54 (57.40%) patients were tested for HIV screening; among them 07/31 (22.58%) tested positive for HIV. The demographic and clinical features of patients who underwent HIV screening and those who did not undergo HIV screening were same. Delayed sputum conversion in the nonrecurrence group was 22.09% and in the recurrence group was 26/54 (48.14%). In all the 54 patients, the posttreatments follow-up after the initial pulmonary TB was 8.2 ± 3.18 years. An analysis of the demographic data and clinical findings on a multivariate basis, it was observed that there was no statistical difference in demographic data such as age, gender, extent of disease, cavitation in the lungs, delayed negative sputum conversion alcoholism, and DM between the patients who developed recurrence and those who did not [Table 1]. There was a statistical significant correlation between the two groups in regards with delayed sputum conversion, DM, and HIV screening positive result ($P < 0.05$), [Table 1].

There was also no difference regarding the doses of RIF, INH, ethambutol, and PZA between the two groups [Table 2]. The rates of treatment compliance or noncompliance (regular or irregular use of the medication) ($P = 0.018$) as well as of HIV-positivity and HIV-negativity ($P = 0.31$) were different between the two groups [Table 1]. There were 07/31 (22.58%) positive HIV test patients in the recurrence group and 09.01% HIV-positive incidence in the nonrecurrence group which was significant statistically ($P < 0.05$), [Table 1]. The overall recurrence was 54/3832 (%) in the present study. The number of patients developing recurrence within 12 months was 23/3832 (0.060%) and between 13 and 24 months was 16 (0.41%), and the remaining 15/3832 (0.39%) were between 25 and 96 months. In the HIV-positive patients, recurrence occurred within 14–49 months (mean of 18 months) after cure, whereas in the HIV-negative patients, recurrence occurred within 32–72 months (mean of 39 months; $P = 0.548$).

DISCUSSION

In the present study, 54 patients were included as per the inclusion criteria form among total number of 3832 patients who were treated for pulmonary TB over

Table 1: The demographic data and correlation between the patients who developed recurrence and without recurrence (n=54)

Observation	Recurrence group	Without recurrence	P
Mean age	38.12±4.60	39.21±6.11	0.612
Gender incidence ratio	1.61: 1	1.66:1	0.725
Extent of disease	Moderate-to-severe	Moderate-to-severe	Moderate-to-severe
Cavitation of lung	85.18%	86.02%	0.601
Alcoholism-19/54	35.18%	36.11%	0.120
irregularity in using medications	38/54-70.37%	49.16%	0.018
Noncompliance of treatment in alcoholics	17/54-31.48%	-	-
Delayed sputum conversion	26/54-48.14%	22.09%	0.044
DM	37.03%	21.54%	0.027
HIV positive	22.58	09.01%	0.031

DM: Diabetes mellitus

Table 2: The treatment doses of patients with recurrence and without recurrence (n=54)

Anti-TB drugs	Recurrence group	No recurrence group	P
Rifampicin	10.3±2.8	10.5±3.57	0.435
INH	6.4±1.5	6.9±1.99	0.610
Ethambutol	18.76±2.7	17.35±6.30	0.723
PZA	28.76±3.5	27.11±7.23	0.813

TB: Tuberculosis, INH: Isoniazid, PZA: Pyrazinamide

10 years. These 54 patients were evaluated in terms of TB symptoms, alcoholism, and DM, as well as being submitted to sputum smear microscopy and chest X-ray. Throughout the treatment period, the patients were monitored monthly using the clinical evolution and sputum tests. Recurrence of TB is defined as a new episode of the disease after the cure of a previous episode. It can occur due to endogenous reactivation or to exogenous reinfection,^[12] which are conditions that are clinically indistinguishable^[13] but can be differentiated by molecular techniques.^[12-14] The molecular techniques are not available at community level health in India, and due to its cost-effectiveness are not used. However, the failure to use these techniques does not cause greater harm to patients since at recurrence; patients again receive the RIF+ INH+ ethambutol+ PZA regimen, which is indicated in cases of endogenous reactivation as well as in cases of reinfection. Review of epidemiological studies shows that in areas of low TB incidence, recurrence is usually due to endogenous reactivation.^[15] In areas of high incidence, the incidence of cases of recurrence attributed to reinfection can reach 75%.^[12] Recurrence due to reinfection is a constant risk over time;^[13] whereas recurrence due to reactivation seems to occur closer to the time of cure.^[16] The overall recurrence was 54/3832 (%) in the present study. The number of patients developing recurrence within 12 months was 23/3832 (0.060%) and between 13 and 24 months was 16 (0.41%) and the remaining

15/3832 (0.39%) were between 25 and 96 months. In the HIV-positive patients, recurrence occurred within 14–49 months (mean of 18 months) after cure, whereas in the HIV-negative patients, recurrence occurred within 32–72 months (mean of 39 months; $P = 0.548$). The recurrences occurring within 12 months in this study may be more likely due to endogenous reactivation. The remaining cases occurred during the observation period (an average of two cases per year), and it was not possible to infer whether they were due to reactivation or to reinfection. Incomplete bacteriological cure, which is usually caused by irregular medication intake, is the most common cause of endogenous reactivation. Endogenous reactivation can also result from the use of regimens with low bactericidal potency, from inadequate treatment duration, from underdosing of the medications or from the inappropriate choice of medications, and ignoring the presence of preexisting resistance.^[4,6,7,13,17,18] In the present study, the regimen used was appropriate in terms of its composition, duration, and indication (treatment-naïve patients living in an area of low prevalence of primary resistance), and doses prescribed. Doses of INH higher than the 5 mg/kg of body weight recommended for adults were used due to the formulation of the capsule (300 mg of RIF and 200 mg of INH), which does not allow the prescription of the ideal INH dose without lowering the RIF dose.^[19] In the present study, only noncompliance and HIV infection proved to be related to higher rates of recurrence. Unlike previous studies, which have demonstrated that recurrence is more frequent in patients with DM, in those with extensive disease, and in those with pulmonary cavitation at the beginning of the treatment, the present study did not confirm that these conditions are risk factors for recurrence. Regarding DM, it is possible that the results of the present study are mainly due to the greater treatment compliance. Alcoholism has been identified as a major predictor of noncompliance from the initiation of TB chemotherapy, being a common cause of abandonment, death, and recurrence of TB.^[20] In recent studies, poor treatment compliance has been a significant risk factor for recurrence of TB in HIV-positive patients.^[6,21] In the present study, alcoholism was more common in patients who did not comply with the treatment than in those who did. However, alcohol abuse, in its relationship with recurrence, is no longer important when noncompliance is considered, since it is not alcoholism that leads to recurrence of TB, but rather treatment noncompliance. A limitation of many of the studies is the lack of information about the degree of immunosuppressant effect of HIV-positive patients, since severity of immunosuppression is a predictor of TB recurrence.^[21,22] In one of those studies, recurrence in HIV-positive patients only occurred in individuals with HIV-related symptoms, which are indicative of a more

advanced stage of immunosuppression.^[5] In other studies, low CD4 counts proved to be associated with a greater likelihood of recurrence.^[21,24] In addition to the limitation imposed by the small number of HIV-positive patients in the present study, this topic was also not investigated. Since AIDS treatment was little effective at the time, the patients were recruited, it is to be presumed that the immunity of many patients was compromised. The results of the present study indicate that noncompliance and HIV infection are independent risk factors for recurrence of TB after cure using the self-administered RIF+ INH+ ethambutol+ PZA regimen.

CONCLUSIONS

The patients cured of TB who present at least one of these risk factors can benefit from the implementation of a posttreatment surveillance system for early detection of possible cases of recurrence. To prevent noncompliance with TB treatment, especially in areas of high prevalence of TB and HIV infection, it becomes more important that supervised treatment be used. For HIV-positive patients, the use of INH after TB is cured can be contemplated. However, clinical and epidemiological studies are needed to calculate the cost-benefit ratio of this chemoprophylaxis, as well as to determine the appropriate duration of treatment.

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