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ORIGINAL ARTICLE

Prevalence and determinants of extrapulmonary involvement in patients with pulmonary tuberculosis in a Sub-Saharan African country: A cross-sectional study

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Abstract

Background: Determinants of extrapulmonary involvement during pulmonary tuberculosis (PTB) have not been extensively investigated. We assessed the prevalence and determinants of extrapulmonary involvement during PTB in a Sub-Saharan African country with a high prevalence of both TB and human immunodeficiency virus (HIV) infection. *Methods:* The medical records of patients aged ≥15 y, admitted for a first episode of TB to the Pneumology Service of Yaoundé Jamot Hospital, Cameroon, between 2009 and 2010 were considered. Determinants of extrapulmonary involvement were investigated through logistic regression. *Results:* A total of 984 patients (58.9% male), with a median age (25^{th}–75^{th} percentiles) of 32 (25–41) y were admitted for a first episode of TB, including 629 (63.9%) with isolated PTB, 127 (12.9%) with isolated extrapulmonary TB (EPTB), and 228 (23.2%) with both PTB and EPTB (PTB/EPTB). Therefore, the prevalence of EPTB among those with PTB was 26.6% (228/857). The main determinants of EPTB among patients with PTB were male sex (adjusted odds ratio (OR) 2.71, 95% confidence interval (95% CI) 1.71–4.03), HIV infection (OR 2.20, 95% CI 1.36–3.55), absence of fibrotic lung lesions (OR 1.96, 95% CI 1.23–3.14), smear-negative PTB (OR 7.20, 95% CI 4.13–12.56), anaemia (OR 1.60, 95% CI 1.03–2.50), and leukopenia (OR 2.59, 95% CI 1.12–5.98). *Conclusions:* About a quarter of patients with PTB in this setting also have extrapulmonary involvement. EPTB is less contagious, less frequent than PTB, and less well addressed by programs in developing countries, while its identification is important for optimizing care. The presence of determinants of EPTB among patients with PTB should motivate active investigation of extrapulmonary involvement in order to improve management.

Keywords: *Pulmonary tuberculosis, extrapulmonary tuberculosis, prevalence, determinants, Cameroon*

Introduction

Tuberculosis (TB) remains a major public health issue in developing countries, particularly those of Sub-Saharan Africa [1]. Although lung involvement is the most frequent infection site, TB can affect virtually any organ [2]. Indeed, extrapulmonary tuberculosis (EPTB) is also frequent and has been reported in about 15–20% of human immunodeficiency virus (HIV)-negative patients with TB [2]. This proportion is much higher in patients with HIV infection [2,3]. While certain forms of EPTB such as pleural or lymph node TB respond very well to anti-TB treatment [2,4], other forms such as meningeal or miliary TB are very challenging to treat and are associated with high mortality rates [5–7]. About 1 in every 6 patients with pulmonary tuberculosis (PTB) also has extrapulmonary involvement [8,9]. Certain characteristics associated with EPTB have been identified, including HIV infection [3], young age [10], female gender [11],

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and hypoalbuminaemia [8]. Moreover, one study has shown that socio-demographic determinants of EPTB vary across geographic regions [12].

It is important to carefully investigate the presence of extrapulmonary extension in patients with PTB (and vice versa) in order to optimize the treatment and improve the outcomes of care. However, this task can be quite challenging in the absence of a good knowledge of the determinants of extrapulmonary involvement in patients with PTB.

The aim of this study was to assess the prevalence and determinants of extrapulmonary involvement in patients with PTB in a highly endemic area for both TB and HIV infection.

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Materials and methods

Study setting and participants

This cross-sectional study was conducted in the Pneumology Service of Yaoundé Jamot Hospital (YJH) between January 2009 and December 2010. The study setting has been described in detail elsewhere [13]. In brief, YJH serves as a referral hospital for TB and chest diseases for the capital city of Cameroon (Yaoundé) and surrounding areas, and is one of the major centres for the diagnosis and treatment of TB in the country. Patients aged ≥ 15 y hospitalized in the chest unit of YJH for a first episode of PTB during the study period were considered for inclusion in the final sample based on data collected from the patient's file and admission/discharge registers.

Work-up and diagnosis of tuberculosis

At YJH, all patients suspected for TB receive a clinical examination including data collection on functional signs (general, pulmonary, and extrapulmonary) and physical signs relating to PTB and EPTB. Overall, all patients receiving care for TB at this centre are seen by a physician, and those with extrapulmonary involvement are systematically seen by 1 of the 7 chest specialist physicians of the hospital. The investigation of extrapulmonary involvement is an integral part of the routine workup of patients with TB, and chest X-ray is systematically requested for all patients with EPTB.

Three direct sputum examinations are systematically performed for all patients who can produce a sputum sample, as well as a standard chest X-ray. The diagnosis of EPTB is based on further radiological exams, bacteriological, cytological, and biochemical examination of fluids collected from the involved organs, histological examination of pathologic tissue samples from the involved organs, or strong clinical evidence consistent with active EPTB, followed by the clinician's decision to treat the patient with a full course of anti-TB chemotherapy. Patients who receive a final diagnosis of TB are also screened for co-infection with HIV subject to informed consent, as previously described [13].

The following international definitions were applied in the service at the time of the study [14,15]: (1) smear-positive PTB: acid-fast bacilli (AFB) found in at least 2 sputum specimens; (2) smear-negative PTB: persisting negativity on 3 sputum examinations after a 10-day course of non-specific antibiotic treatment in a patient with TB-like clinical and radiological signs, and in the absence of any obvious cause; (3) EPTB: TB involving organs other than the lungs, for instance pleura, lymph nodes, abdomen, genito-urinary system, skin, joints and bones, meninges, etc. A patient is classified as a new case (first episode of TB) if he/she has never been exposed to anti-TB treatment for more than 1 month in the past.

Procedures

Admission and discharge registers were used to identify potentially eligible patients. Patient files were then retrieved and reviewed for inclusion and data collection. Socio-demographic data collected included age, sex, and residence (urban vs rural). Past medical history data included current smoking (yes vs no), alcohol consumption (yes vs no), vaccination with bacille Calmette–Guérin (BCG), and co-morbidities (diabetes mellitus). Clinical details included cough, expectoration, haemoptysis, chest pain, asthenia, anorexia, fever, and weight loss. Radiographic data were collected on the type of parenchymatous lesions and their extent, the presence of pleural effusion, and mediastinal or hilar lymph nodes. The assessment of the parenchymatous extension of the lesions was based on the subdivision of each pulmonary lobe into 3 regions [16]. Biological data included the results of the HIV test, full blood count, and CD4 count (for HIV-positive patients only). The study was approved by the administrative authorities of YJH and the Cameroon National Ethics Committee.

Statistical methods

Data were analysed with the use of the SPSS software version 12.0.1 for Windows (SPSS Inc., Chicago, USA). Results are expressed as the mean and standard deviation, median (25^{th}–75^{th} percentiles), and count (percentage). For group comparisons, the Chi-square test or Fisher's exact test for qualitative variables and the Student *t*-test or

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non-parametric equivalents for quantitative variables were used. Logistic regression models were used to investigate potential determinants of extrapulmonary involvement in patients with PTB. Potential candidate predictors were first investigated in univariable analysis. Significant variables (based on a threshold probability <0.1) were entered all together in the same multivariable model. Thereafter, stepwise backward selection procedures (based on the probability threshold of 0.05 for entry and 0.1 for removal) were used to retain variables in the final model. Face validation of this final model was based on the Hosmer and Lemeshow test for calibration and C-statistics for discrimination [17,18]. A p-value of <0.05 was used to characterize statistically significant results.

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Results

Data available and the prevalence and distribution of extrapulmonary tuberculosis

During the study period, a total of 1023 patients aged ≥ 15 y were hospitalized in the service for a first episode of TB. Clinical files were missing for 21 patients and 18 others had incomplete files; they were all excluded. The median age (25^{th}–75^{th} percentiles) of the remaining 984 patients was 32 (25–41) y and 58.9% were male. Among them, 629 (63.9%) patients had isolated PTB, 127 (12.9%) had isolated EPTB, and 228 (23.2%) had both PTB and EPTB (PTB/EPTB). Therefore, the prevalence of EPTB among patients with PTB (857 patients) was 26.6% (228/857).

The distribution of sites of extrapulmonary involvement in patients with PTB is shown in Figure 1. Pleural TB was the most frequent (144, 63.2%), followed by lymph node TB (84, 36.8%) and peritoneal TB (24, 10.5%). Multiple organ extrapulmonary involvement was found in 43 (18.9%) patients.

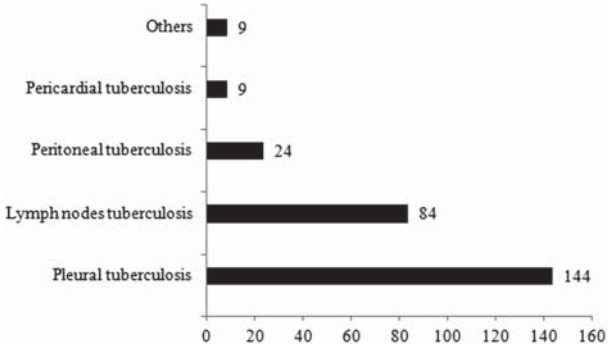

Figure 1. Distribution of extrapulmonary involvement sites in patients with pulmonary tuberculosis.

Pleural TB was histologically confirmed in 86/144 (59.7%) patients and was based on cytology of the pleural fluid (predominantly lymphocytes) in 58/144 (40.3%) patients. Lymph node TB was bacteriologically proven in 8 (9.5%) patients and based on cytology/histology in 63 (75%) patients, or radiographic and clinical findings in 13 (15.5%) patients. For other forms of EPTB (42 patients), the final diagnosis was based on bacteriology in 3 (7.1%) patients, cyto-histology in 9 (21.4%) patients, and radiographic and clinical findings in 30 (71.4%) patients. Overall, the diagnosis of EPTB was bacteriologically or histologically proven in 161 (70.6%) patients, and for 59.9% of all extrapulmonary involvement.

Demographic characteristics and lifestyle of pulmonary tuberculosis patients with and without extrapulmonary involvement

The sex ratio (male/female) was 1.8 in the PTB/EPTB group and 1.3 in the PTB group ($p=0.03$). Alcohol consumption was similar in the 2 groups, but PTB/EPTB patients were less likely to be smokers than isolated PTB patients (13.2% vs 19.6%, $p=0.03$) (Table I).

Medical history and clinical profiles of pulmonary tuberculosis patients with and without extrapulmonary involvement

The distribution of general clinical signs was similar among PTB/EPTB and isolated PTB patients (all $p>0.16$, Table I). The median duration of symptoms was also similar ($p=0.29$). However, PTB/EPTB patients were more likely to have smear-negative PTB (35.8% vs 4.6%, $p<0.001$) and co-infection with HIV (52.6% vs 26.9%, $p<0.001$) compared to patients with isolated PTB (Table I).

Radiographic and biological profiles of pulmonary tuberculosis patients with and without extrapulmonary involvement

Extension of pulmonary lesions to more than 1 zone (61.3% vs 79.2%, $p<0.001$), cavitations (24.6% vs 58.3%, $p<0.001$), and fibrotic lesions (14.0% vs 42.3%, $p<0.001$) were less frequent in PTB/EPTB patients compared to those with isolated PTB (Table II). However, PTB/EPTB patients were more likely to have anaemia, leukopenia, lymphopenia, and neutropenia than patients with isolated PTB (all $p\leq 0.01$, Table II). Among patients with HIV co-infection, the median CD4 count was lower in those with PTB/EPTB than in those with isolated PTB (126 vs 173, $p=0.01$).

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Table I. Demographic profile and clinical characteristics of pulmonary tuberculosis patients with and without extrapulmonary involvement.

Characteristics	Pulmonary and extrapulmonary TB ($n = 228$)	Isolated pulmonary TB ($n = 629$)	p-Value
Age, y, *n* (%)			
< 32	94 (41.2)	323 (51.4)	0.009
≥ 32	134 (58.5)	306 (48.6)	
Sex, *n* (%)			
Male	147 (64.5)	354 (56.3)	0.031
Female	81 (35.5)	275 (43.7)	
Current smoking, *n* (%)			
Yes	30 (13.2)	123 (19.6)	0.031
No	198 (86.8)	506 (80.4)	
Alcohol consumption, *n* (%)			
Yes	56 (24.6)	154 (24.5)	0.981
No	172 (75.4)	475 (75.5)	
BCG vaccination, *n* (%)			
Yes	154 (67.5)	453 (72.0)	0.203
No	74 (32.5)	176 (28.0)	
Diabetes mellitus, *n* (%)			
Yes	3 (1.3)	11 (1.7)	0.659
No	225 (98.7)	618 (98.3)	
HIV infection, *n* (%)			
Yes	120 (52.6)	169 (26.9)	< 0.001
No	108 (47.4)	460 (73.1)	
Anorexia, *n* (%)			
Yes	160 (70.2)	471 (74.9)	0.167
No	68 (29.8)	158 (25.1)	
Asthenia, *n* (%)			
Yes	198 (86.8)	566 (74.1)	0.191
No	30 (13.2)	63 (10.0)	
Weight loss, *n* (%)			
Yes	212 (93.0)	584 (92.8)	0.945
No	16 (7.0)	45 (7.2)	
Fever, *n* (%)			
Yes	203 (89.0)	577 (91.7)	0.222
No	25 (11.0)	52 (8.3)	
Duration of symptoms			
Median (25^{th}–75^{th} percentiles)	12 (8–16)	12 (8–16)	0.287
< 12 weeks, *n* (%)	94 (41.2)	294 (46.7)	0.152
≥ 12 weeks, *n* (%)	134 (58.8)	335 (53.3)	
Type of pulmonary TB, *n* (%)			
Smear-negative	64/179 (35.8)	29/629 (4.6)	< 0.001
Smear-positive	115/179 (64.2)	600/629 (95.4)	

TB, tuberculosis; BCG, bacille Calmette–Guérin; HIV, human immunodeficiency virus.

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Predictors of extrapulmonary involvement in patients with pulmonary tuberculosis

In multivariable adjusted logistic regression, male sex (odds ratio (OR) 2.71, 95% confidence interval (95% CI) 1.71–4.03), HIV infection (OR 2.20, 95% CI 1.36–3.55), absence of fibrotic lung lesions (OR 1.96, 95% CI 1.23–3.14), smear-negative PTB (OR 7.20, 95% CI 4.13–12.56), anaemia (OR 1.60, 95% CI 1.03–2.50), and leukopenia (OR 2.59, 95% CI 1.12–5.98) were the main determinants of extrapulmonary involvement in patients with PTB. In stepwise backward selection procedures, the same variables were retained in the final model, together with smoking and the absence of cavitations, both having only a borderline association with extrapulmonary involvement. The odd ratios for this final model are shown in Table III. This model had very good apparent calibration based on the Hosmer and Lemeshow test (Chi-square = 4.75, $p = 0.78$, df = 8). The apparent discrimination was also good with a C-statistic (95% confidence intervals) of 0.796 (0.755–0.837).

Discussion

In this study conducted in a country with high endemicity for both TB and HIV infection, we found a

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Table II. Radiographic and haematological profiles of pulmonary tuberculosis patients according to the presence of extrapulmonary involvement.

Characteristics	Pulmonary and extrapulmonary TB ($n = 228$)	Isolated pulmonary TB ($n = 629$)	p-Value
Radiographic profile			
Number of radiographic fields involved, *n* (%)			
≤2	86 (38.7)	130/626 (20.8)	<0.001
>2	136 (61.3)	496/226 (79.2)	
Cavitations, *n* (%)			
Present	56 (24.6)	367 (58.3)	<0.001
Absent	172 (75.4)	262 (41.7)	
Retractile lesions, *n* (%)			
Yes	32 (14.0)	266 (42.3)	<0.001
No	196 (86.0)	363 (57.7)	
Haematological profile			
Haemoglobin level, *n* (%)			
<10 g/dl	108 (47.4)	218 (34.7)	0.001
≥10 g/dl	120 (52.6)	411 (65.3)	
Leukocyte count, *n* (%)			
<4000/mm^3	40 (17.5)	23 (3.7)	<0.001
≥4000/mm^3	188 (82.5)	606 (96.3)	
Lymphocyte count, *n* (%)			
<1500/mm^3	112 (49.1)	175 (27.8)	<0.001
≥1500/mm^3	116 (50.9)	454 (72.2)	
Neutrophil count, *n* (%)			
<1500/mm^3	13 (5.7)	14 (2.2)	0.010
≥1500/mm^3	215 (94.3)	615 (97.8)	
CD4[a]			
Median (25th–75th percentile)/mm^3	126 (54–203.25)	173 (87–343)	0.014
<50/mm^3, *n* (%)	26/120 (21.7)	25/169 (14.8)	0.002
50–200/mm^3, *n* (%)	64/120 (53.3)	68/169 (40.2)	
>200/mm^3, *n* (%)	30/120 (25.0)	76/169 (45.0)	

TB, tuberculosis; HIV, human immunodeficiency virus.
[a]CD4 data are only for those patients who tested positive for HIV infection.

high prevalence of extrapulmonary involvement in patients with an active first episode of PTB. The main determinants of extrapulmonary involvement were male sex, HIV co-infection, the absence of fibrotic parenchymatous lesions, smear-negative PTB, anaemia, and leukopenia. The careful exploitation of predictive information from these predictors assessed during the routine diagnosis and care of people with PTB can aid the detection, further investigation, and improvement of the management

Table III. Multivariable adjusted odd ratios (OR) and 95% confidence intervals (95% CI) for the predictors of extrapulmonary involvement during pulmonary tuberculosis in Yaoundé, Cameroon.

	Full model		Final model	
Variables	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age ≥32 y	1.03 (0.68–1.58)	0.873	–	
Male	2.71 (1.71–4.03)	<0.001	2.71 (1.72–4.28)	<0.001
Smoker	0.59 (0.33–1.03)	0.063	0.60 (0.34–1.03)	0.07
HIV infection	2.20 (1.36–3.55)	0.001	2.29 (1.45–3.62)	<0.001
≤2 radiographic fields involved	1.22 (0.75–1.99)	0.424	–	
No cavitation	1.52 (0.98–2.35)	0.06	1.52 (0.99–2.34)	0.06
No retractile parenchymatous lesion	1.96 (1.23–3.14)	0.005	1.89 (1.19–2.99)	0.007
Smear-negative pulmonary TB	7.20 (4.13–12.56)	<0.001	7.17 (4.15–12.38)	<0.001
Haemoglobin level <10 g/dl	1.60 (1.03–2.50)	0.037	1.63 (1.05–2.53)	0.03
Leukocyte count <4000/mm^3	2.59 (1.12–5.98)	0.026	2.43 (1.22–4.83)	0.01
Total lymphocyte count <1500/mm^3	1.26 (0.81–1.96)	0.302	–	
Neutrophil count <1500/mm^3	0.62 (0.19–2.00)	0.419	–	

HIV, human immunodeficiency virus; TB, tuberculosis.

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of this subgroup at risk of a poor outcome due to extrapulmonary involvement.

We are not aware of previous studies that have extensively characterized extrapulmonary involvement in people with PTB in Sub-Saharan Africa. The prevalence of EPTB among patients with PTB in our study was higher than those reported by Kim et al. (12.5%) in Korea [8], Cailhol et al. (10.3%) in France [12], and Noertjojo et al. (9.9%) in Hong Kong [19]. The distribution of extrapulmonary involvement in our sample was similar to that reported in the literature, dominated by pleural, lymph node, and peritoneal TB [2,3].

The prevalence of extrapulmonary involvement in our sample was much higher in the subgroup with HIV infection. Even after adjustment for possible confounders, HIV infection was associated with twice the risk of extrapulmonary involvement in our patients with PTB. The high incidence of EPTB in people with HIV infection has been described extensively [3]. Failure in some previous studies to demonstrate any significant effect of HIV infection on the co-occurrence of extrapulmonary involvement in patients with PTB was probably due only to the lack of statistical power. In the study by Kim et al. [8] for instance, only 5 patients out of a total of 320 had HIV infection, while only 4 patients out of 4967 had HIV infection in the study by Noertjojo et al. in Hong Kong [19].

We also found a higher prevalence of extrapulmonary involvement in men than in women in our sample, which is in line with the findings of Noertjojo in Hong Kong [19], but not those of Kim et al. who found no sex difference in Korea [8]. Differences are possibly explained by the small size of the sub-cohort with combined PTB and EPTB in the study of Kim et al. [8] (only 40 participants). Our findings, however, seem at variance with some studies that have compared patients with isolated PTB to those with isolated EPTB, showing a higher proportion of women in the latter [9]. In general, there have been reports of ill-understood sex differences in the manifestations of TB [12,20]. The gender effect in our study was robust to adjustment for possible confounders, suggesting a likely independent effect that requires further investigation. In general, there is no consensus on the possible effect of ageing on the occurrence of EPTB. There have been suggestions that failing of the immune system with ageing is associated with EPTB, particularly miliary and meningeal TB [21,22]. However, some studies have either found no effect at all [12], or rather a protective effect [8]. We found no effect of age in the current study. Extrapulmonary involvement was more frequent in patients with smear-negative PTB, with a 7-fold higher risk, even after adjustment for potential extraneous determinants. Extrapulmonary extension of TB results at least in part from the incompetence of the cell-mediated immune system [23,24] and is often characterized by the paucibacillary nature of pulmonary involvement. In the study setting, a major provider of cell-mediated immune deficiency is HIV infection, which was more frequent in our subgroup of patients with extrapulmonary involvement. However, in mutually adjusted multivariable logistic regression, both HIV infection and smear-negative PTB emerged as independent predictors of extrapulmonary involvement. PTB in the context of cell-mediated immune deficiency is often characterized by the low frequency of cavitary lesions, which are considered to be rich in Mycobacterium tuberculosis. Indeed, although cavitary lesions were significantly less frequent in patients with extrapulmonary involvement, the difference was no longer significant in multivariable analysis, suggesting a correlation between smear-negative TB and the absence of cavitary pulmonary lesions.

Anaemia and leukopenia were independent predictors of extrapulmonary involvement, in disagreement with the findings of Kim et al. in Korea [8]. This high frequency of haematological abnormalities in PTB/EPTB patients could at least in part be explained by bone marrow involvement. They were less likely to be related to antiretroviral treatment, since the proportion of patients with HIV receiving antiretrovirals was similar in the 2 groups (data not shown).

The current study had some limitations. Data collection using existing patient files is often criticized for the lack of, or poor standardization of measurement procedures and the frequent missing information. During the study period, our centre was staffed by 7 chest physicians who used the same standard protocol to investigate each new patient with TB, which therefore strengthens the quality of the data used in the current study. As expected, files or data were missing for a relatively small proportion of potentially eligible patients (less than 4%), who were excluded. There was no difference in the demographic profile of excluded patients and those included in the final analysis (data not shown). Moreover, given the large number of those included, it is likely that adding the excluded patients would have had only meaningless effects. A parameter like serum albumin, a marker of nutritional status, which has been reported to be associated with EPTB [8], was not available in our sample and therefore precluded the possibility of testing it as a predictor in our population. There have been reports that some strains of M. tuberculosis could be associated with extrapulmonary involvement [25], which is another

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hypothesis we were unable to test. The assessment of some key exposures, such as alcohol intake or smoking habit, was mostly qualitative with no quantification of the intake, which could help to better characterize the observed effects. Our study also had major strengths. These include our large sample size, including almost the totality of adult patients followed in the service during the year of the study. By conducting such a study for the first time in an area highly endemic for both TB and HIV infection, we were able to better and perhaps more reliably characterize the effect of HIV infection on the co-occurrence of both PTB and EPTB. The study hospital, which is a referral centre, provides care on an annual basis to about 1600 to 1800 patients with TB from the capital city, the surrounding areas, and other parts of the country [13]. This figure represents approximately 8% of all patients with TB treated in the country. This large number and the extensive catchment area suggest that patients with TB receiving care at this centre are likely broadly representative of the country's population with TB. However, as our study was conducted only among hospitalized patients (2/3 of those receiving care for TB at the centre [13]), some caution should be taken when extrapolating our prevalence figures to the entire population with TB.

In conclusion, a quarter of adults with PTB in this setting also have extrapulmonary involvement. This proportion is twice as high among those co-infected with HIV. In addition, being male, smear-negative PTB, non-fibrotic pulmonary lesions, anaemia, and leukopenia are associated with extrapulmonary involvement. EPTB, which is less contagious and less frequent than PTB, is often less well addressed by anti-TB programs in developing countries, however identifying extrapulmonary involvement is very important to improve the management of patients and the outcomes of care. Therefore, the presence in patients with PTB of those characteristics found to be associated with EPTB in the current study should trigger intensive investigation of possible extrapulmonary involvement, in order to improve the management of these patients. Studies with active inclusion of patients are needed to confirm the findings of our study.

Declaration of interest: The authors declare that they have no conflict of interest.

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