


# Predictors of delayed sputum smear conversion among pulmonary tuberculosis patients in Kota Kinabalu, Malaysia

## A retrospective cohort study

Khalid Mokti, MD, MPH, DrPH<sup>a,b</sup>, Zaleha Md Isa, BSc, PhD<sup>b</sup>, Julaidah Sharip, MD, MPH<sup>c</sup>, Sahrol Nizam Abu Bakar, MD, MPH, DrPH<sup>c</sup>, Azman Atil, MD, MPH<sup>a,b</sup>, Firdaus Hayati, MD, DrGenSurg<sup>d,\*</sup> , Syed Sharizman Syed Abdul Rahim, MBBch BAO, MPH, DrPH<sup>a</sup>

### Abstract

Smear-positive pulmonary tuberculosis (SPPTB) is the major contributor to the spread of tuberculosis (TB) infection, and it creates high morbidity and mortality worldwide. The objective of this study was to determine the predictors of delayed sputum smear conversion at the end of the intensive phase of TB treatment in Kota Kinabalu, Malaysia.

This retrospective study was conducted utilising data of SPPTB patients treated in 5 TB treatment centres located in Kota Kinabalu, Malaysia from 2013 to 2018. Pulmonary TB (PTB) patients included in the study were those who had at least completed the intensive phase of anti-TB treatment with sputum smear results at the end of the 2nd month of treatment. The factors associated with delayed sputum smear conversion were analyzed using multiple logistic regression analysis. Predictors of sputum smear conversion at the end of intensive phase were evaluated.

A total of 2641 patients from the 2013 to 2018 periods were included in this study. One hundred eighty nine (7.2%) patients were identified as having delayed sputum smear conversion at the end of the intensive phase treatment. Factors of moderate (advanced odd ratio [aOR]: 1.7) and advanced (aOR: 2.7) chest X-ray findings at diagnosis, age range of >60 (aOR: 2.1), year of enrolment 2016 (aOR: 2.8), 2017 (aOR: 3.9), and 2018 (aOR: 2.8), smokers (aOR: 1.5), no directly observed treatment short-course (DOTS) supervisor (aOR: 6.9), non-Malaysian citizens (aOR: 1.5), and suburban home locations (aOR: 1.6) were associated with delayed sputum smear conversion at the end of the intensive phase of the treatment.

To improve sputum smear conversion success rate, the early detection of PTB cases has to be fine-tuned so as to reduce late or severe case presentation during diagnosis. Efforts must also be in place to encourage PTB patients to quit smoking. The percentage of patients assigned with DOTS supervisors should be increased while at the same time ensuring that vulnerable groups such as those residing in suburban localities, the elderly and migrant TB patients are provided with proper follow-up treatment and management.

**Abbreviations:** 95% CI = 95% confidence interval, AFB = acid fast bacilli, aOR = advanced odd ratio, DOTS = directly observed treatment short-course, EPTB = extrapulmonary tuberculosis, Mtb = Mycobacterium tuberculosis, PTB = pulmonary tuberculosis, SPPTB = smear-positive pulmonary tuberculosis, TB = tuberculosis, TBTC = tuberculosis treatment centres.

**Keywords:** Malaysia, pulmonary tuberculosis, retrospective study, sputum

Editor: Ediriweera Desapriya.

There was no funding for this research. However, the publication fee was supported by the Universiti Malaysia Sabah.

This study was approved by the National Medical Research Register (NMRR ID: NMRR-18-3698-40627) and approved by the Medical Research and Ethics Committee (MREC) (MREC Reference No: KKM/NIHSEC/P19-443(11)).

The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

<sup>a</sup> Department of Community and Family Medicine, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia, <sup>b</sup> Department of Community Health, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia, <sup>c</sup> Kota Kinabalu District Health Office, Ministry of Health Malaysia, Kota Kinabalu, Sabah, Malaysia, <sup>d</sup> Department of Surgery, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia.

\* Correspondence: Firdaus Hayati, Department of Surgery, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia (e-mail: firdaushayati@gmail.com, m\_firdaus@ums.edu.my).

Copyright © 2021 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Mokti K, Md Isa Z, Sharip J, Abu Bakar SN, Atil A, Hayati F, Syed Abdul Rahim SS. Predictors of delayed sputum smear conversion among pulmonary tuberculosis patients in Kota Kinabalu, Malaysia: A retrospective cohort study. *Medicine* 2021;100:31(e26841).

Received: 27 November 2020 / Received in final form: 8 July 2021 / Accepted: 9 July 2021

<http://dx.doi.org/10.1097/MD.00000000000026841>

## 1. Introduction

Tuberculosis (TB) is one of the top 10 diseases leading to mortality worldwide. It continues to infect a vast segment of society every year with an estimated 10 million individuals contracting TB and 1.6 million eventually succumbing to the disease in 2017.<sup>[1]</sup> In Malaysia, TB does not only cause morbidity on the pulmonary tuberculosis (PTB), but also on the extra-pulmonary type.<sup>[2–4]</sup> The sputum smear test is widely used to diagnose PTB. PTB treatment targets include sputum smear conversion at the end of the intensive phase of anti-TB treatment. Smear conversion is defined as new smear-positive PTB (SPPTB) cases that have converted to negative after undergoing anti-TB treatment during the intensive phase of treatment.<sup>[5]</sup> Smear conversion, a significant indicator of TB care performance, also predicts treatment failure and relapse.<sup>[6]</sup>

Patients with SPPTB are the main contributors to the spread of TB infection; this situation occurs when they expel droplet nuclei that carry infectious bacilli during coughing or sneezing.<sup>[7]</sup> An untreated PTB patient could potentially infect 10 to 15 people per year.<sup>[8]</sup> Clearance of mycobacteria from sputum is required to achieve individual cure and reduce the PTB transmission. An estimated 80% to 90% of SPPTB patients would undergo smear conversion within 2 to 3 months of therapy.<sup>[9]</sup> The delayed sputum conversion patient has significant public health implications for containing the TB pandemic.

The disappearance of acid-fast bacilli from smears and cultures is the most widely accepted determinant for the treatment of patients with SPPTB.<sup>[10]</sup> The related risk factors for delayed conversion studies were widely conducted worldwide including in Malaysia.<sup>[11]</sup> Several factors have been described as having the potential to delay the smear conversion observed in previous studies. Sociodemographic factors, high-risk behavior factors, past medical background factors, the outcome of an examination after a diagnosis, psychological factors, and healthcare service factors are among them.<sup>[10]</sup> The risk factors of delayed sputum conversion are essential information needed by the health care provider to avoid unfavorable results.<sup>[5]</sup> It also stresses the health care system with disease dissemination.<sup>[12]</sup>

SPPTB also creates high morbidity and death. Delayed sputum smear conversion is associated with unfavorable treatment outcomes including a default of the TB treatment protocol.<sup>[13]</sup> PTB patients who still present positive sputum smear with the regular 6-month regimen at the end of the intense period are at elevated risk of developing drug resistance especially if therapy is not explicitly observed.<sup>[11]</sup> This could lead to an increase in treatment cost, difficulties and the risk of recurrence. Any incidence of delayed conversion of positive sputum smear at the end of the intensive phase of treatment presents a high risk of spreading the infection; this thus necessitates a further period of isolation for the TB patient due to the extension of treatment. Extended periods of isolation and treatment could lead to non-compliance, additional costs for the patient's family and health service, and stigma for the patient himself.<sup>[14]</sup>

This research aimed to determine the predictors of delayed sputum smear conversion at the end of the intensive phase of anti-TB treatment of SPPTB patients in Kota Kinabalu, Malaysia. The findings of the study will contribute towards ascertaining methods to enhance sputum smear conversion as well as identifying patients who require more medical attention and care (such as advanced lung lesions) so as to improve treatment outcomes and consequently reduce time and costs which would

otherwise be necessary for the third month's additional smear test. In addition, awareness of factors associated with delayed sputum smear conversion would be useful for clinicians to perform better patient management and improve treatment outcomes.<sup>[15]</sup>

## 2. Methodology

### 2.1. Study setting

All cases of SPPTB patients registered in the *Sistem Maklumat Tibi* (MyTB) database in Kota Kinabalu District between 2013 and 2018 were evaluated for inclusion. Kota Kinabalu has an estimated population of 500,000 with a population density of 613 persons per km<sup>2</sup>. An estimated TB incidence of 104 per 100,000 population in 2018 put Kota Kinabalu District above the national incidence rate of 92 per 100,000 population.<sup>[16]</sup> Kota Kinabalu District constitutes 16 townships namely Tanjung Aru, Sembulan, Kampung Air, Luyang A, Luyang B, Luyang C, Luyang D, Likas, Pulau Gaya, Laut, Pekan/Taman, Pantai, Timbok, Kionsom, Darat, and Petagas.

Located on the West Coast, Kota Kinabalu is the largest district in Sabah. The district is divided into 5 operational government TB treatment centres (TBTC): Luyang Health Clinic, Inanam Health Clinic, Mangatal Health Clinic, Telipok Health Clinic, and Pusat Rawatan Tibi 1, Queen Elizabeth Hospital. TBTC treatment guidelines include

1. a standardized 6-month rifampicin-based regimen for new cases and an 8-month regimen for re-treatment cases, and
2. the evaluation of acid-fast bacilli (AFB) sputum smear conversion from positive to negative at the end of the intensive phase of treatment with the period set at 2 months for new cases and 3 months for re-treatment cases.

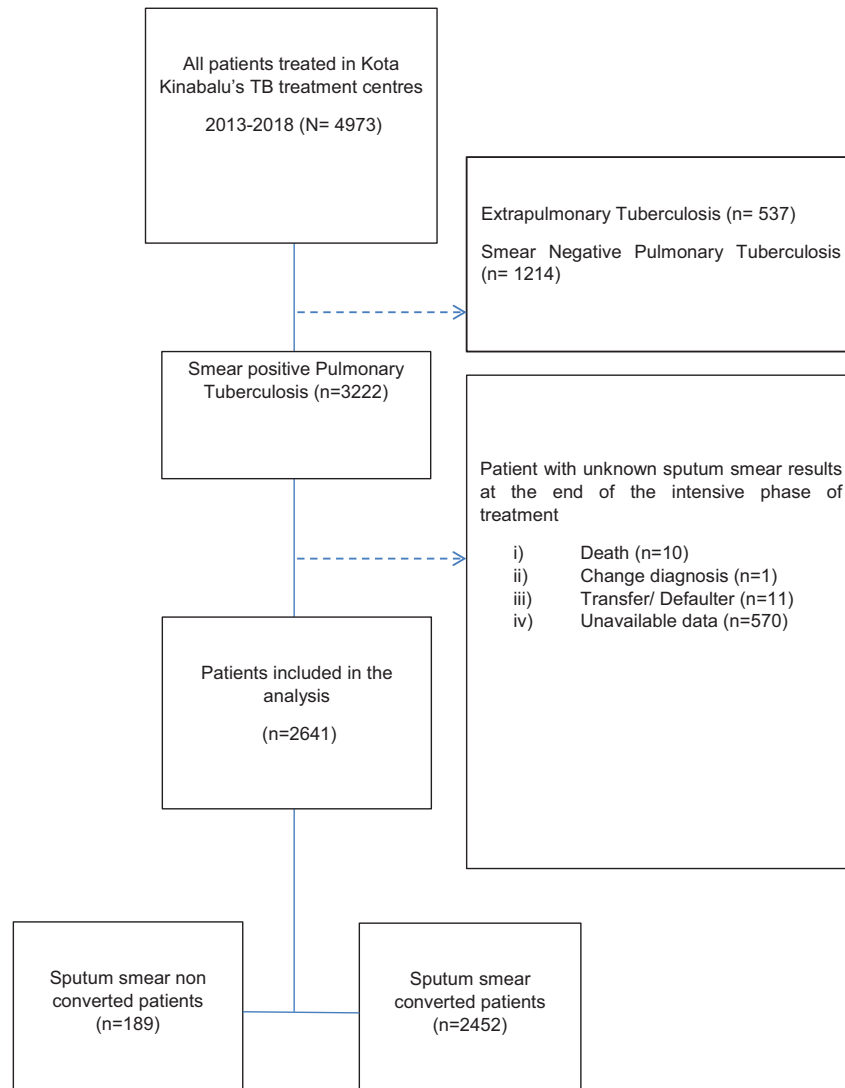
### 2.2. Study design

This retrospective cohort study was based on the assessment of the 2013 to 2018 data of SPPTB patients in the district of Kota Kinabalu, Malaysia. The inclusion criteria for this study were

1. new smear-positive PTB cases with follow-up management at any 5 government TB treatment centers in Kota Kinabalu during the intensive TB treatment and completion of at least the intensive phase of the anti-TB treatment,
2. extrapulmonary TB (EPTB) patients with unknown sputum smear results at the end of the intensive phase of treatment,
3. patients with missing information on one of the variables,
4. patients who were transferred out, and
5. patients who had died or had interrupted treatment before the end of the intensive phase (Fig. 1).

### 2.3. Data collection

Data was obtained from the register of patients in the Malaysian TB Information System or MyTB developed by the Ministry of Health Malaysia. MyTB is a web-based application designed for capturing TB patient information directly from a standardized template form. At facility level, a TB patient's clinical information is collated onto a standardized TB form register by the attending TB nurse and subsequently validated by the local area TB coordinator. A copy of the verified information is then forwarded



**Figure 1.** Algorithm for the sampling of smear-positive TB treated in Kota Kinabalu TB treatment centers between January 2013 to December 2018.

for upload onto the MyTB online system at the district level. Once the data has been uploaded online, it is then available on a server and may be accessed at both district and national levels. Data for the present study were aggregated for all health care facilities in Kota Kinabalu District. The primary factors gathered were the year of diagnosis, patient's sociodemographic (age, gender, education, nationality, working status, and house location) and clinical features (smoker, diabetes mellitus, human deficiency virus, and recurrent TB status), TB management (directly observed therapy supervisor and detection methods), the clinical presentation of TB (chest X-ray severity), and results of sputum smear testing before and during anti-TB treatment. Patient data confidentiality such as name, identification number, and address were not revealed in the analysis.

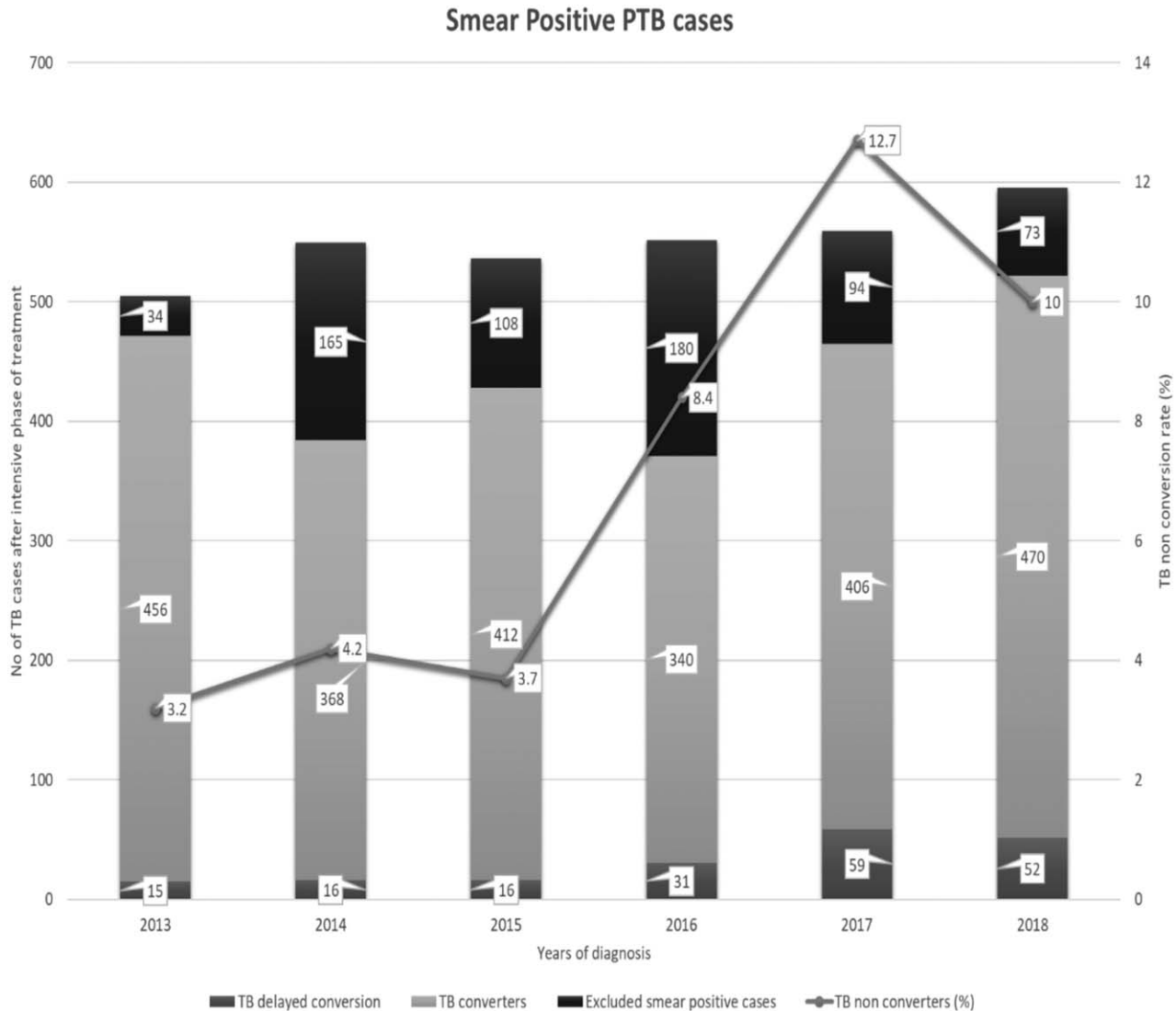
#### 2.4. Data analysis

Data was analyzed with IBM SPSS version 26 software. Bivariate analysis using a simple logistic regression test was conducted to analyze the risk factors. Variables that were statistically

significant in the bivariable analysis were entered into a logistic regression model. Multivariate analysis was applied to obtain a final model describing the significant independent predictors of smear conversion at the end of the intensive phase. A backward stepwise selection was used to identify the independent risk factors for delayed sputum conversion at the end of the intensive phase of anti-TB treatment. Results of the multivariate analysis were presented as beta, standard error, wald, *P* value, adjusted odds ratio, and 95% confidence interval. The fit of the model was assessed with Hosmer Lemeshow and the overall classification percentage. Significance of the statistical tests was taken at a *P* value of .05.

### 3. Results

Between 2013 and 2018, a total of 4973 patients with TB were treated at the various TBTCs in Kota Kinabalu. Of this figure, 537 (10.8%) were EPTB cases, 1214 (24.4%) smear-negative pulmonary TB and 3,222 (64.8%) smear-positive pulmonary TB. EPTB and smear-negative cases were excluded from the analysis.



**Figure 2.** Trends of smear-positive PTB cases and conversion rate in Kota Kinabalu District, 2013 to 2018.

From the total smear-positive cases, 22 (0.7%) cases were transferred/ default/ death/ change diagnosis while 570 (17.7%) cases did not have documented smear results at the end of the intensive phase of treatment. The final case total included in this study was 2641 (82%) which had documented smear results at both treatment initiation and the end of the intensive phase of anti-TB treatment (Fig. 1). Due to incomplete documented data input in the MyTB system, we excluded cases with missing data ranging from 34 cases in 2013 to 180 cases in 2016 (Fig. 2).

From 2013 to 2018, a total of 189 (7.2%) PTB cases were classified as delayed sputum conversion while 2452 (92.8%) patients had a conversion of sputum smear. The annual percentage change of TB non-conversion in new cases significantly had increased in 2016 (8.4%), 2017 (12.7%), and 2018 (10.0%) from 3.2% in 2013. The mean patient age included in the analysis was  $37.1 \pm 16.2$  with 1589 (60.2%) males and 1052 (39.8%) females.

Bivariable analysis (Table 1) indicated that delayed sputum conversion was significantly associated with the year of diagnosis

(2016, 2017 and 2008), the  $\geq 50$  age group, males, non-Malaysian citizens, and those who were illiterate, smokers and residing in suburban areas. They also had absent Bacillus Calmette-Guerin scarring, presented moderate and advanced chest X-ray findings at diagnosis, and were without directly observed treatment, short-course (DOTS) supervisors.

After adjusting for potential confounders in multivariate logistic regression analysis (Table 2), the predictors for delayed sputum smear conversion were ascertained. These included moderate (advanced odd ratio [aOR]: 1.8, 95% confidence interval [95% CI]: 1.3–2.5) and advanced (aOR: 2.7, 95% CI: 1.6–4.5) chest X-ray finding at diagnosis, age  $> 60$  (aOR: 2.1, 95% CI: 1.1–4.0), year of enrolment (2016 (aOR: 2.8, 95% CI: 1.5–5.3), 2017 (aOR: 3.9, 95% CI: 2.1–7.0), 2018 (aOR: 2.8, 95% CI: 1.5–5.0)), smoker (aOR: 1.5, 95% CI: 1.1–2.1), no DOTS supervisor (aOR: 6.9, 95% CI: 2.4–20.0), non-Malaysian citizen (aOR: 1.5, 95% CI: 1.0–2.2), and rural house location (aOR: 1.6, 95% CI: 1.1–2.3). This model fit was based on a non-significant result of Hosmer and Lemeshow Test ( $P = .62$ ) and the overall percentage of 92.8% from the classification table.

**Table 1****Bivariable analysis on associated sociodemographic, comorbid, and clinical factors with delayed sputum smear conversion in Kota Kinabalu TBTC, 2013 to 2018.**

<b>Smear results</b>						
<b>Variable</b>	<b>Total N</b>	<b>Delayed sputum conversion</b>		<b>OR</b>	<b>P value</b>	<b>95% CI</b>
		<b>Yes (n=189) f (%)</b>	<b>No (n=2452) f (%)</b>			
Prevalence	2641	189 (7.2)	2452 (92.8)	–	–	–
Year of enrolment						
2013	471 (17.8)	15 (3.2)	456 (96.8)	–	–	–
2014	384 (14.5)	16 (4.2)	368 (95.8)	1.3	.45	0.7–2.7
2015	428 (16.2)	16 (3.7)	412 (96.3)	1.2	.65	0.6–2.4
2016	371 (14.0)	31 (8.4)	340 (91.6)	2.8	<.01	1.5–5.2
2017	465 (17.6)	59 (12.7)	406 (87.3)	4.4	<.01	2.5–7.9
2018	522 (19.8)	52 (10.0)	470 (90.0)	3.4	<.01	1.9–6.0
Age group						
<20	401 (15.2)	22 (5.5)	379 (94.5)	–	–	–
20–40	1219 (46.2)	79 (6.5)	1140 (93.5)	1.2	.48	0.7–1.9
41–60	776 (29.4)	64 (8.2)	712 (91.8)	1.6	.09	0.9–2.6
>60	245 (9.3)	24 (9.8)	221 (90.2)	1.9	.04	1.0–3.4
Gender						
Female	1052 (39.8)	58 (5.5)	994 (94.5)	–	–	–
Male	1589 (60.2)	131 (8.2)	1458 (91.8)	1.5	<.01	1.1–2.1
Working status						
Working	1289 (48.6)	88 (6.9)	1196 (93.1)	–	–	–
Not working	1357 (51.4)	101 (7.4)	1256 (92.6)	1.1	.56	0.8–1.5
Nationality						
Malaysian	1726 (65.4)	90 (45.2)	1636 (94.8)	–	–	–
Non-Malaysian	915 (34.6)	99 (10.8)	816 (89.2)	2.2	<.01	1.6–3.0
Education level						
Illiterate	993 (37.6)	110 (11.1)	883 (88.9)	3.0	<.01	1.6–5.9
Primary	681 (22.0)	30 (5.2)	551 (94.8)	1.3	.46	0.6–2.7
Secondary	815 (30.9)	39 (4.8)	776 (95.2)	1.2	.59	0.6–2.5
Tertiary	252 (9.5)	10 (4.0)	242 (96.0)	–	–	–
DM						
Yes	205 (7.8)	12 (5.9)	193 (94.1)	–	–	–
No	2436 (92.2)	177 (7.3)	2259 (92.7)	1.3	.45	0.7–2.3
HIV status						
Yes	27 (1.0)	1 (3.7)	26 (96.3)	–	–	–
No	2614 (99.0)	188 (7.2)	2426 (92.8)	2.0	.49	0.3–14.9
Smoker						
Yes	794 (30.1)	76 (9.6)	718 (90.4)	1.6	<.01	1.2–2.2
No	1847 (69.9)	113 (6.1)	1734 (93.9)	–	–	–
House location						
Urban	934 (35.4)	42 (4.5)	892 (95.5)	–	–	–
Sub-Urban	1707 (64.6)	147 (8.6)	1560 (91.4)	2.0	<.01	1.4–2.9
Case status						
New	2487 (94.2)	176 (7.1)	2311 (92.9)	–	–	–
Recurrent	154 (5.8)	13 (8.4)	141 (91.6)	1.2	.54	0.7–2.1
Detection						
Active/Screening	364 (13.8)	19 (5.2)	345 (94.8)	–	–	–
Passive	2277 (86.2)	170 (7.5)	2107 (92.5)	1.5	.13	0.9–2.4
BCG scar						
Yes	1802 (68.2)	98 (5.4)	1704 (94.6)	–	–	–
No	839 (31.8)	961 (10.8)	748 (89.2)	2.1	<.01	1.6–2.9
Chest X-ray at diagnosis						
No lesion /Minimal	1295 (49)	60 (4.6)	1235 (95.4)	–	–	–
Moderate	1179 (44.6)	104 (8.8)	1075 (91.2)	2.0	<.01	1.4–2.8
Advanced	167 (6.3)	25 (15)	142 (85)	3.6	<.01	2.2–6.0
DOT supervisor						
Yes	2625 (99.4)	183 (7.0)	2442 (93)	–	–	–
No	16 (0.6)	6 (37.5)	10 (62.5)	8.0	<.01	2.9–22.3

95% CI = 95% confidence interval, BCG = Bacillus Calmette–Guérin, DM = diabetes mellitus, DOT = directly observed therapy, HIV = human deficiency virus, OR = odds ratio, TBTC = tuberculosis treatment centers.



**Table 2****Multivariable analysis on factors associated with delayed sputum smear conversion at the end of the second month of intensive phase treatment.**

Variable	B	S.E.	Wald	P value	aOR	95% CI
Year of enrolment						
2016	1.02	0.33	9.68	<.01	2.77	1.5–5.3
2017	1.35	0.30	19.99	<.01	3.86	2.1–7.0
2018	1.02	0.31	11.08	<.01	2.77	1.5–5.0
No DOTS Supervisor	1.93	0.55	12.56	<.01	6.89	2.4–20.0
Chest x-rays at diagnosis						
Moderate	0.56	0.17	10.44	<.01	1.75	1.3–2.5
Advanced	0.98	0.27	13.23	<.01	2.67	1.6–4.5
Non-Malaysian	0.41	0.19	4.81	.03	1.50	1.0–2.2
Smoker	0.43	0.16	7.21	<.01	1.54	1.1–2.1
Age >60	0.74	0.33	5.04	.03	2.09	1.1–4.0
Residence of rural area	0.47	0.19	6.15	.01	1.59	1.1–2.3

95% CI = 95% confidence interval, aOR = adjusted odds ratio, DOT = directly observed therapy.

#### 4. Discussion

Analysis of MyTB data between 2013 and 2018 showed that predictors for delayed sputum conversion were the year of diagnosis (2016, 2017, and 2018), absence of DOTS supervisor, chest X-rays at diagnosis (moderate and advanced), non-Malaysian citizens, smokers, aged more than 60 years old, and residing in suburban/rural areas. At the end of the intensive phase of TB treatment, multiple factors could contribute towards the delayed conversion of sputum smear. Ideally, culture is the best way to assess *Mycobacterium tuberculosis* (*Mtb*) viability since non-viable bacteria are microscopy (AFB smear) and remain visible.<sup>[5]</sup> This method unfortunately cannot be used in field conditions particularly in restricted environments such as in developing nations due to factors of cost and the time required to produce the results. Some studies however have indicated a strong correlation between sputum AFB smear and sputum culture.<sup>[11,17]</sup> Therefore, it would be adequate to use microscopic observation as a tool to assess the conversion of sputum smear in this study.

The percentage of smear-positive patients with delayed sputum smear conversion at the end of the intensive phase of anti-TB treatment is an indicator of the performance of the TB programme.<sup>[11,18]</sup> Studies conducted in many settings showed that the proportion of non-conversion sputum smear at the end of the intensive TB treatment phase ranged from 5% to 32%.<sup>[18,19]</sup> In our study, only 7.2% of patients with SPPTB had delayed conversion of sputum smear at the end of the 2nd month of the intensive phase of the treatment, a percentage rate deemed acceptable. However, if categorized by treatment years, the year 2016 (aOR: 2.8, 95% CI: 1.5–5.3), 2017 (aOR: 3.9, 95% CI: 2.1–7.0), and 2018 (aOR: 2.8, 95% CI: 1.5–5.0) were significantly associated with delay in sputum smear conversion at the end of the intensive phase of TB treatment in multivariable analysis. Furthermore, there were major differences of cases that had to be excluded due to incomplete data input in each year from 2013 to 2018 ranging from 34 cases in 2013 to 180 cases in 2016 (Fig. 2). Consequently, we were unable to rule out that the missing data in the MyTB database system might have impacted the results of calculated smear conversion rate in each respective year. As such, the reasons for the low smear conversion rate observed in Kota Kinabalu District in 2016, 2017, and 2018 compared to 2013 could not be ascertained. Previous research had also reported similar results whereby delayed sputum

conversion increased in trend if analyzed by year of diagnosis. Although the exact reasons for this remain unclear, incomplete data reporting of smear results could be a contributing factor. Other factors include non-response to first-line treatment, a consequence of the rise of drug-resistant *Mtb* cases and change in TB case management compared to previous years.<sup>[11]</sup> Further exploration is necessary to understand these results and determine how incomplete smear results might be improved.

One of the reasons for sputum smear conversion delay even after 2 months of intensive phase treatment is inadequate supervision and monitoring of the treatment itself.<sup>[20]</sup> In this study, absence of DOTS supervisors (aOR=6.9, 95% CI: 2.4–20.0) was ascertained as an independent factor for delayed sputum conversion. In the context of Malaysia, all patients are required to have a DOTS supervisor, usually either a family member or health care worker. If the patient is without any DOTS supervisor or where the supervision is inadequate, there is an increased likelihood or tendency of non-compliance. Proper supervision of PTB patients enables the close monitoring of compliance and adherence to the TB treatment which in turn would increase the success rate of sputum conversion.

Unsematham et al found that moderate and advanced X-ray lesions in PTB patients were associated with delayed smear conversion.<sup>[21]</sup> Their findings are in agreement with our study whereby moderate (aOR=1.8, 95% CI: 1.3–2.5) and advanced (aOR=2.7, 95% CI: 1.6–4.5) lesions in chest X-rays at diagnosis were associated with delayed sputum conversion. Late diagnosis is often linked to advanced lung lesions in PTB with cavity and extensive disease presenting higher bacterial loads, a condition which prolongs bacterial clearance.<sup>[22,23]</sup> Earlier detection of TB would reduce the number of patients with advanced and very advanced chest X-ray findings and subsequently lead to faster conversion of sputum smear.

Our analysis showed that smokers (aOR=1.5, 95% CI: 1.1–2.1) were significantly associated with delayed sputum conversion compared to non-smokers in the intensive phase of anti-TB treatment. This association between smoking and delayed sputum conversion has been proven and documented in other studies although there are some conflicting views on the role of smoking in the conversion of sputum smear.<sup>[24–29]</sup> Tobacco smoke inhibits the defence mechanism of the lung against infections.<sup>[26]</sup> It stimulates the alveolar macrophages for inflammatory response together and suppresses the antigen

presentation function to develop a specific immune response thereby causing T-cell anergy.<sup>[30]</sup> Thus the existence of an immunodeficiency pattern among smokers would lead to the delayed clearing of bacilli from their lungs.<sup>[31]</sup> Another study reports that smoking behavior impairs the natural mucociliary clearance of tracheal, bronchial secretions and alveolar macrophage function against *Mtb* in patients with TB. It therefore requires a longer period for smoking TB patients to achieve sputum conversion compared to non-smoking TB patients.

Past research also highlighted an association between age and delayed sputum conversion.<sup>[32–34]</sup> The findings in our study were in concurrence with these reports whereby we found older patients in the age range of >60 (aOR = 2.1, 95% CI: 1.1–4.0) to be more prone to delayed sputum conversion compared to younger patients. Older TB patients demonstrated significantly higher rates of non-conversion due probably to age-related immune deficiencies. Other reasons include delay in seeking health care for the elderly which then leads to the progression of the disease.<sup>[35,36]</sup>

A patient's residence locality, whether suburban or in rural areas, is also a variable that significantly delayed the sputum conversion (aOR = 1.6, 95% CI: 1.1–2.3). Delay in arriving at a definitive diagnosis and in the initiation of optimal treatment increases TB morbidity, mortality, the possibility of emergence of drug resistance, and risk of transmission among rural communities.<sup>[37]</sup> In addition, access to TB diagnosis and treatment for people with TB who live in rural areas is significantly delayed.<sup>[38]</sup> The distance between the patient's home and the corresponding health facility could also affect the adherence to the treatment.<sup>[39,40]</sup> Multiple factors contribute to the delay and lower treatment compliance or completion rates among rural dwellers including individual factors such as distrust of healthcare providers and reliance on alternative medicine. This delay is also oftentimes linked to socio-economic factors such as lack of funds to pay for cost of transportation and treatment, the need to prioritise between either working for their daily livelihood or undergoing treatment, and the inability to access a treatment facility due to distance.<sup>[41,42]</sup>

Our study also found non-Malaysians (OR = 1.5, 95% CI: 1.0–2.2) associated with delayed sputum conversion. The number of such studies among the immigrant population is however limited due to multiple factors such as language barriers, uncertain legal status, lack of access to the health care system, increased geographic mobility, and socio-cultural differences in conceptions about the disease. These factors, taken together, will hinder proper follow-up treatment by health care services among this vulnerable population.<sup>[43]</sup>

Past research also highlighted other reasons for the delay of sputum smear conversion at the end of the intensive phase of anti-TB treatment; among these contributory factors are lack of education, poor patient adherence, co-morbidity, low quality anti-TB drugs, anti-TB drugs doses below the recommended range, drug-resistant TB, heavy bacillary load and recurrent PTB disease.<sup>[33,44,45]</sup> However, our study found these factors as non-significant contributors to the delay in sputum conversion in the local context.

#### 4.1. Limitations

Our study is limited in that the assessment was based solely on information acquired from patient registers with some essential

risk factor information such as the outcome of this study which is post-treatment smear grades missing from the MyTB system. Several studies had reported that at the end of the intensive TB treatment, heavy original bacillary load was recorded as a significant risk factor for delay in sputum smear transformation.<sup>[44–47]</sup> Future improvements or upgrade of MyTB should consider the inclusion of pre-treatment smear grades in the information system. In addition, not all patients who were smear-positive had sputum culture results. Due to this limitation, only sputum smear AFB results were used as the outcomes in this study since no sputum culture was available for use as comparison to the sputum smear. Due to the lack of information and missing data in the MyTB system, our study could only include 2641 (82%) of the 3222 smear-positive pulmonary TB in the analysis. To ensure the MyTB system is solid in content and delivery, future data input has to include these missing data and other critical variables especially sputum smear results, initial smear grading during diagnosis, and socio-economic status of patients.<sup>[48]</sup> These will greatly assist in the optimisation of national TB control measures.

## 5. Conclusion

Our study has shown that delayed smear conversion at 7.4% is considered low and acceptable in following the WHO target and recommendation. Moderate and advanced chest X-ray findings at diagnosis, non-Malaysians, the age range of >35, low education level, smokers, absence of DOTS supervisors, and residence in suburban or rural localities were associated with delayed sputum conversion. To improve sputum smear conversion rate, there is a need to improve early detection of PTB cases to

1. reduce late or severe cases presenting during diagnosis,
2. strengthen quit-smoking management and promotions among PTB patients, and
3. increase the percentage of patients with DOTS supervisors.

In the same instance, the vulnerable population i.e. those residing in suburban localities, the elderly and migrant TB patients must be given access to proper follow-up treatment and management.

## Acknowledgment

We thank the Director-General of Health Malaysia for his permission to publish the output of this research as an article in this journal. In addition, we thank those who were directly or indirectly involved in making the research a success.

## Author contributions

**Conceptualization:** Zaleha Md Isa.

**Data curation:** Azman Atil.

**Formal analysis:** Khalid Mokti.

**Methodology:** Khalid Mokti.

**Project administration:** Firdaus Hayati, Syed Sharizman Syed Abdul Rahim.

**Resources:** Julaidah Sharip, Sahrol Nizam Abu Bakar.

**Supervision:** Zaleha Md Isa.

**Validation:** Zaleha Md Isa.

**Writing – original draft:** Khalid Mokti, Azman Atil.

## References

- [1] World Health Organization. Global tuberculosis report 2018. <https://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf?sequence=1&isAllowed=y>. Accessed July 23, 2021
- [2] Sultan MAH, Hayati F, Azizan N, Haur LC, Sharif SZ. Various presentations of breast tuberculosis and tuberculous lymphadenopathy: a case series of surgical rarity. *Med Med J* 2017;32:33–41.
- [3] Azizan N, Hayati F, Abdul Rashid NF, Abdullah Suhaimi SN. Metastatic papillary thyroid cancer in tuberculous lymphadenopathy: an unfortunate dual pathology. *GMJ* 2018;29:154–6.
- [4] Hoe VC, Khairuddin A, Tan JS, Sharif MS, Azizan N, Hayati F. Incidental hepatic tuberculosis during planned resection of locally advanced ampullary carcinoma: a case report. *BMC Surg* 2020;20:1–4.
- [5] Bouti K, Aharmim M, Marc K, et al. Factors influencing sputum conversion among smear-positive pulmonary tuberculosis patients in Morocco. *ISRN Pulmonol* 2013;2013:1–5.
- [6] Namukwaya E, Nakwagala F, Mulekya F, Mayanja-Kizza H, Mugerwa R. Predictors of treatment failure among pulmonary tuberculosis patients in Mulago hospital, Uganda. *African Health Sciences* 2011;11:105–11.
- [7] Mokti K, Ibrahim MY, Giloi N, et al. Factors contribute to tuberculin skin test (TST) positive among urban islander, Malaysian Borneo. *Gazi Med J* 2020;32:11–6.
- [8] Agarwal S, Chauhan L. Tuberculosis Control in India. New Delhi: Directorate General of Health Services, Ministry of Health and Family Welfare; 2005.
- [9] Toman K, Frieden TR, Organization WH. Toman's Tuberculosis: Case Detection, Treatment, and Monitoring: Questions and Answers/Edited by T Frieden. 2nd edition. 2004;World Health Organization,
- [10] Kuaban C, Bame R, Mouangue L, Djella S, Yomgni C. Non conversion of sputum smears in new smear positive pulmonary tuberculosis patients in Yaounde, Cameroon. *East Afr Med J* 2009;86:219–25.
- [11] Djouma FN, Noubom M, Ateudjieu J, Donfack H. Delay in sputum smear conversion and outcomes of smear-positive tuberculosis patients: a retrospective cohort study in Bafoussam, Cameroon. *BMC Infectious Dis* 2015;15:1–7.
- [12] World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. <https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf>. Accessed July 24, 2021.
- [13] Siddiqui UA, O'Toole M, Kabir Z, et al. Smoking prolongs the infectivity of patients with tuberculosis. *Ir Med J* 2010;103:278–80.
- [14] Mokti K, Isa Z, Manaf MRA, Hayati F, Abd Rahim SSS. Nutritional burden in tuberculosis and inter-sectoral nutritional management for tuberculosis patients in Malaysia. *Türkiye Klinikleri Tip Bilimleri Dergisi* 2020;40:83–95.
- [15] Saffari M, Jolandimi HA, Sehat M, et al. Smear grading and the Mantoux skin test can be used to predict sputum smear conversion in patients suffering from tuberculosis. *GMS Hyg Infect Control* 2017;12:1–6.
- [16] Department of Statistics, Malaysia. Press release monthly manufacturing statistics Malaysia, August 2014. [https://www.dosm.gov.my/v1/images/stories/files/LatestReleases/mms/2014/MMS\\_Aug14BI.pdf](https://www.dosm.gov.my/v1/images/stories/files/LatestReleases/mms/2014/MMS_Aug14BI.pdf). Accessed July 23, 2021.
- [17] Dominguez-Castellano A, Muniain M, Rodriguez-Bano J, et al. Factors associated with time to sputum smear conversion in active pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2003;7:432–8.
- [18] Jayakody W, Harries A, Malhotra S, De Alwis S, Samaraweera S, Pallewatta N. Characteristics and outcomes of tuberculosis patients who fail to smear convert at two months in Sri Lanka. *Public Health Action* 2013;3:26–30.
- [19] Parikh R, Nataraj G, Kanade S, Khatri V, Mehta P. Time to sputum conversion in smear positive pulmonary TB patients on category I DOTS and factors delaying it. *J Assoc Physicians India* 2012;60:22–6.
- [20] World Health Organization. Treatment of tuberculosis: guidelines – fourth edition. [https://apps.who.int/iris/bitstream/handle/10665/44165/9789241547833\\_eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/44165/9789241547833_eng.pdf). Accessed July 23, 2021
- [21] Unsematham S, Kateruttanakul P. Factors predicting sputum smear conversion and treatment outcomes in new smear-positive pulmonary tuberculosis. *J Med Assoc Thai* 2013;96:644–9.
- [22] Augusto VM, Greco DB, Dalcolmo M, Neves MA, Weinreich HR. Pulmonary tuberculosis presentation-Late diagnosis, advanced disease. *Eur Respiratory Soc* 2021;40:P2621.
- [23] Perrin F, Woodward N, Phillips P, et al. Radiological cavitation, sputum mycobacterial load and treatment response in pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2010;14:1596–602.
- [24] Nagu TJ, Spiegelman D, Hertzmark E, et al. Anemia at the initiation of tuberculosis therapy is associated with delayed sputum conversion among pulmonary tuberculosis patients in Dar-es-Salaam, Tanzania. *PLoS One* 2014;9:e91229.
- [25] Babalik A, Kiziltas S, Arda H, Oruc K, Celintas G, Calalettin H. Factors affecting smear conversion in tuberculosis management. *Med Sci* 2012;1:351–62.
- [26] Maciel E, Briosci A, Peres R, et al. Smoking and 2-month culture conversion during anti-tuberculosis treatment. *Int J Tuberc Lung Dis* 2013;17:225–8.
- [27] Dorman SE, Johnson JL, Goldberg S, et al. Substitution of moxifloxacin for isoniazid during intensive phase treatment of pulmonary tuberculosis. *Am J Respir Crit Care Med* 2009;180:273–80.
- [28] Visser ME, Stead MC, Walzl G, et al. Baseline predictors of sputum culture conversion in pulmonary tuberculosis: importance of cavities, smoking, time to detection and W-Beijing genotype. *PLoS One* 2012;7:e29588–129588.
- [29] Slama K, Chiang C, Enarson D, et al. Tobacco and tuberculosis: a qualitative systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2007;11:1049–61.
- [30] Geng Y, Savage SM, Johnson LJ, Seagrave J, Sopori ML. Effects of nicotine on the immune response. I. Chronic exposure to nicotine impairs antigen receptor-mediated signal transduction in lymphocytes. *Toxicol Appl Pharmacol* 1995;135:268–78.
- [31] Rate SC, Grading SS. Factors influencing delay in sputum smear conversion among new smear-positive pulmonary tuberculosis patients of Davangere tuberculosis unit. *Int J Med Sci Public Health* 2017; 6:1565–71.
- [32] Noubom M, Nembot FD, Donfack H, Mfin PSK, Tchasse F. Caracteristiques des patients tuberculeux à l'ouest cameroun: 2000-2009. *Pan Afr Med J* 2014;16:39.
- [33] Lee J, Lee B, Yoon HI, Lee CT, Lee J. Influence of previous tuberculosis treatment history on acid-fast bacilli smear and culture conversion. *Int J Tuberc Lung Dis* 2012;16:1344–8.
- [34] Meiri I, Saad SB, Daghfous H, Khelifa MB, Tritar F. Factors influencing sputum smear conversion delay in tuberculosis. *Eur Respiratory Soc* 2015;46:A2695.
- [35] Gaur S, Dhingra V, Rajpal S, Aggarwal J. Tuberculosis in the elderly and their treatment outcome under DOTS. *Indian J Tuberc* 2004;51:83–7.
- [36] Arora V, Singla N, Sarin R. Profile of geriatric patients under DOTS in revised national tuberculosis control programme. *Indian J Chest Dis Allied Sci* 2003;45:231–6.
- [37] Marahatta SB, Yadav RK, Giri D, et al. Barriers in the access, diagnosis and treatment completion for tuberculosis patients in central and western Nepal: a qualitative study among patients, community members and health care workers. *PLoS One* 2020;15:e0227293.
- [38] Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health* 2008;8:15.
- [39] Akinsola OJ, Yusuf OB, Ige OM, Okonji PE. Models for predicting time to sputum conversion among multi-drug resistant tuberculosis patients in Lagos, South-West Nigeria. *Front Public Health* 2018;6:347.
- [40] Kelly C, Hulme C, Farragher T, Clarke G. Are differences in travel time or distance to healthcare for adults in global north countries associated with an impact on health outcomes? A systematic review. *BMJ Open* 2016;6:e013059.
- [41] Sreeramareddy CT, Qin ZZ, Satyanarayana S, Subbaraman R, Pai M. Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review. *Int J Tuberc Lung Dis* 2014;18:255–66.
- [42] Cai J, Wang X, Ma A, Wang Q, Han X, Li Y. Factors associated with patient and provider delays for tuberculosis diagnosis and treatment in Asia: a systematic review and meta-analysis. *PLoS One* 2015;10:e0120088.
- [43] Essadek HO, Mendioroz J, Guiu IC, et al. Community strategies to tackle tuberculosis according to the WHO region of origin of immigrant communities. *Public Health Action* 2018;8:135–40.
- [44] Pefura-Yone EW, Kengne AP, Kuaban C. Non-conversion of sputum culture among patients with smear positive pulmonary tuberculosis in Cameroon: a prospective cohort study. *BMC Infectious Dis* 2014; 14:138.
- [45] Ukwaja KN, Oshi DC, Oshi SN, Alobu I. Profile and treatment outcome of smear-positive TB patients who failed to smear convert after 2 months of treatment in Nigeria. *Trans R Soc Trop Med Hyg* 2014;108:431–8.
- [46] Tiwari S, Kumar A, Kapoor S. Relationship between sputum smear grading and smear conversion rate and treatment outcome in the patients



- of pulmonary tuberculosis undergoing dots—a prospective cohort study. *Indian J Tuberc* 2012;59:135–40.
- [47] Fanai S, Viney K, Tarivonda L, Roseveare C, Tagaro M, Marais B. Profile of tuberculosis patients with delayed sputum smear conversion in the Pacific island of Vanuatu. *Public Health Action* 2014;4:S19–24.
- [48] Jeffrey MS, Ahmedy F, Avoi R, et al. Integrating digital health for healthcare transformation: conceptual model of smart healthcare for northern Borneo. *Int J Adv Trends Computer Sci Engineering* 2020; 9:110–5.