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.

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 superior segment 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, positivity 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, 92.2% 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.

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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.
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. 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

Figure 1. Flowchart of study design.
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contraindications for HRCT of the lungs. Patients with lesions such as pneumothorax (indicated by CXR), rib fractures (indicated by CXR), mediastinal disease, cardiovascular diseases (diagnosed by echocardiography), esophageal lesions (diagnosed by panendoscopy), pleural effusion (diagnosed by chest sonography), and those <18 years of age (to reduce radiation exposure) were 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 June 2008 to November 2009. The records of 5,005 patients who were older than 18 years with suspicious pulmonary lesions seen in the ED were retrospectively reviewed [15,20,21]. The diagnosis of culture-positive PTB, inactive PTB [22], and non-tuberculosis mycobacterium (NTM) infection [23] were based on culture; diagnosis of pneumonia was based on previous study [24]. The diagnoses of chronic pulmonary diseases were based on pulmonary function tests (PFTs) and clinical history, diagnosis of congestive heart failure was based on echocardiography and clinical history, diagnosis of collagen vascular disease was based on serum titers and pathology, and diagnosis of lung cancer, lymphoma, or metastatic cancer was based on pathology and clinical history [25].

Of the 5,005 patients, 4,195 received HRCT imaging. The 800 patients who did not receive HRCT had a minimal pneumothorax or pleural disease (n = 205), rib fractures (n = 183), cardiac vascular disease (n = 210), and esophageal lesions (n = 200) diagnosed based on chest x-ray, echocardiography, chest sonography, and panendoscopy. These patients did not have culture-positive PTB. In addition, consent had not been received from 10 patients, five patients with AIDS were excluded, and 50 patients did not have a definite diagnosis or were lost to follow-up. Thus, the derivation groups consisted of a total of 4,140 patients.

Validation Phase

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.

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 multidetector 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 evaluated 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 predictors of culture-positive PTB in a stepwise logistic regression analysis by considering CT findings that included CT morphology, 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, in which variables with P ≤ 0.1 were entered into the multivariate models [5]. Then we used a backward elimination process and maintained variables with P < 0.001 to derive an index based on a scoring system [28]. The scoring system weighted each variable based on the β-coefficient from the logistic regression analysis. Analysis of the ROC curve found an advantage to using logistic regression weights, so those were used for the scores predicting culture-positive PTB based on the first phase of the study (Fig. 2). We calculated the culture-positive PTB score for each subject by summing the component variables, and we determined a cutoff value (C value) from the prediction model. The second phase of the study validated the ability of the model to predict culture-positive PTB.

Care Protocol and Measurements. During the validation phase, we reviewed chest radiographs and HRCT scans of patients, along with their charts for previous PTB, diabetes mellitus, steroid usage, gastrectomy, anemia, and liver cirrhosis. For all cases in the culture-positive PTB groups, we determined if the emergency physician had ordered respiratory isolation and if the diagnosis was confirmed by the results of sputum or other specimens after invasive procedure such as bronchoscopy, pleural biopsy, or surgical intervention. We did not use a standardized guideline for respiratory isolation upon admission during the first phase of the study. During the second phase of the study, patients were admitted to a respiratory isolation setting if their score was over 1 based on the ROC curve. In the validation phase, if the score was >1 upon reading the HRCT, the radiologist notified the attending physician and patient was placed in respiratory isolation.

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
($\beta$) 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
$\beta$ value as a base (here, the $\beta$ 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
($\beta$/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 ($\beta$ 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
(2611 male/1397 female) were considered to have other pulmo-
nary 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 $\beta$ 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 $\beta$ 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.
Table 1. Demographic and clinical characteristics of the subjects in derivation phase and validation phase.

| Variables                                      | Derivation Phase (n = 4,140) | Validation Phase (n = 4,105) |
|------------------------------------------------|------------------------------|------------------------------|
| Age, y                                         | G1 (n = 132)                 | G2 (n = 4,008)               | G3 (n = 147)                 | G4 (n = 3,958)               | P    |
| Sex, males                                     | 66.6±10.8                    | 67.1±9.2                    | 67.7±10.2                    | 66.9±8.2                    | 0.573 |
| Anemia (<11 g/dL)                              | 87 (65.9)                    | 261 (65.1)                  | 98 (66.7)                    | 258 (65.3)                  | 0.856 |
| Diabetes mellitus                              | 51 (38.6)                    | 1338 (33.4)                 | 53 (36.1)                    | 1305 (33.0)                 | 0.209 |
| Gastroctomy                                    | 15 (11.4)                    | 357 (8.9)                   | 16 (10.9)                    | 355 (9.0)                   | 0.332 |
| Alcoholism                                      | 14 (10.6)                    | 318 (7.9)                   | 15 (10.2)                    | 315 (8.0)                   | 0.266 |
| Smear-negative, culture positive               | 108 (81.8)                   | 0 (0)                       | <0.001*                      | 100 (68.0)                  | 0 (0) | <0.001* |
| Smear-negative, culture positive               | 24 (18.2)                    | 0 (0)                       | <0.001*                      | 47 (32.0)                   | 0 (0) | <0.001* |
| Bacterial infection (blood culture/effusion/  | 0 (0)                        | 2786 (69.5)                 | 1 (0.7)*                      | 2829 (71.5)                 | <0.001* |
| sputum)                                        |                              |                             |                               |                             |      |
| Mycoplasma infection (elevated titer)          | 0 (0)                        | 261 (6.5)                   | <0.001*                      | 0 (0)                       | 256 (6.5) | <0.001* |
| Viral infection (elevated titer or pathology)  | 0 (0)                        | 1 (0)                       | 1.000                        | 0 (0)                       | 101 (2.5) | <0.001* |
| Non-tuberculosis mycobacterial infection       | 0 (0)                        | 136 (3.4)                   | 0.022                        | 0 (0)                       | 101 (2.5) | <0.001* |
| (culture)                                      |                              |                             |                               |                             |      |
| Fungus (pathology)                             | 0 (0)                        | 4 (0.1)                     | 1.000                        | 0 (0)                       | 3 (0.1) | 1.000 |
| Congestive heart failure                       | 0 (0)                        | 25 (0.6)                    | 1.000                        | 0 (0)                       | 19 (0.5) | 1.000 |
| Chronic bronchitis                             | 0 (0)                        | 325 (8.1)                   | <0.001*                      | 0 (0)                       | 337 (8.5) | <0.001* |
| Collagen vascular disease                      | 0 (0)                        | 20 (0.5)                    | 1.000                        | 0 (0)                       | 17 (0.4) | 1.000 |
| Lung cancer/lymphoma/metastatic cancer to lung | 0 (0)                        | 450 (11.3)                  | <0.001*                      | 1 (0.7)*                     | 396 (10.0) | <0.001* |

Symptoms and signs

| Symptoms and signs                             | Derivation Phase (n = 4,140) | Validation Phase (n = 4,105) |
|------------------------------------------------|------------------------------|------------------------------|
| Fever                                          | 53 (40.2)                    | 1342 (33.5)                  | 60 (40.7)                    | 1858 (46.9)                 | 0.111 |
| Weight loss                                    | 51 (38.6)                    | 1339 (33.4)                  | 59 (40.1)                    | 1619 (40.9)                 | 0.211 |
| Cough                                          | 50 (37.8)                    | 1338 (33.4)                  | 87 (59.2)                    | 2601 (65.7)                 | 0.337 |
| Weakness                                       | 56 (42.4)                    | 1579 (39.4)                  | 61 (41.5)                    | 1616 (40.8)                 | 0.484 |

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.

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

**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 other pulmonary diseases without culture-positive PTB).

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99.3%, 99.7% vs. 99.9%, 92.2% vs. 98.6%, and 99.9% vs. 99.9% s, 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+8, 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+8, 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+8, s9, s10), and cluster nodules/mass (positive in s1, s2, s1+s2). Example combinations are (0, 0, 0, 0, 0), (1, 2, −3, 0, 0), (0, 0, −3, 3, 0), and (0, 0, −3, 0, 3). Thus, a patient with a total score of 0 (0+0+(−3)+0+3) may have negative cavitation s1, s2, s1+s2, consolidation s1, s2, s1+s2, and cluster nodules/mass s1, s2, s1+s2, but positive consolidation s7, s8, s7+8, 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 out of 4140 patients with previous PTB (19 with culture-positive PTB and 614 with other pulmonary diseases), revealed that the relative score was similar to the total patients in the derivation phase (Table S4 in File S1).
Table 2. High-resolution computed tomography findings of subjects in the derivation phase and validation phase.

| Variables                                      | Derivation Phase (n = 4,140) | Validation Phase (n = 4,105) |
|------------------------------------------------|------------------------------|------------------------------|
|                                                 | G1 (n = 132) | G2 (n = 4,008) | P       | G3 (n = 147) | G4 (n = 3,958) | P       |
| Consolidation                                   |                |                |        |                |                |        |
| s1, s2, s1+s2                                   | 102 (77.3)     | 305 (7.6)      | <0.001* | 104 (70.7)     | 317 (8.0)      | <0.001* |
| s3, s4, s5                                      | 20 (15.2)      | 289 (7.2)      | 0.002*  | 15 (10.2)      | 296 (7.5)      | 0.220   |
| s6                                              | 66 (50)        | 65 (1.6)       | <0.001* | 70 (47.6)      | 64 (1.6)       | <0.001* |
| s7, s8, s7+s8, s9, s10                          | 11 (8.3)       | 1356 (33.8)    | <0.001* | 13 (8.8)       | 1342 (33.9)    | <0.001* |
| Cavitation                                      |                |                |        |                |                |        |
| s1, s2, s1+s2                                   | 81 (61.4)      | 34 (0.8)       | <0.001* | 72 (49.0)      | 10 (0.3)       | <0.001* |
| s3, s4, s5                                      | 8 (6.1)        | 88 (2.2)       | 0.004*  | 7 (4.8)        | 64 (1.6)       | 0.004*  |
| s6                                              | 36 (27.3)      | 98 (2.4)       | <0.001* | 32 (21.8)      | 72 (1.8)       | <0.001* |
| s7, s8, s7+s8, s9, s10                          | 8 (6.1)        | 88 (2.2)       | 0.004*  | 5 (3.4)        | 149 (3.8)      | 0.820   |
| Clusters of nodules                             |                |                |        |                |                |        |
| s1, s2, s1+s2                                   | 102 (77.3)     | 6 (0.1)        | <0.001* | 97 (66.0)      | 0 (0)          | <0.001* |
| s3, s4, s5                                      | 17 (12.9)      | 2 (0.05)       | <0.001* | 11 (7.5)       | 0 (0)          | <0.001* |
| s6                                              | 26 (19.7)      | 4 (0.1)        | <0.001* | 23 (15.6)      | 3 (0.1)        | <0.001* |
| s7, s8, s7+s8, s9, s10                          | 23 (17.4)      | 2 (0.05)       | <0.001* | 22 (14.9)      | 0 (0)          | <0.001* |
| Interlobular septal thickening                  | 93 (70.5)      | 2231 (55.7)    | 0.011*  | 89 (60.5)      | 2215 (56.0)    | 0.272   |
| Bronchial wall thickening                       | 103 (78.0)     | 2647 (60.0)    | 0.004*  | 106 (72.1)     | 2604 (65.8)    | 0.112   |
| Ground-glass-opacity                            | 109 (82.6)     | 2757 (68.8)    | 0.001*  | 111 (75.5)     | 2710 (68.5)    | 0.071   |
| Centrilobular nodules with tree-in-bud           | 87 (65.9)      | 1397 (34.9)    | <0.001* | 94 (63.9)      | 1344 (34.0)    | <0.001* |
| Paratracheal adenopathy                         | 66 (50.0)      | 1459 (36.4)    | 0.001*  | 61 (41.5)      | 1437 (36.3)    | 0.199   |
| Fibrosis                                        | 22 (16.7)      | 1202 (30.0)    | 0.001*  | 34 (23.1)      | 1196 (30.2)    | 0.065   |
| Parenchymal Calcification                       | 12 (9.1)       | 754 (18.8)     | 0.005*  | 24 (16.3)      | 750 (18.9)     | 0.425   |

Table 3. Multivariate logistic regression analysis in derivation phase (N = 4,140).

| Variables                        | Estimated β (Std. Err.) | Estimated Odds Ratio (95% CI) | P       | Relative Score |
|----------------------------------|------------------------|-------------------------------|---------|----------------|
| Cavitation                       | 5.060 (1.434)          | 157.6 (9.5, 2619.1)          | <0.001* | 1.5 and 3.7    |
| Consolidation                    | 5.944 (1.487)          | 381.3 (20.7, 7037.9)         | <0.001* | 2               |
| Consolidation s7, s8, s7+s8, s9, s10 | −7.588 (1.529)     | 0.001 (0.001)                | <0.001* | −3              |
| Clusters nodules/mass s1, s2, s1+s2 | 9.669 (1.492)          | 15826.1 (964.1, 2597862.2)   | <0.001* | 3               |
| Consolidation s6                 | 11.728 (1.777)         | 123962.7 (3810.4, 4032857.2) | <0.001* | 3               |

Table 5 summarizes the post-test probability according to the given prevalence and predicted 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

References:
1. [1] Estimated/ (Std. Err.)
2. [2] Estimated Odds Ratio (95% CI)
3. [3] P
4. [4] Relative Score
5. [5] Indicates statistical significance, P<0.05.
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 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. |
|---------------------------------------------------------------|
| **Predictive results from HRCT model**                        |
| **Derived phase**                                             |
| **Culture-positive PTB (n = 132)**                            |
| **Other pulmonary diseases (n = 4,008)**                      |
| Predicted culture-positive PTB                                |
| 130                                                           |
| 11                                                            |
| Predicted absence of PTB                                      |
| 2                                                             |
| 3997                                                          |
| **Validation phase**                                          |
| **Culture-positive PTB (n = 147)**                            |
| **Other pulmonary diseases (n = 3,958)**                      |
| Predicted culture-positive PTB                                |
| 146                                                           |
| 2                                                             |
| Predicted absence of PTB                                      |
| 1                                                             |
| 3956                                                          |
| **Predictive terms**                                          |
| **Sensitivity**                                               |
| 130/132 (98.5%)                                               |
| 146/147 (99.3%)                                               |
| **Specificity**                                               |
| 3997/4008 (99.7%)                                             |
| 3956/3958 (99.9%)                                             |
| **False negative rate**                                      |
| 2/132 (15%)                                                  |
| 1/147 (0.7%)                                                 |
| **False positive rate**                                      |
| 11/4008 (0.3%)                                               |
| 2/3958 (0.1%)                                                |
| **Positive predictive value**                                |
| 130/141 (92.2%)                                              |
| 146/148 (98.6%)                                              |
| **Negative predictive value**                                |
| 3997/3999 (99.9%)                                            |
| 3956/3957 (99.9%)                                            |

*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.

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

| Prevalence of culture-positive PTB | Prediction Score | Pre-test odds | LR+ | Post-test odds | Post-test probability |
|-----------------------------------|-----------------|---------------|-----|---------------|-----------------------|
| Study population in derivation phase | 3.2%*          | 1             | 0.033 | 328.33       | 10.82                 | 91.5%                |
| Study population in validation phase | 3.6%*          | 1             | 0.037 | 328.33       | 12.26                 | 92.5%                |
| High prevalence                    | 5.0%            | 1             | 0.053 | 328.33       | 17.28                 | 94.5%                |
| Moderate prevalence                | 3.0%            | 1             | 0.031 | 328.33       | 10.15                 | 91.0%                |
| Moderate-to-low prevalence         | 1.0%            | 1             | 0.010 | 328.33       | 3.32                  | 76.8%                |

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.

*The prevalence was calculated based on the culture-positive PTB probability in the derivation phase (132/4140).

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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. with the high frequency of bacterial pneumonia in the lower lobe and s10 was a negative factor in our model. This is in accordance with the high frequency of bacterial pneumonia in the lower lobe and s10 was a negative factor in our model. This is in accordance with the high frequency of bacterial pneumonia in the lower lobe.

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.

**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 C-AN. Contributed reagents/materials/analysis tools: J-JY C-AN C-RC. Wrote the paper: J-JY C-AN C-RC CT TC M-TW.

**References**

1. Michele TM, Cronin WA, Graham NM, Dwyer DM, Pope DS, et al. (1997) Transmission of Mycobacterium tuberculosis by a fiberoptic bronchoscope. Identification by DNA fingerprinting. JAMA 278: 1093–1095.

2. Mathar F, Sacks I, Auten G, Sall R, Levy C, et al. (1994) Delayed diagnosis of pulmonary tuberculosis in city hospitals. Arch Intern Med 154: 306–310.

3. Moran GJ, McCabe F, Morgan MT, Talan DA (1995) Delayed recognition and infection control for tuberculosis patients in the emergency department. Ann Emerg Med 26: 280–289.

4. Moran GJ, Talan DA, Abrahamian FM (2000) Diagnosis and management of pneumonia in the emergency department. Infect Dis Clin North Am 22: 53–72, vi.

5. Kanaya AM, Gilchrist DV, Chambers HF (2001) Identifying pulmonary tuberculosis in patients with negative sputum smear results. Chest 120: 349–355.

6. Pinto LM, Dheda K, Theron G, Allwood B, Calligaro G, et al. (2013) Development of a simple reliable radiographic scoring system to aid the diagnosis of pulmonary tuberculosis. PLoS ONE 8: e54235.

7. Elcker L, Peirota CA, Webb R, Leslie KO (2000) High-resolution computed tomography patterns of diffuse interstitial lung disease with clinical and pathological correlation. J Bras Pneumol 34: 715–744.

8. Yeh JJ, Chen SC, Teng WB, Chou CH, Hsieh SP, et al. (2010) Identifying the most infectious lesions in pulmonary tuberculosis by high-resolution multidetector computed tomography. Eur Radiol 20: 2133–2145.

9. Yeh JJ, Yu JK, Teng WB, Chou CH, Hsieh SF, et al. (2012) High-resolution CT for identify patients with smear-positive, active pulmonary tuberculosis. Eur J Radiol 81: 195–201.

10. Kowada A (2013) Cost effectiveness of high resolution computed tomography with interferon-gamma release assay for tuberculosis contact investigation. Eur J Radiol 82: 1353–1358.

11. Agoritsas T, Courvoisier DS, Combescure C, Deom M, Perneger TV (2011) Disease? A randomized trial. J Gen Intern Med 26: 373–378.

12. Paulo S, Mendes S, Vizinho R, Carneiro AV (2004) Diagnostic testing, pre- and post-test probabilities and their use in clinical practice. Rev Port Cardiol 23: 1187–1196.

13. Alkember AK (2007) Understanding diagnostic tests 2: likelihood ratios, pre- and post-test probabilities and their use in clinical practice. Acta Paediatr 96: 407–411.

14. Arroll B, Allan GM, Elley CR, Kenacly T, McCormack J, et al. (2012) Diagnosis in primary care: probabilistic reasoning. J Prim Health Care 4: 166–173.
Corcoran HL, Renner WR, Milstein MJ (1992) Review of high-resolution CT of the lung. Radiographics 12: 917–939; discussion 940–911.

Padley S, Gleson F, Flower CD (1995) Review article: current indications for high resolution computed tomography scanning of the lungs. Br J Radiol 68: 105–109.

Hauser M, Russi EW, Marinecek B (1996) [High-resolution computerized tomography of the lungs: bases, findings, indications]. Schweiz Med Wochenschr 126: 398–408.

Heitkamp DE, Mohammed TL, Kirsch J, Amorosa JK, Brown K, et al. (2012) ACR appropriateness criteria (R) acute respiratory illness in immunocompromised patients. J Am Coll Radiol 9: 164–169.

Kirsch J, Ramirez J, Mohammed TL, Amorosa JK, Brown K, et al. (2011) ACR Appropriateness Criteria (R) acute respiratory illness in immunocompetent patients. J Thorac Imaging 26: W42–W44.

Primack SL, Muller NL (1994) High-resolution computed tomography in acute diffuse lung disease in the immunocompromised patient. Radiol Clin North Am 32: 731–744.

Worthy S, Kang EY, Muller NL (1995) Acute lung disease in the immunocompromised host: differential diagnosis at high-resolution CT. Semin Ultrasound CT MR 16: 353–360.

WHO (1994) WHO tuberculosis programme-Framework for effective tuberculosis control. In. Geneva, Switzerland.

Thomson RM, Yeow WW (2009) When and how to treat pulmonary non-tuberculous mycobacterial diseases. Respiratory 14: 12–26.

Lim WS, Macfarlane JT, Bowell TC, Harrison TG, Rose D, et al. (2001) Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax 56: 296–301.

Nakanishi M, Demura Y, Ameshima S, Kosaka N, Chiba Y, et al. (2010) Utility of high-resolution computed tomography for predicting risk of sputum smear-negative pulmonary tuberculosis. Eur J Radiol 73: 545–550.

Hansell DM, Bankier AA, MacMahon H, McLeod TC, Muller NL, et al. (2008) Fleischner Society: glossary of terms for thoracic imaging. Radiology 246: 697–722.

Nishino M, Itoh H, Hatabu H (2013) A practical approach to high-resolution CT of diffuse lung disease. Eur J Radiol.

Wang JH, Pappas D, De Jager PL, Pelletier D, de Bakker PI, et al. (2011) Modeling the cumulative genetic risk for multiple sclerosis from genome-wide association data. Genome Med 3: 3.

Verbakel JV, Van den Bruel A, Thompson M, Stevens R, Aertsgeert B, et al. (2013) How well do clinical prediction rules perform in identifying serious infections in acutely ill children across an international network of ambulatory care datasets? BMC Med 11: 10.

Piatek AS, van Cleef M, Alexander H, Coggins WL, Rehr M, et al. (2013) GeneXpert for TB diagnosis: planned and purposeful implementation. Global Health: Science and Practice 1:18–23.

Shimura S (1998) Normal chest radiograph and lung function do not necessarily mean normal lungs. Intern Med 37: 901–902.

Wisniwsky JP, Hanschke C, Balemire J, Wilner G, Deloire AM, et al. (2005) Prospective validation of a prediction model for isolating inpatients with suspected pulmonary tuberculosis. Arch Intern Med 165: 453–457.

El-Soll A, Mylotte J, Sheerif S, Serghani J, Grant BJ (1997) Validity of a decision tree for predicting active pulmonary tuberculosis. Am J Respir Crit Care Med 155: 1711–1716.

Mayo JR, Aldrich J, Muller NL (2003) Radiation exposure at chest CT: a statement of the Fleischner Society. Radiology 228: 15–21.

Lee KS, Hwang JW, Chung MP, Kim H, Kwon CJ (1996) Utility of CT in the evaluation of pulmonary tuberculosis in patients without AIDS. Chest 110: 977–984.

Poey C, Verhaegen F, Giron J, Lavaysiere J, Fajadet P, et al. (1997) High resolution chest CT in tuberculosis: evolutive patterns and signs of activity. J Comput Assist Tomogr 21: 601–607.

Coelho LO, Gaspareto TD, Escuissato DL, Marchiori E (2009) Bacterial pneumonia following bone marrow transplantation: HRCT findings. J Bras Pneumol 35: 431–435.

Ikazoe J, Takeuchi N, Jokoh T, Kohno N, Tomiyama N, et al. (1992) CT appearance of pulmonary tuberculosis in diabetic and immunocompromised patients: comparison with patients who had no underlying disease. AJR Am J Roentgenol 159: 1175–1179.

Moran GJ, Barrett TW, Mower WR, Krishnadasan A, Abrahamian FM, et al. (2009) Decision instrument for the isolation of pneumonia patients with suspected pulmonary tuberculosis admitted through US emergency departments. Ann Emerg Med 53: 625–632.

Davidson M (2002) The interpretation of diagnostic test: a primer for physiotherapists. Aust J Physiother 48: 227–232.

Sica GT (2006) Bias in research studies. Radiology 238: 780–789.