

Characteristics of patients with tuberculosis and the associated factors with TB-related mortality in a rural setting in Sarawak, Malaysia: A single-centre study

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ABSTRACT

Introduction: Tuberculosis (TB) in Malaysia has estimated incidence and mortality rates of 81 cases per 100,000 people-year and 4.9 per 100,000 populations, respectively. This study aimed to study the characteristics of rural TB patients and their mortality outcomes.

Materials and methods: This is a retrospective observational study involving real-world data analysis, looking into TB patients in Lubok Antu Health Clinic by obtaining data through clinic cards, from 1 January 2019 till 31 December 2020. Statistical significance was $p < 0.05$.

Results: Eighty-four patients were included. Fifty-two (61.9%) were male. Median age was 58.5 (39–67). Forty-six (54.8%) had smear-positive TB. Seventy-eight (92.9%) were alive at treatment completion. Fifteen (17.9%) experienced adverse drug reactions. Estimated prevalence and mortality rate were 7.1% and 10.7 per 100,000 populations, respectively. Regression analyses revealed that drug reaction was significantly associated with compliance [OR = 8.38 (95% CI: 1.26, 55.53), $p = 0.029$]. Patients compliant with treatment were more likely to survive [OR = 12.5 (95% CI: 1.61, 97.34), $p = 0.028$].

Conclusion: Compliance with TB treatment should be emphasised to reduce TB-related mortality.

KEYWORDS:

Compliance; prevalence; mortality; rural; tuberculosis

INTRODUCTION

Tuberculosis (TB) remains a disease of public health importance in Malaysia. According to World Health Organization (WHO) Global Tuberculosis Report 2020, there were 25,837 cases of the disease nationwide in 2018 with an estimated incidence of 81 cases per 100,000 people-year in this developing country.¹ Although it is lower as compared to worldwide incidence of 130 cases per 100 000 people-year in 2019,² more work still needs to be done in this field. It is one of the top 10 causes of death worldwide, ranking above

HIV/AIDS as a leading cause of death from a single infectious agent. Around 1.3 million deaths among HIV-negative individuals were attributed to TB globally in 2019, with an addition of around 208,000 deaths among HIV-positive people.² South-East Asia has 44% of worldwide TB cases among WHO regions, which has important weightage in TB prevalence.² Malaysia being in among South-East Asia countries has to contribute to this nationwide effort in curbing the expansion of disease. While TB-related mortality in Malaysia showed a reducing trend,³ the number of TB incidence is still significant and has yet to achieve the global end TB milestone.⁴

WHO and the International Union Against TB and Lung Disease recommend the effort of contact tracing in order to improve the detection of TB cases.⁵ Hence, local studies on the epidemiology and population dynamic of the disease need to be supported in order to curb this important public health problem. The risk of developing or reactivation of TB is reported to be higher in high-risk population with predisposing factors such as HIV, DM, and immunocompromised.⁶ Hence, regular screening for asymptomatic high-risk population in high-risk area might be a wise step in TB detection.

Few recent studies have been done to study the local epidemiology and characteristics of TB population in rural area, especially in Sarawak, Malaysia where the incidence of TB is staggering with the high inflow of immigrants, causing TB incidence to be difficult to control. Hence, this study aims to study the characteristics of rural TB patients and their mortality outcomes to supplement the effort of national TB program, in line with the global effort to expand TB care and control. The objectives of this study include determining the prevalence and mortality rate among TB patients in Lubok Antu district; and determining factors associated with TB mortality, factors associated with compliance with anti-tuberculous therapy, factors associated with the development of symptoms and factors associated with the development of adverse drug reactions.

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MATERIALS AND METHODS

Study Patients

This is a retrospective observational study (case series) looking into patients who were diagnosed with TB and receiving treatment in primary healthcare facility in a rural setting, comparing the factors between patients who died from TB and patients who survived.

Data of all patients diagnosed with TB and received treatment in Lubok Antu Primary Healthcare Clinic, Sri Aman Division, Sarawak, Malaysia were obtained retrospectively through a review of their medical records. Lubok Antu Health Clinic is the mother clinic that covers all TB patients within Lubok Antu district which consisted of eight health clinics, namely Lubok Antu Health Clinic, Engkelili Health Clinic, Batang Ai Health Clinic, Merindun Health Clinic, Nanga Kesit Health Clinic, Nanga Stamang Health Clinic, Nanga Delok Health Clinic, and Nanga Patoh Health Clinic. Hence, although this study only involved data collection from a single centre, it represented a wide coverage of the local rural population.

Information collected include patients' age, sex, race, marital status, smoking status, alcohol history, new cases versus previous TB, HIV status, types of TB, chest X-ray findings, sputum smear status, drug resistance status, treatment duration, compliance to treatment, clinical symptoms at presentation, adverse drug reactions upon receiving TB treatment, and TB-related outcomes. Compliance to treatment was assessed by reviewing patients' directly observed treatment (DOT) record.

The inclusion criteria of this study were all patients diagnosed with TB, either through symptom or contact screening, and received treatment in Lubok Antu Health Clinic, from 1 January 2019 till 31 December 2020. The exclusion criteria include patients who were initially treated as TB but later confirmed to be other diagnosis.

Outcome Measure

The end-point of this study was TB-related mortality prior to or upon completion of treatment.

Statistical Analysis

This study was analysed using the IBM SPSS Statistics version 20.0. Quantitative variables are presented in frequency (percentage) for categorical data and median (interquartile range) for continuous data with skewed distribution. Analysis of quantitative variables in comparison between groups was done using Mann-Whitney U test (non-parametric). Analysis of categorical variables was performed through Pearson's chi-square test or Fisher's exact test wherever applicable. Statistical significance was set at $p < 0.05$. Logistic regression analysis was done to determine the independent variables associated with TB mortality.

RESULTS

Patients' Characteristics

A total of 84 patients were recruited into this study, 40 (47.6%) from year 2019 and 44 (52.4%) from year 2020. They

consist of 52 (61.9%) males and 32 (38.1%) females, with a median age of 58.5 (39–67) years. Eighty (95.2%) were Iban, while the rest consisted of 1 (1.2%) Chinese, 2 (2.4%) Bidayuh and 1 (1.2%) foreigner. There was a total of 78 (92.9%) new cases within the 2-year period, 5 (6.0%) with previous pulmonary tuberculosis (PTB) who completed treatment, and 1 (1.2%) with previous PTB but did not complete treatment.

Forty-six (54.8%) had smear-positive TB, while 38 (45.2%) had smear-negative TB. All patients had TB sensitive to a common anti-tuberculous drug regime, and none were rifampicin-resistance or multi-drug resistance (MDR).

Other characteristics of TB patients are stated in Table I.

Sixty-seven (79.8%) received anti-TB treatment for 6 months, 12 (14.3%) received non-standard treatment duration, ranges from 7 to 10 months. Of this group of patients, three were due to delayed sputum conversion, hence prolongation of intensive phase; two were due to the development of hepatitis as a result of adverse drug reaction from standard HREZ regime, hence were changed to alternative anti-tuberculous regime; one was due to development of rash from hypersensitivity to rifampicin and later restarted treatment with HZO regime; one defaulted treatment and needed to restart intensive phase; two were persistently symptomatic despite compliance to treatment, hence prolongation of total duration of treatment; three had persistent chest radiography (CXR) changes.

Seventy-nine (94.0%) were compliant with treatment. One was deemed treatment failure for persistent CXR changes upon completion of standard regime and needing to restart anti-tuberculous therapy. There were 5 (6.0%) who were non-compliant with treatment. Among those, three received treatments under the classification of treatment after default in accordance with Malaysia Clinical Practice Guidelines.⁷

Seventy-eight (92.9%) patients were alive at the end of treatment, while 6 (7.1%) died prior to or upon completion of treatment.

TB-Associated Mortality Outcomes and Associated Factors

Factors involved in TB-associated mortality outcomes are stated in Table II.

Odds of mortality in non-compliant patients is 12.5 times more than those compliant to treatment with statistical significance of p value=0.028.

Other factors such as age, gender, marital status, smoking history, alcoholic, immunocompromised status, chest X-ray findings, sputum smear results, symptoms and drug reactions were found to be insignificant in their association with TB-related mortality.

We explored the crude relationship between TB mortality and each independent variable using simple logistic regression (univariate analyses). Those factors with p value < 0.1 were selected for the multiple logistic regression analysis but the sample size was underpowered for the analysis.

Table I: Characteristics of patients with tuberculosis (n=84)

Characteristics	n (%)
Median age (Q1–Q3) – years	58.5 (39–67)
Gender	
Male	52 (61.9)
Female	32 (38.1)
Ethnic	
Iban	80 (95.2)
Chinese	1 (1.2)
Bidayuh	2 (2.4)
Foreigners	1 (1.2)
Marital status	
Married	63 (79.7)
Single	11 (13.9)
Widowed	4 (5.1)
Divorced	1 (1.3)
Smoker	26 (32.5)
Alcoholic	10 (12.2)
Case category	
New case	78 (92.9)
Previous PTB completed treatment	5 (6.0)
Previous PTB has not completed treatment	1 (1.2)
TB contact	51 (62.2)
Immunocompromised status	
Nil	65 (77.4)
Diabetes mellitus	18 (21.4)
Malignancy	1 (1.2)
HIV	0 (0.0)
ESRF	0 (0.0)
Others	0 (0.0)
CXR findings	
Normal	16 (19.0)
Mild PTB changes	27 (32.1)
Moderate PTB changes	27 (32.1)
Advanced PTB changes	14 (16.7)
Sputum smear	
Positive	46 (54.8)
Negative	38 (45.2)
Drug resistance	
Nil	84 (100.0)
Rifampicin resistance	0 (0.0)
MDR	0 (0.0)
Treatment duration	
6 months	67 (79.8)
Non-standard regime	12 (14.3)
Did not complete treatment (dead)	5 (6.0)
Compliance	
Yes	79 (94.0)
No	5 (6.0)
Outcomes	
Alive	78 (92.9)
Dead	6 (7.1)

CXR, chest radiography; ESRF, end-stage renal failure; HIV, human immunodeficiency virus; MDR, multi-drug resistance; PTB, pulmonary tuberculosis.

Symptoms of TB Experienced by Patients

TB symptoms experienced by patients are stated in Table III.

At diagnosis, 73 (86.9%) patients were symptomatic, while 11 (13.1%) were asymptomatic. The most common symptom experienced was cough, followed by loss of weight, fever, loss of appetite, night sweats and haemoptysis - 59 (70.2%) had cough, 44 (52.4%) had loss of weight, 33 (39.3%) had fever, 30 (35.7%) had loss of appetite, 15 (17.9%) had night sweats and 10 (11.9%) had haemoptysis. None experienced dyspnoea.

Adverse Drug Reactions

Adverse drug reactions experienced by patients are stated in Table IV.

Of the total patients treated, a minority of 15 (17.9%) experienced adverse drug reactions. From the most common to the least, 10 (11.9%) had hepatitis, 3 (3.6%) experienced gout, and 2 (2.4%) had rash. None develop peripheral neuropathy, visual impairment, hearing deficit or thrombocytopenia.

Table II: Factors associated with TB-associated mortality outcomes (n=84)

Factors	Outcomes		Simple logistic regression	
	Alive n (%)	Dead n (%)	Crude OR (95% CI)	p value ^a
Age*				
≤60yo	42 (97.7)	1 (2.3)	1	0.068
>60yo	36 (87.8)	5 (12.2)	5.83 (0.65,52.3)	
Gender				
Male	49 (94.2)	3 (5.8)	1	0.539
Female	29 (90.6)	3 (9.4)	1.69 (0.32,8.93)	
Marital Status*				
Married	59 (93.7)	4 (6.3)	1.02 (0.11,9.78)	0.988
Single/Widow/Divorcee	15 (93.8)	1 (6.2)	1	
Smoking				
Yes	24 (92.9)	2 (7.1)	1.42 (0.22,9.04)	0.716
No	51 (94.8)	3 (5.2)	1	
Alcohol				
Yes	8 (80.0)	2 (20.0)	5.75 (0.83,39.74)	0.100
No	69 (95.8)	3 (4.2)	1	
Immunocompromised*				
Yes	17 (89.5)	2 (10.5)	1.79 (0.30,10.64)	0.553
No	61 (93.8)	4 (6.2)	1	
Chest X-ray				
Normal	15 (93.8)	1 (6.3)	1	0.876
Abnormal	63 (92.6)	5 (7.4)	1.19 (0.13,10.96)	
Sputum smear				
Positive	44 (95.7)	2 (4.3)	0.39 (0.07,2.24)	0.273
Negative	34 (89.5)	4 (10.5)	1	
Compliance				
Yes	75 (94.9)	4 (5.1)	1	0.028
No	3 (60.0)	2 (40.0)	12.5 (1.61,97.34)	
Symptoms*				
Yes	68 (93.2)	5 (6.8)	0.74 (0.08,6.96)	0.794
No	10 (90.9)	1 (9.1)	1	
Drug Reaction*				
Yes	12 (80.0)	3 (20.0)	5.50 (0.99,30.55)	0.060
No	66 (95.7)	3 (4.3)	1	

^a Likelihood Ratio (LR) test.

Factors marked with '*' allowed for non-binary response during data collection.

Table III: Symptoms of TB (n=84)

Symptoms	n (%)
Cough	59 (70.2)
Loss of weight	44 (52.4)
Fever	33 (39.3)
Loss of appetite	30 (35.7)
Night sweats	15 (17.9)
Haemoptysis	10 (11.9)
Dyspnoea	0 (0.0)

Table IV: Adverse drug reactions (n=84)

Adverse drug reactions	n (%)
Hepatitis	10 (11.9)
Gout	3 (3.6)
Rash	2 (2.4)
Peripheral neuropathy	0 (0.0)
Visual impairment	0 (0.0)
Hearing deficit	0 (0.0)
Thrombocytopenia	0 (0.0)

Table V: Factors associated with compliance to anti-tuberculous therapy (n=84)

Factors	Compliance		Simple logistic regression	
	Yes n (%)	No n (%)	Crude OR (95% CI)	p value ^a
Age				
≤60 years old	41 (95.3)	2 (4.7)	1	0.605
>60 years old	38 (92.7)	3 (7.3)	1.62 (0.26,10.22)	
Gender				
Male	50 (96.2)	2 (3.8)	1	0.307
Female	29 (90.6)	3 (9.4)	2.59 (0.41,16.40)	
Marital status				
Married	61 (96.8)	2 (3.2)	1	0.172
Single/widow/divorcee	14 (87.5)	2 (12.5)	0.23 (0.03,1.77)	
Smoking				
Yes	24 (92.3)	2 (7.7)	2.17 (0.29, 16.31)	0.457
No	52 (96.3)	2 (3.7)	1	
Alcohol				
Yes	8 (80.0)	2 (20.0)	8.75 (1.08, 70.89)	0.055
No	70 (97.2)	2 (2.8)	1	
Drug reaction				
Yes	12 (80.0)	3 (20.0)	8.38 (1.26, 55.53)	0.029
No	67 (97.1)	2 (2.9)	1	

^a Likelihood Ratio (LR) test.

Drug Compliance and Associated Factors

Factors associated with drug compliance are stated in Table V.

This study also explored factors which are associated with compliance to anti-TB treatment. Odds of non-compliance in those having drug reaction is 8.38 times more than those without drug reaction, p value=0.029. Odds of non-compliance among smoker and alcohol drinker were 2.17 and 8.75 times more than odds of non-compliance among non-smoker and non-alcohol drinker, respectively. However, these associations were not statistically significant with p value=0.194 and p value=0.055, respectively.

We explored the crude relationship between drug compliance and each independent variable using simple logistic regression (univariate analyses). Those predictors of non-compliance with p value <0.1 were selected for the multiple logistic regression analysis but the sample size was underpowered for the analysis.

DISCUSSION

Lubok Antu is a district with 27,984 populations in the state of Sarawak in Malaysia, consisting of mainly Iban ethnic.⁸ Hence, majority of the patients in this study were Iban. The disease burden in the local area can be translated into 139 cases per 100,000 people-year. This incidence is much higher compared to our national statistic of 81 per 100,000 people-year.¹ Furthermore, there might be under-reporting of the local incidence of TB as some patients attend follow-up in clinics of neighbouring district. There is a slight increment in the number of TB cases from year 2019 to year 2020 (40 and 44 in respective years). It is a disease of male predominance (61.9% male), which is consistent with WHO data of 56% TB cases worldwide being men.²

Note that among the study population, only 28 (32.5%) were smoker, and 10 (12.2%) were alcoholic. This might be due to under-reporting of patients' social history. Not all patients

who contracted TB had TB contact. Hence, healthcare worker needs to be extra vigilant in screening for potential TB patients even for those who were not previously in contact with any known PTB patients.

In this study, 38 (45.2%) patients were smear-negative and 16 (19.0%) had normal chest X-ray. This makes diagnosis of TB difficult and easy to be missed. Moreover, not all TB patients were symptomatic. Hence, high clinical suspicion is necessary to come to the diagnosis for this asymptomatic group. Further work-up might need to be done to ascertain the diagnosis if sputum was smear-negative and CXR was normal but clinical suspicion of TB remains high.

Fortunately for the community, all the TB cases were sensitive to standard anti-tuberculous regime. MDR strain had not evolved among the local community. Further effort to ensure compliance is necessary to maintain the status of drug-sensitive strain. Better compliance was shown to significantly improve mortality from this study, further supporting the findings from other studies.⁹⁻¹¹ Social and mental support can help to improve compliance among patients, which had previously been highlighted by other studies.¹²⁻¹⁷ Hence, early referral to a psychologist for those who were non-compliant with treatment will most likely be beneficial. Education of patients' family in supervising patients and to provide mental support might play a role in improving compliance among patients.

In this rural setting, many patients were from more remote areas which were far away from clinic, requiring hours of boat ride to reach. Hence, logistic challenges to attend clinic follow-up for continuation of treatment remains an important factor. Hence, in our clinic setting, free boat services will be arranged for those patients who were unable to afford transport to attend clinic. Infrastructure development in curbing logistic challenge should be prioritised in order to make patients' attendance at clinic convenient. In our setting, for this group of patients with logistic concern, daily DOT will be supervised by an in-charge

appointed by the clinic staffs among the local villagers. These are exemplary steps to further improve patients' compliance to treatment in rural setting.

Adverse drug reaction should not be a hindrance to compliance with treatment. The minority patients (17.9%) who developed drug reactions were of non-fatal reactions and steps had been taken to ensure subsequent compliance after recovery from the adverse effects.

In this study, we were unable to form a stable model to predict the associated factors. This can be due to two possibilities - inadequate sample size which could inflate the standard error and widen the 95% CI; or the number of event for mortality was very small (6 deaths versus 78 alive). Therefore, the model did not fit.

TB mortality rate in Lubok Antu district was 10.7 per 100,000 populations, which was more than double the national TB mortality rate of 4.9 per 100,000 populations; but half of that of the global TB mortality rate of 20.0 per 100,000 populations.¹ There is still room for improvement in reducing TB mortality with the aim to achieve the global end TB milestone.

TB is an important public health problem in our country. Especially for rural community, TB is often under-diagnosed and under-treated where awareness among the community is low and further complicated by logistic challenges. This has important implications to the rural community as TB is a contagious disease. It can easily spread to involve a large number of people when the local community in rural area usually lives in close proximity within longhouses and have frequent close physical interaction. Steps need to be taken to educate the community in early seeking of treatment for those with symptoms suspicious of TB and to be compliant with treatment once diagnosed. This can help to improve TB-related mortality in the community. The importance of mental support should not be undermined, and thus should be part of the treatment alongside pharmacological therapy.

CONCLUSION

TB mortality prevalence in Lubok Antu population was fortunately low (7.1%), although steps need to be taken to raise the standard of TB care to further reduce mortality and morbidity. Compliance with treatment was found to be significantly associated with mortality and is especially needed to be emphasised in the effort of curbing TB since it is a modifiable factor that carries a significant impact on TB outcome.

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