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# Influence of antimicrobial chemotherapy on spirometric parameters and pro-inflammatory indices in severe pulmonary tuberculosis

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**ABSTRACT: Patients who have completed a treatment for severe pulmonary tuberculosis (TB) are often left with severe respiratory disability. There have been few prospective studies assessing the effect of treatment on lung function in such patients.**

**The influence of antimicrobial chemotherapy on lung function was investigated over a six month period in patients with newly diagnosed pulmonary TB to test the hypothesis that treatment improves lung function, as well as to identify factors that may influence lung function outcome. Seventy-six patients were recruited into the study, of whom 74 completed the treatment programme. Forty-two were current smokers and 13 seropositive for the human immunodeficiency virus.**

**Improvement in lung function occurred in 54% of patients, but residual airflow limitation or a restrictive pattern was evident in 28% and 24% of patients, respectively. The extent of lung infiltration (radiographic score) both at the outset and after chemotherapy was significantly and negatively related to forced expiratory volume in one second ($FEV_1$) (% pred) (r=-0.41, and r=-0.46, respectively). The post-treatment serum C-reactive protein and $\alpha_1$-protease inhibitor levels were negatively associated with $FEV_1$ (% pred) (r=-0.30 and r=-0.35, respectively).**

**These findings demonstrate that, while antimicrobial chemotherapy may lead to improved lung function in patients with pulmonary tuberculosis, a large proportion of patients has residual impairment. The most significant factor influencing post-treatment lung function status, as measured by forced expiratory volume in one second (% predicted), is the pretreatment and post-treatment radiographic score, which acts as a marker of the extent of pulmonary parenchymal involvement in tuberculosis.**
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Patients who have completed a course of treatment for pulmonary tuberculosis (TB) are often left with severe respiratory disability due primarily to fibrocavitary lung disease [1–13]. Some patients have significant hypoxaemia with pulmonary hypertension and considerable ventilatory defects [7]. The diffusing capacity has also been shown to be decreased, which appears to be associated mainly with restrictive disease [11].

Only one previously published prospective study reported that treatment of pulmonary TB improves lung function. However, this conclusion was reached with a small number of patients and the extent of the improvement was based on a two-drug regimen before anti-tuberculous agents such as rifampicin and pyrazinamide [6] were available. Other studies have been cross-sectional and have studied either patients on discharge [9] or recalled patients, who had been treated up to 2 yrs previously [12, 13]. The obvious bias in recall studies is the possibility that patients with persistent respiratory symptoms may be more likely to respond to a request for follow-up evaluation. This may have been the case in one of these studies, in which only 40% of patients could be traced [13].

New cases of pulmonary TB were studied prospectively over a six month period to confirm the hypothesis that treatment improves lung function despite the development of residual fibrosis. The study also attempted to identify factors that may influence lung function outcome, such as smoking habit, extent of lung infiltration on chest radiograph and degree of inflammatory activity, as measured by the erythrocyte sedimentation rate (ESR) and concentrations of C-reactive protein (CRP) and $\alpha_1$-protease inhibitor ($\alpha_1$-PI).

## Materials and methods

This study was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand, Johannesburg, South Africa.

### *Study subjects*

The study assessed patients admitted into the Rietfontein and Charles Hurwitz (South African National Tuberculosis Association) hospitals in the Johannesburg area of

Gauteng, South Africa, between July 1994 and September 1995. Patients were referred for hospital-supervised treatment rather than outpatient therapy by their respective physicians, and this decision was based primarily on the assessment of the patient's personal and socioeconomic circumstances, as well as on the clinical and radiological severity of the infection. In contrast to this population of patients with severe TB, patients who are usually referred for outpatient therapy in Gauteng are considered to be well enough to continue with their usual employment during the treatment period. Seventy six consecutive patients with active pulmonary TB consented to participate in the study and were recruited over an 18 month period. Two of the 76 patients defaulted from treatment. The patients from both hospitals were Black Africans drawn from the same urban population.

Eligibility for entry into the study included typical symptoms of pulmonary TB such as cough, fever, weight loss and night sweats, fibrocavitary lung infiltrate on chest radiography and at least one sputum specimen staining positively with Ziehl-Neelsen for acid-fast bacilli and from which *Mycobacterium tuberculosis* was cultured. Patients with a history of previous treatment for TB were not studied in order to exclude patients with previous lung fibrosis or infection with multi drug-resistant TB.

All patients included in the study were receiving anti-TB treatment at the time of initial assessment but no patient had been on treatment for longer than 2 weeks. Patients with evidence of multi drug-resistant strains of *M. tuberculosis*, by sputum culture, were excluded from the study, as were patients with coexisting lung pathology, defined as any patient with a history of previous respiratory disease or clinical or radiological evidence of lung pathology other than TB, cardiac disease or metabolic problems, including chronic liver disease, renal failure or diabetes mellitus. Patients who tested positive for human immunodeficiency virus (HIV) infection were not excluded from the study unless there was clinical and immunological evidence of advanced immunosuppresion.

The study investigators did not influence patient management in any way and the patients were treated by their respective physicians with four standard anti-tuberculous drugs during the first 2 months, including isoniazid, rifam-picin, pyrazinamide and ethambutol, and at least isoniazid and rifampicin during the subsequent 4 months of treatment. Streptomycin was added initially in some cases where the physician was concerned about the possibility of drug resistance pending the culture result. All patients in this study were treated in hospital for the full six month per-iod, during which time the medication to be swallowed was administered and directly observed by trained nursing staff.

### *Lung function*

A portable Jaeger Flowscreen (version 2.10gb, Wuerzburg, Germany) was used for measurements of flow volume loop, from which the forced expiratory volume in one second ($FEV_1$), forced vital capacity (FVC), $FEV_1$:FVC ratio and $FEV_1$ (% pred) were noted. The lung function was measured by a qualified lung function technologist (L. Page-Shipp). The best of at least three measurements of each parameter was accepted. The pneumotachograph was sterilized in Cidex® (activated glutaraldehyde; Johnson & Johnson, Johannesburg, Sth Africa) for 10 min between patients and disposable mouthpieces were used to prevent cross-infection between patients. The criterion for airway obstruction was an $FEV_1$:FVC ratio of <70%, while restrictive defects were defined as an $FEV_1$:FVC ratio of Š70% with an FVC <80% [9], as has been employed in two previous studies of TB [9, 13]. Normal predicted spirometric values were obtained from regression coefficients using data from COOKSON *et al.* [14].

### *Follow-up*

Each patient underwent clinical assessment on a regular basis to confirm the response to treatment and identify possible complications. Repeat measurements of lung function were undertaken again after 12 weeks in a subgroup of patients selected on a random basis and finally after 6 months of treatment in all of the patients. Sputum examination was repeated until three specimens were negative on Ziehl-Neelsen staining. A chest radiograph was repeated after 6 months. The chest radiographs were reviewed without sight of the lung function data. A scoring system for the radiographs, previously reported by SNIDER *et al.* [9] and summarized in table 1, was used for the initial and final assessment, whereby each lung was divided into thirds and each third was rated on a four-point scale of 0 to 3 for the extent of infiltration, giving a maximum radiographic score of 18.

### *Laboratory investigations*

The ESR and circulating leukocyte counts were measured by standard haematological procedures. Numbers of circulating $CD4^+$ T-lymphocytes were measured in whole blood using an Epics II Profile flow cytometer (Coulter Electronics Corp., Hialeah, FL, USA). Serum levels of the acute phase reactants, CRP and $\alpha_1$-PI, were quantitated by laser nephelometry, while urinary cotinine levels, a measure of smoking status, were measured using a double antibody competitive binding radioimmunoassay procedure, with values of >500 $ng \cdot mL^{-1}$ urine considered as positive (Diagnostic Products Corp., Los Angeles, CA, USA). All of these tests were performed at the outset and after 6 months of antimicrobial chemotherapy. HIV screening was performed by means of enzyme-linked immunosorbent assay (ELISA) procedures and, where necessary, confirmed by Western blot testing, only after pretest counselling and the acquisition of informed consent.

Table 1. – Radiographic scoring system of lung infiltration for pulmonary tuberculosis

| Score | Features |
|---|---|
| 0 | No infiltrate |
| 1 | One third or less of the zone |
| 2 | Infiltrate involving more than one third, but less than two thirds of the zone |
| 3 | Infiltrate involving more than two thirds of the zone |

Each lung was divided into thirds and each third was scored according to the degree of infiltration using the index above. The maximum score was 18.

*Statistical analysis*

The statistical analysis proceeded in three steps. First, the efficacy of treatment was established by comparing initial and post-treatment values using the Student's (two-tailed) paired t-test. Secondly, bivariate correlations between $FEV_1$ (% pred) values and radiographic score coefficients were computed, and thirdly, multivariate regression analysis was used to relate the post-treatment results of the lung function investigations ($FEV_1$ (% pred)) and the radiographic scores, serum levels of CRP and $\alpha_1$-PI and urinary cotinine concentrations.

## Results

The patients were characterized as having severe TB if they were referred for hospital-based rather than outpatient treatment. The characteristics of the patients are summarized in table 2.

All patients, 13 of whom tested seropositive for HIV, showed improvement of symptoms, resolution of fever and weight gain ($p<0.0001$) following 6 months of antimicrobial chemotherapy. Bacteriological eradication of TB was confirmed by demonstrating the clearance of acid-fast bacilli on Ziehl-Neelsen staining on at least three consecutive sputum samples and a negative sputum culture undertaken towards the end of the treatment period. The mean $CD4^+$ cell count at the start of treatment in the HIV-seropositive subgroup of patients was 284 cells·mL$^{-1}$.

*Lung function and radiographic scores*

The results of investigations performed at the outset and after 6 months of chemotherapy are shown in table 3. Lung function improved in 54% of the patients but, despite radiological improvement, it deteriorated or was unchanged in the remaining 46% during the course of treatment. Improvement in lung function did not appear to be affected by smoking habit (table 3). Nineteen patients had lung function measured at 12 weeks, as well as 24 weeks after treatment, to assess early changes in lung function. All showed improvement by 12 weeks ($p<0.01$). The HIV-seropositive group failed to demonstrate any improvement in lung function after treatment. The types of residual lung function abnormality observed after the six month period of antimicrobial chemotherapy are summarized in table 4. Twenty-four per cent of patients showed a restrictive lung pattern, while 28% had airflow limitation. Forty-seven per cent of patients were assessed as having normal lung function at the end of treatment. When the patients were divided into two groups, on the basis of post-treatment lung function data, into obstructive or nonobstructive patterns ($FEV_1$:FVC values of <70% and Š70%, respectively) and their pretreatment radiographic scores were compared, no significant difference was detectable.

The mean radiological score for the entire group was 9.1 before treatment and 4.8 after treatment (table 3), which constituted a highly significant improvement ($p<0.0001$). The HIV-seropositive group showed a pre-treatment radiological score of 10.7 and post-treatment score of 5.1 ($p<0.0001$).

*Laboratory investigations*

Serum levels of CRP and $\alpha_1$-PI, as well as urinary cotinine concentrations, before and after 6 months of antimicrobial chemotherapy, are shown in table 5. Serum levels of both acute phase reactants, especially those of CRP ($p<0.0001$), declined after treatment, with no significant differences observed between the groups of smokers and nonsmokers, either before or after treatment. Urinary cotinine levels increased significantly ($p<0.0001$) after chemotherapy in the group of smokers. The ESR decreased

Table 2. – Characteristics of patients with active pulmonary tuberculosis

| | Total group | HIV-negative | HIV-positive |
|---|---|---|---|
| Number | 74 | 61 | 13 |
| Age yrs* | 35±10 (18–65) | 35±11 (18–65) | 32±7 (23–44) |
| Male:female ratio | 2.3:1 | 2.2:1 | 3.3:1 |
| Smoker:nonsmoker ratio | 1.4:1 | 1.5:1 | 3.3:1 |
| Alcohol:nonalcohol user ratio | 0.76:1 | 0.65:1 | 1.6:1 |

*: mean±SEM (range). HIV: human immunodeficiency virus.

Table 4. – Lung function patterns and change before and after 6 months of treatment in 74 patients with pulmonary tuberculosis

| | Before | After |
|---|---|---|
| Normal | 24 (32) | 35 (47) |
| Obstructive | 8 (11) | 21 (28) |
| Restrictive | 42 (57) | 18 (24) |
| Improved | - | 40 (54) |
| Worse | - | 15 (20) |
| Unchanged | - | 19 (26) |

Values are presented as numbers and percentages in parentheses.

Table 3. – Effects of antimicrobial chemotherapy on spirometric parameters in patients with pulmonary tuberculosis and in the subgroups of nonsmokers and smokers

| Lung function | Entire group (n=74) | | Nonsmokers (n=31) | | Smokers (n=43) | |
|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After |
| $FEV_1$ L | 2.10±0.07 | 2.31±0.07$^+$ | 2.06±0.12 | 2.23±0.11$^\#$ | 2.15±0.09 | 2.37±0.10$^+$ |
| % pred | 69.6±2.02 | 76.4±2.08 | 70.4±3.53 | 75.7±3.49 | 69.0±2.40 | 77.0±2.59 |
| FVC L | 2.52±0.09 | 3.02±0.09$^+$ | 2.40±0.15 | 2.85±0.15$^+$ | 2.61±0.11 | 3.15±0.11$^+$ |
| % pred | 73.7±2.14 | 87.9±2.13 | 72.5±3.55 | 85.5±3.55 | 74.7±2.66 | 89.6±2.60 |
| $FEV_1$/FVC % | 84.49±1.19 | 77.05±1.26 | 86.64±1.77 | 77.82±2.13 | 82.08±1.65 | 75.14±1.66 |
| Radiographic score | 9.11±0.59 | 4.64±9.41$^+$ | 8.77±0.93 | 5.1±0.68$^+$ | 9.37±0.8 | 4.3±0.49$^+$ |

Results are expressed as mean±SEM. $FEV_1$: forced expiratory volume in one second; FVC: forced vital capacity. Significant difference between pretreatment and post-treatment values; $^+$: $p<0.0001$, $^\#$: $p<0.004$.

significantly (p<0.0001) from a mean value of 83 mm·h$^{-1}$ at the outset to 43 mm·h$^{-1}$ after chemotherapy, as did the mean circulating leukocyte count, which declined from an initial mean value of $9.7\times10^6$·mL$^{-1}$ to $5.9\times10^6$·mL$^{-1}$ after treatment (p< 0.0001).

*Correlations of FEV1 (% pred) with radiographic score, CRP and $\alpha_1$-PI*

Bivariate correlations between FEV1 (% pred) values and radiographic scores before and after completion of chemotherapy in the entire group of patients, as well as in the nonsmokers and smokers, are shown in table 6 and figure 1. Statistically significant negative correlations of similar magnitude between FEV1 (% pred) and radiographic score were observed at the outset in all three groups, while the post-treatment correlation was strongest in the group of nonsmokers (r=-0.65, p=0.0003). A statistically significant negative correlation (r=-0.32, p=0.008) was also observed between the initial, pretreatment radiographic score and the final FEV1 (% pred) values on completion of chemotherapy in the entire group, with the nonsmokers contributing more to this (r=-0.40, p=0.035) than the smokers (r=-0.26, p=0.10).

There were no significant correlations between ESR and radiographic score or lung function, nor were there any detectable correlations between initial FEV1 (% pred) values and serum CRP or $\alpha_1$-PI levels. However, on completion of treatment, the FEV1 (% pred) and CRP, and FEV1 (% pred) and $\alpha_1$-PI levels were negatively and significantly correlated (r=-0.30, p=0.014 and r=0.350, p= 0.0056, respectively) in the entire group of patients. This relationship was independent of smoking status for CRP, but was significantly related to smoking for $\alpha_1$-PI (r= -0.3583, p=0.0295).

A weak, statistically insignificant, inverse correlation between FEV1 (% pred) and urinary cotinine was evident, but no correlations between this spirometric parameter and alcohol consumption could be detected.

*Multiple regression analysis of FEV1 (% pred)*

Post-treatment multiple correlations between FEV1 (% pred) values and radiographic scores $\alpha_1$-PI, CRP and cotinine levels were obtained using multiple linear regression. The $F_{1,\ 50}$-value of 13.365 was significant (p=0.00062). The multiple correlation coefficient was 0.599. The coefficients of the radiographic score and $\alpha_1$-PI were negative, with p=0.0001 and p=0.0005, respectively. This corroborates the negative correlations found in the bivariate correlations.

Table 5. – Serum C-reactive protein (CRP), $\alpha_1$-protease inhibitor ($\alpha_1$-PI) and urine cotinine levels before and after chemotherapy in patients with tuberculosis and in the subgroups of nonsmoking and smoking patients with pulmonary tuberculosis

| | CRP µg·mL$^{-1}$ | | $\alpha_1$-PI mg·dL$^{-1}$ | | Cotinine ng·mL$^{-1}$ | |
|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After |
| Entire group (n=66) | 64±6 | 10±1+ | 363±15 | 300±14+ | 1258±238 | 2610±370+ |
| Nonsmokers (n=26) | 63±11 | 8±2+ | 359±25 | 292±20 | 288±61 | 262±23 |
| Smokers (n=40) | 65±7 | 11±2+ | 366±19 | 306±19 | 1920±365 | 4214±483+ |

Results are expressed as mean±SEM. Significant difference between pretreatment and post-treatment values: +: p<0.01–0.0001.

Table 6. – Correlations between forced expiratory volume in one second (% predicted) and radiographic score before and after chemotherapy in 74 patients with pulmonary tuberculosis and in the subgroups of smokers and nonsmokers

| | Before treatment | | | After treatment | | |
|---|---|---|---|---|---|---|
| | Entire group | Nonsmokers | Smokers | Entire group | Nonsmokers | Smokers |
| Correlation coefficient | -0.41 | -0.40 | -0.42 | -0.46 | -0.65 | -0.31 |
| p-values | 0.0005 | 0.04 | 0.007 | 0.0001 | 0.0003 | 0.056 |

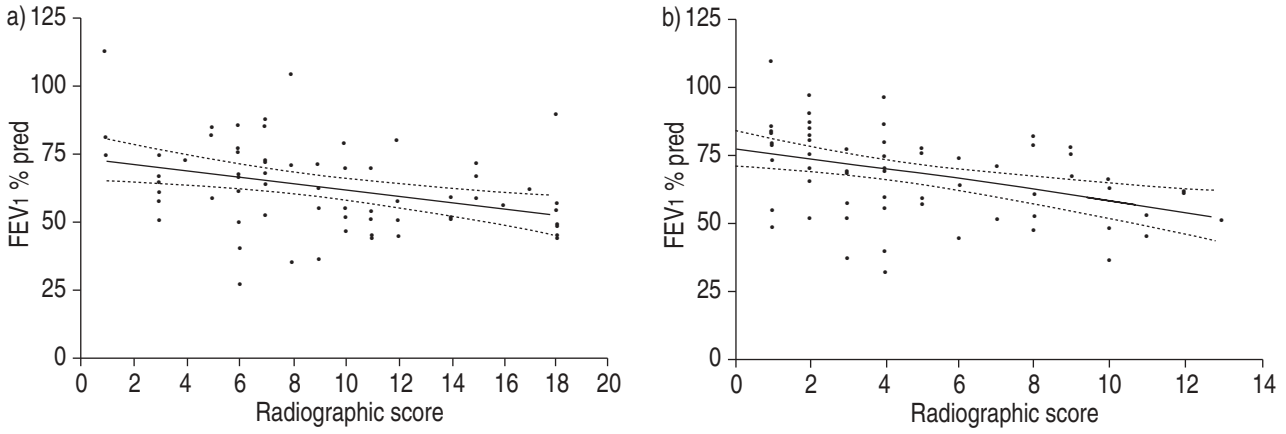


Fig. 1. – Scattergram of bivariate correlations (——: mean; ·····: 95% confidence limits) between the forced expiratory volume in one second (FEV1) (% predicted) values and radiographic scores: a) before and b) after 6 months of antimicrobial chemotherapy in patients with pulmonary tuberculosis.

## Discussion

In this study lung function in hospitalized patients with severe pulmonary TB was investigated, since it was assumed that this group of patients were more likely to have significant impairment of lung function. Various studies [2, 12, 13] have reported that patients with radiological evidence of more advanced disease at the time of initial diagnosis of TB appear to have the worst lung function after treatment. This has, however, not been a consistent finding, and SIMPSON *et al.* [6] found a negative correlation between chest radiographic changes and lung function only in untreated patients. The findings of the present study suggest that cigarette smoking, for which the study design strictly controlled, may account for these differences.

In nonsmokers, strong negative correlations exist not only between the radiographic score and FEV1 (% pred) at the beginning and end of treatment, but also between the initial radiographic score and final FEV1 (% pred). In smokers, however, only the correlation between radiographic score and the FEV1 (% pred) at the outset achieved statistical significance. This lack of correlation between the initial radiographic score and the post-treatment FEV1 (% pred) in cigarette smokers as opposed to nonsmokers suggests that smoking *per se* has an effect on this spirometric parameter. A possible additional complicating factor in smokers relates to the observation that clinical improvement was accompanied by alterations in their smoking habit, as demonstrated by the detection of significant increases in urine cotinine levels. The tendency for patients to have smoked more with clinical improvement is an interesting observation and implies that exposure to any possibly deleterious effects of smoking progressively increased during the course of treatment.

Although the HIV-seropositive group showed symptomatic improvement, weight gain, radiological and sputum clearing after 6 months of anti-TB treatment, the small numbers of patients in this group did not allow for meaningful correlation between radiological scores, lung function and inflammatory indices.

HALLET and MARTIN [3] suggested a relationship between obstructive disease and the extent of TB. However, no correlation was found between the extent of initial radiographic infiltration and the development of airflow limitation. The reported incidence of airway obstruction has varied from 27% in the study by BIRATH *et al.* [8] to 51% in LANCASTER and TOMASCHEFSKY [5]. In this study, multivariate analysis of data demonstrated that the radiographic score, a marker of the extent of parenchymal involvement in TB, is the most important determinant of impairment of lung function as measured by FEV1 (% pred), being superior to smoking status and circulating acute phase reactants. The observation that 27% of pa-tients showed an obstructive lung pattern at the end of treatment should be seen in the context of modern therapy with four or five drugs in a population of patients infected with drug-sensitive organisms. It is difficult to compare lung function outcome between groups of patients who have been given treatment regimens of greatly varying efficacy.

As in the present study, other authors [15, 16] failed to demonstrate an important association between smoking and airway obstruction in patients with TB, in contrast to general population surveys. Although the incidence of endobronchial TB in our patients is unknown, it seems probable that the development of airway disease due to tuberculous inflammation is likely to predominate over more slowly evolving smoking-related airway damage [17].

The patients showed a significant decrease in pro-inflammatory indices including total leukocyte count, ESR, $\alpha_1$-PI and CRP levels after 6 months of treatment, with no difference between smokers and nonsmokers. $\alpha_1$-PI concentrations have been reported to be significantly higher in patients with TB than in normal controls [18] and to decline in response to treatment [19]. No studies have reported a relationship between $\alpha_1$-PI levels and the extent of lung damage. It has, however, been postulated that measurement of serial $\alpha_1$-PI levels can be helpful in selected cases to differentiate between patients who are likely to clear acid-fast bacilli from their sputum and those who have persistently positive sputum after 1 month of chemotherapy [19]. No attempt was made to correlate $\alpha_1$-PI levels with the rapidity of sputum clearance of acid-fast bacilli. In this study, although $\alpha_1$-PI levels were negatively and significantly correlated with post-treatment FEV1 (% pred) in smokers, rather than nonsmokers, smoking is a confounding variable as it has been shown to elevate $\alpha_1$-PI levels in smokers without evidence of coexistent infection [20].

CRP has been reported to be significantly elevated in patients with active TB, normalizing over weeks on therapy, thereby correlating with clinical response [21, 22]. Higher CRP concentrations have also been associated with more severe TB and a poor prognosis [23]. This observation is supported by reports that patients with more severe lung destruction, as evidenced by lung cavitation, had significantly higher CRP levels than patients without cavitation [24]. Furthermore, the CRP levels decreased rapidly after initiation of treatment [24]. In the present study, CRP levels decreased significantly in concert with other acute phase parameters such as ESR and $\alpha_1$-PI levels during clinical recovery and after clearing of acid-fast bacilli from sputum.

In conclusion, the results of this study have demonstrated that although antimicrobial chemotherapy for pulmonary tuberculosis is associated with improved lung function, there is residual impairment in a large proportion of patients. The extent of initial radiographic infiltration predicts the degree of residual lung function impairment after treatment. The failure to correlate the initial extent of radiological infiltrate with the degree of impairment in lung function after treatment in smokers, as opposed to nonsmokers, suggests that smoking may contribute to lung damage in these patients.

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