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Computer-assisted chest radiography reading for tuberculosis screening in people living with diabetes mellitus

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SUMMARY

BACKGROUND: Diabetes mellitus is a significant risk factor for tuberculosis (TB). We evaluated the performance of computer-aided detection for tuberculosis (CAD4TB) in people living with diabetes mellitus (PLWD) in Indonesia.

METHODS: PLWD underwent symptom screening and chest X-ray (CXR); sputum was examined in those with positive symptoms and/or CXR. Digital CXRs were scored using CAD4TB and analysed retrospectively using clinical and microbiological diagnosis as a reference. The area under the receiver operator curve (AUC) of CAD4TB scores was determined, and an optimal threshold score established. Agreement between CAD4TB and the radiologist's reading was determined. **RESULTS:** Among 346 included PLWD, seven (2.0%) had microbiologically confirmed and two (0.6%) had

clinically diagnosed TB. The highest agreement of CAD4TB with radiologist reading was achieved using a threshold score of 70 ($\kappa = 0.41$, $P < 0.001$). The AUC for CAD4TB was 0.89 (95%CI 0.73–1.00). A threshold score of 65 for CAD4TB resulted in a sensitivity, specificity, positive predictive value and negative predictive value of respectively 88.9% (95%CI 51.8–99.7), 88.5% (95%CI 84.6–91.7), 17.0% (95%CI 7.6–30.8) and 99.6% (95%CI 98.2–100). With this threshold, 48 (13.9%) individuals needed microbiological examination and no microbiologically confirmed cases were missed.

CONCLUSIONS: CAD4TB has potential as a triage tool for TB screening in PLWD, thereby significantly reducing the need for microbiological examination.

KEY WORDS: CAD4TB v 5; triage tool; Indonesia

IT HAS LONG BEEN RECOGNISED that people living with diabetes mellitus (PLWD) are disproportionately affected by tuberculosis (TB).¹ Compared with people without diabetes mellitus (DM), PLWD have an increased risk of *Mycobacterium tuberculosis* infection,² at least a two-fold higher risk of developing TB,^{3–6} and experience worse outcomes once diagnosed with TB.⁷ In 2015, there were approximately 10.4 million new TB cases and 1.4 million deaths caused by TB worldwide.⁸ The six countries with the highest number of incident TB cases in 2015 were India, Indonesia, China, Nigeria, Pakistan and South Africa. Of these, Indonesia accounted for 10% of global cases, with an estimated 1 020 000 new TB cases in 2015.⁸ Approximately 9.5% of all TB cases in Indonesia in 2010 were attributable to DM, and this percentage is estimated to increase to 14% by

2030.⁹ The International Diabetes Federation predicts that global DM prevalence will increase from 7% (415 million) in 2015 to 10% (642 million) by 2040.^{10,11} Indonesia has the seventh highest DM prevalence rate worldwide, with 10 million (6.2%) PLWD in 2015; this prevalence has been estimated to increase to 16.2 million people by 2040.¹⁰

To address the double burden of TB and DM and the absence of international guidelines, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease developed a collaborative framework setting out the principles for bidirectional screening and integrated management.¹² Studies on how best to screen for TB in PLWD have mainly focused on symptom screening and chest radiography (CXR).^{13,14} Novel technologies such as the Xpert[®] MTB/RIF assay (Cepheid,

Sunnyvale, CA, USA) and computer-assisted radiography have not been employed.^{15,16}

Computer-aided detection for TB (CAD4TB) is a software system developed for the automated detection of pulmonary TB (PTB).¹⁷ It quantifies various imaging characteristics of a CXR to compute a score from 0 to 100: higher scores indicate more abnormalities and greater likelihood of PTB.¹⁷ Initial studies of CAD4TB have shown encouraging performance characteristics,^{18–25} although it is clear that pre-specified threshold scores are needed for different patient groups and settings.²⁶

We conducted the first performance evaluation of CAD4TB in Indonesia and the first among PLWD, focusing on CAD4TB as a possible triage test in the screening algorithm of TB among PLWD.

METHODS

Setting and study participants

From December 2013 to February 2015, PLWD aged ≥ 18 years accessing DM care were offered TB screening and were recruited consecutively from the endocrine out-patient clinic at Hasan Sadikin General Hospital, Bandung, Indonesia, and 25 of 73 community health centres (CHC) in Bandung. The 25 CHCs were selected because they were 1) among the CHCs with the highest number of TB cases, and 2) had a chronic disease prevention programme in which PLWD and hypertension received routine examinations, medications and education. Participants who underwent digital CXR with available Digital Imaging and Communication in Medicine (DICOM) files were included in this study.

Procedures

A questionnaire was administered to collect sociodemographic and clinical data. Clinical data included symptoms suggestive of TB and past medical history of TB and DM. Human immunodeficiency virus (HIV) testing was not routinely performed, as HIV prevalence in adults aged 15–49 years in Indonesia is 0.4% and PLWD are not considered a high HIV risk population.²⁷ CXRs were obtained from all participants and were read within 48 h by a specialist radiologist (certified by the Indonesian board) and classified as: normal, possible TB, probable TB, and abnormal, non-TB-related. All PLWD with cough > 2 weeks or CXR classified as possible or probable TB were asked to submit two (spot and morning) sputum samples. Sputum samples were investigated using Ziehl-Neelsen staining and liquid culture for *M. tuberculosis* using the microscopic observation drug susceptibility assay. All results were entered into a database using Research Electronic Data Capture (REDCap; Vanderbilt University, Nashville, TN, USA).²⁸ Digital CXRs available were scored retrospectively using CAD4TB v5 (Delft Imaging Systems,

Veenendaal, The Netherlands), with scores from 0 to 100 (0 being completely normal and 100 very suggestive of TB).

Outcomes

The primary outcome (reference standard) of this study was the number of people diagnosed with active PTB. Individuals were diagnosed as having active PTB if they were smear-, culture- or Xpert-positive (microbiologically positive) or if a pulmonologist decided to treat them for TB (clinically positive). The secondary outcome of this study was a CXR reading by a radiologist categorised as ‘not TB’ (‘normal’ and ‘abnormal, non-TB-related’) and ‘suggestive of TB’ (‘probable TB’ and ‘possible TB’).

Statistical analyses

Statistical analyses were performed using Stata v13 (StataCorp, College Station, TX, USA). We assessed different threshold levels of CAD4TB scores to categorise CXRs into normal vs. abnormal, and cross-tabulate the CXR category with the reference standard. We then calculated the sensitivity and specificity of CAD4TB using those thresholds to construct the area under the receiver operating curve (AUC). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CAD4TB, the number needed to screen (NNS) and the number of TB cases missed were calculated against the reference standard, along with their 95% confidence intervals (CIs). CAD4TB results at different thresholds were compared with the reading by the radiologist using κ scores for agreement.

Ethics

Written informed consent was provided by study participants in the main study before inclusion. The study protocol was approved by the Observational/Interventions Research Ethics Committee, London School of Hygiene & Tropical Medicine, London, UK (6449 and 13503), and the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia (377/UN6.C2.1.2/KEPK/PN/2012).

RESULTS

Of the 866 PLWD who were offered TB screening, 809 (93.4%) consented to participate. Fifteen of these were under anti-tuberculosis treatment at the time of recruitment and were therefore excluded from the analysis, leaving a total of 794 PLWD. DICOM files were available for 346 (43.6%) individuals. DICOM files that were missing had been deleted before being accessed for the study by hospital staff as they freed up limited electronic storage space on the routine system. Of 346 PLWD, 232 (67.1%) were recruited in

Table 1 Characteristics of the study population with and without an available DICOM file

Characteristics	DICOM file available (<i>n</i> = 346) <i>n</i> (%)	DICOM file not available (<i>n</i> = 448) <i>n</i> (%)	<i>P</i> value (χ^2)
Age, years, mean \pm SD	59.3 \pm 10.2	58.1 \pm 10.3	0.100
Male sex	151 (43.6)	140 (31.2)	<0.001
Recruitment site			<0.001
Hasan Sadikin General Hospital	238 (68.8)	243 (54.2)	
Community Health Centre	108 (31.2)	205 (45.8)	
Recruitment time period			<0.001
December 2013–April 2014	146 (42.2)	138 (30.8)	
May 2014–September 2014	146 (42.2)	74 (16.5)	
October 2014–February 2015	54 (15.6)	236 (52.7)	
Past history of TB	38 (11.0)	44 (9.8)	0.593
Productive cough \geq 2 weeks	35 (10.1)	24 (5.4)	0.011
Haemoptysis	0	2 (0.4)	0.213
Night sweats	48 (13.9)	52 (11.7)	0.340
Weight loss	103 (29.8)	100 (22.4)	0.019
Breathlessness	57 (16.5)	42 (9.4)	0.003
HIV status			0.140
Negative	3 (0.9)	0	
Positive	1 (0.3)	1 (0.2)	
Unknown	342 (98.8)	447 (99.8)	
Chest X-ray reading			0.236
Normal	176 (50.9)	215 (48.0)	
Possible active TB	11 (3.2)	13 (2.9)	
Probable active TB	34 (9.8)	31 (6.9)	
Abnormal, not TB	124 (35.8)	184 (41.1)	
Missing result	1 (0.3)	5 (1.1)	
Acid-fast bacilli			0.133
Not indicated	276 (79.8)	386 (86.2)	
Negative	49 (14.2)	42 (9.4)	
Scanty	1 (0.3)	0	
1+	0	0	
2++	3 (0.9)	1 (0.2)	
3+++	2 (0.6)	1 (0.2)	
Missing result	15 (4.34)	18 (4.0)	
Culture			0.064
Not indicated	276 (79.8)	386 (86.2)	
Negative	47 (13.6)	36 (8.0)	
Positive	6 (1.7)	5 (1.1)	
Missing result	17 (4.9)	21 (4.7)	
Treated for TB			0.158
No	337 (97.1)	443 (98.9)	
Yes, microbiologically confirmed	7 (2.0)	5 (1.1)	
Yes, clinical diagnosis	2 (0.6)	0	

DICOM = Digital Imaging and Communication in Medicine; SD = standard deviation; TB = tuberculosis; HIV = human immunodeficiency virus.

endocrine out-patient clinics at Hasan Sadikin General Hospital and 114 (32.9%) were from CHCs.

Those with a DICOM file were more likely to be male (43.6% vs. 31.2%) and reported a higher prevalence of symptoms (Table 1). Although the prevalence of microbiologically confirmed and clinically diagnosed TB was not significantly different, prevalence estimates suggested that PLWD with DICOM files had a higher TB prevalence (2.6%, 95%CI 1.2–4.9) than those without (1.1%, 95%CI 0.4–2.6).

In those with available DICOM files, the mean age was 59.3 years (standard deviation [SD] 10.2); 151 (43.6%) were male (Table 1). Few (*n* = 35, 10.0%) reported productive cough \geq 2 weeks, and respectively 48 (13.9%) and 57 (16.5%) reported night sweats and breathlessness. Less than one third had

weight loss. CXR was reported as ‘probable TB’ or ‘possible TB’ in 45 (13.0%) PLWD, 22 (48.9%) of whom had a history of PTB. Normal CXRs were observed in 176 (50.9%) and non-TB-related abnormalities (e.g., cardiomegaly and aortic atherosclerosis) in 124 (35.8%) PLWD.

The prevalence of microbiologically confirmed TB was 2.0% (*n* = 7), and a further two (0.6%) individuals were started on anti-tuberculosis treatment based on clinical diagnosis. Culture results were missing for two individuals overall (Figure 1). Fifteen individuals who were eligible for sputum investigations were either unable to provide sputum or did not provide sputum for unknown reasons. These individuals were included in the denominator.

Figure 2A shows the receiver operating characteristic curve for CADTB in PLWD using different

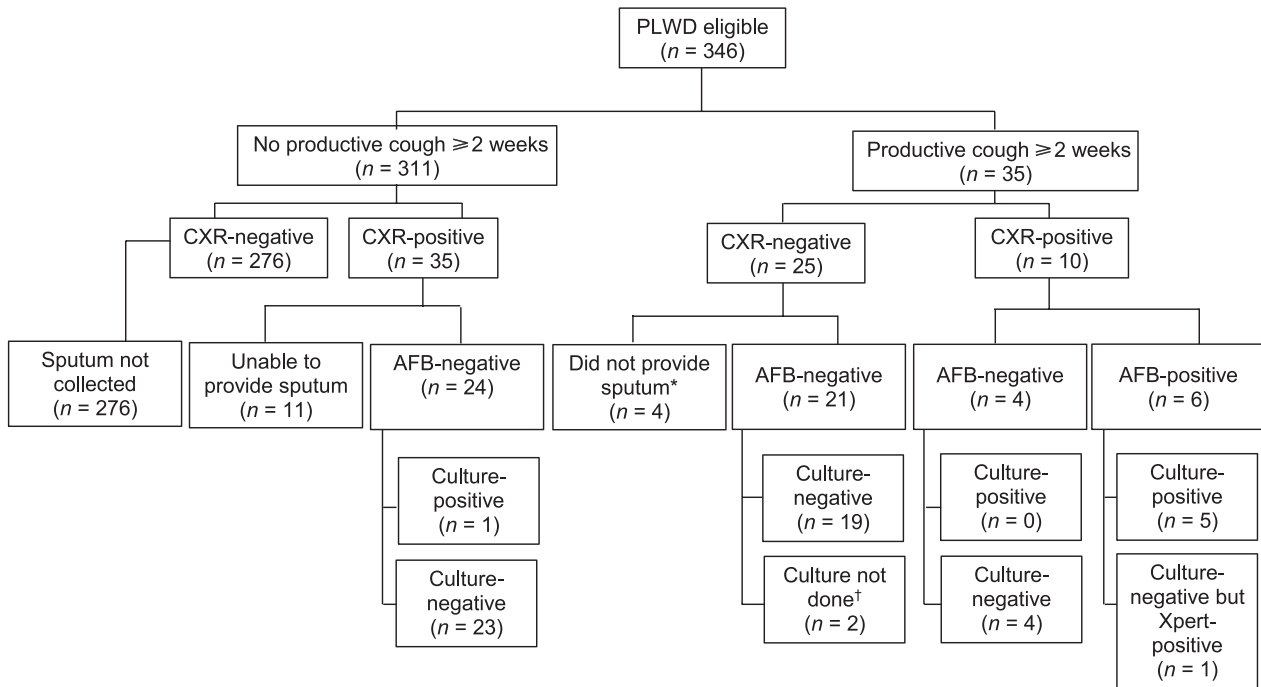


Figure 1 TB screening results in PLWD. *Four PLWD with productive cough but CXR– did not provide sputum for unknown reasons. †Two PLWD with productive cough but CXR– provided sputum for AFB but culture was not done because the samples had been lost. PLWD = people living with diabetes mellitus; CXR = chest X-ray; AFB = acid-fast bacilli.

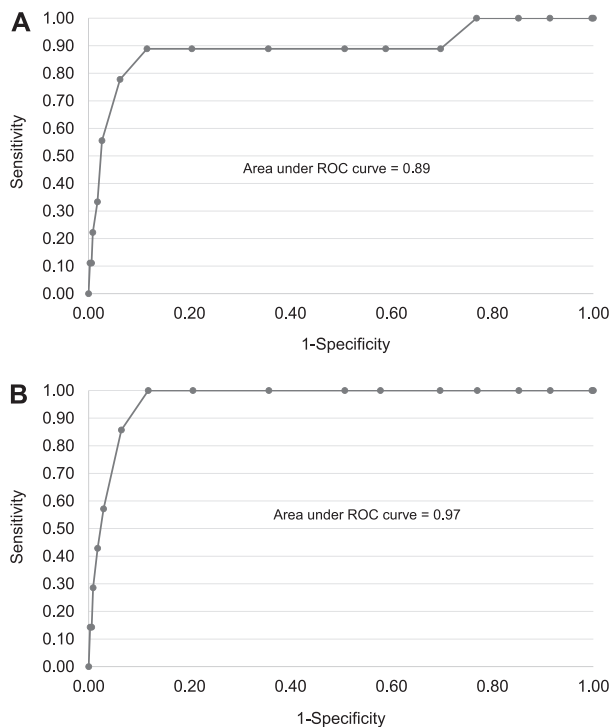


Figure 2 ROC curves in PLWD screened for TB. **A)** Using PLWD with microbiologically confirmed and clinically diagnosed TB as the reference standard (number of positive cases = 9). **B)** Using microbiologically confirmed TB as the reference standard (number of positive cases = 7). ROC = receiver operating characteristic; PLWD = people living with diabetes mellitus.

CAD4TB scoring thresholds. The AUC was 0.89 (95%CI 0.73–1.00). At a threshold score of 65, sensitivity and specificity were 88.9% (95%CI 51.8–99.7) and 88.4% (95%CI 84.5–91.6), respectively. Microbiological investigations would need to be performed on 48 (13.9%, 95%CI 10.4–18.0) out of 346 PLWD to ensure that all seven microbiologically confirmed TB cases and one of the two clinically diagnosed TB cases were diagnosed (Table 2). Lowering the threshold to under 65 did not increase sensitivity, but reduced specificity. The other clinically diagnosed TB case who was missed using a CAD4TB score threshold of 65 had a CXR reported as probable active TB by the radiologist due to a patchy change in one upper lung, and had a CAD4TB score of 38.7. The patient was asymptomatic, and both microscopy and culture results were negative.

When using microbiologically confirmed TB as the reference standard, the AUC was 0.97 (95%CI 0.94–0.99), and 65 remained the optimum threshold (Figure 2B). The sensitivity, specificity, PPV and NPV of CAD4TB using 65 as the threshold score was 100% (95%CI 59.0–100.0), 88.2% (95%CI 84.3–91.4), 14.9% (95%CI 6.2–28.3), and 100% (95%CI 98.8–100.0), respectively.

Table 3 shows the κ agreement and percentage concordance of CAD4TB scores with reading by the radiologist. The highest concordance was achieved using a threshold of 70 (88.7%, 95%CI 85.4–92.1), for which the κ score was 0.41 (standard error 0.052).

Table 2 Sensitivity, specificity, NNS and number of TB cases missed in PLWD by CAD4TB threshold score

Threshold	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	NNS for 1 TB case <i>n</i> (95%CI)	Number of cases missed of all cases (<i>n</i> = 9)
35	100.0 (66.4–100.0)	23.1 (18.7–28.0)	3.4 (1.5–6.3)	100.0 (95.4–100.0)	29.8 (20.4–41.5)	0
40	88.9 (51.8–99.7)	30.3 (25.4–35.5)	3.3 (1.4–6.3)	99.0 (94.7–100.0)	30.4 (20.4–41.5)	1
45	88.9 (51.8–99.7)	42.1 (36.8–47.6)	3.9 (1.7–7.6)	99.3 (96.2–100.0)	25.4 (16.3–34.6)	1
50	88.9 (51.8–99.7)	49.2 (43.8–54.7)	4.5 (1.9–8.6)	99.4 (96.7–100.0)	22.4 (13.8–31.1)	1
55	88.9 (51.8–99.7)	64.4 (59.0–69.5)	6.2 (2.7–11.9)	99.5 (97.5–100.0)	16.0 (9.3–25.6)	1
60	88.9 (51.8–99.7)	79.5 (74.8–83.7)	10.4 (4.6–19.4)	99.6 (97.9–100.0)	9.6 (4.8–18.0)	1
65	88.9 (51.8–99.7)	88.4 (84.5–91.6)	17.0 (7.6–30.8)	99.7 (98.2–100.0)	5.9 (2.1–12.8)	1
70	77.8 (40.0–97.2)	93.8 (90.6–96.1)	25.0 (10.7–44.9)	99.4 (97.7–99.9)	4.0 (1.1–10.0)	1
75	55.6 (21.2–86.3)	97.3 (94.9–98.8)	35.7 (12.7–64.9)	98.8 (96.9–99.7)	2.8 (0.6–8.6)	4
80	33.3 (7.5–70.1)	98.2 (96.2–99.3)	33.3 (7.5–70.1)	98.2 (96.2–99.3)	3.0 (0.6–8.6)	6

NNS = number needed to screen; TB = tuberculosis; PLWD = people living with diabetes mellitus; CAD4TB = computer-aided detection for tuberculosis; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

DISCUSSION

In an urban setting in Indonesia, 9 of 346 PLWD (2.6%, 95%CI 1.2–4.9) had active TB, compared with 0.8% in the general population aged 45–54 years and 1.0% in the general population aged 55–64 years according to the recent Indonesian national prevalence survey, indicating the importance of screening for TB in PLWD.⁸ We assessed CAD4TB with a threshold score of 65 as a triage test to restrict the number of individuals needing sputum examination to a minimum. Only 48 (13.9%, 95%CI 10.4–18.0) PLWD screened for TB would have required sputum examination, and only a single case of clinically diagnosed TB would have been missed among the remaining 298 individuals. The one person who would have been missed was asymptomatic and had negative sputum microscopy and *M. tuberculosis* culture, casting some doubt on the diagnosis of TB disease.

To date, implementation of the recommendation for bidirectional screening for TB and DM has been challenging. In particular, the best and most cost-effective approach to TB screening among PLWD has not been established.²⁹ Even in high TB burden countries, TB prevalence in the general population is rarely >0.5% and the prevalence of TB in PLWD is <2%.^{8,16} A selective screening strategy would thus be an advantage. Possible algorithms include clinical assessment or CXR before sputum testing.³⁰ Symptom screening and clinical examination have low sensitivity and specificity, but also low costs. CXR detects possible TB lesions even in relatively asymptomatic individuals, resulting in earlier diagnosis; however, costs are generally higher.

CAD4TB has several advantages. First, given the extremely short turnaround time of CAD4TB (1–2 min if the software is present on the X-ray machines), triage for further testing can be done immediately,

Table 3 Agreement between CAD4TB and the radiologist according to different CAD4TB threshold scores in PLWD

Threshold	Individuals with CXR above and below the threshold		Individuals with CXR probable TB	Individuals with CXR possible TB	Individuals with normal CXR	Individuals with abnormal, non-TB CXR	Concordance % (95%CI)	Agreement κ
	<i>n</i>	<i>n</i>						
35	Above	179	30	6	85	58	35.0 (29.9–40.0)	0.08
	Below	166	4	5	91	66		
40	Above	243	32	9	118	84	40.5 (35.3–45.6)	0.08
	Below	102	2	2	58	40		
45	Above	203	30	6	97	70	49.1 (43.8–54.4)	0.10
	Below	142	4	5	79	54		
50	Above	179	30	6	85	58	56.1 (50.8–61.3)	0.14
	Below	166	4	5	91	66		
55	Above	128	28	5	55	40	69.1 (64.2–74.0)	0.23
	Below	217	6	6	121	84		
60	Above	77	24	4	19	30	80.9 (76.8–85.1)	0.35
	Below	268	10	7	105	146		
65	Above	47	20	1	11	15	85.6 (81.8–89.3)	0.37
	Below	298	14	10	113	161		
70	Above	28	16	1	5	6	88.7 (85.4–92.1)	0.41
	Below	317	18	10	171	118		
75	Above	14	10	0	2	2	88.7 (85.4–92.1)	0.30
	Below	331	24	11	174	122		
80	Above	9	7	0	1	1	88.4 (85.0–91.8)	0.22
	Below	336	27	11	175	123		

CAD4TB = computer-aided detection for tuberculosis; PLWD = people living with diabetes mellitus; CXR = chest X-ray; TB = tuberculosis; CI = confidence interval.

obviating the need for return visits and maximising retention across the screening process. In addition, radiologists are scarce in many places. CAD4TB can substitute for radiologists in settings where their expertise is lacking. Finally, use of a dynamic and continuous threshold on CAD4TB allows selection of a smaller or larger proportion of patients for further (microbiological) screening based on available resources.

CAD4TB has performed well in other study populations. However, only two studies from Tanzania and Zambia have used CAD4TB for screening. The study conducted in Tanzania used radiological expert consensus as a reference standard.²⁴ A direct comparison between this study and our study is therefore not possible. The other study analysed data from a prevalence survey in Zambia using mycobacterial culture as the reference.²⁵ The Zambian study used the same version of CAD4TB (i.e., v5) as in our study. The AUC was 0.87, similar to that reported in our study.

Our study had several limitations. Digital CXR files could not be retrieved for a substantial proportion of participants; those with available DICOM files were different from those without, particularly with regard to sex and symptoms. Although the removal of DICOM files seemed non-systematic, the difference in baseline variables suggests the possibility of selection bias. It is difficult to predict how this could have influenced the sensitivity of different CAD4TB scores. The relatively small number of TB cases means that the sensitivity estimate was imprecise, with a relatively wide CI. Furthermore, the patients included in our study mostly underwent routine follow-up for DM both in the referral hospital and in the CHC; more extensive studies in different settings are needed to complement our study. According to the parent study algorithm, not everybody was extensively investigated for TB, only those with symptoms or a positive CXR. It is therefore possible that a few active TB patients were missed. We also did not have follow-up data on whether any of the participants developed TB disease over the following few months. Fifteen individuals who were eligible for sputum investigations but who did not provide sputum were included in the denominator, as they had been clinically diagnosed with TB. As such, the prevalence of TB in our study may have been slightly underestimated. Finally, we did not have an independent radiologist reviewing the CXRs to determine the inter-observer variability, nor were CXRs read twice after a time delay to determine intra-observer variability. However, the comparison between CAD4TB reading and reading by a board-certified radiologist reflects the standard of care in Indonesia. In this setting, CXRs are routinely read by the Department of Radiology at Hasan Sadikin General Hospital.

In conclusion, systematic TB screening of PLWD should be considered in settings with a high TB prevalence. However, microbiological laboratory services and expert radiology skills are often the bottleneck in TB screening, and symptom screening with relatively low sensitivity and specificity is likely to miss a substantial proportion of TB, particularly subclinical or incipient cases. Our data suggest that CXR performs well as a triage test in TB screening, and CAD4TB enables the use of CXR without the need for expert radiology review with the added benefit of a very short turnaround time. For future real-life implementation, all PLWD with a positive CXR (CAD4TB score ≥ 65) should undergo microbiological examinations, and to avoid any missed TB cases, those with a negative CXR (CAD4TB score < 65) result should be encouraged to undergo repeat CXR in case of symptoms. Studies of CXRs, along with CAD4TB as a triage test, need to be performed in other settings; cost-effectiveness studies are also required. Other studies may also assess the role of CAD4TB in situations if repeat screening is indicated.

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References

- 1 Lonnroth K, Roglic G, Harries A D. Improving tuberculosis prevention and care through addressing the global diabetes epidemic: from evidence to policy and practice. *Lancet Diabetes Endocrinol* 2014; 2: 730–739.
- 2 Lee M R, Huang Y P, Kuo Y T, et al. Diabetes mellitus and latent tuberculosis infection: a systemic review and meta-analysis. *Clin Infect Dis* 2017; 64: 719–727.
- 3 Jeon C Y, Murray M B. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLOS Med* 2008; 5: e152.
- 4 Kim S J, Hong Y P, Lew W J, Yang S C, Lee E G. Incidence of pulmonary tuberculosis among diabetics. *Tuber Lung Dis* 1995; 76: 529–533.
- 5 Leung C C, Lam T H, Chan W M, et al. Diabetic control and risk of tuberculosis: a cohort study. *Am J Epidemiol* 2008; 167: 1486–1494.
- 6 Kuo M C, Lin S H, Lin C H, Mao I C, Chang S J, Hsieh M C. Type 2 diabetes: an independent risk factor for tuberculosis: a nationwide population-based study. *PLOS ONE* 2013; 8 e78924.
- 7 Baker M A, Harries A D, Jeon C Y, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC Med* 2011; 9: 81.
- 8 World Health Organization. Global tuberculosis report, 2016. WHO/HTM/TB/2016.13. Geneva, Switzerland: WHO, 2016.

- 9 Ruslami R, Arnoutse R E, Alisjahbana B, et al. Implications of the global increase of diabetes for tuberculosis control and patient care. *Trop Med Int Health* 2010; 15: 1289–1299.
- 10 International Diabetes Federation. IDF diabetes atlas. Brussels, Belgium: IDF, 2016. <http://www.diabetesatlas.org/across-the-globe.html> Accessed May 2018.
- 11 Guariguata L, Whiting D R, Hambleton I, Beagley J, Linnenkamp U, Shaw J E. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract* 2014; 103: 137–149.
- 12 World Health Organization & International Union Against Tuberculosis and Lung Disease. Collaborative framework for care and control of tuberculosis and diabetes. WHO/HTM/TB/2011.15. Geneva, Switzerland: WHO, 2011.
- 13 Kumar A, Jain D C, Gupta D, et al. Screening of patients with diabetes mellitus for tuberculosis in India. *Trop Med Int Health* 2013; 18: 646–654.
- 14 Lin Y, Li L, Mi F, et al. Screening patients with diabetes mellitus for tuberculosis in China. *Trop Med Int Health* 2012; 17: 1302–1308.
- 15 Mave V, Nimkar S, Prasad H, et al. Tuberculosis screening among persons with diabetes mellitus in Pune, India. *BMC Infect Dis* 2017; 17: 388.
- 16 Jeon C Y, Harries A D, Baker M A, et al. Bi-directional screening for tuberculosis and diabetes: a systematic review. *Trop Med Int Health* 2010; 15: 1300–1314.
- 17 Pande T, Cohen C, Pai M, Ahmad Khan F. Computer-aided detection of pulmonary tuberculosis on digital chest radiographs: a systematic review. *Int J Tuberc Lung Dis* 2016; 20: 1226–1230.
- 18 Hogeweg L, Mol C, de Jong P A, Dawson R, Ayles H, van Ginneken B. Fusion of local and global detection system to detect tuberculosis in chest radiograph. *Med Image Comput Comput Assist Interv* 2010; 13: 650–657.
- 19 Maduskar P, Muyoyeta M, Ayles H, Hogeweg L, Peters-Bax L, van Ginneken B. Detection of tuberculosis using digital chest radiography: automated reading vs. interpretation by clinical officers. *Int J Tuberc Lung Dis* 2013; 17: 1613–1620.
- 20 Muyoyeta M, Maduskar P, Moyo M, et al. The sensitivity and specificity of using a computer-aided diagnosis program for automatically scoring chest x-rays of presumptive TB patients compared with Xpert MTB/RIF in Lusaka Zambia. *PLOS ONE* 2014; 9: e93757.
- 21 Breuninger M, van Ginneken B, Philipsen R H H M, et al. Diagnostic accuracy of computer-aided detection of pulmonary tuberculosis in chest radiographs: a validation study from sub-Saharan Africa. *PLOS ONE* 2014; 9: e106381.
- 22 Philipsen R H H, Sánchez C I, Maduskar P, et al. Automated chest-radiography as a triage for Xpert testing in resource-constrained settings: a prospective study of diagnostic accuracy and costs. *Sci Rep* 2015; 5: 12215.
- 23 Mendelez J, Sanchez CI, Philipsen R H H M, et al. An automated tuberculosis screening strategy combining X-ray based computer-aided detection and clinical information. *Sci Rep* 2016; 6: 25265.
- 24 Steiner A, Mangu C, van den Hombergh J, et al. Screening for pulmonary tuberculosis in a Tanzanian prison and computer-aided interpretation of chest X-rays. *Public Health Action* 2015; 5: 249–254.
- 25 Mendelez J, Philipsen R H H, Chanda-Kapata P, Sunkutu V, Kapata N, van Ginneken B. Automatic versus human reading of chest X-rays in the Zambia National Tuberculosis Prevalence Survey. *Int J Tuberc Lung Dis* 2017; 21: 880–886.
- 26 Khan F A, Pande T, Tessema B, et al. Computer-aided reading of tuberculosis chest radiography: moving the research agenda forward to inform policy. *Eur Respir J* 2017; 50: 1700953.
- 27 Joint United Nations Programme on HIV/AIDS. HIV and AIDS estimates in Indonesia. Geneva, Switzerland: UNAIDS, 2016. <http://www.unaids.org/en/regioncountries/countries/indonesia>. Accessed May 2018.
- 28 Harris P A, Taylor R, Thielke R, Payne J, Gonzalez N, Conde J G. Research electronic data capture (REDCap). A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42: 377–381.
- 29 Harries A D, Kumar A M V, Satyanarayana S, et al. Diabetes mellitus and tuberculosis: programmatic management issues. *Int J Tuberc Lung Dis* 2015; 19: 879–886.
- 30 World Health Organization. Systematic screening for active TB: principles and recommendation. WHO/HTM/TB/2013. Geneva, Switzerland: WHO, 2013.

R É S U M É

CONTEXTE : Le diabète est un facteur de risque important de tuberculose (TB). Nous avons évalué la performance de la détection de la TB assistée par ordinateur (CAD4TB) parmi les personnes atteintes de diabète (PLWD) en Indonésie.

MÉTHODE : Les PLWD ont bénéficié d'un dépistage basé sur les symptômes et d'une radiographie pulmonaire (CXR) ; les crachats ont été examinés chez ceux qui avaient des symptômes positifs et/ou une CXR suggestive de TB. Les CXR numérisées ont été classées grâce au programme CAD4TB et analysées rétrospectivement, en utilisant le diagnostic clinique et microbiologique comme référence. La zone sous la courbe récepteur opérateur (AUC) des scores CAD4TB a été déterminée et un seuil optimal de score établi. L'accord entre CAD4TB et la lecture du radiologue a été déterminé.

RÉSULTATS : Sur les 346 PLWD inclus, sept (2,0%) ont

eu un diagnostic de TB confirmé par microbiologie et deux (0,6%) par les signes cliniques. L'accord le plus élevé de CAD4TB avec la lecture du radiologue a été atteint en utilisant un seuil de score de 70 ($\kappa=0,41$; $P < 0,001$). L'AUC pour CAD4TB a été de 0,89 (IC95% 0,73–1,00). Un seuil de score de 65 pour CAD4TB a abouti à une sensibilité, une spécificité, une valeur prédictive positive et une valeur prédictive négative de 88,9% (IC95% 51,8–99,7), de 88,5% (IC95% 84,6–91,7), de 17,0% (IC95% 7,6–30,8) et de 99,6% (IC95% 98,2–100), respectivement. Avec ce seuil, 48 (13,9%) individus ont eu besoin d'un examen microbiologique et aucun cas confirmé par microbiologie n'a été manqué.

CONCLUSION : Le CAD4TB est un outil potentiel de tri dans le cadre du dépistage de la TB parmi les PLWD, qui réduit significativement le besoin d'examen microbiologique.

RESUMEN

MARCO DE REFERENCIA: La diabetes representa un importante factor de riesgo de padecer tuberculosis (TB). Se evaluó la eficacia de un programa de detección de la TB asistido por computadores (CAD4TB, por *Computer Aided Detection for Tuberculosis*) en personas con diagnóstico de diabetes (PLWD) en Indonesia.

MÉTODOS: En las PLWD se practicó una detección sintomática de la TB y una radiografía de tórax (CXR) y se examinó el esputo de los pacientes con un resultado positivo de los síntomas, la CXR o ambos. Las CXR digitales se calificaron según la puntuación del programa CAD4TB y se analizaron de manera retrospectiva, tomando el diagnóstico clínico y microbiológico como método de referencia. Se determinó el área bajo la curva de eficacia diagnóstica (AUC) de las puntuaciones del CAD4TB y se definió la puntuación liminar óptima. Se determinó la concordancia de la lectura con el programa CAD4TB y la lectura por un radiólogo.

RESULTADOS: De las 346 PLWD incluidas en el estudio,

se detectaron siete casos de TB con confirmación microbiológica (2,0%) y dos de TB diagnosticada mediante criterios clínicos (0,6%). El mayor grado de concordancia entre el CAD4TB y la lectura por el radiólogo se logró con un umbral de 70 en la puntuación ($\kappa = 0,41$; $P < 0,001$). El AUC del CAD4TB fue 0,89 (IC95% 0,73–1,00). Con una puntuación liminar de 65 del CAD4TB se logró una sensibilidad de 88,9% (IC95% 51,8–99,7), una especificidad de 88,5% (IC95% 84,6–91,7), un valor diagnóstico de un resultado positivo de 17,0% (IC95% 7,6–30,8) y un valor diagnóstico de un resultado negativo de 99,6% (IC95% 98,2–100). Con este umbral, 48 personas necesitaron examen microbiológico (13,9%) y no se pasó por alto ninguno de los casos con confirmación microbiológica.

CONCLUSIÓN: El programa CAD4TB puede ser un instrumento útil en la detección sistemática de la TB de las PLWD y disminuiría de manera considerable la necesidad de practicar el examen microbiológico.