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Sex differences in the impact of diabetes mellitus on tuberculosis recurrence: a retrospective national cohort study

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Declaration of interests

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.

ABSTRACT

Objectives: Whether diabetes mellitus (DM) increases tuberculosis (TB) recurrence risk is debatable. We determined the effect of DM on TB recurrence.

Methods: This retrospective nationwide cohort study included patients with TB who successfully completed TB treatment during 2011–2017 and followed up for TB recurrence until August 2020. We performed subdistribution hazard model analyses stratified by sex to assess diabetes risk related to TB recurrence after successful treatment.

Results: Of 199,571 participants who had received successful TB treatment, 47,952 (24%) had DM. There were more men (64.4%), positive acid-fast bacilli smears (35.9%), and positive cultures (49.5%) in the DM group. There were 6,208 TB recurrences (3.1%) during 5.1 years of follow-up: 38.9% and 26.6% occurred 1 and 1–2 years after treatment completion, respectively. The recurrence rate was higher in the DM group (3.8%) than in the non-DM group (2.9%, $p<0.0001$). DM was associated with a higher TB recurrence risk, especially in men (adjusted hazard ratio [aHR] 1.23, 95% confidence interval [CI] 1.15–1.32) but not in women (aHR 0.96, 95% CI 0.85–1.09).

Conclusions: The TB recurrence rate after successful treatment was higher in patients with DM than in patients without DM. DM is associated with TB recurrence in men.

Keywords: tuberculosis; diabetes mellitus; recurrence; relapse; sex

INTRODUCTION

Tuberculosis (TB) remains a leading cause of morbidity and mortality worldwide. According to a WHO report from 2021, there were 5.8 million new patients with TB, with an estimated 1.5 million fatalities in 2020 (World Health Organization, 2021). Diabetes affects approximately 537 million adults worldwide, with the majority living in low- and middle-income countries. Diabetes was directly responsible for 6.7 million deaths in 2021 (International Diabetes Federation, 2021). The total number of diabetics is projected to increase to 783 million by 2045 (Sun et al., 2022). Over the last three decades, type 2 diabetes has increased dramatically across countries with varying income levels (WHO Health topics on Diabetes, 2021). The prevalence of diabetes mellitus (DM) among patients with pulmonary TB was estimated to be 13.73% globally, 13.59% in the western Pacific, and 14.62% in Southeast Asia (Li et al., 2021).

Diabetes is well known to be an unfavorable companion for TB. Prospective cohort studies and systematic reviews revealed an increased risk of TB in individuals with DM (Baker et al., 2012; Jeon & Murray, 2008). Immune cell function is compromised in people with type 2 DM, and they have a lower capacity to phagocytose *Mycobacterium tuberculosis* (Restrepo et al., 2014). The clinical presentation of TB in diabetic patients is also more severe, with more cavitary patterns on chest X-rays and a greater need for hospitalization at the time of diagnosis (Moreno-Martínez et al., 2015). In addition, unfavorable treatment outcomes were more likely linked to TB-DM comorbid patients. A previous study demonstrated that diabetes is associated with higher TB mortality, treatment failure, and positive culture after two months of treatment (Baker et al., 2011; Degner et al., 2018; Golub et al., 2019; Huangfu et al., 2019).

However, studies identifying the association between DM and TB relapse or recurrence are limited and controversial. A systematic review and meta-analysis revealed that people with diabetes have an increased risk of recurrent TB (Baker et al., 2011; Huangfu et al., 2019). Nevertheless, the majority of the included studies did not assess the significant confounding variables and had a small number of recurrent TB populations. In contrast, a systematic review and meta-analysis showed that DM was not associated with recurrent TB (Qiu et al., 2021).

The increased burden of diabetes can be a challenge to achieve the goal of TB elimination, and the association between DM and TB outcomes is an important public health issue. Furthermore, patients with recurrent TB were more likely to have poor treatment outcomes, especially treatment failure (Ndambuki et al., 2021). We, therefore, conducted a retrospective cohort study using a large nationwide database to determine the impact of DM on TB recurrence.

METHODS

Sources of data and collection

The Korean Tuberculosis and Post-Tuberculosis (TB-POST) cohort was constructed by linking the following three databases: (1) the Korean National Tuberculosis Surveillance System (KNTSS) data regarding people with TB notified between 2011 and 2018, (2) the National Health Information Database (NHID) of people with a history of TB and related diseases between 2006 and 2018, and (3) Statistics Korea data on the causes of death between 2011 and 2018 (Jeong et al., 2022).

Study design and population

This was a retrospective, nationwide cohort study of patients with TB. Initially, 305,260 patients with TB were linked through a combination of the KNTSS and NHID, registered between 2011 to 2018. After excluding 65,412 individuals, 239,848 registered individuals with TB and treated between 2011 and 2017 were identified. We excluded patients with TB who registered in 2018 because the follow-up period for TB recurrence was insufficient. Among them, 199,571 patients with successful treatment were included in the final analysis to assess TB recurrence (Figure 1).

Definition and measurement

Exposure: Diabetes mellitus

Diabetes mellitus was defined by any one of the following criteria 1 year before and after TB diagnosis: (1) at least two claims of the International Classification of Diseases (ICD) coding for

DM (E11-E14), and (2) at least one claim of ICD code for DM and prescription of anti-diabetic drugs for more than four weeks.

Outcome: Recurrence after successful treatment

The treatment outcomes of TB were defined according to the criteria suggested by the World Health Organization (WHO) and reported to the National TB Surveillance System (World Health Organization, 2013). The sum of the cured and treatment completed was designated as treatment success. The primary outcome of this study was TB recurrence, which can be either re-activated with the same strain (i.e., relapse) or re-infected with a new strain. We defined TB recurrence as re-registered patients with TB after treatment success of the initial TB treatment until August 31, 2020.

Covariates

Household income was classified into the 5th quintile (1=the lowest, 5=the highest) among health insurance beneficiaries, according to the national health insurance premium and medical aid beneficiaries were classified into group 0. Variables that may influence the final treatment outcome, including age, sex, nationality, residential region, previous TB treatment history, lesion site, sputum smear results, sputum culture results, comorbidities (end-stage renal disease, cancer and HIV status), and Charlson comorbidity index (CCI) (Canadian Institute for Health Information, 2021) were measured as covariates.

Statistical analyses

Continuous variables are presented as mean (standard deviation) if the variable was normally distributed, otherwise described as median (interquartile range), and categorical variables are expressed as numbers (percentages). The Student's t-test was used if the variable was normally distributed or else Mann–Whitney test was used to compare continuous variables, and the chi square test was used to compare categorical variables appropriately. The cumulative incidence function was used to estimate the recurrence rate, and the subdistribution hazard model was used to assess the risk of diabetes related to TB recurrence after successful treatment, considering competing risks. Model 1 was adjusted for age, region, household income, and nationality. Model 2 was adjusted for TB lesions, previous TB history, hospital joining public–private mix collaboration, AFB smear, and culture in addition to model 1. Model 3 was adjusted for disability and comorbidity, in addition to Model 2. Model 4 was adjusted for disability and CCI scores, in addition to Model 2.

All *p*-values were two-tailed, and a *p*-value of <0.05 was deemed statistically significant. All statistical analyses were performed using SAS Enterprise Guide (SAS Institute Inc., Cary, NC, USA) and STATA/MP version 17 (Stata Corp LLC, College Station, TX, USA).

RESULTS

General characteristics

Of 199,571 participants who had received successful treatment, 47,952 (24%) had DM (Figure 1). During the 5.1-year follow-up period, there were 6,208 (3.1%) patients with TB recurrence, and cumulative recurrence rate was 614.8/100,000 person years (PY). The baseline characteristics of the study participants in the DM and the non-DM groups are shown in Table 1. In DM group, there were more men (64.4%) and older people (age ≥65 years 53.1%) (Table 1). In addition, the proportion of patients with a positive acid-fast bacilli smear (35.9% vs 26.5%), a positive culture (49.5% vs 42.3%), and recurrent TB (3.8% vs 2.9%) was higher in the DM group than in the non-DM group (all $p<0.0001$). The general characteristics of the DM and non-DM groups stratified by sex were compared (Tables 2 and 3). There were 114,916 (57.6%) men and 84,655 (42.4%) women. Among the men and women, there were 4,312 (3.8%) and 1,896 (2.2%) patients with TB recurrence, respectively. Recurrence of TB occurred more commonly in the DM group than in the non-DM group in men (4.8% vs 3.4%, $p<0.0001$, Table 2), but not in women (2.0% vs 2.3%, $p=0.06$, Table 3).

Time table of recurrence after successful treatment

The median time to TB recurrence was 497 (interquartile range, 238–943) days, which was significantly shorter in the DM group (462 days) than in the non-DM group (516 days, $p<0.0001$).

Figure 2 shows the percentage of TB recurrence by follow-up years after successful treatment in DM and non-DM patients. Among 6,208 TB recurrences, 38.9% were within 1 year (40.9% in

DM, 38% in non-DM) and 26.6% were 1–2 years after the completion of the treatment (27.9% in DM and 26% in non-DM). Early recurrence within 2 years after the treatment completion was higher in patients with DM than those without DM (68.9% vs 64%, p=0.007).

The cumulative recurrence rate in patients with DM (856.3/100,000 PY) was significantly higher than that in patients without DM (550.2/100,000 PY, p<0.0001). However, when analyzed by sex, it was only significant in men, as demonstrated in Figure 3.

Different impact of DM on TB recurrence by sex

To identify the impact of DM on TB recurrence, we analyzed the data stratified by sex using a subdistribution hazard model in survival analysis (Table 4).

DM was associated with a higher risk of TB recurrence in men (crude hazard ratio [HR]=1.45, 95% confidence interval [CI] 1.37–1.55, p<0.0001). When we adjusted other covariates in model 1 to model 4, DM was still associated with increased risk for recurrence of TB in men (aHR=1.23, 95% CI 1.15–1.32, p<0.0001 in model 4). However, DM was not linked to an increased risk of TB recurrence in women (crude HR=0.91, 95% CI 0.81–1.03, p=0.13; and aHR=0.96, 95% CI 0.85–1.09, p=0.55 in Model 4).

DISCUSSION

According to our findings from a nationwide cohort analysis, the prevalence of DM in participants who had successfully completed TB treatment was 24%. We discovered a 3.1% TB recurrence during 5.1 years of follow-up with incidence of 614.8/100,000 PY. The recurrence of TB was higher in patients with DM than in non-DM (3.8 % vs 2.9%), and diabetes was associated with a higher risk of TB recurrence, especially in men. In addition, we found that TB recurrence was the highest 2 years after successful treatment, and the time to recurrence was shorter in diabetic patients.

In line with previous studies, patients with DM in the current study have a greater risk of TB recurrence (Baker et al., 2011; Golub et al., 2019; Huangfu et al., 2019). Patients with TB and DM tend to have more severe clinical manifestations, such as severe lung involvement with cavity, positive acid-fast bacilli smear, and a longer sputum culture conversion time, than those without DM (Chiang et al., 2014; Degner et al., 2018; Mi et al., 2013; Naidoo & Dookie, 2018). Several studies have demonstrated that the immunity of people with hyperglycemia is impaired, including reduced polymorphonuclear leukocyte function, neutrophil chemotaxis, and phagocytosis (Delamaire et al., 1997; Restrepo et al., 2014). Alveolar macrophages were less activated in patients with TB and DM, which may increase vulnerability to mycobacterial infection (Wang et al., 1999). Additionally, they are more prone to having delayed immune responses to TB infection (Vallerskog et al., 2010). Therefore, low capacity of mycobacterial control in patients with DM can result in a higher risk of TB development, high bacillary burden, and recurrence of TB.

Another factor that could explain TB recurrence in patients with DM might be the pharmacokinetic and pharmacodynamic effects of anti-TB drugs. A previous study showed that

rifampicin concentrations were anticipated to be lower in patients with DM (Chang et al., 2015). The absorption rate constant and volume of distribution of rifampicin were found to be affected by DM (Chang et al., 2015). Another study showed that patients with DM had lower pyrazinamide concentrations than non-DM (Alfarisi et al., 2018). As a result, reduced anti-TB drug exposure may increase the risk of recurrence of TB. However, this issue remains contentious. Therefore, further research on anti-TB drug concentrations in DM and their impact on TB recurrence should be conducted.

By analyzing the data stratified by sex, we found that DM was significantly associated with a higher risk of recurrent TB in men but not in women. We could not fully explain the reason for this difference in the effect of DM on TB recurrence according to sex in our study.

Men had a higher rate of TB recurrence in some previous studies (Hung et al., 2015; Lee & Kim, 2014). Our findings support the notion that men have a greater rate of TB recurrence. On the other hand, female sex was not a predictor of TB recurrence, implying that other variables such as smoking, alcohol consumption, and chronic obstructive pulmonary disease (COPD) could be confounding factors.

Previous research has revealed that smoking, drinking, and being underweight are risk factors for TB recurrence (Khan et al., 2006; Leung et al., 2015; Lin et al., 2021; Thomas et al., 2019). However, we lacked information on these variables. As a result, confounding factors may explain the sex difference in the effect of DM on TB recurrence. Smoking statistics in the Republic of Korea showed that men smoke more than women (Gunter et al., 2020). Nicotine inhibits macrophage production of tumor necrosis factor-alpha, which is considered to worsen the severity of disease and increase the risk of recurrence (Lin et al., 2021). Sputum smears and

cultures were more likely to remain positive after two months of treatment in smokers (Leung et al., 2015). We could hypothesize that impaired host immunity in diabetic patients, when combined with smoking in men, was associated with increased TB severity and slower microbiological responses. Therefore, men with DM may have a higher rate of TB recurrence.

A study in Taiwan found that COPD was a risk factor for TB recurrence (Hung et al., 2015). In the Republic of Korea, the men had more COPD comorbidity than the women (Lee & Rhee, 2021). As a result, COPD could be another confounder. Further prospective research is required to determine whether smoking, alcohol consumption, and COPD are confounding factors in men with DM.

For DM control status in men and women, we could not find a plausible explanation for the different effects of DM on TB recurrence by sex. In the Republic of Korea, lifestyle modifications, including regular exercise and diet control, are the basic non-pharmacological interventions and recommended to all adults with DM (Hur et al., 2021). However, those who regularly walked for exercise (a minimum of 30 min per day, for ≥5 days per week) accounted for 38.1% of the adults with DM (37.2% in men and 39.4% in women) based on a Korea National Health and Nutrition Examination Survey (Bae et al., 2022). Among adults with DM, 61.4% were receiving oral glucose-lowering medications or insulin; however, only 24.5% of the adults with DM achieved an HbA1c target of <6.5% (Bae et al., 2022). According to a previous study in the Republic of Korea (Choe et al., 2018), women are less likely than men to reach glycemic control targets without significant differences in diabetes treatment. Of our patients with TB-DM in 2013-2018, 79.6% received anti-diabetic medications. The proportion of metformin prescriptions was 38%; sulfonylurea, 24%; and insulin, 20%. We didn't have information on DM control status in our cohort. We cannot conclude whether or not DM severity

and treatment have an impact on sex differences in TB recurrence; therefore, these covariates should be investigated in future research.

In addition to sex, a positive acid-fast bacilli smear, pulmonary TB, previous TB history, and lower household income were also associated with TB recurrence in our study (Supplementary Tables 1 and 2). These findings were consistent with those of previous studies (Bestrashniy et al., 2018; Lee & Kim, 2014; Youn et al., 2022). In particular, low socioeconomic status is associated with multiple biosocial determinants of TB such as malnutrition, risk behaviors, and low access to health service (Ortblad et al., 2015). Lower household income in our study may contribute to TB recurrence as an association with these multiple biosocial determinants of TB (Hargreaves et al., 2011).

This study has several strengths. First, this was a nationwide cohort study that investigated the impact of DM on TB recurrence. This cohort covered all patients with TB and had a long follow-up period. Second, we used an integrated dataset by linking three national databases; thus, we could analyze more relevant covariates such as socioeconomic status and comorbidities. Despite these strengths, this study had some limitations. We could not access some of the information because we used data from a retrospective cohort. We lacked details on diabetic severity (HbA1c) and DM treatment. This information may have an impact on our findings because poorly controlled diabetes may influence the severity of TB and TB recurrence. To overcome this limitation, we used the CCI and household income level as covariates for the adjustment because these factors were also known as contributing factors for poor glycemic control in patients with DM (Cottrell et al., 2020; Wilke et al., 2014). However, in a future study, diabetic severity and DM treatment indicators should be included.

Second, although we collected covariates, such as age, household income, previous TB history, AFB smear, and culture, we were unable to account for potential confounding factors that could have been linked to TB recurrence, including smoking, drinking, body mass index, and occupation. Moreover, factors affecting the severity of TB, particularly smear and culture status after two months of treatment, were not collected. Third, because TB genotyping could not be performed, we were unable to distinguish between relapse and re-infection.

In conclusion, our study demonstrated that DM is associated with TB recurrence, especially in men. These findings support the notion that patients with DM, particularly men, should be prioritized for follow-up after successful TB treatment. Further research should be conducted to determine why TB recurrence predominantly occurs in men with diabetes, as well as whether it is related to smoking, alcohol consumption, COPD, and other sex-specific risk factors.

Contributions

DE contributed to interpretation, initial drafting of the manuscript, manuscript review and revision, and final approval of the version to be submitted. DJ participated in the design of the study, performed the data analysis and interpretation, and revised the manuscript. JM, DJ, HYK, HJK, and HSK contributed to interpretation and critically reviewed the manuscript for important intellectual content. HC and YAK conceptualized and designed the study, acquired and interpreted the data, reviewed and revised the manuscript, funding acquisition, and final approval of the version to be submitted.

Conflict of Interest

All authors declare that they have no competing interests.

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Ethical Approval Statement

The study protocol was reviewed and approved by the institutional review board of the National Evidence-based Healthcare Collaborating Agency (NECAIRB19-008-1). The requirement for informed consent was waived due to the retrospective nature of the study using public de-identified data.

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Figure legends

Figure 1. Flow diagram of the study population

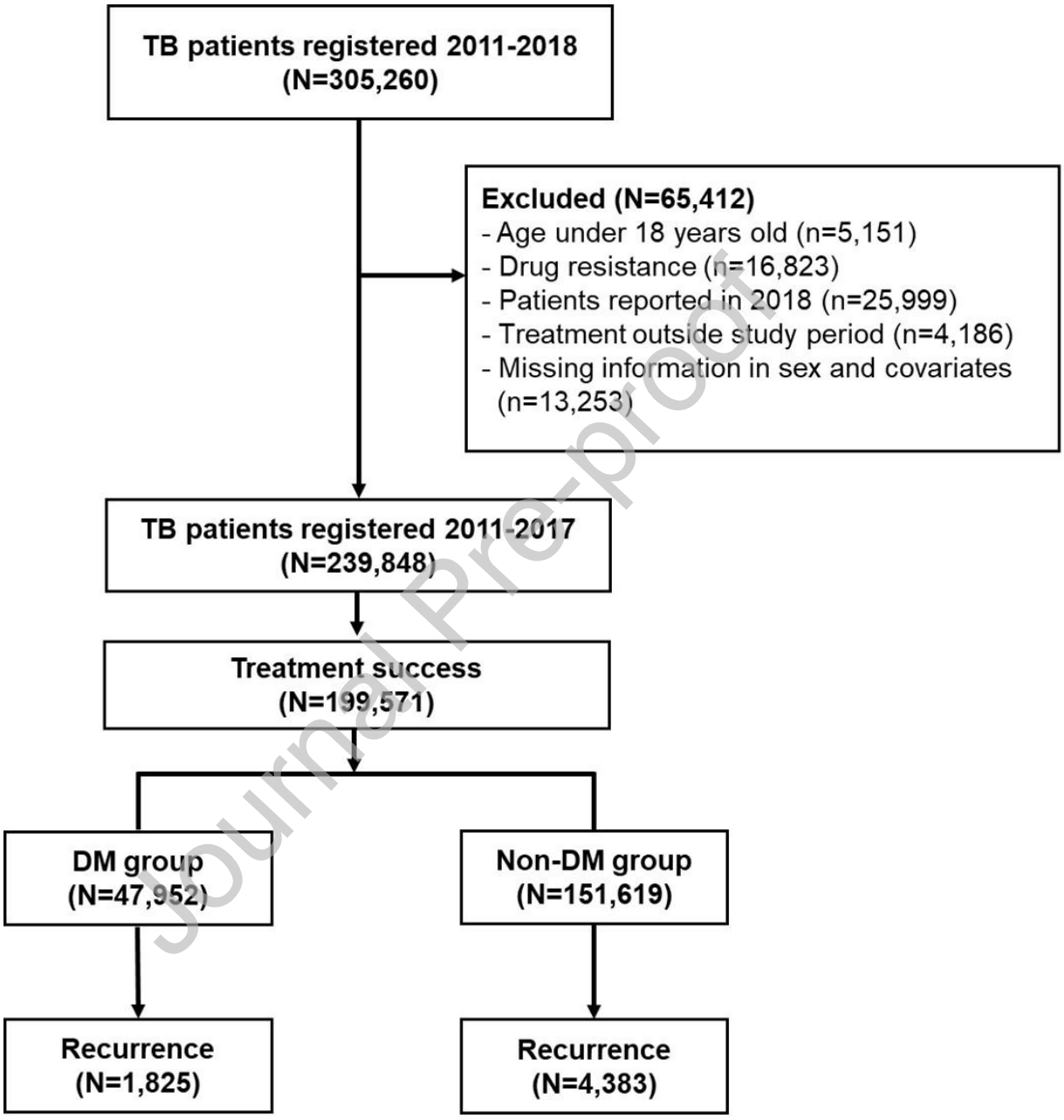

Figure 2. The percentage of TB recurrence by follow-up years after successful treatment in DM and non-DM groups

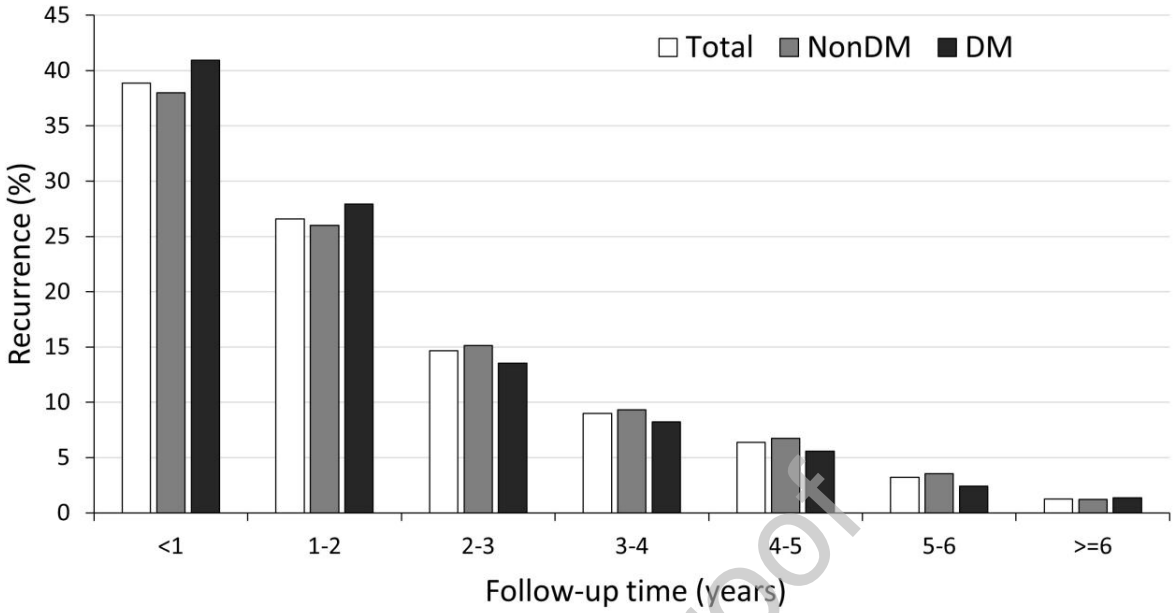

Figure 3. The cumulative recurrence rate after treatment success in DM and non-DM groups by sex

Figure 3a- Cumulative recurrence rate (Total)

Figure 3b- Cumulative recurrence rate (Men)

Figure 3c- Cumulative recurrence rate (Women)

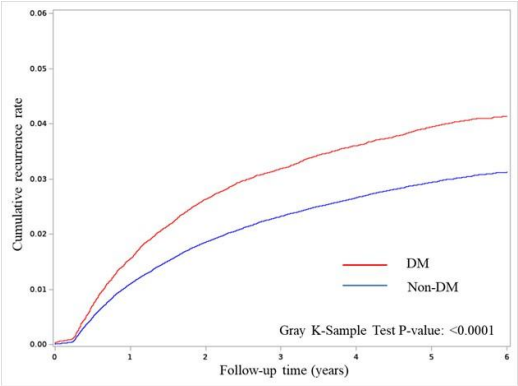

Figure 3a

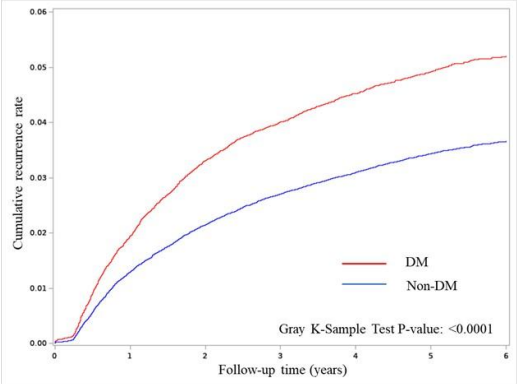

Figure 3b

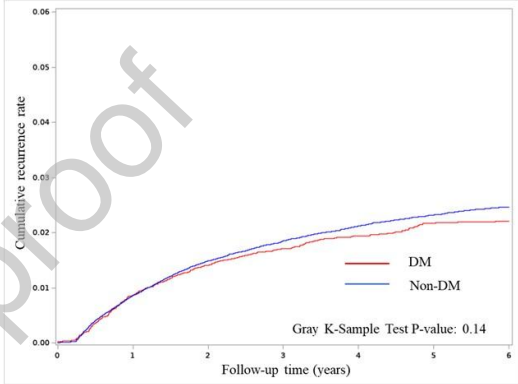

Figure 3c

Table1: General characteristics of the study population

Variables	Total 199,571 n (%)	DM 47,952 n (%)	Non-DM 151,619 n (%)	p-value
Gender				<0.0001
Men	114,916 (57.6)	30,874 (64.4)	84,042 (55.4)	
Women	84,655 (42.4)	17,078 (35.6)	67,577 (44.6)	
Age-group (year)				<0.0001
18-24	14,157 (7.1)	204 (0.4)	13,953 (9.2)	
25-34	26,389 (13.2)	757 (1.6)	25,632 (16.9)	
35-44	26,988 (13.5)	2,858 (6.0)	24,130 (15.9)	
45-54	33,270 (16.7)	7,980 (16.6)	25,290 (16.7)	
55-64	32,474 (16.3)	10,703 (22.3)	21,771 (14.4)	
65-74	30,244 (15.2)	11,820 (24.7)	18,424 (12.2)	
75+	36,049 (18.1)	13,630 (28.4)	22,419 (14.8)	
Age; year, Median [IQR]	54 [38-70]	66 [55-76]	50 [34-66]	<0.0001
Region				<0.0001
Metropolitan	88,844 (44.5)	20,440 (42.6)	68,404 (45.1)	
Others	110,727 (55.5)	27,512 (57.4)	83,215 (54.9)	
Nationality				<0.0001
Korean	194,852 (97.6)	47,583 (99.2)	147,269 (97.1)	
Others	4,719 (2.4)	369 (0.8)	4,350 (2.9)	
Disability				<0.0001
No	175,941 (88.2)	38,577 (80.5)	137,364 (90.6)	
Physical disability	21,208 (10.6)	7,854 (16.4)	13,354 (8.8)	
Internal disability	2,422 (1.2)	1,521 (3.2)	901 (0.6)	
Household income				<0.0001
0 (Lowest)	13,796 (6.9)	5,265 (11.0)	8,531 (5.6)	
1	31,989 (16.0)	7,596 (15.8)	24,393 (16.1)	
2	32,790 (16.4)	6,721 (14.0)	26,069 (17.2)	
3	35,512 (17.8)	7,435 (15.5)	28,077 (18.5)	
4	38,884 (19.5)	8,948 (18.7)	29,936 (19.7)	
5 (Highest)	46,600 (23.4)	11,987 (25.0)	34,613 (22.8)	
Lesion of TB				<0.0001
Pulmonary	170,906 (85.6)	41,800 (87.2)	129,106 (85.2)	
Extra-pulmonary	28,665 (14.4)	6,152 (12.8)	22,513 (14.8)	
TB history				<0.0001
New case	174,967 (87.7)	41,688 (86.9)	133,279 (87.9)	
Previous treated case	24,604 (12.3)	6,264 (13.1)	18,340 (12.1)	
PPM hospitals				<0.0001
Non-PPM	57,750 (28.9)	13,181 (27.5)	44,569 (29.4)	
PPM/Mix	141,821 (71.1)	34,771 (72.5)	107,050 (70.6)	
AFB smear				<0.0001
Positive	57,469 (28.8)	17,236 (35.9)	40,233 (26.5)	
Negative	107,467 (53.8)	23,963 (50.0)	83,504 (55.1)	
UNK	34,635 (17.4)	6,753 (14.1)	27,882 (18.4)	
Culture				<0.0001
Positive	87,794 (44.0)	23,727 (49.5)	64,067 (42.3)	
Negative	56,826 (28.5)	12,335 (25.7)	44,491 (29.3)	
UNK	54,951 (27.5)	11,890 (24.8)	43,061 (28.4)	
CCI score				<0.0001
0	87,383 (43.8)	14,987 (31.3)	72,396 (47.8)	
1	84,634 (42.4)	20,967 (43.7)	63,667 (42.0)	

2	8,616 (4.3)	3,381 (7.1)	5,235 (3.5)	
3 or above	18,938 (9.5)	8,617 (18.0)	10,321 (6.8)	
Co-morbidity				
Transplantation	532 (0.3)	326 (0.7)	206 (0.1)	<0.0001
HIV	221 (0.1)	54 (0.1)	167 (0.1)	0.89
Cancer	4,063 (2.0)	1,515 (3.2)	2,548 (1.7)	<0.0001
ESRD	2,393 (1.2)	1,841 (3.8)	552 (0.4)	<0.0001
Notification year				<0.0001
2011	32,713 (16.4)	6,690 (14.0)	26,023 (17.2)	
2012	32,944 (16.5)	7,280 (15.2)	25,664 (16.9)	
2013	29,564 (14.8)	6,827 (14.2)	22,737 (15.0)	
2014	28,691 (14.4)	6,910 (14.4)	21,781 (14.4)	
2015	26,513 (13.3)	6,806 (14.2)	19,707 (13.0)	
2016	25,561 (12.8)	6,841 (14.3)	18,720 (12.4)	
2017	23,585 (11.8)	6,598 (13.8)	16,987 (11.2)	
Recurrence TB	6,208 (3.1)	1,825 (3.8)	4,383 (2.9)	<0.0001

AFB, acid-fast bacilli; CCI, Charlson comorbidity index; DM, diabetes mellitus; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; IQR, interquartile range; PPM, public private mix; SD, standard deviation; TB, tuberculosis; UNK, unknown.

Table2: General characteristics of the study population in men

Variables	Men		
	DM	**Non-DM**	**p-value**
	30,874	84,042	
	n (%)	n (%)	
Age-group (year)			<0.0001
18-24	121 (0.4)	7,649 (9.1)	
25-34	464 (1.5)	13,199 (15.7)	
35-44	2,240 (7.3)	13,493 (16.1)	
45-54	6,555 (21.2)	15,625 (18.6)	
55-64	8,260 (26.8)	13,650 (16.2)	
65-74	7,227 (23.4)	10,677 (12.7)	
75+	6,007 (19.5)	9,749 (11.6)	
Age; year, Median [IQR]	62 [53-72]	50 [35-64]	<0.0001
Region			<0.0001
Metropolitan	13,577 (44.0)	37,988 (45.2)	
Others	17,297 (56.0)	46,054 (54.8)	
Nationality			<0.0001
Korean	30,648 (99.3)	81,712 (97.2)	
Others	226 (0.7)	2,330 (2.8)	
Disability			<0.0001
No	24,832 (80.4)	74,882 (89.1)	
Physical disability	5,062 (16.4)	8,542 (10.2)	
Internal disability	980 (3.2)	618 (0.7)	
Household income			<0.0001
0 (Lowest)	3,179 (10.3)	4,835 (5.8)	
1	4,969 (16.1)	13,262 (15.8)	
2	4,744 (15.4)	14,749 (17.6)	
3	5,023 (16.3)	15,834 (18.8)	
4	5,862 (19.0)	16,868 (20.1)	
5 (Highest)	7,097 (23.0)	18,494 (22.0)	
Lesion of TB			<0.0001
Pulmonary	27,701 (89.7)	73,678 (87.7)	
Extra-pulmonary	3,173 (10.3)	10,364 (12.3)	
TB history			<0.0001
New case	26,055 (84.4)	72,121 (85.8)	
Previously treated case	4,819 (15.6)	11,921 (14.2)	
PPM hospitals			<0.0001
Non-PPM	8,998 (29.1)	26,905 (32.0)	
PPM/Mix	21,876 (70.9)	57,137 (68.0)	
AFB smear			<0.0001
Positive	11,689 (37.9)	23,108 (27.5)	
Negative	15,681 (50.8)	48,679 (57.9)	
UNK	3,504 (11.4)	12,255 (14.6)	
Culture			<0.0001
Positive	15,932 (51.6)	37,227 (44.3)	
Negative	8,048 (26.1)	25,733 (30.6)	
UNK	6,894 (22.3)	21,082 (25.1)	
CCI score			<0.0001
0	10,974 (35.5)	42,464 (50.5)	
1	13,161 (42.6)	33,576 (40.0)	
2	2,036 (6.6)	2,853 (3.4)	

3 or above	4,703 (15.2)	5,149 (6.1)	
Co-morbidity			
Transplantation	231 (0.8)	144 (0.2)	<0.0001
HIV	47 (0.2)	155 (0.2)	0.25
Cancer	1,136 (3.7)	1,625 (1.9)	<0.0001
ESRD	1,135 (3.7)	298 (0.4)	<0.0001
Notification year			<0.0001
2011	4,396 (14.2)	14,410 (17.2)	
2012	4,753 (15.4)	14,187 (16.9)	
2013	4,480 (14.5)	12,531 (14.9)	
2014	4,344 (14.1)	11,999 (14.3)	
2015	4,349 (14.1)	10,991 (13.1)	
2016	4,387 (14.2)	10,477 (12.5)	
2017	4,165 (13.5)	9,447 (11.2)	
Recurrence TB	1,475 (4.8)	2,837 (3.4)	<0.0001

AFB, acid-fast bacilli; CCI, Charlson comorbidity index; DM, diabetes mellitus; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; IQR, interquartile range; PPM, public private mix; SD, standard deviation; TB, tuberculosis; UNK, unknown.

Table3: General characteristics of the study population in women

Variables	Women		
	DM	**Non-DM**	**p-value**
	17,078	67,577	
	n (%)	n (%)	
Age-group (year)			<0.0001
18-24	83 (0.5)	6,304 (9.3)	
25-34	293 (1.7)	12,433 (18.4)	
35-44	618 (3.6)	10,637 (15.7)	
45-54	1,425 (8.3)	9,665 (14.3)	
55-64	2,443 (14.3)	8,121 (12.0)	
65-74	4,593 (26.9)	7,747 (11.5)	
75+	7,623 (44.6)	12,670 (18.8)	
Age; year, Median [IQR]	73 [62-79]	49 [33-70]	<0.0001
Region			<0.0001
Metropolitan	6,863 (40.2)	30,416 (45.0)	
Others	10,215 (59.8)	37,161 (55.0)	
Nationality			<0.0001
Korean	16,935 (99.2)	65,557 (97.0)	
Others	143 (0.8)	2,020 (3.0)	
Disability			<0.0001
No	13,745 (80.5)	62,482 (92.5)	
Physical disability	2,792 (16.4)	4,812 (7.1)	
Internal disability	541 (3.2)	283 (0.4)	
Household income			<0.0001
0 (Lowest)	2,086 (12.2)	3,696 (5.5)	
1	2,627 (15.4)	11,131 (16.5)	
2	1,977 (11.6)	11,320 (16.8)	
3	2,412 (14.1)	12,243 (18.1)	
4	3,086 (18.1)	13,068 (19.3)	
5 (Highest)	4,890 (28.6)	16,119 (23.9)	
Lesion of TB			0.10
Pulmonary	14,099 (82.6)	55,428 (82.0)	
Extra-pulmonary	2,979 (17.4)	12,149 (18.0)	
TB history			<0.0001
New case	15,633 (91.5)	61,158 (90.5)	
Previously treated case	1,445 (8.5)	6,419 (9.5)	
PPM hospitals			<0.0001
Non-PPM	4,183 (24.5)	17,664 (26.1)	
PPM/Mix	12,895 (75.5)	49,913 (73.9)	
AFB smear			<0.0001
Positive	5,547 (32.5)	17,125 (25.3)	
Negative	8,282 (48.5)	34,825 (51.5)	
UNK	3,249 (19.0)	15,627 (23.1)	
Culture			<0.0001
Positive	7,795 (45.6)	26,840 (39.7)	
Negative	4,287 (25.1)	18,758 (27.8)	
UNK	4,996 (29.3)	21,979 (32.5)	
CCI score			<0.0001
0	4,013 (23.5)	29,932 (44.3)	

1	7,806 (45.7)	30,091 (44.5)	
2	1,345 (7.9)	2,382 (3.5)	
3 or above	3,914 (22.9)	5,172 (7.7)	
Co-morbidity			
Transplantation	95 (0.6)	62 (0.1)	<0.0001
HIV	7 (0)	12 (0)	0.07
Cancer	379 (2.2)	923 (1.4)	<0.0001
ESRD	706 (4.1)	254 (0.4)	<0.0001
Notification year			<0.0001
2011	2,294 (13.4)	11,613 (17.2)	
2012	2,527 (14.8)	11,477 (17.0)	
2013	2,347 (13.7)	10,206 (15.1)	
2014	2,566 (15.0)	9,782 (14.5)	
2015	2,457 (14.4)	8,716 (12.9)	
2016	2,454 (14.4)	8,243 (12.2)	
2017	2,433 (14.3)	7,540 (11.2)	
Recurrence TB	350 (2.0)	1,546 (2.3)	0.06

AFB, acid-fast bacilli; CCI, Charlson comorbidity index; DM, diabetes mellitus; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; IQR, interquartile range; PPM, public private mix; SD, standard deviation; TB, tuberculosis; UNK, unknown.

Table 4: Impact of DM on TB recurrence after successful treatment stratified by sex

	Crude		Model 1		Model 2		Model 3		Model 4	
	HR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI
Total										
Diabetes Mellitus										
no	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
yes	1.35	1.28-1.43	1.26	1.19-1.34	1.22	1.15-1.29	1.22	1.15-1.29	1.22	1.15-1.29
Men										
Diabetes Mellitus										
no	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
yes	1.45	1.37-1.55	1.29	1.20-1.38	1.23	1.15-1.32	1.23	1.15-1.32	1.23	1.15-1.32
Women										
Diabetes Mellitus										
no	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
yes	0.91	0.81-1.03	0.95	0.84-1.08	0.96	0.85-1.09	0.96	0.85-1.09	0.96	0.85-1.09

HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; DM, diabetes mellitus; TB, tuberculosis.

Model 1 was adjusted for age, region, household income, and nationality.

Model 2 was adjusted for TB lesions, previous TB history, PPM hospital, AFB smear, and culture, in addition to Model 1.

Model 3 was adjusted for disability and comorbidity, in addition to Model 2.

Model 4 was adjusted for disability and Charlson comorbidity index (CCI) scores, in addition to Model 2.