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Central Nervous System Tuberculosis: Risk Factors for Mortality in a Propensity Score–Matched Case-Control Study

Michael Asare-Baah,[1,2,©] Lori Johnston,[3] Tatiana Ramirez-Hiller,[4] Marie Nancy Séraphin,[2,5] and Michael Lauzardo[2,5]

[1]Department of Epidemiology, College of Public Health and Health Professions, College of Medicine, University of Florida,Gainesville, Florida, USA, [2]Emerging Pathogens Institute, University of Florida, Gainesville, Florida, USA, [3]Bureau of Tuberculosis Control, Florida Department of Health, Tallahassee, Florida, USA, [4]Pediatric Research Hub, Department of Pediatrics, College of Medicine, University of Florida,Gainesville, Florida, USA, and [5]Division of Infectious Diseases and Global Medicine, College of Medicine, University of Florida,Gainesville, Florida, USA

Background. Despite advancements in tuberculosis (TB) control and treatment in the United States (US), patients with central nervous system TB (CNS-TB) continue to experience significantly higher mortality rates than those without CNS-TB. This raises concerns regarding clinical management and the need for a deeper understanding of the risk factors contributing to these deaths. This study aimed to determine the predictors of mortality in patients with CNS-TB.

Methods. We conducted a retrospective 1:2 propensity score–matched case-control study. Cases were TB patients diagnosed with TB of the meninges, brain, spinal cord, or peripheral nerves, as documented in the Florida Department of Health (FDOH) TB registry, between 2009 and 2021. Controls were TB patients without CNS-TB, also reported in the FDOH TB registry during the same timeframe. We employed conditional logistic regression models to investigate the factors contributing to mortality in cases compared with controls.

Results. We analyzed data from 116 cases and 232 matched controls. Patients with CNS-TB had a 5.69-fold higher risk of death than those without CNS-TB (adjusted odds ratio [aOR], 5.69 [95% confidence interval {CI}, 2.91–11.6]). Increased risk of death was associated with human immunodeficiency virus (HIV) coinfection (aOR, 1.93 [95% CI, .82–4.37]) and diabetes (aOR, 3.13 [95% CI, 1.28–7.47]). Miliary TB and non-HIV immunosuppression were significantly associated with being a case, while cavitary TB was less likely to be associated with being a case.

Conclusions. Clinical management should prioritize screening and close monitoring of patients with HIV coinfection and diabetes to improve patient outcomes.

Keywords. central nervous system tuberculosis; mortality risk; propensity score–matched case-control study; tuberculosis meningitis; tuberculosis mortality.

Central nervous system tuberculosis (CNS-TB) is a rare but devastating clinical manifestation of *Mycobacterium tuberculosis* (*Mtb*) infection of the brain and spinal cord [1, 2]. It results from the hematogenous dissemination of *Mtb* from the primary sites of infection across the blood–brain barrier, leading to cerebral pathology [3–5] and granulomatous inflammation at the base of the meninges [6]. The symptoms of CNS-TB often include a stiff neck, headache, fever, and neurological difficulties resembling those of meningitis [1, 7–9]. Unfortunately, CNS-TB is associated with high mortality rates (10%–20%) and can result in disabling neurological complications (5%–24%) [1, 4, 6, 10, 11]. Although early intervention is critical to achieving successful outcomes [12, 13], diagnosis is difficult owing to the low bacterial load in infected tissues [14, 15]. CNS-TB is often diagnosed at advanced stages, posing significant treatment challenges [16, 17]. Even in high-resource settings, mortality rates and neurological complications can be as high as 50% [2, 3, 6, 11].

Detecting CNS-TB typically requires evaluating clinical, laboratory, and radiological findings [14, 15]. The process involves a thorough medical history and physical examination to evaluate the symptoms and risk factors associated with CNS-TB, laboratory analysis of cerebrospinal fluid (CSF) or biopsy of brain tissue to confirm the presence of *Mtb* infection, and radiological imaging with magnetic resonance imaging and computed tomographic scans of the brain and spine to identify abnormalities such as meningeal enhancement, tuberculomas, hydrocephalus, and infarctions [12]. Although effective, the diagnostic process is laborious and time-consuming, as it takes at least 6 weeks to culture the isolates and obtain the results [18]. This is further compounded by the limited sensitivity of currently available diagnostic tools for detecting low levels of *Mtb* in the CSF or brain tissue. CSF polymerase chain reaction

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Correspondence: Michael Lauzardo, MD, MSc, Emerging Pathogens Institute, University of Florida, 2055 Mowry Road, PO Box 100009, Gainesville, FL 32610, USA (Mike.Lauzardo@medicine.ufl.edu); Marie Nancy Séraphin, PhD, Emerging Pathogens Institute University of Florida 2055 Mowry Road, PO Box 100009, Gainesville, FL 32610, USA (nancy.seraphin@medicine.ufl.edu).

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testing for *Mtb* DNA using Xpert MTB/RIF assay has high sensitivity and is recommended for diagnosing CNS-TB [12, 19]. Nevertheless, diagnostic delays persist even in settings with appropriate access to Xpert MTB/RIF assays [20], potentially because of the low clinical suspicion in high-risk populations.

In settings with low TB burden, CNS-TB accounts for 1%–5% of all TB cases [2, 14]. Its incidence is mainly determined by the local TB prevalence, host immune system, and pathogen virulence state [7, 21]. This condition disproportionately affects young children, human immunodeficiency virus (HIV)–coinfected patients, and immigrants from highly TB-endemic countries in developed countries [1, 3, 14, 22]. The risk of *Mtb* dissemination to the CNS increases with concurrent miliary TB and immunosuppression [2].

Several studies have identified predictors of CNS-TB mortality, such as age, non-US-born persons, HIV coinfection, diabetes, chronic kidney disease, miliary TB, and drug-resistant TB [11, 23–27]. However, these predictors vary across settings and populations and may not be generalizable in all contexts. A limitation of these studies is the need for more representative control groups from the general TB population to compare with CNS-TB patients. This challenge can be addressed using propensity score matching, which reduces the bias caused by confounding variables in observational studies and approximates a randomized experiment [28]. This technique creates a sample of TB patients with CNS-TB that is comparable to a sample of TB patients without CNS-TB based on observed covariates. In our study, using statewide surveillance data allowed for the estimation of propensity scores based on multiple covariates, providing a diverse source of TB patients with or without CNS-TB. In this study, we used a 13-year cohort of TB patients from the Florida Department of Health (FDOH) TB registry to investigate the risk factors that best predict TB-related mortality among patients with CNS-TB compared to a representative control group from the same source population.

MATERIALS AND METHODS

Study Design and Population

We conducted a retrospective case-control study using propensity score matching to determine the risk factors associated with TB-related mortality among cases with CNS-TB compared with controls without CNS-TB within a de-identified surveillance dataset from the FDOH TB registry. The dataset contains demographic, clinical, and epidemiological information on confirmed TB patients notified between January 2009 and December 2021. These patients were locally diagnosed and managed by various county health departments across Florida, and the FDOH TB Control Program centrally collated their data.

The source population included 6762 notified TB cases, of which 116 (1.7%) were classified as CNS-TB and 6646 (98.3%) without CNS-TB. We calculated the propensity score (likelihood of being a case) for all patients in the dataset using logistic regression based on age and birth origin. To create balanced groups with sufficient sample sizes, we matched cases and controls based on their propensity scores in a 1:2 ratio. By matching individuals of similar age, we directed the focus of the analysis on the specific effects of other variables of interest without the confounding effects of age, also matching on birth origin controlled for potential genetic or environmental factors that may be associated with both the exposure (CNS-TB) and the outcome (TB-related mortality). Figure 1 shows a flow diagram of the study design and population.

Measures

Exposure Variable: CNS-TB Status

We analyzed the presence or absence of CNS-TB as a dichotomous variable and primary exposure of interest. We defined a case of CNS-TB according to the Centers for Disease Control and Prevention's report of a verified case of TB criteria as having TB disease affecting the meninges, brain, spinal cord, or peripheral nerves, with laboratory confirmation via any of the following: (1) positive nucleic acid amplification test for *Mtb* complex from CSF or CNS tissue biopsy or (2) positive smear or culture from a CNS specimen. The control group (non–CNS-TB) consisted of TB patients with all forms of TB except those in the CNS-TB category.

Covariates: Patients' Demographics and Clinical and Epidemiological Predictors

Patient demographics included age at diagnosis (0–4, 5–14, 15–24, 25–44, 45–64, ≥65 years), self-reported sex (male, female), birth origin (US-born, non-US-born), and ethnicity (Hispanic/Latino, non-Hispanic/Latino). Clinical predictors were analyzed as categorical variables that indicated the presence, absence, or unknown status of HIV coinfection, diabetes, any form of drug resistance to at least 1 of the first-line anti-TB drugs, non-HIV immunosuppression (hepatitis, chronic kidney, and liver conditions), miliary TB disease, and cavitary TB disease. Epidemiological risk factors were grouped into 2 broad categories because there were fewer observations to be modeled separately. These were lifestyle risks, including patients with a history of 1 or more of the following: past-year alcohol use, injection drug use, noninjection drug use, and congregate risk, which included homelessness, residence in a long-term care facility, and correctional facility.

Outcome Variable: TB-Related Death

The primary outcome of interest was the occurrence of TB-related deaths, defined as death directly caused by TB or complications related to TB, including death at diagnosis or during treatment as indicated in the TB surveillance registry. We analyzed this as a dichotomous variable (died/alive).

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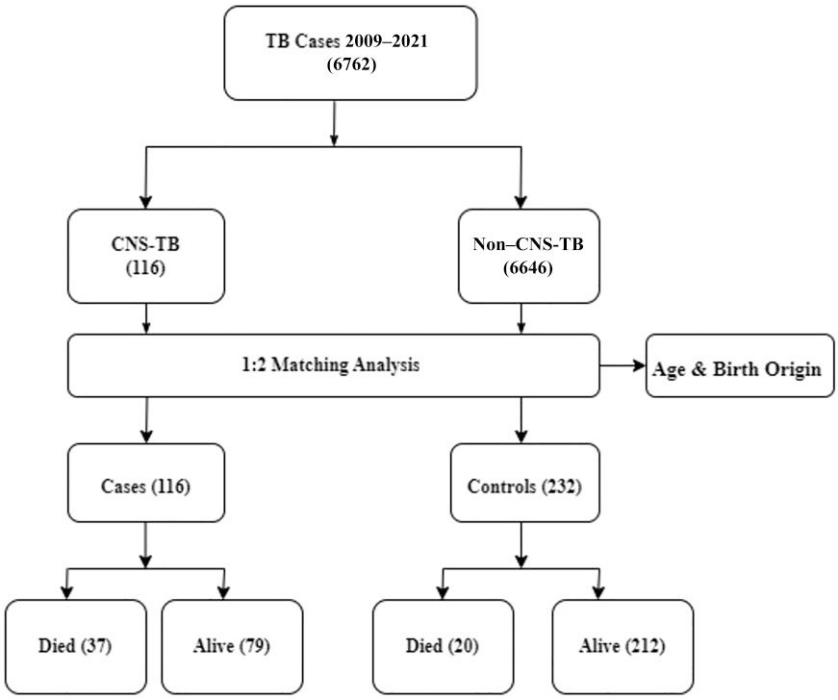

Figure 1. Flow diagram of the study design and population. Abbreviations: CNS, central nervous system; TB, tuberculosis.

Ethics Statement

The study was approved by the institutional review boards (IRBs) of the University of Florida and the FDOH (approval number IRB202201098) under secondary research, for which informed consent was waived.

Statistical Analysis

An initial crude analysis of the baseline characteristics of all 6762 patients was carried out to assess the differences in demographics, epidemiological, and clinical features between patients with and without CNS-TB using the χ^2 or Fisher exact test where necessary. To address the imbalance in baseline characteristics, we used propensity score matching to create 2 groups of participants based on CNS-TB status that were similar in age and birth origin. We generated a multivariable logistic regression model to estimate the propensity scores. The nearest neighbor technique was used to match participants with similar propensity scores, with a caliper width of 0.2 (matched pairs were within 0.2 standard deviations of each other in terms of the propensity score) and a ratio of 1:2. The MatchIt package in R was used to perform propensity score–matching analysis [29, 30].

We conducted univariate and multivariate conditional logistic regression analyses on the matched cohort to assess the effects of the identified variables on the risk of mortality in cases compared with controls. Variables deemed clinically relevant were included in the multivariate logistic analysis using the backward selection technique, and the most parsimonious model was selected based on the Akaike information criterion [31]. The Hosmer-Lemeshow goodness-of-fit test was used to assess the model calibration. We checked for multicollinearity among the predictors in the parsimonious model by calculating the variance inflation factor (VIF) values for each predictor. A VIF value >5 was considered an indication of multicollinearity. We reported odds ratios (ORs) with 95% confidence intervals (CIs) and set the statistical significance at $P < .05$. All analyses were performed using R software version 4.3.0.

RESULTS

Baseline Characteristics of the Initial Study Population Stratified by CNS Status

Patients with CNS-TB had a higher overall risk of TB-related death (31.9% vs 10.5%), including death during diagnosis (7.8% vs 2.7%) and treatment (25.9% vs 8.0%) (Table 1). They were also more likely to be in the age group 0–4 years (4.3% vs 0.7%), female (48.3% vs 34.9%), non-US-born (68.1% vs 57.0%), HIV infected (17.2% vs 11.5%), immunosuppressed (13.8% vs 7.9%), and have miliary TB disease (15.5% vs 4.8%). However, CNS-TB was less common among patients aged ≥65 years (18.1% vs 20.8%), those exposed to lifestyle risk factors such as alcohol and drug use (16.4% vs 22.6%), those resistant to any of the first-line drugs (6.9% vs 8.7%), those exposed to congregate settings (7.8% vs 12.5%), and those with cavitary TB disease (12.9% vs 40.6%).

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Table 1. Baseline Characteristics of the Study Population Stratified by Central Nervous System Tuberculosis Status

Variable	Overall (n = 6762)	CNS-TB (n = 116)	Non–CNS-TB (n = 6646)	*P* Value
Age, y, median (min, max)	49 (0, 98.0)	47 (0, 87.0)	49 (0, 98.0)	.001
Age group, y				.001
0–4	49 (0.7)	5 (4.3)	44 (0.7)	
5–14	39 (0.6)	1 (0.9)	38 (0.6)	
15–24	613 (9.1)	12 (10.3)	601 (9.0)	
25–44	2124 (31.4)	34 (29.3)	2090 (31.4)	
45–64	2536 (37.5)	43 (37.1)	2493 (37.5)	
≥65	1401 (20.7)	21 (18.1)	1380 (20.8)	
Sex, female	2378 (35.2)	56 (48.3)	2322 (34.9)	.004
Non-US-born	3865 (57.2)	79 (68.1)	3786 (57.0)	.021
Hispanic/Latino	1941 (28.7)	34 (29.3)	1907 (28.7)	.967
People with HIV	784 (11.6)	20 (17.2)	764 (11.5)	.159
Lifestyle risk[a]	1520 (22.5)	19 (16.4)	1501 (22.6)	.035
Diabetic	811 (12.0)	13 (11.2)	798 (12.0)	.905
Drug-resistant	589 (8.7)	8 (6.9)	581 (8.7)	.594
Congregate risk[b]	843 (12.5)	9 (7.8)	834 (12.5)	.280
Cavitary TB	2714 (40.1)	15 (12.9)	2699 (40.6)	<.001
Miliary TB	337 (5.0)	18 (15.5)	319 (4.8)	<.001
Non-HIV immunosuppression	544 (8.0)	16 (13.8)	528 (7.9)	.034
Died at diagnosis	191 (2.8)	9 (7.8)	184 (2.7)	.002
Died on treatment	561 (8.3)	30 (25.9)	531 (8.0)	<.001
Overall, death	732 (10.8)	37 (31.9)	695 (10.5)	<.001

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

Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus: TB, tuberculosis.

[a]Includes past-year alcohol use, injection drug use, and noninjection drug use.

[b]Includes homelessness, long-term care, and correctional facility use.

Propensity Score–Matched Comparison of Cases and Controls

The baseline characteristics were distributed evenly between the 2 groups after the matching process (Table 2). The *P* values for age distribution and birth origin were .98 and 1, respectively, indicating no significant differences between cases and controls regarding these baseline characteristics.

Risk Factors Associated With CNS-TB in the Matched Cohort

Patients diagnosed with CNS-TB had a significantly higher likelihood of having miliary TB disease and non-HIV immunosuppressive conditions compared to those without CNS-TB (Table 3). The odds were 5.55-fold for miliary TB disease and 2.96-fold for non-HIV immunosuppressive conditions. Conversely, patients with CNS-TB were found to be less likely to have cavitary TB disease, with odds of 0.23 times compared to patients with non–CNS-TB.

Predictors of TB-Related Mortality in the Matched Cohort

Patients with CNS-TB were found to have a much higher risk of dying, at 5.69 times that of patients without CNS-TB (95% CI, 2.91–11.6). Other factors that significantly increased the risk of death were HIV coinfection (adjusted odds ratio [aOR], 1.93 [95% CI, .82–4.37]) and diabetes (aOR, 3.13 [95% CI, 1.28–7.47]). On the other hand, being female (aOR, 0.60 [95% CI, .29–1.19]) and having resistance to at least 1 of the first-line anti-TB drugs (aOR, 0.34 [95% CI, .05–1.34]) appeared to lower the odds of death, although these associations were not statistically significant (Table 4).

Table 2. Baseline Parameters in the 1:2 Propensity Score–Matched Groups

Variable	Overall (n = 348)	Cases (n = 116)	Controls (n = 232)	*P* Value
Age, y				.982
Mean (SD)	46.4 (20.2)	46.4 (20.3)	46.5 (20.2)	
Median (min, max)	47 (0, 87.0)	47 (0, 87.0)	47 (0, 87)	
Birth origin, No. (%)				1.000
US-born	111 (31.9)	37 (31.9)	74 (31.9)	
Non-US-born	237 (68.1)	79 (68.1)	158 (68.1)	

Abbreviations: SD, standard deviation; US, United States.

DISCUSSION

In a case-control study using propensity score matching, we identified the patient characteristics that best predicted TB-related mortality among CNS-TB patients in a 13-year cohort of TB patients from the FDOH TB registry (2009–2021). The incidence of CNS-TB in our population was 1.7%, consistent with the estimated national average of 1%–5% and the 1.5%–2.7% observed prevalence of TB meningitis in Texas [11, 32].

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Table 3. Characteristics Associated With Central Nervous System Tuberculosis (CNS-TB) Compared to Non–CNS-TB

Variable	Overall (n = 348)	Cases (n = 116)	Controls (n = 232)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted *P* Value
Sex, female	147 (42.2)	56 (48.3)	91 (39.2)	1.45 (.92–2.27)	1.60 (.95–2.70)	.077
Ethnicity, Hispanic/Latino	116 (33.3)	34 (29.3)	82 (35.3)	0.76 (.46–1.22)	…	
People with HIV	45 (12.9)	20 (17.2)	25 (10.8)	1.73 (.90–3.29)	1.17 (.54–2.45)	.7
Lifestyle risk[a]	53 (15.2)	19 (16.4)	34 (14.7)	1.18 (.63–2.17)	…	
Diabetes	48 (13.8)	13 (11.2)	35 (15.1)	0.71 (.35–1.37)	…	
Drug resistance	32 (9.2)	8 (6.9)	24 (10.3)	0.64 (.26–1.42)	…	
Congregate risk[b]	40 (11.5)	9 (7.8)	31 (13.4)	0.55 (.24–1.15)	…	
Cavitary TB	112 (32.2)	15 (12.9)	97 (41.8)	0.23 (.12–.42)	0.23 (.11–.44)	<.001
Miliary TB	28 (8.0)	18 (15.5)	10 (4.3)	5.24 (2.35–12.3)	5.52 (2.11–15.2)	<.001
Non-HIV immunosuppression	31 (8.9)	16 (13.8)	15 (6.5)	2.31 (1.10–4.91)	2.30 (1.01–5.26)	.047
Died	57 (16.4)	37 (31.9)	20 (8.6)	4.96 (2.75–9.21)	4.83 (2.41–10.1)	<.001

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

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus: OR, odds ratio; TB, tuberculosis.

[a]Includes past-year alcohol use, injection drug use, and noninjection drug use.

[b]Includes homelessness, long-term care, and correctional facility use.

Table 4. Predictors of Tuberculosis-Related Mortality in the Matched Cohort

Variables	Overall (n = 348)	Died (n = 57)	Alive (n = 291)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted *P* Value
CNS-TB	116 (33.3)	37 (64.9)	79 (27.1)	4.96 (2.75–9.21)	5.69 (2.91–11.6)	<.001
Sex, female	147 (42.2)	22 (38.6)	125 (43.0)	0.83 (.46–1.48)	0.60 (.29–1.19)	.15
Ethnicity, Hispanic/Latino	116 (33.3)	16 (28.1)	100 (34.4)	0.75 (.39–1.37)	…	
People with HIV	45 (12.9)	11 (19.3)	34 (11.7)	2.48 (1.11–5.29)	1.93 (.82–4.37)	.041
Lifestyle risk[a]	53 (15.2)	13 (22.8)	40 (13.7)	2.03 (.97–4.05)	1.93 (.82–4.37)	.12
Diabetes	48 (13.8)	12 (21.1)	36 (12.4)	1.89 (.88–3.82)	3.13 (1.28–7.47)	.01
Drug resistance	32 (9.2)	2 (3.5)	30 (10.3)	0.32 (.05–1.09)	0.34 (.05–1.34)	.2
Congregate risk[b]	40 (11.5)	4 (7.0)	36 (12.4)	0.56 (.16–1.47)	…	
Cavitary TB	112 (32.2)	10 (17.5)	102 (35.1)	0.43 (.20–.88)	…	
Miliary TB	28 (8.0)	9 (15.8)	19 (6.5)	3.18 (1.28–7.44)	…	
Non-HIV immunosuppression	31 (8.9)	8 (14.0)	23 (7.9)	1.90 (.76–4.34)	…	

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

Abbreviations: CI, confidence interval; CNS, central nervous system; HIV, human immunodeficiency virus: OR, odds ratio; TB, tuberculosis.

[a]Includes past-year alcohol use, injection drug use, and noninjection drug use.

[b]Includes homelessness, long-term care, and correctional facility use.

The high TB-related mortality among patients with CNS-TB, which was 5.69-fold higher compared to those without CNS-TB in our population, despite the availability of well-resourced treatment capabilities and an efficient TB control program in Florida, affirms the difficulties in diagnosis and complexities associated with the clinical management of the condition. Several factors contribute to the high mortality of CNS-TB. First, the nonspecific symptoms of CNS-TB lead to delayed diagnosis and treatment initiation, resulting in disease progression and worse outcomes [33, 34]. This is exacerbated in vulnerable populations with limited healthcare access and inadequate screening methods. Second, patients presenting with advanced CNS-TB, like TB meningitis, are susceptible to neurological complications from high bacterial loads in the CNS [35]. This results in significant morbidity, with many survivors experiencing long-term disability [4]. Ultimately, the complex and variable presentation of CNS-TB makes early recognition and prompt treatment difficult. Coupled with the rapid progression and neurological damage associated with advanced disease, these factors explain the persistently high mortality rates observed in CNS-TB patients, even in well-resourced healthcare systems. This underscores the importance of early treatment, particularly before the onset of neurological signs or changes in consciousness [12]. In most instances, starting treatment without diagnostic confirmation is safer than waiting for test results if efforts are made to confirm the diagnosis later.

Patients with CNS-TB who also have immunosuppressive conditions, such as HIV and diabetes, are at an increased risk

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of death. These comorbidities weaken the immune system, making it more challenging to manage TB infection clinically [33, 36]. This often requires prolonged and complex treatment regimens that can increase the risk of adverse outcomes [37]. To improve patient outcomes, it is essential to integrate TB, HIV, and diabetes care programs to ensure comprehensive clinical management. Clinicians should consider TB as a differential diagnosis for HIV-infected or diabetic patients presenting with neurological symptoms to ensure early diagnosis and initiation of therapy.

The observed association between CNS-TB and miliary TB is consistent with the widespread dissemination of *Mtb* within the bloodstream, a characteristic feature of miliary TB. This dissemination allows *Mtb* to cross the blood–brain barrier and cause cerebral damage. The reason for the dissemination is immunocompromise, specifically cell-mediated immunity. The reduced incidence of CNS-TB among patients with cavitary pulmonary disease is not surprising, given that the very same immune mechanisms necessary to form cavities in some patients with pulmonary TB are the exact immune mechanisms compromised in patients with disseminated TB disease and CNS-TB. This is reflected in our data with a higher number of HIV-infected patients and children <5 years of age.

This retrospective observational study was based on a secondary analysis of surveillance data from FDOH. This study design is prone to residual confounding, which can affect the accuracy of the estimated effects and potentially limit the generalizability of the findings. Additionally, our definition of TB-related mortality does not capture all causes of death and is constrained by the parameters of the dataset. We could ascertain only deaths that occurred at diagnosis and during therapy and not those potentially related to TB that may have occurred after treatment conclusion.

To better understand the factors and mechanisms that drive the high mortality rate in CNS-TB patients, future research should focus on conducting prospective multicenter cohort studies with larger sample sizes than the current study. Additionally, more accurate CNS diagnostic classification methods should be utilized. Patients should be tracked throughout therapy and follow-up to better delineate TB-related deaths. Furthermore, future studies should assess the efficacy of current treatment protocols and regimens and explore alternative options to improve the outcomes and quality of life of patients with CNS-TB.

CONCLUSIONS

Our study showed that CNS-TB was associated with higher mortality rates than non–CNS-TB. Clinical risk factors such as HIV and diabetes are associated with TB-related mortality. Early diagnosis, prompt initiation of appropriate treatment, and comprehensive management of comorbidities are crucial to improve outcomes and reduce mortality rates among patients with CNS-TB. Moreover, strengthening healthcare systems, improving access to healthcare, and implementing enhanced screening methods for high-risk groups are essential for reducing the mortality rates associated with CNS-TB.

Notes

Author contributions. M. A.-B., M. N. S., and M. L. contributed to the generation of ideas, methodology development, statistical analysis, and manuscript drafting. T. R.-H. was involved in the initial discussion of the study design, facilitating the acquisition of the data and submission of the protocol for institutional review board approval. L. J. was involved in data generation, extraction, and contextual interpretation of the data analysis. All authors meticulously reviewed the final version before the approval of the publication.

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Patient consent. This analysis used de-identified data to protect patient privacy and did not include factors necessitating individual patient consent.

Data availability. These data are not publicly available and contain information from the national tuberculosis case report form, which is protected by the Assurance of Confidentiality. This prevents the disclosure of any information that could be used to identify patients.

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