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REVIEW ARTICLE

Prevalence and characteristics of tuberculous meningitis in Malaysia (2015-2020)

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ABSTRACT

Tuberculosis (TB) is one of the top 10 causes of death and the leading cause of morbidity from a single infectious agent. Tuberculous meningitis (TBM) is a subtype of tuberculosis which constitutes about 5% of all extrapulmonary tuberculosis and about 1-2% of active tuberculosis. This study was conducted to analyse the annual incidence of TBM in Malaysia from 2015-2020. Through this study we were also able to study the demographic characteristics and clinical profiles of TBM patients. It was a cross sectional study using data collected from Malaysia national case-based TB registry (MyTB) between year 2015 and 2020. Descriptive analysis was used and univariate analysis was performed using binary logistic regression. All the statistical analyses with p-value less than 0.05 is considered significant with the 95% confidence interval. There were total of 2072 TBM cases from year 2015 until 2020, which comprised of 1.38% of total TB cases within 6 years. Most of the patients were Malaysian (1682 cases (81.2%)) while only 390 (18.8%) cases were reported among foreigners. Most cases were detected among the age group of 35-44 with average of 77.8 (22.5%) cases per year, followed by age group 35-44 with average of 66.8 (19.35%) cases per year. Of all the TBM cases, 23.2% patients were known case of HIV while 1.45% diagnosed as HIV later. TBM is a disease with poor prognosis as the consequence of the half of the affected patient is death or severe disability which is evidenced by 42.7% patients passed away. TBM imposes a great challenge in both diagnosis and management, as most affected patients will be left with severe long-term complications even with treatment. It is important to understand the epidemiology and characteristics of tuberculous meningitis in Malaysia to improve the management and enhance the control of this deadly disease.

Keywords: Tuberculous meningitis; prevalence; characteristics; Malaysia.

INTRODUCTION

Globally, tuberculosis (TB) is one of the top 10 causes of death and the leading cause of morbidity from a single infectious agent. In 2020, an estimation of 9.9 million people worldwide fell ill with TB, while 1,500,000 people died of TB (WHO, 2021). Malaysia is classified as a country with an intermediate burden of TB with notification rate of less than 100 per 100,000 population. The incidence rate in Malaysia is around 92 per 100,000 population for the year 2020, an increase rate of 3.2% as compared to the year 2015. The mortality rate of 6.1 cases per 100,000 population in 2020 is also an increment of 16% as compared to the year 2015 (WHO, 2021). The trend of Malaysia's TB incidence and mortality rate is far from achieving the End TB Strategy by the WHO which is to achieve 20% reduction in incidence and 35% reduction in TB deaths by the year 2020 as compared to the year 2015.

Tuberculous meningitis (TBM), a form of extrapulmonary tuberculosis, is the most devastating and lethal form of tuberculosis. TBM causes sub-acute or chronic inflammation of the meninges as a consequence of *Mycobacterium tuberculosis* bacilli invading the sub-arachnoid space through hematogenous spread (Donovan *et al*., 2020). Globally TBM accounts for about 1% of all current tuberculosis patients and 5–10% of extrapulmonary tuberculosis cases, with the global burden estimated to be more than 100,000 new cases each year (Li *et al*., 2020). The commonest sites of extrapulmonary TB in Malaysia are lymph nodes and pleura. Although the incidence rate of TBM is low, the outcome is devastating with a high fatality rate. The result of TBM is usually death or survivors with catastrophic neurological abnormalities (Donovan *et al*., 2020; Philip *et al*., 2015).

TBM is common in young children aged 2 to 4 years old and also in human immunodeficiency virus (HIV) infected individuals (Seddon *et al*., 2019). It is reported that in high TB burden countries,

TB is the commonest cause of bacterial meningitis in children (22%) followed by *Streptococcus pneumoniae* (4%) and *Klebsiella pneumoniae* (3%) (Cresswell, 2021). Apart from the age group and underlying HIV infection, other contributing factors for TBM include being immunocompromised due to other non-communicable diseases such as malignancy, chronic lung disease and diabetes mellitus (Kee *et al*., 2017).

The common presenting symptoms of TBM are that of subacute meningitis such as fever, headache, neck stiffness, nausea and vomiting. As these symptoms are also present in most bacterial meningitis, it is hard to differentiate TBM from other causes (Török, 2015). Another common presenting symptom in TBM is cranial nerve palsy with cranial nerves II and VI being the most commonly affected (Arshad *et al*., 2020). Additionally, symptoms that persist for more than 5 days are predictive of TBM (Méchaï & Bouchaud, 2019). Advanced TBM may present with severe symptoms such as altered mental status, raised intracranial pressure, coma and convulsions (Török, 2015). The clinical symptoms of TBM are similar irrespective of Bacille Calmette- Guérin (BCG) vaccination status, HIV co-infection and the organism genotype (Méchaï & Bouchaud, 2019; Slane & Unakal, 2022).

The one solid prognostic factor for improved outcomes with decreased neurological deficit and death rate among TBM patients is the timely diagnosis and early initiation of treatment. Unfortunately, this is still not achievable due to the challenges in clinical diagnosis and paucibacillary infection causing delays in microbiological diagnosis (Méchaï & Bouchaud, 2019; Soria *et al*., 2019). Ziehl-Neelson staining of cerebrospinal fluid (CSF) which has been developed more than 100 years ago is a fast technique to test for TBM; however, its sensitivity is only 10% to 20%. Mycobacterial culture has better sensitivity of 60% to 70%, but the drawback of this method is that it takes up to 2 weeks to obtain the results (Méchaï & Bouchaud, 2019). The latest liquid culture technique is better as it can produce results as early as 6 days (Török, 2015). Culturing is also important to determine the antibiotic resistance of the causative organisms (Arshad *et al*., 2020). Nucleic acid amplification tests (NAATs) have been used for the diagnosis of TBM recently (Seddon *et al*., 2019). The most notable NAATs is GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) which is a fully automated real-time polymerase chain reaction (rt-PCR) based assay and is approved by the WHO for the detection of *Mycobacterium tuberculosis* and rifampicin resistance in extra-pulmonary TB specimens in both adults and pediatrics, including CSF samples in suspected TBM cases (Méchaï & Bouchaud, 2019; Török, 2015). Another method endorsed by the WHO is line-probe assays (LPAs), which are being used in middle to high-income countries (Török, 2015). Apart from that, the use of neuroimaging is also helpful in TBM diagnosis (Arshad *et al*., 2020). However, the neuroradiological features of TBM such as basal meningeal enhancement, infarction and hydrocephalus detected in computerized tomography (CT) scans are usually not apparent in the initial stages of the disease because of its low sensitivity – can be as low as 40% (Méchaï & Bouchaud, 2019).

The outcome of TBM can be significantly improved by prompt treatment. Therefore, special attention should be given to understanding the background and nature of the disease. It is recommended that empirical treatment be started as soon as clinical symptoms and CSF features are suggestive of TBM (Marx & Chan, 2011). The present WHO guideline recommends treatment with rifampicin (RMP), isoniazid (INH), pyrazinamide (PZE) and ethambutol (ETB) for 2 months of initiation phase followed by RMP and INH for 7 to 10 months of continuation phase (Marx & Chan, 2011; Philip *et al*., 2015; Török, 2015).

This paper aims to evaluate the prevalence and characteristics of TBM diagnosed in Malaysia which include its distribution based on geographical area, possible risk factors associated with the disease and the treatment outcome. With a better understanding of the disease characteristics, we hope that the findings could be helpful for future guidance in the clinical approach to TBM.

METHODS

Study Design

This is a cross-sectional study where the data from the National Tuberculosis MyTB database was analyzed. All patients with a diagnosis of TBM from the year 2015 to 2020 were included in this study.

Statistical analysis

SPSS version 21.0 for Windows was used to perform all statistical analyses. Univariate logistics regression analysis was executed to determine the independent associations between age group, gender, ethnicity, citizenship, residential area, education level, income status, HIV status, smoking status, diabetes mellitus status and TBM infection.

RESULTS

Between the years of 2015 and 2020, 2072 patients were registered in MyTB database for tuberculous meningitis, accounting for 1.36% of the total 152,660 TB cases. The annual incident rate ranges between 0.96 to 1.2 per 100,000 people in Malaysia. Figure 1 shows that TBM constitutes between 1.2%–1.5% of TB cases each year. The lowest number of incidents (300 cases, 1.2%) was reported in 2016, while the largest number (387, 1.5% cases) was reported in 2017, followed by the year 2019 (374, 1.4% cases). Selangor had the greatest number of cases throughout the 6-year duration with 496 cases (23.93%), followed by Sabah (474 cases, 22.88%) and Sarawak (219 cases 10.57%) (Figure 2).

Variables that showed $p < 0.25$ significance in the univariable analysis (age, citizenship, education level, income status, diabetes mellitus, HIV positivity, smoking and BCG scar) were included in a multiple logistic regression, wherein out of the eight variables, five remained significantly associated with TB meningitis, at the 5% significance level i.e., age, citizenship, HIV positivity, smoking and BCG scar (Table 1).

Non-Malaysian are slightly at higher risk of TBM (AOR 1.61, $p < 0.001$, CI: 1.42, 1.82) compared with Malaysian citizens. Among the Malaysian, the majority of TBM cases registered were of Malay ethnicity (857 cases) followed by Sarawakian (269 cases) and Chinese (244 cases). However, race is not a significant factor for TBM according to the univariate logistic regression as $p > 0.05$. The age group of 15 years and below were most significantly at risk (AOR 4.5, $P< 0.001$, CI: 3.66, 5.53), followed by the age group 25-34 years old (AOR 1.29, $p = 0.002$, CI: 1.10, 1.52) and 15-24 years old (AOR 1.16, $p = 0.100$, CI: 0.97, 1.39). The number of TBM cases is slightly higher among males (1357 cases, 1.4%) compared to female patients (715 cases, 1.3%), but according to univariate logistic regression, gender is not a significant risk factor for TBM as $p > 0.05$. Underlying HIV infection is one of the most significant risk factors for TBM infection both among Malaysian citizens (AOR: 6.36, $p < 0.001$, CI: 5.61, 7.20) and non-Malaysian (AOR: 7.83 $p<0.001$, CI: 5.66, 10.83). Apart from that, individuals with no previous BCG vaccination also possess a higher risk for TBM infection (AOR: 1.23, $p= 0.011$, CI: 1.05, 1.44).

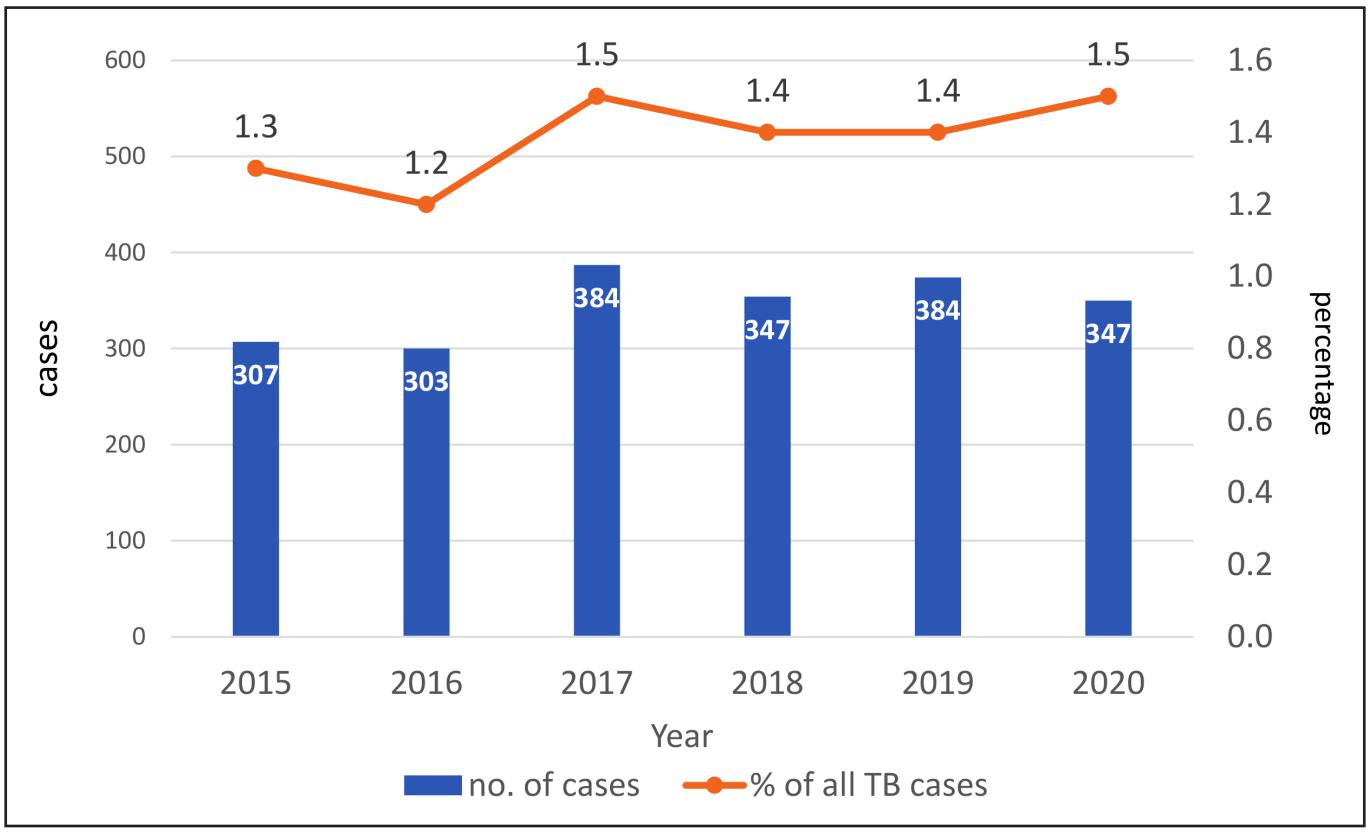

Figure 1. Trends of TBM cases from the year 2015 to 2020.

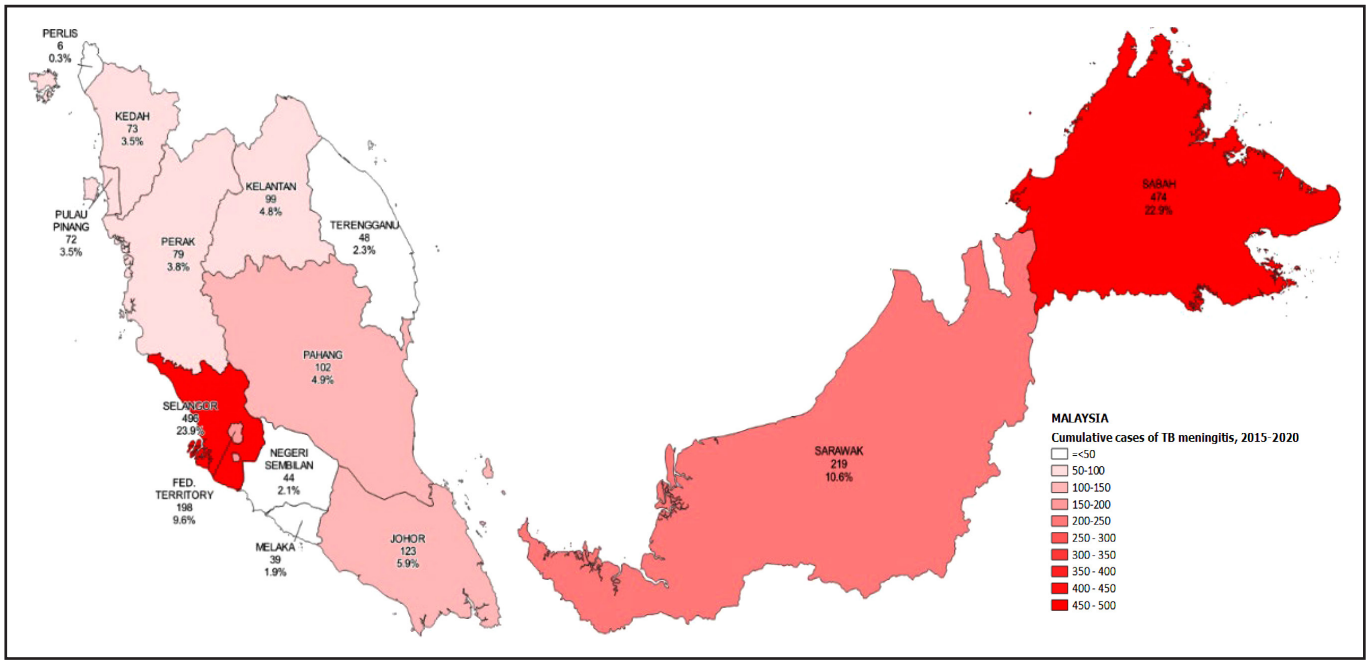

Figure 2. Number of TBM cases according to states in Malaysia.

Patients who are smokers (AOR: 1.25, p<0.001, CI: 1.12, 1.39) are slightly at higher risk of being diagnosed with TBM compared to non-smokers. Other studied factors such as education level, income status, and diabetes mellitus status did not have any significant risk (Table 1 and Table 2).

Upon examination of every possible two-way interaction between the five variables, significant interactions were found between age and citizenship, age and BCG scar and smoking status and BCG scar. Therefore, the analysis was subsequently stratified by citizenship status, with age, HIV positivity, smoking status and BCG scar as the independent variables (Table 3).

Out of 2072 patients diagnosed with TBM, 885 patients (42.7%) passed away while only 806 patients (38.9%) completed their treatment. TBM was stated as the cause of mortality in about 23.44% (173) patients. Out of the 885 patients, 268 (30.28%) patients were diagnosed with HIV. Other common causes of mortality

Table 1. Proportion of tuberculous meningitis cases and crude odds ratio by sociodemographic and clinical factors in Malaysia, 2015–2020 (n = 152,660)

	TB meningitis %	OR (95% CI)	P value
Cases TBM/All TB cases)	1.4 (2072/152,660)		
Sociodemographic			
Age group (years)			
Less than 15	4.1 (167/ 4,043)	4.78 (3.98, 5.74)	<0.001
15-24	1.2 (281/ 22,631)	1.39 (1.20, 1.62)	<0.001
25-34	1.7 (476/ 28,682)	1.87 (1.64, 2.14)	<0.001
35-44	1.5 (397/ 25,669)	1.74 (1.52, 2.00)	<0.001
45-54	1.2 (313/ 25,696)	1.37 (1.18, 1.59)	<0.001
55 and more	0.9 (406 / 45,403)	Ref.	
Gender			
Male	1.4 (1357 / 98,254)	1.05 (0.96, 1.15)	0.28
Female	1.3 (715 / 54,406)	Ref.	
Nationality			
Malaysian	1.3 (1700 / 133,522)	Ref.	
Non-Malaysian	1.9 (372 / 19,138)	1.54 (1.37, 1.72)	<0.001
Race			
Malay	1.3 (857 / 68,368)	0.93 (0.63, 1.35)	0.694
Chinese	1.1 (244 / 22,489)	0.80 (0.54, 1.19)	0.269
Indian	1.4 (124 / 8,703)	1.06 (0.70, 1.60)	0.799
Orang Asli in Peninsular Malaysia	1.7 (20 / 1,172)	1.27 (0.71, 2.26)	0.422
Bumiputera Sarawak	1.4 (269/19,045)	1.05(0.71,1.55)	0.823
Bumiputera Sabah	1.3 (157/11,667)	1.00 (0.66, 1.49)	0.984
Others	1.4 (28/2,072)	Ref.	
Education level			
Not educated	1.6 (448 / 28,834)	0.83(0.57, 1.20)	0.315
Primary	1.2 (296 / 240,30)	0.66(0.45, 0.95)	0.026
Secondary	1.3 (994 / 75,538)	0.70(0.49, 1.00)	0.053
Form 6 / Diploma / Certificate	1.4 (224 / 16,285)	0.73(0.50, 1.07)	0.107
Graduate	1.3 (79 / 6,083)	0.69(0.45, 1.05)	0.083
Others	1.9 (31 /1,658)	Ref.	
Residential			
Urban	1.4 (1146 / 84,225)	1.01 (0.93, 1.10)	0.829
Rural	1.3 (904 / 67,075)	Ref.	
Income status			
No	1.4 (1300 / 91,914)	1.11 (1.02, 1.21)	0.022
Yes	1.3 (772 / 60,514)	Ref.	
Risk Factors			
Diabetes mellitus			
No	1.5 (1812/123,660)	Ref.	
Yes	0.9 (260/28,864)	0.61 (0.54, 0.70)	<0.001
HIV positive			
No	1.1 (1393/124,964)	Ref.	
Yes	6.2 (471/7,557)	5.90 (5.30, 6.56)	<0.001
Smoking			
No	1.4 (1476/103,705)	Ref.	
Yes	1.2 (596/48,819)	0.86 (0.78, 0.94)	0.001
Health care worker			
No	1.3 (2045/150,125)	Ref.	
Yes	1.1 (27/ 2,399)	0.82 (0.56, 1.21)	0.321
BCG scar			
No	1.7 (423/25, 414)	1.29 (1.16, 1.43)	<0.001
Yes	1.3 (1,649/127,110)	Ref.	

Total sample size may not equal 152,660 due to missing data.

Table 2. Multivariate analysis on factors associated with TBM cases in Malaysia, 2015-2020 (n=132,062)

	aOR (95% CI)	*p*-value
Sociodemographic		
Age group (years)		
Less than 15	4.66 (3.79, 5.74)	< 0.001*
15-24	1.19 (0.99, 1.42)	0.063
25-34	1.32 (1.12, 1.55)	< 0.001*
35-44	1.14 (0.97, 1.34)	0.108
45-54	1.05 (0.89, 1.22)	0.591
55 and more	Ref.	
Citizenship		
Malaysian	Ref.	
Non-Malaysian	1.46 (1.22, 1.75)	< 0.001*
Education level		
Not educated	0.91 (0.61, 1.36)	0.645
Primary	0.91 (0.60, 1.37)	0.648
Secondary	0.98 (0.66, 1.46)	0.924
Form 6 / Diploma/Certificate	1.03 (0.68, 1.57)	0.890
Graduate	1.01 (0.64, 1.59)	0.976
Others	Ref.	
Income status		
Yes	1.02 (0.92, 1.13)	0.729
No	Ref.	
Diabetes mellitus		
Yes	1.05 (0.90, 1.22)	0.537
No	Ref.	
HIV positive		
Yes	6.54 (5.82, 7.36)	< 0.001*
No	Ref.	
Smoking		
Yes	1.24 (1.12, 1.38)	< 0.001*
No	Ref.	
BCG scar		
No	1.23 (1.05, 1.44)	0.011*
Yes	Ref.	

among the patients were severe sepsis (18.15%), AIDS (8.13%), and disseminated TB (7.86%) (Table 4).

DISCUSSION

The data analysed in this study was obtained from the MyTB database, a database that registers all the TB cases in Malaysia. Among different forms of TB, TBM is considered the most lethal and disabling with a debilitating prognosis (Li *et al*., 2020). The symptoms of TBM are very similar to those of bacterial meningitis, making the diagnosis of TBM often missed or overlooked. Consequently, it is usually diagnosed at the late stage of the disease with reduced effectiveness of treatment.

The average number of TBM cases in Malaysia is about 346 cases per year. The year 2016 registered the lowest number with 300 cases (1.2% of all TB cases) while the year 2017 had the most with a total of 387 TBM cases (1.5% of all TB cases). With regards to geographical factors, the higher incidence of TB in Selangor state is likely due to its high population and urbanization attracting a high rate of foreign immigration as well as natives moving from other states (Kaur *et al*., 2020)

Our study noted that non-Malaysian citizens have a slightly higher risk to develop TBM. A report by Nissapatorn *et al*. (2007), also showed similar findings of higher TB incidence among foreigners in Malaysia. The spread of TB could be facilitated by most immigrants living in overcrowded conditions with poor socioeconomic status which in turn may explain the higher risk for TBM (Mohidem *et al*., 2021). Unfortunately, there are not many studies on the TBM characteristics among immigrants in Malaysia.

The analysis of our data showed that patients aged less than 15 are at higher risk of developing TBM. This finding is similar to other studies, which revealed that the peak age for TBM is between 0-4 years old (Philip *et al*., 2015; Thwaites *et al*., 2000). Seddon *et al*. (2019) also described similar findings, stating that the median age is ranged from 2 to 4 years according to recent cohorts of children with TBM. The report also states that both the risk of disease progression and the risk of dissemination decrease rapidly in childhood and reach the lowest point at elementary school age. It can be concluded that the risk of developing TB illness, specifically TBM, is age-related with

Table 3. Factors associated with TBM cases among in Malaysia, stratified by citizenship

	Malaysian (n = 115,599)		Non-Malaysian (n = 16,539)	
	aOR (95% CI)[a]	p-value	aOR (95% CI)[b]	p-value
Age group (years)				
Less than 15	3.20 (2.51,4.09)	< 0.001	20.56 (10.88,38.85)	< 0.001
15-24	1.25 (1.04,1.49)	0.015	1.99 (1.05, 3.75)	0.034
25-34	1.34 (1.14, 1.57)	< 0.001	2.47 (1.35, 4.52)	0.003
35-44	1.14 (0.96, 1.35)	0.127	2.17 (1.17, 4.03)	0.015
45-54	1.07 (0.90, 1.27)	0.426	1.48 (0.75, 2.92)	0.263
55 and more	Ref.		Ref.	
HIV positive				
Yes	6.36 (5.61, 7.20)	< 0.001	7.83 (5.66, 10.83)	< 0.001
No	Ref.		Ref.	
Smoking				
Yes	Ref.		Ref.	
No	1.22 (1.09, 1.37)	< 0.001	1.40 (1.05, 1.87)	0.023
BCG scar				
No	1.10 (0.900, 1.34)	0.353	1.47 (1.12, 1.94)	0.006
Yes	Ref.		Ref.	

[a]Hosmer Lemeshow goodness of fit chi square=3.363, p=0.910, percentage correctly classified: 98.7%[b] Hosmer Lemeshow chi square =4.59 p=0.800, percentage correctly classified: 98.0%.

Table 4. Outcome of TBM treatment

Treatment Outcome	2015	2016	2017	2018	2019	2020	Total
Still in treatment	8	3	35	28	24	17	115
Failed treatment	N/A	1	N/A	N/A	1	N/A	2
Deceased	118	132	170	140	172	153	885
Migrated or loss to follow-up	21	8	16	11	10	6	72
Recovered	13	10	9	13	10	19	74
Completed treatment	131	137	125	130	144	139	806
Halted treatment	16	12	19	21	22	13	103
Unknown	N/A	N/A	10	4	1	N/A	15
Total	307	303	384	347	384	347	2072

high incidence among children under the age of two (Donovan *et al*., 2020; Huynh *et al*., 2022).

In this study, we also found that HIV infection is one of the most common risk factors associated to TBM. This finding is consistent with multiple reports finding showing that HIV infection increases the risk for extrapulmonary TB and TBM (Berenguer *et al*., 1992; Seddon *et al*., 2019; Vinnard & MacGregor, 2009). Vinnard & MacGregor (2009) also states that the risk even increases with decreasing level of CD4+ count. In addition to raising the risk of rapid progression of pulmonary tuberculosis (Pormohammad *et al*., 2018), HIV infection also increases the activation of latent TB infection (Vinnard & MacGregor, 2009). It is also known that HIV is associated with higher mortality in TB patients (Katrak *et al*., 2000). According to a study by Dodd *et al*., (2021) it was shown that 35% of the adult patients who died of TBM every year were HIV positive.

Our findings also suggested that individuals who have never received BCG vaccination are more susceptible to TBM infection. According to several studies, BCG has an efficacy of between 75 and 85% preventive rate against TBM (Philip *et al*., 2015; Rock *et al*., 2008). Neonatal BCG immunization was found to protect against TBM in kids up to age 5 with a pooled efficacy of 73% in a global meta-analysis of case-control studies (Huynh *et al*., 2022). Other studies also found that children who received the BCG vaccine and later on diagnosed with TBM had a milder clinical course and better short-term outcomes than their counterparts who did not receive the vaccine (Kumar *et al*., 2005; Rock *et al*., 2008).

In this study, it is noted that smokers are at a slightly higher risk of TBM. Unfortunately, there is no previous research done to directly compare the relationship between TBM and smoking status. There was a study by Quan *et al*. (2022) stated that smoking is a risk factor for TB as smoking hinders the host's immune reaction to *M. tuberculosis*. According to WHO, 21% of Malaysian are smokers as of 2016 (WHO, 2018). This warrants more research to be carried out to study the correlation between TBM and smoking.

It is noted that the mortality rate of TBM is invariably high as 42.7% of patients had passed away. A study by Stadelman *et al*., 2020 states the mortality rate among TBM was 23% at 3 months and 25% at 1 year. Another systemic review and meta-analysis by Wang *et al*. (2019) states the mortality rate was 24.7% among TBM adult patients (95%CI: 18.7–31.9). The study also states that the mortality rate among HIV-positive patients was 50% compared to HIV-negative patients (17%) (Wang *et al*., 2019). Another study conducted in Kota Kinabalu, Sabah indicates that the rate of mortality and severe neurological sequelae were high among TBM patients compared to other central nervous system infections irrespective of anti-tubercular treatment or steroid administration (Lee *et al*., 2016). Therefore, more research is essential to be carried out for a better understanding of TBM pathogenesis which in turn will lead to the discovery of treatment options with better prognosis in patients.

These research findings are valuable in recognizing the epidemiological factors and the nature of TBM in Malaysia. As there are not many studies focusing on the epidemiological data of TBM in Malaysia among both citizens and immigrants in Malaysia, this study could provide a basic and current ideology for further research. On the other hand, the main disadvantage of this study is the inability to explore the clinical features and investigation findings of these TBM patients due to the limitations of the MyTB dataset in addition to the highly variable cause of death reported in MyTB database. To improve future research outcomes, we suggest that the cause of death be standardized in the MyTB database.

TBM still poses a threat to the health care system as it causes a higher rate of mortality and morbidity despite the preventive efforts through BCG vaccination. The best clinical approach to TBM in reducing mortality and morbidity is timely diagnosis and treatment. However, the greatest challenge faced by clinicians is the non-specific clinical symptoms and paucibacillary nature of the infection making the diagnosis very difficult. Clinicians would require a high suspicion in their approach to patients with meningitis symptoms so that the diagnosis of TBM is not missed. It is hoped that with more research carried out focusing on TBM, a faster and more reliable diagnostic method can be developed and improvement in the existing diagnostic tools can be done as well. Apart from improvements in the clinical settings, preventive measures through the reduction of malnutrition, poverty, and low-income households will have a significant impact on TB prevention and control.

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Conflict of Interest

The author declares that there is no conflict of interests in the publication of this study.

Ethical Approval

Medical Research and Ethical Committee (MREC) has approved this research on 15th February 2022 NMRR ID-21-02308-I2N (IIR).

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