JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Factors associated with all-cause mortality in tuberculosis patients in a Malaysian tertiary hospital

Chee Kuan Wong[1], Kee Seong Ng[1], Sarah Qian Rou Choo[1], Choon Jiat Lee[1], Yik Pheng Teo[1], Su May Liew[2], Karuthan Chinna[3], Ee Ming Khoo[2], Wei Leik Ng[2], Peter Seah Keng Tok[4], Yan Shen Kee[1], De Min Chiang[1]

[1] Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
[2] Department of Primary Care Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
[3] Faculty of Business and Management, UCSI University, Kuala Lumpur, Malaysia
[4] Department of Social and Preventive Medicine, Centre for Epidemiology and Evidence-Based Practice, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Abstract

Introduction: The all-cause mortality for tuberculosis is 1 in every 10 patients in Malaysia. The currently available national surveillance database does not record patients' variables such as socio-economic factors, existing co-morbidities, and risk behavior for investigation. An electronic medical record system can capture this missing information and use it to determine all-cause mortality factors more accurately. Our study aims to determine the factors associated with all-cause mortality in a cohort of tuberculosis patients in a Malaysian tertiary hospital which is equipped with an electronic medical record system.

Methodology: Records of patients diagnosed with tuberculosis from 1st January 2018 to 30th September 2019 were retrieved. Sociodemographic and clinical data were extracted. Treatment outcomes and all-cause mortality were recorded at 1 year after diagnosis. Univariate, multivariate, and stepwise regression were used to determine the factors associated with all-cause mortality.

Results: Four-hundred and seventy-one patients were reviewed. The mean age was 46.6 ± 19.7 years. The all-cause mortality rate at one year of diagnosis was 15.3%. Factors identified were age [aOR 1.026 (95% CI: 1.004-1.049)], chronic kidney disease [aOR 3.269 (1.508-7.088)], HIV positive status [aOR 4.743 (1.505-14.953)], active cancer [aOR 5.758 (1.605-20.652)], liver disease [aOR 6.220 (1.028-37.621)], and moderate to advanced chest X-ray findings [aOR 3.851 (1.033-14.354)].

Conclusions: On average, one in seven patients diagnosed with TB died within a year in a Malaysian tertiary hospital. Identification of this vulnerable group using the associated factors found in this study may help to reduce the risk of mortality through early intervention strategies.

Key words: tuberculosis; TB; factors; mortality; Malaysia.

J Infect Dev Ctries 2023; 17(8):1138-1145. doi:10.3855/jidc.16967

(Received 16 June 2022 – Accepted 06 February 2023)

Introduction

Tuberculosis (TB) is an important global public health issue. The World Health Organisation (WHO) estimated that there were 10 million people diagnosed with TB, and an estimated 1.4 million TB deaths globally in 2019 [1]. Malaysia is a country with intermediate TB burden, and a reported incidence rate of 92 per 100,000 population in 2019 based on the WHO TB country, regional and global profiles. According to the Malaysian national TB cohort data from years 2014 to 2017, the all-cause mortality was 1 in every 10 patients, while TB treatment success rate was 81% in 2017, which was below the recommended target of at least 90% by WHO [2,3].

There were numerous studies on TB all-cause mortality using the databases collected from country specific TB reporting systems. The United State of America found that the diagnosis of multi-drug resistant TB, end-stage renal disease, human immunodeficiency virus (HIV) infection, older age and immunosuppression were significant risk factors associated with TB mortality [4]. A study conducted in Shanghai found that underlying disease such as chronic obstructive pulmonary disease, diabetes mellitus and having cancer were significantly associated with TB mortality, apart from older age, male gender, positive sputum smear test, and multidrug resistant TB [5]. Two Malaysian studies have also shown that older age, male gender, Malaysian nationality, rural residence, lower education level, passive detection of TB, underlying diabetes mellitus, extrapulmonary TB, advanced chest X-ray findings, and positive HIV were associated with

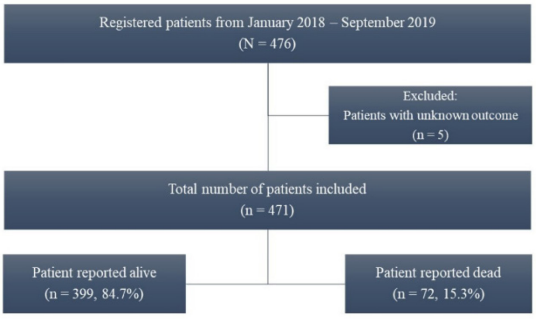
all-cause mortality in TB [3]. However, all these studies were limited by using multiple sources such as death certificate, interviews by health inspectors, and manual data entry into the reporting system. The currently available Malaysian national surveillance database is unable to obtain certain patient variables such as socio-economic factors, existing co-morbidities, and risk behavior for investigation. [3] This led to issues such as missing data and limited clinical information that may significantly affect the all-cause mortality. In our study, we aimed to investigate the factors of all-cause mortality in TB patients who attended a tertiary teaching hospital equipped with an electronic medical record (EMR) system, which would minimize missing data and ease the collection of important clinical data.

Methodology

Study design and population

A retrospective cohort study was conducted at a university tertiary hospital located in Kuala Lumpur, the capital of Malaysia. All records of patients diagnosed with TB (fulfilled the criteria for International Classification of Diseases Tenth Revision (ICD-10) code A15-19) in the hospital from 1st January 2018 to 30th September 2019 were included. Patients with unknown treatment outcome at one-year surveillance were excluded. The hospital had started a TB registry since 2018 and data were collected using an electronic TB information system (TBIS) 10A form, which was completed by the attending doctor at the point of diagnosis. Medical histories, including sociodemographic characteristics, smoking history and comorbidities were retrieved from the filled TBIS 10A form. Data that was missing in the form was traced by using the patient's electronic medical records. The variable definitions of comorbidities are provided in Supporting File 1. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and approval from University of Malaya Medical Ethics Committee was obtained before commencement of the study (approval number 201945-7299).

Figure 1. Proportion of treatment outcomes of patients with TB.



Diagnosis of tuberculosis

All registered patients in the study were either bacteriologically confirmed or clinically diagnosed with TB [6]. A bacteriologically confirmed TB case is one from whom a biological specimen was tested positive by smear microscopy, culture, or new molecular tests. A clinically diagnosed TB case refers to one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed to have active TB by a clinician and started on a full course of TB treatment. This includes cases diagnosed by chest X-ray with characteristic abnormalities or suggestive histology, and extrapulmonary cases that could not be confirmed by laboratory testing. The final diagnosis of the patients was recorded as pulmonary TB (PTB) or extrapulmonary TB (EPTB).

PTB referred to any bacteriologically confirmed or clinical diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary and disseminated TB were classified under PTB as there were lesions in the lungs. A patient with both PTB and EPTB was classified as a case of PTB. EPTB referred to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs.

Outcome

The WHO defines TB death as a TB patient who dies for any reason before starting or during the course of treatment [6]. In our study, we used all-cause mortality as a surrogate marker of mortality attributable to TB [7].

Data analysis

Data was analyzed using IBM Statistical Package for the Social Sciences (SPSS) software version 23.0 (SSPS Inc., Chicago, IL, USA). All quantitative data were tested for normality. Normally distributed data were expressed as mean and standard deviation, or as median and interquartile range. Categorical data were described as frequency and percentages. Univariate and multivariate logistic regression procedures were used, with all-cause mortality as the dependent outcome. All variables with a p value ≤ 0.25 in univariate analyses were included in the multivariate analysis. Finally, stepwise analysis was performed. In the final analysis, the level of significance was set as 0.05.

Results

Sociodemographic and clinical characteristics

There was a total of 476 TB patients registered in the period from 1st January 2018 to 31st September 2019. Five patients were excluded due to unknown outcome. Out of the 471 patients, 15.3% were reported dead after diagnosis of TB during the 1-year surveillance (Figure 1).

The sociodemographic characteristics of the study population are summarized in Table 1. The mean age of the patients was 46.6 ± 19.7 years. Majority of the patients were Malaysians (88.1%) and males (59%), while 33.8% of them were unemployed.

Table 2 summarizes the clinical features of the study population. Most of them (96%) were detected by passive case finding, and 366 (77.7%) of them had PTB. Out of these PTB patients, 59.6% were sputum smear positive. 74.3% had BCG vaccination scar. As for risk behavior, 27.6% of them were ever smoker, 3% were ever illicit drug user and 2.1% were dependent on alcohol. As for the chronic medical diseases, 24.6% had diabetes mellitus, 10.2% had chronic kidney disease, 6.4% had HIV infection, 3.6% were on immunosuppressive therapy, 3.4% had active cancer, 3% had asthma, 2.8% had chronic obstructive pulmonary disease and 1.5% had liver disease. 16.6% had one comorbidity, 7.9% had two comorbidities and 4.4% had at least three comorbidities. Out of the 48 patients with chronic kidney disease (CKD), 17 (35.4%) were on hemodialysis and out of these 17 patients, 11 (64.7%) have died. Among the patients in this study, 16 had co-existing active cancer. One third of them had lung cancer, and 9 (56.3%) of them had died. As for the chest X-ray findings, 56.2% had moderate to advanced radiological changes.

Table 1. Sociodemographic characteristics of study population.

Variables	n (%)
Age (Mean age ± SD)	46.61 ± 19.73
Gender	
Male	278 (59.0)
Female	193 (41.0)
Nationality	
Malaysian	415 (88.1)
Non-Malaysian	56 (11.9)
Occupation	
High skilled white collar	72 (15.3)
Low skilled white collar	60 (12.7)
High skilled blue collar	18 (3.8)
Low skilled blue collar	64 (13.6)
Armed force	2 (0.4)
Students	48 (10.2)
Unemployed	159 (33.8)
Health care workers	21(4.5)
Not known	48 (10.2)

Factors associated with the all-cause mortality

The factors associated with the all-cause mortality in TB patients using univariate, multivariate and stepwise regression analyses are summarized in Tables 3 and 4. Based on the final analysis, factors that were associated with all-cause mortality were age [aOR 1.026 (95% CI: 1.004-1.049)], chronic kidney disease [aOR 3.269 (1.508-7.088)], positive HIV status [aOR 4.743 (1.505-14.953)], active cancer [aOR 5.758 (1.605-20.652)], liver disease [aOR 6.220 (1.028-37.621)], and moderate to advanced chest X-ray (CXR) findings [aOR 3.851 (1.033-14.354)].

Table 2. Clinical features of the study population.

Variables	n (%)
Type of TB detection (passive)	452 (96.0)
Smoking status (ever smoker)	131 (27.9)
BCG scar (present)	350 (74.3)
Illicit drug use (ever user)	14 (3.0)
Alcohol dependence	10 (2.1)
Diabetes mellitus	116 (24.6)
Chronic kidney disease	48 (10.2)
Liver	7 (1.5)
Immunosuppressive therapy	17 (3.6)
Active cancer	16 (3.4)
Chronic obstructive pulmonary disease	13 (2.8)
Asthma	14 (3.0)
HIV status	
Positive	30 (6.4)
Negative	371 (78.8)
Unknown	70 (14.8)
Number of comorbidities	
None	335 (71.1)
One	78 (16.6)
Two	37 (7.9)
Three and above	21 (4.4)
Chest X ray findings	
No lesion	60 (13.0)
Minimal	143 (30.9)
Moderate advanced and far advanced	260 (56.2)
Types of tuberculosis (tuberculosis)	
Pulmonary TB	366 (77.7)
Sputum Smear Positive	218 (59.6) [a]
Sputum Smear Negative	111 (30.3) [a]
Sputum Smear Not Done	37 (10.1) [a]
Extra-pulmonary TB	105 (22.3)
Lymph node	43 (41.0)[a]
Pleural	19 (18.1)[a]
Abdominal	12 (11.4)[a]
CNS	12 (11.4)[a]
Skeletal	9 (8.6)[a]
Cutaneous	5 (4.8)[a]
Others	5 (4.8)[a]

[a] Percentages of the specific outcome.

Table 3. Univariate and multivariate analysis of mortality.

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p* value	Adjusted Odds ratio (95% CI)	*p* value
Age	1.047 (1.032 – 1.064)	**0.000***	1.025 (1.002-1.048)	**0.031***
Male	1.187 (0.708 – 1.991)	0.515		
Malaysian[a]	1.574 (0.949 – 3.861)	0.315		
Occupation				
High skilled white collar	0.348 (0.154-0.787)	**0.005**[b]*	0.912 (0.323-2.577)	0.469
Low skilled white collar	0.147 (0.044-0.493)	**0.011***	0.261 (0.051-1.330)	0.862
High skilled blue collar	0.557 (0.154-2.021)	**0.002***	1.304 (0.273-6.234)	0.106
Low skilled blue collar	0.236 (0.089-0.628)	0.374	0.910 (0.288-2.882)	0.860
Armed force	0.000 (0.000)	**0.004***	0.000 (0.000)	0.873
Students	0.000 (0.000)	0.999	0.000 (0.000)	0.999
Not known	0.828 (0.387-1.771)	0.997	2.154 (0.839-5.530)	0.997
Unemployed	1	0.627	1	0.111
Passive TB Case Detection	0.961 (0.272 – 3.390)	0.950		
Smoking status (ever smoker)	1.100 (0.631 – 1.915)	0.737		
BCG scar (present)	1.563 (0.835 – 2.488)	0.189	0.746 (0.380 – 1.464)	0.394
Alcohol dependence	2.435 (0.615 – 9.644)	0.205	1.589 (0.272-9.294)	0.607
Illicit drug use (ever used)	1.534 (0.417 – 5.639)	0.520		
Diabetes Mellitus	2.090 (1.227 – 3.558)	**0.007***	0.796 (0.375-1.688)	0.552
Chronic Kidney Disease	5.096 (2.679 – 9.694)	**0.000***	3.172 (1.332-7.557)	**0.009***
Liver disease	7.765 (1.700 – 35.463)	**0.008***	4.591 (0.717-29.404)	0.108
Immunosuppressive therapy	1.747 (0.553 – 5.516)	0.342		
Active Cancer	8.000 (2.876 – 22.251)	**0.000***	6.488 (1.739-24.203)	**0.005***
COPD	1.691 (0.454 – 6.302)	0.434		
Asthma	0.921 (0.202 – 4.206)	0.916		
HIV status		0.380		**0.025***
Negative	1		1	
Positive	1.826 (0.746 – 4.467)	0.187	5.290 (1.587-17.631)	**0.007***
Unknown	1.241 (0.625 – 2.466)	0.537	1.125 (0.468-2.707)	0.793
Number of comorbidities		**0.000***		0.322
None	1		1	
One	2.143 (1.120 – 4.103)	**0.021***	1.392 (0.632-3.066)	0.411
Two	3.076 (1.377 – 6.872)	**0.006***	1.212 (0.429-3.422)	0.717
Three and above	7.551 (2.998 – 19.014)	**0.000***	2.832 (0.917-8.747)	0.071
Chest X ray findings		**0.000***		**0.019***
No lesion	1		1	
Minimal	1.740 (0.473 – 6.404)	0.404	2.572 (0.542-12.219)	0.142
Moderate and advanced	5.098 (1.538 – 16.900)	**0.008***	6.323 (1.334-29.114)	**0.020***
Types of tuberculosis				
Pulmonary TB	1		1	
Extra-pulmonary TB	0.658 (0.340 – 1.276)	0.215	1.827 (0.694-4.808)	0.222

[a] Reference group is non-Malaysian; [b] The minimum expected count is 0.31; * Factors with significant *p* value of < 0.05.

Table 4. Results from stepwise regression for mortality.

Variables	Adjusted Odd Ratio (95% CI)	*p* value
Age	1.026 (1.004-1.049)	**0.019***
Chronic kidney disease	3.269 (1.508 – 7.088)	**0.003***
Active cancer	5.758 (1.605-20.652	**0.007***
Liver disease	6.220 (1.028-37.621	**0.047***
HIV status		**0.029***
Negative	1	
Positive	4.743 (1.505-14.953)	**0.008***
Unknown	0.962 (0.409-2.263)	0.929
Chest X ray findings		**0.019***
No lesion	1	
Minimal	1.664 (0.391-7.071)	0.490
Moderate and advanced	3.851 (1.033-14.354)	**0.045***

* Factors with significant *p* value of < 0.05.

Discussion

The all-cause mortality rate in a year was about 1 in 7 patients (15.3%) in our study. The factors that were significantly associated include increasing age, chronic kidney disease, patient with positive HIV status, active cancer, liver disease, and moderate to advanced CXR findings.

The 1-year mortality rate based on Malaysia National TB registry data from 2014 to 2017 was approximately 1 in 10 patients (10.2%) [3]. This is lower than the all-cause mortality rate that we found in our study. This finding is not unexpected as this study population is that of a tertiary hospital, which caters to patients that have more complicated and severe illnesses as compared to the majority of TB cases in the national cohort that are usually treated at community health clinics. A study in South Korea also reported that the TB mortality rate was higher in a suburban tertiary hospital compared to its national TB mortality rate [8].

Increasing age was a factor that was significantly associated with mortality in our study. The immunity in a person declines as a person ages, which is due to age-related changes in the immune system referred to as immunosenescence. This leads to decreased ability to fight against infections. [9] Aging is associated with a decrease in the cellularity of the bone marrow which causes decline in the adaptive immune response [10]. Our study finding corresponded to several local and foreign studies [5,8,11]. A study in Hong Kong showed that older patients had higher proportion with comorbidities and more advanced disease at the time of diagnosis. However, our study found that age was an independent factor even with the inclusion of comorbidities. We did not include the severity of the comorbidities into the analysis and this may act as mediating factors for our findings. Another possibility is that there were other associated factors that were not analyzed in this study.

CKD was found to be significantly associated with mortality among TB patients in this study. Immune deficiency due to decline in kidney function predisposes CKD patients to infection, particularly to TB and may also cause reactivation of latent TB infection (LTBI) and mortality [12,13]. Lack of symptoms, missing bacteriological proof and higher frequency of extrapulmonary TB are challenges that delayed the diagnosis in patients with hemodialysis [14]. However, a study conducted in Saudi Arabia reported lower mortality in patients with CKD owing to early diagnosis and treatment with high clinical suspicion in this group of patients [14]. This highlights the importance of early identification of patients that are vulnerable to allow for intervention strategies that can ameliorate the risk.

Patients with positive HIV status had higher all-cause mortality rates in our study. This is in concordance with findings from other local and foreign studies. [3,15] One explanation for the higher mortality may be that HIV replication is enhanced by host responses to *Mycobacterium tuberculosis*, which leads to accelerated depression of cellular immunity [16]. Other factors involved in the increased mortality include not being on antiretroviral therapy (ART) and the presence of other morbidities like neoplastic diseases and illicit drug use in HIV-TB co-infected patients [17,18].

In our study, active cancer was associated with a significant higher mortality rate in TB patients. Studies in Brazil and Korea reported increased TB mortality in patients diagnosed with hematological malignancies and lung cancer [19,20]. This is because active cancer patients who received cytotoxic chemotherapy are immunosuppressed, where both cell-mediated immunity and immunoglobulin production are reduced, thus predisposing them with a wide spectrum of infective complications and TB infection. [21] In addition, co-existence of TB and lung cancer poses a diagnostic challenge to clinicians as one could mask the presence of the other disease leading to a delay in diagnosis and initiation of treatment [21].

Liver disease was shown to be significantly associated with all-cause mortality in TB patients. This is concordant with findings from Australia and Taiwan [7,22]. Anti-tuberculosis medication such as isoniazid, rifampicin and pyrazinamide are mainly metabolized by liver and poses a risk of drug induced liver injury (DILI), especially in patient with liver disease such as Hepatitis B and/or C infections. Several studies have shown that hepatitis B and C coinfection increase the risk of DILI [23]. Hence, patients with prior liver disease are at higher risk of hepatotoxicity. [24] However, our sample size was too small and a bigger sample size would be much more meaningful.

More advanced CXR features were significantly associated with all-cause mortality in TB, similar to the findings from Malaysia National TB Registry Data and a study from Korea [3,25]. The high number of moderate to advanced CXR cases in our study, similar to a study conducted in the state of Sabah where TB rates are highest in the country, suggests that delay in the diagnosis of TB remains frequent within our population [26]. This again highlights the need for earlier diagnosis.

Our study has shown that smoking was not significantly associated with the all-cause mortality in TB, which is in line with the findings from Malaysia National TB Registry Data [3]. However, another study from Malaysia revealed a significant association between ever smokers and TB mortality [27]. The discordance in result could be possibly due to the higher prevalence of smokers in Khan *et al* (46.2%) as compared to our study (27.9%). Multiple foreign studies also show significant association between ever smokers and poorer treatment outcome in TB patients [28,29]. A thorough smoking history including number of pack years should be collected to properly investigate its association with TB outcome and mortality as the discrepancy could be possibly due to the nature of data collection for smoking in this study, which was self-reporting by patients.

Historically, patients with combined diabetes mellitus (DM) and TB have had a worse prognosis than TB only patients [30]. However, our study shared the similar findings with Liew *et al,* which did not illustrate a significant association between DM and all-cause mortality in TB. The possible explanation to this may be attributed to their better treatment adherence and monitoring for chronic diabetes management. HbA1c is used as a marker for short term glycemic control, and serial HbA1c may be a better gauge and identifier to assess diabetic related complications for long term glycemic control. This is proven by a study from Taiwan that TB treatment outcome was not proportionately related to single HbA1c reading [31]. However, the relation between the long-term glycemic control and the TB treatment outcome was not examined in our study partly due to underutilization of the test in our study population. Further research is required to investigate the validity of this statement [32].

Strengths and limitations

Missing data from the registry could be traced by using the electronic medical database. This had reduced the amount of missing data and allowed for better accuracy of results. The database also allowed collection and analysis of clinical data which is not included in the national TB registry. One of the limitations in the study was that all-cause mortality was used instead of actual cause of death. The actual cause of death that were concluded in the hospital mortality reviews were not captured in our hospital EMR, eventually lead to difficulty in concluding the relationship of TB to the cause of death. Information in the TBIS form, particularly on comorbidities, is subject to clinician's judgement. Important data such as household income was not recorded, in both TBIS and EMR, and occupation was used instead as a surrogate marker to represent the socioeconomic status.

Recommendations

The use of an electronic medical database is strongly recommended for recording the information of patients with TB, particularly the detailed clinical history and investigation results for future epidemiology studies and research purposes. This would help develop proper risk and prognostic scores to risk stratify patients and identify those in high risk so that early intervention could be done to reduce the mortality rate in TB. TB patients with older age, CKD, liver disease, HIV positive status and active cancers should be tagged as having high risk of mortality. Strategies to reduce mortality in these groups should comprise improvement of time to diagnosis and early effective treatment with close monitoring. Apart from that, a strategic framework tackling tuberculosis in these patients should include transmission prevention, active screening, as well as preventive treatment of vulnerable groups with latent TB infection using the risk factors identified in this study. This could translate to improved survival and quality of life, which in turn will reduce hospital stay and total healthcare costs [5,15].

Conclusions

On the average, 1 in 7 patients with TB in a Malaysian university tertiary hospital died from all-cause mortality in a year. The key findings of this study highlighted the clinical variables, comorbidities, and severity of disease of the vulnerable group in a tertiary hospital. Increasing age, chronic kidney disease, positive HIV status, active cancer, liver disease, and moderate to advanced CXR findings were the factors that were significantly associated with all-cause mortality in TB patients in this study. Identification of this vulnerable group using the associated factors found in this study may help to reduce the risk of mortality through early intervention strategies.

Acknowledgements

The authors wish to thank the following individuals for their contributions in the process of writing the paper: Anisha Gill A/P Awtar Singh, Chee Sher Weyne, Diyaanah Binti Nasir, Evonne Tan Yee Wern, Janice Ong, Lim Qun Ya, Lim Sze Zee, Lim Zhan Foong, Muhammad Amir Johari, Muhammad Anis bin Abdul Aziz, A Roovam, P Balasubramaniam, See Hai Liang, A Suneesa, P Som Sak, Tan Jia Kai, Tang Ching

Wen, Teh Chui Jiun, Teh Kai Li Kylie, Teh Le Ni, Woon Shi Shien, Yeo Audrey and Yong Qing Hui.

Authors' contributions

Chee Kuan Wong, Kee Seong Ng, Sarah Qian Rou Choo, Choon Jiat Lee, Yik Pheng Teo, Yan Shen Kee, De Min Chiang: conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, visualization, writing - original draft, writing - review and editing

Su May Liew, Karuthan Chinna, Ee Ming Khoo, Wei Leik Ng, Peter Seah Keng Tok: conceptualization, investigation, methodology, project administration, supervision, writing - review and editing

References

1. WHO (2020) Global tuberculosis report. Available: https://www.who.int/publications-detail-redirect/9789240013131. Accessed: 27 March 2022.
2. WHO (2021) Global tuberculosis report. Available: https://www.who.int/publications-detail-redirect/9789240037021. Accessed: 4 May 2022.
3. Tok PSK, Liew SM, Wong LP, Razali A, Loganathan T, Chinna K, Ismail N, Kadir NA (2020) Determinants of unsuccessful treatment outcomes and mortality among tuberculosis patients in Malaysia: a registry-based cohort study. PLoS One 15: e0231986. doi: 10.1371/journal.pone.0231986.
4. Hannah HA, Miramontes R, Gandhi NR (2017) Sociodemographic and clinical risk factors associated with tuberculosis mortality in the United States, 2009-2013. Public Health Rep 132: 366-375. doi: 10.1177/0033354917698117.
5. Liu Y, Zheng Y, Chen J, Shi Y, Shan LY, Wang S, Wang WB, Shen X, Zhang Y (2018) Tuberculosis-associated mortality and its risk factors in a district of Shanghai, China: a retrospective cohort study. Int J Tuberc Lung Dis 22: 655-660. doi: 10.5588/ijtld.17.0726.
6. WHO (2013) Definitions and reporting framework for tuberculosis. revision: Updated December 2014 and January 2020. Available: https://apps.who.int/iris/handle/10665/79199. Accessed: 4 May 2022.
7. Lin CH, Lin CJ, Kuo YW, Wang JY, Hsu CL, Chen JM, Cheng WC, Lee LN (2014) Tuberculosis mortality: patient characteristics and causes. BMC Infect Dis 14: 5. doi: 10.1186/1471-2334-14-5.
8. Kim CW, Kim SH, Lee SN, Lee SJ, Lee MK, Lee JH, Shin KC, Yong SJ, Lee WY (2012) Risk factors related with mortality in patient with pulmonary tuberculosis. Tuberc Respir Dis (Seoul) 73: 38-47. doi: 10.4046/trd.2012.73.1.38.
9. Goronzy JJ, Weyand CM (2013) Understanding immunosenescence to improve responses to vaccines. Nat Immunol 14: 428-436. doi: 10.1038/ni.2588.
10. Sadighi Akha AA (2018) Aging and the immune system: an overview. J Immunol Methods 463: 21-26. doi: 10.1016/j.jim.2018.08.005.
11. Chan-Yeung M, Noertjojo K, Tan J, Chan SL, Tam CM (2002) Tuberculosis in the elderly in Hong Kong. Int J Tuberc Lung Dis 6: 771-779.
12. Shu CC, Wei YF, Yeh YC, Lin HH, Chen CY, Wang PH, Cheng SL, Wang JY, Yu CJ (2020) The impact on incident tuberculosis by kidney function impairment status: analysis of severity relationship. Respir Res 21: 51. doi: 10.1186/s12931-020-1294-5.
13. Fried LF, Katz R, Sarnak MJ, Shlipak MG, Chaves PHM, Jenny NS, Stehman-Breen C, Gillen D, Bleyer AJ, Hirsch C, Siscovick D, Newman AB (2005) Kidney function as a predictor of non-cardiovascular mortality. J Am Soc Nephrol 16: 3728-3735. doi: 10.1681/ASN.2005040384.
14. El Kabbaj D, Bahadi A, Oualim Z (2010) Prevalence of tuberculosis in hemodialysis patients. Saudi J Kidney Dis Transpl 21: 164-167.
15. Karo B, Krause G, Hollo V, van der Werf MJ, Castell S, Hamouda O, Haas W (2016) Impact of HIV infection on treatment outcome of tuberculosis in Europe. AIDS 30: 1089-1098. doi: 10.1097/QAD.0000000000001016.
16. Toossi Z (2003) Virological and immunological impact of tuberculosis on human immunodeficiency virus type 1 disease. J Infect Dis 188: 1146-1155. doi: 10.1086/378676.
17. Ismail I, Bulgiba A (2013) Predictors of death during tuberculosis treatment in TB/HIV co-infected patients in Malaysia. PLoS One 8: e73250. doi: 10.1371/journal.pone.0073250.
18. Ruiz-Navarro MD, Espinosa J, Hernández MJ, Franco AD, Carrillo CC, García AD, Fulgueiras AG, Diz PG, de Valdivielso MJ, Fernández M (2005) Effects of HIV status and other variables on the outcome of tuberculosis treatment in Spain. Archivos de bronconeumologia 41: 363-370. doi: 10.1016/S1579-2129(06)60242-5.
19. Silva FA, Matos JO, de Q Mello FC, Nucci M (2005) Risk factors for and attributable mortality from tuberculosis in patients with hematologic malignances. Haematologica 90: 1110-1115.
20. Hong S, Mok Y, Jeon C, Jee SH, Samet JM (2016) Tuberculosis, smoking and risk for lung cancer incidence and mortality. Int J Cancer 139: 2447-2455. doi: 10.1002/ijc.30384.
21. Ho JC, Leung CC (2018) Management of co-existent tuberculosis and lung cancer. Lung Cancer 122: 83-87. doi: 10.1016/j.lungcan.2018.05.030.
22. Walpola HC, Siskind V, Patel AM, Konstantinos A, Derhy P (2003) Tuberculosis-related deaths in Queensland, Australia, 1989-1998: characteristics and risk factors. Int J Tuberc Lung Dis 7: 742-750.
23. Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R (2008) Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol 23: 192-202. doi: 10.1111/j.1440-1746.2007.05207.x.
24. Girling DJ (1978) The hepatic toxicity of antituberculosis regimens containing isoniazid, rifampicin and pyrazinamide. Tubercle 59: 13-32. doi: 10.1016/0041-3879(77)90022-8.
25. Min J, Kim JS, Kim HW, Shin AY, Koo HK, Lee SS, Kim YK, Shin KC, Chang JH, Chun G, Lee J, Park MS, Park JS (2019) Clinical profiles of early and tuberculosis-related mortality in South Korea between 2015 and 2017: a cross-sectional study. BMC Infect Dis 19: 735. doi: 10.1186/s12879-019-4365-9.
26. Goroh MMD, Rajahram GS, Avoi R, Van Den Boogaard CHA, William T, Ralph AP, Lowbridge C (2020) Epidemiology of tuberculosis in Sabah, Malaysia, 2012-2018. Infect Dis Poverty 9: 119. doi: 10.1186/s40249-020-00739-7.
27. Khan AH, Sulaiman SAS, Hassali MA, Khan KU, Ming LC, Mateen O, Ullah MO (2020) Effect of smoking on treatment

outcome among tuberculosis patients in Malaysia; a multicenter study. BMC Public Health 20: 854. doi: 10.1186/s12889-020-08856-6.
28. Gegia M, Magee MJ, Kempker RR, Kalandadze I, Chakhaia T, Golub JE, Blumberg HM (2015) Tobacco smoking and tuberculosis treatment outcomes: a prospective cohort study in Georgia. Bull World Health Organ 93: 390-399. doi: 10.2471/BLT.14.147439.
29. Leung CC, Yew WW, Chan CK, Chang KC, Law WS, Lee SN, Tai LB, Leung EC, Au RK, Huang SS, Tam CM (2015) Smoking adversely affects treatment response, outcome and relapse in tuberculosis. Eur Respir J 45: 738-745. doi: 10.1183/09031936.00114214.
30. Boucot KR (1957) Diabetes mellitus and pulmonary tuberculosis. J Chronic Dis 6: 256-279. doi: 10.1016/0021-9681(57)90007-3.
31. Chiang CY, Bai KJ, Lin HH, Chien ST, Lee JJ, Enarson DA, Lee TI, Yu MC (2015) The influence of diabetes, glycemic control, and diabetes-related comorbidities on pulmonary tuberculosis. PLoS One 10: e0121698. doi: 10.1371/journal.pone.0121698.
32. Liew SM, Khoo EM, Ho BK, Lee YK, Mimi O, Fazlina MY, Asmah R, Lee WK, Harmy MY, Chinna K, Jiloris FD (2015) Tuberculosis in Malaysia: predictors of treatment outcomes in a national registry. Int J Tuberc Lung Dis 19: 764-771. doi: 10.5588/ijtld.14.0767.

Corresponding author

Wong Chee Kuan, MD.
Department of Medicine, University of Malaya,
Lembah Pantai, 59100 Kuala Lumpur, Malaysia.
Tel: +60178712807
Fax: +60379562253
Email: ckwong@ummc.edu.my

Conflict of interests: No conflict of interests is declared.

Annex – Supplementary Items

Variables definition

Chronic kidney disease: Patients with eGFR < 60 mL/min/1.73m^2 (Stage 3 and above) at baseline for a duration of ≥ 3 months or evidence of markers of kidney damage such as albumin: creatinine ratio (ACR) ≥ 30 mg/g [1].

Liver disease (irreversible liver damage): Patients were recruited based on the prognostic child-pugh score. Patients with a score of ≥ 5 points (child-pugh A and above) were defined as liver disease patients.

Diabetes mellitus (DM) patients: Patients with newly diagnosed DM at the point of diagnosis of tuberculosis (TB) or previously diagnosed by medical doctor with 2 abnormal glucose results (asymptomatic) or 1 abnormal glucose result (symptomatic) or HbA1c > 6.3%. Patient on oral antidiabetic agent or insulin or regular follow up for diabetes mellitus at any healthcare facilities also considered as DM patient [2].

Active cancer: Patients who were recorded as having an active cancer with or without treatment or on palliative treatment or conservative treatment at the point of diagnosis of TB in the electronic medical records.

Chronic obstructive pulmonary disease (COPD): Patients with previously diagnosed COPD with lung function test ($FEV_1/FVC < 0.7$), with or without treatment or with newly diagnosed COPD were recruited based on GOLD 2020 diagnostic criteria at the point of diagnosis of TB [3].

Asthma: Patients with previously diagnosed asthma with or without treatment and currently on regular follow up or with newly diagnosed asthma based on GINA 2020 diagnostic criteria at the point of diagnosis of TB [4].

Positive human immunodeficiency virus (HIV): patients with previously diagnosed positive HIV testing with or without treatment or newly diagnosed HIV positive status at the point of diagnosis of TB.

Immunosuppressive therapy: Patients who are on agent that suppress the immune response of a patient, such as steroids, non-steroidal immunosuppressant, anti-TNF alpha agent, DMARDs and biologics agents.

Alcohol dependence: Based on ≥ 3 of DSM-IV dependence criteria of substance use disorders within a 12-month period [5].

Illicit drug use: Patients who consume non-medical variety of drugs that are prohibited by international law, including amphetamine-type stimulants, cannabis, cocaine, heroin and other opioids, and MDMA (ecstasy).

Other comorbidities: Patients with pre-existing medical conditions as recorded in the EMR including hypertension, ischemic heart disease, thyroid disease and endocrinological disease, dyslipidaemia, cerebral vascular disease, autoimmune conditions, skin disease, psychiatric disorders, gastritis, Down's syndrome, musculoskeletal disease, transverse myelitis, nephrotic syndrome, deep vein thrombosis, pulmonary embolism, cerebral palsy, lupus nephritis, gout, Parkinson's disease and seizure.

Loss of weight: Documented loss of more than 5 percent of usual body weight over 6 to 12 months in EMR or from patient's history.