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Distinct Clinical Features of Extrapulmonary and Disseminated Tuberculosis in HIV- and Non-HIV-Associated Immunosuppression: A Retrospective Cohort Study

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Background. There is scarce information regarding the clinical differences between extrapulmonary and disseminated tuberculosis (TB) in patients with different types of immunosuppression. We aimed to compare the clinical characteristics and outcomes of extrapulmonary and disseminated TB in patients with non–human immunodeficiency virus (HIV)–associated and HIV-associated immunocompromise.

Methods. In this retrospective cohort study, we included immunocompromised adults with extrapulmonary or disseminated TB in a referral center in Mexico City from January 2000 to December 2023. We compared clinical characteristics, treatments, and death. Multivariate logistic regression analysis for death-related characteristics and Kaplan-Meier survival estimates were performed.

Results. We included 180 patients: 81 with non-HIV-associated and 99 with HIV-associated immunosuppression ($CD4^+$ <200 cells/μL). Most were male (62%), with a median age of 34 (interquartile range, 29–47) years. Among all patients, 55% had HIV infection and 33% had autoimmune disease. Disseminated disease was more frequent in the HIV group (80% vs 63%, $P = .02$). Infections by *Mycobacterium bovis* were more prevalent in the non-HIV group (54% vs 36%, $P = .02$). Death occurred in 23% of cases. Factors related to death (odds ratio [95% confidence interval]) were age (1.05 [1.01–1.10]), unemployment (31.62 [1.65–605.18]), tobacco use (4.21 [1.03–17.21]), disseminated disease (6.13 [1.24–30.35]), and central nervous system (CNS) involvement (10.10 [1.91–53.53]) in the non-HIV group, and malignancy (33.82 [2.37–483.33]) and intensive care unit admission (7.26 [1.93–27.29]) in the HIV group.

Conclusions. Disseminated TB was more frequent in the HIV group. Factors associated with mortality differed, highlighting CNS involvement in the non-HIV group and malignancy in the HIV group.

Keywords. disseminated tuberculosis; extrapulmonary tuberculosis; HIV; immunocompromise; tuberculosis.

In 2023, tuberculosis (TB) returned to be the world's leading infectious cause of mortality worldwide, following the coronavirus disease 2019 pandemic. Globally, an estimated 10.8 million new cases were reported—the highest rate since 1995—with an increasing trend since 2020 [1].

According to the World Health Organization (WHO) and the National Center for Preventive Programs and Disease Control, a Mexican Ministry of Health agency responsible for coordinating and implementing disease prevention and control strategies, approximately 30 000 new TB cases are reported annually in Mexico [1, 2]. In 2021, 20 255 cases were documented; 16.5% were extrapulmonary and 4.7% disseminated disease [2]. The most common comorbidities associated with TB in Mexico include diabetes (30%), malnutrition (16%), tobacco use (16%), alcoholism (14%), substance abuse (12%), and human immunodeficiency virus (HIV) infection (9%) [2].

The pathogenesis of extrapulmonary TB dissemination is influenced by the virulence of mycobacteria, its transmission

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pathways, and the host's immune status. Proposed mechanisms for dissemination include the infection of alveolar macrophages, enabling passage through the lymphatic and circulatory systems; and direct infection of lung-dwelling antigen-presenting dendritic cells then spreading to lymph nodes [3].

Immunosuppressed patients with rheumatic diseases, whether treatment-naive or receiving steroids or anti–tumor necrosis factor (TNF) therapy, have an increased risk of TB reactivation, with approximately 21%–26% presenting in an extrapulmonary site, frequently involving the lymphatic system [4–6]. Evidence indicates a strong association between disseminated TB and advanced HIV disease, with a reported prevalence of 10% [2, 7], and an increased risk of dissemination in cases of advanced disease [8, 9].

However, few reports describe extrapulmonary and disseminated TB in patients with other forms of immunosuppression. Given the diagnostic challenges associated with these conditions, a thorough understanding of TB in these scenarios is highly relevant for improving clinical outcomes. Our study aims to describe and compare the clinical features and outcomes of extrapulmonary and disseminated TB in patients with HIV-associated and non-HIV-associated immunocompromise.

MATERIALS AND METHODS

Study Design and Population

This retrospective cohort study was conducted at a third-level national referral center for adult patients in Mexico City, specializing in treating adults with complex, multisystemic, and immunocompromising medical conditions. Using our center's Clinical Microbiology Laboratory database, we identified all clinical cultures positive for *Mycobacterium tuberculosis* and *Mycobacterium bovis* between January 2000 and December 2023. We reviewed medical records and selected adult immunocompromised patients who were diagnosed with extrapulmonary or disseminated TB, and followed up at our institution for up to 24 months after diagnosis. Patients with exclusive pulmonary TB, incomplete information in the medical records, and those referred to other centers for medical attention were excluded.

Immunocompromise was defined when at least 1 of the following conditions was met: (*i*) HIV infection with $CD4^+$ count <200 cells/μL; (*ii*) solid organ or bone marrow transplant on systemic immunosuppressants; (*iii*) active malignant neoplasm receiving systemic chemotherapy in the past 6 months; (*iv*) use of systemic steroids (prednisone >15 mg/day or its equivalent for 2 or more consecutive weeks) [10]; or (*v*) use of other systemic immunosuppressive drugs in the last 6 months (eg, anti-TNF-α, anti-metabolites, anti-CD20 monoclonal antibodies) [11]. Two infectious disease specialists reviewed all TB diagnoses. Extrapulmonary TB was defined as a positive culture for *M tuberculosis* or *M bovis* from any anatomical site other than the lungs, including cases where the lungs were also involved. Disseminated TB was defined as 1 of the following: (*i*) involvement of 2 or more noncontiguous organs; (*ii*) isolation of *M tuberculosis* or *M bovis* in blood, bone marrow, or bone; or (*iii*) miliary pattern on chest imaging and positive culture from any site other than blood or bone marrow [3, 12].

Patients were categorized as receiving early TB treatment if active anti-TB therapy (isolate susceptible by subsequent in vitro testing) was initiated within 7 days of diagnosis. All-cause mortality was recorded within 24 months of diagnosis, from medical records. Based on the WHO recommendations, this timeframe was selected to account for patients with drug-resistant TB, for whom 24 months of anti-TB treatment is the standard of care in our country [13, 14].

Microbiology Procedures

During the study period, mycobacterial identification began with the digestion and decontamination of samples using the N-Acetyl-L-Cysteine-Sodium Hydroxide method for all samples except cerebrospinal fluid. The processed samples were then inoculated into Lowenstein-Jensen medium, Stonebrink medium, and MGIT tubes (Becton-Dickinson, Sparks, Maryland, USA). Up to 2018, positive cultures were confirmed using DNA probes (AccuProbe, San Diego, California, USA). From January 2019 to November 2021, confirmation was performed using the GenoType Mycobacterium CM/AS assay (Hain Lifescience GmbH, Nehren, Germany). Since November 2021, species complex identification was made using matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry (BD Bruker Maldi Biotyper Daltonics, Bremen, Germany) [15, 16]. Drug susceptibility testing for rifampin, streptomycin, isoniazid, and ethambutol was done using the radiometric (before 2005) or the BD BACTEC MGIT 960 systems (Becton-Dickinson) [15]. Prior to the implementation of DNA probes and mass spectrometry, conventional biochemical tests were the only method employed for species identification. *Mycobacterium tuberculosis* was identified by niacin production, positive nitrate reductase activity, and heat-stable catalase, while *M bovis* was identified by niacin production, nitrate reduction, and pyrazinamidase deamidation. Since the implementation of MALDI-TOF, pyrazinamidase deamidation has been done for *M bovis* species identification [16].

Statistical Analysis

Patients' sociodemographic and clinical characteristics were summarized as percentages, mean and standard deviation, or median and interquartile range (IQR), as appropriate. Comparisons between patients with HIV-associated and non-HIV-associated immunocompromise were made by Fisher exact test or Wilcoxon rank-sum test, according to the variables being analyzed. Univariate and multivariate logistic regression analyses for factors associated with death 24 months

after diagnosis were performed separately for each study group. Age, sex, and variables with a P value ≤.10 [17] in the univariate analysis were included in the multivariate models. Univariate time-to-event analysis was performed using Kaplan-Meier survival estimates and log-rank tests. A 2-sided P value ≤.05 was considered statistically significant for all comparisons. Missing data were not imputed. All statistical analyses were performed using R version 4.3.1 and RStudio version 2023.03.2 software.

RESULTS

We identified 5610 positive cultures in 3153 patients. Of the 3153 patients, 2973 were excluded for the following reasons: samples from other healthcare centers (n = 2350), exclusive pulmonary TB (n = 241), lack of immunocompromise (n = 224), referral to other centers (n = 105), and incomplete medical records (n = 53). We included 180 patients: 81 with non-HIV-associated immunocompromise (45%) and 99 with HIV-associated immunocompromise (55%). The study population consisted of 180 patients, of whom 111 (61.7%) were male. The median age was 34 years (IQR, 29–47 years). *Mycobacterium bovis* was identified in 44% of all cases (80/180). Positive tuberculin skin test (TST) (>5 mm) was more frequent in the non-HIV group (50% vs 21%, $P = .02$). The rest of the baseline clinical characteristics and their distribution between groups are shown in Table 1.

Overall, the 2 most common sites of organ involvement in cases of extrapulmonary TB were lymph nodes (16/50 [32%]) and central nervous system (CNS) (15/50 [30%]). The distribution of extrapulmonary organ involvement in both study groups is shown in Table 2. Lung and CNS was the most common combination of disseminated TB for the non-HIV group, whereas lung and gastrointestinal was the most common for the HIV group. The 10 most common combinations of organ involvement in cases of disseminated TB are shown in Figure 1 for both groups. Twenty-six patients had a positive blood culture, with 20 of them in the HIV group (15 *M tuberculosis*/11 *M bovis*). Of these, 8 of 26 died (30%). The complete lists of organ involvement and their combinations are shown in Supplementary Table 1 and Supplementary Table 2.

Non-HIV-Associated Immunocompromise Group

Infection due to *M bovis* accounted for 54% (44/81) of infections in this group. The most common comorbidities were rheumatic autoimmune diseases (72/81), with systemic lupus erythematosus as the most frequent (48/72). All patients were receiving pharmacologic systemic immunosuppression. Two patients had an isoniazid-monoresistant isolate (1 *M tuberculosis*, 1 *M bovis*) and 1 had an isolate resistant to isoniazid and rifampin (*M tuberculosis*). Multivariate analysis showed that age (odds ratio [OR], 1.05 [95% confidence interval {CI}, 1.01–1.10]), unemployment (OR, 31.62 [95% CI, 1.65–605.18]), tobacco use (OR, 4.21 [95% CI, 1.03–17.21]), and disseminated TB (OR, 6.13 [95% CI, 1.24–30.35]) were independently associated with death.

HIV-Associated Immunocompromise Group

Disseminated disease was the most prevalent disease presentation in this group (80%). The median $CD4^+$ cell count was 77 cells/μL (IQR, 42–122 cells/mL) in the extrapulmonary TB group and 44 cells/mL (IQR, 23–102 cells/mL) in the disseminated disease group ($P = .08$). No differences were observed in the proportion of patients with undetectable viral load (1/20 and 9/79) or on antiretroviral therapy (5/20 and 36/59). Malignancy (OR, 33.82 [95% CI, 2.37–483.33]) and intensive care unit (ICU) admission (OR, 7.26 [95% CI, 1.93–27.29]) were significantly associated with mortality. HIV patients with malignancy [4] were receiving chemotherapy for lymphoma (3/4) and visceral Kaposi sarcoma (1/4). Five patients had isolates resistant to isoniazid (3 *M tuberculosis*, 2 *M bovis*), 2 patients had isolates resistant to rifampin (1 *M tuberculosis*, 1 *M bovis*), and 2 patients had isolates resistant to isoniazid and rifampin (1 *M tuberculosis*, 1 *M bovis*).

Treatment, Disease Severity, and Survival

Overall, 91% of patients (163/180) received anti-TB treatment. Isoniazid-rifampicin-pyrazinamide-ethambutol fixed-dose oral combination, per local guidelines, was the most common treatment (153/163). Ten patients received intravenous therapy due to compromise of the gastrointestinal tract and/or septic shock. Seventeen patients (9%) did not receive anti-TB treatment; all were diagnosed postmortem. Death occurred in 41 of 180 (23%) patients: 22 in the non-HIV group (median time to death, 3 months [IQR, 0–7 months]), and 19 in the HIV group (median time to death, 2 months [IQR, 0–7 months]) ($P = .35$). Early treatment was inversely associated with death in both groups (non-HIV group: OR, 0.21 [95% CI, .05–.95]; HIV group: OR, 0.28 [95% CI, .08–.98]). Hospitalization was required for 89% of the study population (160/180), with 20% (36/180) requiring ICU admission. CNS involvement was associated with death in the non-HIV group (OR, 10.10 [95% CI, 1.91–53.53]) (Table 3). Survival analysis showed no significant differences between extrapulmonary and disseminated disease, independently assessing both study groups (Figure 2).

DISCUSSION

We found relevant and distinct clinical features of extrapulmonary and disseminated TB by comparing immunosuppressed patients with and without HIV infection. Extrapulmonary TB presents significant diagnostic challenges due to its mimicry

Table 1. Baseline Clinical Characteristics

Variable	All Patients (n = 180)	Non-HIV-Associated Immunocompromise (n = 81)	HIV-Associated Immunocompromise (n = 99)	*P* Value
Age, y, median (IQR)	34.35 (29.10–47.24)	37.83 (30.28–52.59)	33.56 (29.07–45.13)	.07
Sex, male	111 (62)	24 (30)	87 (88)	<.001
Unemployed	99 (55)	61 (75)	38 (38)	<.001
Tobacco use	76 (43)	27 (34)	49 (51)	.04
Alcohol use	91 (51)	27 (34)	64 (66)	<.001
Drug use	33 (19)	3 (4)	30 (31)	<.001
Community bacillus exposure	34 (20)	16 (21)	18 (19)	.86
Comorbidity	180 (100)	81 (100)	99 (100)	.86
Chronic hypertension	19 (10)	16 (20)	3 (3)	.001
Diabetes mellitus	6 (3)	4 (5)	2 (2)	.50
HbA1c, %, median (IQR)	8.45 (7.72–9.18)	9.90 (9.90–9.90)	7.00 (7.00–7.00)	.317
Autoimmune disease	59 (33)	58 (72)	1 (1)	<.001
Systemic lupus erythematosus	28 (48)	28 (48)	0	
Rheumatoid arthritis	6 (10)	6 (10)	0	
Idiopathic inflammatory myopathy	5 (9)	5 (9)	0	
Thyroiditis	4 (7)	3 (5)	1 (100)	
Systemic sclerosis	3 (5)	3 (5)	0	
Juvenile idiopathic arthritis	1 (2)	1 (2)	0	
Autoimmune hepatitis	2 (3)	2 (3)	0	
ANCA-associated vasculitis	2 (3)	2 (3)	0	
Primary sclerosing cholangitis	1 (2)	1 (2)	0	
Primary Sjögren disease	1 (2)	1 (2)	0	
Other	6 (10)	6 (10)	0	
Malignancy[a]	14 (8)	10 (12)	4 (4)	.07
Solid organ malignancy	7 (50)	4 (40)	3 (75)	
Hematological malignancy	7 (50)	6 (86)	1 (14)	
Organ transplant	5 (3)	5 (6)	0	.04
Kidney	4 (80)	4 (80)		
Bone marrow	1 (20)	1 (20)		
Cardiovascular disease	6 (3)	5 (6)	1 (1)	.13
Chronic lung disease	6 (3)	5 (6)	1 (1)	.13
End-stage renal disease	4 (2)	3 (4)	1 (1)	.48
Inflammatory bowel disease	4 (2)	4 (5)	0	.08
Crohn disease	1 (25)	1 (25)	0	
Ulcerative colitis	2 (50)	2 (50)	0	
Nonspecified	1 (25)	1 (25)	0	
Chronic neurological disease	1 (1)	1 (1)	0	.92
Pharmacologic systemic immunosuppression	85 (48)	81 (100)	4 (4)	
Steroids	32 (18)	32 (40)	0	
Chemotherapy	11 (6)	8 (10)	3 (3)	
Other	39 (22)	38 (47)	1 (1)	
Not specified	4 (2)	4 (3)	0	
$CD4^+$ count, cells/μL, median (IQR)	NA	NA	50 (26–105)	
IGRA (n = 14)				.08
Positive	6 (46)	5 (71)	1 (14)	
Negative	8 (62)	2 (29)	6 (86)	
TST (n = 72)				.02
<5 mm	46 (64)	19 (50)	27 (79)	
>5 mm	26 (36)	19 (50)	7 (21)	
Mycobacterium tuberculosis complex species				.02
M tuberculosis	100 (56)	37 (46)	63 (64)	
M bovis	80 (44)	44 (54)	36 (36)	
Type of disease				.02
Extrapulmonary	50 (28)	30 (37)	20 (20)	
Disseminated	130 (72)	51 (63)	79 (80)	

Table 1. Continued

Variable	All Patients (n = 180)	Non-HIV-Associated Immunocompromise (n = 81)	HIV-Associated Immunocompromise (n = 99)	*P* Value
Days from diagnosis to treatment, median (IQR)	5.00 (1.00–15.00)	8.50 (2.75–20.50)	3.00 (1.00–9.00)	.003
Hospitalization	160 (89)	69 (85)	91 (92)	.23
ICU stay	36 (20)	14 (17)	22 (22)	.52
Death 24 mo after diagnosis	41 (23)	22 (28)	19 (19)	.35
Time to death, mo, median (IQR)	2 (0–7)	3 (0–7)	2 (0–7)	.50

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ANCA, anti-neutrophil cytoplasmic autoantibody; HbA1c, glycated hemoglobin; HIV, human immunodeficiency virus; ICU, intensive care unit; IGRA, interferon-γ release assay; IQR, interquartile range; NA, not available; TST, tuberculin skin test.

[a]Five lymphoma, 5 leukemia/myelodysplastic syndrome, 2 solid organ, 1 visceral Kaposi sarcoma, 1 germinal cell tumor.

Table 2. Organ Involvement and Deaths in Cases of Extrapulmonary Tuberculosis

		Non-HIV-Associated Immunocompromise (n = 30)		HIV-Associated Immunocompromise (n = 20)		
Variable	All (n = 50)	Cases	Deaths	Cases	Deaths	*P* Value (Cases)
Tuberculous lymphadenitis	16 (32)	7 (23)	0	9 (45)	1	.194
Central nervous system	15 (30)	9 (30)	4	6 (30)	1	1.000
Gastrointestinal system	11 (22)	8 (27)	1	3 (15)	0	.531
Genitourinary system	6 (12)	4 (13)	0	2 (10)	0	1.000
Skin and soft tissues	2 (4)	2 (7)	0	0	…	.659

Data are presented as No. (%) unless otherwise indicated.

Abbreviation: HIV, human immunodeficiency virus.

of organ-specific conditions and the difficulty in obtaining culture samples, given its paucibacillary nature [18].

Many studies suggest an association between HIV and an increased risk of extrapulmonary TB, particularly when compared to pulmonary TB in people with HIV (PWH). However, HIV infection also significantly increases the risk of disseminated TB (OR, 2.65 [95% CI, 2.10–3.35]) compared to localized extrapulmonary involvement [19, 20]. This higher risk is strongly associated with lower $CD4^+$ lymphocyte counts and higher viral loads [8, 9, 21]. Our study findings indicate that disseminated TB is more common among PWH, particularly those with low $CD4^+$ cell counts. We did not find a significant difference in $CD4^+$ cell counts between patients with HIV who had extrapulmonary or disseminated TB, although we included only HIV patients with a $CD4^+$ count <200 cells/μL. Of note, 91 of 99 patients had $CD4^+$ <50 cells/μL.

Autoimmune diseases were the most prevalent comorbidity in this study among the non-HIV group, likely due to the referral nature of our center. However, several studies have suggested a potential link between autoimmune diseases and TB, possibly mediated by shared autoantibodies found in autoimmune diseases [22]. Also, this population frequently uses immunosuppressive treatments, such as steroids or targeted therapies (ie, TNF-α inhibitors), which are known to increase the risk of active TB, including extrapulmonary and disseminated forms [23]. This observation is replicated in our study, seeing that steroids were the most common systemic immunosuppressive therapy.

Alcohol abuse, tobacco use, and substance abuse were more prevalent in the HIV-associated immunocompromise group (66%, 51%, and 31%, respectively), which is consistent with the association between these comorbidities previously reported in the literature [24]. Previous studies have identified alcohol abuse as an independent risk factor for both latent and active TB (risk relations [RR], 3.33 [95% CI, 2.14–5.19]), linking it to higher bacillary loads, delayed diagnosis, reduced treatment adherence, and increased rates of treatment failure and relapse [25, 26]. Although our study did not find an association between this and death, we did not stratify alcohol consumption. Interestingly, unemployment and tobacco use were significantly associated with death in the non-HIV group. We hypothesize that this may be related to 2 factors. First, although not registered, this group may lack the universal free healthcare that is offered to PWH in our country. Second, PWH have very close outpatient monitoring, which may not necessarily be the case for immunocompromised patients without HIV. However, there could be other explanations, and further research into the social determinants of health related to death in immunocompromised patients with TB is needed.

Although significant variability exists among observational studies regarding the strength of the association and causality between diabetes and TB [9, 21, 27], people with diabetes

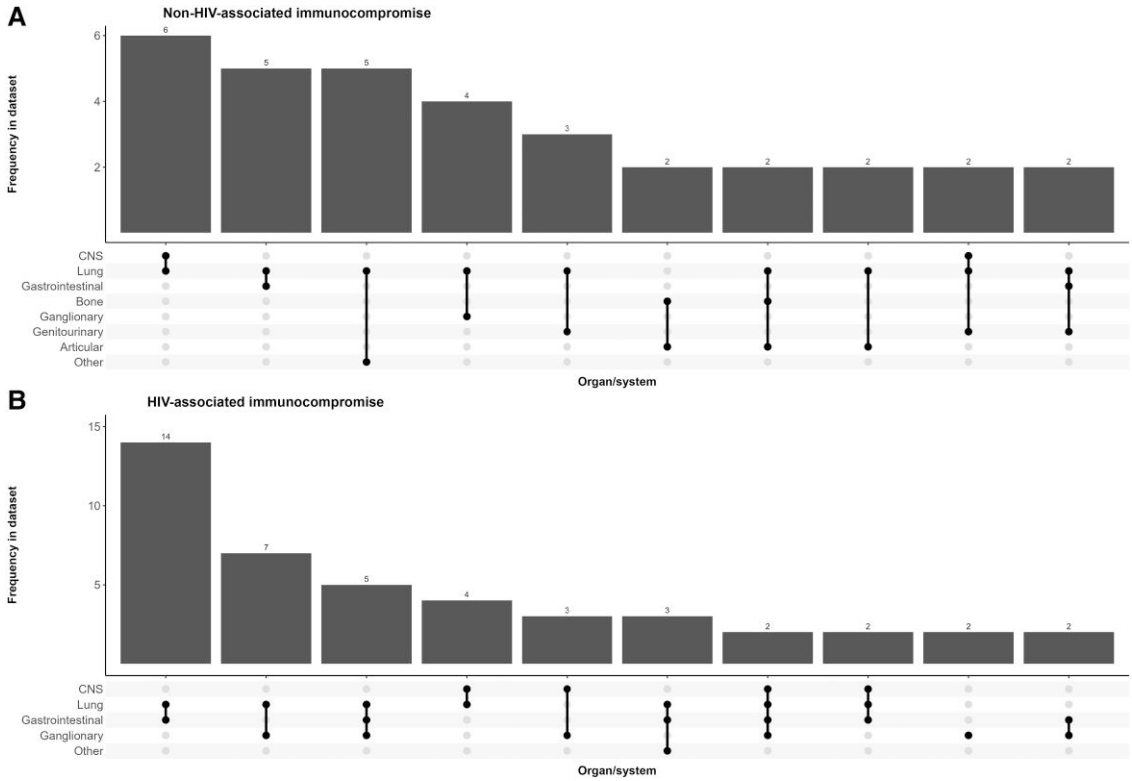

Figure 1. The 10 most common organs/systems involved in cases of disseminated tuberculosis. The black dots vertically connected with lines represent the combinations of the different organs or systems simultaneously involved. *A*, Non–human immunodeficiency virus (HIV)–associated immunocompromise. *B*, HIV-associated immunocompromise. *Positive blood culture. Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus.

have a 3-fold higher risk of active TB compared to the general population (RR, 3.11 [95% CI, 2.27–4.26]), with trends indicating worse outcomes in mortality and recurrence [28]. The coexistence of diabetes and TB is often associated with low education levels, high unemployment rates, and poor treatment adherence [2, 27, 29]. Interestingly, diabetes was infrequent in our study population, affecting <5%. Data on the relationship between diabetes and extrapulmonary TB are lacking, and more studies are needed [28].

Our study highlights differences in the distribution of *M tuberculosis* complex species in patients with different types of immunosuppression. HIV infection is recognized as an important risk factor for *M bovis* infection, being associated with advanced immunosuppression, abdominal involvement, and increased mortality [30]. In our center, the frequency of *M bovis* isolates in clinical samples has increased in recent years, rising from 7.8% in 2000 to 28.4% in 2014 [31]. In a retrospective study conducted at our institution involving immunosuppressed and nonimmunosuppressed patients, *M bovis* was found to be significantly associated with extrapulmonary TB (adjusted OR, 1.80 [95% CI, 1.21–2.69]) and steroid use (adjusted OR, 2.27 [95% CI, 1.42–3.63]) [32]. Considering that the reported prevalence of extrapulmonary TB in PWH is 13.8% [33], an increasing number of *M bovis* cases could be expected.

The most prevalent extrapulmonary sites identified in our study were lymphatic and CNS involvement. In contrast, national-level data from Mexico show miliary, lymphatic, and pleural TB as the most commonly affected sites [2]. A previous study in our center found that extrapulmonary TB is more frequent than pulmonary TB in patients with systemic lupus erythematosus, with abdominal and CNS involvement as the most prevalent organs involved [34]. These differences may be explained by the high prevalence of HIV infection in our population, which is strongly associated with lymphatic, meningeal, and disseminated forms of TB [8, 35]. Interestingly, disseminated disease was more frequent in the HIV group and extrapulmonary disease in the non-HIV group. Even though <50% were evaluated with interferon-γ release assay (IGRA) or TST, positivity was more common in the non-HIV group. We think this may be related to the timing of TB infection and the disease pathogenesis. We hypothesize that TB reactivation led to extrapulmonary involvement in the non-HIV group (as shown by positive IGRA/TST). In contrast, recent infection in the setting of low $CD4^+$ counts led to dissemination in the HIV group.

Results from our study show a high prevalence (21%) of mycobacteremia in the HIV group, in which most patients had disseminated disease. It has been shown that in approximately 50% of disseminated cases, the initial clinical presentation is

Table 3. Factors Associated With Death 24 Months After Extrapulmonary or Disseminated Tuberculosis Diagnosis

	Non-HIV-Associated Immunocompromise						HIV-Associated Immunocompromise					
	Univariate			Multivariate			Univariate			Multivariate		
Characteristic	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value
Age	1.03	(.99–1.06)	.08	1.05	(1.01–1.10)	.003	1.01	(.97–1.05)	.58	1.00	(.96–1.05)	.88
Sex, female	2.31	(.69–7.74)	.18	1.54	(.28–8.42)	.61	2.40	(.64–9.01)	.20	2.79	(.54–14.25)	.21
Unemployment	9.98	(1.25–79.77)	.03	31.62	(1.65–605.18)	.02	1.58	(.58–4.34)	.37	…	…	
Tobacco use	2.56	(.93–7.08)	.07	4.21	(1.03–17.21)	.04	0.97	(.35–2.71)	.96	…	…	
Alcohol use	0.89	(.31–2.53)	.82	…	…		0.77	(.28–2.22)	.63	…	…	
Drug use	NA	…		…	…		1.55	(.53–4.49)	.42	…	…	
$CD4^+$ <50 cells/μL	NA	…		…	…		1.35	(.48–3.78)	.57	…	…	
Undetectable HIV viral load	NA	…		…	…		0.48	(.06–4.06)	.50	…	…	
Antiretroviral treatment	NA	…		…	…		1.04	(.38–2.85)	.95	…	…	
Chronic hypertension	0.87	(.25–3.05)	.83	…	…		2.17	(.19–25.22)	.54	…	…	
Autoimmune disease	1.08	(.36–3.23)	.89	…	…		NA	…		…	…	
Malignancy	1.96	(.50–7.75)	.34	…	…		14.81	(1.45–151–65)	.02	33.82	(2.37–483.33)	.009
Organ transplant	0.66	(.07–6.20)	.71	…	…		NA	…		…	…	
Cardiovascular disease	1.87	(.29–12.00)	.51	…	…		1.82	(.28–11.76)	.53	…	…	
Chronic lung disease	1.87	(.29–11.99)	.51	…	…		NA	…		…	…	
Mycobacterium species			.60						.32			
M tuberculosis	Ref	…		…	…		Ref	…		…	…	
M bovis	1.30	(.48–3.52)		…	…		0.57	(.19–1.72)		…	…	
Days to treatment	0.99	(.96–1.02)	.56	…	…		1.01	(1.01–1.03)	.04	…	…	
Early treatment	0.39	(.13–1.13)	.08	0.21	(.05–.95)	.04	0.31	(.11–.89)	.03	0.28	(.08–.98)	.04
ICU admission	3.47	(1.05–11.45)	.04	2.67	(.63–11.40)	.18	6.30	(2.12–18.72)	<.001	7.26	(1.93–27.29)	.003
Type of disease			.10			.03			.26			
Extrapulmonary	Ref	…		Ref	…		Ref	…		…	…	
Disseminated	2.50	(.81–7.69)		6.13	(1.24–30.35)		2.47	(.52–11.70)		…	…	
Organ involvement												
CNS	3.02	(1.03–8.84)	.04	10.10	(1.91–53.53)	.007	2.70	(.94–7.75)	.07	2.52	(.66–9.58)	.17
Lymph nodes	0.51	(.13–1.97)	.33	…	…		0.56	(.20–1.63)	.29	…	…	
Gastrointestinal	0.86	(.29–2.54)	.78	…	…		0.38	(.12–1.14)	.08	0.37	(.09–1.57)	.18
Genitourinary	0.95	(.30–3.03)	.93	…	…		0.81	(.21–3.15)	.76			
Skin/soft tissue	0.51	(.06–4.67)	.56	…	…		1.43	(.14–14.51)	.75			
Lung	1.49	(.55–4.03)	.43	…	…		2.63	(.80–8.65)	.11			
Joints	1.65	(.43–6.31)	.46	…	…		3.02	(.45–19.49)	.25			
Positive blood culture	6.33	(1.07–37.49)	.04	…	…		1.07	(.31–3.66)	.92	…	…	

Abbreviations: CI, confidence interval; CNS, central nervous system; HIV, human immunodeficiency virus; ICU, intensive care unit; NA, not available; OR, odds ratio.

characterized by mycobacteremia, with a high likelihood of concurrent pulmonary coinfection [8, 35]. This observation is consistent with a study in which positive blood cultures were not linked to HIV status, but rather to abdominal TB and a body mass index <18 kg/m² [36].

CNS involvement remains one of the most severe forms of TB, particularly in PWH [9, 21, 35]. It is associated with the highest mortality rates, comparable to those seen in peritoneal involvement [9]. In consistence with this, in our study, CNS involvement was associated with higher odds of death, but only in the non-HIV-associated immunocompromise group. We hypothesize that this may be related to lower clinical suspicion of meningeal TB and delayed treatment in this group. Most disseminated cases in both study groups involved the lungs, reinforcing the hypothesis that lung involvement is the primary site of infection. This supports the well-established pathogenesis of mycobacteria breaching the lung barriers, thereby facilitating the spread of the disease [3].

The early initiation of anti-TB therapy largely determines survival outcomes in patients diagnosed with TB [37, 38]. In our study, both groups showed significantly lower odds of death when treatment was initiated within 7 days from diagnosis. Of note, the time from diagnosis to treatment initiation was significantly shorter in the HIV group compared to the non-HIV group (3 vs 8.5 median days, $P = .003$). We consider that this difference is likely related to a lower suspicion of TB in people without HIV and to a more exhaustive diagnostic workup in PWH. Mortality among critically ill TB patients reaches 68.7%, with acute respiratory failure and/or septic shock being the primary drivers [37]. In our study, ICU admission was strongly associated with death in the HIV group.

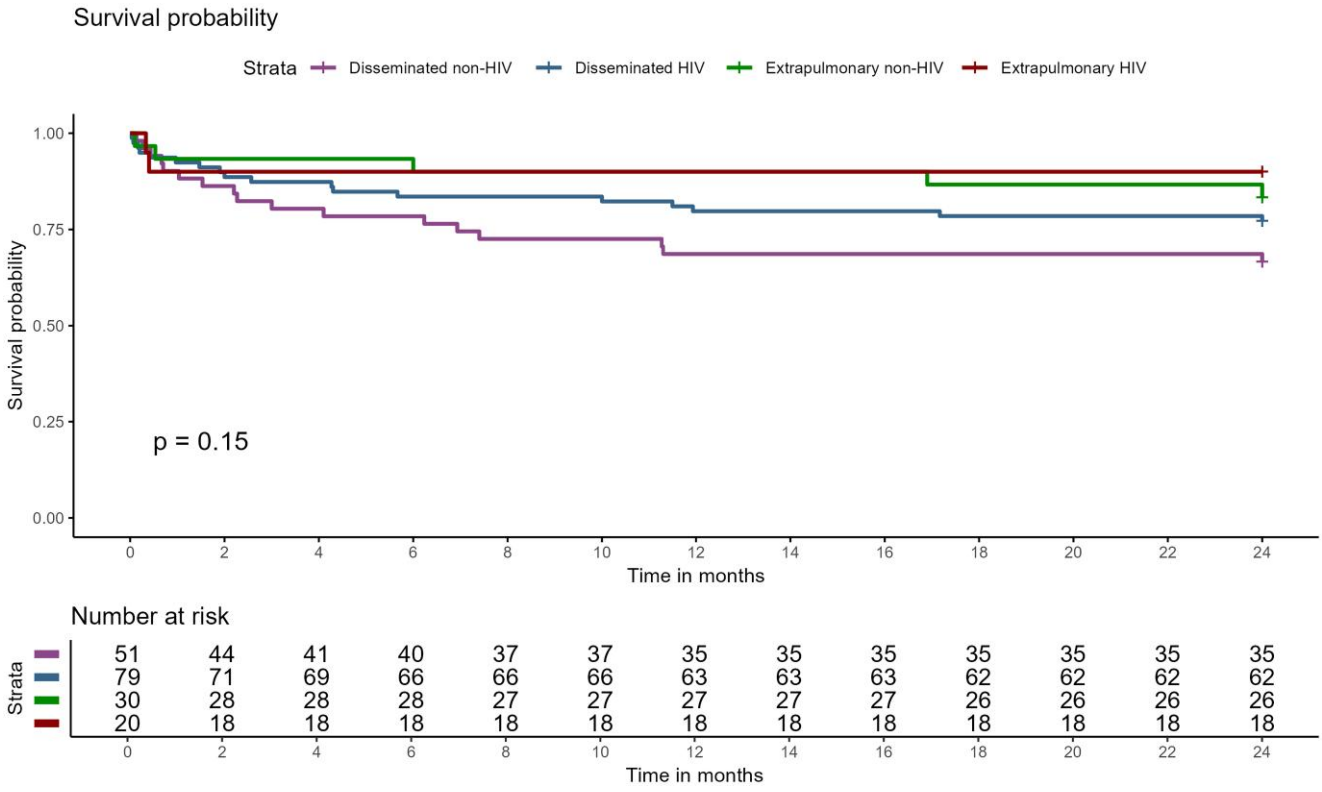

Figure 2. Extrapulmonary and disseminated tuberculosis survival probability 24 months after diagnosis by immunosuppression group. Abbreviation: HIV, human immunodeficiency virus.

Limitations of our study include its retrospective nature and a relatively small sample size. Some of the risk factors for death found in the logistic regression analysis show wide CIs, which is possibly related to the small sample size. While supporting differences between the study groups, additional studies with larger sample sizes need to confirm these observations. Additionally, due to the low number of resistant isolates, we could not assess further risk factors for resistance or evaluate treatment outcomes according to anti-TB drug resistance patterns. However, since Mexico is a country with a low prevalence of drug-resistant TB, this was expected [1]. Strengths of our study include contrasting patients with different types of immunocompromise, long-term follow-up, and careful description of all organs/systems involved in disseminated TB. This is the first study to characterize and compare the sociodemographic and clinical features, treatment regimens, and outcomes of extrapulmonary and disseminated TB between patients with non-HIV-associated and HIV-associated immunocompromise, providing valuable insights into their similarities and differences.

In summary, extrapulmonary and disseminated TB exhibit distinct clinical characteristics and outcomes in patients with different types of immunosuppression. Mortality rates are high and closely linked to disease severity and the timeliness of anti-TB therapy. CNS involvement is associated with death, especially in non-HIV-associated immunocompromised patients.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Ethics approval. This protocol was reviewed and approved by the Research and Ethics in Research Committees at Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (REF 5015-24-24-1). Due to the retrospective nature of the study, the informed consent form was waived.

Data availability. The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Potential conflicts of interest. The authors: No reported conflicts of interest.

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