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Published in:
Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

DOI:
10.1016/j.jctube.2019.01.003

Publication date:
2019

Document version
Publisher's PDF, also known as Version of record

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Citation for published version (APA):
Rastoder, E., Shaker, S. B., Naqibullah, M., Wille, M. M. W., Lund, M., Wilcke, J. T., ... Jensen, S. G. (2019). Chest x-ray findings in tuberculosis patients identified by passive and active case finding: A retrospective study. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases, 14, 26-30. https://doi.org/10.1016/j.jctube.2019.01.003
Chest x-ray findings in tuberculosis patients identified by passive and active case finding: A retrospective study

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ARTICLE INFO

Keywords:
Tuberculosis
Chest x-ray changes
Passive case finding
Active case finding
Chest x-ray assessment
Normal chest x-ray

ABSTRACT

Background: Chest x-ray is central in screening and diagnosis of tuberculosis. However, sputum culture remains gold standard for diagnosis.

Aim: To establish the rate of normal chest x-rays in tuberculosis patients found by spot sputum culture screening, and compare them to a group identified through passive case finding.

Method: Chest x-rays from 39 culture-positive patients, identified by spot sputum culture screening in Copenhagen from 2012 to 2014, were included in the study (spot sputum culture group(SSC)). 39 normal chest x-rays from persons screened by mobile x-ray, and 39 chest x-rays from tuberculosis-patients identified through passive case finding(PCF) were anonymised and randomised. Two respiratory physicians and two radiologists assessed the chest x-rays.

Results: The normal chest x-ray rate was higher in the non-tuberculosis control group (median = 32 (82.1%), range = 74.4%–100%), compared to the SSC group (median = 7 (17.9%), range = 10.3%–33.3%), and the PCF controls (median = 3(7.7%), range = 2.6%–15.4%). In the SSC group 14 (35.9%) were categorized as normal by at least one study participant.

Conclusion: A substantial minority of patients diagnosed with tuberculosis by spot sputum culture screening, and through passive case finding would not have been identified with chest x-ray alone, highlighting that a normal chest x-ray does not exclude pulmonary tuberculosis.

1. Introduction

In 2016 the tuberculosis(TB) incidence rate in Denmark was 5.7/100,000 [1], but the incidence rate is not decreasing as it is seen in our neighboring countries: Finland, Norway and Sweden [2]. As in other low incidence countries, TB is most common in high-risk groups in Denmark. Limited access to the health care system may cause ongoing transmission among alcoholics, drug users, immigrants and homeless people. Thus, active screening among TB high-risk groups is pivotal in gaining TB control.

Several studies using chest x-ray (CXR) to screen for TB have been published, describing the method as effective with immediate results [3–8]. From September 2012 through June 2014 seven screening rounds, using spot sputum, were performed at 11 locations in Copenhagen. The participants with positive sputum smear microscopy, -culture or -nucleic acid amplification tests (NAAT) were referred to further investigation including CXR screening.

Results from this retrospective study were published in 2015. In total 1075 participants were screened and 36(3.35%) TB patients identified. The physicians assessing the chest x-rays had not been blinded to the fact that the patients had participated in the project. They concluded that 22.2% of TB patients found by spot sputum screening did not have CXR changes suggestive of TB [9].

The aim of this study was, in a blinded setting, to establish the rate of normal CXRs in tuberculosis patients found by spot sputum culture screening, and to compare the rate of CXR changes in this group, to a group of tuberculosis patients identified through passive case finding.

2. Methods

2.1. Patients and controls

Spot Sputum Culture (SSC) group: 39 TB-patients identified by spot sputum screening in eight screening rounds from September 2012 to
Table 1
Population characteristics at baseline, in the three patient/control groups: Patients found by spot sputum culture screening (SSC group); Patients identified by passive case finding (PCF controls); Participants who were screened by mobile chest x-ray and did not have tuberculosis (non-TB controls).

|                                | SSC group n (%) | PCF controls n (%) | Non-TB controls n (%) | Total n (%) | P value* |
|--------------------------------|-----------------|--------------------|-----------------------|-------------|---------|
| Patients screened              | 39 (33.33)      | 39 (33.33)         | 39 (33.33)            | 117         | 0.4150  |
| Age, year, mean (SD)           | 50.19 (9.7)     | 50.28 (14.5)       | 50.25 (9.2)           | 50.24 (11.4)| 0.2824  |
| Sex                            |                 |                    |                       |             |         |
| Male                           | 28 (71.8)       | 32 (82.1)          | 28 (71.8)             | 88 (75.2)   | 0.2824  |
| Substance abuse**              |                 |                    |                       |             |         |
| Alcohol abuse                  |                 |                    |                       |             |         |
| Yes                            | 23 (58.97)      | 16 (41.03)         | /NA                   | 39 (33.3)   | 0.2739  |
| Smoking                        |                 |                    |                       |             |         |
| Yes                            | 28 (71.79)      | 18 (46.1%)         | /NA                   | 46 (39.3)   | 0.0706  |
| Cannabis                       |                 |                    |                       |             |         |
| Yes                            | 22 (56.41)      | 9 (23.08)          | /NA                   | 31 (26.5)   | 0.0108  |
| Illicit drugs                  |                 |                    |                       |             |         |
| Yes                            | 2 (5.13)        | 3 (7.69)           | /NA                   | 5 (4.3)     | 0.7444  |
| Homeless***                    |                 |                    |                       |             |         |
| Yes                            | 21 (53.85)      | 10 (25.64)         | /NA                   | 31 (26.5)   | 0.0379  |
| No                             | 17 (43.9)       | 24 (61.54)         | /NA                   | 41 (35.0)   |         |
| Other****                      | 1 (2.56)        | 3 (7.69)           | /NA                   | 4 (3.4)     |         |
| Originating from high incidence country | |                  |                       |             |         |
| Yes                            | 27 (69.3)       | 23 (59.0)          | /NA                   | 50 (42.7)   | 0.1569  |
| No                             | 10 (25.6)       | 16 (41.0)          | /NA                   | 26 (22.2)   |         |
| Unknown                        | 2 (5.1)         | 0 (0)              | /NA                   | 2 (1.7)     |         |
| Greenland                      |                 |                    |                       |             |         |
| Yes                            | 19 (48.7)       | 8 (20.5)           | /NA                   | 27 (23.1)   | 0.0063  |
| Culture samples                |                 |                    |                       |             |         |
| Positive                       | 38 (97.4)       | 30 (76.92)         | /NA                   | 68 (58.1)   | 0.0067  |

* P value between the SSC group and the PCF controls.
** Information about substance abuse was not available in 1 SSC case and in 2 PCF controls cases. These three patients are categorized as having no substance abuse.
*** Home status was not available in two cases in PCF controls; these two patients are not included in the analysis.
**** These patients are in prison.

In this project we used digital x-rays with 2 views. They were analysed on high resolution screens, and the readers had unlimited time to read the images. The images were anonymised, numbered from one to one hundred and seventeen, and put in random order to avoid recognition of the patient groups.

Four independent readers (two respiratory physicians and two radiologists) assessed the chest radiographs. The respiratory physicians have been in the profession for 26 and 21 years respectively, for the radiologists it is 11 and 20 years. They filled in questionnaires prepared for the study. Inspired by two papers [10, 11] CXRs were classified as normal, acute CXR changes and chronic CXR changes, followed by a sub-categorisation of the acute and chronic changes. Acute: (a) The suspicion of active TB is high, (b) CXR changes compatible with active TB, (c) Chronic CXR changes not suggestive of active TB. In the tables a and b have been merged to the category, acute changes suggestive of tuberculosis. Chronic: (a) Rib fractures, (b) CXR changes typical of healed TB and (c) Chronic pulmonary changes of unknown origin [10, 11].

2.3. Analyses of data

Data in the article is presented using median and range calculated among the four readers.

The Chi-squared test was used to compare CXRs in the SSC group and the PCF control group.

We used the kappa statistics to assess agreement among physicians and radiologists. In this study strength of agreement is defined as follows:

- Kappa-value < 0.20 = Poor
- Kappa-value 0.21–0.40 = Fair
- Kappa-value 0.41–0.60 = Moderate
- Kappa-value 0.61–0.80 = Good
- Kappa-value 0.81–1.00 = Very good

Sensitivity was calculated using the x-ray results of culture positive patients from the SSC and the PCF group; and specificity was calculated using the x-ray results of non-TB patients examined by mobile CXR. The
sensitivities and the specificities reported are the means of the sensitivity and the specificities of the readers (respiratory physicians and radiologists).

2.4. Ethics

The study was a cross-sectional register study as confirmed by the Central Ethics Committee of Denmark (protocol no. H-15007396). Permission to access and process data was given by the Danish Data Protection Agency (j.nr.: 2007 – 58 – 0015).

3. Results

We analysed 2 × 39 CXRs from patients diagnosed with TB, and 39 from persons without TB. Table 1 shows the three groups, and their baseline characteristics. 1(2.6%) patient in the SSC group and 9(23.1%) patients in the PCF group were culture negative. Patients in the SSC group were significantly more likely to be homeless compared to the PCF controls (p value = 0.0379), and they were significantly more likely to have a cannabis abuse (p value = 0.0108). 48.7% in the SSC group were Greenlanders compared to, 20.5% in the PCF controls (p value = 0.0063). There was no statistically significant difference in the age and sex distribution among the three groups.

Table 2 shows the x-ray results of the SSC group and the PCF controls. As expected, the rate of normal CXRs was highest in the non-TB control group (median = 32 (82.1%) and range = 74.4% – 100%) compared to the SSC group (median = 7 (17.9%), range = 10.3% – 33.3%) and the PCF controls (median = 3 (7.7%), range = 2.6%–15.4%). In the SSC group 14 (35.9%) were categorized as normal by at least one reader.

In Table 3 the results from patients with culture-negative TB have been excluded, thus, solely including results from patients with culture positivity by at least one reader. In this study, respiratory physicians and radiologists had unlimited time to assess each CXR. In daily work evaluation of CXRs may not be as thorough because of time limitations. It is therefore likely that the number of normal CXRs might be around 36% or perhaps even higher. This is an important finding, because of CXRs central role in TB diagnostics and screening [4–6, 12–22] and may indicate the complementary roles of CXR and sputum analysis in screening for tuberculosis in high risk groups.

Table 1 illustrates that 1 individual in the SSC group had microscopy verified tuberculosis, and was therefore included. The 9 patients in the PCF group were defined as TB patients based on a combination of chest x-ray findings, symptoms, such as weight loss, fatigue, and haemoptysis, and a good response to anti-tuberculosis treatment. According to ECDC guidelines diagnoses of culture-negative pulmonary tuberculosis should be based on above mentioned criteria.

Table 2

Chest x-ray results from patients found by spot sputum culture screening (SSC group), and patients identified by passive case finding (PCF controls); Assessed by two respiratory physicians and two radiologists.

|          | Respiratory physicians |          | Radiologists |
|----------|------------------------|----------|--------------|
|          | Physician 1            | Physician 2 | Radiologist 1 | Radiologist 2 |
| Abnormal |                        |          |              |              |
| Acute changes | 23 (59.0) | 21 (53.9) | 0.2340 | 20 (51.3) | 21 (53.9) | 0.8206 |
| Chronic changes | 13 (33.3) | 12 (30.8) | 0.8083 | 7 (18.0) | 13 (33.3) | 0.1197 |
| Total* | 35 (84.6) | 36 (92.3) | 0.2877 | 26 (66.7) | 33 (84.6) | 0.0648 |
| Normal |                        |          |              |              |
| Acute changes | 32 (82.1) | 30 (78.3) | 0.7613 | 26 (66.7) | 24 (61.5) | 0.4653 |
| Chronic changes | 8 (20.5) | 13 (33.3) | 0.2018 | 10 (25.6) | 13 (33.3) | 0.3264 |
| Total* | 35 (89.7) | 36 (92.3) | 0.6920 | 31 (79.5) | 38 (97.4) | 0.0131 |

* Total represents the number of patients with some kind of abnormality. Each abnormality is only counted for once.

4. Discussion

In this blinded study we established that in the SSC group of TB-patients 17.9% had CXRs categorized as normal, furthermore 35.9% of the CXRs in this group were categorized as normal by at least one of the participating respiratory physicians and/or radiologists. This highlights the fact that a normal CXR does not exclude active TB. We found a higher percentage of normal CXRs in the SSC group (17.9%), compared to the PCF controls (7.7%). Our results support the findings of Jensen et al. study from 2015, where 22.2% of TB patients found by spot sputum screening had no CXR changes suggestive of TB [9].

The respiratory physicians and radiologists participating in this study were presented with nothing except a CXR of each patient, whereas in the study by Jensen et al physicians were aware of the patients’ symptoms and their positive sputum samples or positive microscopy. A study published in 2012 by Vant-Hoog et al. showed a sensitivity of 100% when symptoms and CXR assessments were combined, an awareness of symptoms increased sensitivity. Surprisingly in our study we found the opposite to be true: Fewer patients from the SSC group were categorized as normal (17.9%) compared to Jensen et al. non-blinded study (22.2%). In their daily work, the four readers do not assess CXRs with such a high TB incidence, which could have led to an over-reporting of normal CXRs. However our results suggest that spot sputum culture examination identifies TB patients that would not have been found by CXR screening alone.

Almost 36% of CXRs in the SSC group were categorized as normal by at least one reader. In this study, respiratory physicians and radiologists had unlimited time to assess each CXR. In daily work evaluation of CXRs may not be as thorough because of time limitations. It is therefore likely that the number of normal CXRs might be around 36% or perhaps even higher.
A similar but non-significant difference in rate of abnormal CXRs between PCF controls and culture positive SSC patients was seen (Table 3). 

Two readers reported significantly more frequent CXR changes among culture positive PCF controls compared to culture positive SSC patients (Table 3). A similar but non-significant difference in rate of abnormal CXRs between PCF controls and SSC patients were seen in the results from the two other readers. The patients in the SSC group may be in an early stage of their disease and therefore have less pulmonary infiltrations. Whereas, the PCF controls seek help from health care authorities, which implies that they have more pronounced symptoms and perhaps their TB stage is more advanced, leading to progressive pulmonary infiltrations. As shown in Table 1, patients in the SSC group are significantly more likely to be homeless and have an abuse (cannabis) compared to the PCF controls. Thus, access to health care providers and awareness of TB symptoms may be limited in this group; therefore we would expect them to have a more progressive stage of TB when diagnosed. This is not found in our study where the SSC group had a higher median of normal CXRs (17.9%) compared to the PCF group (7.7%), highlighting that the SSC patients in this study were found at an early stage. To establish the stage of TB we would need to know about the onset of symptoms, but there has been no data available for that. 

Table 4 shows an equally, good agreement among the respiratory physicians and radiologists when evaluating chest x-rays for culture positive and negative patients. Categorizations: Normal, with acute changes and with changes specifically suggestive of active TB. 

Table 3 Chest x-ray results from patients found by spot sputum culture screening (SSC group, n = 38), and patients identified by passive case finding (PCF controls, n = 30); assessed by two respiratory physicians and two radiologists. Only culture positive patients were included.

|                  | Respiratory physicians | Physician 2 | P value | Radiologists | Physician 2 | P value |
|------------------|------------------------|-------------|---------|--------------|-------------|---------|
|                  | PCF controls n (%)     | PCF controls n (%) |         | PCF controls n (%) | PCF controls n (%) |         |
|                  | Physician 1             | PCF controls n (%) |         | Physician 2 | PCF controls n (%) |         |
| Normal           | 12 (31.6)              | 3 (10.0)     | 0.0331  | 7 (18.4)    | 0 (0)        | 0.0131  |
| Abnormal         | 4 (10.5)               | 1 (3.3)      | 0.5716  | 26 (68.4)   | 26 (68.4)    | 0.0782  |
| Acute changes    | 24 (60.5)              | 24 (80.0)    | 0.0844  | 20 (52.6)   | 18 (60.0)    | 0.5434  |
| Acute changes, suggestive of TB | 15 (39.5) | 18 (60.0) | 0.0926 | 12 (31.6) | 15 (50.0) | 0.1232 |
| Chronic changes  | 8 (26.7)               | 7 (18.4)     | 0.5038  | 2 (5.3)     | 0 (0)        | 0.4354  |
| Total*           | 33 (86.8)              | 29 (96.7)    | 0.1561  | 26 (68.4)   | 27 (90.0)    | 0.0331  |

* Total represents the number of patients with some kind of abnormality. Each abnormality is only counted for once.

Two readers reported significantly more frequent CXR changes among culture positive PCF controls compared to culture positive SSC patients (Table 3). A similar but non-significant difference in rate of abnormal CXRs between PCF controls and SSC patients were seen in the results from the two other readers. The patients in the SSC group may be in an early stage of their disease and therefore have less pulmonary infiltrations. Whereas, the PCF controls seek help from health care authorities, which implies that they have more pronounced symptoms and perhaps their TB stage is more advanced, leading to progressive pulmonary infiltrations. As shown in Table 1, patients in the SSC group are significantly more likely to be homeless and have an abuse (cannabis) compared to the PCF controls. Thus, access to health care providers and awareness of TB symptoms may be limited in this group; therefore we would expect them to have a more progressive stage of TB when diagnosed. This is not found in our study where the SSC group had a higher median of normal CXRs (17.9%) compared to the PCF group (7.7%), highlighting that the SSC patients in this study were found at an early stage. To establish the stage of TB we would need to know about the onset of symptoms, but there has been no data available for that. 

Table 4 shows an equally, good agreement among the respiratory physicians and radiologists when evaluating chest x-rays for culture positive and negative patients. Categorizations: Normal, with acute changes and with changes specifically suggestive of active TB. 

Table 4 Overall levels of agreement between respiratory physicians and radiologists when evaluating chest x-rays for culture positive and negative patients. Categorizations: Normal, with acute changes and with changes specifically suggestive of active TB.

|                    | Respiratory physicians | Radiologists | Physician 2 | Radiologists | Physician 2 | P value |
|--------------------|------------------------|--------------|-------------|--------------|-------------|---------|
|                    | PCF controls n (%)     | PCF controls n (%) |         | PCF controls n (%) | PCF controls n (%) |         |
|                    | Physician 1             | PCF controls n (%) |         | Physician 2 | PCF controls n (%) |         |
| Normal             | 12 (31.6)              | 3 (10.0)     | 0.0331  | 7 (18.4)    | 0 (0)        | 0.0131  |
| Abnormal           | 4 (10.5)               | 1 (3.3)      | 0.5716  | 26 (68.4)   | 26 (68.4)    | 0.0782  |
| Acute changes      | 24 (60.5)              | 24 (80.0)    | 0.0844  | 20 (52.6)   | 18 (60.0)    | 0.5434  |
| Acute changes, suggestive of TB | 15 (39.5) | 18 (60.0) | 0.0926 | 12 (31.6) | 15 (50.0) | 0.1232 |
| Chronic changes    | 8 (26.7)               | 7 (18.4)     | 0.5038  | 2 (5.3)     | 0 (0)        | 0.4354  |
| Total*             | 33 (86.8)              | 29 (96.7)    | 0.1561  | 26 (68.4)   | 27 (90.0)    | 0.0331  |

* Total represents the number of patients with some kind of abnormality. Each abnormality is only counted for once.

Conflict of interest

We have no conflict of interest.

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