

Risk factors for recurrence of pulmonary tuberculosis in properly treated patients and declared healed

Facteurs de risque de récurrence de la tuberculose pulmonaire chez les patients ayant reçu un traitement adéquat

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ABSTRACT

Introduction: Despite the national tuberculosis control program in Tunisia, and the efforts made by the health authorities, a relapse-free cure for pulmonary tuberculosis (TB) remains elusive and not always guaranteed. This study aimed to identify risk factors for pulmonary tuberculosis recurrence among adequately treated patients who had been declared healed.

Methods: We collected records of patients treated for the first episode of TB in the pulmonology department of Charles Nicolle Hospital of Tunis between 2013 and 2021. Every patient had at least one year follow-up after the end of treatment. Two groups were identified: patients with TB recurrence (G1) and patients without TB recurrence (G0).

Results: We analyzed data of 140 patients treated for TB, and 12 patients had a TB recurrence (G1: 8.6%). G1 patients were significantly older (45 years vs 42 years, $p=0.013$). There was no significant difference between groups in terms of gender-ratio ($p>0.05$), tobacco intoxication ($p>0.05$), substance abuse ($p>0.05$), nor comorbidities ($p>0.05$). However, G1 patients had a more frequent history of incarceration ($p<0.001$). Time to consult and time to bacteriological confirmation of TB didn't differ between groups. Evolution was characterized by a slower clinical improvement ($p=0.006$) and a longer time of bacilloscopic negativity in G1 ($p=0.048$). Multivariate analysis showed that the delay in clinical improvement beyond 30 days ($OR=9.79$; 95% $CI=1.77-54.05$; $p=0.009$) and the delay in bacilloscopic negativity ($OR=4.93$; 95% $CI=1.06-22.92$; $p=0.042$), were independent risk factors associated with TB recurrence.

Conclusions: Pulmonary TB recurrence concerns mainly patients with a delayed time to bacilloscopic negativity and a slower clinical improvement, particularly beyond 30 days. These at-risk patients require specific follow-up to prevent this complication.

Key words: Tuberculosis, recurrence, relapse, risk factor

RÉSUMÉ

Introduction: Malgré les avancées thérapeutiques en Tunisie, un remède sans rechute contre la tuberculose pulmonaire (TB) reste insaisissable et pas toujours garanti. Cette étude visait à rechercher les facteurs de risque de récurrence de la tuberculose pulmonaire chez les patients correctement traités.

Méthodes: Nous avons recueilli des dossiers de patients traités pour un premier épisode de tuberculose pulmonaire au service de pneumologie de l'hôpital Charles Nicolle de Tunis entre 2013 et 2021. Nous avons suivi pendant au moins un an après la fin du traitement. Deux groupes ont été identifiés : les patients présentant une récurrence de la tuberculose (G1) et les patients sans récurrence de tuberculose (G2).

Résultats : Nous avons analysé les données de 140 patients traités pour la tuberculose, dont 12 patients présentaient une récurrence de la tuberculose (G1 : 8,6 %). Les patients de G1 étaient significativement plus âgés (45 ans contre 42 ans, $p=0,013$). Il n'y a pas eu de différence significative entre les groupes en termes d'apparence de genre ($p>0,05$), d'intoxication au tabac ($p>0,05$), de toxicomanie ($p>0,05$) ni de comorbidités ($p>0,05$). Cependant, les patients G1 avaient un historique d'emprisonnement plus élevé ($p<0,001$). Le temps pour consulter et le temps pour la confirmation bactériologique de la tuberculose n'ont pas varié selon les groupes. L'évolution s'est caractérisée par une amélioration clinique plus lente ($p=0,006$) et une durée plus longue de négativité bacilloscopique en G1 ($p=0,048$). L'analyse multivariée a montré que le retard d'amélioration clinique dépasse 30 jours ($OR = 9,79$; $IC \text{ à } 95 \% = 1,77 \text{ à } 54,05$; $p = 0,009$) et le retard de négativité bacilloscopique ($OR = 4,93$; $IC \text{ à } 95 \% = 1,06 \text{ à } 22,92$; $p = 0,042$), étaient des facteurs de risque indépendants associés à la récurrence de la tuberculose.

Conclusions: La récurrence de la tuberculose pulmonaire concerne principalement les patients présentant un délai retardé jusqu'à la négativité bacilloscopique et une amélioration clinique plus lente, en particulier au-delà de 30 jours. Ces patients à risque nécessitent un suivi spécifique pour prévenir cette complication.

Mots clés: Tuberculose Récurrence, Rechute, Facteurs de risque

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INTRODUCTION

Tuberculosis, a well-known contagious infectious disease caused mainly by *Mycobacterium tuberculosis* (1), remains today a major public health challenge affecting all countries and all age groups. Despite being both treatable and preventable, it continues to cause significant morbidity. According to the WHO organization, 10.8 million people fell ill with TB worldwide, including 6.0 million men, 3.6 million women, and 1.3 million children, with a total of 1.25 million deaths from TB in 2023 (2). The African region is the highest tuberculosis burden globally and accounts for around a third of tuberculosis cases among those under 15 years of age worldwide. Two-thirds of these children are undiagnosed due to the lack of resources (3), meaning that despite the international progress to reduce its incidence rates, the disease is still concentrated among populations with low socioeconomic status (4).

In Tunisia, despite stable and relatively high tuberculosis treatment success rates, with an incidence rate that decreased from 28/100,000 inhabitants in 2018 to 22.46/100,000 inhabitants in 2021 (5), TB recurrence remains a common complication. To date, there has been no analysis of country-wide data in Tunisia to describe the number and proportion of TB patients with recurrent disease. Recurrent TB is when a patient has been treated for pulmonary TB and healed but later develops the disease again. Recurrence of tuberculosis (RT) can be associated with the risk of resistance. For this purpose, we looked for possible predictive factors of TB recurrence to prevent this complication and to take early care of these patients.

METHODS

We conducted a descriptive study with retrospective data collection of patients treated for a first episode of pulmonary TB in the pneumonology department of Charles Nicolle Hospital of Tunisia between January 2013 and July 2021. Diagnosis of Pulmonary TB was suspected by the presence of clinical and radiological signs and confirmed by detecting acid-alcohol resistant bacille in Sputum smear microscopy, or by identifying *Mycobacterium tuberculosis* in Culture of sputum on solid or liquid media, or by Nucleic acid amplification tests (NAAT), including Xpert MTB/RIF assay, for rapid and specific identification (2).

All patients were followed up for at least one year after the end of treatment. Patients were divided into two groups:

- G1: patients with RT during the setback period.
- G0: patients without RT during the setback period.

We analyzed the data of the first episode of TB.

Clinical improvement was defined by improvement of initial symptoms and weight gain. Performance status was used to evaluate patient's well-being and ability to perform daily activities. This scale ranges from 0 to 5, with lower scores indicating better function.

- 0: Fully active, able to carry on all pre-disease activities without restriction
- 1: Restricted in physically strenuous activity but ambulatory and able to do light work
- 2: Ambulatory, capable of self-care but unable to work; up and about >50% of waking hours
- 3: Limited self-care; confined to bed or chair >50% of waking hours
- 4: Completely disabled; confined to bed or chair, no self-care possible

Criteria for declaring TB "cured" were adherence to full and standard regimen of treatment, negative sputum microscopy/culture at the end (5th months) for patients with initial positive bacilloscopy, no persistence or reversion to positivity during the last months of treatment, resolution of symptoms and radiological improvement or stability (1).

Delayed bacilloscopic negativity was defined as the persistence of alcohol-acid-resistant bacilli in sputum two months after starting anti-tuberculosis treatment.

TB recurrence refers to the situation where a patient who was previously declared cured or who completed TB treatment subsequently develops a new episode of TB.

A comparative analysis was conducted by using SPSS software. Percentages were compared using Pearson's chi-square test, and in case of invalidity, Fisher's test. Means were compared using Student's t-test, and in case of invalidity, non-parametric tests were used. In all statistical tests, the significance level was set at 0.05. We compare socio-demographic features, clinical presentation, and evolution characteristics of both groups.

The risk factors for RT were determined after multivariate analysis or logistic regression. Patients' identification was not revealed, and as it was a retrospective study, patient consent was not required.

RESULTS

We included 140 patients treated for a first episode of pulmonary TB with a gender ratio of 4.8 (men=113; 80.7 %). The mean age was 44.3 years $\pm$ 17.5 [17- 87 years]. More than two-thirds of patients were smokers (72.1%) with a mean tobacco consumption of 35.4 pack-years. Patients' characteristics are detailed in Table I.

All patients received a well-conducted anti-tuberculosis treatment. Co-infection tuberculosis and Human immunodeficiency virus (HIV) was systematically investigated, and no cases were found. No drug-resistant TB was found among patients. Mean follow-up time was 4.88 years $\pm$ 2.54 years.

The first group (G1) included 12 patients (8.6%). Relapses were clinically suspected and had been confirmed bacteriologically.

Table 1. Clinical Feature of patients with pulmonary tuberculosis

Parameters	
Age (years)	44 ± 17.4
Gender	113 males vs 27 females
Tobacco smokers (patients)	101 (72%)
Average tobacco consumption (Pack-years)	35 ± 24
Drug addiction (patients)	15 (10.7%)
Chronic alcoholism (patients)	47 (33%)
Incarceration stay (patients)	Current stay: 22 Past stay: 4
Socio-economic condition (patients)	Poor: 77 (55%) Moderate: 52 (37%) Good: 11 (8%)
Diabetes (patients)	21 (15%)
Hepatitis (patients)	1 (0.7%)
Renal chronic failure (patients)	2 (1.4%)
High blood pressure (patients)	16 (11.4%)
Cardiopathy (patients)	2 (1.4%)
Chronic obstructive pulmonary disease (patients)	2 (1.4%)
Asthma (patients)	1 (0.7%)
Pulmonary cancer	2 (1.4%)
Bronchiectasis	
Average body mass index (Kg/m ²)	19 ± 3.9
PS≥2 (patients)	24(17.1%)

Socio-demographic factors

G1 patients were significantly older than G0 patients (44 years vs 42 years, $p=0.01$) with no difference in gender ratio ($p=0.6$).

Patients with RT had a significantly lower socio-economic level ($p=0.02$) as well as more frequent past or current incarceration ($p=0.001$).

Tobacco smoking, alcohol consumption, and drug addiction did not differ between groups (respectively: $p=0.2$, $p=0.1$, and $p=0.1$).

Clinical features

There was no significant difference in the prevalence of comorbidities between G1 and G0 ($p>0.05$), particularly diabetes, hypertension, and kidney failure. Time between onset of symptoms and first medical consultation did not differ between the 2 groups (G1: 48 days vs G0: 67 days; $p=0.3$). Body mass index (BMI) was similar in both groups ($p>0.05$), as well as the assessment of general condition using the Performance Status scale (G1 with PS≥2: 4patients vs G0 with PS≥2: 20 patients; $p=0.5$). Bacteriological confirmation time didn't differ (G1: 11.5±11days vs G0: 7.9±7.6 days; $p=0.1$).

Table 2 shows demographic and clinical features of G1' patients.

Table 2. Demographic and clinical features of patients with TB recurrence (G1)

Parameters	G1 (n=12)	G0 (n=128)	p
Age (years)	44 ± 11	44±18	0.01
Gender	11 males 1 female	102 males 26 females	0.6
Tobacco smokers (patients)	11	90	0.2
Average tobacco consumption (Pack-year)	22 ± 6	34±24	0.3
Drug addiction (patients)	2	13	0.1
Chronic alcoholism (patients)	2	45	0.1
Incarceration stay (patients)	Current stay: 1 Past stay: 3	21 1	0.001
Socio-economic condition (patients)	Poor: 3 Moderate: 6 Good: 3	74 46 8	0.02
Diabetes (patients)	2	19	0.8
Hepatitis (patients)	0	1	
Renal chronic failure (patients)	0	2	
High blood pressure (patients)	2	14	0.1
Cardiopathy (patients)	2	0	0.06
Chronic respiratory disease (patients)	0	2	
Average body mass index (Kg/m ²)	18.6 ± 2.1	19±4	0.8
PS≥2 (patients)	4	20	0.5
Average time to consultation (days)	48 ± 25	63±55	0.3
Average time to confirm TB (days)	11.5 ± 11	8±8	0.1

Evolution under treatment

All patients received anti-tuberculosis drugs, and treatment's adverse effects did not differ between the 2 groups ($p>0.05$).

During treatment follow-up, we noticed a slower clinical improvement in G1 patients (G1=35 ± 35 days vs G0=22 ± 20 days; $p=0.006$). Indeed, 83% of G1 patients didn't describe an improvement of their initial symptoms and weight after 30 days of treatment beginning vs 16% of G0 patients ($p<0.001$). Bacilloscopy negativity was delayed in G1 (4.2 ± 3.9 months vs 2.14 ± 1.58 months in G0, $p=0.01$). Table 3 summarizes the evolution of TB in both groups.

Table 3. TB treatment and evolution in both groups

	G1 (n=12)	G0 (n=128)	p-value
Combined TB treatment (patients)	11	125	0.2
Cutaneous side effects (patients)	2	5	0.6
Hepatic side effects (patients)	2	4	0.4
Average clinical improvement time (days)	35	22	0.006
Average time to negativity of bacilloscopy (months)	4.2	3.9	0.01
Average radiological improvement time (months)	2.2	2.8	0.1
Radiological sequelae (patients)	6	8	0.02

Multivariate analysis

Multivariate analysis showed that two significant independent risk factors for TB recurrence were identified.

- Delay to clinical improvement beyond 30 days: The odds ratio (OR) for this factor was 9.79 with 95% confidence interval (CI) of 1.77-54.05 and a p-value of 0.009. This suggests that patients who do not show clinical improvement within 30 days of treatment may be at higher risk of experiencing TB recurrence.

- Delayed bacilloscopy negativity: This factor had an odds ratio of 4.93, with a 95% CI of 1.06–22.92 and a p-value of 0.042. This indicates that patients who take longer time to achieve negative bacilloscopy results were also at a higher risk for recurrence.

DISCUSSION

Since the establishment of the Tunisian National Tuberculosis Control Program in 1959, Tunisia has made significant strides in the prevalence, management, and prognosis of TB. Despite these advancements, TB recurrence remains a notable complication. In our monocentric study, we observed a recurrence rate of 8.6% among patients who were correctly treated for pulmonary tuberculosis.

Recurrence of TB refers to the re-emergence of the disease in patients who have been previously treated and declared healed. This condition can be alarming as it not only indicates potential treatment failures but also raises concerns about the risk of drug resistance.

In the literature review, several studies sought to identify the risk factors for the recurrence of TB, and their results have varied significantly. A meta-analysis has indicated that low adherence to TB treatment increased the risk of recurrence of TB (6). However, in our study, all patients demonstrated acceptable adherence to their treatment regimens, suggesting that this particular risk factor did not contribute to the recurrence observed in our cohort. Many studies found that patients' age was not associated with TB recurrence (7–11), while other authors found that an advanced age was a risk factor for TB recurrence (12). In this study, patients with recurrent TB were significantly older [$p=0.013$], yet multivariate analysis revealed that age was not an independent risk factor for recurrence. Tobacco smoking and alcohol consumption were also considered as independent factors in the recurrence of pulmonary TB according to some authors (13,14), contrary to our study.

Additionally, it had been reported that HIV infection was a risk factor for the recurrence of TB (12,15). However, no patient was diagnosed with HIV infection among our population given that Tunisia is a low HIV-burden country. Furthermore, an initial drug resistance was described as a risk factor for the recurrence of TB (13). In practice, the anti-tuberculosis drug resistance test was carried out in patients with recurrence of TB or patients with delayed bacilloscopy negativity. No cases of anti-tuberculosis drug resistance were identified in our population.

Several studies have consistently identified poor treatment compliance as a predictor of TB recurrence (7,16). Additionally, BMI has been associated with increased risk of recurrence (15,17). These factors warrant further investigation in future research to better understand their role in TB management and patient outcomes.

In this study, a delay in bacilloscopy negativity was identified as a significant factor that can alter the course of TB. This finding aligns with previous research indicating that delayed negativity may suggest slower treatment response, persistent bacterial activity, or potential treatment challenges (18). Despite the implications of this factor, there is currently a lack of studies specifically investigating the relationship between delayed bacilloscopy negativity and TB recurrence.

In addition, delayed clinical improvement, particularly beyond 30 days after the start of treatment, was of concern, but the association between this event and tuberculosis relapse was not very robust given the wide confidence interval in the statistical study. Despite these observations, there appears to be a lack of research specifically examining the direct correlation between clinical improvement and tuberculosis recurrence. Although studies have explored various factors contributing to recurrence, none has focused solely on this aspect of delayed clinical improvement as a stand-alone risk factor [1,14].

CONCLUSION

This study underscores the critical importance of timely clinical improvement in TB treatment and bacilloscopy negativity as predictor factors for TB recurrence. Delays beyond 30 days of clinical evolution and two months for bacilloscopy negativity significantly elevate the risk of relapse, highlighting the need for close monitoring and potentially more aggressive interventions in patients who do not show expected improvements early in their treatment regimen.

Addressing the identified risk factors can lead to improved patient outcomes and more effective strategies for managing TB in the population. Future studies should aim to explore these factors in larger, more diverse cohorts to enhance our understanding and inform public health interventions effectively.

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