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The yield of chest X-ray based versus symptom-based screening among patients with diabetes mellitus in public health facilities in Addis Ababa, Ethiopia

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ABSTRACT

Background: Patients with diabetes mellitus (DM) are at increased risk of developing TB, but the best screening algorithm for early detection and treatment of TB remains unknown. Our objective was to determine if combining routine chest X-ray screening could have a better yield compared with symptom-based screening alone.

Methods: We conducted this cross-sectional study between September 2020 and September 2021 in 26 public health facilities in Addis Ababa, Ethiopia. All DM patients attending the clinics during the study period were offered chest X-ray and symptom screening simultaneously followed by confirmatory Xpert testing. We analyzed the number and proportion of patients with TB by the diagnostic algorithm category and performed binary logistic regression analysis to identify predictors of TB diagnosis.

Results: Of 7394 patients screened, 54.6 % were female, and their median age was 53 years. Type-2 diabetes accounted for 89.6 % of all participants of the patients. Of 172 symptomatic patients, chest X-ray suggested TB in 19, and 11 of these were confirmed to have TB (8 bacterilogicially confirmed and 3 clinically diagnosed). Only 2 of the 152 asymptomatic patients without X-ray findings had TB (both bacteriologically confirmed). X-ray was not done for one patient. On the other hand, 28 of 7222 symptom-negative patients had X-ray findings suggestive of TB, and 7 of these were subsequently confirmed with TB (6 clinically diagnosed). When combined with 8 patients who were on treatment for TB at the time of the screening, the overall point prevalence of TB was 380 per 100,000. The direct cost associated with the X-ray-based screening was 42-times higher.

Conclusion: Chest X-ray led to detection of about a third of TB patients which otherwise would have been missed but the algorithm is more expensive. Its full cost implication needs further economic evaluation.

1. Background

Tuberculosis (TB) and diabetes mellitus (DM) are significant public health problems both individually and as co-epidemics causing huge constraints on the health system and patient outcomes [1,2]. People with DM are at increased risk of developing TB. They are also at increased risk of relapse, treatment failure and death [3–6]. Recent estimates suggest that about 537 million adults were living with DM in 2021, 24 million of these were estimated to be residing in the African region, about 54 % these were undiagnosed and nearly half a million died of DM associated causes [7,8]. Type 2 diabetes (T2D) is projected to increase to more than eight thousand per 100,000 population by 2040, and the trend for lower-income countries is of significant concern [9]. According to a recent systematic review, 13.7 % of patients with active TB have DM [10]. In Addis Ababa, where this study was conducted, 14.8 % of adult patients attending public health facilities had DM [11]. In our own recent health-facility based study, 8.3 % of patients with active TB had DM which is more than twice the national prevalence estimate, a

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half of these were undiagnosed during TB treatment initiation, and a simple risk scoring system was found to be helpful in identifying patients at higher risk of TB [12]. With the projected massive increase in the number of people living with DM, identifying the optimum algorithm for early detection of TB in patients with DM would have huge impact in improving the quality of care for patients with co-morbidities.Fig. 1..

Despite the recommendations for bidirectional screening of the two diseases being in place for over a decade now [13], evidence on the extent of integrated screening remains limited, suggesting a need for more data in this area [14]. The updated WHO guidelines on TB screening provide detailed guidance on TB screening for the general population and some specific high-risk groups [15,16]. The guideline clearly outlines that systematic TB screening may be done among the general population if TB disease prevalence is estimated to be 0.5 % or higher. The specific subgroups in which systematic screening for TB is recommended include subpopulations with structural risk factors for TB, like people living with HIV, close contacts of people with pulmonary TB, and prisons and penitentiary institutions. DM is among the key risk factors that should be considered in the prioritization of TB screening among people attending health clinics. However, there is no consensus as to which screening algorithm is the best in terms of yield and cost for people living with diabetes. Symptom-only based screening, for example, requires less resources but its yield has been low. On the other hand, routine chest X-ray-based screening can be resource-intensive and difficult to interpret due to atypical radiological features, often involving lower lobes and cavitary lesions [17].

Studies that evaluated screening algorithms among other high-risk groups have shown varying yields. In Sri Lanka, for example, a study that employed sequential algorithm of systematic symptom-based screening followed by further investigation and clinical evaluation including chest X-ray based on indications was found to be effective only among older male patients with uncontrolled blood sugar [18]. Performance of computer-aided detection for TB (CAD4TB) among people living with diabetes and other risk groups also showed its beneficial role as triage test [19–21]. In the study that compared CAD4TB with symptom screening among household contacts, 42 % of bacteriologically confirmed TB patients were negative on symptom screen [21].

Studies that compare chest X-ray-based screening against symptom-based screening among patients with DM are scarce. Our objective was to assess the yield of TB screening in patients with DM using symptom-based screening alone or sequential algorithm of symptom-based screening followed by chest X-ray in those with symptoms.

2. Methods

2.1. Design and setting

This was a cross-sectional, health facility-based study carried out between September 2020 and September 2021. We conducted this study in 7 public hospitals and 26 health centers in Addis Ababa. The choice of these health care facilities was purposeful as they constituted the major centres for diabetes care in Addis Ababa, the capital city of Ethiopia. All these facilities have TB diagnostic and treatment services, but treatment follow-up was mostly organized at health center level.

2.2. Participants

All consecutive DM patients visiting the health facilities during the above stated period were screened for TB symptoms (≥2 weeks of cough, weight loss, fever and loss of appetite) using nationally approved symptom screening checklists. Patients with cough or two or more of the other symptoms were classified as “screen positive” while those without

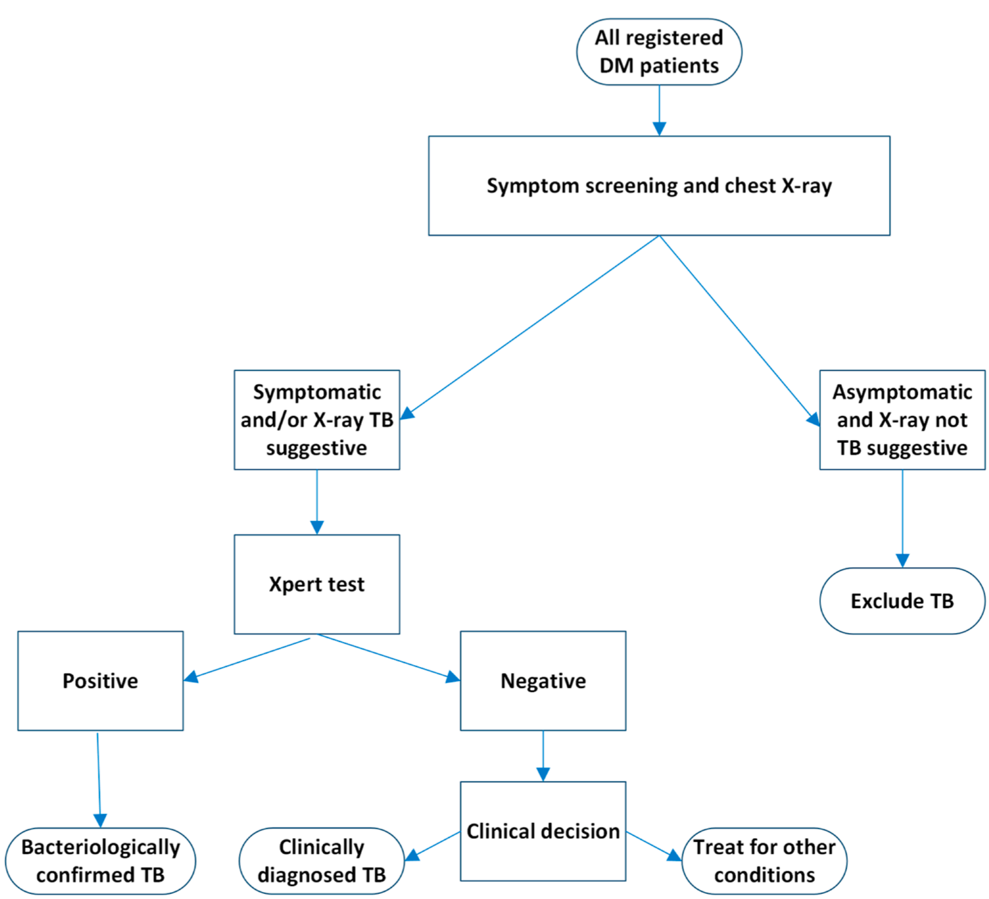

Fig. 1. Overview of the screening algorithm.

were classified as “screen negative”.

Patients were offered chest X-ray screening irrespective of their symptom status. In facilities where there is shortage or lack of chest radiography services, patients were linked to private diagnostic centers where the cost of the X-ray was covered under a contractual agreement signed between the health facility and the project coordination office.

Consultant radiologists interpreted the X-ray findings as part of their routine practice. The treating physician classified radiologists’ reports as “suggestive of TB” or “not suggestive of TB” based on the notes by the radiologists. Final TB diagnosis was made by the treating physician based on clinical, radiological, and bacteriological tests. All patients with productive cough received Xpert testing.

2.3. Training and quality assurance

All clinicians working in the diabetes clinics received additional on-site orientation on the TB screening algorithm. Also, district TB officers were oriented on the screening approach. They in turn supervised and mentored clinicians in the hospitals and health centers during the implementation of the study.

2.4. Data collection, entry, and analysis

At the end of each calendar month, project officers (a medical doctor and two nurses) visited each project site, reviewed clinical records, and collected individual level patient data on a standardized data abstraction form. A data clerk, under supervision of the project coordinator, entered the data in the Statistical Package for Social Sciences (SPSS) version 25.0 [22]. The lead author cleaned and analyzed the data.

The main outcome of interest was confirmed diagnosis of TB as per the national guideline. Accordingly, a patient can have bacteriologically or clinically confirmed TB. Bacteriologically confirmed pulmonary TB (BCTB) is defined as a person in whom a molecular WHO-recommended rapid diagnostic test (mWRD) detects *Mycobacterium tuberculosis* (*M.tb*); or a person who has at least 1 positive test result on acid-fast bacilli (AFB) microscopy. In this study, we relied on the Xpert MTB/RIF test for the confirmation of diagnosis as AFB microscopy was done inconsistently. A person in whom an Xpert MTB/RIF test showed no M.tb and a decision was made by a clinician to empirically treat with a full course of anti-TB treatment based on additional clinical evidence, was defined as having clinically diagnosed TB (CDTB). Confirmation of TB diagnosis outside the lung parenchyma was defined as extra-pulmonary TB (EPTB). Combination of all the three categories were defined as all forms of TB (AFTB) [23].

We used binary logistic regression (LR)technique to identify factors associated with increased risk of TB diagnosis. In the LR, we first performed univariate analysis of socio-demographic and clinical factors associated and moved those with a P-value < 0.25 to a multivariate analysis. We further analyzed the number and proportion of patients with any form of TB by the diagnostic algorithm category and presented the results in a flow diagram. We estimated the direct cost of X-ray examinations based on the WHO unit cost estimates [24]. As an indirect measure of cost effectiveness and effort, we calculated number needed to screen (NNS) and number needed to test (NNT) values for the two screening algorithms.

2.5. Ethics

The Ethics review committee of Addis Ababa City Council Health Bureau reviewed and approved the study protocol. Study participants provided informed verbal consent before being enrolled in the study. Patient data was handled confidentially, and anonymized data base was used for analysis. Patients who were diagnosed with TB received appropriate care according to the standard of care.

3. Results

Of 7394 DM patients screened, 54.6 % were female, the median (IQR) age of participants was 53 (45–61) years, and about a half were recruited from health centres. T2D accounted for 89.6 % of all participants. Ninety-nine per cent of all the participants were receiving some type of medication, with over 70 % being on a non-insulin-based regimen. Fasting plasma glucose (FPG) values were available for 99.4 % of the participants, their median (IQR) FPG level was 149 g/dL (122–189), and 71.2 % had FPG level $\geq$126 g/dL. Fifty-two (0.7 %) of the participants reported a history of TB, of whom two had had drug-resistant TB (DR-TB), and eight (0.1 %) patients were under treatment for active TB.

History of cough for two or more weeks was the most frequently reported symptom at 2.4 % (179 patients). Out of these, 162 (90.5 %) were determined to have presumptive TB (screen positive). Other symptoms were much less common including fever in 0.8 % (61 patients), night sweats in 0.7 % (49 patients), loss of appetite in 0.3 % (22 patients), and history of close contact in just 0.1 % (6 patients). Overall, symptom screening suggested presumptive TB in 172 patients, and only 10 of these were due to criteria other than cough. Of the 172 patients with presumptive TB on symptom screening, chest X-ray suggested TB disease in 11.2 % (19/172) − 11 of which were subsequently confirmed to have TB (8 BCTB and 3 CDTB). In the other 152 who had a chest X-ray which did not suggest TB disease, 2 had BCTB. Fig. 2 summarizes the yield of the screening algorithm.

All but two DM patients with presumptive TB received chest X-ray-based screening which suggested TB in 47 patients (0.6 %). A final diagnosis of TB disease was confirmed in 20 patients, of whom 11 had BCTB and 9 were diagnosed clinically i.e had CDTB. Of the 20 patients with a final diagnosis of TB, 18 had chest X-ray findings suggestive of TB, and 13 had a history of prolonged cough. The overall point prevalence of newly diagnosed active TB was thus 270 per 100,000. When the eight patients already on treatment are added, the prevalence increases to 380 per 100,000. Out of the 7,222 patients in whom TB symptom screen was negative, chest X-ray suggested TB disease in 28 - of whom7 were subsequently confirmed to have TB (1 BCTB and 6 CDTB).

Using a direct cost estimate of USD $8 per X-ray, the total direct cost associated with X-ray examinations was USD $59,136. If the order of the screening were reversed, i.e doing X-ray in those with TB symptom screen positive only, we would have spent USD $1,376 on chest X-rays. Thus, the routine X-ray based screening led to a 42-fold increase in the direct cost of X-rays.

In bi-variate analyses, having clinical symptoms and being male were significantly associated with higher rates of TB diagnosis. Table 1 shows unadjusted associations between clinical and demographic factors and final TB diagnosis. Neither age group nor the type of diabetes was associated with TB diagnosis.

The NNS for symptom-only screening was 569 compared with 370 for X-ray. Table 2 summarizes the NNS and NNT values for the two screening algorithms.

In an adjusted analysis, male sex was significantly associated with TB diagnosis (aOR), 95 % CI; 7.06 [1.92, 25.93]; $p < 0.01$). Also, having chronic cough [aOR, 95 % CI; 15.49 (3.74–64.18)] and night sweats [aOR, 95 % CI; 14.27 (3.73–54.59)] showed significant association with TB diagnosis. However, neither age group not loss of appetite had significant association (Table 3).

4. Discussion

In this study, the rate of TB disease amongst patients with DM was 380 per 100,000 which is nearly thrice the national TB incidence estimate of 132 per 100,000 in the general population [25], confirming the heightened risk of TB among this group of patients. Routine chest Xray, irrespective of absence of TB symptoms, helped detect almost a third of the newly detected TB patients, which otherwise would have been

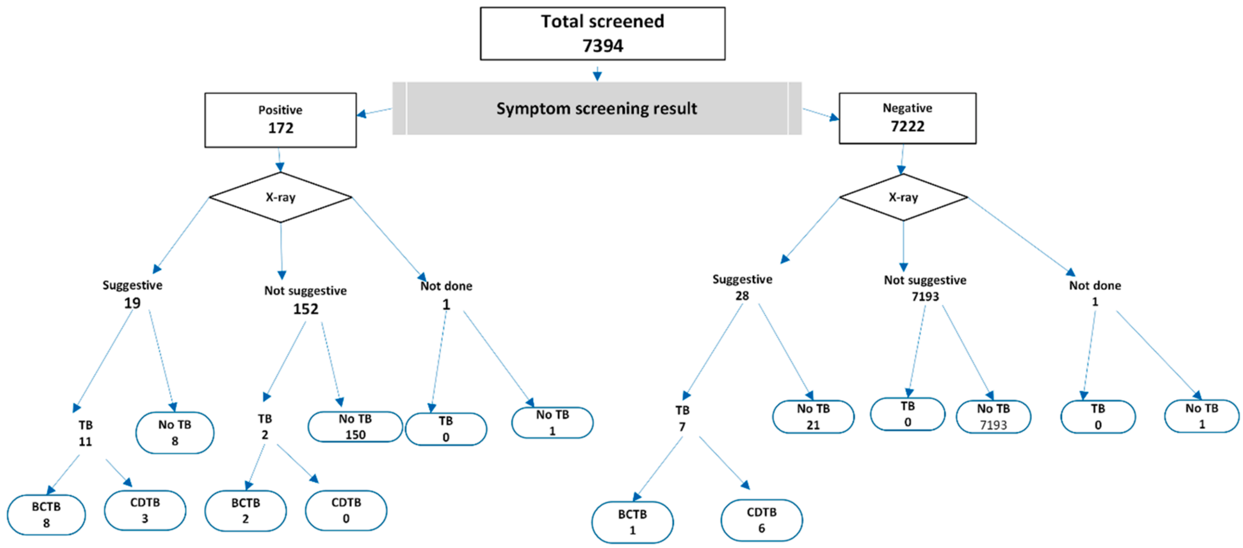

Fig. 2. Profile of patients screened and diagnosed for TB.

Table 1
Frequency of baseline clinical and laboratory data in patients with or without final TB diagnosis.

	Number (%)		
Variable	No TB	TB	Chi square; p-value
TB symptom-cough ≥2 weeks			
Yes	166 (2.2 %)	13 (65)	332; <0.001
No	7206 (97.8)	7 (35)	
Fever			
Yes	55 (0.7)	6 (30)	208.5; <0.001
No	7315 (99.3)	14 (s70)	
Night sweats			
Yes	39 (0.5)	10 (50)	741; <0.001
No	7330 (99.5)	10 (50)	
Loss of appetite			
Yes	20 (2.7)	2 (10)	63.6; <0.001
No	7348 (97.3)	18 (90)	
Type of health facility			
Hospital	3791 (51.4)	6 (30)	3.67; 0.16
Health Centre	3579 (48.6)	14 (70)	
Sex			
Male	3305 (45)	17 (85)	13.01; <0.001
Female	4033 (55)	3 (15)	
Age group			
1–64 yr	6001 (81.8)	19 (95)	2.33; 1.27
65+	1332 (18.2)	1 (5)	
Type of diabetes			
Type 1	766 (10.4)	2 (10)	0.01; 0.99
Type 2	6604 (89.6)	18 (90)	
Latest FBS (g/dl)			
<126 g/dl	2109 (28.8)	5 (25)	0.13; 0.7
>=126 g/dl	5222 (71.2)	15 (75)	
Type of medication			
Insulin	1583 (21.5)	3 (15)	5.6; 0.6
Oral hypoglycemic	942 (12.8)	4 (20)	
Metformin	2167 (29.4)	5 (25)	
Diet and exercise only	85 (1.2)	0	
Oral hypoglycemic and Metformin	1954 (26.6)	7 (35)	
Insulin and Metformin	532 (7.2)	0	
Insulin and Oral hypoglycemic	95 (1.3)	1 (0.5)	

Table 2
NNS and NNT values per screening algorithm.

Indicators	Symptom-only	X-ray added
Number of individuals identified with TB (A)	13	20
Number of individuals screened (B)	7394	7394
Number of individuals tested (C)	172	200
NNS (A/B)	569	370
NNT (A/C)	13	10

Table 3
Adjusted analysis of factors associated with TB diagnosis.

Variable	Unadjusted OR (95 %)	Adjusted OR (95 % CI)
Sex (Male vs Female)	6.91 (2.02, 23.62)	7.06 (1.92, 25.93)
Age group (<65 yr vs 65 +)	4.21 (0.56, 31.53)	4.44 (0.53, 36.6)
TB symptom-cough ≥2 weeks (yes vs no)	80.62 (31.76, 204.66)	15.49 (3.74, 64.18)
Fever (yes vs no)	57 (21.13, 153.78)	2.99 (0.8, 10.77)
Night sweats (yes vs no)	187.95 (74.06, 476.98)	14.27 (3.73, 54.59)
Loss of appetite (yes vs no)	40.82 (8.88, 187.65)	1.29 (0.2, 7.92)

missed. However, it should be noted that only one out of these seven cases were bacteriologically confirmed, with the other six being clinically confirmed TB cases. Hence, it is likely that the risk of transmission from these seven "missed" patients would be minimal.

While there are many studies that have addressed the prevalence of DM in patients attending TB clinics, studies looking at the prevalence of TB among diabetics are much fewer. In most of this small number of studies, the algorithm includes a chest X-ray only for patients who have a positive symptom screen [26,27]. A study in Karachi, Pakistan did include DM patients with and without symptoms suggestive of TB. However, the number without presumptive TB who took up screening was too small to comment on the yield of TB among those tested for TB without any suggestive symptoms [28]. Thus, although these studies confirm the wider finding of a higher prevalence of TB disease in those patients with diabetes mellitus, they do not show whether the routine use of chest X-ray in all patients attending diabetic clinics irrespective of TB symptoms.

Our results highlight the potential role of routine chest X-ray examination for patients under diabetic care at an interval to be determined in further studies. But inclusion of routine X-ray examination for all diabetic patients, irrespective of TB symptoms, increased the direct cost of diagnostics 42-fold. A screening programme conducted in Jiangyin City of Jiangsu Province, China from 2016 to 2018, concluded that it was feasible but uneconomical to conduct large-scale and regular chest X-ray screening for tuberculosis (TB) in diabetic patients [29].

The introduction of active screening for TB needs to consider the screening interval, target population, screening methods, and other logistical issues. A reasonable screening frequency can be determined based on the infection rate and the incidence rate of TB and financial affordability. The authors of the paper from China recommended that it was more economical to implement active TB screening (including a chest Xray) every 2 years rather than every year, focusing on the high-risk groups (given as patients with a low body mass index, high fasting blood glucose, and decreased triglycerides) for TB screening than to select all diabetes patients [29]. In our study, majority of the patients had FPG levels exceeding the threshold for DM diagnosis. If that is taken as an uncontrolled DM, that will still be too large to consider for routine screening.

Presence of additional risk factors should be considered in prioritizing patients for routine chest X-ray screening. In Bangladesh, for example, female patients and those with undernutrition were found to be at higher risk of developing TB [30]. The higher TB rate in our study is in line with the general global trend that TB burden is higher among males [31], but the Bangladesh finding of a higher TB rate among female patients with diabetes is in sharp contrast to ours. Others also found increased risk of TB among DM patients who used insulin for DM treatment and in those with longer duration in diabetes care. The use of insulin was associated with increased risk of TB in a national cohort of DM patients in Australia, as insulin use is an indirect indicator of poor glycemic control with oral hypoglycemic agents [32]. Although the small number of patients with TB diagnosis did not allow us to make adequate comparison by DM treatment regimen, we did not find significant association by regimen type. We did not include information about nutritional status and other risk factors such as smoking in our study, and indicators of disease such as Hemoglobin A1c were not included, which are among the limitations of this study. We also did not do a thorough economic evaluation of the X-ray screening, which would have helped with making choices between the tradeoffs of missing cases and spending more money.

5. Conclusion

A screening algorithm that integrated chest X-ray examination within the existing symptom-based screening irrespective of the patients' symptom status led to detection of about a third more TB patients among people with DM who otherwise would have been missed. Clearly, doing chest X-ray for every DM patient is more expensive than symptom-guided screening, but its full cost implication to TB programmes needs further economic evaluation. Further studies are also needed to determine the optimum frequency of such screening schedules.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. This project was funded by Dr. C. de Langen Stichting voor Mondiale Tuberculosebestrijding.

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