A Prospective Study on Treatment Outcome Among Tuberculosis Patients With Diabetes Mellitus

Raghavendra F.N.[1], Sowmya G.R.[2]

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Abstract

Introduction: Tuberculosis (TB) remains a significant global health challenge, causing substantial morbidity and mortality, particularly in low- and middle-income countries (LMICs). Despite global efforts to control and eliminate TB, the disease continues to affect millions, with an estimated 10 million new cases and 1.5 million deaths reported in 2019 alone. The burden of TB is further complicated by the increasing prevalence of diabetes mellitus (DM), a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.

Material and Method: This study was a prospective, non-interventional and observational study was carried out in the Department of General Medicine at Ballari Medical College and Research Centre, Ballari. The source of data for this study comprised tuberculosis (TB) patients with known diabetes mellitus (DM) and newly diagnosed diabetes mellitus visiting the TB Cell Hospital. Confirmed pulmonary tuberculosis as evidenced by either sputum for Acid-Fast Bacilli (AFB), Cartridge-Based Nucleic Acid Amplification Test (CBNAAT), or radiological investigations.

Result: A vast majority of the participants (91.0%, 131 participants) had negative sputum status, while 9.0% (13 participants) did not have their sputum status reported. No participants had positive sputum status at the end of treatment. The p-value of < 0.001 suggests a highly statistically significant difference in sputum status at the end of treatment. The majority of the participants (91.0%, 131 participants) were cured, while 9.0% (13 participants) died. The p-value of 0.006 indicates a statistically significant difference in treatment outcomes. In this study, participants who were cured had lower mean FBS (135.4 ± 33.7 mg/dL), PPBS (206.9 ± 46.8 mg/dL), and median HbA1c (6.5%) at baseline compared to those who were not cured (FBS: 174.9 ± 46.5 mg/dL, PPBS: 252.2 ± 62.9 mg/dL, HbA1c (7.8%, IQR: 7.2 - 8.6%).

Conclusion: This study provides valuable insights into the factors influencing treatment outcomes in patients with TB-DM comorbidity and underscores the need for personalized management strategies, routine DM screening, and appropriate treatment modalities to improve outcomes in this vulnerable population. Future research should focus on developing and evaluating targeted interventions to optimize treatment outcomes and reduce mortality in patients with TB-DM comorbidity.

Keywords: Tuberculosis, Diabetes mellitus, Acid-Fast Bacilli.

Author's Affiliation: [1]Professor, [2]Postgraduate, Department of General Medicine, Ballari Medical College and Research Centre, Ballari, Karnataka 58310, India.

Corresponding Author: Sowmya G.R., Postgraduate, Department of General Medicine, Ballari Medical College and Research Centre, Ballari, Karnataka 58310, India.

E-mail: sowmyagr27@gmail.com

INTRODUCTION

Significant morbidity and death are caused by tuberculosis (TB), which continues to be a major worldwide health concern, especially in low- and middle-income countries (LMICs). An estimated 10 million new cases and 1.5 million deaths from tuberculosis were recorded in 2019 alone, despite international efforts to manage and eradicate the illness.[1] The rising incidence of diabetes mellitus (DM), a chronic metabolic disease marked by hyperglycemia brought on by abnormalities in insulin production, action, or both, exacerbates the burden of tuberculosis.[2] TB-DM comorbidity, the co-occurrence of TB and DM, presents a special therapeutic difficulty since both conditions negatively impact one another, which results in less favorable treatment outcomes.[3]

For many years, it has been known that TB and DM interact, and historical evidence suggests that people with DM are more likely to have TB than people without DM.[4] Chronic hyperglycemia's immunosuppressive effects, which weaken the host's immunological response to Mycobacterium tuberculosis (Mtb) infection, are thought to be the cause of this connection. It has been demonstrated that hyperglycemia changes the activity of macrophages, lowers T-cell responses, and hinders the synthesis of cytokines and chemokines that are necessary for efficient immune responses against Mtb[5]. As a result, people with diabetes mellitus are more vulnerable to developing primary TB infection, latent TB reactivation, and more severe TB infections, such as multidrug-resistant TB (MDR-TB).[6]

Furthermore, because of its effects on insulin resistance and glucose metabolism, TB might make it more difficult to control diabetes mellitus by causing a hyperglycemic condition.[7] Pro-inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are elevated in the inflammatory response to Mtb infection. These cytokines disrupt insulin signaling pathways and encourage insulin resistance.[8] Additionally, by accelerating the metabolism of insulin and oral hypoglycemic medications, TB treatment itself, especially when combined with rifampicin, a strong inducer of hepatic enzymes, can impact glycemic control.[9]

A thorough and interdisciplinary strategy is necessary to handle TB-DM comorbidity because of the reciprocal link between TB and DM. This entails treating both illnesses as soon as possible,

checking blood sugar levels often, and modifying anti-TB and antidiabetic medications as required. According to studies, TB patients with diabetes mellitus have greater rates of treatment failure and recurrence, delayed sputum culture conversion, and higher mortality rates than TB patients without diabetes mellitus[10,11]. These unfavorable results highlight the necessity of individualized treatment plans and careful monitoring in order to enhance the prognosis of patients with TB-DM.

MATERIAL AND METHOD

The study was carried out in the Department of General Medicine at Ballari Medical College And Research Centre, Ballari.

Inclusion Criteria

Participants were included in the study if they met the following criteria:

1. Confirmed pulmonary tuberculosis as evidenced by either sputum for Acid-Fast Bacilli (AFB), Cartridge-Based Nucleic Acid Amplification Test (CBNAAT), or radiological investigations.
2. Age above 18 years.
3. Diagnosed with diabetes mellitus or newly diagnosed during the study.

Exclusion Criteria

Participants were excluded from the study based on the following criteria:

1. Age below 18 years.
2. Diagnosed TB patients with HIV positive status, liver diseases, renal diseases, pulmonary diseases, or any other underlying comorbidities.
3. Patients with extrapulmonary tuberculosis.
4. Pregnant women and women in the postpartum period less than six weeks from delivery.

METHODOLOGY

1. **Patient Enrolment:**
   - Patients fulfilling the inclusion criteria were enrolled in the study after obtaining informed consent.
   - Demographic data, medical history, and clinical examination findings were recorded.

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- Patients were screened for diabetes via Random Blood Sugar (RBS > 200 mg/dl) and subjected to further investigations including Fasting Blood Sugar (FBS > 126 mg/dl), Postprandial Blood Sugar (PPBS > 200 mg/dl), and Hemoglobin A1c (HbA1c > 6.5%) based on criteria referenced from Harrison's Principles of Internal Medicine.

2. **Measurement of Glucose Concentration:**
   - All patients underwent fasting blood glucose testing at the initiation of TB treatment. Values above 126 mg/dl were considered abnormal.
   - A 2-hour plasma glucose sample was collected after a 75-gram Oral Glucose Tolerance Test (OGTT). Values above or equal to 200 mg/dl were considered for further HbA1c measurement and HbA1c >6.5% included in the study.

3. **Follow-Up:**
   - Symptoms at the time of presentation were recorded.
   - Mycobacterial load was assessed, and sputum studies were performed at 2 months and at the end of treatment.

- Monitoring of blood sugar levels was done two monthly, and patients were regularly followed up to observe the outcome on an inpatient or outpatient basis as recorded in the study proforma.

RESULTS

Table 1: Tb Diagnostic Methods Used in the Study Participants

TB Diagnostic Method	Frequency (%)	P-value
Sputum AFB	58 (40.3%)	
Sputum CBNAAT	45 (31.3%)	0.002
Chest X-ray	22 (15.2%)	
Sputum TRUNAT	19 (13.2%)	

Sputum AFB was the most commonly used TB diagnostic method (40.3%), followed by Sputum CBNAAT (31.3%), Chest X-ray (15.2%), and Sputum TRUNAT (13.2%), with a statistically significant difference (p=0.002) in the utilization of these diagnostic methods among the study participants.
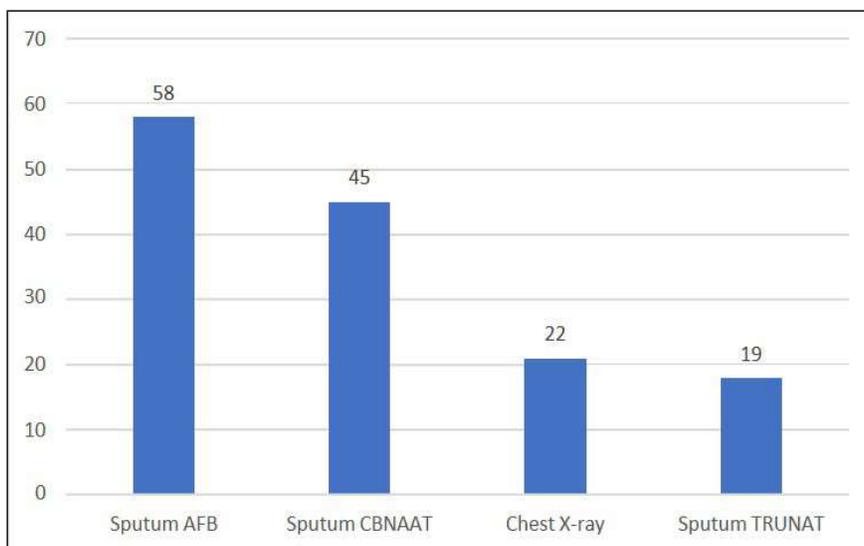

Fig. 1: Bar diagram showing TB diagnostic methods used in the study participants

Table 2: Sputum Status at the End of Treatment of Study Participants

Sputum Status	Frequency (%)	P-value
Negative	131 (91.0%)	
Positive	0 (0.0%)	< 0.001
Not reported	13 (9.0%)	

Table 2 displays the sputum status at the end of treatment. A vast majority of the participants (91.0%, 131 participants) had negative sputum status, while 9.0% (13 participants) did not have their sputum status reported. No participants had positive sputum status at the end of treatment. The p-value of <0.001 suggests a highly statistically significant difference in sputum status at the end of treatment
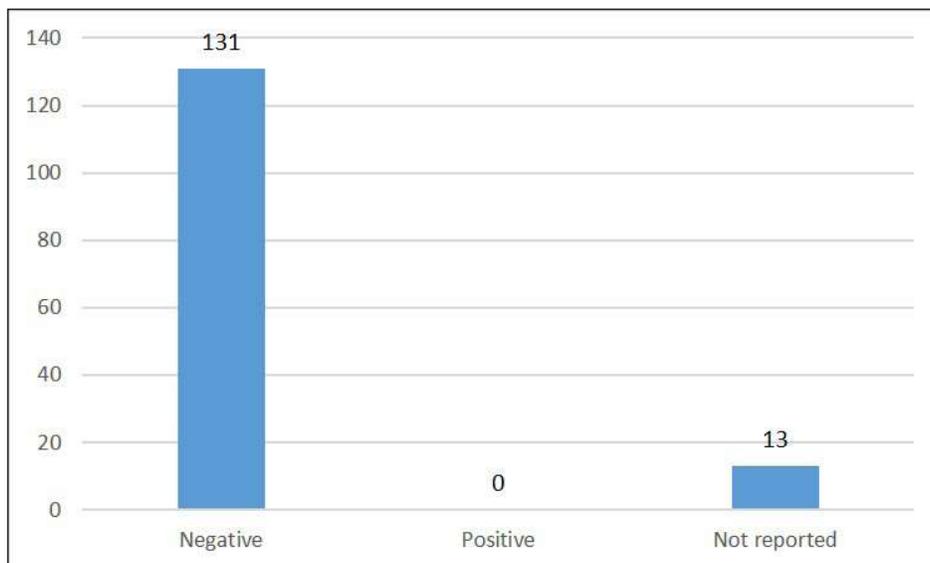

Fig. 2: Bar diagram showing sputum status at the end of the treatment of study participants

Table 3: Treatment Outcomes of Study Participants

Treatment Outcome	Frequency (%)	P-value
Cured	131 (91.0%)	0.006
Died	13 (9.0%)	

Table 3 represents the treatment outcomes. The majority of the participants (91.0%, 131 participants) were cured, while 9.0% (13 participants) died. The p-value of 0.006 indicates a statistically significant difference in treatment outcomes
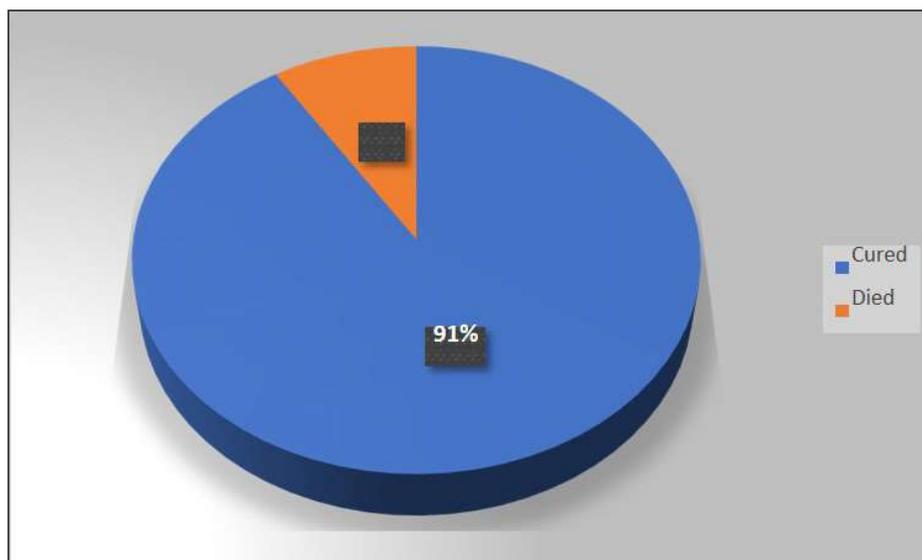

Fig. 3: Pie Chart showing treatment outcomes of study participants

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Table 4: Association Between Glycemic Control and Treatment Outcomes

Glycemic Control Parameter	Cured (Mean ± SD)	Not Cured (Mean ± SD)	Odds Ratio (95% CI)	P-Value
FBS at Baseline (mg/dL)	135.4 ± 33.7	174.9 ± 46.5	0.82 (0.68 - 0.98)	0.032
PPBS at Baseline (mg/dL)	206.9 ± 46.8	252.2 ± 62.9	0.76 (0.62 - 0.94)	0.011
HbA1c at Baseline (%)	6.5 (5.9 - 7.2)*	7.8 (7.2 - 8.6)*	0.68 (0.52 - 0.89)	0.005

In this study, participants who were cured had lower mean FBS (135.4 ± 33.7 mg/dL), PPBS (206.9 ± 46.8 mg/dL), and median HbA1c (6.5%, IQR: 5.9 - 7.2%) at baseline compared to those who were not cured (FBS: 174.9 ± 46.5 mg/dL, PPBS: 252.2 ± 62.9 mg/dL, HbA1c(7.8%, IQR: 7.2 - 8.6%). The odds ratios and p-values (FBS: OR = 0.82, p = 0.032; PPBS: OR = 0.76, p = 0.011; HbA1c: OR = 0.68, p = 0.005) suggest that better glycemic control at baseline was significantly associated with improved treatment outcomes.
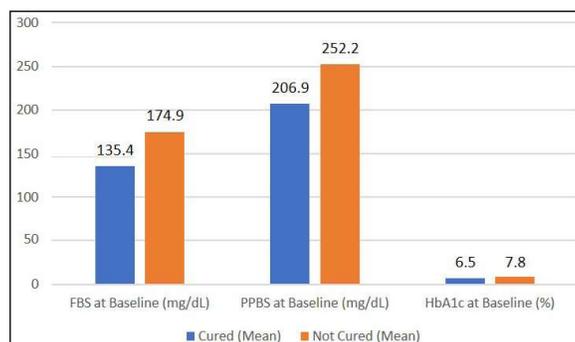

Fig. 4: Bar diagram showing association between glycemic control and treatment outcomes

Table 5: Treatment Outcomes of Age Groups Among Study Participants

Age Group	Cured (%)	Died (%)	P-value
< 30 years	6 (100%)	0 (0%)	
30-49 years	51 (94.4%)	3 (5.6%)	
50-69 years	66 (91.7%)	6 (8.3%)	0.042
≥ 70 years	8 (66.7%)	4 (33.3%)	

Table 5 displays the treatment outcomes by age groups. The highest cure rate was observed in the <30 years age group (100%, 6 participants), followed by the 30-49 years age group (94.4%, 51 participants), the 50-69 years age group (91.7%, 66 participants), and the ≥ 70 years age group (66.7%, 8 participants). The mortality rate was highest in the ≥ 70 years age group (33.3%, 4 participants). The p-value of 0.042 indicates a statistically significant difference in treatment outcomes across age groups
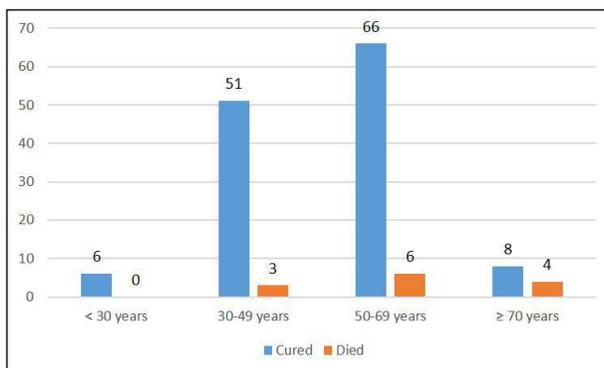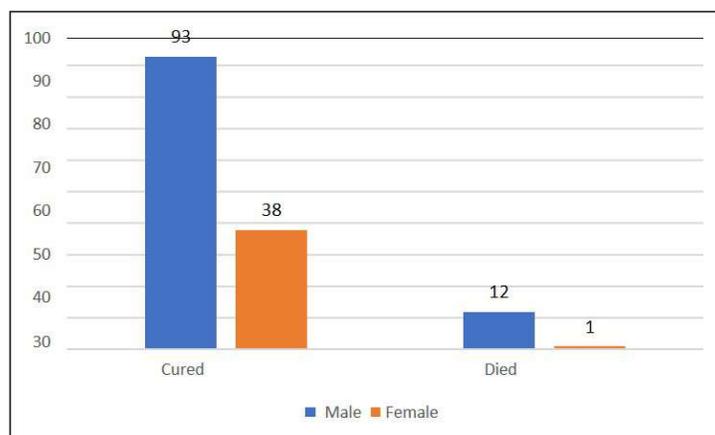

Fig. 5: Bar diagram showing treatment outcomes of age groups among study participants

Table 6: Treatment Outcomes of Gender Among Study Participants

Gender	Cured (%)	Died (%)	P-value
Male	93 (88.6%)	12 (11.4%)	
Female	38 (97.4%)	1 (2.6%)	0.623

Table 6, shows the treatment outcomes by gender. Females had a higher cure rate (97.4%, 38 participants) and a lower mortality rate (2.6%, 1 participant) compared to males (88.6% cured, 93 participants; 11.4% died, 12 participants). However, the p-value of 0.623 suggests that the difference in treatment outcomes between genders was not statistically significant.

Fig. 6: Bar diagram showing treatment outcomes of gender among study participants

Table 7: Treatment Outcomes of Bmi Categories Among Study Participants

BMI Category	Cured (%)	Died (%)	P-value
Underweight	24 (80.0%)	6 (20.0%)	
Normal	84 (94.3%)	5 (5.6%)	
Overweight	21 (91.3%)	2 (8.7%)	0.032
Obese	2 (100%)	0 (0%)	

Table 7, presents the treatment outcomes by BMI categories. The cure rate was highest in the obese category (100%, 2 participants), followed by the normal weight category (94.3%, 84 participants), the overweight category (91.3%, 21 participants), and the underweight category (80.0%, 24 participants). The mortality rate was highest in the underweight category (20.0%, 6 participants). The p-value of 0.032 indicates that the difference in treatment outcomes across BMI categories was statistically significant. The median BMI was 21.4 kg/m², with an interquartile range (IQR) of 18.6 - 24.5 kg/m².
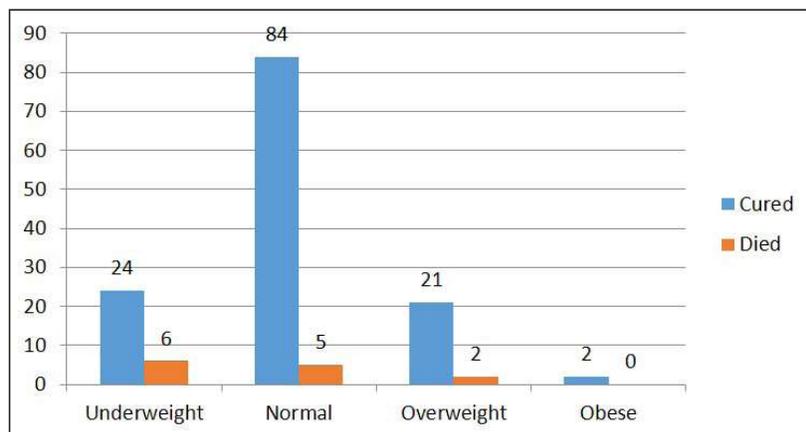

Fig. 7: Bar diagram showing treatment outcomes of BMI categories among study participants

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Table 8: Treatment Outcomes of Smoking Among Study Participants

Smoking Status	Cured (%)	Died (%)	P-value
Smoker	42 (82.4%)	9 (17.6%)	0.032
Non-smoker	89 (95.7%)	4 (4.3%)	

Table 8 displays the treatment outcomes by smoking status. Non-smokers had a higher cure rate (95.7%, 89 participants) and a lower mortality rate (4.3%, 4 participants) compared to smokers (82.4% cured, 42 participants; 17.6% died, 9 participants). The p-value of 0.032 suggests a statistically significant difference in treatment outcomes between smokers and non-smokers.
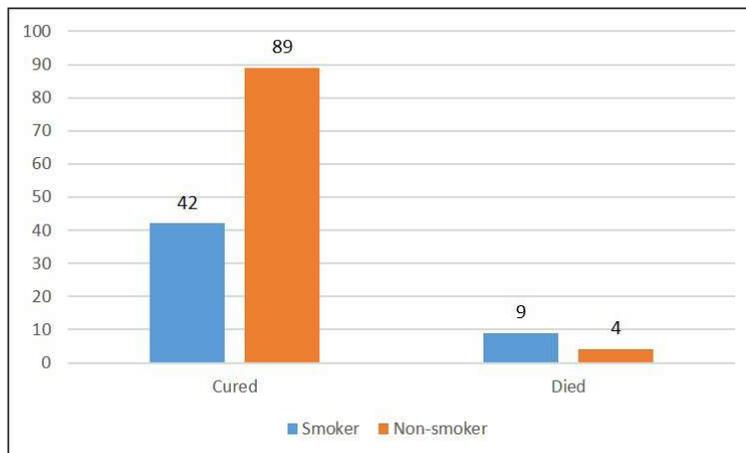

Fig. 8: Bar diagram showing treatment outcomes of smoking among study participants

Table 9: Treatment Outcomes of Alcohol Consumption Among Study Participants

Alcohol Consumption	Cured (%)	Died (%)	P-value
Consumer	36 (80.0%)	9 (20.0%)	0.011
Non-consumer	95 (96.0%)	4 (4.0%)	

Table 2.9 shows the treatment outcomes by alcohol consumption. Non-consumers had a higher cure rate (96.0%, 95 participants) and a lower mortality rate (4.0%, 4 participants) compared to consumers (80.0% cured, 36 participants; 20.0% died, 9 participants). The p- value of 0.011 indicates a statistically significant difference in treatment outcomes between alcohol consumers and non-consumers.
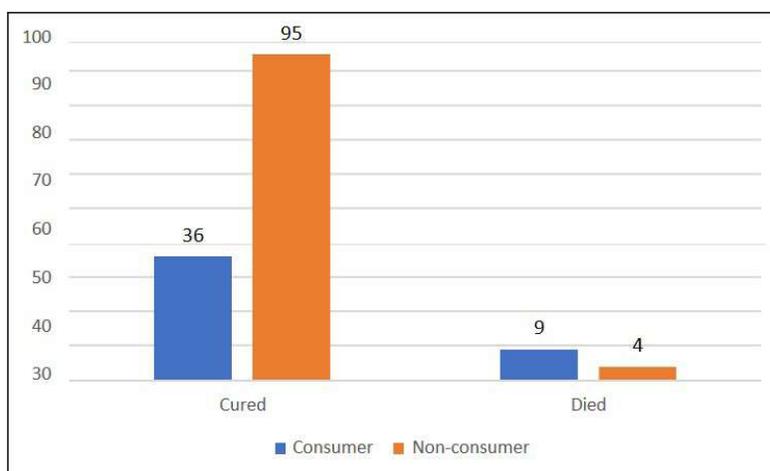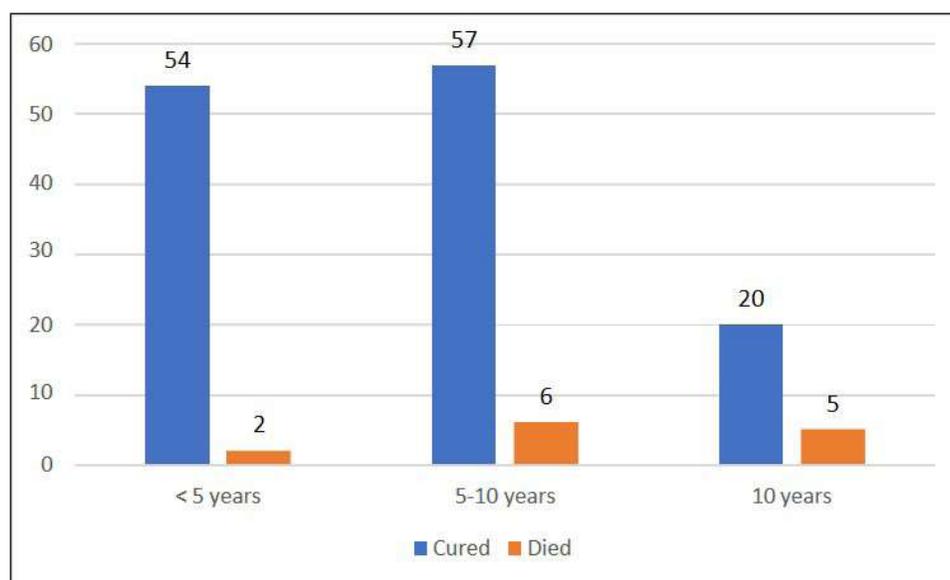

Fig. 9: Bar diagram showing treatment outcomes of alcohol consumption among study participants

Table 10: Treatment Outcomes of Diabetes Duration Among Study Participants

Diabetes Duration	Cured (%)	Died (%)	P-value
< 5 years	54 (96.4%)	2 (3.6%)	
5-10 years	57 (90.5%)	6 (9.5%)	0.048
> 10 years	20 (80.0%)	5 (20.0%)	

Table 10 presents the treatment outcomes by diabetes duration. The cure rate was highest in the < 5 years duration group (96.4%, 54 participants), followed by the 5-10 years duration group (90.5%, 57 participants), and the > 10 years duration group (80.0%, 20 participants). The mortality rate was highest in the > 10 years duration group (20.0%, 5 participants). The p-value of 0.048 suggests a statistically significant difference in treatment outcomes across diabetes duration categories.

Fig. 10: Bar diagram showing treatment outcomes of diabetes duration among study participants

DISCUSSION

The present study investigated the treatment outcomes of tuberculosis among patients with diabetes mellitus and analyzed the factors associated with these outcomes. The findings of this study highlight the importance of considering various demographic, clinical, and lifestyle factors when managing TB-DM comorbidity.

Age was found to be a significant factor in treatment outcomes, with the highest cure rate observed in the youngest age group (< 30 years) and the lowest in the oldest age group (≥ 70 years). This finding is consistent with previous studies that have reported age as a significant predictor of TB treatment outcomes. A meta-analysis by Huangfu *et al*. (2019) found that older age was associated with an increased risk of adverse treatment outcomes in TB patients (OR = 1.56, 95% CI: 1.23-1.98).[12]

Similarly, a study by Nhamoyebonde and Leslie (2014) reported that older age was associated with a higher risk of TB treatment failure and mortality (p < 0.001).[13] The increased risk of adverse outcomes in older patients may be attributed to a decline in immune function, a higher prevalence of comorbidities, and potential drug interactions.

Gender was not found to be significantly associated with treatment outcomes in the present study (p = 0.623). This finding contrasts with some previous studies that have reported gender differences in TB treatment outcomes. For example, a systematic review by Horton *et al*. (2016) found that male patients had a higher risk of unsuccessful treatment outcomes compared to females (OR = 1.19, 95% CI: 1.07-1.32).[14] However, the lack of a significant association between gender and treatment outcomes in the present study is consistent with the findings of a meta-analysis by Feng *et al*. (2012), which reported no significant difference in treatment success rates between male

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and female TB patients (OR = 1.03, 95% CI: 0.93-1.14).[15]

BMI was significantly associated with treatment outcomes in the present study (p = 0.032). The underweight category had the lowest cure rate (80.0%) and the highest mortality rate (20.0%) compared to other BMI categories. This finding is in line with previous studies that have reported a higher risk of adverse treatment outcomes in underweight TB patients. A meta-analysis by Lai *et al.* (2017) found that underweight BMI was associated with an increased risk of TB treatment failure (OR = 1.66, 95% CI: 1.16-2.37) and mortality (OR = 2.45, 95% CI: 1.75-3.44) compared to normal BMI.[16]

Smoking status was significantly associated with treatment outcomes in the present study (p= 0.032), with smokers having a lower cure rate (82.4%) and a higher mortality rate (17.6%) compared to non-smokers (95.7% cured, 4.3% died). This finding is consistent with previous studies that have reported smoking as a risk factor for adverse TB treatment outcomes. A meta-analysis by Alavi-Naini *et al.* (2013) found that smoking was associated with an increased risk of TB treatment failure (OR = 1.69, 95% CI: 1.16-2.46) and mortality (OR = 1.56, 95% CI: 1.23-1.98). [17] The negative impact of smoking on TB treatment outcomes may be attributed to the immunosuppressive effects of tobacco smoke, reduced lung function, and potential drug interactions.

Alcohol consumption was also significantly associated with treatment outcomes in the present study (p = 0.011), with consumers having a lower cure rate (80.0%) and a higher mortality rate (20.0%) compared to non-consumers (96.0% cured, 4.0% died). This finding is in agreement with previous studies that have reported alcohol consumption as a risk factor for adverse TB treatment outcomes. A systematic review by Imtiaz *et al.* (2017) found that alcohol use disorder was associated with an increased risk of TB treatment default (RR = 2.00, 95% CI: 1.70-2.35) and mortality (RR = 1.63, 95% CI: 1.27-2.08).[18]

Diabetes duration was significantly associated with treatment outcomes in the present study (p = 0.048), with the highest cure rate observed in the < 5 years duration group (96.4%) and the lowest in the > 10 years duration group (80.0%). This finding is consistent with previous studies that have reported a longer duration of diabetes as a risk factor for adverse TB treatment outcomes. A study by Viswanathan *et al.* (2014) found that patients with a diabetes duration of > 10 years had a higher risk of TB treatment failure (OR = 2.83, 95% CI: 1.05-

7.65) and mortality (OR = 3.38, 95% CI: 1.14-10.03) compared to those with a duration of < 5 years[19]

Glycemic control at baseline, as measured by FBS, PPBS, and HbA1c, was significantly associated with treatment outcomes in the present study. Participants who were cured had lower mean FBS (135.4 ± 33.7 mg/dL), PPBS (206.9 ± 46.8 mg/dL), and median HbA1c (6.5%, IQR: 5.9 - 7.2%) at baseline compared to those who were not cured (FBS: 174.9 ± 46.5 mg/dL, PPBS: 252.2 ± 62.9 mg/dL, HbA1c: 7.8%, IQR: 7.2 - 8.6%).This finding is in line with previous studies that have reported poor glycemic control as a risk factor for adverse TB treatment outcomes in patients with DM[20]

HbA1c, a marker of long-term glycemic control, was also found to be significantly associated with treatment outcomes in the present study. The present study also found a significant improvement in FBS and PPBS levels during TB treatment (p < 0.001). A study by Kumpatla *et al.* (2013) reported similar findings.[21]

The majority of the participants in the present study achieved negative sputum conversion (56.3%) at 2 months and were cured (91.0%) at the end of treatment. This finding is consistent with previous studies that have reported high treatment success rates in TB patients with DM. A systematic review by Baker *et al.* (2011) found that the pooled treatment success rate among TB patients with DM was 85.8% (95% CI: 81.9-89.7%) However[22], the mortality rate in the present study (9.0%) was similar to what was reported in some previous studies. For example, a study by Mave *et al.* (2021) reported a mortality rate of 10% among TB patients with DM.[23]

In conclusion, the present study found that age, BMI, smoking status, alcohol consumption, diabetes duration, and glycemic control at baseline were significantly associated with treatment outcomes among TB patients with DM. The findings of this study highlight the need for tailored interventions and close monitoring of TB patients with DM, particularly those with risk factors for adverse outcomes. Future studies with larger sample sizes and multi-center designs are needed to confirm these findings and to explore the effectiveness of targeted interventions for improving treatment outcomes in this high-risk population.

CONCLUSION

This study provides valuable insights into the factors influencing treatment outcomes in patients

with TB-DM comorbidity and underscores the need for personalized management strategies, routine DM screening, and appropriate treatment modalities to improve outcomes in this vulnerable population. Future research should focus on developing and evaluating targeted interventions to optimize treatment outcomes and reduce mortality in patients with TB-DM comorbidity.

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