Electronic Journal of General Medicine
2024, 21(2), em579
e-ISSN: 2516-3507
https://www.ejgm.co.uk/

MODESTUM

Original Article

OPEN ACCESS

HIV–A prognostic factor of tuberculous meningitis: A retrospective cohort study among adults in peninsular Malaysia

King-Fang Tan [1], Nyi Nyi Naing [2], Nadiah Wan-Arfah [3*], John Tharakan [4], Hanip Rafia [5], Irfhan Ali Hyder Ali [6], Noor Aliza Tarekh [7], Vetriselvan Subramaniyan [8,9], Ling Shing Wong [10**], Siddharthan Selvaraj [11,12]

[1] Sultan Azlan Shah Training Institute of Ministry of Health Malaysia, Ministry of Health Malaysia, Perak, MALAYSIA
[2] Faculty of Medicine, Universiti Sultan Zainal Abidin, Kuala Terengganu, Terengganu, MALAYSIA
[3] Faculty of Health Sciences, Universiti Sultan Zainal Abidin, Kuala Terengganu, Terengganu, MALAYSIA
[4] Department of Neurosciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, MALAYSIA
[5] Department of Neurology, Hospital Kuala Lumpur, Ministry of Health Malaysia, Wilayah Persekutuan, Kuala Lumpur, MALAYSIA
[6] Department of Respiratory, Hospital Pulau Pinang, Ministry of Health Malaysia, Pulau Pinang, MALAYSIA
[7] Department of Respiratory, Hospital Sultanah Aminah, Ministry of Health Malaysia, Johor Bahru, Johor, MALAYSIA
[8] Pharmacology Unit, Jeffrey Cheah School of Medicine and Health Sciences, Monash University, Jalan Lagoon Selatan, Bandar Sunway, 47500 Selangor Darul Ehsan, MALAYSIA
[9] Center for Transdisciplinary Research, Department of Pharmacology, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, 600077, INDIA
[10] Faculty of Health and Life Sciences, INTI International University, Nilai, MALAYSIA
[11] Faculty of Dentistry, AIMST University, Bedong, Kedah, MALAYSIA
[12] Centre for Global Health Research, Saveetha Medical College and Hospital, Chennai, Tamil Nadu, INDIA
***Corresponding Author:** wanwaj@unisza.edu.my
****Corresponding Author:** lingshing.wong@newinti.edu.my

Citation: Tan K-F, Naing NN, Wan-Arfah N, Tharakan J, Rafia H, Hyder Ali IA, Tarekh NA, Subramaniyan V, Wong LS, Selvaraj S. HIV–A prognostic factor of tuberculous meningitis: A retrospective cohort study among adults in peninsular Malaysia. Electron J Gen Med. 2024;21(2):em579. https://doi.org/10.29333/ejgm/14402

ARTICLE INFO

Received: 02 Aug. 2023

Accepted: 14 Oct. 2023

ABSTRACT

Background: Tuberculous meningitis is a major public health issue, despite showing low incidence, tuberculous meningitis causes substantial mortality. For better clinical management, identification of prognostic factors is crucial to reduce health risk of Malaysian society. Therefore, the aim of this study was to determine the prognostic factors of adult tuberculous meningitis in peninsular Malaysia.

Materials & methods: Initially, a retrospective cohort study and one-year of follow-up period was carried out. In addition, a total of 217 adult tuberculous meningitis patients treated or had follow-up in four tertiary hospitals in peninsular Malaysia were recruited. Cox proportional hazards regression was employed to perform multivariable analysis.

Results: The overall survival probability of adult tuberculous meningitis was 36.8% with median survival time 244 days. Significant prognostic factors were Glasgow coma scale score (aHR=0.71, 95% CI=0.65, 0.76; p<0.001), HIV status (aHR=1.94, 95% confidence interval [CI]=1.19, 3.15; p=0.008), headache (aHR=0.48, 95% CI=0.31, 0.76; p=0.002) and meningeal enhancement (aHR=0.47, 95% CI=0.30, 0.74; p=0.001), nausea (aHR=2.21, 95% CI=1.33, 3.66; p=0.002), and vomit (aHR=0.58, 95% CI=0.36, 0.93; p=0.023).

Conclusions: Evidently, the survival of among adults with tuberculous meningitis was low. Since HIV positive has a significant influence in mortality; early screening, diagnosis, and prompt treatment in this subgroup of patients play a key role in survival.

Keywords: prognosis, meningeal enhancement, tuberculosis, tuberculous meningitis, epidemiology, health risk

INTRODUCTION

Tuberculosis is caused by *mycobacterium tuberculosis* infection commonly in lungs, which is called pulmonary tuberculosis. Extrapulmonary tuberculosis is usually caused by dissemination of *mycobacterium tuberculosis* by blood or lymph vessel to other organs in the body. It occurs when the bacteria disseminated to the brain and eventually causes infection in meninges. Tuberculous meningitis is believed to be increased in trend following the increase of tuberculosis and HIV prevalence; thus, our study provides insights on the association between HIV and tuberculous meningitis among the adults in peninsular Malaysia.

Tuberculosis is a global epidemic. World Health Organization (WHO) estimates that one third of the world's population has latent tuberculosis and is infected by *mycobacterium tuberculosis*. Each year, a total of nine million new cases were diagnosed and more than one million cases were HIV positive while half a million cases were multidrug resistance tuberculosis (MDR-TB) and nearly two million deaths were caused by tuberculosis [1].

In year 2012, the largest number of new tuberculosis cases occurred in Asia, accounting for 58.0% of new cases globally [1]. Although Malaysia is not listed in WHO high TB burdened country, out of 29 million population in Malaysia, 22,710 of people were reported to have tuberculosis and 1,414 deaths were caused by tuberculosis in year 2012 [2]. Besides that, in year 2012 itself, a total of 21,249 new cases of tuberculosis were reported, which 2,300 cases were tuberculosis with HIV positive and 2,945 cases were extra-pulmonary tuberculosis [3].

Tuberculous meningitis is the most critical form of tuberculosis associated with high mortality and morbidity rate despite its low incidence rate. Mortality rate of tuberculous meningitis worldwide is around 15.3% to 38.9% [4-6]. A local study reported 27.5% of death, 25.0% morbidity and 47.5% survive without complication [7]. The median time of death was reported at 64 days [5]. In HIV-infected patients, the median survival time was estimated from 20 days (range one to 172 days) to three month (95% confidence interval [CI]=2, 4) [8]. Corticosteroids is reported to reduce the mortality rate by 20.0% (RR=0.8, 95% CI=0.7, 0.9, NNT=10) in all stage of tuberculous meningitis [9]. There are relatively few prognostic studies of tuberculous meningitis that had been done nationally and worldwide. Therefore, the main aim of this study was to determine the survival and prognostic factors of adult tuberculous meningitis patients in peninsular Malaysia.

MATERIALS & METHODS

A retrospective cohort study was conducted among patients aged 18 and above, admitted with a diagnosis of tuberculous meningitis to the Hospital Kuala Lumpur (HKL), Hospital Universiti Sains Malaysia (HUSM), Hospital Pulau Pinang (HPP), and Hospital Sultanah Aminah (HSA). These tertiary hospitals were purposively selected in this study to cover the area of peninsular Malaysia.

The calculation of sample size was based on the level of significance (α=0.05) and pre-determined power (1-β=0.80) by using power, from the expert opinion obtained from previous studies by using PS sample size calculation software in the year 2020 [10, 11]. An estimated 20.0% was added in anticipation of missing data or loss to follow-up. The predetermined sample size was 205 patients. There was no probability sampling method applied. All available folders in HUSM, HPP, and HAS been reviewed. In HKL, medical folders were reviewed until the required sample size was met.

Study Factors & Outcome

The patient's medical records were reviewed, and the following information was extracted: demographic characteristics, underlying disease, clinical features, image studies, use of steroids, mannitol, day in which treatment started and clinical outcome. Brain computed tomography (CT) scans or magnetic resonance imaging (MRI) studies were done for most patients after admission. Findings consistent with tuberculous meningitis in brain CT and MRI scans were, as follows: hydrocephalus, meningeal enhancement, tuberculoma, vasculitis or infarcts. The event in this study was the survival time defined as the time interval between time of clinical onset and time of event measured in days. The censored observations were those who complete recovery, survived with sequelae and who were lost to follow-up.

Statistical Analysis

The continuous variables were expressed as median (IQR) and categorical variables as a proportion of the total number of patients. Kaplan-Meier method was used to perform survival estimates while the log-rank test for comparison of survival distribution.

Cox proportional hazards regression model was employed to perform univariable analysis and multivariable analysis of the variables, respectively. To eliminate confounding factors in predicting the risk for mortality, varia-bles with p-values≤0.25 by univariable analysis were selected for multivariable Cox proportional hazard regres-sion model for further assessment. All statistical calculations were analyzed using Stata SE version 11.0. Results were expressed as adjusted hazard ratios and corresponding 95% confidence interval (CI). A p-value of <0.05 was regarded as significant.

RESULTS

Among the 217 cases, 157 (72.3%) were Malaysia citizens and 60 (27.7%) were foreigners. Cases are predominantly male (68.7%) and Malay (44.7%). Among 120 non-Malay cases, other race (foreigners) comprised the majority with 62 (28.6%), Chinese 31 (14.3%), and followed by Indian 27 (12.4%). The age of the cases was ranged between 18 to 73 years old, median (IQR)=39 (19). There were 98 (45.2%) who had extra-meningeal tuberculosis and 81 (37.3%) were having active infection of pulmonary tuberculosis.

The duration to onset of anti-tuberculosis treatment (duration of clinical symptom to-day of treatment started) were one to 289 days with median (IQR)=15 (22). Adjunctive steroid therapy was used in 162 (74.7%) of the cases (**Table 1**).

Table 1. Demographic & clinical characteristics of tuberculous meningitis patients according to death outcome (n=217)

Socio-demographic characteristics	Frequency (%)		Median (IQR)	
	Death	Censored	Death	Censored
Age (year)			40 (22)	38 (19)
Gender				
Male	70 (74.5)	79 (64.2)		
Female	24 (25.5)	44 (35.8)		
Race				
Malay	38 (40.4)	59 (48.0)		
Chinese	15 (16.0)	16 (13.0)		
Indian	9 (9.6)	18 (14.6)		
Others	32 (34.0)	30 (24.4)		
Occupation				
Labor workers	14 (14.9)	13 (10.6)		
Non-labor	21 (22.3)	46 (37.4)		
Inmates	17 (18.1)	5 (4.0)		
Not available	42 (44.7)	59 (48.0)		
HIV status				
Positive	27 (28.7)	27 (21.9)		
Negative	67 (71.3)	96 (78.1)		
Diabetes mellitus				
Yes	19 (20.2)	12 (9.8)		
No	75 (79.8)	111 (90.2)		
Hypertension				
Yes	19 (20.2)	20 (16.3)		
No	75 (79.8)	103 (83.7)		
Extra meningeal tuberculosis				
Yes	52 (55.3)	46 (37.4)		
No	42 (44.7)	77 (62.6)		

Table 1 (Continued). Demographic & clinical characteristics of tuberculous meningitis patients according to death outcome (n=217)

Socio-demographic characteristics	Frequency (%)		Median (IQR)	
	Death	Censored	Death	Censored
Active pulmonary tuberculosis				
Yes	38 (30.9)	43 (45.7)		
No	85 (69.1)	51 (54.3)		
Nausea				
Yes	34 (36.2)	28 (22.8)		
No	60 (63.8)	95 (77.2)		
Vomiting				
Yes	39 (41.5)	66 (53.7)		
No	55 (58.5)	57 (46.3)		
Headache				
Yes	52 (55.3)	87 (70.7)		
No	42 (44.7)	36 (29.3)		
Kernig's sign				
Negative	85 (90.4)	101 (82.1)		
Positive	9 (9.6)	22 (17.9)		
Altered level of consciousness				
Yes	72 (76.7)	76 (61.8)		
No	22 (23.4)	47 (38.2)		
Loss of consciousness				
Yes	53 (56.4)	26 (21.1)		
No	41 (43.6)	97 (78.9)		
Convulsion				
Yes	31 (33.0)	34 (27.6)		
No	63 (67.0)	89 (72.4)		
Altered sensorium				
Yes	63 (67.0)	67 (54.5)		
No	31 (33.0)	56 (45.5)		
Focal limb weakness				
Yes	62 (66.0)	62 (50.4)		
No	32 (34.0)	61 (49.6)		
Numbness				
Yes	7 (7.4)	16 (13.0)		
No	87 (92.6)	107 (87.0)		
Cranial nerve palsy				
Yes	62 (66.0)	78 (63.4)		
No	32 (34.0)	45 (36.6)		
Hydration				
Normal	49 (52.1)	82 (66.7)		
Dehydrate	43 (45.8)	41 (33.3)		
Overload	2 (2.1)	0 (0.0)		
Hydrocephalus				
Yes	64 (68.1)	70 (56.9)		
No	30 (31.9)	53 (43.1)		
Infarction				
Yes	41 (43.6)	49 (39.8)		
No	53 (56.4)	74 (60.2)		
Meningeal enhancement				
Yes	42 (44.7)	64 (52.0)		
No	52 (55.3)	59 (48.0)		
Tuberculoma				
Yes	42 (44.7)	50 (40.6)		
No	52 (55.3)	73 (59.4)		
CSF glucose level			[a]2.20 (2.2)	[a]2.00 (1.85)
CSF protein level (g/L)			[a]1.54 (1.9)	[a]1.35 (1.36)
GCS score			[b]5.00 (5.0)	[b]13.0(6.00)
BMRC stage				
I	[b]2 (2.2)	[b]40 (34.2)		
II	[b]5 (5.4)	[b]36 (30.8)		
III	[b]85 (92.4)	[b]41 (35.0)		
Mechanical ventilated				
Yes	[c]69 (80.2)	[c]37 (31.9)		
No	[c]17 (19.8)	[c]79 (68.1)		
Days to onset of anti-tuberculous treatment			14.5 (24.0)	16.0 (22.0)

Table 1 (continued). Demographic & clinical characteristics of tuberculous meningitis patients according to death outcome (n=217)

Socio-demographic characteristics	Frequency (%)		Median (IQR)	
	Death	Censored	Death	Censored
Use of steroids				
Yes	68 (72.3)	94 (76.4)		
No	26 (27.7)	29 (23.6)		
Use of dexamethasone				
Yes	68 (72.3)	92 (74.8)		
No	26 (27.7)	31 (25.2)		
Use of prednisolone				
Yes	4 (4.3)	9 (7.3)		
No	90 (95.7)	114 (92.7)		
Use of mannitol				
Yes	6 (6.4)	7 (5.7)		
No	88 (93.6)	116 (94.3)		

Note. [a]Available data 171 (78.8%); [b]Available data 209 (96.3%); & [c]Available data 202 (93.1%)

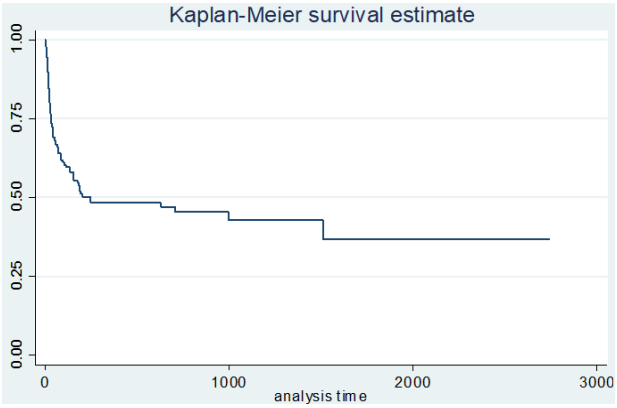

Figure 1. Kaplan-Meier curve for overall survival estimate of adult tuberculous meningitis in peninsular Malaysia (n=217) (*median survival time from onset of symptom to death) (Source: Authors' own elaboration)

The overall survival probability from Kaplan-Meier estimate was 36.8% (SE=0.07) 95% CI=0.23, 0.50. The median survival time from onset of symptom to death for adult tuberculous meningitis patients was 244 days (SE=269.72) (**Figure 1**).

The prognostic factors of tuberculous meningitis patients based on health characteristics by simple Cox proportional hazards regression found that the presence of extra-meningeal tuberculosis, active tuberculosis and HIV positive status had significant higher risk of dying compared to absence and negative status. Retrovirus positive patients had 81.0% higher risk of dying compared to retrovirus negative patients. Clinical characteristics such as absence of headache, altered level of consciousness, loss of consciousness, altered sensorium, abnormal hydration status, BMRC stage III, decrease of GCS score and mechanical ventilation were found as significant prognostic factors of adult tuberculous meningitis.

Patients who were not presented with headache had higher risk of dying by 51.0% compared to patients who developed headache. BMRC stage III patients had 23.63 times higher risk of dying compared to BMRC stage I patients. Decrease of one unit of GCS score had increased 25.0% risk of dying. Patients who were mechanically ventilated had 5.66 times higher risk of dying compared to those who were not mechanically ventilated. However, simple Cox proportional hazards regression analysis found no significant risk difference among treatment characteristics (**Table 2**).

Table 2. Prognostic factors of adult tuberculous meningitis patients using simple Cox proportional hazards regression

Variable	Simple Cox proportional hazards regression			
	[a]RC	[b]CHR (95% CI)	Wald test	p-value
Gender				
Male	0.54	1.72 (1.08, 2.74)	2.28	0.023
Female	0	1		
Race				
Malay	-0.60	0.55 (0.34, 0.88)	-2.47	0.014
Chinese	-0.42	0.66 (0.36, 1.22)	-1.32	0.186
Indian	-0.68	0.51 (0.24, 1.07)	-1.79	0.073
Others	0	1		
Occupation				
Labor workers	0.97	2.64 (1.33, 5.25)	2.77	0.006
Non-labor	0	1		
Inmates	1.52	4.58 (2.41, 8.70)	4.64	<0.001
Not available	0.43	1.54 (0.91, 2.61)	1.62	0.106
Extra meningeal tuberculosis				
Yes	0.55	1.73 (1.15, 2.60)	2.65	0.008
No	0	1		
Active PTB				
Yes	0.51	1.67 (1.11, 2.5)	2.48	0.013
No	0	1		
HIV status				
Positive	0.59	1.81 (1.15, 2.8)	2.57	0.010
Negative	0	1		
Diabetes mellitus				
Yes	0.35	1.42 (0.86, 2.3)	1.37	0.172
No	0	1		
Hypertension				
Yes	-0.05	0.95 (0.58, 1.5)	-0.18	0.857
No	0	1		
Altered level of consciousness				
Yes	0.61	1.84 (1.14, 2.9)	2.49	0.013
No	0	1		
Loss of consciousness				
Yes	1.16	3.19 (2.11, 4.8)	5.50	<0.001
No	0	1		
Altered sensorium				
Yes	0.46	1.59 (1.03, 2.4)	2.10	0.035
No	0	1		
Focal limb weakness				
Yes	0.35	1.4 (0.92, 2.17)	1.59	0.112
No	0	1		
Numbness				
Yes	-0.50	0.61 (0.28, 1.3)	-1.26	0.207
No	0	1		
Hydration status				
Normal	0	1		
Dehydrate	0.62	1.86 (1.23, 2.8)	2.91	0.004
Overload	2.78	16.2 (3.7, 69.6)	3.74	<0.001
CSF glucose level	-0.02	0.98 (0.85, 1.1)	-0.36	0.717
CSF protein level (g/L)	0.04	1.04 (0.95, 1.1)	0.85	0.393
Hydrocephalus				
Yes	0.36	1.44 (0.93, 2.2)	1.63	0.103
No	0	1		
Infarction				
Yes	0.20	1.23 (0.82, 1.8)	0.98	0.327
No	0	1		
Meningealenhancement				
Yes	-0.26	0.77 (0.5, 1.16)	-1.23	0.219
No	0	1		
Tuberculoma				
Yes	-0.04	0.96 (0.6, 1.45)	-0.17	0.862
No	0	1		
BMRC stage				
I	0	1		
II	0.99	2.7 (0.52, 13.9)	1.19	0.236
III	3.16	23.6 (5.8, 96.3)	4.33	<0.001
Day onset to treatment	-0.003	1.0 (0.99, 1.00)	-1.09	0.277
Use of steroids				
Yes	-0.18	0.84 (0.53, 1.3)	-0.77	0.439
No	0	1		
Use of dexamethasone				
Yes	-0.08	0.92 (0.59, 1.4)	-0.34	0.733
No	0	1		
Use of prednisolone				
Yes	-0.72	0.49 (0.18, 1.3)	-1.40	0.162
No	0	1		

Note. [a]RC: Crude regression coefficient & [b]CHR: Crude hazards ratio

Table 3. Prognostic factors of adult tuberculous meningitis patients in peninsular Malaysia using multiple Cox proportional hazards regression on forward LR method (n=217)

Variable	Multiple Cox proportional hazards regression			
	RC (b)	[a]AHR (95% CI)	[b]WS (df)	[c]p-value
GCS	-0.35	0.7 (0.65, 0.76)	-8.74	<0.001
HIV status				
Yes	0.66	1.94 (1.2, 3.15)	2.67 (1)	0.008
No	0	1		
Headache				
Yes	-0.73	0.48 (0.3, 0.76)	-3.13 (1)	0.002
No	0	1		
Meningeal enhancement				
Yes	-0.75	0.47 (0.3, 0.74)	-3.26 (1)	0.001
No	0	1		
Nausea				
Yes	0.79	2.2 (1.33, 3.66)	3.08 (1)	0.002
No	0	1		
Vomiting				
Yes	-0.54	0.58 (0.36, 0.9)	-2.27 (1)	0.023
No	0	1		

Note. RC: Regression coefficient; AHR: Adjusted hazards ratio; WS: Wald statistics; Multiple proportional hazards Cox regression model: Forward stepwise LR selection method was applied; Multicollinearity & interaction were unlikely; Global test, p=0.820, model proportional hazards assumption was checked & reported to be proportionate & constant over time; Regression diagnostic was performed by estimated residuals Cox-Snell, martingale, & deviance & influential analysis; Influential outliers were identified by checking percent changes in regression coefficient set at 20%; & No influential outlier was found, & model fit well with observations

The multivariable analysis found that only GCS, HIV status, headache, meningeal enhancement, nausea, and vomiting significantly predict the risk of mortality (**Table 3**).

The increase of one unit of Glasgow coma scale score had reduced the probability of dying by 29.0% (HR=0.71, 95% CI=0.65, 0.76, p<0.001). HIV positive patients had 94.0% higher risk of dying compared to HIV negative patients (HR=1.94, 95% CI=1.19, 3.15, p=0.008). Patients who had headache was 52.0% lower risk of dying compared to patients who did not have headache (HR=0.48, 95% CI=0.31, 0.76, p=0.002). Patients who had nausea was 2.21 times higher risk of dying compared to patients who did not have nausea (HR=2.21, 95% CI=1.33, 3.66, p=0.002). Patients who had vomiting episodes had 42.0% lower risk of dying compared to pa-tients who did not have vomiting (HR=0.58, 95% CI=0.36, 0.93, p=0.023). Patients with meningeal enhancement in imaging finding had 53% lower risk of dying compared to patient without meningeal enhancement (HR=0.47, 95% CI=0.30, 0.74, p=0.001).

DISCUSSION

In this study, out of 217 adult tuberculous meningitis patients, 94 (43.3%) died, 17 (7.8%) survive with sequelae, 41 (18.9%) survive without sequelae and 65 (30.0%) lost to follow up. This finding was slightly higher compared with previous finding of overall mortality 15.3% to 38.9% [12, 14]. A total of 75.0% of death in this study occurred within 69 days (started from the first day clinical symptom), which was three time longer compared to 21 days in the previous study [15]. The overall median survival time of this study was 244 days and overall survival rate was 36.8% (over seven years study period and one year follow up). This indicates that the tuberculous meningitis is an acute disease with high mortality. The high percentage in survived with sequelae, later contribute to further morbidity and mortality. A previous local study reported 25.0% survived with sequelae and 47.5% survived without sequelae [16].

Compared to the previous study, our study showed less survival with sequelae (7.8%) and less survival without sequelae (18.9%). The survival probability in female (55.5%) was higher compared to male (24.2%). Median survival time for female cannot be estimated in this study, whereas male patients had only 155 days of median survival time, which was 89 days shorter than the overall median survival time. A previous study reported that, there was a low female: male ratio in prevalence of tuberculosis [17]. A meta-analysis in Brazil also revealed a marginally significant male bias in exposure to *mycobacterium tuberculosis* (random-effects OR=1.16, 95% CI=1.00, 1.36; n=6,725 subjects) [18]. A genetic study suggested that sexual hormones may play a part in protection or susceptibility to tuberculosis.

The possible role of sex steroids in tuberculosis was also strengthened by the fact that the progression-to-disease and mortality rates are higher in females during their reproductive years, after which such rates turn again to be higher in men. The study in female mice demonstrated more resistant to infection with bacteria of two species related to *mycobacterium tuberculosis.* This showed that the difference of gender may have different innate resistance mechanism mediate by phagocytes. Estrogens in female has been shown to increase the activity of IFNc gene promoter, which then causes increase IFNc production and activate protective Th1 response. However, the levels of steroid hormones vary not only between the sexes, but also with age and physiological state (e.g., menstrual cycles and gestation) [19].

The occupation of the patients significantly predicted the survival probabilities. Inmates (17.1%) had the lowest survival rate, followed by labor workers (26.5%), unknown occupation (44.5%) and non-labor workers (53.8%). The median survival time for inmates was only 16 days, whereas, 43 days for labor worker and 191 days for unknown occupation (p<0.001, log rank test). These might probably because the proportion of HIV positive among inmates was large. In this study, out of 17 deaths among inmates, 12 (70.6%) were HIV positive, 11 (64.7%) were intravenous drug user (IVDU), nine (52.9%) had extra meningeal tuberculosis, eight (47.1%) had active pulmonary tuberculosis, and one (5.9%) had diabetes mellitus. Besides that, the confined space and crowded area in the prison, detention or rehabilitation camp causes infection of pulmonary tuberculosis, malnutrition and further reduces of immune system of HIV positive inmates. Thus, reduced the survival of inmates.

Extra meningeal tuberculosis patients had significantly lower survival probability 23.5% versus 48.7% in patients without extra meningeal tuberculosis. The median survival time in extra meningeal tuberculosis patients was 11 days shorter than patients who did not have extra meningeal tuberculosis (p=0.007, log rank test). However, extra meningeal tuberculosis was found insignificant in both univariable (p=0.074) and multivariable analysis (p=0.845). Patients with active pulmonary tuberculosis were also had similar finding in this study. Compared to extra meningeal tuberculosis, patients with concomitant active pulmonary tuberculosis had a lower survival probability (19.2%) and a shorter median survival time (83 days). The difference might be due to the concomitant effect of active pulmonary tuberculosis, which causes systemic infection thus further weakened the immune system. In addition, miliary tuberculosis were reported as an independent predictor for death in previous study [20].

HIV positive patients (27.7%) had lower survival probability compared to HIV negative patients (46.0%). The median survival time in retrovirus positive patients was 153 days, which was significantly shorter than patients with negative status (704 days) (p=0.009, log rank test). This is like other study, which reported that the six-to-nine-month survival rate was significantly decreased in HIV infected patients [21, 22]. The significant difference among HIV positive and HIV negative patients were studied in few studies. A prospective cohort study in Vietnam revealed that HIV infection did not alter the neurological presentation of tuberculous meningitis, although additional extrapulmonary tuberculosis was more likely to occur in HIV infected patients [22] In this study, 29 (53.7%) HIV positive patients had extra meningeal tuberculosis and 18 (62.1%) of them died. Whereas 23 (42.6%) HIV positive patients had concomitant active pulmonary tuberculosis and 15 (55.6%) of them died. A previous study in HIV-associated tuberculosis had shown clear survival benefit in patients receiving antiretroviral therapy (ART) during tuberculosis therapy [23]. However, immediate ART was found not significantly associated with nine-month mortality [24, 25]. Whereas starting ART prior to or during tuberculosis treatment may be associated with lower mortality in patients with HIV associated tuberculosis [26]. In our study, seven (63.6%) patients with ART and 20 (46.5%) patients without ART died. The survival of ART therapy group was lower but no significant difference between groups was found.

Also, headache was reported among tuberculous meningitis patients 139 (64.1%) and only 52 (37.4%) of them died compared to 42 (44.7%) death in patients without symptom of headache. This profound clinical manifestation had revealed a higher survival probability of 40.6% compared to 33.4% who had not presented it. The median survival time for patients with the absence of headache was 69 days, whereas the median survival time increased significantly to 996 days with the presence of headache (p=0.001, log rank test). This finding was like previous study, which reported headache as an independent predictor in univariable [27] and multivariable analysis [28]. Headache as a predictor might be due to its strong disturbance in activity of daily living (ADL) of patients thus promote earlier seek for treatment and earlier diagnosis of tuberculous meningitis. Altered level of consciousness (29.7%) was found to significantly reduce the survival probability of tuberculous meningitis patients compared to normal conscious patients (54.2%). Patients with altered level of consciousness had only 155 days of median

survival time (p=0.011, log rank test). Loss of consciousness, another more severe form of change of conscious level, where no response was given by the patients can be transient or prolonged coma. In this study, the survival probability for loss of consciousness was only 22.0% compared to without loss of consciousness 48.4%. Patients with loss of consciousness had only 52 days of survival, which was three times shorter than in altered level of consciousness alone. Similar study also reported higher odds of death among comatose patients [29]. Besides that, altered sensorium was also found significantly influence the survival probability of tuberculous meningitis patients. Patients with altered sensorium had a survival probability of 25.3% and median survival time of 185 days only, similar finding was reported [30]. These clinical manifestations were closely related to the clinical changes in the brain, hydrocephalus, which might give rise to either obstructive or communicating causes increase in intracranial pressure, which thus altered brainstem function.

Hydration level was found significant in predicting the median survival time (p<0.001, log rank test). Patients with overload hydration status had only five days median survival time compared to dehydration (96 days) and normal hydration (1510 days). Cerebral salt wasting syndrome [31] and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [32] were found to explain the relationship between hydration level and death of tuberculous meningitis in detail.

Over the decades, BMRC stage was used to classify the severity of disease and it was found significantly predictive of the survival among tuberculous meningitis patients. In this present study, stage III patients were found to have significant lower survival probability (10.5%) compared to stage I (86.6%) and stage II (75.0%). Median survival time for stage III patients was only 43 days. Thus, severity of disease was found significantly associated with mortality [33]. Mechanical ventilated patients had 43 days of median survival time and a significantly lower survival probability of 20.1% compared to patients who had not been mechanically ventilated (59.3%) (p<0.001, log rank test). The needs of mechanical ventilation were presented by the disease severity and the brainstem involvement.

In univariable analysis, institution, gender, race, occupation, presence of extra meningeal tuberculosis, concomitant active pulmonary tuberculosis, HIV status, presence of headache, altered level of consciousness, loss of consciousness, altered sensorium, hydration status, BMRC stage, GCS score and mechanical ventilated were identified as prognostic factor for adult tuberculous meningitis. GCS score was found as a more significant independent prognostic factor for death of tuberculous meningitis compared to BMRC stage and APACHE II [34].In this study, an increase of one unit score of GCS was found to reduce the risk of dying by 25.0% (HR=0.75, 95% CI=0.71, 0.80; p<0.001), with the minimum GCS score of three and maximum score of 15. This predictor role was also found highly significant in the multivariable analysis with a higher hazards' ratio (adjusted HR=0.71, 95% CI=0.65, 0.76; p<0.001).

In the multivariable analysis, GCS score, HIV status, and headache continued to be significant independent predictors for tuberculous meningitis. Whereas meningeal enhancement, nausea and vomiting were found significant to predict death for adult tuberculous meningitis in conjunction with other independent predictors. Presence of meningeal enhancement was found to reduce the risk of dying by 53.0% (adjusted HR=0.47, 95% CI=0.30, 0.74; p=0.001). This might be due to classical presentation of meningeal enhancement in tuberculous meningitis, which promotes early diagnosis and treatment thus increase the survival of the patients. Besides that, the presence of vomiting in presentation also significantly reduced the risk of dying by 42.0% (adjusted HR=0.58, 95% CI=0.36, 0.93; p=0.023). Vomiting is a profound clinical presentation among tuberculous meningitis, which was usually associated with changes of intracranial pressure and hydrocephalus. Therefore, the presence of vomiting usually sped up the diagnosis of the disease and commence of treatment. Nausea was found as prognostic factor for tuberculous meningitis, which had increased the risk of dying by 2.21 time (adjusted HR=2.21, 95% CI=1.33, 3.66, p=0.002). This is because nausea is less distressing, less prominent clinical manifestation and theoretically less meaningful in differential diagnosis of disease, thus causing the diagnosis and treatment delay.

Benefits of Study

Our study findings, aid in the advancement of knowledge on prognostic factors of tuberculous meningitis and provides facts, refinement of current hypotheses and offers insights and potential solutions.

Limitations of Study

A small sample size may limit generalizability of findings to a larger population. Our participants' responses may be impacted by how questions are worded or the context in which they are presented, resulting in skewed conclusions if it does not appropriately represent the diversity of the community.

CONCLUSIONS

Overall, the survival of adult tuberculous meningitis was low. Adult patients with lower GCS score, HIV positive status, presented with nausea, absence of headache, absence of meningeal enhancement and absence of vomiting had a higher risk of dying from tuberculous meningitis. Current drug therapy and diagnostic test however did not reduce the mortality among tuberculous meningitis patients. Therefore, further screening plan and treatment plan are needed for earlier diagnosis and treatment to prevent mortality.

Author contributions: All authors have sufficiently contributed to the study and agreed with the results and conclusions.

Funding: No funding source is reported for this study.

Acknowledgements: The authors would like to thank the Director General of Ministry of Health Malaysia for permission to publish this article, and the whole staff in medical records, chest clinics in Hospital Kuala Lumpur, Hospital Universiti Sains Malaysia, Hospital Pulau Pinang, and Hospital Sultanah Aminah.

Ethical statement: The authors stated that the study received approval from Human Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/272.3. [1.5]) and Malaysia Research & Ethics Committee (NMRR-13-771-16977). Written informed consents were obtained from the participants.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

REFERENCES

1. Glaziou P, Floyd K, Raviglione MC. Global epidemiology of tuberculosis. Semin Respir Crit Care Med. 2018;39(3):271-85. https://doi.org/10.1055/s-0038-1651492 PMid: 30071543
2. Diah IM, Aziz N, Ahmad N. Relative risk estimation of tuberculosis with standardized morbidity ratio in Malaysia. Glob J Pure Appl Math. 2016;12(5):4011-9.
3. Adejumo OA, Daniel OJ, Otesanya AF, et al. Factors associated with TB/HIV co-infection among drug sensitive tuberculosis patients managed in a secondary health facility in Lagos, Nigeria. Afr J Infect Dis. 2017;11(2):75-82. https://doi.org/10.21010/ajid.v11i2.10 PMid:28670643 PMCid:PMC5476816
4. Jullien S, Ryan H, Modi M, Bhatia R. Six months therapy for tuberculous meningitis. Cochrane Database Syst Rev. 2016;9(9):CD012091. https://doi.org/10.1002/14651858.CD012091.pub2 PMid:27581996 PMCid:PMC5018659
5. Schaller MA, Wicke F, Foerch C, Weidauer S. Central nervous system tuberculosis: Etiology, clinical manifestations and neuroradiological feature. Clin Neuroradiol. 2019;29(1):3-18. https://doi.org/10.1007/s00062-018-0726-9 PMid: 30225516
6. Ozturk-Engin D, Popescu CP. Tuberculous meningitis. In: Sener A, Erdem H, editors. Extrapulmonary tuberculosis. Springer; 2019. p. 101-120. https://doi.org/10.1007/978-3-030-04744-3_8
7. Sy MCC, Espiritu AI, Pascual 5th JLR. Global frequency and cinical features of stroke in patients with tuberculous meningitis: A systematic review. JAMA Netw Open. 2022;5(9):e2229282. https://doi.org/10.1001/jamanetworkopen.2022.29282 PMid:36048445 PMCid:PMC9437750
8. Rewari BB, Kumar A, Mandal PP, Puri AK. HIV TB coinfection-perspectives from India. Expert Rev Respir Med. 2021;15(7):911-30. https://doi.org/10.1080/17476348.2021.1921577 PMid:33900861
9. Donovan J, Figaji A, Imran D, Phu NH, Rohlwink U, Thwaites GE. The neurocritical care of tuberculous meningitis. Lancet Neurol. 2019;18(8):771-83. https://doi.org/10.1016/S1474-4422(19)30154-1 PMid:31109897
10. Urlacher BR. Complexity, causality, and control in statistical modeling. Am Behav Sci. 2020;64(1):55-73. https://doi.org/10.1177/0002764219859641
11. Young C, Walzl G, Du Plessis N. Therapeutic host-directed strategies to improve outcome in tuberculosis. Mucosal Immunol. 2020;13(2):190-204. https://doi.org/10.1038/s41385-019-0226-5 PMid:31772320 PMCid:PMC7039813
12. Cresswell FV, Te Brake L, Atherton R, et al. Intensified antibiotic treatment of tuberculosis meningitis. Expert Rev Clin Pharmacol. 2019;12(3):267-88. https://doi.org/10.1080/17512433.2019.1552831 PMid:30474434
13. Wen L, Li M, Xu T, Yu X, Wang L, Li K. Clinical features, outcomes and prognostic factors of tuberculous meningitis in adults worldwide: Systematic review and meta-analysis. J Neurol. 2019;266(12):3009-21. https://doi.org/10.1007/s00415-019-09523-6 PMid:31485723
14. Stadelman AM, Ellis J, Samuels THA, et al. Treatment outcomes in adult tuberculous meningitis: A systematic review and meta-analysis. Open Forum Infect Dis. 2020;7(8):ofaa257. https://doi.org/10.1093/ofid/ofaa257 PMid:32818138 PMCid:PMC7423296
15. Abdulaziz ATA, Li J, Zhou D. The prevalence, characteristics and outcome of seizure in tuberculous meningitis. Acta Epileptol. 2020;2(1):1-8. https://doi.org/10.1186/s42494-020-0010-x
16. Selvaraj JU, Sujalini BB, Rohitson MS, George AA, Arvind VH, Mishra AK. Identification of predictors of cerebrovascular infarcts in patients with tuberculous meningitis. Int J Mycobacteriol. 2020;9(3):303-8. https://doi.org/10.4103/ijmy.ijmy_107_20 PMid:32862165
17. Horton KC, Hoey AL, Béraud G, Corbett EL, White RG. Systematic review and meta-analysis of sex differences in social contact patterns and implications for tuberculosis transmission and control. Emerg Infect Dis. 2020;26(5):910-9. https://doi.org/10.3201/eid2605.190574 PMid:32310063 PMCid:PMC7181919
18. Chidambaram V, Tun NL, Majella MG, et al. Male sex is associated with worse microbiological and clinical outcomes following tuberculosis treatment: A retrospective cohort study, a systematic review of the literature, and meta-analysis. Clin Infect Dis. 2021;73(9):1580-8. https://doi.org/10.1093/cid/ciab527 PMid:34100919 PMCid:PMC8563313
19. Al-Ghafli H, Varghese B, Enani M, et al. Demographic risk factors for extra-pulmonary tuberculosis among adolescents and adults in Saudi Arabia. PloS One. 2019;14(3):e0213846. https://doi.org/10.1371/journal.pone.0213846 PMid:30917151 PMCid:PMC6436801
20. Hsu P-C, Yang C-C, Ye J-Jr, Huang P-Y, Chiang P-C, Lee M-H. Prognostic factors of tuberculous meningitis in adults: A 6-year retrospective study at a tertiary hospital in Northern Taiwan. J Microbiol Immunol Infect. 2010;43(2):111-8. https://doi.org/10.1016/S1684-1182(10)60018-7 PMid: 20457427
21. Wilkinson RJ, Rohlwink U, Misra UK, et al. Tuberculous meningitis. Nat Rev Neurol. 2017;13(10):581-98. https://doi.org/10.1038/nrneurol.2017.120 PMid:28884751
22. Thakur KT, Boubour A, Saylor D, Das M, Bearden DR, Birbeck GL. Global HIV neurology: A comprehensive review. AIDS. 2019;33(2):163-84. https://doi.org/10.1097/QAD.0000000000001796 PMid:29547440 PMCid:PMC6139090
23. Viktorova IB, Zimina VN, Degtyareva SY, Kravtchenko AV. Respiratory diseases in HIV-infected patients. J Infectol. 2020;12(4):5-18. https://doi.org/10.22625/2072-6732-2020-12-4-5-18
24. Cresswell FV, Te Brake L, Atherton R, et al. Intensified antibiotic treatment of tuberculosis meningitis. Expert Rev Clin Pharmacol. 2019;12(3):267-88. https://doi.org/10.1080/17512433.2019.1552831 PMid:30474434
25. Hamada Y, Getahun H, Tadesse BT, Ford N. HIV-associated tuberculosis. Int J STD AIDS. 2021;32(9):780-90. https://doi.org/10.1177/0956462421992257 PMid: 33612015 PMCid:PMC8236666
26. Sereti I, Sheikh V, Shaffer D, et al. Prospective international study of incidence and predictors of immune reconstitution inflammatory syndrome and death in people living with human immunodeficiency virus and severe lymphopenia. Clin Infect Dis. 2020;71(3):652-60. https://doi.org/10.1093/cid/ciz877 PMid:31504347 PMCid: PMC7384325

27. Kirdlarp S, Srichatrapimuk S, Kiertiburanakul S, Phuphuakrat A. Clinical features of adult patients with a definite diagnosis of central nervous system tuberculosis in an endemic country: A 13-year retrospective review. J Clin Tuberc Other Mycobact Dis. 2020;21:100190. https://doi.org/10.1016/j.jctube.2020.100190 PMid: 32995572 PMCid:PMC7501451
28. Seddon JA, Tugume L, Solomons R, Prasad K, Bahr NC, Tuberculous Meningitis International Research Consortium. The current global situation for tuberculous meningitis: Epidemiology, diagnostics, treatment and outcomes. Wellcome Open Res. 2019;4:167. https://doi.org/10.12688/wellcomeopenres.15535.1 PMid: 32118118 PMCid:PMC7029758
29. Logan C, Mullender C, Mirfenderesky M, et al. Presentations and outcomes of central nervous system TB in a UK cohort: the high burden of neurological morbidity. J Infect. 2021;82(1):90-7. https://doi.org/10.1016/j.jinf.2020.10.028 PMid:33137354
30. Raberahona M, Rakotoarivelo RA, Razafinambinintsoa T, Andrianasolo RL, de Dieu Randria MJ Clinical features and outcome in adult cases of tuberculous meningitis in tertiary care hospital in Antananarivo, Madagascar. Biomed Res Int. 2017;2017:9316589. https://doi.org/10.1155/2017/9316589 PMid:28396873 PMCid:PMC5371227
31. Misra UK, Kalita J, Kumar M. Safety and efficacy of fludrocortisone in the treatment of cerebral salt wasting in patients with tuberculous meningitis: A randomized clinical trial. JAMA Neurol. 2018;75(11):1383-91. https://doi.org/10.1001/jamaneurol.2018.2178 PMid: 30105362 PMCid:PMC6248117
32. Li QJ, Song J, Li XY, et al. Differentiation of intraspinal tuberculosis and metastatic cancer using magnetic resonance imaging. Infect Drug Resist. 2020;13:341-9. https://doi.org/10.2147/IDR.S224238 PMid:32099425 PMCid:PMC7007797
33. Maheswari EU, Bhoopathy RM, Bhanu K, Anandan H. Clinical spectrum of central nervous system tuberculosis and the efficacy of revised national tuberculosis control program in its management. J Neurosci Rural Pract. 2019; 10(01):71-7. https://doi.org/10.4103/jnrp.jnrp_163_18 PMid:30765974 PMCid:PMC6337963
34. Loddenkemper R, Lipman M, Zumla A. Clinical aspects of adult tuberculosis. Cold Spring Harb Perspect Med. 2016;6(1):a017848. https://doi.org/10.1101/cshperspect.a017848 PMid:25659379 PMCid:PMC4691808