

The Footprint of Diabetes Mellitus on the Characteristics and Response to Anti-Tuberculous Therapy in Patients with Pulmonary Tuberculosis from Saudi Arabia

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Background: Right now, a tuberculosis (TB) and diabetes mellitus (DM) syndemic is re-emerging worldwide. Given the contradictory results of the impact of DM on the natural history of pulmonary TB (PTB), this study was undertaken to shed light on the precision of this hypothesis from a community with a substantial caseload of both diseases.

Methods: The present 5-year, retrospective, cohort study involved 487 (60.8% males, and 39.2% females) adult PTB patients (mean age 53.71 ± 15.78 years) selected from Dr. Soliman Fakeeh Hospital (DSFH), Jeddah, Kingdom of Saudi Arabia (KSA). The relevant patients' clinical, radiological and microbiological data were extracted from the hospital medical and laboratory database.

Results: In our study, the cumulative prevalence of DM among PTB subjects was 27.1%. Both diabetic and non-diabetic groups were matched with regard to gender ($p = 0.46$); however, diabetic patients were significantly older ($p = 0.0001$). Patients with concomitant DM displayed higher frequency of the classic clinical presentations of PTB and were 1.8 times more likely to have cavitory lesions on imaging studies ($p = 0.012$). Furthermore, diabetic patients showed higher initial sputum acid-fast bacillus (AFB) smear grade ($p = 0.0001$) and were more prone to have delayed culture conversion as compared to their non-diabetic counterparts (77.55 ± 37.74 versus 54.95 ± 27.67 days, respectively; $p = 0.0001$) which points out to less favorable treatment outcome.

Conclusion: DM showed an impact on different aspects of PTB. Accordingly, integrated bi-directional screening programs for both diseases in the KSA need to be implemented to upgrade health-care services of patients with dual diagnosis.

Keywords: pulmonary, tuberculosis, diabetes, comorbidity, impact

Introduction

Despite 9 decades of effective vaccination campaigns and 6 decades of anti-tuberculous medications, tuberculosis (TB) remains the most common cause of death from a single infectious agent worldwide.¹ Pulmonary tuberculosis (PTB) is an airborne communicable disease caused by *Mycobacterium tuberculosis* (MTB) bacilli, which are transmitted from person to person via inhalation of droplet nuclei classically generated by coughing.² Recently, it is estimated that about 25% of the world's population have been infected with MTB.³ Unfortunately, COVID-19 pandemic was associated with a negative influence on TB control in terms of delayed diagnosis and increased severity of clinical manifestations of TB.⁴

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In the Kingdom of Saudi Arabia (KSA), TB constitutes a public health concern owing to the population dynamics of the Kingdom, including an enormous number of emigrants from TB-endemic countries and the annual inflow of millions of hajjis during the Hajj and Umrah periods.⁵ Although a tangible advancement in the notification as well as the treatment of TB cases had occurred in Saudi Arabia, a reasonable infection rate is published, heretofore, as opposed to other countries.⁶

In contrast to TB, diabetes mellitus (DM), is a non-communicable, metabolic disorder attributed to many factors. It is characterized by abnormally high blood glucose level secondary to disturbances in insulin secretion, insulin action or both.⁷ In 2019, DM was the fifth leading cause of global mortality, with approximately 463 million adults diagnosed with diabetes. By 2045, projection up to 548 million is anticipated.⁸

Historically, the correlation between DM and TB dates back to the beginning of the 1900s. Thereafter, this association was ignored due to the innovation of powerful treatment modalities for either disease.⁹ Globally, re-birth of this comorbidity was noticed because of current progress in the number of diabetic patients brought about by dramatic changes in the life-style. A meta-analysis observed that DM triples the possibility of developing active TB.¹⁰

The precise pathophysiology of DM as a detrimental factor for TB is not fully explored. It is believed that DM jeopardizes both specific and non-specific immune mechanisms. Diabetic patients have impaired chemotaxis, activation of phagocytic cells and presentation of the antigens of *MTB* bacilli.¹¹ In addition, compromised T cell-mediated immunity (CMI), decreased function of alveolar macrophages, reduced production of hydrogen peroxide and low levels of interferon- γ are noticed.¹²

To the extent of our knowledge, few studies have been done in the Middle East countries to investigate the association between DM and TB. For that etiology, this study was designed to (i) assess the prevalence of DM in patients with PTB, (ii) review the impact of DM on the clinical, radiological and microbiological characteristics of patients diagnosed with PTB and (iii) evaluate the response of PTB cases with and without DM to anti-TB drugs, retrospectively, during a 5-year study period in patients attending Dr. Soliman Fakeeh Hospital (DSFH), Jeddah, KSA.

Patients and Methods

Study Eligibility, Design and Setting

The study design was approved by the institutional review board (IRB) of DSFH (Approval No. 154/IRB/2020). In this retrospective cohort study, all confirmed adult (>18 years) patients with active PTB attending DSFH and notified to the Saudi Ministry of Health (MOH) in the period from June 2015 to May 2020 were eligible to the study. DSFH is a 500-bedded private hospital in Jeddah, KSA. It provides both inpatient and outpatient tertiary-care for the residents of the Kingdom.

Pulmonary TB Diagnostic Criteria

During the study interval, 487 (296 males and 191 females) adult patients (mean age 53.71 ± 15.78 years) with newly diagnosed active PTB were identified based on their initial clinical presentation, radiologic findings as well as sputum acid-fast bacillus (AFB) smear results. The AFB smear microscopy was performed at the Microbiology Laboratory of DSFH using Ziehl-Neelsen (ZN) stain and smears were graded as +, ++, or +++ based on the criteria set by the International Union Against Tuberculosis and Lung Disease (IUATLD).¹³ Also, sputum specimens from the enrolled patients were cultured on Lowenstein-Jensen media in accordance with the standardized protocols of the hospital laboratory.

Pulmonary TB Treatment Regimen

Patients diagnosed with PTB were prescribed anti-TB medications according to the WHO recommendations.¹⁴ The patients were subjected to repeat sputum testing using Ziehl-Neelsen-stained smears as well as culture at the end of the initiation phase and after treatment completion.

Diagnosis of DM Among the Enrolled Patients

Patients with concurrent DM were identified based on the diagnostic scheme of the American Diabetes Association (ADA).¹⁵ DM was considered poorly controlled if HbA1c was >8%.¹⁶ The study cohort was further subdivided into 2 groups; group (1): patients suffering from both PTB and DM (DM/PTB group) and group (2): patients diagnosed with PTB only without DM (non-DM/PTB group).

Patients' Demographic, Clinical and Radiologic Data

Patients' medical record numbers (MRN) were used to capture the relevant data to the study cohort, including

(1) demographic data; age at time of diagnosis, gender, nationality, occupation, (2) past history of PTB, (3) history of contact to PTB cases, (4) body mass index “BMI”, (5) special habits including cigarette smoking and or alcohol consumption, (6) clinical presentation of PTB, (7) chest X-ray (CXR) and computed tomography (CT) findings, (8) results of the laboratory investigations and (9) response to anti-TB therapy based on sputum culture outcome.

Exclusion Criteria

Pediatric patients (<18 years), pregnant TB women and PTB patients with concomitant extrapulmonary TB, hepatitis B, hepatitis C, human immunodeficiency virus (HIV), autoimmune disease (s) or malignancy were excluded from the study. Also, patients receiving immunosuppressive therapy were not eligible to our study.

Statistical Analysis

The data were entered and analyzed using IBM® SPSS® Statistics program version 26.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as numbers and percentages with Pearson's Chi-Square (χ^2) test used to define the statistical significance of the data, meanwhile Fischer's Exact test was used as a correction for χ^2 test when >25% of the cells have count <5 in 2×2 tables. Continuous variables were described as means \pm standard deviation (SD) for parametric data after testing normality using Kolmogorov–Smirnov test.

The Independent Samples *T*-Test was used to compare the means of 2 independent groups. Odds ratios (OR) with 95% confidence intervals (CI) were determined. For sputum culture conversion time, a Kaplan–Meier plot was constructed and Log rank test was used for significance testing. A multivariate logistic regression analysis was performed to define the association of predictor variables with the outcome variable. *p*-values <0.05 (2-tailed) were considered statistically significant.

Results

Demographic and Baseline

Characteristics of the Study Participants

From June 2015 to May 2020, 487 patients (60.8% males and 39.2% females) with a mean age of 53.71 ± 15.78 years and a mean BMI of 24.37 ± 3.70 kg/m² were eligible to the current study. About two-thirds of the enrolled patients were Saudi nationals. While about 45% of our

cohort were self-employed, 5% and 4.7% were migrant-workers and college students, respectively.

Amongst our cohort, DM/PTB group (group 1) included 132 patients (27.1%), whereas non-DM/PTB group (group 2) comprised 355 patients (72.9%). A statistically significant difference was detected between both groups in relation to the age ($p = 0.0001$); however, they were matched with reference to gender ($p = 0.46$). At the time of PTB diagnosis, the BMI showed higher means \pm SD among comorbid patients compared to those without DM, with a statistically significant difference (Table 1).

Glycemic Outlines of the Study Cohort

Amongst 132 DM/PTB patients, the mean HbA1c% was $10.58 \pm 2.33\%$ compared to $5.09 \pm 0.56\%$ in non-DM/PTB group ($p = 0.0001$). Other glycemic parameters are presented in Table 2. Almost 86% of our diabetic cohort had poor glycemic control based on HbA1c%, while 13.6% showed marginal HbA1c concentration ($7.74 \pm 0.16\%$).

Two-thirds of our patients had previous diagnosis of DM of 2.5–17 years' duration (mean 5.4 ± 7.8 years), meanwhile it was diagnosed in the other third during their follow-up visits in the hospital for PTB. About 89.4% of DM/PTB patients were on oral hypoglycemic pills and the remaining patients were scheduled insulin injections.

Clinical Manifestations of Pulmonary TB Patients with and without DM

Overall, productive cough was the most dominant clinical presentation of PTB in both DM/PTB and non-DM/PTB groups (78.9%), followed by fever (75.6%), night sweats (65.7%) and unexplained weight loss (40%). With the exception of chest pain and malaise, diabetic patients showed statistically significant differences in relation to the typical presentations of PTB as compared to non-diabetics (Table 3).

Radiologic Findings of Pulmonary TB Patients According to Their DM Status

On CXR and CT scan, patients having both comorbidities showed higher frequency of pulmonary consolidation as compared to those with PTB only (43.9% versus 30.1%), with a considerably significant difference (OR: 1.82, 95% CI: 1.2–2.74, $p = 0.005$). In the same way, pulmonary cavitory lesions were observed more commonly among diabetic patients (31.8% versus 20.6%, OR: 1.8, 95% CI:

Table 1 Baseline Characteristics of the Study Population

| Parameters | DM/PTB Group n = 132 (%) | Non-DM/PTB Group n = 355 (%) | χ^2 | p-value |
|---|--------------------------|------------------------------|----------|---------|
| Age, years (\pm SD) ^a | 61.17 \pm 11.33 | 50.94 \pm 16.3 | 7.79 | 0.0001* |
| Gender | | | | |
| Males | 84 (63.6%) | 212 (59.7%) | 0.62 | 0.46 |
| Females | 48 (36.4%) | 143 (40.3%) | | |
| Nationality | | | | |
| Saudi | 85 (64.4%) | 271 (76.3%) | 11.55 | 0.14 |
| Egyptian | 19 (14.4%) | 33 (9.3%) | | |
| Filipino | 15 (11.4%) | 29 (8.2%) | | |
| Others | 13 (9.8%) | 22 (6.2%) | | |
| Occupation | | | | |
| Self-employed | 56 (42.4%) | 162 (45.6%) | 16.89 | 0.18 |
| Un-employed | 48 (36.4%) | 132 (37.2%) | | |
| Business-owner | 21 (15.9%) | 20 (5.6%) | | |
| Migrant-worker | 5 (3.8%) | 20 (5.6%) | | |
| College student | 2 (1.5%) | 21 (5.9%) | | |
| BMI, kg/m ² (\pm SD) ^a | 25.15 \pm 3.59 | 24.08 \pm 3.71 | 2.85 | 0.005* |
| Past history of PTB | 13 (9.8%) | 24 (6.8%) | 1.31 | 0.34 |
| Contact to PTB case | 90 (68.2%) | 215 (60.6%) | 2.38 | 0.14 |
| Cigarette smoking | 99 (75%) | 250 (70.4%) | 0.33 | 0.37 |
| Alcohol drinking | 22 (16.7%) | 43 (12.1%) | 3.9 | 0.23 |

Notes: ^aSignificance was tested using the independent samples T-test; **p* < 0.05 (statistically significant).

Abbreviations: DM/PTB, diabetes mellitus and pulmonary tuberculosis; n, number; χ^2 , Pearson's Chi-Square test; SD, standard deviation; BMI, body mass index.

Table 2 Baseline Glycemic Parameters in Diabetic versus Non-Diabetic Pulmonary Tuberculosis Patients

| Parameters | DM/PTB Group n = 132 (%) | Non-DM/PTB Group n = 355 (%) | 95% CI | p-value |
|---------------------|--------------------------|------------------------------|---------------|---------|
| FPG (mg/dL) | 210.59 \pm 42.69 | 109.69 \pm 10.98 | 96.08–105.73 | 0.0001* |
| 2-hours PPG (mg/dL) | 328.51 \pm 66.38 | 180.8 \pm 17.19 | 140.19–155.21 | 0.0001* |
| HbA1c% | 10.58 \pm 2.33% | 5.09 \pm 0.56% | 5.23–5.75 | 0.0001* |

Notes: **p* < 0.05 (statistically significant). Data are expressed as means \pm standard deviation (SD).

Abbreviations: DM/PTB, diabetes mellitus and pulmonary tuberculosis; n, number; CI, confidence interval; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; HbA1c, glycosylated hemoglobin.

1.15–2.82, *p* = 0.012). However, involvement of the lower lung lobes, pulmonary nodules as well as pleural effusion had more or less similar rates between both groups (*p*-values = 0.16, 0.54 and 0.21, respectively). Data are summarized in Table 3.

A subsequent multivariate logistic regression analysis revealed that age was not an independent risk factor for pulmonary cavitory lesions, meanwhile DM remained a significant predictor (OR: 2.01, 95% CI: 1.24–3.24, *p* = 0.004). On the other hand, additional multivariate analysis indicated that patients aged 30–44 years were 2.67 times

more likely to have pulmonary consolidation (*p* = 0.001), which reflects a potential confounding effect of age. However, DM was also the most statistically significant factor (OR: 2.39, 95% CI: 1.53–3.74, *p* = 0.0001).

Microbiological Profile of the Study Participants

In our study, the proportion of patients with a preliminary positive AFB smear was statistically higher amongst the DM/PTB cohort as compared to the non-diabetics (79.6% versus 60.8%). In addition, 2 months after anti-TB therapy,

Table 3 Clinical and Radiologic Findings of Pulmonary Tuberculosis Among Diabetic versus Non-Diabetic Patients

| Parameters | DM/PTB Group n = 132 (%) | Non-DM/PTB Group n = 355 (%) | OR (95% CI) | p-value |
|-------------------------------|--------------------------|------------------------------|------------------|---------|
| Clinical findings | | | | |
| Cough | 116 (87.9%) | 268 (75.5%) | 2.35 (1.32–4.19) | 0.004* |
| Fever | 110 (83.3%) | 258 (72.7%) | 1.88 (1.13–3.14) | 0.01* |
| Night sweating | 97 (73.5%) | 223 (62.8%) | 1.64 (1.05–2.55) | 0.03* |
| Dyspnea | 70 (53%) | 96 (27%) | 3.05 (2.01–4.61) | 0.0001* |
| Weight loss | 68 (51.5%) | 127 (35.8%) | 1.9 (1.27–2.86) | 0.002* |
| Anorexia | 59 (44.7%) | 113 (31.8%) | 1.73 (1.15–2.61) | 0.01* |
| Malaise | 52 (39.4%) | 112 (31.5%) | 1.4 (0.93–2.14) | 0.1 |
| Chest pain | 43 (32.6%) | 110 (31%) | 1.08 (0.70–1.65) | 0.74 |
| Hemoptysis | 36 (27.3%) | 63 (17.7%) | 1.74 (1.08–2.78) | 0.02* |
| Pulmonary radiologic findings | | | | |
| Consolidation | 58 (43.9%) | 107 (30.1%) | 1.82 (1.2–2.74) | 0.005* |
| Cavitation | 42 (31.8%) | 73 (20.6%) | 1.8 (1.15–2.82) | 0.012* |
| Lower lung lesions | 26 (19.7%) | 51 (14.4%) | 1.46 (0.87–2.46) | 0.16 |
| Nodules | 20 (15.2%) | 45 (12.7%) | 1.23 (0.69–2.17) | 0.54 |
| Pleural effusion | 13 (9.8%) | 23 (6.5%) | 1.6 (0.77–3.21) | 0.21 |

Notes: * $p < 0.05$ (statistically significant). Data are expressed as numbers and percentages.

Abbreviations: DM/PTB, diabetes mellitus and pulmonary tuberculosis; n, number; OR, odds ratio; CI, confidence interval.

negative sputum smears were more probably to be detected among non-DM/PTB group in contrast to diabetics (67.6% versus 43.9%, respectively). Details are illustrated in Table 4.

Notably, 57.6% of the diabetic patients had their sputum culture converted to negative after 2 months of anti-TB therapy, in comparison to 77.7% of the non-diabetics ($p = 0.0001$). Kaplan–Meier curves revealed a considerably delayed sputum culture conversion to negative ($\chi^2 = 43.14$, $p = 0.0001$) among diabetic as compared to non-diabetic patients (mean time; 77.55 ± 37.74 and 54.95 ± 27.67 days, respectively). Data are shown in Figure 1.

To assess the effect of further confounders as predictors for sputum culture conversion, we generated a multivariate regression analysis. Intriguingly, DM was the most statistically significant predictor for delayed sputum culture conversion ($p = 0.001$), with diabetics were 2.28 times more likely to experience delayed culture conversion (Table 5). However, 45–60 years of age had a confounding effect on the treatment response of PTB ($p = 0.01$).

Discussion

To date, TB and DM comorbidity represent a serious public health challenge despite deliberate efforts to decrease the burden of either disease. Though numerous prospective

Table 4 Sputum Acid-Fast Bacillus (AFB) Smear Results in This Study

| Parameters | DM/PTB Group n = 132 (%) | Non-DM/PTB Group n = 355 (%) | χ^2 | p-value |
|--|--------------------------|------------------------------|----------|---------|
| Baseline sputum smear results | | | | |
| Negative | 27 (20.5%) | 139 (39.2%) | 18.71 | 0.0001* |
| Grade ++ | 69 (52.3%) | 163 (45.9%) | | |
| Grade +++ | 36 (27.3%) | 53 (14.9%) | | |
| Two months' post-treatment smear results | | | | |
| Negative | 58 (43.9%) | 240 (67.6%) | 43.32 | 0.0001* |
| Grade + | 48 (36.4%) | 103 (29.0%) | | |
| Grade ++ | 26 (19.7%) | 12 (3.4%) | | |

Notes: * $p < 0.05$ (statistically significant). Data are expressed as numbers and percentages.

Abbreviations: DM/PTB, diabetes mellitus and pulmonary tuberculosis; n, number; χ^2 , Pearson's Chi-Square test.

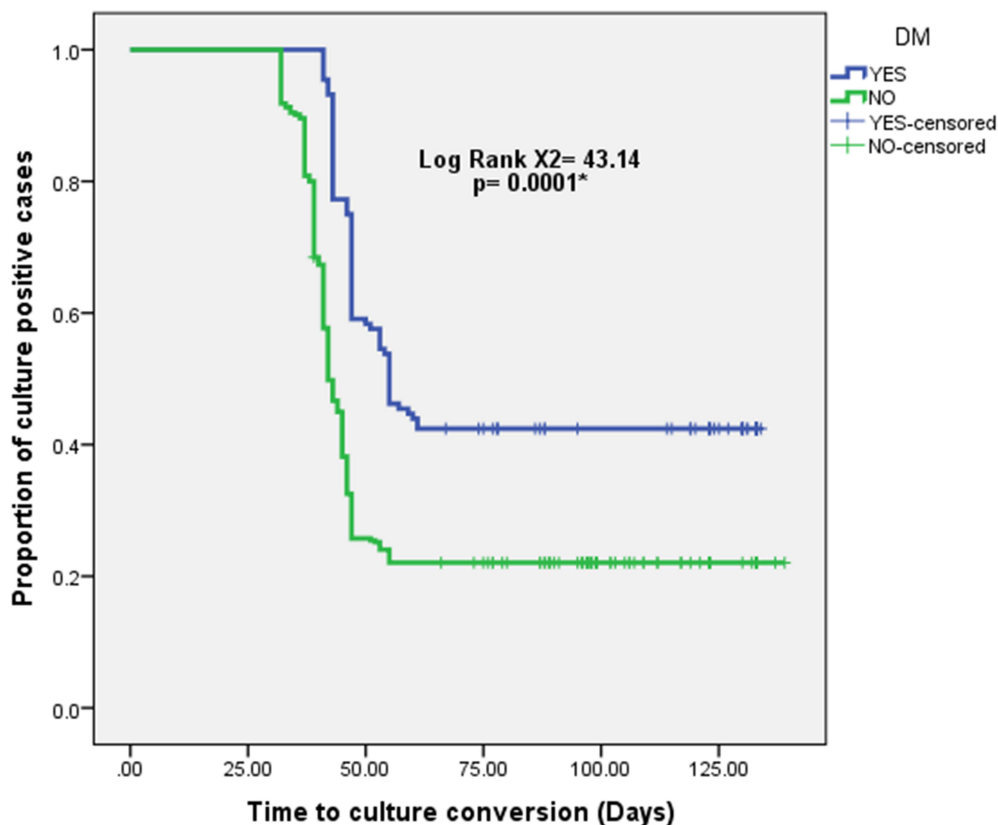


Figure 1 Kaplan–Meier plot of the time to sputum culture conversion after treatment initiation among pulmonary TB (PTB) patients with and without diabetes mellitus (DM). Kaplan–Meier curves revealed significantly longer sputum time to culture conversion into negative among DM/PTB patients (mean time: 77.55 ± 37.74 days) as compared to their non-diabetic counterparts (mean time: 54.95 ± 27.67 days). Significance was tested using the Log rank test ($\chi^2 = 43.14$, $p = 0.0001$). Of note, 57.6% of the diabetic cohort had their sputum culture converted to negative after 2 months of anti-TB therapy, in contrast to 77.7% of the non-diabetics. * $p < 0.05$ (statistically significant).

and retrospective studies have investigated the correlation between both conditions, currently available data from the KSA, in this perspective, are limited. With this in mind, we performed this 5-year retrospective study.

Overall, 487 patients diagnosed with PTB during the study interval were found to fulfill our inclusion criteria. DM was identified in 27.1% of the study group. This prevalence is supported by the findings of a recent study performed in King Khalid University Hospital, Riyadh, Saudi Arabia, where DM was detected in 26.7% of their TB cohort.¹⁷ This high prevalence of DM among PTB patients from the KSA warrants prompt efforts from the policymakers. Parallel to that, a prevalence rate of 27.7% has been declared from analogous study conducted in Egypt.¹⁸ Likewise, an overall prevalence of 25.3% has been reported from another study conducted in India,¹⁹ which is the head TB-burden country all over the world.²⁰

Recently, a South Asian systematic review concluded that DM accounted for 21% among the enrolled TB patients. The investigators acclaimed this rate to the fact

that most of the Asians suffer from adiposity, poor glycaemic control, reduced functional pancreatic β -cell mass as well as decreased insulin secretion.²¹ On the other hand, a Brazilian study noticed that the mean prevalence of TB/DM comorbidity during the study period was 11.29%.²² Dissimilar results could be explained by dissimilar ethnic, economic and epidemiological characteristics among different nations.

Interestingly, a prevalence about 3% was disclosed from an earlier study performed in Mozambique. Furthermore, an estimated prevalence of 1% was observed in Beira, the second largest city in Mozambique. This result was attributed to the lack of some of the risk factors for DM such as obesity, old age (>45 years), hypertension and smoking.²³ In light of that, Di Gennaro and his colleagues recommended DM screening in resource-poor countries, including the aforementioned ones, using a single blood sugar testing irrespective of other factors like education, social background and availability of qualified health-care workers.²⁴

In the present work, patients with co-occurring DM and PTB tended to be significantly older in age compared to those with PTB only ($p = 0.0001$). This variance could be related to the possibility of PTB reactivation in elderly patients along with increased incidence of DM among this age group. Our finding is in keeping with the results from a prior nationwide cohort study. In that retrospective study, Gil-Santana and his associates noticed that TB/DM patients were considerably older ($p < 0.001$) than non-diabetics enrolled at a TB primary care facility in Brazil between 2004 and 2010.²⁵ Conversely, an earlier Iranian study found no significant age difference amongst the recruited group.²⁶

When stratified with gender, a male preponderance was noted in both diabetic and non-diabetic subjects; however, the difference did not reach a statistical significance ($p = 0.46$). Our result is concordant with the observation of a cross-sectional study from Pakistan.²⁷ This finding could partly be explained by differences in lifestyle, as we noticed a higher rate of cigarette smoking and alcohol consumption, in the present study, among males compared to the females (p -values = 0.01 and 0.006, respectively) which are both risk factors for PTB.²⁸

In favor of our results, a Brazilian study disclosed that diabetic individuals were more likely to have classic clinical manifestations of PTB.²⁹ Additionally, input from a Chinese study deduced that DM was independently related to worse chest symptoms in PTB patients.³⁰ This could be traced to the deranged innate and adaptive immune mechanisms in patients with coincident DM. Consequently, failure to eliminate *MTB* bacilli enables bacterial multiplication and dissemination to occur more rapidly, contributing to aggravated clinical features in hyperglycemic patients.³¹ Given the fact that most of the herein diabetic patients (86%) had HbA1c $>8\%$ (poorly controlled DM) and the remaining subjects had borderline mean HbA1c% of $7.74 \pm 0.16\%$, we were not able to conduct a sub-group analysis of our DM cohort according to their degree of dysglycemia.

Compatible with our results, previous studies have also explored conceivable effects of DM on the radiologic findings of PTB. An earlier study conducted in Riyadh, KSA and another one from Bangladesh endorsed that diabetic patients had pulmonary cavities more often than non-diabetics (p -values = 0.02 and 0.001, respectively).^{32,33} This could be ascribed to the immune dysfunction in diabetic patients induced by hyperglycemia.³⁴

Up till now, treatment response in DM/PTB patients is questionable. Sputum AFB smear and culture negativity

are key leaders of treatment outcome after commencing anti-TB therapy. In our study, patients with concurrent DM showed a higher initial sputum smear grade (which is the milestone of *MTB* bacilli density) as compared to non-diabetics. Also, 2 months after anti-TB therapy, non-diabetic patients were more likely to have negative sputum smears (Table 4). Observations of this study are consistent with the findings of previous authors.^{35–37} Quite the reverse, an earlier case-control study contradicted this result.³⁸ That incompatible conclusion could be explained by differences in the duration of their study, demographics of the study participants, baseline *MTB* load as well as their relatively small sample size.

More importantly, the lag time till conversion of sputum cultures to negative during anti-TB therapy is used for forecasting treatment response. Of the total 132 DM/PTB patients, 76 (57.6%) got their sputum culture converted to negative, in contrast to 276 (77.7%) non-diabetic patients ($p = 0.0001$), with the mean duration for sputum culture conversion to negative was significantly longer in DM/PTB patients compared to non-DM/PTB group (details are given in Figure 1). In the multivariate logistic regression analysis, DM remained the most significant predictor for delayed sputum culture conversion (Table 5).

In agreement with our findings, a study from Georgia and another one from Qatar ascertained unfavorable outcome of sputum culture conversion amongst diabetics.^{39,40} On the other side, a recent prospective study from India affirmed that DM has no adverse impact on sputum culture results. Nevertheless, the follow-up period in that study was only 18 months which could contribute to this discordance.⁴¹ Many investigators have endeavored to provide clarifications for delayed sputum culture conversion among diabetic subjects. For example, Lyu and his co-workers acknowledged that long-term hyperglycemia decreases the secretion of gastric hydrochloric acid, which adversely interferes with the pharmacokinetic parameters of rifampicin.⁴² Furthermore, other authors suggested that diabetic gastroparesis could partly contribute to impaired gastrointestinal absorption of anti-TB medications.⁴³

In addition to that, our multivariate analysis indicated that 45–60 years of age had a confounding effect on treatment outcome of PTB ($p = 0.01$). Lately, a study from Italy addressed factors contributing to adverse events (AEs) and poor treatment outcome of PTB. The research group found that aging and DM are amongst the predictors of AEs for PTB.⁴⁴ Accordingly, frequent follow-up of

Table 5 Multivariate Logistic Regression Analysis of the Predictors for Sputum Culture Conversion in This Study

| Parameters | Culture Conversion | No Culture Conversion | Univariate <i>p</i> -value | Multivariate | |
|---|--------------------|-----------------------|----------------------------|------------------|-----------------|
| | | | | OR (95% CI) | <i>p</i> -value |
| Age group | | | | | |
| <30 years | 25 (7.1%) | 6 (4.4%) | 0.007* | 0.54 (0.2–1.42) | 0.21 |
| 30–44 years | 87 (24.7%) | 22 (16.3%) | | 0.55 (0.31–0.98) | 0.45 |
| 45–60 years | 121 (34.4%) | 39 (28.9%) | | 0.53 (0.33–0.87) | 0.01* |
| >60 years | 119 (33.8%) | 68 (50.4%) | | – | – |
| Gender | | | | | |
| Male | 219 (62.2%) | 77 (57%) | 0.3 | 0.72 (0.47–1.09) | 0.12 |
| Female | 133 (37.8%) | 58 (43%) | | | |
| DM | | | | | |
| Yes | 76 (21.6%) | 56 (41.5%) | 0.0001* | 2.28 (1.39–3.72) | 0.001* |
| No | 276 (78.4%) | 79 (58.5%) | | | |
| Sputum smear grade (Baseline) | | | | | |
| Negative | 122 (34.7%) | 44 (32.6%) | 0.81 | 1.02 (0.56–1.87) | 0.95 |
| ++ | 168 (47.7%) | 64 (47.4%) | | 0.98 (0.56–1.73) | 0.95 |
| +++ | 62 (17.6%) | 27 (20%) | | – | – |
| Sputum smear grade (2 months after treatment) | | | | | |
| Negative | 228 (64.8%) | 70 (51.9%) | 0.03* | 0.93 (0.43–2.02) | 0.85 |
| + | 99 (28.1%) | 52 (38.5%) | | 1.47 (0.67–3.26) | 0.34 |
| ++ | 25 (7.1%) | 13 (9.6%) | | – | – |

Note: **p* <0.05 (statistically significant).

Abbreviations: DM, diabetes mellitus; OR, odds ratio; CI, confidence interval.

those patients by the health-care professionals is of utmost importance. Currently, there is a growing interest for the potential use of chest ultrasound (CUS) to diagnose and monitor PTB cases. Di Gennaro and others concluded that CUS is a promising imaging modality for recognition of TB-related conditions.⁴⁵ Given the availability and safety issues, CUS should be employed in different health-care facilities for optimum follow-up of PTB patients, especially those with likely AEs.

With regard to the prevalence of multidrug-resistant (MDR)-*MTB* in Saudi Arabia, 4% of the total isolates identified in the central tuberculosis laboratory in Al-Madinah Al-Monawarah in the period from January 2012 to December 2014 were MDR.⁴⁶ This high rate could be related to the unique nature of Al-Madinah, where millions of Muslims including those from TB-endemic regions frequently visit this holy place, especially during Hajj and Umrah seasons. Another study from Tabuk province, north of the KSA, demonstrated that 3.3% of the isolates were MDR.⁴⁷ Unfortunately, susceptibility testing for *MTB* isolates was not routinely done at the Microbiology Laboratory of DSFH during the study interval.

Accordingly, we were not able to gauge the extent of this problem.

Of note, our study has some limitations that worth-mentioning. First, the retrospective nature of our study makes it liable to selection bias of the study cohort. Second, cultural characteristics of the Saudi society may force some of the enrolled patients to deny smoking or alcohol drinking, which could modify our results related to behavioral risk factors for coincident DM and PTB. Finally, we were not able to figure out susceptibility pattern of *MTB* isolates to anti-TB drugs because of the shortage of data from our Microbiology laboratory records in this regard.

Conclusion

Generally, our tertiary-care facility showed a high prevalence of PTB/DM comorbidity. In addition, DM had an unpromising effect on the clinical, radiological and microbiological profile of PTB subjects as well as their treatment outcome from a country with a considerable concern of either disease. This underscores the need to reciprocal screening for PTB and DM, which could act as a gateway in timely detection and management of whichever disease.

Also, public awareness regarding truths and myths of PTB and DM should be underlined on a large scale in different communities regardless of their educational level. Finally, it is mandatory to manage all TB patients taking into account their increased risk of non-communicable diseases, including DM.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional review board (IRB) of DSFH (Approval No. 154/IRB/2020) and the need for informed consent was waived since all data were anonymized before analysis. Patients' data privacy and confidentiality were respected in all levels of the study.

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Disclosure

The authors have no conflicts of interest for this work to declare.

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