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Treatment outcomes of extended versus non-extended intensive phase in pulmonary tuberculosis smear positive patients with delayed sputum smear conversion: A retrospective cohort study at primary care clinics in Kota Kinabalu

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Abstract

Introduction: Delayed sputum smear conversion in patients with smear-positive pulmonary tuberculosis is a crucial problem at primary care clinics in Sabah resulting in poor treatment outcomes. This study aimed to compare the treatment outcomes between extended and non-extended intensive phase treatments among patients with delayed sputum smear conversion and to identify the factors associated with unsuccessful treatment outcomes.

Methods: This retrospective cohort study was conducted using data from a Malaysian tuberculosis registry, medical records and clinic referral emails from five primary care clinics in Kota Kinabalu from January 2014 to December 2018. A total of 163 patients with delayed sputum smear conversion were selected and divided into cohort groups: 90 patients received 3 months of intensive phase treatment (extended intensive phase), and 73 patients received 2 months of intensive phase treatment (non-extended intensive phase).

Results: Of the 163 patients, 33.7% had unsuccessful treatment outcomes (25.2% had treatment failure; 0.6% died; 3.7% defaulted; and 4.3% transferred out), and 3.7% had relapse. There were no significant differences in the prevalence of unsuccessful treatment outcomes (37.6% vs 28.6%, OR=1.51, CI=0.77–2.94, P=0.226) and relapse (2.2% vs 5.7%, OR=0.36, CI=0.65–2.04, P=0.404) between the extended and non-extended intensive phase groups. High sputum acid-fast bacilli grade (AFB) at 2 months, drug resistance and lack of directly observed treatment, short-course supervision (DOTS) were associated with unsuccessful treatment outcomes.

Conclusion: Extended intensive phase treatment in patients with delayed sputum smear conversion does not prevent unsuccessful treatment outcomes and relapse.

Introduction

Tuberculosis (TB) is a major public health concern and remains one of the leading causes of death worldwide. Approximately 1.4 million patients died, and 10 million people developed TB in 2019.[1] Malaysia has an intermediate burden of TB. This disease is of major significance in Sabah primarily owing to the influx of immigrants from neighbouring countries with a high prevalence of TB.[2] Sabah's estimated incidence of TB (128/100,000) far exceeds the national rate (92/100,000).[3] The treatment success rate in Sabah is 83% for patients with drug-sensitive TB and 36% for those with multidrug-resistant TB,[4] remaining below the World Health Organization (WHO) recommended target of ≥90%.

TB treatment aims to provide the safest and most effective treatment in the shortest possible time.[5] Isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z) are the first-line drugs for treating patients with TB caused by drug-susceptible *Mycobacterium tuberculosis*. The WHO recommends patients who are newly diagnosed with active pulmonary TB to receive 2 months of intensive phase treatment (2EHRZ), followed by 4 months of maintenance phase treatment (4HR).[6] The initial indicator of successful TB treatment is the change in the bacteriological status of

patients' sputum from acid-fast bacilli (AFB) positivity to AFB negativity, which is referred to as sputum smear conversion. The mean time from treatment initiation to sputum smear conversion has been reported to be 1.99 months.[7]

The smear conversion rate at the end of 2 months of the intensive phase is an important operational indicator in the National TB Control Program. It provides objective evidence for patients' response to therapy and hence the treatment outcome. Delayed sputum smear conversion is defined as persistent sputum AFB positivity after 2 months of intensive phase treatment. The worldwide prevalence of delayed sputum smear conversion is 5.0–32.1% among all patients with smear-positive pulmonary TB.[8–16] Factors such as male sex, elderly age, high initial sputum AFB grade, presence of cavitation or extensive pulmonary disease have been identified to be associated with delayed sputum smear conversion.[8-18] Persistent smear positivity at the end of 2 months of treatment is significantly associated with unfavourable treatment outcomes, especially lower cure rate, treatment failure and relapse.[13-19]

The WHO has previously recommended extending the intensive phase to 3 months in patients with pulmonary TB and positive sputum smear at the end of the second month of treatment; this strategy has become the standard in the national TB programmes of many countries. However, since 2010, the WHO no longer recommends the extension of the intensive phase in patients with delayed sputum smear conversion.[6] Nevertheless, such extension continues to be widely practiced in Malaysia. There are no guidelines available for the treatment of delayed sputum smear conversion or severe pulmonary TB in Malaysia.[20] Previous studies have shown inconsistent findings on the effectiveness of treatment extension in patients with delayed sputum smear conversion. Extension of the intensive phase by 1 month may reduce relapse but not failure and may not increase the acquired resistance.[21] Another literature found no evidence of reduced recurrent TB in patients who received extended treatment; the extension subjected patients to high direct costs of medications and investigations.[22] However, these studies did not focus on patients with severe pulmonary TB, who may benefit from treatment extension.

Delayed sputum smear conversion is a critical problem at primary healthcare clinics in Sabah resulting in poor treatment outcomes. The knowledge about the effectiveness of extension of the intensive phase in patients with delayed sputum smear conversion and the factors associated with unsuccessful treatment outcomes is expected to be useful for clinicians to decide on the clinical management of patients. The results are expected to help in bridging knowledge gaps and to improve patient outcomes.

Hence, this study aimed to compare the treatment outcomes (i.e. unsuccessful treatment outcome and relapse) between extended and non-extended intensive phase treatments and to identify the factors associated with unsuccessful treatment outcomes in patients with delayed sputum smear conversion who attended primary care clinics in Kota Kinabalu.

Methods

This 5-year retrospective cohort study investigated patients with smear-positive pulmonary TB and delayed sputum smear conversion registered under five primary care clinics in Kota Kinabalu, namely Klinik Kesihatan (KK) Menggatal, KK Luyang, KK Inanam, KK Telipok and Pusat Rawatan 1 Queen Elizabeth Hospital from January 2014 to December 2018. This study was conducted using data from the Malaysian National Tuberculosis Surveillance Registry, Tuberculosis Information System (TBIS), medical records and clinic referral emails.

Regardless of age, all patients who were diagnosed with smear-positive pulmonary TB with or without extrapulmonary TB and at least one positive sputum smear at 2 months of treatment after completion of the intensive phase and treated with the standard treatment regimen using the first-line anti-TB drugs were eligible for enrolment into the study cohort. Patients who were previously treated for TB, who did not have the treatment outcome evaluated or who had a change in diagnosis were excluded. The enrolled patients were then divided into extended (3EHRZ) and non-extended intensive phase (2EHRZ) groups for comparison of their treatment outcomes.

The dependent variables were the treatment outcomes, including the unsuccessful and successful treatment outcomes, as the primary endpoint of treatment and relapse as the secondary endpoint of treatment.

The independent variables were selected on the basis of their potential association with the treatment outcomes based on the available data from the TB registry and medical records: sociodemographic profiles, clinical profiles and treatment profiles.

The definitions of the categories of TB cases, treatment outcome operational terms and chest radiograph severity are presented in **Table 1**.

Table 1. Definitions of the categories of TB cases, treatment outcomes and chest radiograph severity.[20,23]

Definition of TB cases	
New smear- positive PTB	A patient who has never received treatment for TB or who has taken anti-TB drugs for less than 30 days and who has: • two or more initial sputum smear examinations positive for AFB; OR • one sputum examination positive for AFB plus radiographic abnormalities consistent with active PTB as determined by a clinician; OR • one sputum specimen positive for AFB and at least one sputum specimen culture-positive for AFB
Extrapulmonary TB	TB of organs other than the lungs, such as the pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones and meninges. Diagnosis should be based on one culture-positive specimen or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of anti-TB chemotherapy.
Previously treated	A patient previously treated for TB including relapse, failure and default cases
Definition of treatment outcomes	
Successful treatment	The sum of patients who are cured and completed treatment
Unsuccessful treatment	The sum of patients who have treatment failure, died, defaulted and transferred out.
Cured	A patient with a former positive smear who shows a negative smear in the last month of treatment and on at least one previous occasion
Completed treatment	A patient who has completed treatment but who does not meet the criteria to be classified either as a cure or a failure
Died	A patient who dies for any reason during the course of treatment
Treatment failure	A patient whose sputum smears positive at 5 months or later during treatment
Defaulted	A patient who has interrupted treatment for 2 or more consecutive months
Transferred out	A patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known
Not evaluated	A patient who does not have the treatment outcome evaluated
Relapse	A patient whose most recent treatment outcome is 'cured' or 'treatment completed' and who is subsequently diagnosed with bacteriologically positive TB via sputum smear microscopy or culture within 2 years after completed treatment
Chest radiograph severity	
Minimal	Slight lesions with no cavity; confined to small parts of one or both lungs but with the total extent not exceeding the upper zone
Moderately advanced	Dense confluent lesions not exceeding one third of one lung OR disseminated slight to moderate density in one or both lungs not exceeding the volume of one lung. The total diameter of the cavity does not exceed 4 cm.
Far advanced	Lesions are more extensive than those in moderately advanced cases.

TB = tuberculosis
PTB = pulmonary tuberculosis
AFB = acid-fast bacilli
EPTB = extrapulmonary tuberculosis

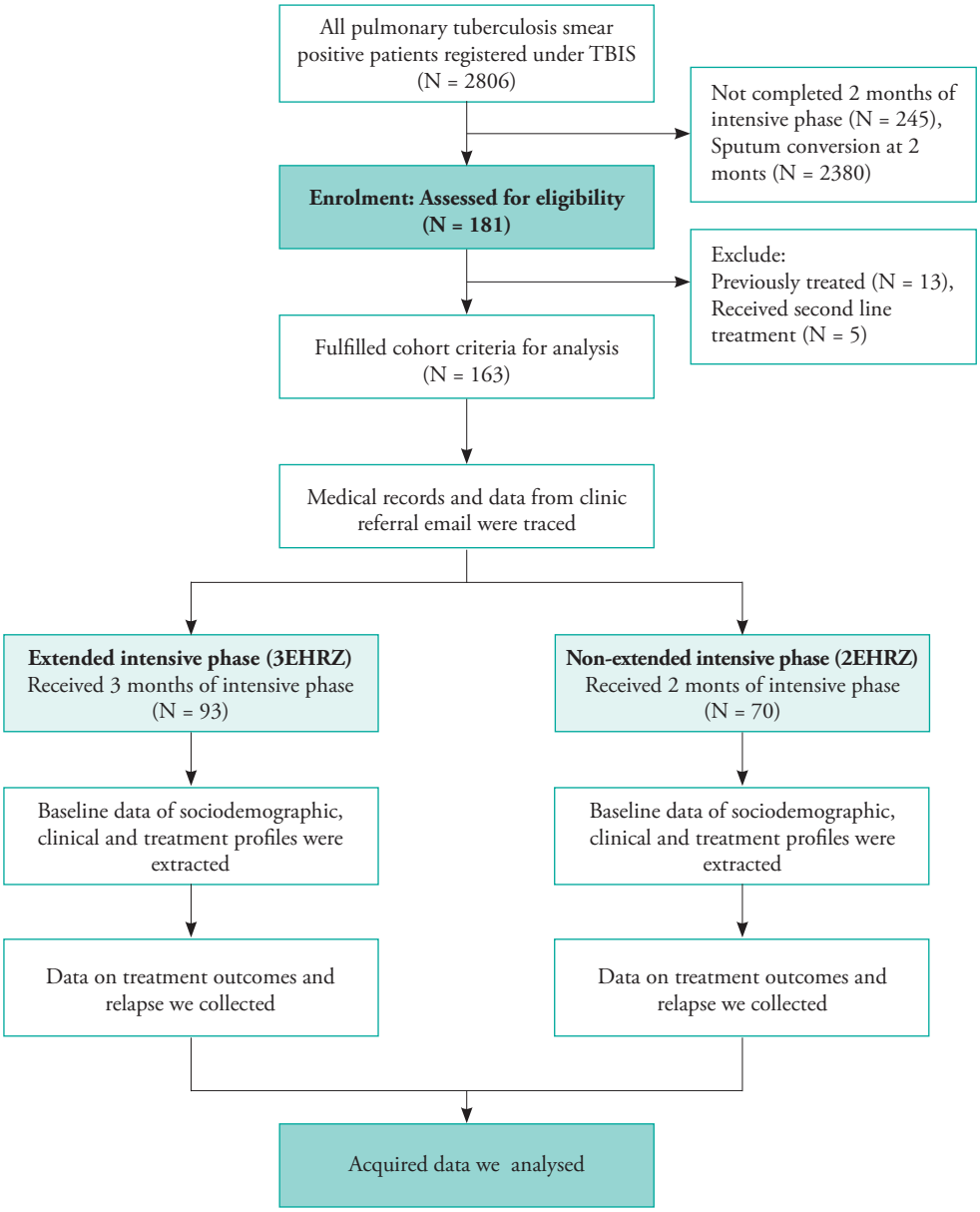

Figure 1. Flowchart of enrolment of eligible participants.

Figure 1 illustrated the enrolment flow of the eligible participants. Patients' identification and registration numbers were used to trace their medical records, chest radiographs and sputum microbiology results, including sputum for AFB, sputum for MTB culture and sensitivity, sputum for GeneXpert and sputum for line probe assay. For patients whose files were missing or had been disposed, data were retrieved from the clinic referral emails to the respiratory team. Of the 163 patients, 93 (57%) received 3 months of intensive phase treatment (extended intensive phase), while the other 70 (43%) received 2 months of intensive phase treatment (non-extended intensive phase).

The baseline sociodemographic, clinical and treatment profiles of the patients were extracted. Both groups received 4–7 months of maintenance phase treatment. The DOTS programme in Sabah provided medications to patients on a daily basis during the intensive phase and on a fortnightly basis during the maintenance phase of the treatment. The patients were switched to separate tablet regimens when there was intolerance or adverse drug reactions to fixed-dose combination (AkuriT). Data on the treatment outcomes and relapse were collected. Relapse cases were traced in the TBIS using the patients' name and identification number in subsequent 2 years after the patients completed TB treatment. A data collection form was used to record the data collected from the TB registry, medical records and clinic referral emails.

Data were analysed using Statistical Package for Social Sciences (SPSS) version 26.0. Continuous data were reported as means and standard deviations and categorical data as frequencies and percentages. A bivariate analysis using an independent t-test, the chi-square test and Fisher's exact test was applied to compare the patient profiles and treatment outcomes between the extended and non-extended intensive phase groups. Single imputation using mode values was used to account for missing data in the categorical variables of interest. Univariate and multivariate logistic regression analyses were used to assess the potential determinants of unsuccessful treatment outcomes. The crude and adjusted odds ratios (ORs), 95% confidence intervals (CIs) and P-values were reported for each independent variable. The independent variables with P-values of <0.25 in the univariate analysis were included in the multivariate logistic regression analysis (enter selection method). The Hosmer–Lemeshow test and Nagelkerke pseudo R^2 were used to assess the fit of the model. In all tests, a P-value of <0.05 was considered statistically significant.

Ethical approval for this study was obtained from the Medical Research and Ethics Committee of the Ministry of Health Malaysia (NMRR-19-4064-52225).

Results

Sociodemographic, clinical and treatment profiles of the patients

Table 2 shows the sociodemographic, clinical and treatment profiles of the patients with delayed sputum smear conversion. The profiles of the patients were relatively similar between the two groups. Of the 163 patients, the mean (σ) age was 38.9 (15.9) years, and most patients were aged from 25 to 44 years (42.9%). Male sex was more predominant (68.7%), with a male-to-female sex ratio of 2:1. More than half of the patients were non-Malaysians (52.8%), had low educational levels (59.5%) and were unemployed (54.0%). The majority of the patients were diagnosed with smear-positive pulmonary TB (97.5%). Approximately one tenth of the patients had diabetes mellitus (12.3%), and one third of the patients were smokers (39.3%). Most patients had severe pulmonary TB with moderately advanced chest radiograph severity (57.7%), lung cavitation (81.0%) and high sputum AFB grade (3+) (54.0%) at diagnosis. More than half of the patients had scanty AFB detected in the sputum at 2 months (58.9%). Approximately 82.2% of the patients had MTB complex detected from the sputum culture at baseline, while only 6.7% had positive sputum MTB culture at 2 months. Further, 9.2% were found to have drug resistance to the first-line anti-TB drugs.

Table 2. Sociodemographic, clinical and treatment profiles of patients who received extended and non-extended intensive phase treatments.

Variable	Total		Extended intensive phase (3EHRZ)		Non-extended intensive phase (2EHRZ)		P-value
	N=163	%	n=93	%	n=70	%	
Age (year), mean, σ	38.9±15.9		38.9±16.3		38.9±15.6		0.989[a]
<24	36	22.1	24	25.8	12	17.1	0.516[b]
25–44	70	42.9	36	38.7	34	48.6	
45–64	45	27.6	26	28.0	19	27.1	
>65	12	7.4	7	7.5	5	7.1	
Sex							
Male	112	68.7	69	74.2	43	61.4	0.082[b]
Female	51	31.3	24	25.8	27	38.6	
Nationality							
Non-Malaysian	86	52.8	52	55.9	34	48.6	0.353[b]
Malaysian	77	47.2	41	44.1	36	51.4	
Race							
Filipino	84	51.5	50	53.8	34	48.6	
Sabah Native	65	39.9	33	35.5	32	45.7	
Chinese	9	5.5	7	7.5	2	2.9	
Malay	3	1.8	1	1.1	2	2.9	
Indonesian	2	1.2	2	2.2	0	0	

Table 2. Continued

Variable	Total		Extended intensive phase (3EHRZ)		Non-extended intensive phase (2EHRZ)		P-value
	N=163	%	n=93	%	n=70	%	
Highest educational level							
None	97	59.5	58	62.4	39	55.7	0.186[b]
Primary school	25	15.3	10	10.8	15	21.4	
Secondary school	32	19.6	21	22.6	11	15.7	
College or university	9	5.5	4	4.3	5	7.1	
Occupation							
Unemployed	88	54.0	51	54.8	37	52.9	0.802[b]
Employed	75	46.0	42	45.2	33	47.1	0.989[b]
TB diagnosis							
Smear-positive PTB	159	97.5	91	97.8	68	97.1	1.000[c]
Smear-positive PTB with EPTB	4	2.5	2	2.2	2	2.9	
Comorbidity							
Diabetes mellitus	20	12.3	13	14.0	7	10.0	0.443[b]
HIV infection	2	1.2	0	0	2	2.9	0.183[c]
Smoking	64	39.3	37	39.8	27	38.6	0.875[b]
BCG vaccination	91	55.8	50	53.8	41	58.6	0.541[b]
Chest radiograph severity							
Minimal	47	28.8	26	28.0	21	30.0	0.951[b]
Moderately advanced	94	57.7	54	58.1	40	57.1	
Far advanced	22	13.5	13	14.0	9	12.9	
Lung cavitation							
Present	132	81.0	75	80.6	57	81.4	0.900[b]
Absent	31	19.0	18	19.4	13	18.6	
Sputum AFB grade							
At diagnosis							
Scanty	6	3.7	4	4.3	2	2.9	0.138[b]
1+	21	12.9	15	16.1	6	8.6	
2+	48	29.4	31	33.3	17	24.3	
3+	88	54.0	43	46.2	45	64.3	
At 2 months							
Scanty	96	58.9	50	53.8	46	65.7	0.281[b]
1+	42	25.8	27	29.0	15	21.4	
2+	20	12.3	14	15.1	6	8.6	
3+	5	3.1	2	2.2	3	4.3	
Sputum MTB culture							
At diagnosis							
Not performed	2	1.2	2	2.2	0	0	**0.002[b]**
No AFB seen or isolated	27	16.6	8	8.6	19	27.1	
MTB complex detected	134	82.2	83	89.2	51	72.9	
At 2 months							
Not performed	27	16.6	15	16.1	12	17.1	0.405[b]
No AFB seen or isolated	125	76.7	73	78.5	52	74.3	
MTB complex detected	11	6.7	5	5.4	6	8.6	
Drug resistance							
Any drug resistance	15	9.2	11	11.8	4	5.7	0.181[b]
No drug resistance	148	90.8	82	88.2	66	94.3	
Duration of the maintenance phase							
≤4 months	60	36.8	23	24.7	37	52.9	<0.001[b]
5–6 months	58	45.6	48	51.6	10	14.3	
≥7 months	45	27.6	22	23.7	23	32.9	

Table 2. Continued

Variable	Total		Extended intensive phase (3EHRZ)		Non-extended intensive phase (2EHRZ)		P-value
	N=163	%	n=93	%	n=70	%	
Total duration of treatment							
≤6 months	48	29.4	11	11.8	37	52.9	**<0.001**[b]
7–8 months	26	16.0	16	17.2	10	14.3	
≥9 months	89	54.6	66	71.0	23	32.9	
DOTS							
Yes	138	84.7	76	81.7	62	88.6	0.230[b]
No	25	15.3	17	18.3	8	11.4	
Drug combination							
Fixed-dose combination	129	79.1	68	73.1	61	87.1	**0.029**[b]
Separate tablet regimen	34	20.9	25	26.9	9	12.9	

σ Standard deviation; [a]Independent t-test; [b]Chi-square test; [c]Fisher's exact test Level of significance: P<0.05
3EHRZ = 3 months of ethambutol, isoniazid, rifampicin and pyrazinamide treatment
2EHRZ = 2 months of ethambutol, isoniazid, rifampicin and pyrazinamide treatment
PTB = pulmonary tuberculosis **EPTB** = extrapulmonary tuberculosis
HIV = human immunodeficiency virus **BCG** = *bacillus Calmette–Guérin*
AFB = acid-fast bacilli **MTB** = *Mycobacterium tuberculosis*
DOTS = directly observed therapy, short-course

Primary and secondary treatment outcomes

Table 3 compares the primary and secondary endpoints of treatment outcomes between the extended and non-extended intensive phase groups among the patients with delayed sputum smear conversion. Of the 163 patients with delayed sputum smear conversion, the treatment success rate was 66.3% (65.0% were cured, and 1.2% completed treatment), while 33.7% had unsuccessful treatment outcomes (25.2% had treatment failure; 0.6% died; 3.7% defaulted; and 4.3% transferred out), and 3.7% had relapse.

There were no significant differences in the prevalence of unsuccessful treatment outcomes (37.6% vs 28.6%, OR=1.51, CI=0.77–2.94, P=0.226) and relapse (2.2% vs 5.7%, OR=0.36, CI=0.65–2.04, P=0.404) between the extended and non-extended intensive phase groups. A clear benefit of extended intensive phase treatment in the prevention of failure and defaulting apart from improving the cure rate could not be identified in the subgroup analysis of the patients with unsuccessful and successful outcomes. The differences in the rates of failure (28.0% vs 21.4%, P=0.343), default (4.3% vs 2.9%, P=0.630) and cure (60.2% vs 71.4%, P=0.139) between both groups were not significant.

Table 3. Primary and secondary endpoints of treatment outcomes between extended and non-extended intensive phase treatments.

Outcome	Total		Extended intensive phase (3EHRZ)		Non-extended intensive phase (2EHRZ)		P-value	OR	95% CI
	N=163	%	n=93	%	n=70	%			
Treatment outcome									
Unsuccessful	55	33.7	35	37.6	20	28.6	0.226[a]	1.51	0.77–2.94
Treatment failure	41	25.2	26	28.0	15	21.4	0.343[a]	1.42	0.69–2.95
Died	1	0.6	0	0	1	1.4	NA		
Defaulted	6	3.7	4	4.3	2	2.9	NA		
Transferred out	7	4.3	5	5.4	2	2.9	NA		
Successful	108	66.3	58	62.4	50	71.4			
Cured	106	65.0	56	60.2	50	71.4	0.139[a]	0.61	0.31–1.18
Completed treatment	2	1.2	2	2.2	0	0	NA		

Table 3. Continued

Outcome	Total		Extended intensive phase (3EHRZ)		Non-extended intensive phase (2EHRZ)		P-value	OR	95% CI
	N=163	%	n=93	%	n=70	%			
Relapse									
Yes	6	3.7	2	2.2	4	5.7	0.404[b]	0.36	0.65–2.04
No	157	96.3	91	97.8	66	94.3			

[a]**Chi-square test;** [b]**Fisher's exact test**
Level of significance: P<0.05
3EHRZ = 3 months of ethambutol, isoniazid, rifampicin and pyrazinamide treatment
2EHRZ = 2 months of ethambutol, isoniazid, rifampicin and pyrazinamide treatment
Unsuccessful outcomes = Treatment failure, died, defaulted and transferred out
Successful outcomes = Cured and completed treatment
NA = P-value not generated for these variables owing to an insufficient sample

Determinants of unsuccessful treatment outcomes

Table 4 presents the factors associated with unsuccessful treatment outcomes in the patients with delayed sputum smear conversion in the univariate and multivariate analyses. The variables in the univariate analysis that showed significant associations with unsuccessful treatment outcomes were far advanced chest radiograph severity (OR=3.27, CI=1.12-9.58, P=0.031), high sputum AFB grade at 2 months (≥2+) (OR=5.33, CI=2.09–13.63, P<0.001), any drug resistance (OR=4.58, CI=1.48–14.16, P=0.008), 7-month duration of the maintenance phase (OR=2.88, CI=1.27–6.51, P=0.011) and no DOTS supervision (OR=11.77, CI=4.11–33.72, P<0.001). The duration of intensive phase treatment was not significantly associated with unsuccessful treatment outcomes. Factors with P<0.25 in the univariate analysis, including the duration of the intensive phase, age, sex, diabetes mellitus, chest radiograph severity, sputum AFB grade at 2 months, sputum MTB culture at 2 months, drug resistance and DOTS supervision, were entered into the multiple logistic regression analysis.

In our final model, after adjustments for other factors in the multiple logistic regression analysis, high sputum AFB grade at 2 months (≥2+) (OR=10.87, CI=2.72–43.30, P=0.001), presence of any drug resistance (OR=4.60, CI=1.16–18.17, P=0.029) and no DOTS supervision (OR=16.66, CI=3.82–72.71, P<0.001) were the factors significantly associated with unsuccessful treatment outcomes. This model fit was based on a non-significant Hosmer–Lemeshow test result (P=0.869), an overall 76.1% classifier from the classification table, an 79.8% area under the receiver operating characteristic curve and a 0.357 Nagelkerke pseudo R^2.

Table 4. Univariate and multivariate analyses of the factors associated with unsuccessful treatment outcomes.

Variable	Unsuccessful outcomes		Successful outcomes		Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
	n=55	%	n=108	%				
Duration of the intensive phase								
Non-extended (2EHRZ)	20	28.6	50	71.4	1.00 (ref)		1.00 (ref)	
Extended (3EHRZ)	35	37.6	58	62.4	1.51 (0.77–2.94)	0.227	1.27 (0.49–3.26)	0.625
Age (year)								
<24	8	22.2	28	77.8	1.00 (ref)		1.00 (ref)	
25–44	23	32.9	47	67.1	1.71 (0.68–4.34)	0.257	1.22 (0.35–4.27)	0.753
45–64	18	40.0	27	60.0	2.33 (0.87–6.26)	0.092	0.75 (0.16–3.63)	0.724
>65	6	50.0	6	50.0	3.50 (0.88–13.88)	0.075	2.26 (0.32–15.83)	0.410
Sex								
Female	12	23.5	39	76.5	1.00 (ref)		1.00 (ref)	
Male	43	38.4	69	61.6	2.03 (0.96–4.29)	0.065	1.51 (0.54–4.23)	0.434
Smoking								
No	33	33.3	66	66.7	1.00 (ref)			
Yes	22	34.4	42	45.6	1.05 (0.54–2.04)	0.891		
Diabetes mellitus								
No	45	31.5	98	68.5	1.00 (ref)		1.00 (ref)	
Yes	10	50.0	10	50.0	2.18 (0.85–5.60)	0.106	4.04 (0.98–16.62)	0.053

Table 4. Continued

Variable	Unsuccessful outcomes		Successful outcomes		Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
	n=55	%	n=108	%				
Chest radiograph severity								
Minimal	11	23.4	36	76.6	1.00 (ref)		1.00 (ref)	
Moderately advanced	33	35.1	61	64.9	1.77 (0.80–3.93)	0.160	1.47 (0.49–4.48)	0.495
Far advanced	11	50.0	11	50.0	3.27 (1.12–9.58)	**0.031**	1.43 (0.27–7.63)	0.675
Lung cavitation								
No	8	25.8	23	74.2	1.00 (ref)			
Yes	47	35.6	85	64.4	1.59 (0.66–3.83)	0.302		
Sputum AFB grade								
Baseline								
Scanty	2	33.2	4	66.7	1.00 (ref)			
1+	8	38.1	13	61.9	1.23 (0.18–8.33)	0.831		
2+	12	25.0	36	75.0	0.67 (0.10–4.11)	0.662		
3+	33	37.5	55	62.5	1.20 (0.21–6.92)	0.838		
At 2 months								
Scanty	24	25.0	72	75.0	1.00 (ref)		1.00 (ref)	
1+	15	35.7	27	64.3	1.67 (0.76–3.64)	0.201	1.77 (0.62–5.08)	0.291
≥2+	16	64.0	9	36.0	5.33 (2.09–13.63)	**<0.001**	10.87 (2.72–43.40)	**0.001**
Sputum MTB culture								
Baseline								
No AFB seen or isolated	8	29.6	19	70.4	1.00 (ref)			
MTB complex detected	46	34.3	88	65.7	1.24 (0.51–3.05)	0.638		
At 2 months								
No AFB seen or isolated	45	36.0	80	64.0	1.00 (ref)		1.00 (ref)	
MTB complex detected	7	63.6	4	36.4	3.11 (0.86–11.21)	0.083	1.60 (0.26–9.92)	0.614
Drug resistance								
No drug resistance	45	30.4	103	69.6	1.00 (ref)		1.00 (ref)	
Any drug resistance	10	66.7	5	33.3	4.58 (1.48–14.16)	**0.008**	4.60 (1.16–18.17)	**0.029**
Duration of the maintenance phase								
≤4 months	16	26.7	44	73.3	1.00 (ref)			
5–6 months	16	27.6	42	72.4	1.05 (0.47–2.36)	0.911		
≥7 months	23	51.1	22	48.9	2.88 (1.27–6.51)	**0.011**		
DOTS								
Yes	35	25.4	103	74.6	1.00 (ref)		1.00 (ref)	
No	20	80.0	5	20.0	11.77 (4.11–33.72)	**<0.001**	16.66 (3.82–72.71)	**<0.001**
Drug combination								
Separate tablet regimens	11	32.4	23	67.6	1.00 (ref)			
Fixed-dose combination	44	34.1	85	65.9	1.08 (0.48–2.42)	0.847		

Level of significance: P<0.05
3EHRZ = 3 months of ethambutol, isoniazid, rifampicin and pyrazinamide treatment
2EHRZ = 2 months of ethambutol, isoniazid, rifampicin and pyrazinamide treatment
AFB = Acid-fast bacilli **MTB** = *Mycobacterium tuberculosis*
DOTS = directly observed therapy, short-course

Discussion

In this retrospective cohort study, the sputum smear non-conversion rate at 2 months was 6.5%. There were no significant differences in the treatment outcomes between the extended and non-extended intensive phase groups particularly in terms of reducing unsuccessful outcomes and relapse. Additionally, the study found that high sputum AFB grade (≥2+) at 2 months, presence of drug resistance and lack of DOTS supervision were the factors contributing to the unsuccessful outcomes.

In general, the patients' sociodemographic and clinical profiles are almost similar to those in existing studies from other countries.[8-18] Patients were predominantly men,[8,9,11,18] with a mean age of 40 years,[8,10,14,15] had low educational levels and were unemployed.[24] Most patients with sputum non-conversion at 2 months had a high baseline sputum AFB grade (3+)[8-11,15,16,18] and cavitation or extensive pulmonary disease.[9,10,12,17,18]

Our findings are comparable to those from previous studies worldwide, with a varying sputum smear non-conversion rate at 2 months of 7.3–8.3%.[8,11,13] In contrast, this finding is much lower than that reported in a study conducted in Cleveland: rate of delayed sputum smear conversion of 32.1%.[10] Meanwhile, a slightly lower sputum non-conversion rate at 2 months was reported in Morocco at 5.0%.[12]

Non-conversion of sputum smear at the end of 2 months of intensive phase treatment has been shown to be associated with unsuccessful treatment outcomes.[13-19] The prevalence of unsuccessful treatment outcomes in the patients with delayed sputum smear conversion is equivalent to that in a previous study in India at 36.5%, with comparable rates of failure (27%), TB death (1.4%) and defaulting (8.1%).[17] The mortality rate among patients with delayed sputum smear conversion reached up to 8.5% in a study in Bafoussam.[14] Variations in the rate of unsuccessful treatment outcomes in patients with delayed sputum smear conversion might be related to the differences in the comorbidity, severity of TB, socioeconomic status of patients and strength of TB control programmes.

One of the possible reasons for the incline of unsuccessful treatment outcomes over the past few years could be the influx of an increasing number of people from neighbouring countries seeking employment in Malaysia.[25] Foreigners prefer to be transferred to their countries or defaulted from the treatment owing to fear of compulsory expulsion by immigration authorities.[26] Therefore, specific measures such as early identification of defaulters are needed to improve compliance with treatment, prevent loss of follow-up and reduce mortality rates.

Contrary to expectations, the current study showed no significant difference in the prevalence of unsuccessful treatment outcome and relapse among the patients with delayed sputum smear conversion who received 2 or 3 months of intensive phase treatment. These results corroborate previous reports that treatment failure cannot be prevented by a 1-month extension of the intensive phase in case of a positive sputum smear at 2 months.[21] However, this study was unable to demonstrate reduced relapse in patients who received extended intensive phase treatment. The prolonged maintenance phase in this study might reduce the relapse rate and the difference between the two groups.

The latest guidelines no longer recommended extending the intensive phase of treatment in cases of non-conversion of the sputum smear at the end of the phase.[6] We support the WHO recommendations of not extending the intensive phase in patients with delayed sputum smear conversion but monitoring sputum AFB and culture. The CDC recommends prolonging the maintenance phase to 7 months in patients with lung cavitation, extensive pulmonary disease or culture-positive sputum after 2 months of the intensive phase.[5] There was insufficient evidence of the effectiveness of prolonged maintenance phase treatment, which was not explored in the current study. This study lays the groundwork for future investigations and studies to evaluate this gap of knowledge.

A better understanding of the factors associated with unsuccessful treatment outcomes is essential to help plan effective interventions and strategies for reducing morbidity and mortality from TB infections. A positive sputum smear for AFB may show non-viable bacilli, especially in small amounts and a lower sputum AFB grade.[27] It can only be distinguished by sputum MTB culture; however, it would take too long for clinical practice relevance to be realised. Thus, rapid culture modalities such as GeneXpert MTB/RIF should be utilised, especially in patients with high sputum AFB grades at 2 months (≥2+) and high risks of drug-resistant TB. Prolonging the treatment may subject patients to adverse drug reactions and non-adherence to treatment, which increases the risk of developing drug-resistant TB. The DOTS strategy can help patients comply with their medications with continuous monitoring and prevent the risk of defaulting or loss.[28] The implementation of the DOTS strategy in the national TB programme in Malaysia has yielded better results in monitoring patients. Comprehensive care and control of TB and diabetes mellitus are vital owing to the increasing trend of diabetes mellitus worldwide, including in Malaysia. Diabetes mellitus increases the risk of unsuccessful outcomes among patients with TB[29,30], but the association is not significant in this study. Planned implementation strategies and key activities under the national TB programme in the future should then accordingly target these factors.

This study was subject to the potential limitations inherent to any retrospective study. There are possibilities of information bias, such as missing, unreported or incomplete data from the TB registry and medical records. Less than 5% of missing observations were noted for the sputum AFB grade, sputum MTB culture, presence of drug resistance and lung cavitation; these were imputed accordingly. This study had a relatively small sample size, which may undermine the significance of the analysis. The absolute differences of 9% for the unsuccessful treatment outcomes and 3.5% for relapse between the extended and non-extended intensive phase groups are of concern despite not being significant. Finally, it is unknown whether the results of this study can be generalised to other settings in Malaysia or other countries.

This study revealed that extension of intensive phase treatment to 3 months in patients with delayed sputum smear conversion made no significant difference in preventing unsuccessful treatment outcomes and reducing relapse compared with non-extension. High sputum AFB grade at 2 months (≥2+), presence of drug resistance and lack of DOTS supervision emerged as the associated factors of unsuccessful treatment outcomes in the patients with delayed sputum smear conversion. Identification of these factors can guide measures for risk assessment and stratification of patients with TB and delayed sputum smear conversion and establish appropriate surveillance and management strategies. The findings also provide feedback to existing national TB control programmes and highlight future areas of focus.

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Author contributions
A.A., T.S.F., and N.S. contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

Ethical approval
Approval to conduct the study was obtained from the Medical Research and Ethics Committee of the Ministry of Health Malaysia (NMRR-19-4064-52225) and the Research and Ethics Committee of Universiti Kebangsaan Malaysia (FF- 2020-084).

Conflicts of interest
All authors declare no conflicts of interest.

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Data sharing statement
The data of this article are available upon reasonable request to the corresponding author.

How does this paper make a difference in general practice?

- This initial study in Malaysia provides evidence on the effectiveness of extended treatment in patients with persistent sputum smear positivity at 2 months.
- The study comprehensively assessed the possible factors related to unsuccessful treatment outcomes in patients with delayed sputum smear conversion.
- Identification of associated factors can guide strategies for risk assessment and stratification of patients with TB and delayed sputum smear conversion and establish appropriate protocols of surveillance and management.
- The findings provide feedback to the existing national TB control programme and highlight future areas of focus.

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