Time to develop tuberculosis and its predictors among adult diabetes mellitus patients on follow-up at chronic outpatient department of hospitals in Southwest Shewa Zone, Oromia, Ethiopia: A retrospective cohort study

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ABSTRACT

Background: Diabetes mullites (DM) is a risk factor of tuberculosis (TB) and the two are often coexist and influence each other. Developing countries are suffering from DM which further exposes individuals to active TB infection. However, there is limited evidence on the time to develop TB and its predictors among adult diabetes mullites (DM) patients on treatment. Thus, this study aimed to determine time to develop TB and its predictors among adult DM patients on follow-up in hospitals in Southwest Shewa zone, Oromia Regional State, Ethiopia.

Methods: A retrospective cohort study was conducted among 346 DM patients on follow-up in hospitals found in Southwest Shewa Zone from 2013-2022. A systematic random sampling method was used to select the participants. A structured questionnaire and data extraction checklist were used to collect data. Descriptive statistics were used to summarize the characteristics of the participants. Kaplan-Meir curve was employed to show survival probability between groups for significantly associated variables. Cox-proportional hazard model was used to determine predictors of time to TB develop.

Results: Of the total 346 DM patients, 11.5% were developed TB during follow-up period, and more than 55% of TB incidences occurred within five years of follow-up. The overall TB incidence density was 2.2 per 100 (95% CI: (1.5–4.6)) person-year observations (PYOs). Age older than 50 year (AHR = 6.0, 95%CI:1.6–21.6), having smoking history (AHR = 5.8, 95%CI: 1.1–13.7), previous TB treatment history (AHR = 5.2, 95% CI: 2.2–2.6), being HIV sero-reactive (AHR = 3.5, 95% CI:1.6–8.2), being alcohol user (AHR = 3.5, 95% CI:1.6–7.6) and forgetfulness (AHR = 2.4, 95% CI: 1.2–4.9) were significantly predicted time to develop TB.

Conclusion: The incidence of TB in DM patients was considerable (11.5%), and more than 55% of TB incidences occurred within five years of follow-up. Interventions that targeted DM patients who smoke cigarette, drink alcohol, and have forgetfulness are vital to increase time to develop TB in DM patients.

Keywords: Diabetes, Tuberculosis, Infectious diseases, Bacteriology

Citation: Merga BS, Muse TB, Desta HO. Time to develop tuberculosis and its predictors among adult diabetes mellitus patients on follow-up at chronic outpatient department of hospitals in Southwest Shewa Zone, Oromia Regional State, Ethiopia: A retrospective cohort study. *HAJHBS*. 2024, 1(1): 9–15: DOI:
Edited by Derara Girma Tufa

Submitted: April 10, 2024 | Revised: June 12, 2024 | Published: October 31, 2024

BACKGROUND

TB is a communicable disease caused by the bacterium *Mycobacterium tuberculosis*. It spreads when individuals with active TB release the bacteria into the air by coughing, sneezing, laughing, or singing. The disease typically affects the lungs, namely pulmonary TB but can affect other sites like lymph nodes, bone, pleura, intra abdomen, and other organs (1).

DM is a chronic metabolic disease, that increases the susceptibility of individuals to TB primary due to chronic inflammation, characterized by an increase in proinflammatory cytokines and a decrease in immunomodulatory cytokines (2,3).

The link between TB and DM is a significant risk factors that complicates TB control efforts. Currently, the global prevalence of DM has risen more rapidly than ever, reaching (11.7%) (4,5). This surge has increased the incidence of TB and complicating the management of co-infected patients (4,5). Recent studies have indicated that approximately 15% of TB cases worldwide are linked to DM (5,6). Patients with TB/DM comorbidities have a two-fold higher risk of death during TB treatment and a higher risk of TB relapse after treatment, primarily due to late detection of the diseases or poor glycemic control (7).

The prevalence of DM among patients with pulmonary TB (PTB) is estimated to be 13.7% with approximately 13.7% of patients with active TB estimated to have DM

in Africa (8). Ethiopia is one of the 30 high TB burden countries, and it is gradually reducing to the burden of TB to meet the set target. Currently, the incidence of TB in the general population is 140 cases per 100,000 people (1).

Although TB is prevalent among DM patients, there is evidence limitation on time to develop TB and its predictors among DM patients. Therefore, this study was aimed to determine time to develop TB and its predictors among adult diabetic patients on follow-up in hospitals found in Southwest Shewa Zone, Oromia Regional State of Ethiopia. The findings of this study are important for TB control program in decision to screening TB and to design interventions that targeted predictors of time to develop TB among DM patients.

METHODS

Study settings, design and period

A facility-based retrospective cohort study was conducted in hospitals found in Southwest Shewa Zone, Oromia Region State of Ethiopia. The zone has 11 districts with has an estimated total population of 1,101,129. (9). Six hospitals are present in five districts of the zone which serving the communities of the districts and other population live in nearby districts. All except Wolliso Hospital are providing diabetic care services for more than ten years. Wolliso Hospital started healthcare services in 2020 and there is no data before that time. The data covers period from June 28, 2013, to June 27, 2020. However, medical charts and registration books of the patients were reviewed from December 17, 2022, to March 06, 2023, to retrieve the data on the intended variables.

Inclusion and exclusion criteria

DM patients who were older than 17 years and on follow-up from June 28, 2013, to June 27, 2020 at the hospitals found in Southwest Shewa Zone were included in this study. However, DM patients with gestational DM and transferred in from other health facilities within this study period were excluded.

Sample size calculation

The sample size for this study was calculated by using Mark Weaver and Freedman principles of survival sample size calculations formula by assuming the proportion of allocation 0.5, adjusted hazard ratio (AHR) of 4.0 from previous study for previous alcohol use as exposure variable (10), and 10% non-response rate. Finally, a total of 346 sample size was determined.

Data collection tools and procedures

The data was collected by checklist that developed based on previous study reported from Ethiopia (10,12). Structured questionnaire was prepared and used for data collection from selected participants through interview. Five nurses were collected data, and one nurse supervised data collection process. The participants were selected by systematic random sampling method by using outpatient follow-up registration at chronic disease follow up clinic. The selected patients were interviewed by the developed questionnaire, and additional factors were retrieved from the registration starting from the date of DM follow-up initiation (first follow-up visit) to the end of the study period using data collection checklists. All data was collected by trained nurses.

Data quality assurance

The questionnaire and the checklist were properly designed. One day training was given for data collectors and supervisors on the questionnaire, and data collection tools as well as ethical principles. The data extraction checklist and questionnaire prepared in English and translated to Afan Oromo for data collection. The collected data was reviewed and checked daily for completeness, accuracy, and consistency by the supervisor and the investigators.

Data processing and analysis

The data was entered to epi-info version 7.2.5.0 and exported to Statistical Package for Social Science (SPSS) version 20 for cleaning and analysis. Descriptive statistics such as frequency, percent, mean with standard deviation or median with interquartile range were used to summarize the characteristics of the participants.

Event in this analysis was development of TB during the follow up of DM, while censored those who not developed TB, died, lost to follow up. A Kaplan-Meier survival curve was used to estimate survival time, and log-rank test was conducted to compare the equivalence of survival curves. Bivariable Cox-proportional hazard model was fitted for each explanatory variable and those with p-value ≤ 0.25 were included to multivariable Cox-proportional hazard model. Cox-proportional hazard assumption model was checked using the Schoenfeld residual test (p-value = 0.1) and log-log plots. Adjusted Hazard Ratio (AHR) with 95% confidence interval (CI) and p-value < 0.05 were used to measure the strength of association and significance.

RESULTS

Demographic characteristics of study the participants

A total of 331 participants with a response rate of 95.7% were included in the analysis, while 15 cards were excluded due to incompleteness. The median age of the participants was 50 years with (IQR = 23). Majority-

Table 1: Sociodemographic characteristics of diabetes patients on treatment follow-up in Hospitals of Southwest Shewa Zone from June 28, 2013, to June 27, 2022

Variables	Categories	Frequency	Percentage	PYO	TB	TBID
Age	18-35	80	24.2	385.63	5	0.013
	36-49	104	31.4	522.27	12	0.023
	>=50	147	44.4	794.51	21	0.026
Sex	Male	223	67.4	1069.5	22	0.021
	Female	108	32.6	646.43	16	0.025
Place of residence	Rural	220	66.5	1130.47	29	0.026
	Urban	111	33.5	585.46	9	0.015
	Single	39	11.8	199.49	3	0.015
Marital status	Married	255	77.0	1272.95	31	0.024
	Widowed and divorced	37	11.2	243.49	4	0.016
	No formal education	143	43.2	824.52	22	0.027
Educational status	Primary	100	30.2	473.41	10	0.021
	Secondary and above	88	26.6	418	6	0.014
	Farmer	203	61.3	1052.77	27	0.026
	Merchant	26	7.9	126.07	2	0.016
Occupation	Government employee	35	10.6	177.22	2	0.011
	Student and others*	67	20.2	359.87	3	0.008

**Daily laborers, drivers; PYO-Person-year observation; TB-Tuberculosis; TBID-TB incidence density*

(44.4%) of the participants were older than 50 years. About two-thirds (67.4%) of participants were male. Of the total participants, 220(66.5%) were rural residents, and 143(43.2%) had no formal education (Table 1).

Clinical and behavioural characteristics

Of the total participants, 240(72.5%) were diagnosed for type II DM, and 314(94.8%) were HIV-negative. Nearly two-third (63.5%) of the patients had fasting blood glucose greater than 130 in their recent test record or at the time of TB diagnosis. Majority (60.7%) of the participants were using oral hypoglycemic agents' medications, while 111(33.5) using insulin. The majority (92.1%) of the participants had recent creatinine level of 0.65-1.3 mg/dl. Of the total participants, 324(97.9%) had hemoglobin >10 mg/dl and 256(76.4%) had a BMI of 18.5-24.9 kg/m^2.

Eight-nine (26.9%) of the participants forgot to take medications for more than two days within a month, and 26(7.9%) had a history of discontinuing medication of DM for more than a month. Twenty-four (7.3%) of the participants had a history of previous TB treatment, and 13(3.9%) had a contact history with TB patients from the workplace or household close contact (Table 2).

Table 2: Clinical and behavioral characteristics of diabetes patients on treatment in hospitals found in Southwest Shewa Zone from June 28, 2013, to June 27, 2022

Variables	Categories	Frequency	Percentage	PYO	TB	TBID
History of forgetting medication	Yes	89	26.9	494.98	20	0.040
	No	242	73.1	122.95	18	0.146
History of discontinuing DM medication	Yes	26	7.9	141.85	4	0.028
	No	305	92.1	1574.08	34	0.022
History of previous TB treatment	Yes	24	7.3	108.38	9	0.083
	No	307	92.7	1607.55	29	0.018
Contact history with TB patients	Yes	13	3.9	64.33	2	0.031
	No	318	96.1	1651.6	36	0.022
Type of DM	Type I	91	27.5	457.87	14	0.031
	Type II	240	72.5	1258.06	24	0.019
HIV status of patients	Non-reactive	314	94.8	1627.97	34	0.021
	Reactivre	17	5.2	87.96	4	0.045
Cigarette smoking history	Yes	5	1.5	16.96	2	0.118

	No	326	98.5	1698.97	36	0.021
Chewing chat	Yes	7	2.1	24.56	2	0.081
	No	324	97.9	1691.37	36	0.021
Fasting blood glucose (mg/dl)	<70	6	1.8	44.41	2	0.045
	71-130	114	34.4	598.9	9	0.015
	>130	211	63.7	1072.62	27	0.025
Creatinine (mg/dl)	<0.65	14	4.2	85.44	2	0.023
	0.65-1.3	305	92.1	1566.16	33	0.021
	>1.3	12	3.6	64.33	3	0.047
Hemoglobin (mg/dl)	<=10	7	2.1	38.48	2	0.052
	>10.01	324	97.9	1667.45	36	0.021
DM medications	OHGA	201	60.7	1065.73	22	0.021
	Insulin	111	33.5	550.31	13	0.024
	Both	19	5.7	99.89	3	0.03
Alcohol use history	Yes	58	17.5	254.84	12	0.047
	No	273	82.5	1461.09	26	0.018
BMI (kg/m2)	<18.5	63	19	318.39	12	0.038
	18.5-25	253	76.4	1324.3	25	0.019
	>25	15	4.5	73.24	1	0.014

PYO-Person-year observation; TB-Tuberculosis; TBID-TB incidence density; BMI-Body Mass Index; DM-Diabetes Mellitus; OHGA-Oral Hypoglycemic Agent

Incidence rate of tuberculosis

At the end of follow-up period, 1759.32 Person Years of Observation (PYOs) were obtained. During ten-year period, 38 new TB incidences occurred; of those 17 had pulmonary TB and the remaining 21 had extrapulmonary TB. The cumulative incidence rate of TB development was 38 (11.5%) within 193.6 PYOs. The overall incidence density of TB was 2.2 per 100 (95% CI: 1.5-4.6) PYO. More than 55% of TB incidences were occurred within five years of follow-up after DM follow up commenced.

TB-free survival status of diabetes mullites patients

The mean survival time was 5.2 year, while median 5.3 year, and the range 3.9 year. Two hundred ninety-three (88.5%) observations were censored at the end of the follow-up time. During the follow up period 1551.2 Person-years of risk time was observed [Figure 1].

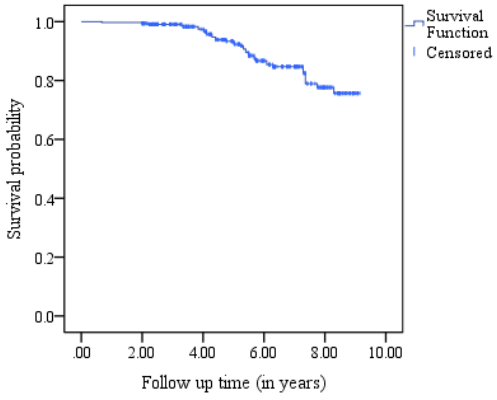

Figure 1: The overall TB-free survival probability of diabetes mellitus patients in hospitals found in Southwest Shewa, Oromia Region State, Ethiopia, 2022

Predictors of time to TB development among DM patients

The results indicate that there was a significant difference in the survival function of the categorical variable particularly the HIV status of the patients. The hazard rate of developing TB for DM patients who have HIV during treatment was consistently and significantly shorter than those who did not have HIV [Figure 2].

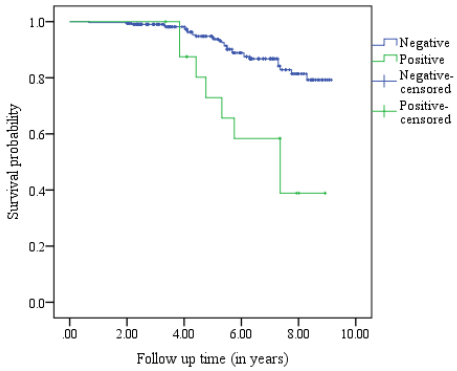

Figure 2: Kaplan-Meier survival curves comparing TB-free survival probability of DM patients based in HIV status

In bivariable Cox-proportional hazard model, HIV status, age, place of residence, history of forgetting to take medication, smoking history, chewing khat, DM medication type, history of previous TB treatment, and history of alcohol consumption were significantly association with time to develop TB (Table 3). In a multivariable Cox-proportional hazard model, previous TB treatment history (AHR = 5.2, 95% CI: 2.2–12.6), being older than50 year (AHR = 6.0, 95% CI: 1.6–21.6), history of alcohol use (AHR = 3.5, 95% CI: 1.6–7.6), cigarette smoking history (AHR=5.8, 95% CI: 1.1–13.7), forgetting to take medication (AHR = 2.4, 95% CI: 1.2–4.9), and being HIV sero-reactive (AHR = 3.5, 95% CI: 1.6–8.2) were significantly associated with time to develop TB (Table 3).

Table 3: Predictors of time to develop TB among diabetes mellitus patients on follow-up in hospitals in Southwest Shewa zone, Oromia region, Ethiopia from June 28, 2013, to June 27, 2022.

Variables		CHR (95%CI)	AHR (95%CI)
Age	18-35	1.0	1.0
	36-49	1.8 (0.62–5.0)	1.6(0.51–4.3)
	>50	1.8 (0.66–4.7)	6.0 (1.6–21.6) **
Forgetting the medications	No	1.0	1.0
	Yes	2.5 (1.3–4.8)	2.4 (1.2–4.9) *
Previous TB treatment history	No	1.0	1.0
	Yes	4.0 (1.8–9.2)	5.2 (2.2–12.6) **
HIV sero-status	Non-reactive	1.0	1.0
	Reactive	3.9 (1.8–8.6)	3.5 (1.6–8.0) **
Cigarette smoking	No	1.0	1.0
	Yes	7.3 (1.7–30.7)	5.8 (1.1–13.7) *
Alcohol use history	No	1.0	1.0
	Yes	2.9 (1.5–5.9)	3.5 (1.6–7.6) **

*AHR-Adjusted Hazard Ratio; CHR-Crude Hazard Ratio; CI-Confidence Interval; **-significant at p-value <0.01; *-Significant at p-value <0.05; 1-reference category*

DISCUSSION

Collaborative works of TB program for populations at high-risk of chronic diseases like DM is implemented to achieve WHO 2030 End TB epidemic control strategies (1). Despite several interventions, TB remains a global public health concern, especially in low-and-middle-income countries. The finding of this study indicated that the incidence of TB in DM patients of the study area was found to be 2.2 per 100 PYOs. It is consistent with a study reported from India (2.2 per 100 PYs) (13) and with the study reported from Debra Markos 2.4 per 100 PYOs (10).

In contrast the incidence of TB in DM patients in the present study is higher than the results of previous studies reported from different countries. For instance, the study reported from China showed that the incidence of TB in DM patient is 119.85 per 100,000 person-years (14). Still the study reported from China indicated that the incidence of TB in DM patients is 51.3 per 100,000 PYs) (15). Similarly the study reported from Tanzania showed that the incidence of TB in DM patients is 1.7 per 100 PYs) (16). The variation between the present study results and the findings of previous studies might be due to difference in study settings, follow-up periods, TB burden in the study are, and sociodemographic characteristics of study participants. In addition, the difference could be due to TB screening and diagnostic techniques used in different countries. Moreover, the incidence of TB in DM patients in the current study is lower than the findings of previous studies reported from different settings. A stydy reported from Australia indicated that the incidence of TB in DM patients is 5.8 per 100 PYs (17), while study reported from Addis Ababa, revealed 3.8 per 100PYs (18). Moreover, the study reported from Dessie reported higher (6.2 per 100PYs) incidence of TB among DM patients (19) than the current study result. The most probable reason of difference on the incidence of TB between the present study result and previous studies finding is study population, TB burden, follow up period, TB screening method and sociocultural difference in the study areas.

In the present study being older than 50 years increased time to develop TB six times than DM patients aged 18–35 years. This finding is approximately similar to a previous study reported from Eritrea (20). Even though a small number of the patients (5.2%) were HIV sero-reactive in the current study, it increased time to develop TB by 3.5 times compared to HIV negative DM patients. This finding is supported by the result of the study reported from South Africa (21). This could be due to lack of viral suppression and treatment non-adherence.

In the current study, a history of alcohol consumption was significantly associated with time to develop TB.

Time to develop TB is speed upped by 3.5 times in DM patients who had history of alcohol consumption than those did not have history of alcohol consumption. This result is in line with the study findings reported from Australia (17) and India (13). In addition, findings reported from different studies conducted in Ethiopia (10,12,22) are also supported the present study finding in which alcohol consumption significantly speed upped time to develop TB in DM patients. There are also previous studies reported from United Kingdom (23) and China (24) showed a contradicting results with the current study findings. The difference between the present study and previous studies could be attributable to the level of awareness and sociodemographic characteristics difference between study participants.

Having previous TB treatment history was speed upped time to develop TB among DM patients by five times. The current study finding is similar with previous studies reported from different areas of Ethiopia (18,19,25) in which having previous TB treatment speed up time to develop TB in DM patients. Cigarette smoking is also six times speed upped time to develop TB among DM patients who had history of cigarette smoking than those had not cigarette smoking history. The current study finding is lower than the results of previous study reported from South Africa (26). The difference of the results of current study and previous studies might be due to higher number of cigarette smokers exist in South Africa than in Ethiopia. However, the present study finding is higher than the results reported from Australia (17) and the United Kingdom (23). This discrepancy between previous studies and the current study results might be due to sample size difference, Tb burden, follow-up time, and study settings. However, the present study finding is similar with the previous study result reported from Southern Ethiopia (27).

Data were collected through both patient interviews and data extraction from records to gather information on potential predictors. However, this study also has limitations. It was conducted using retrospective hospital records, which may have resulted in missing data on important factors such as hemoglobin, creatinine, and quantitative blood glucose levels. This could limit the analysis of factors associated with the time taken to develop TB based on the variables accessed from the secondary data.

CONCLUSION

Time to develop TB among DM patients was shorter than previously reported studies. The incidence rate of TB among DM patients was 2.2 person/100 years and cumulative incidence of 11.5%. More than half of TB incidences occurred within five years of follow-up after DM treatment started. Age >50 years, cigarette smoking, history of previous TB treatment, HIV sero-reactive, alcohol consumption, and forgetting medication taking were significantly associated with time to develop TB among DM patients. Implementing regular TB screening among DM patients is crucial to TB control and management of DM. Interventions that target factors associated with time to develop TB are required to increase time to develop TB among DM patients on care.

List of abbreviations

AFB-Acid Fast Bacilli; AOR-Adjusted Odd Ratio; AHR-Adjusted Hazard Ratio; BMI-Body Mass Index; CI-Confidence Interval; DM-Diabetic Mellitus; HIV-Human Immunodeficiency Virus; HR-Hazard Ratio; OHGA-Oral Hypoglycemic Agents TB-Tuberculosis; WHO-World Health Organization

Declarations

Ethical consideration

Ethical clearance was obtained from the ethical review board of Ambo University, College of Medicine and Health Sciences with reference number: AU/PGC/536/2015 on 06/12/2022.

Permission to access data and the patients was secured from the Southwest Shewa health office and respective hospitals. Written informed consent was obtained from each participant after thorough explanation of the objective and procedure of the study. Confidentiality of the participates was maintained through not collecting data on variables that expose the identity of the participants, and limiting data access.

Availability of data and materials

The data set used in this study is available from the corresponding author upon reasonable request.

Authors' contributions

BSM conceived the study, conduct analysis and draft the manuscript. TBM and HOD reviewed the manuscript critically, and approved submission. All authors approved the submission of the manuscript.

Acknowledgments

The authors acknowledge management team of included hospitals for their cooperation during data collection. The authors also appreciate all data collectors and participants for their tolerance and commitment during data collection.

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