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Epidemiology and factors associated with Extra-pulmonary tuberculosis in a Low-prevalence area

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ABSTRACT

Background: Tuberculosis is a global public health problem. Extra-pulmonary tuberculosis accounts for an increasing proportion of cases worldwide, although information about epidemiological, clinical, or microbiological factors is lacking.
Methods: We conducted a retrospective observational study of tuberculosis cases diagnosed between 2016 and 2021, classified into Pulmonary and Extra-pulmonary tuberculosis. Univariable and multivariable logistic regression models were used to investigate risk factors of Extra-pulmonary tuberculosis.
Results: 20.9% of overall cases were classified as Extra-pulmonary tuberculosis, with a rising trend from 22.6% in 2016 to 27.9% in 2021. Lymphatic tuberculosis accounted for 50.6% of cases, followed by pleural tuberculosis (24.1%). 55.4% of cases belonged to foreign-born patients. Microbiological culture tested positive in 92.8% of Extra-pulmonary cases. Logistic regression analysis showed that women were more predisposed to develop Extra-pulmonary tuberculosis (aOR 2.46, 95% CI 1.45–4.20) as well as elderly patients (aged $\geq$ 65 years) (aOR 2.47, 95% CI 1.19–5.13) and persons with previous history of tuberculosis (4.99, 95% CI 1.40–17.82).
Conclusions: Extra-pulmonary Tuberculosis have increased within our study period. A profound decline occurred in 2021 tuberculosis cases, probably due to COVID-19. Women, elderly population, and persons with previous history of tuberculosis are at higher risk of developing Extra-pulmonary tuberculosis in our setting.

1. Introduction

Tuberculosis (TB) is a global public health problem. Actually, before COVID-19 pandemic it was the ninth leading cause of death worldwide [1] and according to 2021 WHO Global TB report it remains the leading cause of mortality among infectious diseases [2,3].

Due to the implications that COVID-19 pandemic has had on health care systems all around the globe, there was a large global drop in the number of new TB cases in 2020, a trend that continued during the first semester of 2021 and derived in a disruption of treatment services [2,3].

Pulmonary tuberculosis (PTB) is the most frequent clinical manifestation of the disease, accounting for 85% of reported TB cases worldwide. When TB affects any part of the body other than the lungs, it is referred to as extrapulmonary TB (EPTB). The most common anatomic sites for EPTB are lymph nodes and pleura, although it can be found almost anywhere in the body [4,5].

EPTB accounts for a significant proportion of TB cases worldwide. According to the 2022 ECDC Report, a total of 33 148 TB cases were reported in 2020. Of all these cases, 73.1% corresponded to PTB, compared to the 21.5% reported as EPTB. The remaining were reported as concurrent pulmonary-extrapulmonary TB or had no TB site reported [6]. In recent decades, an increase in EPTB rates in developed countries has been observed, in contrast to a decrease in PTB rates. Despite this, EPTB is not usually incorporated into TB control programs probably due to its lower transmissibility [7].

Traditionally, the main reported risk factors associated with the development of EPTB include extremes of age (<15 and > 65 years of age), female sex, people who migrate from high incidence TB countries, and immunosuppression [8–12]. However, there is a lack of information about other epidemiological, clinical, or even microbiological factors.

In order to comprehensively understand the epidemiology of EBTB, we conducted an observational study with the aim to describe the epidemiology, distribution and factors associated with EPTB in a low-burden TB area and secondly, to analyze the changes derived from the

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COVID-19 pandemic and their impact on TB diagnosis.

2. Materials and Methods

2.1. Data collection

We conducted a retrospective observational study of all TB cases diagnosed at Hospital Universitario 12 de Octubre, a tertiary care hospital with > 1,200 beds located in Madrid, Spain, that provides medical care to more than half a million inhabitants. Our study covered a period of over 6-year (January 2016 - December 2021). All TB cases reported during the study period were added, including pediatric cases. Among them, bacteriologically confirmed or clinically diagnosed cases were differentiated. PTB was defined as a TB case affecting the lung parenchyma, the tracheobronchial tree, or the larynx. EPTB was defined as TB involving organs or anatomical sites other than the lungs (such as pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, or meninges). Patients with concurrent EPTB and PTB and those with disseminated TB were excluded from our study because their illnesses were not distinctly classifiable as either PTB or EPTB.

We reviewed demographic and clinical variables from available electronic records belonging to both Microbiology and Preventive Medicine departments, to conduct comparative analyses between PTB and EPTB cases, including sex, age, country of birth, previous TB episode, HIV status and any other non-HIV immunosuppression.

2.2. Statistical analysis

All cases were grouped into PTB and EPTB for descriptive and comparative purpose.

Quantitative variables were expressed as mean (CI 95%) and compared with Studenťs *-t* test. Categorical variables were expressed as number (%) and compared by Pearson's chi squared test or Fisher's exact test if any n < 5. Results were considered significant when p-values were < 0.05.

We used univariable and multivariable logistic regression models to investigate risk factors associated with EPTB and calculate OR with 95% confidence intervals relative to PTB. Multivariate adjusted model included clinical and demographic baseline characteristics: sex, age, immunosuppression status, history of disease and nationality. Statistical analysis was performed using STATA software, version, 15.1 (StataCorp LP, College Station, TX, USA).

2.3. Ethical considerations

This study was designed and performed in accordance with the ethical standards of the Helsinki Declaration. The study protocol was approved by the Clinical Research Ethics Committee of our institution (Instituto de Investigación Sanitaria Imas12, Hospital Universitario 12 de Octubre). The need for written informed consent was waived due to the non-interventional study design.

3. Results

3.1. Tuberculosis cases

Between 2016 and 2021, a total of 398 patients with TB were diagnosed at Hospital Universitario 12 de Octubre. Out of these patients, 20.9% (n = 83) were diagnosed with EPTB, 60.8% (n = 242) with PTB, 8.5% (n = 34) presented disseminated TB, and 3.8% (n = 15) were classified as concurrent extrapulmonary-pulmonary tuberculosis; 24 cases (6%) had missing data for major disease site. During this period, overall TB cases decreased from 84 in 2016 to 57 in 2018. An isolated increase was observed in the number of global cases in 2019, with a downward trend that continues from 2020 to 2021, when the lowest number of global cases were reported (Fig. 1a). The overall trend of EPTB regarding global cases of TB shows an increase from 22.6% in 2016 to 27.9% in 2021 (Fig. 1b).

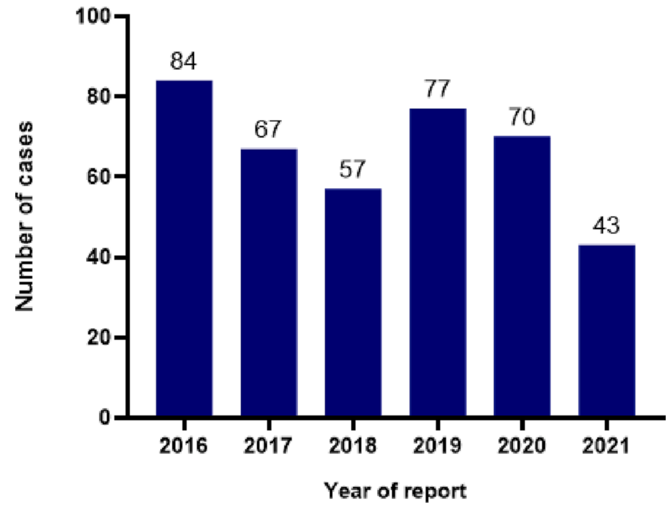

Fig. 1a. Annual distribution of overall TB cases.

The most common presentation of EPTB cases was lymphatic TB (50.6%, 42), followed by pleural TB (24.1%, 20), abdominal TB (8.4%, 7) and bone TB (8.4%, 7) (Fig. 2). We did not find any confirmed case of meningeal TB. Over the course of the study period, an increase in the incidence rate was only observed in lymphatic TB, whereas the trend for the remaining forms of EPTB moved towards stabilization with even a slight decline in some cases.

3.2. Demographic characteristics of EPTB cases

The mean age of patients with EPTB was 49.6 (CI 95% 45.0–54.2). The greatest burden of EPTB was recorded in the group aged 25–44 years (n = 28, 33.7%), followed by patients aged over 65 years (n = 22, 26.5%). Pediatric cases (<18 years) accounted for the 4,8% (n = 4) of EPTB cases.

More than half of the EPTB patients were female (n = 50, 60.2%). Lymphatic and pleural involvement were more frequently associated with female sex (76.2%, *p* = 0.003 and 55.0%, *p* = 0.583; respectively), while genitourinary and abdominal TB were more related to males (83.3%, *p* = 0.024 and 71.4%, *p* = 0.074; respectively).

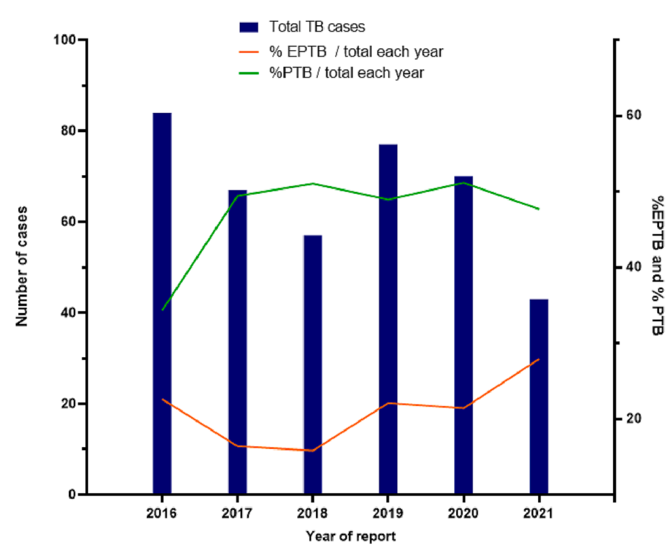

Fig. 1b. Evolution and progression of EPTB vs PTB cases during the study period.

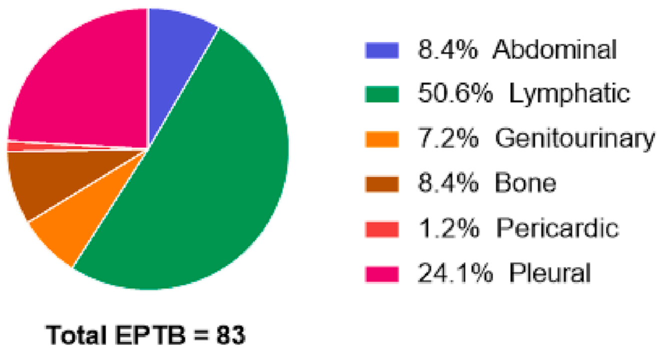

Fig. 2. Distribution of EPTB in anatomic locations.

Lymphatic TB was the most frequent form in all age groups (ranging from 52.4% to 66.7%) except for the 25–44 age group, in which pleural TB was as frequently seen as lymphatic TB (35.7% for both locations). In patients aged under 25, lymphatic TB accounted for the 66.7% of the cases, followed by pleural TB (25.0%).

Regarding the country of origin, of the 83 EPTB reported cases, 55.4% belonged to foreign-born patients whereas 44.6% corresponded to Spain-born patients. Higher proportions of foreign-born EPTB cases were observed in all age groups (ranging from 61.9% to 82.4%) except in the group aged over 65, in which the 95.5% of EPTB cases occurred in Spain-born patients. During the study period, the proportion of foreign-born patients increased significantly, from 58.5% in 2016 to 69.2% in 2021.

The greatest percentage of foreign-born patients in both PTB and EPTB cases corresponded to Bolivia (n = 30, 9.3%), Romania (n = 26, 8.0%), Peru and Republic of Ecuador (n = 22, 6.8% for each nationality), although when focusing only in EPTB cases, the highest incidence was found in Ecuador (n = 9, 10.9%) followed by Morocco (n = 4, 4.8%).

3.3. Comparison between EPTB and PTB cases

Table 1 summarizes characteristics of EPTB patients compared to PTB patients. The percentage of women was higher among EPTB rather than PTB cases (35.2% versus 64.8%, $p \leq 0.001$). EPTB patients were 7.6 years older than PTB patients (CI 95% 2.5–12.7 years). The percentage of cases with previous TB treatment was lower in EPTB (2.4% versus 10.8%, $p = 0.020$). Foreign-born patients were predominant in both EPTB and PTB groups, although this predominance was greater from 2018 onwards.

TB diagnosis was confirmed by a positive culture in 99.2% (240 / 242) of PTB cases, which was significantly higher than the percentage for EPTB cases (92.8%, 77 / 83; $p = 0.004$).

Regarding the total of culture-positive cases (N = 317, 97.5%), drug susceptibility testing yielded results in all of them. Only 7 (2.9%) MDR-TB cases were identified in the PTB group whereas no cases of antibiotic resistance were found in the EPTB group.

The results of the logistic regression analysis (Table 2) showed that women rather than men, were more predisposed to develop EPTB (aOR 2.46, 95% CI 1.45–4.20). Elderly patients (aged ≥ 65 years) were found to be more likely to have EPTB (aOR 2.47, 95% CI 1.19–5.13). Patients with a previous TB episode, had a higher risk of developing EPTB compared to patients without previous history of TB (4.99, 95% CI 1.40–17.82). HIV infection did not show any relation with the development of EPTB. Immunosuppression other than HIV and country of origin loosed statistical significance from univariate to multivariate analysis.

Table 1
Comparison of demographic, clinical and microbiological characteristics among PTB and EPTB patients in Hospital 12 de Octubre, Madrid, 2016–2021.

Variable	PTB (N = 242)	EPTB (N = 83)	*p* value
Sex, n (%)	93 (38.4)149	50 (60.2)33	0.001
Female	(61.6)	(39.8)	
Male			
Age, (IC 95%)	42.1	49.6	0.004
	(39.8–44.3)	(45.0–54.2)	
Type of case, n (%)	214	80	0.019
New case	(88.4)28	(96.4)3	
Previous TB	(11.6)	(3.6)	
Origin of birth, n (%)	165	46	0.036
Foreign	(68.2)77	(55.4)37	
Spain	(32.8)	(44.6)	
Region of birth, n (%)	77 (31.8)13	37 (44.6)9	0.054
Spain	(5.4)13	(10.8)5	
African Region	(5.4)37	(6.0)7	
Eastern Mediterranean	(15.3)92	(8.4)22	
RegionEuropean Region	(38.0)2	(26.5)2	
(Spain excluded)	(0.8)8	(2.4)1	
Region of the Americas	(3.31)	(1.2)	
South-East Asian Region			
Western Pacific Region			
VIH status, n (%)	7 (2.9)235	82 (98.8)1	0.392
No	(97.1)	(1.2)	
Yes			
Inmunosupression (no VIH related), n (%)	226	71	0.685
	(93.4)16	(85.5)12	
No	(6.6)	(14.5)	
Yes			
Drug susceptibility testing, n (%)[a]	233	77	0.202*
Not MDR	(97.1)7	(100)0	
MDR	(2.9)	(0)	
Xpert Ultra determination, n (%)[b]	38	8	0.366
Negative	(20.2)150	(27.6)21	
Positive	(79.8)	(72.4)	
Culture, n (%)	2	6	0.004
Negative	(0.8)240	(7.2)77	
Positive	(99.2)	(92.8)	

PTB: pulmonar tuberculosis. EPTB: extrapulmonar tuberculosis. MDR: multi drug resistant. [a]Excludes 8 patients with unknown drug susceptibility testing. [b]Excludes 107 patients without Xpert Ultra determination at diagnosis. * Reciprocal continuity correction for cells with zero events.

Table 2
Univariate and multivariate analysis of clinical and demographic characteristics of EPTB.

	Univariate analysis			Multivariate analysis		
Characteristics	OR	IC 95%	p-value	aOR	IC 95%	p-value
Female Sex	2.43	1.46 – 4.04	0.001	2.46	1.45 – 4.20	0.001
Age ≥ 65 years	2.76	1.47 – 5.16	0.002	2.47	1.19 – 5.13	0.015
New case	3.49	1.03 – 11.80	0.044	4.99	1.40 – 17.82	0.013
VIH status	0.41	0.05 – 3.38	0.407	0.96	0.10 – 8.87	0.973
Inmunosupresion (VIH not included)	2.38	1.08 – 5.28	0.032	1.47	0.61 – 3.56	0.388
Spanish nationality	1.72	1.03 – 2.87	0.037	1.43	0.80–2.57	0.222

4. Discussion

The present study describes the epidemiologic and clinical characteristics of EPTB patients attending to a tertiary care hospital in Madrid, Spain, over a period of six years and identifies risk factors associated with the occurrence of EPTB. The proportion (20.9%) of EPTB among all the TB cases found in our study is comparable with the range of what has been reported for other developed countries such as The Netherlands (38%), United States (27%), and Germany (21.6%) [11,13,14].

Regarding the evolution of cases over time and in line with what has been reported elsewhere [2,3,6,8,11,12], while a decrease in the global number of TB cases was observed throughout the study period, opposite trends were observed between both EPTB and PTB. This observation may be explained due to the fact that control program measures effectively focus on reducing contagious PTB cases but may be less effective against EPTB. Demographic changes favoring populations with higher prevalence of EPTB may also contribute to the consistency of EPTB [11,13].

One of the aims of this study was to observe to what extend COVID-19 pandemic has had an influence on TB detection and reporting in our setting. Spanish lockdown lasted from 14th March 2020 to 21st June 2020, a situation shared by many other countries around the globe, including developed and undeveloped ones. Throughout 2020, deep declines in the number of reported TB cases were notified globally while in contrast, the number of TB-related deaths increased considerably. Particularly, this changes were mostly seen in areas with low-incomes and the highest TB incidence rates [2,3,6]. Interestingly, in our hospital only a small decrease in the number of reported TB cases was observed during 2020 whereas a large drop was observed in 2021. The explanation may reside in the fact that our country has a relatively low prevalence of TB and thus the detection of cases was not greatly affected by the initial lockdown. Social distancing and the hygienic measures created to prevent COVID-19 infection, could have led to a decrease in the circulation of TB and therefore a reduction in the number of diagnosed cases in 2021. [2,3,15–17].

The sites of EPTB vary by age group and gender across different populations studied. However, in line with other studies, lymph nodes and pleura were the most commonly reported sites in our setting [9,11,18,19]. The distribution of the organ affected by EPTB across gender does not seem to follow a clear pattern as various studies also describe [9,11,19,20]. Notably, during the study period we observed an increase in lymphatic TB cases while pleural TB cases decreased. Consistently with other studies [11,12,14] we found an association between EPTB and either female sex or absence of previous TB episode.

We observed that age groups carrying the highest risk of having EPTB were those over 65 years, followed by the 25–44 year group, a finding that agrees with a recent national study conducted in our country [8]. Some groups have suggested that young patients are more likely to be affected by EPTB than elderly ones [21,22] In contrast, other studies report no association between age and risk of EPTB [23]. Although previous studies have showed that the presence of HIV infection is the main EPTB risk factor [23,24] we found similar odds for HIV infection among EPTB and PTB cases. Our lack of association is likely attributable to the small number of HIV-infected patients included in the study.

Unlike other studies [8,11,25], we did not find an increased association between EPTB and the country of origin. In fact, EPTB rates in foreign-born patients were lower than those found in the national population. This may be due to the higher proportion in our population of middle-aged patients and patients aged > 65 years, having these two groups a predominance of Spain-born patients. Of note, microbiological culture provided a larger number of positive results than expected [8,9] for both EPTB (92.8%) and PTB (99.2%). We believe that this discrepancy may be explained due to some limitations when tracking patients from electronic records who only had a clinical diagnosis of TB, thus an underestimation of these patients may have occurred.

Our study has some limitations. First, our retrospective research only collected data of TB cases from a single hospital, therefore limiting the overall scope of our findings. Secondly, there is limited available information regarding some of the studied variables, such as date of entry and duration of stay in our country regarding foreign-born patients and some missed behavioral and social factors that could lead to the progression from latent TB infection to TB disease. Moreover, due to this lack of information regarding clinical records, details of previous TB episodes and its treatment are very limited, allowing us to only classify the cohort between previous TB infection or not. Finally, the reduced population size regarding certain variables, such as HIV infection, could act as a confounding factor in the statistical analysis.

In conclusion, our data show that although overall TB cases have been following a downward trend for the last years, proportion of EPTB cases compared to PTB have increased within our study period, denoting a lack of effectiveness in control programs regarding EPTB. Of note, it is to mention the profound decline in the number of cases diagnosed in 2021, probably directly derived from the impact of the COVID-19 pandemic. Women, elderly population ($>$65 years of age), and persons with previous history of TB are at higher risk for developing extrapulmonary TB in our setting.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authoŕs contributions

Study design: Paula López Roa. Data collection: Marta Rolo, Beatriz González Blanco and Nicolás Rosillo. Data analysis: Carmen Alhena Reyes. Manuscript writing/revision: Marta Rolo, Beatriz González Blanco and Paula López Roa. Contribution to draft and finalising of the manuscript: Marta Rolo, Nicolás Rosillo and Carmen Alhena Reyes. All authors revised the manuscript and approved the final version.

References

[1] Houda Ben A, Makram K, Chakib M, Khaoula R, Fatma H, Fatma S, et al. Extrapulmonary Tuberculosis: Update on the Epidemiology, Risk Factors and Prevention Strategies. Int J Trop Dis 2018;1(1).

[2] Chakaya J, Petersen E, Nantanda R, Mungai BN, Migliori GB, Amanullah F, *et al.* The WHO Global Tuberculosis 2021 Report – not so good news and turning the tide back to End TB. Int J Infect Dis 2022; 124:S26–9. https://doi.org/10.1016/j.ijid.2022.03.011.

[3] Global tuberculosis report 2022. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

[4] Arega B, Mersha A, Minda A, Getachew Y, Sitotaw A, Gebeyehu T, *et al.* Epidemiology and the diagnostic challenge of extra-pulmonary tuberculosis in a teaching hospital in Ethiopia. Quinn F, editor. PLOS ONE 2020; 15(12):e0243945. https://doi.org/10.1371/journal.pone.0243945.

[5] Baykan AH, Sayiner HS, Aydin E, Koc M, Inan I, Erturk SM. Extrapulmonary tuberculosıs: an old but resurgent problem. Insights Imaging 2022;13(1):39. https://doi.org/10.1186/s13244-022-01172-0.

[6] European Centre for Disease Prevention and Control, WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2022 – 2020 data. Copenhagen: WHO Regional Office for Europe and Stockholm: European Centre for Disease Prevention and Control; 2022. Licence: CC BY 3.0 IGO.

[7] Sharma SK, Mohan A, Kohli M. Extrapulmonary tuberculosis. Expert Rev Respir Med 2021;15(7):931–48. https://doi.org/10.1080/17476348.2021.1927718.

[8] Culqui-Lévano DR, Rodriguez-Valín E, de Donado-Campos J, M.. Analysis of extrapulmonary tuberculosis in Spain: 2007–2012 National Study. Enfermedades

Infecc Microbiol Clínica 2017;35(2):82–7. https://doi.org/10.1016/j.eimc.2016.06.002.
[9] García-Rodríguez JF, Álvarez-Díaz H, Lorenzo-García MV, Mariño-Callejo A, Fernández-Rial Á, Sesma-Sánchez P. Extrapulmonary tuberculosis: epidemiology and risk factors. Enfermedades Infecc Microbiol Clínica 2011;29(7):502–9. https://doi.org/10.1016/j.eimc.2011.03.005.
[10] Mor Z, Pinsker G, Cedar N, Lidji M, Grotto I. Epidemiology of extra-pulmonary tuberculosis in Israel, 1999–2010. int j tuberc lung dis 2013;17(2):229–33.
[11] Peto HM, Pratt RH, Harrington TA, LoBue PA, Armstrong LR. Epidemiology of Extrapulmonary Tuberculosis in the United States, 1993–2006. Clin Infect Dis 2009;49(9):1350–7. https://doi.org/10.1086/605559.
[12] Pang Yu, An J, Shu W, Huo F, Chu N, Gao M, et al. Epidemiology of Extrapulmonary Tuberculosis among Inpatients, China, 2008–2017. Emerg Infect Dis 2019;25(3):457–64.
[13] Forssbohm M, Zwahlen M, Loddenkemper R, *et al*. Demographic characteristics of patients with extrapulmonary tuberculosis in Germany. *Eur Respir J*; 2008 Jan 1;**31** (1):99–105. https://doi.org/10.3201/eid2503.180572.
[14] te Beek LA, van der Werf MJ, Richter C, Borgdorff MW. Extrapulmonary Tuberculosis by Nationality, the Netherlands, 1993–2001. Emerg Infect Dis 2006; 12(9):1375–82. https://doi.org/10.3201/eid1209.050553.
[15] Dheda K, Perumal T, Moultrie H, Perumal R, Esmail A, Scott AJ, et al. The intersecting pandemics of tuberculosis and COVID-19: population-level and patient-level impact, clinical presentation, and corrective interventions. Lancet Respir Med 2022;10(6):603–22.
[16] Shen X, Sha W, Yang C, Pan Q, Cohen T, Cheng S, et al. Continuity of TB services during the COVID-19 pandemic in China. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis 2021;25(1):81–3.
[17] Hogan AB, Jewell BL, Sherrard-Smith E, Vesga JF, Watson OJ, Whittaker C, *et al*. Potential impact of the COVID-19 pandemic on HIV, tuberculosis, and malaria in low-income and middle-income countries: a modelling study. Lancet Glob Health 2020; 8(9):e1132–41. https://doi.org/10.1016/S2214-109X(20)30288-6.
[18] Gomes T, Reis-Santos B, Bertolde A, Johnson JL, Riley LW, Maciel EL. Epidemiology of extrapulmonary tuberculosis in Brazil: a hierarchical model. BMC Infect Dis 2014;14:9. https://doi.org/10.1186/1471-2334-14-9.
[19] Sunnetcioglu A, Sunnetcioglu M, Binici I, Baran AI, Karahocagil MK, Saydan MR. Comparative analysis of pulmonary and extrapulmonary tuberculosis of 411 cases. Ann Clin Microbiol Antimicrob 2015;14:34. https://doi.org/10.1186/s12941-015-0092-2.
[20] Sreeramareddy CT, Panduru KV, Verma SC, Joshi HS, Bates MN. Comparison of pulmonary and extrapulmonary tuberculosis in Nepal- a hospital-based retrospective study. BMC Infect Dis 2008;8(1):8. https://doi.org/10.1186/1471-2334-8-8.
[21] Noertjojo K, Tam CM, Chan SL, Chan-Yeung MM. Extra-pulmonary and pulmonary tuberculosis in Hong Kong. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis 2002;6(10):879–86.
[22] Lewinsohn DA, Gennaro ML, Scholvinck L, Lewinsohn DM. Tuberculosis immunology in children: diagnostic and therapeutic challenges and opportunities. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis 2004;8(5):658–74.
[23] Yang Z, Kong Y, Wilson F, Foxman B, Fowler AH, Marrs CF, et al. Identification of Risk Factors for Extrapulmonary Tuberculosis. Clin Infect Dis 2004;38(2):199–205.
[24] Huebner RE, Castro KG. The changing face of tuberculosis. Annu Rev Med 1995;46: 47–55. https://doi.org/10.1146/annurev.med.46.1.47.
[25] Luque L, Rodrigo T, García-García JM, Casals M, Millet JP, Caylà J, et al. Factors Associated With Extrapulmonary Tuberculosis in Spain and Its Distribution in Immigrant Population. Open Respir Arch 2020;2(3):119–26.