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Extrapulmonary tuberculosis in China: a national survey

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Abstract

Background: Extrapulmonary TB (EPTB) is not a notifiable infectious disease in China but brought heavy burden to public health. However, epidemic situation of EPTB nationwide was unclear yet. This study aimed to investigate the magnitude and main subtypes of EPTB in China.

Methods: A national cross-sectional study with multistage, stratified cluster random sampling was conducted during 2020-2021. Proportions of EPTP in all TB patients by organs were calculated. Logistic regression models were used to estimate odds ratios by characteristics.

Results: A total of 6,843 TB patients were included. 24.6% of them were patients with EPTB, and the proportion of EPTB solo was 21.3%. Higher EPTB burden was observed in children, female, clinically diagnosed patients, provincial-level and prefectural-level health facilities, and Central and West China. EPTB occurred most frequently in respiratory (35.5%), musculoskeletal (15.8%) and peripheral lymphatic (15.8%) systems with top three subtypes including tuberculous pleurisy (35.0%), spinal TB (9.8%) and cervical tuberculous lymphadenopathy (7.9%). With the increase of age, proportion of peripheral lymphatic TB decreased, and proportion rank of genitourinary TB rose.

Conclusion: It is essential to strengthen diagnosis and treatment capacity of EPTB in primary medical facilities. EPTB should be list into National Tuberculosis Program as a notifiable disease.

Keywords: extrapulmonary tuberculosis, epidemiology, subtypes, national survey

Introduction

As an infectious disease attracting worldwide attention, tuberculosis (TB) brought a high disease burden of an estimated 9.9 million people infected in 2020, and was the
leading cause of death from a single pathogen until the pandemic of COVID-19 (World Health Organization, 2021). Though majority of TB cases come on firstly from the lungs and transmitted through respiratory tract, Mycobacterium tuberculosis may develop lymphatic or blood dissemination when the body's immunity is weakened, and cause extrapulmonary tuberculosis (EPTB) invading any human organ outside the lungs other than teeth, hair, and nails (Dunrong Zhang, 2000; World Health Organization, 2013). Compared with pulmonary tuberculosis (PTB), EPTB is characterized by atypical clinical symptoms, difficult diagnosis, high disability and mortality rate, which not only seriously threatens patients' health, but also brings heavy economic burden to patients, families and society (Ananthakrishnan R, et al., 2012; Banta JE, et al., 2020; Owusu-Edusei K, et al., 2017; Prasanna T, et al., 2018). Therefore, diagnosis, treatment and prevention of EPTB cannot be neglected. Globally, based on the report of World Health Organization (WHO), the number of EPTB notified in 2019 accounted for 16% of the total number of notified TB cases and the proportion was highest in East-Mediterranean region (24%), followed by Southeast Asia (19%), Europe (16%), Africa and America (15%), and Western Pacific region was the lowest (8%) (World Health Organization, 2020). Because the prevalence and risk of EPTB varies in different subpopulations, including different settings for patients’ treatment, gender, and ageing population, etc (Yang S, et al., 2021; Yang Z, et al., 2004), the control of EPTB is more complicated. Obviously, to reach the ambitious vision and its milestones of the “End TB Strategy” posted by WHO with zero disease, zero death and zero suffering due to the disease (World Health Organization, 2015), EPTB should be effectively controlled together with PTB.

China has historically been a country with a high prevalence of TB, and ranked the number two in the world behind India in 2020 (World Health Organization, 2021). In China, for timely recording and reporting TB cases, a specially designed system named Tuberculosis Information Management System (TBIMS) (Huang F, et al., 2014) is widely used around the mainland China. Three-level TB management units are established with the basic units centralized at the county level, and designated TB health facilities at each level were set up by health authorities for TB diagnostic and treatment (Chinese Center for Disease Control and Prevention, 2021). According to China's national law of infectious diseases control (National People’s Congress, 2005), only PTB cases are reported to national Infectious Diseases Reporting System.
and transferred to designated facilities for further diagnosis and treatment, while EPTB is not a mandatorily reported infectious disease even it is also encouraged to be reported to TBIMS. Therefore, there was no representative data of EPTB magnitude, let alone the frequency among extrapulmonary organs at the national level of China, and the available studies of EPTB in China were mainly based on data collected by local health facilities. Based on an observational study from a tertiary TB specific hospital in Beijing, up to 31.3% of hospitalized TB patients had EPTB (Pang Y, 2019). However, the proportion was much lower in Shenzhen City’s outpatients of 7% (Jiansheng H, 2000), and in other regional studies that did not involve tuberculous pleurisy, including 10.4% in Tianjin City (Jingxin Li, et al., 2019), and 19.1% in Qiannan of Guizhou Province (Cao Y, et al., 2022). Previous studies also showed that the proportion of EPTB in some regions of China had gradually increased during the past decades (Cao Y, et al., 2022; Jingxin Li, et al., 2019). Hence, it is essential to grasp the epidemic situation of EPTB nationwide and take countermeasures, but the previous studies mainly provided regional evidence of China, and the forms of EPTB were not fully covered.

In this study, we carried out a nationwide retrospective cross-sectional study with stratified cluster random sampling based on clinical records to better understand the magnitude of EPTB in China. We believe our findings can provide the basis for further improving National TB Program (NTP) strategies and strengthening the diagnosis, treatment, and management of EPTB in China.

Methods

Study design

A retrospective cross-sectional study (World Health Organization, 2012) based on reviewing clinical data from different level health facilities was conducted by the National Center for Tuberculosis Control and Prevention (NCTB) of Chinese Center for Disease Control and Prevention (China CDC) from 2020 to 2021, which is in charge of National TB Program (NTP) in mainland China. All clinical records of patients with laboratory bacteriologically confirmed and clinically diagnosed TB in
these facilities in 2019 were extracted and reviewed to describe the epidemiology of EPTB. According to the WHO's definition of EPTB, EPTB refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs (World Health Organization, 2013). In this study, patients with EPTB were defined as patients who were diagnosed as at least one subtype of TB other than pulmonary tuberculosis (PTB), including patients only with lesions out of the lungs and patients with EPTB and PTB concurrence. The detailed process was as follows.

Sampling of health facilities

A multistage, stratified cluster random sampling was conducted in this survey. All of 9337 county-level or above health facilities in mainland China which have reported at least one TB case in 2019 were included in the sampling process as the sampling cluster. Based on the 5.0% of EPTB proportion in total TB patients registered in national TBIMS, 20.0% of tolerance error, 3 of design effect (DEFF), 0.05 of α value, and 10.0% of patients with unverifiable information, a total of 6100 TB patients were needed in this survey. After comprehensively considering the differences in diagnosis capacity and number of TB patients diagnosed in the different levels of health facilities, a total 31 health facilities were randomly selected among 21 provinces around mainland China, including 2 provincial-level health facilities, 4 prefectural-level health facilities, and 14 county-level health facilities. The 31 selected health facilities included 9 facilities located in East, 9 facilities in Central and 13 facilities in West regions, respectively. The detailed process of sampling and geographical distribution of the selected health facilities were shown in Appendix Text S1, Appendix Figure S1 and S2.

Data collection and cleaning

After trained by NCTB of China CDC, primary investigators (staffs from local CDC) collected and reviewed medical records in 2019 of the selected health facilities. A password protected electronic database were developed to store the data, including patients’ national ID number, name, sex, age, address, diagnosis, laboratory test
results, department for treatment, and name and address of the health facility. For facilities with electronic Hospital Information System (HIS), investigators retrieved HIS with “结核” (TB in Chinese characters) and extracted all the matched records into a password protected electronic database. For facilities with paper-based records, all patients, outpatients, laboratories records were reviewed, and all of the TB-related records were double-checked and entered into the electronic database by investigators.

The medical data recorded in the electronic database were further verified and cleaned by provincial-level investigators after the primary data collection. The records were deduplicated by patients’ national ID number or, if the ID number was unavailable, identified by the same name and manually check and determined by investigators with age, gender, similar home address and other related information. The original diagnosis in different records of the same patient were combined and checked by physicians for finalizing the diagnosis. The diagnosis of PTB was based on the standards provided in Diagnosis for Pulmonary Tuberculosis (WS288-2017) National Health and Family Planning Commission, 2017). The diagnosis of EPTB in different systems was based on the Technical Guide for Tuberculosis Prevention and Control in China (Chinese Center for Disease Control and Prevention, 2021), patients’ symptoms and signs, imaging characteristics and other relevant laboratory testing results were considered comprehensively in the diagnostic process. Based on ICD-11 and actual disease status of Chinese cases (World Health Organization, 2018), EPTB was classified as 11 subtypes in body system level (including respiratory (excluding PTB), musculoskeletal, digestive, genitourinary, endocrine, peripheral sympathetic, nervous, circulatory system, other system, multisystem and TB of unspecified system) and 48 subtypes in body organ level (Appendix Table S1).

After excluding intra- and inter-facility duplication and non-TB patients, NCTB’ staffs anonymized the sensitive information (i.e., ID, name, etc) in the database, and exported the data for further analysis.
Statistical analysis

Descriptive statistics were used to describe the characteristics of diagnosed TB cases at investigated health facilities. We calculated the proportion of EPTB as number of EPTB cases accounted for total diagnosed TB cases. The proportions of EPTB’s subtypes in different systems and organs among all patients with EPTB were also calculated for describing the nationwide compositions of EPTB. Mann-Whitney U test was used to compare the median age between PTB patients and EPTB patients because it was not normally distributed. Chi-square test was used to compare the categorical variables between PTB patients and EPTB patients, and the compositions of EPTB by characteristics. Univariable and multivariable logistic regression models were used to estimate the crude and adjusted odds ratios (ORs and aORs, respectively) and 95% CIs of being diagnosed as EPTB by characteristics.

A two-sided p value of 0.05 or less was regarded as significant. Statistical analyses were done with SPSS, version 21.0 (IBM Corp) and R version 4.0.3 (R Core Team). Mapping was done with ArcGIS, version 10.0 (Esri).

Ethics

Permission for the study was sought from the National Center for Tuberculosis Control and Prevention, Beijing, China. As this study involved analysis of routinely collected secondary data, the academic committee waived off the need for informed consent and approved this study (NCTB-2022015).

Results

General information
A total of 28,599 TB-related medical records were extracted from the 31 health facilities. After excluding 17,504 duplication, 3,405 non-TB patients, and 847 presumptive TB patients without laboratory confirmation or clinical diagnosis, 6,843 clinically diagnosed or laboratory confirmed tuberculosis patients were included in this study, including 5,162 patients only with PTB and 1,681 patients with EPTB (Figure 1). Among the patients with EPTB, 1,459 patients (86.8%) were only with lesions out of pulmonary organs, and 222 patients (13.2%) diagnosed as EPTB concurrent with PTB (Table 1).

The overall M: F ratio was 1.9:1, and the median age was 52.0 (IQR: 35.0-65.0) years. Most of them were clinically diagnosed TB without laboratory confirmation (80.8%), outpatients (63.3%), and treated at designated TB facilities (68.4%). Among these TB patients, a total of 124 patients (1.8%) were infected with HIV. In addition, patients were evenly distributed regionally with 32.2% in East, 34.7% in Central, and 33.1% in West regions, respectively. (Table 1) Compared with PTB patients, patients with EPTB were more female (45.3% vs 31.6%), clinically diagnosed (96.5% vs 75.7%), treated in provincial-level facilities (30.6% vs 11.3%) and non-designated facilities (44.6% vs 27.3%) (p<0.05) (Table 1).

Proportion of EPTB
Among all TB patients, 24.6% (95%CI: 23.4-25.8%, 1,681 patients) of them were patients with EPTB, and the proportion of patients only with lesions out of pulmonary organs was 21.3% (95%CI: 20.3-22.4%, 1,459 patients). In the East region of China, 13.5% (95%CI: 12.0-15.0%) of TB patients were diagnosed as EPTB, while the proportion of the Central of China was 26.5% (95%CI: 24.5-28.6%) and that of West region was 33.4% (95%CI: 31.1-35.8%). (Table 2)

The proportion of EPTB in female patients was 31.8% (95%CI: 29.7-34.1%), which was higher than that in male patients (P< EPTB: 20.7%, 95%CI: 19.4-22.0%; adjusted
OR (aOR): 1.60, 95% CI: 1.41-1.81, p<0.001). Children aged under 15 years had a significantly higher EPTB proportion than other age group reaching up to 50.5% (95% CI: 38.2-65.8%, p<0.001). 29.3% (95% CI: 28.0-30.8%) of clinically diagnosed patients were diagnosed as EPTB, which was seven times higher than patients with laboratory confirmation (4.4%, 95% CI: 3.4-5.6%; aOR: 9.23, 95% CI: 6.99-12.20, p<0.001). Similar proportions of EPTB were observed between patients infected with HIV (29.0%, 95% CI: 21.0-39.3) and HIV negative patients (24.5%, 95% CI: 23.3-25.7, p>0.05). No significant difference in EPTB's proportion was observed in inpatients compared with outpatients (aOR: 1.05, 95% CI: 0.91-1.20, p>0.05), and in non-designated TB health facilities compared with designated TB facilities (aOR: 1.10, 95% CI: 0.94-1.30, p>0.05). As for the different levels of health facilities, Provincial-level (46.9%, 95% CI: 43.0-51.0%; aOR: 4.87, 95% CI: 4.06-5.85, p<0.001) and prefectural-level (23.6%, 95% CI: 21.6-25.6%; aOR: 1.85, 95% CI: 1.59-2.15, p<0.001) health facilities diagnosed higher proportions of EPTB than county-level facilities (18.2%, 95% CI: 16.8-19.7). In addition, the EPTB's proportion was significantly higher in West (aOR: 2.60, 95% CI: 2.18-3.10, p<0.001) and Central (aOR: 1.87, 95% CI: 1.57-2.23, p<0.001) regions than East region of China. (Table 2)

Proportion of EPTB's subtypes

EPTB occurred most frequently in respiratory (excluding PTB, 35.5%), musculoskeletal (15.8%) and peripheral lymphatic (15.8%) systems with the top three subtypes including tuberculous pleurisy (35.0%), spinal TB (9.8%) and cervical tuberculous lymphadenopathy (7.9%) (Figure 2 and 3, Appendix Table S2-S3). The highest proportion of EPTB's subtype in different systems were tuberculous pleurisy (98.8%) in respiratory system TB excluding PTB, spinal TB (62.1%) in musculoskeletal system, peritoneum TB (44.4%) in digestive system, renal TB (38.7%) in genitourinary system, breast TB (50.0%) in endocrine system, cervical tuberculous lymphadenopathy (50.2%) in peripheral lymphatic system, tuberculous meningitis (68.9%) in nervous system, tuberculous pericarditis (90.9%) in circulatory system, and oral TB (61.7%) in other systems, respectively. (Figure 3, Appendix Table S4-S12)
The proportion of peripheral lymphatic and genitourinary TB was higher in female than male (peripheral lymphatic: 20.8% vs 11.6%, genitourinary TB: 11.4% vs 8.3%), which the proportion of respiratory TB (excluding PTB) was lower in female (28.8% vs 41.0%) (p<0.001) (Appendix Table S2, Figure S3). The proportion of peripheral lymphatic TB was the highest in children under 15-years-old (41.7%). With the increase of age, the proportion of peripheral lymphatic system TB decreased, while respiratory TB (excluding PTB) became the top one EPTB in proportion after 15-years-old, and the proportion rank of genitourinary TB rose sharply from Rank 8 in children (0-14 years) to Rank 3 in young adults (25-34 years) and maintained at Rank 4 in the later age groups (Figure 4).

Most of the laboratory confirmed EPTP were respiratory TB (excluding PTB) (63.8), and the proportion of respiratory TB (excluding PTB) in EPTB inpatients (41.4%) was also higher than outpatients (30.5%, p<0.001) (Appendix Table S2, Figure S5-S6). The proportion of peripheral lymphatic TB was higher in patients infected with HIV (47.2%) than HIV negative patients (15.1%), while the proportion of respiratory TB (excluding PTB) was lower in patients infected with HIV (16.7% vs 35.9%) (Appendix Table S2, Figure S7). A higher proportion of respiratory TB (excluding PTB) was diagnosed and treated in county-level and prefectural-level health facilities than provincial-level facilities (40.6% vs 42.1 vs 22.2%, p<0.001), which was also shown in designated TB facilities than non-designated facilities (43.1% vs 25.9%, p<0.001) (Appendix Table S2, Figure S8-S9). In addition, the proportion of peripheral lymphatic system TB in the West region (22.8%) was significantly higher than Central (7.9%) and East (14.5%) regions (p<0.05) (Appendix Table S2, Figure S10).

Discussion

This study was the first to reveal the nationwide epidemic situation of EPTB in mainland China. The estimated overall EPTB’s proportion of 24.6% and the proportion of 21.3% in patients only with lesions out of the lungs among all TB patients were observed, which was higher than the overall level of the world (16%), and was about to reach the highest proportion of 24% in the East-Mediterranean region, which indicated that China was also a country with a high burden of EPTB (World Health...
Organization, 2020). While the proportion of EPTB in China was lower than some developing countries in Asia and Africa, of which the reported proportion of EPTB was 41.67% in Karnataka, India (Prakash SR, et al., 2013), 38.8% in Addis Ababa, Ethiopia (Fentie AM, et al., 2020), 38% in Lebanon (O'Son L, et al., 2020), and 36.5% in Laayoune, Morocco (Eddabra R, et al., 2020). In a large population study of 13,148 TB patients in Botswana, EPTB patients accounted for 22.7% among all TB patients, which was similar to our finding (Mudiayi TK, et al., 2020). Compared with other regional studies in China, the EPTB’s proportion reported in this study was much lower than the 31.3% reported in Beijing’s TB inpatients (Pang Y, et al., 2019). The data from TB designated or specialized hospital probably have high selection bias with relative high TB patient proportion among all cases and better diagnosis and treatment ability, and our study showed a higher EPTB’s proportion in provincial-level health facilities than prefectural-level and county-level facilities (46.9% vs 23.6% vs 18.2%). In addition, the EPTB’s proportion in this study was obviously higher than studies which did not involve tuberculous pleurisy, especially for a more than twice higher than Tianjin’ study (Jingxin Li, et al., 2019), which was because the tuberculous pleurisy (40.7%) was one of the main subtype of EPTB in China.

Our study implied that the leading subtypes of EPTB were tuberculous pleurisy, spinal TB and tuberculous peripheral lymphadenopathy. The rank was similar with that in the United States reported in 2017 (Sevgi DY, et al., 2017) and the South Korea reported in 2013 (Lee JY, 2015), while was different from Oman (Gaifer Z, 2017), Afghanistan (Fader T, et al., 2010) and Turkey (Sunnetcioglu A, et al., 2015) where the lymphatic TB was the most common subtype of EPTB. These variations may be related to the differences in geographical and social environments, ethnic, economic and health service capacity (Sunnetcioglu A, et al., 2015). Though more male than female had EPTB (M/F: 1.2/1), which was consistent with the previous studies in Colombia (Arciniegas W, et al., 2006), Turkey (Ozbay B, et al., 2002), Bosnia and Herzegovina (Cukic V, et al., 2018), and China (Kang W, et al., 2020; Pang Y, et al., 2019), the EPTB’s proportion was significantly higher among female than male (31.8% vs 20.7%; aOR:1.60, 95% CI: 1.41-1.81, p<0.001). The female gender’s significant association to EPTB also supported the findings of two previous studies conducted in Turkey and northern Italy, respectively (Di Nuzzo M, et al., 2018; Musellim B, et al., 2005). We also found that the proportions of peripheral lymphatic and
genitourinary TB in female were about 1.7 times (20.8% vs 11.6%) and 1.4 times (11.4% vs 8.3%) higher than male, which posed an additional risk for female and further supported the evidences provided by previous studies (Pang Y, et al., 2019; Lee JY, 2015; Obene SA, et al., 2019; Sanches I, et al., 2015; Qian X, et al., 2018). Female with genital system TB often had involved fallopian tubes (Grace GA, et al., 2017), which was an important cause of female infertility; and infection of the lymph nodes allowed the Mycobacterium tuberculosis to spread through the lymph system throughout the body. Therefore, as a kind of socially marginalized population, the disease burden of EPTB in women should be brought to the forefront.

In China, children had the highest EPTB proportion of 50.5%, which was about 1.6-2.6 times of the proportion in other age groups. The most common subtypes among children was peripheral lymphatic TB (41.7%), of which the supporting evidences also came from Colombia (Sepulveda EVF, et al., 2017), Spain (Santiago-Garcia B, et al., 2016), European Union (Sandgren A, et al., 2013) and Bunin’s studies (Ade S, et al., 2014). The phenomenon could be explained by the immature lymphatic system and cellular immunity in children. The change of major subtypes might be partly related to human body’s growth, development and aging. With the age-dependent maturation of immune system (Licastro F, et al., 2005; Lurie MB, 1941), the proportion rank of peripheral lymphatic TB decreased from the first place in children aged 0-14 years to the second place in age groups of 15-34 years, and then decreased to the third place after 45-years-old. On the contrary, with the development and functional maturity of the genital system, the rank of genitourinary TB increased rapidly from the eighth place in children aged under 14 years to the third or fourth place after 25 years. Therefore, for the effective prevention and control of EPTB, the characteristics of different age groups should be considered comprehensively.

As an important comorbidity of tuberculosis, HIV infection has been considered as a risk factor for EPTB by several studies (Gonzalez OY, et al., 2003; Naing C, et al., 2013; Shivakoti R, et al., 2017). However, in this study, no significant difference in EPTB’s proportion was observed in HIV-seropositive patients compared with HIV negative patients (aOR: 0.96, 95%CI: 0.63-1.45, p>0.05), which was similar with Di Nuzzo M, et al.’s study in northern Italy in which no single comorbidity was
associated with EPTB though multimorbidity was significantly associated to the development of EPTB (Di Nuzzo M, et al., 2018). This phenomenon in our study might be related to the low rate of HIV infection among TB patients in China, of which the HIV infection rate was only 1.7% among PTB-only patients and 2.1% among EPTB patients. This finding needs to be further verified in local HIV high-prevalence areas of China.

In the diagnosis and treatment of EPTB, different from the relatively evenly distributed subtypes of EPTB in outpatients, the leading subtype of EPTB in inpatients was respiratory TB represented by tuberculous pleurisy, which was consistent with the finding in a large-scale multicenter study of inpatients in China (Kang W, et al., 2020). A prominent problem in EPTB’s diagnosis was the extremely low rate of etiological diagnosis (3.5%). Lack of active sampling for pathogen testing and inadequate TB pathogen testing capacity in primary health facilities combined to result in a very low proportion of EPTB patients with laboratory-confirmed results. The phenomenon led to that the diagnosis and treatment of EPTB was mainly empirical, and medicine use could not be determined based on drug susceptibility results, which might increase the possibility of treatment failure (Pang Y, et al., 2019). Therefore, it is of great importance to strengthen and popularize the laboratory testing methods for EPTB with high accuracy, easy for detection and suitable for primary health facilities.

The proportion of EPTB diagnosed in designated TB health facilities seemed higher than in non-designated facilities (34.7% vs 19.9%), but adjusted in multi-variable analysis, the difference was not significant. However, the level of facilities seemed more determinant in the proportion difference, especially in provincial-level facilities (46.9%) with higher health capacity to provide EPTB-related health services. If the differential diagnosis capacity of the health facilities is inadequate, especially for primary health facilities, it is more likely to misdiagnosed EPTB as other diseases, resulting in misdiagnosis, such as confusing tuberculous meningitis with viral meningitis, bone TB with rheumatoid arthritis, and so on, which may hinder the early diagnosis and treatment of EPTB. Therefore, it is necessary to strengthen the training of non-TB specialist physicians to improve the diagnosis and treatment capacity for EPTB in health facilities, especially for primary medical facilities.
addition, there was regional imbalance in the proportion of EPTB, which was much lower in East region. Several reasons could explain the phenomenon. Previous studies had indicated that poverty level of regions, families or individuals had positive associations with TB's disease burden (Marmot M, et al., 2012; Newman L, et al., 2015; Zuo Z, et al., 2020). In terms of GDP, China's Central and Western regions lag behind the eastern coastal provinces (The People's Daily, 2022). More economically underdeveloped rural areas were in the Central and Western regions than East region, and Pang et al's study indicated that patients from rural areas were more likely to have EPTB in China (Pang Y, et al., 2019). In addition, there was also a regional imbalance in TB treatment capacity in China. The proportion of designated TB health facilities in all kinds of facilities with the ability of TB diagnosis and treatment was higher in East region (Du xin, et al., 2021), which could facilitate early detection and treatment of TB patients in East region, thereby preventing the disease from reactivating in other organs.

The limitation of this study was that this was a nationwide survey that could not provide the subnational evidence of EPTB’s proportion. However, this is the pioneering study to reveal the nationwide epidemiology of EPTB and the main subtypes of EPTB in mainland China, which covered all types of EPTB and patients. Our findings provide the basis for further improving of TB prevention and control in China. In the future TB management and decision-making, we should be aware that EPTB should not be ignored. Towards to End TB strategy goals, it is essential to strengthen the diagnosis and treatment capacity of EPTB in health facilities, especially for primary medical facilities. In addition, we could design wider and content rich specific investigation to substantiate and expand our findings, including population mobility, more comorbidities and the culture level of the patients tested with TB and EPTB. What is more important, EPTB should be list into National Tuberculosis Program as a notifiable disease. We would add stricter requirements of notifying all EPTB in our NTP surveillance system and establish sentinel surveillance sites in order to obtain the trends and more precise information of EPTB.
Declarations

Conflict of Interest

We declare no competing interests.

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Ethical Approval statement

Permission for the study was sought from the National Center for Tuberculosis Control and Prevention, Beijing, China. As this study involved analysis of routinely collected secondary data, the academic committee waived off the need for informed consent and approved this study (NCTB-2022015).

Author contributions

TL, XD, YZ and ZJ were responsible for the study design; FH, NW, NN and JR contributed to data collection, data management and data cleaning; XY and TL contributed to data analysis; the first draft of the manuscript was written by TL and XY and all authors commented on previous versions of the manuscript. All authors have reviewed and approved the final manuscript.
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Figure 3. Distribution of organ-level extrapulmonary tuberculosis (EPTB) in different systems

Figure 4. Ranking change of extrapulmonary tuberculosis (EPTB)’s subtypes with age
Figure 1. Study profile flowchart

Notes: TB= tuberculosis, PTB= pulmonary tuberculosis, EPTB= extrapulmonary tuberculosis.
Figure 2. Compositions of extrapulmonary tuberculosis (EPTB) in mainland China

Notes: TB= tuberculosis, HML TB= Hilar and mediastinal lymph node tuberculosis, PTB= pulmonary tuberculosis, LGTB= Liver and gallbladder tuberculosis, TBPL= tuberculous peripheral lymphadenopathy, TBL= tuberculous lymphadenopathy, TBM= Tuberculous meningitis, TBME: Tuberculous meningoencephalitis
Figure 3. Distribution of organ-level extrapulmonary tuberculosis (EPTB) in different systems

Notes: TB= tuberculosis, HML= Hilar and mediastinal lymph node tuberculosis, PTB= pulmonary tuberculosis, LGTB= Liver and gallbladder tuberculosis, TBPL= tuberculous peripheral lymphadenopathy, TBL= tuberculous lymphadenopathy, TBM= Tuberculous meningitis, TBME: Tuberculous meningoencephalitis
Figure 4. Ranking change of extrapulmonary tuberculosis (EPTB)’s subtypes with age

Note: * Respiratory tuberculosis (excluding pulmonary tuberculosis)
Table 1. Characteristics of pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB) patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (N=6843) n (%)</th>
<th>PTB-only (N=5162) n (%)</th>
<th>EPTB (N=1681) n (%)</th>
<th>EPTB-only (N=1459) n (%)</th>
<th>EPTB with PTB (N=222) n (%)</th>
<th>p value&lt;sup&gt;+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>4452 (65.1)</td>
<td>3532 (68.4)</td>
<td>920 (54.7)</td>
<td>766 (52.5)</td>
<td>154 (69.4)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2391 (34.9)</td>
<td>1630 (31.6)</td>
<td>761 (45.3)</td>
<td>693 (47.5)</td>
<td>68 (30.6)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>median (IQR)</td>
<td>52.0 (35.0-65.0)</td>
<td>53.0 (35.0-66.0)</td>
<td>49.0 (32.0-62.0)</td>
<td>49.0 (33.0-62.0)</td>
<td>49.5 (27.8-63.0)</td>
</tr>
<tr>
<td>------------</td>
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<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>0-14</td>
<td>95 (1.4)</td>
<td>47 (0.9)</td>
<td>48 (2.9)</td>
<td>45 (3.1)</td>
<td>3 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>15-24</td>
<td>776 (11.3)</td>
<td>582 (11.3)</td>
<td>194 (11.5)</td>
<td>153 (10.5)</td>
<td>41 (18.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25-34</td>
<td>831 (12.1)</td>
<td>609 (11.8)</td>
<td>222 (13.2)</td>
<td>194 (13.3)</td>
<td>28 (12.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>35-44</td>
<td>720 (10.5)</td>
<td>499 (9.7)</td>
<td>221 (13.1)</td>
<td>203 (13.9)</td>
<td>18 (8.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>45-54</td>
<td>1285 (18.8)</td>
<td>932 (18.1)</td>
<td>353 (21.0)</td>
<td>312 (21.4)</td>
<td>41 (18.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>55-64</td>
<td>1336 (19.5)</td>
<td>1047 (20.3)</td>
<td>289 (17.2)</td>
<td>248 (17.0)</td>
<td>41 (18.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥65</td>
<td>1785 (26.1)</td>
<td>1437 (20.3)</td>
<td>348 (20.7)</td>
<td>298 (20.4)</td>
<td>50 (20.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missing</td>
<td>15 (0.2)</td>
<td>9 (0.2)</td>
<td>6 (0.4)</td>
<td>6 (0.4)</td>
<td>0 (0.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Methods of diagnosis <0.001
- Laboratory confirmed
  - 1311 (19.2) 1253 (24.3) 58 (3.5) 16 (1.1) 42 (18.9)
- Clinically diagnosed
  - 5532 (80.8) 3909 (75.7) 1623 (96.5) 1443 (98.9) 180 (81.1)

Source of patients <0.001
- Outpatients
  - 4332 (63.3) 3420 (66.3) 912 (54.3) 819 (56.1) 93 (41.9)
- Inpatients
  - 2511 (36.7) 1742 (33.7) 769 (45.7) 640 (43.9) 129 (58.1)

HIV status 0.244
- Negative
  - 6719 (98.2) 5974 (98.3) 1645 (97.9) 1433 (98.2) 212 (95.5)
- Positive
  - 124 (1.8) 88 (1.7) 36 (2.1) 26 (1.8) 10 (4.5)

Level of health facilities <0.001
- County-level
  - 3488 (51.0) 2853 (55.3) 635 (37.8) 557 (38.2) 78 (35.1)
- Prefectural-level
  - 2258 (33.0) 1726 (33.4) 532 (31.6) 392 (26.9) 140 (63.1)
- Provincial-level
  - 1097 (16.0) 583 (11.3) 514 (30.6) 510 (35.0) 4 (1.8)

Designated TB health facilities <0.001
- Yes
  - 4684 (68.4) 3752 (72.7) 932 (55.4) 741 (50.8) 191 (86.0)
- No
  - 2159 (31.6) 1410 (27.3) 749 (44.6) 718 (49.2) 31 (14.0)
<table>
<thead>
<tr>
<th>Region</th>
<th>TB</th>
<th>PTB</th>
<th>EPTB</th>
<th>IQR</th>
<th>Chi-square test</th>
</tr>
</thead>
<tbody>
<tr>
<td>East</td>
<td>2201 (32.2)</td>
<td>1905 (36.9)</td>
<td>296 (17.6)</td>
<td>281 (19.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Central</td>
<td>2375 (34.7)</td>
<td>1746 (33.8)</td>
<td>629 (37.4)</td>
<td>549 (37.6)</td>
<td>80 (36.0)</td>
</tr>
<tr>
<td>West</td>
<td>2267 (33.1)</td>
<td>1511 (29.3)</td>
<td>756 (45.0)</td>
<td>629 (43.1)</td>
<td>127 (57.2)</td>
</tr>
</tbody>
</table>

Note: TB = tuberculosis, PTB = pulmonary tuberculosis, EPTB = extrapulmonary tuberculosis, IQR = interquartile range.

EPTB-only meant patients only with lesions out of the lungs.

Chi-square test was used to compare the characteristics between patients infected only with PTB and patients with EPTB (the group included patients only with lesions out of the lungs and patients with EPTB and PTB concurrence).
Table 2. Comparison of proportion of extrapulmonary tuberculosis (EPTB) by characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Proportion of EPTB</th>
<th>OR (95% CI)</th>
<th>p value</th>
<th>aOR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20.7 (19.4-22.0)</td>
<td>1.00</td>
<td>-</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>31.8 (29.7-34.1)</td>
<td>1.79 (1.60-2.01)</td>
<td>&lt;0.001</td>
<td>1.60 (1.41-1.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-14</td>
<td>50.5 (38.2-65.8)</td>
<td>1.00</td>
<td>-</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>15-24</td>
<td>25.0 (21.7-28.6)</td>
<td>0.33 (0.21-0.50)</td>
<td>&lt;0.001</td>
<td>0.33 (0.21-0.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25-34</td>
<td>26.7 (23.4-30.3)</td>
<td>0.36 (0.23-0.55)</td>
<td>&lt;0.001</td>
<td>0.37 (0.24-0.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>35-44</td>
<td>30.7 (26.9-34.9)</td>
<td>0.43 (0.28-0.67)</td>
<td>&lt;0.001</td>
<td>0.42 (0.27-0.66)</td>
<td>&lt;0.001</td>
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<tr>
<td>45-54</td>
<td>27.5 (24.8-30.4)</td>
<td>0.37 (0.24-0.57)</td>
<td>&lt;0.001</td>
<td>0.38 (0.25-0.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>55-64</td>
<td>21.6 (19.3-24.2)</td>
<td>0.27 (0.18-0.41)</td>
<td>&lt;0.001</td>
<td>0.28 (0.18-0.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥65</td>
<td>19.5 (17.6-21.6)</td>
<td>0.24 (0.16-0.36)</td>
<td>&lt;0.001</td>
<td>0.27 (0.17-0.41)</td>
<td>&lt;0.001</td>
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<tr>
<td>Missing</td>
<td>40.0 (38.8-77.8)</td>
<td>0.65 (0.22-1.98)</td>
<td>0.451</td>
<td>2.23 (0.66-7.48)</td>
<td>0.195</td>
</tr>
<tr>
<td><strong>Methods of diagnosis</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Laboratory confirmed</td>
<td>4.4 (3.4-5.6)</td>
<td>1.00</td>
<td>-</td>
<td>1.00</td>
<td>-</td>
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<tr>
<td>Clinically diagnosed</td>
<td>29.3 (28.0-30.8)</td>
<td>8.97 (6.85-11.74)</td>
<td>&lt;0.001</td>
<td>9.23 (6.99-12.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Source of patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatients</td>
<td>21.1 (19.7-22.4)</td>
<td>1.00</td>
<td>-</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>Inpatients</td>
<td>30.6 (28.5-32.8)</td>
<td>1.66 (1.48-1.85)</td>
<td>&lt;0.001</td>
<td>1.05 (0.91-1.20)</td>
<td>0.495</td>
</tr>
<tr>
<td><strong>HIV status</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>24.5 (23.3-25.7)</td>
<td>1.00</td>
<td>-</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Level of health facilities</td>
<td>Designated TB health facilities</td>
<td>Region</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
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<td>---------------------------------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>29.0 (21.0-39.3)</td>
<td>1.26 (0.85-1.87)</td>
<td>0.245</td>
<td>0.96 (0.63-1.45)</td>
<td>0.843</td>
</tr>
<tr>
<td></td>
<td></td>
<td>County-level</td>
<td>Prefectural-level</td>
<td>Provincial-level</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>18.2 (16.8-19.7)</td>
<td>1.00 (1.22-1.58)</td>
<td>3.96 (3.42-4.59)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prefectural-level</td>
<td>1.00</td>
<td>4.87 (4.06-5.85)</td>
<td>0.843</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Provincial-level</td>
<td>1.59 (1.22-1.58)</td>
<td>1.85 (1.59-2.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Designated TB health facilities</td>
<td>Yes</td>
<td>19.9 (18.7-21.2)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>34.7 (32.3-37.2)</td>
<td>2.14 (1.81-2.40)</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>Region</td>
<td>East</td>
<td>13.5 (12.0-15.0)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Central</td>
<td>26.5 (24.5-28.6)</td>
<td>2.32 (1.99-2.70)</td>
<td>&lt;0.001</td>
<td>1.87 (1.57-2.23)</td>
</tr>
<tr>
<td></td>
<td>West</td>
<td>33.4 (31.1-35.8)</td>
<td>2.23 (2.77-3.74)</td>
<td>&lt;0.001</td>
<td>2.60 (2.18-3.10)</td>
</tr>
</tbody>
</table>

Note: TB = tuberculosis, EPTB = extrapulmonary tuberculosis, OR = odds ratio, aOR = adjusted odds ratio, CI = confidence interval. 
* Sex, age, methods of diagnosis, source of patients, HIV status, level of health facilities, designated TB health facilities, and region were included in the multivariable logistic regression.