



Contents lists available at ScienceDirect

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

journal homepage: www.elsevier.com/locate/jctube

Chest X-ray predicts cases of pulmonary tuberculosis among women of reproductive age with acute respiratory symptoms: A multi-center cross-sectional study

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ARTICLE INFO

Keywords:

Chest X-ray
Pulmonary tuberculosis
Women of reproductive age
EXIT-TB
Acute respiratory symptoms
Ethiopia

ABSTRACT

Background: Tuberculosis (TB) prevalence is increasing among women of reproductive age (WRA) in sub-Saharan Africa, yet undiagnosed and untreated cases remain rather high with serious health and socio-economic consequences. We aimed to assess the prevalence and predictors of TB in WRA seeking health care for acute respiratory symptoms.

Methods: We consecutively enrolled outpatient WRA with acute respiratory symptoms seeking care at four healthcare facilities in Ethiopia between July 2019 and December 2020. Data on sociodemographic characteristics and clinical information were collected using a structured questionnaire administered by trained nurses. Posteroanterior chest X-ray was performed in non-pregnant WRA and interpreted independently by two radiologists. Sputum samples were collected from all patients and tested for pulmonary TB using Xpert MTB/RIF and/or smear microscopy. Predictors of bacteriologically confirmed TB cases were determined using binary logistic regression, with clinically relevant variables included in the final Firth's multivariate-penalized logistic regression model.

Results: We enrolled 577 participants, of whom 95 (16%) were pregnant, 67 (12%) were living with HIV, 512 (89%) had cough of less than 2 weeks, and 56 (12%) had chest-x-ray findings suggestive of TB. The Overall prevalence of TB was 3% (95% CI: 1.8%-4.7%) with no significant difference observed between patient groups categorized by duration of cough or HIV serostatus (*P-value* = 0.9999). In multivariable analysis, TB-suggestive CXR abnormality (AOR 18.83 [95% CI, 6.20–57.18]) and history of weight loss (AOR 3.91 [95% CI, 1.25–12.29]) were associated with bacteriologically-confirmed TB cases.

Conclusions: We found a high TB prevalence among low-risk women of reproductive age with acute respiratory symptoms. Routine CXR may improve early case detection and thereby TB treatment outcomes.

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<https://doi.org/10.1016/j.jctube.2023.100383>

Available online 8 June 2023

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1. Introduction

Tuberculosis (TB) is a leading infectious cause of morbidity and mortality, including in women of reproductive age (WRA) between the ages of 15 and 49, with an estimated 1.6 million deaths in 2021 [1–3]. Of all HIV-related TB deaths worldwide in 2020, about half are women [4] and almost 90% of HIV-related TB deaths in women occur in sub-Saharan Africa (SSA) [5]. Although most TB cases are still diagnosed in men [1], reported cases in WRA are increasing in SSA [2,6]. Most available anti-TB regimens are safe and effective even during pregnancy, with a good compliance rate reported [7,8]. Yet TB patients are often diagnosed late in the disease course, with 60% of the estimated number of cases going undiagnosed or unreported in 2021 [1,9]. In TB-endemic countries, untreated TB remains a notorious cause of infertility and poor maternal and perinatal outcomes [5,8,10,11].

The literature reports that the prevalence of TB in WRA age is high, even in asymptomatic or acutely symptomatic patients [6,12–15]. A study also found a high prevalence of pulmonary TB in patients presenting to outpatient clinics for a cough lasting less than two weeks [16]. In contrast, some studies have reported a low TB prevalence in predominantly HIV-negative pregnant cohorts, regardless of the duration of respiratory symptoms [17–19], and a cough lasting longer than two weeks has been suggested as a better criterion for HIV-negative pregnant women [18].

Recognizing the importance of early TB case detection, recent WHO guidelines have included tools that increase the sensitivity of TB case detection, namely chest X-ray (CXR), C-reactive protein (CRP) in people living with HIV, and rapid molecular diagnostic tests [9]. However, performing CXR raises safety concerns in pregnant women [20], and molecular diagnostic tests may not be sensitive in patients living with HIV [14,21] or unavailable in most health facilities where patients first encounter the healthcare system [22]. Physicians reported seeing a large number of patient cases in reproductive and child health (RCH) clinics and tend to focus on “more common” diagnoses as available resources do not allow them to follow guidelines [18].

In WRA, there is a need to improve case detection capabilities [10], however, which patients should be tested to maximize case detection while giving due consideration to resource implications remains a topic of research and controversy. Besides, optimal TB case-finding methods for pregnant women are ill-investigated. This study aimed to assess the prevalence and predictors of pulmonary TB in WRA seeking healthcare for acute respiratory symptoms.

2. Methods

2.1. Study design setting

This study was part of the EXIT-TB (Scaling up Evidence Based Multiple Focus Integrated Intensified TB Screening to End TB research project; a multi-center implementation study that implements and evaluates EXIT-TB package to increase TB case detection in the East African region [23–26]. The study followed a quantitative, multicenter cross-sectional study design. It was conducted in four health institutions in Ethiopia from July 2019 to December 2020; two hospitals were in urban areas, namely, Hiwot Fana Specialized University Hospital found in Harari Region and Zewditu Memorial Hospital found in Addis Ababa City Government, and one hospital and one health center located in rural areas, thus Chelenko Primary Hospital and Melka Jebdu Health Center found in Oromia Region. Site selection was done using stratified random sampling taking into account the difference between urban and rural settings [23] and referral bias.

2.2. Participants

Participants were WRA with acute respiratory symptoms seeking outpatient care in the four study facilities. Acute respiratory symptom

was defined primarily as a cough of less than two weeks duration. The Sample size was estimated using a single proportion formula with a 95% confidence level, 80% power, 3% margin of error, 15% contingency, and an assumed bacteriologically-confirmed pulmonary TB prevalence among WRA of 5.3% [12]. These reached a final sample size of 577. Participants with diabetes, HIV/AIDS, alcohol use disorders, smoking and malnutrition were considered high-risk groups for developing TB according to guidelines [9].

2.3. Data collection procedures

WRA attending outpatient clinics for acute respiratory symptoms with no confirmed pulmonary TB and consented to participate in the study were consecutively enrolled in the study. To determine the prevalence and predictors of bacteriologically confirmed TB in WRA age who presented with cough of acute duration, four trained data collectors administered a structured and pre-tested questionnaire that included socioeconomic and demographic variables, risk factors for TB, and active respiratory symptoms.

All study participants, except pregnant women, underwent quality-controlled posteroanterior CXRs, and two experienced radiologists blinded to clinical information interpreted the films. Inter-observer agreement for all CXR films obtained as part of the project was checked and we found an adequate agreement for TB suggestive findings [$\kappa = 95\%$ (95% CI: 87.598.6%)].

All study participants gave sputum specimens which were tested for TB using Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) and/or smear microscopy based on the national TB guideline [24]. Laboratory-confirmed cases were referred and linked to treatment.

2.4. Statistical analysis

Collected data were cleaned, entered into EpiData version 3.1 and then transferred to Stata version 14.2 (StataCorp, College Station, Texas, USA) for statistical analysis. First, descriptive statistics were generated for sociodemographic variables, TB risk factors, and active respiratory symptoms and associations with TB status checked using Fisher’s exact test. Subsequently, predictors of bacteriologically confirmed TB cases were determined using binary logistic regression, with clinically relevant variables included in the final multivariate-penalized logistic regression model (firthlogit). Odds ratios with 95% confidence intervals (CIs) were reported and a *P-value* of less than 5% was considered statistically significant.

2.5. Ethical approval

This study was approved by the Institutional Review Board of the College of Health Sciences, Addis Ababa University, and the Institutional Health Research Ethics Review Committee of the College of Health and Medical Sciences, Haramaya University. Written consent was obtained from each participant or parents as applicable, and assent was sought from children under the age of 18. All patients received standard care according to national guidelines and those diagnosed with TB were linked to TB treatment clinics [27].

3. Results

3.1. Sociodemographic characteristics of study participants

A total of 577 WRA were included, of whom 95 (16%) were pregnant. The participants had a mean age (SD) of 29.8 (9) years and 262 (46%) were in the 25–34 age group. Four participants were under the age of 18. Descriptive statistics on sociodemographic variables and classification by bacteriologically-confirmed TB status are presented in Table 1.

Table 1
Sociodemographic characteristics of study participants and associations with bacteriologically-confirmed TB cases at health facilities, Ethiopia.

Socio-demographic Characteristics	N = 577 %	Smear/X pert Positive	Smear/X pert negative	P-value*	
Health Facility					
Melka Jebdu Health center	181 (31)	1	180	0.0700	
Hiwot Fana University Hospital	178 (31)	8	170		
Zewditu Memorial Hospital	120 (21)	4	116		
Chelenko Primary Hospital	98 (17)	4	94		
Clinic					
Out-patient department	475 (82.4)	17	458	0.2850	
Antenatal care	94 (16.2)	0	94		
Diabetic clinic	3 (0.5)	0	3		
Family planning	1 (0.2)	0	1		
Labor ward	1 (0.2)	0	1		
Postnatal care	3 (0.5)	0	3		
Age category					
15–24	169 (29)	7	162		0.5430
25–34	262 (46)	7	255		
35–49	146 (25)	3	143		
Level of education					
Never attended	295 (51)	9	286	0.6510	
Primary Education	138 (24)	3	135		
Secondary Education	80 (14)	3	77		
Vocational Training	20 (3)	0	20		
Tertiary education	27 (5)	2	25		
Traditional Education	17 (3)	0	17		
Marital Status					
Single	102 (18)	4	98	0.1070	
Married	410 (71)	9	401		
Separated	23 (4)	1	22		
Divorced	20 (3)	0	20		
Widow/Widower	22 (4)	3	19		
Occupation					
Student	51 (9)	1	50	1.0000	
Employed	87 (15)	2	85		
Peasant	65 (11)	2	63		
Housewife	342 (59)	11	331		
Business owner	32 (6)	1	31		
Residence					
Rural	278 (48)	11	267	0.1280	
Urban	299 (52)	5	293		

*p-values are expressed from Fisher’s exact tests; N: absolute frequency; %: percentage.

3.2. Clinical symptoms and TB risk factors

Of the total, 67 (12%) of the participants were living with HIV and 51 (76%) of them were on ART. Five hundred twelve (89%) participants had a cough less than two weeks, and 306 (53%) reported one or more accompanying respiratory symptoms such as fever, hemoptysis, chest pain, or shortness of breath. CXR was performed in 482 non-pregnant participants, of whom 56 (12%) had findings suggestive of TB (Table 2).

Xpert MTB/RIF was done for all participants and sputum smear microscopy was performed in all except 11 participants. 17 patients [3% (95% CI: 1.8%-4.7%)] had bacteriologically confirmed TB. In pregnant WRA, there were no diagnosed cases of TB. Similarly, no clinically diagnosed TB case was recorded in this study. The prevalence of TB in

Table 2
Clinical risk factors and symptoms of study participants and their association with bacteriologically-confirmed TB cases at health facilities, Ethiopia.

Risk factors and Clinical Presentation	N = 577 %	Xpert/Smear positive	Smear/X pert negative	P-value
HIV serostatus				
Positive	67 (12)	2	65	0.9999
Negative	510 (88)	15	495	
Is the patient on ART				
Yes	51 (76)	1	50	0.4180
No	16 (24)	1	15	
TB contact history				
Yes	67 (12)	5	62	0.0390
No	503 (87)	12	491	
Not sure	7 (1)	0	7	
Chronic diseases				
Chronic disease/s present	28 (5)	0	28	0.9999
No chronic disease	549 (95)	17	532	
Alcohol intake				
Yes	90 (16)	3	87	0.7380
No	487 (84)	14	473	
Cigarette smoking				
Yes	12 (2)	1	11	0.3040
No	565 (98)	16	549	
Duration of cough				
Cough < 2 weeks	512 (89)	15	497	0.9999
Cough ≥ 2 weeks	65 (11)	2	63	
fever				
Yes	236 (41)	4	232	0.2100
No	341 (59)	13	328	
Hemoptysis				
Yes	80 (14)	4	76	0.2750
No	497 (86)	13	484	
Chest pain				
Yes	15 (3)	0	17	0.9999
No	560 (97)	17	543	
Shortness of breath				
Yes	8 (1)	0	8	0.9999
No	569 (99)	17	552	
Night sweat				
Yes	310 (54%)	10	300	0.8070
No	267 (46%)	7	260	
Weight loss				
yes	88 (15)	6	82	0.0320
No	489 (85)	11	478	
Chest X-ray				
Suggestive of TB	56 (10)	11	45	0.0001
Normal/Non-suggestive	426 (74)	6	420	
Not done	95 (16)	0	95	

N: absolute frequency; %: percentage; ART: antiretroviral treatment

WRA with coughs lasting less than 2 weeks was 2.93%, which was comparable to those with chronic coughs at 3.08% (Fisher’s exact p-value = 0.9999) (Table 2). Likewise, no significant difference in TB prevalence was found between WRA living with or without HIV (Fisher’s exact p-value = 0.9999).

3.3. Association between participant characteristics and pulmonary TB

A CXR abnormality suggestive of TB was strongly associated with

bacteriologically confirmed TB cases, even after controlling for confounders ($P < 0.0001$) (Table 3). The odds of TB diagnosis in patients with TB-suggestive CXR findings were 19 times higher than those with normal CXR findings or non-TB-suggestive abnormal findings (AOR, 18.83 [95% CI, 6.20–57.18]). In addition, patients with weight loss had 4 times odds to be diagnosed with TB (AOR, 3.91 [95% CI, 1.25–12.29]). We observed an association between previous contact with a known TB patient and diagnosed TB cases although it does not reach statistical significance when other variables are accounted for ($P = 0.1300$). There was also no significant difference in the odds of being diagnosed with TB depending on the duration of cough ($P = 0.4900$) and the presence of established risk factors for TB (Table 3).

4. Discussion

This study aimed to determine the prevalence and predictors of bacteriologically-confirmed pulmonary TB among WRA with acute respiratory symptoms visiting healthcare facilities for treatment. CXR abnormality suggestive of TB and a history of weight loss had significant associations with bacteriologically-confirmed TB cases.

This study found a higher TB prevalence among out-patients with acute duration of cough than previously reported study in Ethiopia, at 1.9% [16], although lower than the prevalence in chronic coughers [12,16]. In the first study, however, only 46% of the study participants were women and no data was available on how many were in the reproductive age groups [16]. There were no confirmed TB cases among pregnant women in our study, which was comparable with a previous study [17] that reported no culture-confirmed cases out of 174 pregnant women with a cough duration of more than 2 weeks. No significant difference in TB prevalence was observed among WRA living with or without HIV, unlike studies from elsewhere that noted limited TB cases in HIV-negative women [12,13,18,19]. A possible explanation for the observed difference could be that the previous studies have enrolled comparatively higher number of women living with HIV/AIDS [12,13]. In addition, some of the studies have included a confirmatory culture test [13], or addressed only chronically coughing WRA [12].

In this study, the prevalence of TB was fairly comparable among participants presenting with a duration of cough of less or more than two weeks, as also reported elsewhere [24]. Although there are previous studies that questioned cough duration as a significant risk factor, they reported a discrepant occurrence of TB in the two groups [28,29]. In addition, a recent study from Eswatini found no difference in TB prevalence between symptomatic and asymptomatic patients [13]. Currently, symptom-based screening for TB, even modified to include

patients with cough of any duration, is becoming less preferred as it missed to detect a significant number of TB cases [14,30] although it was found to have good specificity [31] and cost-effectiveness. The findings of this study challenge the use of 2-week cough criteria to prioritize patients for the limited TB diagnostic resources. A separate study found a TB prevalence of 14% among all acutely coughing outpatients and recommended that patients with acute cough should undergo a TB workup including CXR [23]. Despite the low TB prevalence of 3% we found in WRA, the same recommendations can be made considering the grave consequences of TB in these patients.

A CXR abnormality suggestive of TB was found to be better at predicting cases in the present study, and it may outperform cough duration-based algorithms in assigning low-risk WRA to different TB likelihood categories. Furthermore, CXR has documented benefits in improving TB case detection compared to symptom-based screening in adults [30,31] and there is increasing interest in adopting CXR-based screening in national TB programs in line with WHO recommendations [9]. It is important to keep in mind that 35% of TB cases occurred in patients who did not have suggestive CXR findings. Although computer-aided detection of TB suggestive findings may have improved the performance and feasibility of CXR-based diagnosis in a study setting, it is not widely available today [32,33].

We could not perform a subgroup analysis in pregnant women as no TB case was identified among them. Although we included few pregnant women in our study, a sputum sample was obtained from all and analyzed according to national guidelines. However, bacteriological TB diagnostic tests, particularly smear microscopy, are known to have low sensitivity in pregnant women [8,15]. There is also a recent study reporting reduced sensitivity of molecular diagnostic tests in pregnant women compared to confirmatory culture [14]. In multivariable analysis, patients with suggestive CXR abnormalities and weight loss had higher odds of being diagnosed with TB. As is well known, physicians hesitate to order CXR in pregnant women, and these patients are less likely to present with weight loss [7]. However, TB can present with acute respiratory symptoms during pregnancy and shielded CXR is an option to improve case detection [8]. A clinically diagnosed case of TB was also not documented among enrolled patients, possibly reflecting the ingrained thinking of health workers that associates TB with a cough lasting longer than 2 weeks. The wider clinical, public health, social and structural forces are all important in decisions surrounding TB screening, diagnosis, and management [34–39].

This study reported solid evidence about the prevalence and predictors of TB in WRA seeking health care for acute respiratory symptoms in one of the high TB burden countries, Ethiopia. However, the study has

Table 3

Multivariable Logistic Regression of Factors Associated with Bacteriologically confirmed TB cases at health facilities, Ethiopia. (n = 577).

Variables	Categories	COR 95% CI	P	AOR 95% CI	P
Age category	15–24	2.06 (0.52–8.11)	0.30	2.74 (0.66–11.32)	0.1600
	25–35	1.31 (0.33–5.14)	0.70	1.14 (0.27–4.81)	0.8600
	36–49	—	—	—	—
HIV serostatus	Positive	1.02 (0.23–4.54)	0.98	1.33 (0.27–6.57)	0.7200
	Negative	—	—	—	—
TB contact History	Yes	3.30 (1.13–9.68)	0.03	0.38 (0.11–1.27)	0.1300
	No	—	—	—	—
Duration of cough	< 2 weeks	—	—	—	—
	≥ 2 weeks	0.95 (0.21–4.25)	0.95	0.59 (0.13–2.64)	0.4900
Other respiratory symptoms*	Present	0.79 (0.30–2.08)	0.64	0.57 (0.19–1.67)	0.3100
	Absent	—	—	—	—
Night sweat	Yes	1.24 (0.46–3.29)	0.67	0.45 (0.14–1.42)	0.1700
	No	—	—	—	—
Weight loss	Yes	3.18 (1.14–8.83)	<0.01	3.91 (1.25–12.29)**	0.0200
	No	—	—	—	—
CXR finding	TB suggestive	17.23 (6.08–48.81)	<0.001	18.83 (6.20–57.18) ***	<0.0001
	Not TB suggestive	—	—	—	—

*Other respiratory symptoms: fever, hemoptysis, chest pain and shortness of breath; **Statistically significant for tuberculosis at P value <0.05; ***Statistically significant for tuberculosis at P value <0.0001; CI: confidence interval; COR: crude odds ratio; AOR: Adjusted odds ratio.

some limitations. First, most study participants were nonpregnant, low-risk WRA, and the results may not be generalizable to high-risk WRA. Second, we did not include as many women with chronic symptoms, which may have reduced the number of cases identified and influenced the comparison.

5. Conclusion

TB is prevalent in low-risk women of reproductive age with acute respiratory symptoms. Routine CXR may improve early case detection and thereby TB treatment outcomes, thus should be performed and interpreted with TB in mind to identify and put more cases into treatment. More studies that included a larger number of pregnant and HIV-positive women are recommended to provide better insight into the TB burden among high-risk women.

Funding

This work was funded by the European and Developing Countries Clinical Trials Partnership (EDCTP2) program supported by the European Union under grant number CSA2016S-1608.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the College of Health Sciences, Addis Ababa University, and the Institutional Health Research Ethics Review Committee of the College of Health and Medical Sciences, Haramaya University, Ethiopia.

Consent for publication

Study participants have given their full consent for publication.

Availability of data and materials

The datasets used and/or analyzed during the current study will be available from the corresponding author on reasonable request.

CRedit authorship contribution statement

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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.

Acknowledgments

The authors thank the Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University, Ethiopia, for providing technical support and managing the grant. The authors thank Haramaya University for supporting the execution of the project.

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