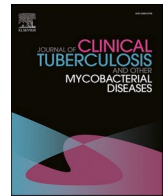Contents lists available at ScienceDirect

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Risk factors for mortality and multidrug resistance in pulmonary tuberculosis in Guatemala: A retrospective analysis of mandatory reporting

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ABSTRACT

Background: Risk factors for mortality and MDR-TB in Guatemala are poorly understood. We aimed to identify risk factors to assist in targeting public health interventions.
Methods: We performed a retrospective study of adults with pulmonary TB reported to the Guatemalan TB Program between January 1, 2016 and December 31, 2017. The primary objective was to determine risk factors for mortality in pulmonary TB. The secondary objective was to determine risk factors associated with MDR-TB.
Results: Among 3,945 patients with pulmonary TB, median age was 39 years (IQR 25–54), 59% were male, 25% of indigenous ethnicity, 1.1% had MDR-TB and 3.9% died. On multivariable analysis, previous TB treatment (odds ratio [OR] 3.57, CI 2.24–5.68 [p < 0.001]), living with HIV (OR 3.98, CI 2.4–6.17 [p < 0.001]), unknown HIV diagnosis (OR 2.65, CI 1.68–4.18 [p < 0.001]), indigenous ethnicity (OR 1.79, CI 1.18–2.7 [p = 0.005]), malnutrition (OR 7.33, CI 3.24–16.59 [p < 0.001]), and lower educational attainment (OR 2.86, CI 1.43–5.88 [p = 0.003]) were associated with mortality. Prior treatment (OR 53.76, CI 25.04–115.43 [p < 0.001]), diabetes (OR 4.13, CI 2.04–8.35 [p < 0.001]), and indigenous ethnicity (OR 11.83, CI 1.46–95.73 [p = 0.02]) were associated with MDR-TB.
Conclusions: In Guatemala, both previous TB treatment and indigenous ethnicity were associated with higher TB mortality and MDR-TB risk among patients with pulmonary TB.

1. Introduction

Tuberculosis (TB) was the leading cause of mortality from a single infectious agent in 2019, with an estimated 1.4 million deaths worldwide. [1] Risk factors for TB mortality include HIV infection, diabetes, anemia, chronic lung, heart, and liver disease. [2]

Multidrug resistant tuberculosis (MDR-TB), defined as resistance to isoniazid and rifampin, is a growing threat and a significant burden on health systems worldwide. The World Health Organization (WHO) estimated that in 2019, there were 465,000 estimated new cases of rifampin resistant TB (RR-TB) or MDR-TB worldwide, with 182,000 associated deaths. [1] RR-TB, detectable by readily available point-of-care testing, is an excellent surrogate marker for concomitant INH resistance, with INH resistance identified in 90% on RR-TB cases. [3] Among new TB cases in 2019, 3.3% were MDR-TB, of which 17.7% had previously been treated. [1] MDR-TB is associated with higher cost of

treatment, lower cure rates, and higher mortality than non-MDR-TB, highlighting its public health importance. [4–6] One study from 2000 to 2012 in Peru found that less education, history of prior TB, diabetes, and HIV infection were associated with increased mortality in patients with MDR-TB. [7] A *meta*-analysis with > 20,000 patients found that previous TB disease and prior TB treatment, non-completion of TB treatment, and failure of TB treatment were strongly associated with MDR-TB. [8] Another systematic review found HIV was not associated with the incidence of MDR-TB but was associated with primary MDR-TB. [9] However, a study from Peru noted a ten-fold increased risk of MDR-TB in people living with HIV (PLWHIV). [10] Other studies from Latin America identified male sex, diabetes, and smoking as risk factors for MDR-TB. [11–13]

In 2019, Guatemala reported 3,716 new cases of TB and estimated 130 cases of RR-TB/MDR-TB, an indication of success in the efforts to improve access to TB diagnostics, care, and treatment that warranted a

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change in Guatemala's TB burden status from moderate to low by the Global Fund to Fight AIDS, Tuberculosis, and Malaria. [1,14] However, significant disparities still exist in access to healthcare in rural and indigenous communities in Guatemala that are frequently subject to discrimination and language barriers. [15–16] A Guatemalan National TB Program (GNTBP) report in 2015 found that the Central and Northwestern regions had the highest rates of TB, and that in >15% of TB cases, HIV diagnosis was unknown. [17] A single-center study from Guatemala found that the most significant risk factor for treatment failure was resistance to ≥ 2 TB drugs (OR 6.4, CI 2.3–17.8), where resistance to isoniazid (19%), streptomycin (18%) and rifampin (3%) were the most commonly seen, but only 2.8% had resistance to both isoniazid and rifampin. [18]

The intent of this study was to identify risk factors for mortality and MDR-TB in adults with pulmonary TB in Guatemala.

2. Methods

2.1. Study design

We conducted a retrospective study of all adults with pulmonary TB reported to the GNTBP from January 1, 2016 to December 31, 2017. The Human Research Protection Office at Washington University in St. Louis and the Research Ethical Committee at the Guatemalan Ministry of Health approved the study with a waiver of informed consent.

2.2. Data collection

The GNTBP database collects standardized information on TB cases from all public healthcare facilities in the country, as TB case reporting is mandatory in Guatemala. The form collects age, sex, level of education, occupation, condition at diagnosis as defined by the WHO (i.e., new case, recurrent TB, previous loss to follow up, or treatment failure), site of infection (pulmonary vs. extrapulmonary), resistance profile (non-MDR-TB vs. MDR-TB), prior treatment history, and method used for the diagnosis (Supplementary Figure 1). Standard TB treatment regimens used are described in the Guatemalan Ministry of Public Health and Social Assistance's TB treatment protocol. [19]

We included all adults ≥ 18 years old at the time of the case notification. We excluded patients with extrapulmonary disease and those with unknown mortality status at the time of data collection. Date of death was validated using the Guatemalan National Registry of Persons database (*Registro Nacional de Personas* [RENAP]).

2.3. Variable definitions

TB disease was defined microbiologically, histopathologically or clinically confirmed. Microbiological diagnosis was based on acid-fast bacilli (AFB) visualized on stain, culture positive for *Mycobacterium tuberculosis complex,* or a positive molecular test (i.e. GeneXpert assay or in-house Mycobacterium tuberculosis [MTB] PCR testing) from respiratory specimens. Histopathological diagnosis was defined as tissue biopsy with granulomatous inflammation and/or AFB on specific stains from respiratory tract tissue samples. Clinical diagnosis was based on symptoms suggestive of TB as determined by the treating physician and supported by improvement after TB therapy, consistent radiographic findings, positive lipoarabinomannan assay, positive TB skin testing and/or interferon gamma release assay. MDR-TB cases were defined as having a positive rpoB rifampin-resistance mutation by the Xpert MTB/RIF (Cepheid, Sunnyvale, CA) test or resistance to both isoniazid (INH) and rifampin on drug susceptibility testing. Non-MDR-TB cases were defined as cases that did not fit the case definition for MDR-TB. Lower educational level was defined as fewer than six years of formal education (i.e. incomplete primary school). Indigenous ethnicity was determined by self-identification as Mayan, Garífuna, or Xinca. Guatemalan regions were based on the eight geopolitical definitions used by the Guatemalan

government (Metropolitan, North, Northeast, Southeast, Central, Southwest, Northwest, Petén) using the patients residence address at the time of notification. [20] Malnourishment was defined as body mass index (BMI) < 18.5 kg/m2 at the time of the case notification, as obtained from local medical records. HIV diagnosis, receipt of antiretroviral therapy (ART), diabetes, hypertension, chronic liver or kidney disease, history of previous TB treatment, drug or alcohol abuse, incarceration history, and pregnancy were obtained from non-mandatory reporting captured in the case-report form.

2.4. Statistical analysis

The primary outcome was all-cause mortality after the diagnosis of pulmonary TB and the secondary outcome was MDR-TB. Pearson Chi2 or Fisher's exact tests, and *t* test or Mann-Whitney *U* test were used for descriptive statistics, as appropriate. Variables significantly associated with mortality in the univariate analysis (p < 0.2) were included in the multivariable model. Multivariate binary logistic regression was used to evaluate risk factors associated with mortality and MDR-TB. In the multivariate logistic regression model, we adjusted for significant risk factors identified in the univariate analysis. For mortality, we adjusted for HIV diagnosis, prior TB treatment, education level, ethnicity, diabetes, and MDR-TB. For MDR-TB, we adjusted for previous TB treatment, education level, diabetes, and the patient's Guatemalan region of residence. All statistical tests were two-tailed, and significance was set at α = 0·05. All statistical analyses were done using SPSS (IBM, Armonk, New York, USA, version 26).

3. Results

3.1. Demographics and clinical characteristics

Of 5,959 patients with TB, 202 patients with extrapulmonary TB and 1,812 with unknown death status were excluded. Among 3,945 patients included in the analysis, the median age was 39 years (IQR 25–54), 59% were male, 25% were of indigenous ethnicity, and 83.9% had a low education level (Table 1). The Southwest region had the highest proportion of TB cases (30.6%), followed by the Central (22.9%), Metropolitan (21.4%), Northeast (8.8%), Northwest (7.4%), North (3.7%), Southeast (3.3%), and Petén (1.8%). Of 3,881 patients with a sputum AFB stain result, 2944 (75.8%) were positive. TB molecular testing, cultures, and biopsies were positive in 492 (12.5%), 80 (2%), and 92 (2.4%) of patients, respectively. Of 3,514 (89.6%) patients with a known HIV test result, 303 (8.6%) were PLWHIV. For 58 patients for whom receipt or lack thereof of ART was known, 39 (67.2%) were on ART.. Diabetes was present in 540 (13.7%) patients and 41 patients (1%) were malnourished. Alcohol abuse was documented in 52 patients (1.3%) and recreational drug use in 11 patients (0.3%). Previous incarceration was noted in 222 (5.6%) patients. Two-hundred twenty-nine (6.6%) patients had been previously treated for TB, and 43 (1.1%) had MDR-TB. Overall, 154 (3.9%) patients died.

3.2. Univariate analysis

Overall mortality was higher in patients who were older (45 vs 38 years, p < 0.001), of indigenous ethnicity (38.4% vs 24.5%, p < 0.001), and had lower education level (94.2% vs 83.5%, p < 0.001) (Table 1). There were mortality differences amongst regions with the highest mortality seen in the Northwest (14.9%), Northeast (12.3%), and Northern (5.2%) regions of Guatemala (p = 0.005). Higher mortality was also seen in patients with malnutrition (6.5% vs 0.6%, p < 0.001), previous TB treatment (21% vs 6%, p < 0.001), and a clinical diagnosis of TB (14% vs 7.8%, p = 0.014). The proportion of clinically diagnosed TB was higher in PLWHIV (26.8% vs 8.8%, p < 0.001) and indigenous population (12.6% vs 9.4%, p = 0.004) (data not shown). Indigenous ethnicity was also associated with malnutrition (1.7% vs 0.8%, p = 0.01)

Table 1
Characteristics of 3,945 patients with pulmonary tuberculosis, by mortality, Guatemala, 2016–17.

Variable	Alive (n = 3791)	Deceased (n = 154)	p value	OR (95% CI)*
Demographics, no. (%)				
Median (IQR) age in years	38 (27–54)	45 (31–60)	<0.001	———
Male sex	2249 (59.3)	90 (58.4)	0.827	0.96 (0.69–1.33)
Indigenous ethnicity[a]	926 (24.5)	59 (38.3)	<0.001	1.92 (1.37–2.68)
Lower education level	3165 (83.5)	145 (94.2)	<0.001	3.18 (1.61–6.28
Geographical Regions, no. (%)				
Metropolitan (1)	814 (21.5)	32 (20.8)	0.005	———
North	140 (3.7)	8 (5.2)		1.45 (0.65–3.22)
Northeast	329 (8.7)	19 (12.3)		1.46 (0.82–2.62)
Southeast	125 (3.3)	4 (2.6)		0.81 (0.28–2.34)
Central	875 (23.1)	29 (18.8)		0.84 (0.50–1.40)
Southwest	1171 (30.9)	35 (22.7)		0.76 (0.46–1.23)
Northwest	270 (7.1)	23 (14.9)		2.16 (1.24–3.76)
Petén	67 (1.8)	4 (2.6)		1.51 (0.52–4.42)
Diagnostic Method, no. (%)				
Microbiologic (1)	3397 (89.6)	131 (85.1)	0.009	———
Clinical	303 (8.0)	22 (14.3)		1.88 (1.18–3.0)
Histopathologic	91 (2.4)	1 (0.6)		0.28 (0.39–3.0)
Risk factors, no. (%)				
HIV diagnosis				
HIV uninfected (1)	3119 (82.8)	92 (59.7)	<0.001	———
Unknown	377 (10)	30 (19.5)	<0.001	2.17 (1.44–3.28)
People living with HIV	271 (7.2)	32 (20.8)	<0.001	3.38 (2.24–5.1)
ART** [a]	32 (0.8)	7 (4.5)	<0.001	5.68 (2.46–13.10)
Diabetes	527 (13.9)	13 (8.4)	0.055	0.57 (0.32–1.01)
Hypertension	21 (0.6)	0 (0)	1	———
Previously treated for TB	228 (6)	31 (21)	<0.001	3.93 (2.59–5.97)
Malnutrition	31 (0.8)	10 (6.5)	<0.001	8.42 (4.05–17.51)
Alcohol abuse	49 (1.3)	3 (1.9)	0.456	1.51 (0.46–4.92)
Drug abuse	11 (0.3)	0 (0)	1	———
Incarceration history	216 (5.8)	6 (4.2)	0.580	0.71 (0.31–1.63)
Microbiologic characteristics, no. (%)				
MDR-TB	38 (1)	5 (3.2)	0.025	3.31 (1.28–8.54)
Sputum smear microscopy positive	2839 (75.9)	105 (73.44)	0.487	0.87 (0.59–1.27)
Molecular testing positive	472 (12.5)	20 (13)	0.843	0.84 (0.65–1.69)
LAM positive	14 (0.4)	1 (0.6)	0.450	1.76 (0.23–13.49)
Culture positive	75 (2)	5 (3.5)	0.219	1.77 (0.70–4.44)

MDR-TB multidrug resistant tuberculosis. OR Odd ratio, CI Confidence Interval, HIV Human Immunodeficiency Virus, PLWHIV People Living with HIV. ART Antiretroviral Therapy. Microbiologic diagnosis includes positive acid-fast bacilli (AFB) stain, culture, and molecular tests. Histopathologic diagnosis refers to tissue biopsy with granulomatous inflammation and/or positive AFB. Clinical diagnosis is based on clinical and/or radiological findings as determined by the treating clinician. Reference category marked with the number 1. *Only for categorical variables. **Only includes PLWHIV. [a]Data missing in 21.7% and 82% of patients for variables ethnicity and receipt of ART for PLWHIV, respectively.

and lower educational level (91.1% vs 81.5%, p < 0.001) (data not shown). PLWHIV (20.8% vs 7.2%, p < 0.001), being on antiretroviral therapy (4.5% vs 0.8%, p < 0.001), unknown HIV diagnosis (19.5% vs 10%, p < 0.001), and MDR-TB (3.2% vs 1%, p = 0.025) were associated with higher mortality.

Patients with MDR-TB had lower education level compared to those with non-MDR-TB (100% vs 83.7%, p = 0.001) (Table 2). There was a significant difference in geographical distribution of MDR-TB, with less MDR-TB cases in the Metropolitan region (2.3% vs 21.7%) compared to the Central (39.5% vs 22.7%) and Southwest regions (44.2% vs 30.4%) (p = 0.003). Patients with MDR-TB were also more likely to have diabetes (41.9% vs 13.4%, p < 0.001) and to have received prior TB therapy (79.1% vs 5.8%, p < 0.001) compared to those with non-MDR-TB.

Table 2
Characteristics of 3,945 patients with pulmonary tuberculosis, by presence or absence of multidrug resistance (MDR-TB), Guatemala, 2016–2017.

Variable	Non-MDR-TB (n = 3902)	MDR-TB(n = 43)	p value	OR (95% CI)*
Demographics, no. (%)				
Age, median (IQR)	39 (28–54)	38.5 (28.5–45.25)	0.778	———
Male sex	2314 (59.3)	25 (58.1)	0.877	0.95 (0.51–1.75)
Indigenous ethnicity	984 (25.2)	1 (2.3)	0.001	14.16 (1.94–103.04)
Lower education level	3267 (83.7)	43 (100)	0.001	———
Geographical Regions, no. (%)				
Metropolitan (1)	845 (21.7)	1 (2.3)	0.003	———
North	147 (3.8)	1 (2.3)		5.74 (0.35–92.41)
Northeast	346 (8.9)	2 (4.7)		4.88 (0.44–54.04)
Southeast	129 (3.3)	0 (0)		———
Central	887 (22.7)	17 (39.5)		16.19 (2.15–121.96)
Southwest	1187 (30.4)	19 (44.2)		13.52 (1.80–101.23)
Northwest	292 (7.5)	1 (2.3)		2.89 (0.18–46.41)
Petén	69 (1.8)	2 (4.7)		24.49 (2.19–273.51)
Risk factors, no (%)				
HIV diagnosis				
Uninfected (1)	3577 (92.2)	41 (95.3)	0.771	———
PLWHIV	301 (7.8)	2 (4.7)	0.771	0.58 (0.14–2.40)
ART[a]	39 (1)	0 (0)		———
Unknown diagnosis	404 (10.4)	3 (7)	0.618	0.64 (0.19–2.09)
Diabetes	552 (13.4)	18 (41.9)	<0.001	4.66 (2.52–8.60)
Hypertension	21 (0.5)	0 (0)	1	———
Previously treated for TB	225 (5.8)	34 (79.1)	<0.001	61.73 (29.25–130.29)
Malnutrition	41 (1.1)	0 (0)	1	———
Alcohol abuse	52 (1.3)	0 (0)	1	———
Incarceration history	221 (5.7)	1 (16.7)	0.298	3.30 (0.38–28.44)
Drug abuse	11 (0.3)	0 (0)	1	———

MDR-TB Multidrug Resistant Tuberculosis. OR Odd Ratio, CI Confidence Interval, HIV Human Immunodeficiency Virus, PLWHIV People Living with HIV. ART Antiretroviral Therapy. *Only for categorical variables. Reference category marked with the number 1. [a] Data missing for 21.7% and 82% of patients for ethnicity and receipt of ART for PLWHIV, respectively.

3.3. Multivariate analysis

In the multivariate analysis, higher odds of mortality was associated with previous TB treatment (OR 3.57, CI 2.24–5.68 [p < 0.001]), PLWHIV (OR 3.98, CI 2.4–6.17 [p < 0.001]), unknown HIV diagnosis (OR 2.65, CI 1.68–4.18 [p < 0.001]), indigenous ethnicity (OR 1.79, CI 1.18–2.7 [p = 0.005]), malnutrition (OR 7.33, CI 3.24–16.59 [p < 0.001]), and lower educational level (OR 2.86, CI 1.43–5.88 [p = 0.003]). The c-statistic for this model was 0.73 (CI 0.68–0.77, p < 0.001). There were no significant associations between mortality and diabetes (OR 0.72, CI 0.4–1.32 [p = 0.29]) or MDR-TB (OR 1.8, CI 0.6–5.2 [p = 0.282]).

Regarding MDR-TB, multivariate analysis showed that previous TB treatment (OR 53.76, CI 25.04–115.43 [p < 0.001]), diabetes (OR 4.13, CI 2.04–8.35 [p < 0.001]), and indigenous ethnicity (OR 11.83, CI 1.46–95.73 [p = 0.02]) were associated with higher odds of MDR-TB. The c-statistic for this model was 0.90 (CI 0.84–0.96, p < 0.001) (Table 3).

4. Discussion

In our study we found that of 3,945 cases of pulmonary TB in Guatemala, 154 (3.9%) died and 43 (1.1%) had MDR-TB over a two-year period. By comparison, WHO estimated that in 2017 alone, Guatemala had 4,300 cases of TB, of which, 370 (8.6%) had death as an outcome and 130 were MDR/RR-TB (3.0%). [21] The discrepancy in the number of cases in our study might be partially attributable to including only adults with pulmonary TB, but could also reflect systematic under-reporting. [22–23] WHO also reported that among patients with TB, PLWHIV had lower mortality than people without HIV (0.41 per 100,000 population vs 1.8 per 100,000 population). [21] In our study PLWHIV had 3.98 times higher odds of death than patients without HIV coinfection, findings consistent with a previous *meta*-analysis that found a four-fold increase in mortality in TB/HIV coinfected patients. [24] The WHO estimates of HIV testing rates (94%) in patients with TB in Guatemala are in keeping with what was observed in this study (89.7%). Unknown HIV diagnosis was associated with higher odds of mortality in

our study. Limited local testing availability in remote areas or difficulties accessing the healthcare system may account for the mortality difference seen among those with an unknown HIV diagnosis. According to UNAIDS, 32% of PLWHIV in Guatemala do not know their diagnosis, and a recent study found that nearly 60% have a CD4 count $\leq$ 200 cell/mm^3 at the time of diagnosis. [25–26] Lack of information on CD4 count and viral load in PLWHIV included in our study is a limitation that could provide insight to the associations found.

We also found that clinically-diagnosed cases had higher odds of mortality, and PLWHIV were more likely to receive a clinical diagnosis. The diagnosis of TB can be difficult, and in individuals with advanced HIV disease, who tend to have atypical clinical presentations, diagnostic testing yield is lower. [27] Additionally, without microbiological confirmation, these patients may have harbored another infection with similar manifestations, such as histoplasmosis, suggesting the need for reliable point of care diagnostic tests. Reinhardt *et al.* found that 11.4% of Guatemalan patients with an AIDS-defining illness at HIV diagnosis had histoplasmosis. [26] Furthermore, in Latin America, the estimated incidence of histoplasmosis is equivalent to TB in PLWHIV and the overall prevalence of previous exposure to histoplasmosis was highest in Guatemala, although this was largely based on older studies using the histoplasmin test. [26,28–29] The higher mortality seen in clinically-diagnosed TB is in keeping with recently published data suggesting that in severely immunosuppressed, ART-naïve PLWHIV, empirical treatment for tuberculosis was not superior to test-guided treatment in reducing mortality. [30]

Lower educational level was associated with greater odds of mortality and MDR-TB, although the latter was not significant on multivariate analysis. In Peru, less education was also associated with higher mortality in patients with MDR-TB (OR 3.06, CI 1.43–6.55), and more education was associated with less loss to follow-up and lower mortality (OR 0.39, CI 0.16–0.94). [7,31] Primary school or lower education has also been associated with higher mortality in China (OR 2.51, CI 1.34–4.70) [32] and higher rates of MDR-TB have been associated with less education in studies from Pakistan and Turkey. [33–34] Similarly, the odds of mortality and MDR-TB were greater for those of indigenous ethnicity. Cerón *et al.* demonstrated that indigenous people in Guatemala experience multiple barriers to care, including language barriers and discrimination, likely contributing to the disparity of outcomes. [16] We found indigenous people had lower educational level, more malnutrition and more commonly had a clinical diagnosis, reflecting underlying social disparities. We also found that patients with malnutrition had a seven-fold increased odds of mortality, a finding particularly worrisome as Guatemala has one of the highest rates of malnutrition in Latin America. [35] However, malnutrition at the time of notification may be related to TB disease itself as consumption is fairly common in people with advanced TB disease.

Previously reported risk factors associated with MDR-TB were also seen in our study, particularly diabetes mellitus and prior TB treatment. A *meta*-analysis that included studies from fifteen countries, including Mexico and Peru, found that diabetes was a significant risk factor for development of MDR-TB (OR 1.97, CI 1.58–2.45). [11,36] A single-center, prospective study of patients diagnosed with pulmonary TB in Guatemala found that prior TB treatment for more than two weeks (OR 3.0; CI 1.5–10.3) was associated with resistance to $\geq$ 2 antituberculous antimicrobials. [18]

This is the first study to assess risk factors associated with TB mortality and with MDR-TB using nationwide mandatory reporting in the Central American region. Limitations of our study include its retrospective nature, the limited number of variables obtained from mandatory reporting forms, and the significant amount of missing data. The standardized reporting form allows only for mutually-exclusive selection of pulmonary or extrapulmonary TB at the time of the notification, likely leading to the exclusion of patients with extrapulmonary TB who also had pulmonary involvement. Additionally, the limited number of variables and incomplete data are reflective of the usual

Table 3

Risk factors associated with mortality and with multidrug resistance in a multivariable binomial logistic regression analysis of adult patients with pulmonary tuberculosis, Guatemala, 2016–2017.

RISK FACTORS	ODDS RATIO (95% CI)	P VALUE
MORTALITY		
HIV diagnosis*		
Unknown HIV diagnosis	2.65 (1.68–4.18)	<0.001
PLWHIV	3.98 (2.4–6.17)	<0.001
On ART**	0.43 (0.16–1.15)	0.09
Previous TB treatment	3.57 (2.24–5.68)	<0.001
Indigenous ethnicity	1.79 (1.18–2.7)	0.005
Diabetes	0.72 (0.4–1.32)	0.29
MDR-TB	2.08 (073.-6.01)	0.168
Lower education	2.86 (1.43–5.88)	0.003
Malnutrition	7.33 (3.24–16.59)	<0.001
MDR TB		
Previous treatment	53.76 (25.04–115.43)	<0.001
Diabetes	4.13 (2.04–8.35)	<0.001
Indigenous ethnicity	11.83 (1.46–95.73)	0.02
Guatemalan Regions***		
Metropolitan	0.24 (0.01–4.40)	0.342
Northeast	1.35 (0.10–17.11)	0.816
Central	2.31 (0.26–19.93)	0.446
Southwest	2.40 (0.28–20.58)	0.424
Northwest	2.35 (0.11–50.26)	0.582
Petén	3.19 (0.22–45.66)	0.392

HIV human immunodeficiency virus, PLWHIV People living with HIV, ART antiretroviral therapy, MDR-TB multidrug resistant tuberculosis. * Reference category for HIV is negative test. **only applicable to PLWHIV. ***The northern region of Guatemala was used as reference category.

standard of data gathering on cases in the country, as the mandatory reporting form was not designed for research purposes. Furthermore, data collection on all comorbidies is not mandatory nor standardized, likely leading to underreporting as reflected by the low prevalences seen. Self-reporting ethnicity might have led to missclassification, and the relevant amount of missing data for this variable (21.7%). The overall small number of MDR-TB cases reported hinders the representativeness of the associations found with MDR-TB. Use of rifampin resistance as a surrogate marker for MDR-TB may also have led to an overestimation in the number of MDR-TB cases. Lastly, the primary outcome was all-cause mortality and deaths might have not been directly related to TB. However, WHO assumes the proportion of deaths attributable to TB is the same as the observed proportion in recorded deaths (i.e. overall mortality). [37]

In this two-year study of patients with pulmonary TB in Guatemala, we found that PLWHIV, unknown HIV diagnosis, prior TB treatment, indigenous ethnicity, lower education level, and malnutrition were significantly associated with overall mortality risk. Risk of MDR-TB was higher in patients with indigenous ethnicity, prior treatment for TB, and diabetes. Higher TB mortality and MDR-TB risk in indigenous polulations might reflect social disparities seen in Guatemala and other Latin American countries. Additional studies are needed to further characterize TB morbidity and mortality in Central America.

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CRediT authorship contribution statement

Kevin Montes: Data curation, Writing – original draft, Visualization. **Himachandana Atluri:** Data curation, Writing – original draft. **Hibeb Silvestre Tuch:** Data curation, Resources, Writing – review & editing. **Lucrecia Ramirez:** Resources, Data curation. **Juan Paiz:** Resources, Data curation. **Ana Hesse Lopez:** Resources, Data curation. **Thomas C. Bailey:** Supervision, Writing – review & editing. **Andrej Spec:** Supervision, Writing – review & editing. **Carlos Mejia-Chew:** Conceptualization, Methodology, Visualization, Writing – review & editing, Project administration.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2021.100287.

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