Original Article

Prevalence of Pulmonary Tuberculosis, Failure of Treatment, and its Related Factors in Kashan During 2004-2017

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Abstract

Background: *Mycobacterium tuberculosis* affects the lungs in 85% of all cases and the remaining 15% through extra pulmonary affecting other parts of the body such as lymph nodes, pleura, and the genitourinary system. This study aimed to investigate extra-pulmonary tuberculosis (TB) associated factors, failure of treatment, and trends between 2004-2017 in Kashan, Iran.

Materials and Methods: This study was conducted during 2004-2017 on newly registered extrapulmonary tuberculosis patients referred to TB Referral Center in Isfahan province, Kashan city, Iran. Information (demographic characteristics, related factors of the disease, and treatment status) of 197 extrapulmonary tuberculosis (EPTB) patients was extracted from Medical case records.

Results: In total, 527 cases of Tuberculosis were reported, of which, 159 (30.17%) were confirmed extrapulmonary TB. Eighty-five (53.5%) and 74 (46.5%) were male and female, respectively. Also, 74 (46.5%), and 84 (53.5%) of EPTB were from Iran, and Afghanistan immigrants, respectively. The average age of patients was 41.9±2.18. Among underlying diseases in extrapulmonary TB positive, diabetes mellitus (DM) was predominant with a prevalence of 31 (19.5%), while, 128 (80.5%) cases did not show any underlying disease. Most of the patients were in the age group (21-40 years) with a frequency of 60 (37.7%), and the lowest of patients belonged to the age group (>80 years) with a frequency of 9 (5.7%). No correlation was found between related factors and infection with EPTB ($p > 0.05$).

Conclusion: Our findings showed that the prevalence of EPTB in Kashan was relatively high, but, a relative decrease was shown during 2004-2017, which with preventative measures can be reduced the prevalence.

Keywords: Epidemiology, Tuberculosis, Prevalence

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Introduction

Nowadays, Tuberculosis (TB) is considered one of the most common infectious diseases worldwide[1]. It can infect all organs of the body, but the lungs are affected in 85% of cases, and 15% of cases in an extra-pulmonary form infected other organs such as lymph nodes, pleura, genitourinary system, bones, joints, and meningitis[2, 3]. The last report from WHO in 2017 showed an estimation of 6.3 million new TB cases

globally, of which 16% were Extra-pulmonary TB (EPTB); incidence rates ranged from 8% in the Western Pacific Region to 24% in the Eastern Mediterranean Region[4]. With develop of acquired immunodeficiency syndrome (AIDS) infection, the incidence of EPTB is also increasing and becomes an international problem[5]. EPTB is responsible for 15 to 20 % of all forms in individuals who do not have human immunodeficiency virus (HIV) infection[6, 7].

EPTB is somewhat neglected and compared to pulmonary tuberculosis (PTB) rising in prevalence in low-burden countries[8]. Thus, it has specific challenges in both diagnostic and management aspects[9]. In most cases, the detection of EPTB is often hard due to unclear clinical signs and the need for revascularization[10]. The EPTB appears with diverse signs in various situations; for this reason, it is known as "thousand faces infection[11]. Also, owing to EPTB having a different manifestation which may mimic other diseases it will make it more diagnostically challenging for laboratories, epidemiologists, and physicians[12]. Therefore, diagnostic delay confers its higher capability for creating disease, predominantly tuberculous meningitis (TBM), for that, EPTB merits further focus[13, 14].

Iran is a country with an intermediate TB burden, with the report of 10290 new TB cases in 2015, of which 2863 (28.26%) were EPTB and 299 (2.95%) relapse cases[15]. The TB control strategy aims to reach <1 case per 1 million yearly by 2050 and an 80% decrease in TB incidence until 2030, in comparison with 2015[16, 17]. But, similar to many other countries, TB remained a major cause of disease in Iran[18].

Several risk factors are defined for the dissemination of EPTB, including patients who were age ≥45 years, female, HIV+, excessive alcohol use, abnormal chest radiographs end-stage renal disease (ESRD), and diabetes[19, 20].

Reviewing the trend of TB incidence during the time affords important measures to evaluate the outcome of controlling and managing programs and health policies for governments, and implanting the best control strategies[21].

Treatment failure is the presence of persistent or repeatedly positive cultures during the treatment of tuberculosis. Usually, after 3 months of multi-drug therapy for pulmonary tuberculosis produced by the drug-susceptible bacterium, 90–95% of patients will have negative cultures and indicate clinical enhancement. Patients whose sputum cultures stay positive after 4 months of anti-tuberculosis therapy should be categorized as treatment failures[18]. The reasons for treatment failure in patients receiving appropriate anti-tuberculosis regimens are Non-adherence, drug resistance, malabsorption of drugs, and laboratory error. If treatment failure happens the patient should be referred to a local center. *M. tuberculosis* strains should be sent to a referral laboratory for drug-susceptibility testing against both first, and second-line drugs[2]. Therefore, this present study aimed to investigate the epidemiology, and trend of extrapulmonary tuberculosis, and the failure of treatment from 2004-2017 in Kashan, Iran.

Methods

Study population and data extraction: A non-experimental, retrospective cross-sectional study was conducted from 2004-2017 with newly registered extrapulmonary tuberculosis patients referred to the Referral Center for Tuberculosis in Kashan city, Isfahan province, Iran. In general, information on 159 extra-pulmonary TB patients was extracted from Medical case records. The Medical records were filled and completed by the trained personnel in this center. In this study, a newly diagnosed extrapulmonary tuberculosis case was described as a diagnosis based on; one culture-positive, histological, or strong clinical evidence accordant with the extrapulmonary disease. TB-specific deaths included TB patients in whom TB was cited as the cause of death. Independent variables such as occupation, education, gender, nationality, history, age, and other related factors were studied and their correlation with EPTB was investigated. This should be noted that all patients declared that they didn't use narcotic drugs and alcohol. Lastly, the trend of extrapulmonary tuberculosis between 2004-2017 was depicted for EPTB patients of Kashan, Iran.

Identification procedures: In the diagnosis of Tuberculosis, direct smear microscopy alongside culture sputum specimens was used. Clinical specimens were homogenized with equal volumes of 50 mM NaOH comprising 0.5% N-acetyl-l-cysteine (NALC) and decontaminated with 10% sodium hydroxide, and then incubated at 37 °C. Consequently, Ziehl- Neelson

staining was used for TB diagnosis (*21*). Furthermore, clinical manifestations and radiographic parameters were assessed in all patients suspected to have tuberculosis.

Ethical considerations: This study was approved by the ethics committee of the Kashan University of Medical Science; IR.KAUMS.REC.1399.052.

Statistical analysis: Data were analyzed using SPSS software (version 19) by Kolmogorov-Smirnov, Chi-square, and Fisher's exact tests. *P values* of less than *0.05* were regarded as statistically significant.

Results

In total, 527 cases of Tuberculosis were reported, of which, 159 (30.17%) were confirmed extrapulmonary TB-positive cases. Eighty-five (53.5%) and 74 (46.5%) were male and female, respectively. Also, 74 (46.5%), and 84 (53.5%) of EPTB were from Iran, and Afghanistan immigrants, respectively. The average age of patients was 41.9±2.18. Among underlying diseases in extrapulmonary TB-positive, diabetes mellitus (DM) was predominant with a prevalence of 31 (19.5%), while, 128 (80.5%) cases did not show any underlying disease. Most of the patients were in the age group (21-40 years) with a frequency of 60 (37.7%), and the lowest of patients belonged to the age group (>80 years) with a frequency of 9 (5.7%). According to the occupational status, most of the patients were housewives with a frequency of 66 (41.5%), followed by workers at 36 (22%). Most of the patients were illiterate with a prevalence of 129 (81.1%), and only 9 (5.7%) patients had an academic education. In total, only 41 (25.8%) of patients had previous contact history with TB-positive patients. No correlation was found between the related factors listed in Table 1 and infection with EPTB (*P*> 0.05) (Table 1).

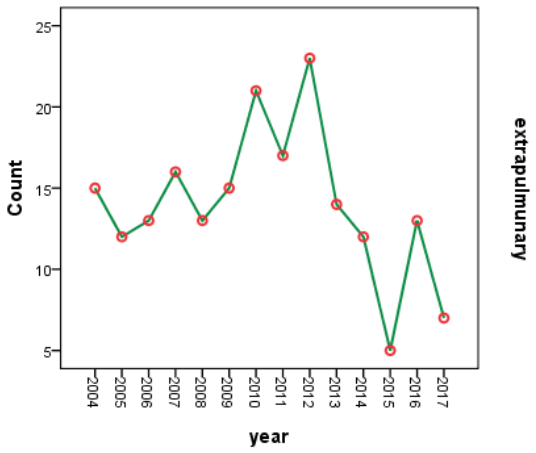

Figure 1. Annual trend of extrapulmonary tuberculosis cases since 2004-2017 in Kashan, Iran.

No cases of concurrent EPTB with PT have been documented. The cases of EPTB smear positive since 2004-2010 were not recorded in medicinal records, but since 2011-2017, 67 out of 73 cases (92%) were smeared positive. In total, 41 patients had the culture positive.

As shown in Table 2, 137 (86.2%) patients completed the treatment period, and 22 (13.8%) were absent from the treatment process. Of 159 patients, 150 (94.3%) were new cases, 4 (2.5%) were patients that had a previous TB relapse, and 5 (3.1%) cases were imported from other cities in Iran or other foreign countries. Also, 155 (97.5%) were treated with first-line anti-TB drugs and 4 (2.5%) with second-line anti-TB drugs. Moreover, of total extrapulmonary TB, 69 (43.4%) were outpatient (Patients were referred to the TB center by physicians, health centers, or patients themselves referred to the health centers), and 90 (56.6%) of patients were hospitalized. Among types of extrapulmonary TB, most cases belonged to lymph nodes (19.5%), followed by each of the pleura, and bone, with a prevalence rate of 18.9%. But, the lowest was related to genital type with frequency 2 (1.3%).

Annual case rates of EPTB have been recorded in Kashan since 2004. A relative drop in the rate of incidence was reported in the initial period of 2005. Then, a slight increase was evident from 2005-2007. A gradual increase was observed from 2007 until 2011, followed by a sharp increase in 2012, and also, a sharp decrease in 2013. From 2014-2017, there was a variation as a slight increase/decrease trend. In total, a consistent level of EPTB cases in Kashan about 30% of the total reported TB cases yearly explains the incidence rate of EPTB reported during 2004-2017. But, from the initial (2004) until the recent (2017), a relative decrease was observed (Figure 1). Also, we did not find any relationship between associated factors and failure of treatment (P>0.05).

internationally decreased by 37% in the community[22].

Table 1: Demographic characteristic of registered extrapulmonary tuberculosis patients referred to the Kashan Referral Center for Tuberculosis.

Characteristics		Number(N)	Percent (%)	P value
Gender	Male	85	53.5	0.2
	Female	78	46.5	
Nationality	Iran	74	46.5	0.06
	Afghanistan	85	53.5	
Age groups	0-20	28	17.6	0.2
	21-40	60	37.7	
	41-60	38	23.9	
	61-80	24	15.1	
	>80	9	5.7	
Education	Illiterate	129	81.1	0.2
	Diploma	21	13.2	
	>Diploma	9	5.7	
Underlying diseases	Yes	31	19.5	0.2
	No	128	80.5	
History contact with TB	Yes	41	25.8	0.1
	No	118	74.2	
Occupation	Student	9	5.7	0.1
	House- wives	66	41.5	
	Worker	35	22	
	Employee	2	1.3	
	Farmer	8	5	
	Retired	13	8.2	
	Unemployed	8	5	
	Free	10	6.3	
	Other	8	5	

Table 2: Variables and factors related to registered extrapulmonary tuberculosis patients referred to the Kashan Referral Center for Tuberculosis.

Variables		Number(N)	Percent (%)
Status	Outpatient	69	43.4
	Hospitalized	90	56.6
Type of extra TB	Pleura	30	18.9
	Lymph-node	31	19.5
	Bone	30	18.9
	Gastro	17	10.7
	Skin	5	3.1
	Genital	2	1.3
	Urinary	6	3.8
	CNS	4	2.5
	Other	34	21.4
Case disease	New	150	94.3
	Import	5	3.1
	Relapse	4	2.5
Therapeutic regimen	Anti-TB first-line drugs	155	97.5
	Anti-TB second-line drugs	4	2.5
Results of treatment	Complete treatment	137	86.2
	Absent of treatment	22	13.8

Discussion

Tuberculosis (TB) still has remained a major health concern worldwide[3]. In recent decades active TB rate especially pulmonary tuberculosis (PTB) has Nevertheless, the frequency of extrapulmonary tuberculosis (EPTB) has stayed constant almost worldwide[23]. Extra-pulmonary TB indicates tuberculosis infection which has spread from the lung hematogenous or through the lymphatic system[24]. In

contrast to pulmonary tuberculosis (PTB), studies about EPTB are significantly smaller and have received less attention from authorities, particularly, in developing countries, probably because extrapulmonary TB is less transmissible than pulmonary,[25] or difficulties in diagnosis[26].

The incidence rate of EPTB in this study was 159 (30.17%), the results obtained are comparable with data reported by Iranian Center for Diseases Control and Prevention (CDC) in 2011 reported the prevalence of pulmonary as 14.6 per 100000 people, of which 4.12 had extrapulmonary TB[27]. In neighboring countries of us, such as Oman[28], India[29], and Saudi Arabia[30], EPTB accounted for respectively 37%, 16%, and 57.5% of all reported TB cases. Other studies from Iran showed such a pattern previously. Similarly, Rafiee et al. in northeast Iran[18], Ghaffari-Fam et al. in North Iran (Babol)[31], and Yahyavi et al. in Southwest Iran(Baghmalek)[27] reported prevalence rates of 23%, 25%, and 12.5%, respectively.

The annual trend case of EPTB in Kashan from 2004 showed a relative drop in the rate of incidence in the initial period to 2005. Then, a slight increase was evident from 2005-2007. As well, a gradual increase was observed from 2007 until 2011, followed by a sharp increase in 2012, and also, a sharp decrease in 2013. From 2014-2017, there was a variation as a slight increase/decrease trend. In total, a consistent level of EPTB cases in Kashan about 30% of the total reported TB cases annually explains the prevalence rate of EPTB reported during 2004-2017. But, from the initial (2004) until the recent (2017), a relative decrease was recorded.

For our acknowledge, the Center for Disease Control and Prevention (CDC), reported that the ratio of EPTB among all TB cases remained high, and the decrease in TB from 1953 has almost belonged to pulmonary TB reduction and not to EPTB[32]. This variation and difference in extra-pulmonary TB between the present study and mentioned studies possibly referred to the variation in diagnostic methods; highly heterogeneous manifestation of EPTB, the lower yield of laboratory diagnostic tests for detection of EPTB from extrapulmonary samples, use of molecular and conventional methods in different locations, cytological studies, and/or pericardoscopy in recent years[27].

Based on our findings, lymph nodes followed by the pleura and bone were the main sites for EPTB aligned with many other studies reporting the same[28, 33-35]. Also, in the USA, a nationwide report shows lymphatic TB (40.4%) as the most frequent followed by pleural TB (19.8%), bone and joints TB (11.3%)[23], while, in the European Union (EU), the trend was different as it showed a higher predominance of pleural TB (36.7%), followed by lymphatic TB (30.5%)[34].

In the present study, multivariable analyses were not found a correlation between factors included in the study (gender, age, occupation, history, nationality, education, and underlying disease) and infection with EPTB. Our findings are in contrast to other studies that revealed a relationship between the female sex[23, 36], and age[37] as risk factors for EPTB. In general, extrapulmonary TB affects individuals in young children (<15 years of age) and older adults (>65 years of age)[38, 39]. But contrary to these reports, our study showed that most of the patients were in the age group (21-40), followed by the age group (41-60). But in fact, no correlation was found between the age factor and EPTB.

In the current study, among underlying diseases in extrapulmonary TB-positive, diabetes mellitus (DM) was predominant, but we did not find any relationship between DM and EPTB. In agreement with our study, a study from China[38], Taiwan[40], and Brazil[25] reported the same, and also they did not report a significant association. But contrasting findings from a study conducted in the United States showed the correlation between diabetes and increasing extrapulmonary TB risk[41].

Tuberculosis is more common among men than women particularly in adults with difficult occupations[42], accordingly, among Iranian people; tuberculosis prevalence is also higher among males than females[43]. Our study showed a higher prevalence of EPTB in males than females. This subject might be explainable by the presence of men in the community, and more exposure to the carriers and risk factors of EPTB[43], although, the present study did not show a significant relationship between independent factors (sex, and occupation) and EPTB. The epidemiological profile in the current study reflects the nationality of patients, with a predominance of Afghanistan immigrant patients than Iranian, as more than half of EPTB cases belonged

to Afghan refugees. According to the report of the UN Refugee Agency, by end of 2005, Iran had been the host of the third largest refugee population in all over the world, with a total of 716,000 refugees[43]. The prevalence of tuberculosis in the population of immigrants is very high and often reflects the undesirable situation of the disease in Afghanistan[44]. Immigrants mostly encounter many obstacles to accessing diagnostic and medicinal settings[45], and they certainly have a significant impact on the epidemiology of tuberculosis in Iran[46].

Most of the patients in our study were illiterate, although was not found a significant relationship between education and the EPTB, However, this causes a longer diagnostic delay among illiterate patients[47]. Also, most of the patients were housewives, or laborers, while, no correlation was found between occupation and EPTB. Nevertheless, patients living at low economic levels, and in poverty, exposing to an increased risk of poor health outcomes, unsuitable use of medications, and delay in referring to physicians, and treatment[48, 49].

The outcome of treatment in the present study showed that almost all patients were exposed and treated with anti-TB first-line drugs. Almost patients completed the treatment and there was no treatment failure, and also, no case of death was observed. Contrary to our findings, others reported failure between 7-34%[50, 51]. The important reasons for this failure were; irregular treatment followed by alcohol abuse, illiteracy, and smoking[52, 53]. Also, Tekle et al. have declared the reasons for the failure of treatment as being a lack of family support, inadequate knowledge of treatment duration, and side effects of drugs[50].

Adama Diallo and et. al showed that the delay between initiation of treatment and first sputum-smear investigation, also weight loss between diagnosis and first sputum-smear investigation were factors related to treatment failure of first-line pulmonary tuberculosis.

Moreover, high bacterial load at the first sputum-smear investigation was similarly related to first-line pulmonary tuberculosis treatment failure. Furthermore, they showed that the patient's weight loss between the diagnosis and the first bacilloscopic examination augmented the odds of treatment failure[54]. Among patients, the most common reason for the failure of TB drugs includes; traveling journeys, the finish of health facilities during strikes, and the absence of healthcare personnel to afford TB drugs[55]. Finally, the high rate of EPTB in Kashan and all over Iran might be due to poor case detection of EPTB; and illegal and legal immigrants from neighboring countries with a high burden of TB, this requires further assessment by examining case detection strategies in the country. Also, positive patients would be subjected to anti-tuberculosis drugs before being allowed entrance into our country.

Conclusion

Our findings showed that the prevalence of EPTB was significant in Kashan, but, a relative decrease was observed from 2004-2017. Also, a high rate of EPTB associated with Afghan patients was recorded in Kashan. This requires that illegal and legal immigration of people affected by tuberculosis be considered from other countries with a high burden of disease, and positive patients would be subjected to anti-tuberculosis drugs before being allowed entrance into our country.

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