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Clinical significance of low forced expiratory flow between 25% and 75% of vital capacity following treated pulmonary tuberculosis

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References: 25

ABSTRACT

Objectives: The aim of this study was to assess the prevalence and determinants of post-tuberculosis chronic respiratory signs, and to assess the clinical impact of a low forced expiratory flow between 25% and 75% ($FEF_{25-75\%}$) in a group of individuals previously treated successfully for pulmonary tuberculosis.

Design: This was a cross-sectional study involving individuals in their post-tuberculosis treatment period. They all underwent a spirometry following the 2005 criteria of the American Thoracic Society /European Respiratory Society. Distal airflow obstruction (DAO) was defined by a $FEF_{25-75\%} < 65\%$ and a ratio forced expiratory volume during the first second (FEV_1)/forced vital capacity (FVC) ≥ 0.70. Logistic regression models were used to investigate the determinants of persisting respiratory symptoms following anti-tuberculous treatment.

Setting: This study was carried out in the tuberculosis diagnosis and treatment centre at Yaounde Jamot Hospital, which serves as a referral centre for tuberculosis and respiratory diseases for the capital city of Cameroon (Yaounde) and surrounding areas.
Participants: All consecutive patients in their post-tuberculosis treatment period were consecutively enrolled between November 2012 and April 2013.

Results: Of the 177 patients included, 101 (57.1%) were men and median age (25^{th}-75^{th} percentiles) was 32 (24-45.5) years. At least one chronic respiratory sign was present in 110 (62.1%) participants and DAO was found in 67 (62.9%). Independent determinants of persisting respiratory signs were the duration of symptoms prior to tuberculosis diagnosis higher than 12 weeks (adjusted odd ratio 2.91; 95% confidence interval: 1.12-7.60, p=0.029) and presence of DAO (2.22; 1.13-4.38, p=0.021).

Conclusions: $FEF_{25-75\%} < 65\%$ is useful for the assessment and diagnosis of post-tuberculous DAO. Mass education targeting early diagnosis of pulmonary tuberculosis can potentially reduce the prevalence of post-tuberculosis respiratory signs and distal airflow obstruction.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a cross-sectional study, precluding any inference about the direction of the relationships found in the study.
- It is likely that distal airflow obstruction in our study was the consequence of pulmonary tuberculosis, considering that all patients with known chronic bronchitis prior to tuberculosis occurrence were excluded.
- The relatively large number of patients included is a major strength.
- This study uses robust methods to assess the relation between post-tuberculosis chronic respiratory symptoms and distal airflow obstruction

INTRODUCTION

Pulmonary tuberculosis, the commonest form of tuberculosis, is an important public health challenge worldwide.[1] The clinical presentation of pulmonary tuberculosis usually combines general signs with chronic respiratory signs including cough and expectoration.[2] The presence of dyspnoea during pulmonary tuberculosis usually indicates the extensive nature of the pulmonary lesions.[2] Radiographic and functional sequels are very frequent following tuberculosis treatment, and ad-integrum restitution of the lungs is rather less frequent.[3-5] While functional sequels are mostly due to restrictive or mixed functional disorders,[6-8] post-tuberculosis airflow obstruction is also present in an important number of patients.[8-11] The prevalence of post-tuberculosis airflow obstruction ranges between 5% and 30% across published studies.[12-15] Furthermore, pathophysiological studies suggest that lesions affecting exclusively the distal respiratory pathways are possible during pulmonary tuberculosis.[10]

We are not aware of published studies on post-tuberculosis distal airflow obstruction (DAO) and the possible connection with persistence of respiratory signs following treatment for pulmonary tuberculosis. The assessment of DAO in routine practice is still a challenge with regard to the indices to be used; however, many have suggested mean median expiratory flow or forced expiratory flow between 25% and 75% ($FEF_{25-75\%}$) to be useful for this purpose. The wide variability of this index limits the possibility of defining a reliable optimal threshold for diagnosing DAO.[16] The thresholds of 65% or 60% have been applied in children to characterise distal airflow obstruction.[17, 18] The aim of this study was to determine the prevalence and factors associated with post-tuberculosis chronic respiratory signs, and to assess the clinical impact of a low $FEF_{25-75\%}$ in a group of patients successfully treated for pulmonary tuberculosis.

MATERIALS AND METHODS

Study setting and participants

This study was conducted in the Center for Diagnosis and Treatment of tuberculosis (CDT) of the Yaounde Jamot Hospital (YJH) between November 2012 and April 2013 (6 months duration). This centre has been described in details previously.[19, 20] In short, YJH is the reference centre for tuberculosis and chest diseases for the Capital city of Cameroon

(Yaounde) and surrounding areas. Over the last five years, the centre has diagnosed and treated an average of 1600 to 1800 patients with tuberculosis per year.

All patients age 18 years and above, successfully treated for bacteriologically proven pulmonary tuberculosis (new case or re-treatment) were invited to take part in the study. Bacteriological proofs of pulmonary tuberculosis was based on the presence of acid fast bacillary (AFB) on at least one direct sputum smear examination,[21] or a positive sputum culture for *Mycobacterium tuberculosis*. Patients with any of the following conditions were excluded: patients with treatment failure, on-going bacterial pneumonia or within the four weeks preceding inclusion, chronic respiratory condition before TB diagnosis, on-going treatment with beta blockers, physical or mental inability to perform spirometry test.

Pulmonary tuberculosis treatment

Tuberculosis treatment at the CDT follows to the guidelines of the Cameroon National Tuberculosis Control Program (NTCP) and the World Health Organization (WHO) recommendations.[22, 23] Antituberculosis drugs are dispensed free of charge, and treatment regimens used are standard regimens of category I for new patients and of category II for re-treatment cases. New cases are treated with a regimen that includes an intensive phase of two months duration with rifampicin (R), isoniazid (H), ethambutol (E) and pyrazinamide (Z), followed by a 4-month continuation phase with rifampicin and isoniazid (2RHEZ/4RH). During re-treatment, category I medications (R, H, E, Z) are completed with streptomycin (S). Therefore, re-treatment cases are treated with RHEZS for two months, followed by one month on RHEZ and five months on RHE (2RHEZS/1RHEZ/5RHE). During the intensive phase, adherence is directly monitored by the healthcare team for patients admitted, and during weekly drug collection in those treated as outpatients. The continuation phase is conducted on the outpatient basis and adherence assessed during monthly visits for scripts renewal and drugs collection.

Monitoring and outcomes of pulmonary tuberculosis treatment

During treatment, sputum smear positive patients are re-examined for AFB at the end of month 2, 5 and 6 for new cases, and at the end of month 3, 5 and 8 for re-treated patients. At the end of the treatment, patients are ranked into mutually exclusive categories[22, 23] as: 1) cured – patient with negative smear at the last month of treatment and at least one of the preceding; 2) treatment completed – patient who has completed the treatment and for whom the smear result at the end of the last month is not available; 3) failure – patient with positive

smear at the 5th month or later during treatment; 4) death – death from any cause during treatment; 5) defaulter – patient who's treatment has been interrupted for at least two consecutive months; 6) transfer – patient transferred to complete his treatment in another centre and who's treatment outcome is unknown.

Procedures

Baseline data collection

In this cross-sectional study, baseline data were collected on socio-demographic, clinical, radiological and biological characteristics of patients. Socio-demographic data collected included age, sex, residence (urban vs. rural) and formal level of education. Past medical history data included current or former smoking (yes vs. no), past history of tuberculosis and co-morbidities (diabetes mellitus). Clinical details included: duration of symptoms prior to tuberculosis diagnosis, persistent of respiratory symptoms (cough, expectoration, dyspnoea). Radiographic data were collected on the extension of lungs involvement (number of fields affected), the type of lung lesions (cavities, fibrotic lesions), the presence of pleural effusion and mediastinal or hilar lymph nodes. Biological data included the results of the HIV test result. The study was approved by the administrative authorities of the YJH and institutional review board of the Faculty of Medicine and Biomedical Sciences of University of Yaounde 1.

Ventilatory variables measurement

Spirometric measurements were acquired with a digital turbine pneumotachograph (Spiro USB, Care fusion, Yorba Linda-USA) following the 1994 American Thoracic Society (ATS) standards.[24] All the pulmonary volumes and flow rates were automatically corrected for body temperature and pressure saturation. Measurements were done under the direct supervision of an experienced pneumologist who is also certified in lung function testing (EWPY). The different respiratory indices were measured without bronchodilators and included: forced vital capacity (FVC), forced expiratory volume during the first second (FEV1), forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25-75\%}$) and the ratio FEV1/FVC. The acceptability and reproducibility criteria recommended by the ATS and European Respiratory Society (ERS) guidelines (ATS/ERS guidelines) were respected.[16] At least three manoeuvres up to a maximum of eight were performed as required to obtain the flow rate curve (FVC curve). A one minute resting period was observed between consecutive

manoeuvres. Satisfactory exhalation was considered in the presence of any of the following: 1) no change in exhaled volume (plateau on the volume-time curve) for 1 second after an exhalation time of at least 6 seconds; 2) the presence of a reasonable duration or plateau in the volume-time curve; 3) inability of the subject to continue to exhale.[16, 24] The largest values for FEV1 and FVC from three acceptable manoeuvres were retained. The authorized difference between the largest values of FVC or FEV1 of the three acceptable manoeuvres was inferior or equal to 0.150 L or 5%. The manoeuvre with the largest sum of FEV1 plus FVC was used to determine $FEF_{25-75\%}$. Predicted values were calculated using reference values based on the Global Lung Initiative (GLI) reference spirometric equations for black.[25] Included participants were categorised according to their $FEF_{25-75\%}$ into 3 mutually exclusive groups: normal ($FEF_{25-75\%} \geq 80\%$), intermediate ($65\% \leq FEF_{25-75\%} < 80\%$) and low ($FEF_{25-75\%} < 65\%$). DAO was based on $FEF_{25-75\%} < 65\%$.

Statistical analysis

Data were analysed with the use of SPSS v17 for Windows®. We have presented categorical variables as count (percentages) and quantitative variables as mean (standard deviation) or median (25^{th}-75^{th} percentiles. Group's comparison used chi square tests for categorical variables and Student's t-test for non-parametric equivalents for quantitative variables. Logistic regressions were then used to investigate the determinants of persisting chronic respiratory signs. Potential candidate determinants were first investigated in univariate analysis. Significant predictors (based on a threshold probability <0.1) were entered all together in the same multivariable model. A p-value<0.05 was used to characterise statistically significant results.

RESULTS

General characteristics of the study population and prevalence of chronic respiratory signs

A total of 189 patients were invited to take part in the study. One refused to consent, ten had incorrect spirometry records while one had a FEV1/FVC<0.70. Of the 177 participants included, 101 (57.1%) were men and median age (25^{th}-75^{th} percentile) was 32 (24-45.5) years. Thirty-five (19.8%) patients were current or ex-smokers, 23 (13%) had a prior history of pulmonary tuberculosis and 47 (26.6%) had co-incident HIV infection. At least one chronic respiratory sign (CRS) was found in 110 (62.1%) patients at the completion of the anti-

tuberculosis treatment. In details, 87 (49.2%), 62 (35%) and 99 (55.9%) patients had persisting cough, expectoration and dyspnoea respectively at treatment completion (Table 1).

Table 1: Characteristics of study population at the end of tuberculosis treatment

Characteristics	n=177 (%)
Baseline clinical characteristics	
Male sex	101 (57.1)
Age, years, median (25^{th}-75^{th})	32 (24-45.5)
Median duration of symptoms before diagnosis, weeks (25^{th}-75^{th})	8 (4-12)
Current of past smoking	35 (19.8)
Previous pulmonary tuberculosis	23 (13)
HIV infection	47 (26.6)
Diabetes mellitus	4 (2.3)
Radiological signs	
Extension of tuberculosis lesions > 4 zones	52/148 (35.1)
Cavitary disease	81/148 (45.8)
Persisting respiratory symptoms at the end of tuberculosis treatment	
Any respiratory symptoms	110 (62.1)
Cough	87 (49.2)
Expectoration	62 (35.0)
Dyspnoea	99 (55.9)
Spirometry values at the end of tuberculosis treatment	
FEV1, %, mean (SD)	76.3 (19.0)
FVC, %, mean (SD)	74.8 (18.2)
FEV1/FVC	0.86 (0.07)
$FEF_{25-75\%}$, %, median (25^{th}-75^{th})	74 (56-94.5)

FEV1, forced expiratory volume in 1^{st} second; FVC, forced vital capacity;
$FEF_{25-75\%}$, forced expiratory flow between 25 and 75% FVC;
SD, standard deviation

Relationship between $FEF_{25-75\%}$ and chronic respiratory signs

Table 2 shows the distribution of chronic respiratory signs at treatment completion, according to $FEF_{25-75\%}$ categories. Seventy-five patients (42.4%) had normal $FEF_{25-75\%}$, 35 (19.8%) had intermediate $FEF_{25-75\%}$, while 67 (37.9%) had low $FEF_{25-75\%}$. Persisting cough, expectoration and dyspnoea were significantly more frequent among patients with low $FEF_{25-75\%}$. The frequency of at least one persisting chronic respiratory sign was 52% in patients with normal $FEF_{25-75\%}$ and 74.6% among those with low $FEF_{25-75\%}$ (p=0.005). The related odd ratio was 2.72 (95% confidence interval: 1.33-5.57).

Table 2: Frequency of persistent respiratory symptoms and spirometry indices according to $FEF_{25-75\%}$

Symptoms	$FEF_{25-75\%} \geq 80\%$, n=75 (%)	$FEF_{25-75\%}$ between 65% and 80%, n=35(%)	p-value$^{\$}$	$FEF_{25-75\%} < 65\%$, n=67 (%)	p-value$^{\mu}$
chronic cough	28 (37.3)	17 (48.6)	0.264	42 (62.7)	0.003
Chronic expectoration	20 (26.7)	11 (31.4)	0.605	31 (46.3)	0.015
Chronic dyspnoea	38 (50.7)	16 (45.7)	0.628	45 (67.2)	0.046
Any chronic respiratory symptoms	39 (52.0)	21 (60.0)	0.433	50 (74.6)	0.005
FEV1, L, median (25^{th}-75^{th} percentiles)	89(82-100)	73(62-82)	<0.001	64(52-73)	<0.001
CVF, L, (25^{th}-75^{th} percentiles)	83(74-92)	72(61-83)	<0.001	64(53-77)	<0.001
FEV1/FVC, mean (SD)	0.89(0.04)	0.86(0.05)	0.005	0.81(0.06)	<0.001

FEV1, forced expiratory volume in 1^{st} second; FVC, forced vital capacity; $FEF_{25-75\%}$, forced expiratory flow between 25 and 75% FVC; SD, standard deviation
$FEF_{25-75\%}$, forced expiratory flow between 25 and 75% of forced vital capacity
$^{\$}$, for comparison between normal and intermediate $FEF_{25-75\%}$;
$^{\mu}$, for comparison between normal and low $FEF_{25-75\%}$;

Predictors of persisting respiratory signs at the completion of antituberculosis treatment

Univariable and multivariable adjusted determinants of persisting respiratory signs are shown in Table 3. Independent predictors of persisting signs were longer duration of symptoms prior

to tuberculosis diagnosis [odd ratio 2.91 (95% confidence interval: 1.91-7.60) for symptoms duration greater than 12 weeks], and DAO [2.22 (1.13-4.38)].

Table 3: Determinants of persistent of chronic respiratory symptoms at the end of tuberculosis treatment

Facteurs	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Male sex	1.31 (0.71-2.44)	0.387	/	/
Age	1.01 (0.98-1.03)	0.646	/	/
Duration of symptoms > 12 weeks	3.31 (1.29-8.50)	0.013	2.91(1.12-7.60)	0.029
Smoking	1.68 (0.75-3.76)	0.209	/	/
Previous pulmonary tuberculosis	1.86 (0.69-4.98)	0.218	/	/
HIV infection	0.76 (0.39-1.51)	0.439	/	/
Extension of pulmonary lesions > 4 zones	1.48 (0.71-3.07)	0.292	/	/
Cavitary disease	1.12 (0.57-2.20)	0.751	/	/
Fibrotic lesions	1.24 (0.59-2.62)	0.571	/	/
$FEF_{25-75\%}$	2.45 (1.26-4.77)	0.008	/	/
≥ 80%	1 (reference)			/
65%-79%	1.39 (0.61-3.13)	0.433	/	/
< 65%	2.72 (1.33-5.54)	0.006	2.22 (1.13-4.38)	0.021

$FEF_{25-75\%}$, forced expiratory flow between 25 and 75% of forced vital capacity; OR, odds ratio; CI, confidence interval

Relationship of $FEF_{25-75\%}$ with other spirometry indices

In this study, FEV1 and FVC were significantly low in patients with low or intermediate $FEF_{25-75\%}$ compared to those with normal $FEF_{25-75\%}$ ($p<0.001$). The ratio FEV1/FVC was higher in patients with normal (0.89) than in those with intermediate (0.86) or low (0.81) $FEF_{25-75\%}$ (Table 2).

DISCUSSION

The main findings from this study conducted among patients successfully treated for pulmonary tuberculosis in a region of medium endemicity for tuberculosis are the following : 1) the prevalence of persisting chronic respiratory signs after treatment is very high ; 2) about two in five patients with normal FEV1/FVC have DAO ; 3) DAO is more frequent among patients with persisting chronic respiratory signs after anti-tuberculosis treatment ; 4) long duration of symptoms prior to tuberculosis diagnosis is a predictive factor for persisting respiratory signs following successful treatment for tuberculosis.

Functional post-tuberculosis sequels have been largely characterised.[4, 10, 11] However, few studies have reported on persisting chronic respiratory signs following the treatment of pulmonary tuberculosis. Even in the absence of functional sequels, post-tuberculous persisting chronic respiratory signs can negatively impact on the quality of life of individuals. In our series, three fifths of patients had persisting chronic respiratory signs following treatment for pulmonary tuberculosis. In a recent review from South Africa, chronic bronchitis and dyspnoea were two to seven times more frequent in people with a history of tuberculosis than in those who had never had tuberculosis.[11]

Persisting chronic respiratory signs were associated with prolonged duration of symptoms prior to tuberculosis diagnosis in our study. Lee and co-workers also found that the presence of bronchial obstruction in the post-pulmonary tuberculosis treatment period was influenced by the duration of symptoms prior to starting treatment.[13] Distal bronchial obstruction was found in over a third of our participants. It was independently associated with persisting chronic pulmonary signs, and further associated with a worse profile of spirometry indices. These independent associations suggest that, in addition to confirming the bacteriological cure of the infection, people completing treatment for pulmonary tuberculosis should also be investigated for the presence of functional respiratory signs and indicators of distal airways lesions, in order to optimise their management. There are several interrelated mechanisms to explain the occurrence of post-tuberculous distal bronchial obstruction. Bronchial endothelial inflammation during pulmonary tuberculosis could lead to localised or generalised bronchial obstruction, pulmonary fibrosis, and increase airways' resistance. The destruction of the lung' parenchyma could also reduce the pulmonary compliance and cause the small airways to collapse.[10]

The cross-sectional nature is the main limitation of this study, precluding any inference about the direction of the relationships found in the study. However, in on historical cohort, Hnidzo and co-workers found a gradual decrease in the pulmonary function with the increasing episodes of tuberculosis.[7] It is likely that DAO in our study was the consequence of pulmonary tuberculosis, considering that all patients with known chronic bronchitis prior to tuberculosis occurrence were excluded. The relatively large number of patients included is a major strength.

In conclusion, low $FEF_{25-75\%}$ is useful criteria for diagnosing distal airflow obstruction in patients treated for pulmonary tuberculosis and who otherwise, have normal FEV1/FVC ratio. Persisting chronic respiratory signs following treatment for tuberculosis are very frequent and often associated with DAO. Furthermore, prolonged duration of symptoms prior to starting treatment appears to be a major determinant of persisting post-tuberculous chronic respiratory signs. Sensitisation of the population to consult early with tuberculosis-like symptoms has a potential for improving early diagnosis/treatment and reduction of the prevalence of post-tuberculosis DAO.

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Contributors: EWPY conceived the study, collected data, co-analysed the data and drafted the manuscript. APK contributed to study design, data analysis, drafting and critical revision of the manuscript. PETK collected data, co-analysed data and critical revised the manuscript. EAZ supervised data collection and critically revised the manuscript. All authors approved the final version of the manuscript.

Competing interests: None for all authors.

Data Sharing Statement: No additional data

Ethics approval: Ethics approval was provided by the Institutional Review Board of Yaounde Jamot Hospital.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	*5*
Study size	10	Explain how the study size was arrived at	/
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	/
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9,10
		(*b*) Report category boundaries when continuous variables were categorized	9,10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	/
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11,12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Clinical significance of low forced expiratory flow between 25% and 75% of vital capacity following treated pulmonary tuberculosis: a cross-sectional study

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Clinical significance of low forced expiratory flow between 25% and 75% of vital capacity following treated pulmonary tuberculosis: a cross-sectional study

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ABSTRACT

Objectives: The aim of this study was to assess the prevalence and determinants of post-tuberculosis chronic respiratory signs, and to assess the clinical impact of a low forced expiratory flow between 25% and 75% ($FEF_{25-75\%}$) in a group of individuals previously treated successfully for pulmonary tuberculosis.

Design: This was a cross-sectional study involving individuals in their post-tuberculosis treatment period. They all underwent a spirometry following the 2005 criteria of the American Thoracic Society /European Respiratory Society. Distal airflow obstruction (DAO) was defined by a $FEF_{25-75\%} < 65\%$ and a ratio forced expiratory volume during the first second (FEV_1)/forced vital capacity (FVC) ≥ 0.70. Logistic regression models were used to investigate the determinants of persisting respiratory symptoms following anti-tuberculous treatment.

Setting: This study was carried out in the tuberculosis diagnosis and treatment center at Yaounde Jamot Hospital, which serves as a referral center for tuberculosis and respiratory diseases for the capital city of Cameroon (Yaounde) and surrounding areas.
Participants: All consecutive patients in their post-tuberculosis treatment period were consecutively enrolled between November 2012 and April 2013.

Results: Of the 177 patients included, 101 (57.1%) were men and median age (25^{th}-75^{th} percentiles) was 32 (24-45.5) years. At least one chronic respiratory sign was present in 110 (62.1%) participants and DAO was found in 67 (62.9%). Independent determinants of persisting respiratory signs were the duration of symptoms prior to tuberculosis diagnosis higher than 12 weeks (adjusted odd ratio 2.91; 95% confidence interval: 1.12-7.60, p=0.029) and presence of DAO (2.22; 1.13-4.38, p=0.021).

Conclusions: $FEF_{25-75\%} < 65\%$ is useful for the assessment and diagnosis of post-tuberculous DAO. Mass education targeting early diagnosis of pulmonary tuberculosis can potentially reduce the prevalence of post-tuberculosis respiratory signs and distal airflow obstruction.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a cross-sectional study, precluding any inference about the direction of the relationships found in the study.
- It is likely that distal airflow obstruction in our study was the consequence of pulmonary tuberculosis, considering that all patients with known chronic bronchitis prior to tuberculosis occurrence were excluded.
- The relatively large number of patients included is a major strength.
- This study uses robust methods to assess the relation between post-tuberculosis chronic respiratory symptoms and distal airflow obstruction

INTRODUCTION

Pulmonary tuberculosis, the commonest form of tuberculosis, is an important public health challenge worldwide.[1] The clinical presentation of pulmonary tuberculosis usually combines general signs with chronic respiratory signs including cough and expectoration.[2] The presence of dyspnoea during pulmonary tuberculosis usually indicates the extensive nature of the pulmonary lesions.[2] Radiographic and functional sequels are very frequent following tuberculosis treatment, and ad-integrum restitution of the lungs is rather less frequent.[3-5] While functional sequels are mostly due to restrictive or mixed functional disorders,[6-8] post-tuberculosis airflow obstruction is also present in an important number of patients.[8-11] The prevalence of post-tuberculosis airflow obstruction ranges between 5% and 30% across published studies.[12-15] Furthermore, pathophysiological studies suggest that lesions affecting exclusively the distal respiratory pathways are possible during pulmonary tuberculosis.[10]

We are not aware of published studies on post-tuberculosis distal airflow obstruction (DAO) and the possible connection with persistence of respiratory signs following treatment for pulmonary tuberculosis. The assessment of DAO in routine practice is still a challenge with regard to the indices to be used; however, many have suggested mean median expiratory flow or forced expiratory flow between 25% and 75% ($FEF_{25-75\%}$) to be useful for this purpose. The wide variability of this index limits the possibility of defining a reliable optimal threshold for diagnosing DAO.[16] The thresholds of 65% or 60% have been applied in children to characterise distal airflow obstruction.[17, 18] The aim of this study was to determine the prevalence and factors associated with post-tuberculosis chronic respiratory signs, and to assess the clinical impact of a low $FEF_{25-75\%}$ in a group of patients successfully treated for pulmonary tuberculosis.

MATERIALS AND METHODS

Study setting and participants

This study was conducted in the Center for Diagnosis and Treatment of tuberculosis (CDT) of the Yaounde Jamot Hospital (YJH) between November 2012 and April 2013 (6 months duration). This centre has been described in details previously.[19, 20] In short, YJH is the reference centre for tuberculosis and chest diseases for the Capital city of Cameroon

(Yaounde) and surrounding areas. Over the last five years, the centre has diagnosed and treated an average of 1600 to 1800 patients with tuberculosis per year.

All patients age 18 years and above, successfully treated for bacteriologically proven pulmonary tuberculosis (new case or re-treatment) were invited to take part in the study. Bacteriological proofs of pulmonary tuberculosis was based on the presence of acid fast bacillary (AFB) on at least one direct sputum smear examination,[21] or a positive sputum culture for *Mycobacterium tuberculosis*. Sputum culture and drugs susceptibility test (DST) were done for all retreatment cases. Patients with any of the following conditions were excluded: patients with treatment failure, patients with resistance to at least one antituberculosis drug, on-going bacterial pneumonia or within the four weeks preceding inclusion, chronic respiratory condition before TB diagnosis, on-going treatment with beta blockers, physical or mental inability to perform spirometry test.

Pulmonary tuberculosis treatment

Tuberculosis treatment at the CDT follows to the guidelines of the Cameroon National Tuberculosis Control Program (NTCP) and the World Health Organization (WHO) recommendations.[22, 23] Antituberculosis drugs are dispensed free of charge, and treatment regimens used are standard regimens of category I for new patients and of category II for re-treatment cases. New cases are treated with a regimen that includes an intensive phase of two months duration with rifampicin (R), isoniazid (H), ethambutol (E) and pyrazinamide (Z), followed by a 4-month continuation phase with rifampicin and isoniazid (2RHEZ/4RH). During re-treatment, category I medications (R, H, E, Z) are completed with streptomycin (S). Therefore, re-treatment cases are treated with RHEZS for two months, followed by one month on RHEZ and five months on RHE (2RHEZS/1RHEZ/5RHE). During the intensive phase, adherence is directly monitored by the healthcare team for patients admitted, and during weekly drug collection in those treated as outpatients. The continuation phase is conducted on the outpatient basis and adherence assessed during monthly visits for scripts renewal and drugs collection.

Monitoring and outcomes of pulmonary tuberculosis treatment

During treatment, sputum smear positive patients are re-examined for AFB at the end of month 2, 5 and 6 for new cases, and at the end of month 3, 5 and 8 for re-treated patients. At the end of the treatment, patients are ranked into mutually exclusive categories[22, 23] as: 1) cured – patient with negative smear at the last month of treatment and at least one of the

preceding; 2) treatment completed – patient who has completed the treatment and for whom the smear result at the end of the last month is not available; 3) failure – patient with positive smear at the 5th month or later during treatment; 4) death – death from any cause during treatment; 5) defaulter – patient who's treatment has been interrupted for at least two consecutive months; 6) transfer – patient transferred to complete his treatment in another centre and who's treatment outcome is unknown.

Procedures

Baseline data collection

In this cross-sectional study, baseline data were collected on socio-demographic, clinical, radiological and biological characteristics of patients. Socio-demographic data collected included age, sex, residence (urban vs. rural) and formal level of education. Past medical history data included current or former smoking (yes vs. no), past history of tuberculosis and co-morbidities (diabetes mellitus). Clinical details included: duration of symptoms prior to tuberculosis diagnosis, persistent of respiratory symptoms (cough, expectoration, dyspnoea). Patients whose symptoms continued at the end of TB treatment were considered as having persistent respiratory symptoms. Radiographic data were collected on the extension of lungs involvement (number of fields affected), the type of lung lesions (cavities, fibrotic lesions), the presence of pleural effusion and mediastinal or hilar lymph nodes. Biological data included the results of the HIV test result. The study was approved by the administrative authorities of the YJH and institutional review board of the Faculty of Medicine and Biomedical Sciences of University of Yaounde 1.

Ventilatory variables measurement

The spirometric measurements were done in the month following the completion of TB treatment. Spirometric measurements were acquired with a digital turbine pneumotachograph (Spiro USB, Care fusion, Yorba Linda-USA) following the 1994 American Thoracic Society (ATS) standards.[24] All the pulmonary volumes and flow rates were automatically corrected for body temperature and pressure saturation. Measurements were done under the direct supervision of an experienced pneumologist who is also certified in lung function testing (EWPY). The different respiratory indices were measured without bronchodilators and included: forced vital capacity (FVC), forced expiratory volume during the first second (FEV1), forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25-75\%}$) and the

ratio FEV1/FVC. The acceptability and reproducibility criteria recommended by the ATS and European Respiratory Society (ERS) guidelines (ATS/ERS guidelines) were respected.[16] At least three manoeuvres up to a maximum of eight were performed as required to obtain the flow rate curve (FVC curve). A one minute resting period was observed between consecutive manoeuvres. Satisfactory exhalation was considered in the presence of any of the following: 1) no change in exhaled volume (plateau on the volume-time curve) for 1 second after an exhalation time of at least 6 seconds; 2) the presence of a reasonable duration or plateau in the volume-time curve; 3) inability of the subject to continue to exhale.[16, 24] The largest values for FEV1 and FVC from three acceptable manoeuvres were retained. The authorized difference between the largest values of FVC or FEV1 of the three acceptable manoeuvres was inferior or equal to 0.150 L or 5%. The manoeuvre with the largest sum of FEV1 plus FVC was used to determine $FEF_{25-75\%}$. Predicted values were calculated using reference values based on the Global Lung Initiative (GLI) reference spirometric equations for black.[25] Included participants were categorised according to their $FEF_{25-75\%}$ into 3 mutually exclusive groups: normal ($FEF_{25-75\%} \geq 80\%$), intermediate ($65\% \leq FEF_{25-75\%} < 80\%$) and low ($FEF_{25-75\%} < 65\%$). DAO was based on $FEF_{25-75\%} < 65\%$.

Statistical analysis

Data were analysed with the use of SPSS v17 for Windows®. We have presented categorical variables as count (percentages) and quantitative variables as mean (standard deviation) or median (25^{th}-75^{th} percentiles. Group's comparison used chi square tests for categorical variables and Student's t-test for non-parametric equivalents for quantitative variables. Logistic regressions were then used to investigate the determinants of persisting chronic respiratory signs. Potential candidate determinants were first investigated in univariate analysis. Significant predictors (based on a threshold probability <0.1) were entered all together in the same multivariable model. A p-value<0.05 was used to characterise statistically significant results.

RESULTS

General characteristics of the study population and prevalence of chronic respiratory signs

A total of 189 patients were invited to take part in the study. One refused to consent, ten had incorrect spirometry records (not acceptable and/or not reproducible manoeuvres) while one

had a FEV1/FVC<0.70. Of the 177 participants included, 101 (57.1%) were men and median age (25^{th}-75^{th} percentile) was 32 (24-45.5) years. Thirty-five (19.8%) patients were current or ex-smokers, 23 (13%) had a prior history of pulmonary tuberculosis and 47 (26.6%) had co-incident HIV infection. At least one chronic respiratory sign (CRS) was found in 110 (62.1%) patients at the completion of the anti-tuberculosis treatment. In details, 87 (49.2%), 62 (35%) and 99 (55.9%) patients had persisting cough, expectoration and dyspnoea respectively at treatment completion (Table 1 and Figure 1).

Table 1: Characteristics of study population at the end of tuberculosis treatment

Characteristics	n=177 (%)
Baseline clinical characteristics	
Male sex	101 (57.1)
Age, years, median (25^{th}-75^{th})	32 (24-45.5)
Median duration of symptoms before diagnosis, weeks (25^{th}-75^{th})	8 (4-12)
Current of past smoking	35 (19.8)
Previous pulmonary tuberculosis	23 (13)
HIV infection	47 (26.6)
Diabetes mellitus	4 (2.3)
Radiological signs	
Extension of tuberculosis lesions > 4 zones	52/148 (35.1)
Cavitary disease	81/148 (45.8)
Persisting respiratory symptoms at the end of tuberculosis treatment	
Any respiratory symptoms	110 (62.1)
Cough	87 (49.2)
Expectoration	62 (35.0)
Dyspnoea	99 (55.9)
Spirometry values at the end of tuberculosis treatment	
FEV1, %, mean (SD)	76.3 (19.0)
FVC, %, mean (SD)	74.8 (18.2)
FEV1/FVC	0.86 (0.07)
$FEF_{25-75\%}$, %, median (25^{th}-75^{th})	74 (56-94.5)

FEV1, forced expiratory volume in 1^{st} second; FVC, forced vital capacity;
$FEF_{25-75\%}$, forced expiratory flow between 25 and 75% FVC;
SD, standard deviation

Relationship between $FEF_{25-75\%}$ and chronic respiratory signs

Table 2 shows the distribution of chronic respiratory signs at treatment completion, according to $FEF_{25-75\%}$ categories. Seventy-five patients (42.4%) had normal $FEF_{25-75\%}$, 35 (19.8%) had intermediate $FEF_{25-75\%}$, while 67 (37.9%) had low $FEF_{25-75\%}$. Persisting cough, expectoration and dyspnoea were significantly more frequent among patients with low $FEF_{25-75\%}$. The frequency of at least one persisting chronic respiratory sign was 52% in patients with normal $FEF_{25-75\%}$ and 74.6% among those with low $FEF_{25-75\%}$ (p=0.005). The related odd ratio was 2.72 (95% confidence interval: 1.33-5.57).

Table 2: Frequency of persistent respiratory symptoms and spirometry indices according to $FEF_{25-75\%}$

Symptoms	$FEF_{25-75\%} \geq 80\%$, n=75 (%)	$FEF_{25-75\%}$ between 65% and 80%, n=35(%)	$FEF_{25-75\%} < 65\%$, n=67 (%)	p-value
chronic cough	28 (37.3)	17 (48.6)	42 (62.7)	0.011
Chronic expectoration	20 (26.7)	11 (31.4)	31 (46.3)	0.050
Chronic dyspnoea	38 (50.7)	16 (45.7)	45 (67.2)	0.056
Any chronic respiratory symptoms	39 (52.0)	21 (60.0)	50 (74.6)	0.020
FEV1, %, median (25^{th}-75^{th} percentiles)	89(82-100)	73(62-82)	64(52-73)	<0.001
FVC, %, (25^{th}-75^{th} percentiles)	83(74-92)	72(61-83)	64(53-77)	<0.001
FEV1/FVC, mean (SD)	0.89(0.04)	0.86(0.05)	0.81(0.06)	<0.001

FEV1, forced expiratory volume in 1^{st} second; FVC, forced vital capacity; $FEF_{25-75\%}$, forced expiratory flow between 25 and 75% FVC; SD, standard deviation
$FEF_{25-75\%}$, forced expiratory flow between 25 and 75% of forced vital capacity

Predictors of persisting respiratory signs at the completion of antituberculosis treatment

Univariable and multivariable adjusted determinants of persisting respiratory signs are shown in Table 3. There is no association between smoking volume (pack-years) and persistent of CRS (data not shown). Independent predictors of persisting signs were longer duration of symptoms prior to tuberculosis diagnosis [odd ratio 2.91 (95% confidence interval: 1.91-7.60) for symptoms duration greater than 12 weeks], and DAO [2.22 (1.13-4.38)].

Table 3: Determinants of persistent of chronic respiratory symptoms at the end of tuberculosis treatment

Facteurs	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Male sex	1.31 (0.71-2.44)	0.387	/	/
Age	1.01 (0.98-1.03)	0.646	/	/
Duration of symptoms > 12 weeks	3.31 (1.29-8.50)	0.013	2.91(1.12-7.60)	0.029
Smoking	1.68 (0.75-3.76)	0.209	/	/
Previous pulmonary tuberculosis	1.86 (0.69-4.98)	0.218	/	/
HIV infection	0.76 (0.39-1.51)	0.439	/	/
Extension of pulmonary lesions > 4 zones	1.48 (0.71-3.07)	0.292	/	/
Cavitary disease	1.12 (0.57-2.20)	0.751	/	/
Fibrotic lesions	1.24 (0.59-2.62)	0.571	/	/
$FEF_{25-75\%}$	2.45 (1.26-4.77)	0.008	/	/
≥ 80%	1 (reference)			/
65%-79%	1.39 (0.61-3.13)	0.433	/	/
< 65%	2.72 (1.33-5.54)	0.006	2.22 (1.13-4.38)	0.021

$FEF_{25-75\%}$, forced expiratory flow between 25 and 75% of forced vital capacity; OR, odds ratio; CI, confidence interval

Relationship of $FEF_{25-75\%}$ with other spirometry indices

In this study, FEV1 and FVC were significantly low in patients with low or intermediate $FEF_{25-75\%}$ compared to those with normal $FEF_{25-75\%}$ ($p<0.001$). The ratio FEV1/FVC was higher in patients with normal (0.89) than in those with intermediate (0.86) or low (0.81) $FEF_{25-75\%}$ (Table 2).

DISCUSSION

The main findings from this study conducted among patients successfully treated for pulmonary tuberculosis in a region of medium endemicity for tuberculosis are the following : 1) the prevalence of persisting chronic respiratory signs after treatment is very high ; 2) about two in five patients with normal FEV1/FVC have DAO ; 3) DAO is more frequent among patients with persisting chronic respiratory signs after anti-tuberculosis treatment ; 4) long duration of symptoms prior to tuberculosis diagnosis is a predictive factor for persisting respiratory signs following successful treatment for tuberculosis.

Functional post-tuberculosis sequels have been largely characterised.[4, 10, 11] However, few studies have reported on persisting chronic respiratory signs following the treatment of pulmonary tuberculosis. Even in the absence of functional sequels, post-tuberculous persisting chronic respiratory signs can negatively impact on the quality of life of individuals. In our series, three fifths of patients had persisting chronic respiratory signs following treatment for pulmonary tuberculosis. In a recent review from South Africa, chronic bronchitis and dyspnoea were two to seven times more frequent in people with a history of tuberculosis than in those who had never had tuberculosis.[11]

Persisting chronic respiratory signs were associated with prolonged duration of symptoms prior to tuberculosis diagnosis in our study. Lee and co-workers also found that the presence of bronchial obstruction in the post-pulmonary tuberculosis treatment period was influenced by the duration of symptoms prior to starting treatment.[13] Distal bronchial obstruction was found in over a third of our participants. It was independently associated with persisting chronic pulmonary signs, and further associated with a worse profile of spirometry indices. These independent associations suggest that, in addition to confirming the bacteriological cure of the infection, people completing treatment for pulmonary tuberculosis should also be investigated for the presence of functional respiratory signs and indicators of distal airways lesions, in order to optimise their management. There are several interrelated mechanisms to explain the occurrence of post-tuberculous distal bronchial obstruction. Bronchial endothelial inflammation during pulmonary tuberculosis could lead to localised or generalised bronchial obstruction, pulmonary fibrosis, and increase airways' resistance. The destruction of the lung' parenchyma could also reduce the pulmonary compliance and cause the small airways to collapse.[10]

The cross-sectional nature is the main limitation of this study, precluding any inference about the direction of the relationships found in the study. However, in on historical cohort, Hnidzo and co-workers found a gradual decrease in the pulmonary function with the increasing episodes of tuberculosis.[7] It is likely that DAO in our study was the consequence of pulmonary tuberculosis, considering that all patients with known chronic bronchitis prior to tuberculosis occurrence were excluded. The relatively large number of patients included is a major strength.

In conclusion, low $FEF_{25-75\%}$ is useful criteria for diagnosing distal airflow obstruction in patients treated for pulmonary tuberculosis and who otherwise, have normal FEV1/FVC ratio. Persisting chronic respiratory signs following treatment for tuberculosis are very frequent and often associated with DAO. Furthermore, prolonged duration of symptoms prior to starting treatment appears to be a major determinant of persisting post-tuberculous chronic respiratory signs. Sensitisation of the population to consult early with tuberculosis-like symptoms has a potential for improving early diagnosis/treatment and reduction of the prevalence of post-tuberculosis DAO.

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Competing interests: None for all authors.

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Ethics approval: Ethics approval was provided by the Institutional Review Board of Yaounde Jamot Hospital.

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Figure legend

Figure 1: Spirometric indices of study population

FEV1, forced expiratory volume in 1s; FVC, forced vital capacity; FEF25-75%, forced expiratory flow between 25% and 75%

Clinical significance of low forced expiratory flow between 25% and 75% of vital capacity following treated pulmonary tuberculosis: a cross-sectional study

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ABSTRACT

Objectives: The aim of this study was to assess the prevalence and determinants of post-tuberculosis chronic respiratory signs, and to assess the clinical impact of a low forced expiratory flow between 25% and 75% ($FEF_{25-75\%}$) in a group of individuals previously treated successfully for pulmonary tuberculosis.

Design: This was a cross-sectional study involving individuals in their post-tuberculosis treatment period. They all underwent a spirometry following the 2005 criteria of the American Thoracic Society /European Respiratory Society. Distal airflow obstruction (DAO) was defined by a $FEF_{25-75\%} < 65\%$ and a ratio forced expiratory volume during the first second (FEV_1)/forced vital capacity (FVC) ≥ 0.70. Logistic regression models were used to investigate the determinants of persisting respiratory symptoms following anti-tuberculous treatment.

Setting: This study was carried out in the tuberculosis diagnosis and treatment center at Yaounde Jamot Hospital, which serves as a referral center for tuberculosis and respiratory diseases for the capital city of Cameroon (Yaounde) and surrounding areas.

Participants: All consecutive patients in their post-tuberculosis treatment period were consecutively enrolled between November 2012 and April 2013.

Results: Of the 177 patients included, 101 (57.1%) were men and median age (25^{th}-75^{th} percentiles) was 32 (24-45.5) years. At least one chronic respiratory sign was present in 110 (62.1%) participants and DAO was found in 67 (62.9%). Independent determinants of persisting respiratory signs were the duration of symptoms prior to tuberculosis diagnosis higher than 12 weeks (adjusted odd ratio 2.91; 95% confidence interval: 1.12-7.60, p=0.029) and presence of DAO (2.22; 1.13-4.38, p=0.021).

Conclusions: $FEF_{25-75\%} < 65\%$ is useful for the assessment and diagnosis of post-tuberculous DAO. Mass education targeting early diagnosis of pulmonary tuberculosis can potentially reduce the prevalence of post-tuberculosis respiratory signs and distal airflow obstruction.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a cross-sectional study, precluding any inference about the direction of the relationships found in the study.
- It is likely that distal airflow obstruction in our study was the consequence of pulmonary tuberculosis, considering that all patients with known chronic bronchitis prior to tuberculosis occurrence were excluded.
- The relatively large number of patients included is a major strength.
- This study uses robust methods to assess the relation between post-tuberculosis chronic respiratory symptoms and distal airflow obstruction

INTRODUCTION

Pulmonary tuberculosis, the commonest form of tuberculosis, is an important public health challenge worldwide.[1] The clinical presentation of pulmonary tuberculosis usually combines general signs with chronic respiratory signs including cough and expectoration.[2] The presence of dyspnoea during pulmonary tuberculosis usually indicates the extensive nature of the pulmonary lesions.[2] Radiographic and functional sequels are very frequent following tuberculosis treatment, and ad-integrum restitution of the lungs is rather less frequent.[3-5] While functional sequels are mostly due to restrictive or mixed functional disorders,[6-8] post-tuberculosis airflow obstruction is also present in an important number of patients.[8-11] The prevalence of post-tuberculosis airflow obstruction ranges between 5% and 30% across published studies.[12-15] Furthermore, pathophysiological studies suggest that lesions affecting exclusively the distal respiratory pathways are possible during pulmonary tuberculosis.[10]

We are not aware of published studies on post-tuberculosis distal airflow obstruction (DAO) and the possible connection with persistence of respiratory signs following treatment for pulmonary tuberculosis. The assessment of DAO in routine practice is still a challenge with regard to the indices to be used; however, many have suggested mean median expiratory flow or forced expiratory flow between 25% and 75% ($FEF_{25-75\%}$) to be useful for this purpose. The wide variability of this index limits the possibility of defining a reliable optimal threshold for diagnosing DAO.[16] The thresholds of 65% or 60% have been applied in children to characterise distal airflow obstruction.[17, 18] The aim of this study was to determine the prevalence and factors associated with post-tuberculosis chronic respiratory signs, and to assess the clinical impact of a low $FEF_{25-75\%}$ in a group of patients successfully treated for pulmonary tuberculosis.

MATERIALS AND METHODS

Study setting and participants

This study was conducted in the Center for Diagnosis and Treatment of tuberculosis (CDT) of the Yaounde Jamot Hospital (YJH) between November 2012 and April 2013 (6 months duration). This centre has been described in details previously.[19, 20] In short, YJH is the reference centre for tuberculosis and chest diseases for the Capital city of Cameroon

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(Yaounde) and surrounding areas. Over the last five years, the centre has diagnosed and treated an average of 1600 to 1800 patients with tuberculosis per year.

All patients age 18 years and above, successfully treated for bacteriologically proven pulmonary tuberculosis (new case or re-treatment) were invited to take part in the study. Bacteriological proofs of pulmonary tuberculosis was based on the presence of acid fast bacillary (AFB) on at least one direct sputum smear examination,[21] or a positive sputum culture for *Mycobacterium tuberculosis*. Sputum culture and drugs susceptibility test (DST) were done for all retreatment cases. Patients with any of the following conditions were excluded: patients with treatment failure, patients with resistance to at least one antituberculosis drug, on-going bacterial pneumonia or within the four weeks preceding inclusion, chronic respiratory condition before TB diagnosis, on-going treatment with beta blockers, physical or mental inability to perform spirometry test.

Pulmonary tuberculosis treatment

Tuberculosis treatment at the CDT follows to the guidelines of the Cameroon National Tuberculosis Control Program (NTCP) and the World Health Organization (WHO) recommendations.[22, 23] Antituberculosis drugs are dispensed free of charge, and treatment regimens used are standard regimens of category I for new patients and of category II for re-treatment cases. New cases are treated with a regimen that includes an intensive phase of two months duration with rifampicin (R), isoniazid (H), ethambutol (E) and pyrazinamide (Z), followed by a 4-month continuation phase with rifampicin and isoniazid (2RHEZ/4RH). During re-treatment, category I medications (R, H, E, Z) are completed with streptomycin (S). Therefore, re-treatment cases are treated with RHEZS for two months, followed by one month on RHEZ and five months on RHE (2RHEZS/1RHEZ/5RHE). During the intensive phase, adherence is directly monitored by the healthcare team for patients admitted, and during weekly drug collection in those treated as outpatients. The continuation phase is conducted on the outpatient basis and adherence assessed during monthly visits for scripts renewal and drugs collection.

Monitoring and outcomes of pulmonary tuberculosis treatment

During treatment, sputum smear positive patients are re-examined for AFB at the end of month 2, 5 and 6 for new cases, and at the end of month 3, 5 and 8 for re-treated patients. At the end of the treatment, patients are ranked into mutually exclusive categories[22, 23] as: 1) cured – patient with negative smear at the last month of treatment and at least one of the

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preceding; 2) treatment completed – patient who has completed the treatment and for whom the smear result at the end of the last month is not available; 3) failure – patient with positive smear at the 5th month or later during treatment; 4) death – death from any cause during treatment; 5) defaulter – patient who's treatment has been interrupted for at least two consecutive months; 6) transfer – patient transferred to complete his treatment in another centre and who's treatment outcome is unknown.

Procedures

Baseline data collection

In this cross-sectional study, baseline data were collected on socio-demographic, clinical, radiological and biological characteristics of patients. Socio-demographic data collected included age, sex, residence (urban vs. rural) and formal level of education. Past medical history data included current or former smoking (yes vs. no), past history of tuberculosis and co-morbidities (diabetes mellitus). Clinical details included: duration of symptoms prior to tuberculosis diagnosis, persistent of respiratory symptoms (cough, expectoration, dyspnoea). Patients whose symptoms continued at the end of TB treatment were considered as having persistent respiratory symptoms. Radiographic data were collected on the extension of lungs involvement (number of fields affected), the type of lung lesions (cavities, fibrotic lesions), the presence of pleural effusion and mediastinal or hilar lymph nodes. Biological data included the results of the HIV test result. The study was approved by the administrative authorities of the YJH and institutional review board of the Faculty of Medicine and Biomedical Sciences of University of Yaounde 1.

Ventilatory variables measurement

The spirometric measurements were done in the month following the completion of TB treatment. Spirometric measurements were acquired with a digital turbine pneumotachograph (Spiro USB, Care fusion, Yorba Linda-USA) following the 1994 American Thoracic Society (ATS) standards.[24] All the pulmonary volumes and flow rates were automatically corrected for body temperature and pressure saturation. Measurements were done under the direct supervision of an experienced pneumologist who is also certified in lung function testing (EWPY). The different respiratory indices were measured without bronchodilators and included: forced vital capacity (FVC), forced expiratory volume during the first second (FEV1), forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25-75\%}$) and the

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ratio FEV1/FVC. The acceptability and reproducibility criteria recommended by the ATS and European Respiratory Society (ERS) guidelines (ATS/ERS guidelines) were respected.[16] At least three manoeuvres up to a maximum of eight were performed as required to obtain the flow rate curve (FVC curve). A one minute resting period was observed between consecutive manoeuvres. Satisfactory exhalation was considered in the presence of any of the following: 1) no change in exhaled volume (plateau on the volume-time curve) for 1 second after an exhalation time of at least 6 seconds; 2) the presence of a reasonable duration or plateau in the volume-time curve; 3) inability of the subject to continue to exhale.[16, 24] The largest values for FEV1 and FVC from three acceptable manoeuvres were retained. The authorized difference between the largest values of FVC or FEV1 of the three acceptable manoeuvres was inferior or equal to 0.150 L or 5%. The manoeuvre with the largest sum of FEV1 plus FVC was used to determine $FEF_{25-75\%}$. Predicted values were calculated using reference values based on the Global Lung Initiative (GLI) reference spirometric equations for black.[25] Included participants were categorised according to their $FEF_{25-75\%}$ into 3 mutually exclusive groups: normal ($FEF_{25-75\%} \geq 80\%$), intermediate ($65\% \leq FEF_{25-75\%} < 80\%$) and low ($FEF_{25-75\%} < 65\%$). DAO was based on $FEF_{25-75\%} < 65\%$.

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Statistical analysis

Data were analysed with the use of SPSS v17 for Windows®. We have presented categorical variables as count (percentages) and quantitative variables as mean (standard deviation) or median (25^{th}-75^{th} percentiles. Group's comparison used chi square tests for categorical variables and Student's t-test for non-parametric equivalents for quantitative variables. Logistic regressions were then used to investigate the determinants of persisting chronic respiratory signs. Potential candidate determinants were first investigated in univariate analysis. Significant predictors (based on a threshold probability <0.1) were entered all together in the same multivariable model. A p-value<0.05 was used to characterise statistically significant results.

RESULTS

General characteristics of the study population and prevalence of chronic respiratory signs

A total of 189 patients were invited to take part in the study. One refused to consent, ten had incorrect spirometry records (not acceptable and/or not reproducible manoeuvres) while one

had a FEV1/FVC<0.70. Of the 177 participants included, 101 (57.1%) were men and median age (25^{th}-75^{th} percentile) was 32 (24-45.5) years. Thirty-five (19.8%) patients were current or ex-smokers, 23 (13%) had a prior history of pulmonary tuberculosis and 47 (26.6%) had co-incident HIV infection. At least one chronic respiratory sign (CRS) was found in 110 (62.1%) patients at the completion of the anti-tuberculosis treatment. In details, 87 (49.2%), 62 (35%) and 99 (55.9%) patients had persisting cough, expectoration and dyspnoea respectively at treatment completion (Table 1 and Figure 1).

Table 1: Characteristics of study population at the end of tuberculosis treatment

Characteristics	n=177 (%)
Baseline clinical characteristics	
Male sex	101 (57.1)
Age, years, median (25^{th}-75^{th})	32 (24-45.5)
Median duration of symptoms before diagnosis, weeks (25^{th}-75^{th})	8 (4-12)
Current of past smoking	35 (19.8)
Previous pulmonary tuberculosis	23 (13)
HIV infection	47 (26.6)
Diabetes mellitus	4 (2.3)
Radiological signs	
Extension of tuberculosis lesions > 4 zones	52/148 (35.1)
Cavitary disease	81/148 (45.8)
Persisting respiratory symptoms at the end of tuberculosis treatment	
Any respiratory symptoms	110 (62.1)
Cough	87 (49.2)
Expectoration	62 (35.0)
Dyspnoea	99 (55.9)
Spirometry values at the end of tuberculosis treatment	
FEV1, %, mean (SD)	76.3 (19.0)
FVC, %, mean (SD)	74.8 (18.2)
FEV1/FVC	0.86 (0.07)
$FEF_{25-75\%}$, %, median (25^{th}-75^{th})	74 (56-94.5)

FEV1, forced expiratory volume in 1^{st} second; FVC, forced vital capacity;
$FEF_{25-75\%}$, forced expiratory flow between 25 and 75% FVC;
SD, standard deviation

Relationship between $FEF_{25-75\%}$ and chronic respiratory signs

Table 2 shows the distribution of chronic respiratory signs at treatment completion, according to $FEF_{25-75\%}$ categories. Seventy-five patients (42.4%) had normal $FEF_{25-75\%}$, 35 (19.8%) had intermediate $FEF_{25-75\%}$, while 67 (37.9%) had low $FEF_{25-75\%}$. Persisting cough, expectoration and dyspnoea were significantly more frequent among patients with low $FEF_{25-75\%}$. The frequency of at least one persisting chronic respiratory sign was 52% in patients with normal $FEF_{25-75\%}$ and 74.6% among those with low $FEF_{25-75\%}$ (p=0.005). The related odd ratio was 2.72 (95% confidence interval: 1.33-5.57).

Table 2: Frequency of persistent respiratory symptoms and spirometry indices according to $FEF_{25-75\%}$

Symptoms	$FEF_{25-75\%} \geq 80\%$, n=75 (%)	$FEF_{25-75\%}$ between 65% and 80%, n=35(%)	$FEF_{25-75\%} < 65\%$, n=67 (%)	p-value
chronic cough	28 (37.3)	17 (48.6)	42 (62.7)	0.011
Chronic expectoration	20 (26.7)	11 (31.4)	31 (46.3)	0.050
Chronic dyspnoea	38 (50.7)	16 (45.7)	45 (67.2)	0.056
Any chronic respiratory symptoms	39 (52.0)	21 (60.0)	50 (74.6)	0.020
FEV1, %, median (25^{th}-75^{th} percentiles)	89(82-100)	73(62-82)	64(52-73)	<0.001
FVC, %, (25^{th}-75^{th} percentiles)	83(74-92)	72(61-83)	64(53-77)	<0.001
FEV1/FVC, mean (SD)	0.89(0.04)	0.86(0.05)	0.81(0.06)	<0.001

FEV1, forced expiratory volume in 1^{st} second; FVC, forced vital capacity; $FEF_{25-75\%}$, forced expiratory flow between 25 and 75% FVC; SD, standard deviation
$FEF_{25-75\%}$, forced expiratory flow between 25 and 75% of forced vital capacity

Predictors of persisting respiratory signs at the completion of antituberculosis treatment

Univariable and multivariable adjusted determinants of persisting respiratory signs are shown in Table 3. There is no association between smoking volume (pack-years) and persistent of CRS (data not shown). Independent predictors of persisting signs were longer duration of symptoms prior to tuberculosis diagnosis [odd ratio 2.91 (95% confidence interval: 1.91-7.60) for symptoms duration greater than 12 weeks], and DAO [2.22 (1.13-4.38)].

Table 3: Determinants of persistent of chronic respiratory symptoms at the end of tuberculosis treatment

Facteurs	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Male sex	1.31 (0.71-2.44)	0.387	/	/
Age	1.01 (0.98-1.03)	0.646	/	/
Duration of symptoms > 12 weeks	3.31 (1.29-8.50)	0.013	2.91(1.12-7.60)	0.029
Smoking	1.68 (0.75-3.76)	0.209	/	/
Previous pulmonary tuberculosis	1.86 (0.69-4.98)	0.218	/	/
HIV infection	0.76 (0.39-1.51)	0.439	/	/
Extension of pulmonary lesions > 4 zones	1.48 (0.71-3.07)	0.292	/	/
Cavitary disease	1.12 (0.57-2.20)	0.751	/	/
Fibrotic lesions	1.24 (0.59-2.62)	0.571	/	/
$FEF_{25-75\%}$	2.45 (1.26-4.77)	0.008	/	/
≥ 80%	1 (reference)			/
65%-79%	1.39 (0.61-3.13)	0.433	/	/
< 65%	2.72 (1.33-5.54)	0.006	2.22 (1.13-4.38)	0.021

$FEF_{25-75\%}$, forced expiratory flow between 25 and 75% of forced vital capacity; OR, odds ratio; CI, confidence interval

Relationship of $FEF_{25-75\%}$ with other spirometry indices

In this study, FEV1 and FVC were significantly low in patients with low or intermediate $FEF_{25-75\%}$ compared to those with normal $FEF_{25-75\%}$ ($p<0.001$). The ratio FEV1/FVC was higher in patients with normal (0.89) than in those with intermediate (0.86) or low (0.81) $FEF_{25-75\%}$ (Table 2).

DISCUSSION

The main findings from this study conducted among patients successfully treated for pulmonary tuberculosis in a region of medium endemicity for tuberculosis are the following : 1) the prevalence of persisting chronic respiratory signs after treatment is very high ; 2) about two in five patients with normal FEV1/FVC have DAO ; 3) DAO is more frequent among patients with persisting chronic respiratory signs after anti-tuberculosis treatment ; 4) long duration of symptoms prior to tuberculosis diagnosis is a predictive factor for persisting respiratory signs following successful treatment for tuberculosis.

Functional post-tuberculosis sequels have been largely characterised.[4, 10, 11] However, few studies have reported on persisting chronic respiratory signs following the treatment of pulmonary tuberculosis. Even in the absence of functional sequels, post-tuberculous persisting chronic respiratory signs can negatively impact on the quality of life of individuals. In our series, three fifths of patients had persisting chronic respiratory signs following treatment for pulmonary tuberculosis. In a recent review from South Africa, chronic bronchitis and dyspnoea were two to seven times more frequent in people with a history of tuberculosis than in those who had never had tuberculosis.[11]

Persisting chronic respiratory signs were associated with prolonged duration of symptoms prior to tuberculosis diagnosis in our study. Lee and co-workers also found that the presence of bronchial obstruction in the post-pulmonary tuberculosis treatment period was influenced by the duration of symptoms prior to starting treatment.[13] Distal bronchial obstruction was found in over a third of our participants. It was independently associated with persisting chronic pulmonary signs, and further associated with a worse profile of spirometry indices. These independent associations suggest that, in addition to confirming the bacteriological cure of the infection, people completing treatment for pulmonary tuberculosis should also be investigated for the presence of functional respiratory signs and indicators of distal airways lesions, in order to optimise their management. There are several interrelated mechanisms to explain the occurrence of post-tuberculous distal bronchial obstruction. Bronchial endothelial inflammation during pulmonary tuberculosis could lead to localised or generalised bronchial obstruction, pulmonary fibrosis, and increase airways' resistance. The destruction of the lung' parenchyma could also reduce the pulmonary compliance and cause the small airways to collapse.[10]

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The cross-sectional nature is the main limitation of this study, precluding any inference about the direction of the relationships found in the study. However, in on historical cohort, Hnidzo and co-workers found a gradual decrease in the pulmonary function with the increasing episodes of tuberculosis.[7] It is likely that DAO in our study was the consequence of pulmonary tuberculosis, considering that all patients with known chronic bronchitis prior to tuberculosis occurrence were excluded. The relatively large number of patients included is a major strength.

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In conclusion, low $FEF_{25-75\%}$ is useful criteria for diagnosing distal airflow obstruction in patients treated for pulmonary tuberculosis and who otherwise, have normal FEV1/FVC ratio. Persisting chronic respiratory signs following treatment for tuberculosis are very frequent and often associated with DAO. Furthermore, prolonged duration of symptoms prior to starting treatment appears to be a major determinant of persisting post-tuberculous chronic respiratory signs. Sensitisation of the population to consult early with tuberculosis-like symptoms has a potential for improving early diagnosis/treatment and reduction of the prevalence of post-tuberculosis DAO.

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Competing interests: None for all authors.

Ethics approval: Ethics approval was provided by the Institutional Review Board of Yaounde Jamot Hospital.

Contributors: EWPY conceived the study, collected data, co-analysed the data and drafted the manuscript. APK contributed to study design, data analysis, drafting and critical revision of the manuscript. PETK collected data, co-analysed data and critical revised the manuscript. EAZ supervised data collection and critically revised the manuscript. All authors approved the final version of the manuscript.

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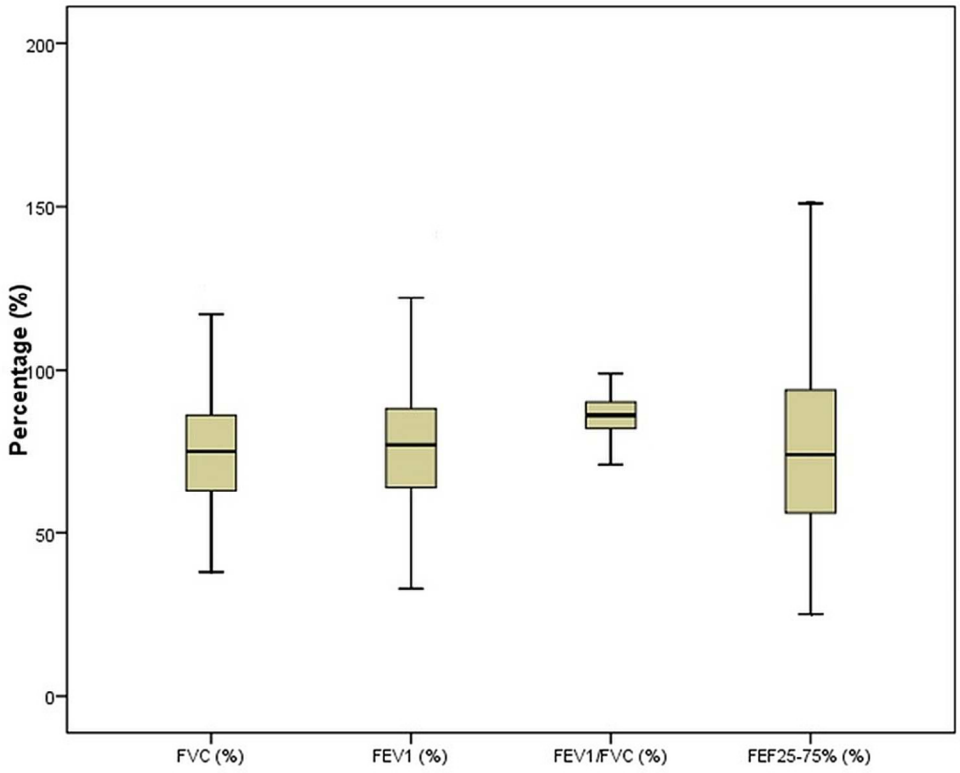

Figure 1: Spirometric indices of study population
FEV1, forced expiratory volume in 1s; FVC, forced vital capacity; FEF25-75%, forced expiratory flow between 25% and 75%
90x71mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	*5*
Study size	10	Explain how the study size was arrived at	/
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	/
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7,8
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9,10
		(*b*) Report category boundaries when continuous variables were categorized	9,10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	/
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11,12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.