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Diabetic Status and Other Risk Factors for Developing Pulmonary Tuberculosis: A Retrospective Cohort Study at King Abdul Aziz University Hospital, Jeddah

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Pulmonary and extrapulmonary tuberculosis is an emerging public health challenge among diabetic (DM) patients. Diabetes is a known cause of immunosuppression and is recognized as an independent risk factor for tuberculosis (TB). Diabetes and tuberculosis frequently coexist and influence each other [1]. This study investigates diabetes mellitus as a risk factor for developing pulmonary tuberculosis (PTB) compared to extra-pulmonary tuberculosis (EPTB).
Materials and Methods: This retrospective cohort study included all culture-confirmed, and PCR-positive TB patients (PTB 522 and EPTB 173) reported to King Abdul Aziz University Hospital, Jeddah, between January 2012 to January 2021. The categorical baseline characteristic of PTB and EPTB patients has been compared with DM status using Pearson chi-square and Fisher's exact test. The univariable and multivariable logistic regression model was used to estimate the association between DM and different sites of TB (PTB and EPTB).
Results: Of 695 diagnosed TB patients, 215 (30.94%) are diabetic. The percentage of PTB is (75.11%), and EPTB is (24.89%) as a risk factor; DM shows a significant association with PTB in both univariate and multivariate logistic regression analysis. Age, smoking status, dyslipidemia, and other comorbidities are also significantly associated with PTB (P value <0.05).
Conclusion: In this study, we found a high rate of pulmonary tuberculosis (PTB) among diabetic patients. Proper management of DM and TB infection might increase TB control and prevent PTB and EPTB development in the Saudi population.

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Keywords: Diabetes mellitus; pulmonary tuberculosis; extrapulmonary; risk factor.

1. INTRODUCTION

Tuberculosis (TB) remains a significant source of morbidity and mortality. Worldwide, one-third of the population is estimated to be infected with *Mycobacterium tuberculosis* [2]. Globally, about nine million annual incidents of active TB cases [3,4]. In 2014, the estimated worldwide prevalence of diabetes mellitus (DM) was 387 million people (8.3%) in adults and was expected to exceed 590 million people by 2035 [5]. The risk of having active TB disease in patients with DM is approximately 3 times higher compared to the population who does not have diabetes. Furthermore, 15% of active TB cases worldwide are attributable to DM [2,6,7]. Patients with DM usually have a greater risk of poor TB outcomes, including relapse and death [2]. The reason for poor outcomes in patients with TB is most probably due to immune impairment, which DM causes [8,9]. Moreover, the treatment of TB sometimes becomes more complex as these TB cases with DM develop drug-resistant TB [10].

According to previously done studies, it has been proven that the relation between TB and DM is like a two-ended sword; as DM increases the risk of developing TB infection, patients with TB have higher rates of having a medical history of DM [11–13]. Moreover, TB can even cause DM in cases not previously known to be diabetic [14]. TB and DM are hypothetically lethal combinations with a synergistic effect. It is also a rising public health problem in countries where both diseases are most likely to converge [15]. Therefore, the health system needs to monitor and ensure the continuity of the long-time care for DM, and immediate care is required for TB control [12].

Approximately 15% of global TB cases are diagnosed as extra-pulmonary tuberculosis (EPTB). EPTB cases are challenging to treat and control as they are harder to diagnose and sometimes associated with worse outcomes than pulmonary tuberculosis (PTB) [16,17]. Incidence of EPTB more commonly occurs in a person with impaired innate immunity, renal disease, and HIV [18–22]. Studies have indicated that the sites of EPTB may vary according to geographic location and population. Clinical manifestations of TB are variable and depend on several factors associated with the microbe, the host, and the environment [21,23–25]. The role of host-related factors which are responsible for the occurrence of TB at extrapulmonary sites is inadequate. However, global data related to DM and TB patients are limited. More precisely, few studies have been done to explore the relation of DM with PTB and EPTB. We have yet to see any study that reported the distribution of DM among the PTB and EPTB cases to explain the actual situation that will direct the efforts to halt both epidemics. Thus, in this study, we investigated whether DM is a risk factor for developing either PTB or EPTB and explored other risk factors associated with PTB.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

A retrospective cohort study included all the TB-positive patients diagnosed by culture or PCR positive results and treated in King Abdul Aziz University Hospital (KAUH), Jeddah, between 1st January 2012 to 31st January 2021. King Abdul Aziz University is one of the largest tertiary care hospitals in the western region of Saudi Arabia [26].

2.2 Study Population

This study included all patients over 17 years old diagnosed with TB confirmed by culture or positive PCR. We extracted 695 TB (522 PTB and 173 EPTB) confirmed cases, out of which 215 (30.94%) cases were found to have diabetes.

2.3 Data Collection Procedures

All the data were collected by reviewing the electronic medical record. The socio-demographic data, including age, gender, nationality, marital status, history of smoking habit, alcohol drinking status, and history of relapse, was collected from the history taking part in the electronic record review. The data for comorbidities including diabetes mellitus, hypertension, cardiac disease, HIV, dyslipidemia, and other comorbidities (thyroid disease, gynecological issues in female patients, and benign prostatic hyperplasia in case of male patients) were collected from patient's statements, reports of different laboratory investigations which are done during the period of hospital admission of the patient, and by different medication that given to the patient for treatment purpose. The main risk factor of our study, diabetes mellitus (DM), was diagnosed

based on a blood test known as a glycosylated hemoglobin test (HbA1C). In our study, If the HbA1c test result is ≥ 6.5, the patient was considered to have DM. Furthermore, the result of fasting blood sugar (FBS) is also included in this study. The usual range of FBS is from 3.9 to 5.6 mmol/l. ≥7 mmol/l of FBS is considered abnormal in this study. The diagnosis of TB was made by reviewing the test reports of blood culture for TB and the PCR test. Either it is PTB or EPTB; this information was collected from medical records reviewing TB patients' radiological findings and physician reports.

2.4 Ascertainment of Key Variables

2.4.1 Pulmonary TB

The patient with at least one sputum specimen positive for acid-fast bacilli (AFB), including any scanty result. Moreover, Chest x-ray abnormalities with active TB were diagnosed by a qualified physician.

2.4.2 Extrapulmonary TB

Radiological findings by a qualified physician confirm a patient with TB of different organs other than the lungs.

2.4.3 Diabetes mellitus (DM)

Diabetes mellitus is diagnosed based on the blood test HbA1C; If the HbA1c test result is ≥ 6.5, the patient is considered to have DM. Also, according to WHO criteria as follows, fasting blood glucose ≥ 7.0 mmol/L (126mg/dl) or 2-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dl) and self- statement of a person known as diabetic or on anti-diabetic medication. New cases of diabetes were those diagnosed for the first time in the study, and the old cases were those previously diagnosed by physicians and/or medical records of taking anti-diabetic medications for high blood glucose levels.

2.5 Statistical Analysis

Categorical baseline characteristics of TB cases in including age (18 - ≤ 39, ≥ 40 - ≤ 60, > 60), gender (male or female), nationality (Saudi or non-Saudi), marital status (single, married, others), BMI (< 18.5, ≥ 18.5 – ≤ 24.9, ≥ 25 - ≤ 29.9, ≥ 30 - ≤ 39.9, ≥ 40), history of smoking (non-smoker, smoker, unknown), alcohol drinking status (non-alcoholic, alcoholic, unknown), history of relapse (yes or no), Drug sensitivity of TB (drug-sensitive TB and drug-resistant TB) were compared with the site of TB, PTB, and EPTB by Pearson's chi-square test. Different comorbidities include diabetes (diabetic or non-diabetic), hypertension (hypertensive or non-hypertensive), cardiac disease (present or absent), HIV (positive or negative), dyslipidemia (present or absent), and other comorbidities (present or absent) were also compared with the site or TB (PTB and EPTB) by Pearson's chi-square test. Univariate and multivariate logistic regression models were used to estimate the association between diabetes and the site of TB (PTB and EPTB). To find out the confounder in this study, backward elimination logistic regression analysis was done. We found that body mass index (BMI) and dyslipidemia a confounder. Our model has been adjusted for the confounders. The statistical tests were considered significant (2-sided) at $p < 0.05$. All the statistical analysis of this study was performed by using Stata version 13.0 (Stata Corp, College Station, Texas, USA).

3. RESULTS

A total of 695 TB-positive cases are included in this study. PTB cases are 522 (75.11%), and EPTB cases are 173 (24.89%). The mean age of the TB-positive patients is 43.78 ± 18.26 years. Most of the TB cases are male, 55.97%. More than half are married, 62.01%. Foreign citizens are most likely to develop TB, 61.87% compared to Saudi citizens. The mean body mass index (BMI) among TB patients is 22.78 ± 4.93, which indicates an average body weight. Only 16.55% of TB cases have a history of smoking. The percentage of relapse TB patients is only 7.05%. 13.24% TB positive cases are resistant to 1st line anti TB drugs.

As shown in Table 1, PTB is most frequently seen in the young age group (18 – 39 years old) of cases 242 (46.36%). Compared to females, males are commonly affected with PTB 298 (57.09%). The non-Saudi citizen population is more in percentage by 330 (63.22%) than the Saudi population. Married people are more prone to have PTB 326 (62.45%). TB cases with normal BMI are more likely to have PTB 269 (51.53%). Only 40 (7.66%) TB cases are diagnosed as PTB. The percentage of 1st line anti-TB drug resistance in PTB cases is 69 (13.22%); in EPTB cases, the percentage is 23 (13.29%). Among the socio-demographic data, age and smoking status significantly differ between PTB and EPTB (P-value < 0.05).

Table 1. Baseline characteristics and socio-demographic data of TB-positive cases of King Abdul Aziz University Hospital, Jeddah, from 1st January 2012 to 31st January 2021. (n = 695)

Characteristics	Pulmonary TB (n = 522)		Extra-pulmonary TB (n = 173)		P value
	N	%	N	%	
Age (years)					
Young age (18 – 39)	242	46.36	99	57.23	
Middle age (40 – 60)	142	27.20	45	26.01	**0.02**
Older age (>60)	138	26.44	29	16.76	
Gender					
Male	298	57.09	91	52.60	0.30
Female	224	42.91	82	47.40	
Nationality					
Saudi	192	36.78	73	42.20	0.20
Non-Saudi	330	63.22	100	57.80	
Marital status					
Single	181	34.67	59	34.10	0.35
Married	326	62.45	105	60.69	
Divorced	15	2.87	9	5.20	
BMI (Kg/m^2)					
Underweight (<18.5)	101	19.35	22	12.72	
Normal weight (≥ 18.5 - <25)	269	51.53	87	50.29	
Overweight (≥ 25 - <30)	93	17.82	39	22.54	
Obese (≥ 30 - ≤ 39)	31	5.94	17	9.83	0.10
Morbid obese (≥ 40)	28	5.36	8	4.62	
Smoking status					
Non- smoker	295	56.51	109	63.01	
Smoker	102	19.55	14	7.51	**0.001**
Unknown	125	23.95	51	29.48	
Alcohol drinking status					
Non-alcoholic	157	30.08	62	35.84	
Alcoholic	1	0.19	0	0.00	0.32
unknown	364	69.73	111	64.16	
History of Relapse					
Yes	482	92.34	164	94.80	0.27
No	40	7.66	9	5.20	
Drug sensitivity of TB					
Drug sensitive TB	453	86.78	150	86.71	0.98
Resistant TB	69	13.22	23	13.29	

Table 2 illustrates that in case PTB cases majority of the patients are non-hypertensive 396 (75.86%), have no cardiac disease 462 (88.51%), HIV negative 456 (87.52%), have no dyslipidemia 472 (90.6%) and other comorbidities are absent 368 (70.63%). In the case of EPTB also, the mass of the population is non-hypertensive 138 (79.77%), having no cardiac disease 157 (90.75%), HIV negative 149 (86.13%), having no dyslipidemia 170 (98.27%) and other comorbidities are absent 140 (80.92%). Among the data for comorbidities in PTB and EPTB cases, variables like diabetes, dyslipidemia, and other comorbidities show a significant difference between PTB and EPTB groups. (P-value < 0.05).

Table 3 reveals the association of laboratory investigation with pulmonary tuberculosis (PTB) and extra-pulmonary tuberculosis (EPTB) patients. The majority of the PTB cases have a higher percentage of 177 (33.91 %) high HbA1c level (≥ 6.5), and in the case of EPTB, the high level of HbA1c is only 36 (20.81%). In the case of fasting blood sugar (FBS), PTB patient has a more significant percentage,177 (33.91%), of having high FBS level. 34 (19.65 %) of EPTB cases has FBS level more than the normal range.

Table 2. Association between comorbidities with PTB and EPTB patients of KAUH from January 2012 to January 2021. (n = 695)

Characteristics	Pulmonary TB (n = 522)		Extra pulmonary TB (n = 173)		P value
	N	%	N	%	
Diabetes mellites					
Diabetic	180	34.48	35	20.23	**0.00**
Non-diabetic	342	65.52	138	79.77	
Hypertension					
Hypertensive	126	24.14	35	20.23	0.29
Non-hypertensive	396	75.86	138	79.77	
Cardiac disease					
Present	60	11.49	16	9.25	0.41
Absent	462	88.51	157	90.75	
HIV					
Positive	65	12.48	24	13.87	0.63
Negative	456	87.52	149	86.13	
Dyslipidemia					
Present	49	9.40	3	1.73	**0.001**
Absent	472	90.60	170	98.27	
Comorbidity					
Present	153	29.37	33	19.08	**0.008**
Absent	368	70.63	140	80.92	

Table 3. Association between laboratory investigation with PTB and EPTB cases of KAUH from 2012 to 2021. (n = 695)

Lab investigation	Pulmonary TB (n = 522)	Extra pulmonary TB (n = 173)	P value
HbA1c			
Normal level	176 (33.72 %)	74 (42.77 %)	
High level	177 (33.91 %)	36 (20.81 %)	**0.004**
Investigation not done	169 (32.38 %)	63 (36.42 %)	
Fasting blood sugar (FBS)			
Normal level	340 (65.13 %)	137 (79.19 %)	
High level	177 (33.91%)	34 (19.65 %)	**0.002**
Low level	5 (0.96 %)	2 (1.16 %)	

Table 4 shows that diabetic cases in PTB are 180 (34.48%) and in EPTB 35 (20.23%). In univariable analysis, diabetes significantly correlates with PTB (OR: 2.07, 95% CI, 1.37 – 3.13). In the case of multivariable analysis, it also shows a significant association with PTB (OR: 2.06, 95% CI, 1.32 – 3.23). Our model is adjusted for BMI and dyslipidemia.

Table 5 illustrates the association between different risk factors and sites of TB (PTB and EPTB). In univariable logistic regression analysis, PTB is significantly associated with DM (OR: 2.07, 95% C.I, 1.37 – 3.13), dyslipidemia (OR: 2.95, 95% C.I, 1.80 – 19.1), age (OR: 2.63, 95% C.I, 1.00 – 1.02), BMI (OR: 0.95, 95% C.I, 0.92 – 0.99), HbA1c (OR: 1.31, 95% C.I, 1.05 – 1.63) and FBS (OR: 1.97, 95% C.I, 1.34 – 2.92).

In multivariable analysis, PTB is significantly associated with DM (OR: 2.06, 95% C.I, 1.32 – 3.23), dyslipidemia (OR: 2.46, 95% C.I, 1.37 – 15.5), age (OR: 1.02, 95% C.I, 1.00 – 1.03), BMI (OR: 0.94, 95% C.I, 0.90 – 0.97), HbA1c (OR: 1.01, 95% C.I, 0.73 – 1.37) and FBS (OR: 1.81, 95% C.I, 1.13 – 2.87).

In both univariate and multivariate logistic regression analysis, PTB is not significantly associated with hypertension, cardiac disease, HIV, gender, and relapse.

Table 4. Association between diabetes and site of TB (PTB and EPTB) (n = 695)

Total TB patient (n = 695)	Diabetic (n = 215)		Non-diabetic (n = 480)		Univariable analysis		Multivariable analysis	
	No.	%	No.	%	OR (95% C.I)	P value	a OR ** (95% C.I)	P value
Pulmonary TB (n = 522)	180	34.48	342	65.52	2.07 (1.37 – 3.13)	**0.001**	2.06 (1.32 – 3.23)	**0.002**
Extra-pulmonary TB (n = 173)	35	20.23	138	79.77				

*** Adjusted for BMI and dyslipidemia*

Table 5. Association between the site of TB (PTB and EPTB) and its risk factors among TB cases of KAUH

Risk factors of PTB *vs.* EPTB	Univariable analysis		Multivariable analysis	
	OR (95% C.I)	P value	a OR **(95% C.I)	P value
Age	1.01 (1.00 – 1.02)	**0.008**	1.02 (1.00 – 1.03)	**0.02**
Gender	0.83 (059 – 1.17)	0.30	0.98 (0.63 – 1.30)	0.60
Body mass index (BMI)	0.95 (0.92 – 0.99)	**0.01**	0.94 (0.91 – 0.98)	**0.00**
Relapse	1.51 (0.72 – 3.18)	0.27	1.43 (0.66 – 3.12)	0.36
Diabetes mellitus (DM)	2.07 (1.37 – 3.13)	**0.00**	2.06 (1.32 – 3.23)	**0.00**
Hypertension	1.05 (0.82 – 1.91)	0.29	0.65 (0.38 – 1.09)	0.10
Cardiac disease	1.27 (0.71 – 2.27)	0.41	0.70 (0.37 – 1.35)	0.29
Dyslipidemia	2.95 (1.80 – 19.1)	**0.00**	2.46 (1.37 – 15.5)	**0.01**
HIV	0.88 (0.53 – 1.46)	0.63	0.84 (0.49 – 1.41)	0.51
Other comorbidities	2.63 (1.15 – 2.69)	**0.00**	1.59 (1.01 – 2.52)	**0.04**
HbA1c	1.31 (1.05 – 1.63)	**0.02**	1.01 (0.73 – 1.37)	**0.03**
Fasting Blood sugar (FBS)	1.97 (1.34 – 2.92)	**0.00**	1.81 (1.13 – 2.87)	**0.01**

*** Adjusted for BMI, dyslipidemia, and marital status*

4. DISCUSSION

This retrospective cohort study included 695 adult TB-positive cases in KAUH, Jeddah, demonstrating that diabetes mellitus is a risk factor for developing PTB. Till now, few studies have examined the association between diabetes and the site of TB (PTB and EPTB). A recent cross-sectional study in Bangladesh (2021) reveals that the prevalence of DM is higher in PTB cases, and DM has a significant association with PTB [27]. A population-based study on TB patients by *Garcia-Rodrigues et al.* in Galicia, Spain, stated that there are non-significant increased odds of having PTB *vs.* EPTB in patients with diabetes (OR: 1.48, 95% CI, 0·89 - 2·47) [28].

This research showed a significant difference in the age group (P value < 0.05). A study by *T. Sreeramareddy et al.* (2008) described that being younger than 25 is a risk factor for PTB relative to EPTB [29]. Also, some studies from USA and Turkey have reported that younger age is an independent risk factor for developing PTB or EPTB [21,24].

We did not find a gender difference in our study; this outcome is different from the studies which were done previously. Some previously done studies observed gender differences in developing and developed countries, most probably due to exposure to TB infection and the prevalence of susceptibility risk factors like smoking [23,30–32]. Body mass index (BMI) significantly correlates with PTB in both Univariate and multivariate logistic regression analyses. Our finding is not different from the study done in the past and explains that BMI is significantly associated with pulmonary TB [33]. Moreover, a study done in 2017 found that lower BMI is positively associated with PTB [34].

In our study, we noted a significant association between smoking with PTB; our finding is similar to a study done in Nepal [29]. Furthermore, our result is consistent with a meta-analysis that reported smoking is a risk factor for TB infection, and PTB [35]. History of relapse did not indicate any positive association with PTB in this. However, some studies suggested that a history of previous TB or relapse is associated with PTB compared to EPTB [29]. Studies from many developed countries have reported an increasing trend of PTB among HIV-positive cases. HIV infection is also associated with EPTB [36,37]. However, in this study, we could not find any significant association between HIV and PTB. Most probably due to an inadequate number of HIV patients admitted to KAUH during the study duration period (January 2012 to January 2021). Other comorbidities included all the diseases not stated independently in this study, like anemia, thyroid disease, history of a previous stroke, gynecological disease in females, and benign prostatic hyperplasia (BPH) in males. Other comorbidities show a positive association with PTB; this finding is not different from the studies done in the past [29]. To diagnose and follow up diabetes, HbA1c is regularly done in KAUH. Therefore, we use the information on HbA1c to investigate the diabetes status of TB-positive patients. Although HbA1c and fasting blood sugar (FBS) shows a significant difference between PTB and EPTB group. This finding is the same as a newly done study done by Habib Sheul et al. [27].

There is a massive number of missing data on alcohol drinking habits of TB-positive patients. 219 (31.51%) patients out of 695 TB cases are non-alcoholic, only 1 (0.14%) case has a history of alcohol intake, and in 475 (68.35%) cases, we cannot find any record of the information on alcohol intake history. Hence, maybe a lack of information in the electronic medical record due to social stigma.

The study's strengths include (i) the inclusion of two common clinical types of TB (PTB and EPTB) as the study population that is not often assessed and compared for DM, (ii) no studies done in KSA on PTB and EPTB to explore their association with diabetes. This study has some limitations; first, it is conducted based on a medical record review of TB patients at a selected hospital, which may lead to information bias. Moreover, as we searched from previous medical records, due to missing data, we cannot collect adequate information on respiratory diseases like asthma and COPD in TB-positive cases, which could be a crucial factor in finding out the associated risk factors of PTB. Secondly, this study was performed in a tertiary hospital, not in the TB Centre of Jeddah, and the data of the labor screening program is not included, which enables the detection of most cases in ex-pats.

5. CONCLUSION

In conclusion, this study reveals that DM is a risk factor for developing PTB. Also, the laboratory investigation, including HbA1c and Fasting glucose, shows uncontrolled DM is associated with Pulmonary TB development compared to extrapulmonary TB. It indicates that more active TB treatment and follow-up are required for patients with DM. All TB Positive cases need diabetes screening and regular monitoring of glycemic levels. PTB and EPTB patients may benefit from the intervention as the proportion of DM is considerably more significant in TB positive population, and a remarkable association has been observed. Policymakers can emphasize regular screening and monitoring of DM as a part of standard care.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Ethical approvals of our study were obtained from the Bio-medical Ethical Committee of King Abdul Aziz University Hospital, Jeddah.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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