*Original Article*

# TUBERCULOSIS-SPECIFIC AND NON-TUBERCULOSIS-SPECIFIC MORTALITY IN A DISTRICT

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## ABSTRACT

Tuberculosis (TB) is a communicable disease that contributes to major ill health. Worldwide, it is one of the leading causes of death from a single infectious agent. The study aimed to describe the epidemiology and factors associated with TB-specific and non-TB-specific mortality in Manjung District, Perak, Malaysia. All confirmed TB cases from 2015 to 2020 registered in Manjung District under "Sistem Maklumat Tibi" (MyTB) were included. Factors associated with TB-specific and non-TB-specific mortality were analysed by u sing simple and multiple logistic regression analysis. A total of 742 TB cases were included in the analysis, 34 (28.1%) and 87 (71.9%) died from TB-specific and non-TB-specific causes respectively. From multiple logistic regression analyses, male gender, non-Malaysian, cases notified by government hospitals, Human Immunodeficiency Virus (HIV) positive status and HIV testing not offered/unknown were significantly associated with TB-specific mortality. For non-TB-specific mortality two factors were significant, age group 65 and above, and HIV-positive status. To strengthen and reduce both the TB-specific and non-TB-specific mortality rate in Manjung District, targeted approaches, such as close monitoring should be practised especially among male gender, non-Malaysians, those with HIV and cases presented to the hospital.

**KEYWORDS:** tuberculosis-specific, non-tuberculosis-specific,TB mortality, risk factors, logistic regression

## INTRODUCTION

Tuberculosis (TB) is a communicable disease that contributes to a major cause of ill health and is one of the leading causes of death worldwide from a single infectious agent (1). It is caused by Mycobacterium tuberculosis, which typically affects the lungs (pulmonary TB). It can also affect other sites; however, it is curable and preventable (2).

The World Health Organisation's (WHO) "End TB Strategy" set a 2020 milestone aimed at a reduction of 35% of the total TB deaths from the 2015 baseline. However, only a 9.2% reduction was achieved, reaching about one-quarter of the milestone. The COVID-19 pandemic caused disruptions to the diagnosis and treatment of all diseases, including TB (3). However, this only partially explains the shortfalls in milestone progress, as by 2019, the reduction in TB deaths was only 14% compared to the 2015 baseline, which was far below the 35% target (1).

In Malaysia, TB cases have remained high despite improvements in diagnosis and treatment. The estimated TB incidence rate in 2021 was 97 (with a range of 79 to 106) per 100,000 population with an estimated TB mortality rate of 4 cases per 100,000 population (4,5). Most studies on TB mortality have examined mainly all-cause risk factors mortality, rather than TB-specific mortality (6). One study done in 2017, compared the risk factors between TB-specific and non-TB-specific mortality. However, this study was done in the United States which is a low-burden setting for TB as compared to Malaysia which is classified by WHO as an intermediate TB burden country (7). We aimed to further explore the factors associated with TB-specific and non-TB-specific mortality to identify key similarities and differences between the two groups. Understanding these factors could help develop targeted interventions to reduce overall TB mortality, with a particular focus on preventing TB-specific mortality.

Manjung is a district in the south-western part of Perak, Malaysia, with a total population of 245,683. The most common ethnic groups are Malays (57.5%), Chinese (28.4%), Indians (12.6%) and others (1.5%) (8). The major sectors of the economy in Manjung District are agriculture and tourism. Manjung is the third biggest district in Perak by population, with one of the highest TB cases and mortality in Perak. Hence, it is essential to investigate the underlying contributing factors. To the best of our knowledge, there is no published study on TB-specific and non-TB-specific death epidemiology in the Manjung district. Therefore, this study was conducted to describe the epidemiology of TB mortality and its associated factors with TB-specific and non-TB-specific patients on treatment in the Manjung district from 2015 to 2020.

## MATERIALS AND METHODS

A retrospective cohort study was conducted between 1 May and 9 June 2022 for all confirmed TB cases reported to the Manjung District Health Office. Cases were registered in the national online system called "Sistem Maklumat Tibi"(MyTB) over six years (2015–2020).

In Malaysia, all confirmed TB cases in government or private healthcare facilities are required by law to be reported under the Prevention and Control of Infectious Diseases Act 1988 (Act 342) (9). MyTB was developed and is run by the Ministry of Health, Malaysia to standardise the reporting, investigation, and case findings at the district, state, and national levels for the control and prevention of TB.

From the extracted TB cases, excluded cases from the analysis were patients whose diagnosis changed, cases transferred out or lost during follow-up, defaulted treatment and incomplete information in the MyTB. All TB mortality cases were discussed in the TB mortality audit by a panel consisting of a respiratory physician, treating physicians and representatives from the district health office to determine if the death is TB-specific (death caused by TB) or non-TB-specific (death caused by other than TB). Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia (NMRR ID-22-01238-3OX (IIR)).

**Definitions**

Cases for TB-specific mortality were defined as mortality amongst TB patients before they completed their anti-TB treatment and the death was determined as TB-specific during the mortality audit. Cases for non-TB-specific mortality were defined as mortality amongst TB patients before they completed their anti-TB treatment and the death was determined as non-TB-specific by the mortality audit panellists.

The notification centre was categorised into three groups based on the institutions that diagnosed and notified the TB cases, such as government health clinics, private health clinics and hospitals. Active case detection was when contacts of newly diagnosed patients were systematically screened. Patients presenting to health services with symptoms and later being confirmed of TB were termed as passive case detection. Meanwhile, TB cases detected from various screening, such as workers screening, medical screening and screening of TB in HIV and diabetes patients, were termed as detection from screening (10).

Extrapulmonary TB was defined as TB diagnosed in organs other than the lungs, such as the lymph nodes, pleura, gastrointestinal tract or central nervous system (11). Smear-positive pulmonary TB (PTB) was defined as a PTB patient with at least one or more initial sputum smear examinations (direct smear microscopy) positive for acid-fast bacilli (AFB), or with one sputum specimen positive for AFB and radiographic abnormalities consistent with active PTB, or with one sputum specimen positive for AFB and culture positive for Mycobacterium tuberculosis (12). Smear-negative PTB was defined as a PTB patient with at least three negative results in direct smear sputum microscopy but with radiographic results suggestive of active TB or sputum culture positive for Mycobacterium tuberculosis (12).

**Statistics**

Data collection and analysis were conducted at the Manjung District Health Office. Data were downloaded from MyTB. This was followed by importing and analysing the data using IBM Statistical Package for Social Science (SPSS) version 24.0 software.

We used descriptive statistics to report the risk factors of interest and Pearson's Chi-square tests to determine the differences between TB-specific and non-TB-specific mortality. To analyse the odds of TB-specific mortality and non-TB-specific mortality for each risk factor, we compared each group of patients with the group of all living patients with TB. The risk factors were evaluated through univariate and multivariate logistic regression. Variables with a p-value of less than 0.25 or considered clinically significant from the univariate analysis were selected and considered for multiple logistic regression analysis. We used the stepwise, forward-selection and backwards-elimination strategies to choose the final regression model. Only variables selected by all three strategies were included in the final model. Multicollinearity and interaction were checked for the final model. The fitness of the model was tested by using the Hosmer-Lemeshow goodness-of-fit test, classification table and area under the receiver

operating characteristics (ROC) curve in SPSS software. All TB cases from 2015 to 2020 were analysed. The significance level for all statistical tests was set at 0.05 unless otherwise stated.

## RESULTS

### Characteristics of the reported cases

Of the 822 patients with the diagnosis of TB reported in the Manjung District in the MyTB from 2015 to 2020, 742 (90.3%) met the eligibility criteria for the study and 80 cases were discarded, as shown in Figure 1. About 121 (16.3%) patients died before completing their TB treatment, and 34 were audited to have died due to TB (TB-specific mortality). A total of 621 (83.7%) were still alive. Figure 2 shows the number of patients who were alive at the end of treatment and patients who died due to TB-specific and non-TB-specific causes according to year. The annual proportion of TB patients who died because of TB ranged from 3.0% to 8.6% and the annual proportion of TB patients who died of causes other than TB ranged between 7.0% to 17.1%. The proportion of TB patients who died of causes other than TB was higher for all the years except for the year 2016, where it was similar for both at 7.0%.

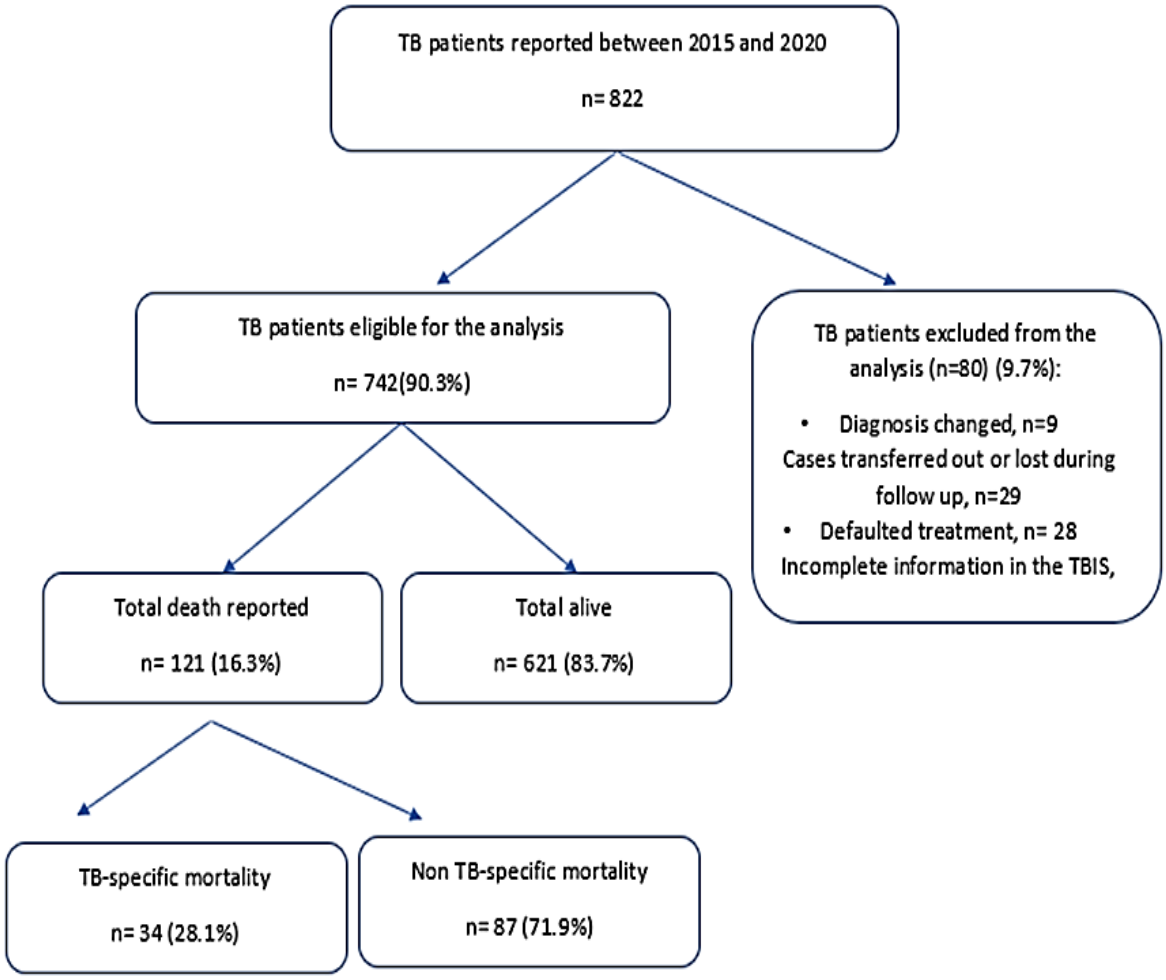


**Figure 1.** Flow diagram of 822 patients with TB reported to the MyTB between 2005 and 2010

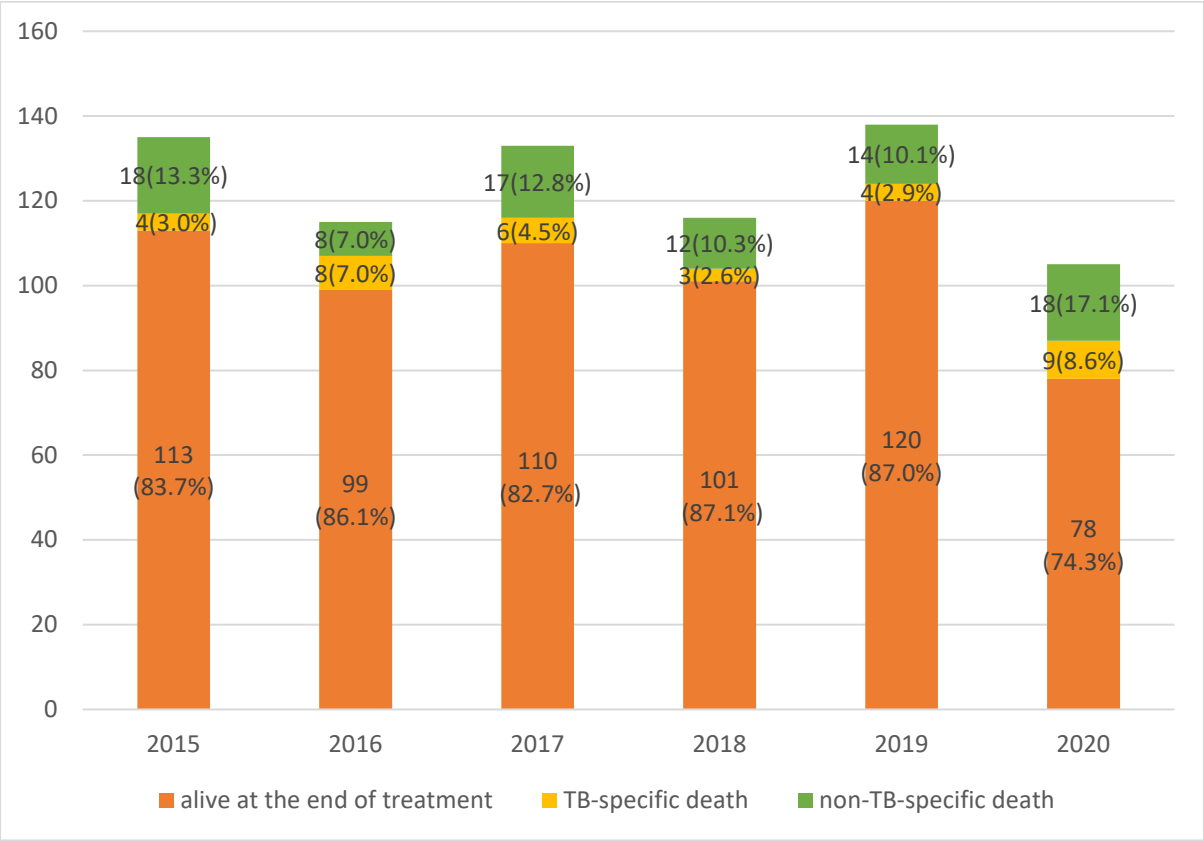


**Figure 2.** Cases with patients who were alive at the end of treatment, TB-specific, and non-TB-specific death according to year

Table 1 presents the characteristics of the 742 reported TB cases in Manjung district, categorised by their sociodemographic risk factors based on TB-specific mortality, non-TB-specific mortality and status of alive at the end of treatment. Significant differences were seen in the sociodemographics of the age group, gender, citizenship, notification centre, TB category and HIV status at the time of diagnosis among the three groups as analysed by Pearson's Chi-Squared test.

**Table 1.** TB-specific mortality, non-TB-specific mortality and alive at the end of treatment by sociodemographics among reported TB cases in Manjung District Health Office from 1st January 2015 to 31st December 2020 (n=742)

| Variable | N (%) | | | |
|---|---|---|---|---|
| | Alive (n=621) | TB-specific mortality (n=34) | Non-TB-specific mortality (n=87) | *p*-value |
| Sociodemographics | | | | |
| Age (years) | | | | <0.001 |
| <14 year | 13 (2.1) | 0 (0.00) | 0 (0.0) | |
| 15-24 years | 83 (13.4) | 2 (5.9) | 4 (4.6) | |
| 25-44 years | 220 (35.4) | 13 (38.2) | 21(24.1) | |
| 45-64 years | 224 (36.1) | 14 (41.2) | 32 (36.8) | |
| >65 years | 81 (13.0) | 5 (14.7) | 30 (34.5) | |
| Gender | | | | <0.001 |
| Female | 251 (40.4) | 2 (5.9) | 31 (35.6) | |
| Male | 370 (59.6) | 32 (94.1) | 56 (64.4) | |
| Citizenship | | | | <0.001 |
| Malaysian | 603 (97.1) | 27 (79.4) | 83 (95.4) | |
| Non-Malaysian | 18 (2.9) | 7 (20.6) | 4 (4.6) | |
| Education Level | | | | 0.064 |
| None/Primary | 49 (7.9) | 3 (8.8) | 13 (14.9) | |
| Secondary | 507 (81.6) | 30 (88.2) | 70 (80.5) | |
| Tertiary | 65 (10.5) | 1 (3.0) | 4 (4.6) | |
| Case Detection | | | | 0.638 |
| Passive | 556 (89.5) | 33 (97.1) | 78 (89.7) | |
| Active | 44 (7.1) | 1 (2.9) | 7 (8.0) | |
| Screening | 21 (3.4) | 0 (0.00) | 2 (2.3) | |
| Notification Centre | | | | <0.001 |
| Government Clinic | 180 (29.0) | 2 (5.9) | 5 (5.7) | |
| Private Facility | 62 (10.0) | 0 (0.0) | 1 (1.2) | |
| Government Hospital | 379 (61.0) | 32 (94.1) | 81 (93.1) | |
| Diabetes | | | | 0.077 |
| No | 437 (70.4) | 29 (85.3) | 56 (64.4) | |
| Yes | 184 (29.6) | 5 (14.7) | 31 (35.6) | |

| | | | | |
|---|---|---|---|---|
| Smoking Status | | | | 0.440 |
| No | 426 (68.6) | 20 (58.8) | 57 (65.5) | |
| Yes | 195 (31.4) | 14 (41.2) | 30 (34.5) | |
| BCG Scar | | | | 0.076 |
| No | 70 (11.3) | 8 (23.5) | 13 (14.9) | |
| Yes | 551 (88.7) | 26 (76.5) | 74 (85.1) | |
| TB Category | | | | 0.049 |
| PTB smear negative | 128 (20.6) | 5 (14.7) | 28 (32.2) | |
| PTB smear positive | 429 (69.1) | 28 (82.4) | 51 (58.6) | |
| Extra PTB | 64 (10.3) | 1 (2.9) | 8 (9.2) | |
| Healthcare Workers | | | | 0.579 |
| No | 603 (97.1) | 34 (100.0) | 85 (97.7) | |
| Yes | 18 (2.9) | 0 (0.0) | 2 (2.3) | |
| HIV status at the time of diagnosis | | | | <0.001 |
| Negative | 584 (94.0) | 24 (70.6) | 69 (79.3) | |
| Positive | 11 (1.8) | 6 (17.6) | 10 (11.5) | |
| Testing not offered/unknown | 26 (4.2) | 4 (11.8) | 8 (9.2) | |

*p*-values are based on a chi-squared test.

Factors associated with TB-specific and non-TB-specific mortality

For factors associated with TB-specific mortality, simple logistic regression analysis identified gender, citizenship, diabetes status, notification centre, presence of a BCG scar, and HIV status at the time of diagnosis as significant variables to be included in the multiple logistic regression analysis. Age and smoking status were also included, despite having a *p*-value greater than 0.25, as they were considered clinically significant. In the multiple logistic regression analysis, four factors were found to be significantly associated with TB-specific mortality after adjusting for other variables. These factors were male gender, non-Malaysian citizenship, government hospital notification, and HIV status (positive or testing not offered/unknown at the time of diagnosis), as shown in Table 2.

For factors associated with non-TB-specific mortality, simple logistic regression analysis selected age, education level, diabetes status, HIV status at the time of diagnosis and TB category for inclusion in the multiple regression analysis, as shown in Table 3. After adjusting for other factors, two variables were found to be significant: age 65 years and above and being HIV-positive. Although the adjusted odds ratio for HIV status at the time of diagnosis (not offered/unknown) was less than 0.05, it was considered not significant, as the 95% confidence interval crossed the value of one.

**Table 2.** Simple and multiple logistic regression analysis of factors associated with TB-specific mortality in Manjung District from 1st January 2015 to 31st December 2020 (n=34)

| Variable | Wald statistic | df[a] | Crude OR[b] (95% CI[c]) | *p*-value | Adj. OR[b] (95% CI[c]) | *p*-value |
|---|---|---|---|---|---|---|
| **Sociodemographics** | | | | | | |
| Age (years) | 26.284 | 4 | | | | |
| <14 year | | | <0.001 | 0.999 | <0.001 | 0.999 |
| | | | (0.01, 0.01) | | (0.01, 0.01) | |
| 15-24 years | | | 1 | | 1 | |
| 25-44 years | | | 1.92 | 0.246 | 1.72 | 0.346 |
| | | | (0.64, 5.74) | | (0.56, 5.34) | |
| 45-64 years | | | 2.86 | 0.054 | 2.82 | 0.065 |
| | | | (0.98, 8.32) | | (0.94, 8.45) | |
| ≥65 years | | | 7.41 | <0.001 | 7.40 | 0.001 |
| | | | (2.50,211.95) | | (2.38,23.06) | |
| Gender | | | | | | |
| Female | 121.718 | 1 | 1 | | | |
| Male | | | 1.14 | 0.590 | | |
| | | | (0.71, 1.81) | | | |
| Citizenship | | | | | | |
| Malaysian | 301.290 | 1 | 1 | | | |
| Non-Malaysian | | | 1.21 | 0.724 | | |
| | | | (0.41, 3.58) | | | |
| Education Level | | | | | | |
| None/Primary | 19.987 | 2 | 1 | | | |
| Secondary | | | 0.52 | 0.052 | | |
| | | | (0.27, 1.01) | | | |
| Tertiary | | | 0.24 | 0.018 | | |
| | | | (0.08, 0.79) | | | |
| Case Detection | | | | | | |
| Passive | 0.354 | 2 | 1 | | | |
| Active | | | 1.18 | 0.704 | | |
| | | | (0.51, 2.70) | | | |
| Screening | | | 0.72 | 0.660 | | |
| | | | (0.17, 3.13) | | | |

| | | | | |
|---|---|---|---|---|
| Notification Centre | | | | |
| Government | 23.084 | 2 | 1 | |
| Clinic | | | | |
| Private Facility | | | 0.59 | 0.630 |
| | | | (0.07, 5.12) | |
| Government Hospital | | | 7.17 | 0.751 |
| | | | (2.86, 17.99) | |
| Diabetes | | | | |
| No | 224.438 | 1 | 1 | 0.195 |
| Yes | | | 1.37 | |
| | | | (0.85, 2.18) | |
| Smoking Status | | | | |
| No | 213.906 | 1 | 1 | 0.629 |
| Yes | | | 1.12 | |
| | | | (0.70, 1.80) | |
| BCG Scar | | | | |
| No | 35.773 | 1 | 1 | 0.419 |
| Yes | | | 0.77 | |
| | | | (0.41, 1.45) | |
| Tuberculosis Category | | | | |
| PTB smear negative | 56.156 | 2 | 1 | |
| PTB smear positive | | | 0.53 | 0.103 |
| | | | (0.32, 0.87) | |
| Extra PTB | | | 0.59 | 0.210 |
| | | | (0.25, 1.35) | |
| Healthcare Workers | | | | |
| No | 304.222 | 1 | 1 | 0.808 |
| Yes | | | 0.83 | |
| | | | (0.19, 3.65) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| HIV status at the time of diagnosis | | | | | | |
| Negative | 293.433 | 2 | 1 | | 1 | |
| Positive | | | 5.18 | <0.001 | 6.12 | 0.041 |
| | | | (2.28,11.77) | | (2.49,15.01) | |
| Testing not offered/ unknown | | | 2.35 | 0.178 | 1.84 | 0.035 |
| | | | (1.04, 5.33) | | (0.76, 4.49) | |

Constant -2.345

Manual method applied

No multicollinearity (highest variance inflation factor value was 3.43) and no interaction detected

Hosmer-Lemeshow test, *p*-value=0.116

Classification table 88.0% correctly classified

The area under receiver operating characteristic (ROC) was 80.6

## DISCUSSION

It was found that between 2015 and 2020 16.3% of TB patients living in the Manjung District died before completing their treatment. This was higher than the Malaysian reported TB mortality of 10.2% between 2014 and 2017 (13). The highest TB mortality was in 2020 when 25.7% of cases died. This was the year when the COVID-19 pandemic started and the impact of the pandemic had reversed years of global progress in reducing the number of deaths from TB. According to the WHO, the number of estimated TB deaths in 2020 worldwide returned to the level seen before 2017 (14).

However, a further breakdown, as shown in Figure 1, reveals that in the Manjung district, only 34 (28.1%) of all deaths were attributed to TB. A large proportion of the deaths (71.9%) were due to causes other than TB. The only factor significantly associated with both TB-specific and non-TB-specific mortality was HIV status at the time of diagnosis. Several previous studies have reported findings comparable to those of the present study regarding HIV and TB mortality. This study reported that those with HIV-positive status were about three times to die from TB-specific and more than six times from non-TB-specific causes during treatment. Meanwhile, those with testing not offered or unknown were 3.57 times more likely to die from TB-specific and almost two times more from non-TB-specific causes during TB treatment. A study conducted by Marks et al. with the National Tuberculosis Surveillance System data from 1997 to 2005 found that patients infected with HIV had higher odds of TB diagnosis at death and death during TB treatment than patients who were HIV negative (15). Later, a similar study conducted by Haylea et al. using data from 2009–2013 reported similar findings (6). A meta-analysis reported that HIV positive had a hazard ratio of 2:6 for TB mortality (16). HIV increases the risk of TB infection and the severity of TB disease and mortality. Furthermore, TB may also act as a cofactor in the progression of HIV infection by increasing the HIV viral load (17). This explains why HIV patients with TB are at higher risk of mortality from both TB-specific and non-TB-specific causes.

The three other factors significant for TB-specific mortality were male gender, non-Malaysian citizenship and cases notified by the government hospitals. Males were 11.09 times more likely than females to die from TB-specific causes during their TB treatment. A study on TB mortality in Taiwan also reported that males were more likely to die from TB-specific death (18). Similarly, a study in Saudi Arabia reported that males had a double the mortality rate as compared to females for all-cause TB mortality (19). While various previous studies have consistently shown that males are prone to both

TB-specific death or all-cause TB mortality, none have reported odds as high as observed in our study. Of the 34 reported TB-specific mortality, only two were reported among females. Some possible explanations include males tend to delay seeking treatment at health clinics, only doing so when their worsens and have lower adherence to TB treatment compared to females, increasing their risk of TB-specific mortality among males (20).

Non-Malaysians were over ten times more likely to die from TB-specific mortality as compared to Malaysian citizens. Studies showed that immigrants had higher TB mortality for infectious diseases as compared to locals (21,22). Non-citizens were more vulnerable to death from infectious diseases, such as TB, due to a series of risk factors associated with migration. The migrants in Manjung District are majority labour-class workers; hence, their exposure risk in their living conditions predisposed them to be infected with TB. They are more likely to be diagnosed in the later stage of the infection; therefore, increasing the risk of TB-specific mortality. Problems and barriers to accessing healthcare and lack of knowledge about the healthcare system might also contribute to their higher mortality rate (23).

Interestingly, notification centre was significantly associated with TB-specific mortality. As compared to TB cases notified by government clinics, cases notified by government hospitals were 5.12 times more likely to die from TB-specific causes. TB cases that were presented to government hospitals were more severe and required hospitalisation. Whereas, government clinics primarily detected TB cases from the screening of symptomatic or close contact with TB cases, which were clinically more stable. Studies showed that the TB mortality rate was about 52% higher among late presenters than in early presenters (24).

The only other factor significant for non-TB-specific mortality aside from HIV status was the age of 65 and above. As compared to the 15–24-year-old age group, the 65 and above age group had 7.40 times higher odds of non-TB-specific mortality. This is not surprising as the age group has a higher mortality rate in general as compared to the 15-24 years age group.

The strength of this study lies in the fact that all causes of death among the patients were assessed and audited by a panel, which reduced the potential for misclassification of TB-specific and non-TB-specific mortality. However, since the study population was limited to those from the Manjung District, the results cannot be generalized to other populations. Given the relatively small number of outcome events, the precision of the study may be affected, and the results should be interpreted with caution. Due to the limitations of secondary data, we did not have access to external information beyond the online notification database. We also lacked adequate data regarding the duration of treatment, which could have influenced TB-specific mortality. For a more comprehensive understanding of factors associated with TB mortality, future researchers may consider expanding the current analysis to more to achieve a larger sample.

Based on the findings of this study, it is recommended that TB screening and awareness in primary healthcare be optimised, particularly among high-risk groups, to reduce TB-specific mortality. These groups include males, non-Malaysians, individuals with HIV, and those who presented late to the hospital. Close monitoring of these groups during TB treatment is crucial to assess the worsening of their condition and ensure adherence, which will help reduce both TB-specific and non-TB-specific mortality.

## CONCLUSION

About 16% of TB patients died during the treatment course in Manjung District from both TB-specific and non-TB-specific causes. To strengthen and reduce both the TB-specific and non-TB-specific mortality rate in Manjung District, targeted approaches, such as close monitoring should be practised, especially among male gender, non-Malaysians, those with HIV and cases presented to the Hospital.

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