Delay in Diagnosis of Pulmonary Tuberculosis is Associated with Increased Risk of Transmission in Pastoralist Setting, Ethiopia

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Abstract

Background To comprehend the effect of delayed care on risk of tuberculosis (TB) transmission in a TB prevalent but low case detection area, this study examined the association of diagnosis delay with patient infectiousness (cavitation and smear positivity) and determined the threshold delay that optimizes infectiousness. It also assessed transmission drivers in Somali region of Ethiopia, an area with ample pastoralist population. Methods A cross-sectional study was conducted using 434 new pulmonary TB patients, aged ≥15 years, who were recruited prospectively in five major facilities between December 2017 and October 2018. Data were collected on delays in diagnosis, socio-demographics, clinical and epidemiological information using interview, record-review, anthropometry, sputum microscopy and chest radiography techniques. Log-binomial regression models were used to reveal predictors of cavitation and smear positivity at p<0.05 using Stata/SE®14. C-statistics was applied to determine predictive ability and threshold delay that classifies infectiousness. Results Median age of participants was 30 years. Majorities were male (62.9%), nearly half (46.5%) were pastoralist and 2.3% TB/HIV co-infected. Median delay from debut of illness to diagnosis was 49 days (IQR=37). Among all cases, 45.6% [95%CI: 40.9-50.4] had pulmonary cavity and 42.0% [95%CI: 37.3–46.9] were smear positive. On multivariable analysis, cavitation was higher in patients delayed over a month [P<0.001], ≤35 years [APR (95%CI) =1.3(1.01-1.6)], with chronic diseases [APR (95%CI) =1.8(1.2-2.6)] and low MUAC*female [APR (95%CI) =1.8(1.2-2.8)]. Smear positivity was higher in patients delayed >49 days [p=0.02], ≤35 years [APR (95%CI) =1.4(1.1-1.8)], low BMI [APR (95%CI) =1.3(1.01-1.7)] and low MUAC [APR (95%CI) =1.5(1.2-1.9)]. Delay discriminates cavitation [AUC (95%CI) =0.67(0.62-0.72)] at 43 days optimal cutoff and 74.6% sensitivity. Conclusion This study highlights that delay in diagnosis of pulmonary TB remains high and is associated with increased risk of cavitation and smear positivity in pastoral setting in Ethiopia. In pastoral settings, this may call upon a socio-cultural tailored TB prevention and control strategies.

Background

Tuberculosis (TB), caused by *Mycobacterium Tuberculosis (MTB)*, remains the leading killer of infectious diseases. Globally, it caused an estimated 10 million cases, 1.3 million deaths, and 300,000 deaths among HIV-positive people in 2017. In the same year, Ethiopia ranked 11th among the 22 high burden, 4th in Africa and one of 14 countries with triple burden of TB, MDR-TB and TB/HIV with an estimated 172, 000 new cases [1]. The prevalence was found to be higher in pastoral communities (316/100,000) than the national level (277/100,000) [2]. To curb the global epidemics of this deadliest disease, the End-TB strategy sets early diagnosis and treatment of cases as pillars to ending TB epidemics by 2030 [3]. For the most part, the national TB control program (NTP) of Ethiopia detects TB cases when people with presumptive symptoms present themselves to health facilities (passive case finding strategy) [4].

However, this passive approach struggles to achieve the required case detection rates in resource-limited settings, allowing millions of potentially infectious cases undiagnosed in communities [5, 6]. Nearly one-third of TB cases in Ethiopia were not notified in 2017 [1]. Local-specific reports indicated the number of undetected infectious cases in community equals the number of notified cases [7], and another study

reported up to two-thirds of active cases remained undetected by the passive system [6]. In Somali Regional State of Ethiopia (SRS), new case detection rate has not exceeded 50% in recent years [8]. This implies a high number of infectious cases exist in households and communities without obtaining proper diagnosis and treatments, which is likely influenced by patients' healthcare seeking behavior and health system deficiencies [9, 10]. Extreme delay in diagnosis and treatment of TB has been challenging in Ethiopia, and median delay exceeding two months was reported in pastoral settings [11].

Failures to timely detect cases and initiate treatment worsen the disease, increase risk of death, increase risk of treatment failure and drug resistance, and exacerbate ongoing transmission in households and congregate settings. Devastating damages occur in lung tissues as patients delay longer without proper treatment, the classical hallmark is cavity formation [12, 13]. Cavities are sites of excessive TB bacilli accumulation and release higher bacilli load in aerosols [14]. Moreover, cavities slow smear conversion following treatment (prolongs contagious period), and are associated with high treatment failure and relapse, emergence of drug resistance, disease dissemination and permanent lung impairments [15]. Findings have indicated a call for extended treatment of Cavitary TB with a combination of new drugs and new treatment strategies [16], yet no special strategy is currently in place in Ethiopia.

In addition to influencing infectiousness, delay prolongs contagious period and extends contact time between index case and close contacts [17]. This highlights the need for assessing the effect of delays on risk of TB transmission to assess the effectiveness of TB control programs in controlling the disease and interrupting its transmission. However, the effect of delays on risk of transmission, to the best of our knowledge, was not addressed in pastoral settings in Ethiopia. There is also limited data on cavitary TB and the acceptable delays from clinical and programmatic perspectives. Hence, this study was intended to assess the association of delay in diagnosis with infectiousness of patients and determine threshold delays that optimize cavitation and smear positivity as proxy measures of infectiousness. We have also assessed household drivers of transmission in Somali regional state of Ethiopia where majorities of the population lead pastoral life and households inhabit in cramped transitory huts [18].

Methods

Study Setting

Four hospitals (Kharamara, Dege-habour, Kebri-Daher and Gode) and one health center (Abilelie) in Somali Regional State of Ethiopia were selected purposefully based on their patient flow, presence of radiologic facility, and geographic location in the administration. Kharamara hospital and Abilelie health center are located in the regional capital, Jigjiga. The rest facilities are found in less-urbanized, pastoral-dominant and semi-arid zones of the region. Approximately 85% of the region's population lead a nomadic or agro-pastoral way of life [18]. The nomads rear livestock, migrate seasonally while agro-pastoralists are relatively permanent, and carry out mixed herding and farming [11]. The hospitals and selected health centers provide TB services as per the National guideline, which involves two spot-spot

smear microscopy examination spaced by 30 minutes (morning on demand), chest radiography, molecular (GeneXpert), pathology and clinical investigations [4].

Figure 1: Map of the study area

Study Design and Population

A facility-based cross-sectional study was conducted to determine the effect of delay in diagnosis and/or treatment on the infectiousness (pulmonary cavitation and sputum smear positivity) of patients diagnosed with pulmonary TB (PTB). All newly arriving clinically confirmed patients aged ≥15 years were included between December 1, 2017 and October 31, 2018 regardless of smear status and treatment category. Patients aged ≥15 years manifest similar pathological features and the same diagnosis approaches are used [4]. People in this age category are believed to acquire competent immunity that is key in cavity formation [19], cover 80% of all TB cases and account for almost 100% of disease transmissions [20]. Patients with lung co-morbidities (bronchitis, pneumonia and lung cyst) were excluded.

Sample Size and Sampling Technique

The minimum sample size estimated using OpenEpi303 for cross-sectional studies was 282. This assumed 95% CI, 80% power, 1:1 ratio of non-delayed/delayed, 27.5% of non-delayed and 45% of delayed patients had cavitation in related study [12], 5% precision and 10% non-response rate, and given delay above 30 days as critical point at which risk of transmission increases [21]. We included all the available samples in the analysis to increase the power of the test, which raised the final sample size to 434. Patients were recruited sequentially from the first date of data collection. As the patients arrived to the Directly Observed Therapy-Short Course (DOTS) facilities for treatment initiation, all upcoming eligible PTB patients were recruited for the study before initiating treatment.

Data Collection: Questionnaire, Microscopy and Chest X-ray

A mix of methods including interview, anthropometry, Acid-Fast Bacilli (AFB) microscopy and chest radiography were used in addition to the standard medical examination (record review). A structured and pre-tested questionnaire was employed to obtain data on delays in diagnosis, socio-demographics, self-reported medical conditions, and environmental drivers of transmission. Records were reviewed to substantiate co-morbidities. Mid-Upper Arm Circumference (MUAC) was measured using inelastic paper tapes, and Body Mass Index (BMI) was computed from weight (kilograms) and height (meter-square) measures. Nurses working in DOTS clinics carried out recruitment, interview, record review and anthropometry procedures. Training was provided on sampling and data collection procedures by the principal investigator and a local research assistant.

AFB Examination

Upon completion of interviews, the DOTS providers linked patients to radiology and laboratory units using request forms prepared for this purpose. Three sputum specimens from each patient were collected; morning sputum at home, and two spot specimens spaced by 30 minutes after the patient delivered the morning specimen. A pair of smears was prepared from each specimen, air dried and heat fixed. One slide of each pair was examined at hospital laboratories using Ziehl Neelsen (ZN) staining technique. The rest three smears were transported and examined blindly at Armaur Hansen Research Institute (AHRI) TB laboratory in Addis Ababa, Ethiopia. The results were interpreted as negative (no AFB), scanty (1-9 AFB/100 field), 1+ (10-99 AFB/100 field), 2+ (1-10 AFB/field), 3+(>10 AFB/field) [4].

Figure 2: Procedure of AFB examination

Chest Radiography

All patients underwent Chest X-ray examinations to identify lung cavitation, measure cavity size and count the number of cavities. A senior radiologist at Kharamara hospital examined all the X-ray films and digital imaging. The radiologist was blinded to radiologic and AFB results reported during the standard initial diagnosis. Sample of X-ray films (n=41) were randomly picked and blindly re-checked by another radiologist to ensure the reliability of X-ray readings. As of rechecking, we found levels of 95.1% [84.6-100%] kappa agreement for cavity identification, 0.84 [0.64, 0.93] Cohen's kappa coefficient for cavity size, and 85.7% [63.7-96.9%] Cohen's proportion of zero difference for cavity count.

Data Processing and Analysis

Data were double entered and validated using EpiData version 3.1; and analyzed using Stata/SE®14 (*StataCorp, College Station, Texas 77845 USA*). Descriptive statistics was performed to summarize delays in diagnosis, patient infectiousness, explanatory and environmental factors of transmission. Prevalence ratios along with 95% confidence intervals (CI) were used to compare cavitation and smear positivity between categories of predictors, and multivariable analyses were fitted using Log-binomial regression models. Statistical significances were determined at p-value ≤0.05; and p-value ≤ 0.2 in bivariate analysis was used as a cutoff point for inclusion in final models. C-statistics or Receiver Operating Characteristic (ROC) was employed to determine the discriminatory ability and threshold/optimal cutoff points of diagnosis delay that classify patient infectiousness at maximum sum of sensitivity and specificity, and positive likelihood ratio (LR+), given sensitivity (>70%).

Operational/standard definition of terms

Pulmonary Tuberculosis: is a patient with lung TB of either smear-positive or negative forms. A smear AFB positive patient is confirmed if at least one AFB positive smears; A smear negative patient is diagnosed if: at least two AFB smear negative results, no response to a course of broad-spectrum antibiotics, again two AFB negative smears and radiological abnormalities consistent with TB; Or two AFB smear negative results but culture positive for *MTB* [4].

New Case: is a patient who has never had treatment for TB before or has not yet initiated anti-TB treatment.

Retreatment case: is a patient who was treated for any form of TB before but has developed the disease again following relapse or default or failure to cure during the 1st regimen.

Newly Diagnosed Patient: a patient who was prospectively diagnosed with Pulmonary TB during the study period. This excludes patients who were on treatment.

Diagnosis delay: is defined as the period from debut of the first symptom(s) particularly cough or other (chest pain, haemoptysis, weight loss, night sweating) to the date of TB diagnosis.

Infectiousness: is the capability of a PTB patient to transmit TB infection into a susceptible person, characterized by the existence of pulmonary cavity and/or AFB positive smear.

Pulmonary cavity: is an air-containing lucent space within a consolidation or a mass or nodule surrounded by infiltrate or fibrotic wall identified upon radiological examination [19, 22].

Figure 3: Photo of a patient with cavity on the right chest (arrow), [*captured by the radiologist*]

Results

Socio-demographic and Clinical Characteristics

All the 434 pulmonary TB patients recruited in the study had complete chest radiography, and 421 of them had complete AFB results. The participants had a median age of 30 years, ranging from 15 to 82 years. The majority was male (62.9%; M:F ratio=1.7:1), illiterate (61.5%), new cases (90.3%) and smear negative (57.6%), presented with cough (94.9%) and chest pain (57.6%). Close to half (46.5%) were reliant on pastoralism (within, 36% nomadic) and 2.3% co-infected with HIV (Table 1).

The median diagnosis delay from debut of respiratory symptoms to the date of TB diagnosis was 49 days (IQR=37), ranging 8 to 362 days. Four rural patients received care longer than 254 days after the onset of the early respiratory illnesses.

Figure 4: Box plot illustrating the distribution of diagnosis delay in days

Cavitation and Smear Positivity

Out of the 434 pulmonary TB cases, 45.6% [95%CI: 40.9-50.4%] had single-to-five cavities on chest X-ray (mean, 1.8±0.9 cavities) with mean diameter of 2.8±1.0 centimeters. Of the non-cavitary cases, 5.5% had consolidated lesions but not duly branded as cavity. Overall, 42.0% [95%CI: 37.3 46.9%] of patients were smear positive upon rechecking at AHRI TB laboratory. The AFB identification rate and loads were similar between the three sputum samples. Individual specimens produced equivalent smear positivity rates (i.e. morning=42%; first spot=41.8%; second spot=41.7%) and grading (correlation≥0.95) with the combined 42% smear positivity (Table 2). In hospital laboratories, 19.2% of smear positive patients were misidentified as smear negative and 2.9% of smear negative as smear positive. Smear positivity was multifold among patients with cavities (75.3%) compared to without cavities (13.7%) [APR (95%CI): 5.5 (3.9-7.7), p<0.001]. Conversely, 82.5% [95%CI: 76.1%, 87.8%] of smear positive patients had cavities. Smear examination truly identified 75.3% [95%CI: 68.6 – 81.2%] of patients with cavitation (sensitivity) and 86.3% [95%CI: 81.2 90.5%] without cavitation (specificity) (Table 3).

Risk Factors of Cavitation and Smear Positivity

The rate of cavitation and smear positivity showed no difference between sex, diabetes, HIV, co-infection, history of TB, residence and pastoralism categories [p>0.05]. Cavitation was considerably higher in patients aged 35 years or younger [APR (95%CI) =1.3(1.01–1.6), p=0.04] and with chronic diseases *(Hypertension/chronic Heart/Renal Disease)* [APR (95%CI) =1.8 (1.2–2.6), p=0.006], and in female patients with low MUAC [APR (95%CI) =1.8 (1.2–2.8), p=0.01] (Table 4). Similarly, smear positivity was higher in patients aged 35 years or younger [APR (95%CI) =1.4 (1.1–1.8), p=0.007], with low BMI [APR (95%CI) =1.3 (1.01–1.7), p=0.04] and low MUAC [APR (95%CI) =1.5(1.2–1.9), p=0.003] (Table 5).

Delay in diagnosis of patients is associated with the risk of cavitation [p<0.001]. Cavitation increased in patients who delayed 31-49 days [APR (95%CI) =1.8 (1.2–2.8), p=0.006], 50-70 days [APR (95%CI) =2.4 (1.6–3.7), p<0.001] and 71+ days [APR (95%CI) = 2.7 (1.8–4.1), p<0.001] compared to those who received care within 30 days. Ninety percent (90%) of patients with cavitation delayed more than 30 days (Table 4). Smear positivity was not associated at 30 days delay in diagnosis [p>0.05], but it was significantly higher in patients who delayed above median delay (49 days) [APR (95%CI) =1.3 (1.1–1.6), p=0.02] than their counterparts (Table 5).

Discriminative Ability of Delay to Detect Thresholds of Infectiousness

The ROC analysis indicated that diagnosis delay has significant predictive ability and detects optimal cutoff point as prognosis test of pulmonary cavitation (p<0.001). The area under curve (AUC) of the empirical ROC was 0.67 [95%CI: 0.62 - 0.72]. The optimal cutoff point was determined at 43 days when the resulting sensitivity, specificity and the likelihood ratio for positive test result were 74.6%, 52.1% and 1.6, respectively (Figure 5). Using this cutoff point, delay correctly classifies 62.4% of patients with or without cavitation, and 60.0% of patients delayed above this point. The predict test revealed that the probability of cavitation increases as a day in delay increases (Figure 6). The median diagnosis delay

had also significant association with smear positivity (p=0.02). Nonetheless, it revealed poor discriminative ability to classify smear status [AUC (95%CI): 0.56 (0.51-0.62)] (Figure 7).

Figure 5: Area under the ROC curve of diagnosis delay as a prognosis test of pulmonary cavitation

Figure 6: The predicted probability of pulmonary cavitation at each value of the observed diagnosis delay

Figure 7: Area under the ROC curve of diagnosis delay as a prognosis test of smear positivity

Distribution of Environmental Catalysts of TB Transmission

Two hundred three patients (46.8%) live in narrow, windowless and small dam-shaped huts. Of whom, 93.1% had evident cough. Out of the patients living in modern mud/cement-made homes, 34.5% live and 59.8% sleep in single rooms. Of the patients with recognized infectiousness, 77.8% of Cavitary and 76.8% of smear positive patients shared sleeping rooms with family members (mean, 6.6±2.8). Similarly, 73.7% of Cavitary and 76.3% of smear positive patients spit sputum everywhere. Regarding knowledge of TB transmission, 55.5% of patients thought TB is transmissible; of whom, 84.7% said via airborne droplets, 6.6% via contaminated food or drink, 5.8% via sexual intercourse and others (2.9%) (Table 6).

Discussion

The present finding reveals that close to half (45.6%) of all and 82.5% of smear positive patients with pulmonary TB had one or more cavities; 42% were sputum smear positive, and half of them delayed more than seven weeks and few nearly a year without medical care. Cavitation increased continuously as patients delayed longer than four weeks, and optimized at threshold delay of 43 days. Similarly, smear positivity was higher in patients who delayed above seven weeks.

Cavitation and smear positivity were reciprocally illustrative, and the majority of patients had either cavitation or was smear positive. Cavities are the stockpiles of mycobacterial accumulation, and connected to airflow they release high bacillary load in sputum and nasal droplets, the channel for transmission [23]. This connotes the large majority of patients had intricate form of the disease and was capable of transmitting TB prior to diagnosis or treatment. This cavitation rate matches with the maximum assumption of 50% rate that happens if patients do not receive treatment during the entire course of the disease [24, 25], and it surpassed the 34.0% [26] and 21% [23] rates elsewhere. It was also drastically higher in smear positive patients, almost twice to previous reports of 49.9% [23] and 38.3% [27] in other places. On the other hand, the smear positivity was comparable to other reports in Ethiopia [28-30].

Cavitation and smear positivity were notably higher in delayed patients. The median delay was higher than the threshold delay (43 days) that optimizes the risk of cavitation, and it was the significant delay at which smear positivity increases. To be precise, the majority of patients (60%) delayed above the threshold delay of cavitation without obtaining care. Delay in care does not only worsen cavitation and

smear positivity as figured out [12, 13], but it also prolongs the period of contagiousness and contact time between patients and contacts [17]. The majority of infectious patients (90% of cavitary and 84% of smear positive) delayed more than a month in poor housing, crowding and inadequate ventilation conditions implies higher prospect of transmission. Four out of five patients who delayed above the threshold and over three-fourth of patients with Cavitary- or smear positive-TB used to share sleeping rooms/beds with average six-plus household members. This signals an ongoing transmission and is an existing threat in a pastoral community bearing in mind the transitory huts with narrow and closed indoor spaces.

In addition to delay, cavitation and smear positivity were also higher in younger (≤35) and undernourished patients as well as in those co-infected with chronic diseases after adjusting for potential confounders. Younger and immune competent patients are documented to have higher risk of cavitation than elders do [31, 32]. Concomitant and weakening physical conditions in older people blunt inflammatory responses which then constrain cavitation [33]. The increased risk of cavitation and smear positivity in undernourished patients could be either way: under-nutrition led to immune-deficiency and enhanced disease progression [34, 35] or the disease itself might lead to under-nutrition [36]. Moreover, other evidences revealed diabetes, smoking, low income and absence of HIV [37-39] as independent predictors of cavitation and smear positivity. The reason why it is not witnessed in the current study might be due to the small number of cases that cohabit these factors. Nonetheless, our data revealed that cavitation and smear positivity were not different between sex, treatment and livelihood categories.

The impact of cavitation is not only limited to transmission but also associated with increased risks of treatment failure, relapse, emergence of drug resistance and permanent lung impairments upon complete treatments as well as dissemination of the disease to other organs [16]. Hence, evaluating the effects of cavitation on treatment outcomes and transmission will have strategic importance in the prevention and control of TB in places where cavitary TB is prevalent.

Limitation: We can anticipate under-reporting of cavitation and smear-positivity. The reduced sensitivity of Chest X-ray might underestimate cavitation, and salivary sputum and missed smear examinations could underrate smear positivity. Recall bias might influence the precision of diagnosis delay. Moreover, the proportion of pastoralists seems less represented contrasted to their proportion in the general population. This might be due to the reduced case notification that was observed during dry seasons when pastoralists moved to remote areas for pasture.

Conclusion

This study highlights that delay in diagnosis and/or treatment and infectiousness of patients with pulmonary tuberculosis have remained high in pastoral settings in Ethiopia. The indices of infectiousness, cavitation and smear positivity, were extra-prevalent in patients with substantial delays, and in younger and undernourished patients. Excessive delay has strong association with infectiousness and a delay of 43 days looks the threshold delay that optimizes pulmonary cavitation. The majority of

patients with remarkable infectiousness live in large families under deprived housings and hazardous conditions for extensive periods. Thus, the ongoing transmission would potentially be huge in pastoralist settings. To control the disease and interrupt the risk of transmission, strategies for pastoralist population need to be revisited, and socio-cultural tailored strategies are needed to address delay in detection and treatment of ill cases in the pastoralist areas of the country.

Abbreviations

AFB: Acid Fast Bacilli

AHRI: Armaur Hansen Research Institute

APR: Adjusted Prevalence Ratio

AUC: Area Under the Curve

BCG: Bacillus Calmette-Guerin

BMI: Body Mass Index

CI: Confidence Interval

CM: Centimeters

CT: Computed Tomography

DOTS: Directly Observed Therapy-Short Course

FMOH: Federal Ministry of Health

HIV: Human Immunodeficiency Virus

IQR: Inter-Quartile Range

Kg: Kilogram

M: Meter

MDR: Multi-Drug Resistant

MTB: Mycobacterium Tuberculosis

MUAC: Mid-Upper Arm Circumference

NTP: National TB Control Program

PR: Prevalence Ratio

PTB: Pulmonary Tuberculosis

ROC: Receiver operating characteristic

SRS: Somali Regional State

TB: Tuberculosis

WHO: World Health Organization

Declarations

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Availability of Data and Materials

The dataset supporting the conclusions of this article is included within the article. The collected data contain confidential information, and consent has not been obtained for public sharing of raw data with identifiers. However, the datasets used and/or analyzed are available at the hands of the corresponding author and can be shared upon reasonable requests.

Authors' Contributions

FG conceived this research, developed draft protocol, coordinated fieldwork, led data analysis, and wrote draft manuscript. MD enriched the conception, revised and approved all drafts of the protocol and manuscript. AW directed data analysis, and revised and approved all drafts of protocol and manuscript. TG, BS and RT directed the fieldwork, and revised and approved all drafts of the protocol and manuscript.

GA led laboratory examinations. MG led Chest X-ray imaging and examinations. All the authors read and approved the final manuscript version sent for publication.

Ethical Approval and Consent to Participate

Ethical clearance was obtained from Institutional Health Research Ethics Review Committee (IHRERC) of Haramaya University, College of Health and Medical Sciences (Ref.No: IHRERC/009/2016), and AHRI/ALERT Ethical Review Committee (Ref.No: P001/17). Written consent was obtained upon provision of information for participants and parents/guardians of 15-17 years old participants as well as assent from 15-17 years old participants. Participation was self-determined and discontinuation was guaranteed.

Consent to publish

Consent was obtained from all participants or parents/guardians of 15-17 years old participants to publish data without individual identifiers.

Competing Interests

None of the authors have any competing interests.

References

1. WHO: Global tuberculosis report 2018: World Health Organization; 2018.

2. Kebede AH, Alebachew, Tsegaye ZF, Lemma E, Abebe A, Agonafir M *et al*: The first population-based national tuberculosis prevalence survey in Ethiopia, 2010-2011. INT J TUBERC LUNG DIS2014; 18(6):635–639. http://dx.doi.org/610.5588/ijtld.5513.0417.

3. Lönnroth K, Raviglione M: The WHO's new End TB Strategy in the post-2015 era of the Sustainable Development Goals. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2016; 110(3):148-150.

4. FMOH: National Guidelines for TB, DR-TB and Leprosy in Ethiopia. In. Edited by Ethiopian Federal Ministry of Health, 6th edn. Addis Ababa; 2017.

5. Ho J, Fox GJ, Marais BJ: Passive case finding for tuberculosis is not enough. *International journal of mycobacteriology* 2016; 5(4):374-378.

6. Tadesse T, Demissie M, Berhane Y, Kebede Y, Abebe M: Two-Thirds of Smear-Positive Tuberculosis Cases in the Community Were Undiagnosed in Northwest Ethiopia: Population Based Cross-Sectional

Study. *PLoS ONE* 2011; 6(12):e28258.

7. Hamusse S, Demissie M, Teshome D, Hassen MS, Lindtjorn B: Prevalence and Incidence of Smear-Positive Pulmonary Tuberculosis in the Hetosa District of Arsi Zone, Oromia Regional State of Central Ethiopia. *BMC Infect Dis* 2017; 17(1):214.

8. RHB: regional health sector performance report for 2010 Ethiopian calender. In. Edited by Planning MaED. Jigjiga: Regional Health Bureau; 2017.

9. Getnet F, Demissie M, Assefa N, Mengistie B, Worku A: Delay in diagnosis of pulmonary tuberculosis in low-and middle-income settings: systematic review and meta-analysis. *BMC pulmonary medicine* 2017; 17(1):202.

10. Li Y, Ehiri J, Tang S, Li D, Bian Y, Lin H *et al*: Factors associated with patient, and diagnostic delays in Chinese TB patients: a systematic review and meta-analysis. *BMC Medicine* 2013; 11:156:http://www.biomedcentral.com/1741-7015/1711/1156.

11. Gele AA, Bjune G, Abebe F: Pastoralism and delay in diagnosis of TB in Ethiopia. *BMC public health* 2009; 9:5-5.

12. Cheng S, Chen W, Yang Y, Chu P, Liu X, Zhao M *et al*: Effect of Diagnostic and Treatment Delay on the Risk of Tuberculosis Transmission in Shenzhen, China: An Observational Cohort Study, 1993-2010. *PLoS One* 2013; 8(6):e67516.

13. Virenfeldt J, Rudolf F, Camara C, Furtado A, Gomes V, Aaby P *et al*: Treatment delay affects clinical severity of tuberculosis: a longitudinal cohort study. *BMJ open* 2014; 4(6):e004818.

14. Squeglia F, Ruggiero A, Berisio R: Collagen degradation in tuberculosis pathogenesis: the biochemical consequences of hosting an undesired guest. *The Biochemical journal* 2018; 475(19):3123-3140.

15. Ravimohan S, Kornfeld H, Weissman D, Bisson GP: Tuberculosis and lung damage: from epidemiology to pathophysiology. *European respiratory review : an official journal of the European Respiratory Society* 2018; 27(147).

16. Saeed W: Cavitating pulmonary tuberculosis: a global challenge. *Clinical medicine (London, England)* 2012; 12(1):40-41.

17. Mathema B, Andrews JR, Cohen T, Borgdorff MW, Behr M, Glynn JR *et al*: Drivers of Tuberculosis Transmission. *The Journal of infectious diseases* 2017; 216(suppl_6):S644-s653.

18. CSA: Population Projection of Ethiopia for All Regions: At Wereda Level from 2014 – 2017. In. Addis Ababa: Central Statistical Agency of Federal Democratic Republic of Ethiopia; 2013.

19. Gadkowski LB, Stout JE: Cavitary pulmonary disease. *Clinical microbiology reviews* 2008; 21(2):305-333.

20. Hunter RL: Pathology of post primary tuberculosis of the lung: an illustrated critical review. *Tuberculosis (Edinburgh, Scotland)* 2011; 91(6):497-509.

21. Lin X, Chongsuvivatwong V, Lin L, Geater A, Lijuan R: Dose-response relationship between treatment delay of smear-positive tuberculosis patients and intra-household transmission: a cross-sectional study. *Trans R Soc Trop Med Hyg* 2008; 102(8):797-804.

22. Palaci M, Dietze R, Hadad DJ, Ribeiro FKC, Peres RL, Vinhas SA *et al*: Cavitary disease and quantitative sputum bacillary load in cases of pulmonary tuberculosis. *Journal of clinical microbiology* 2007; 45(12):4064-4066.

23. Zhang L, Pang Y, Yu X, Wang Y, Lu J, Gao M *et al*: Risk factors for pulmonary cavitation in tuberculosis patients from China. *Emerging microbes & infections* 2016; 5(1):1-11.

24. Curvo-Semedo L, Teixeira L, Caseiro-Alves F: Tuberculosis of the chest. *European journal of radiology* 2005; 55(2):158-172.

25. Nachiappan AC, Rahbar K, Shi X, Guy ES, Mortani Barbosa EJ, Jr., Shroff GS *et al*: Pulmonary Tuberculosis: Role of Radiology in Diagnosis and Management. *Radiographics : a review publication of the Radiological Society of North America, Inc* 2017; 37(1):52-72.

26. Huang Q, Yin Y, Kuai S, Yan Y, Liu J, Zhang Y *et al*: The value of initial cavitation to predict re-treatment with pulmonary tuberculosis. *European journal of medical research* 2016; 21(1):20.

27. Manzano KR: Prevalence and Risk Factors of Cavitary Lung Lesions in a Metropolitan Hospital at San Juan Puerto Rico. *Chest infections* 2015; 148(4):143A.

28. Belay M, Bjune G, Ameni G, Abebe F: Diagnostic and treatment delay among Tuberculosis patients in Afar Region, Ethiopia: a cross-sectional study. *BMC public health* 2012; 12:369.

29. Gebreegziabher SB, Bjune GA, Yimer SA: Patients' and health system's delays in the diagnosis and treatment of new pulmonary tuberculosis patients in West Gojjam Zone, Northwest Ethiopia: a cross-sectional study. *BMC Infect Dis* 2016; 16(1):673.

30. Seid A, Metaferia Y: Factors associated with treatment delay among newly diagnosed tuberculosis patients in Dessie city and surroundings, Northern Central Ethiopia: a cross-sectional study. *BMC public health* 2018; 18(1):931.

31. Perez-Guzman C, Torres-Cruz A, Villarreal-Velarde H, Vargas MH: Progressive age-related changes in pulmonary tuberculosis images and the effect of diabetes. *American journal of respiratory and critical care medicine* 2000; 162(5):1738-1740.

32. Mathur M, Badhan RK, Kumari S, Kaur N, Gupta S: Radiological Manifestations of Pulmonary Tuberculosis - A Comparative Study between Immunocompromised and Immunocompetent Patients. *Journal of clinical and diagnostic research : JCDR* 2017; 11(9):Tc06-tc09.

33. Perez-Guzman C, Vargas MH, Torres-Cruz A, Villarreal-Velarde H: Does aging modify pulmonary tuberculosis?: A meta-analytical review. *Chest* 1999; 116(4):961-967.

34. Chandrasekaran P, Saravanan N, Bethunaickan R, Tripathy S: Malnutrition: Modulator of Immune Responses in Tuberculosis. *Frontiers in immunology* 2017; 8:1316.

35. Anuradha R, Munisankar S, Bhootra Y, Kumar NP, Dolla C, Kumaran P *et al*: Coexistent Malnutrition Is Associated with Perturbations in Systemic and Antigen-Specific Cytokine Responses in Latent Tuberculosis Infection. *Clinical and vaccine immunology : CVI* 2016; 23(4):339-345.

36. Kant S, Gupta H, Ahluwalia S: Significance of nutrition in pulmonary tuberculosis. *Critical reviews in food science and nutrition* 2015; 55(7):955-963.

37. de Albuquerque Mde F, Albuquerque SC, Campelo AR, Cruz M, de Souza WV, Ximenes RA *et al*: Radiographic features of pulmonary tuberculosis in patients infected by HIV: is there an objective indicator of co-infection? *Revista da Sociedade Brasileira de Medicina Tropical* 2001; 34(4):369-372.

38. Alkabab YM, Enani MA, Indarkiri NY, Heysell SK: Performance of computed tomography versus chest radiography in patients with pulmonary tuberculosis with and without diabetes at a tertiary hospital in Riyadh, Saudi Arabia. *Infection and drug resistance* 2018; 11:37-43.

39. Nijenbandring de Boer R, Oliveira e Souza Filho JB, Cobelens F, Ramalho Dde P, Campino Miranda PF, Logo K *et al*: Delayed culture conversion due to cigarette smoking in active pulmonary tuberculosis patients. *Tuberculosis (Edinburgh, Scotland)* 2014; 94(1):87-91.

Tables

Table 1: Socio-demographic and clinical characteristics of TB patients in Somali region, Ethiopia, December 2017 to October 2018

Characteristics of patients (N=434)		Frequency (%)
Sex	Male	273 (62.9)
	Female	161 (37.1)
Age group	15 to 23	115 (26.5)
	24 to 30	112 (25.8)
	31 to 50	123 (28.3)
	51+	84 (19.4)
Literacy level	Illiterate	267 (61.5)
	Primary	45 (10.4)
	Secondary	64 (14.7)
	Tertiary	58 (13.4)
Marital status	Single	131(30.2)
	Married	265 (61.1)
	Divorced/separated/widowed	38 (8.7)
Residence	Rural	215 (49.5)
	Urban	215 (49.5)
	Refugee/displaced	4 (1.0)
Livelihood	Pastoralism	202 (46.5)
	Other	232 (53.5)
Income	Saving	54(12.5)
	Income=expense	303 (69.8)
	Indebt	77 (17.7)
Cough	Yes	412 (94.9)
	No	22 (5.1)
Haemoptysis	Yes	33 (7.6)
	No	401 (92.4)
Chest pain	Yes	250 (57.6)
	No	184 (42.4)

Breathing difficulty	Yes	93 (21.4)
	No	341 (78.6)
Functional status	Good	60 (13.8)
	Ambulatory	360 (83.0)
	Bedridden	14 (3.2)
Treatment category	New	392 (90.3)
	Retreatment	42 (9.7)
Prior History of tuberculosis	Yes	65 (15.0)
	No	369 (85.0)
Smear status	Positive	184 (42.4)
	Negative	250 (57.6)
HIV status	Positive	10 (2.3)
	Negative	422 (97.2)
	Unknown	2 (0.5)
Diabetes mellitus	Yes	16 (3.7)
	No	412 (94.9)
	Unknown	6 (1.4)
Smoking history	Ever smoker	45 (10.4)
	Never smokers	389 (89.6)
Khat chewing	Ever chewer	58 (13.4)
	Never chewer	376 (86.6)

Table 2: Sputum AFB grading of TB Patients in Somali region, Ethiopia, December 2017 to October 2018

AFB Grading (n=421)	Sputum Specimens		
	Morning Specimen	1st Spot Specimen	2nd Spot Specimen
Negative	243 (58.0)	244 (58.2)	245 (58.3)
Scanty	27 (6.4)	30 (7.2)	28 (6.7)
1+	52 (12.4)	52 (12.4)	47 (11.2)
2+	40 (9.6)	43 (10.3)	48 (11.4)
3+	57 (13.6)	50 (11.9)	52 (12.4)

Key: *AFB: Acid-Fast Bacilli*

Table 3: sputum Smear positive versus cavitation matrix of TB patients

		Cavitary TB		
		Yes (%)	**No (%)**	**Total**
AFB result	**Positive**	146 (75.3)	31 (13.7)	177 (42.04)
	Negative	48 (24.7)	196 (86.3)	244 (57.96)
	Total	194	227	421

Key*: The percentages indicate the proportions of smear positive and negative patients among Cavitary and non-Cavitary cases*

Table 4: Predictors of Pulmonary cavitation in TB patients in Somali region, Ethiopia, December 2017 to October 2018

Characteristics (n=434)		Total PTB cases n (%)	Cavitary TB n (%)	*P*-value	PR (95%CI)	*P*-value	APR (95%CI)
Sex	Female	161 (37.1)	70 (43.5)	0.49*	1	–	–
	Male	273 (62.9)	128 (46.9)		1.1 (0.9, 1.3)		
Age	15 to 35	251 (57.8)	125 (49.8)	0.04	1.3 (1.01, 1.6)	0.04	1.3 (1.01, 1.6)
	36+	183 (42.2)	73 (39.9)		1		1
Livelihood	Pastoralism	202 (46.5)	96 (47.5)	0.45*	1.1 (0.9, 1.3)	–	–
	Non-pastoralism	232 (53.5)	102 (44.0)		1		
Smoking	Ever smoker	45 (10.4)	23 (51.1)	0.40*	1.1 (0.8, 1.5)	–	–
	Never smoker	389 (89.6)	175 (45.0)		1		
BCG scar	Yes	52 (12.0)	26 (50.0)	0.48*	1.1 (0.8, 1.5)	–	–
	No	382 (88.0)	172 (45.0)		1		
Chronic diseases (HTP/CHD/CRD)	Yes	20 (4.6)	12 (60)	0.13	1.3 (0.9, 1.9)	0.006	1.8 (1.2, 2.6)
	No	414 (95.4)	186 (44.9)		1		1
MUAC female (n=161)	Low (≤23 cm)	93 (57.8)	51 (54.8)	0.002	2.0 (1.3, 3.0)	0.01	1.8 (1.13 , 2.8)
	High (>23 cm)	68 (42.2)	19 (27.9)		1		1
MUAC male (n=273)	Low (≤23 cm)	154 (56.4)	74 (48.1)	0.63*	1.1 (0.8, 1.4)	–	–
	High (>23	119	54		1		

	cm)	(43.6)	(45.4)				
BMI	Low (<18.5)	304 (70.0)	149 (49.0)	0.04	1.3 (1.01, 1.7)	0.23	1.2 (0.9, 1.5)
	High (≥18.5)	130 (30.0)	49 (37.7)		1		1
Prior history of TB	Yes	65 (15.0)	31 (47.7)	0.71*	1.1 (0.8, 1.4)	--	--
	No	369 (85.0)	167 (45.3)		1		
Delay in medical care (days)	30 or less	90 (20.7)	20 (22.2)	1	1	--	1
	31 to 49	138 (31.8)	58 (42.0)	0.004	1.9 (1.2, 2.9)	0.006	1.8 (1.2, 2.8)
	50 to 70	98 (22.6)	54 (55.1)	<0.001	2.5 (1.6, 3.8)	<0.001	2.4 (1.6, 3.7)
	71 or more	108 (24.9)	66 (61.1)	<0.001	2.8 (1.8, 4.2)	<0.001	2.7 (1.8, 4.1)

Table 5: Predictors of smear positivity in TB patients in Somali region, Ethiopia, December 2017 to October 2018

Characteristics (n=434)		Total PTB cases n (%)	Smear positive TB n (%)	*P*-value	PR (95%CI)	*P*-value	APR (95%CI)
Sex	Female	157 (37.3)	58 (36.9)	0.11	1	0.17	1
	Male	264 (62.7)	119 (45.1)		1.2 (0.9, 1.5)		1.2 (0.9, 1.5)
Age	15 to 35	245 (58.2)	119 (48.6)	0.002	1.5 (1.2, 1.9)	0.007	1.4 (1.1, 1.8)
	36+	176 (41.8)	58 (33.0)		1		1
Livelihood	Pastoralism	194 (46.1)	81 (41.8)	0.91	0.98 (0.79, 1.24)	-	–
	Non-pastoralism	227 (53.9)	96 (42.3)		1		
Smoking	Ever smoker	43 (10.2)	22 (51.2)	0.17	1.2 (0.9, 1.7)	0.28	1.2 (0.8, 1.6)
	Never smoker	378 (89.8)	155 (41.0)		1		1
BCG scar	Yes	52 (12.4)	23 (44.2)	0.61	1.01 (0.7, 1.4)	-	–
	No	369 (87.6)	154 (41.7)		1		
Chronic diseases (HTP/CHD/CRD)	Yes	20 (4.8)	8 (40.0)	0.85	0.95 (0.5, 1.6)	-	–
	No	401 (95.2)	169 (42.1)		1		
MUAC	Low (≤23 cm)	235 (55.8)	119 (50.6)	<0.001	1.6 (1.3, 2.1)	0.003	1.5 (1.2, 1.9)
	High (>23 cm)	186 (44.2)	58 (31.2)		1		1
BMI	Low (<18.5)	294 (69.8)	135 (45.9)	0.02	1.4 (1.1, 1.8)	0.04	1.3 (1.01, 1.7)
	High	127	42 (33.1)		1		1

	(≥18.5)	(30.2)					
Prior history of TB	Yes	65 (15.4)	22 (33.8)	0.17	0.8 (0.5, 1.1)	0.25	0.8 (0.6, 1.2)
	No	356 (84.6)	155 (43.5)		1		1
Delay in medical care (days)	49 or less	222 (52.7)	83 (37.4)	0.04	1	0.02	1
	50 or more	199 (47.3)	94 (47.2)		1.3 (1.01, 1.6)		1.3 (1.1, 1.6)

Key:

*MUAC and BMI Cutoffs were 23 cm and 18.5 Kg/M2 (FANTA's finding for developing countries) ; 1 indicates reference category; *indicates the variable not included in multivariable regression analysis; BCG: Bacillus Calmette-Guerin; AFB: Acid-Fast Bacilli; PR prevalence ratio; APR Adjusted prevalence ratio; HTP/CHD/CRD Hypertension/Chronic Heart Disease/Chronic Renal Disease*

Table 6: Transmission catalysts among delayed, Cavitary and smear-positive patients in Somali region, Ethiopia, December 2017 to October 2018

Environmental catalysis		Total PTB cases (= 434) n (%)	Delayed above optimal cutoff (=256) n (%)	Cavitary TB (=198) n (%)	Smear positive (=177) n (%)
House type	Traditional hut	203 (46.8)	136 (53.1)	93 (47.0)	82 (46.3)
	Wood & metal roof	173 (39.9)	93 (36.3)	82 (41.4)	70 (39.6)
	Cement/concrete	58 (13.3)	27 (10.6)	23 (11.6)	25 (14.1)
Shares sleeping room with family	Yes	350 (80.6)	212 (82.8)	154 (77.8)	136 (76.8)
	No	84 (19.4)	44 (17.2)	44 (22.2)	41 (23.2)
Where do spit Sputum	Spit anywhere	320 (73.7)	187 (73.1)	146 (73.7)	135 (76.3)
	Prepared container	107 (24.7)	66 (25.8)	50 (25.3)	40 (22.6)
	Other	7 (1.6)	3 (1.2)	2 (1.0)	2 (1.1)
Thought TB is transmissible	Yes	241 (55.5)	139 (54.3)	122 (61.6)	104 (58.7)
	No	112 (25.8)	62 (24.2)	44 (22.2)	49 (27.7)
	I don’t know	81 (18.7)	55 (21.5)	32 (16.2)	24 (13.6)
Action to prevent transmission	Mouth cover (cough)	164 (37.8)	95 (37.1)	80 (40.4)	72 (40.7)
	Separate sleep	25 (5.8)	14 (5.5)	11 (5.6)	11 (6.2)
	Separate meal utensil	4 (0.9)	2 (0.8)	2 (1.0)	1 (0.6)
	Nothing to prevent	241 (55.5)	145 (56.6)	105 (53.0)	93 (52.5)

Key:

Delayed case: patients delayed above optimal cut-off point for augmented infectiousness (43 days).

Mean family size= 6.6±2.8 household members

Figures

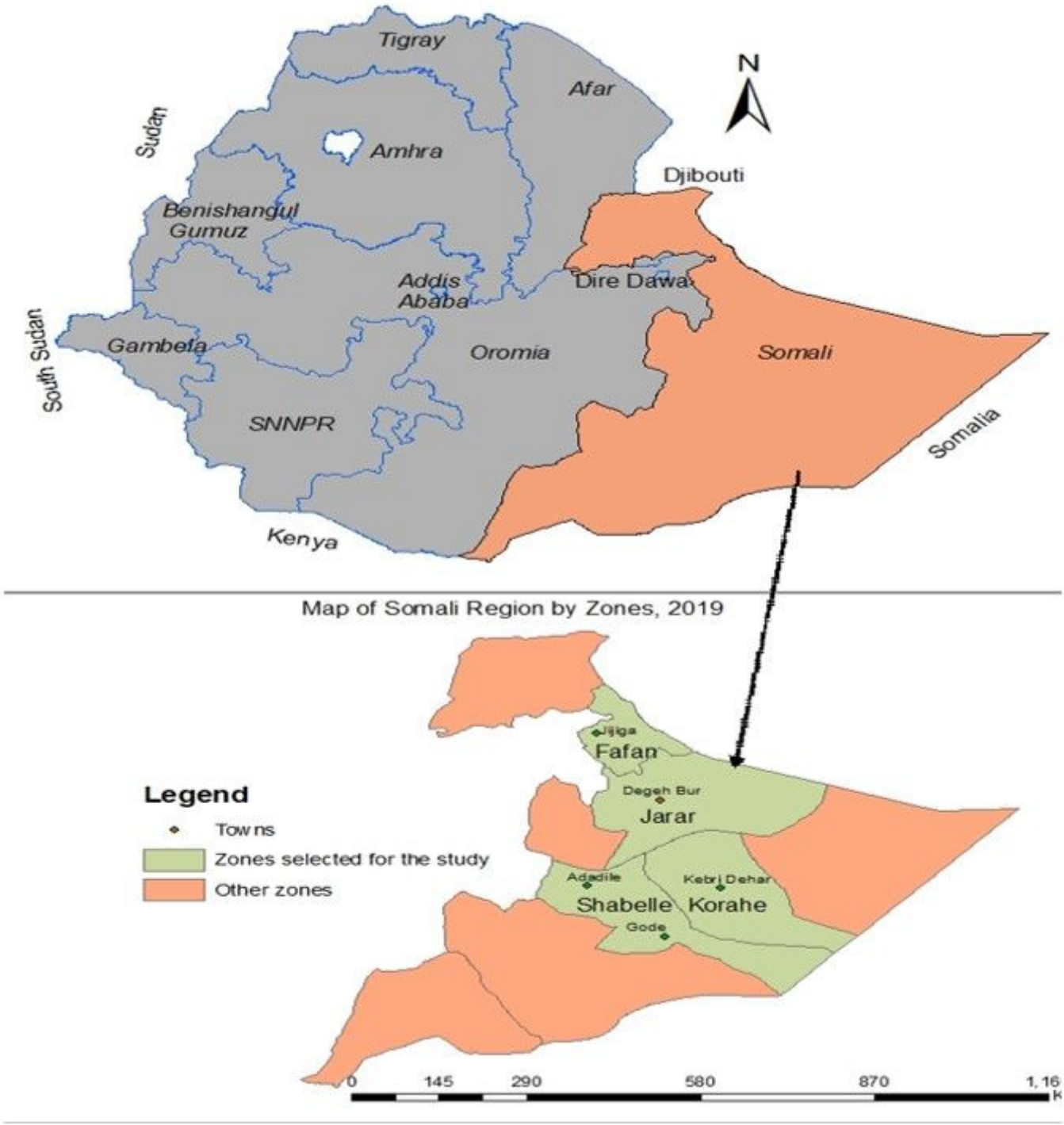

Figure 1

Map of the study area

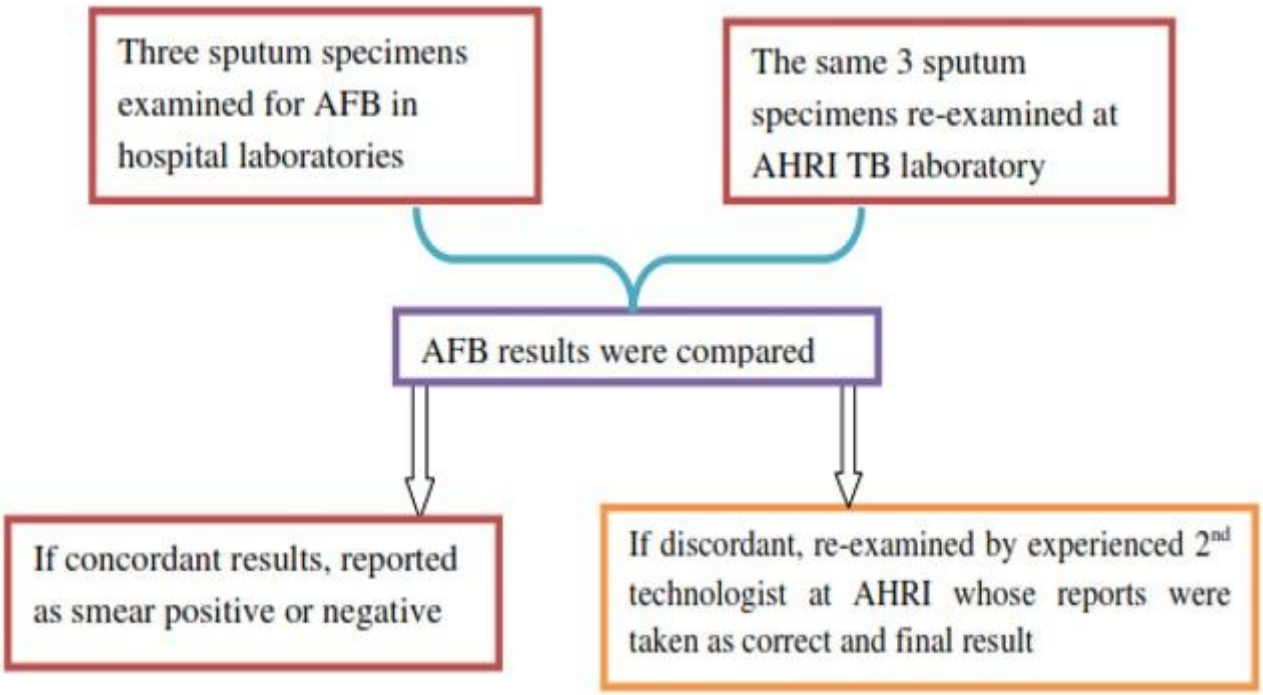

Figure 2

Procedure of AFB examination

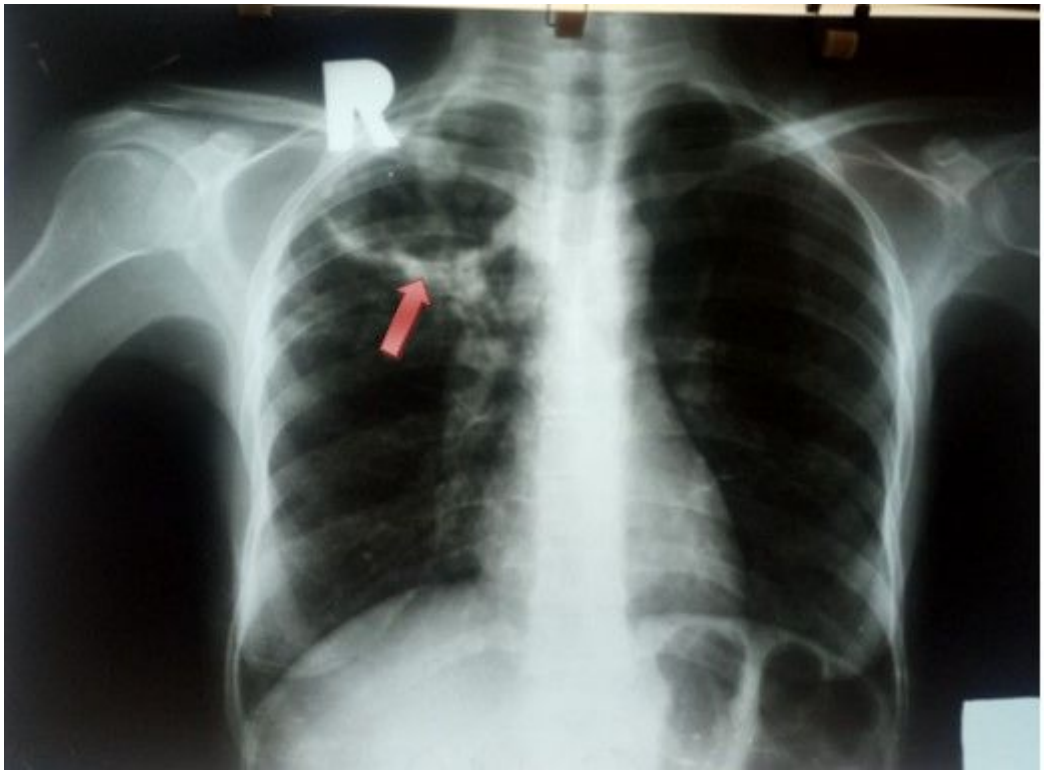

Figure 3

Photo of a patient with cavity on the right chest (arrow), [captured by the radiologist]

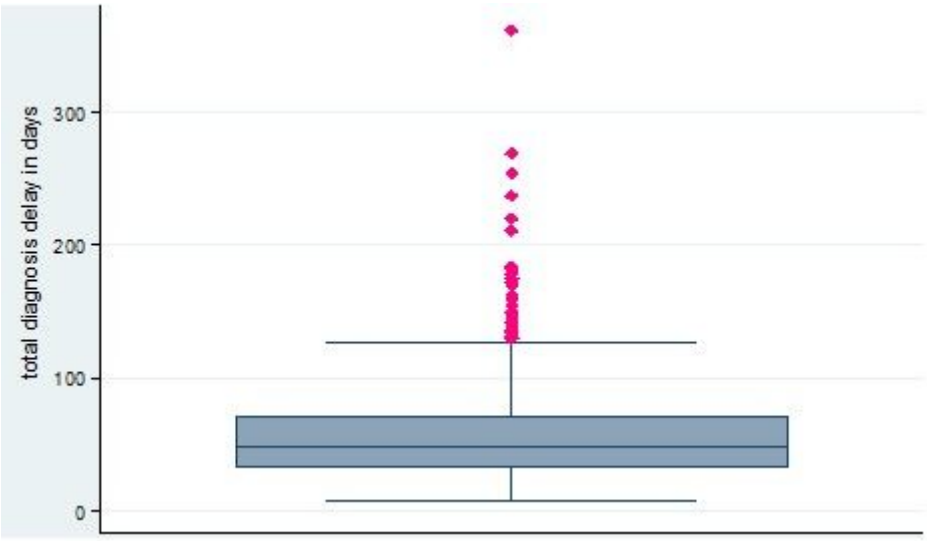

Figure 4

Box plot illustrating the distribution of diagnosis delay in days

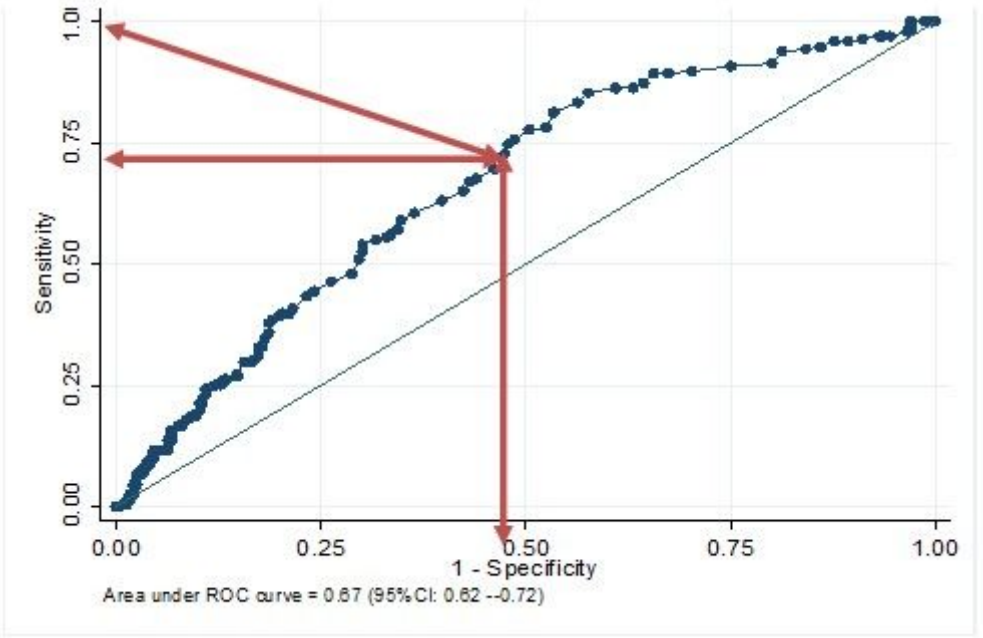

Figure 5

Area under the ROC curve of diagnosis delay as a prognosis test of pulmonary cavitation

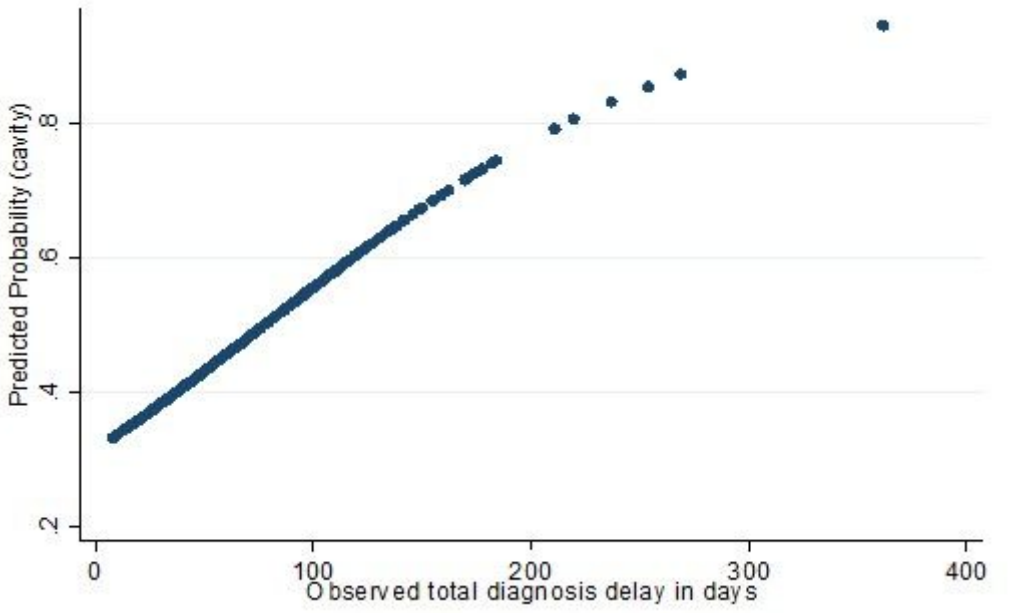

Figure 6

The predicted probability of pulmonary cavitation at each value of the observed diagnosis delay

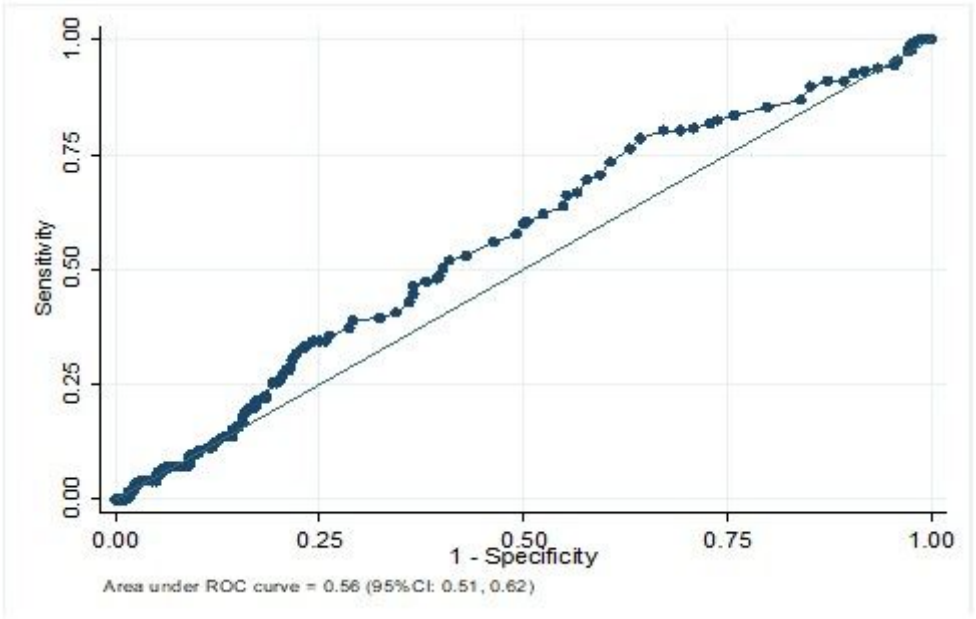

Figure 7

Area under the ROC curve of diagnosis delay as a prognosis test of smear positivity