ORIGINAL ARTICLE

Tuberculosis-HIV Co-infection: Factors Associated With Its Mortality in Malaysia

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ABSTRACT

Introduction: About ten million people were diagnosed with Tuberculosis (TB) in 2019. It has been one of the top ten causes of death worldwide with 1.4 million recorded cases, and 15% of them were people with Human Immunodeficiency Virus (HIV). This study aims to identify factors associated with mortality among patients with TB-HIV co-infection in Malaysia. **Methods:** A retrospective cohort study was conducted using secondary data from the TB Information System (TBIS) in Malaysia from 2015 to 2019. A Kaplan-Maier survival curve and a Cox regression analysis were applied. **Results:** The factors associated with mortality among TB-HIV co-infection patients regarding foreign nationality include no level of education, no directly observed therapy (DOT) supervision, passive case detection, far-advanced findings on chest radiography, no highly active antiretroviral therapy (HAART), and no co-trimoxazole preventive therapy (CPT) treatment. **Conclusion:** The above findings provide a better picture of the current situation of TB-HIV co-infection on a national level. Therefore, the Ministry of Health Malaysia should give more focus and priority to addressing the challenge of reducing the dual burden disease of TB and HIV in Malaysia.

Keywords: Tuberculosis; HIV Coinfections; Risk factor; Mortality; Malaysia

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INTRODUCTION

Tuberculosis (TB) is one of the oldest infectious illnesses globally due to Mycobacterium tuberculosis and is transferred from one person to another via air. According to an interactive TB map from the Stop TB Partnership for the year 2019, about ten million individuals were diagnosed with tuberculosis (TB), which was one of the top ten causes of mortality globally, with 1.4 million documented deaths, 15% of whom were persons infected with Human Immunodeficiency Virus (HIV). The goals monitored under the Sustainable Developmental Goals (SDGs) were to reduce the incidence rate by 80% and the number of TB deaths by 90% in 2030 (1). However, under the WHO End TB Strategy, the reduction was higher, at 90% and 95%, respectively, for the number of TB deaths and TB incidence rate (2).

TB-HIV co-infection happens when a TB patient is infected with HIV or when HIV patients are infected with TB. TB occurred earlier during HIV infection than many other opportunistic infections. Despite various studies published since the year 2000, TB-HIV co-infection has remained a significant global health challenge to this day despite all the implementation and monitoring of control actions for it (3-6).

Every nation, including Malaysia, pledged to end the TB epidemic even though the burden for the year 2017 recorded a notification rate of 81 per 100,000 population and a mortality rate of 6.5 per 100,000 population. Malaysia has a moderate burden of TB disease, with TB cases ranging from 90 to 94 cases per 100,000 population from 2015 until 2019. Annually, about 1,400 to 1,500 deaths were recorded during that same period. Even though the prevalence of TB has increased from 2000 to 2018, the prevalence of TB-HIV co-infection has decreased since 2008, remaining at less than 6% (5). The latest TB-HIV co-infection in Malaysia as of 2019 was 5.9% (6). With the trend of TB-HIV co-infection patients' deaths steadily decreasing, it is critical to further develop our healthcare system and educate patients to meet the SDG and WHO End TB Strategy targets. A prior local investigation was conducted utilising the national TB patient cohort from 2013 to 2017, although it was limited by the number of patients and location. Despite the government's efforts, a vacuum exists that may be filled to assure the future success of TB treatment, particularly in patients with TB-HIV co-infection.

This study aims to add to the knowledge of the predictors of mortality among TB-HIV co-infection patients at a nationwide level using the most recent cohort of patients. As a result, policymakers and healthcare staff will be able to focus on the target demographic and enhance treatment outcomes.

MATERIALS AND METHODS

Data sources

This study was a retrospective cohort study of TB-HIV patients for the whole of Malaysia between 2015 and 2019. All microbiologically proven and clinical cases of TB must be reported to the Ministry of Health (MOH) Department, which records them in a secure computerised database, TBIS. Sociodemographic, patient factors, healthcare system, and characteristics of disease data were obtained from a positive case and updated in the TBIS.

Definitions

TB-HIV co-infection patients were considered to have a diagnosis of active TB and tested positive for HIV. For the analysis, independent variables were grouped into four sections: sociodemographic, patient, health care system, and disease.

Youth participants are between 15 and 24 years old. Adults are participants between 25 and 64 years old. Participants 65 years of age and older are seniors. Ethnicity referred to a group of people that share some inherent physical traits, culture, or beliefs that classify them as Malay, Chinese, Indian, or others.

Treatment outcome, the health care system and disease factors followed the classification by WHO definitions and reporting framework for TB (7).

When a patient succumbs to death, a mortality audit for the cause of death must be conducted within 3 months after the incident. A meeting between the chest physician from the tertiary centre, hospitals and the local health district office involved with the diagnosis and treatment of patients will be conducted. This is to determine if any subpar treatment was given and better improve the outcome of other patients in the future. The meeting concludes with a form called 10J to be filled up and updated in the TBIS by a medical officer.

The HIV status of patients upon diagnosis of TB is determined using an HIV rapid test kit. Once there is a positive result, a subsequent enzyme-linked immunosorbent assay (ELISA) is conducted for further adjustment of the patient's treatment.

Highly active antiretroviral therapy (HAART) and co-trimoxazole preventive therapy (CPT) are recorded as initiated or not. If either treatment is provided, the date is recorded in TBIS.

Data analysis

The reference population was patients registered as having TB-HIV co-infection in TBIS from 2015 to 2019, with a total of 7250 as the sampling frame. Cases were defined as patients from 15 to more than 65 years old, diagnosed from January 1, 2015, till December 31, 2019, with only treatment outcomes of "cured", "completed", and "died" included. The study excluded patients with incomplete information, children, and treatment outcomes apart from the above-mentioned.

Data were entered and analysed in SPSS Version 26. Continuous data were reported as the mean and standard deviation (SD) for descriptive analysis since the data were regularly distributed. The frequency (n) and percentage (%) were presented for categorical data. The survival rates were calculated using the Kaplan-Meier method.

Univariate and multivariate Cox regression models were used to assess the relevant factors of death while controlling for confounding factors. The magnitude of the association was measured by the hazard ratio (HR), and its statistical significance was evaluated using the HR condition interval (CI) and the p-value. The level of significance was set at $p < 0.05$.

Ethical considerations

This study made use of secondary data that had been stripped of personal information and patient identification. Because all instances were anonymised, no formal informed permission from individual patients was obtained. The study was conducted in accordance with approval by the Medical Review & Ethics Committee (MREC), the Ministry of Health, and the Malaysia National Medical Research Ethics Committee (NMRR).

RESULTS

A total of 128,682 TB patients were registered in the TBIS from 2015 through 2019. However, only 7,250 patients were diagnosed with TB-HIV co-infection. Of these, cases with incomplete data (265), children (39), treatment failures (36), treatment defaulted (679), loss to follow-up (109), and change of diagnosis (301) were excluded from the study. Of the remaining 5,821, TB-HIV co-infection patients included in this study, only 2033 (34.9%) patients died, while another 3788 (65.1%) were alive.

The sociodemographic, patient factor, health care system, and characteristic of disease data of all atients included in the research (N = 5,821) are shown in Table I. The mean age (±SD) of patients was 39.39 (±10.47). The median survival curve was 78 weeks, as shown in Figure 1.

Table I : Socio-demographic, patient factor, health care system and characteristic of disease of the study population

Socio-demographic characteristics	n	%
Age group		
Youth	330	5.67
Adult	5375	92.34
Senior	116	1.99
Gender		
Female	716	12.30
Male	5105	87.70
Ethnicity		
Chinese	845	14.52
Indian	436	7.49
Malay	3589	61.65
Others	951	16.34
Nationality		
Malaysian	5529	94.98
Foreigner	292	5.02
Education level		
Tertiary	947	16.27
Secondary school	3765	64.68
Primary school	599	10.29
None	510	8.76
Patient factor		
Smoking		
No	3035	52.14
Yes	2786	47.86
Diabetes mellitus		
No	5507	94.61
Yes	314	5.39
Health care system		
Case detection		
Active	538	9.24
Passive	5283	90.76
DOT supervision[1]		
HCW	4505	77.39
Non HCW	1249	21.46
No supervision	67	1.15
Characteristic of disease		
Type of TB		
Extra PTB	1428	24.53
PTB with Extra PTB	426	7.32
PTB	3967	68.15
TB case category		
New case	4971	85.40
Retreatment case	850	14.60
Chest x-ray		
No lesion	3864	66.38
Moderately advanced	1717	29.50
Far advance	240	4.12
HAART		
No	1397	24.00
Yes	4424	76.00
CPT		
No	412	7.08
Yes	5409	92.92

DOTS = directly observed treatment short course; HCW = health care worker; PTB = pulmonary tuberculosis; HAART = highly active antiretroviral therapy; CPT = Co-trimoxazole preventive therapy.

[1]DOT supervision during intensive phase of treatment.

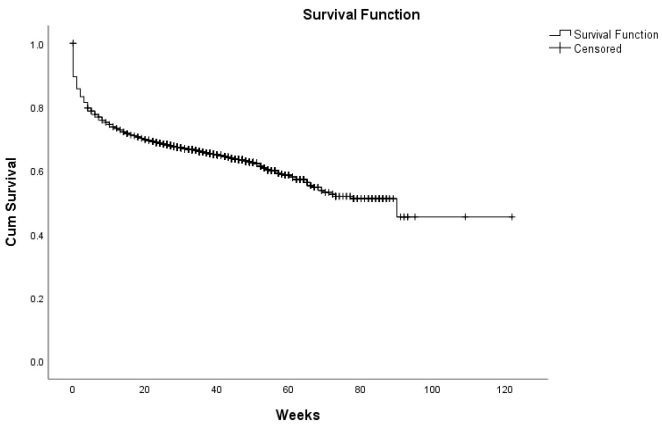

Figure 1 : Kaplan-Meier survivor curves of TB-HIV co-infection patients. The median survival curve was 78 weeks with the mean age (±SD) of patients was 39.39 (±10.47).

All variables that were analysed in the univariate analysis were included in the multivariate analysis. The variables that remained in the final model are shown in Table II.

Table II : Factors associated with socio-demographic, patient factor, health care system and characteristic of disease of the study population

Variables	Alive n (%)	Died n (%)	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age group				< 0.001		0.034
Youth	249 (4.3)	81 (1.4)	1		1	
Adult	3470 (59.6)	1905 (32.7)	1.523 (1.220 - 1.903)	< 0.001	1.274 (1.017 - 1.595)	0.035
Senior	69 (1.2)	47 (0.8)	1.889 (1.319 - 2.706)	0.001	1.602 (1.103 - 2.326)	0.013
Gender						
Female	435 (7.5)	281 (4.8)	1	0.007		
Male	3353 (57.6)	1752 (30.1)	0.842 (0.742 - 0.955)			
Ethnicity				0.037		
Chinese	590 (10.1)	255 (4.4)	1			
Indian	280 (4.8)	156 (2.7)	1.211 (0.992 - 1.478)	0.060		
Malay	2304 (39.6)	1285 (22.1)	1.207 (1.055 - 1.381)	0.006		
Others	614 (10.5)	337 (5.8)	1.219 (1.036 - 1.434)	0.017		
Nationality						
Malaysia national	3645 (62.6)	1884 (32.4)	1	< 0.001	1	0.002
Foreign national	143 (2.5)	149 (2.5)	1.850 (1.565 - 2.186		1.460 (1.149 - 1.855)	
Education level				< 0.001		< 0.001
Tertiary	712 (12.3)	235 (4.0)	1		1	
Secondary school	2450 (42.1)	1315 (22.6)	1.481 (1.289 - 1.702)	< 0.001	1.328 (1.151 - 1.531)	< 0.001
Primary school	350 (6.0)	249 (4.3)	1.828 (1.530 - 2.185)	< 0.001	1.515 (1.260 - 1.821)	< 0.001
None	276 (4.7)	234 (4.0)	2.161 (1.803 - 2.590)	< 0.001	1.559 (1.272 - 1.912)	< 0.001
Smoking						
No	2000 (34.4)	1035 (17.8)	1	0.294		
Yes	1788 (30.7)	998 (17.1)	1.048 (0.960 - 1.143)			
DM						
No	3584 (61.6)	1923 (33.0)	1	0.892		
Yes	204 (3.5)	110 (1.9)	1.013 (0.836 - 1.228)			
Case detection						
Active	367 (6.3)	171 (2.9)	1	0.105	1	0.038
Passive	3421 (58.8)	1862 (32.0)	1.138 (0.973 - 1.331)		1.182 (1.009 - 1.383)	
DOT supervision[1]				< 0.001		< 0.001
HCW	2730 (46.9)	1775 (30.5)	1		1	
Non HCW	1045 (18.0)	204 (3.5)	0.311 (0.237 - 0.408)	< 0.001	0.360 (0.311 - 0.418)	< 0.001
No supervision	13 (0.2)	54 (0.9)	0.109 (0.080 - 0.147)	< 0.001	2.884 (2.193 - 3.792)	< 0.001
Type of TB				0.036		
Extra PTB	955 (16.4)	473 (8.1)	1			
PTB with extra PTB	265 (4.5)	161 (2.8)	1.193 (0.997 - 1.426)	0.054		
PTB	2568 (44.2)	1399 (24.0)	1.135 (1.023 - 1.261)	0.017		

TB case category						
New case	3247 (55.8)	1724 (29.6)	1	0.904		
Retreatment case	541 (9.3)	309 (5.3)	1.007 (0.893 - 1.137)			
Chest x-ray				< 0.001		< 0.001
No Lesion	2689 (46.2)	1175 (20.2)	1		1	
Moderately Advanced	1003 (17.2)	714 (12.3)	1.501 (1.368 - 1.647)	< 0.001	1.449 (1.314 - 1.599)	< 0.001
Far Advanced	96 (1.6)	144 (2.5)	2.742 (2.306 - 3.262)	< 0.001	2.446 (2.047 - 2.923)	< 0.001
HAART						
Yes	1020 (17.5)	377 (6.5)	1	< 0.001	1	< 0.001
No	2768 (47.6)	1656 (28.4)	1.493 (1.335 - 1.670)		1.283 (1.133 - 1.453)	
CPT						
Yes	315 (5.4)	97 (1.6)	1	< 0.001	1	0.009
No	3473 (59.7)	1936 (33.3)	1.682 (1.372 - 2.063)		1.348 (1.076 - 1.688)	

DOTS = directly observed treatment short course; HCW = health care worker; PTB = pulmonary tuberculosis; HAART = highly active antiretroviral therapy; CPT = Co-trimoxazole preventive therapy.
[1]DOT supervision during intensive phase of treatment.

DISCUSSION

Our study on the five years of TB surveillance data showed that passive case detection of TB-HIV patients leads to higher mortality in our local setting. Almost 91% of patients in our study were detected and diagnosed when they sought treatment which is in line with Peru (8). However, this should not be the norm as inadequate knowledge, attitude and practice among patients will reduce the health-seeking behaviour and further increase the disease burden among the population (9–11). As part of the healthcare system factor, it is vital to reorient healthcare services to actively find cases in the community to break the chain of transmission (12). Thus, emphasis on the importance of getting early treatment for a better treatment outcome is of utmost importance. Other mortality factors are age group, nationality, education level, DOT supervision, CXR, HAART, and CPT, which are common in most studies.

The senior age group is one of the socio-risk factors for mortality in our study. This discovery is related to an increased likelihood of decreased immunity and lack of nutrition as a person ages, making them more prone to infections and leading to poor outcomes found similar to other studies (10-13). Besides that, the lack of social support and availability of geriatric care services further associate them with mortality (17,18).
Migration, particularly for foreign workers from countries with a high TB prevalence, is a risk factor for TB (19). According to Malaysia's Department of Statistics, as of 2021, 2.7 million (8.4%) foreign nationals comprise 32 million of the population. Foreigners usually defer public health care due to the costly additional fee unless the employers cover an emergency case or cost found in a cross-sectional survey (14). Malaysia has a few health policies for migrant workers that mandate them to undergo a medical examination before entry. Even after entering the country, foreign employees must undergo pre-employment medical tests at private clinics recognised by the Foreign Workers Medical Examination and Monitoring Agency (FOMEMA) (21). According to the International Health Regulation, every foreign worker diagnosed with an infectious disease on the list must be notified and treated before being sent back to their home country. Several studies found that their low socioeconomic status and overcrowded and impoverished living conditions could increase the chance of disease worsening (17-19). It could lead to the transmission of infectious diseases among the community and increase the burden on the current healthcare system. Besides, the high expense of seeking healthcare services and language problems hampers foreign patient management (26,27). Immigrants tend to default and lost to follow-up, increasing the chances of an unsuccessful TB treatment outcome.

The education level among TB-HIV co-infection patients in our study is another socio-risk factor associated with mortality. The lack of education results in a lack of knowledge and behaviour. As a result, patients do not practice the proper cough etiquette, the health-seeking nature for early intervention, and the need for adherence to a treatment regime found in similar studies (20-21, 24-26). Patients without a proper education are less likely to work and have a lower socioeconomic status, affecting their food security and access to health care services (26,27).

DOT supervision, a low-cost, systematic approach

to recording and reporting, is the most decisive factor associated with mortality outcomes among patients in the study. A meta-analysis review supports our similar findings (35). Patients with the dual burden of infectious disease have better management of their drug treatment with close monitoring of HAART and anti-TB medications are closely monitored for early signs of side effects. These can further be related to other studies (17, 26, 30, 34-36).

Radiography is the most basic, readily available, low-cost, easily maintained, and minimal radiation-exposure available tool for TB imaging among patients. In addition, a correlation of atypical chest radiography findings with a culture sample to establish the diagnosis of active tuberculosis before starting anti-TB medication (38). Early identification of aberrant lung imaging findings would allow for early referral to tertiary centres, other advanced diagnostic tools for further confirmation, and a better patient mortality result. Characteristics of disease found among patients with moderately and far advanced chest radiography presentations to be significantly associated with death which is in line with other studies (26-27, 32, 35-36). These would indicate a delay in seeking treatment by the patient upon diagnosis, further favouring mortality outcome as found in those studies.

As TB-HIV patients have a higher chance of opportunistic infections, the emphasis is on antiretroviral initiation. However, our study found HAART initiation was only among a quarter of patients. Since the introduction of HAART, studies have seen favourable outcomes among TB-HIV co-infected patients (40–44). Thus, emphasis on the initiation of antiretroviral therapy immediately upon confirmation of the diagnosis to strengthen patients' immune systems irrespective of their CD4 cell count. Furthermore, similar local studies have shown better survival for patients with simultaneous anti-TB and HAART treatment (45,46).

Similar to HAART, not even ten per cent of patients were on CPT in our study. CPT is primarily used to treat HIV infections and prevent opportunistic infections. According to WHO, consideration for CPT should be for everyone with the risk of exposure to HIV, which includes HIV patients in a severe or advanced stage of disease, TB-HIV patients, and infants with a risk of vertical transmission (47). Therefore, managing the two conditions more effectively during this pivotal phase to enhance patients' survival and quality of life is crucial. According to a slew of scientific studies, CPT measures are associated with a considerable reduction in the incidence and mortality associated with TB-HIV co-infection (42–46).

Several limitations to our study as this research used retrospective secondary data. The TB unit at state and national levels schedules audits and routinely monitor the data to ensure information completeness. Possible selection bias concerning patients' treatment outcomes was found in our study to evaluate the risk factors for mortality. Only audited and registered TB-HIV co-infected patients with the result of death were included in the study. Besides that, laboratory characteristics of patients, i.e. the total white blood cell and CD4 counts attainable from the National AIDS Registry, were excluded from this study because of unavailable data. Including that information would reduce bias in determining the progression to mortality. These findings should guide and influence future research into the risk factors for mortality. The strength of our study is the national-level surveillance data, adaptable to other nations with a similar sociodemographic and disease burden for future research. The TB data, which also represent the population under study and is replicable at the state level, were obtained from a trustworthy source.

CONCLUSION

Our study highlighted the recent picture of the current situation of TB-HIV co-infection on a national level. The findings show that more work is needed to lower death rates in specific groups, including the elderly, persons of foreign origin, and those without education. As a result, this requires more targeted actions towards the current public health programmes and mitigation measures to reduce the risk factors for mortality. In the present study, the passive method detected most cases. We even observed that the use of HAART and CPT had an association with mortality. These support the early identification of cases through active case finding and attention to prophylaxis treatment commencement among TB-HIV co-infected patients. As a result, there is a pressing need for integrating HIV and TB care to provide integrated therapy for both illnesses and properly control adverse medication effects. To conclude, managing HIV and TB simultaneously is critical for patient survival.

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