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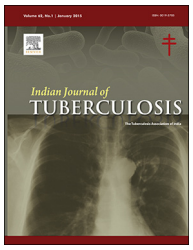

Original Article

Initial airflow obstruction in new cases of pulmonary tuberculosis: Complication, comorbidity or missed?

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ABSTRACT

Tuberculosis (TB) may have a similar spirometry findings as a chronic obstructive pulmonary disease but the prevalence of TB-induced airflow obstruction (AO) is still unknown.
Objectives: To measure frequency of AO in new TB cases at the beginning of treatment and to evaluate factors associated with obstructive abnormalities following TB diagnosis.
Materials and Methods: 317 patients that have no history of prior AO were recruited into the study with a median age of 39.0 years (IQR, 30.0–49.0). AO was defined using the $FEV_1/F(VC) <$ LLN.
Results: AO was detected in 29.97% (95/317) new TB cases. These patients had a more severe clinical manifestation of TB with a greater likelihood of cough, OR = 5.47 (95%CI 1.90–15.70) and wheezing, OR = 10.51 (95%CI 5.72–19.27), $p < 0.001$. The frequency of AO was positively associated with bronchoscopic evidence of narrowing of the main airways. Furthermore, from multiple logistic regression analysis we would assume that higher FEV_1 value in TB patients with AO was related to greater BMI and inversely associated with older age, female sex and radiographic extent ($p < 0.05$).
Conclusions: Obstructive pattern on spirometry frequently occurs in new TB cases without previously detected AO. This category of patients should be targeted for detailed follow-up, particularly, in high TB burden countries.

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1. Introduction

Tuberculosis (TB) is a growing problem in Ukraine because existing military conflict adds to the pre-existing challenges, such as a high rate of drug resistance and human immunodeficiency virus (HIV) co-infection.[1] However, TB case detection based on annual chest radiology rather than sputum smear microscopy (in 2015 there were only 2.6% TB cases identified by finding acid-fast bacilli (AFB) in primary health care)[27] leads to a delay in diagnosis with extensive lung lesions. Unfortunately, pulmonary dysfunction is a significant obstacle in achieving a desirable treatment outcome among TB patients.[12–14]

Airflow obstruction (AO) associated with active TB is often missed in routine practice.[3,7,33] AO may prolong sputum conversion time and delay healing of lung cavities,[9,14,35] despite effective TB treatment usually minimizes a restrictive ventilatory defect.[31] The prevalence of an obstructive abnormality (heterogeneous definitions) varies between 12.5 and 88.2% among different categories of TB patients.[2,35] Some authors considered airflow limitation as a "red flag" diagnostic tool for chronic obstructive pulmonary disease (COPD),[9,19] although others highlight active TB as an independent etiology of this phenomenon.[10,20,22,35] Nevertheless, discrepancies in study design and characteristics of selected participants, including sequelae of previous treatment[16] as well as coexistence of other diseases (HIV),[33] bronchial asthma (BA),[12] bronchiectasis[18] etc.), complicate estimates of the rate of AO among newly diagnosed TB patients.

Thus, the aim of the present study was to determine the frequency of initial AO among patients with new cases of pulmonary TB and to evaluate factors associated with obstructive abnormalities following TB diagnosis.

2. Study population and methods

2.1. Study design and participants

The present prospective cross-sectional study was carried out at the Regional Tuberculosis Dispensary in Vinnytsia from August 2007 to March 2012. Out of 2226 consecutively admitted patients aged 18 years or older with new cases of pulmonary tuberculosis, 352 (15.8%) were randomly selected and invited to participate in this study.

Inclusion criteria: 1) patients above 17 years of age with confirmed (culture positive) new case of pulmonary tuberculosis (a case never having previously received drug treatment for active TB or having received anti-TB drugs for less than one month); 2) at the time of spirometry test all participants could take anti-tuberculosis treatment, but not longer than one week.

Patients with any of the following conditions were *excluded*: 1) ever diagnosed with COPD, BA, bronchiectasis; 2) non-consenting patients; 3) ongoing treatment with β-blockers or corticosteroids; 4) pregnancy; 5) radiological evidence of lung pathology other than TB; 6) lack of cooperation; 7) technical difficulties; 8) mental or physical inability to perform the pulmonary function testing; 9) experience of smoking ≥10 pack/years; 10) intense/prolonged occupational exposure to noxious particles or gases; 11) exacerbation of allergic diseases; 12) HIV-positive patients.

Post-randomization exclusion of non-eligible patients ($n = 35$) was performed due to the following reasons: study personnel errors, $n = 4$; COPD, $n = 10$; bronchiectasis, $n = 1$; BA, $n = 3$; lung cancer/metastases, $n = 2$; ongoing treatment with corticosteroids, $n = 1$; allergy, $n = 2$; poor efforts during spirometry, $n = 4$; informed refusal patients, $n = 5$; HIV-positive individuals, $n = 3$.

The median age of the subjects ($n = 317$) was 39.0 years (IQR, 30.0–49.0). Comparative analysis of demographic characteristics between participants and adult population with new cases of pulmonary TB is shown in Table 1. Population data from 2010 was preferred for comparison as a midpoint of our study duration (2007–2013).

This study was approved by the Bioethics Committee at the National Pirogov Memorial Medical University of Vinnytsia and all participants gave written informed consent.

2.2. Methods

All patients underwent a standard evaluation that included complains, history, physical examination, chest radiography (CXR), laboratory investigations and lung function study.

2.3. Pulmonary function tests (PFTs)

Spirometry was performed and interpreted according to American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force on pulmonary function standards.[26,30] Measurements of forced expiratory volume in one second (FEV_1), vital capacity (VC), forced vital capacity (FVC) and forced expiratory flow between 25% and 75% of the FVC ($FEF_{25–75\%}$) were made using a portable Microlab Spiro (version 1.32, Rochester, UK) following the valid reference values of the European Community for Steel and Coal (ECCS). Pulmonary function tests (PFTs) were done in sitting position by qualified technologist under the direct supervision of the principal investigator.

Airflow obstruction was defined using the $FEV_1/F(VC)$ ratio of less than the lower limit of normal (LLN) for relevant healthy population. The baseline VC or FVC has been chosen as a preferred parameter for diagnostic ratio calculating whichever was larger.[23] We analyzed flow-volume loop configurations to suspect predominant occurrence of the airway obstruction. Post-bronchodilator testing was performed if baseline spirometry showed an obstructive pattern. Significant reversibility was determined if after inhalation of 400 mcg salbutamol (four separate doses with 30-s intervals) and 15 min re-measurement - per cent/absolute changes in FEV_1 and/or FVC ≥12% and 200 ml compared with baseline values.[26]

Mouthpiece and transducer were cleaned and disinfected between patients to prevent the transmission of infection via direct contact with biological fluids.

2.4. Flexible fiberoptic bronchoscopy

Flexible fiberoptic bronchoscopy (FB) was performed in the procedure room via the oral route (Olympus; BF-PE2 or BF-TE2; Japan). There were standard indications: cough or

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Table 1 – Characteristics of participants (n = 317) and adult population with new cases of pulmonary tuberculosis* (n = 30,314) in Ukraine.

Characteristics	Participants (n = 317)	Population (n = 30,314)	p-value
Male, n (%)	236 (74.4)	21,039 (69.4)	
Female, n (%)	81 (25.6)	9275 (30.6)	0.0545**
Rural residence, n (%)	123 (38.8)	10,358 (34.2)#	0.086**
Current smokers, n (%)	110 (34.7)	not available	
Ex-smokers, n (%)	19 (6.0)	not available	
Age distribution yrs., n (%)			
18–24	34 (10.7)	3290 (10.9)	
25–34	72 (22.7)	8161 (26.9)	
35–44	87 (27.4)	7402 (24.4)	
45–54	69 (21.8)	5868 (19.4)	
55–64	36 (11.4)	3181 (10.5)	
≥65	19 (6.0)	2412 (8.0)	0. 93,624##

* Ministry of Health report.[30]
\# Available data from mixed (adults + children) population with new TB cases.
** 2-sample z-test;
\## Mann–Whitney U test.

breathlessness unexplained due to the radiologic abnormalities (clinical suspicion of bronchial involvement), diffuse lung process on the CXR, recurrent hemoptysis, unexplained hoarseness, smear-negative cases (bacteriological confirmation of diagnosis), abrupt changes in the amount of sputum etc. More than half of the study participants have refused the FB through a fear of the discomfort during this procedure either they found the FB unnecessary or intolerable.

2.5. *Statistical analysis*

Data were analyzed with the use of statistical software SPSS V.20 and GraphPad Prism V.6 for Windows. We assessed the normality of the distribution by histogram and Shapiro-Wilks W test. Mean with 95% confidence interval (CI) and median with 25th–75th percentile (inter-quartile range (IQR)) presented normally and non-normally distributed variables, as appropriate. Multivariable logistic regression model was used to evaluate the independent predictors of airflow obstruction on spirometry. We rejected "the null hypothesis" if p-value was less than the threshold (0.05).

3. Results

Airflow obstruction has been detected in 29.97% (95/317) hospitalised patients with new pulmonary TB. The frequency of complaints and auscultatory findings accompanying with AO (FEV_1/F(VC) ratio below LLN) are given in Table 2. We also analyzed the differences between the probability of clinical sings happening among patients with AO and subjects without an obstructive pattern on spirometry (Fig. 1). Thus, odds ratio

Table 2 – Percentages of clinical signs and auscultatory findings combined with AO.

Findings	% of subjects, n = 95
Cough	95.8 (91)
Dyspnea	84.2 (80)
Wheezes	83.2 (79)
Fever	71.6 (68)
Loss of appetite	50.5 (48)
Weakness	46.3 (44)

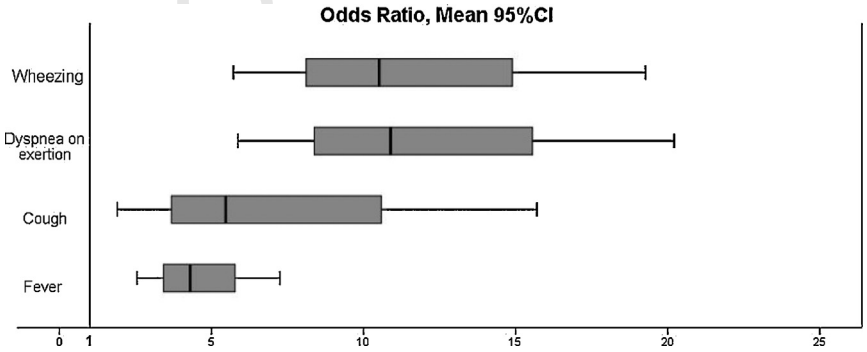

Fig. 1 – Association between airflow obstruction and probability of clinical signs in new TB cases. Legend: Pearson Chi-Square test, $p < 0.001$ for all cases

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(OR) was calculated for cough OR = 5.47 (95% CI 1.90–15.70); dyspnea on exertion OR = 10.89 (95%CI 5.87–20.21); wheezing 10.51 (95%CI 5.72–19.27) and fever OR = 4.30 (95%CI 2.55–7.25), $p < 0.001$ for all cases. Of note, among underweight (BMI < 18.5) TB patients with airflow limitation, BMI value did not significantly correlate with FEV_1 (L) ($r = 0.35$, $p = 0.24$).

Radiographic manifestation of pulmonary TB were directly proportional to the frequency of obstructive abnormality on spirometry in subjects ($r = 1$, $p = 0.01$) – Fig. 2. Nevertheless, there were weak correlations with FEV_1 (L) ($r = -0.24$, $p = 0.018$) and respiratory impairment severity ($r = 0.32$, $p = 0.002$), classified according to ERS/ATS Task Force [33].

Significant post-bronchodilator reversibility was obtained in 53.5% (51/95) TB patients with AO. Meanwhile, only 37.9% (36/95) new TB cases with AO had post-bronchodilator FEV_1/F (VC) ratio less than LLN. Overall, flow-volume loop configurations revealed that majority of TB patients with AO had lower airway obstruction 37.9% (36/95) and dynamic central or intrathoracic upper airway obstruction 30.5% (29/95) (Fig. 3). To evaluate differences in endoscopic tracheobronchial pathology between TB patients with AO and without obstructive pattern on PFTs, we prospectively investigated 104 patients by FB. Table 3 summarizes the distribution of endobronchial findings in the target groups. Thus, any endobronchial pathology in new cases of pulmonary TB increased chances of obstructive abnormality on spirometry OR = 4.90 (95%CI 2.37–10.13) of what it would have been a normal endoscopic picture.

A binomial logistic regression was performed to evaluate the effects of age, gender, CXR pattern, smear microscopy, lung destruction, smoking, BMI and biomass/coal exposure on the likelihood that subjects have airflow obstruction, $\chi^2(9) = 17.67$, $p = 0.039$. The model explained 7.7% (Nagelkerke R^2) of the variance in AO and correctly classified 69.7% of cases. Only increasing age was associated with slightly greater likelihood of presence obstructive abnormality on PFTs - adjusted OR 1.02 (95% CI 1.00–1.04), $p = 0.02$.

Table 4 summarizes the stepwise multiple regression analysis. Unsurprisingly, BMI demonstrated the greatest positive impact on FEV_1 value whilst age, gender, domestic fuel and radiographic extent were associated with the biggest negative linear relation to operating margin.

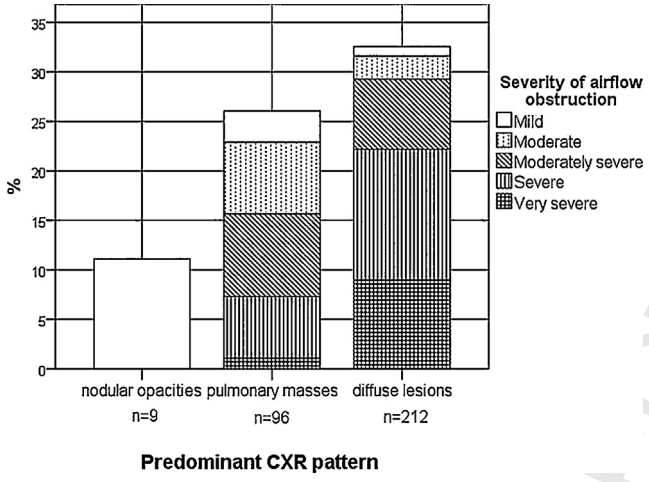

Fig. 2 – The relationship between pulmonary involvement due to TB and the frequency of airflow obstruction stratified by severity grading.

4. Discussion

The present study provides evidence that almost a third of hospitalised new cases with pulmonary TB (culture-confirmed) had AO (FEV_1/F(VC) < LLN) in Ukraine. We suggest AO might act as a surrogate marker of the severity of the clinical presentation and the extent of radiographic abnormality in newly diagnosed TB patients. However, the frequency of AO at first presentation with TB was greater than that noted by *Plit et al.* (11%), although his population was younger (median 35 versus 39 years in this study) and found by new inpatients rather than active annual CXR screening.[31]

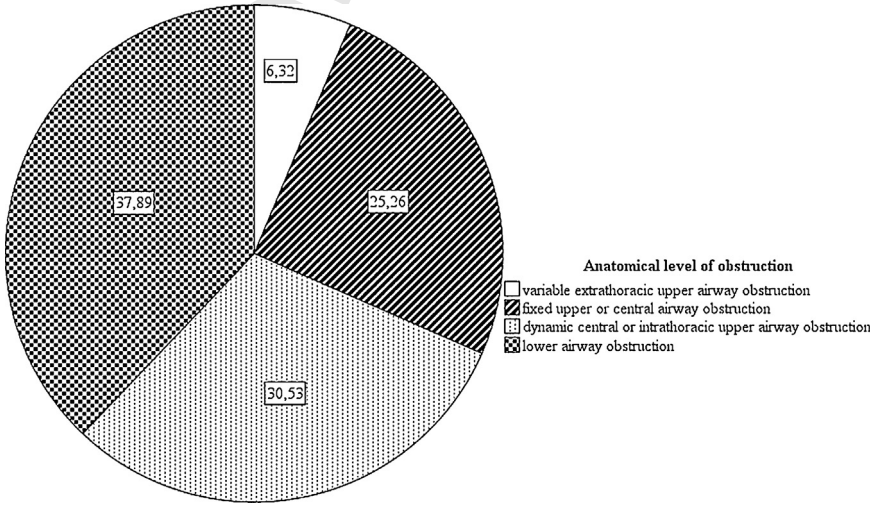

Fig. 3 – The frequency of airflow obstruction originating from different anatomical level.

Table 3 – Bronchoscopic findings and results of spirometry in new TB cases.

Endoscopic changes	FEV1/F(VC) < LLN (n = 58)	FEV1/F(VC)≥LLN (n = 46)
Normal endoscopic appearance, n (%)	3 (56.9)	36 (78.3)
Nonspecific inflammation, n (%)	19 (32.8)	7 (15.2)
Tuberculous endobronchitis, n (%)	6 (10.3)	None
Malignancy, n (%)	None	3 (6.5)*

TB, tuberculosis; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; LLN, less than the lower limit of normal for relevant healthy population.
* Mann–Whitney U test, $p = 0.4593$.

Table 4 – Results of multiple regression analysis with FEV_1(L) as dependent variable among TB patients with airflow obstruction.

Dependend variable	Predictors	Correlation coefficient	p-value	Standardized β coefficient	p-value
FEV_1, L	BMI	0.14*	0.173	0.22	0.013
	Domestic fuel	−0.20**	0.057	−0.20	0.024
	Sex	−0.32**	0.002	−0.34	<0.001
	Radiographic extent	−0.20#	0.058	−0.22	0.014
	Age	−0.40*	<0.001	−0.34	<0.001

Model summary: $F = 9.91$, $R^2 = 0.36$, $p < 0.001$. FEV_1, forced expiratory volume in one second; TB, tuberculosis.
* Pearson's Correlation Coefficient.
** Chi-squared test.
# Spearman's Coefficient of Rank Correlation.

Overdiagnosis of COPD or BA in patients with TB-induced airway narrowing can occur as a result of endobronchial lesions,[16] compression by enlarged mediastinal lymph nodes,[5,13] paravertebral[28] or retropharyngeal abscess[6] and even cellular bronchiolitis.[7]

Bronchospasm or bronchial hyperresponsiveness may play a key role in the development of AO in TB patients.[29,35] Proinflammatory cytokines by airway epithelial cells, contamination of cavities by *Aspergillus* and by nontuberculous mycobacteria may also contribute to hypersensitivity disorders (including AO).[8,11,24]

In accordance with previous findings,[2,9] the clinical significance of AO depends on its severity and cause. AO can be considered as a self-limiting disorder under standard chemotherapy either effectively cured by taking broncholitics/corticosteroids[31,35] or may remain as a progressive, irreversible abnormality (defined as COPD) in the post-treatment period.[2,25] Post-bronchodilator reversibility was detected in 15.0% of new TB cases with positive smear microscopy and fibrocavitary lesions[32] and 6.3% of patients with severe dyspnea and post-tuberculous lung destruction.[34] Unlike previous data, we found reversibility in half (52.82%) of new TB patients, but it does not rule out positive clinical response to bronchodilators in another half of the subjects.[30] Nevertheless, we determined that the post-bronchodilator ratio FEV_1/F(VC) was <LLN in 11.4% new active TB cases, while in population-based cross-sectional study carried out in Latin America[25] the prevalence of post-bronchodilator AO was 30.7% among individuals with a history of TB. Therefore, development of adjuvant interventions to prevent or to suspend further deterioration of lung function in individuals with TB could be useful tool for vast majority of patients.

Our results were consistent with several studies noting the important relationships between AO and chest radiographic pattern of TB patients.[3,15,17] Although we calculated no significant correlation between FEV_1(L) and CXR changes ($r = -0.20$, $p = 0.058$) in comparison to earlier published literature ($r = -0.41$, $p < 0.001$)[31] because only patients with airflow limitation were taken into account. The logistic regression has determined only increasing age as an important predictor of initial AO among new TB patients ($p = 0.02$), whereas *Radovic et al.* were focused on pulmonary TB cases with "extensive" lesions and normal PFTs at the beginning of treatment.[32] Therefore, this approach seems to need exclusion of the vast majority of such TB patients that might have restrictive, mixed or obstructive abnormalities.[3]

Multiple regression analysis in our study revealed strong evidence about negative associations between FEV_1 (L) and female sex. In Ukraine women traditionally are more exposed to fuel by heating with coal or wood. Positive impact of BMI on FEV_1 (L) among TB patients could be explained by less proportion of malnourished or cachectic patients with severe clinical presentation and skeletal muscle wasting. Interestingly, the frequency of AO in patients with prior TB was irrespective to more hard smoking history, as confirmed earlier.[19]

The main strengths of our study were prospective design, using strong criteria for participants selection (culture-confirmed TB cases, low limit of normal value on spirometry with post-bronchodilator testing), relatively large sample and avoidance of self-reported measurements.

We would like to note some limitations of this study. First, cross-sectional design cannot prove causality. Second, we did not estimate the effect of passive smoking in our sample. Nonetheless, Ukraine has one of the highest smoking rates in the world and AO might have an inverse relationship with second hand smoking. Third, we had no opportunity to perform methacholine challenge test and chest computed

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tomography in our clinic. Therefore, concomitant BA and bronchiectasis cannot be fully excluded even without typical clinical presentation and no prior history of allergy. The present analysis has not focused on family income, dietary intake and living in correctional settings, although these factors may increase risk of AO.[21]

The main difficulty was to distinguish restrictive defect from mixed dysfunction (restrictive and obstructive). However, alternative methods of lung volumes measurement, e.g. the body plethysmography and nitrogen washout have also limited application in active TB patients due to potential harm of contamination.[23,30] In this context non-contact lung function assessment is a perspective option.

5. Conclusions

We found that new cases of pulmonary TB were frequently accompanied by initial AO. This category of patients was older and had more severe clinical manifestation of TB, as well as more often endobronchial pathology. We encourage further investigations to establish the clinical significance of AO associated with TB and consensus in treatment strategy: who should be treated, how long and which drugs are preferred.

Conflicts of interest

The authors have none to declare.

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[4].

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