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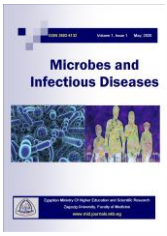

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Original article

Clinical and epidemiological profile of extra-pulmonary tuberculosis in Kasr Al-Ainy Hospitals, Cairo, Egypt

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ABSTRACT

Background: Tuberculosis (TB) remains a significant public health challenge in Egypt, particularly concerning extrapulmonary tuberculosis (EPTB). **Aim:** To delineate the sociodemographic and clinical characteristics, risk factors, and treatment outcomes of EPTB patients. **Methods:** This study was conducted on 244 patients (144 had EPTB, compared to 94 with pulmonary TB (PTB) & 6 patients had concurrent PTB and EPTB) at Kasr Al-Ainy Hospitals, Cairo University, between October 2023 and August 2024. Data was collected during visits to the clinic. **Results:** The study included 244 patients with TB. Concerning patients with EPTB (150), their mean age was 34.9 ± 14.9 years, with a slight female predominance (53%). Urban residents account for 49.3% of cases. The most common extrapulmonary forms were lymphadenitis (36%), pleural, and musculoskeletal TB (15.3% each). Diabetes was present in 20.7% of cases, human immunodeficiency virus (HIV) co-infection in 4%, and smoking prevalence was 38.2%. Histopathology (46.7%) and Xpert mycobacterium/rifampcin (MTB/RIF) assay (33.3%) were the main diagnostic tools. Compared to 94 PTB patients (more frequently diagnosed using microbiological smears), EPTB cases had lower percentage of cigarette smoking, chronic obstructive pulmonary disease (COPD) and asthma, longer treatment durations and adjuvant steroids. **Conclusion:** The common forms of EPTB were lymphatic, pleural and skeletal TB. Younger patients, residents of urban areas, and people diagnosed with diabetes had a higher risk of EPTB. Effective management and prevention programs would be a major step toward controlling the spread of the disease and improving patient outcomes in Egypt.

Introduction

Tuberculosis (TB) is a leading cause for morbidity and mortality worldwide. It mostly affects the lungs and can spread to other organs in the body [1]. Extrapulmonary tuberculosis (EPTB) may present general symptoms such as unexplained weight loss, prolonged night sweats, and fever, along with additional symptoms depending on the affected organ [2]. Tuberculosis (TB) is among the top ten major causes of mortality in low and low-to-middle-income countries [3]. Approximately 85% of patients who got infected with TB can be effectively treated with a 6-month medication regimen, thus the disease is preventive and curable. [4].

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On an international scale, there was a 3.6% increase in the TB incidence rate per 100,000 people annually from 2020 to 2021 [5]. The occurrence of TB cases per 100,000 people varies significantly across countries, with rates ranging from fewer than 10 to over 500 new and relapse cases annually [6]. Without treatment, the mortality rate for TB is significant, approximately 50%. Despite being adherent to the currently recommended treatments consisting of a 4 to 6-month regimen of anti-TB drugs nearly 85% of individuals can achieve recovery [5].

In Egypt, tuberculosis prevalence rate has declined, with TB incidence dropping from 26 cases per 100,000 in 2000 to 10 per 100,000 in 2021 [7]. This improvement may be attributed to increased treatment success rates, which stood at 86%. The estimated TB treatment coverage reached 69% in 2019. Additionally, TB mortality decreased from 3.5 to 0.43 per 100,000 population [2]. Understanding the risk factors of EPTB is a crucial step in targeting preventive strategies. The risk factors are diverse and require increased attention due to the diversity in the pathogenesis of each EPTB site [8].

The study aimed to describe the basic sociodemographic, clinical characteristics, and risk factors of extrapulmonary tuberculosis and to study the outcome of the anti-tuberculosis treatment given to patients

Material and methods

Study design and ethical consideration

This cross-sectional study was conducted on 244 patients diagnosed with TB at the endemic medicine department and the tuberculosis clinic in the chest department, in Kasr-Al-Ainy Hospitals, Cairo University over the period from October 2023 to August 2024. The Institutional Review Board and ethics committee of faculty of medicine at Cairo University approved this study (MS-414-2023).

Data collection

Informed consent was obtained from all patients for participation in the study. Patients of both sexes diagnosed with EPTB (144 and 6 with concurrent EPTB & pulmonary TB (PTB)) for comparative purpose 94 patients with only PTB were included. Patients were subjected to detailed history including sociodemographic data, history of present illness, concomitant medications, and comorbidities. Close contact with a case of TB or admission to fever hospital, any family history for TB and clinical examination together with determination of treatment regimen and any complication during course of the treatment were also asked. All data was collected during the visits to the clinic. The study excluded patients who refused to participate or those with incomplete data.

Sample collection

Patients were diagnosed by microbiological tests, radiological findings, and biopsy with histopathological analysis or molecular testing. Samples were collected at the microbiological laboratory attached to the clinic. Smear microscopy was performed on processed sediments using auramine-O fluorochrome staining and confirmed with Ziehl-Neelsen (ZN) staining, The processed sediments were inoculated into Middlebrook 7H10 solid slants, as well as liquid broth Mycobacterial Growth Indicator Tubes (MGIT) [9]. Molecular study by GeneXpert was done for patients. Radiological assessment was performed at the radiology department. Biopsies were obtained at chest or endemic medicine departments.

They were divided into two parts, one was fixed in formalin and sent for histopathological examination by an expert pathologist to identify the caseating granuloma with Langhans and foreign body giant cells, the other was crushed and sent in special GeneXpert containers fixed in saline to study the GeneXpert assay [10].

Case definitions for PTB & EPTB were done according to National TB control guidelines in Egypt (2017); where PTB referred to a case of TB involving the lung parenchyma, with smear positive or in case of smear negative; radiological abnormalities, whereas EPTB referred to a case of TB involving organs other than the lungs. Diagnosis was based on at least one specimen with confirmed *Mycobacterium TB* or histological or strong evidence consistent with active EPTB [11]

Follow-up included clinical assessments and observation of adverse effects, particularly elevated liver enzyme levels, one month after starting treatment.

Statistical analysis

Data was entered and statistically analyzed on the Statistical Package of Social Science Software program, version 25 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data was presented using mean, standard deviation, median and interquartile range for

quantitative variables and frequency and percentage for qualitative ones. Comparison between groups for qualitative variables was performed using Chi square or Fisher's exact tests while for quantitative variables the comparison was conducted using independent t-test (for normally distributed data) or Mann Whitney test (for skewed data). *P* values less than or equal to 0.05 were considered statistically significant.

Results

This cross-sectional study was conducted on 244 patients with TB. Of these patients, 59% (144) had exclusively extrapulmonary tuberculosis (EPTB), 38.5% (94) had exclusively pulmonary tuberculosis (PTB), whereas 6 patients (2.5%) had concurrent PTB and EPTB. The sociodemographic features and sites for EPTB (n=150) are shown in **table (1)**. Eighty patients were females (53.3%) with mean age 34.9 ± 14.9 years. Patients living in urban areas represented 49.3% (n=74). The most common forms were lymphatic TB (36%, n=54), followed by pleural TB (15.3%, n=23), musculoskeletal TB (15.3%, n=23), and intestinal TB (14.7%, n=22). Comorbidities, management and treatment outcomes for patients with EPTB are represented in **table (2)**. Ninety-seven patients (64.7%) had no comorbidity. Patients with diabetes represented 20.7% followed by hypertension which represented 12%. About 40% of the patients were smokers, whereas 8.7% were drug addicts. Four percent of the patients were people living with HIV as shown in **figure (1).** Most of the patients were either diagnosed with histopathology (46.7%, n=70) or the molecular Xpert MTB/RIF assay (33.3%, n=50). Regarding anti-tubercular treatment regimens, 28% (n=42) of the patients with EPTB received treatment for 6 months, whereas treatment was extended to 9 months in 48.7% (n=73) of patients and to 12 months in 22.7% (n=34). Steroids were added to the treatment regimen in 15.3% (n=23) of the patients. Fifty six percent of patients with EPTB (n=84) completed treatment and 34.7% (n=52) were still on treatment, while 3 patients died before the end of their treatment regimen. Observing the antitubercular drugs complications, more than 95% of patients did not develop any adverse events.

There was no statistically significant difference between both studied groups (EPTB & PTB) as regards age, residence or history of imprisonment of patients (p =0.29, p =0.40, p =0.45) respectively. There was a statistically significant higher percentage of female patients who had EPTB (p< 0.001). Regarding occupation, there was a statistically significantly lower percentage of not working with patients who had EPTB (p= 0.022) as shown in **table (3).**

There was a statistically significant higher percentage of cigarette smoking, chronic obstructive pulmonary disease (COPD) and asthma among patients who had PTB compared to those who had EPTB **(**p <0.001 and p =0.02, respectively). Risk factors and management for the two studied groups (PTB & EPTB) are demonstrated in **table (4)**.

The study reported a statistically significant higher percentage of EPTB patients definitively diagnosed with histopathology and molecular Xpert MTB/RIF assay compared to patients with PTB who were diagnosed using microbiological smear methods (p<0.001). Extension of treatment duration and adding steroids to antitubercular drugs were resorted to in a statistically significant higher percentage of EPTB patients compared to PTB patients (p<0.001). There was a significantly higher percentage of patients who are still on treatment among the patients with EPTB than patients with PTB (p<0.001). Mortality was reported in 3 patients with EPTB (2.1%) and 1 patient with PTB (1.1%)**.** Concerning those who died with EPTB, the first was 37 years old diagnosed with TB meningitis, anti TB drugs were initiated and well tolerated for 1 week, then developed convulsions and died 1 day later. The second was 59 years old diagnosed with TB meningitis, received anti- TB drugs for 2 days and died due to sepsis, the third was 27 years old diagnosed as POTT'S disease, start of anti TB drugs was done, 4 days later she developed hypoxia and passed away. A 66-year-old patient diagnosed with pulmonary TB, started anti- TB drugs and 2 days later, passed away due to hypoxia.

Table 1. Sociodemographic features and sites of lesions for Tuberculosis in the patients with extrapulmonary TB.

(1.A) Sociodemographic features of patients with EPTB	**N= 150 * (%)**
Age (in years)	
Range	9 – 70
Mean (SD)	34.9 ± 14.9
Median (IQR)	30 (24 - 45)
Gender	
Male	70 (46.7)
Female	80 (53.3)
Residence	
Urban	74 (49.3)
Rural	58 (38.7)
Immigrant	18 (12)
Occupation	
Working	88 (58.7)
Not working / housewife	42 (28)
Student	20 (13.3)
History of Prison	
Yes	10 (6.7)
No	140 (93.3)

(1.B) Sites for extrapulmonary TB **	**N= 150 * (%)**
Lymph node	54 (36)
Pleural	23 (15.3)
Musculoskeletal	23 (15.3)
Intestinal	22 (14.7)
Peritoneal	9 (6)
Meningeal	9 (6)
Genitourinary	7 (4.7)
Breast	4 (2.7)
Omental	3 (2)
Pancreatic	3 (2)
Pericardial	3 (2)
Uveitis	2 (1.3)
Suprarenal	1 (0.7)
Cutaneous	1 (0.7)
Miliary	1 (0.7)
Spleen	1 (0.7)

***** Includes 144 patients with exclusively EPTB and 6 patients with concurrent EPTB and PTB, SD=standard deviation, IQR= interquartile range, EPTB: extrapulmonary Tuberculosis

** Some patients had more than one site

Table 2. Comorbidities, risk factors, management and outcome for patients with extrapulmonary TB.

(2.A) Comorbidities of patients with EPTB **	**N=150 * (%)**
None	97 (64.7)
Diabetes	31 (20.7)
Hypertension	18 (12)
Systemic lupus erythematosus	3 (2)
Chronic kidney disease	3 (2)
Rheumatoid arthritis	2 (1.3)
Psoriasis	2 (1.3)
Hepatitis C	1 (0.7)
Kidney transplantation	1 (0.7)
Ischemic heart disease	1 (0.7)
Hypothyroidism	1 (0.7)
Ulcerative colitis	1 (0.7)
Breast cancer on chemotherapy	1 (0.7)
Primary immunodeficiency	1 (0.7)
Familial mediterranean fever	1 (0.7)
Autoimmune hepatitis	1 (0.7)
Silicosis	1 (0.7)
(2.B) Management of patients with EPTB	**N=150 * (%)**
Diagnostic methods ***	
Histopathology	70 (46.7)
Xpert MTB/RIF assay	50 (33.3)
Mycobacteria Growth Indicator Tube (MGIT)	13 (8.7)
Adenosine deaminase (ADA)	6 (4)
Radiological findings	9 (6)
Microbiological smear	7 (4.7)
Duration of anti TB drugs	
6 months	42 (28)
9 months	73 (48.7)
12 months	34 (22.7)
18 months	1 (0.6)
Total	150 (100)
Additional management	
None	118 (78.7)
Steroids	23 (15.3)
Ultrasound-guided drainage	5 (3.3)
Debridement	4 (2.7)
Treatment outcomes	
Completed treatment	84 (56)
Still on treatment	52 (34.7)
Loss of follow up	9 (6)
Relapse	6 (4)
Discontinue treatment	5 (3.3)
Death	3 (2)
Complications	
No	143 (95.4)
Increased transaminases	5 (3.3)
Intestinal obstruction	2 (1.3)

***** includes 144 patients with exclusively EPTB and 6 patients with concurrent EPTB and PTB, SD=standard deviation, IQR= interquartile range, EPTB: extrapulmonary Tuberculosis, HIV: Human immunodeficiency virus, Xpert MTB/RIF: xpert mycobacterium/rifampcin

****** Patients had more than one comorbidity

** * Patients diagnosed by combined methods

Table 3. The sociodemographic features of the two studied groups (extrapulmonary and pulmonary TB).

Sociodemographic Data of the studied population	**PTB(n=94) N (%)**	**EPTB(n=144) N (%)**	***p*-value ***
Age			
Range	12-73	9-70	
Mean ± SD	37.3 ±16.1	34.4 ±14.8	
Median (IQR)	33 (23-50)	30 (24-45)	0.29
Gender			
Male	64 (68.1)	66 (45.8)	
Female	30 (31.9)	78 (54.2)	< 0.001
Residence			
Urban	41 (43.6)	71 (49.3)	0.40
Rural	44 (46.8)	55 (38.2)	
Immigrant	9 (9.6)	18 (12.5)	
Occupation			
Working	48 (51.1)	85 (59)	0.022
Not working/ housewife	40 (42.6)	39 (27.1)	
Student	6 (6.4)	20 (13.9)	
History of Prison			
Yes	9 (9.6)	9 (6.2)	0.45
No	85 (90.4)	135 (93.8)	

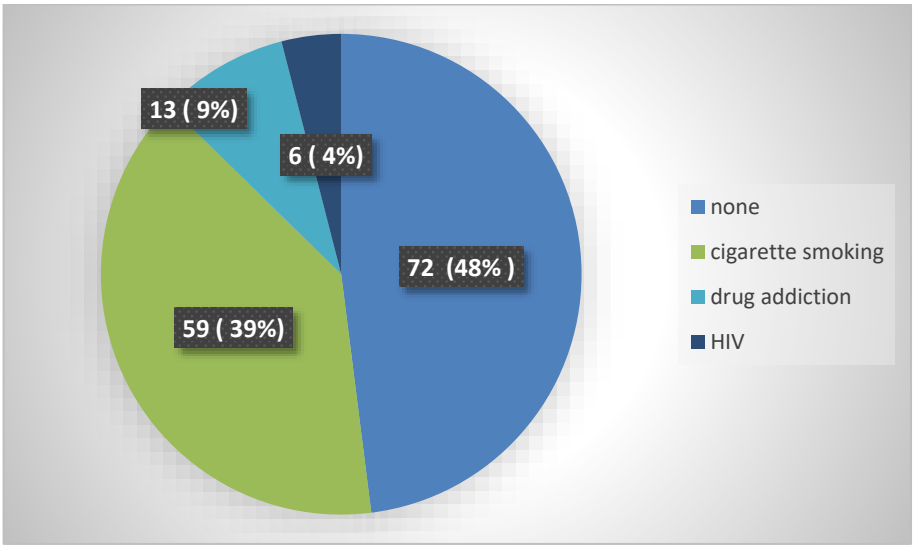
*$p \leq 0.05$ = statistically significant, SD=standard deviation, IQR= interquartile range, EPTB: extrapulmonary Tuberculosis, PTB: pulmonary Tuberculosis

Table 4. Risk factors, management for the two studied groups (extrapulmonary and pulmonary TB).

	PTB (N=94) N (%)	**EPTB (N=144) N (%)**	***p*-value ***
Risk Factors of the studied population			
Cigarette Smoking	57 (60.6)	55 (38.2)	< 0.001
Drug Addiction	12 (12.8)	12 (8.3)	0.27
HIV	2 (2.1)	6 (4.2)	0.49
Management of the studied population			
Diagnostic methods			
Histopathology	2 (2.1)	68 (47.2)	< 0.001
Xpert MTB/RIF assay	12 (12.8)	49 (34)	< 0.001
Mycobacteria Growth Indicator Tube (MGIT)	1 (1.1)	10 (6.9)	0.05
Adenosine deaminase (ADA)	0 (0)	6 (4.2)	0.08
Radiological findings	2 (2.1)	6 (4.2)	0.49
Microbiological smear	77 (81.9)	7 (4.9)	< 0.001
Duration of treatment			
6 months	78 (83)	41 (28.5)	< 0.001
9 months	16 (17)	69 (47.9)	
12months	0 (0)	33 (22.9)	
18 months	0 (0)	1 (0.7)	
Additional management			
None	94 (100)	111 (77.1)	
Steroids	0 (0)	23 (16)	< 0.001
Debridement	0 (0)	4 (2.8)	
Ultrasound-guided drainage	0 (0)	4 (2.8)	
Intestinal obstruction	0 (0)	2 (1.4)	

*$p \leq 0.05$ = statistically significant, SD=standard deviation, IQR= interquartile range, EPTB: extrapulmonary Tuberculosis, PTB: pulmonary Tuberculosis, HIV: Human immunodeficiency virus, Xpert MTB/RIF: xpert mycobacterium/rifampcin

Figure 1. Risk factors for patients with extrapulmonary TB.



HIV: human immunodeficiency virus. Patients have more than one risk factor

Discussion

In Egypt, TB remains a significant public health issue, leading the National Tuberculosis Control Program to apply diagnosis, notification, registration and provision of treatment of TB cases all over the country [12]. The disease typically affects the lungs causing pulmonary TB which is the most concerning form because of its role in disease transmission. However, TB can affect nearly any organ through hematogenous or lymphatic dissemination of *Mycobacterium tuberculosis*, resulting in extrapulmonary TB (EPTB). Previous studies have reported that EPTB accounts for 15-40% of all TB infections, and this proportion is still rising. EPTB can exist alone or coexist with pulmonary TB (PTB) simultaneously [13]. EPTB has various clinical presentations and poses a diagnostic challenge to physicians because of its obscure paucibacillary nature and difficulties in obtaining suitable samples as opposed to sputum. Given the public health burden of TB, and insufficient epidemiological data on EPTB in Egypt, the aim of the study was to describe the epidemiological and clinical characteristics & treatment outcome of patients diagnosed with EPTB.

The study included 244 patients, 144 of whom were diagnosed with exclusively EPTB in addition to six patients with concurrent PTB. The increasing prevalence of EPTB is consistent with its growing trend at the global level. A recently published systematic review reported a 26% pooled prevalence of EPTB among TB patients in African countries. This is similar to that reported from Japan (25.3%) and Germany (21.6%) but lower than that in Australia (40%) and Italy (31.6%) [14]. In the past, patients with EPTB were overlooked and missed due to the limitations of traditional techniques, the insidious clinical presentation, and the poor performance of diagnostic tests. However, in recent years, advances in diagnostic modalities have led to an increased number of confirmed cases of EPTB [15]. Another factor to this finding is that the study hospital is a tertiary hospital equipped with more sensitive diagnostic options for identifying EPTB and dealing with complex TB patients. In this study, different types of EPTB occurred at different frequencies, with tuberculous lymphadenitis (36%), followed by pleural (15.3%), musculoskeletal (15.3%) and intestinal TB (14.7%) being the most prevalent types. Tuberculous lymphadenitis occurs due to the lymph nodes serving as niches for *Mycobacterium tuberculosis* growth and persistence. Reactivation of latent TB can begin in the lymph nodes, leading to the dissemination of bacteria to the lungs and other organs [16]. Pleural TB frequently results from the rupture of subpleural lesions in the lungs, allowing *Mycobacterium tuberculosis* to invade the pleural cavity [17].

A similar pattern was previously observed in studies conducted in Egypt and identified lymphatic and pleural tuberculosis as the most common sites for EPTB [12]. **El Bouhy et al.** [18] reported that lymphatic TB constituted the largest group (29.13%) of EPTB cases in Assiut followed by genitourinary (22.82%) [18]. Also, **El-**

Shabrawy et al. [19] reported that the most frequently affected extrapulmonary site in Sharkia Governorate was lymph nodes (30.2%) followed by bone (28.4%), and then pleura [19]. Comparable findings have been reported in other countries, including the Netherlands & the United Kingdom, Saudi Arabia, The USA and Iran [20-23]. Musculoskeletal TB is common in developing countries, affecting approximately 10% of those with active disease [24]. The authors speculate that the observed increase in skeletal TB may be driven by the improvement in diagnostic techniques.

In this study, the mean age of patients with EPTB was in the fourth decade. A similar finding was reported by **Zedan et al.** [25] who found a mean age of 37.5 ±16.0 years among Egyptian patients with tuberculosis [25]. This age group may be at higher risk of exposure due to the higher prevalence of smoking behavior, and physical, mental, and occupational stress.

It is important to note that this age group represents the most productive segment of the national population, underscoring the urgence for targeted attention in national control programs [26]. In the study, the incidence of EPTB was slightly higher in females (53%), consistent with the findings of **Shirzad et al.** [19] this could be due to certain factors such as hormonal variations, cultural aspects, and differences in immune system responses [23, 27]. A study conducted by **Sanches et al. [**28] in northern Portugal reported that the female gender is an independent risk factor for EPTB [28]. However, **Nour et al.** [29] reported a higher incidence of EPTB in males in Egypt [29]. The current study revealed more urban residents than rural residents among EPTB patients. Similar findings were reported in studies conducted in Giza, Shakira and Ismailia among Egypt governorates. This can be explained by the possibility of overcrowding in the urban areas, with a lack of adequate aeration and an increase of air pollution. On the contrary, previous studies from El-Behira, Dakahlia, Qalyobia, Minofia, Assiut, Sohag, and Aswan among Egypt governorates showed that TB cases were higher in rural areas owing to poverty, drinking contaminated milk, exposure to cough spray from infected cattle, or close physical contact with infected animals [26]. There has been an increased rate of immigration to Egypt in recent years, largely attributed to the political conflicts in the region [30].

We observed that immigrants accounted for 12.5% of EPTB cases in this study. A WHO descriptive analysis of TB burden in Egypt showed that the estimated incidence rate per 100000 population decreased to 10 in 2021, compared to neighboring countries: 59 in Libya and 58 in Sudan [29]. In this study, 18 patients with TB had a history of imprisonment. A study conducted in a Thai prison found that the prevalence of TB among prisoners was 10 times higher than in the general population [31]. This elevated risk was attributed to factors such as the overcrowded conditions and duration of incarceration. People who are coinfected with TB and human immunodeficiency virus (HIV) are 21-34 times more likely to develop active TB disease than people without HIV. The ratio of EPTB to PTB in people with late stages of HIV increases to 50:50 from 20:80 in the early stages [32].

In spite of this, the low rate of HIV co-infection in our study (4.2%) may be due to referral bias, as most HIV-positive patients are referred to fever hospitals. This likely leads to underrepresentation in study sample. In the study, drug addiction was present in 8.3% of patients with EPTB. TB infection among drug users is linked to various factors, including the risky lifestyle of drug users, crowded living conditions, isolation for drug consumption, sharing of items such as pipes, malnutrition, and higher prevalence of HIV [33].

Chronic diseases can lead to abnormalities in immune function, leading to an increased incidence of EPTB. Diabetes mellitus (DM) is a risk factor that strongly impacts the diagnosis and treatment of TB, with the proportion of DM in all TB patients varying from 15% to 25%. While DM increases the overall risk of infections, the exact mechanisms through which DM predisposes individuals to TB remain unclear [34]. In our study, DM was present in 20% of our EPTB patients, a finding consistent with studies conducted by **Balakrishnan et al.** and **Shanmuganathan et al.** [35, 36]. Alongside DM, we found that hypertension was present in 12% of our EPTB patients. There appears to be no direct link between TB and the prevalence of hypertension, except through the common association between DM and hypertension [37].

The study observed that chronic kidney disease (CKD) was present in 2% of patients with EPTB. A study by **Hussein et al.** [38] found that TB in patients with chronic renal failure (CRF) often

localizes to extrapulmonary sites, most commonly presenting as tuberculous peritonitis and lymphadenitis. They attributed this to a weakened T-cell response, defects in antigen-presenting cells, and persistent inflammation caused by uremia and dialysis treatment. Additionally, factors such as malnutrition, vitamin D deficiency, and hyperparathyroidism contribute to immune suppression, increasing susceptibility to TB in extrapulmonary sites. Patients with EPTB who previously underwent kidney transplantation accounted for 0.7% of our cases [38]. **Ai et al.** [39] found that patients who undergo organ transplantation are 20 times more susceptible to TB than the general population, primarily due to the use of immunosuppressive drugs [39]. In this study, we compared the characteristics, management strategies and outcomes of patients with exclusively EPTB to patients with isolated PTB as a comparative group. Regarding co-morbidities, there was a higher percentage of cigarette smoking, COPD and asthma among patients who had PTB compared to those who had EPTB. Chronic obstructive pulmonary disease (COPD) and asthma can affect immune responses in a way that increases susceptibility to PTB [40].

However, they are not considered to have the same level of immunocompromising effects in EPTB [41]. A study by **Ai et al.** [39] reported that the relative risk of TB infection in tobacco smokers, compared to non-smokers, ranges from 2 to 3.4 [39]. Tobacco smoking directly affects the lungs by impairing local immune responses, such as alveolar macrophage function, and damaging respiratory tissues, contributing to increased susceptibility to lung infections like PTB [42].

There was an apparent difference between the studied groups as regards the method of definitive diagnosis of tuberculosis. In about half of our patients with EPTB, histopathology was useful for the definitive diagnosis.

This was in line with a study by **Shirzad et al.** [23]. Histopathology can detect the characteristic granulomas with caseous necrosis and can exclude other potential differential diagnoses that present similarly to EPTB [43]. With improved sensitivity and specificity than conventional methods, the xpert mycobacterium/rifampcin (Xpert MTB/RIF) assay is recommended as a diagnostic tool for EPTB [44]. This was the case in our study in which about one-third of the patients with EPTB were diagnosed with Xpert MTB/RIF assay. A study done by **Agrawal et al.** [45] found that Xpert MTB/RIF assay has a higher sensitivity than Acid fast bacilli smear microscopy even in respiratory samples, it can be a useful tool for the early diagnosis of patients with high clinical suspicion of pulmonary tuberculosis [45].

On the other hand, the majority of diagnosed pulmonary TB cases (82%) were smear-positive compared to a much lower yield of microbiological smears in EPTB (5%) which can be explained by fewer Mycobacterium bacilli in EPTB samples limiting the identification of acid-fast bacilli using microscopy. The standard treatment regimen for TB is a 2-month administration of rifampicin, isoniazid, ethambutol and pyrazinamide followed by a 4-month administration of rifampicin and isoniazid. This was the case in most patients with PTB (83%). On the contrary, only 28% of the patients with EPTB received treatment for 6 months whereas extension of treatment duration was resorted to in the remaining patients. The treatment regimen may need to be modified in EPTB, according to different sites and drug resistance, such as elongating treatment time to 9-12 months for central nervous system (CNS) and skeletal TB, and addition of steroids for meningeal and pericardial TB. Corticosteroids have been used as an adjunctive in the treatment of EPTB for the prevention of complications like neurological disability, pleural fibrosis and constrictive pericarditis [46].

Surgical debridement and imaging-guided drainage play a role in the management of relevant complications. There was a significantly higher percentage of patients who are still on treatment among patients with EPTB than patients with PTB. This observation can be attributed to the shorter treatment duration for PTB patients compared to EPTB patients, whose treatment periods often exceeded six months. Treatment of patients with tuberculosis requires careful monitoring for adverse drug effects.

Since hepatotoxicity may be caused by isoniazide (INH), rifampcin (RIF), or pyrazinamide (PZA), patients receiving antituberculous therapy with first-line drugs should undergo baseline measurement of liver enzymes [47]. In the study we found that 3.3% of EPTB patients developed increased transaminases. Another complication that our patients developed was intestinal obstruction in patients who had TB enteritis. Intestinal obstruction occurs because of intestinal luminal narrowing, multiple strictures, or adhesions [48]. Few

limitations to the analysis should be noted. Firstly, the reduced population size regarding certain variables, such as HIV infection. Secondly, the collection of data on EPTB cases from one tertiary hospital limits the overall scope of our findings. Thirdly, lack of further classification according to extrapulmonary sites prior to further analysis of clinical characteristics. Despite these limitations, this study on patients with EPTB in Kasr Al-Ainy hospitals has generated valuable knowledge about their epidemiological and clinical characteristics and might provide helpful guidance on their management.

Conclusion

This study describes the epidemiological and clinical characteristics of patients with EPTB, in a tertiary university hospital in Cairo, and helps to identify the risk factors associated with the disease. The common forms of EPTB were lymphatic, pleural and skeletal TB. Younger patients, residents of urban areas, and people diagnosed with diabetes had a higher risk of EPTB. Considering the rising burden of EPTB cases, heightened clinical awareness, effective management of comorbid conditions, promotion of socioeconomic development in control strategies and improving diagnostic tools would be a major step toward controlling the spread of the disease and improving patient outcomes in Egypt.

Conflict of interest

The authors report no conflict of interest.

Funding

Non-declared.

Authors' contribution

Sherief Musa: Conception and design of the study, revising the draft critically for important intellectual content. Sabah Ahmed Hussein: Data collection, revising the data critically for important intellectual content. Hala Abdulnasser Alammari: Data collection, intertpretation of data, drafting the article. Mira Atef: Drafting, revision of the article and submitting the article. All authors have approved the final article.

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