Incidence, risk factors and clinical characteristics of extra-pulmonary tuberculosis patients: a ten-year study in the North of Iran

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Abstract

OBJECTIVE To determine the incidence of extra-pulmonary tuberculosis (EPTB) and examine the risk factors and the clinical features of the disease over a ten-year period.

METHODS Retrospective study of records of patients who were followed and registered in the TB registry programme in the health district of Gorgan, Iran from January 1, 2008, through December 31, 2017.

RESULTS Among 2280 TB records, 609 (26.71%) were EPTB. They were mostly female patients (53.7%) and residents in rural areas (56.5%) with a mean age of 40.55 years [ ± 16]. The average age of female patients (37.55 years [ ± 16.99]) was lower than of male patients (44.07 years [ ± 20.59]). The median of the incidence rate was 7.5 per 100,000 inhabitants for EPTB; biopsy and pathology were the best methods for the detection of EPTB. The most frequent forms of EPTB were lymphatic TB (193/609 = 31.7%) and pleural TB (158/609 = 25.9%). In most cases (245/609 = 40.2%), one to three months elapsed between occurrence of symptoms and final confirmation of EPTB. The outcome of EPTB was weaker than of pulmonary TB (PTB).

CONCLUSION Our most important finding was the increasing incidence of EPTB, which shows the importance of attention to this disease. Lymph node and pleural tissue were the most commonly infected tissues. Skeletal TB presents a challenge in the diagnosis and treatment of EPTB.

KEYWORDS extra-pulmonary tuberculosis, burden disease, risk factors, outcome, lymphatic tuberculosis

Sustainable Development Goals (SDGs): SDG 3 (good health and well-being), SDG 5 (gender equity)

Introduction

*Mycobacterium tuberculosis* complex (MTBC) causes Tuberculosis (TB), one of the oldest and most lethal infectious diseases in the world. Despite all efforts to reduce its disease burden, TB still remains a major public health problem, especially in developing countries [1]. Ten million people (range, 9.0–11.1 million) had TB in 2018, including 5.7 million men, 3.2 million women and 1.1 million children; and 1.6 million died from TB in the same year. *Mycobacterium tuberculosis* infects about a quarter of the people on earth, and about 10% of them have the potential to get sick [1].

In recent years, the incidence of the disease has decreased in most countries, but not fast enough to reach the first WHO goal in 2020, ‘end TB strategy until 2030’. Overall, the TB incidence rate declined by 1.6% per year between 2000 and 2017 and by 2.0% between 2017 and 2018 [1].

Annually, WHO analyses all data from the world for its global TB report; but unfortunately because of a lack of facilities in some areas, many people with remain unrecognised or unreported. One reason for this is extra-pulmonary tuberculosis (EPTB). In most countries, the incidence of EPTB has increased and it can be a challenge for the strategy of reducing TB and the ‘end TB strategy’ set by WHO [2–4]. On average, 15% of the clinical forms of TB can be EPTB; its rate varies from 8% in the western Pacific region to 30% in the eastern Mediterranean region [5–7].

Mostly, MTBC can disseminate to different organs with the lymph nodes and the pleura at the top. Other
The present retrospective study analysed 10 years of data on EPTB patients who were followed and registered on the TB registry programme of the health district of Gorgan, Iran. Gorgan is in the north of Iran, with 473,000 inhabitants in 2018 and the second-highest incidence rate in Iran because of the common border with countries with a high burden of TB including Afghanistan [1]. We collected the data from the TB registry electronic database and patients’ files from January 1, 2008, through December 31, 2017. Tuberculosis cases were surveyed by the health centres and diagnosed and reported by physicians. All patients were interned in the TB treatment programme according to the WHO Guidelines [1].

The ethics committee of Golestan University of Medical Science reviewed and approved the study. All required information was anonymised and the names of patients were de-identified. As the study evaluated data from the TB registry system, informed consent was not necessary.

Definitions
In Iran’s surveillance TB programme, clinical TB (active TB) and EPTB cases were defined under the WHO definitions and guidelines [1, 17]. Patients with at least one of the following criteria were defined as an EPTB case: having compatible histopathology and cytology in organs other than the lungs; one culture-positive specimen in an aspiration sample obtained from the cerebrospinal/pleural/ascetic fluid; strong clinical evidence of TB in the other part of the body except lungs, followed by a decision by a clinician to treat with a full course of anti-TB drugs and giving an answer. In our analysis, we excluded the patients who had both pulmonary TB (PTB) and EPTB from the study.

Data collection and analysis
The demographic and clinical characteristics of the patients were collected using standard data extraction forms. They were included age, sex, place of residence, past medical and co-infection histories (diabetes, HIV infection, chronic obstructive pulmonary disease (COPD), cancer, immunosuppressive treatment and other diseases) and the lifestyle (smoking, alcohol) of the patients. The anatomical locations of EPTB were recorded including lymph nodes, gastrointestinal system, plural, genitourinary tract, skin, joints and bones, meninges and other organs. Other information was also extracted from the files, including symptoms of the disease (general symptoms including fever, chronic fatigue, night sweats, dyspnoea and weight loss and different specific signs) and diagnostic methods including imaging (computed tomographic (CT), magnetic resonance imaging (MRI) and chest x-ray), microbiology cultivation and staining, histopathology methods, and/or clinical evidence (Tables 1 and 2). Outcomes were categorised and recorded as treated, loss of follow-up, and/or abandon the treatment, failed and death.

We used SPSS software version 16 (package for windows, SPSS Incorporation, Chicago, Illinois, USA) to process and analyse the data. At first, variables were expressed by frequencies and mean with standard deviation. Chi-square and Fisher exact tests were done to calculate the comparison of the different variables. When important anatomical sites include the genitourinary system, the gastrointestinal tract, the bones and the central nervous system [8–11]. Several types of EPTB, such as meningitis and miliary TB, have a high mortality rate and are categorised as severe disease [12, 13].

The reasons and mechanisms of how the bacterium spreads and why it infects certain organs remain largely unknown. Probably, due to individual weakness of the immune system and macrophage dysfunction, the bacteria can spread between tissues through body fluids such as blood and lymph [14]. Some risk factors are involved, such as host–pathogen interactions and the immune system. The main risk factors associated with EPTB vary widely and include human immunodeficiency virus (HIV) co-infection, female sex, age (young children and/or above 65 years of age), race and diabetes [5, 13, 15]. Some of these factors lead to the immune system dysfunction due to decreased number of immune cells, production of cytokines and proliferation of tissue cells [8, 16].

EPTB diagnosis is more difficult than PTB diagnosis and requires invasive procedures such as biopsy or surgery, along with routine procedures. This difficulty leads to delay in the diagnosis and treatment of EPTB and increases the rate of mortality [11].

The results of different geographical studies are controversial; hence determining the main risk factors associated with EPTB clinical phenotype is a necessary step to improve detection and treatment of patients and to expand suitable protocols for managing EPTB according to each geographical area. Finally, it helps us reach our worldwide goal, ‘end TB strategy’. Thus the aim of this study was to evaluate the risk factors of EPTB and its clinical manifestations.

Methods
Study setting

The present retrospective study analysed 10 years of data on EPTB patients who were followed and registered on the TB registry programme of the health district of Gorgan, Iran. Gorgan is in the north of Iran, with 473,000 inhabitants in 2018 and the second-highest incidence rate in Iran because of the common border with countries with a high burden of TB including Afghanistan [1]. We collected the data from the TB registry electronic database and patients’ files from January 1, 2008, through December 31, 2017. Tuberculosis cases were surveyed by the health centres and diagnosed and reported by physicians. All patients were interned in the TB treatment programme according to the WHO Guidelines [1].

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each $P$-value was less than 0.05, the related result was considered statistically significant.

**Results**

**Study population**

From 2008 to 2017, 2280 TB records were included in the study. Among them, 1150, 521 and 609 records were PTB (smear $+$), PTB (smear $-$) and pure EPTB, respectively. The study focused on pure EPTB cases that had only EPTB without any pulmonary involvement and complications of PTB. Seven patients had EPTB with PTB, which categorised in the TB records and were excluded from the study because the primary location of the infection was unclear. All EPTB cases had no smear results, because there were patients who were not initially suspected of having TB and were not evaluated for the existence of MTB. In this regard, only the available information about EPTB cases that had smear results is reported in this section. Based on clinical manifestations, positive results in the Ziehl–Neelsen staining belonged to pleural (16 out of 142 cases), lymph node fluid (12 out of 183 cases) and urinary tract (one from two cases) samples. Other patients were not evaluated for this test. The overall prevalence of smear-positive EPTB was 19 of 327 cases (5.8%).

The proportion of female patients (53.7%) and residents in rural areas (56.5%) was higher. The total mean age of the patients was 40.55 years [±16]. The average age of female patients (37.55 years [±16.99]) was lower than of male patients (44.07 years [±20.59]).

| Variables                  | Frequency (%) | Variables                  | Frequency (%) |
|----------------------------|---------------|----------------------------|---------------|
| Year of diagnosis          |               | Diabetes                   |               |
| 2008                       | 40 (6.6)      | Yes                        | 241 (39.6)    |
| 2009                       | 42 (6.9)      | No                         | 228 (37.4)    |
| 2010                       | 62 (10.2)     | Unknown                    | 140 (23)      |
| 2011                       | 52 (8.5)      | High Blood pressure        |               |
| 2012                       | 58 (9.5)      | Yes                        | 184 (30.2)    |
| 2013                       | 78 (12.8)     | No                         | 419 (68.8)    |
| 2014                       | 73 (12)       | Unknown                    | 6 (1.0)       |
| 2015                       | 76 (12.5)     |                            |               |
| 2016                       | 65 (10.7)     | Yes                        | 211 (34.6)    |
| 2017                       | 63 (10.3)     | No                         | 394 (64.7)    |
| Gender                     |               | Unknown                    | 4 (0.7)       |
| Male                       | 282 (46.3)    | CKD                        |               |
| Female                     | 327 (53.7)    | Yes                        | 216 (35.5)    |
| Age (mean ± SD)/range      |               | No                         | 383 (62.9)    |
| Age group                  |               | Unknown                    | 10 (1.6)      |
| 0-15                       | 30 (4.9)      | Injectable Addict          |               |
| 16-30                      | 94 (15.4)     | Yes                        | 258 (42.4)    |
| 31-45                      | 198 (32.5)    | No                         | 235 (38.6)    |
| 46-64                      | 166 (27.3)    | Unknown                    | 116 (19)      |
| ≥65                        | 121 (19.9)    | Smoking                    |               |
| Residence                  |               | Yes                        | 435 (71.5)    |
| Urban                      | 265 (43.5)    | No                         | 150 (24.6)    |
| Rural                      | 344 (56.5)    | Unknown                    | 24 (3.9)      |
| TB history                 |               | Alcohol                    |               |
| Yes                        | 59 (9.7)      | Yes                        | 120 (19.7)    |
| No                         | 488 (80.1)    | No                         | 356 (58.5)    |
| Unknown                    | 62 (10.2)     | Unknown                    | 133 (21.8)    |
| HIV status                 |               | Detection methods          |               |
| Yes                        | 42 (6.9)      | Biopsy and histopathological | 436 (71.6)  |
| No                         | 213 (35)      | Imaging                    | 137 (22.5)    |
| Unknown                    | 354 (58.1)    | Smear and culture          | 36 (5.9)      |

TB, Tuberculosis; HIV, the human immunodeficiency virus; COPD, chronic obstructive pulmonary disease; CKD, Chronic kidney disease.
youngest and oldest patients were 2 (female) and 90 (male) years old, respectively. Most numbers of the patients were in the age range of 31–45 years (32%), followed by 27% aged 46–64 years. A total of 9.7% and 6.9% had a TB history in the past and co-infection with HIV, respectively; diabetes (39.57%) and drug addiction (42.36%) were the other important factors related to EPTB based on the past medical history and

Table 2  Frequency distribution of extra-pulmonary tuberculosis cases in each involved organ and the most common symptom observed on each organ

| Site of disease (N = 609) | Frequency (%) | The most common symptom (%) * |
|-------------------------|---------------|-------------------------------|
| Lymph nodes             | 193 (31.7)    | Fever† (58) + swollen lymph nodes (49.7) |
| Pleura                  | 158 (25.9)    | Dyspnoea (76.6) + chest pain (70.9) |
| Spine                   | 76 (12.5)     | Backache (92.1)               |
| Breast                  | 67 (11)       | Breast mass (97)              |
| Bones                   | 21 (3.4)      | Wounds and discharge from wounds (76.2) |
| Adrenal glands          | 15 (2.5)      | Anorexia (93.3)               |
| Gastrointestinal        | 12 (2)        | Anorexia (100)                |
| Genitalia               | 12 (2)        | Night sweats (83.3)           |
| Uterus                  | 10 (1.6)      | Fever/ night sweats (80) + abdominal mass (50) |
| Eye                     | 10 (1.6)      | Reduced vision (80)           |
| Miliary                 | 10 (1.6)      | Fever/ night sweats/ fatigue (100) |
| Meninges                | 8 (1.3)       | Fever (100)                   |
| Joints                  | 5 (0.8)       | Movement restrictions (100)   |
| Skin                    | 3 (0.5)       | Wounds and discharge from wounds (100) |
| Ovaries                 | 3 (0.5)       | Infertility (66.6)            |
| Urinary tract           | 2 (0.3)       | Fever/night sweats/anorexia (100) |
| Chest wall              | 2 (0.3)       | Wounds and discharge from wounds (100) |
| Larynx                  | 2 (0.3)       | Throat mass (100)             |

*Percentage of the symptom that observed on the most cases based on the frequency in each infected organ.
†All frequency of signs and symptoms of extra-pulmonary tuberculosis cases included fever (40.9%), fatigue (39.9%), night sweats (37.9%), dyspnoea (35.1%), weight loss (33.8%), chest pain (30%), anorexia (28.1%), backache (13.8%), breast mass (10.7%), swollen lymph nodes (9.4%), wounds and discharge from wounds (8.5%), cough and sputum (6.6%), movement restrictions (3.3%), abdominal mass (3%), reduced vision (1.3%), throat mass (1.3%), infertility (1%), neck pain (1%), axillary wound (0.5%).

Figure 1  Trends in the incidence rate of extra-pulmonary tuberculosis (EPTB) with respect to total, male and female cases, Iran 2008–2017 (number per 100 000 populations).
lifestyle. Table 1 shows all demographic and clinical characteristic data.

Based on the population of the region, the median of the incidence rate was 7.5 per 100 000 inhabitants for EPTB. Figure 1 shows the annual incidence rate (2008–2017) per 100 000 inhabitants in total, and in male and female populations. Table 1 presents the characteristics of the laboratory detection methods of the infection. Biopsy and histopathology were the best methods for the detection of EPTB, confirming EPTB in 71.6% of the patients. Clinical grounds, imaging methods and response to treatment helped confirm EPTB in 22.5%. Findings of EPTB on X-ray, CT, MRI and sonography helped confirm EPTB in 20.3%, 19.2%, 9% and 3.6% of patients, respectively. Another method for the detection of EPTB was smear evaluation and culture of fluids of the body. The two main and frequent forms of infection were lymphatic TB (193/609 = 31.7%) and pleural TB (158/609 = 25.9%). There were also several rare infection sites such as breast, eyes, skin, larynx and meninges, as shown in Table 2. However, these sites were divided into seven main categories for statistical purposes. Rare cases were categorised as ‘other’ group. In this regard, sites of infection were categorised as lymph nodes (193/609 = 31.7%), pleural (158/609 = 25.9%), bone and joint (102/609 = 16.74%), breast (67/609 = 11%), urogenital system (42/609 = 6.89%), gastrointestinal system (12/609 = 1.97%) and meninges (8/609 = 1.31%) groups (Table 3).

The statistical analysis showed that TB infection is associated with sex in some organs of the body. All meningeval TB (8/8) happened in male patients. Furthermore, most of the bone and joint (73/102 = 71.56%), and plural (97/158 = 61.39%) cases were seen in males (P ≤ 0.05). On the contrary, most infections in the lymph nodes (116/193 = 60.10%), breast (65/67 = 97.01%) and urogenital (25/42 = 59.52%) organs were seen in women. Age difference could be significantly related to the sites of infection. Most of the bone and joint (67/102 = 65.68%) and urogenital (28/42 = 66.66%) cases were older than the average age (40.55) of patients, whereas most of the breast cases (47/67 = 70.14%) were younger (Table 3).

The interval between onset of symptoms and definitive diagnosis of EPTB was categorised into four groups. Most number of cases (245/609 = 40.2%) had one to three months between symptom onset and final confirmation of EPTB. 175 (28.7%) cases had a faster diagnosis time and were diagnosed within a month, whereas 15.8% experienced a delay of over six months (96/609) and 15.3% of three to six months (93/609). The longest duration time of disease’s diagnosis (over six months) was for the skin (3/3), joint (5/5), urinary tract (2/2) and spine (14/76 = 53.94%) TB cases. Ovary (3/3) and larynx (2/2) TB cases were diagnosed fastest. Based on infection site categories, most bone and joint cases (52/102 = 50.98%) were diagnosed after six months. All meningitis cases (8/8) and most of the pleural (129/158 = 81.64%) TB patients were diagnosed in less than three months (Table 3).

**Signs and symptoms**

Clinical signs were seen in two types, general and specific to each involved organ. Logically, general symptoms were seen in most patients, including fever (40.9%), fatigue (39.9%), night sweating (37.9%), weight loss (33.8%) and anorexia (28.1%). Specific clinical symptoms were very variable in each case and related to each

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**Table 3** Proportion of each involved organ according to the characteristics of the Extra-Pulmonary Tuberculosis patients

| Organ          | Frequency (%) | ≤40.55 | >40.55 | P-value | Gender | Diagnosis time (month) | P-value |
|----------------|--------------|--------|--------|---------|--------|------------------------|---------|
| Lymph nodes    | 193 (31.7%)  | 101    | 92     | 0.517   | Female | ≤1                      | 0.005   |
|                |              |        |        |         | Male   | 1–3                    | 0.001   |
|                |              |        |        |         | 3–6    | >6                     | <0.001  |
|                |              |        |        |         |        | ≥6                     | <0.001  |

*Spine + bone + joint.
†Adrenal glands + genitalia + uterus + ovaries + urinary tract.
‡Eye + milary + skin + chest wall + larynx.

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affected organ. Table 2 shows the most symptoms in each infected organ. For example, backache and deteriorating vision were common in spinal (70/76 = 92.10%) and ocular TB patients (8/10 = 80%), respectively.

Treatment

After confirmation of the infection, all 609 patients immediately began drug therapy according to Iran’s Ministry of Health Protocol based on WHO guidelines [18,19]. Patients received a combination of isoniazid, rifampicin, pyrazinamide and either ethambutol or streptomycin, along with other required treatments.

Regardless of treatment outcome, the mean duration was 7.14 (median = 7.5) months. 95 (15.6%) patients were treated for less than 1.5 months. 40 (6.6%) cases were treated for 1.5–3 months, 147 (24.1%) for 3–6 months, 54 (8.9%) for 6–9 months and 270 (44.3%) for 9–12 months. Three (0.5%) patients were treated for more than 12 months (Table 4). Half (49.4%) completed treatment and were cured and 38.9% either left treatment or were lost to follow-up. 11.7% died. The highest mortality rate was observed in the disseminated EPTB (miliary TB) and meningeal TB. By comparison, 75% of 1671 PTB cases were cured, 17.5% had treatment failure or left treatment, and 7.5% died. The rate of treatment failure and death in was significantly lower for PTB than EPTB.

Trends of different TB forms

By year, the incidence of EPTB cases increased from 9.67 to 13.11 per 100,000 population, but the trend was not statistically significant. Regarding the anatomic site of the infection, there was no change in disease status in different years.

Discussion

One difficulty in achieving the WHO goal of reducing TB is EPTB. This type of TB is generally underestimated, and its diagnosis is often delayed by clinicians, which can lead to an increase in drug-resistant strains or mortality rates. Therefore, although risk factors for this disease have been studied [2, 8, 13], updated information is helpful for faster detection of ERPTB, especially in complicated cases.

Between 2008 and 2017, the average incidence rate of PTB was decreasing in Iran, which met WHO goals [1]. By contrast, similar to other studies, we found a slight increase in the incidence rate of EPTB in our study [2]. In recent years, the incidence of EPTB has been varied, but in most reports, the rate of reporting and incidence of the disease has slightly increased; therefore, special attention should be paid to it. This may be because of the improved quality of epidemiological studies and/or detection methods of EPTB cases, which can lead to more attention to underestimated cases [20–22]. Moreover, comorbidities including diabetes or HIV are on the increase and can contribute to the spread of EPTB cases. Other researchers also highlighted that diabetes is a risk factor for both PTB and EPTB [11, 16, 23, 24]. Diabetes can weaken the immune system and help the bacteria to disseminate in different organs, due to a drop in the number of activated macrophages, the production capacity of interleukin 10, and different cytokines [16].
In a study in Qatar, the proportion of EPTB in 2005 was 29% that subsequently increased to about 50% in 2015 [25]. In a study in Denmark, which analysed the TB cases between 2009 and 2014, 21.1% of all TB cases were EPTB and the incidence of EPTB increased between 2009 and 2013 and then decreased in 2014 [26]. A similar trend was observed in the present study and after an increase in the incidence rates of EPTB in the first few years under study, EPTB incidence declined slightly.

The rate of female EPTB patients with the lower age range in this study was similar to previous reports, although the total mean age of our patients was higher. Qian et al. analysed the data of EPTB in the state of Texas, USA and found that females were at significantly elevated risk of EPTB [27]. The higher incidence of EPTB in women could be because of variability in endocrine hormones, cultural aspects and immune-related factors [8]. Furthermore, Pang et al. found an association between EPTB and both female sex and younger age of patients [28]. Toure et al. also reported that one of the main risk factors of EPTB could be younger age (0–40) vs. 60 years and over [9].

In two reports from Senegal and the European Union, the most affected patients by EPTB were in the age ranges of 30–44 and 25–44 years [29, 30]. Similar to these results, most affected patients by EPTB were in the same age range (31–43 years) in the present study. These results suggested that EPTB should be considered more in this group of people.

Similar to the results of previous studies, our patients with infections that affect the immune system (HIV) and chronic diseases (diabetes, COPD) had a higher chance to be infected with EPTB [2, 20]. Bukhary et al. highlighted that immunosuppression disease, diabetes mellitus, chronic use of steroids and HIV were some important risk factors in EPTB patients in Saudi Arabia [31]. Chronic disease can lead to abnormalities of immune function, as can drug addiction. EPTB may be associated with immunosuppression more than PTB [28]. Therefore, based on the American Thoracic Society guideline, all patients with chronic and/or immunosuppressive diseases with a complicated condition should be screened for TB by a tuberculin skin test (TST) or IFN-γ releasing assay (IGRA) [32].

Along with most previous studies, we found that the two main infection sites were lymph nodes and pleural. In a study in the USA, lymph nodes followed by pleural and osteoarticular were the main infection sites [4]. Lymph nodes were also the most common site of EPTB in several studies from Saudi Arabia [2]. In the European Union, most countries showed a higher prevalence of lymphatic TB as the first site including The Netherlands (39%) and the United Kingdom (37%), whereas pleural TB was seen in Poland (36%) and Romania (58%) as the most prevalent form [33–36]. Biopsy and histopathological findings appear to be the best diagnostic procedures. When symptoms of an infectious disease occur in an organ and clinicians suspect EPTB, biopsy can be useful for the definitive diagnosis.

Fever and night sweating were the most frequent complaints. In a systematic review study, fever (45%) and night sweating (55%) were the main cardinal systemic symptoms among EPTB cases [5]. Along with the general symptoms of the disease in most EPTB cases, specific symptoms are related to the part of the infected organ: spinal TB may cause back pain, as reported by Garg et al. [37]. Possible involvement of TB in the organs of the body should be taken into consideration by physicians in patients who have systemic symptoms and who are at high risk for TB disease.

Early detection and treatment of TB are very important for TB control programmes to reduce the chance of transmission within the community and reduce TB incidence. The average time of diagnosis was about three months. In some cases, it was much longer. For example, most spine TB cases were diagnosed after six months. Generally, normal PTB cases are diagnosed in less than one month. The difference in the detection time can be alarming. Delay in diagnosis can lead to drug-resistant strains besides imposing additional treatment costs. Diagnosis of EPTB can be very complex, and the present data could help clinicians to better understand its clinical features.

Another difference to PTB is treatment duration. A 6-month standard treatment regimen is recommended in patients with drug-susceptible PTB [17], whereas in the present study, the average duration time of treatment was one year in many EPTB patients. Longer treatment imposes more suffering and costs on patients, and subsequently, health systems may lose track of patients' treatment plans, and patients become lost. Unfortunately, EPTB is less noticeable than PTB, and the outcome of EPTB patients is often underestimated and not reported to the TB registry and control programmes. Compared to PTB, EPTB treatment outcomes can be a challenge without knowledge regarding the risk factors and comorbidity. Therefore, the information should always be updated [26]. In the present survey, almost half of the patients were treated and cured. However, in some studies, the rate of recovery was higher. The treatment success rate was 67.6% in the Hayat Khan et al. report [38]. Ohene et al. reported 69% had successful treatment in Ghana [39]. In Denmark, the treatment success rate was even higher and increased from 79.4% in 2009 to 90.9% in 2014 [26]. One reason for the lower success rate of
treatment in our study may be that we had lots of skeletal TB cases that took a long time to be diagnosed and required a long treatment period. This again showed the importance of rapidly diagnosing this type of TB. Most patients had chronic comorbidities in the present study, which could affect the treatment. Ohene et al. showed that one of the important risk factors for death in EPTB patients was HIV co-infection [39]. Another important finding is the significant difference in treatment success rate between EPTB and PTB. It was significantly lower than in EPTB compared to PTB. This again shows the importance of early diagnosis of EPTB to improve treatment outcomes and reduce the risk of progression of the disease to its lethal forms.

While our study provides an opportunity to evaluate risk factors and clinical characteristics of EPTB, it has limitations. We only used the TB registry data of one province in Iran. Moreover, as the information was already recorded, it did not allow us to perform further analysis on some variables such as living standards (travel and socio-economic stratum), patients’ information (full lifestyle features) and the reason for leaving the treatment regime. Incomplete documentation was also another issue. Further and broader studies regarding these limitations may help clinicians to better control the disease.

**Conclusion**

This study helps to identify risk factors associated with EPTB. Being female, or younger, or having chronic illnesses such as diabetes can be important risk factors for the disease. The two main and frequent forms of EPTB are lymphatic and pleural TB, which reflect the spread of bacteria through body fluids such as lymph. Skeletal TB can be very important and is difficult to diagnose and treat. Late diagnosis and long-term treatment of skeletal TB can be a challenge for physicians. More consideration of the results can enhance TB control programmes and may contribute to an earlier diagnosis of EPTB patients to achieve better therapeutic outcomes.

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