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Increasing Number and Volume of Cavitary Lesions on Chest Computed Tomography Are Associated With Prolonged Time to Culture Conversion in Pulmonary Tuberculosis

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Background. Cavitary lesions (CLs) primarily identified by chest x-ray (CXR) have been associated with worse clinical outcomes among patients with pulmonary tuberculosis (PTB). Chest computed tomography (CT), which has better resolution and increased sensitivity to detect lung abnormalities, has been understudied in PTB patients. We compared detection of CLs by CT and CXR and assessed their association with time to sputum culture conversion (tSCC).

Methods. This was a retrospective cohort study of 141 PTB patients who underwent CT. We used multivariate Cox proportional hazards models to evaluate the association between CLs on CXR and the number and single largest volume of CLs on CT with tSCC.

Results. Thirty (21%) and 75 (53%) patients had CLs on CXR and CT, respectively. CT detected cavities in an additional 44 patients (31%) compared with CXR. After multivariable adjustment, we observed a negative association between CLs and tSCC, with an adjusted hazard ratio (aHR) of 0.56 (95% confidence interval [CI], 0.32 to 0.97) for single CLs and 0.31 (95% CI, 0.16 to 0.60) for multiple CLs present on CT. Patients with a CL volume ≥25 mL had a prolonged tSCC (aHR, 0.39; 95% CI, 0.21 to 0.72). CLs on CXR were not associated with increased tSCC after multivariable adjustment.

Conclusions. CT detected a larger number of cavities in patients with PTB relative to CXR. We observed an association between increasing number and volume of CLs on CT and delayed tSCC independent of sputum microscopy result. Our findings highlight a potential role for CT in the clinical and research setting as a tool to risk-stratify patients with PTB.

Keywords. cavitary lesion; chest computed tomography; chest x-ray; pulmonary tuberculosis; sputum culture conversion.

Cavitary lesions (CLs) are a hallmark of pulmonary tuberculosis (PTB) infection. CLs can facilitate the diagnosis of PTB, and although they have been associated with high bacillary loads in PTB patients [1], there are conflicting data regarding their association with treatment outcomes and their utility as a biomarker to determine treatment length [2–12]. Pharmacokinetic (PK) studies have shown suboptimal penetration of antituberculosis drugs into CLs, providing a rationale for the association of CLs with delayed culture conversion and poor clinical treatment outcomes [13–16]. Yet observational studies assessing the role of CLs on treatment outcomes have shown inconsistent associations [2–8, 11, 12], and randomized controlled trials (RCTs) of shortened 4-month, relative to 6-month, regimens in patients with noncavitary PTB have not consistently met noninferiority criteria [9, 10]. A limitation of the previously cited studies is their use of chest x-ray (CXR) to determine the presence of CLs. Although chest computed tomography (CT) has become more available in recent years, its use to measure CLs in PTB is limited.

CT has advantages relative to CXR. Variable film and CXR reader quality can affect detection of CLs, and studies have shown poor interobserver agreement in detection of CLs on CXR [17, 18]. CT is more sensitive and specific for detection of CLs than CXR [4, 19, 20], has higher intra- and inter-reader agreement [20], and thus may better characterize the relationship between CLs and treatment response. In addition, although classic CT findings for tuberculosis (TB) other than CLs have been characterized [19–21], their association with treatment response remains understudied.

Given the international TB agenda's priority of identifying risk stratification tools to shorten treatment duration and the absence of reliable serum biomarkers [22], CLs should remain an important area of study. Using CT to better characterize

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CLs may provide new insight into the relationship between the number and size of CLs and treatment outcomes. CT may also play an important role in research settings to reduce misclassification of CL presence. In addition, ATS/CDC/IDSA drug-susceptible PTB treatment guidelines recommend a 7-month treatment continuation phase among patients with CLs on CXR and persistent positive sputum culture after 2 months of treatment, they do not address CL detected by CT [23]. More importantly, due to the high cost and limited availability in high burden TB countries, determining the clinical utility of chest CT is paramount to help decide if its use in PTB care should be expanded.

We performed a secondary analysis of a retrospective cohort study of PTB patients at Grady Memorial Hospital (GMH) in Atlanta, Georgia, to assess the utility of CT in predicting treatment response, as measured by time to sputum culture conversion (tSCC). GMH is a 1000-bed safety net hospital located in Fulton Country with an incidence of 7.7 cases per 100 000 persons in 2015, 3 times that of the United States [24]. Our objectives were (1) evaluate the agreement in CL detection between CT and CXR; (2) assess the effect of CLs as identified by CT and CXR on tSCC; and (3) test the association between additional radiographic findings on CT and tSCC. We hypothesized CT would be more sensitive in detecting CLs relative to CXR and an increasing number and volume of CLs on CT would be associated with prolonged tSCC.

METHODS

Adults (≥18 years) with sputum culture-confirmed TB treated between January 2008 and October 2015 with both CXR and CT images available for review were eligible for inclusion. Patients with incomplete treatment or sputum culture results were excluded. After discharge, patients were referred to county public health departments for follow-up. Detailed study methods have been described previously [25].

Data Collection

Electronic medical record (EMR) abstraction was performed to obtain demographic, clinical, and radiographic characteristics of patients during their initial PTB hospital admission. Follow-up data was collected from local health departments and the Georgia State Electronic Notifiable Surveillance System; last accessed December 2016. Data was recorded in case report forms and entered into an online REDCap database [26].

Radiology

CXR and CT were included in our sample if they were obtained <1 month before or after index admission for pulmonary tuberculosis and prior to initiation of treatment. Data were obtained from radiology reports and included presence of multi-lobar or bilateral disease, CLs, pleural effusions, and miliary pattern. CT examinations were included if they had a minimum slice thickness of 2.5 millimeters. CT images were extracted and jointly reviewed by 2 Emory University thoracic radiologists, who evaluated the following: degree of involvement of each lung lobe, presence and number of pulmonary nodules, presence of and highest percent involvement of lobes with tree-in-bud (TiB) nodularity, CLs, maximum diameter and wall thickness of the largest cavity, pleural effusion, lymphadenopathy (LAD), and miliary pattern. Radiologists were blinded to CXR findings associated with CT. Disagreements on any characteristics between the 2 thoracic radiologists were discussed until consensus was reached. CT imaging was ordered at clinicians' discretion during the study period.

Laboratory

Sputum specimens underwent acid-fast bacilli (AFB) smear microscopy, were cultured in Middlebrook 7H11 agar and liquid media using the BacT/ALERT 3D, and were concentrated and examined by fluorescent microscopy (Auramine stain) with grading according to international standards [27]. Sputum samples were collected weekly while inpatient and every 7–14 days until culture conversion after discharge at county health departments. Follow-up sputum samples from county clinics were sent to the Georgia Public Health Laboratory, where smear microscopy and culture in both solid Lowenstein-Jensen media and liquid Middlebrook 7H9 media in MGIT were performed. Firstline drug testing was performed per American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America (ATS/CDC/IDSA) guidelines [28].

Variables

Our primary outcome, tSCC, was defined as the number of days from initiation of PTB treatment to the first of 2 consecutive negative sputum culture results at least 30 days apart [29].

Our primary exposures were presence of CL on CXR and CT and volume of largest cavity by CT. CXR CLs were classified as present/absent and CT CLs as absent/single/multiple. CT volume of largest cavity was calculated assuming an ellipsoid form with radii measurements in millimeters using the following formula: $\frac{4}{3}*\pi*r_{LA}*r_{SA}*r_{CC}$ (LA = long axis, SA = short axis, CC = cranio-caudal) and multiplied by 1000 to convert to milliliters. Cavitary volume was categorized as 0 (ie, absence of CL), 0–24, and ≥25 mL based on the distribution of our data. Percent lung involvement, TiB, and LAD were included in multivariable models.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). For patients with missing height on admission (n = 12), BMI was inferred from recorded weight under the assumption that the height of respondents fell between the 2.5th and 97.5th percentile of age- and sex-matched members of the US population [30]. PTB-specific characteristics included prior diagnosis

of TB, isoniazid resistance, baseline smear grade, and directly observed therapy (DOT) adherence. Isoniazid resistance was defined as *M. tuberculosis* isolates with growth at an isoniazid concentration of ≥0.2 μg/mL [28]. Poor DOT adherence was defined as receiving ≤40 daily (Monday through Friday) doses of any antituberculous medication during the first 3 months.

Statistical Analysis

First, we compared the demographic and clinical characteristics of patients who underwent CT with those who did not to assess for selection bias and ensure internal generalizability of our results. Second, we assessed the agreement in detection of CL between CXR and CT. Third, we examined relationships between demographic, clinical, and radiographic characteristics with tSCC. Fourth, we developed 3 multivariable models with tSCC as the outcome and the following exposures: (1) single, multiple, or absent CL on CT; (2) CL volume 0, 0–24.9, and ≥25 mL; and (3) presence or absence of CL on CXR. Bivariate associations were tested using chi-square and Fisher exact tests for proportions and Wilcoxon and Kruskall-Wallis tests for comparisons of continuous variables. Median differences with 95% confidence intervals (CIs) were calculated using Hodges-Lehmann estimation. Agreement in detection of CLs between CXR and CT was evaluated with Kappa statistics [31]. Cox proportional hazard models were used to assess the association between CT characteristics and tSCC. Models were built using purposeful selection [32]; confounders were identified through literature review and bivariate analyses. Evaluation of collinearity preceded modeling procedures. Modeling proceeded as follows: (1) Models included all variables associated with the exposure of interest and a P value <.2, and we performed backward selection by removing variables in order from the largest to smallest P value, until all remaining variables had a P value <.1 or the removal of a variable resulted in a change in the exposure hazard ratio by >20%. (2) Variables that were initially excluded from our models ($P \geq .2$) were introduced in the model and retained in the model if their P value was <.1 or they changed the hazard ratio of the exposure by >20%. (3) We assessed for intermediate variables and interaction between variables in our models. (4) Proportional hazards assumptions were evaluated visually by log-log plots and statistically using time-rank tests if they were deemed to violate the assumption upon visual examination [33]. Adjusted Kaplan-Meier curves were created for our exposures of interest.

RESULTS

Study Population

We identified 242 PTB cases with complete data, of whom 93% achieved culture conversion. Study population characteristics are shown in Appendix Table 1. Patients were mostly male (76%), aged 40–59 years (60%), black (82%), and US-born (74%). Forty-six percent reported a history of homelessness, 55% reported alcohol use, 26% reported drug use, and 58% smoked tobacco. BMI was <18.5 in 22% of patients, 45% had a baseline albumin <3.0 g/dL, 15% had DM, and 36% were HIV-infected. Ten percent had a prior diagnosis of PTB. Baseline sputum microscopy was negative in 29%, 1–2+ in 21%, and 3–4+ in 50% of patients. One-fourth were reported to have isoniazid resistance. DOT adherence in the first 3 months of therapy was available for 188 patients, of whom 14 (7%) had poor adherence. Forty-six patients (19%) had cavitary CXR on admission. Patients who underwent CT evaluation at baseline (n = 175) were less likely to report homelessness compared with their non-CT counterparts (41% vs 60%; P = .01) and more likely to have DM (18% vs 8%; P = .046). The 2 groups were similar in all other measured characteristics, including baseline isoniazid resistance and DOT adherence. (Appendix Table 1).

Chest CT was performed in 178 (74%) patients; 34 images were unavailable due to institutional changes in EMR, and 3 CTs were excluded because they were obtained after initiation of treatment and 2, 5, and 6 months after admission. Therefore, 141 images were included in our final sample (Appendix Figure 1). Disagreements between radiologists regarding the presence/size of CLs and the percentage of lung involvement were present in 2 (1.4%) and 9 (6.3%) cases, respectively. The mean time from admission to CT was 1.9 days (95% confidence interval [CI], 1.2 to 2.7 days), and from admission to initiation of treatment was 9.1 days (95% CI, 7.0 to 11.1 days).

Cavitary Detection Among CT and CXR

Among 141 patients with CT, 75 (53%) were classified as having any CL, including 42 (30%) with multiple CLs. Comparisons of CL detection between CT and CXR overall and by selected characteristics are shown in Table 1. CT identified a CL in 44 (31%) patients without CL on CXR. Overall and subgroup comparisons (ie, HIV status, sputum smear grade, and diabetes mellitus) of agreement between CT and CXR revealed slight agreement (Kappa values, 0.22–0.39).

CT Findings and Time to Culture Conversion

Detailed CT characteristics by demographic and clinical characteristics are shown in Table 2. Most patients had TiB abnormality (83%) with a median (interquartile range [IQR]) highest percent lobar TiB involvement of 37.5% (12.5%–62.5%). The median percent total lung involvement was 31% (14.6%–52.1%), and 69% had lymphadenopathy. Among patients with a CL, the median volume of the largest cavity (IQR) was 24.5 (8.4–109.1) mL. Black, US-born, patients with a history of homelessness, and albumin <3.0 g/dL had a higher median largest cavity volume than their counterparts. Patients with a BMI <18.5 or >25 had a higher percentage of single and multiple cavitary lesions relative

Table 1. Comparison of Detection in Cavitary Lesions Between CXR and CT Overall and by Subgroup Among 141 Patients With Pulmonary TB, Grady Memorial Hospital, Atlanta, GA, 2008–2015

	Radiographic Findings[a]			
	CXR(-) and CT(-)	CXR(+) and CT(+)	CXR(-) and CT(+)	
	No. (%)			Kappa Statistic (95% CI)[c]
Total (n = 140)[b]	66 (47.1)	30 (21.4)	44 (31.4)	0.39 (0.27 to 0.51)
HIV status				
Infected (n = 46)	40 (87.0)	0 (0.0)	6 (13.0)	NA
Uninfected (n = 94)	26 (27.7)	30 (31.9)	38 (40.4)	0.30 (0.18 to 0.43)
Sputum smear				
Negative (n = 41)	34 (82.9)	1 (2.4)	6 (14.8)	0.22 (–0.14 to 0.58)
1–2+ (n = 26)	9 (34.6)	5 (19.2)	12 (46.2)	0.22 (0.02 to 0.43)
3–4+ (n = 73)	23 (31.5)	24 (32.9)	26 (35.6)	0.36 (0.22 to 0.52)
Diabetes mellitus				
Yes (n = 28)	10 (35.7)	8 (28.6)	10 (35.7)	0.36 (0.12 to 0.61)
No (n = 112)	56 (50.0)	22 (19.6)	34 (30.4)	0.39 (0.26 to 0.53)

CXR(-) = absence of cavitary lesion on CXR; CT(-) = absence of cavitary lesion on CT; CXR(+) = presence of cavitary lesion on CXR; CT(+) = presence of cavitary lesion on CT.

Abbreviations: CI, confidence interval; CT, chest computed tomography; CXR, chest x-ray; TB, tuberculosis.

[a]There were no instances where a CXR was classified as cavitary and CT as noncavitary.

[b]One patient with a CT did not undergo CXR on admission.

[c]Agreement is classified based on Kappa statistic as follows: 0.01–0.20 poor; 0.21–0.40 slight; 0.41–0.60 fair; 0.61–0.80 good; 0.81–0.92 very good; 0.93–1.00 excellent [31].

to normal-BMI patients. The presence, number, and volume of CLs increased as the smear grade positivity increased.

Percent culture conversion at 28 and 56 days and median tSCC by study characteristics are shown in Table 3. Overall, 83% of patients achieved culture conversion by 56 days, and the median tSCC (IQR) was 30 (12.5–50.0) days. The median tSCC increased with baseline sputum smear grade ($P < .0001$). The presence of a CL on CXR and TiB on CT were associated with increased tSCC ($P < .003$). An increasing number of CLs and volume of the largest CL ($P < .05$) were significantly associated with increased median tSCC.

To assess the added value of CLs detected by CT over (1) CLs on CXR and (2) baseline smear grade, we compared the median difference in tSCC between (1) CT with and without CLs among patients without CLs on CXR and (2) stratified by baseline smear grade regardless of CL presence on CXR. Among patients without a CL on CXR, detection of CL on CT was associated with an increased tSCC (median difference, 16 days; 95% CI, 7 to 25 days; $P = .0008$). Similar results were observed among patients with baseline 3–4+ sputum smear grade (median difference, 19.5 days; 95% CI, 8 to 31 days; $P = .001$). Comparisons among sputum smear–negative and 1–2+ patients were not statistically significant (data not shown).

Adjusted hazard ratios (aHRs) from multivariate models are shown in Table 4. Relative to patients with no CLs, those with single and multiple CLs had prolonged tSCC (aHR, 0.56; 95% CI, 0.32 to 0.97; and aHR, 0.31; 95% CI, 0.16 to 0.60; respectively). Similarly, patients with cavitary lesions ≥25 mL had a prolonged tSCC compared with patients without CL (aHR, 0.39; 95% CI, 0.21 to 0.72). CXR CL and CT TiB, percent total lung involvement, and LAD were not associated with tSCC after multivariate adjustment. Adjusted Kaplan-Meier curves for number and volume of CLs on CT are shown in Figure 1.

DISCUSSION

Our study of 141 PTB patients who underwent CT evaluation yielded 3 important findings. First, we confirmed the increased sensitivity of CT relative to CXR to detect CLs including among patients co-infected with HIV and those with pauci-bacillary disease. Second, we highlighted delays in tSCC in patients with CLs present on CT but not on CXR. Third, we observed an independent dose–response association between increasing number of CLs and volume of the largest CL and tSCC. To our knowledge, this is the first study to examine the association between CLs detected by CT and their detailed characteristics with tSCC in PTB. Our results suggest that CT provides more nuanced measurements of CLs relative to CXR and that, if confirmed by further study, it has potential to be utilized as a risk stratification tool using number and size of CLs to determine treatment duration, length, and response to therapy.

Our study highlighted 2 important aspects in the performance of CT when compared with CXR. First, CT identified additional CLs in 31% of patients relative to CXR, including in 15% of patients with a negative sputum smear and 13% of HIV-infected patients. The increased sensitivity in detecting CLs on CT may improve early clinical management of HIV-infected and AFB sputum smear microscopy–negative PTB suspects, groups in which diagnosis is often delayed and, in settings without culture, frequently missed. The presence of a CL may increase the suspicion of TB, leading to both further work-up and potentially earlier initiation of empiric anti-TB treatment. Second, among

Table 2. Chest CT Characteristics by Demographic and Clinical Characteristics of 141 Patients With Pulmonary TB, Grady Memorial Hospital, Atlanta, GA, 2008–2015

	CT Characteristic					
	Percent Total Lung Involvement	LAD	TiB Abnormality	Cavitary Lesion		Volume of Largest Cavity, mL[a]
	n = 141			n = 75		
				Single	Multiple	
Characteristic[b]	Median (IQR)	No. (%)	No. (%)	No. (%)		Median (IQR)
Total	31.3 (14.6–52.1)	97 (68.8)	117 (83.0)	33 (23.4)	42 (29.8)	24.5 (8.4–109.1)
Demographics						
Age, y						
18–39	30.2 (16.7–50.0)	26 (68.4)	31 (81.6)	9 (23.7)	6 (15.8)	19.6 (4.7–72.6)
40–59	31.3 (12.5–93.8)	57 (69.5)	66 (80.5)	18 (22.0)	27 (32.9)	28.0 (17.1–112.9)
65+	33.3 (20.8–56.3)	14 (66.7)	20 (95.2)	6 (28.6)	9 (42.9)	24.2 (4.5–103.7)
Sex						
Female	36.5 (9.4–50.0)	24 (75.0)	24 (75.0)	6 (18.8)	10 (31.3)	22.4 (19.0–121.4)
Male	29.2 (16.7–54.2)	73 (67.0)	93 (85.3)	27 (24.8)	32 (29.4)	24.8 (5.8–104.4)
Race						
Nonblack	35.4 (18.8–52.1)	19 (73.0)	22 (84.6)	9 (34.6)	7 (26.9)	**21.5 (4.9–38.2)**
Black	29.2 (12.5–54.2)	78 (67.8)	95 (82.6)	24 (20.9)	35 (30.4)	**33.6 (12.7–113.9)**
US-born						
Yes	32.3 (16.7–54.2)	71 (69.6)	87 (85.3)	23 (22.6)	33 (32.4)	**38.1 (7.9–120.2)**
No	20.8 (10.4–50.0)	26 (66.7)	30 (76.9)	10 (25.6)	9 (23.1)	**18.7 (11.4–24.5)**
History of homelessness or shelters						
Yes	25.0 (16.7–43.8)	39 (68.4)	46 (80.7)	10 (17.5)	17 (29.8)	**52.6 (17.1–143.8)**
No	35.4 (12.5–56.3)	58 (69.1)	71 (84.5)	23 (27.4)	25 (29.8)	**23.2 (4.9–66.2)**
Alcohol use						
Yes	35.4 (16.7–51.0)	50 (65.8)	65 (85.5)	19 (25.0)	27 (35.5)	24.5 (5.8–103.7)
No	27.1 (10.4–56.3)	47 (72.3)	52 (80.0)	14 (21.5)	15 (23.1)	24.5 (17.0–126.5)
Drug use						
Yes	25.0 (14.6–37.5)	20 (58.8)	26 (76.5)	8 (23.5)	5 (14.7)	24.2 (12.7–38.9)
No	35.4 (14.6–56.3)	77 (72.0)	91 (85.1)	25 (23.4)	37 (34.6)	24.7 (7.4–112.9)
Tobacco use						
Smoker	32.3 (16.7–47.9)	54 (65.9)	68 (82.9)	21 (25.6)	25 (30.5)	26.1 (5.8–104.4)
Nonsmoker	27.1 (10.4–87.5)	43 (72.9)	49 (83.1)	12 (20.3)	17 (28.8)	24.5 (17.0–109.5)
Clinical						
BMI, kg/m^2						
<18.5	43.8 (25.0–60.4)	20 (60.6)	29 (87.9)	**9 (27.3)**	**15 (45.5)**	49.7 (16.6–120.1)
18.5–24.9	25.0 (12.5–47.9)	57 (68.7)	70 (84.3)	**16 (19.3)**	**19 (22.9)**	24.2 (7.4–82.5)
≥25	31.3 (10.4–52.1)	20 (80.0)	18 (72.0)	**8 (32.0)**	**8 (32.0)**	23.2 (8.6–55.7)
Albumin at admission, g/dL						
<3.0	**43.8 (18.8–60.4)**	41 (74.6)	48 (87.3)	8 (14.6)	20 (36.4)	**93.5 (23.6–152.1)**
≥3.0	**25.0 (10.4–43.8)**	56 (65.1)	69 (80.2)	25 (29.1)	22 (25.6)	**20.5 (5.7–45.0)**
Type 2 diabetes						
Yes	30.2 (16.7–50.0)	19 (67.9)	22 (78.6)	10 (35.7)	8 (25.6)	24.3 (12.7–45.0)
No	31.3 (12.5–54.2)	78 (69.0)	95 (84.0)	23 (20.4)	34 (30.1)	24.8 (8.4–109.5)
HIV status						
Infected	**17.7 (10.4–35.4)**	34 (73.9)	**29 (63.0)**	**4 (8.7)**	**2 (4.4)**	16.0 (5.8–38.9)
Uninfected	**37.5 (18.8–56.3)**	63 (66.3)	**88 (92.6)**	**29 (30.5)**	**40 (42.1)**	24.8 (12.7–109.1)
Tuberculosis-specific						
Previous diagnosis of MTB						
Yes	38.5 (29.2–56.3)	9 (64.3)	13 (92.9)	1 (7.1)	6 (42.9)	38.9 (24.2–184.5)
No	31.3 (12.5–87.5)	88 (69.3)	104 (81.9)	32 (25.2)	36 (28.4)	24.1 (6.9–106.4)
Isoniazid resistance						
Yes	22.9 (12.5–56.3)	23 (67.7)	26 (76.5)	7 (20.6)	8 (23.5)	24.2 (5.7–113.9)
No	35.4 (14.6–52.1)	74 (69.2)	91 (85.1)	26 (24.3)	34 (31.8)	24.7 (13.6–106.8)
Smear grade of index specimen						
Negative	**16.7 (6.3–27.1)**	26 (63.4)	**27 (65.9)**	**6 (14.6)**	**1 (2.4)**	**4.7 (1.6–11.4)**
1–2+	**22.9 (10.4–60.4)**	16 (61.5)	**22 (84.6)**	**12 (46.2)**	**5 (19.2)**	**14.4 (3.5–24.2)**
3–4+	**42.7 (27.1–56.3)**	55 (74.3)	**68 (91.9)**	**15 (20.3)**	**36 (48.7)**	**39.6 (20.9–113.9)**
Achieved culture conversion						
Yes	29.2 (12.5–47.9)	84 (66.7)	103 (81.8)	30 (23.8)	34 (27.0)	24.1 (7.9–68.3)
No	54.2 (35.4–75.0)	13 (86.7)	14 (93.3)	3 (20.0)	8 (53.3)	113.9 (23.0–184.5)

Abbreviations: BMI, body mass index; CT, chest computed tomography; IQR, interquartile range; TB, tuberculosis; TiB, tree-in-bud.

[a]Calculations performed only among patients with a cavitary lesion present on CT.

[b]Numbers in bold represent associations with a *P* value <.05.

Table 3. Time to Sputum Culture Conversion by Demographic, Clinical, and Radiographic Characteristics of 141 Patients With Pulmonary TB, Grady Memorial Hospital, Atlanta, GA, 2008–2015

	Achieved Culture Conversion[a]			
	≤28 d	≤56 d	Time to Culture Conversion, d	
Characteristic	No. (%)		Median (IQR)	*P* Value[c]
Total (n = 126)[b]	56 (44.4)	104 (82.5)	30.0 (12.5–50.0)	-
Demographics				
Age, y				.5
18–39	19 (54.3)	27 (77.2)	23.0 (10.0–55.0)	
40–59	31 (41.9)	65 (87.9)	30.5 (14.0–47.0)	
≥60	6 (35.3)	12 (70.6)	34.0 (21.0–67.0)	
Sex				.07
Female	15 (53.6)	25 (89.3)	22.5 (8.5–39.5)	
Male	41 (41.8)	79 (80.6)	31.0 (14.0–51.0)	
Race				.3
Nonblack	14 (56.0)	18 (72.0)	23.0 (11.0–61.0)	
Black	42 (41.6)	86 (85.2)	31.0 (14.0–50.0)	
US-born				.3
Yes	37 (42.1)	74 (84.2)	31 (13.5–50.5)	
No	19 (50.0)	30 (79.0)	28.5 (11.0–46.0)	
History of homelessness				.2
Yes	20 (38.5)	44 (84.7)	32.5 (14.0–50.5)	
No	36 (48.7)	60 (81.1)	29.0 (11.0–50.0)	
Alcohol use				.2
Yes	33 (47.8)	59 (85.5)	29.0 (12.0–47.0)	
No	23 (40.4)	45 (79.0)	34.0 (12.0–50.0)	
Drug use				.07
Yes	16 (50.0)	32 (100.0)	27.5 (11.0–40.5)	
No	40 (42.6)	72 (76.6)	30.0 (14.0–55.0)	
Tobacco use				.2
Smoker	33 (43.4)	63 (82.9)	30.5 (14.0–52.0)	
Nonsmoker	23 (46.0)	41 (82.0)	29.0 (9.0–47.0)	
Clinical				
BMI, kg/m^2				.1
<18.5	11 (36.7)	22 (73.4)	45.5 (12.0–70.0)	
18.5–24.9	33 (44.6)	63 (85.1)	29.5 (14.0–42.0)	
≥25	12 (54.6)	19 (86.4)	20.5 (7.0–42.0)	
Albumin at admission, g/dL				.2
<3.0	18 (42.6)	35 (83.1)	30.0 (12.0–53.0)	
≥3.0	38 (45.2)	69 (82.1)	30.0 (11.5–46.5)	
Type 2 diabetes				.4
Yes	8 (30.8)	23 (88.5)	30.0 (23.0–50.0)	
No	48 (48.0)	81 (81.0)	29.5 (23.0–50.0)	
HIV status				.004
Infected	24 (57.1)	39 (92.8)	20.0 (10.0–35.0)	
Uninfected	32 (38.1)	65 (77.4)	34.5 (17.0–54.5)	
Tuberculosis-specific				
Previous diagnosis of TB				.2
Yes	7 (58.3)	10 (83.3)	18.0 (8.5–48.5)	
No	49 (43.0)	94 (82.5)	30.0 (13.0–51.0)	
Isoniazid resistance				.2
Yes	11 (36.7)	26 (86.7)	39.0 (14.0–53.0)	
No	45 (46.9)	78 (81.3)	29.0 (11.5–48.0)	
Treatment with quinolones				.2
Yes	17 (43.6)	37 (94.9)	30.0 (12.0–40.0)	
No	39 (44.8)	67 (77.0)	30.0 (11.0–54.0)	

Table 3. Continued

Characteristic	Achieved Culture Conversion[a] ≤28 d No. (%)	Achieved Culture Conversion[a] ≤56 d No. (%)	Time to Culture Conversion, d Median (IQR)	*P* Value[c]
Baseline smear grade				<.0001
Negative	26 (66.7)	34 (87.2)	12.0 (5.0–34.0)	
1–2+	12 (50.0)	22 (91.7)	28.5 (15.5–41.0)	
3–4+	18 (28.6)	48 (76.2)	39.0 (23.0–55.0)	
Radiographic				
Admission CXR				.003
Cavity absent	51 (51.5)	82 (82.8)	25.0 (10.0–46.0)	
Cavity present	5 (19.2)	21 (80.7)	40.5 (30.0–55.0)	
Admission CT				
Total lung involvement				.2
0%–24.9%	28 (50.0)	47 (83.9)	26.5 (8.0–44.0)	
25.0%–49.9%	13 (33.3)	30 (76.9)	34.0 (17.0–54.0)	
≥50%	15 (48.4)	27 (87.1)	29.0 (14.0–53.0)	
TiB abnormality				.003
Present	42 (40.8)	82 (79.6)	33.0 (14.0–54.0)	
Absent	14 (60.9)	22 (95.7)	14.0 (7.0–30.0)	
Lymphadenopathy				.2
Present	37 (44.1)	68 (81.0)	31.0 (14.0–50.5)	
Absent	19 (45.2)	36 (85.7)	29.0 (9.0–50.0)	
Cavitary lesion				<.0001
Absent	38 (61.3)	55 (88.7)	15.0 (7.0–35.0)	
Single	14 (46.7)	25 (83.4)	31.0 (17.0–52.0)	
Multiple	4 (11.8)	24 (70.6)	42.5 (33.0–59.0)	
Volume of largest cavity				<.0001
0 mL	38 (61.3)	55 (88.7)	15.0 (7.0–35.0)	
0–24.9 mL	15 (41.7)	30 (83.4)	34.0 (19.0–52.5)	
≥25 mL	3 (10.7)	19 (67.8)	46.5 (32.0–60.0)	

Abbreviations: BMI, body mass index; CT, chest computed tomography; IQR, interquartile range; TB, tuberculosis; TiB, tree-in-bud.

[a]Percentages achieving culture conversion in 28 and 56 days are cumulative.

[b]Fifteen patients did not achieve culture conversion.

[c]*P* value for median difference using 1-sided probability for Wilcoxon test for binary variables and Kruskal-Wallis test for variables with more than 2 categories.

Table 4. Crude and Adjusted Hazard Ratios for Sputum Culture Conversion by Patient Characteristics of 141 Patients With Pulmonary TB, Grady Memorial Hospital, Atlanta, GA, 2008–2015

Characteristic	Time to Sputum Culture Conversion HR (95% CI)	Time to Sputum Culture Conversion aHR (95% CI)	*P* Value
Model 1: CT cavitary lesion[a]			
Absent	Ref.	Ref.	
Single	0.71 (0.46–1.10)	0.56 (0.32–0.97)	.04
Multiple	0.39 (0.25–0.60)	0.31 (0.16–0.60)	.0005
Model 2: volume of largest cavity CT[a]			
0 mL	Ref.	Ref.	
0.1–24.9 mL	0.62 (0.41–0.94)	0.52 (0.29–0.92)	.02
≥25.0 mL	0.41 (0.26–0.64)	0.39 (0.21–0.72)	.003
Model 3: CXR cavitary lesion[a]			
Absent	Ref.	Ref.	
Present	0.78 (0.50–1.20)	1.01 (0.63–1.62)	.96

Abbreviations: aHR, adjusted hazard ratio; CT, chest computed tomography; TB, tuberculosis.

[a]Adjusted for age, sex, baseline smear grade, alcohol use, cocaine/crack/meth/heroin use, body mass index, albumin, and previous TB.

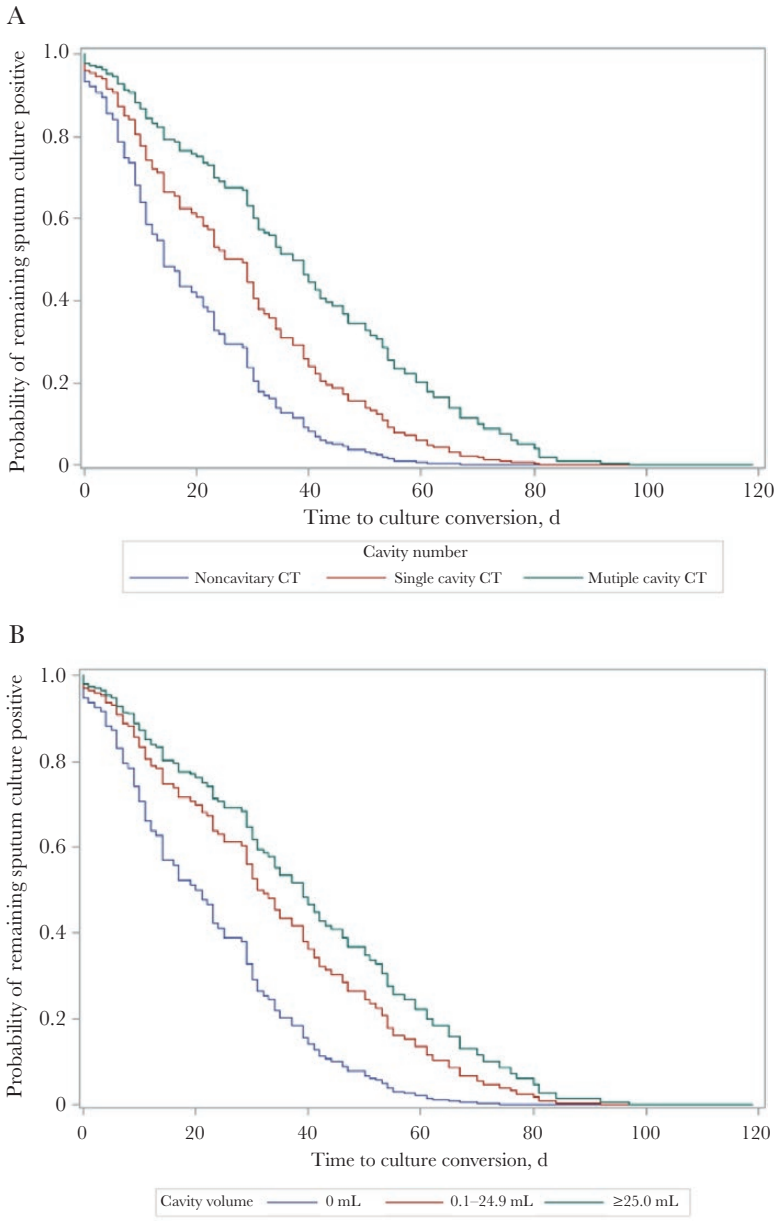

Figure 1. Adjusted Kaplan-Meier curves for cavitary lesions on chest computed tomography. Curves adjusted for age, sex, smear result, alcohol and drug use, body mass index, albumin, and previous PTB. A, Association between cavity number and time to sputum culture conversion. B, Association between cavity volume and time to sputum culture conversion.

patients with a noncavitary CXR, the presence of a cavity on CT resulted in a 2-week median increase in tSCC. This finding highlights the importance of CLs that are not detected by CXR and reinforces the theory that CLs are important determinants of treatment response. In addition, the difference in detection of CLs between CXR and CT in our study suggests that there may be misclassification of cavitary disease in previous studies and highlights a potential role for improving measurement bias in future clinical trials seeking to study shorter treatment courses among PTB patients without CLs.. Recent advances in imaging technology have decreased the radiation dose typically associated with CT, resulting in safer and more widespread use. Low-dose protocols deliver ~0.5–1.5 millisieverts (mSv), compared with ~0.1 mSv for chest radiography, for an estimated lifetime cancer risk of 0.01%–0.06% [34]. With increasing use of CT, the presence of CLs in PTB patients needs to be addressed in future tuberculosis guideline modifications.

Beyond its improved performance relative to CXR, the use of CT highlighted how better measurements of CLs could be used in clinical risk stratification in PTB patients. Our models demonstrated a dose–response relationship between the number of CLs and the volume of the largest CL and tSCC.

Furthermore, our results suggested a possible volume threshold (≥25 mL) at which cavitary lesions may require more intensive treatment modalities; the ongoing Predict TB trial is studying CL volume as a stratification tool to determine treatment length arm [35]. The use of CT may facilitate personalization of PTB therapy by combining CL features with pharmacokinetic data. For example, rifampin and pyrazinamide have demonstrated adequate concentrations in caseum [15], and quinolones less so, although moxifloxacin may have improved caseum penetration relative to gatifloxacin and levofloxacin [36]. In the absence of validated biomarkers, our data suggest that CT could play a larger role in the design of clinical trials testing shortened therapy for patients without identifiable CL and optimization of treatment regimens for patients with CL based on antituberculous PK properties.

In contrast to prior studies demonstrating an association between increasing percentage of lung involvement and delayed time to culture conversion in CXR [3, 7], increasing percentage of lung involvement, TiB, or LAD on CT was not significantly associated with tSCC. One explanation is the difference in outcomes; prior studies evaluated percent achieving culture conversion at 2 months, whereas we used tSCC. Nevertheless, the lack of association observed in our study with characteristics other than CLs suggests that the latter may be the most important determinant of sputum culture conversion.

Our study has several limitations. First, 19% of patients had evidence of CL on CXR, which is lower than in high-incidence settings, with prevalence of cavitary CXR ranging from 48% to 89% [2, 4, 12]. Thus, our results require external validation before application in high-incidence environments. Second, CT scans were read by chest radiologists with a priori knowledge of PTB diagnosis, possibly resulting in misclassification bias. Of 141 CTs evaluated, 7 were reclassified as having CLs, and 1 was reclassified as noncavitary after chest radiologist evaluation. Third, 34 CTs were unavailable for further characterization; however, all 33 of these were from before 2010, which coincides with hospital transition to EMR, and 1 was not uploaded; thus the lack of image availability is likely random. Fourth, we did not have dedicated study radiologists read initial CXRs, which may have underestimated the presence of CLs on initial CXR. However, initial reads were performed by experienced chest radiologists in an academic teaching hospital with a high PTB rule-out rate. Fifth, cavitary disease in pulmonary tuberculosis is higher among diabetics relative to nondiabetics [37]. The prevalence of diabetes was higher in our subsample (17.7%) relative to the entire cohort (7.5%), raising concerns for selection bias. However, the higher detection of CLs among diabetics have been documented for both CT and CXR [37, 38]; we would therefore not expect an increased detection of CL in CT alone. This is supported in our data by the similar percentage of CLs detected on CT but no CXR among diabetics relative to nondiabetics (36% vs 30%). Sixth, the retrospective design of our study made it difficult to ascertain the indication for and assess differential ordering of CTs among study patients. Sensitivity analyses comparing the characteristics of patients who did and did not undergo CT were similar. Finally, tSCC is an imperfect predictor of cure and failure/relapse, but has been extensively used to evaluate new treatments and as a surrogate of treatment outcomes in observational studies [39, 40].

CONCLUSIONS

This is the first study assessing the association between CT CLs and other characteristics with tSCC in PTB. We observed an independent dose–response relationship between increasing number and volume of CLs on CT and delayed tSCC independent of baseline sputum smear and highlighted the increased sensitivity of CT in detecting CLs relative to CXR. Our findings suggest an important role for CT in clinical and research settings to risk-stratify patients to determine treatment length and possibly predict treatment failure and relapse.

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Appendix Table 1. Demographic and Clinical Characteristics Overall and by Chest Computed Tomography Status of 242 Patients With Pulmonary TB, Grady Memorial Hospital, Atlanta, GA, 2008–2015

		Chest CT Performed		
	Total (n = 242)	Yes (n = 175)[a]	No (n = 67)	
Characteristic		No. (%)		*P* Value[e]
Demographics				
Age, y				.3
18–39	70 (28.9)	51 (29.1)	19 (28.4)	
40–59	145 (59.9)	101 (57.7)	44 (65.6)	
≥60	27 (11.2)	23 (13.2)	4 (6.4)	
Sex				.4
Female	57 (23.5)	44 (25.1)	13 (19.4)	
Male	185 (76.4)	131 (74.9)	54 (80.6)	
Race				.7
Nonblack	43 (17.7)	32 (18.3)	11 (16.4)	
Black	199 (82.2)	143 (81.7)	56 (83.6)	
US-born				.6
Yes	178 (73.6)	127 (72.6)	51 (76.1)	
No	64 (26.4)	48 (27.4)	16 (23.9)	
History of homelessness[b]				.01
Yes	111 (46.3)	72 (41.1)	39 (60.0)	
No	129 (53.8)	103 (58.9)	26 (40.0)	
Alcohol use[b]				.2
Yes	132 (54.8)	91 (52.0)	41 (62.1)	
No	109 (45.2)	84 (48.0)	25 (37.9)	
Drug use[b]				.5
Yes	63 (26.4)	44 (25.3)	19 (29.2)	
No	176 (73.6)	130 (74.7)	46 (70.8)	
Tobacco use				.8
Smoker	141 (58.3)	103 (58.9)	38 (56.7)	
Nonsmoker	101 (41.7)	72 (41.1)	29 (43.3)	
Clinical				
BMI, kg/m^2				.3
<18.5	53 (21.9)	38 (21.7)	15 (22.4)	
18.5–24.9	139 (57.4)	105 (60.0)	34 (50.7)	
≥25	50 (20.7)	32 (18.3)	18 (26.9)	
Albumin at admission, g/dL				.9
<3.0	109 (45.0)	79 (45.1)	30 (44.8)	
≥3.0	133 (55.0)	96 (54.9)	37 (55.2)	
Diabetes mellitus				.05
Yes	36 (14.9)	31 (17.7)	5 (7.5)	
No	206 (85.1)	144 (82.3)	62 (92.5)	
HIV status				.3
Infected	88 (36.4)	60 (34.3)	28 (41.8)	
Uninfected	154 (63.6)	115 (65.7)	39 (58.2)	
Tuberculosis-specific				
Previous diagnosis of TB				.9
Yes	25 (10.3)	18 (10.3)	7 (10.5)	
No	217 (89.7)	157 (89.7)	60 (89.5)	
Isoniazid resistance				.6
Yes	60 (24.8)	42 (24.0)	18 (26.9)	
No	182 (75.2)	133 (76.0)	49 (73.1)	
Baseline smear grade				.5
Negative	69 (28.5)	49 (28.0)	20 (29.9)	
1–2+	51 (21.1)	34 (19.4)	17 (25.4)	
3–4+	122 (50.4)	92 (52.6)	30 (44.8)	

Appendix Table 1. Continued

Characteristic	Total (n = 242)	Chest CT Performed		*P* Value[e]
		Yes (n = 175)[a]	No (n = 67)	
		No. (%)		
Poor DOT adherence in the first 3 mo of therapy[c]				.2
Yes	14 (7.4)	10 (7.8)	4 (6.8)	
No	174 (92.6)	119 (92.3)	55 (93.2)	
Radiographic				
Chest x-ray at admission[d]				.5
Cavity absent	192 (79.3)	136 (79.5)	56 (83.6)	
Cavity present	46 (19.0)	35 (20.5)	11 (16.4)	

Abbreviations: BMI, body mass index; CT, chest computed tomography; TB, tuberculosis.

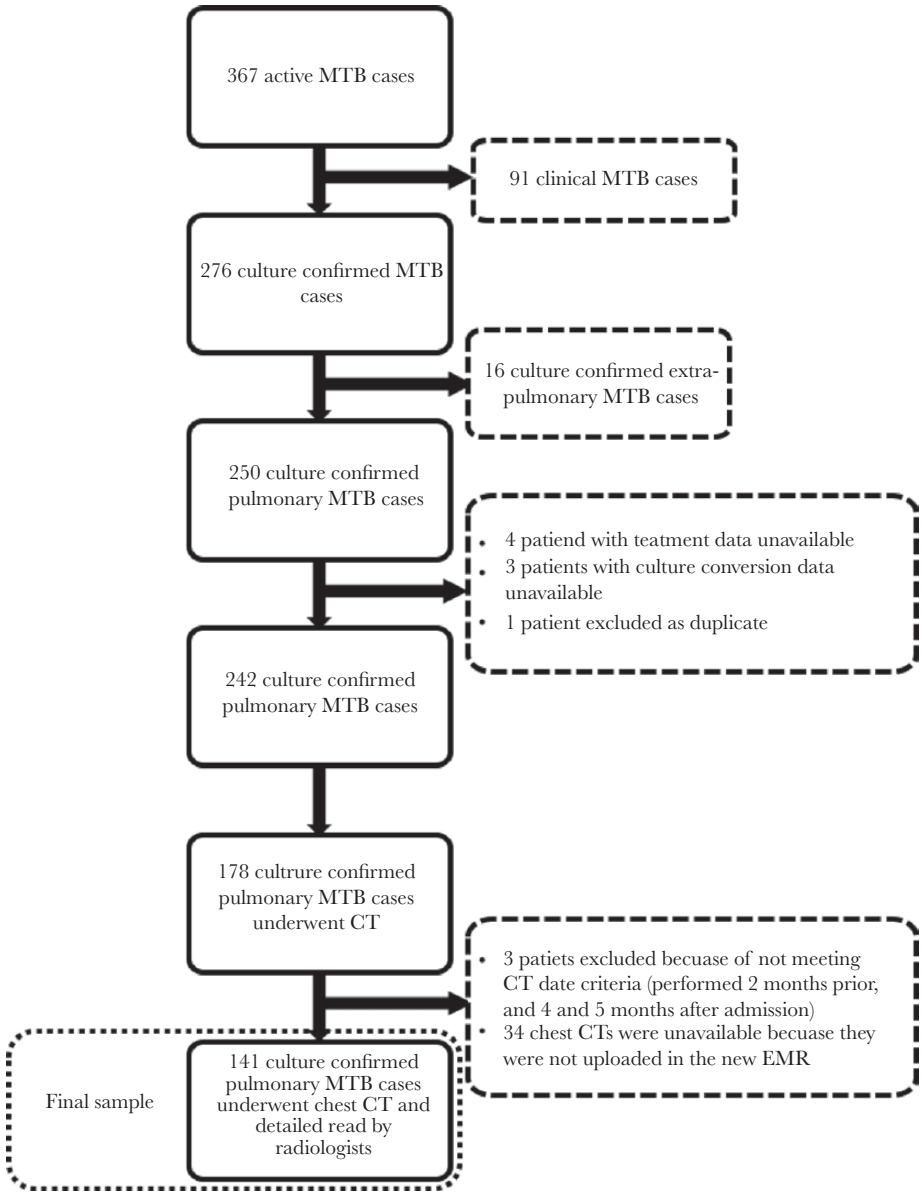
[a]Three individuals who underwent a CT of the chest were classified as not having chest CT done given that it was done at a different admission.

[b]Two, 1, and 3 patients had missing values for homelessness, alcohol use, and crack, cocaine, or heroin use, respectively.

[c]Defined as ≤40 doses. Excluded patients with missing directly observed therapy sheet and who had <90 days of treatment. Information available only for 188 patients.

[d]Two individuals did not undergo chest x-ray during admission.

[e]*P* values reflect the results of chi-square tests or Fisher exact tests where cell numbers are ≤5.



Appendix Figure 1. Flowchart of study population selection in a retrospective cohort study of 242 patients with pulmonary TB, Grady Memorial Hospital, Atlanta, GA, 2008–2015. Abbreviations: CT, chest computed tomography; EMR, electronic medical record; TB, tuberculosis.