A High Resolution Computer Tomography Scoring System to Predict Culture-Positive Pulmonary Tuberculosis in the Emergency Department

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Abstract

This study evaluated the use of high-resolution computed tomography (HRCT) to predict the presence of culture-positive pulmonary tuberculosis (PTB) in adult patients with pulmonary lesions in the emergency department (ED). The study included a derivation phase and validation phase with a total of 8,245 patients with pulmonary disease. There were 132 patients with culture-positive PTB in the derivation phase and 147 patients with culture-positive PTB in the validation phase. Using imaging evaluation of pulmonary lesions included morphology and segmental distribution. The post-test probability ratios between both phases in three prevalence areas were analyzed. In the derivation phase, a multivariate analysis model identified cavitation, consolidation, and clusters/nodules in right or left upper lobe (except anterior segment) and consolidation of the right or left lower lobe as independent positive factors for culture-positive PTB, while consolidation of the right or left lower lobe (except superior segment) were independent negative factors. An ideal cutoff point based on the receiver operating characteristic (ROC) curve analysis was obtained at a score of 1. The sensitivity, specificity, positive predictive value, and negative predictive value from derivation phase were 98.5% (130/132), 99.7% (3997/4008), 92.2% (130/141), and 99.9% (3997/3999). Based on the predicted positive likelihood ratio value of 328.33 in derivation phase, the post-test probability was observed to be 91.5% in the derivation phase, 92.5% in the validation phase, 94.5% in a high TB prevalence area, 91.0% in a moderate prevalence area, and 76.8% in moderate-to-low prevalence area. Our model using HRCT, which is feasible to perform in the ED, can promptly diagnose culture-positive PTB in moderate and moderate-to-low prevalence areas.

Introduction

Tuberculosis (TB) outbreaks are common in hospitals, and delayed diagnosis of hospitalized patients with active pulmonary tuberculosis (PTB) is an important factor in nosocomial infections [1]. Many patients experience delays in diagnosis, which can be due to varied symptoms and atypical chest X-ray (CXR) findings [2,3]. Proposed models to predict culture-positive PTB are based on medical history, clinical symptoms and signs, and chest radiographs [2,4–6]. However, testing ability with respect to post-test probability was reported in only one study [5].

Chest computed tomography (CT), particularly high-resolution computed tomography (HRCT), is feasible to perform in the emergency department (ED), and is well-suited to reveal changes in lung structure [7–9]. It has been shown that HRCT can detect culture-positive PTB and predict the risk of sputum smear-negative and sputum-positive PTB [8–10]. A recent study has reported the cost-effectiveness of using HRCT for detecting culture-positive PTB [10].

The goal of this study is to investigate the efficacy of a HRCT screening protocol for detecting the presence or absence of culture-positive PTB, and to examine the post-test probability in areas with different prevalence of tuberculosis [5,11–14].

Materials and Methods

Study Design

This study was approved by the Ethics Review Board of Ditmanson Medical Foundation Chia-Yi Christian Hospital. As the derivation phase was a retrospective review of medical records, the requirement of informed patients consent was waived. All participants in validation phase of this study signed an informed consent document after being fully informed of the study protocol.

This was a two-phase study that first identified risk factors for culture-positive PTB in Southern Taiwanese, and then validated those factors. The patients in this study were divided into two groups, those with culture-positive PTB and those with other pulmonary diseases. The overall study design is illustrated in the flowchart presented in Figure 1.
The indications for the use of HRCT of the lungs included the following [15–17]. Evaluation of diffuse pulmonary disease discovered on chest radiographs, conventional CT of the chest, or other CT examinations that include portions of the chest, including selection of the appropriate site for biopsy of diffuse lung disease. 2) Evaluation of the lungs in patients with clinically suspected pulmonary disorders with normal or equivocal chest radiographs. 3) Evaluation of suspected small and/or large airway disease. 4) Quantification of the extent of diffuse lung disease for evaluating effectiveness of treatment. There were no absolute

Derivation Phase

The indications for the use of HRCT of the lungs included the following [15–17]. Evaluation of diffuse pulmonary disease discovered on chest radiographs, conventional CT of the chest, or other CT examinations that include portions of the chest, including selection of the appropriate site for biopsy of diffuse lung disease.
Validation Phase

Groups consisted of a total of 4,140 patients. These patients did not have culture-positive PTB. In on chest x-ray, echocardiography, chest sonography, and panen-
or pleural disease (n = 205), rib fractures (n = 185), cardiac vascular
diagnosis of lung cancer, lymphoma, or
the diagnosis of collagen vascular disease was based on serum titers
diagnosis of pneumonia was based on previous study [24]. The
diagnoses of chronic pulmonary diseases were based on pulmonary
mycobacterium (NTM) infection [23] were based on culture;
culture-positive PTB, inactive PTB [22], and non-tuberculosis
the ED were retrospectively reviewed [15,20,21]. The diagnosis of
were older than 18 years with suspicious pulmonary lesions seen in
June 2008 to November 2009. The records of 5,005 patients who
were admitted from the ED. This validation phase prospectively
in-hospital isolation of patients with culture-positive PTB who
excluded from receiving HRCT imaging. Heitkamp et al. [18] and
Kirsch et al. [19] published reports after our study which agree
with the inclusion and exclusion criteria used in this study.
A total of 15,800 patients visited the ED of our hospital from
Of the 5,005 patients, 4,195 received HRCT imaging. The 800
Guidelines were developed from the identified HRCT factors
as explained in the subsequent section) to guide choices regarding
in-hospital isolation of patients with culture-positive PTB who
were admitted from the ED. This validation phase prospectively
validated these guidelines by evaluating their ability to diagnose
4,105 adult patients with suspicious pulmonary lesions admitted
from the ED between December 2009 and October 2010. These
patients were enrolled with the same inclusion and exclusion
criteria as the patients in the derivation phase.

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criteria as the patients in the derivation phase.

HRCT Imaging

All patients received chest CT scans with a 64-MDCT scanner
(Brilliance, Philips Medical Systems, Cleveland, OH, USA) set to
0.625 mm collimation, 100–120 kV, 250 mAs, a table speed of
57.5 mm/sec, a rotation time of 0.75 sec, and a pitch of 1.07. The
images were acquired during a single breath-hold lasting 5–
8 seconds, which rendered respiratory motion artifacts uncommon.
The spiral mode was used to scan the whole thorax, and the
total radiation dose was about 7.0 mSv. The raw data were
0.625 mm (conventional CT is 5 mm thick), and CT reformation
yielded HRCT images that were 1 mm thick. The images were
reconstructed with a 1-mm slice thickness in the axial plane (no
gap) and in the coronal plane (5-mm apart) using a high spatial-
frequency algorithm, and then sent to the picture archiving
and communication system (PACS) for review. All thin-section multi-
detector CT (MDCT) images were displayed on a monitor at the
pulmonary window level setting (level, -600 HU; width, 1200 HU).

HRCT Evaluation

CT Morphology and anatomy distribution. Definitions of
morphology and anatomical distribution were adopted from
previously described information [9,26,27].

Image Interpretation Criteria. The HRCT scans were
interpreted by 3 radiologists. Each had over 15 years of experience
reading thoracic radiological studies, and was unaware of the
sputum smear and clinical examination results. All patients in the
study received a chest x-ray, and the x-ray results were available to
the radiologists. The request form for the CT examination did not
provide any clinical details or any suggestions as to the possible
clinical diagnosis. All three radiologists thoroughly read and
interpreted all CT images independently on a daily basis. The
radiologists thoroughly interpreted the CT images including all 18
segments over both lungs without any focus or view of interest.
The locations of lung involvement were reported as one or more of
the 18 designated lung segments. In the late afternoon every day,
all three radiologists discussed any discrepancies in their findings
and any were resolved by consensus.

Development of Derivation Set and Validation of Receiver Operating Characteristic (ROC) Curve. We identified pre-
dictors of culture-positive PTB in a stepwise logistic regression
analysis by considering CT findings that included CT morphol-
ogy, anatomic distribution, and number of areas of consolidation,
cavitations, and clusters of nodules. We identified potential
predictive variables for culture-positive PTB using univariate
analysis by considering CT findings that included CT morphol-
ogy, anatomy distribution, and any were resolved by consensus.
The localization of lung cancer, lymphoma, or
and any were resolved by consensus.

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analysis by considering CT findings that included CT morphol-
ogy, anatomy distribution, and any were resolved by consensus.
Post-test probability was subsequently calculated according to
the given prevalence and predicted positive likelihood ratio (LR).

Statistical Analysis

Statistical analyses were performed with SPSS 15.0 statistics
software (SPSS Inc., Chicago, IL, USA). Continuous data were
presented as mean ± standard deviation, and categorical data by
group as number with percentage (%). Two-sample t-test was
performed to compare the differences between groups for
continuous data. The Pearson’s chi-square test or Fisher’s exact
test was used to compare differences in categorical data between groups. A multiple logistic regression model was performed to identify the predictors of culture-positive PTB. The estimated beta (β) with standard error (SE) and odds ratio (OR) with 95% confidence interval (CI) were calculated for the multivariate logistic regression. A relative score was given by using the lowest β value as a base (here, the β value of cavitation of s1, s2, and s1+s2 was the lowest). For the other variables selected in multivariate logistic regression, the relative score was given as 2 when the ratio (β/5.060) was >1 and <1.5, and as 3 when the ratio was ≥1.5 and <2.5. Since the effect of consolidation of s7, s8, s7+s8, s9, s10 was inverse (β value is negative), the relative score was set as negative. The area under the ROC curve (AUC) indicated the best cutoff point based on maximization of the Youden index. All statistical analyses were considered significant at P<0.05.

Results

The model was derived from 4,140 patients (2,698 males), and validated with 4,105 patients (2,684 males). The age and sex distributions of the derivation group and validation group showed no significant difference (both, P>0.05; results not shown). Among the patients in the derivation phase, 132 patients (87 male/45 female) were diagnosed with culture-positive PTB, while the others (2,611 male/1,397 female) were considered to have other pulmonary diseases. Demographic characteristics, medical history, and clinical symptoms and signs were all similar between the culture-positive PTB and the other pulmonary diseases groups. The frequency of smear-positive, culture-positive and smear-negative, culture-positive PTB were different between the derivation phase and the validation phase, but the frequency of culture-positive PTB was similar between the two phases (3.2% [132/4140] vs. 3.6% [147/4105], P=0.654) (Table 1).

When CT morphology and anatomic examinations were compared between the culture-positive PTB and other pulmonary diseases groups, the culture-positive PTB group had higher values in consolidation, cavitation, clusters of nodules, ground-glass-opacity, and centrilobular nodules with tree-in-bud appearance, but had lower values in fibrosis (all, P<0.05) (Table 2). Anatomic examination found that the culture-positive PTB group had significantly higher values for consolidation of s1, s2, s1+s2, s3, s4, s5, and s6, for cavitation of s1, s2, s1+s2, s3, s4, s5, and s6, and for all the clusters of nodules/mass. Vice versa, lower values for consolidation of s7, s8, s7+s8, s9, s10 were found in the culture-positive PTB group (all, P<0.05). The kappa value for both inter-observer and intra-observer variation (including the interpretation of HRCT morphology and the score of HRCT report) was >0.9 indicating excellent reliability.

Multivariate logistic regression identified multiple independent predictors of culture-positive PTB in the derivation group (Table 3). We then developed a “relative score”, which was based on the ratio of each estimated β to the lowest one (i.e., the estimated cavitation of s1, s2, s1+s2 of 5.060). The relative score was 2 for ratios >1 and <1.5, and 3 for ratios >1.5 and <2.5. If the β effect was inverse, the score assigned was negative. The relative score was used in the multivariate logistic regression model. The ROC curve derived from the multivariate logistic regression had an AUC of 0.997 (95% CI 0.991 to 1.000, P<0.001; Fig. 2). The best observed sensitivity and specificity was found at a cutoff score of 1. The model had a predictive ability with a sensitivity, specificity, positive predictive value, and negative predictive value for the derivation vs. validation phase of 98.5% vs.

Figure 2. Receiver operating characteristic (ROC) curve from the multivariate logistic regression model analysis of the derivation group. The area under the ROC (AUC) = 0.997 (95% confidence interval [CI] 0.991 to 1.000, P<0.001).

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Table 1. Demographic and clinical characteristics of the subjects in derivation phase and validation phase.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Derivation Phase (n = 4,140)</th>
<th>Validation Phase (n = 4,105)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.6±10.8</td>
<td>67.1±9.2</td>
<td>0.573</td>
</tr>
<tr>
<td>Sex, males</td>
<td>87 (65.9)</td>
<td>2611 (65.1)</td>
<td>0.856</td>
</tr>
<tr>
<td>Anemia (&lt;11 g/dL)</td>
<td>51 (38.6)</td>
<td>1338 (33.4)</td>
<td>0.209</td>
</tr>
<tr>
<td>Gastroctomy</td>
<td>15 (11.4)</td>
<td>357 (8.9)</td>
<td>0.332</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>63 (47.7)</td>
<td>1710 (42.7)</td>
<td>0.247</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>14 (10.6)</td>
<td>318 (7.9)</td>
<td>0.266</td>
</tr>
<tr>
<td>Received steroids</td>
<td>44 (33.3)</td>
<td>1077 (26.9)</td>
<td>0.100</td>
</tr>
<tr>
<td>Albumin &lt;2.5 g/dL</td>
<td>52 (39.4)</td>
<td>1327 (31.3)</td>
<td>0.132</td>
</tr>
<tr>
<td>Smear-positive, culture positive</td>
<td>108 (81.8)</td>
<td>0 (0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Smear-negative, culture positive</td>
<td>24 (18.2)</td>
<td>0 (0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Bacterial infection (blood culture/effusion/sputum)</td>
<td>0 (0)</td>
<td>2786 (69.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mycoplasma infection (elevated titer)</td>
<td>0 (0)</td>
<td>261 (6.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Viral infection (elevated titer or pathology)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Non-tuberculosis mycobacterial infection (culture)</td>
<td>0 (0)</td>
<td>136 (3.4)</td>
<td>0.022</td>
</tr>
<tr>
<td>Fungus (pathology)</td>
<td>0 (0)</td>
<td>4 (0.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0 (0)</td>
<td>25 (0.6)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>0 (0)</td>
<td>325 (8.1)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Collagen vascular disease</td>
<td>0 (0)</td>
<td>20 (0.5)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Lung cancer/lung lymphoma/metastatic cancer to lung (pathology)</td>
<td>0 (0)</td>
<td>450 (11.3)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Symptoms and signs

| Fever                                          | 53 (40.2)                    | 1342 (33.5)                 | 0.111 |
| Weight loss                                    | 51 (38.6)                    | 1339 (33.4)                 | 0.211 |
| Cough                                          | 50 (37.8)                    | 1338 (33.4)                 | 0.337 |
| Weakness                                       | 56 (42.4)                    | 1579 (39.4)                 | 0.484 |

| HRCT Predicts Culture-Positive TB               |

G1, patients with culture-positive PTB in derivation group; G2, patients other pulmonary diseases in the derivation group; G3, patients with culture-positive PTB in validation group; G4, patients other pulmonary diseases in the validation group. Data are presented as mean ± standard deviation for continuous variables, and n (%) for categorical variables. PTB, pulmonary tuberculosis; NA, not assessed.

*Indicates statistical significance between G1 and G2 in derivation phase or between G3 and G4 in validation phase, P<0.05.

†Comparison of the incidence of culture-positive PTB of the derivation group with the validation group (3.2% [132/4140] vs. 3.6% [147/4105], P = 0.654).

Note: Combined disease such as bacterial infection with culture-positive PTB (n = 1), and lymphoma with culture-positive PTB (n = 1) were grouped as culture-positive PTB. In the derivation phase there were 633 patients with previous PTB (19 with culture-positive PTB and 614 with other pulmonary diseases without culture-positive PTB).

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According to the scoring system for predicting culture-positive PTB (total score >1) and other pulmonary diseases (total score ≤1) shown in Table S1 in File S1. The predictive model combined the results of cavitation (positive in s1, s2, s1+s2), consolidation (positive in s1, s2, s1+s2), consolidation (positive in s6), consolidation (positive in s7, s8, s7+s8, s9, s10), and cluster nodules/mass (positive in s1, s2, s1+s2), and the relative scores were derived thereafter. The frequency of patients with culture-positive PTB based on the scoring system in the derivation and validation phases is shown in Table S2 in File S1.

As another example, in this study a total score of 0 was based on the combination of the patterns in cavitation (positive in s1, s2, s1+s2), consolidation (positive in s1, s2, s1+s2), consolidation (positive in s6), consolidation (positive in s7, s8, s7+s8, s9, s10), and cluster nodules/mass (positive in s1, s2, s1+s2), and cluster nodules/mass (positive in s1, s2, s1+s2), but positive consolidation s7, s8, s7+s8, s9, s10, and consolidation s6. Among the 47 patients in the validation phase who were smear negative, 34 patients received a total score of 3, nine received a total score of 2, three received a total score of 5, and one received a total score of 1 (Table S3 in File S1).

Multivariate logistic regression analysis in the subgroup of derivation phase for 633 patients with previous PTB (19 with culture-positive PTB and 614 other pulmonary diseases without culture-positive PTB), revealed that the relative score was similar to the total patients in the derivation phase (Table S4 in File S1).

99.3%, 99.7% vs. 99.9%, 92.2% vs. 98.6%, and 99.9% vs. 99.9% respectively (Table 4). Details of the scoring system for predicting culture-positive PTB (total score >1) and other pulmonary diseases (total score ≤1) are shown in Table S1 in File S1. The predictive model combined the results of cavitation (positive in s1, s2, s1+s2), consolidation (positive in s1, s2, s1+s2), consolidation (positive in s6), consolidation (positive in s7, s8, s7+s8, s9, s10), and cluster nodules/mass (positive in s1, s2, s1+s2), and the relative scores were derived thereafter. The frequency of patients with culture-positive PTB based on the scoring system in the derivation and validation phases is shown in Table S2 in File S1.

Examples of the scoring can be seen by referring to Table S1 in File S1. If the patient had negative cavitation s1, s2, s1+s2, consolidation s1, s2, s1+s2, consolidation s6, and cluster nodules/mass s1, s2, s1+s2, but positive consolidation of s7, s8, s7+s8, s9, s10, then the patient would receive a total score of -3 (0+0+(-3)+0+0). As another example, in this study a total score of 0 was based on the combination of the patterns in cavitation (positive in s1, s2, s1+s2), consolidation (positive in s1, s2, s1+s2), consolidation (positive in s6), consolidation (positive in s7, s8, s7+s8, s9, s10), and cluster nodules/mass (positive in s1, s2, s1+s2), and cluster nodules/mass (positive in s1, s2, s1+s2), but positive consolidation s7, s8, s7+s8, s9, s10, and consolidation s6. Among the 47 patients in the validation phase who were smear negative, 34 patients received a total score of 3, nine received a total score of 2, three received a total score of 5, and one received a total score of 1 (Table S3 in File S1).

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3.2% patients had culture-positive PTB. The post-test probability derivation phase, the HRCT screening protocol identified that given prevalence and predicted positive LR [5,29]. In the superior segment of right or left lower lobe; s7, medical basal segment of right lower lobe; s8, anterior basal segment of right lower lobe; s7, lateral segment of right middle lobe or superior segment of left lingual lobe; s5, medial segment of right middle lobe or inferior segment of left lingual lobe; s6, medial-anterior basal segment of left lower lobe; and s10, posterior basal segment of right or left lower lobe.

**Table 2.** High-resolution computed tomography findings of subjects in the derivation phase and validation phase.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Derivation Phase (n = 4,140)</th>
<th>Validation Phase (n = 4,105)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G1 (n = 132)</td>
<td>G2 (n = 4,008)</td>
</tr>
<tr>
<td>Consolidation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>s1, s2, s1+2</td>
<td>102 (77.3)</td>
<td>305 (7.6)</td>
</tr>
<tr>
<td>s3, s4, s5</td>
<td>20 (15.2)</td>
<td>289 (7.2)</td>
</tr>
<tr>
<td>s6</td>
<td>66 (50)</td>
<td>65 (16.6)</td>
</tr>
<tr>
<td>s7, s8, s7+8, s9, s10</td>
<td>11 (8.3)</td>
<td>1356 (33.8)</td>
</tr>
<tr>
<td>Cavitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>s1, s2, s1+2</td>
<td>81 (61.4)</td>
<td>34 (0.8)</td>
</tr>
<tr>
<td>s3, s4, s5</td>
<td>8 (6.1)</td>
<td>88 (2.2)</td>
</tr>
<tr>
<td>s6</td>
<td>36 (27.3)</td>
<td>98 (2.4)</td>
</tr>
<tr>
<td>s7, s8, s7+8, s9, s10</td>
<td>8 (6.1)</td>
<td>88 (2.2)</td>
</tr>
<tr>
<td>Clusters of nodules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>s1, s2, s1+2</td>
<td>102 (77.3)</td>
<td>6 (0.1)</td>
</tr>
<tr>
<td>s3, s4, s5</td>
<td>17 (12.9)</td>
<td>2 (0.05)</td>
</tr>
<tr>
<td>s6</td>
<td>26 (19.7)</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td>s7, s8, s7+8, s9, s10</td>
<td>36 (27.3)</td>
<td>98 (2.4)</td>
</tr>
<tr>
<td>Interlobular septal thickening</td>
<td>93 (70.5)</td>
<td>2231 (55.7)</td>
</tr>
<tr>
<td>Bronchial wall thickening</td>
<td>103 (78.0)</td>
<td>2647 (60.0)</td>
</tr>
<tr>
<td>Ground-glass-opacity</td>
<td>109 (82.6)</td>
<td>2757 (68.8)</td>
</tr>
<tr>
<td>Centrilobular nodules with tree-in-bud</td>
<td>87 (65.9)</td>
<td>1397 (34.9)</td>
</tr>
<tr>
<td>Paratracheal adenopathy</td>
<td>66 (50.0)</td>
<td>1459 (36.4)</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>22 (16.7)</td>
<td>1202 (30.0)</td>
</tr>
<tr>
<td>Parenchymal Calcification</td>
<td>12 (9.1)</td>
<td>754 (18.8)</td>
</tr>
</tbody>
</table>

G1, patients with culture-positive PTB in derivation group; G2, patients other pulmonary diseases in the derivation group; G3, patients with culture-positive PTB in validation group; G4, patients other pulmonary diseases in the validation group. Data are expressed as number (%). s1, apical segment; s2, posterior segment right upper lobe; s1+s2, apico-posterior segment left upper lobe; s3, anterior segment of right upper lobe or left upper lobe; s4, lateral segment of right middle lobe or superior segment of left lingual lobe; s5, medial segment of right middle lobe or inferior segment of left lingual lobe; s6, superior segment of right or left lower lobe; s7, medical basal segment of right lower lobe; s8, anterior basal segment of right lower lobe; s7+8, medial-anterior basal segment of left lower lobe; s9, lateral basal segment of right or left lower lobe; s9, lateral basal segment of right or left lower lobe; s10, posterior basal segment of right or left lower lobe.

*Indicates statistical significance between G1 and G2 in derivation phase or between G3 and G4 in validation phase, P<0.05.

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Table 5 summarizes the post-test probability according to the given prevalence and positive LR [5,29]. In the derivation phase, the HRCT screening protocol identified that 3.2% patients had culture-positive PTB. The post-test probability was derived as 91.5% based on the predicted positive LR+ value of 328.33. In the validation phase, the HRCT screening protocol identified that 3.6% patients had culture-positive PTB, and the post-test probability was derived as 92.5%. Moreover, the post-test

<table>
<thead>
<tr>
<th>Estimated</th>
<th>Estimated Odds Ratio (95% CI)</th>
<th>P</th>
<th>Relative Scorea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavitation s1, s2, s1+2</td>
<td>5.060 (1.434)</td>
<td>157.6 (9.5, 2619.1)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Consolidation s1, s2, s1+2</td>
<td>5.944 (1.487)</td>
<td>381.3 (20.7, 7037.9)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Consolidation s7, s8, s7+8, s9, s10</td>
<td>–7.588 (1.529)</td>
<td>0.001 (0, 0.010)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Clusters nodules/mass s1, s2, s1+2</td>
<td>9.669 (1.428)</td>
<td>7832.6 (964.1, 259786.2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Consolidation s6</td>
<td>11.728 (1.777)</td>
<td>123962.7 (3810.4, 4032857.2)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

s1, apical segment; s2, posterior segment right upper lobe; s1+s2, apico-posterior segment left upper lobe; s6, superior segment of right or left lower lobe; s7, medical basal segment of right lower lobe; s8, anterior basal segment of right lower lobe; s7+8, medial-anterior basal segment of left lower lobe; s9, lateral basal segment of right or left lower lobe; and s10, posterior basal segment of right or left lower lobe.

*Relative score is based on the ratio of each estimated j with the lowest one (5.060) as base = 1. The relative score was set as 2 when the ratio (j/5.060) was ≥1 and <1.5, and as 3 when the ratio was ≥1.5 and <2.5. Since the effect of consolidation of s7, s8, s7+8, s9, s10 was inverse, the relative score was set as negative.

*Indicates statistical significance, P<0.05.

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Table 3. Multivariate logistic regression analysis in derivation phase (N = 4,140).
probability were also estimated as 94.5%, 91.0%, and 76.8% when the pre-diagnosed probability (or prevalence of culture-positive PTB) were high prevalence (5.0%), moderate prevalence (3%), and moderate-to-low prevalence prevalence (1.0%) (Table 5).

### Discussion

The rapid diagnosis of culture-positive PTB is critical for preventing spread of the disease. If CXR is the only means of diagnosis, the cost of isolation (over diagnosis) and nosocomial spread (under diagnosis) will be great. The use of GeneXpert for diagnosing PTB promises to provide rapid and accurate diagnosis, but the test cannot be performed without sputum [30]. Many patients in this study were not able to produce sputum in the ED, and while bronchoscopy can be used to obtain sputum it is invasive and also a source of nosocomial infection. Though HRCT is associated with the use of ionizing radiation the impact of this is minimal in most adult patients, and in this study patients younger than 18 were excluded in order to reduce the impact of radiation. Also, this study utilized spiral CT, and the radiation dose was approximately 7 mSV. Taking the cost of isolation rooms, training of personnel with the CT equipment, and training of the radiologist into consideration, HCRT is feasible and a more cost-effective method for allocating resources for the isolation of patients [10,31–34].

Our model identified consolidation of s1, s2, s1+s2 and s6; cavitation of s1, s2, and s1+s2; and clusters of nodules in s1, s2, and s1+s2 as positive factors predictive of culture-positive PTB, while consolidation of s7, s8, s7+s8, s9, and s10 were negative factors. Together, these factors had an overall high sensitivity (130/132, 98.5%), specificity (3997/4008, 99.7%), high positive predictive value (130/141, 92.2%) and high negative predictive value (3997/3999, 99.9%). The high sensitivity and high specificity contribute to the OR being as high as 328.33 [13]. In addition, high post-test probabilities in high (94.5%), moderate (91.0%), and moderate-to-low (76.8%) prevalence areas were obtained.

The most important finding in this study is that non-cavitation such as consolidation in s1, s2, s1+s2 and s6; cavitation of s1, s2, and s1+s2; and clusters of nodules/mass in s1, s2, and s1+s2 were associated with the highest positive predictive score. These findings largely agree with recent HRCT studies showing that not only cavitation of s1, s2, and

### Table 4. Predictive ability of HRCT in derivation phase and validation phase.

<table>
<thead>
<tr>
<th></th>
<th>Derivation phase</th>
<th>Validation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Culture-positive PTB (n = 132)</td>
<td>Other pulmonary diseases (n = 4,008)</td>
</tr>
<tr>
<td>Predicted results from HRCT model*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted culture-positive PTB</td>
<td>130</td>
<td>11</td>
</tr>
<tr>
<td>Predicted absence of PTB</td>
<td>2</td>
<td>3997</td>
</tr>
<tr>
<td>Predictive terms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>130/132 (98.5%)</td>
<td>146/147 (99.3%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>3997/4008 (99.7%)</td>
<td>3956/3958 (99.9%)</td>
</tr>
<tr>
<td>False negative ratea</td>
<td>2/132 (1.5%)</td>
<td>1/147 (0.7%)</td>
</tr>
<tr>
<td>False positive rateb</td>
<td>11/4008 (0.3%)</td>
<td>2/3958 (0.1%)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>130/141 (92.2%)</td>
<td>146/148 (98.6%)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>3997/3999 (99.9%)</td>
<td>3956/3957 (99.9%)</td>
</tr>
</tbody>
</table>

*The cutoff value from the predictive score to classify patients as culture-positive PTB with total score>1 and other pulmonary diseases with total score≤1.

aFalse negative rate, 1-sensitivity.
bFalse positive rate, 1-specificity.
doi:10.1371/journal.pone.0093847.t004

### Table 5. Summary of post-test probability according to the prevalence and predicted positive likelihood ratio.

<table>
<thead>
<tr>
<th></th>
<th>Prevalence of culture-positive PTB</th>
<th>Prediction Score</th>
<th>Pre-test odds</th>
<th>LR+</th>
<th>Post-test odds</th>
<th>Post-test probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population in derivation phase</td>
<td>3.2%a</td>
<td>1</td>
<td>0.033</td>
<td>328.33</td>
<td>10.82</td>
<td>91.5%</td>
</tr>
<tr>
<td>Study population in validation phase</td>
<td>3.6%b</td>
<td>1</td>
<td>0.037</td>
<td>328.33</td>
<td>12.26</td>
<td>92.5%</td>
</tr>
<tr>
<td>High prevalence</td>
<td>5.0%</td>
<td>1</td>
<td>0.053</td>
<td>328.33</td>
<td>17.28</td>
<td>94.5%</td>
</tr>
<tr>
<td>Moderate prevalence</td>
<td>3.0%</td>
<td>1</td>
<td>0.031</td>
<td>328.33</td>
<td>10.15</td>
<td>91.0%</td>
</tr>
<tr>
<td>Moderate-to-low prevalence</td>
<td>1.0%</td>
<td>1</td>
<td>0.010</td>
<td>328.33</td>
<td>3.32</td>
<td>76.8%</td>
</tr>
</tbody>
</table>

LR+, predicted positive likelihood ratio. The LR+ = 328.33 derived from the equation (sensitivity/1-specificity) with a sensitivity = 98.5% and specificity = 99.7% in derivation phase.

aThe prevalence was calculated based on the culture-positive PTB probability in the derivation phase (132/4140).
bThe prevalence was calculated based on the culture-positive PTB probability in validation phase (147/4105).
doi:10.1371/journal.pone.0093847.t005
s1+s2 [8] but also consolidation in s1, s2, s1+s2, and s6 [25] and clusters of nodules/mass in s1, s2, and s1+s2 [8] are predictive of culture-positive PTB. This observation is also in accordance with other previous studies [35,36]. Consolidation of s7, s8, s7+s8, s9, and s10 was a negative factor in our model. This is in accordance with the high frequency of bacterial pneumonia in the lower lobe (73.3%) as reported by Coelho et al. [37]. Meanwhile, Yeh et al. [8] reported that only 16% (13/84) of smear-positive and 15% (6/40) of smear-negative culture-positive PTB patients had consolidation in s7, s8, s7+s8, s9, or s10. Furthermore, CT findings of culture-positive PTB in immunocompromised patients, such as those with diabetes, are similar to our findings [38]. This supports that consolidation of s7, s8, s7+s8, s9, and s10 was also a negative factor in predicting culture-positive PTB in the prior study by Yeh et al. [8].

Ideally, a decision instrument would have 100% sensitivity, specificity, and negative predictive value, and no patients with the disease would be missed [39]. In our model, the sensitivity, specificity, and negative predictive value are all >95%. We utilized the given prevalence rates to test the ability of the model [5]. The high OR contributes to the high post-test probability in moderate and moderate-to-low prevalence areas.

As previously reported by Kanaya et al. [5], a post-test probability of 5% is the threshold for withholding empiric treatment for patients with suspected PTB but with negative sputum results. In contrast, in high to moderate prevalence areas the threshold is more conservative. In our study, high post-test probability was observed in moderate and moderate-to-low prevalence areas. This finding implies that our model may be useful in deciding to initiate treatment or isolation in patients with suspected culture-positive PTB in different prevalence areas if post-test probability is >60% in these areas. Conversely, in very low prevalence area the risk and cost benefit must be considered [14,40].

Our HRCT predictive model also produced lower a false positive rate based on the results from the validation phase. This implies that the necessity of respiratory isolation could be better determined based on our HRCT screening protocol, thereby reducing unnecessary cost and manpower in the management of this specific population of patients in high to low prevalence areas.

Limitations

Our study has several limitations. Its scope was limited to the reliability and reproducibility of the five variables predictive of culture-positive PTB, and we focused on adult patients in the ED. While the validation phase showed good results at our ED, the prediction model was not tested in other areas. Other areas such as those with a different prevalence of TB or AIDS may also have patients with different demographic and clinical characteristics to which this model may not be applicable. There were some differences in the range of scores between the derivation and validation groups. However, this difference didn’t affect the results of the prediction model, and the sensitivity and specificity were high in the two phases implying that the results are reproducible in our hospital and in other regional hospitals. There are a number of potential sources of bias in this study. However, we have attempted to reduce the sources of bias in a number of ways [41]. 1) The observer (radiologist) was not aware of the culture results. 2) The observer was not aware of the clinical manifestations. 3) Discrepancies were resolved by consensus. 4) Multiple logistic regression analysis was used to obtain the β values. 5) The number of patients was large. 6) The results of the derivation phase are valid and generalizable to the target population (high post-test probability in the validation phase). 7) The kappa values for inter-observer and intra-observer reliability were >0.9, indicating excellent reliability. Finally, combined disease was a limitation of this study and needs further investigation.

Conclusions

Our prediction model using HRCT, which is feasible to perform in the ED, can promptly diagnose culture-positive PTB in moderate and moderate-to-low prevalence areas.

Supporting Information

File S1 Supplementary tables (Tables S1–S4). (DOC)

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Author Contributions

Conceived and designed the experiments: J-JY M-TW. Performed the experiments: J-JY C-AN C-RC. Analyzed the data: J-JY M-TW. Contributed reagents/materials/analysis tools: J-JY C-AN. Wrote the paper: J-JY C-AN C-RC TY TC M-TW.

References


