

Screening for Tuberculosis with Computer-Aided Detection in Diabetic Patients in Armenia

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Abstract

Background: Computer-aided detection (CAD) software products are increasingly used as a tool to enhance the feasibility and accuracy of chest radiography interpretation. The research objectives of this study include: evaluation of the diagnostic accuracy of CAD strategy for screening and detection of TB in diabetic patients and assessment of the feasibility of using CAD within TB screening programs among patients with diabetes mellitus (DM). **Methods:** This study has a cross-sectional design considering the individuals with DM to be screened for TB by CAD. As a qualitative component of the study, we carried out in-depth interviews with key informants to understand acceptability of using CAD for TB screening activities. **Results:** Of 380 study participants screened and analyzed, only one case was confirmed bacteriologically (0.3%, 95% CI: 0 - 0.8) and two participants were confirmed for TB in total (0.5%, 95% CI: 0 - 1.3). One pulmonary tuberculosis case was missed by CAD and confirmed by sputum Gene-Xpert test. The feasibility and acceptability of using CAD within TB screening programs among patients with DM is obvious, given not only the yield of results and interpretations but also the outcome and expectations of in-depth interviews. All interviewees accepted CAD as a screening tool for TB detection, not only among DM patients but also in the other risk groups. **Conclusion:** Utilization of CAD is feasible to perform in PHC setting for any population, including key populations such as people living with DM. Further studies devoted to CAD screening in DM patients are reasonable to conduct with application of CAD at a threshold lower than 70, as at least one PTB case was missed by CAD and confirmed by sputum GeneXpert test.

Keywords

Tuberculosis, Screening, Diabetes, Computer-Aided Detection

1. Introduction

Chest radiography (CXR) plays a key role in the detection of pulmonary tuberculosis (TB). Along with the World Health Organization (WHO) recommended guidelines on bacteriological or molecular testing, the integration of CXR into screening and triaging algorithms can assist with early detection of TB, given its high sensitivity as a screening tool, including among non-symptomatic patients, and utility in detecting people who require further diagnostic testing thereby guiding the effective allocation of molecular WHO-recommended rapid diagnostic tests (mWRD) [1]. As such, CXR can improve case detection and cost-efficiency and facilitate early detection and treatment initiation, and reduce the likelihood of onward transmission [2] [3]. Since 2020, WHO has included computer-aided detection (CAD) technologies for TB detection in TB screening guidelines and recommendations for adults over the age of 15 years in place of human readers for interpretation of digital CXR in both screening and triage for TB disease [4] [5]. CAD utilizes artificial intelligence (AI) to analyze CXR for abnormalities suggestive of pulmonary TB, which produces an abnormality score to determine the need for follow-on diagnostic testing for TB relative to a selected threshold. CAD software products are increasingly used as a tool to enhance the feasibility and accuracy of CXR interpretation worldwide as a way to replace or augment human expert interpretation of plain CXR when screening for pulmonary TB and reduce inter-reader variability and delays in reading radiographs when skilled personnel are scarce [6].

In Armenia, the first CAD device was received in 2022, with an additional seven CAD machines delivered in 2023, which coincided with the planning of TB screening activities for TB cases among specific populations, including patients with diabetes [7].

The links between TB and diabetes are well established and diabetes is recognized as a key risk factor for TB [8] [9]. People with diabetes have a twofold to threefold risk of developing TB disease, a twofold risk of death during TB treatment, a fourfold risk of TB relapse after treatment completion and a twofold risk of developing multidrug-resistant TB (MDR-TB) [9]. In Armenia, the number of patients with diabetes type 1 and type 2 has increased in two-fold in the last 30 years and reached to 109,286 in 2021 [10]. According to the diabetes mellitus (DM) management guidelines, patients with DM are supposed to have annual fluorography examinations, however, the experience shows that TB vigilance is low among primary health care (PHC) doctors in Armenia. TB screening is not routinely carried out among all eligible populations. The prevalence of TB among patients with DM is not known (no prevalence survey was conducted so far), while the proportion of those having DM among diagnosed TB cases is more than 10%.

In order to enhance TB screening among patients with diabetes in Armenia, this study aimed to evaluate the diagnostic accuracy of CAD strategy for screening and detection of TB in diabetic patients and assessment of the feasibility/acceptability of using CAD within TB screening programs among patients with DM.

2. Methods

2.1. Study Design

This was a mixed-methods study comprising a quantitative, cross-sectional survey to screen presenting DM patients for TB using CAD and qualitative in-depth interviews with key informants to understand acceptability of using CAD for TB screening activities.

2.1.1. Study Setting

The cross-sectional study recruited participants with DM registered in Artashat Medical Center—a big health care facility serving around 100,000 population of Artashat town and surrounding villages (Ararat region)—with about 1000 registered patients with DM. The outpatient clinic of Artashat Medical Center was selected also for the advantage of having a TB outpatient service in its structure with an operating GeneXpert MTB/RIF machine available.

2.1.2. Study Objectives

- 1) To evaluate the diagnostic accuracy of CAD strategy (at determined calibration) for screening and detection of TB in diabetic patients by comparing the performance of CAD in detecting probable pulmonary TB against a bacteriological reference standard in Armenia; and
- 2) To evaluate the feasibility/acceptability of using CAD within TB screening programs among patients with DM.

2.2. Participants

The following participants were considered eligible for the cross-sectional study: current DM patient registered at Artashat Medical Center and resident of the service area of Artashat Medical Center; diagnosed with type 1 or 2 diabetes with documented prescription of either oral and/or insulin treatment; aged 18 and above; had at least one recorded visit to PHC facility during the 6 months prior to recruitment and provided consent for participation and willingness to undergo CXR and bacteriological laboratory tests. Pregnant women or participants with medical conditions that were not compatible with performing a CXR and children under 18 years were excluded from the study. The cross-sectional study sample included 402 patients with DM in total, all of whom completed the survey. Out of 402 study participants, digital images of CXR were interpreted by CAD and NCP radiologist independently for 380 people.

2.3. Study Tools/Data Collection

Recruitment of study participants, fieldwork and data collection lasted around 6 months.

Clinical variables were measured on-site or retrieved from the ambulatory forms. CAD technician visited the study site twice a week to examine the screened by W4SS questionnaire patients with DM. The mWRD—GeneXpert MTB/RIF—was used as a TB diagnosis reference standard for the study. The outcome of CAD test

(“TB”/“non-TB”) was compared with bacteriological confirmation of TB. Definition of “TB case” is based on both radiological evidence and bacteriological confirmation of TB.

To assess the feasibility of using CAD for screening among DM patients, the data on the following process indicators were collected: number of DM patients eligible for TB screening; number of DM patients having TB symptoms; number of patients refused to participate in the survey; number of patients able to produce sputum; number of patients undergone CXR with CAD; number of TB cases detected as a result of screening all participants; and reliability of interpretation results between CAD radiologist and laboratory confirmation.

Data collection of the qualitative component was retrieved from open-ended questionnaires completed by key informants. Upon receiving informed written consent, the interviews were conducted via trained interviewers, audio recorded, transcribed and analyzed.

2.4. Study Procedures

The study started in January 2023 and was completed in November 2023.

PHC endocrinologist organized recruitment of diabetic patients visiting the health care facility during the period of study fieldwork, with relation to diabetic complications and complaints. Patients were screened for eligibility criteria, asked for informed consent and invited to participate in the survey. Patients underwent the following TB screening activities: clinical symptom screen using the WHO-recommended four-symptom screen questionnaire (W4SS; current cough, fever, night sweats, and/or weight loss), followed by CXR and parallel interpretation by CAD and radiologist. For CAD, a threshold of 70 was used to categorize images either as “TB” or “non-TB”. For the radiologist, expert opinion was used to classify images as “TB”, “non-TB” and “TB suspect”. The patients meeting one of the following criteria were further referred for bacteriological testing (GeneXpert MTB/RIF and culture) and asked to provide sputum samples: at least three TB clinical symptoms, contact with a confirmed TB case, CAD or radiologist reading as “TB”, and “non-TB” or “TB suspect”, respectively.

Within the period of August-October 2023, in-depth “face to face” interviews with key informants (specialists of different levels of health care system, such as radiologists, TB clinicians, endocrinologists and project managers) were carried out to assess the experience, professional attitude and challenges related to the CAD implementation for screening purposes in the TB care field. Participation was voluntary and all participants were informed about the confidentiality.

2.5. Data Management and Analysis

Statistical data analyses were carried out by the principal investigators and main study team at the central level using Microsoft Excel software. Descriptive analyses included frequencies and percentages for categorical variables, and measures of the central tendency (mean, standard deviation/median, IQR) with 95% confidence

intervals for continuous variables. No associations between the explanatory and outcome variables were tested, given the fact that two TB cases were detected only. For the qualitative component of the study, thematic analyses of interview transcripts and inductive coding segments of text relevant to the study questions were conducted. Coding was focused on identifying perceived barriers and facilitating features (personal and organizational) related to CAD use in various settings, as well as other unanticipated key themes that may emerge.

2.6. Ethical Aspects

All the research meets the ethical guidelines, including adherence to the legal requirements of Armenia. The study was approved by the local Ethics Review Committee of Healthcare Research and Development Initiative of Armenia NGO (The study was approved by the Ethics Review Committee of Healthcare Research and Development Initiative of Armenia (number of the approval: HRDI-ERC-2020-003, date: 05-May-2020). All study participants provided written informed consent.

3. Results

3.1. CAD Screening

However, CXR was interpreted for only 380 participants due to technical difficulties that occurred in the process of digitalization of radiological images and CAD equipment. On average, participants were female (71%), lived in rural areas (75%), aged between 46 - 75 years (87%) and had a median age of 64. Nearly all (97%) of the study population had type 2 diabetes, with median age at the first diagnosis of 55 (Table 1).

Table 1. Demographic and social characteristics of the study population.

Characteristics	Women		Men		Total	
	n	%	n	%	n	%
Total sample	287	71.4	115	28.6	402	100
Age range						
18 - 25	1	0.3	0	0.0	1	0.2
26 - 35	2	0.7	1	0.9	3	0.7
36 - 45	19	6.6	6	5.2	25	6.2
46 - 55	36	12.5	14	12.2	50	12.4
56 - 65	117	40.8	49	42.6	166	41.3
66 - 75	100	34.8	36	31.3	136	33.8
76 - 85	12	4.2	9	7.8	21	5.2
Ethnic origin						
Armenian	283	99.0	112	97.4	395	98.3
Other	4	1.0	3	2.6	7	1.7

Continued

Education							
Primary	2	0.8	0	0.0	2	0.5	
Secondary	144	55.4	71	67.0	215	58.7	
Technical/vocational	90	34.6	23	21.7	113	30.9	
University	24	9.2	12	11.3	36	9.8	
Occupation							
Unemployed	212	80.3	77	76.2	289	79.2	
Employed	52	19.7	24	23.8	76	20.8	
Residence							
Urban	72	25.0	30	26.0	102	25.4	
Rural	215	75.0	85	74.0	300	74.6	
Housing							
Private house	229	82.1	92	81.4	321	81.9	
Apartment	49	17.5	21	18.6	70	17.9	
Shelter	1	0.4	0	0.0	1	0.3%	
Heating							
Yes					388	96.5	
No					14	3.5	
Migration history							
Yes	47	17.5	12	11.0	59	15.6	
No	221	82.5	97	89.0	318	84.3	
Monthly income/per person							
Up to 150\$	258	92.1	104	92.0	362	92.1	
150 - 350\$	22	7.9	8	7.1	30	7.6	
350 - 700\$	0	0.0	1	0.9	1	0.3	
Family composition							
Single	20	7.4	4	3.7	24	6.3	
1 - 2 members	56	20.6	25	23.1	81	21.3	
>3 members	196	72.1	79	73.1	275	72.4	
Smoking							
Yes	1	0.4	52	45.2	53	13.2	
No	284	99.6	63	54.8	347	86.8	
Alcohol use							
Yes	1	0.4	37	32.2	38	10.0	
No	284	99.6	78	67.8	362	90.0	
Substance use							
Yes	0	0.0	1	0.9	1	0.3	
No	280	100.0	114	99.1	392	99.7	

Continued

Type DM						
Type I	7	2.5	5	4.3	12	3.0
Type II	271	95.1	107	93.0	378	94.5
Unknown	7	2.5	3	2.6	10	2.5
Anti-diabetic medicine						
Oral	230	80.1	88	76.5	318	79.1
Injecting	50	17.4	25	21.7	75	18.7
Both	7	2.4	2	1.7	9	2.2
Last CXR (self-reported)						
In the same year	27	9.4	6	5.2	33	8.2
Last 2 - 5 years	102	35.5	42	36.5	144	35.8
Do not answer/not remember	158	55.1	67	58.3	225	56.0
BG last measured						
Previous day	114	42.4	48	45.3	162	43.2
Within one month	127	47.2	45	42.5	172	45.9
Earlier than 1 month	28	10.4	13	12.3	41	10.9
BG last measurement (mmol/l)						
<6.0	17	6.2	8	7.5	25	6.6
6.1 - 10.0	152	55.5	54	50.9	206	54.2
10.1 - 15.0	74	27.0	34	32.1	108	28.4
>15.1	31	11.3	10	9.4	41	10.8
BG measurement (mmol/l) on the day of survey						
<6.0	29	10.1	9	7.9	38	9.5
6.1 - 10.0	120	41.7	45	39.5	165	41.0
10.1 - 15.0	83	28.8	36	31.6	119	29.6
>15.1	56	19.4	24	21.1	80	20.0
BP systolic (mm/Hg)						
90 - 140	151	54.9	71	65.1	222	57.7
140 - 160	75	27.3	20	18.3	95	24.7
160 - 220	49	17.8	18	16.5	67	17.4
BMI						
<18.5	2	0.5	2	0.7	0	0.0
18 - 25	41	10.2	20	7.0	21	18.3
25 - 30	114	28.4	75	26.2	39	33.9
30 - 35	142	35.4	102	35.7	40	34.8
35 - 40	60	15.0	51	17.8	9	7.8
>40	42	10.5	36	12.6	6	5.2

Continued

Comorbidities							
CVD	146	50.9	57	49.6	203	50.5	
Neurological	179	62.4	63	54.8	242	60.2	
Vision impairment	146	50.9	55	47.8	201	50.0	
Liver	19	6.6	5	4.3	24	6.0	
Kidneys	22	7.7	6	5.2	28	7.0	
BLE	105	36.6	30	26.1	135	33.6	
Tumor	16	5.6	1	0.9	17	4.2	
COPD	13	4.5	6	5.2	19	4.7	
Musculoskeletal	154	53.7	49	42.6	203	50.5	
Dermatological	12	4.2	3	2.6	15	3.7	
HIV infection	0	0.0	0	0.0	0	0.0	
People having 3 and more comorbidities	164	57.1	48	41.7	212	52.7	
History of TB							
Yes	1	0.3	5	4.3	6	1.5	
No	286	99.7	114	95.7	396	98.5	
TB clinical symptoms							
0 - 2	230	80.1	97	84.3	327	81.3	
>3	57	19.9	18	15.7	75	18.7	
Cough more than 2 weeks	31	10.8	29	25.2	60	14.9	
Fever more than 2 weeks	7	2.4	2	1.7	9	2.2	
Dyspnea	35	12.2	18	15.7	53	13.2	
Chest pain	25	8.7	11	9.6	36	9.0	
Hemoptysis	0	0.0	1	0.9	1	0.2	
Night sweat	192	66.9	62	53.9	254	63.2	
Appetite loss	59	20.6	15	13.0	74	18.4	
Weight loss	93	32.4	28	24.3	121	30.1	
Contact with TB patient	5	1.7	0	0.0	5	1.2	

Two participants reported TB in their families, however, none of them was a TB suspect by symptoms and CXR. Nevertheless, three and more TB signs (particularly night sweat, weight loss and cough for more than 2 weeks) were reported in 19% of study participants based on W4SS results.

In total, 402 DM patients participated in the study, for whom questionnaires were completed, screening for TB with W4SS questionnaire was carried out and CXR with CAD portable equipment was conducted. Out of 402 study participants, digital images of CXR were interpreted by CAD and NCP radiologists independently for 380 participants (**Table 2**).

Table 2. CAD and radiologists' screening results.

		CAD			
		TB+		TB-	
CAD+	True Positive	1	False Positive	1	2
CAD-	False Negative	1	True Negative	377	378
Total		2		378	380
Sensitivity	TP/TP + FN = 1/2, 50%				
Specificity	TN/TN + FP = 377/378, 99.7%				
		Radiologist			
Radiologist+	True Positive	2	False Positive	7	9
Radiologist-	False Negative	0	True Negative	371	371
Total		2		378	380
Sensitivity	TP/TP + FN = 2/2, 100.0%				
Specificity	TN/TN + FP = 371/378, 98.1%				

Out of 402 screened patients, only 25 were able to produce sputum for bacteriological confirmation by sample direct microscopy, GeneXpert MTB/RIF and culture test.

While in total 75 DM patients screened by W4SS questionnaire had three or more symptoms and were referred to bacteriological testing, only seven produced sputum. However, none of those seven patients' CXR images were interpreted as "TB suspect" by either CAD and the radiologist, or further confirmed bacteriologically. Only two CXR images were interpreted by CAD as "TB suspect" (**Table 3**).

The radiologist interpreted both these cases as "TB". The case TBS-A-153 was negative by GeneXpert MTB/RIF. The case TBS-A-394 had completed treatment for pulmonary TB with a "cured" outcome and the result of the post-treatment follow-up sputum culture test was negative (March 31, 2023).

In total, the radiologist interpreted nine CXR images as "TB suspect" and "TB". Out of these nine cases, one was TB-positive and four were TB-negative by GeneXpert MTB/RIF, one patient refused to continue with bacteriological analysis, the other participant was not able to produce sputum, and one patient was lost-to-follow-up (moved abroad). The last patient (TBS-A-394) had negative sputum culture result during post-treatment follow-up (**Table 3**).

Thus, out of the 380 study participants screened and analyzed, only one case was confirmed bacteriologically (0.3%, 95% CI: 0 - 0.8) and two participants were confirmed for TB in total (0.5%, 95% CI: 0 - 1.3). Both TB confirmed cases were males from rural settings aged 77 and 48 years old. They were diagnosed with DM 21 and 3 years ago, respectively. Blood glucose in two TB-confirmed patients were measured at 10.8 mmol/l and 14.1 mmol/l at the time of visit and BMI equal to 24 and 45 respectively.

Table 3. Screening outcomes.

No.	Patient code	Gender	Age	TB contact	DM duration, year	Clinical symptoms (N)	CAD interpretation	Radiologist's interpretation	GeneXpert MTB/RIF result	Clinical outcome
1	TBS-A-86	F	73	no	6	2	non-TB	TB suspect	no sputum	TB excluded
2	TBS-A-110	M	77	no	21	0	non-TB	TB suspect	positive	TB confirmed
3	TBS-A-143	M	68	no	29	1	non-TB	TB suspect	LTFU	LTFU
4	TBS-A-153	M	75	no	23	3	TB	TB suspect	negative	not evaluated
5	TBS-A-184	M	64	no	3	1	non-TB	TB suspect	negative	not evaluated
6	TBS-A-197	F	81	no	12	2	non-TB	TB suspect	negative	not evaluated
7	TBS-A-199	M	70	no	13	2	non-TB	TB suspect	refused	refused
8	TBS-A-388	M	65	no	16	1	non-TB	TB suspect	negative	not evaluated
9	TBS-A-394	M	48	no	3	2	TB	TB	n/a	see Notes*

LTFU: Lost-to-follow-up. Notes*: The patient completed treatment for TB with treatment outcome “cured” in September 2021. Sputum sample was taken on 31.03.2023 and examined within the framework of the post-treatment follow-up with culture-negative outcome.

3.2. In-Depth Interviews

Even though interviewees' experience related to CAD was limited, all of them mentioned CAD application for screening purposes only within the scope of their professional activities. One interviewee considered it useful to apply CAD in TB hospital for diagnostic purposes. All interviewees accepted the possibility of the patients' mistrust towards CAD, however, they also believed that education and enlightenment could help overcome this. The participants stated that the double review of X-ray images by radiologists was believed to increase trust in screening results. The interviewees found it important to explain to the people that CAD screening was just the initial step and additional examinations should be performed for the final diagnosis.

4. Discussion

While the DM patients cannot be considered as a primary target risk group for TB screening, the present study and a number of similar screenings may emphasize the importance of continuing this exercise to yield more evidence. To evaluate the diagnostic accuracy of CAD strategy (at determined calibration: 70) for screening and detection of TB in diabetic patients by comparing the performance of CAD in detecting probable pulmonary TB against a bacteriological reference standard in Armenia, the following results were found: the only one bacteriologically confirmed case was classified as “tuberculosis” by the radiologist and missed by CAD, the other case was confirmed by CAD and radiologist but the GeneXpert test was negative. Thus, it may be assumed that the CAD threshold set at 70 could have missed the “true” TB case. The availability of CAD in Armenia is a great opportunity to evaluate the diagnostic accuracy and feasibility of CAD application for

TB screening activities among the patients with diabetes. This experience may pave the way for programmatic implementation of screening strategy with CAD in Armenia, which will enable to increase the active screening and detect TB not only among diabetic patients but also in other groups exposed to a higher risk of developing TB.

Despite the provision of counseling to study participants, asymptomatic individuals demonstrated a low willingness to submit sputum samples. Reasons include but are not limited to: stigma and fear of being associated with TB, fear of results, discomfort and effort needed, practical barriers, lack of understanding of importance of sputum analyses, no proper instructions, and so on. This finding suggests that sputum examination may have limited applicability as a screening tool within populations presumed to be healthy and increases value of mobile CAD X-rays as a TB screening tool.

Nevertheless, feasibility and acceptability of using CAD within TB screening programs among patients with DM is obvious, given not only the yield of results and interpretations but also the outcome and expectations of in-depth interviews. All interviewees accepted CAD as a screening tool for TB detection, not only among DM patients but also in the other risk groups, especially for remote and hard-to-reach destinations. Participants indicated the lack of enough experience of working with CAD and mistrust to the accuracy and reliability of AI as the main shortcomings. It is worth mentioning that only one participant highlighted the importance of calibration of CAD when discussing the accuracy of interpretation. This can be explained in a way that other interviewees did not keep in mind or neglected the significance of CAD calibration related to the sensitivity and susceptibility of the device for TB detection. Nevertheless, the vast majority of participants acknowledged advantages of CAD in terms of mobility, as well as saving time and human resources.

Advantages of CAD: Participants acknowledged many advantages of CAD, such as: high quality of images, mobility, small size and feasibility in transportation to remote destinations, time-saving and quick interpretation, better safety compared with conventional X-ray devices, easy exploitation and high patient throughput in a comparatively short time, possibility to use the device for bedridden or disabled patients with movement limitations. Regarding the advantages of CAD for DM patients, the interviewees did not mention any specific features compared with the general population, however, they admitted the necessity to screen this population as a high-risk group and considered CAD as a helpful tool for this purpose.

“CAD as a ‘universal’ device for screening among various groups, including DM patients” —endocrinologist, Artashat Medical Center.

Potential barriers and challenges of CAD utilization in the health care facilities: the participants mentioned different preconditions to introduce and scale up CAD, such as: experience required for operating CAD.

“Interpretations of CAD coincide with the physician’s interpretation in 30% of

cases only, the AI interpretation is not reliable because it is 'human-made' and 'just a device'.

"It is important for technical proficiency to choose the right cutoff and scale for certain purposes".

Comparative analyses carried out for research conducted elsewhere with utilization of CAD technology in different settings demonstrate similar findings and recommendations.

Conclusions of the present study do not contradict with analogous research in comparable subject risk groups such as people living with diabetes mellitus [11] [12].

5. Limitations

The present study was limited in several ways.

CAD equipment was calibrated by default at 70, therefore, no other options of calibration below or above 70 were possible. Some TB suspects were lost to follow-up.

6. Conclusion

Taking into account all the findings and above discussion around the study objectives, we came up with the following conclusions. Utilization of CAD is feasible to perform in PHC setting for any population, including key populations such as people living with DM. Further studies devoted to CAD screening in DM patients are reasonable to conduct with application of CAD at a threshold lower than 70, as at least one PTB case was missed by CAD (calibrated at the threshold of 70) and confirmed by sputum GeneXpert test.

7. Recommendations

Based on the data presented in this manuscript, literature review and results of the in-depth interviews, the following recommendations were formulated.

- To have more accurate outcomes and not miss a TB suspect case in the patients with DM, we recommend reducing the CAD threshold to less than 70.
- The proper training of specialists will improve the CAD-reading outcomes. Thus, diagnostic accuracy of CAD will improve. In this light, accumulated practice and experience will be needed to promote and expand CAD diagnostic capacity in the country.
- To reduce the time interval between the screening and further clinical and laboratory examination of TB suspected cases as much as possible. On-site and proper counseling on this matter would definitely help overcome the challenge.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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