



## Survival Analysis of Tuberculosis Patients Based on Diabetes Mellitus Status in West Sumatra

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### Abstract

Tuberculosis (TB) is still one of the main problems in tropical countries, especially in Indonesia. The existence of conditions that cause decreased immune systems, such as Diabetes Mellitus (DM), can lead to an increased risk of death in people with Tuberculosis. This study aimed to analyze the survival of Tuberculosis patients with a history of DM in West Sumatra Province. This research was conducted from April to October 2022. It is a retrospective cohort study with all TB patients recorded in the TB03 SO data register in West Sumatra Province in 2021 (N=8,299). The samples were all candidates who met the research criteria in the data (n=1,125 TB patients). Data analysis was performed using survival analysis. The results showed that 177 TB patients (15.73%) had a history of DM, and 948 (84.27%) did not. The cumulative probability of survival for TB patients based on non-DM cases on day 150 is 0.95. In contrast, the cumulative probability of survival for patients with a history of DM is lower, namely 0.90. The group of TB patients who suffered from DM, male and more than 45 years old, experienced a more significant decrease in survival.

### Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. This bacterium usually attacks the lungs but does not rule out attacking other organs. Common symptoms of active pulmonary TB are coughing for more than two weeks, accompanied by phlegm (sometimes it bleeds), chest pain, fatigue, loss of appetite, weight loss, fever, and night sweats. Tuberculosis bacteria are transmitted through the air when TB sufferers actively cough, laugh, and sneeze and can die within a few hours in the open air or when exposed to sunlight. TB is included in one of the world's Sustainable Development Goals (SDGs) targets. Until now, Tuberculosis is still one of the world's top ten causes of death. In 2019, 1.4 million people died from Tuberculosis (WHO, 2020).

As many as 44% of TB sufferers come from Southeast Asia, followed by Africa at 25%. Of the 30 countries with the highest TB burden globally, Indonesia ranks second after India (WHO, 2020). In 2019, there were 845,000 TB cases in Indonesia, consisting of 562,000 notified cases and 283,000 unnotified cases. The number of TB sufferers in Indonesia is dominated by men, who are 1.4 times larger than women. As many as 48% of patients are male, 35% are female, and 17% are cases in children (Kemenkes RI, 2019). However, community research in tuberculosis determinants published in various health journals in Indonesia is still limited (Ratnasari & Handayani, 2023).

Based on several studies that have been conducted, it was found that certain conditions and diseases can affect the condition of TB sufferers. The chances of developing TB disease

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are much higher among people affected by risk factors such as malnutrition, diabetes, HIV, smoking, and alcohol consumption (WHO, 2020). Worldwide, it is estimated that there are 9.6 million new patients with active TB each year, and of these, one million experience TB and DM (TB-DM) (Lönnroth *et al.*, 2014; WHO, 2020). At one time, the number of patients with comorbid TB-DM was higher than that of patients with TB-HIV worldwide (Ruslami *et al.*, 2010).

In 2015, a systematic review study identified 59 studies on DM and TB from 10 countries in the Middle East, showing that the prevalence of TB-DM comorbidities varies widely between studies (Alkabab *et al.*, 2015). An observational study conducted in North Semarang found that Diabetes mellitus has a relationship with the incidence of pulmonary TB (Dian Saraswati, 2014). A meta-analysis by Hayashi found that the risk of active TB in people with DM was higher than without DM. The review by Lönnroth *et al.* also found that someone with DM affects a person's risk of getting TB disease three times compared to those who don't (Hayashi & Chandramohan, 2018; Lönnroth *et al.*, 2014). West Sumatra is a province with high health problems of Tuberculosis and diabetes mellitus. Based on the 2018 Riskesdas Indonesia data, there were 20,663 people with Tuberculosis (prevalence of 0.31%) and 37,063 people diagnosed with Diabetes Mellitus in all age groups in West Sumatra Province (Kemenkes RI, 2018). So, this research aimed to analyze the survival of Tuberculosis patients with a history of DM in West Sumatra Province.

## Methods

This research is an observational analytic study using a retrospective population-based cohort study. It was conducted in West Sumatra Province from April to October 2022. The population for this study was TB patients whose DM status was recorded in the TB03 SO (Drug Sensitive) data register in West Sumatra Province in 2021 (N=8,299). The number of samples used in this study included all candidates who meet the research criteria in the data set, namely 1,125 people. This study was analyzed using survival analysis, where

the outcome variable was the time (days) until an event occurred or until the end of the research period (endpoint). The starting point for measuring survival time was the patient's diagnosis date. Survival status was categorized into the event of the patient's death at the end of the study period and the sensor's if the patient was still alive or cured. This study obtained ethics approval from the Faculty of Public Health, Universitas Andalas research ethics committee, with registered number 15/UN16.12/KEP-FKM/2022.

## Result and Discussion

The survival of TB patients was obtained from two variables, namely, the survival status of TB patients and the patient's survival time (days). The patient's survival status consists of two categories: event and sensor. An event is a condition in which a patient experiences death from being diagnosed with TB. There were 66 (5.87%) patients experienced an event, and 1,059 (94.13%) did not experience an event (sensor).

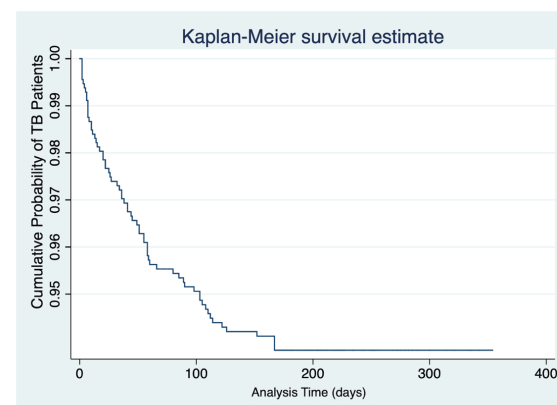


Figure 1. Kaplan Meier Curve of Survival Probability of TB Patients

Based on Figure 1, the survival probability curve for TB patients in West Sumatra in 2021 shows a decline. On day 30, the survival rate for TB patients was 0.97. This means that if there are 100 people with TB, there are 97 people who survive. At day 365, the probability of survival decreased to 0.94. So, if there are 100 TB sufferers, only 94 people will survive. Survival decreased steadily with increasing observation time. Median patient survival cannot be calculated because until the

end of the observation, less than 50% of TB patient deaths have occurred.

Our study shows that the probability of TB patients surviving in West Sumatra in 2021 has decreased over time. It is similar to research in Southern Brazil; most of the deaths occurred within two months after the diagnosis, during the intensive phase of the treatment (Dos Santos *et al.*, 2021). The result of our study also shows that by 12 months, the survival rate declined to 0.94. This finding is in line with survival research in Liberia. The patients were followed up for a mean period of 10 months and showed a decreased survival rate. Of 337 patients, 33 (9.8%) died, resulting in a 90.2% survival rate at 21 months (Carter *et al.*, 2021). Research by Xie *et al.* also shows the 1-year cumulative survival rate of patients with TB decreased to 94.11% (Xie *et al.*, 2020).

Table 1. Cumulative Probability of Survival of TB Patients Based on DM Status

| No | Survival Time (days) | Non-DM | DM     |
|----|----------------------|--------|--------|
| 1  | 2                    | 0.9958 | 0.9944 |
| 2  | 12                   | 0.9863 | 0.9718 |
| 3  | 30                   | 0.9757 | 0.9661 |
| 4  | 60                   | 0.9620 | 0.9322 |
| 5  | 90                   | 0.9578 | 0.9266 |
| 6  | 120                  | 0.9525 | 0.9096 |
| 7  | 150                  | 0.9504 | 0.9040 |
| 8  | 365                  | 0.9483 | 0.9040 |

Source: TB03 SO data register in West Sumatra. 2021

In this study, 177 (15.73%) TB patients also had DM, and 948 (84.27%) TB patients did not suffer from DM. The cumulative probability of survival for TB patients based on non-DM cases on day 150 is 0.95, which means that out of 100 TB patients, only 95 survive for one year. Meanwhile, the cumulative survival probability of patients with a history of DM on day 150 is lower, namely 0.90. This means that out of 100 people with TB, only 90 survive on day 150 (Table 1).

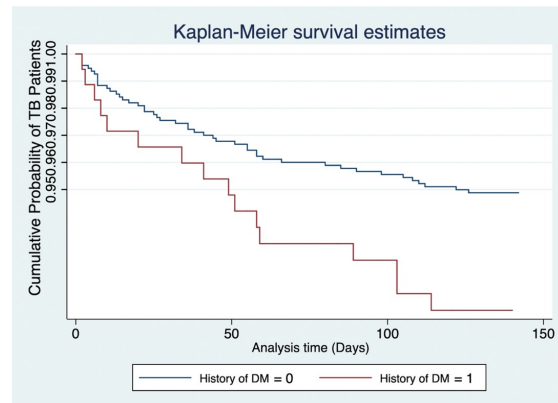


Figure 2. Kaplan Meier Curve Probability of Survival in TB Patients Based on DM Status

In Figure 2, it can be seen that each group has decreased since the first month. The group of TB patients who suffered from DM experienced a more significant reduction compared to the group of TB patients who did not suffer from DM.

Most deaths occurred in male TB patients (6.63%), with a survival probability of 0.93 (Table 2). This is following research in Taiwan that shows patients with male gender had significantly higher mortality. male gender is associated with older age, more co-morbidities, and worse treatment outcomes (Feng *et al.*, 2012). It is consistent with another study that found the risk of death was 1.847 times higher for male patients (Xie *et al.*, 2020). Research in Southern Brazil by Santos *et al.* found that male TB patients had a risk of death that was 6.49 times higher than that of female patients. In the study, sex and age are intercepted, producing different risk effects for death (Dos Santos *et al.*, 2021). Gender disparities in the diagnosis and treatment of pulmonary TB are reflected in elevated disease transmission and reactivation rates and inferior treatment outcomes, particularly among men, that contribute to mortality (Jiménez-Corona *et al.*, 2006).

In terms of age characteristics, our study found that most deaths occur at the age of more than 45 years (9.74%), with a survival probability of 0.90 (Table 2). Using the likelihood ratio chi-square test, research in Ethiopia found that a patient's age, with a p-value less than 0.05, has a relatively strong association with the death of TB patients (Haile *et al.*, 2021). With each year of increase in age, the risk of death

Table 2. Survival of TB Patients Based on Patient Characteristics in 1-Year

| No | Variable          | Event     | Sensor      | Total       | 1-year cumulative probability of survival of a TB patient |
|----|-------------------|-----------|-------------|-------------|-----------------------------------------------------------|
|    |                   | n (%)     | n (%)       | n (%)       |                                                           |
| 1  | Sex               |           |             |             |                                                           |
|    | Male              | 45 (6.63) | 634 (93.37) | 679 (60.36) | 0.93                                                      |
|    | Female            | 21 (4.71) | 425 (95.29) | 446 (39.64) | 0.95                                                      |
| 2  | Age (years old)   |           |             |             |                                                           |
|    | <= 18             | 2 (1.37)  | 144 (98.63) | 146 (12.98) | 0.99                                                      |
|    | 19 – 45           | 16 (3.29) | 470 (96.71) | 486 (43.20) | 0.97                                                      |
|    | > 45              | 48 (9.74) | 445 (90.26) | 493 (43.82) | 0.90                                                      |
| 3  | Diabetes Mellitus |           |             |             |                                                           |
|    | DM                | 17 (9.60) | 160 (90.40) | 177 (15.73) | 0.90                                                      |
|    | Non-DM            | 49 (5.17) | 899 (94.83) | 948 (84.27) | 0.95                                                      |

Source: TB03 SO data register in West Sumatra. 2021

increased by 1.059 times. Advanced age is associated with a higher risk of death, possibly related to low immunity, atypical symptoms, longer onset time, primary diseases, and poor health awareness in elderly patients. Therefore, it is crucial to strengthen TB screening in the elderly population to enable early detection, diagnosis, and treatment (Rahmanian *et al.*, 2018; Xie *et al.*, 2020). Some researchers also found the same result about older people related to decreased survival of Tuberculosis (Geleso, 2020; Moosazadeh *et al.*, 2014; Selvaraju *et al.*, 2021; Teketelew *et al.*, 2022).

Our study found that most deaths occurred in TB patients with DM, which was 9.6% with a survival probability of 0.9. Whereas in the group of patients who did not have DM, the mortality was 5.17% with a survival probability of 0.95 (Table 2). This is in line with a survival analysis study by Liu *et al.* in China that, within one year of observation, Diabetes Mellitus was significantly associated with death in TB patients (Liu *et al.*, 2022). A study of TB patients treated with comorbidities found that DM prolonged culture positivity on examination 2-3 months of TB care. DM also increases the risk of death with an RR of 1.89 (95% CI 1.52 to 2.36) (Baker *et al.*, 2011).

Diabetes is a metabolic disease caused by inflammation that results from a complex immunological process. When insulin resistance occurs due to insulin signaling inhibition, it triggers immune responses that worsen the inflammatory state. Many studies

have been conducted to determine how diabetes-related mechanisms interfere with the host's defense against pathogens. These mechanisms include cytokine production suppression, phagocytosis defects, immune cell dysfunction, and the inability to eliminate microbes (Berbudi *et al.*, 2020). DM potentially contributes to poor control and changes the natural history of TB infection. It also exacerbates the clinical manifestations of TB. Diabetic patients with TB are more likely to complain of physical symptoms, such as dyspnea, fatigue, asthenia, body aches, and headaches. Over time, DM causes functional and structural changes in the circulation of TB development, which causes differences in healing time between TB-DM and TB-non-DM patients. The determinant of the emergence of complications in TB-DM patients is ongoing hyperglycemia, which causes biochemical and structural abnormalities in blood vessels and peripheral nerves. Endothelial damage appears to be a triggering factor for the pathogenesis of microvascular complications associated with symptoms of DM complications in TB patients (Leal *et al.*, 2017).

### Conclusion

Most deaths occurred in male TB patients and patients aged over 45 years. The group of TB patients who suffer from DM experienced a more significant decrease in survival compared to the group of TB patients who do not suffer from DM. TB-DM patients should get more

attention on side effects, symptoms, care, and support from their families and health workers. The joint force for collaboration DM and TB-related activities should be developed more, which has to be reflected in the national or local plans, respectively.

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