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Artificial intelligence-reported chest X-ray findings of culture-confirmed pulmonary tuberculosis in people with and without diabetes

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ABSTRACT

Objectives: We applied computer-aided detection (CAD) software for chest X-ray (CXR) analysis to determine if diabetes affects the radiographic presentation of tuberculosis.
Methods: From March 2017-July 2018, we consecutively enrolled adults being evaluated for pulmonary tuberculosis in Karachi, Pakistan. Participants had same-day CXR, two sputum mycobacterial cultures, and random blood glucose measurement. We identified diabetes through self-report or glucose >11.1mMol/L. We included participants with culture-confirmed tuberculosis for this analysis. We used linear regression to estimate associations between CAD-reported tuberculosis abnormality score (range 0.00 to 1.00) and diabetes, adjusting for age, body mass index, sputum smear-status, and prior tuberculosis. We also compared radiographic abnormalities between participants with and without diabetes.
Results: 63/272 (23%) of included participants had diabetes. After adjustment, diabetes was associated with higher CAD tuberculosis abnormality scores ($p < 0.001$). Diabetes was not associated with frequency of CAD-reported radiographic abnormalities apart from cavitary disease; participants with diabetes were more likely to have cavitary disease (74.6% vs 61.2% $p = 0.07$), particularly non-upper zone cavitary disease (17% vs 7.8%, $p = 0.09$).
Conclusions: CAD analysis of CXR suggests diabetes is associated with more extensive radiographic abnormalities and with greater likelihood of cavities outside upper lung zones.

1. Introduction

Diabetes mellitus is a substantial risk factor for active tuberculosis [1] of increasing epidemiologic importance. A *meta*-analysis pooling data of 2.3 million people with active tuberculosis estimated a diabetes prevalence of 15.3% at diagnosis [2], and it is projected that worldwide diabetes prevalence will increase from 463 million to 578 million by 2030 [3]. Diabetes is believed to modulate tuberculosis risk by affecting immune responses, hence it is plausible that diabetes may affect the clinical presentation of tuberculosis [4]. Increased prevalence of lower lung lesions has been observed in the radiographic presentation of tuberculosis for individuals with diabetes compared to those without diabetes [5], along with increased cavitation [6]. However, other studies have not found differences in the radiographic appearance of tuberculosis in association with diabetes [7]. Artificial intelligence-based radiographic analysis, often referred to as computer-aided detection (CAD), offers a new tool for addressing this uncertainty. CAD-based chest X-ray (CXR) analysis will be increasingly used in tuberculosis diagnostic pathways following the technology's approval by the World Health Organization in 2021 [8].

In the present report, using data from a study undertaken to estimate the diagnostic accuracy of CAD for detecting culture-confirmed

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pulmonary tuberculosis, we assess whether diabetes status was associated with the radiographic presentation of tuberculosis as reported by CAD. While we previously found that diabetes was not associated with sensitivity or specificity of two commercially-available deep learning-based CAD in this dataset, our prior work did not assess for associations between diabetes and type and distribution of particular radiographic findings as reported by CAD [9].

2. Methods

In the original study, between March 10, 2017 and July 13, 2018, we consecutively enrolled individuals 15 years and older presenting with symptoms of tuberculosis, or identified as household contacts exposed to tuberculosis, at the Ghori TB Clinic of the Indus Hospital in Karachi, Pakistan [9]. Participants completed a standardized questionnaire, submitted three sputa (one for nucleic acid amplification test per routine standard of care at the clinic, and two for smear microscopy and mycobacterial cultures as part of the research protocol), and underwent digital CXR, height and weight measurements, and a random glucose test. We excluded individuals within one year of completion of active tuberculosis treatment. Pulmonary tuberculosis was confirmed if at least one of two liquid cultures was positive for *Mycobacterium tuberculosis*, and excluded if both cultures were negative at 6 weeks of incubation. For the present analysis, we included all individuals with culture-confirmed pulmonary tuberculosis. Individuals were classified as having diabetes if they self-reported diabetes, or if they had a random blood glucose >11.1 mMol/L (200 mg/dL). The institutional review boards of Interactive Research and Development and the Research Institute of the McGill University Health Centre approved the study. Informed consent was obtained from all participants and included consent for future use of data in other studies.

For this report, we analyzed CXR with a commercially-available deep learning-based CAD software, qXR version 3.0 (qure.ai, India). For each type of radiographic abnormality reported (e.g. nodule, consolidation, etc.), qXR outputs abnormality scores on a 100-point scale (0.00 to 1.00, higher scores indicate greater abnormality) and also provides a binary classification indicating if the abnormality has been detected. The radiologic abnormalities reported include cardiomegaly, consolidation, fibrosis, nodule, pleural effusion, costophrenic angle, cavity, emphysema, opacity, and hilar enlargement. For cavity, consolidation, fibrosis, nodule, and opacity qXR provides the anatomical location — upper, middle, or lower zone, and left or right. All involved zones are reported. qXR also outputs a tuberculosis abnormality score and a binary classification of the CXR as compatible with tuberculosis or not.

To determine if diabetes was associated with results of CAD analysis amongst participants with tuberculosis, we first compared the median tuberculosis abnormality scores between participants with and without diabetes using the Wilcoxon Rank Sum test. To account for potential confounding of associations between diabetes and CAD tuberculosis abnormality scores by other covariates, we used multivariable linear regression to estimate the average difference in CAD score associated with diabetes, while adjusting for age, sex, prior tuberculosis, body mass index (BMI), and sputum smear status (acid fast bacilli positive vs negative). These covariates were selected for inclusion in the regression model, as age, sex, prior tuberculosis, BMI, and smear status are all known factors that could be associated with both diabetes and CXR analysis for tuberculosis detection [10]. We used a logit-transformation to model CAD tuberculosis abnormality scores, since modeling the continuous CAD score violated the assumptions of linear regression. Interpreting an association on the logit-transformed CAD score is nonintuitive, hence we back-transformed results to provide estimates of the association between diabetes and CAD score, for which we applied the delta method to estimate 95% confidence intervals [11]. For these interpretable estimates, we had to assume values for each covariate in the model; because of the importance of having data for both females and males, we calculated sex-specific estimates assuming sex-specific average age and BMI, and no prior tuberculosis. Because prior studies have shown that smear status significantly affects sensitivity of CAD thresholds, we further stratified the back-transformed estimates by smear [9,10]. Next, we compared the prevalence of the individual abnormalities (e.g. nodule) between participants with and without diabetes using Fisher's Exact test. Finally, we assessed for associations between diabetes and location of radiographic abnormalities. For each abnormality, we compared proportion of radiographs with lower, versus mid, versus upper, versus lower and mid, versus upper and mid, versus lower and upper, versus all zones. We also compared the proportion of participants without any upper zone involvement, as the upper lung fields are the classic location for tuberculosis. To determine if there was a propensity for laterality, we compared proportions with right, versus left, versus bilateral disease. As a post-hoc exploratory analysis to assess for potential differences amongst those newly diagnosed with diabetes, we compared the CAD results for participants diagnosed with diabetes at enrollment versus those self-reporting a prior diagnosis. We interpreted p-values less than 0.05 as statistically significant. Adjustments for multiple comparisons were not performed. All analyses were performed using R version 4.0.2 [12].

3. Results

We included 272 participants with culture-confirmed pulmonary tuberculosis. The median age (interquartile range, IQR) was 29 (22, 45), and 48% (n = 130) were female. Of the 272 participants, 23% (n = 63) were classified as having diabetes, 22% (n = 14) by self-report alone and 78% (n = 49) by elevated random glucose measurement. Those with diabetes were older (48 vs 25, $p < 0.0001$), had higher BMI (21.4 vs 17.3, $p < 0.0001$), were less likely to previously had tuberculosis (4.8% vs 15.8%, $p = 0.02$), and were more likely to self-report fever (96.8% vs 87.4%, $p = 0.03$) at time of enrollment (Table 1). There were no significant differences between those with and without diabetes who reported a cough, night sweats, weight loss, hemoptysis, or as a household contact for someone with active tuberculosis. Diabetes was not associated with sex, smoking status, nor sputum smear-positivity.

The median (IQR) tuberculosis abnormality score was similar for those with and without diabetes (0.94 (0.90, 0.96) vs 0.94 (0.86, 0.97), $p = 0.46$). Table 2 provides a summary of the multivariable linear regression. After adjusting for age, sex, prior tuberculosis, BMI, and sputum smear, CAD tuberculosis abnormality scores were on average higher amongst people with diabetes compared to those without ($p <$

Table 1
Comparison of participants with and without diabetes, amongst those with culture-confirmed pulmonary tuberculosis (n = 272). All value N (%) unless otherwise specified.

Characteristic	Diabetes (N = 63)	No Diabetes (N = 209)	p-value
Age in years, median (IQR)	48 (37, 59)	25 (20, 36)	<0.0001
Female	30 (47.6)	100 (47.8)	1
Body Mass Index, median (IQR)[a]	21.4 (18.5, 25.0)	17.3 (15.6, 19.3)	<0.0001
Prior tuberculosis	3 (4.8)	33 (15.8)	0.02
Tobacco smoking	6 (9.5)	22 (10.5)	1
Cough	61 (96.8)	206 (98.6)	0.33
Fever[b]	60 (96.8)	181 (87.4)	0.03
Night sweats[c]	49 (77.8)	145 (70.0)	0.30
Weight loss[d]	58 (92.1)	193 (92.8)	0.79
Hemoptysis	22 (34.9)	55 (26.3)	0.24
Household contact of someone with active tuberculosis	16 (25.4)	78 (37.3)	0.11
Sputum smear acid fast bacilli positive	51 (81.0)	160 (76.6)	0.58

[a]One individual with diabetes and two with no diabetes had missing information. [b]One individual with diabetes and two with no diabetes had missing information. [c]Two individuals with no diabetes had missing information. [d]One individual with no diabetes had missing information.

Table 2
Multivariable linear regression model – summary of associations of participant characteristics with logit-transformed CAD tuberculosis score.

Covariate	Coefficient[a]	p-value
Age	−0.02	<0.01
Female	−0.24	0.17
Body mass index	−0.09	<0.0001
Prior tuberculosis	−0.40	0.10
Sputum smear-negative	−1.37	<0.0001
Diabetes	0.85	<0.001

[a] Note that coefficient estimates are of the effect of the covariate on the logit of the CAD score, rather than on the CAD score scale as output by the software. Applying the delta method for back-transformation, and assuming no prior tuberculosis and sex-specific average age and body mass index, the average per-unit change in CAD score associated with diabetes were: +0.04 (95% confidence interval (CI): 0.03, 0.06) and +0.04 (95% CI: 0.02, 0.05) for women and men, respectively, with smear-positive tuberculosis; and +0.12 (95% CI: 0.07, 0.17) and +0.12 (95% CI: 0.07, 0.16) for women and men, respectively, for smear-negative tuberculosis.

0.001). Assuming sex-specific average age and BMI, no prior tuberculosis, and smear-positivity, diabetes was associated with an increase in the tuberculosis abnormality score of +0.04 (95% confidence interval (CI): 0.03, 0.06) amongst women and +0.04 (95% CI: 0.02, 0.05) amongst men. For smear-negative disease, diabetes was associated with an increase of tuberculosis abnormality score of +0.12 (95% CI: 0.07, 0.17) and +0.12 (95% CI: 0.07, 0.16) for women and men, respectively.

Participants with and without diabetes had similar prevalence of blunted costophrenic angle, cardiomegaly, consolidation, emphysema, fibrosis, hilar enlargement, nodule, opacity and pleural effusion (Table 3). A greater proportion of participants with diabetes were classified as having tuberculosis (98.4% vs 91.4%, p = 0.09) and cavitary disease (74.6% vs 61.2% p = 0.07), albeit neither difference reached the threshold for statistical significance. While most cavities were situated in upper zones regardless of diabetes status, cavitary disease affecting solely the lower or mid zones was over twice as prevalent amongst people with diabetes (17% vs 7.8%, p = 0.09) (Table 3). A detailed breakdown on anatomical distribution of particular abnormalities is provided in Table 4. Apart from cavities, there was no

Table 3
Comparison of computer-aided detection analysis of chest radiographs from participants with and without diabetes, amongst those with confirmed tuberculosis only (n = 272). All value N (%).

Abnormality	Diabetes (N = 63)	No Diabetes (N = 209)	p-value
Prevalence of particular radiographic abnormalities			
Tuberculosis	62 (98.4)	191 (91.4)	0.09
Blunted costophrenic angle	1 (1.6)	5 (2.4)	1
Cardiomegaly	1 (1.6)	1 (0.5)	0.41
Cavity	47 (74.6)	128 (61.2)	0.07
Consolidation	58 (92.1)	184 (88.0)	0.49
Emphysema	10 (15.9)	41 (19.6)	0.58
Fibrosis	51 (81.0)	170 (81.3)	1
Hilar enlargement	0 (0.0)	0 (0.0)	
Nodule	55 (87.3)	175 (83.7)	0.56
Opacity	62 (98.4)	205 (98.1)	1
Pleural Effusion	6 (9.5)	29 (13.9)	0.52
Location of particular radiographic abnormalities			
Cavity			
No upper zone	8 (17.0)	10 (7.8)	0.09
Any upper zone	39 (83.0)	118 (92.2)	
Consolidation			
No upper zone	5 (8.6)	27 (14.7)	0.27
Any upper zone	53 (91.4)	157 (85.3)	
Fibrosis			
No upper zone	5 (9.8)	14 (8.2)	0.78
Any upper zone	46 (90.2)	156 (91.8)	
Nodule			
No upper zone	3 (5.5)	7 (4.0)	0.71
Any upper zone	52 (94.5)	168 (96.0)	
Opacity			
No upper zone	6 (9.7)	31 (15.1)	0.40
Any upper zone	56 (90.3)	174 (84.9)	

Table 4
Comparison of CAD-reported anatomical location of particular radiographic abnormalities between participants with and without diabetes, amongst those with culture-confirmed pulmonary tuberculosis. All value N (%).

Location of radiographic abnormalities	Diabetes (N = 63)	No Diabetes (N = 209)	p-value
Zone of radiographic abnormalities			
Cavity			
Lower	0 (0.0)	0 (0.0)	0.08
Mid	3 (6.4)	9 (7.0)	
Upper	9 (19.1)	27 (21.1)	
Lower & mid	5 (10.6)	1 (0.8)	
Upper & mid	27 (57.4)	77 (60.2)	
Lower & upper	0 (0.0)	1 (0.8)	
All	3 (6.4)	13 (10.2)	
Consolidation			
Lower			0.40
Mid	0 (0.0)	1 (0.5)	
Upper	1 (1.7)	0 (0.0)	
Lower & mid	5 (8.6)	26 (14.1)	
Upper & mid	24 (41.4)	74 (40.2)	
Lower & upper	0 (0.0)	0 (0.0)	
All	28 (48.3)	83 (45.1)	
Fibrosis			
Lower	0 (0.0)	0 (0.0)	0.71
Mid	1 (2.0)	4 (2.4)	
Upper	0 (0.0)	7 (4.1)	
Lower & mid	4 (7.8)	10 (5.9)	
Upper & mid	35 (68.6)	114 (67.1)	
Lower & upper	0 (0.0)	0 (0.0)	
All	11 (21.6)	35 (20.6)	
Nodule			
Lower	0 (0.0)	0 (0.0)	0.46
Mid	1 (1.8)	0 (0.0)	
Upper	0 (0.0)	3 (1.7)	
Lower & mid	2 (3.6)	7 (4.0)	
Upper & mid	15 (27.3)	57 (32.6)	
Lower & upper	0 (0.0)	0 (0.0)	
All	37 (67.3)	108 (61.7)	
Opacity			
Lower	0 (0.0)	3 (1.5)	0.54
Mid	1 (1.6)	3 (1.5)	
Upper	0 (0.0)	8 (3.9)	
Lower & mid	5 (8.1)	25 (12.2)	
Upper & mid	28 (45.2)	80 (39.0)	
Lower & upper	0 (0.0)	0 (0.0)	
All	28 (45.2)	86 (42.0)	
Laterality of radiographic abnormalities			
Cavity			
Left	20 (42.6)	46 (35.9)	0.27
Right	23 (48.9)	58 (45.3)	
Bilateral	4 (8.5)	24 (18.8)	
Consolidation			
Left	15 (25.9)	53 (28.8)	0.58
Right	24 (41.4)	62 (33.7)	
Bilateral	19 (32.8)	69 (37.5)	
Fibrosis			
Left	13 (25.5)	35 (20.6)	0.61
Right	16 (31.4)	49 (28.8)	
Bilateral	22 (43.1)	86 (50.6)	
Nodule			
Left	7 (12.7)	19 (10.9)	0.53
Right	13 (23.6)	32 (18.3)	
Bilateral	35 (63.6)	124 (70.9)	
Opacity			
Left	9 (14.5)	32 (15.6)	0.65
Right	17 (27.4)	44 (21.5)	
Bilateral	36 (58.1)	129 (62.9)	

association between diabetes and the zone, nor laterality of particular radiographic abnormalities (Table 4).

3.1. Exploratory analysis comparing imaging findings between newly versus previously diagnosed diabetes

Of the 63 participants with diabetes, 27% (n = 17) were newly diagnosed at enrollment and 73% (n = 46) were previously diagnosed. There was no difference in the median (IQR) tuberculosis abnormality score for participants newly diagnosed and previously diagnosed with diabetes (0.94 (0.89, 0.96) vs 0.94 (0.90, 0.97), p = 0.48). The proportion of participants classified as having tuberculosis was similar for those newly diagnosed with diabetes versus those previously diagnosed (100% vs 97.8%, p = 1). Participants newly diagnosed with diabetes had a lower prevalence of cavitary disease (52.9% vs 82.6%, p = 0.02) and nodules (70.6% vs 93.5% p = 0.03).

4. Discussion

To our knowledge, this is the first report applying deep learning-based CAD software to assess for associations between diabetes and the radiographic presentation of tuberculosis. After adjusting for potential confounding variables, we found that the tuberculosis abnormality score was on average higher amongst people with diabetes than those without diabetes. These results suggest those with diabetes had more severe pulmonary disease at presentation. An actionable interpretation of these data is that alternate CAD threshold scores will not be needed to ensure adequate sensitivity for diagnosing tuberculosis in the presence of diabetes. Diabetes was also associated with increased cavitary disease outside the upper lung zones, though cavities in upper zones were the most common location for tuberculous cavities regardless of diabetes status. Concordance of these results with studies in which humans read radiographs [5,6] further supports the World Health Organization's approval of CAD software as an alternative to human readers for interpreting CXR for tuberculosis [8], even amongst individuals with diabetes. Our work also underscores the importance of screening for tuberculosis amongst people with diabetes in high-TB burden areas.

Our study has several strengths. First, the use of CAD software provided a novel approach for addressing whether diabetes is associated with the radiographic presentation of tuberculosis. CAD allowed for a quantitative continuous measure of disease severity that could not be done using human readers, and which permitted adjustment for potential confounders. Another advantage of using CAD is that it provides an objective reading and eliminates within and between reader variability that is well-known to occur with human readers and that limits generalizability and reproducibility of studies based on human reading. Our study also includes a high participation rate, completeness of data, use of sputum induction, and liquid culture as the reference standard for pulmonary tuberculosis, reducing selection bias and misclassification bias [9].

Some limitations should be considered. This was a single-centre study, limiting the generalizability of our results. Second, we were unable to assess if duration or type of diabetes, glycemic control, or the use of medication for diabetes would further modify the association. In addition, although we adjusted for potential confounders, there is a possibility that residual confounding remains. Lastly, we only reported on results from one CAD software.

In summary, we gained new insights into associations between diabetes and the radiographic presentation of culture-confirmed pulmonary tuberculosis through the novel application of deep learning-based CAD software for CXR analysis. CAD analysis suggests that diabetes is independently associated with more extensive radiographic abnormalities at tuberculosis presentation, particularly cavitary disease, and also increases the likelihood that cavities will be found outside the upper lung zones. There is a need to determine if these associations are modified by glycemic control and duration of diabetes, and also if they can be replicated in other populations, in particular amongst people living with HIV.

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Consent

The institutional review boards of Interactive Research and Development and the Research Institute of the McGill University Health Centre approved the study. Informed consent was obtained from all participants.

CRediT authorship contribution statement

Coralie Geric: Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Arman Majidulla:** Data curation, Writing – review & editing. **Gamuchirai Tavaziva:** Formal analysis, Writing – review & editing. **Ahsana Nazish:** Data curation, Writing – review & editing. **Saima Saeed:** Data curation, Writing – review & editing. **Andrea Benedetti:** Methodology, Formal analysis, Writing – review & editing. **Aamir J. Khan:** Conceptualization. **Faiz Ahmad Khan:** Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CG, AM, GT, AN, SS, and AB have no potential conflicts of interest to disclose. Aamir J. Khan has had financial interests in the company Alcela, of which qure.ai is a client, and has provided technical assistance to quire.ai data scientists on the development of an all-in-artificial intelligence algorithm for mass CXR screening in public health programs. Consulting started in Q4 2019 and ended in Q2 2020. Solution was not finalized, and the planned product was not made commercially available. Aamir J. Khan had helped conceive and design the included study from Pakistan in 2016 to 2017, but was never directly involved in data collection, analysis or reporting of that study and his relationship with Alcela arose after the completion of data collection for that study. Aamir J. Khan was not involved in the design, analysis, reporting, writing, editing, or decision to submit the work reported in the present manuscript. As Principal Investigator, Faiz Ahmad Khan received the grant from the Canadian Institutes of Health Research (CIHR) to undertake the original study of CAD diagnostic accuracy in Pakistan whose data are analyzed for the present work. The present work is partially funded by a peer-reviewed grant from l'Observatoire International sur les Impacts Sociétaux de l'IA et du Numérique, which is a publicly funded observatory of the Fonds de Recherche du Quebec, which itself is the provincial research funding agency in the province of Quebec. FAK currently holds a grant from CIHR to study CAD in Canada. FAK also reports salary support from the Fonds de Recherche du Quebec Santé. Qure.ai (India) the developer and owner of qXR, the software evaluated

in this study, provide our lab with free access to their software. They have no access to data, and no role in collection, analysis and interpretation of data; nor in the writing of reports; nor in the decision to submit work for publication. Delft (Netherlands) the developer and owner of CAD4TB, provide ou rlab with reduced research pricing access to their software. They have no access to data, and no role in collection, analysis and interpretation of data; nor in the writing of reports; nor in the decision to submit work for publication.

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References

[1] Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med* 2008;5:e152. doi: 10.1371/journal.pmed.0050152.

[2] Noubiap JJ, Nansseu JR, Nyaga UF, Nkeck JR, Endomba FT, Kaze AD, Agbor VN, Bigna JJ. Global prevalence of diabetes in active tuberculosis: a systematic review and meta-analysis of data from 2·3 million patients with tuberculosis. *Lancet Glob Health* 2019;7:e448-e460. doi: 10.1016/s2214-109x(18)30487-x.

[3] Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract 2019;157:107843. https://doi.org/10.1016/j.diabres.2019.107843.

[4] Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis 2009;9:737–46. https://doi.org/10.1016/s1473-3099(09)70282-8.

[5] Patel AK, Rami KC, Ghanchi FD. Radiological presentation of patients of pulmonary tuberculosis with diabetes mellitus. Lung India 2011;28:70. https://doi.org/10.4103/0970-2113.76308.

[6] Perez-Guzman C, Torres-Cruz A, Villarreal-Velarde H, Vargas MH. Progressive age-related changes in pulmonary tuberculosis images and the effect of diabetes. Am J Respir Crit Care Med 2000;162:1738–40. https://doi.org/10.1164/ajrccm.162.5.2001040.

[7] Ruslami R, Aarnoutse RE, Alisjahbana B, van der Ven AJ, van Crevel R. Implications of the global increase of diabetes for tuberculosis control and patient care. Trop Med Int Health 2010;15:1289–99. https://doi.org/10.1111/j.1365-3156.2010.02625.x.

[8] World Health Organization. WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease. Geneva: World Health Organization; 2021.

[9] Ahmad Khan F, Majidulla A, Tavaziva G, Nazish A, Abidi SK, Benedetti A, Menzies D, Johnston JC, Khan AJ, Saeed S. Chest x-ray analysis with deep learning-based software as a triage test for pulmonary tuberculosis: a prospective study of diagnostic accuracy for culture-confirmed disease. Lancet Digit Health 2020;2:e573-e581. doi: 10.1016/s2589-7500(20)30221-1.

[10] Tavaziva G, Harris M, Abidi SK, Geric C, Breuninger M, Dheda K, et al. Chest X-ray analysis with deep learning-based software as a triage test for pulmonary tuberculosis: an individual patient data meta-analysis of diagnostic accuracy. Clin Infect Dis 2022;74:1390–400. https://doi.org/10.1093/cid/ciab639.

[11] Cox C. Delta Method. Encyclopedia of Biostatistics, 2005.

[12] R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Vienna, Austria, 2020.