

Epidemiology of Extrapulmonary TB and its risk factors in Damascus, Syria.

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Abstract

Background:

Tuberculosis (TB) is a major public health concern worldwide and is the 13th leading cause of death, and the second deadliest infectious disease after COVID-19 worldwide¹. Extrapulmonary tuberculosis (EPTB) cases accounted for 15% of the 7.2 million cases of TB worldwide in 2019. ² global statistics indicate that Tuberculosis causes 4,500 deaths every day¹. We aim to study the epidemiology of EPTB and its risk factors.

Methods:

A multicenter retrospective study was conducted at the National Center for Tuberculosis Control in Damascus in the year 2020 to analyze the patients with extrapulmonary tuberculosis.

Results:

205 patients were diagnosed with extrapulmonary tuberculosis in Damascus and its countryside in the year 2020, and the most common site of extrapulmonary tuberculosis was Lymph Nodes (102) 49.75%, while ear and breast were the least common (1 case of each). Cervical nodes were the most affected with EPTB (80.40%), while Mediastinal nodes were the least affected (1.96%). The most incidence rate was in patients between 25 and 34 years old, while the least incidence rate was in patients older than 65 years old. The percentage of infected females was approximately 66%, while the percentage of infected males was approximately 34%. The majority of infected patients were residents in the city (78.68%) compared to infected patients from the countryside (21.31%). The most common comorbidity was Hypertension: 23.41% of cases, while kidney diseases were the least common. Smoking was the most common risk factor. The most common general symptom associated with extrapulmonary tuberculosis was fever 55.60%, while night sweats were the least common symptom 14.63%.

Conclusion:

Tuberculosis is a major public health concern worldwide that can cause death or cause long-lasting complications but still can be prevented by vaccination and avoiding the possible risk factors that were studied in this study.

Introduction

Tuberculosis is a major public health concern worldwide. Globally, tuberculosis is the 13th leading cause of death and the second deadliest infectious disease after COVID-19. ¹Although tuberculosis most commonly affects the lungs, it can also affect other sites and is known as extrapulmonary tuberculosis. In 2020, an estimated 10 million people got infected with tuberculosis (TB) worldwide. 5.6 million men, 3.3 million women, and 1.1 million children. TB is present in all countries and age groups but 98% of cases occur in developing countries¹. Extrapulmonary tuberculosis (EPTB) cases accounted for 15% of the 7.2 million cases of TB worldwide in 2019. ² Although it is a preventable and treatable disease, global statistics indicate that this disease kills about 4,500 patients every day¹.

Methods

Subjects: The sample of the study included patients with extrapulmonary tuberculosis who met the inclusion criteria.

Inclusion and Exclusion criteria: All patients with confirmed extrapulmonary tuberculosis were included in the study. Cases of pulmonary tuberculosis, suspected and probable cases that have not been confirmed with EPTB, cases with insufficient data, and patients who did not return to the center after diagnosis were excluded.

Instrumentation and procedure: The study was conducted in a retrospective design, and included all EPTB cases in the year 2020 that met the inclusion criteria after obtaining the ethical approvals. The authors collected clinical data from the patient's medical records that were kept in the National Center for Tuberculosis Control in Damascus. This center contains data on all TB cases admitted to all hospitals and TB centers in Damascus. Medical files of all the patients of our study sample were thoroughly studied, and the mentioned patients were contacted by the data collecting team to obtain further information. Then specifically designed forms were filled up with the gathered data which included; the patient's gender, age, area of living (rural or urban), place of living (healthy or unhealthy), occupation, symptoms, clinical manifestations, comorbidities, habits (like smoking and drinking).

Data Analysis: The variables and data were entered and encoded in Excel, and then entered and decoded in SPSS-25 to analyze relationships, graphs, and statistical tables through it. Chi-square was used and a P-value < 0.05 has been considered statistically significant.

Ethical considerations: Ethical approval was obtained from the Institutional Review Board (IRB) Faculty of Medicine, Syrian Private University, and the National Center for Tuberculosis Control in Damascus Institutional Review Board (IRB). Verbal consent was obtained from each patient when contacting them for data collection purposes.

Results

205 patients were diagnosed with extrapulmonary tuberculosis in Damascus and its countryside in the year of 2020 and the sites of extrapulmonary tuberculosis were distributed as follows: Lymph nodes (102) 49.75%, Peritoneum (28) 13.66%, Pleura (26) 12.68%, Spine (11) 5.36%, Meninges (8) 3.90%, Bones (7) 3.41%, Skin and Soft tissues (5) 2.44%, Genitourinary system (5) 2.44%, Pericardium (3) 1.46%, Eye (3) 1.46%, Ear (1) 0.49%, Breast (1) 0.49%.

Lymph nodes TB, gastrointestinal TB, Eye TB, Breast TB, and Peritoneal TB were most common in females, while other EPTB types were most common in males. **(Table 1)**

In diagnosing tuberculosis of the lymph nodes by biopsy the affected nodes were distributed as follows: Cervical nodes: 82/102 cases (80.40%), Axillary nodes: 7/102 cases (6.86%), Supraclavicular nodes: 5/102 cases (4.90%), Submandibular nodes: 3/102 cases (2.94%), Mesenteric nodes: 3/102 cases (2.94%), Mediastinal nodes: 2/102 cases (1.96%).

The highest incidence rate was in patients between 25 and 34 years old, while the lowest incidence rate was in patients older than 65 years old. The percentage of infected females was approximately 66%, while the percentage of infected males was approximately 34%. **(Table 2)**

The majority of infected patients were residents in the city (78.68%) compared to infected patients from the countryside (21.31%).

The most common comorbidities among patients with extrapulmonary tuberculosis in the study were: Hypertension: (48/205) 23.41%, Diabetes Mellitus: (31/205) 15.12%, Chronic obstructive pulmonary disease (COPD): (5/205) 2.4%, Kidney disease: (3/205) 1.5%, COVID-19: (20/205) 9.75% were diagnosed, 9 of which were confirmed by PCR testing, and 11 cases were diagnosed clinically. 17 of those infected with Covid-19 had lymph nodes tuberculosis, two had urogenital tuberculosis, and one case with pleural tuberculosis. **(Table 3)**

Possible risk factors for extrapulmonary tuberculosis: Smoking (cigarettes, hookah, passive): 79/205 (38.53%), Unhealthy housing: 48/205 (23.41%) living in an unventilated or unsunny environment, forced displacement: 43/205 (20.97%) were displaced, which forced them to live in crowded and unhealthy places, Imprisonment: 6 (2.92%). **(Table 4)**

The most common general symptom associated with extrapulmonary tuberculosis was fever 55.60%, while night sweats were the least common symptom 14.63%. **(Table 5)**

In non-adherence to tuberculosis treatment: 9 cases were recorded (4.39%) and were distributed as follows: 4/102 (6.86%) of the patients with Lymphocytic TB, 1/26 (3.84%) of the patients with Pleural TB, 1/11 (9.09%) of patients with Pott's disease, 1/5 (20%) of patients with skin and soft tissue TB, 1/3 (33.33%) of patients with Pericardial TB, 1/1 (100%) of patients with Breast Tb.

In Relapse Cases: 12/205 (5.85%) cases were recorded and were distributed as follows: 7/102 (6.86%) of Lymphocytic TB cases, 2/28 (7.14%) of Peritoneal TB, 2/11 (18.18%) of Spine TB cases in the study, 1/8 (12.50%) of Meningeal TB cases.

Declarations

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Availability of data and materials:

All data related to this paper's conclusion are available and stored by the authors. All data are available from the corresponding author on a reasonable request.

Conflict of interest:

The authors declare that they have no conflict of interest.

Authors' contributions:

AJ, MF, MN, SA, and FK conceptualized the study, wrote the study protocol, performed the statistical analysis, participated in data collection, and did the literature search. YM did a literature search and revision of the draft. All authors read and approved the final draft.

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Tables

Table 1. represents the prevalence of extrapulmonary tuberculosis types between males and females

TB Type	Males [n=70]	Females [n=135]	Total [n=205]
Lymph Nodes TB	25/70 (35.71%)	77/135 (57.03%)	102/205 (49.75%)
Pleural TB	15/70 (21.42%)	11/70 (8.14%)	26/205 (12.68%)
Meningeal TB	5/70 (7.14)	3/135 (2.22%)	8/205 (3.90%)
Skin and Soft tissue TB	2/70 (2.85%)	3/135 (2.22%)	5/205 (2.44%)
gastrointestinal TB	0/70 (0.00%)	5/135 (3.70%)	5/205 (2.44%)
Eye Tb	1/70 (1.43%)	2/135 (1.48%)	3/135 (1.46%)
Breast TB	0/70 (0.00%)	1/135 (0.74%)	1/205 (0.49%)
Peritoneal TB	6/70 (8.57%)	22/135 (16.29%)	28/205 (13.66%)
Pott's disease	5/70 (7.14%)	6/135 (4.44%)	11/205 (5.36%)
Skeletal TB	5/70 (7.14%)	2/135 (1.48%)	7/205 (3.41%)
Genitourinary TB	2/70 (2.85%)	3/135 (2.22%)	5/205 (2.44%)
Pericardial TB	3/70 (4.28%)	0/135 (0.00%)	3/205 (1.46%)
ENT Tb	1/70 (1.43%)	0/135 (0.00%)	1/205 (0,49%)

Table 2. represents the prevalence of extrapulmonary tuberculosis by age and gender.

Age	Male [n = 70]	Female [n = 135]	Total [n = 205]
0-4 years	(7/70) 10.00%	(6/135) 4.44%	(13/205) 6.34%
5-14 years	(11/70) 15.27%	(16/135) 11.85%	(27/205) 13.17%
15-24 years	(9/70) 12.85%	(28/135) 20.74%	(37/205) 18.04%
25-34 years	(16/70) 22.85%	(30/135) 22.22%	(46/205) 22.43%
35-44 years	(10/70) 14.28%	(18/135) 13.33%	(28/205) 13.65%
45-54 years	(11/70) 15.27%	(21/135) 15.55%	(33/205) 16.09%
55-64 years	(3/70) 4.28%	(10/135) 7.40%	(13/205) 6.43%
older than 65 years	(3/70) 4.28%	(6/135) 4.44%	(9/205) 4.39%

Table 3. represents the distribution of comorbidities among the extrapulmonary TB patients

Comorbidity	Number of patients with it Number (%)	Number of patients without it Number (%)	Chi-Square Value	P-Value
Hypertension	48 (23.4)	157 (76.6)	57.956	<0.05
Diabetes Mellitus	31 (15.1)	174 (84.9)	99.751	<0.05
COPD	5 (2.4)	200 (97.6)	185.488	<0.05
Kidney Disease	3 (1.5)	202 (98.5)	193.176	<0.05
Covid-19	20 (9.8)	185 (90.2)	132.805	<0.05

Table 4. represents the possible risk factors for extrapulmonary TB patients

Possible risk factors	Number of patients with it	Number of patients without it	Chi-Square	P-Value
Smoking	79	126	10.776	< 0.05
Unhealthy housing	48	157	57.956	< 0.05
Forced displacement	43	162	69.078	< 0.05
Imprisonment	6	199	181.702	< 0.05

Table 5. represents the types of extrapulmonary tuberculosis with its associated general symptoms

TB Type	Symptoms associated General					
Lymph Nodes TB	Fever	Site Swelling	Single Lymphadenopathy	Multiple Lymphadenopathy	Tenderness	
	(47/102) 46.07%	(92/102) 90.19%	(90/102) 88.23%	(12/102) 11.76%	(35/102) 34.31%	
Pleural TB	Fever	Coughing	Chest Pain	Dyspnea		
	(17/26) 65.38%	(21/26) 80.76%	(19/26) 73.07	(12/26) 46.15%		
Peritoneal TB	Fever	Abdominal Pain	Ascites	Nausea and Vomiting	Diarrhea	Jaundice
	(23/28) 82.14%	(23/28) 82.14%	(28/28) 100%	(23/28) 82.14%	(6/28) 21.42%	(11/28) 39.28%
Meningeal TB	Fever	Headache	Nausea and Vomiting	Mental Confusion	Neck Stiffness	
	(5/8) 62.50%	(5/8) 62.50%	(3/8) 37.50%	(3/8) 37.50%	(5/8) 62.50%	
Pott's disease	Fever	Back Pain	Abnormalities Morphological	Abscesses	Nerve (hemiplegia) injury	
	(6/11) 54.54%	(10/11) 90.90%	(4/11) 36.36%	(7/11) 63.63%	(2/11) 18.18%	
Skeletal TB	Localized warmth	Skeletal Pain	Swellings	Movement Limitations		
	(4/7) 57.15%	(6/7) 85.72%	(5/7) 71.50%	(7/7) 100%		
Skin and tissue TB Soft	Fever	Painful Areas Erythematous	Hard Painless Ulcer			
	(3/5) 60%	(1/5) 20%	(4/5) 80%			
Genitourinary TB	Fever	Lower Abdominal Pain	Urinary Symptoms	Menstrual Changes	Sterility	
	(1/5) 20%	(2/5) 40%	(1/5) 20%	(2/5) 40%	(3/5) 60%	
TB gastrointestinal	Fever	Abdominal Pain	Bowel Habits Changes	Weight Loss	Right Iliac Fossa Mass	Nausea and Vomiting
	(2/5) 40%	(4/5) 80%	(1/5) 20%	(3/5) 60%	(1/5) 20%	(2/5) 40%
Pericardial TB	Fever	Coughing	Chest Pain	Dyspnea		
	(3/3) 100%	(2/3) 66.66%	(2/3) 66.66%	(3/3) 100%		
Eye Tb	Redness Eye	Gradual Vision Loss				
	(3/3) 100%	(3/3) 100%				

Table 6. Number of Extrapulmonary TB cases between 2003 and 2020 in Damascus:

Year	Number of Cases	Year	Number of Cases
2003	315 Case	2012	701 Case
2004	295 Case	2013	772 Case
2005	330 Case	2014	800 Case
2006	326 Case	2015	611 Case
2007	375 Case	2016	391 Case
2008	330 Case	2017	303 Case
2009	339 Case	2018	254 Case
2010	272 Case	2019	231 Case
2011	410 Case	2020	205 Case

Discussion

The data shows that lymph node TB is the dominant type of extrapulmonary tuberculosis in Damascus city. Several studies in different countries have shown that the dominant type of extrapulmonary tuberculosis differs with different geographical locations. For example, lymph node TB was the most common type in the Netherlands (39%), the United States (40%), and the United Kingdom (37%)³⁻⁴⁻⁵, while pleural tuberculosis was the most common in Poland (36%) and Romania (58%).⁶ There could be a possible reason for the difference in the most common sites of EPTB between Syria and other countries, which is that the BCG vaccine that is used in Syria, provides immunity to various types of TB, and thus may cause the absence or decrease in the appearance of certain types of TB, while in countries where this vaccine is not given, the rates of emergence of the types that the BCG vaccine decreases may be higher.⁷⁻⁸

The highest infection rate among the patients in the sample was in the age range 25-34 years (22.43%), this age range was also the most age range associated with extrapulmonary TB in a similar Indian study.⁹ Although extrapulmonary tuberculosis primarily affects adults, 19.51% of cases occurred in children under the age of 15 years, and this may be because of the lack of vaccination due to the war in Syria and due to displacement cases, which amounted to 20.97%.

The majority of patients infected with extrapulmonary TB were females (65.85%), this was also the case in an Iranian study, which indicates that there's a relation between the female gender and extrapulmonary TB.¹⁰

As mentioned previously, the percentage of patients infected with extrapulmonary tuberculosis was higher in the city of Damascus compared to its countryside, at a rate of 78.68%. This may have been contributed by the far distance between the city center where most of the hospitals and TB centers are located and the countryside, and thus decreasing the number of patients coming from the countryside, and the movement of most of the rural population to the city, especially during the war years.

In cases that were associated with chronic diseases, the study showed that Hypertension was the most common accompanying disease with a rate of 23.41%, as well as in a Taiwanese and an Indian study.¹¹⁻¹² In studying the relationship between hypertension and extrapulmonary TB there was a statistical significance for not having Hypertension. In studying the relationship between diabetes mellitus and extrapulmonary TB there was a statistical significance for not having diabetes mellitus, this was also the case in a Brazilian and Taiwanese study.¹³⁻¹⁴ In studying the relationship between COPD and extrapulmonary TB there was a statistical significance for not having COPD. In studying the relationship between kidney disease and extrapulmonary TB there was a statistical significance for not having kidney disease. In studying the relationship between Covid-19 and extrapulmonary TB there was a statistical significance for not having Covid-19. As for the relationship between AIDS and extrapulmonary tuberculosis, the National Center for Tuberculosis Control in Damascus stopped conducting all HIV-related tests in 2011 to this day due to the war's circumstances.

On the other hand, extrapulmonary tuberculosis (EPTB) was not associated with Pulmonary TB risk factors, as in studying the relation between having them and extrapulmonary TB, there was a statistical significance for not having them. Although smoking is considered common in Syria, only 73 cases were recorded of smoking between active and passive smoking. Perhaps this is due to the small sample size, or the absence of an actual connection between smoking as a risk factor and between the infection with extrapulmonary tuberculosis which was the case in a Taiwanese study.¹⁵

The most common presentation in lymph nodes TB was site swelling near the infected nodes (90.19%), while in a study conducted in India, the most common presentation was painless single node enlargement with fever. The most common symptom of pleural tuberculosis was dry nonproductive cough (80.76 %), followed by pleural pain (73.07%). These results are similar to what was mentioned in a Turkish study by Cohen and Richard about the most common symptoms of pleural tuberculosis.¹⁶ The results of Pott's disease "spinal tuberculosis" were similar to those of an Indian study, where the most common symptoms were spinal pain and back pain.¹⁷ In urogenital tuberculosis, the results were similar to those in an Indian study.¹⁸ In Peritoneal tuberculosis, the most common symptom was ascites 28/28 (100%), followed by fever, abdominal pain, and vomiting, 23/28 (82.14%) for each. In meningial tuberculosis, the most common symptoms were fever, headache, stiff neck, and confusion. These results are similar to a study

conducted in Turkey.¹⁹ Tuberculosis of the skin and soft tissues had various symptoms such as hard, painless ulcers 4/5 (80%), fever 3/5 (60%), and painful erythematous area 1/5 (20%). In Skeletal tuberculosis, limitation of joint movement was the most common presentation with a percentage of 7/7 (100%), similar to a study conducted in northern Iran.¹⁰ In gastrointestinal tuberculosis, the common symptoms were abdominal pain 4/5 (80%), weight loss 3/5 (60%), and nausea and vomiting 2/5 (40%). Abdominal pain was also the most common (74%) in a study conducted in the United Kingdom, while nausea and vomiting accounted for (31%) of the symptoms and were the second most common symptom.²⁰ In Pericardial tuberculosis, the most common symptoms were fever and dyspnea (100%), followed by coughing and chest pain (66%). In Ocular tuberculosis, eye redness and gradual vision loss were the most common (100%). As for ear tuberculosis, we had one patient who suffered from gonorrhoea and progressive hearing loss. Regarding breast tuberculosis, there was one affected woman who had a painful lump in the right breast.

In the cases of recurrence, the rate of recurrence in Pott's disease was the highest (18.18%) compared to the rates of recurrences in other extrapulmonary TB types.

According to the records of the National Center for Tuberculosis Control in Damascus over 18 years (2003-2020), it was found that the rate of extrapulmonary tuberculosis was almost stable between 2003 and 2010, but in 2011 and 2015 there was a significant increase in the infection rates before they returned to their usual rates between the years 2016 and 2020, this increase may be strongly attributed to the war that took place in Syria, where not all children were able to obtain the national vaccination program, which led to an increase in the incidence of many diseases, including tuberculosis, in addition to the re-emergence of other diseases such as polio for example.

Conclusion

Tuberculosis is a major public health concern worldwide that can cause death or cause long-lasting complications but still can be prevented by vaccination and avoiding the possible risk factors that were studied in this study.

Figures

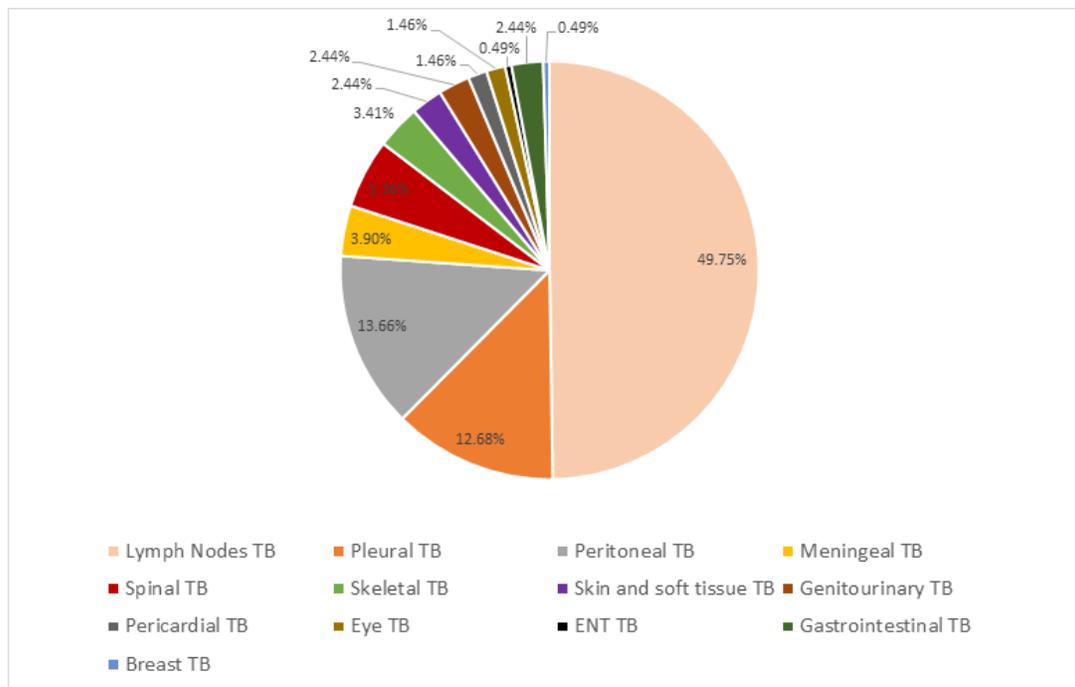


Figure 1

Prevalence of Extrapulmonary TB