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Glycemic trajectories and the risk of tuberculosis in diabetic patients: a retrospective cohort study

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Abstract

Diabetic patients with poor glycemic control had increased risk of tuberculosis, but glycemic control may change overtime. We conducted a retrospective cohort study to investigate whether glycemic trajectories influence the risk of active tuberculosis, using the Taipei Medical University Clinical Research Database.

Among patients with baseline HbA1C > 9.0%, the incidence rate (IR) of tuberculosis was 97.09 per 100 person-years among those with poor glycemic trajectory and 43.36 per 100 person-years in those with good glycemic trajectory (incidence rate ratio (IRR) 2.24; adjusted hazard ratio (aHR) 4.88, 95% confidence interval (CI) 1.19–20.02).

Among patients with baseline HbA1C 7.1–9.0%, the IR of tuberculosis was 169.49 per 100 person-years among those with poor glycemic trajectory and 24.97 per 100 person-years in those with good glycemic trajectory (IRR 6.79; aHR 4.02, 95% CI 1.58–10.23).

Among patients with baseline HbA1C ≤ 7.0% at baseline, the IR of tuberculosis was 98.23 per 100 person-years among those with poor glycemic trajectory and 34.30 per 100 person-years in those with good glycemic trajectory (IRR 6.79; aHR 3.00, 95% CI 1.10 -81.82).

We concluded that glycemic trajectory was associated with subsequent risk of active tuberculosis.

(Word count 190)

Introduction

The International Diabetes Federation has estimated that there are 537 million adults living with diabetes globally. The number of diabetic patients will increase to 643 million by 2030 and 783 million by 2045.[1] Diabetes mellitus (DM) is an important risk factor for tuberculosis (TB). Patients with DM have an increased risk of TB compared with people without DM. A systemic review and meta-analysis reported that DM was associated with a 3-fold higher risk of TB in cohort studies compared with patients without DM; case control studies also revealed an increased risk of TB among diabetic patients, although findings were heterogeneous[2]. The rising burden of DM may have a significant impact on global TB prevention and care.

Patients with DM are not homogenous. Glycemic control measured by fasting plasma glucose or glycated hemoglobin A1C (HbA1C) varies among patients [3]. Studies have reported that patients with inadequate glycemic control had a significantly higher risk of TB, whereas those with adequate glycemic control did not[4]. One limitation of these studies was that glycemic control was assessed only once for each cohort participant[3,4]. Glycemic control is not constant and may change overtime. Patients with inadequate glycemic control may subsequently improve through dietary modification, increased physical activity [5], and changes in anti-diabetic treatment. Likewise, patients with adequate glycemic control at baseline may experience deterioration during follow-up. Therefore, classification based only on baseline glycemic control may result in misclassification because it does not capture changes in glycemic control over time.

The Taipei Medical University Clinical Research Database (TMUCRD)[6], created in 2015, is a comprehensive repository of real world data containing electronic medical records of 4.15 million patients who visited three affiliated hospitals, namely Taipei Medical University Hospital, Wan Fang Hospital and Shuang Ho Hospital, from 2004–2021[6–9]. It provides an opportunity to assess the changes in glycemic control over time among a cohort of patients with DM and to evaluate the association between glycemic trajectories and the risk of active TB.

Results

There were 101,217 patients with DM in the TMUCRD between 1 January 2004-31 December 2016. Patients diagnosed before 2004 (n = 9,976), patients who had no prescription of DM medication (n = 38,835), patients who were treated with DM drugs for less than 30 days within one year (n = 6,995), patients who had no HbA1C or fasting plasma glucose results (n = 13,412), patients who had less than two tests of HbA1C or fasting plasma glucose within the first 24 months (n = 16,399) and patients with active TB diagnosed within 3-month of enrollment (n = 299) were excluded. The remaining 32,008 patients were enrolled in this study (Fig. 1). Their mean age was 59.5 years. 17,265 (53.9%) were male. Overall, 9,887 (30.9%) had cancer, 5,114 (16.0%) had liver disease, and

5,649 (17.7%) had chronic obstructive pulmonary disease. A total of 26,957 (84.2%) were treated with biguanides, 8,149 (25.5%) with dipeptidyl peptidase-4 inhibitors, and 5,409 (16.9%) with insulins or insulin analogues. At baseline, 14,637 (45.7%) had HbA1C ≤ 7.0%, 9,302 (29.1%) had HbA1C 7.1–9.0%, and 8,069 (25.2%) had HbA1C > 9% at baseline (Supplement Table 1).

Table 1
Incidence rate of tuberculosis in patients with poor glycemic trajectory (n = 612) and patients with good glycemic trajectory (n = 14025) among diabetic patients with HbA1C < = 7% at baseline and incidence rate ratios of poor glycemic trajectory vs good glycemic trajectory

	Poor glycemic trajectory			Good glycemic trajectory			IRR, poor vs good trajectory
	Events	Person-years follow up	IR*	Events	Person-years follow up	IR	
All	5	5.09	98.23	158	460.6	34.30	2.86
Gender							
Female	2	1.83	109.29	64	173.76	36.83	2.97
Male	3	3.26	92.03	94	286.84	32.77	2.81
Age (years)							
< 65	2	0.27	740.74	50	168.81	29.62	25.01
65–85	2	3.69	54.20	97	267.96	36.20	1.50
> 85	1	1.13	88.50	11	23.84	46.14	1.92

Table 2
Incidence rate of tuberculosis in patients with poor glycemic trajectory (n = 164), patients with fair glycemic trajectory (n = 370), and patients with good glycemic trajectory (n = 8766) among diabetic patients with HbA1C 7.1-9% at baseline and incidence rate ratios of poor vs good and fair vs goo glycemic trajectory

	Poor glycemic trajectory			Fair glycemic trajectory			Good glycemic trajectory			IRR,	IRR,
	Events	Person-years follow up	IR*	Events	Person-years follow up	IR*	Events	Person-years follow up	IR*	poor vs good trajectory	fair vs good trajectory
ALL	2	1.18	169.49	5	3.33	150.15	115	460.6	24.97	6.79	6.01
Gender											
Female	1	0.8	125.00	1	0.34	294.12	48	148.8	32.26	3.88	9.12
Male	1	0.38	263.16	4	2.99	133.78	67	149.01	44.96	5.85	2.98
Age group											
< 65 yrs	1	0.45	222.22	1	0.4	250.00	49	124.7	39.29	5.66	6.36
65–85	-	-	-	4	2.93	136.52	55	146.22	37.62	-	3.63
> 85	1	0.73	136.99	-	-	-	11	26.89	40.91	3.35	-

Table 3
Incidence rate of tuberculosis in patients with poor glycemic trajectory (n = 1018) and patients with good glycemic trajectory (n = 7051) among diabetic patients with HbA1C > 9% at baseline and incidence rate ratios of poor glycemic trajectory vs good glycemic trajectory

	Poor glycemic trajectory			Good glycemic trajectory			IRR, poor vs good trajectory
	Events	Person-years follow up	IR*	Events	Person-years follow up	IR	
All	10	10.3	97.09	123	283.7	43.36	2.24
Gender							
Female	5	3.69	135.5	53	117.16	45.24	3
Male	5	6.61	75.64	70	166.54	42.03	1.8
Age (years)							
< 65	6	4.19	143.2	83	208.98	39.72	3.61
65–85	3	4.88	61.48	36	70.38	51.15	1.2
> 85	1	1.23	81.30	4	4.35	91.95	0.88

Table 4
The association between glycemic trajectories and risks of tuberculosis in diabetic patients estimated by cox proportional hazard models, stratified by baseline HbA1C

	Univariable		Multivariable	
	HR (95% CI)	P-value	aHR (95% CI)	P-value
Baseline HbA1C > 9%				
Good trajectory	Reference		Reference	
Poor trajectory	2.02(0.50–8.15)	0.32	4.88(1.19–20.02)	0.01
Baseline HbA1C 7.1-9%				
Good trajectory	Reference		Reference	
Poor trajectory	3.26(1.33–7.97)	0.01	4.02(1.58–10.23)	< 0.01
Fair trajectory	1.65(1.43–1.90)	< 0.01	1.17(0.40–6.59)	0.50
Baseline HbA1C ≤ 7%				
Good trajectory	Reference		Reference	
Poor trajectory	1.88(0.77–4.57)	0.17	3.00(1.10-81.82)	0.03

Of the 14,637 patients with baseline HbA1C ≤ 7.0%, 14025 (95.8%) had good glycemic trajectory, among whom 158 had developed active TB during 460.6 person-years of follow-up (incidence rate 34.30 per 100 person-years); 612 (4.3%) had poor glycemic trajectory in whom 5 had developed active TB during 5.09 person-years of follow-up (incidence rate 98.23 per 100 person-years; poor vs good glycemic trajectory, incidence rate ratio 2.86). In multivariable Cox proportional hazards regression model, poor glycemic trajectory was associated with a higher risk of active TB than good glycemic trajectory (adjusted hazard ratio (aHR) 3.00, 95% confidence interval (95% CI) 1.10 -81.82).

Of the 9,302 patients with baseline HbA1C 7.1–9.0%, 8766 (94.2%) had good glycemic trajectory, among whom 115 developed active TB during 460.6 person-years of follow-up (incidence rate 24.97 per 100 person-years). A total of 370 (4.0%) had fair glycemic trajectory, among whom 5 developed active TB during 3.33 person-years of follow-up (incidence rate 150.15 per 100 person-years; fair vs good glycemic trajectory incidence rate ratio 6.01). A total of 164 (1.8%) had poor glycemic trajectory, among whom 2 had developed active TB during 1.18 person-years of follow-up (incidence rate 169.49 per 100 person-years, poor vs good

glycemic trajectory, incidence rate ratio 6.79). In the multivariable Cox proportional hazards regression model, poor glycemic control was associated with a higher risk of active TB than good glycemic trajectory (aHR 4.02, 95% CI 1.58–10.23).

Of the 8,069 patients with baseline HbA1C > 9% at baseline, 7051 (87.4%) had good glycemic trajectory, among whom 123 developed active TB during 283.7 person-years of follow-up (incidence rate 43.36 per 100 person-years). A total of 1018 (12.6%) had poor glycemic trajectory in whom 10 had developed active TB within 10.3 person-years of follow-up (incidence rate 97.09 person-year; poor vs good glycemic control, incidence rate ratio 2.24). In the multivariable Cox proportional hazards regression model, poor glycemic trajectory was associated with a higher risk of active TB than good glycemic trajectory (adjHR 4.88, 95% CI 1.19–20.02).

Discussion

Our study revealed that glycemic control was heterogeneous among diabetic patients and may change overtime. Evolution of glycemic control had significant influence on the risk of developing active TB. Among patients with baseline high HbA1C (> 9.0%), improved glycemic control was achievable in most of our study population, and was associated with lower active TB risk compared with poor persistent glycemic control. Among patients with baseline HbA1C ≤ 7.0%, most maintained good glycemic control during follow-up, whereas a small proportion experienced deterioration which was associated with increased risk of TB. A similar pattern was observed among patients with baseline HbA1C 7.1–9.0% in whom deteriorating glycemic control was associated with higher TB risk compared with improved glycemic control. Overall, these findings suggest that longitudinal glycemic control may be clinically relevant for TB risk stratification among patients with DM.

Taiwan is an aging society driven by both increasing life expectancy and low fertility rates [10]. Studies have shown that the prevalence of DM is increasing, especially among the older patients [11,12]. Diabetes care, including diagnosis and treatment of diabetes and management of diabetes related complications, is covered by the National Health Insurance in Taiwan and the coverage rate of the National Health Insurance in Taiwan is 99.9% of the population. To strengthen glycemic control in diabetic patients, the Bureau of National Health Insurance has implemented a pay-for-performance (P4P) program for DM since 2001. In addition to reimbursement for routine diabetes care on a fee-for-services basis, the program provides “case management fees” that covers a package of defined services, including the initial enrolment visit, comprehensive follow-up visits and an annual evaluation visit during which HbA1C and fasting plasma glucose levels are assessed on a quarterly basis [13–15]. The P4P program for DM was associated with increase in clinical guideline adherence and regular follow-up visits[14–16], and was found to yield positive cost-benefit net value[17].

The association between glycemic control and TB risk have been investigated previously. Leung et al enrolled a cohort of older people at Elderly Health Service centers in Hong Kong and conducted prospective follow-up to ascertain the development of TB. They reported that the risk of active TB among diabetic patients varied by glycemic control. Patients with DM and HbA1C < 7% at enrollment were not at increased risk of TB compared to patients without DM, whereas patients with baseline HbA1C ≥ 7% had higher risks of active TB compared to diabetic patients with HbA1c < 7%.[3] However, Leung et al. did not assess changes in glycemic control after enrollment.

Lee et al enrolled a large cohort of individuals who participated in a community-based health screening service in northern Taiwan. Glycemic control was assessed by fasting plasma glucose during screening. They matched the cohort of patients to the national health insurance database to identify patients who developed active TB during follow-up. They reported that patients with diabetic and poor glycemic control, defined as fasting plasma glucose > 130 mg/dl, had a significantly higher hazard of TB compared with patients without diabetes. However, the risk of TB in diabetic patients with good glycemic control, defined as fasting plasma glucose ≤ 130 mg/dl, did not differ significantly from that among nondiabetic individuals.[4] Lee et al. also did not assess the changes in glycemic control after screening, and therefore did not account for the influence of glycemic trajectory after enrollment.

The influence of strengthening glycemic control on active TB risk has been indirectly investigated by Lo et al[13], who investigated whether diabetic patients enrolled in the P4P program (DM- P4P) had a reduced risk of active TB as compared to diabetic patients not enrolled in the P4P program (DM-non-P4P). They enrolled a relatively large random samples of patients with DM and non-DM and matched these patients with the National TB Registry maintained by Taiwan Centers of Disease Control (CDC) to determine whether they had developed TB during follow up. Lo et al. found that the average annual incidence of TB was significantly higher

among DM-non-P4P, but that among DM-P4P and that among non-DM patients did not differ significantly. Lo et al. concluded that enhanced case management of DM may reduce risk of TB among patients with DM.[13] While the findings were encouraging, glycemic data were unavailable in that study.

Antonio-Arques et al. accounted for changes in glycemic control when investigating the association between glycemic control and the risk of TB. They constructed time-dependent models in which HbA1c values were updated whenever a new value became available. Three cut-off values of HbA1c, 7.5%, 8% and 9%, were applied. They reported that people with DM and worse glycemic control showed a trend toward a higher risk of developing TB, although the association was not statistically significant. Our study was unique that we strategically took the change of glycemic control into account and showed that those who had improved glycemic control after enrolment had reduced risk of active TB and those who had deteriorated glycemic control had increased risk of active TB.

Glycemic control is not only associated with the risk of active TB, but also with manifestations of TB and outcomes of treatment. Chiang et al. investigated whether glycemic control influenced radiographic manifestations of pulmonary TB[18]. They reported that TB patients with poor glycemic control were significantly more likely to have opacity over lower lung fields, extensive parenchymal lesions, any cavity, multiple cavities and large cavities. Furthermore, the proportions of patients with any symptoms, cough, hemoptysis, tiredness and weight loss were highest among patients with DM with poor glycemic control (HbA1C > 9%). Moreover, diabetic patients with poor glycemic control were significantly more likely to be smear positive as compared with non-diabetic patients, but not those with good glycemic control [19]. The influence of glycemic control on TB treatment outcomes was recently confirmed by a systematic review and meta-analysis [20]. The prevalence of TB infection among diabetic patients with poor glycemic control has been reported to be higher than among those with good glycemic control [21].

TB screening among patients with DM has been recommended by the World Health Organization (WHO), and computer-assisted detection tools may play a role [22]. Our findings suggest that those with poor glycemic control or deteriorating glycemic trajectory may be reasonable candidates for targeted TB screening and preventive treatment for TB infection.

Our study has several strengths. The sample size was relatively large, allowing for classification of patients by baseline HbA1c and assessment of glycemic trajectories across different baseline glycemic control strata. The follow-up period was relatively long, allowing detection of a substantial number of active TB cases for better quantification of the risk of TB. This study had also limitations. Glycemic trajectory was defined only during the first 12 months after enrollment. Given that diabetes care is covered by the National Health Insurance in Taiwan and that the P4P program for DM has been implemented for 25 years, the majority of patients with DM would likely have maintained the trajectory of glycemic control and the risk of mis-classification is likely to be relatively low.

In conclusion, longitudinal glycemic trajectory was associated with active tuberculosis risk among patients with diabetes; improvement in glycemic control was associated with lower TB risk, whereas deterioration was associated with higher TB risk.

Ethical Considerations

This study was approved by the Institutional Review Board (IRB) of Taipei Medical University (N202304103). The requirement for informed consent was waived because the research involved secondary analysis of de-identified data from the TMUCRD. All study procedures were conducted in accordance with the principles of the Declaration of Helsinki and relevant local regulations governing the use of health data for research purposes.

Declarations

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Declaration of Generative AI and AI-assisted technologies in the writing process:

No generative artificial intelligence (AI) nor AI-assisted technologies were used in creating content or assisting with writing or manuscript preparation.

Disclosure of Competing Interests: none declared

Data and Resource Availability

All data generated or analyzed during this study are included in the published article (and its online supplementary files).

IR, Incidence rate per 100 person-years; IRR, incidence rate ratio

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HR, hazard ratio; aHR adjusted hazard ratio, adjusted for age, sex, Previous history of TB, Rheumatoid arthritis, Chronic obstructive pulmonary disease, Chronic kidney disease, End-stage renal disease, Cancer, Organ transplantation, Pneumoconiosis, and Liver disease (Detail models in supplementary Table 2–4)

Author Contribution

Conception and design of study: J.C.H., P.A.N., S.M.L, T.I.L W.H.H. and C.Y.C. Acquisition of data and analysis: P.A.N., S.M.L, and C.Y. Interpretation of the results: J.C.H., S.M.L, T.I.L W.H.H. and C.Y.C. Drafting of manuscript: J.C.H. and C.Y.C. Revision and Approval of final version of manuscript: J.C.H., P.A.N., S.M.L, C.Y., T.I.L W.H.H. and C.Y.C.

Data Availability

All data generated or analyzed during this study are included in the published article (and its online supplementary files).

Methods

We hypothesized that glycemic trajectories are associated with the risk of developing active TB among patients with DM and that improvement or deterioration of glycemic control during follow-up may influence TB risk. Specifically, among patients with poor glycemic control at enrollment, those who subsequently achieve improved glycemic control may have a lower risk of active TB than those whose glycemic control remains poor. Conversely, among patients with adequate glycemic control at enrollment, those who subsequently experience deterioration in glycemic control may have a higher risk of active TB than those who maintain good glycemic control.

Study Design

We conducted a retrospective cohort study using data from the Taipei Medical University Clinical Research Database[6]. The study was designed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Eligible patients were enrolled between 2005 and 2016 and followed for up to 10 years, until December 31, 2021, or until study endpoints were reached.

Study Population

Participants were outpatients diagnosed with DM, identified through both a DM-related ICD-9-CM code (250) or ICD-10-CM codes (E08, E09, E10, E11, E13), and prescription of at least one month of antidiabetic medication. To ensure adequate monitoring of glycemic status, we included only patients with at least two tests of either HbA1c or fasting plasma glucose within the first 12 months after enrollment and at least one test annually thereafter. Patients who did not meet these criteria were excluded.

Exposure of Interest

The primary exposure of interest was glycemic control, primarily assessed via HbA1c. HbA1c results were recorded for the month of testing, with interpolation between test months according to standardized rules[23]. When HbA1c results were unavailable, fasting plasma glucose was converted to HbA1c values using the validated equation proposed by Nathan and colleagues[24]. At baseline, patients were stratified into three groups according to HbA1c levels: ≤7.0% (good control), 7.1–9.0% (fair control), and greater than 9.0% (poor control). Longitudinal glycemic control during the first 12 months after enrollment was further categorized using the slope (β) of HbA1c trends estimated by linear regression trend-line models[23]. For patients with baseline HbA1c ≤ 7.0%, those with $\beta \leq 0$ were classified as having good glycemic trajectory, whereas those with $\beta > 0$ were considered to have poor glycemic trajectory. For patients with baseline HbA1c between 7.1% and 9.0%, a slope $\beta \leq 0.5$ indicated good glycemic trajectory, $-0.5 < \beta < 0.5$ indicated fair glycemic trajectory, and $\beta > 0.5$ indicated good glycemic trajectory. For patients with baseline HbA1c > 9.0%, those with $\beta \leq 0$ were classified as having good glycemic trajectory, whereas those with $\beta > 0$ were considered to have poor glycemic trajectory.

Outcome of Interest

The primary endpoint was incident active TB during follow-up. Active TB was defined as the presence of a TB-related ICD-9 code (010–018) or ICD-10 code (A15–A19) in combination with prescription of at least two anti-TB medications for a minimum of 28 days. Anti-TB medications included isoniazid, rifampin, ethambutol, pyrazinamide, prothionamide, cycloserine, PAS, aminoglycosides, bedaquiline, delamanid, pretomanid, linezolid, clofazimine, and fluoroquinolones. Patients who were diagnosed with TB within three months of enrollment were excluded to minimize the influence of misclassification due to delayed diagnosis.

Covariates

Covariates were identified using ICD codes and included prior history of active TB (ICD-9-CM: 137.0–137.4; ICD-10-CM: B90.0–B90.9, Z86.11), rheumatoid arthritis (ICD-9-CM: 714.0, 714.30; ICD-10-CM: M05.7–M06.3, M06.8, M06.9, M08.0, M08.2–M08.4), HIV infection (ICD-9-CM: 042–044; ICD-10-CM: B20–B24), chronic obstructive pulmonary disease (ICD-9-CM: 490–496; ICD-10-CM: J40, J43–J45, J47, J67), chronic kidney disease (ICD-9-CM: 585, 403, 404; ICD-10-CM: N18.4–N18.9, I12.0, I12.9, I13.11, I13.2), end-stage renal disease (ICD-9-CM: V45.1, 586; ICD-10-CM: Z99.2, N19), cancer (ICD-9-CM: 140–239; ICD-10-CM: C00–C90, C4A, C7A, C7B, C96.4, C96.9, C96.Z, D3A.8, E31.22, J91.0, R18.0, Z51.12), organ transplantation (ICD-9-CM: V42.0, V42.1, V42.6–V42.7, V42.81–V42.9, 996.80–996.86; ICD-10-CM: Z94.0–Z94.4, Z94.8–Z94.9, D89.81, T86.0–T86.8), pneumoconiosis (ICD-9-CM: 500–503, 505; ICD-10-CM: J60–J65), and liver disease (ICD-9-CM: 571.2, 571.5; ICD-10-CM: K70.2, K70.30, K70.31, K74).

Data Source

The Taipei Medical University Clinical Research Database integrates longitudinal data from the hospital information system database of three affiliated medical centers located in northern Taiwan, covering the period 2004–2021[6]. Clinical information includes demographic characteristics, diagnoses, prescriptions, laboratory results, and outcomes of outpatient, inpatient and emergency records. It combines comprehensive structured data (such as basic patient information, visits, laboratory tests, diagnosis results, treatment, surgery, and medication, etc.) and unstructured data (such as physician records, pathology reports, radiological reports, discharge papers). The database involved electronic medical records of 61.5 million outpatient visits, 3 million emergency visits, and 1.1 million hospital admissions. The mean (median, interquartile range) observation period of patients was 1451 (419, 1-2607) days. The Taipei Medical University Clinical Research Database became available for application in January 2020. Two modes of service were provided: 1) Data to go: applicants can receive released data to conduct their analyses, but the number of patients included is less than 1% of the total population in the database; 2) Report to go: applicants can access various types of data and can analyze their study research in a designated ‘clean room’ in which individuals are prohibited from bringing in any external devices or items, ensuring that only verified reports intended for publication can be carried out[6]. We adopted the “Report to go” mode to analyze clinical data from 2004–2021 related to diabetes patients in the Taipei Medical University Clinical Research Database, and to generate Tables and Figures for this manuscript.

Follow-up

Participants were followed from enrollment until the earliest occurrence of one of the following: the development of active TB, loss to follow-up, discontinuation of DM medications (defined as at least 12 months without prescription), absence of HbA1c or FPG monitoring for at least 12 months, completion of 10 years of follow-up, death, or the study endpoint on December 31, 2021.

Statistical Analysis

Baseline characteristics were compared across HbA1c strata using analysis of variance (ANOVA) for continuous variables and Fisher's exact test for categorical variables. The association between glycemic trajectories and the risk of active TB was evaluated using multivariable Cox proportional hazards regression models adjusting for age, sex, previous history of TB, chronic obstructive pulmonary disease, chronic kidney disease, end stage renal disease, rheumatoid arthritis, cancers, pneumoconiosis, liver disease, and organ transplantation, with hazard ratios (HRs) and 95% confidence intervals (CIs) reported. Good glycemic trajectory served as the reference category. The final models were built using a backward selection procedure, initially including all variables with a P value < 0.20 in univariable analysis and retaining those with a P value < 0.10; age and sex were considered a priori confounders and were included in all models regardless of P value. Time-to-event data were illustrated using Kaplan–Meier survival curves, and group differences were tested with the log-rank test. Age- and sex-stratified incidence rates of TB were also calculated to explore potential effect modification. All statistical tests were two-sided, and a *p*-value of < 0.05 was considered statistically significant. Data management and statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

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Figures

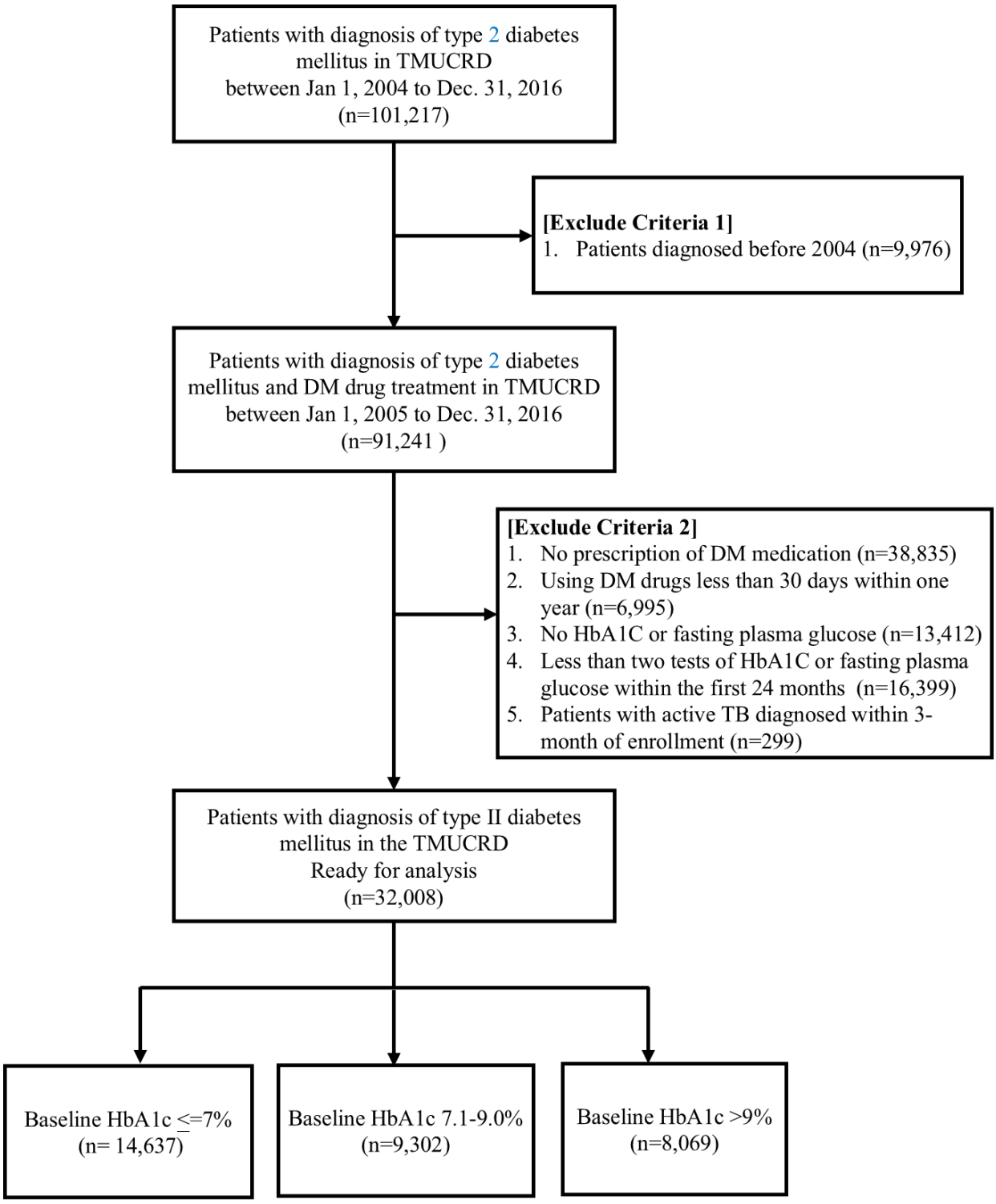


Figure 1

Flow diagram of patient enrollment

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