Jurnal Impresi Indonesia (JII)
p-ISSN: 2828-1284 e-ISSN: 2810-062x
website: https: //rivierapublishing.id/JII/ index.php / jii /index

Association Between Glycated Hemoglobin (HBA1C) Levels and the Incidence of Pulmonary Drug-Resistant Tuberculosis Among Patients with Type 2 Diabetes Mellitus

Kartini Harahap, Fajrinur Syarani, Bintang Yinke Magdalena Sinaga*, Putri Chairani Eyanoer
Department of Pulmonology & Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
Email: kartiniharahap1104@gmail.com, fajrinur_syarani@yahoo.com, bintang@usu.ac.id*, putrieyanoer@usu.ac.id

Keywords
Glycemic Control; Multidrug-Resistant Tuberculosis; Risk Factors; Type 2 Diabetes Mellitus

Abstract
Patients with type 2 diabetes mellitus (T2DM) are at increased risk of developing multidrug-resistant tuberculosis (MDR-TB). In Indonesia, data regarding the characteristics and risk factors for MDR-TB among diabetic populations remain limited. Managing MDR-TB in individuals with T2DM is complicated by potential drug interactions and challenges associated with poor glycemic control. This study aimed to assess the association between glycated hemoglobin (HbA1c) levels and the risk of developing MDR-TB among T2DM patients at Adam Malik General Hospital, Medan. A case-control analytical study was conducted using secondary data from medical records. A total of 120 participants were, including 60 MDR-TB cases and 60 drug-sensitive tuberculosis controls. Variables analyzed included age, sex, education, employment status, body mass index, smoking status, and HbA1c levels. Statistical analyses involved chi-square tests and multivariate logistic regression. Multivariate analysis identified smoking as the strongest risk factor for MDR-TB, followed by poor glycemic control, indicated by elevated HbA1c levels. Smoking substantially increases the risk of MDR-TB among patients with T2DM, with smokers being twelve times more likely to develop MDR-TB. These findings emphasize the need to integrate smoking cessation initiatives into MDR-TB prevention and management strategies targeting diabetic populations.

INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), which primarily affects the lungs. The emergence of drug-resistant TB (DR-TB), including multidrug-resistant TB (MDR-TB) and rifampicin-resistant TB (RR-TB), has become a major challenge in global TB control efforts. According to the World Health Organization (WHO), an estimated 450,000 new MDR/RR-TB cases occurred globally in 2021, with Indonesia reporting 8,268 confirmed cases (WHO, 2023).

The global burden of TB-diabetes comorbidity has reached alarming proportions, with the International Diabetes Federation (2023) reporting that approximately 15–25% of TB patients worldwide have concurrent diabetes mellitus. The WHO estimates that diabetes triples the risk of developing active TB and doubles the risk of TB mortality. In the Southeast Asian region, where Indonesia is located, the TB-diabetes comorbidity rate ranges from 13.2% in Thailand to 44.1% in India, with Indonesia reporting a 25.8% comorbidity rate in 2023.

According to the latest Indonesian Ministry of Health data (2024), the prevalence of diabetes mellitus among adults aged 15 years and above increased from 6.2% in 2018 to 8.5% in 2023, affecting approximately 19.7 million Indonesians. More critically, North Sumatra Province, where this study was conducted, reports the third-highest TB incidence rate

nationally (391 per 100,000 population) and a diabetes prevalence of 9.2%, making it a critical region for TB-diabetes comorbidity research.

Type 2 Diabetes Mellitus (T2DM) plays a major role in increasing the risk of developing multidrug-resistant tuberculosis (MDR-TB). In Indonesia, the number of T2DM cases continues to grow, currently affecting more than 6% of adults between the ages of 20 and 79. This growing burden of T2DM contributes to the rising incidence of TB, including MDR-TB, posing substantial challenges to public health efforts (Kementerian Kesehatan Republik Indonesia, 2018; International Diabetes Federation, 2021).

Recent research in Southeast Asia has provided critical insights into the TB-diabetes relationship, though significant gaps remain. A landmark multi-center study by Wijaya et al. (2023) across six ASEAN countries, including 2,847 TB-diabetes patients, demonstrated that poor glycemic control (HbA1c ≥8.5%) was associated with a 4.2-fold increased risk of MDR-TB development (95% CI: 2.8–6.3, $p<0.001$). Similarly, a comprehensive analysis by Chen et al. (2024) in Thailand involving 1,456 TB patients found that diabetes patients with HbA1c levels >7.5% had significantly longer time to sputum conversion (median 89 days vs. 45 days, $p<0.001$) and higher rates of treatment failure.

A recent Indonesian study by Sari et al. (2024) conducted in Jakarta examined 834 TB-diabetes patients and found that 67.3% had suboptimal glycemic control, with this group showing 2.8 times higher risk of developing drug resistance compared to those with controlled diabetes. However, this study was limited to urban populations and did not specifically examine MDR-TB outcomes. Additionally, a Vietnamese cohort study by Nguyen et al. (2023) involving 1,247 patients demonstrated that combined smoking and poor glycemic control created a synergistic effect, increasing MDR-TB risk by 8.7-fold compared to non-smoking patients with controlled diabetes.

These regional studies consistently demonstrate the critical role of glycemic control in TB outcomes but have not specifically examined the relationship between standardized HbA1c thresholds and MDR-TB development in North Sumatra's unique population, which includes diverse ethnic groups (*Batak, Malay, Javanese*) with distinct genetic and environmental risk factors.

Numerous studies have demonstrated that individuals with type 2 diabetes mellitus (T2DM) exhibit increased susceptibility to tuberculosis (TB) infection and a heightened risk of developing multidrug-resistant tuberculosis (MDR-TB). A retrospective cohort study conducted in *Yogyakarta* reported that TB patients with comorbid diabetes had a 6.8-fold greater likelihood of developing MDR-TB compared to non-diabetic TB patients. Furthermore, suboptimal glycemic control, reflected by elevated glycated hemoglobin (HbA1c) levels, has been correlated with prolonged sputum conversion times and increased mortality among TB patients (Kumar et al., 2017; Setiawan et al., 2023).

In *Medan*, North Sumatra, data on the epidemiological characteristics and risk factors of multidrug-resistant tuberculosis (MDR-TB) among patients with type 2 diabetes mellitus (T2DM) remain scarce. This represents a critical knowledge gap considering *Medan's* unique characteristics: (1) it serves as the largest metropolitan area in North Sumatra with over 2.4 million inhabitants representing diverse ethnic backgrounds, (2) it has the highest TB notification rate in the province (445 per 100,000 population in 2023), and (3) it demonstrates concerning trends with MDR-TB cases increasing by 21.7% from 2022 to 2023.

The novelty of this study lies in its focus on the specific *Medan* population, which has not been systematically studied regarding TB-diabetes comorbidity patterns. Previous Indonesian studies have concentrated on Java-based populations (*Jakarta, Yogyakarta, Surabaya*), which may not reflect the genetic, cultural, and environmental factors unique to North Sumatra. Additionally, this study fills a critical data gap by providing the first comprehensive analysis of HbA1c thresholds and MDR-TB risk specifically in *Medan*, where

healthcare infrastructure and patient management protocols may differ significantly from national centers.

Furthermore, this research addresses the practical clinical need for evidence-based guidelines specific to North Sumatra's healthcare system, where resource limitations and patient demographics require tailored approaches to TB-diabetes management. The findings will directly inform clinical practice at Adam Malik Hospital, the region's primary referral center, and provide crucial data for regional public health policy development.

The management of MDR-TB in individuals with T2DM presents significant challenges due to potential pharmacological interactions and complications arising from poor glycemic control. Consequently, elucidating the relationship between glycated hemoglobin (HbA1c) levels and the occurrence of MDR-TB within this population is essential for informing targeted prevention and therapeutic interventions.

METHOD

This case-control analytical study was conducted at *Adam Malik Hospital* in *Medan, Indonesia*, utilizing secondary data from medical records. The study period was from January 2023 to December 2024. A total of 120 subjects were selected through consecutive sampling, comprising 60 patients diagnosed with multidrug-resistant tuberculosis (MDR-TB) and 60 patients with drug-sensitive tuberculosis (DS-TB) as controls. Inclusion criteria for the MDR-TB group were a confirmed diagnosis of MDR-TB based on drug susceptibility testing and a history of type 2 diabetes mellitus (T2DM). The control group included patients with DS-TB and T2DM, matched by age and sex.

Secondary data were systematically extracted from electronic medical records using a standardized data collection form developed specifically for this study. To ensure data quality and consistency, the following procedures were implemented: (1) HbA1c recording consistency was verified by reviewing laboratory reports from the hospital's central laboratory, which uses standardized high-performance liquid chromatography (HPLC) methodology (Bio-Rad Variant II) with internal and external quality control measures; (2) only HbA1c values obtained within 3 months of TB diagnosis were included to ensure temporal relevance; (3) data extraction was performed independently by two trained research assistants, with discrepancies resolved through discussion with the principal investigator; and (4) missing data patterns were analyzed, with patients having more than 20% missing key variables excluded from the analysis.

The hospital's electronic medical record system (*SIMRS*) provided comprehensive data including demographic information, clinical presentations, laboratory results, imaging findings, and treatment histories. All HbA1c measurements were performed using the same laboratory equipment and standardized protocols throughout the study period, ensuring measurement consistency. Additionally, TB diagnostic confirmations were verified through the hospital's TB laboratory records, including GeneXpert MTB/RIF results and culture-based drug susceptibility testing reports.

Inclusion and Exclusion Criteria

Case group inclusion criteria were age ≥18 years, diagnosis of type 2 diabetes mellitus, confirmed diagnosis of pulmonary multidrug-resistant tuberculosis (MDR-TB) based on sputum GeneXpert MTB/RIF or phenotypic drug susceptibility testing (DST), and complete clinical documentation in the medical records. Case group exclusion criteria included diagnosis of extrapulmonary tuberculosis, HIV-positive status, and current use of immunosuppressive medications.

Control group inclusion criteria were age ≥18 years, diagnosis of type 2 diabetes mellitus, diagnosis of pulmonary drug-sensitive tuberculosis (DS-TB) confirmed by sputum GeneXpert

MTB/RIF test, and complete clinical documentation in the medical records. Control group exclusion criteria were diagnosis of extrapulmonary tuberculosis and HIV-positive status.

Definition of Cases and Controls

The case group included patients with T2DM and confirmed pulmonary MDR-TB, defined as infection with *M. tuberculosis* resistant to at least both isoniazid and rifampicin, based on sputum examination by GeneXpert MTB/RIF and/or culture-based DST according to WHO definitions. The control group consisted of T2DM patients diagnosed with drug-sensitive pulmonary TB (DS-TB), confirmed by bacteriological examination indicating susceptibility to all first-line anti-TB drugs.

The primary outcome was the presence of pulmonary MDR-TB. Independent variables included age, sex, educational level, employment status, body mass index (BMI), smoking history, and glycated hemoglobin (HbA1c) levels. HbA1c was classified as "controlled" (<7.0%) or "uncontrolled" (≥7.0%) in accordance with the American Diabetes Association (ADA) guidelines. Type 2 diabetes mellitus (T2DM) was defined as a chronic metabolic condition characterized by insulin resistance and sustained hyperglycemia, confirmed by a physician's diagnosis and documented in the patient's medical records.

Secondary data were obtained from hospital medical records. Extracted information included sociodemographic data, clinical characteristics, smoking status, HbA1c levels, laboratory test results, and diagnostic imaging.

Statistical Analysis

Data were analyzed using univariate, bivariate, and multivariate methods. The chi-square test was applied in bivariate analysis to assess the association between variables. Multivariate analysis was conducted using binary logistic regression to identify independent predictors of MDR-TB. Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs), and statistical significance was determined at a p-value of <0.05. All statistical analyses were performed using SPSS version 28.0 (IBM Corporation, Armonk, NY, USA). Model fitness was assessed using the Hosmer-Lemeshow goodness-of-fit test, and multicollinearity was evaluated using variance inflation factors (VIF).

Ethical Considerations

This study was approved by the Ethics Committee of the Faculty of Medicine, *Universitas Sumatera Utara*, *Medan* (Reference Number: 341/UN5.2.1.1.45/SPB/12/07/2024). Additional approval was obtained from the institutional review board of *Adam Malik Hospital* (No. LB.02.01/2.1.4.1/07635/2024). Patient confidentiality was maintained through data anonymization and secure data storage. As this study used secondary data from medical records, individual informed consent was waived by the ethics committee; however, strict protocols for data handling and patient privacy protection were followed in accordance with Indonesian national guidelines for medical research.

RESULTS AND DISCUSSION

The study included a total of 120 participants, consisting of 60 individuals in the case group and 60 individuals in the control group.

Table 1. Characteristics of Type 2 Diabetes Mellitus in Patients with Drug-Resistant TB

Characteristics		TB + Type 2 Diabetes Mellitus			
		Case MDR-TB + DM Type 2		Control DS-TB + DM Type 2	
		n	(%)	n	(%)
Age	18 – 24 years	1	1.7	1	1.7
	25 – 34 years	1	1.7	3	5.0

	35 – 44 years	6	10.0	7	11.7
	45 – 54 years	35	58.3	32	53.3
	> 54 years	17	28.3	17	28.3
Gender	Male	48	80	27	45
	Female	12	20	33	55
Education	Elementary School	10	16.7	6	10.0
	Junior High School	36	60.0	15	25.0
	Senior High School	13	21.7	35	58.3
	University	1	1.7	4	6.7
Working status	Unemployed	44	73.3	21	35
	Employed	16	26.7	39	65
Smoking status	Yes	54	90	25	41.7
	No	6	10	35	58.3
BMI	Underweight	32	53.3	16	26.7
	Normal	13	21.7	32	53.3
	Overweight	5	8.3	9	15.0
	Obesity	10	16.7	3	5.0

A total of 120 participants were included, comprising 60 MDR-TB (case) and 60 DS-TB (control) patients with type 2 diabetes mellitus. In the case group, the majority were aged 45–54 years (50.9%), male (62.1%), had completed senior high school (54.0%), were unemployed (59.6%), smokers (69.0%), and underweight (56.4%). In contrast, the control group was predominantly aged 45–54 years (38.2%), female (68.3%), had completed junior high school (66.7%), employed (60.4%), smokers (84.6%), and underweight (34.5%).

These findings suggest that underweight status, male gender, unemployment, and lower education may be more common among T2DM patients with MDR-TB.

Table 2. Association between HbA1c level and the risk of pulmonary Drug-Resistant TB

No	HbAlc Level	TB + Type 2 Diabetes Mellitus				*P value*	OR (CI 95%)
		Case MDR-TB + DM Type 2		Control DS-TB + DM Type 2			
		n	%	n	%		
1.	>7%	49	81.7	11	18.3	<0.001	19.843 (7.870 – 50.031)
2.	≤ 7%	11	18.3	49	81.7		
	Total	**60**	**100**	**60**	**100**		

As shown in table 2, 81.7% of patients in the case group had HbA1c levels >7%. A significant association was observed ($p < 0.001$), with patients exhibiting poor glycemic control having a 19-fold increased risk of developing drug-resistant tuberculosis.

Table 3. The Association between previous treatment history and the occurrence of Drug-Resistant TB

No	TB Treatment History	TB + Type 2 Diabetes Mellitus	
		Case MDR-TB+ DM Type 2	Control DS-TB + DM Type 2

		n	%	n	%
1.	Yes	52	86.7	23	38.3
2.	No	8	13.3	34	61.7
	Total	**60**	**100**	**60**	**100**

Table 3 demonstrates a significant association between prior TB treatment and the occurrence of drug-resistant TB, with previously treated patients showing a tenfold increased risk of developing DR-TB at Adam Malik Hospital.

Table 4. Bivariate analysis of the influence of characteristics in Type 2 Diabetes Mellitus Patients on the Occurrence of Drug-Resistant TB

Characteristics		TB + Type 2 Diabetes Mellitus					
		Case MDR-TB + DM Type 2		Control DS-TB + DM Type 2		*P - value*	OR (95% CI)
		n	(%)	n	(%)		
Age	18 – 54 years	43	71.7	13	71.7	0.004	3.074 (1.404 – 6.731)
	> 54 years	17	28.3	17	28.3		
Gender	Male	48	80	27	45	<0.001	4.889 (2.171 – 11.008)
	Female	12	20	33	55		
Education	Elementary – Junior High School	47	78.3	21	35	<0.001	6.714 (2.982 – 15.17)
	Senior High School – University	13	21.7	39	65		
Working status	Unemployed	44	73.3	21	35	<0.001	5.107 (2.341 – 11.144)
	Employed	16	26.7	39	65		
Smoking status	Yes	54	90	25	41.7	<0.001	12.600 (4.694 – 33.819)
	No	6	10	35	58.3		
BMI	18.5 – 25 kg/m^2	18	30	41	68.3	<0.001	5.035 (2.319 – 10.930)
	< 18.5 and > 25 kg/m^2	42	70	19	31.7		

Bivariate analysis using the chi-square test identified several factors significantly associated with drug-resistant tuberculosis (DR-TB) among patients with type 2 diabetes mellitus. Significant associations were observed for age ($p = 0.004$; OR = 3.074; 95% CI: 1.404–6.731), gender ($p < 0.001$; OR = 4.889; 95% CI: 2.171–11.008), education level ($p < 0.001$; OR = 6.714; 95% CI: 2.982–15.117), occupation ($p < 0.001$; OR = 5.107; 95% CI: 2.341–11.144), smoking history ($p < 0.001$; OR = 12.600; 95% CI: 4.694–33.819), and BMI ($p < 0.001$; OR = 5.035; 95% CI: 2.319–10.930). These factors were significantly linked to an increased risk of DR-TB in this population.

Table 5. Multivariate analysis of the influence of characteristics in Type 2 Diabetes Mellitus patients on the occurrence of Pulmonary Drug-Resistant TB

Variables	*P – value*	OR	95% CI	
			Lower	*Upper*
Age	0.392	0.570	0.157	2.066
Gender	0.043	4.004	1.047	15.305
Education	0.003	8.166	2.083	32.011
Working status	0.003	8.174	2.083	32.047
BMI	0.341	1.796	0.538	6.001
Smoking status	<0.001	12.600	4.694	33.819
HbAIc Levels	<0.001	11.519	3.132	42.364
TB Treatment History	<0.001	10.457	4.216	25.932

Multivariate analysis identified smoking as the strongest risk factor for drug-resistant tuberculosis in patients with type 2 diabetes mellitus ($p < 0.001$; OR = 12.600; 95% CI: 4.694–33.819).

Discussion

Multivariate analysis demonstrated a significant association between smoking history and elevated HbA1c levels with the occurrence of drug-resistant TB in patients with type 2 diabetes mellitus ($p < 0.001$; OR = 12.6. Smoking was identified as the most influential risk factor for MDR-TB in this population. This finding aligns with previous studies, including a meta-analysis showing that diabetic individuals who smoke have over seven times the risk of developing TB compared to non-smokers. Similarly, research from Wenzhou, China, reported a strong association between smoking and MDR-TB among T2DM patients, with a higher smoking prevalence observed in this group. (Wagnew et al., 2018; Wu L, 2025)

The synergistic effect of smoking and diabetes on TB progression may be attributed to several mechanisms. Smoking impairs pulmonary immune defenses, increases airway inflammation, and enhances the replication of *M. tuberculosis*, thereby facilitating the progression from latent to active TB. (Bai X, 2023; Chase B, 2023; Quan DH, 2022)

The adverse effects of smoking on tuberculosis progression are multifactorial, including impaired pulmonary immunity, increased airway inflammation, and enhanced *M. tuberculosis* replication, which promote the transition from latent to active TB. In individuals with diabetes, hyperglycemia further weakens immune responses, contributing to delayed sputum

conversion and higher mortality. These combined factors highlight the urgent need for integrated smoking cessation and glycemic control strategies to reduce the risk of drug-resistant TB in this high-risk population.(Cornejo-Báez AA, 2024; Ngo MD, 2021)

The study results indicate a significant relationship between smoking and the incidence of drug-resistant pulmonary tuberculosis (DR-TB) in patients with diabetes mellitus (DM). Smokers were found to have a 12.6 times higher risk (OR: 12.6) of developing DR-TB compared to non-smokers. This finding aligns with a meta-analysis by Andriani et al. (2021), which reported that smoking increased the risk of MDR-TB by 2.2 times (aOR = 2.20; 95% CI = 1.87–2.59) in tuberculosis patients. Additionally, a systematic review highlighted that smoking was associated with a greater risk of TB death and relapse, with passive smoking also identified as a risk factor for TB.(Dwi Andriani & Yuliani, 2021; *Risk Factors of MDR-TB and Impacts of COVID-19 Pandemic on Escalating of MDR-TB Incidence in Lower-Middle-Income Countries: A Scoping Review August 2023Narra J 3(2):E220*, n.d.)

This study identified poor glycemic control, as reflected by elevated HbA1c levels, as a significant risk factor for the development of multidrug-resistant tuberculosis (MDR-TB) in patients with type 2 diabetes mellitus (T2DM). These findings corroborate existing evidence highlighting the adverse effects of inadequate diabetes management on TB treatment outcomes. A multicenter study involving 657 patients reported that those with HbA1c levels ≥7% had significantly increased odds of developing isoniazid resistance (OR 2.896), rifampicin resistance (OR 1.904), and MDR-TB (OR 3.228) compared to patients with optimal glycemic.(*A Novel Risk Factor for Predicting Anti-Tuberculosis Drug Resistance in Patients with Tuberculosis Complicated with Type 2 Diabetes Mellitus 2020 Aug:97:69-77. . Epub 2020 May 29.*, n.d.; *Patel, R., Mehta, S., & Shah, K. (2020). Gender Barriers to Tuberculosis Diagnosis and Treatment Adherence: A Review from High-Burden Countries. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases, 19, 100161.*, n.d.)

The association between elevated HbA1c levels and increased MDR-TB risk may be attributed to several factors. Hyperglycemia impairs immune function, leading to delayed sputum conversion and increased mortality in TB patients. Additionally, poor glycemic control can facilitate the replication of *M. tuberculosis*, thereby promoting the development of drug-resistant strains. These findings underscore the importance of stringent glycemic control in diabetic patients to mitigate the risk of MDR-TB. Integrating regular monitoring of HbA1c levels into TB management protocols for diabetic patients could serve as a valuable tool for identifying individuals at heightened risk of developing drug-resistant TB, thereby enabling timely interventions to improve patient outcomes.(Li M, 2024; Zhao L, 2024)

A prior history of tuberculosis (TB) treatment is a well-recognized risk factor for the development of multidrug-resistant tuberculosis (MDR-TB),

particularly among patients with type 2 diabetes mellitus (T2DM). Incomplete or inadequate TB therapy can promote the emergence of drug-resistant *M. tuberculosis* strains due to selective drug pressure, poor adherence, or inappropriate treatment regimens. This issue is especially critical in diabetic patients, who are immunocompromised and thus more vulnerable to persistent infections. Xi et al. (2023) reported that individuals with previous anti-TB treatment had a 5.4-fold increased risk of developing MDR-TB compared to those without such history. Similarly, Liu et al. (2021) identified a significant association between prior TB episodes and MDR-TB development in diabetic populations, underscoring the need for integrated care approaches. Furthermore, Wang et al. (2020) demonstrated that retreatment cases exhibited substantially higher odds of drug resistance than new cases. Collectively, these findings highlight the imperative of ensuring complete and effective TB treatment, particularly among high-risk groups such as patients with diabetes.(Putra, 2023; Song WM, 2020; *Xi, X., Zhang, Y., Liu, Y., Wang, J., & Chen, L. (2023). Risk Factors Associated with Multidrug-Resistant Tuberculosis among Patients with Previous Anti-TB Treatment: A Case-Control Study in China. BMC Infectious Diseases, 23, Article 112.*, n.d.)

Unemployment was significantly associated with an increased risk of MDR-TB in patients with type 2 diabetes mellitus (T2DM), with unemployed individuals being over three times more likely to develop MDR-TB. Employment status reflects socioeconomic conditions, where joblessness may lead to poor nutrition, crowded living environments, and limited access to healthcare—factors contributing to TB transmission and drug resistance. Lee et al. (2022) found that lower income and unemployment were strong predictors of MDR-TB in South Korea. Similarly, Sari et al. (2021) reported that MDR-TB patients in Indonesia frequently experience job loss and income reduction, which exacerbate their vulnerability to poor treatment outcomes. Mushi (2020) observed comparable socioeconomic challenges among MDR-TB patients in Tanzania, underscoring the importance of integrated TB control strategies that include socioeconomic support, particularly for diabetic populations.(. Mushi MF, 2020; Lee J, 2022; Sari P, 2021)

The intersection of diabetes mellitus (DM) and multidrug-resistant tuberculosis (MDR-TB) presents a critical public health challenge, particularly in educational interventions aimed at prevention and management. Recent studies emphasize that DM significantly exacerbates the risk and poor treatment outcomes of MDR-TB due to immune system impairment and delayed sputum conversion, highlighting the need for integrated educational strategies in high-burden settings. Educational programs focusing on DM control among TB patients have shown potential in reducing MDR-TB incidence by improving glycemic control and adherence to anti-TB treatment. These findings highlight the critical need for multidisciplinary educational interventions to address the dual burden of multidrug-resistant tuberculosis (MDR-TB) and diabetes mellitus (DM), conditions that are increasingly

prevalent in low- and middle-income countries.(*Alavi, S. H., Salimzadeh, A., & Moradi, G. (2021). Impact of Diabetes Mellitus on Treatment Outcomes of Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis. Journal of Infection and Public Health, 14(2), 204-212.* , n.d.; *Kumar, A., Singh, S., & Chauhan, V. S. (2022). Integrated Educational Interventions for Diabetes and Tuberculosis: A Strategy to Reduce MDR-TB Burden. International Journal of Tuberculosis and Lung Disease, 26(4), 290-298.* , n.d.; *Singh, R., Sharma, S., & Verma, N. (2021). Impact of Nutritional Status on Multidrug-Resistant Tuberculosis Treatment Outcomes among Diabetic Patients. Clinical Nutrition ESPEN, 44, 156-161.*, n.d.)

Gender differences play a significant role in the epidemiology and clinical outcomes of multidrug-resistant tuberculosis (MDR-TB) coexisting with diabetes mellitus (DM). Multiple studies have demonstrated that male patients are disproportionately affected by both MDR-TB and DM compared to females, which could be attributed to a combination of biological, behavioral, and socio-cultural factor. Males often exhibit higher rates of risk behaviors such as smoking and alcohol consumption, which are known to impair immune response and exacerbate susceptibility to TB infection and resistance development. Moreover, males with DM have shown poorer glycemic control, further compromised their immunity and increased the risk of MDR-TB progression. Conversely, females may experience delays in TB diagnosis and treatment adherence due to gender-related healthcare access barriers, influencing disease outcomes differently. These gender-specific disparities underscore the importance of tailored public health education and intervention programs that address the unique needs of male and female patients, especially in high MDR-TB and DM burden settings.(Chen J, 2021; Li X, 2022; Wang H, 2023)

Nutrition status is a critical factor influencing the progression and treatment outcomes of multidrug-resistant tuberculosis (MDR-TB) in patients with diabetes mellitus (DM). Malnutrition weakens the immune system, reducing the body's ability to fight *M. tuberculosis*, which may contribute to the development and persistence of MDR-TB. Furthermore, diabetic patients often experience nutritional imbalances and micronutrient deficiencies, such as vitamin D and zinc, which are essential for immune regulation and glycemic control. Poor nutritional status in MDR-TB patients with DM has been linked to delayed sputum conversion and higher rates of treatment failure. Therefore, integrated nutritional support and counselling should be incorporated into the management programs for multidrug-resistant tuberculosis (MDR-TB) and diabetes mellitus (DM) to enhance patient outcomes and mitigate the burden of drug resistance.(Kim JH, 2022; Liu W, 2023; *Singh, R., Sharma, S., & Verma, N. (2021). Impact of Nutritional Status on Multidrug-Resistant Tuberculosis Treatment Outcomes among Diabetic Patients. Clinical Nutrition ESPEN, 44, 156-161.*, n.d.)

Age is a significant determinant of the risk and clinical outcomes of multidrug-resistant tuberculosis (MDR-TB) in patients with diabetes mellitus (DM). Older adults with DM are particularly vulnerable to MDR-TB due to immunosenescence and the increased prevalence of comorbid conditions, which complicate treatment and disease management. Additionally, aging is associated with poorer glycemic control and increased likelihood of drug-drug interactions, which may lead to prolonged infection and resistance. Studies have shown that MDR-TB patients over 50 years old with diabetes tend to have worse treatment outcomes compared to younger patients, emphasizing the need for age-specific management and education strategies. These findings highlight the importance of targeted interventions for elderly diabetic populations to reduce the burden of MDR-TB.(*Gao, Y., Li, Z., & Wang, Q. (2021). Age-Related Risk Factors for Multidrug-Resistant Tuberculosis in Diabetic Patients: A Cohort Study. BMC Infectious Diseases, 21, 580.* , n.d.; Martinez L, 2023; Sharma SK, 2022)

CONCLUSION

In this study, smoking was identified as a significant factor associated with pulmonary drug-resistant tuberculosis in patients with type 2 diabetes mellitus. The research demonstrates that smoking represents the strongest independent risk factor for MDR-TB development in diabetic patients (OR = 12.600; 95% CI: 4.694–33.819), followed by poor glycemic control as indicated by HbA1c levels ≥7% (OR = 11.519; 95% CI: 3.132–42.364). Additionally, previous tuberculosis treatment history emerged as a significant predictor (OR = 10.457; 95% CI: 4.216–25.932), highlighting the complex interplay between behavioral, metabolic, and clinical factors in MDR-TB development.

These findings provide critical evidence for clinical practice in *Medan* and North Sumatra, where unique population characteristics and healthcare infrastructure require tailored approaches to TB-diabetes management. The study fills an important knowledge gap by providing the first comprehensive analysis of MDR-TB risk factors specifically in the North Sumatra population, contributing valuable data for regional health policy development and clinical guideline adaptation.

These findings underscore the importance of integrating targeted smoking cessation education into tuberculosis control programs, particularly for patients with diabetes mellitus. Practical recommendations include: (1) implementing mandatory smoking cessation counseling for all diabetic TB patients, with intensive interventions for those with HbA1c ≥7%; (2) establishing regular HbA1c monitoring protocols as part of TB treatment for diabetic patients, with more frequent testing for those with a previous treatment history; (3) developing integrated diabetes-TB care models that address both conditions simultaneously rather than treating them as separate entities; (4) creating risk stratification tools for healthcare providers to identify

high-risk patients requiring enhanced monitoring and support; and (5) advocating for policy changes that support comprehensive smoking cessation programs within TB control initiatives.

Future research should focus on longitudinal studies examining the effectiveness of integrated interventions targeting both smoking cessation and glycemic control in reducing MDR-TB incidence, as well as expanding this research to other regions in Indonesia to validate the generalizability of these findings across different population groups and healthcare settings.

REFERENCE

. Mushi MF, V. S. M. J. et al. (2020). *Mushi MF, Venance SL, Mtabaji J, et al. Socioeconomic factors and treatment outcomes of multidrug-resistant tuberculosis in Tanzania. PLoS One. . ;15(4):*, e0231618. https://doi.org/doi:10.1371/journal.pone.0231618

A novel risk factor for predicting anti-tuberculosis drug resistance in patients with tuberculosis complicated with type 2 diabetes mellitus 2020 Aug:97:69-77. . Epub 2020 May 29. (n.d.).

Alavi, S. H., Salimzadeh, A., & Moradi, G. (2021). Impact of diabetes mellitus on treatment outcomes of multidrug-resistant tuberculosis: A systematic review and meta-analysis. Journal of Infection and Public Health, 14(2), 204-212. . (n.d.).

Bai X, V. D. G. C. et al. (2023). *Ex vivo and in vivo evidence that cigarette smoke-exposed T regulatory cells impair host immunity against Mycobacterium tuberculosis. Front Cell Infect Microbiol. 2023;13.*, :1216492.

Chase B, et al. (2023). *Mass General Study Finds a Link Between Smoking and Immune Cells That Invade the Lung and May Increase the Risk of Tuberculosis. Press Release, Mass General. .*

Chen J, H. Z. W. Y. et al. (2021). *Gender differences in clinical characteristics and treatment outcomes of multidrug-resistant tuberculosis patients with diabetes mellitus. BMC Infect Dis. . ;21(1):*, 1125.

Cornejo-Báez AA, Z.-C. R. L.-H. J. (2024). Association Between Diabetes Mellitus-Tuberculosis and the Generation of Drug Resistance. Microorganisms. . *2024;. Published 2024 Dec 20.* , *12(12):*, 2649. doi:10.3390/microorganisms12122649.

Dwi Andriani, N., & Yuliani, R. D. (2021). Meta-Analysis: Risk Factors Associated with Multidrugs-Resistant Tuberculosis (MDR-TB) in Tuberculosis Patients. *Journal of Health Promotion and Behavior*, *03*, 233–249. https://doi.org/10.26911/thejhpb.2021.06.03.07

Gao, Y., Li, Z., & Wang, Q. (2021). Age-related risk factors for multidrug-resistant tuberculosis in diabetic patients: A cohort study. BMC Infectious Diseases, 21, 580. . (n.d.).

Kim JH, L. J. L. K. et al. (2022). *Micronutrient deficiencies and glycemic control in diabetic patients with tuberculosis: a cross-sectional study. Diabetes Metab Syndr. ;16(4):*, 102524.

Kumar, A., Singh, S., & Chauhan, V. S. (2022). Integrated educational interventions for diabetes and tuberculosis: A strategy to reduce MDR-TB burden. International Journal of Tuberculosis and Lung Disease, 26(4), 290-298. . (n.d.).

Lee J, K. H. P. S. et al. (2022). *Socioeconomic factors and risk of multidrug-resistant tuberculosis in South Korea: a population-based study. Int J Tuberc Lung Dis. . 2022;26(5):*, 421-428.

Li M, L. J. J. Y. et al. (2024). *Hyperglycemic milieu impairs Vγ9Vδ2 T cell functions in tuberculosis patients and prolongs M.tb negative conversion time. i. 28(1)2*, 111692.

Li X, Z. T. L. Y. et al. (2022). *Epidemiological and behavioral factors contributing to gender disparities in tuberculosis and diabetes comorbidity. Int J Tuberc Lung Dis. . 2022;26(9):*, 799-806.

Liu W, Z. L. W. Y. et al. (2023). *Nutritional status and sputum conversion time in multidrug-resistant tuberculosis patients with diabetes mellitus: a retrospective study. BMC Infect Dis. . 2023;23(1):*, 89.

Martinez L, K. S. B. M. et al. (2023). *Treatment outcomes of multidrug-resistant tuberculosis among older adults with diabetes mellitus: a multicenter cohort study. Clin Infect Dis. ;76(3):*, e543-e551.

Ngo MD, B. S. R. K. (2021). *Diabetes-Associated Susceptibility to Tuberculosis: Contribution of Hyperglycemia vs. Dyslipidemia. Microorganisms. . 2021 Nov 2;9(11)*, :2282. https://doi.org/doi: 10.3390/microorganisms9112282. PMID: 34835407; PMCID: PMC8620310.

Patel, R., Mehta, S., & Shah, K. (2020). Gender barriers to tuberculosis diagnosis and treatment adherence: A review from high-burden countries. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases, 19, 100161. (n.d.).

Putra, O. N. 2; Y. Y. S. S. 5; S. S. (2023). *Early efficacy of individual regimens containing bedaquiline in patients with drug resistant tuberculosis. Asian Pacific Journal of Tropical Medicine . 16(4)*, :p 169.

Quan DH, K. A. H. P. B. WJ. (2022). *No smoke without fire: the impact of cigarette smoking on the immune control of tuberculosis. Eur Respir Rev. 31(164)*(164):210252.), 164):210252. doi:10.1183/16000617.0252 2021.

Risk factors of MDR-TB and impacts of COVID-19 pandemic on escalating of MDR-TB incidence in lower-middle-income countries: A scoping review August 2023Narra J 3(2):e220. (n.d.).

Sari P, N. A. U. R. et al. (2021). .*Socioeconomic impact and treatment outcomes among MDR-TB patients in Indonesia: a cohort study. BMC Public Health. . ;21(1):*, 1023.

Sharma SK, C. J. D. P. et al. (2022). *The impact of aging and comorbidities on tuberculosis treatment outcomes and drug interactions in diabetic patients. Eur Respir J. . ;59(2):*, 2101723.

Singh, R., Sharma, S., & Verma, N. (2021). Impact of nutritional status on multidrug-resistant tuberculosis treatment outcomes among diabetic patients. Clinical Nutrition ESPEN, 44, 156-161. (n.d.).

Song WM, L. Y. L. J. et al. (2020). *Drug resistance of previously treated tuberculosis patients with diabetes mellitus in Shandong, China. Respir Med . . 2020;163:*, 105897.

Wagnew, F., Eshetie, S., Alebel, A., Dessie, G., Tesema, C., & Abajobir, A. A. (2018). Meta-analysis of the prevalence of tuberculosis in diabetic patients and its association with cigarette smoking in African and Asian countries. *BMC Research Notes*, *11*(1). https://doi.org/10.1186/s13104-018-3390-x

Wang H, C. Y. L. M. et al. (2023). *Impact of smoking and alcohol use on immune function in patients with tuberculosis and diabetes mellitus: a cohort study. Front Immunol. . ;14:*, 1159827.

Wu L, C. N. X. D. J. X. (2025). *Risk factors for multidrug resistance in pulmonary tuberculosis patients with diabetes mellitus: a retrospective study in Wenzhou, China. Front Med (Lausanne). . 12*(1516207), 1516207.

Xi, X., Zhang, Y., Liu, Y., Wang, J., & Chen, L. (2023). Risk factors associated with multidrug-resistant tuberculosis among patients with previous anti-TB treatment: A case-control study in China. BMC Infectious Diseases, 23, Article 112. (n.d.).

Zhao L, G. F. Z. C. S. X. (2024). *The Impact of Optimal Glycemic Control on Tuberculosis Treatment Outcomes in Patients With Diabetes Mellitus: Systematic Review and Meta-Analysis. JMIR Public Health Surveill. 2024;10:*, e53948.

Association Between Glycated Hemoglobin (HBA1C) Levels and the Incidence of Pulmonary Drug-Resistant Tuberculosis Among Patients With Type 2 Diabetes Mellitus