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TANAFFOS

A Five-Year Epidemiological Study of Extra-Pulmonary Tuberculosis and Its Related Risk Factors in Iran

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Background: Tuberculosis is the most common worldwide cause of death from microbial diseases. Extra-pulmonary tuberculosis accounts for 20% to 25% of all cases. In this study, we used generalized estimation equations to investigate the trend of changes in extra-pulmonary tuberculosis incidence.

Materials and Methods: The recorded data of all patients with extra-pulmonary tuberculosis from 2015 to 2019 in Iran's National Tuberculosis Registration Center were included. The trend of standardized incidence changes in provinces of Iran was calculated and reported linearly. Also, we identified the risk factors related to the extra-pulmonary tuberculosis incidence in five consecutive years using generalized estimating equations.

Results: We studied the data of 12,537 patients with extra-pulmonary tuberculosis, of whom 50.3% were female. The mean age of the subjects was 43.61±19.88 years. Around 15.4% of all patients had a history of contact with a tuberculosis patient, 43% had a history of hospital stay, and 2.6% had a human immunodeficiency virus infection. Regarding disease types, 25% were lymphatic, 22% were pleural, and 14% were bone. Golestan province had the highest (average of 28.50 ± 8.65 cases), and Fars province had the lowest (average of 3.06 ± 0.75 cases) standardized incidences in these five years. Also, time trend ($P < 0.001$), employment rate ($P = 0.037$), and average annual rural income ($P = 0.001$) had a significant effect on reducing extra-pulmonary tuberculosis incidence.

Conclusion: Extra-pulmonary tuberculosis has a decreasing trend in Iran. Still, Golestan, Sistan and Baluchestan, Hormozgan, and Khuzestan provinces have a higher incidence rate compared to the other provinces.

Key words: Extra-pulmonary tuberculosis; Epidemiology; Longitudinal studies; Generalized estimating equations model; Iran

INTRODUCTION

Tuberculosis is a common infectious disease, and it is fatal in many cases. It is caused by different species of Mycobacteria, commonly known as *Mycobacterium tuberculosis* (1). In general, a relatively small proportion (5%-15%) of people infected with *M. tuberculosis* develops tuberculosis disease during their lifetime. However, people living with human immunodeficiency virus (HIV), as well as those who have risk factors, such as malnutrition, diabetes, smoking, and alcohol consumption, are much more likely to develop tuberculosis (2).

As the most common type of tuberculosis, pulmonary tuberculosis is epidemiologically important due to its highly contagious nature (3). According to the World Health Organization (WHO) classification criteria, extra-

pulmonary tuberculosis is defined as infection by *M. tuberculosis* that affects tissues and organs outside the pulmonary parenchyma. It accounts for 20% to 25% of all tuberculosis cases worldwide (4). Compared to patients with pulmonary tuberculosis, the percentage of extra-pulmonary tuberculosis cases varies in different countries and depends on its related diseases, plus geographical, social, ethnic, and economic parameters.

In general, extra-pulmonary tuberculosis affects people with diabetes and HIV, as well as children (younger than 15 years old) and older adults (older than 65 years old) (5,6). The most common sites of extra-pulmonary TB are the lymph nodes, pleura, bones and joints, the genitourinary system, and the central nervous system (7). Tuberculosis ranks tenth among the global diseases. About two billion cases, or one-third of the world's population, are infected with this disease, and 1.5 million people die from this disease per year (8).

Regarding tuberculosis control priorities, WHO has recommended a new strategy: "transitioning from stopping TB to ending TB." Based on this strategy, the incidence rate of TB must be decreased up to 90% by 2035 (9). According to the WHO report, there were 10.4 million new cases and 1.67 million deaths from tuberculosis in 2017 (10). In 2015, more than 87% of tuberculosis cases were from 30 countries, and 61% of them were in Asia (11). The disease incidence is more noticeable in developing, low-income, and middle-income countries. More than 95% of tuberculosis mortality cases occur in these countries. It is one of the three main causes of death in 15 to 44 years old women (12).

The prevalence of tuberculosis varies at different ages. In countries where its incidence has dropped dramatically (such as the United States), tuberculosis is mainly a disease of the elderly and those with an at-risk immune system (13). According to Iran's Ministry of Health, 14.4 per 100,000 people in Iran are diagnosed with tuberculosis every year (14). The incidence of extra-pulmonary tuberculosis in Iran decreased from 5.3% per 100,000 people in 2001 (3,382 cases) to 3.6% in 2007 (2,604 cases) (15).

Considering that tuberculosis is an important disease with a high prevalence in Iran (16), it is necessary to determine its epidemiological status according to the specific geographical conditions in different regions of the country (17). Therefore, we did this longitudinal study to investigate its related risk factors, including demographic, economic, and underlying disease factors (age, sex, marital status, nationality, employment rate, history of hospital stay with tuberculosis, HIV, etc.) over five years.

Regarding longitudinal data, correlated observations are obtained by repeating measurements in each province. Thus, the usual analysis without using this correlation is not fit for such data and we need an analytical method (18). One of the possible methods is the marginal model, an extension of the generalized linear model for longitudinal data. A parameter of estimation in marginal models is the generalized estimating method that Liang and Zeger first introduced in 1986. The correlation between observations within a province was modeled by assuming a correlation structure or hypothetical (practical) correlation matrix. A single correlation structure is often accepted in all provinces. We will have better results if this structure is identified more accurately (19). This structure shows the dependencies between observations during a period. This study investigated the epidemiological aspects of extra-pulmonary tuberculosis and its related risk factors using the generalized estimating equations (GEE) model in Iran for five years.

MATERIALS AND METHODS

Study design

In this descriptive-analytical, retrospective study, we examined the recorded data of all the patients with extra-pulmonary tuberculosis provided by the Iran National Tuberculosis Registration Center database. All the patients were diagnosed from April 2015 to December 2019.

Diagnosis of extra-pulmonary tuberculosis had been based on bacteriological evidence (at least one positive culture sample) and pathological evidence (histology changes in favor of tuberculosis) (20).

Data collection

The required information, including age, sex, diagnosis date, reporting source, tuberculosis type, nationality, location, hospital stay history, history of contact with tuberculosis patients, and co-infection with HIV, was gathered in an Excel spreadsheet. The data were retrieved with the formal permission of our university. Also, we used the data of the Statistics Center of Iran for any other required information.

Data analysis

We used descriptive statistics to describe the data. The extra-pulmonary tuberculosis incidence was calculated using the estimated population of the provinces during the studied years. Most diseases affect the age groups disproportionately. To eliminate the effect of age, age-specific incidence rates were calculated per 100,000 people. The standardized age incidence rate was calculated by direct standardization method using the global standard population. Hence, we first calculated the age-specific incidence rate for different age groups. Then, these rates were multiplied by the relative frequency of the standard population in the same age groups. Finally, their sum was reported as the standardized age incidence rate.

To indicate the relationship between social and economic factors (sex ratio, employment rate, population density, etc.) and extra-pulmonary tuberculosis incidence, we used a generalized linear model (GEE).

During the studied years, ArcGIS 10.4 software was used to draw the spatial distribution map. Because the data obtained from the extra-pulmonary tuberculosis examinations were measured for five consecutive years, it causes correlated responses. Therefore, their analysis requires a statistical method that can take into account the correlation between responses for each province. Therefore, we used GEE to determine the effect of each covariate variable on extra-pulmonary tuberculosis prevalence (21, 22). In this study, the correlation structure was Auto regressive (1). In this structure, it is assumed that as the time intervals between measurements increase, their correlation decreases. We did the data analysis with the statistical package for social sciences (SPSS) software version 24 and the confidence level was 95%.

RESULTS

In Iran's National Tuberculosis Registration System, 12,537 cases of extra-pulmonary tuberculosis had been registered from April 2015 to December 2019. This included 6,304 (50.3%) women and 6,233 (49.7%) men. Regarding marital status, 23.2% were single, 68% were married, 2.1% were divorced, and 6.6% were widowed. Their mean age was 43.61 ± 19.88 years old. The 25-44 years old age group had the highest frequency of patients (35.6%). In addition, 18.8% of the patients were younger than 25 years old, 18.8% were 45-64 years old, and 17.3% were older than 64 years old. Also, 86.4% of the patients were Iranian, and 13.1% were Afghan. About 75% of the patients reported living in urban areas.

Totally, 15.4% had a history of contact with tuberculosis patients, 43% had a history of hospital stay, and 2.6% had HIV infection. Lymph node (24.9%), pleura (21.9%), and bone (13.6%) tuberculosis were the most common types of extra-pulmonary tuberculosis. Also, pleural tuberculosis was the most common place in men with a prevalence of 29.8% and in women with lymph node tuberculosis with a prevalence of 29.9%.

The average standardized incidence rates in 2015, 2016, 2017, 2018, and 2019, were 12.14 (±8.42), 10.26 (± 6.43), 8.72 (± 6.39), 7.79 (± 6.39), and 5.55 (±4.05), respectively. Golestan province had the highest number of extra-pulmonary cases in these five years (average of 28.50 ±

8.65). Fars province had the lowest number of standardized incidence rates (average of 3.06 ± 0.75; Table 1).

GIS is an important epidemiological tool that can be useful in identifying geographical areas and population groups with a high risk of disease (23). Using the prepared GIS map, we identified areas that need intensive care in Iran and marked them with dark colors (Figure 1). It was prepared based on the average standardized incidence rate during the studied five years. Figure 2 also shows the decreasing trend of extra-pulmonary tuberculosis in the whole country during the studied years. We investigated the relationship between the incidence of extra-pulmonary tuberculosis and time trend covariant variables, sex ratio, marital status, nationality, age, body mass index, HIV, history of hospital stays because of tuberculosis, contact history with tuberculosis-infected patients, population density, average annual income, and employment rate (Table 2).

The results of generalized estimating equations indicated that the time trend has a significant effect on reducing extra-pulmonary tuberculosis prevalence ($P < 0.001$). Thus, as each year passes, the average incidence decreases by 1.53 units. The employment rate also has a significant effect on reducing extra-pulmonary tuberculosis incidence (P=0.037). When the employment rate increased, the average extra-pulmonary tuberculosis incidence decreased by 1.05 units. Also, the average annual rural income had a significant effect on reducing extra-pulmonary tuberculosis incidence (P = 0.001). In areas with a higher rural income, there is less extra-pulmonary tuberculosis incidence, and increasing the annual rural income by 4.13 units reduces the average standardized incidence.

Other variables, including marital status, which increased the incidence rate by 0.04, were not statistically significant (p=0.059). Sex ratio (P=0.418), location (P=0.305), nationality (p=0.419), HIV (P=0.112), history of contact with a tuberculosis-infected patient (P=0.732), population density (P=0.143), average of urban income (P=0.182), and unemployment rate (P=0.279) increased the disease incidence rate, but not significantly. Finally, age (P=0.607), body mass index (P=0.709), and hospital stay history because of tuberculosis (P=0.549) had no significant associations with reduced extra-pulmonary tuberculosis incidence.

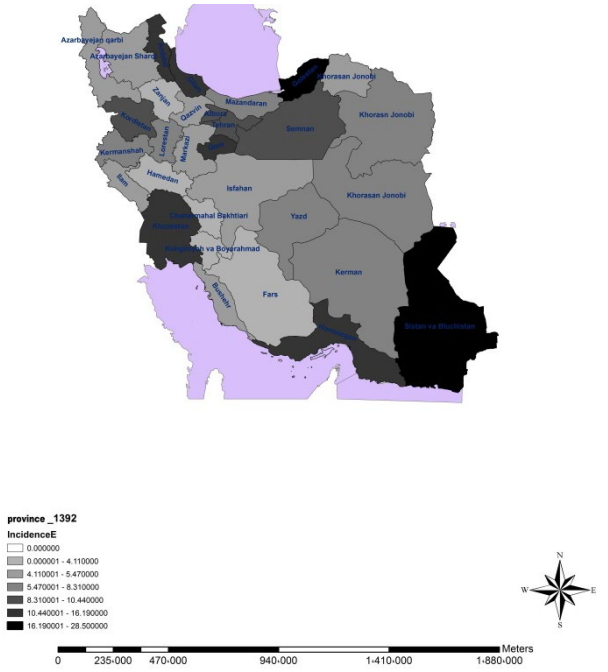


Figure 1. Location of the study area, Provinces of Iran .The map was created using ArcGIS 10.5

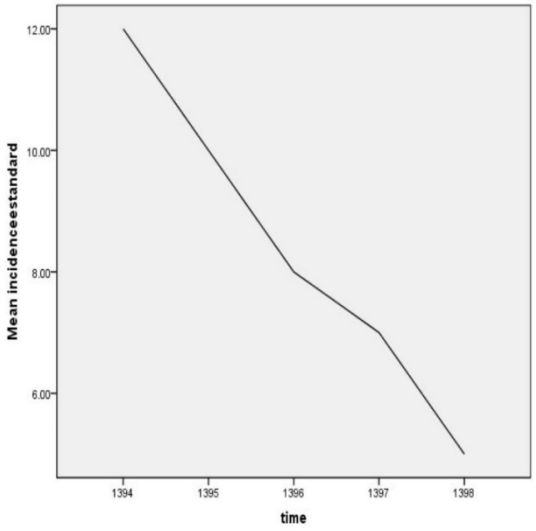


Figure 2. The time trend of extra-pulmonary tuberculosis in the whole country from April 2015 to December 2019

Table 1. Frequency distribution of the most common type of extra-pulmonary tuberculosis, average percentage of changes and trend chart of changes by provinces during April 2015 to December 2019

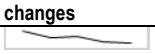
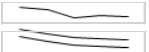
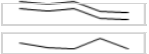
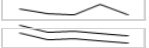
Provinces	Common types of extra-pulmonary	Frequency (%)	Mean of standard incidence (standard deviation)	Average coefficient of variation	trend chart of changes
Ardebil	Lymph node	68 (26%)	12.11(3.01)	0.25	
Mazandaran	pleura	147 (31%)	7.64(2.35)	0.31	
Bushehr	Lymph node	27 (31%)	5(1.72)	0.34	
Chaharmahal Bakhtiari	Lymph node	16 (40%)	3.13(1.73)	0.55	
East Azarbaijan	Lymph node	89 (26%)	5.16(2.97)	0.58	
Isfahan	Lymph node	125(25%)	5.25(1.49)	0.28	
Fars	Lymph node	70(26%)	3.06(0.75)	0.25	
Gilan	pleura	188(34%)	13.12(2.49)	0.19	
Golestan	pleura	195(25%)	28.50(8.65)	0.30	
Khorasan Razavi	pleura	332(28%)	10.28(2.92)	0.28	
Hamedan	Lymph node	30(23%)	4.11(1.59)	0.39	
Hormozgan	Lymph node	147(37%)	16.24(4.31)	0.27	
Ilam	pleura - Lymph node	15(25%)	5.49(1.99)	0.36	
Alborz	Lymph node	93(23%)	9.48(5.13)	0.54	
Tehran	Lymph node	497(20%)	10.44(1.92)	0.18	
Kerman	Lymph node	101(30%)	6.73(2.10)	0.31	
Kermanshah	Lymph node	68(25%)	7.87(3.26)	0.41	
North Khorasan	pleura	16(23%)	4.11(2.33)	0.57	
South Khorasan	Lymph node	43(36%)	8.31(3.32)	0.45	
Khuzestan	pleura	363(34%)	16(3.81)	0.24	
Kohgiloyeh Boyerahmad	Lymph node	26(54%)	3.94(1.58)	0.40	
Kurdistan	pleura	60(23%)	8.83(2.89)	0.33	
Lorestan	Lymph node	63(27%)	8.19(3.03)	0.37	
Markazi	pleura	30(22%)	4.91(2.31)	0.47	
Ghazvin	pleura	26(22%)	4.82(2.14)	0.44	
Semnan	Lymph node	30(25%)	8.81(3.53)	0.40	
Sistan and Baluchestan	Lymph node	347(33%)	26.64(7.04)	0.26	
West Azarbaijan	Lymph node	57(21%)	5.14(2.11)	0.41	
Yazd	Lymph node	33(22%)	7.35(3.02)	0.41	
Zanjan	bone	17(20%)	3.86(1.40)	0.36	
Qom	Lymph node	61(23%)	12.83(4.10)	0.32	

Table 2. Results from the estimating generalized equations method, to investigate the effect of covariant variables on the standardized incidence rate

Variables	Estimation	SE	Test statistics	P-value
Time	-1.53	0.1792	73.488	0.001***<
Sex Ratio	0.005	0.0059	0.656	0.418
Marital status	0.040	0.0213	3.570	0.059
Location	0.059	0.0575	1.052	0.305
Nationality	0.021	0.0260	0.653	0.419
Age	-0.030	0.0589	0.265	0.607
BMI	-0.032	0.0858	0.140	0.709
AIDS	0.065	0.0407	2.519	0.112
Hospitalization history	-0.006	0.0103	0.360	0.549
History of contact with a TB infected patient	0.007	0.0195	0.118	0.732
Population density	0.010	0.0067	2.148	0.143
Average urban income	1.18	8.85	1.783	0.182
Average annual rural income	-4.13	1.22	11.493	0.001**
Unemployment rate	4.06	3.75	1.175	0.279
Employment rate	-1.05	5.03	4.369	0.037*

DISCUSSION

To our knowledge, using the GEE model, the first nationwide investigation on the trend of changes and risk factors of extra-pulmonary tuberculosis in Iran. Totally, the data of 12,537 patients with extra-pulmonary tuberculosis were studied over a five-year period. The average annual standard incidence in Iran was 8.88 per 100,000 people. Our results showed that extra-pulmonary tuberculosis incidence decreased in all provinces during the studied years by 54% on average. Golestan, Sistan and Baluchestan, Hormozgan, and Khuzestan provinces had the highest average standard incidence with 28.50, 26.64, 16.24, and 16 cases, respectively. Fars and Chaharmahal and Bakhtiari provinces had the lowest average standard incidence with 3.06 and 3.13 cases, respectively.

In a study on extra-pulmonary tuberculosis in China from 2008-2017, Yu et al. concluded that the proportion of extra-pulmonary tuberculosis cases in China has increased from 29.8% to 31.4% [24]. In another study, Holden et al. observed no changes in Denmark's average extra-pulmonary tuberculosis incidence from 2004-2009 (1.17-1.23 per 100,000 people) (25). In Hamedan province, Iran during 2005-2011, Saatchi et al. found an average incidence of 2.1 per 100,000 people (1.8-2.4 per 100,000) (26). In Urmia, Iran, 2004-2007, Gholami and Moosavi found an average annual incidence of 4.1 (3.76-4.44 per 100,000 people) (15). In Gorgan province, Iran during 2001-2004, Khodabakhshi et al. reported a prevalence of 9.9 to 13.7 per 100,000 people for extra-pulmonary tuberculosis, showing an increase in the studied years (27). Also, in Zahedan province, Iran, Metanat et al. reported an average incidence of 17.5 per 100,000 people in a five-year period (28). The highest incidence in their study was 19.4 per 100,000 people in 1998.

In this study, 50.3% of the patients were women. Men and women had an almost equal chance of developing extra-pulmonary tuberculosis disease. Yu et al. reported that women were more likely to develop extra-pulmonary tuberculosis than pulmonary tuberculosis (39.7% vs. 29.9%, OR = 1.37) (24). In the study by Holden et al., 40.3% of the patients were Danish women, of whom 50.9% were women who had immigrated to Denmark (25). In a study in Malaysia during 2006-2008, Khan et al. found that the incidence of this disease is 1.31 times higher in women (29). In the study by Saatchi et al., 54% of the patients were women (26). Jamshidi et al. (30) in Ilam province, Iran, reported that the percentage of women was two times higher than men. Metanat et al. (28) reported that in Zahedan province, this was 1.5 times higher in women. However, in Gholami et al. in Urmia and Yazdani et al. in Mazandaran province, announced that men were more infected than women (15, 31).

The mean age in our study was 43.61 years old. The highest frequency of patients was in the 25 to 44 years old age group. In the study by Pang et al. (24), the age group younger than 25 years old was more prone to extra-pulmonary tuberculosis than pulmonary tuberculosis (OR=1.72), and the risk of extra-pulmonary tuberculosis decreased with increasing age (OR=1.5, age group 25-44 versus 45-64 years old). In the study by Holden et al. (25), the mean age was 35 years. Kim et al. (32) examined extra-pulmonary tuberculosis prevalence in patients with pulmonary tuberculosis in Korea during 2004-2006 and found that the mean age of the patients was 45 years old. In the studies by Saatchi et al. (26) and Gholami and Moosavi (15), the mean age was 43.6 and 40.3 years, respectively. Still, unlike most studies, Mohammadi Azni et al. (33) in Damghan, Iran, reported that the highest frequency of patients was older than 70 years. In a case-control study in Nepal (34), young age and female gender were identified as two risk factors for extra-pulmonary tuberculosis.

In our study, the most commonly infected body parts were lymph nodes (25%), pleura (22%), and bones (14%). Yu et al. reported that the highest increase in frequency during the studied years was related to pleural tuberculosis (17.3% to 35.7%), and the largest decrease in lymphatic tuberculosis was from 8.1% to 3.2% (24). In the study by Holden et al., the most commonly infected body parts were lymph nodes (55.4%) and pleura (13.4%) [25].

Saatchi et al. revealed that the most common types of extra-pulmonary tuberculosis were lymphatic (39.1%), pleural (13.5%), and skin (10%) (26).

In our study, 15.4% of patients had a history of contact with tuberculosis-infected patients, 43% had a history of hospital stay, and 2.6% of patients had HIV infection. In many studies, the association of HIV with extra-pulmonary tuberculosis has been confirmed (15, 35, 36).

The incidence of tuberculosis in Golestan province is almost three times higher than the national average. There can be significant differences in the distribution of tuberculosis incidence in Iran. The high incidence in the eastern regions can be because of the frontiers with neighboring countries and migration from those countries to these provinces of Iran. In a previous study (17), the Sistani and Baluch ethnic groups suffered from tuberculosis disease more than any other Iranian ethnic group living in the Golestan province. In Sistan and Baluchestan province, the incidence is very high due to its proximity to Afghanistan and Pakistan (they are among the 22 most infected countries in the world). On the other hand, according to studies (37), the incidence of this disease is higher in places with windy weather and hot and dry climates. Using GIS to predict tuberculosis incidence in Khuzestan province, it was shown that the risk of tuberculosis is higher in very hot climates (38). Also, 35.6% of patients in the whole country are in the 25-44 years old age group. Also, the average age of patients in the four provinces that have a high incidence is lower than in most provinces (i.e., 40.82 ± 18.59 years old in Golestan, 37.25 ± 22.84 years old in Sistan and Baluchestan, 38.76 ± 17.57 years old in Khuzestan, and 39.70 ± 17.43 in Hormozgan). Since these age groups are economically active in society, their sickness can lead to a lot of financial losses and reduce the income of these provinces. The multivariate analysis of our study showed that the employment rate is significantly associated with the incidence of extra-pulmonary tuberculosis. On the other hand, rural income has a significant relationship with the incidence of extra-pulmonary tuberculosis as well. Because in the Golestan, Sistan and Baluchestan, Khuzestan, and Hormozgan provinces, 49.5%, 42.5%, 21.5%, and 31% of patients, respectively, are from rural areas, and most patients are young, it seems that better economic and social situations in cities compared to villages might be the reason for this significant difference.

CONCLUSION

Assessing the disease process and its changes over time can be effective for control, prevention, and treatment strategies. Besides examining the epidemiological characteristics of patients with extra-pulmonary tuberculosis, we investigated the trend of changes in its incidence and its related risk factors in Iran. Our data showed that the most common types of extra-pulmonary tuberculosis are related to lymph nodes, pleura, and bone and the 25-44 years old age group was at the highest risk. The prevalence of extra-pulmonary tuberculosis decreased in all provinces of Iran in the studied five years. However, Golestan, Sistan and Baluchestan, Hormozgan, and Khuzestan provinces still have a higher-than-average incidence rate compared to other provinces. Also, we found that the decrease in extra-pulmonary tuberculosis incidence is related to time trends, employment rate, and average rural income.

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