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Predictors of extrapulmonary tuberculosis among diabetic patients at Debre Markos compressive specialized hospital, Ethiopia, 2021: A retrospective cohort study

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ABSTRACT

Background: Extrapulmonary tuberculosis is an emerging public health problem among diabetic patients. Diabetes, which causes immunosuppression, is increasingly being recognized as an independent risk factor for tuberculosis, and the two often coexist and impact each other. Therefore, this study aimed to investigate the incidence and predictors of extra pulmonary tuberculosis among diabetic patients at Debre Markos referral hospital, Northwest Ethiopia.

Methods: This institutionally-based retrospective cohort study was undertaken among 433 diabetic patients of Debre Markos compressive specialized hospital between January 2016 to December 2020. All eligible diabetic patients who full filled the inclusion criteria were included in the study. Data were entered using Epi-data Version 3.1 and analyzed using STATA Version 14. The survival time of diabetic patients was estimated using the Kaplan-Meier survival curve, and the survival time between different categorical variables was compared using the log rank test. Both bi-variable and multivariable Cox-proportional hazard regression models were fitted to identify independent predictors of tuberculosis among diabetic patients.

Results: Among a cohort of 433 diabetic patients at Debre Markos compressive specialized hospital, 17(3.9%) developed extra pulmonary tuberculosis during the follow-up time. The total time allotted to follow up the study participants was 1101.5 person-years (PY). The overall extra pulmonary tuberculosis incidence rate was 1.5 per 100 PY with 95% CI. Using the multivariable Cox-regression analysis, age (AIR 4.8 (95% CI (1.2–20.7), 0.03), diabetic medication (AIR 1.4 (95% CI(1.24–16), 0.03), having past history of PTB before diabetic follow up initiation (AID 1.5(95% CI (3.2–6.9),0.01) and having history of alcohol (AIR (95%CI (4(1.2–13),0.02) were significantly increased the risk of extra pulmonary tuberculosis while BMI (18.5–25) AIR(95% CI (0.22 (0.06–0.76), 0.02) was associated with a rate reduction for the incidence of extra pulmonary tuberculosis.

Conclusions: In this study, we found a high rate of extra pulmonary tuberculosis among diabetic patients. Factors significantly linked with increased risk of extra pulmonary tuberculosis included: age, using insulin as hypoglycemic medication, having past history of PTB before diabetic follow up initiation and alcoholic history while BMI was associated with a rate reduction of EPTB. Early screening and treatment for extra pulmonary tuberculosis is highly recommended at diabetes mellitus follow up for patients with the above risk factors.

1. Background

TB remains a serious public health challenge throughout the world, most notably in low and middle income countries ranking above HIV/AIDS [1]. Globally, around 10.4 million people fell ill with TB and 1.7 million died from the disease in 2016. The dynamics of the transmission varies geographically, the largest number of new TB cases occurred in Asia and Africa with 45% and 25% respectively [2,3].

Extrapulmonary tuberculosis is an emerging public health problem among diabetic patients. Diabetes, which causes immunosuppression, is

Abbreviations: AFB, Acid Fast Bacilli; BMI, Body Mass Index; DM, Diabetes Mellitus; DOTS, Direct Observed Therapy; EPTB, xtra Pulmonary Tuberculosis; HbA1c, Glycosylated Hemoglobin; MTB, Mycobacterium Tuberculosis; NTLCP, National Tuberculosis and Leprosy Program; PLWD, People living with Diabetes; PPG, Post Prandial Glucose; SDG, Sustainable Development Goal; TBDM, Tuberculosis with Diabetes Comorbidity; TB, Tuberculosis; TBNDM, Tuberculosis with Non-Diabetes Mellitus; USA, United States of America; WHO, World Health Organization.

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increasingly being recognized as an independent risk factor for tuberculosis. The association of extra pulmonary tuberculosis and diabetes mellitus is a concern for the health sectors as the coexistence of those two highly prevalent diseases has made the already existing treatments very complex [4]. The link between TB and DM is considered to be more prominent in developing countries where TB is endemic and the burden of diabetes mellitus is increasing. Accordingly, it is estimated that about 1.6 million deaths were directly caused by diabetes which is 1.69 times more likely to develop TB than none DM individuals in 2015, [5,6].

Currently, the worldwide prevalence of DM has been increased more quickly than ever (11.7%) that increases the incidence of EPTB and made the already existing treatments very complex among the co–infected patients [7]. The prevalence of DM and the incidence of TB in Ethiopia was found to be 6.5 % and 140/100 population respectively [1,8].

2. Methods

2.1. Study design and setting

This institutionally-based retrospective cohort study was undertaken between January 2016 to December 2020 in the chronic follow-up care unit of Debre Markos compressive specialized hospital. Debre Markos town is located 300 km from Addis Ababa, the capital city of Ethiopia, and 256 km from Bahir-Dar, the capital of Amhara Regional State. Debre Markos compressive and specialized Hospital is the only referral hospital found in East Gojjam Zone. The hospital serves >3.5 million people in its catchment area.

2.2. Population

The population for this study were all adult (≥18 years old) diabetic patients who were registered in Debre Markos referral hospital for chronic follow-up care from January 1st, 2016 to December 2020.

2.3. Inclusion criteria and exclusion criteria

All diabetic patients who fulfilled the inclusion criteria and registered from January, 1st 2016 to December 30/2020,' in chronic care follow up clinic of Debre Markos compressive specialized hospital were included in the study. However, we excluded diabetic patients with gestational DM, incomplete data or unavailable medical records, who were transferred in and who had been with EPTB at the time of DM diagnosis from the study as far as the exclusion criteria is concerned.

2.4. Data collection procedures

A five-year institution-based retrospective follow up study was conducted using chart review at Debre Markos compressive and specialized hospital chronic care follow up clinic on adult diabetic patients who had been registered from January 1st 2016 to December 30,2020. All eligible patients were included in the study (census method) after ethical clearance was obtained from the Institutional Review Committee of the College of Health Sciences, Debre Markos University (Ref. Res/Com/ser/&Post gra/Coor/Off: 781/11/10) and verbal informed consent was obtained from the patients. The medical record number (MRN) of the patients was identified from electronic database and health management information system (HMIS) registry books that had been used for the routine care of DM from January 1st, 2016 to December 2020). Then by using the MRN of the diabetic patients their medical records were identified and their status was assessed for the development of EPTB starting from the date of diabetic follow up initiation (first follow-up visit) to the end of the study period using validated data collection checklists.

2.5. Variables of the study

The dependent variable for this study was incidence of EPTB among diabetic patients. The independent variables were: socio-demographic factors (age, sex, and residence), personal behaviors (smoking, alcohol use and both smoking and alcohol use) and clinical characteristics (type of DM, BMI, duration of DM, glycemic control, anti-diabetic medications, past history of TB treatment, close contact with TB patients, history of renal failure).

2.6. Data analysis

Data collection checklist tools adapted from previous study in Ethiopia were used for the data collection [9]. We used Epi-data Version 4.1 for data entry and STATA Version 14 statistical software for data analysis. The necessary assumption of Cox-proportional hazard regression model was checked using the Schoenfeld residual test and the Log-Log plot. The diabetic cohort characteristics of continuous data were described in terms of central tendency (mean or median), dispersion (standard deviation or inter quartile range) and in the frequency distribution for categorical data. In the bi-variable Cox-regression analysis, significant predictors (p-value ≤ 0.25) of extra pulmonary tuberculosis included: HIV Sero status, history of renal failure, family history of DM, blood glucose level, body mass index, type of DM, diabetic medication, past history of TB and history of alcohol. To determine the independent predictors of EPTB a multivariable Cox-proportional hazard adjusted model was fitted after the proportional hazard assumption was checked with (global test = 0.94). log rank test for significantly associated variables at the multivariable analysis (body mass index = 0.02, Past history of PTB = 0.001, age = 0.00, diabetic medication = 0.02 and alcoholic history = 0.02) and by graphically assessment method

Finally, the outcomes of diabetic patients were dichotomized into censored or event categories. The Kaplan Meier survival curve was used to estimate survival time, and log rank test was used to compare the survival curves. Bi-variable Cox proportional hazards regression model was fitted for each explanatory variable and those variables having p-value ≤ 0.25 in bivariate analysis were fit into the multivariable Cox-proportional hazard regression model. Hazard ratio with 95% confidence interval and p-values were used to measure the strength of association and to identify statistically significant predictors. In the multivariable analysis, variables having P-value < 0.05 were considered as significant predictors of extrapulmonary tuberculosis.

3. Result

3.1. Socio demographic characteristics of study participants

In this retrospective cohort study, a total of 433 diabetic patients at Debre Markos compressive specialized Hospital from the period of January 1st, 2016 to December 30, 2020 were included. Fig. 1. In this study about 187(43.2%) of diabetic patients were under the age category of 18–35 years. The median age of the patients was 39 years with minimum and maximum age of 18 and 79 years respectively. In addition, 241 (55.7%) participants were males and 270 (62.5%) were rural residents.

3.2. Clinical and behavioral characteristics of the diabetic patients

This study revealed that about 33(7.6%) patients were positive for HIV and 34 (7.9%) had a history of renal failure. The duration of DM in all patients varied from date of initiation to 5 years of follow up. In the study 53 (12.2 %) participants had a family history of DM and 224 (51.7 %) were with type-I DM. About 197 (45.5%) patients were on oral hypoglycemic agents and 362(83.6%) were above 18Kg/m2 for their BMI. About 8(1.9%) were smokers, 16(3.7%) had alcoholic history and only 5 (1.2%) of the study subjects had both history of alcohol and smoking.

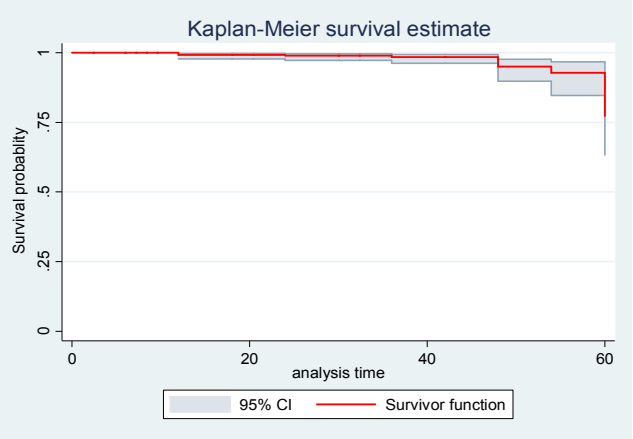

Fig. 1. Kaplan-Meier curve of Extra pulmonary tuberculosis survival proportion for diabetic patients at Debre Markos specialized compressive hospital from January 01/2015 to December 30/2019.

(Table 1)

3.3. Incidence of extra pulmonary tuberculosis among diabetic patients

The patients were followed for 1101.5 total person years. The mean, median and range of the follow-up time was found to be 2.5, 2 and 4.8 years with (IQR = 3) respectively. During the follow up time, about 17 (3.9%) of the patients were with new EPTB cases (7/41.2% Bone, 5/29.4% lymphoid, 4/23.5% and 3/17.6% others). The overall incidence rate ratio of EPTB was found to be 3.9 per 100PY with 95% CI. Among the 17 individuals reporting extra pulmonary tuberculosis 9 (52.9 %) of them were males and 8(47%) had a past history of PTB. More over a relatively higher proportion of EPTB, 8(47%) was diagnosed among the age group of 35–50. In addition, the incidence was higher among rural residents 12(70.6%) and who had a duration of 1–3 years 13 (76.5%) follow-up. In this study, we observed that more than half 11(64.7%) of the EPTBDM patients were with type I DM. Fig. 1

3.4. Tuberculosis incidence density

In this retrospective cohort study, a total of 433 study participants were followed for different periods in five years and produced 1101.5 PY of observation. The mean, median and range of the follow-up time was 2.5, 2 and 4.8 years with (IQR = 3) respectively. Within the follow-up period, 17 patients were found to have post DM EPTB (new cases) with the overall EPTB incidence density (ID) of 3.9 per 100 with 95%CI. (Table2), Figs. 2-6.

3.5. Predictors of time to EPTB occurrence among diabetic patients

At the multivariable analysis only age, past history of PTB, diabetic medication body mass index and alcoholic history remained significant predictors for EPTB ($p < 0.05$). Accordingly, people who are at age of 18–50 years were 4.8 times more likely to develop EPTB than its counter parts (>50 years) (adjusted incidence ratio 4.8 (95% confidence interval 1.2–20.7), 0.03). On the other hand, people living with DM who had a history of PTB were 1.5 times at higher risk of developing EPTB as compared to those who had no past history of PTB (incidence rate ratio (95% CI: 1.5(3.2, 6.9), p: 0.01) and patients who used insulin were 1.4 times at higher risk of developing EPTB as compared to those who used oral hypoglycemic agents only (incidence rate ratio (95%CI: 1.4(1.2,16), p: 0.03) and patients with history of alcohol were 4 times more likely to develop EPTB than its counterparts(incidence rate ratio (95%CI: 4 (1.2–13)). Conversely patients with BMI >=18.5 were less likely to develop EPTB (Incidence rate ratio (95%CI: 0.22(0.6, 0.8), p: 0.02) than those who were underweight weight (<18.5 kg/m^2) counter parts.

4. Discussion

Despite numerous interventions made to prevent EPTB, it remains a serious global public health concern, especially in low- and middle-income countries. Therefore, we conducted this retrospective cohort study to determine the incidence of extra pulmonary tuberculosis among diabetic patients at Debre Markos compressive specialized hospital, Northwest Ethiopia. Accordingly, the overall incidence rate of EPTB was found to be was 1.5 per 100 PY with 95% CI among diabetic patients. This finding is higher than studies conducted in Texas (0.31/100PY), [10]. The above variations between studies could be explained, in part, by the differences in sample size, study settings, follow-up period, and socio-demographic characteristics of study participants. In addition, the distinction might be use of sophisticated screening and diagnostic techniques for early testing and detection prior to the disease progression in developed countries like Texas and china. This is supported by other studies, showed that sophisticated screening and diagnostic techniques for early testing and detection reduce the incidence of TB disease[7,11].

However, the finding of this study is consistent with the study conducted in India (2.2/100 PY) [12] and Tanzania (1.7/100 PY) [10] but inconsistent with the study in North India(0.655/100 PY) [13]. This might be due to the difference in population and the study layout (prospective study was conducted on patients with type II DM) in North India which have relatively decent insulin secretion and glycemic control which prevent developing of complications and co-infections as compared to type I DM.

Conversely, our finding is much lower than TB incidence reported in, Ethiopia at Dessie referral hospitals 6.2/100PY [14]). In the same way the above variations between studies could be explained, in part, by the differences in sample size, study settings, follow-up period, and socio-demographic characteristics of study participants. In this study nearly half(48%) of the respondents were type II DM which is more common in advanced ages with minimal complications including EPTB because of having relatively decent insulin secretion for glycemic control [15]. In addition, most respondents in this study were rural residents that might have socio-economic and demographic factors as a problem to visit the health care organization.

In this cohort study, people who are at age of18-50 years were 4.8 times more likely to develop EPTB than its counter parts (>50 years) (adjusted incidence ratio 4.8 (95% confidence interval 1.2–20.7), 0.03). This might be due to the high proportion of type I DM among young population than type II DM which is relatively with many complications including EPTB due to absolute deficiency of insulin among type I DM. Having history of alcohol was significantly associated with EPTB, accordingly, Patients with a history of alcohol are four times more likely to develop TB than patients with no history of PTB counter parts (incidence rate ratio 4 times more likely to develop EPTB than its counterparts (incidence rate ratio (95%CI: 4 (1.2–13)). This is consistent with studies in Texas [16], Australia [17] India [18] and Ethiopia [19]. However, this study contradicts findings reported from US [20], UK [21] and China [22]. These variations between studies could be the differences in sample size, study settings, follow-up period, and socio-demographic characteristics of study participants.

Furthermore, one of the most significant predictors for the incidence of EPTB among diabetic patients was having past history of PTB. Accordingly patients with a history of PTB are 1.5 times at higher risk of developing EPTB as compared to those who had no past history of PTB (incidence rate ratio (95% CI: 1.5(3.2, 6.9), p: 0.01) which is consistent with a study conducted in Australia [17] and studies in Ethiopia [19,14,23] .

Conversely patients who were normal and over weight (BMI >=18.5) were less likely to develop EPTB (Incidence rate ratio (95%CI: 0.22(0.6, 0.8), p: 0.02) than those who were underweight and over

Table 1
Baseline socio demographic, clinical and behavioral characteristics of people living with diabetes at Debre Markos referral hospital from January, 1st 2016 to December 30/2020.,'.

Variables	Characteristics	Frequency	Percent (%)	PY	EPTB	EPTBID
Sex						
	Male	241	55.7	55.7	9	0.52
	Female	192	44.3	44.3	8	0.25
Age						
	18–35	187	43.2	489.9	3	0.002
	36–50	157	36.3	385.2	8	0.005
	>50	89	20.6	226.4	6	0.004
	Median	39.9				
Place of residence						
	Urban	163	37.6	441.3	7	0.004
	Rural	270	62.4	660.2	12	0.07
BMI						
	< 18.5	71	16.4	212.5	4	0.003
	>=18.5	362	83.6	889	13	0.01
HIV Sero-status						
	Positive	33	7.6	79.4	3	0.01
	Negative	400	92.4	1022.1	14	0.04
Type of DM						
	Type I	224	51.7	593.1	11	0.06
	Type II	209	48.3	508.4	6	0.01
Blood glucose level (mg/dl)						
	≤ 70	14	3.2	47	2	0.02
	70–130	165	38.1	417.3	8	0.03
	≥ 130	254	58.7	637.2	7	0.02
Past history of PTB						
	Yes	9	2.1	23.5	5	0.02
	No	424	97.9	1078	12	0.07
History of close contact						
	Yes	5	1.1	10	3	0.3
	No	428	98.8	1091.5	2	0.15
Duration of EPTB since DM diagnosis						
	≤ 1 year	12	46.2	27	4	0.02
	1–3 year	14	53.9	63.5	13	0.01
DM medications had been/being used						
	OHGA	197	45.5	492.3	6	0.01
	Insulin	226	52.2	580	11	0.03
History of smoking						
	Yes	8	1.9	22	1	0.05
	No	425	98.2	1079.5	16	0.09
History of alcohol						
	Yes	16	3.7	47	3	0.01
	No	417	96.3	1054.5	14	0.04
Both smoking and alcohol						
	Yes	5	1.2	10	1	0.001
	No	428	98.9	1091.5	16	0.02

*BMI: body mass index, DM: diabetic mellitus TB: tuberculosis, OHGA: oral hypoglycemic agents, HIV: human immune virus.

weight (<18.5 kg/m2) counter parts which contradicts with the previous studies conducted in south-eastern Amhara [24], systematic review in Ethiopia [19], Egypt [25], US [20,26] and China (AHR (95%CI: 0.89 (0.76,1.03) [22]. The above variations between studies could be explained, in part, by the differences in sample size, study settings, follow-up period, and socio-demographic characteristics of study participants. In this study half (52%) of the respondents were type I DM in which more expected to be underweight. Similarly this study finding contradicts with the study conducted in Ethiopia at Black lion hospital [9]. This could be due to the difference in socio-demographic characteristics as more than half of the respondents in this study were rural residencies and underweight. It is known that most commonly underweight patients are considered to be Immuno compromised to withstand TB infection. In addition, most respondents in this study were rural residents that might have socio-economic and demographic factors as a problem to visit the health care organization. Furthermore, patients who are on insulin were 1.4 times more likely to develop EPTB than who are on oral hypoglycemic agents only (adjusted incidence ratio 1.4 (1.24–16), 0.03). More than half of the respondents in this study were type I DM. It is known that most commonly type I DM patients are considered to be Immuno compromised due to the absolute deficiency of insulin to withstand complications including EPTB. In addition, So this might be the possible justification for diabetic patients having insulin medication is significantly associated with EPTB.

5. Limitations

Despite strengths, this study has a number of limitations. Firstly, the study was institutional; therefore, diabetic patients at home could be missed. Moreover, secondary data were used, consequently some

Table 2
Tuberculosis incidence density rate stratified by socio-demographic, clinical and behavioral characteristics of Diabetic patients at Debre Markos referral hospital from January, 1st 2016 to December 30/2020.

Variables	Frequency	PY	EPTB	EPTB IDR	CHR (95%CI)	AHR (95% CI)	p-value
Sex							
Male	241	55.7	9	0.52	1.8(1.2–3.2)		
Female	192	44.3	8	0.25	1.00		
Age							
18–35	187	489.9	3	0.002	4(2–31)	4.8(1.2–20)	0.031
36–50	157	385.2	8	0.005			1
>50	89	226.4	6	0.004			1
Place of residence							
Urban	163	441.3	7	0.004	1.00		
Rural	270	660.2	12	0.07	0.72(0.04–11)		
Clinical characteristics							
HIV Sero-status							
Positive	33	79.4	3	0.01	1.00		
Negative	400	1022.1	14	0.04	0.52(0.15–1.7)		
History of renal failure							
Yes	34	78.1	2	0.002	1.00		0.99
No	399	1023	15	0.02	1.1(0.24–4.3)		
Family history of DM							
Yes	53	89.4	2	0.003	1.00		
No	380	1011.7	15	0.04	1.1(0.35–3)		0.96
Type of DM							
Type I	224	593.1	11	0.03	1.00	1.00	
Type II	209	508.4	6	0.01	0.4 (0.2–1	1.6(0.29–8.4)	0.24
BMI							
<18.5	71	212.5	4	0.05	1.00	1.00	
>=18.5	362	889	13	0.01	0.2(0.1–0.6)	0.34 (0.14–0.80)	0.02*
Blood glucose level (g/dl)							
< 70	14	47	1	0.01	1.00		
70–130	165	417.3	8	0.02	1.1(0.12–8.1)		0.99
≥ 130	254	637.2	8	0.03	1.00		
Past history of TB							
Yes	9	23.5	5	0.02	24(6.6–52)	12 (3–39)	0.001*
No	424	1078	12	0.04	1.00	1.00	1
Duration of TB since DM diagnosis							
≤ 1 year	12	27	12	0.4	1.00		
1–3 years	14	63.5	15	0.5	0.4(0.2–1.1)		
DM medications							
OHGA	197	492.3	6	0.01	1.00		1
Insulin	226	580	11	0.03	2.7(1.1–6)	2.8(0.46–16)	0.02
Behavioral characteristics							
History of smoking							
Yes	8	22	1	0.05	1.00		
No	425	1079.5	16	0.09	0.6(0.1–4.3)		
History of alcohol							
Yes	16	47	3	0.01	8.5(1.4–11)	4(1.2–13)	0.02*
No	417	1054.5	14	0.04	1.00	1.00	
History of smoking and alcohol							
Yes	5	10	1	0.001			
No	428	1091.5	16	0.02			

* BMI: body mass index, DM: diabetic mellitus TB: tuberculosis, OHGA: oral hypoglycemic agents, HIV: human immune virus.

important variables like a history of Cancer, chemotherapy, adherence status, glaciated hemoglobin, and organ transplantation could be missed. Furthermore, in this study, the impact of providers' training, supplies, equipment, and setup have not been explored.

6. Conclusion

In five years of diabetic cohort, the overall incidence of Extra pulmonary tuberculosis has been high among diabetic patients. Age, history of alcohol, past history of TB and insulin are found to be independent predictors of TB. However, being normal and overweight (BMI, >=18.5) is found to be an independent positive factor associated with decreased risk of EPTB. Special attention should be given for patients who have a history of alcohol, past history of TB and with low body mass index to reduce the risk of EPTB incidence by improving modifiable risk factors. All diabetic patients should be screened in clinical practice to prevent the occurrences of EPTB as early as possible. Furthermore, prospective cohort study should be conducted to make clear relations between predictors and EPTB incidence among diabetic patients.

7. Declarations

7.1. Ethics approval and consent to participate

Ethical clearance was obtained from the Institutional Review Committee of the College of Health Sciences, Debre Markos University with

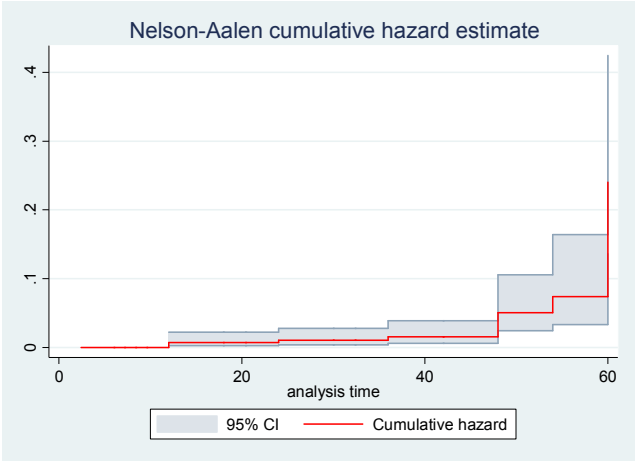

Fig. 2. Nelson Aalen cumulative hazard estimate of extra pulmonary tuberculosis among diabetic patients at Debre Markos specialized compressive hospital from January 01/2015 to December 30/2019.

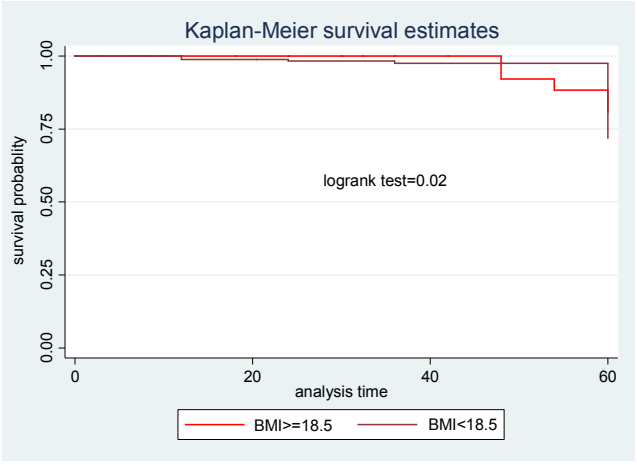

Fig. 3. The Kaplan-Meier survival curves comparing the extra pulmonary tuberculosis free survival probabilities of diabetic patients based their body mass index.

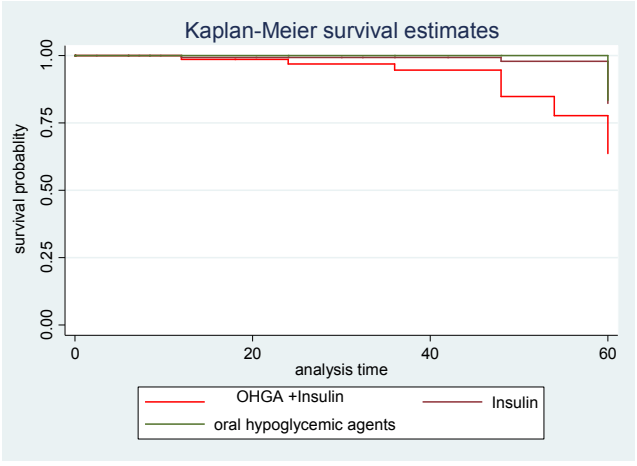

Fig. 4. The Kaplan-Meier survival curves comparing the tuberculosis free survival probabilities of diabetic patients based on their diabetic medication.

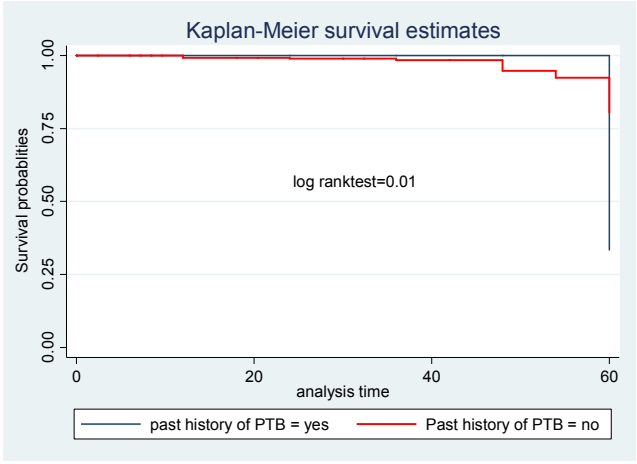

Fig. 5. The Kaplan-Meier survival curves comparing the extra pulmonary tuberculosis free survival probabilities of diabetic patients based on their alcoholic history.

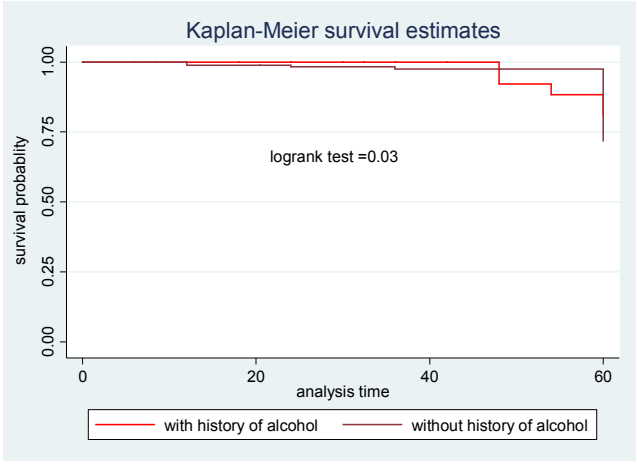

Fig. 6. The Kaplan-Meier survival curves comparing the extra pulmonary tuberculosis free survival probabilities of diabetic patients based on their alcoholic history.

Ref. Res/Com/ser/&Post gra/Coor/Off: 781/11/10. Oral permission was obtained from hospital administrations. Each diabetic patient received an explanation about the purpose of study, and verbal informed consent was obtained from each participant prior to proceeding. The ethical committee formally waived the need of formal written consent since the study was done through interviewing and reviewing of medical record of the couples. Therefore, the committee declared that this study is less invasive as much as confidentiality is maintained. To ensure confidentiality, all collected data were coded and locked in a separate room prior to the data entry process. Participant names were not included in the data collection format, and the data were not disclosed to any person other than principal investigators.

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.

Acknowledgements

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Availability of data and materials

"The dataset will not be shared in order to protect the participants' identities" but it is available from the corresponding author on reasonable request

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