Risk factors for extrapulmonary dissemination of tuberculosis and associated mortality during treatment for extrapulmonary tuberculosis

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Abstract
Many environmental, host, and microbial characteristics have been recognized as risk factors for dissemination of extrapulmonary tuberculosis (EPTB). However, there are few population-based studies investigating the association between the primary sites of tuberculosis (TB) infection and mortality during TB treatment. De-identified population-based surveillance data of confirmed TB patients reported from 2009 to 2015 in Texas, USA, were analyzed. Regression analyses were used to determine the risk factors for EPTB, as well as its subsite distribution and mortality. We analyzed 7007 patients with exclusively pulmonary TB, 1259 patients with exclusively EPTB, and 894 EPTB patients with reported concomitant pulmonary involvement. Age ≥45 years, female gender, human immunodeficiency virus (HIV)-positive status, and end-stage renal disease (ESRD) were associated with EPTB. ESRD was associated with the most clinical presentations of EPTB other than meningeal and genitourinary TB. Patients age ≥45 years had a disproportionately high rate of bone TB, while foreign-born patients had increased pleural TB and HIV+ patients had increased meningeal TB. Age ≥45 years, HIV+ status, excessive alcohol use within the past 12 months, ESRD, and abnormal chest radiographs were independent risk factors for EPTB mortality during TB treatment. The epidemiologic risk factors identified by multivariate analyses provide new information that may be useful to health professionals in managing patients with EPTB.

Introduction
Tuberculosis (TB), especially with human immunodeficiency virus (HIV) co-infection, is a leading cause of death worldwide1. Individuals infected with Mycobacterium tuberculosis (Mtb) may either be asymptomatic (latent TB infection, LTBI) or develop active TB disease2. For active TB disease, a small subset of patients (19.3–39.3%) present with either primary extrapulmonary tuberculosis (EPTB) or EPTB concurrent with pulmonary involvement, while the majority of patients develop pulmonary TB (PTB)3, 4. Some studies have suggested that the proportion of EPTB among all TB cases has been increasing in the United States (USA) (21% in 2013 compared to 16% in 1993) mainly because of the increasing prevalence of HIV infection5, 6. Typically, Mtb infection leads to spatial and temporal lesion dynamics not only within a single individual but also between individuals5, 8. The most common extrapulmonary sites of TB infection are the lymph nodes, the pleura, the genitourinary system, the gastrointestinal tract, the bones, and the central nervous system. To date, the mechanisms for extrapulmonary dissemination remain
largely unknown. It has been found that host–pathogen interactions such as pathogen-associated molecular pattern signaling, antigen presentation, and immune recognition may be used by Mtb to mediate latency induction and pathogen reactivation. These factors are believed to be important in establishing the site of disease presentation and dissemination. One recent study, which assessed within-host bacterial population dynamics in a macaque TB model by using a genome barcoding system coupled with serial 18F-fluorodeoxyglucose radiotracers and positron emission tomography co-registered with computed tomography (PET/CT), suggested that in the first 6 weeks after infection, granuloma size but not bacterial burden is correlated with risk of local dissemination (<10 mm away) in the lungs. Furthermore, genomic analyses of samples from lung and extrapulmonary biopsies of HIV-co-infected patients have demonstrated that the dissemination of Mtb from the lungs to extrapulmonary sites may occur as frequently as between lung sites. Importantly, Mtb sublineages were differentially distributed throughout the lungs of these immunocompromised patients. Therefore, data from Lieberman and co-workers suggest that biopsies from the upper airway represent only a small fraction of the population diversity. These data are also consistent with a nonhuman-primate-model study which showed barcodes recovered from gastric and bronchoalveolar lavage samples represented only a fraction (3.75%) of all bacterial barcodes. Additionally, there has been a study evaluating the immune response profile of inflammatory cytokines such as interferon-γ, interleukin (IL)-1β, and tumor necrosis factor (TNF)-β in HIV-negative children with TB disease. At the time of TB diagnosis, the immune response in all pediatric TB patients (suppressed proinflammatory cytokines and increased regulatory T cell frequency) was not significantly different between PTB and EPTB patients. However, the recovery of the immune response was observed in children with PTB but not in children with EPTB after 6 months of TB treatment. These findings suggest that the host immune response following treatment is specific to the disease (PTB vs. EPTB) rather than due to the within-host defense and cannot explain why one individual develops PTB while another develops EPTB.

Clinically, EPTB is still underrecognized, and diagnoses are often delayed due to its paucibacillary nature and atypical presentations. In fact, many characteristics such as HIV and female gender have been recognized as risk factors for EPTB dissemination. However, there are few population-based studies in the USA investigating the association between primary sites of Mtb infection and mortality during TB treatment. For instance, one study analyzed the epidemiology and risk factors of EPTB from 1993 through 2006 but did not analyze risk factors for patient mortality. Another study demonstrated risk factors for EPTB and mortality at 6 months after TB diagnosis from 1995 through 1999 in Harris County, Texas, but this study analyzed data at the county level and not at the state or country level. The third example is the association of Mtb lineage with the site of TB disease in a study that analyzed US data from 2004 through 2008; the study reported that the Euro-American, Indo-Oceanic, and East African-Indian bacterial lineages were found exclusively in EPTB. Given the variety of organ-specific clinical scenarios and the nonspecific systemic symptoms of EPTB, a more profound understanding of the site distribution of EPTB, as well as the risk factors associated with extrapulmonary dissemination and mortality, is important for developing suitable protocols to manage EPTB patients. Accordingly, this analysis aimed to determine the characteristics associated with EPTB dissemination and mortality during TB treatment by using recent epidemiological data from Texas.

Materials and methods

De-identified surveillance data of all confirmed TB patients reported to the Centers for Disease Control and Prevention’s TB Genotyping Information Management System (TBGMIS) between January 2009 and December 2015 from the state of Texas, USA, were analyzed. TB disease was classified as exclusively PTB, exclusively EPTB or EPTB with concurrent PTB involvement. Sites of EPTB include pleural, lymphatic, bone, genitourinary, peritoneal, and meningeal locations, among others. All patients received anti-TB treatment, and their outcomes were recorded as “completed”, “died”, or “unknown”.

Cases were categorized by site of disease. Differences across groups (exclusively PTB, exclusively EPTB and EPTB with concurrent PTB involvement) were determined by the chi-squared test or Fisher’s exact test as appropriate. Logistic regression was used to determine the characteristics that were associated with patients having exclusively PTB compared to individuals identified to have (1) exclusively EPTB, (2) EPTB with concurrent PTB involvement, or (3) any EPTB (patients with exclusively EPTB and EPTB with concurrent PTB involvement). Odds ratios (OR), adjusted odds ratios (aOR), and 95% confidence intervals (CI) were reported. Multiple logistic regression modeling was also used to determine the risk of patient mortality during treatment in patients with exclusively EPTB. Analyses were performed with SPSS 16.0 (SPSS, Inc., Chicago, Illinois, USA) and Stata MP14.2 (StataCorp LP, College Station, TX, USA). A p-value of <0.05 was considered statistically significant.

Results

Study population and characteristics

From 2009 to 2015, there were 9246 confirmed TB patients in Texas recorded in the TBGIMS database. After
excluding 86 patients because their EPTB site was unknown, we included 9160 TB patients in the analysis (Fig. 1). The patients’ demographic and clinical characteristics are presented in Table 1. The majority of exclusively EPTB patients were male (55.4%) and foreign born (59.1%). The proportions of patients age 25–44 years (39.6%) and Hispanic patients (46.6%) with exclusively EPTB were higher than the proportions of other age or ethnic groups with exclusively EPTB. The percentage of TB contact history was higher in patients with exclusively EPTB (3.7%) than in patients with PTB (9.0%) or EPTB with concurrent PTB (6.9%). In patients with exclusively EPTB, 448/1259 (35.6%) had abnormal chest radiographs and 17/1259 (1.4%) had culture-positive specimens. Multidrug-resistant TB (MDR-TB) was identified in 0.4% of exclusively EPTB cases, 0.1% of EPTB cases with concurrent PTB, and 0.8% of exclusive PTB cases. Two extensively drug-resistant cases were identified in PTB patients. The most prevalent Mtb lineages of exclusively EPTB were Euro-American L4, East Asian L2, and Indo-Oceanic L1.

Sites of EPTB

The distribution of EPTB sites is shown in Fig. 2a. Of the patients with exclusively EPTB, the most common sites of TB disease included pleural (15.7%), lymphatic (32.3%), bone (12.2%), and meningeal (7.5%) sites. The most common sites of TB disease in patients having EPTB with concomitant PTB were also pleural (38.1%), lymphatic (20.8%), bone (7.9%), and meningeal (6.7%) areas.

Risk factors for EPTB and its specific sites

Multivariable analyses were performed in order to identify associations between sociodemographic, microbiologic, and clinical characteristics of EPTB patients and sites of EPTB. Female patients (OR 1.32, 95% CI 1.19–1.46), as well as patients with HIV+ status (OR 1.77, 95% CI 1.47–2.13), immunosuppression (OR 1.31, 95% CI 1.00–1.77), and ESRD (OR 3.42, 95% CI 2.39–4.88) were at a significantly elevated risk of EPTB (Table 2). Patients with a history of contact with a known TB index case within 2 years (OR 0.44, 95% CI 0.35–0.55) and those with diabetes (OR 0.61, 95% CI 0.52–0.71) were less likely to have EPTB than PTB (Table 2).

ESRD was associated with most subtypes of EPTB, excluding meningeal and genitourinary TB (Table 3). Patients age ≥45 years had a disproportionately high rate of bone TB (OR 1.47, 95% CI 1.04–2.08), while foreign-born patients had more pleural TB (OR 1.77, 95% CI 1.31–2.41) and HIV+ patients had more meningeal TB (OR 5.73, 95% CI 3.43–9.56) (Table 3).

Risk factors for mortality during treatment in patients with exclusively EPTB

Among the 1111 patients with exclusively EPTB who had mortality-related data available, 50 (4.5%) died during anti-TB treatment. Mortality was highest among those patients presenting with meningeal (9.6%) or peritoneal TB (8.5%) and lower among those individuals with lymphatic TB (0.7%) (Fig. 2b). During treatment, no mortality was reported among patients having either laryngeal or multisite TB. Age ≥45 (OR 3.75, 95% CI 1.71–8.22), HIV+ status (OR 4.70, 95% CI 1.54–14.32), excessive alcohol use within the past 12 months (OR 3.34, 95% CI 1.45–7.67), ESRD (OR 4.45, 95% CI 1.38–14.33), and abnormal chest radiographs (OR 2.18, 95% CI 1.09–4.35) were risk factors for TB mortality with adjusted odds ratio (Table 4).

Discussion

Although risk factors for the development of exclusively EPTB compared to PTB have been described in several studies5, 12, 16, 17, there are still inconsistent findings among studies from different regions, including substantial state-level heterogeneity in the reported epidemiological data18. We performed an analysis of EPTB patients in the state of Texas. We found that patients who were age ≥45 years, female, HIV+, and suffering from ESRD were at a significantly elevated risk of EPTB. In particular, age ≥45 years, HIV+, excessive alcohol use
Table 1  Characteristics of tuberculosis patients with pulmonary and extrapulmonary locations in Texas, USA, 2009–2015

| Variable                           | Total   | Exclusively PTB | Exclusively EPTB | EPTB with PTB | p-Value |
|------------------------------------|---------|-----------------|------------------|---------------|---------|
| N                                  | 9160    | 7007            | 1259             | 894           | <0.01   |
| Age (years)                        |         |                 |                  |               |         |
| 0–4                                | 395 (4.3) | 297 (4.2)   | 63 (5.0)         | 35 (3.9)      | <0.01   |
| 5–14                               | 213 (2.3) | 146 (2.1)   | 43 (3.4)         | 24 (2.7)      |         |
| 15–24                              | 1048 (11.4) | 808 (11.5) | 129 (10.2)       | 111 (12.4)    |         |
| 25–44                              | 3054 (33.3) | 2245 (32.1) | 498 (39.6)       | 311 (34.8)    |         |
| 45–64                              | 3015 (33.0) | 2403 (34.3) | 361 (28.7)       | 251 (28.1)    |         |
| ≥65                                | 1435 (15.7) | 1108 (15.8) | 165 (13.1)       | 162 (18.1)    |         |
| Gender                             |         |                 |                  |               | <0.01   |
| Male                               | 5954 (65.0) | 4684 (66.8) | 697 (55.4)       | 573 (64.1)    |         |
| Female                             | 3206 (35.0) | 2323 (33.2) | 562 (45.6)       | 321 (35.9)    |         |
| Ethnicity                          |         |                 |                  |               | <0.01   |
| White                              | 1103 (12.0) | 911 (13.0)  | 108 (8.6)        | 84 (9.4)      |         |
| Black                              | 1717 (18.7) | 1524 (17.9) | 262 (20.8)       | 201 (22.5)    |         |
| Asian                              | 1517 (16.6) | 1052 (15.0) | 297 (23.6)       | 168 (18.8)    |         |
| Hispanic                           | 4771 (52.1) | 3752 (53.6) | 587 (46.6)       | 432 (48.3)    |         |
| Other                              | 52 (0.6) | 38 (0.5)       | 5 (0.4)          | 9 (1.0)       |         |
| HIV status                         |         |                 |                  |               | <0.01   |
| Negative                           | 7128 (77.8) | 5518 (78.7) | 959 (76.2)       | 651 (72.9)    |         |
| Positive                           | 608 (6.7) | 409 (5.9)     | 77 (6.1)         | 122 (13.6)    |         |
| Not offered                        | 1424 (15.5) | 1080 (15.4) | 223 (17.7)       | 121 (13.5)    |         |
| Homeless                           |         |                 |                  |               | <0.01   |
| No                                 | 8682 (94.8) | 6600 (94.2) | 1229 (97.6)      | 853 (95.4)    |         |
| Yes                                | 478 (5.2) | 407 (5.8)     | 30 (2.4)         | 41 (4.6)      |         |
| History of TB contacta             |         |                 |                  |               | <0.01   |
| No                                 | 8417 (91.9) | 6373 (91.0) | 1212 (96.3)      | 832 (93.1)    |         |
| Yes                                | 743 (8.1) | 634 (9.0)     | 47 (3.7)         | 62 (6.9)      |         |
| Excessive alcoholb                 |         |                 |                  |               | <0.01   |
| No                                 | 7494 (81.8) | 5633 (80.4) | 1138 (90.4)      | 723 (80.9)    |         |
| Yes                                | 1666 (18.2) | 1374 (19.6) | 121 (9.6)        | 171 (19.1)    |         |
| Injecting drug use                 |         |                 |                  |               | 0.03    |
| No                                 | 8930 (97.5) | 6819 (97.3) | 1241 (98.6)      | 870 (97.3)    |         |
| Yes                                | 230 (2.5) | 188 (2.7)     | 18 (1.4)         | 24 (2.7)      |         |
| Non-injecting drug use             |         |                 |                  |               |         |
| No                                 | 8263 (90.2) | 6257 (89.3) | 1202 (95.5)      | 804 (89.9)    | <0.01   |
| Yes                                | 897 (9.8) | 750 (10.7)    | 57 (4.5)         | 90 (10.1)     |         |
| Origin                             |         |                 |                  |               | 0.01    |
| US born                            | 4108 (44.8) | 3188 (45.5) | 515 (40.9)       | 405 (45.3)    |         |
| Foreign born                       | 5052 (55.2) | 3819 (54.5) | 744 (59.1)       | 489 (54.7)    |         |
Table 1 continued

| Variable                             | Total       | Exclusively PTB | Exclusively EPTB | EPTB with PTB | p-Value |
|--------------------------------------|-------------|-----------------|------------------|---------------|---------|
| **Diabetes**                         |             |                 |                  |               | <0.01   |
| No                                   | 7800 (85.2)| 5883 (84.0)     | 1122 (89.1)      | 795 (88.9)    |         |
| Yes                                  | 1360 (14.8)| 1124 (16.0)     | 137 (10.9)       | 99 (11.1)     |         |
| **End-stage renal disease**          |             |                 |                  |               | <0.01   |
| No                                   | 9024 (98.5)| 6935 (99.0)     | 1230 (97.7)      | 859 (96.1)    |         |
| Yes                                  | 136 (1.5)  | 72 (1.0)        | 29 (2.3)         | 35 (3.9)      |         |
| **Immunosuppression**                |             |                 |                  |               | 0.01    |
| No                                   | 8936 (97.6)| 6854 (97.8)     | 1217 (96.7)      | 865 (96.8)    |         |
| Yes                                  | 224 (2.4)  | 153 (2.2)       | 42 (3.3)         | 29 (3.2)      |         |
| **Previous TB**                      |             |                 |                  |               | 0.08    |
| No                                   | 8819 (96.3)| 6733 (96.1)     | 1226 (97.4)      | 860 (96.2)    |         |
| Yes                                  | 341 (3.7)  | 274 (3.9)       | 33 (2.6)         | 34 (3.8)      |         |
| **Inmate of a correctional facility**|             |                 |                  |               | <0.01   |
| No                                   | 8210 (89.6)| 6161 (87.9)     | 1192 (94.7)      | 857 (95.9)    |         |
| Yes                                  | 950 (10.4) | 846 (2.1)       | 67 (5.3)         | 37 (4.1)      |         |
| **Resident of long-term care facility**|         |                 |                  |               | 0.56    |
| No                                   | 9046 (98.8)| 6921 (98.8)     | 1240 (98.5)      | 885 (99.0)    |         |
| Yes                                  | 114 (1.2)  | 86 (1.2)        | 19 (1.5)         | 9 (1.0)       |         |
| **Specimen smear**                   |             |                 |                  |               | <0.01   |
| Negative                             | 4097 (44.7)| 2832 (40.4)     | 707 (56.2)       | 558 (62.4)    |         |
| Positive                             | 3585 (39.1)| 3423 (48.9)     | 5 (0.4)          | 157 (17.6)    |         |
| Not done/Unknown                     | 1478 (16.1)| 752 (10.7)      | 547 (43.4)       | 179 (20.0)    |         |
| **Specimen culture**                 |             |                 |                  |               | <0.01   |
| Negative                             | 2449 (26.7)| 1462 (20.9)     | 669 (53.1)       | 318 (35.6)    |         |
| Positive                             | 5185 (56.6)| 4782 (68.2)     | 17 (1.4)         | 386 (43.2)    |         |
| Not done/Unknown                     | 1526 (16.7)| 763 (10.9)      | 573 (45.5)       | 190 (21.3)    |         |
| **Chest radiography**                |             |                 |                  |               | <0.01   |
| Abnormal                             | 7694 (84.0)| 6485 (92.6)     | 448 (35.6)       | 761 (85.1)    |         |
| Normal                               | 1024 (11.2)| 233 (3.3)       | 700 (55.6)       | 91 (10.2)     |         |
| Not done/Unknown                     | 442 (4.8)  | 289 (4.1)       | 111 (8.8)        | 42 (4.7)      |         |
| **Radiographic cavity**              |             |                 |                  |               | <0.01   |
| No                                   | 5140 (56.1)| 4031 (57.5)     | 437 (34.7)       | 672 (75.2)    |         |
| Yes                                  | 2540 (27.7)| 2441 (34.8)     | 11 (0.9)         | 88 (9.8)      |         |
| Unknown                              | 1480 (16.2)| 535 (7.7)       | 811 (64.4)       | 134 (15.0)    |         |
| **DST profile**                      |             |                 |                  |               | 0.11    |
| None to RIF/INH                      | 6183 (67.5)| 4902 (70.0)     | 684 (54.3)       | 597 (66.8)    |         |
| RIF or INH                           | 512 (5.6)  | 420 (6.0)       | 44 (3.5)         | 48 (5.4)      |         |
| MDR                                  | 69 (0.7)   | 63 (0.8)        | 5 (0.4)          | 1 (0.1)       |         |
| XDR                                  | 2 (0.1)    | 2 (0.1)         | 0 (0.0)          | 0 (0.0)       |         |
within the past 12 months, ESRD, and abnormal chest radiographs were risk factors for EPTB mortality during treatment.

The observed demographics of female gender and foreign-born origin in the USA have been previously reported as risk factors for EPTB. Similarly, we found that female gender and Hispanic ethnicity were associated with patients who presented with exclusively EPTB after adjusting for other confounding factors. We further noted that ethnicity was not associated with any specific site of EPTB and that female gender was associated with lymphatic and peritoneal TB.

The risk of TB development in the foreign-born population was substantially elevated even more than 5 years after entering the USA. In our study population, more than half (55.2%) of the patients were born outside the USA. The cervical lymphatic site was found to be a more common disease site among foreign-born EPTB.

Table 1 continued

| Variable                  | Total      | Exclusively PTB | Exclusively EPTB | EPTB with PTB | p-Value |
|---------------------------|------------|-----------------|------------------|---------------|---------|
| Unavailable               | 2394 (26.1)| 1620 (23.1)     | 526 (41.8)       | 248 (27.7)    | <0.01   |
| Global Mtb Lineage        |            |                 |                  |               |         |
| Indo-Oceanic L1           | 634 (6.9)  | 483 (6.9)       | 93 (7.4)         | 58 (6.5)      |         |
| East Asian L2             | 1121 (12.2)| 918 (13.1)      | 98 (7.8)         | 105 (11.7)    |         |
| East African-Indian L3    | 174 (1.9)  | 115 (1.6)       | 37 (2.9)         | 22 (2.5)      |         |
| Euro-American L4          | 4344 (47.4)| 3569 (50.9)     | 376 (29.9)       | 399 (44.6)    |         |
| M. bovis                  | 105 (1.1)  | 52 (0.8)        | 36 (2.9)         | 17 (1.9)      |         |
| Other                     | 28 (0.3)   | 12 (0.2)        | 8 (0.6)          | 8 (0.9)       |         |
| Unknown                   | 2754 (30.2)| 1838 (26.5)     | 611 (48.5)       | 285 (31.9)    |         |
| Death at time of diagnosis|            |                 |                  |               | 0.04    |
| No                        | 8964 (97.9)| 6870 (98.0)     | 1220 (96.9)      | 874 (97.8)    |         |
| Yes                       | 196 (2.1)  | 137 (2.0)       | 39 (3.1)         | 20 (2.2)      |         |
| Death during TB treatment |            |                 |                  |               | <0.01   |
| No                        | 8610 (94.0)| 6592 (94.1)     | 1209 (96.0)      | 809 (90.5)    |         |
| Yes                       | 551 (6.0)  | 416 (5.9)       | 50 (4.0)         | 85 (9.5)      |         |

PTB pulmonary tuberculosis, EPTB extrapulmonary tuberculosis, HIV human immunodeficiency virus, RIF rifampin, INH isoniazid, MDR multidrug resistant, XDR extensively drug resistant. Differences across groups were compared using the chi-square test or Fisher’s exact test, as appropriate.

*Patients with a history of contact with a known TB index case within 2 years.

**Excessive alcohol use within the past 12 months.

Fig. 2 Distribution of extrapulmonary tuberculosis by site and associated mortality. a Distribution of extrapulmonary sites in patients with concurrent pulmonary tuberculosis (PTB) or exclusively extrapulmonary tuberculosis (EPTB). b Mortality distribution by extrapulmonary sites in patients with exclusively EPTB.
Table 2  Multivariable analyses of patients’ characteristics with extrapulmonary tuberculosis in Texas, USA, 2009–2015

| Characteristics | Exclusively EPTB vs. exclusively PTB | EPTB with PTB vs. exclusively PTB | Any EPTB vs. exclusively PTB |
|----------------|--------------------------------------|----------------------------------|-------------------------------|
|                | OR (95% CI)                          | aOR (95% CI)                     | OR (95% CI)                   |
| Age (years)    |                                      |                                  |                               |
| 0–4            | (reference)                          | (reference)                      | (reference)                   |
| 5–14           | 1.42 (1.04–1.96)                     | 1.19 (0.85–1.68)                 | 0.81 (0.55–1.19)              |
| 15–24          | 1.98 (1.35–2.88)                     | 2.33 (1.56–3.46)                 | 1.12 (0.71–1.79)              |
| 25–44          | 1.07 (0.83–1.37)                     | 1.10 (0.85–1.42)                 | 0.90 (0.73–1.22)              |
| 45–64          | 1.49 (1.23–1.80)                     | 1.57 (1.29–1.91)                 | 0.95 (0.77–1.16)              |
| ≥65            | 1.01 (0.82–1.23)                     | 1.22 (0.99–1.49)                 | 0.71 (0.58–0.88)              |
| Gender (female)|                                      |                                  |                               |
| White          | (reference)                          | (reference)                      | (reference)                   |
| Black          | 0.84 (0.33–2.15)                     | 0.92 (0.35–2.38)                 | 0.39 (0.18–0.83)              |
| Asian          | 0.76 (0.61–0.94)                     | 0.80 (0.63–1.02)                 | 0.68 (0.32–1.42)              |
| Hispanic       | 1.34 (1.14–1.57)                     | 1.34 (1.12–1.60)                 | 0.67 (0.32–1.42)              |
| Other          | 1.81 (1.55–2.11)                     | 1.57 (1.34–1.85)                 | 0.49 (0.23–1.01)              |
| Homeless       | 0.56 (0.38–0.83)                     | 0.57 (0.40–0.84)                 | 0.78 (0.56–1.08)              |
| History of TB  |                                      |                                  |                               |
| contacta       | 0.39 (0.29–0.53)                     | 0.28 (0.21–0.39)                 | 0.75 (0.57–0.98)              |
| Excessive      | 0.61 (0.49–0.75)                     | 0.60 (0.48–0.74)                 | 1.12 (0.91–1.38)              |
| drug use       | 1.08 (0.64–1.82)                     | 1.04 (0.62–1.76)                 | 1.00 (0.63–1.60)              |
| Non-injecting  | 0.53 (0.39–0.72)                     | 0.52 (0.40–0.71)                 | 0.87 (0.67–1.14)              |
| drug use       | 0.63 (0.51–0.77)                     | 0.61 (0.50–0.74)                 | 0.65 (0.51–0.82)              |
| Diabetes       |                                      |                                  | 0.61 (0.49–0.77)              |
| HIVf           | 1.14 (0.87–1.49)                     | 1.20 (0.92–1.55)                 | 2.65 (2.10–3.35)              |
| Immunosuppression | 1.44 (1.00–2.07)       | 1.36 (0.95–1.95)                 | 1.20 (0.78–1.83)              |
| ESRD           | 2.51 (1.58–3.99)                     | 2.59 (1.63–4.17)                 | 4.30 (2.78–6.64)              |
| Foreign born   | 1.04 (0.89–1.22)                     | 0.92 (0.80–1.06)                 | 1.06 (0.89–1.28)              |
| Previous TB    | 0.68 (0.47–1.00)                     | 0.69 (0.47–1.01)                 | 0.99 (0.68–1.43)              |

EPTB extrapulmonary tuberculosis, PTB pulmonary tuberculosis, OR odds ratio, aOR adjusted odds ratio, CI confidence interval, HIV human immunodeficiency virus, ESRD end-stage renal disease, TB tuberculosis

aPatients with a history of contact with a known TB index case within 2 years
bExcessive alcohol use within the past 12 months
cHIV unknown categorized as negative
Significant odds ratios (p<0.005) are in bold

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Table 3  Risk factors associated with subsites of exclusively extrapulmonary tuberculosis compared to pulmonary tuberculosis in Texas, USA, 2009–2015

| Characteristics       | Pleural (n = 198) | Lymphatic (n = 407) | Bone (n = 154) | Genitourinary (n = 65) | Peritoneal (n = 71) | Meningeal (n = 94) | Others (n = 212) |
|-----------------------|------------------|--------------------|--------------|-----------------------|-------------------|-------------------|----------------|
| Age (>45 years)       | 1.04 (0.76–1.40) | 0.56 (0.44–0.71)   | 1.17 (1.04–2.08) | 1.00 (0.60–1.68)      | 1.06 (0.64–1.74)  | 0.75 (0.48–1.17)  | 1.06 (0.79–1.42) |
| Gender (female)       | 0.91 (0.67–1.25) | 2.04 (1.66–2.51)   | 0.69 (0.48–0.99) | 1.34 (0.87–2.04)      | 1.96 (1.20–3.21)  | 1.22 (0.79–1.88)  | 1.39 (1.05–1.86) |
| Ethnicity (White)     | 0.73 (0.46–1.14) | 0.47 (0.29–0.77)   | 1.14 (0.69–1.88) | 1.26 (0.50–3.22)      | 0.62 (0.23–1.63)  | 0.82 (0.39–1.72)  | 0.77 (0.45–1.30) |
| Homeless              | 0.90 (0.48–1.68) | 0.29 (0.09–0.92)   | 0.54 (0.19–1.50) | 0.47 (0.06–3.57)      | 0.69 (0.16–2.95)  | 0.38 (0.09–1.63)  | 0.72 (0.29–1.82) |
| Excessive alcohol     | 1.17 (0.80–1.71) | 0.38 (0.23–0.63)   | 0.42 (0.23–0.75) | 0.92 (0.35–1.90)      | 1.30 (0.77–2.95)  | 0.54 (0.26–1.14)  | 0.30 (0.16–0.57) |
| Injecting drug use    | 0.91 (0.35–2.34) | 0.63 (0.15–2.68)   | 0.87 (0.20–3.79) | 0.83 (0.10–3.63)      | 0.80 (0.10–6.36)  | 2.20 (0.60–8.05)  | 0.84 (0.20–3.62) |
| Non-injecting drug use| 0.82 (0.49–1.38) | 0.37 (0.18–0.74)   | 0.70 (0.33–1.53) | 0.12 (0.02–1.05)      | 0.58 (0.19–1.76)  | 0.39 (0.14–0.97)  | 0.58 (0.27–1.24) |
| Diabetes              | 0.68 (0.43–1.07) | 0.35 (0.23–0.54)   | 0.92 (0.60–1.42) | 0.54 (0.24–1.22)      | 0.71 (0.35–1.44)  | 0.51 (0.23–1.13)  | 0.84 (0.35–1.66) |
| HIV                   | 0.62 (0.30–1.28) | 1.0 (0.74–1.75)    | 0.49 (0.19–1.50) | 0.64 (0.15–2.66)      | 1.13 (0.40–3.17)  | 0.57 (0.13–2.20)  | 1.52 (0.86–2.68) |
| Immunosuppression     | 0.80 (0.28–2.23) | 0.88 (0.41–1.90)   | 2.54 (1.30–4.97) | 1.57 (0.76–3.28)      | 2.29 (0.77–6.85)  | 1.79 (0.62–5.12)  | 0.95 (0.38–2.38) |
| ESRD                  | 2.74 (1.06–7.10) | 2.96 (1.28–6.87)   | 4.05 (1.82–8.98) | 1.72 (0.22–13.32)     | 3.56 (1.01–12.56) | –                 | 1.40 (0.43–4.61) |
| Foreign born           | 1.77 (1.31–2.41) | 0.88 (0.71–1.10)   | 0.98 (0.68–1.40) | 0.37 (0.19–0.70)      | 0.70 (0.41–1.18)  | 0.97 (0.62–1.51)  | 0.84 (0.62–1.14) |
| Previous TB           | 0.27 (0.07–1.10) | 0.80 (0.43–1.49)   | 1.37 (0.63–2.98) | 0.37 (0.23–1.89)      | 0.37 (0.05–2.70)  | 0.76 (0.24–2.43)  | 0.52 (0.20–1.43) |

*aOR adjusted odds ratio, CI confidence interval, HIV human immunodeficiency virus, ESRD end-stage renal disease
Analysis excluded subjects with multiple subsite involvement (n = 57) and laryngeal sites (n = 3)

*Excessive alcohol use within the past 12 months
#HIV unknown categorized as negative
Significant odds ratios (p<0.005) are in bold

Risk factors and the elderly remain the groups at highest risk. In the US, the rate of PTB among those ≥65 years old is twice the rate of PTB among those <65 years old. Similarly, in Europe, the risk of PTB among those ≥65 years old is almost three times the rate of PTB among those <65 years old. In both regions, the elderly population has a significantly higher risk of developing LTBI and TB disease. In addition, non-injecting drug use was also higher in patients and non-injecting drug use was also higher in patients and non-injecting drug use was associated with patients having genitourinary TB. In our population, HIV was associated with EPTB with concurrent pulmonary infection. This is consistent with previous studies, which have found that HIV co-infection is more common among patients with EPTB than in patients with PTB. In our analysis, we found that patients age >45 years were at an increased risk of EPTB compared to patients age ≤45 years. However, EPTB was more common in non-homeless patients than in homeless patients, as previously reported. It is well known that patients with HIV have an increased risk of EPTB. In our population, HIV was associated with EPTB and non-injecting drug use was also higher in patients with HIV-co-infected EPTB than in patients with PTB. In addition, low CD4 lymphocyte counts in hospitalized patients with HIV-co-infected EPTB were found to be add-on risk factors. In our study, the number of homeless cases was significantly higher in patients with PTB than in patients with exclusively EPTB. We further identified that being homeless was likely to be associated with the most common subsite-specific TB. In our study, the prevalence of injecting drug use was found to be higher in patients with PTB than in patients with EPTB. Similarly, the prevalence of injecting drug use was higher in patients with PTB than in patients with EPTB. In our study, we found that injecting drug use was also higher in patients with PTB than in patients with exclusively EPTB. In addition, non-injecting drug use was also higher in patients with EPTB compared to patients having exclusively EPTB. In addition, the prevalence of injecting drug use was higher in patients with PTB than in patients with EPTB. Similarly, the prevalence of injecting drug use was higher in patients with PTB than in patients with EPTB.
Table 4  Risk factors for mortality during anti-tuberculosis treatment in patients with extrapulmonary tuberculosis in Texas, USA, 2009–2015

| Variable          | Treatment completed (n = 1061) | Died during treatment (n = 50) | Mortality risk (%) | Crude OR (95% CI) | Adjusted OR (95% CI) | Adjusted p-Value |
|-------------------|-------------------------------|-------------------------------|--------------------|------------------|----------------------|------------------|
| Age (years)       |                               |                               |                    |                  |                      |                  |
| 0–14              | 105 (9.9%)                    | 0 (0.0%)                      | 0.0%               | –                |                      |                  |
| 15–24             | 116 (10.9%)                   | 2 (4.0%)                      | 1.7%               | (reference)      |                      |                  |
| 25–44             | 438 (41.3%)                   | 9 (18.0%)                     | 2.0%               | 1.19 (0.25, 5.59) |                      |                  |
| 45–64             | 292 (27.5%)                   | 17 (34.0%)                    | 5.5%               | 3.38 (0.77, 14.85) |                      |                  |
| ≥65               | 110 (10.4%)                   | 22 (44.0%)                    | 16.7%              | 11.60 (2.66, 50.49) |                      |                  |
| Age (years)       |                               |                               |                    |                  |                      |                  |
| <45               | 659 (62.1%)                   | 11 (22.0%)                    | 1.6%               | (reference)      | (reference)          |                  |
| ≥45               | 402 (37.9%)                   | 39 (78.0%)                    | 8.8%               | 5.81 (2.94, 11.48) | 3.75 (1.71, 8.22)   | 0.001            |
| Gender            |                               |                               |                    |                  |                      |                  |
| Female            | 491 (46.3%)                   | 20 (40.0%)                    | 3.9%               | (reference)      |                      |                  |
| Male              | 570 (53.7%)                   | 30 (60.0%)                    | 5.0%               | 1.29 (0.72, 2.30) |                      |                  |
| Race              |                               |                               |                    |                  |                      |                  |
| White             | 84 (7.9%)                     | 9 (18.0%)                     | 9.7%               | (reference)      |                      |                  |
| Black             | 209 (19.7%)                   | 11 (22.0%)                    | 5.0%               | 0.49 (0.20, 1.23) |                      |                  |
| Hispanic          | 501 (47.2%)                   | 24 (48.0%)                    | 4.6%               | 0.45 (0.20, 1.00) |                      |                  |
| Asian             | 262 (24.7%)                   | 6 (12.0%)                     | 2.2%               | 0.21 (0.07, 0.62) |                      |                  |
| Other             | 5 (0.5%)                      | 0 (0.0%)                      | 0.0%               | 1.00 (0.00, 0.00) |                      |                  |
| Race              |                               |                               |                    |                  |                      |                  |
| Non-White         | 977 (92.1%)                   | 41 (82.0%)                    | 4.0%               | (reference)      |                      |                  |
| White             | 84 (7.9%)                     | 9 (18.0%)                     | 9.7%               | 2.55 (1.20, 5.43) |                      |                  |
| HIV status        |                               |                               |                    |                  |                      |                  |
| Negative          | 847 (79.8%)                   | 21 (42.0%)                    | 2.4%               | (reference)      | (reference)          |                  |
| Positive          | 53 (5.0%)                     | 6 (12.0%)                     | 10.2%              | 4.57 (1.77, 11.79) | 4.70 (1.54, 14.32)  | 0.01             |
| Unknown           | 161 (15.2%)                   | 23 (46.0%)                    | 12.5%              | 5.76 (3.11, 10.66) | 6.55 (3.19, 13.44)  | <0.001           |
| Homeless          |                               |                               |                    |                  |                      |                  |
| No                | 1040 (98.0%)                  | 46 (92.0%)                    | 4.2%               | (reference)      | (reference)          |                  |
| Yes               | 21 (2.0%)                     | 4 (8.0%)                      | 16.0%              | 4.31 (1.42, 13.06) | 1.57 (0.40, 6.17)   | 0.52             |
| Excessive alcohol use |                 |                               |                    |                  |                      |                  |
| No                | 973 (91.7%)                   | 37 (74.0%)                    | 3.7%               | (reference)      | (reference)          |                  |
| Yes               | 88 (8.3%)                     | 13 (26.0%)                    | 12.9%              | 3.88 (1.99, 7.58) | 3.34 (1.45, 7.67)   | 0.01             |
| Injecting drug use |                 |                               |                    |                  |                      |                  |
| No                | 1050 (99.0%)                  | 48 (96.0%)                    | 4.4%               | (reference)      |                      |                  |
| Yes               | 11 (1.0%)                     | 2 (4.0%)                      | 15.4%              | 3.98 (0.86, 18.44) |                      |                  |
| Foreign born      |                               |                               |                    |                  |                      |                  |
| No                | 415 (39.1%)                   | 29 (58.0%)                    | 6.5%               | (reference)      |                      |                  |
| Yes               | 646 (60.9%)                   | 21 (42.0%)                    | 3.1%               | 0.47 (0.26, 0.83) |                      |                  |
| Diabetes          |                               |                               |                    |                  |                      |                  |
Table 4 continued

| Variable                                      | Treatment completed (n = 1061) | Died during treatment (n = 50) | Mortality risk (%) | Crude OR (95% CI) | Adjusted OR (95% CI) | Adjusted p-Value |
|-----------------------------------------------|--------------------------------|--------------------------------|--------------------|-------------------|----------------------|-----------------|
| No                                            | 948 (89.3%)                    | 40 (80.0%)                     | 4.0%               | (reference)       | (reference)          |                 |
| Yes                                           | 113 (10.7%)                    | 10 (20.0%)                     | 8.1%               | 2.10 (1.02, 4.31) | 1.55 (0.65, 3.69)    | 0.32            |
| End-stage renal disease                        |                                |                                |                    |                   |                      |                 |
| No                                            | 1043 (98.3%)                   | 44 (88.0%)                     | 4.0%               | (reference)       | (reference)          |                 |
| Yes                                           | 18 (1.7%)                      | 6 (12.0%)                      | 25.0%              | 7.90 (2.99, 20.88) | 4.45 (1.38, 14.33)   | 0.01            |
| Immunosuppression (medical condition or medication) |                                |                                |                    |                   |                      |                 |
| No                                            | 1027 (96.8%)                   | 44 (88.0%)                     | 4.1%               |                   |                      |                 |
| Yes                                           | 34 (3.2%)                      | 6 (12.0%)                      | 15.0%              |                   | 4.12 (1.64, 10.32)   |                 |
| Previous TB                                    |                                |                                |                    |                   |                      |                 |
| No                                            | 1033 (97.4%)                   | 50 (100.0%)                    | 4.6%               |                    |                      |                 |
| Yes                                           | 28 (2.6%)                      | 0 (0.0%)                       | 0.0%               |                    |                      |                 |
| Inmate of a correctional facility              |                                |                                |                    |                   |                      |                 |
| No                                            | 967 (94.8%)                    | 48 (98.0%)                     | 4.7%               | (reference)       |                      |                 |
| Yes                                           | 53 (5.2%)                      | 1 (2.0%)                       | 1.9%               | 0.38 (0.05, 2.81)  |                      |                 |
| Resident of long-term care facility            |                                |                                |                    |                   |                      |                 |
| No                                            | 1048 (98.8%)                   | 47 (94.0%)                     | 4.3%               | (reference)       | (reference)          |                 |
| Yes                                           | 13 (1.2%)                      | 3 (6.0%)                       | 18.8%              | 5.15 (1.42, 18.67) | 2.15 (0.50, 9.26)    | 0.31            |
| AFB smear                                      |                                |                                |                    |                   |                      |                 |
| Negative                                      | 627 (99.4%)                    | 17 (94.4%)                     | 2.6%               | (reference)       |                      |                 |
| Positive                                      | 4 (0.6%)                       | 1 (5.6%)                       | 20.0%              | 9.22 (0.98, 86.93) |                      |                 |
| Culture                                        |                                |                                |                    |                   |                      |                 |
| Negative                                      | 602 (97.6%)                    | 12 (92.3%)                     | 2.0%               | (reference)       |                      |                 |
| Positive                                      | 15 (2.4%)                      | 1 (7.7%)                       | 6.3%               | 3.34 (0.41, 27.40) |                      |                 |
| TB-CXR                                         |                                |                                |                    |                   |                      |                 |
| No                                            | 611 (62.8%)                    | 15 (33.3%)                     | 2.4%               | (reference)       | (reference)          |                 |
| Yes                                           | 362 (37.2%)                    | 30 (66.7%)                     | 7.7%               | 3.38 (1.79, 6.36)  | 2.18 (1.09, 4.35)    | 0.03            |
| Cavitation on CXR                              |                                |                                |                    |                   |                      |                 |
| No                                            | 354 (97.8%)                    | 30 (100.0%)                    | 7.8%               |                    |                      |                 |
| Yes                                           | 8 (2.2%)                       | 0 (0.0%)                       | 0.0%               |                    |                      |                 |
| DST profile                                    |                                |                                |                    |                   |                      |                 |
| Sensitive to RIF and INH                      | 560 (52.8%)                    | 40 (80.0%)                     | 6.7%               |                   |                      |                 |
| Resistant to RIF or INH                       | 39 (3.7%)                      | 0 (0.0%)                       | 0.0%               |                   |                      |                 |
| MDR-TB                                         | 3 (0.3%)                       | 0 (0.0%)                       | 0.0%               | (reference)       |                      |                 |
| Unavailable                                    | 459 (43.3%)                    | 10 (20.0%)                     | 2.1%               | 0.31 (0.15, 0.62)  |                      |                 |
| Genotyping lineage                            |                                |                                |                    |                   |                      |                 |
| Indo-Oceanic (L1)                             | 80 (7.5%)                      | 4 (8.0%)                       | 4.8%               | 0.79 (0.20, 3.05)  |                      |                 |
| East Asian (L2)                                | 79 (7.4%)                      | 5 (10.0%)                      | 6.0%               | (reference)       |                      |                 |
associated with meningeal TB and disseminated TB in a single hospital study in the USA\textsuperscript{13}.

The prevalence of end-stage renal disease (ESRD) continues to rise by approximately 20,000 cases per year in the USA\textsuperscript{29}. Consistent epidemiologic evidence has shown that this population is at risk for developing active TB\textsuperscript{30}. ESRD as a risk factor for EPTB has also been reported in studies in Taiwan and the US state of Georgia \textsuperscript{17, 31}. Accordingly, ESRD was associated with exclusively EPTB, EPTB with concurrent pulmonary involvement, and all cases of EPTB compared to PTB in our population-based analysis. We also found that ESRD was specifically associated with pleural, lymphatic, bone and peritoneal TB. Thus, patients with ESRD are at a high risk of progressing to EPTB. One possibility regarding the underlying mechanisms is that the persistence of impaired cell-mediated immunity in ESRD may leave these patients susceptible to \textit{Mtb} infection or activation of latent infection\textsuperscript{32}. This phenomenon has also been observed in organ transplantation receipts who receive post-transplant immunosuppressive medications that specifically target T cell-mediated immunity\textsuperscript{33, 34}. In regard to the screening strategy among patients with chronic renal disease (CRD), both the American Thoracic Society\textsuperscript{35} and American Transplant Society\textsuperscript{36} guidelines recommend that all immunocompromised subjects and transplant candidates be screened for TB with a tuberculin skin test (TST) or IFN-\textgamma releasing assay (IGRA). The WHO provides more specific guidance on screening all dialysis patients with TST or IGRA\textsuperscript{37}. Beyond the screening strategy, diagnosis of EPTB remains difficult because of the paucibacillary nature. Thus, it is necessary to advance knowledge about the association of CRD/ESRD and EPTB and strategies to improve the prevention, detection, and treatment of EPTB with ESRD.

Consistent with the current literature, our analyses showed that age \geq 45 years, ESRD, HIV+ status, excessive alcohol use within the past 12 months, and abnormal chest radiography were significantly associated with mortality during anti-TB treatment in patients with exclusively EPTB\textsuperscript{17, 38}. In the USA, excess alcohol use may represent a large portion of TB burden\textsuperscript{38}. The relationship between excessive alcohol use and the development of TB disease as well as TB-associated morbidity and mortality has been presumed to be due to impaired immune function\textsuperscript{39}. Other confounding factors such as older age, diabetes, ESRD, and HIV are all related to decreased immune function. HIV was highly associated with mortality during treatment in our analysis, which is consistent with other epidemiologic and observational studies with mortality ranging from 6% to 32\%\textsuperscript{40}. Another important finding of our study was that ESRD was associated with more than quadruple the odds of mortality during anti-TB treatment in patients having exclusively EPTB. Given these findings, we suggest that patients with decreased immune function or immunosuppression are at an increased risk of mortality during treatment and that host immune response may determine the difference in survival. Approaches to meet the objective of optimizing efficacy and safety of treatment, especially for TB-HIV co-infection as well as ESRD, to reduce mortality both in adults and children are urgently required. As shown in a prospective cohort study that enrolled hospitalized HIV co-infected patients with microbiologically confirmed drug-susceptible TB in South Africa, mortality within 12 weeks was positively associated with elevated

### Table 4 continued

| Variable               | Treatment completed (n = 1061) | Died during treatment (n = 50) | Mortality risk (%) | Crude OR (95% CI) | Adjusted OR (95% CI) | Adjusted p-Value |
|------------------------|--------------------------------|-------------------------------|--------------------|------------------|---------------------|------------------|
| East African-Indian (L3) | 35 (3.3%)                      | 1 (2.0%)                      | 2.8%               | 0.45 (0.05, 4.01) |                     |                  |
| Euro-American (L4)     | 300 (28.3%)                    | 27 (54.0%)                    | 8.3%               | 1.42 (0.53, 3.81) |                     |                  |
| \textit{M. bovis}     | 27 (2.5%)                      | 3 (6.0%)                      | 10.0%              | 1.76 (0.39, 7.84) |                     |                  |
| Other                  | 8 (0.8%)                       | 0 (0.0%)                      | 0.0%               | 1.00 (0.00, 0.00) |                     |                  |
| Unknown                | 532 (50.1%)                    | 10 (20.0%)                    | 1.8%               | 0.30 (0.10, 0.89) |                     |                  |
| Genotyping lineage     |                                |                               |                    |                  |                     |                  |
| Not East Asian         | 354 (97.8%)                    | 30 (100.0%)                   | 7.8%               | (reference)      | (reference)         |                  |
| East Asian (L2)        | 8 (2.2%)                       | 0 (0.0%)                      | 0.0%               | 1.38 (0.53, 3.58) | 1.58 (0.53, 4.74)  | 0.42             |

\textit{TB} tuberculosis, HIV human immunodeficiency virus, \textit{TB-CXR} tuberculosis chest X-ray, DST drug susceptibility test, RIF rifampin, INH isoniazid, MDR-TB multidrug-resistant tuberculosis, OR odds ratios

Analysis was performed on 1111 patients with extrapulmonary tuberculosis only and having treatment outcome information available.
concentrations of procalcitonin, activation of the innate immune system, and anti-inflammatory markers. Procalcitonin, a product induced by TNF-α and IL-2 during a bacterial infection, has already shown its value in distinguishing TB from bacterial pneumonia and TB meningitis from bacterial meningitis. A higher level of serum procalcitonin was associated with a poorer prognosis in TB meningitis. Moreover, serum procalcitonin has been reported as an appropriate indicator of infection in ESRD patients. Therefore, identifying a correlation between the host’s immunologic phenotypes and the severity of disease or comorbidities, as well as treatment response, would enable the direct selection of host-directed therapeutics and a potentially beneficial and improved TB outcome.

Another important consideration for the risk of EPTB is diabetes status, as several studies have identified diabetes as a risk factor for developing active TB and poor treatment outcomes. For instance, a study in the UK has reported that patients with diabetes had an increased risk of developing TB compared to a control group. Among patients undergoing TB treatment, patients with diabetes had an increased mortality risk compared to those without diabetes. However, compared to the control group, TB patients with diabetes had an increased probability of having PTB as opposed to EPTB. Furthermore, both our study and a cohort study in the US state of Georgia found TB patients with diabetes to have an increased probability of EPTB as opposed to PTB, and diabetes was not associated with EPTB mortality during TB treatment. In an additional study, diabetes did not contribute to TB-related death in adult patients in the USA. Thus, the inconsistent findings encourage further investigations on the impact of diabetes in PTB and EPTB patients. It is worth emphasizing that the incidence of ESRD is higher in the diabetic population than in the non-diabetic population. Since ESRD is an independent risk factor for EPTB as shown in our study, it may be necessary to account for the association between diabetes and ESRD as a co-epidemic, which would potentially account for the risk of EPTB as well as treatment outcomes.

Among available data for patients with exclusively EPTB, the most prevalent Mtb lineages were Euro-American L4, followed by East Asian L2 and Indo-Oceanic L1. This finding was consistent with a previous nationwide study in the USA. Click et al. suggested that the percentage of cases with exclusively EPTB differs for the four lineages—East Asian, 13.0%; Euro-American, 13.8%; Indo-Oceanic, 22.6%; and East African-Indian, 34.3%—while EPTB with pulmonary involvement did not. However, Click’s study did not show data for M. bovis. Consistent with the results of previous studies, we found a higher proportion of M. bovis in patients with exclusively EPTB than in patients with exclusively PTB or EPTB with pulmonary involvement. Geographically, patients with M. bovis residing along the US–Mexico border had a disproportionately high incidence of M. bovis. This may also be reflected in our results, as Texas is a US state bordering Mexico. The tradition of raw milk and cheese consumption, especially in Hispanic communities, may be another common reason for M. bovis infection. Additionally, we found that positive smear and culture, direct susceptibility test profile and genotyping lineage were not risk factors for mortality from exclusively EPTB during TB treatment. These results may be limited due to many individuals with unknown Mtb status, either because the test was not performed or because the results were not recorded. Instead of bacterial factors, host risk factors such as HIV, age ≥45, excessive alcohol use, and abnormal chest X-ray findings were associated with mortality during treatment of EPTB in our study.

One important limitation of our study is the unavailability of data in some categories. Therefore, the reported crude and adjusted odds ratios could be biased due to unmeasured covariates or unknown confounders. State TB surveillance reporting does not include the depth of clinical information necessary to further investigate recognized risk factors in the epidemiology of EPTB (e.g., CD4 lymphocyte counts for HIV patients and smoking status). An observational design in a large cohort will be necessary to assess the true effect of these factors. Given that Texas has one of the highest TB prevalence rates of any US state and has a more diverse population than many other states, findings from our analysis may not apply to settings elsewhere in the country.

**Conclusion**

The present study characterized the important differences in the population-level dynamics of EPTB, as well as its specific sites, which included demographic factors and clinical characteristics in addition to the heterogeneities within sites of EPTB during the 7-year study period. Age ≥45 years, HIV+ status, and ESRD were identified as risk factors for both EPTB establishment and resulting mortality during treatment. Although the scientific question of the extrapulmonary dissemination remains to be answered, the study’s findings could allow us to design supportive treatments for specific subgroups of patients with increased mortality, such as those with a HIV+ status and those with compromised renal function, in order to improve their outcomes and ultimately minimize the transmission of TB.

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Conflict of interest
The authors declare that they have no conflict of interest.

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