



## The Epidemiology of Tuberculosis in Tabriz, Iran: A Five Year Retrospective Study

Mehrdad Asghari<sup>1</sup>, Siamak Heidarzadeh<sup>2</sup>, Ziba Vaise Malekshahi<sup>3</sup>, Maryam Hemmatzadeh<sup>4</sup>, Mohammad Javad Razzaghe Karimi<sup>4</sup>, Hamideh Ashrafi<sup>5</sup>, Fatemeh Fallah<sup>6</sup>, Raheleh Sadat Sajadi Nia<sup>7\*</sup>

<sup>1</sup> Students Research Committee, Faculty of Paramedicine, Tabriz University of Medical Sciences, Tabriz, IR Iran

<sup>2</sup> Department of Pathobiology, School of Public Health, Tehran University of Medical Sciences, Tehran, IR Iran

<sup>3</sup> Department of biology, Faculty of Science, Shahed University, Tehran, IR Iran

<sup>4</sup> Department of Laboratory Sciences, Faculty of Paramedicine, Tabriz University of Medical Sciences, Tabriz, IR Iran

<sup>5</sup> Tuberculosis and Lung Disease Research Center, Tabriz University of Medical Sciences, Tabriz, IR Iran

<sup>6</sup> Department of Microbiology, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

<sup>7</sup> Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

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### ABSTRACT

**Background:** Tuberculosis is one of the most important causes of morbidity and mortality worldwide. Approximately 10-20% of tuberculosis is Extra-pulmonary tuberculosis (EPTB), which is much higher (50%) in patients suffering from immunity defects such as AIDS. EPTB diagnosis is difficult mostly because of various clinical manifestations and aggressive procedures needed for its diagnosis. The main goal of this study was to determine the prevalence of EPTB in the north west of Iran and also to investigate the different clinical characteristics of the studied population, the various clinical manifestations and organ involvement of EPTB, as well.

**Methods:** This study was carried out retrospectively using the data from Tabriz Tuberculosis and Lung Disease Research Center from 2007 through 2011. Questionnaires were designed to extract relevant information to describe characteristics of EPTB affected population and also various clinical manifestations and organ involvement of the disease among the patients.

**Results:** The study included 203 EPTB cases notified from 2007 through 2011 including, 91 (44.83%) males and 112 (55.17%) females. The mean age of the patients was  $46.55 \pm 18.3$ . The main extra pulmonary involvements of the studied population were lymphadenitis (9.35%), pleural (7.39%) and spinal (5.42%) among males and lymphadenitis (17.24%), ocular (7.88%), pleural (6.40%) and spinal (5.91%) among females, respectively.

**Conclusion:** Since EPTB diagnosis is a challenging and time sparing attempt even by the expert physicians, there is a need to perform further researches in order to identify the main clinical manifestations and organ involvement of EPTB in patients.

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\* Corresponding Author: Raheleh Sadat Sajadi Nia, MD., Shahid Beheshti University of Medical Sciences, Tehran, IR Iran. Tel: +98-9126967489, E-mail: rahelehshajadinia@yahoo.com

## Introduction

Tuberculosis is one of the most important causes of morbidity and mortality worldwide (1). Approximately 2 billion people have latent infection, 8 million are affected with active disease and 2-3 million die due to tuberculosis annually (2-4). The disease frequently involves pulmonary system however it can disseminate through hematogenous or lymphogenous circulation and thus may involve any other organ, which is then called Extra Pulmonary Tuberculosis (EPTB) (4-6).

Approximately 10-20% of tuberculosis is EPTB, that is much higher (50%) in patients suffering from immunity defects such as AIDS (7). The most common sites of EPBT involvement are reported to be lymph nodes and pleura and mean age of involvement is under 35 years old (8, 9). EPTB incidence is higher in developing countries, however number of patients with EPTB has increased in developed countries during the last two decades as well which can be as a result of increased mobility of people, resistance against antibiotics and growing number of patients with suppressed immune system (10). EPTB diagnosis is difficult mostly because of various clinical manifestations and aggressive procedures needed for its diagnosis (11).

The main goal of this study was to determine the prevalence of EPTB in the north west of Iran and also to investigate the different clinical characteristics of the studied population, the various clinical manifestations and organ involvement of EPTB, as well.

## Methods

This study was carried out retrospectively using the data from Tabriz Tuberculosis and Lung Disease Research Center obtained during 2007 through 2011.

From the questionnaires which were designed to extract relevant information to describe characteristics of EPTB affected population, personal data including age, sex, weight, place of residence, nationality, date of EPTB diagnosis, diagnostic criteria, TB type (i.e. “new case”, where a first time TB diagnosis is made and reported, or “re- treated cases”), involved organs, rate of End Stage Renal Disease (ESRD) due to EPTB, family history of TB, history of BCG vaccination and referral center were collected. We followed standard methods for EPTB diagnosis, which has been designed to identify tuberculosis such as: staining (acid-fast) of samples obtained from skin, bone marrow, Cerebrospinal fluid (CSF), sputum with Ziehl-Neelsen method and culturing in solid egg medium (Lowenstein-Jensen), measuring levels of Niacin-Nitrate reduction, semiquantitative catalase, urease, arylsulfatase, tellurite reduction in the specimens, and evaluation of tuberculin test. Specimen processing for the recovery of acid-fast bacilli involves a number of complex procedures, each of which must be carried out with precision. Specimens from sterile site can be inoculated directly to media (small volume), other specimens required decontamination and concentration. All incomplete questionnaires were rechecked and full filled. Data analysis was carried out using SPSS software (version 16; SPSS Inc, Chicago, IL). Descriptive statistics

(frequencies and means) were used to describe the demographic characteristics.

**Ethics**

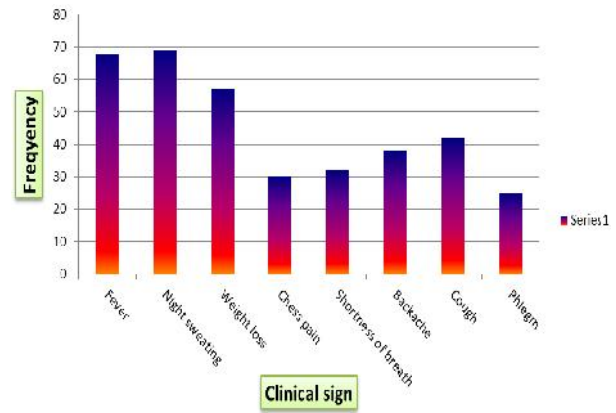
The protocol for this study was reviewed and granted by the Research Deputy of Tabriz University of Medical Sciences and was found to be public health surveillance and not a human subject research.

**Results**

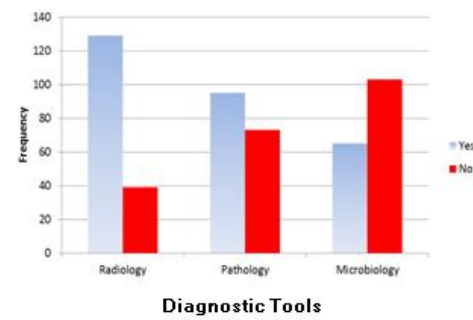
The study included 203 EPTB cases notified from 2007 through 2011 including, 91 (44.83%) males and 112 (55.17%) females.

The most common EPTB manifestations were night sweating (33.99%), chronic fever lasting more than 2 weeks (33.50%) and weight loss (28.80%), respectively (Figure 1) (Table 4, 5). The mean age of the patients was  $46.55 \pm 18.3$  ( $46.38 \pm 18.79$  among males and  $46.68 \pm 17.79$  among females) (Table 1). The main extra pulmonary involvements of the studied population were lymphadenitis (9.35%), pleural (7.39%) and spinal (5.42%) among males and lymphadenitis (17.24%), ocular (7.88%), pleural (6.40%) and spinal (5.91%) among females, respectively (Table 2, 3). Genital TB, TB peritonitis and pericarditis were more dominant among females, however epididymal and also bladder TB were found only in males.

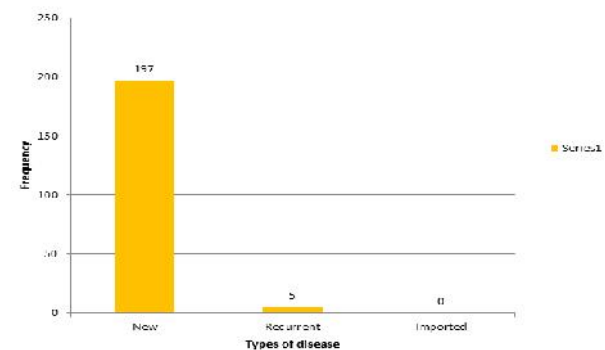
It should be noted that the most useful method for EPTB diagnosis in this study was imaging, by which 129 cases were identified (Figure 2), and the most prevalent type of TB among the studied group were new cases (Figure 3).



**Figure 1.** EPTB manifestations among the patients referred to Tabriz Tuberculosis and Lung Disease Research Center from 2007 through 2011



**Figure 2.** Diagnostic methods for EPTB in patients referred to Tabriz Tuberculosis and Lung Disease Research Center from 2007 through 2011



**Figure 3.** Types of TB in patients referred to Tabriz Tuberculosis and Lung Disease Research Center from 2007 through 2011

**Table 1.** Age and sex distribution of the patients with EPTB referred to Tabriz Tuberculosis and Lung Disease Research Center from 2007 through 2011

Age level		0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	Total	
Gender	Male	Count	1	4	20	17	27	17	14	8	4	91
		%	0.9	3.6	17.9	15.2	24.1	15.2	12.5	7.1	3.6	100.0
	Female	Count	4	6	11	9	23	16	14	7	1	112
		%	4.4	6.6	12.1	9.9	25.3	17.6	15.4	7.7	1.1	100.0
Total	Count	5	10	31	26	50	33	28	15	5	203	
	%	2.5	4.9	15.3	12.8	24.6	16.3	13.8	7.4	2.5	100.0	

**Table 2.** Clinical characteristics and different organ involvements of the patients with EPTB referred to Tabriz Tuberculosis and Lung Disease Research Center from 2007 through 2011

	Miliary tuberculosis	Bladder tuberculosis	Abdominal tuberculosis	Renal tuberculosis	Bone tuberculosis	Gastrointestinal tuberculosis	Thyroid tuberculosis	Meninges tuberculosis	Dermal tuberculosis	Lymphadenitis
Radiology %	100	66.7	0	25	70	100	0	100	90.9	63.3
Pathology %	0	0	50	25	50	100	0	0	100	83.7
Microbiology %	50	100	50	100	40	100	100	100	36.4	26.5
PPD	0	26±12.72	9.5±0.7	16.75±13.14	14±6.14	0	0	0	15.28±10.41	19.29±2.28
ESR	45	6.5±2.12	40.5±14.84	33.25±29.21	62.25±32.27	69±53.74	0	0	22.22±30.57	22.72±3.54
Family history	1	0	1	2	1	0	0	0	3	7
Vaccine history	0	1	0	0	2	1	0	0	3	8
AIDS	0	0	0	0	0	0	0	0	0	1
Cancer	0	1	0	0	0	0	0	0	0	1
Diabetes	0	0	0	0	0	0	0	0	0	2
New disease	1	4	3	5	10	3	1	1	12	52
Recurrent	1	0	0	0	1	0	0	0	1	1

## Discussion

Extra-pulmonary tuberculosis is caused by the spread of TB bacilli from a pulmonary focus (12). Spreading is carried out mainly through hematogenous dissemination or lymphogenous spread from a primary, usually a pulmonary, focus. This hematogenous spread may happen years before the onset of progressive tuberculosis (6, 13).

Although some damages caused by tuberculosis and extra-pulmonary tuberculosis heal up in most patients, but granuloma containing TB bacilli usually stay alive for decades (12). The organism gains access to the blood stream via the lymphohematogenous route and may then

affect any organ (6, 14). The next failures related to damages could reactivate the extra-pulmonary disease once again (12). Since there is no particular sign of infection, therefore reactivation of the disease may not be recognized clinically (12).

There are many reports of unidentified extra-pulmonary tuberculosis that could be distinguished only by necrosis (12). Diagnosis is often difficult, but successful outcomes are possible when made at an early stage (15).

In many different studies the role of various factors on the incidence of pulmonary and extra-pulmonary tuberculosis has been surveyed (16).

**Table 3.** Clinical characteristics and different organ involvements of the patients with EPTB referred to Tabriz Tuberculosis and Lung Disease Research Center from 2007 through 2011

	Pleural tuberculosis	Ocular tuberculosis	Spinal tuberculosis	Genital tuberculosis	Pericardial tuberculosis	Liver tuberculosis	Epididymal tuberculosis	Peritoneum tuberculosis
<b>Radiology %</b>	100	93.8	95	55.6	100	100	50	67.7
<b>Pathology %</b>	40	6.3	50	44.4	50	50	50	50
<b>Microbiology %</b>	40	25	15	66.7	25	50	50	50
<b>PPD</b>	15.13±7.08	29.92±14.18	23.15±3.67	24.44±13.42	26.25±36.83	0	13.75±11.05	16±5.35
<b>ESR</b>	31.95±26.8	28.05±31	42.88±33.27	31.30	14.33±7.02	-	23±29	32.33±14.64
<b>Family history</b>	3	2	1	2	0	0	2	1
<b>Vaccine history</b>	1	0	2	1	0	0	1	0
<b>AIDS</b>	0	0	0	0	0	0	0	0
<b>Cancer</b>	0	0	0	0	0	0	0	0
<b>Diabetes</b>	2	0	1	0	1	0	1	1
<b>New disease</b>	26	27	23	11	5	2	5	6
<b>Recurrent</b>	2	0	0	0	0	0	0	0

**Table 4.** Clinical manifestations of EPTB in patients referred to Tabriz Tuberculosis and Lung Disease Research Center from 2007 through 2011

	Miliary tuberculosis	Bladder tuberculosis	Abdominal tuberculosis	Renal tuberculosis	Bone tuberculosis	Gastrointestinal tuberculosis	Thyroid tuberculosis	Meninges tuberculosis	Dermal tuberculosis	Lymphadenitis
<b>Age mean</b>	63±24	62±12.19	54.33±18.50	41.8±18.47	39.36±30.62	31.33±14.74	29±0	59±0	41.15±15.45	43.61±18.57
<b>Frequency</b>	2	4	3	5	11	3	1	1	13	54
<b>G</b>										
<b>Male</b>	2	4	1	2	7	2	0	1	5	19
<b>Female</b>	0	0	2	3	4	1	1	0	8	35
<b>Fever</b>	2	2	2	0	2	0	0	0	2	20
<b>Weight loss</b>	1	1	3	2	4	1	0	0	1	15
<b>Sweating</b>	2	1	3	1	3	0	0	0	3	18
<b>Chest pain</b>	0	0	0	0	2	1	0	0	0	7
<b>Shortness of breath</b>	0	0	0	1	2	0	0	0	0	8
<b>Backache</b>	0	0	1	1	3	1	0	0	3	5
<b>Cough (more than 2 week)</b>	1	0	1	2	1	0	0	0	1	12
<b>Phlegm (mucus)</b>	0	0	0	1	0	0	0	0	2	9

G = Gender

**Table 5.** Clinical manifestations of EPTB in patients referred to Tabriz Tuberculosis and Lung Disease Research Center from 2007 through 2011

	Pleural tuberculosis	Ocular tuberculosis	Spinal tuberculosis	Genital tuberculosis	Pericardial tuberculosis	Liver tuberculosis	Epididymal tuberculosis	Peritoneum tuberculosis
<b>Age mean</b>	48.5±19.4	53.11±11.9	54.6±17.4	35.6±5.6	60.4±14.4	46±5.6	50.4±17.2	52.6±9.6
<b>Frequency</b>	28	27	23	11	5	2	5	6
<b>Gender</b>								
<b>Male</b>	15	10	11	2	4	0	5	1
<b>Female</b>	13	16	12	9	1	2	0	5
<b>Fever</b>	22	1	10	2	2	0	0	2
<b>Weight loss</b>	12	1	7	2	3	1	0	3
<b>Sweating</b>	16	4	12	2	2	0	0	3
<b>Chest pain</b>	12	0	2	2	2	1	0	3
<b>Shortness of breath</b>	13	0	6	1	3	0	0	0
<b>Backache</b>	9	1	11	2	2	0	0	0
<b>Cough (more than 2 week)</b>	17	1	3	2	1	0	0	2
<b>Phlegm (mucus)</b>	11	1	1	0	1	0	0	0

Extra-pulmonary tuberculosis after observance of HIV infection has become more common (17). It has been investigated among 50% of the patients affected simultaneously with tuberculosis and AIDS (17, 18) and therefore extra-pulmonary tuberculosis most probably is an index of immune deficiency (19). Black men and women have a higher rate of EPTB incidence (19). Furthermore, extra-pulmonary tuberculosis is most common among young patients with active tuberculosis and usually diagnosed as a cancer inadvertently (20).

More than 3.8 million cases of extra-pulmonary tuberculosis were reported to WHO in 2001, 90% of them came from developing countries (21, 22). Among patients with AIDS up to two thirds of infection was either in combined involvement of lungs and extra-pulmonary or extra-pulmonary tuberculosis alone (23). Among 26283 cases with tuberculosis reported to the Centers for Disease Control and Prevention (CDC) in the United States until 1991, 18% of them had extra-pulmonary tuberculosis but following AIDS epidemic, the cases of extra-pulmonary tuberculosis increased and thus 30-60% of patients affected with AIDS and tuberculosis had extra-pulmonary tuberculosis (24).

Annual average incidence rate of tuberculosis in Iran is 17.9 in 100000 patients. Tuberculosis incidence is higher in Balochistan, Khorasan, Golestan Gilan, Kurdistan, Western Azerbaijan, Khuzestan, and southern coasts of Iran (16).

During 2001-2006, pulmonary tuberculosis and extra-pulmonary tuberculosis has had a decreased rate of incidence especially in Birjand

(-18.6%) and Eastern Azerbaijan (-10.2%) cities whereas from 2006 through 2008, it has had an upward move particularly in Sabzevar (+24.9%). Throughout this period 56629 were affected with tuberculosis and 23442 of patients were suffering from extra-pulmonary tuberculosis (25).

In a study performed by Iran Pasteur Institute in 1982, of the patients suffering from tuberculosis, 22.5% were diagnosed with EPTB and the most common organs involved were reported to be lymph nodes (39%) joints and bones (18%), meninges (16%), urinary tract (12%), endometrial tissue (5%). These findings were repeated in another study conducted by the same institute in 1997 (16).

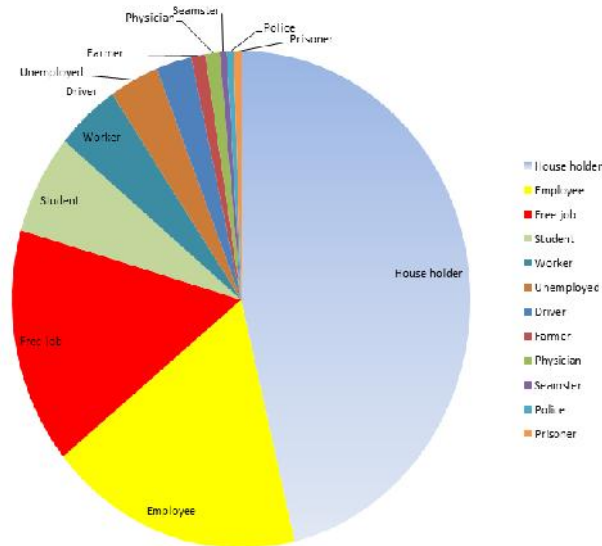
In our study it was shown that the prevalence of EPTB among women (which may be due to having contact with TB affected animals in the farms) is higher than men which is in contrast with the researches by Tam *et al.* in Hong Kong and Lado Lado *et al.* in Santiago (26, 27).

In our study, EPTB incidence was found more commonly (38.9%) between 25-40 years of age, however it was rarely reported in over 65 years old individuals (13%). The most common sites of EPTB involvement were lymph nodes (26.60%), pleural (13.79%), ocular (13.30%) and spinal (10.0%) which is similar to other studies performed in Germany and Netherlands, however in a research by Demiralay in Turkey, the most common sites of EPTB involvement were pleural (52.8%) and lymph nodes, respectively (26.0%) (28).



## Conclusion

Since EPTB diagnosis is a challenging and time sparing attempt even by the expert physicians, there is a need to perform further researches in order to identify the main clinical manifestations and organ involvement of EPTB in patients.



**Figure 4.** Occupation of patients with EPTB referred to Tabriz Tuberculosis and Lung Disease Research Center from 2007 through 2011

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