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Negative tuberculin skin test result predicts all-cause mortality among tuberculosis patients with HIV and diabetes comorbidity

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ABSTRACT

Purpose: The purpose of this study was to determine if a negative tuberculin skin test (TST) result is associated with increased risk of mortality during tuberculosis (TB) treatment.
Methods: We conducted a retrospective cohort study among patients aged ≥15 years with culture-positive TB reported to the Georgia State Electronic Notifiable Disease Surveillance System from 2009 to 2014. TST positivity was defined by the US Centers for Disease Control guidelines. All-cause mortality during TB treatment as well as HIV, diabetes, and end-stage renal disease status were collected from surveillance data. Log-binomial regression was used to estimate adjusted risk ratios and 95% confidence intervals.
Results: Among 1186 culture-confirmed TB patients, 780 (65.8%) with a valid TST and TB treatment outcomes were eligible. Nearly one-third (242/780) had a negative TST result, and 5.6% died during treatment. The highest risk of death was observed among patients with a negative TST and HIV (12.5%) and a negative TST and diabetes (15.4%). Adjusting for confounders, the risk of death among patients with a negative TST was significantly greater compared with those with a positive TST (adjusted risk ratio 2.33 95% confidence interval 1.23–4.43).
Conclusions: A negative TST was associated with more than twice the risk of mortality during TB treatment after adjusting for immunosuppressive conditions.

Introduction

An estimated one-quarter of the world's population is infected by *Mycobacterium tuberculosis* [1] and 10.4 million people are newly diagnosed with tuberculosis (TB) disease annually [2]. TB remains the most common infectious disease cause of death and was estimated to cause >4000 deaths per day in 2016 [2]. Although the greatest burden of TB disease and mortality exists in low- and middle-income countries, deaths from TB remain an important clinical problem in high-income countries. In the United States (US), nearly 5% of patients with TB disease died in 2015 [3]. While the global TB mortality rate declined during the past 4 years [2, 4], achieving further reductions in the TB morality rates remains a central pillar of the End TB Strategy [2]. Developing simple and inexpensive tools to identify patients at higher risk of death during TB treatment will be vital to substantially reduce TB mortality [5].

Approximately, 10%–30% of patients with culture-confirmed TB have a negative tuberculin skin test (TST) [6–9]. Previous work from the United States suggests that a negative TST is associated with increased risk of TB mortality [6]. However, mechanisms underlying the association between a negative TST and increased risk of mortality during TB treatment remain unclear. It is well established that TB mortality risk is greater for patients with immunosuppressive comorbidities such as diabetes mellitus, HIV infection, end-stage renal disease (ESRD) [10–13]. But whether the association between a negative TST and TB mortality is differentially affected by the presence of immunosuppressive comorbidities is unknown.

Conflict of interest: The authors have no conflict of interest to declare.

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Because the TST relies partially on cell-mediated immune responses to *M. tuberculosis* [7, 14], it is an unreliable screening tool among persons with immunosuppression comorbidities [15]. For example, persons living with HIV with lower CD4 cell counts may have a smaller TST induration size or may be nonreactive (i.e., anergic) despite the presence of TB infection [16]. Among patients with TB disease and comorbid HIV, diabetes, or ESRD, it is unknown whether a negative TST is a marker of inadequate immune response. If a negative TST result among patients with TB and immunosuppressive comorbidities is associated with increased risk of mortality, a negative TST could be a simple indicator for increased clinical monitoring during TB treatment.

Given existing gaps in knowledge regarding TST results and TB mortality, we aimed to (1) estimate the prevalence of the common immunosuppressive comorbidities of diabetes, HIV, and ESRD among TB patients with a negative TST result and (2) determine whether the relationship between TST result and risk of all-cause mortality during TB treatment differed by the presence of immunosuppressive comorbidities.

Methods

Setting, study design, and measures

We conducted a retrospective cohort study among adult patients with TB disease (≥15 years old) reported to the Georgia Department of Public Health's State Electronic Notifiable Disease Surveillance System (SENDSS) from 2009 to 2014. All health care providers and laboratories are required by law to report TB cases to Georgia public health authorities using standardized form (i.e., Report of Verified Case of Tuberculosis form) within SENDSS which then transferred to the Tuberculosis Information Management System and US Centers for Disease Control and Prevention (CDC) servers [17]. All adults with culture-confirmed pulmonary or extrapulmonary TB at time of TB diagnosis were eligible for this study. Patients received individualized TB treatment regimens prescribed by health department affiliated providers, typically under directly observed therapy. TB treatment end date and outcomes were extracted from SENDSS.

The primary exposure for this study was TST result. The tuberculin testing was administered by health care workers in county health departments, hospitals, or community clinics. As recommended by the US CDC guidelines, in the state of Georgia, the TST and Interferon-Gamma Release Assays (IGRAs) are used as an aid to establish TB diagnosis, but are not required for all cases [18]. TST induration size was measured and defined as positive based on US CDC guidelines: (1) >5 mm for persons with high risk of TB, (2) > 10 mm for persons with low to medium risk of TB, and (3) > 15 mm for persons with no known TB risk factors [19]. The primary outcome for this study was all-cause mortality during TB treatment which was reported and confirmed by death certificate records in SENDSS.

Relevant covariates in our study, including the immunosuppressive comorbidities of HIV infection, diabetes mellitus, and ESRD, were defined according to SENDSS records. Covariate definitions and categories utilized in this analysis, including patients' demographic characteristics, TB clinical manifestation, behavioral risk factors, history of latent TB infection/TB treatment, and drug-resistance profile, were previously described [20].

Statistical analyses

χ^2 and Fisher's exact tests were performed to assess the bivariate association between patients' characteristics and both TST results and all-cause mortality during TB treatment. We performed log-binomial regression to compare the relative risk of all-cause mortality among patients with a negative TST to patients with a positive TST. Covariates included in regression models were based on observed associations in the bivariate analyses, confounding factors established from published literature, and directed acyclic graph theory [21]. Statistical and biological interactions between TST and comorbid conditions (e.g., HIV and diabetes) were assessed to determine if the association between TST result and all-cause mortality varied by immunosuppressive comorbidities status. Statistical interaction was tested using cross-product terms within multivariable models. Biological interaction was assessed using three measures: (1) relative excess risk due to interaction (RERI), (2) attributable proportion (AP) due to biologic interaction, and (3) synergy index [22]. We defined the absence of biological interaction if the 95% confidence interval (CI) of the RERI and AP included 0 and the 95% CI of synergy index included 1.0. Analyses were performed using SAS version 9.4 (Cary) with a two-sided *P*-value <.05 considered significant in all analyses.

Sensitivity analyses

Sensitivity analyses were performed to quantify systematic errors because of (1) misclassification of TST results, (2) unmeasured confounders, (3) distribution assumptions used in regression analyses, and (4) mis-specification of covariate selection for the multivariable models. To quantify error from misclassification of TST results, we performed additional regressions including those with a missing TST to determine changes in our estimates. We also compared the risk of mortality across different groups of TST induration. We used the approach of Lash et al. [23] to externally adjust the association between negative TST and all-cause mortality during TB treatment based on the unmeasured confounders of smoking, nonadherence to TB treatment, and HIV severity (CD4 count). We compared our log-binomial regression to Cox proportional hazard models to assess whether a negative TST was associated with a higher hazard rate of death during TB treatment. Finally, to assess covariate misspecification, we reported results from several multivariable models to compare changes in the estimated risk ratios with different subsets of covariates.

Institutional review board

This study was approved by the Institutional Review Boards at Georgia State University, Emory University, and the Georgia Department of Public Health, Atlanta, USA.

Results

Study population and baseline characteristics

There were 2202 patients with TB disease reported to SENDSS from 2009 to 2014, of whom 2049 (93%) were 15 years or older (Fig. 1). Among these patients diagnosed with TB, 58% (1186/2049) had culture-confirmed disease. Of those with a positive culture, 68.2% (809/1186) had a valid TST result, of whom most (96.4%, 780/890) had a documented TB treatment and, thus, were included in the final analyses. Among those with culture-confirmed TB, those with valid TST results ($n = 809$) were similar to those with a missing TST result ($n = 377$) with regard to gender, country of birth, history of homelessness and imprisonment, diabetes status, presence of cavitary or miliary disease, and TB site of disease ($P > .05$, Supplemental Table 1). However, HIV infection and ESRD were more prevalent among those with missing TST ($P < .01$). Of the 780 patients included in the final analyses, 242 (31.0%, 95% CI 27.9%–34.3%) had a negative TST (Table 1). The overall prevalence of HIV

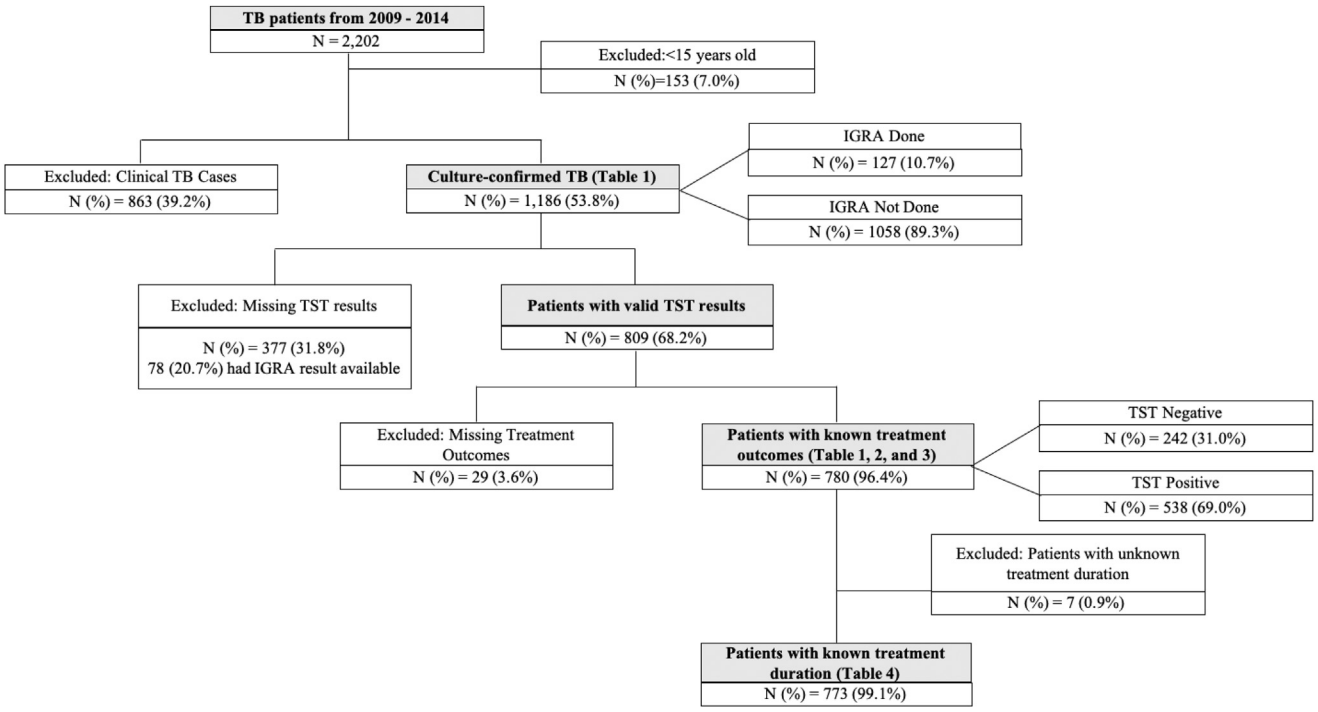

Fig. 1. Study flow diagram of among adult patients with culture-confirmed TB, Georgia, 2009–2014.

Table 1
Tuberculin skin test status among adult patients with culture-confirmed TB, Georgia, 2009–2014 ($n = 780$)

Patient characteristic	TST results			*P*-value (χ^2)
	Negative N % = 242 (31.0)	Positive* N % = 538 (69.0)	Total $n = 780$	
	N %†	N %†	N %†	
Age group (y)				
15–24	18 (7.4)	85 (15.8)	103 (13.2)	**<.01**
25–44	84 (34.7)	214 (39.8)	298 (38.2)	
45–64	93 (38.4)	184 (34.2)	277 (35.5)	
≥ 65	47 (19.4)	55 (10.2)	102 (13.1)	
Male gender	177 (73.1)	365 (67.8)	542 (69.5)	.14
Race, black	104 (43.0)	271 (50.5)	375 (48.1)	.05
Foreign-born	84 (34.7)	255 (47.4)	339 (43.5)	**<.01**
Homeless	37 (15.3)	68 (12.6)	105 (13.5)	.32
History of imprisonment	4 (1.7)	39 (7.3)	43 (5.5)	**<.01**
History of contact with TB patient	19 (8.1)	95 (18.0)	114 (15.0)	**<.01**
History of TB disease	8 (3.3)	32 (5.9)	40 (5.1)	.12
Illicit drug use	28 (11.7)	67 (12.5)	95 (12.2)	.75
Alcohol abuse	44 (18.3)	94 (17.5)	138 (17.8)	.78
HIV status, positive	40 (17.5)	46 (8.7)	86 (11.4)	**<.01**
Diabetes	39 (16.7)	59 (11.2)	98 (12.9)	**.04**
ESRD	4 (1.7)	3 (0.6)	7 (0.9)	.21
History of LTBI prophylaxis	2 (0.8)	31 (5.9)	33 (4.3)	**<.01**
Positive smear at baseline	168 (69.7)	361 (67.2)	529 (68.0)	.49
Abnormal CXR reading at baseline	214 (96.0)	475 (92.8)	689 (93.7)	.10
Cavitary disease	70 (31.8)	196 (38.5)	266 (36.5)	.09
Miliary disease	15 (6.8)	9 (1.8)	24 (3.3)	**<.01**
INH-monoresistant TB	36 (15.6)	60 (11.6)	96 (12.8)	.13
TB site				
Pulmonary	210 (86.8)	495 (92.0)	705 (90.4)	**.04**
Pulmonary + extrapulmonary	27 (11.2)	32 (6.0)	59 (7.6)	
Extrapulmonary only	5 (2.0)	11 (2.0)	16 (2.1)	
TB treatment outcome				
Completed	207 (85.5)	505 (93.9)	712 (91.3)	**<.01**
Died	26 (10.7)	18 (3.4)	44 (5.6)	
Lost to follow-up	6 (2.5)	13 (2.4)	19 (2.4)	
Uncooperative/refused to continue treatment	0 (0.0)	1 (0.2)	1 (0.1)	
Stopped due to adverse reaction	3 (1.24)	1 (0.2)	4 (0.5)	

Bold indicates statistical significance (two-sided *P*-value <.05).
CXR = chest x-ray; ESRD = end-stage renal disease; HIV = human immunodeficiency virus; INH = isoniazid; LTBI = latent TB infection; TNF = tumor necrosis factor; TST = tuberculin skin.
* Classification of positive TST results based on US Centers for Disease Control and Prevention guidelines [19].
† Percentages may not precisely reflect the absolute figures due to missing values.

Table 2
Bivariate analyses of all-cause mortality during treatment among adult patients with culture-confirmed TB, Georgia, 2009–2014 ($n = 780$)

Patient characteristic		Treatment outcome		cRR (95% CI)
	Total $n = 780$*	Not died† N % = 736 (94.4)	Died N % = 44 (5.6)	
	N %	N %	N %	
TST results				
Negative	242 (31.0)	216 (89.3)	26 (10.7)	**3.21 (1.80–5.74)**
Positive	538 (69.0)	520 (96.6)	18 (3.4)	Reference
Age group (y)				
15–24	103 (13.2)	102 (99.0)	1 (1.0)	0.48 (0.06–3.96)
25–44	298 (38.2)	292 (98.0)	6 (2.0)	Reference
45–64	277 (35.5)	261 (94.2)	16 (5.8)	**2.87 (1.14–7.22)**
≥ 65	102 (13.1)	81 (79.4)	21 (20.6)	**10.23 (4.25–24.63)**
Gender				
Female	238 (30.5)	231 (97.1)	7 (2.9)	Reference
Male	542 (69.5)	505 (93.2)	37 (6.8)	**2.32 (1.05–5.13)**
Race				
Nonblack	404 (51.9)	388 (96.0)	16 (4.0)	Reference
Black	375 (48.1)	347 (92.5)	28 (7.5)	**1.89 (1.04–3.42)**
Foreign-born				
No	441 (56.5)	405 (91.8)	36 (8.2)	Reference
Yes	339 (43.5)	331 (97.6)	8 (2.4)	**0.29 (0.14–0.61)**
Homeless				
No	675 (86.5)	636 (94.2)	39 (5.8)	Reference
Yes	105 (13.5)	100 (95.2)	5 (4.8)	0.82 (0.33–2.04)
History of imprisonment				
No	736 (94.5)	692 (94.0)	44 (6.0)	Reference
Yes	43 (5.5)	43 (100.0)	0 (0.0)	N/A*
History of contact with TB patient				
No	648 (85.0)	609 (94.0)	39 (6.0)	Reference
Yes	114 (15.0)	110 (96.5)	4 (3.5)	0.58 (0.21–1.60)
History of TB disease				
No	740 (94.9)	698 (94.3)	42 (5.7)	Reference
Yes	40 (5.1)	38 (95.0)	2 (5.0)	0.88 (0.22–3.51)
Illicit drug use				
No	682 (87.8)	644 (94.4)	38 (5.6)	Reference
Yes	95 (12.2)	91 (95.8)	4 (4.2)	0.76 (0.28–2.07)
Alcohol abuse				
No	639 (82.2)	612 (95.8)	27 (4.2)	Reference
Yes	138 (17.8)	123 (89.1)	15 (10.9)	**2.57 (1.41–4.71)**
HIV status				
Negative	671 (88.6)	639 (95.2)	32 (4.8)	Reference
Positive	86 (11.4)	78 (90.7)	8 (9.3)	1.95 (0.93–4.10)
Diabetes				
No	664 (87.1)	628 (94.6)	36 (5.4)	Reference
Yes	98 (12.9)	91 (92.9)	7 (7.1)	1.32 (0.60–2.88)
ESRD				
No	755 (99.1)	713 (94.4)	42 (5.6)	Reference
Yes	7 (0.9)	6 (85.7)	1 (14.3)	2.57 (0.41–16.14)
History of LTBI prophylaxis				
No	729 (95.7)	686 (94.1)	43 (5.9)	Reference
Yes	33 (4.3)	33 (100.0)	0 (0.0)	N/A*
Baseline smear				
Negative	249 (32.0)	235 (94.4)	14 (5.6)	Reference
Positive	529 (68.0)	500 (94.5)	29 (5.5)	0.98 (0.53–1.81)
Baseline CXR reading				
Normal	46 (6.3)	46 (100.0)	0 (0.0)	Reference
Abnormal	689 (93.7)	647 (93.9)	42 (6.1)	N/A*
Cavitary disease				
No	463 (63.5)	436 (94.2)	27 (5.8)	Reference
Yes	266 (36.5)	251 (94.4)	15 (5.6)	0.97 (0.52–1.79)
Miliary disease				
No	699 (96.7)	659 (94.3)	40 (5.7)	Reference
Yes	24 (3.3)	23 (3.4)	1 (4.2)	0.73 (0.10–5.08)
Mono-INH resistant				
No	652 (87.2)	617 (94.6)	35 (5.4)	Reference
Yes	96 (12.8)	89 (92.7)	7 (7.3)	1.36 (0.62–2.97)
TB Site				
Pulmonary	705 (90.4)	667 (94.6)	38 (5.4)	Reference
Pulmonary + extrapulmonary	59 (7.6)	55 (93.2)	4 (6.8)	1.26 (0.47–3.40)
Extrapulmonary only	16 (2.1)	14 (87.5)	2 (12.5)	2.32 (0.62–8.79)

A. Patients completed TB treatment based on Georgia Department of Public Health's guidelines.
B. Patients with adverse TB treatment outcomes including lost to follow-up, stopped due to adverse events, and refused to continue treatment.
Bold indicates statistical significance (two-sided *P*-value <.05).
CI = confidence interval; CXR = chest x-ray; cRR = crude risk ratio; ESRD = end-stage renal disease; HIV = human immunodeficiency virus; INH = isoniazid; LTBI = latent TB infection; MDR = multidrug resistant; TNF = tumor necrosis factor, TST = tuberculin skin test.
* Crude risk ratios were not calculated due to zero "0" value in one of the cells.
† All-cause mortality was categorized dichotomously and patients with adverse outcomes (i.e., loss to follow-up, refusal to continue TB treatment, or stopped TB treatment due to adverse reaction) were classified as survivors (i.e., not died).

infection and diabetes in this group were 11.4% (95% CI 9.3%–13.8%) and 12.9% (95% CI 10.6%–15.4%), respectively. ESRD was reported among 0.9% (95% CI 0.4%–1.8%) of study participants. The overall all-cause mortality rate was 5.6% (95% CI 4.2%–7.4%) with a median time to death of 69.5 days (IQR 25.0–132.0 days) post-TB treatment initiation.

Factors associated with a negative TST

Compared with TB patients with a positive TST, patients with a negative TST were significantly older (i.e., 44.4% vs. 57.8% ≥ 45 years old) and less likely to be foreign-born (47.4% vs. 34.7%, $P < .05$), but more likely to have miliary TB (1.8% vs. 6.8%, $P \leq .01$) or concurrent pulmonary and extrapulmonary TB (6.0% vs. 11.2%) ($P = .04$) (Table 1). Compared with patients with a positive TST, the prevalence of HIV infection and diabetes were significantly higher among those with a negative TST (8.7% vs. 17.5% for HIV, $P \leq .01$; 11.2% vs. 16.7% for diabetes, $P = .04$). The prevalence of ESRD was also slightly higher among patients with a negative TST (0.6% vs. 1.7%, $P = .21$), but this difference was not statistically significant.

Negative TST and all-cause mortality during TB treatment

The risk of all-cause mortality among patients with a positive TST was significantly lower compared with those with a negative TST (3.4% vs. 10.7%, $P \leq .01$) (Table 2). The all-cause mortality risk was highest among patients with a negative TST with HIV coinfection (5/40, 12.5%) and those with a negative TST with concomitant diabetes (6/39, 15.4%) (Table 3) compared with those with a positive TST and no comorbidity factor (14/431, 3.3%) ($P \leq .01$). After adjusting for age, gender, HIV status, diabetes status, ESRD, cavitary and miliary disease, alcohol abuse, and foreign-born status, we found that the risk of all-cause mortality among those with a negative TST was more than twice the risk of those with a positive TST (adjusted risk ratio [aRR] 2.33 95% CI 1.23–4.43) (Table 3).

Statistical and biological interaction between TST results and comorbidity factors

We found that the multiplicative effect of TST status on mortality risk was nonsignificantly different across HIV and diabetes status (statistical interaction $P > .05$). For example, the risk ratio of all-cause mortality during TB treatment comparing those with negative TST to those with positive TST was 3.73 (95% CI 1.88–7.40) among those without HIV infection and 1.92 (95% CI 0.49–7.52) among those with HIV infection (Table 3). We also observed that the risk ratio of mortality comparing those with a negative TST to those with a positive TST was 9.08 (95% CI 1.14–72.51) among those with diabetes and 3.01 (95% CI 1.59–5.68) among patients without diabetes. In additional analyses to assess biologic interaction between a negative TST and HIV infection, we did not find evidence of biological interaction (adjusted RERI = 4.31, 95% CI −4.80 to 13.42; adjusted AP = 0.50, 95% CI −0.11 to 1.11; and adjusted synergy index = 2.30, 95% CI 0.52–10.15). Similarly, no biological interaction was observed between a negative TST and diabetes (adjusted RERI = 1.36, 95% CI −1.61 to 4.32; adjusted AP = 0.44, 95% CI −0.23 to 1.11; and adjusted synergy index = 2.85, 95% CI 0.23–35.17) (Supplemental Table 2).

Sensitivity and subgroup analyses

After including patients with missing TST results ($n = 377$) in our analyses, the adjusted risk of all-cause mortality during TB treatment among patients with a missing TST was 2.64 (95% CI 1.51–4.63) times the risk of those with a positive TST (Table 4). In the model where we classified all patients with a missing TST as TST negative, the aRR of all-cause mortality during TB treatment comparing patients with a negative TST with a positive TST was 2.47 (95% CI 1.45–4.20). When classifying all patients with a missing TST as TST positive, the risk of all-cause mortality during TB treatment among patients with a negative TST was 28% higher compared with those with a positive TST (aRR 1.28, 95% CI 0.81–2.03). The aRR of all-cause mortality during TB treatment among those with 0 mm induration was 1.95 (95% CI 1.01–3.79) and 0.88 (95% CI 0.20–3.91) among those with 1–10 mm induration when compared with those with induration >10 mm (Table 4).

In sensitivity analyses to quantify bias for unmeasured confounders, we found that the risk ratio for all-cause mortality during TB treatment ranged from 3.27 to 5.38 when externally adjusting for smoking, and 2.84 to 7.05 when externally adjusting for treatment adherence (Table 4). Among TB patients with HIV, the range of aRRs for all-cause mortality comparing those with negative TST

Table 3
Statistical interaction between TST status with immunocompromised comorbidities among adult patients with culture-confirmed TB, Georgia, 2009–2014 ($n = 780$)

Comorbidities	TST results	Mortality (%)	cRR (95% CI)	aRR (95% CI)*
Total cohort	Negative	26/242 (10.7)	**3.21 (1.80–5.74)**	**2.33 (1.23–4.43)**†
	Positive	18/538 (3.4)	Reference	Reference
Statistical interaction				
HIV infection				
No	Negative	19/189 (10.1)	**3.73 (1.88–7.40)**	**2.30 (1.12–4.73)**
	Positive	13/482 (2.7)	Reference	Reference
Yes	Negative	5/40 (12.5)	1.92 (0.49–7.52)	1.91 (0.44–8.29)
	Positive	3/46 (6.5)	Reference	Reference
Diabetes				
No	Negative	20/195 (10.3)	**3.01 (1.59–5.68)**	**2.10 (1.08–4.09)**
	Positive	16/469 (3.4)	Reference	Reference
Yes	Negative	6/39 (15.4)	**9.08 (1.14–72.51)**	7.13 (0.78–65.01)
	Positive	1/59 (1.7)	Reference	Reference
ESRD				
No	Negative	25/230 (10.9)	**3.36 (1.85–6.09)**	**2.18 (1.16–4.09)**
	Positive	17/525 (3.2)	Reference	Reference
Yes	Negative	1/4 (25.0)	N/A‡	N/A‡
	Positive	0/3 (0.0)	Reference	Reference

Bold indicates statistical significance (two-sided *P*-value <.05).
aRR = adjusted risk ratio; cRR = crude risk ratio; ESRD = end stage renal disease; HIV = human immunodeficiency virus; TST = tuberculin skin test.
* Adjusted for age, gender, and foreign-born status.
† Adjusted age, gender, HIV status, diabetes status, ESRD, cavitary and miliary disease, alcohol abuse, and foreign-born status.
‡ Risk ratios were not calculated due to zero "0" value in one of the cells.

Table 4
Sensitivity and subgroup analyses to assess the role of negative TST on all-cause mortality during TB treatment among adult patients with culture-confirmed TB, Georgia, 2009–2014

No	Various sensitivity analyses	Measure of association	TST results	Crude estimates	Adjusted estimates*
1	TST misclassification ($n = 1186$)				
	Including patients with invalid TST results	Risk ratio (95% CI)	TST not done	**3.94 (2.32–6.68)**	**2.64 (1.51–4.63)**
			TST negative	**3.21 (1.80–5.74)**	**2.21 (1.19–4.09)**
			TST positive	Reference	Reference
	Patients with TST missing/not done classified as TST negative	Risk ratio (95% CI)	TST negative	**3.64 (2.20–6.02)**	**2.47 (1.45–4.20)**
			TST positive	Reference	Reference
	Patients with TST missing/not done classified as TST positive	Risk ratio (95% CI)	TST negative	1.49 (0.97–2.30)	1.28 (0.81–2.03)
			TST positive	Reference	Reference
	TST induration classification	Risk ratio (95% CI)	0 mm	2.73 (1.49–5.01)	**1.95 (1.01–3.79)**
			1–10 mm	0.85 (0.20–3.57)	0.88 (0.20–3.91)
			>10 mm	Reference	Reference
2	Unmeasured confounding† ($n = 780$)				
	Externally adjusted for smoking	Risk ratio range	TST negative	—	3.27–5.38
			TST positive		Reference
	Externally adjusted for treatment adherence	Risk ratio range	TST negative	—	2.84–7.05
			TST positive		Reference
	Externally adjusted for CD4 count suppression (among $n = 86$ patients with HIV)	Risk ratio range	TST negative	—	0.49–1.50
			TST positive		Reference
3	Model specification ($n = 773$)				
	Cox proportional hazard model	Hazard rate ratio (95% CI)	TST negative	**2.65 (1.39–5.04)**	**2.08 (1.05–4.12)**
			TST positive	Reference	Reference
4	Covariate misspecification				
	Multiple log-binomial logistic regression models‡ ($n = 780$)	Risk ratio range	TST negative	—	2.10–2.37
			TST positive		Reference
	Multiple Cox proportional hazard regression models§ ($n = 773$)	Hazard rate ratio range	TST negative	—	1.72–2.15
			TST positive		Reference

Bold indicates statistical significance (two-sided *P*-value <.05).
* Adjusted for age, gender, HIV, diabetes, ESRD, cavitary disease, miliary disease, alcohol abuse, and foreign-born status.
† Range of risk ratio was calculated using 2 × 2 table according to Lash et al. [23]
‡ Results were available in Supplemental Table 3.
§ Results were available in Supplemental Table 4.

to those with positive TST after externally accounting for CD4 count was 0.49–1.50. Using Cox proportional models to estimate the hazard rate of mortality, we found that the adjusted hazard of all-cause mortality among patients with a negative TST was 2.08 (95% CI 1.05–4.12) times the hazard rate among those with a positive TST after adjusting for age, gender, HIV status, diabetes status, ESRD, cavitary disease, miliary TB, alcohol abuse, and foreign-born status (Table 4). In models to assess covariate misspecification, the risk ratio of all-cause mortality comparing patients with negative TST to positive TST ranged from 2.10 (95% CI 1.13–3.93) to 2.37 (95% CI 1.27–4.42) when using log-binomial logistic regression (Supplemental Table 3), and 1.72 (95% CI 0.88–3.37) to 2.15 (95% CI 1.11–4.17) when using Cox proportional hazard model (Supplemental Table 4).

Discussion

In this large observational cohort study, we found that one-third of patients with culture-confirmed TB had a negative TST result and that the risk of death in these patients was nearly 11%, a risk almost 2.5 times greater than that of patients with a positive TST. Furthermore, the relative effect of a negative TST was three times greater among patients with both TB and diabetes, as compared with patients without diabetes. Although further risk prediction and validation studies are needed, our results confirm existing empirical evidence suggesting that a negative TST result may be a simple, widely available, and inexpensive clinical marker of increased mortality risk during TB treatment.

Our study results suggesting an association between a negative TST result and an increased risk of death are consistent with previous studies [6,24–26]. For example, a retrospective cohort study among children with TB disease from Peru found that TST induration <5 mm among children was predictive of all-cause mortality during TB treatment (aHR 3.01, 95% CI 2.15–4.21) [26]. In addition, a prospective cohort study conducted in Uganda among TB patients living with HIV infection found that a negative TST was significantly associated with an increased hazard rate of death compared with those with positive TST (cHR 1.9, 95% CI 1.42–2.77) [25]. Third, previous analyses of US National Tuberculosis Surveillance System data found that TST positivity was associated with significantly lower odds of death during TB treatment (aOR 0.33, 95% CI 0.30–0.36) [6]. However, unlike our study, previous studies findings did not adjust for common comorbidities among patients with TB such as diabetes and ESRD. Thus, our study adds new information on the synergistic effect of a negative TST and common comorbidities on mortality risk during TB disease treatment.

Plausible mechanisms regarding how a negative TST result may increase the risk of mortality during TB treatment are likely linked to an insufficient immune response. Anergy, defined as the absence of normal immune response to a particular antigen (e.g., purified protein derivative), is common among patients with malnutrition, HIV infection, and chronic inflammatory diseases such as diabetes and ESRD [27]. These patients may have lower expression of cytokines such as interleukin-2 and interferon-γ [24, 28], which may preclude a positive TST result, even in the face of confirmed TB disease. Previous studies among HIV-negative individuals also reported that CD4 cell counts in TB patients with a negative TST were significantly lower than those with a positive TST [29, 30]. Thus, a negative TST could be a signal of impaired cytokine expression and serve as a proxy for immunosuppression, either relative or absolute, in the setting of active TB disease.

We found that almost one-third of patients diagnosed with culture-confirmed TB did not have a documented TST result, indicating that either a TST was not performed or patients did not return for reading. Notably, approximately one-third of these culture-confirmed TB patients with a missing TST had a negative or

missing smear. Among these, a limited proportion (29%) had IGRA results recorded in SENDSS system. Such patients typically had lower socioeconomic status and other conditions indicating social instability (e.g., homelessness and alcohol abuse), and a TST may have been less likely to be placed among these patients. Because patients in our study with negative TST results were at higher risk of mortality during TB treatment, increased efforts to document TST results in settings where TST is still commonly used may help identify TB patients with highest risk of death.

This study was subject to limitations. First, our primary analyses only included patients with culture-confirmed TB, an available TST result, and a documented TB treatment outcome. Consequently, our findings may not be generalizable to patients with culture-negative TB, those who did not have a TST performed, or those who were lost to follow-up during treatment. However, results from our sensitivity analyses indicated that the demographic and clinical characteristics of patients included in the final analyses were similar to those excluded. The generalizability of our findings may also be limited by the potential cohort effects due to changes in TST and IGRA use during the study period. Second, we did not have information on the date TST was performed. Thus, we were unable to confirm whether the TST results in our data were part of a diagnostic evaluation for TB disease or whether they were performed as part of routine TB screening among high-risk groups, such as homeless individuals. Furthermore, as we used TB surveillance data, we did not have access to patients' detailed clinical records including blood glucose level, CD4 counts, smoking status, hematologic malignancies, TB treatment adherence, the use of hypoglycemic or antiretroviral therapy, or specific cause of death. Our study did not estimate the direct and indirect effects (via negative TST) of immunosuppressed conditions on the risk of mortality during TB treatment. In addition, as patients with TB are not systematically checked for diabetes in the state of Georgia, misclassification on diabetes status is possible. Finally, the lack of statistical significance in our models assessing the multiplicative and additive effects of a negative TST and various comorbidities may suggest that our study was underpowered. However, our various sensitivity analyses indicated robust and consistent findings regarding the increased risk of mortality among patients with a negative TST even after accounting for multiple types of biases due to systematic errors.

Conclusions

We found that a negative TST result among patients with culture-confirmed TB indicated an increased risk of mortality during TB treatment. To determine the clinical prognostic role of the widely available TST among presumptive TB or patients diagnosed with TB disease, further experimental or quasi-experimental research is warranted, especially among patients with immunosuppressive conditions. Our results also highlight the need for clinicians to screen for immunosuppressive comorbidities, particularly diabetes, among patients with a negative TST. Importantly, our findings indicate that patients with TB and a negative TST should receive regular clinical monitoring in an effort to reduce the risk of death during TB treatment.

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Appendix

Supplemental Table1
Comparison between culture-confirmed patients with valid TST results and patients with missing TST in the state of Georgia, 2009–2014 (N = 1186)

Variables	No TST	TST	Total	*P*-value
	N % = 377 (31.8)	N % = 809 (68.2)	N % = 1186 (100.0)	
Age (y)				
15–24	31 (8.2)	109 (13.5)	140 (11.8)	**<.01**
25–44	127 (33.7)	311 (38.4)	438 (36.9)	
45–64	165 (43.8)	282 (34.9)	447 (37.7)	
≥ 65	54 (14.3)	107 (13.2)	161 (13.6)	
Gender				
Female	102 (27.1)	245 (30.3)	347 (29.3)	.26
Male	275 (72.9)	564 (69.7)	839 (70.7)	
Race				
Non-black	176 (46.8)	428 (53.0)	604 (51.0)	**.05**
Black	200 (53.2)	380 (47.0)	580 (49.0)	
Missing	1	1	2	
Foreign-born				
No	198 (52.5)	450 (55.6)	648 (54.6)	.32
Yes	179 (47.5)	359 (44.4)	538 (45.4)	
Occupation				
Employed	124 (33.9)	363 (45.0)	487 (41.6)	**<.01**
Unemployed	160 (43.7)	290 (36.0)	450 (38.4)	
Ineligible for employment, student, retired	82 (22.4)	153 (19.0)	235 (20.1)	
Missing	11	3	14	
Homelessness				
No	311 (82.7)	702 (86.8)	1013 (85.5)	.07
Yes	65 (17.3)	107 (13.2)	172 (14.5)	
Missing	1	0	1	
History of imprisonment				
No	348 (96.9)	756 (94.4)	1104 (95.2)	.06
Yes	11 (3.1)	45 (5.6)	56 (4.8)	
Missing	18	8	26	
Resident of long-term care facility				
No	369 (98.1)	801 (99.0)	1170 (98.7)	.21
Yes	7 (1.9)	8 (1.0)	15 (1.3)	
Missing	1	0	1	
Contact with TB patient				
No	332 (91.7)	675 (85.6)	1007 (87.5)	**<.01**
Yes	30 (8.3)	114 (14.5)	144 (12.5)	
Missing	15	20	35	
TB history				
No	348 (92.3)	769 (95.1)	1117 (94.2)	.06
Yes	29 (7.7)	40 (4.9)	69 (5.8)	
Illicit drug use				
No	329 (87.5)	709 (88.0)	1038 (87.8)	.82
Yes	47 (12.5)	97 (12.0)	144 (12.2)	
Missing	1	3	4	
Alcohol abuse				
No	299 (80.0)	667 (82.8)	966 (81.9)	.24
Yes	75 (20.0)	139 (17.2)	214 (18.1)	
Missing	3	3	6	
HIV status				
Negative	287 (82.0)	693 (88.7)	980 (86.7)	**<.01**
Positive	63 (18.0)	88 (11.3)	151 (13.4)	
Unknown/missing	27	28	55	
Diabetes				
No	309 (85.4)	689 (87.3)	998 (86.7)	.36
Yes	53 (14.6)	100 (12.7)	153 (13.3)	
Missing	15	20	35	
ESRD				
No	351 (97.0)	782 (99.1)	1133 (98.4)	**<.01**
Yes	11 (3.0)	7 (0.9)	18 (1.6)	
Missing	15	20	35	
History of LTBI prophylaxis				
No	352 (97.2)	756 (95.8)	1108 (96.3)	.24
Yes	10 (2.8)	33 (4.2)	43 (3.7)	
Missing	15	20	35	
Baseline smear				
Negative	127 (34.1)	260 (32.2)	387 (32.8)	.53
Positive	246 (65.9)	547 (67.8)	793 (67.2)	
Missing	4	2	6	
Baseline CXR reading				
Normal	28 (8.0)	47 (6.2)	75 (6.7)	.25
Abnormal	321 (92.0)	716 (93.8)	1037 (93.3)	

(*continued on next page*)

Supplemental Table1 (*continued*)

Variables	No TST	TST	Total	*P*-value
	N % = 377 (31.8)	N % = 809 (68.2)	N % = 1186 (100.0)	
Missing	28	46	74	
Cavitary				
No	233 (67.0)	483 (63.8)	716 (64.8)	.31
Yes	115 (33.0)	274 (36.2)	389 (35.2)	
Missing	29	52	81	
Miliary				
No	333 (97.1)	726 (96.8)	1059 (96.9)	.80
Yes	10 (2.9)	24 (3.2)	34 (3.1)	
Missing	34	59	93	
TB site				
Pulmonary	328 (87.0)	730 (90.2)	1058 (89.2)	.16
Pulmonary + extrapulmonary	41 (10.9)	61 (7.5)	102 (8.6)	
Extrapulmonary	8 (2.1)	18 (2.2)	26 (2.2)	
Mono-INH resistant				
No	320 (87.7)	678 (87.4)	998 (87.5)	.89
Yes	45 (12.3)	98 (12.6)	143 (12.5)	
Missing	12	33	45	
MDR-TB				
No	371 (99.7)	794 (98.8)	1165 (99.1)	.19 F
Yes	1 (0.3)	10 (1.2)	11 (0.9)	
Missing	5	5	10	
TB treatment duration				
≤ 6 months	87 (23.1)	110 (13.6)	197 (16.6)	**<.01**
7–12 months	254 (67.4)	600 (74.2)	854 (72.0)	
> 12 months	36 (9.6)	99 (12.2)	135 (11.4)	
TB treatment outcome				
Completed	294 (84.2)	712 (91.3)	1006 (89.1)	**<.01**
Died	46 (13.2)	44 (5.6)	90 (8.0)	
Lost to follow-up	6 (1.7)	19 (2.4)	25 (2.2)	
Uncooperative/refused to continue treatment	2 (0.6)	1 (0.1)	3 (0.3)	
Stopped due to adverse reaction	1 (0.3)	4 (0.5)	5 (0.4)	
Missing	28	29	57	

CXR = chest x-ray; INH = isoniazid; MDR = multidrug resistant.

Supplemental Table 2
Assessment of biologic interaction* between TST results and key immunosuppressive comorbidities (i.e., diabetes and HIV) among adult patients with culture-confirmed TB, Georgia, 2009–2014 (N = 780)

Immunosuppressive comorbidities	TST results	Died	Not died	aRR† (95% CI)	aRERI† (95% CI)	aAP† (95% CI)	aS† (95% CI)
HIV infection					4.31 (−4.80 to 13.42)	0.50 (−0.11 to 1.11)	2.30 (0.52–10.15)
Negative	Positive	13	469	Reference			
Negative	Negative	19	170	2.72 (1.29–5.72)			
Positive	Positive	3	43	2.60 (0.70–9.67)			
Positive	Negative	5	35	8.63 (2.81–26.56)			
Diabetes					1.36 (−1.61 to 4.32)	0.44 (−0.23 to 1.11)	2.85 (0.23–35.17)
No	Positive	16	453	Reference			
No	Negative	20	175	2.24 (1.13–4.43)			
Yes	Positive	1	58	0.49 (0.06–3.79)			
Yes	Negative	6	33	3.09 (1.13–8.47)			

aRERI = adjusted relative excess risk due to interaction; aAP = adjusted attributable proportion due to interaction; aS = adjusted synergy index; HIV = human immunodeficiency virus.

* We defined the absence of biological interaction if the 95% confidence interval (CI) of the RERI and AP included 0 and the 95% CI of synergy index included 1.0.

† Model adjusted for age, gender, HIV status, diabetes status, ESRD, cavitary disease, miliary TB, alcohol abuse, and foreign-born status.

Supplemental Table 3
Covariate selection sensitivity analyses of multivariable log-binomial logistic models for all-cause TB mortality among adult patients with culture-confirmed TB, Georgia, 2009–2014 (N = 780)

Models	Adjusted risk ratio (95% CI)	Wald χ^2 *P*-value	Covariates included in the model
Crude			N/A
TST negative	3.21 (1.80–5.74)	<.01	
TST positive	Reference		
Model 1			Age and gender
TST negative	2.31 (1.25–4.26)	.01	
TST positive	Reference		
Model 2			Age, gender, HIV status, and diabetes status
TST negative	2.23 (1.20–4.14)	.01	
TST positive	Reference		
Model 3			Age, gender, HIV status, diabetes status, and ESRD
TST negative	2.22 (1.19–4.13)	.01	
TST positive	Reference		
Model 4			Age, gender, HIV status, diabetes status, ESRD, and foreign-born status
TST negative	2.13 (1.14–3.96)	.02	
TST positive	Reference		
Model 5			Age, gender, HIV status, diabetes status, ESRD, and occupation
TST negative	2.18 (1.18–4.07)	.01	
TST positive	Reference		
Model 6			Age, gender, HIV status, diabetes status, ESRD, foreign-born status and occupation
TST negative	2.10 (1.13–3.93)	.02	
TST positive	Reference		
Model 7			Age, gender, HIV status, diabetes status, ESRD, and smear
TST negative	2.12 (1.14–3.95)	.01	
TST positive	Reference		
Model 8			Age, gender, HIV status, diabetes status, ESRD, and cavitary disease
TST negative	2.30 (1.23–4.27)	.01	
TST positive	Reference		
Model 9			Age, gender, HIV status, diabetes status, ESRD, cavitary disease, and miliary TB
TST negative	2.37 (1.27–4.42)	.01	
TST positive	Reference		
Model 10*			Age, gender, HIV status, diabetes status, ESRD, cavitary disease, miliary TB, alcohol abuse, and foreign-born status
TST negative	2.33 (1.23–4.43)	.01	
TST positive	Reference		

* Model used in the article.

Supplemental Table 4
Covariate selection sensitivity analyses of multivariable hazard models for sputum culture conversion among adult patients with culture-confirmed TB, Georgia, 2009–2014 (N = 773)

Models	Hazard rate ratio (95% confidence interval)	Wald χ^2 *P*-value	Covariates included in the model
Crude			N/A
TST negative	2.65 (1.39–5.04)	<.01	
TST positive	Ref		
Model 1			Age and gender
TST negative	1.91 (0.99–3.67)	.05	
TST positive	Ref		
Model 2			Age, gender, HIV status, and diabetes status
TST negative	1.86 (0.96–3.62)	.07	
TST positive	Ref		
Model 3			Age, gender, HIV status, diabetes status, and ESRD
TST negative	1.85 (0.95–3.61)	.07	
TST positive	Ref		
Model 4			Age, gender, HIV status, diabetes status, ESRD, and foreign-born status
TST negative	1.95 (1.01–3.78)	.05	
TST positive	Ref		
Model 5			Age, gender, HIV status, diabetes status, ESRD, and occupation
TST negative	1.79 (0.92–3.49)	.09	
TST positive	Ref		
Model 6			Age, gender, HIV status, diabetes status, ESRD, foreign-born status and occupation
TST negative	1.72 (0.88–3.37)	.11	
TST positive	Ref		
Model 7*			Age, gender, HIV status, diabetes status, ESRD, and smear
TST negative	1.83 (0.94–3.55)	.08	
TST positive	Ref		
Model 8			Age, gender, HIV status, diabetes status, ESRD, and cavitary disease
TST negative	1.99 (1.02–3.88)	.04	
TST positive	Ref		
Model 9			Age, gender, HIV status, diabetes status, ESRD, cavitary disease, and miliary TB
TST negative	2.15 (1.11–4.17)	.02	
TST positive	Ref		
Model 10*			Age, gender, HIV status, diabetes status, ESRD, cavitary disease, miliary TB, alcohol abuse, and foreign-born status
TST negative	2.08 (1.05–4.12)	.04	
TST positive	Ref		

* Model used in the article.