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Diabetes Mellitus as a Risk Factor for Drug Resistance Tuberculosis: A Retrospective Cohort Study at King Abdul Aziz University, Jeddah

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: The association between tuberculosis (TB) and diabetes mellitus (DM) is re-emerging with the epidemic of type II diabetes. Both TB and DM were of the top 10 causes of death.[1] This study explores diabetes mellitus as a risk factor for developing the different antitubercular drug-resistant (DR) patterns among TB patients.
Methods: A retrospective cohort study has been conducted on all TB cases reported to the King Abdul Aziz University Hospital, Jeddah, between January 2012 to January 2021. All culture-confirmed and PCR-positive TB cases were included in this study. Categorical baseline characteristic of TB patient has been compared with DM status by using Fisher's exact and Pearson chi-square test. The univariable and multivariable logistic regression model was used to estimate the association between DM and different drug resistance patterns.
Results: Of the total 695 diagnosed TB patients, 92 (13.24%) are resistant to 1st line anti TB

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drugs. Among 92 DR-TB patients, 36 (39.13%) are diabetic. The percentage of different patterns of DR-TB with DM, in the case of mono DR (12.09%), poly DR (4.19%) MDR (0.547%). As a risk factor, DM has a significant association with DR-TB, mono drug-resistant, and pyrazinamide-resistant TB (P-value <0.05). The MDR and PDR separately do not show any significant association with DM, but for further analysis, it shows a significant association with DM when we combined.

Conclusion: Our study identified diabetes mellitus as a risk factor for developing DR-TB. Better management of DM and TB infection caring programs among DM patients might improve TB control and prevent DR-TB development in KSA.

Keywords: Tuberculosis; drug resistance; diabetes; the risk factor; KSA.

1. INTRODUCTION

In 2017 Globally, there were approximately 10 million new tuberculosis (TB) cases and an estimated 400 million diabetes cases, of which 558,000 were multidrug-resistant TB (MDR-TB defined as resistance to at least rifampicin and isoniazid) or rifampicin-resistant TB (RR-TB). Both TB and diabetes mellitus (DM) were among the top 10 causes of death [1].

According to the World health organization (WHO), 3.3% of newly diagnosed and 20% of previously treated TB are resistant to isoniazid and rifampicin.[1] Recently, along with the DM and TB epidemics, the high prevalence of DM among MDR TB patients is a severe cause of concern, with the range of 20 – 23 % of MDR-TB patients are diagnosed with DM [2][3][4].

Drug-sensitive TB has a cure rate of 96% compared to only 54% among MDR TB. The treatment for patients infected with MDR TB strains is exceptionally challenging due to the complexity and increasing treatment duration of the chemotherapy regimen and the associated side effects of the alternative drugs, which also increases the cost of the treatment [5].

The association of TB and DM was investigated for decades [6]. Although several studies have shown a negative association, a recent systemic analysis and meta-analysis (2018) have concluded that people with type 2 DM have 1.5 fold increased risk for developing active TB compared to those who did not have diabetes [7]. Another systemic review published in the same year showed a significant association between DM and the development of multidrug-resistant tuberculosis. Patients with type II DM are known to have altered immunity, specifically a chronic inflammatory state in which many cytokines and chemokines are upregulated. These patients are usually susceptible to superimposed bacterial infections, like Mycobacterium tuberculosis. Immunodeficiency in HIV/AIDS is an important cause for developing MDR-TB and now extensive drug-resistant TB (XDR TB), both of which threaten recent advancements in the control of TB in multiple countries [8].

As the WHO has previously stated, TB ranks 11th among the leading causes of death in Saudi Arabia. Around 64,345 new TB cases were reported in KSA from 1991 to 2010 [9]. As the rate of DR-TB is increasing worldwide; it is crucial to investigate the problem in KSA and their risk factors. In Saudi Arabia, the absolute magnitude of this problem is still unknown as, before 2013, the country never conducted any national survey to measure the burden of TB drug resistance patterns [10]. A single national study reported that the MDR-TB rate is about 4%. Till now, there has been no other study that investigates the MDR-TB rate in Saudi Arabia.

Most of the studies conducted till now discussed only multidrug resistance is associated with DM or not [8,11]. This study aims to identify which type of TB drug resistance is more common in diabetic patients (mono, poly, or multidrug resistance).

Substantial evidence is required to prove that DM is strongly associated with the development of DR-TB. Good diabetes and TB control screening programs among diabetic patients might be necessary to control DR-TB. Our study aims to investigate diabetes mellitus as a risk factor for developing different patterns of antitubercular drug-resistant among TB patients.

2. METHODS

2.1 Setting and Participants

Between 1st January 2012 to 31st January 2021, a retrospective cohort study of all the patients diagnosed with tuberculosis and treated at King

Abdulaziz University hospital was included. King Abdulaziz University Hospital (KAUH) is one of the largest tertiary care hospitals in the western region. KAUH is well equipped with the most advanced technology and has about 4000 healthcare providers and administrators [12]. This study includes all patients over 17 years old diagnosed with tuberculosis confirmed by culture or PCR positive with drug susceptibility test. We extracted a total of 695 TB positive patients with drug susceptibility data and information on diabetes. Out of the total of 695 TB-positive patients, 215 (30.94%) cases suffered from diabetes. Moreover, sociodemographic and clinical characteristics including age, gender, nationality, body mass index (BMI), smoking habits (smokers vs. non-smokers), site of TB (either pulmonary or extrapulmonary TB), associated co-morbidities were collected by medical record review. Patients infected with non-tuberculosis mycobacteria (NTM) were excluded (n = 195).

2.1.1 Data from laboratory diagnosis and others

The sociodemographic data, including age, sex, marital status, drinking, smoking, previous history of TB, was collected from the history taking part by the electronic record review. The co-morbidities including hypertension, asthma, COPD, HIV, and malignancy from the physician's report, patient's statement which found during medical record review, by reviewing the medication that given to the patient and different laboratory tests which are done during the period when the patient was admitted in the hospital for treatment purpose. The main risk factor, diabetes, was diagnosed based on a blood test (HbA1c). If the HbA1c test result is ≥ 6.5, the patient was considered to have diabetic in this study. The diagnosis of DM is made based on the HbA1C test, an OGTT, which is a gold standard method for diagnosis DM, is not found in the electronic medical record of KAUH. The diagnosis of TB was made by reviewing the test report of blood culture for TB and the PCR test. A drug susceptibility test was also reviewed with this test result to find that the patient is resistant to any 1st line anti TB drug or not. To find out the confounder in this study, backward elimination of logistic regression analysis was done. We found that age and hypertension as a confounder. Our model has been adjusted for the confounders (Table number 4).

Definitions of the outcome of this study [13] TB-DM and TB without DM were defined as TB-positive patients with or without having type 2 diabetes. Mono drug resistance tuberculosis (mono DR-TB) refers to resistance to at least one of any 1st line anti TB drugs. Polydrug resistance tuberculosis Poly DR-TB refers to resistance to more than one first-line anti-TB drug other than both isoniazid and rifampicin. Multidrug-resistant tuberculosis (MDR-TB) refers to resistance to both isoniazid and rifampicin [14].

2.2 Statistical Analysis

Categorical baseline characteristics of TB cases including age (18-30, 31- 50, >51), gender (male or female), nationality (Saudi or non-Saudi), marital status (single, married, other), BMI (<18.5, 18.5 – <25, 25 - <30, >=30), alcohol drinking status (yes, no), smoking (smoker, non-smoker, unknown), site of TB (pulmonary or extrapulmonary), history of previous TB (yes or no), were compared by DM status by Pearson chi-square test. To estimate the association among diabetes and different drug-resistant profiles (all kinds of resistant, mono drug-resistant, PDR, MDR, resistant to each of the first line antitubercular drugs-like isoniazid, rifampicin, pyrazinamide, ethambutol), univariable and multivariable logistic regression models were used. Similarly, the logistic regression model also was applied to explore the other risk factors of anti TB-DR. Factors including age, gender, nationality, marital status, BMI, drinking, smoking, previous history of having TB, radiological finding (cavity present or not), and all other co-morbidities (hypertension, cardiac disease, dyslipidemia, malignancy, HIV were adjusted for the multivariable logistic regression model. All statistical analyses of these studies were performed by using Stata version 13.0 (Stata Corp, College Station, Texas, USA)

3. RESULTS

3.1 Baseline Characteristics and Risk Factors

A total of 695 patients were enlisted in the study. Out of which 92 patients have been confirmed to have DR-TB. As shown in Table 1, 57.61% of DR-TB cases were male. The mean age for Diagnosed DR-TB patients is 43.19 ± 16.71. More than half (57.61%) were married. Foreign citizens are more likely to be diagnosed as positive tuberculosis patients (61.87%). The mean BMI of the TB patient with DR is 23.41± 5.13, which almost indicates an average body weight. Three forth the patient with DR-TB has pulmonary tuberculosis (75.11%). 7.61% of DR-

TB patients have a previous history of TB. Among all diagnosed TB patients, one-third (30.94%) has DM, but only among the resistant TB cases, the frequency of diabetic patients was 39.13%. 16.30% of DR-TB patients are hypertensive, and 8.70% have a chronic cardiac disease. In the case of DR-TB, the frequency of dyslipidemia is 3.26%. Among DR-TB cases, 8.70% are HIV positive. Except for particularly mentioned risk factors in this study, other co-morbidities, including anaemia, thyroid disease, and benign prostatic hyperplasia in the case of male TB patients, are 26.80%. Almost half (49.78%) of the patient with TB is taking other medication (except in the 1st line anti TB medication) including medication for diabetes, anti-hypertensive, medication for chronic heart disease, Antiretroviral medication for AIDS, chemotherapy, etc. In the radiological finding, nearly half (42.39%) of DR-TB patients show cavity in their chest x-ray.

3.2 Drug Resistance Profile

Out of 695 TB patients, any of the 1st line anti-TB-DR are found in 92 (13.24%); among them, the person with diabetes is 36 (16.74%). MDR is 8 (1.15%), and diabetic among this MRD-TB patient is 1 (0.47%), PDR is 22 (3.17%), and PDR-TB with diabetes is 9 (4.19%). Finally, mono DR is 62 (8.92%), and mono DR-TB with DM is 26 (12.09). In an additional analysis, when we combined MDR-TB and PDR TB is detected that 30 (4.32%) TB patients were found to have drug resistance in more than one 1st line anti TB drug.

Table 1. Baseline characteristics and co-morbidities of diagnosed TB positive patient of KAUH, from 2012 to 2021 (n = 695)

Characteristics	Anti Tb drug Resistant (n =92)		Anti TB Not – resistant (n = 603)		p- value
	No.	%	No.	%	
Gender					
Male (n = 389)	53	57.61	336	55.72	0.73
Female (n = 306)	39	42.39	267	44.28	
Age					
Young age (n = 219)	28	30.43	186	31.10	0.94
Middle age (n = 229)	32	34.78	197	32.94	
Older age (n = 247)	32	34.78	215	35.95	
Nationality					
Saudi (n = 265)	31	33.70	234	38.81	0.35
Non-Saudi (n = 430)	61	66.30	369	61.19	
Marital status					
Single (n = 240)	36	39.13	204	33.83	0.61
Married (n = 431)	53	57.61	378	62.69	
Others (n = 24)	3	3.26	21	3.48	
BMI (Kg/m^2)					
Under weight (n =123)	13	14.13	110	18.24	0.39
Normal weight (n = 356)	53	57.61	303	50.25	
Overweight (n = 132)	16	17.39	116	19.24	
Obese (n = 48)	10	10.87	42	7.36	
Site of TB					
Extra pulmonary (n = 522)	23	25.0	150	24.88	0.98
Pulmonary (n =173)	69	75.11	453	75.12	
History of the previous TB					
No (n = 646)	85	92.39	561	93.03	0.82
Yes (n = 49)	7	7.61	42	6.97	
Smoking status					
Non – Smoker (n = 404)	58	63.04	346	85.64	0.75
Smoker (n =115)	13	14.13	102	88.70	
Unknown (n = 175)	21	22.83	154	25.54	
Radiological Finding					
Not done (n = 213)	27	29.35	186	30.85	0.15
Normal finding (n = 42)	5	5.43	41	6.80	
Cavity (n = 226)	39	42.39	187	31.01	
Bilateral Disease (n = 210)	21	31.34	189	31.34	

Table 2. Association between baseline characteristics and co-morbidities of drug-resistant adult TB patients with or without DM (n = 92) in King Abdulaziz University Hospital, Jeddah, 2012 to 2021

Characteristic	Resistant without diabetes (n = 56)		Resistant with diabetes (n = 36)		P value
	No.	%	No.	%	
Age (years)					
Young age (18 – 30)	25	44.64	3	8.33	0.00
Middle age (31 – 50)	22	39.29	9	25.00	
Older age (>51)	9	16.07	24	66.67	
Sex					
Male	31	55.36	22	61.11	0.59
Female	25	44.64	14	38.89	
Nationality					
Saudi	21	37.50	10	27.78	0.34
Non-Saudi	35	62.50	26	72.22	
Marital status					
Single	29	51.79	6	16.67	0.03
Married	25	44.64	29	80.56	
Others	2	3.57	1	2.78	
BMI (Kg/m^2)					
Under weight (<18.5)	8	14.29	5	13.89	0.15
Normal weight (>=18.5 - <25)	36	64.29	17	47.22	
Overweight (>=25 - <30)	9	16.07	7	19.44	
Obese (>=30)	3	5.36	7	19.44	
Smoking status					
Non- smoker	42	75.00	17	47.22	0.02
Smoker	5	8.93	7	19.44	
Unknown	9	16.07	12	33.33	
Type of TB					
Pulmonary	40	71.43	29	80.56	0.32
Extrapulmonary	16	28.57	7	19.44	
Radiological finding					
Normal finding	3	5.36	2	5.56	0.97
Cavity	22	39.29	16	44.44	
Bilateral disease	14	25.00	8	22.22	
Not done	17	30.36	10	27.78	
History of the previous TB					
Yes	7	12.50	0	0.00	
No	49	87.50	36	100.00	0.03
Comorbidities					
Hypertension					
Yes	3	5.36	13	36.11	0.00
No	53	94.64	23	63.89	
Cardiac disease					
present	2	3.57	6	16.67	0.03
absent	54	94.43	30	3.57	
HIV					
Yes	6	10.71	2	5.56	0.39
No	50	89.29	34	94.44	
Malignant disease					
Yes	1	1.79	0	0.00	0.42
No	55	98.21	36	100.00	
Dyslipidemia					
Yes	1	1.79	2	5.56	0.32
No	55	98.21	34	94.44	
Other co-morbidities					
Yes	13	23.32	9	25.00	0.84
No	43	76.79	27	75.00	
Other medication					
Yes	17	30.36	27	75.00	0.00

Characteristic	Resistant without diabetes (n = 56)		Resistant with diabetes (n = 36)		P value
	No.	%	No.	%	
No	39	69.64	9	25.00	

Comparing DR-TB with and without DM group with sociodemographic characteristics reveals that age, marital status, smoking, and previous history of TB have a significant association with diabetes with DR-TB (p-value <0.05)

Table 3. Drug resistance profile among TB-DM and TB without DM patients of KAUH from 2012 to 2021

Total TB patient (n=695)	Diabetic (n = 215)		Non- diabetic (n = 480)		P value
	No.	%	No.	%	
Drug sensitive (n = 603)	179	83.26	424	88.33	0.07
Drug Resistant (n = 92)	36	16.74	56	11.67	
Different Drug resistance profile					
Mono drug resistance TB (n = 62)	26	12.09	36	7.50	0.049
Poly drug resistance TB (n = 22)	9	4.19	13	2.71	0.26
Multi drug resistant TB (n = 8)	1	0.47	7	1.46	0.31
Combination of PDR and MDR					
Resistant to >1 Anti TB drug (n = 30)	10	4.65	20	4.17	0.77
A subtype of Mono drug resistance					
Isoniazid (n = 36)	1	3.85	6	16.67	0.36
Rifampicin (n = 14)	2	7.69	4	11.11	0.89
Pyrazinamide (n = 46)	16	61.54	17	47.22	0.03
Streptomycin (n = 31)	6	23.08	9	25.00	0.45

Table 4 illustrates the association between DM and primary anti TB drug resistance profile. In the univariable analysis diabetes mellitus was not significantly associated with DR-TB (OR: 1.52, 95% C.I, 0.97 – 1.39), mono drug resistance (OR: 1.62, 95% C.I, 0.99 – 2.88), PDR (OR: 1.52, 95% C.I, 0.66 – 3.73), MDR (OR: 0.31, 95% C.I, 0.04 – 2.58), Isoniazid resistance (OR: 0.37, 95% C.I, 0.04 – 3.08), rifampicin resistance (OR: 1.12, 95% C.I, 0.20 – 6.15), streptomycin resistance(OR: 1.50, 95% C.I, 0.53 – 4.27). Among subgroup mono DR Only pyrazinamide resistance shows significant association with DM in univariable analysis. (OR: 2.18, 95% C.I, 1.08 – 4.42).

In the case of multivariable analysis, DM shows significant association with any kind of DR-TB with DM (aOR: 2.05, 95% CI, 1.24 – 3.36), mono DR resistance is also revealed significant association with DM (aOR: 2.01, 95% CI, 1.17 – 3.48), poly DR (aOR: 1.70, 95% CI, 0.59 – 4.90) and MDR (aOR: 0.89, 95% CI, 0.09 – 9.04) are not significant in multivariable analysis. As the number of PDR and MDR-TB patients is too little in KAUH from 2012 to 2021, for further analysis, we combined these two groups (more than one anti-TB-DR group), and it shows a significant association with diabetes (aOR: 2.59, 95% CI, 1.05 – 6.35) in multivariable analysis. The multivariable analysis for each of the 1st line anti-TB drug only pyrazinamide shows significant association with DM (aOR: 2.85, 95% CI, 1.21 – 6.69), isoniazid (aOR: 0.66, 95% CI, 0.56 – 7.69), rifampicin (aOR: 1.09, 95% CI, 0.15 – 8.02), and streptomycin (aOR: 1.65, 95% CI, 0.47 – 5.81), does not exhibit any significant association with DM.

4. DISCUSSION

This retrospective cohort study included 695 TB-positive cases in KAUH, Jeddah, revealed that diabetes mellitus is a risk factor for developing 1st line anti TB-DR including any DR-TB, Mono DR-TB, resistance to more than one Anti TB-DR, Pyrazinamide resistant TB compared to not DR-TB. Our study suggests that diabetes can make people susceptible to DR-TB stains, Which is similar to the result of other studies done by AC Tarikulu et al., M al Ammari et al. and W Song et al. [3,14,15].

In Table 4 that there is a statistically significant association of DM as a risk factor for DR-TB. It is 2.05 times more likely to develop DR-TB in diabetic patients compared to being non-diabetic. Similarly, many previously done research has confirmed these findings and suggested that the risk of developing TB in a patient with DM is two to three times higher than in the general population. [7,8,15, 16].

Table 4. Association between diabetes and different pattern of Anti-TB drug resistance

Type of drug resistance	Univariable analysis		Multivariable analysis	
	OR (95% C.I)	P value	aOR* (95% C.I)	P value
Not resistant	Reference	Reference	Reference	Reference
Any Drug Resistance (n = 92)	1.52 (0.97 – 1.39)	0.07	2.05 (1.24 -3.36)	0.005
Mono drug Resistance (n =62)	1.62 (0.99 – 2.88)	0.05	2.01(1.17 – 3.48)	0.01
Poly drug Resistance (n = 22)	1.52 (0.66 – 3.73)	0.31	1.70 (0.59 – 4.90)	0.32
Multidrug Resistance (n = 8)	0.31 (0.04 – 2.58)	0.28	0.89 (0.09 – 9.04)	0.92
MDR and PDR (n = 30)	1.12 (0.51 – 2.44)	0.77	2.59 (1.05 –6.35)	0.04
Isoniazid resistance (n = 7)	0.37 (0.04 – 3.08)	0.36	0.66 (.056 - 7.69)	0.74
Rifampicin resistance (n = 6)	1.12 (0.20 – 6.15)	0.89	1.09 (0.15– 8.02)	0.93
Pyrazinamide resistance (n =33)	2.18 (1.08 – 4.42)	0.03	2.85 (1.21 – 6.69)	0.02
Streptomycin resistance (n =15)	1.50 (0.53 – 4.27)	0.45	1.65 (0.47 – 5.81)	0.44

**Adjusted for Confounders (age and hypertension)*

It is widely accepted that Impaired immunity due to diabetes increases the susceptibility to infection with drug-resistant strains [8] for example, diabetes patients tented to be associated with abnormally regulated cytokine response to mycobacterium tuberculosis [17]. The drug susceptibility increases due to some mediators like short-chain fatty acid, which are altered in an individual with diabetes. Though, the potential biological mechanism remains largely unclear [17,18]. Previously done studies also show a negative association between diabetes and the development of DR-TB. A study done in China on 621 TB-positive patients by *Fengling Mi et al.* does not reveal any association between diabetes and DR-TB [19].

In Table 4, unexpectedly, we did not find a significant association between MDR-TB and DM in univariable and multivariable analyses. It is possibly due to the limited number of MDR-TB patients in KAUH from January 2012 to January 2021. Some reports, including a recent meta-analysis done by *S Hayashi et al.,* have described a significant association between diabetes and MRD-TB [7]. A 1:1 matched case-control study conducted by *Wei-bin Li et al.* in Henan, China, conducted that MDR-TB cases were more likely to suffer from diabetes, cardiovascular disease, respiratory diseases, and cancer. [20]. Moreover, when we did further analysis by combining the patient of MDR-TB and PDR-TB, it showed a significant association with DM (aOR: 2.59 (1.05 –6.35)) in multivariable analysis. This analysis explains that having DM, the chance of being resistant to more than one 1st line anti TB drug is 2.59 times higher than the group who do not have diabetes.

In multivariable logistic regression analysis, DR-TB's mono drug resistance pattern shows a positive association with DM (aOR: 2.01, 95% CI: 1.17 – 3.48).

In the case of subgroup analysis in mono drug resistance, the resistance to pyrazinamide was the most frequently seen (33 patients had pyrazinamide mono drug-resistant TB out of 92 DR-TB patients), and among all mono DR-TB, only pyrazinamide resistance shows significant association with DM (a OR 2.88, 95% CI: 0.94 – 8.87) in both univariable and multivariable analysis, unfortunately, we did not find any positive relation between isoniazid resistance and diabetes. Similarly, a study from British Colombia done by *A Moniruzzaman et al*. did not find any connection between INH-R TB and diabetes [21]. besides, A study performed by *Takashi Hirama. et al*. (2016) illustrates a significant relationship between the two variables. [22].

Our study disclosed that DR-TB with diabetes males (61.11%) are higher in percentage than females (38.89%). However, there is no significant difference between them. Our finding is not different from other previously done research. There are some studies which also shows male has a higher percentage of having DR-TB with DM [19].

In our study, it does not show any association with obesity with DR-TB and DM, but some studies show different findings from ours, that obesity (higher BMI) has a greater risk of having DR-TB with DM [16].

In Table 2, we found that hypertension is associated with DR-TB with DM. Our finding is similar to the finding of other studies where being hypertensive is also associated with DR-TB.[16] Having prior TB treatment is associated with DR-TB, similar to previous research [3][22]. A study

conducted by *A Cetin Tanrikulu et al*. to find the risk factor for DR-TB in turkey found that a history of previous TB treatment has a significant association with DR-TB and MDR-TB. [3] Similarly, the other study in Madrid, Spain, done by *I Suárez-García et al.* also reveals that MDR-TB is associated with previous tuberculosis treatment. [23].

A systematic review conducted in Europe to find the risk factors of developing DR-TB, previous history of TB was the most potent determining factor of MDR-TB in Europe, and the pooled risk of MDR-TB was 10.23 times higher in previously treated patients compared to patients without having previous TB [24].

We did not find any positive association between HIV with DR-TB in our study. Research done in Toronto, Canada, by *Takashi Hirama et al.* shows MDR-TB is associated with HIV infection in the younger age group. Not only this but also a recent meta-analysis was done by *Susan van den Hof et al.* to find out the HIV as a risk factor for MDR reveals that HIV-positive tuberculosis patients are at greater risk of developing multidrug-resistant TB compared with HIV-negative patients. [25].

Other co-morbidity (Table 2) includes diseases not mentioned in this study separately like anaemia, thyroid disease, Benign prostatic hyperplasia (BPH) in the male patients, any other gynaecological disease in the female patient's history of the previous stoke, etc.

In our study, there is a massive number of missing data on alcohol drinking habits, out of 695 patient's information, 219 (31.51%) is non-alcoholic, and 1 (0.14%) is found to have of alcohol drinking habit, and 475 (68.35%) has no information about their alcohol drinking habit. Probably due to social stigma, the information of alcohol drinking status is missing.

This study is based on a medical record review. Due to missing data, we cannot find information about respiratory diseases like COPD and asthma cases in TB patients.
To diagnose DM, we used the information of HbA1c to investigate the diabetes status of the patient. HbA1c is routinely done to diagnose and follow-up DM as KAUH.

As shown in Table 2, we find a positive relationship between smoking habits and DR-TB. A study done to see the association between tobacco smoking and drug-resistant tuberculosis in China performed by *A Cetin Tanrikulu et al*. found substantial evidence that tobacco smoking is associated with an increase in the risk of developing any DR-TB. [26] Other studies also show an association between smoking history and DR-TB [16].

The study's strength is that total DR-TB has been categorized into different subgroups such as mono DR, poly DR, and multi-DR-TB. Resistant to each of the 1st line anti TB drug-like INH resistant TB, rifampicin-resistant, pyrazinamide resistant, ethambutol resistant, and streptomycin-resistant TB also investigated to see that DM as a risk factor has any association with them or not, which would make it possible for us to find DM a risk factor for each pattern of anti TB our resistant strain. Our study is also the first study in KSA, conducted to see the association of DM as a risk factor for a different pattern of DR-TB.

This study also has several limitations. First, this study is conducted based on a medical record review of the TB patient of KAUH; therefore, it may lead to information bias. Secondly, the gold standard laboratory test for diabetes is OGTT; in the electronic medical record in KAUH, the data for OGTT are not found. So, we took the data of HbA1c to diagnose the diabetic patient in our study. Thirdly, as we conducted this study in a tertiary hospital (KAUH), not in the TB Centre of Jeddah, the labor screening program data is also not included, which enables detecting most cases in ex-pats. So, our study may not apply to the general TB population of Jeddah.

The few previous studies done in KSA on TB did not explore the relation of different DR-TB and DM as risk factors for developing DR-TB. Most of those studies were done on the TB survey or focused on MDR-TB cases.

5. CONCLUSION

In conclusion, our results explain that a more robust TB treatment and follow-up might be necessary for patients with DM. Considering the global DM epidemic, this study emphasizes the message that there is a great need for a bi-directional screening and co-management approach in the effort to halt the TB-DM co-morbidity.

Attempts to control DM can have a considerable beneficial effect on TB outcomes. Policymakers can focus on new targets be relevant to an

enhanced care plan for DM patients with TB, particularly among the slightest evidence of problems with adherence or prolonged and complicated infections. Furthermore, focusing on the early identification and treatment of individuals with co-morbidity can improve treatment outcomes. We recommend prospective cohort studies focusing on bacteriologically confirmed TB cases that objectively diagnose diabetes mellitus with clearly defined types of TB and DM coupled with solid controls for potential confounding.

CONSENT

The patient's informed consent was not required as the study was limited to reviewing existing electronic medical records.

ETHICS APPROVAL

Ethical approvals of our study were attained from the Bio-medical Ethical Committee of King Abdulaziz University Hospital, Jeddah.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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