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FACTORS DELAYING SPUTUM CONVERSION IN SMEAR POSITIVE PULMONARY TUBERCULOSIS: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Tuberculosis (TB) has existed for decades and remains a major global health problem globally and also in Malaysia. TB is one of the top ten causes of death worldwide. The pulmonary tuberculosis patients with sputum smear positive become the main source in transmitting the infection, in which one untreated patient able to infect another 10 to 15 person annually. Therefore, delayed sputum smear conversion is important clinically. Apart from a possible continuity of infectiousness, prior studies have indicated that delayed smear conversion is a risk factor for TB treatment failure, emergence of drug-resistant TB and potential increase in TB mortality. The aim of this article is to analyze the factors in delaying sputum conversion among smear positive pulmonary tuberculosis.

Materials and Methods: A scoping systematic review of literature using electronic databases of PubMed, ScienceDirect, Google Scholar was done on 19th to 25th February 2018. Subsequently, more articles and reports were identified by combing through the references from the relevant literatures. The search keywords include; ‘factors delayed sputum conversion’, ‘sputum positive’ and ‘sputum non conversion’.

Result and Discussion: A total of 454 articles and theses within past 10 years (2007-2017) were obtained and 20 articles were selected for final analysis. The analysis and findings are presented based on factors delaying sputum conversion. From previous studies, male gender, older age, unemployment, low BMI, having DM, HIV, smoker, alcohol consumption, high AFB load, advanced or cavitation in CXR, prolonged symptoms and non-adherence to TB treatment were significant factors in delaying sputum conversion.

Conclusion: A total of 454 articles and theses within past 10 years (2007-2017) were obtained and 20 articles were selected for final analysis. The analysis and findings are presented based on factors delaying sputum conversion. From previous studies, male gender, older age, unemployment, low BMI, having DM, HIV, smoker, alcohol consumption, high AFB load, advanced or cavitation in CXR, prolonged symptoms and non-adherence to TB treatment were significant factors in delaying sputum conversion.

Keywords: Factors of delayed, sputum conversion, pulmonary tuberculosis, smear positive

1.0 Introduction

Pulmonary Tuberculosis (TB) remains a leading health problem worldwide. Globally, about 10 million people each year were infected with this disease (WHO, 2017). This large pool of infected people means that TB will continue to be a major problem in the foreseeable future. Tuberculosis has the highest mortality rate among communicable diseases in Malaysia (5.56 per 100,000 population), but then this disease is preventable (National Health and Morbidity Survey [NHMS], 2015). Incidence of tuberculosis in Malaysia is increasing in-trend with the latest incident rate is 79.45 per 100,000 population. (NHMS, 2015). Despite the long and continuous efforts to battle it, TB continues to rise in the country. The absolute number of TB cases in Malaysia is still increasing every year. With this increasing trend of TB cases, TB control should be strengthened in order to decrease the TB burden. Case detection, early treatment and contact tracing are among the fundamental approaches to prevent further spread of the disease (MOH, 2011).

Duration for sputum to convert or sputum conversion become one of the most concerned indicator in TB treatment in view of TB infectivity and prognosis of the disease. TB is transmitted from person to person via droplets from the throat and lungs of people with active respiratory TB disease. The main source for TB spreading is from smear positive pulmonary TB patient. One untreated infectious tuberculosis patient is likely to infect 10-15 persons annually (Styblo, 1978). Sputum conversion also can predict the success of the treatment or treatment outcome. Sputum smear and culture play an important role in monitoring treatment response in patients with tuberculosis especially in multidrug resistance tuberculosis (MDR-TB), and sputum culture conversion is a clinical tool used to predict therapeutic efficacy. Monthly sputum monitoring is essential for earlier detection of treatment failure.

Currently, sputum smear microscopy for acid-fast bacilli (AFB) is the most important and widely available technique for the diagnosis of pulmonary TB in low and middle income countries. Smear conversion in other hand, is defined as new smear-positive PTB cases who became smear negative after a period of anti-TB treatment and are therefore no longer infectious (confirmed by at least two consecutive negative sputum acid fast bacillus) (Bouti, 2013). In general, it is expected that 80 to 90% of patients will undergo smear conversion within two to three months of treatment (Frieden, 2004).

TB program in Malaysia has a comprehensive set of indicators to monitor TB prevention and control (Malaysia Country Progress Report, 2014). Related to pulmonary tuberculosis patient with smear positive sputum, sputum conversion rate (SCR) after 2 months of intensive phase and cure rate has been monitored, as recommended by WHO. These quality assurance indexes have been monitored to view effectiveness of the treatment and effort to reduce the disease transmission. In Malaysia, for the latest 5 years (2012-2016), SCR was reported in range of 60 to 80% and the cure rate, nationally is 75 to 78% despite of national goal, 80% for Malaysian citizen (Sector of Tuberculosis and Leprosy Disease, Disease Control Division, Ministry of Health, 2016- unpublished).

Delayed sputum smear conversion is important clinically. Apart from a possible continuity of infectiousness, prior studies have indicated that delayed smear conversion is a risk factor for TB treatment failure, emergence of drug-resistant TB and potential increase in TB mortality. Several factors have been identified that may delay the time to smear conversion found in previous studies. These include sociodemographic factors, high risk behaviour factors, previous medical history factors, result of investigation upon diagnosis, psychological factors, and health service factors. So, the aim of this article is to analyze the factors delaying sputum conversion in smear positive pulmonary tuberculosis.

2.0 Materials and Methods

The researchers conducted a manual search of articles, journals and related publications by various sources such as academic institutions and international organizations pertaining to the factors delaying sputum conversion in smear positive pulmonary tuberculosis. In the initial phase, the available literatures were accessed on 19th to 25th February 2018 from three electronic databases – Pubmed, PMC, PLoS and public domain databases – Google and Google Scholar. Subsequently, more articles and reports were identified by combing through the references from the relevant literatures. The search keywords include; 'factors delayed sputum conversion', 'sputum positive' and 'sputum conversion'.

A sum of 454 articles, reports and theses within the past 10 years (2007-2017) were obtained. Three stages screening methods were used: the primary screening was done by reviewing only titles, then secondary screening was done by reviewing titles and abstracts, while in the final screening, full text of the articles were reviewed. Charting of the data was done using PRISMA flowchart. Finally, a total of 20 articles and theses were selected and an analysis was done. The analysis and findings are presented based on factors delaying sputum conversion in smear positive pulmonary tuberculosis.

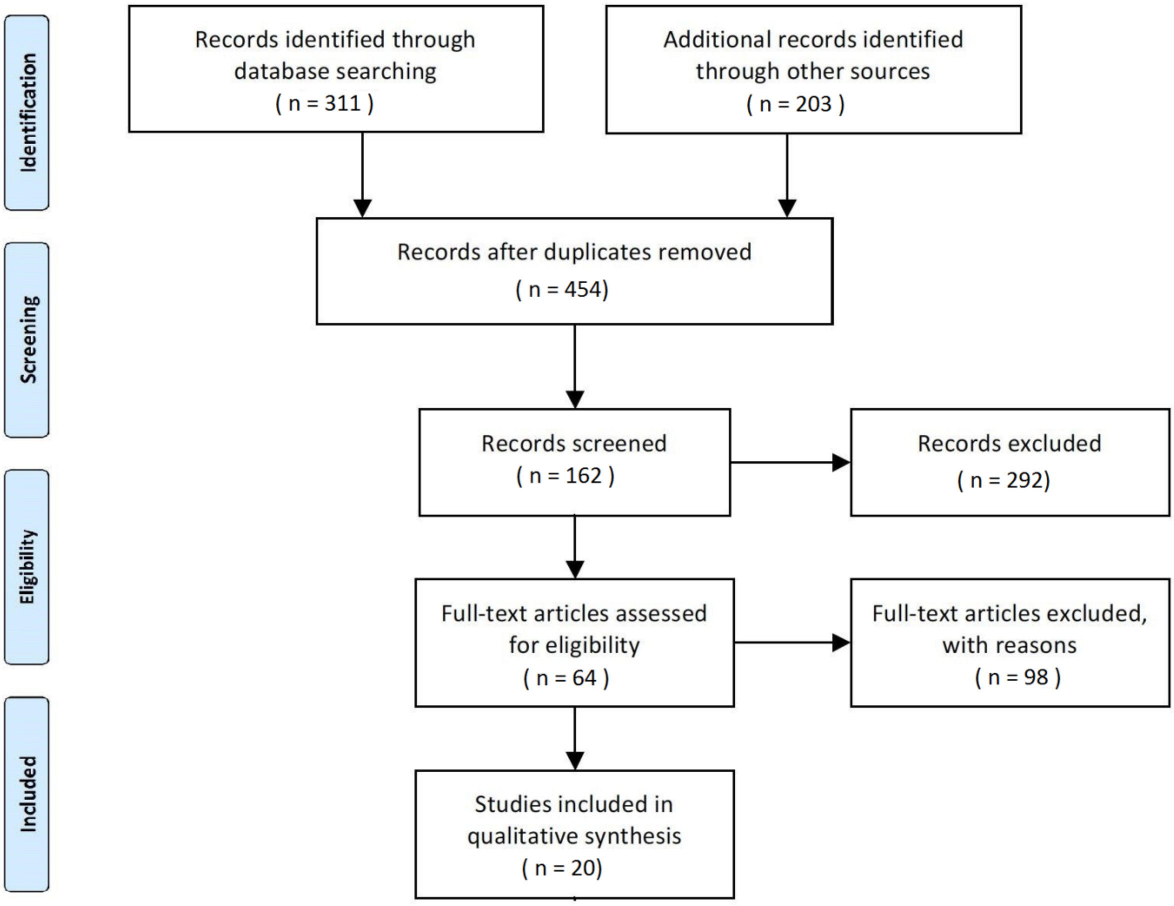

Figure 1: PRISMA Flowchart for factors delaying sputum conversion in smear positive pulmonary tuberculosis.

3.0 Result

Multiple studies have been conducted to explain the factors delaying sputum conversion in smear positive pulmonary tuberculosis patients. The findings from these 20 articles were categorized into socio-demographic characteristics, body mass index (BMI), previous medical history and high-risk behavior (diabetes mellitus, HIV, smoking status, alcohol consumption), investigation results upon diagnosis (AFB grade/bacillary load, CXR, prolonged symptoms) and adherence on treatment. All the factors are summarized in Table 1.

Table 1: **Articles on Factors Delaying Sputum Smear Conversion in Smear Positive Pulmonary Tuberculosis**

Independent Variables (Factors in delaying sputum conversion)		**Country**	**Study citation**	**Study design /study population**	**Finding**
Socio-demographic characteristic	**Gender**	Cameroon	Djouma, Nouborn, Ateudjieu & Donfack, 2015	6 years Retrospective cohort, all smear positive PTB	Male sex RR 1.2 (95%CI 0.7,1.9; p=0.55)
		Turkey	Guler, Unsal, Dursun, Aydln & Capan, 2006	5 years cohort, all PTB	Male OR 2.53 (95%CI 0.92,6.96; p= 0.07)
		Uganda	Bwire, et al., 1999	26 months cohort, all smear positive PTB	Female aOR 0.5 (95%CI 0.3,0.8)
		Thailand	Satung, et al., 2016	3 years retrospective cohort, all smear positive PTB	male sex aRR 1.36 (95%CI 1.12-1.64)
	Age	India	Banu Rekha, et al., 2007	Retro cohort, new smear positive pulmonary TB	Older OR 1.80 (95%CI 1.02,3.16; p=0.03)
		Cameroon	Djouma, Nouborn, Ateudjieu & Donfack, 2015	6 years Retrospective cohort, all smear positive PTB	Age 33 years old aRR 1.5 (95%CI 0.9,2.4; p=0.07)
		Spain	Domínguez-Castellano, et al., 2003	2 years Retrospective cohort, all smear positive PTB	Younger age OR 0.35 (p= 0.013)
		Rwanda	Kayigamba, et al., 2013	3 months retrospective cohort, all forms of TB	Age >45 OR 1.39 (95%CI 0.48,4.01)
		USA	Magee, et al., 2014	3 years cohort, all types of TB	35-44 aHR 0.81 (95%CI 0.69,0.95) 45-54 aHR 0.80 (95%CI 0.66,0.96) *sputum converted
		Thailand	Satung, et al., 2016	3 years retrospective cohort, all smear positive PTB	older age aRR 1.41 (95%CI 1.04,1.91)
		Johor	Tok, Salvaraji, Rosli, & Badrul, 2016	1 year Retrospective cohort	Older OR 1.03 (95% CI 1.01,1.04)
	Employment status	Penang	Atif, et al., 2014	1 year cohort cohort, all new smear positive PTB patients	Unemployment aOR 0.07 (95%CI 0.18,0.84)
		Uganda	Atwine, et al., 2017	Cohort, all sample form Rifatox trial, all types of PTB	Social service aRR 3.0 (95%CI 1.10,8.19)
	BMI	India	Jindal, Bhatt, &	1 year prospective cohort, New Sputum	per unit increase in BMI leads to an early smear

			Malik, 2015	Positive (NSP) TB patients in Category I	conversion with a regression coefficient of -0.121 (95 % Cl-0.242 to -0.001, p= 0.047)
		USA	Magee, et al., 2014	3 years cohort, all types of TB	<18.5 aHR 0.64 (0.54, 0.76) >25 aHR 1.27 (1.02, 1.59) *sputum converted
		Kuala Lumpur	Shariff & Safian, 2015	Case control, smear positive PTB	Underweight OR 1.67 (95%CI 0.80,3.49)
Previous Medical History and High Risk Behaviour	**Diabetes mellitus**	Penang	Atif, et al., 2014	1 year cohort cohort, all new smear positive PTB patients	Concurrent diabetes aOR 6.80 (95% CI 2.98,15.51)
		Turkey	Guler, Unsal, Dursun, Audln & Capan, 2006	5 years cohort, all PTB	DM OR 2.39 (95%CI 1.04,5.48; p= 0.04)
		USA	Magee, et al., 2014	3 years cohort, all types of TB	DM RR 1.20 (95%CI 0.87,1.65)
		China	Mi et al., 2013	10 months Retrospective cohort	DM RR 3.85 (95%CI 2.24,6.63)
		Thailand	Satung, et al., 2016	3 years retrospective cohort, all smear positive PTB	DM RR 1.00 (95%CI 0.77,1.30)
		Kuala Lumpur	Shariff & Safian, 2015	Case control, smear positive PTB	DM OR 4.01 (95%CI 1.61,9.96)
		India	Viswanathan, et al., 2013	3 months retrospective cohort, all types of sputum	DM RR 3.9 (95% CI 1.5,10.6).
		Taiwan	Chang, et al., 2011	1 year cohort	DM in Rx failure aOR 10.91 (95%CI 2.26,52.76; p=0.003)
		Johor	Tok, Salvaraji, Rosli, & Badrul, 2016	1 year Retrospective cohort	DM OR 1.21 (95% CI 0.70,2.10)
	HIV	Rwanda	Kayigamba, et al., 2013	3 months retrospective cohort, all forms of TB	HIV OR 2.99 (95%CI 1.33,6.71)
		Uganda	Bwire, et al., 1999	26 months cohort, all smear positive PTB	HIV aOR 0.9 (95%CI 0.5,1.6) *sputum converted
		Thailand	Satung, et al., 2016	3 years retrospective cohort, all smear positive PTB	HIV aRR 0.45 (95%CI 0.033,0.59) *sputum converted
		USA	Telzak, 1997	Years cohort	HIV p>0.05
	Smoker	Penang	Atif, et al., 2014	1 year cohort cohort, all new smear positive PTB patients	Smoker aOR 2.43 (95% 1.18,5.03)
		Penang	Gillani, Syed Sulaiman & Ali 2010	18 months Retrospective cohort, all smear positive TB	Non smoker OR 0.312 (95%CI 0.17-0.57; p < 0.001)

		Turkey	Guler, Unsal, Dursun, Audln & Capan, 2006	5 years cohort, all PTB	Smoking RR 0.56 (95%CI 0.21,1.45; p= 0.23) *sputum converted
		India	Jindal, Bhatt & Malik, 2015	1 year prospective cohort, New Sputum Positive (NSP) TB patients in Category I	Consumption of tobacco OR 2.405 (95%CI 1.031,5.607)
		USA	Magee, et al., 2014	3 years cohort, all types of TB	Smoker aHR 0.77 (0.68, 0.88) *sputum converted
	Alcohol consumption	USA	Liu, Shilkret, & Ellis, 1999	1 year prospective cohort, all types of TB	Excess alcohol use HR 1.29 (95%CI 1.03,1.63)
		USA	Magee , et at., 2014	3 years cohort, all types of TB	Alcohol use aHR 0.62 (95%CI 0.46, 0.83)
Investigation results upon diagnosis	**AFB grade / bacillary load**	Kuwait	Abal, et al., 2004	Cohort, exposure smoker, all smear positive TB	+++ OR 0.445 (95%CI 0.22,0.89; p=0.022) *sputum converted
		India	Banu Rekha, et al., 2007	Retro cohort, new smear positive pulmonary TB	Smear grading OR 2.64 (95%CI 1.76,3.96; p <0.001)
		Morocco	Bouti, et al, 2013	6 months prospective cohort, all smear positive TB	Smear grading 3+ OR7.1 (95%CI 2.5,11.2)
		South Africa	Brust, et al., 2013	Cohort, MDRTB + HIV	Sputum grading aOR 3.45 [1.39-8.59]).
		Cameroon	Djouma, Nouborn, Ateudjieu & Donfack, 2015	6 years Retrospective cohort, all smear positive PTB	2+ RR 9.9 (95%CI 2.4,42.4; p<0.01) 3+ RR 10.6 (95%CI 2.5,44.5; p<0.01)
		Spain	Fortun, et al., 2006	9 years prospective cohort, smear positive PTB	high bacillary counts in sputum smears at diagnosis OR 2.86 (95%CI 1.20,6.66)
		Turkey	Guler, Unsal, Dursun, Audln & Capan, 2006	5 years cohort, all PTB	AFB positivity OR 1.48 (95%CI 1.06,2.05; p=0.01)
		India	Jindal, Bhatt & Malik, 2015	1 year prospective cohort, New Sputum Positive (NSP) TB patients in Category I	bacterial load RR 1.38 (95% CI 0.21,2.74)
		Rwanda	Kayigamba, et al., 2013	3 months retrospective cohort, all forms of TB	2+ OR 1.54 (95%CI 0.63,3.77) 3+ OR 2.69 (95%CI 1.09,6.63)
		USA	Magee, et al., 2014	3 years cohort, all types of TB	3+ aHR 0.70 (95%CI 0.57, 0.86) 4+ aHR 0.52 (95%CI 0.42, 0.66) *sputum converted
	CXR	Kuwait	Abal, et al., 2004	Cohort, exposure smoker, all smear positive TB	Advanced OR 0.390 (95%CI 0.21,0.76; p=0.006) *sputum converted

		Pakistan	Basit et al., 2014	Retrospective cohort, All confirmed pulmonary MDR-TB	cavitation at baseline OR 0.35 (p=0.006) *sputum converted
		Penang	Atif, et al., 2014	1 year cohort cohort, all new smear positive PTB patients	Cavities at the start of the treatment aOR 2.67 (95% 1.29,5.77)
		India	Banu, et al., 2007	Retro cohort, new smear positive pulmonary TB	No of zonal involved OR 1.31 (95% 1.09,1.57; p= 0.01)
		Morocco	Bouti, et al., 2013	6 months prospective cohort, all smear positive TB	Bilateral radiologic lesions OR 13.4 (95%CI 1.8,55.6)
		Spain	Domínguez-Castellano, et al., 2003	2 years Retrospective cohort, all smear positive PTB	Advanced OR 9.26 (p=0.036)
		Spain	Fortun, et al., 2006	9 years prospective cohort, smear positive PTB	Lung cavitations OR 4.0 (95% CI 1.63,9.09)
		Turkey	Guler, Unsal, Dursun, Audln & Capan, 2006	5 years cohort, all PTB	Radiology OR 13.44 (95% 5.89,30.67; p<0.001)
		India	Jindal, Bhatt & Malik, 2015	1 year prospective cohort, New Sputum Positive (NSP) TB patients in Category I	Cavitation on CXR RR 2.50 (95% CI 1.57,3.44), Bilateral lesions RR 1.23 (95% CI 0.38,2.09)
		USA	Magee, et al., 2014	3 years cohort, all types of TB	Cavitation aHR 0.63 (0.54, 0.73) *sputum converted
		Thailand	Satung, et al., 2016	3 years retrospective cohort, all smear positive PTB	Cavitation aRR 0.84 (95% 0.73,0.96) *sputum converted
	Prolonged Symptoms	Spain	Fortun, et al., 2006	9 years prospective cohort, smear positive PTB	Prolonged period of symptoms OR 3.57 (95% CI 1.43,3.57).
		India	Jindal, Bhatt & Malik, 2015	1 year prospective cohort, New Sputum Positive (NSP) TB patients in Category I	Delayed starting treatment OR 3.726 (95% 1.42, 9.72)
		India	Singla, et al., 2013	Case control, smear positive PTB	Duration of illness >2m aOR 8.29 (95% 2.10,32.70)
Adherence on treatment	**No of Days missing pills**	Kuala Lumpur	Shariff & Safian, 2015	Case control, smear positive PTB	Non adherent OR 2.85 (95% 1.21,6.74)
		India	Singla, et al., 2013	Case control, smear positive PTB	No of interruption in IP 1-2 aOR 4.74 (95%CI 1.21,18.49) No of interruption in IP 3 or more aOR 15.56 (95%CI 2.14,112.88)

4.0 Discussion

4.1 Socio-demographic Characteristics

By socio-demographic characteristics, most of the study reported that being a male and older age increases the risk for delaying in sputum conversion in pulmonary TB patients. Balasubramanian, Garg & Santha (2004) in their study of gender differences in distribution of TB, reported that male patients were frequently found to have treatment failure associated with taking medications irregularly as compared to women, which could also explain the increased risk of delayed sputum conversion among male patients. By age, pre-existing comorbidities among older patients and decreased in immunity could be associated with a risk of reduced compliance to TB medications and thus, increases the risk of delayed sputum conversion (Arora, Singla & Sarin, 2003). Being unemployment also found to be a risk factor in delayed sputum conversion. This could be because of obstacle in seeking healthcare services due to financial constraint and also environment of unemployment were exposed to different spectrum of population. A study done in Portugal reported that unemployed TB patients had higher prevalence rates of current alcohol consumption, smoking, and HIV positivity, so these are the potential confounders (Mota, Carvalho, Valente, Braga & Duarte, 2012). Another risk factor found in socio-demographic characteristics is people with low BMI. Low BMI is significant in people with malnutrition and possibly lead to lower immunity.

4.2 Previous Medical History and High Risk Behavior

Majority of the studies reported that delayed in sputum conversion also associated with having diabetes mellitus and HIV. In these both conditions, people with uncontrolled diabetes mellitus and people living with HIV, has low immunity to fight another concurrent disease. These could be different among people with controlled diabetes mellitus or people living with HIV but started on anti-retroviral treatment and having stable immunity. Regarding HIV positivity, there are contradictive results from previous studies. Some studies indicated that HIV status does not negatively influence TB smear conversion, since its positivity has been associated with lower bacillary load expressed, by a lower prevalence of cavitary disease among these patients (Senkoro, Mfinanga & Mørkve, 2010). Whereas cigarette smoking, shows evidences that active and passive smokers has an increased risk of contracting active TB compared to non-smokers (Leung et al., 2010).

4.3 Investigation Result upon Diagnosis

Bilateral radiological involvement and higher colony count are also factors for delayed TB smear conversion. These is due to the high baseline bacillary burden of those patients (Mota, Carvalho, Valente, Braga & Duarte, 2012). Most of the studies reported that patients with high pre-treatment smear grade (3+/4+) were less likely to convert compared to patients with low pre-treatment grade (1+/2+). This persistent smear positivity is associated with higher pre-treatment grade due to the initially high mycobacterial burden (Canetti, 1965). All these result could be influenced by patients' internal factors and behaviour and exposure to TB (duration, source and contact). So prolonged symptoms of TB also could influence the result of investigation.

4.4 Adherence on Treatment

Previous studies found that the longer period of missing treatment could result in greater chance for having sputum non-conversion. The effectiveness of anti TB will be disrupted and patients will not achieve bactericidal activity, thus M. tuberculosis will remain active and progressive. This also could possibly lead to drug resistant and sputum will further not converted if same regime being used.

5.0 Conclusion and recommendation

Sputum smear conversion plays a vital role in the effort towards prevention and control of TB in any population. Clinically delayed sputum smear conversion increase the morbidity and mortality among pulmonary TB patients. Besides that, sputum smear conversion is of public health importance to prevent and control disease among the population. Delayed sputum smear conversion burdens the healthcare system further with increasing spread of the disease.

There are several factors that contribute to delayed sputum smear conversion which can be categorized into socio-demographic, high risk behavior, previous medical history, investigation result upon diagnosis and adherence to treatment. Among all these factors, there are certain factors (namely high risk behavior and adherence to treatment) that could be controlled or modified to further enhance TB treatment, prevention and control. Therefore prevention and control efforts should focus more on these modifiable factors. Modifying these factors contributing to delayed sputum smear conversion through primary, secondary and tertiary prevention measures.

Health education on TB among the general population to educate on the disease nature, symptoms, prevention methods, and importance of medical attention seeking needs to be highlighted. Early diagnosis and prompt treatment needs to be sustained by dynamically updating healthcare provider with latest diagnosis methods and treatment options available. Among the TB patients importance of adherence to treatment in order to limit morbidity and prevent mortality need to be properly counseled and made understood to the TB patients. Further study on specific population is needed to expend body of knowledge and for better outcome in TB management especially in isolation and usage of mask issues.

Declaration

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Authors contribution

Author 1: information gathering, preparation and editing of manuscript

Author 2: information gathering, review of manuscript and editing

Author 3: information gathering, review of manuscript and editing

Author 4: information gathering, review of manuscript and editing

References

Arora, V.K., Singla, N., Sarin, R. (2003). Profile of geriatric patients under DOTS in Revised National Tuberculosis Control Programme. The Indian Journal of Chest Diseases & Allied Sciences; 45(4), 231–235.

Atif, M., Syed Sulaiman, S. A., Shafie, A. A., Ali, I, Asif, M., Babar, Z. U. D. (2014). Treatment outcome of new smear positive pulmonary tuberculosis patients in Penang, Malaysia. BMC Infectious Diseases, 14, 399. Retrieved from http://www.biomedcentral.com/1471-2334/14/399

Atwine, D., Orikiriza, P., Taremwa, I., Ayebare, A., Logoose, S., … Bonnet, M. (2017). Predictors of delayed culture conversion among Ugandan patients. BMC Infectious Diseases; 17, 299. Doi: 10.1186/s12879-017-2335-7

Balasubramanian, R., Garg, R., Santha, T. (2004). Gender disparities in tuberculosis: report from a rural DOTS programme in south India. International Journal of Tuberculosis and Lung Disease; 8(3), 323–332

Banu Rekha, V. V., Balasubramanian, R., Swaminathan, Ramachandran, R., Rahman, F., … Narayanan, P.R. (2007). Sputum conversion at the end of intensive phase of Category-1 regimen in the treatment of pulmonary tuberculosis patients with diabetes mellitus or HIV infection: An analysis of risk factors. Indian Journal of Medicine Repiratory; 126, 452-458

Basit, A., Ahmad, N., Khan, A. H., Javaid, A., Syed Sulaiman, S. A., … Ahmad, I., (2014). Predictors of two months culture conversion in multidrug-resistant tuberculosis: Findings from a retrospective cohort study. PLoS ONE; 9(4): e93206. doi: 10.1371/journal.pone.0093206

Bouti, K., Aharmim, M., Marc, K., Soualhi, M., Zahraoui, R., Benamor, J., Bourkadi, J. E., Iraqi, G. (2013). Factors Influencing Sputum Conversion among Smear-Positive Pulmonary Tuberculosis Patients in Morocco. International Scholarly Research Notices. Doi: 10.1155/2013/486507

Brust, J. C. M., Berman, A. R., Zalta, B., Haramati, L. B., Ning, Y., … Gandhi, N. R. (2013). Chest radiograph findings and time to culture conversion in patients with multidrug-resistant tuberculosis and HIV in Tugela Ferry, South Africa. PLoS ONE; 8(9): e73975. doi:10.1371/journal.pone.0073975

Canetti, G. (1965). Present aspects of bacterial resistance in tuberculosis. American Reviews of Respiratory; 687-703

Chang, J. T., Dou, H. Y., Yen, C. L. Wu, Y. H., Huang, R. M., … Shieh, C. C. (2011). Effect of type 2 diabetes mellitus on the clinical severity and treatment outcome in patients with pulmonary tuberculosis: A potential role in the emergence of multidrug-resistance. Journal of the Formosan Medical Association;110(6), 372–381

Djouma, F. N., Nouborn, M., Ateudjieu, J., Donfack, H. (2015). Delay in sputum smear conversion and outcomes of smear-positive tuberculosis patients: a retrospective cohort study in Bafoussam, Cameroon. BMC Infectious Diseases; 15, 139. Doi:10.1186/s12879-015-0876-1

Fortun, J., Davila, P. M., Molina, A., Navas, E., Hermida, J. M., … Moreno, S. (2007). Sputum conversion among patients with pulmonary tuberculosis: are there implications for removal of respiratory isolation? Journal of Antimicrobial Chemotherapy; 59, 794–798. Doi:10.1093/jac/dkm025

Frieden, T. (2004) Toman's Tuberculosis Case Detection, Treatment, and Monitoring—Questions and Answers (2nd ed.). World Health Organisation; Geneva.

Gillani, W. S., Syed Sulaiman, S. A., Ali, J. A. (2010). Clinical Modalities and Therapeutic Outcomes; Between Ever-Smokers Versus Never-Smokers of Tuberculosis Patients in Penang, Malaysia. European Journal of General Medicine; 7(4), 389-397

Guler, M., Unsal, E., Dursun, B., Aydln, O., Capan, N. (2006). Factors influencing sputum smear and culture conversion time among patients with new case pulmonary tuberculosis. International Journal of Clinical Practice; 61(2), 231–235. Doi: 10.1111/j.1742-1241.2006.01131.x

Jindal, H. H. A., Bhatt, B., Malik, J. S. (2015). A study on the smear conversion time and its associated factors in sputum positive Category I Tuberculosis DOTS cases in District Rohtak. Scholars Journal of Applied Medical Sciences (SJAMS); 3(9D), 3391-3399. Online: ISSN 2320-6691

Kayigamba, F. R., Bakker, M. I., Mugisha, V., Naeyer, L. D., Gasana, M., … van der Loeff, M. S. (2013). Adherence to tuberculosis treatment, sputum smear conversion and mortality: a retrospective cohort study in 48 Rwandan clinics. PLoS ONE; 8(9). Online: e73501

Liu, Z., Shilkret, K. L., & Ellis, H. M. (1999). Predictors of sputum culture conversion among patients with tuberculosis in the era of tuberculosis resurgence. Archieve of Internal Medicine; 159, 1110-1116

Leung, C.C., Lam, T.H., Ho, K.S., Yew, W.W., Tam, C.M., Chan, W.M. et al. (2010). Passive smoking and tuberculosis. Arch Internal Medicine; 170 (2010), 287-292

Magee, M. J., Kempker, R. R., Kipiani, M., Tukvadze, N., Howards, P. P., … Blumberg, H. M. (2014). Diabetes mellitus, smoking status, and rate of sputum culture conversion in patients with multidrug-resistant tuberculosis: a cohort study from the country of Georgia. PLoS ONE; 9(4). Online: e94890

Mi, F., Tan, S., Liang, L., Harries, A. D., Hinderaker, S. G., … Du, Jian. (2013). Diabetes mellitus and tuberculosis: pattern of tuberculosis, two-month smear conversion and treatment outcomes in Guangzhou, China. Tropical Medicine and International Health; 18(11), 1379-1385. Doi:10.1111/tmi.12198

Ministry of Health [MOH] of Malaysia, 2011. National Strategic Plan for Tuberculosis Control, 2011-2015.

Mota, P.C., Carvalho, A., Valente, I., Braga, R., Duarte, R. (2012). Predictors of delayed sputum smear and culture conversion among a Portugese population with pulmonary tuberculosis. Revista Portugesa de Pneumologia; 18(2), 72-79

National Health and Morbidity Survey [NHMS] (2015). Ministry of Health, retrieved from http://www.iku.gov.my/images/IKU/Document/REPORT/nhmsreport2015vol2.pdf.

Satung, J., Kaewkungwal, J., Silachamroon, U., Pokaew, P., Rattanajiamrangsree, S., Kasetjareon, Y., Lawpoolsri, S. (2016). Treatment outcomes among diabetic patients with tuberculosis in Thailand. Southeast Asian Journal of Tropical Medicine and Public Health; 47(6)

Senkoro, M., Mfinanga, S.G., Mørkve, O. (2010). Smear microscopy and culture conversion rates among smear positive pulmonary tuberculosis patients by HIV status in Dar es Salaam, Tanzania. BMC Infectious Disease; 10 (2010), 210

Shariff, N. M., Safian, N. (2015). Diabetes mellitus and its influence on sputum smear positivity at 2nd month of treatment among pulmonary tuberculosis patients in Kuala Lumpur, Malaysia: A case control study. International Journal of Mycobacteriology; 4, 323-329.

Singla, R., Bharty, S. K., Gupta, U. A., Khayyam, K. U., Vohra, V., … Behera, D. (2013). Sputum smear positivity at two months in previously untreated pulmonary tuberculosis patients. International Journal of Mycobacteriology; 2, 199-205.

Styblo, K. (1985). Current state of the question : epidemiology of tuberculosis . Bulletin of the International Union Against Tuberculosis and Lung Disease; 53, 53-66 .

Telzak, E. E., Fazal, B. A., Pollard, C. L., Turett, G. S., Justman, J. E., & Blum, S. (1997). Factors influencing time to sputum conversion among patients with smear positive pulmonary tuberculosis. Clinical Infectious Diseases; 25, 666-670

Tok, P, Salvaraji, L.,Rosli, N., Badrul, H. A. S. (2016). Impact of diabetes mellitus on the sputum conversion among new smear positive pulmonary tuberculosis patients in Johor Bahru, Malaysia. Jurnal Kesihatan Johor; 12.

Viswanathan, V., Vigneswari, A., Selvan, K., Satyavani, K., Rajeswari, R., Kapur, A. (2013). Effect of diabetes on treatment outcome of smear positive pulmonary tuberculosis – A report from South India. Journal of Diabetes and Its Complications. Doi: 10.1016/j.jdiacomp.2013.12.003

World Health Organization (WHO). (2015). Global Tuberculosis Report 2015. Geneva.

World Health Organization (WHO). (2017). Global Tuberculosis Report 2017. Geneva.