Khan et al. BMC Public Health (2020) 20:854
https://doi.org/10.1186/s12889-020-08856-6

BMC Public Health

RESEARCH ARTICLE Open Access

Effect of smoking on treatment outcome among tuberculosis patients in Malaysia; a multicenter study

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Abstract

Background: Smoking plays a key role in the development of tuberculosis (TB) infection and is also a predictor of poor TB treatment prognosis and outcomes. The current study was conducted to determine the prevalence of smoking and to assess the effects of smoking on treatment outcomes among TB patients.

Methods: A multi-center retrospective study design was used to collect data from TB patients in four different states of Malaysia, namely Penang, Sabah, Sarawak, and Selangor. The study included medical records of TB patients admitted to the selected hospitals in the period from January 2006 to March 2009. Medical records with incomplete data were not included. Patient demographics and clinical data were collected using a validated data collection form.

Results: Of all patients with TB (9337), the prevalence of smokers was 4313 (46.2%). Among smokers, 3584 (83.1%) were associated with pulmonary TB, while 729 (16.9%) were associated with extrapulmonary TB. Male gender (OR = 1.43, 95% CI 1.30–1.58), Chinese ethnicity (OR = 1.23, 95% CI 1.02–1.49), Sarawak indigenous ethnicity (OR = 0.74, 95% CI 0.58–0.95), urban residents (OR = 1.46, 95% CI 1.33–1.61), employed individuals (OR = 1.21, 95% CI 1.09–1.34), alcoholics (OR = 4.91, 95% CI 4.04–5.96), drug abusers (OR = 7.43, 95% CI 5.70–9.60) and presence of co-morbid condition (OR = 1.27, 95% CI 1.16–1.40) all showed significant association with smoking habits. This study found that 3236 (75.0%) patients were successfully treated in the smokers' group, while 4004 (79.7%) patients were non-smokers. The proportion of deaths (6.6%, $n = 283$), defaulters (6.6%, $n = 284$) and treatment interruptions (4.7%, $n = 204$) was higher in the smokers' group.

Conclusions: Smoking has a strong influence on TB and is a major barrier towards treatment success (OR = 0.76, 95% CI 0.69–0.84, $p < 0.001$). Therefore, the findings indicate that smoking cessations are an effective way to decrease treatment failure and drug resistance.

Keywords: Smoking, Treatment outcome, Tuberculosis

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Background

Global data on tuberculosis (TB) provided by the World Health Organization revealed that 10.0 million people (range, 9.0–11.1 million) were ill with TB in 2018. In addition, in 2018, there were 1.2 million TB fatalities among people who are HIV negative and 251,000 deaths among those who are HIV positive. Since 2007, TB has been the leading cause of death from a single infectious agent, ranking above HIV/AIDS [1]. Smoking and tuberculosis remain two major health concerns worldwide [2]. Some studies from China and India reported that smoking increases the severity and mortality rate of tuberculosis [2, 3]. In 2010, the WHO suggested a stronger focus on preventing exposures to tuberculosis [4]. In addition to cancer and coronary heart disease, numerous studies have identified smoking as a risk factor in the development of TB [5, 6]. Tobacco-associated deaths are projected to increase to 8.4 million by 2020 [7], along with TB, both of which are major sources of mortality and morbidity. Various components of the cigarette smoke such as free radicals of oxygen, acrolein, formaldehyde and carbon monoxide increase the oxidative stress in smokers, thus affecting the bronchial mucosa and increasing the threat of *Mycobacterium tuberculosis* infection [8]. This might be the reason for less effective TB treatment outcomes among specific populations [9, 10]. Although the prevalence of TB in Malaysia decreased significantly compared to the early 1990s, Malaysia was still ranked as an intermediate burden country by the World Health Organization (WHO) in 2018 with an incidence rate of 92/100,000 and estimated mortality rate of 4.9/100,000 population [1].

Despite increasing pieces of evidence showing a strong association between tobacco smoking and TB [1, 11], there are only a few observational studies highlighting the association between smoking and TB treatment outcomes with limited study population [7] and or single-center studies [12, 13] which are difficult to generalize. Previous studies have typically identified potential risk factors for poor results of TB treatment [7, 9, 10]. In this study, the prevalence of smoking in TB patients in Malaysia was determined and the impact that smoking has on the outcomes of tuberculosis treatment was investigated.

Methods

Study design and location

A multicenter retrospective study was conducted among the TB patients in four states of Malaysia (Sabah, Sarawak, Selangor, and Penang) — two representative states from west Malaysia and two from peninsular Malaysia — selected based on the highest burden of TB patients [14].

Inclusion & exclusion criteria

All TB patients (new, relapse, treatment failure and treatment defaulters) of both genders, either with or without co-morbidity, who presented at the chest clinic of Penang hospital from January 2006 to March 2009 were included in the study. Patients with incomplete medical records were removed from the study. Disease classification, treatment protocol and treatment outcomes were defined as per the Malaysian tuberculosis treatment guidelines [15], which are aiming to meet World Health Organization criteria. Sputum smear examinations were done at the end of two, four and 6 months of treatment in new cases and at the end of two, three, five and 8 months in retreatment cases. Sputum examination was repeated again after 1 month if positive at 2 months of treatment. Treatment outcomes initially recorded as cured, treatment completed, defaulted, transferred out, expired and treatment continued were then classified into two categories: successful or unsuccessful treatment. Cured and treatment-completed patients were placed in the successful treatment category, and the remainder was placed in the unsuccessful treatment category. Owing to the main objective of the study, patients were grouped into either ever smokers (those who smoked cigarettes at the time of TB diagnosis or who had previously smoked) or never smokers (those who had never smoked or had smoked less than 100 cigarettes in their lifetime).

Data collection

A purpose-developed pre-validated data collection form was used to collect demographic and clinical data. Demographic data included patients' gender, age, weight, ethnicity, residential area, marital status, and smoking and alcohol consumption status. Clinical data collected included clinical presentation, serum biochemistry results, nature of TB case (new, retreatment - failure, default and relapse), site of TB infection (pulmonary or extrapulmonary), presence of the co-morbid condition along with respective medications, results of sputum cultures, and treatment outcomes.

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS), version 20.0 (SPSS, Inc., Chicago, IL, USA). Percentages and frequencies were used for categorical variables, while means ± standard deviations were calculated for continuous variables. Univariate and multivariate binary regression analyses were used to examine whether tobacco smoking had contributed to poor treatment outcomes in TB patients. The results are presented as *P*-value, odds ratio (OR) and 95% confidence interval (CI). A *P*-value ≤0.05 was considered statistically significant.

Results

Out of 9337 TB patients, the prevalence of smokers was 4313 (46.2%) while 5024 (53.8%) were non-smokers. The

mean age of patients among smokers and non-smokers was 42.18 ± 15.97 and 41.12 ± 17.05 years old, respectively, while the mean weight was 42.02 ± 10.48 and 41.53 ± 9.77 kg, respectively. The male gender was more predominant among both smokers and non-smokers: 3261 (75.6%) and 3181 (63.3%) patients, respectively. There was a high male-to-female ratio in the smoker's group (3:1). Most of the cases in the smoker group lie in the age group 26–55 years. Malay ethnicity (28.6%, n = 1232) followed by Chinese ethnicity (26.7%, n = 1153) were in a higher proportion in the smokers' group. About 2958 (68.6%), 3159 (73.2%) and 3010 (69.8%) smoker patients belong to urban areas, were unmarried and were unemployed, respectively. The prevalence of alcohol and drug abusers was also higher in the smokers' group than non-smokers' group: 18.6% (n = 802) and 14% (n = 602), respectively. The majority of the smoker patients (83.1%, n = 3584) had PTB while co-morbidity was observed in 44.2% (n = 1907) of patients (Table 1).

Patient variables were further analyzed based on smoking habits using univariate and multivariate analysis. Multivariate binary logistic regression in Table 2 shows that the odds of smoking showed a significant association with male gender (OR = 1.43, 95% CI 1.30–1.58), Chinese ethnicity (OR = 1.23, 95% CI 1.02–1.49), and Sarawak indigenous ethnicity (OR = 0.74, 95% CI 0.58–0.95). The odds were high and statistically significant with urban residents (OR = 1.46, 95% CI 1.33–1.61), employed individuals (OR = 1.21, 95% CI 1.09–1.34), alcoholics (OR = 4.91, 95% CI 4.04–5.96), drug abusers (OR = 7.43, 95% CI 5.70–9.60) and those with a co-morbid condition (OR = 1.27, 95% CI 1.16–1.40).

Table 3 is based on the clinical signs and symptoms and shows that significant differences exist among both the smokers' and non-smokers' groups. Despite this, data analysis indicated that the prevalence of night sweats (1462, 33.9%), coughs (3579, 83%), shortness of breath (1911, 44.3%), fever (2794, 64.8%), weight loss (2969, 68.8%) and loss of appetite (3181, 73.8%) was significantly higher in the smokers' group.

This study revealed that the overall success rate was 77.5% (n = 7240) patients out of which 75% (3236) patients were successfully treated in the smokers' group while 4004 (79.7%) patients belonged to non-smokers group. The rates of mortality (6.6%, n = 283), defaulters (6.6%, n = 284) and treatment interruption (4.7%, n = 204) were high in the smokers' group. In multivariate analysis, treatment completion (aOR 0.87, 95% CI 0.78–0.96, $p < 0.01$), death rate (aOR 1.57, 95% CI 1.31–1.89, $p < 0.001$), defaulters (aOR 1.57, 95% CI 1.31–1.89, $p < 0.001$) and treatment interruption (aOR 1.49, 95% CI 1.21–1.84, $p < 0.001$) showed significant associations with smoking habit. The chances of treatment success

Table 1 Sociodemographic distribution of TB patients according to smoking habit

Patient Variables	Total ***N*** = 9337	Never smoked ***N*** = 5024	Ever smoked ***N*** = 4313
Weight (mean ± SD)	41.75 ± 10.11	41.53 ± 9.77	42.02 ± 10.48
Gender			
Male	6442 (69)	3181 (63.3)	3261 (75.6)
Female	2895 (31)	1843 (36.7)	1052 (24.4)
Age (mean ± SD)	41.61 ± 16.57	41.12 ± 17.05	42.18 ± 15.97
< 15	265 (2.8)	172 (3.4)	93 (2.2)
16–25	1472 (15.8)	876 (17.4)	596 (13.8)
26–35	1878 (20.1)	1001 (19.9)	877 (20.3)
36–45	1754 (18.8)	872 (17.4)	882 (20.4)
46–55	1674 (17.9)	880 (17.5)	794 (18.4)
56–65	1279 (13.7)	673 (13.4)	606 (14.1)
> 65	1015 (10.9)	550 (10.9)	465 (10.8)
Race			
Malay	2504 (26.8)	1272 (25.3)	1232 (28.6)
Chinese	2211 (23.7)	1058 (21.1)	1153 (26.7)
Indian	671 (7.2)	350 (7)	321 (7.4)
Indigenous Sarawak	976 (10.5)	614 (12.2)	362 (8.4)
Indigenous Sabah	1702 (18.2)	1003 (20)	699 (16.2)
Indonesian immigrants	631 (6.8)	372 (7.4)	259 (6)
Philippine immigrants	493 (5.3)	287 (5.7)	206 (4.8)
Others	149 (1.6)	68 (1.4)	81 (1.9)
Area			
Urban	5959 (63.8)	3001 (59.7)	2958 (68.6)
Rural	3378 (36.2)	2023 (40.3)	1355 (31.4)
Marital status			
Single	6706 (71.8)	3547 (70.6)	3159 (73.2)
Married	2631 (28.2)	1477 (29.4)	1154 (26.8)
Employment status			
Employed	2531 (27.1)	1228 (24.4)	1303 (30.2)
Unemployed	6806 (72.9)	3796 (75.6)	3010 (69.8)
Alcohol drinkers			
Yes	941 (10.1)	139 (2.8)	802 (18.6)
No	8396 (89.9)	4885 (97.2)	3511 (81.4)
Intravenous drug user (IVDU)			
Yes	670 (7.2)	68 (1.4)	602 (14)
No	8667 (92.8)	4956 (98.6)	3711 (86)
TB-type			
PTB	7781 (83.3)	4197 (83.5)	3584 (83.1)
EPTB	1556 (16.7)	827 (16.5)	729 (16.9)
Co-morbidity			
Yes	3414 (36.6)	1507 (30)	1907 (44.2)
No	5923 (63.4)	3517 (70)	2406 (55.8)

Table 2 Distribution of TB patients according to smoking habit based on multivariate analysis

Patient variables	Univariate analysis			Multivariate analysis		
	Crude OR	95% CI	*p*-Value	aOR	95% CI	*p*-Value
Gender						
Male	1.79	1.64–1.96	**< 0.001**	1.43	1.30–1.58	**< 0.001**
Female	1.00	–		1.00	–	
Age						
< 15	0.62	0.48–0.80	**< 0.001**	0.86	0.66–1.14	0.31
16–25	0.75	0.67–0.85	**< 0.001**	0.92	0.81–1.04	0.22
26–35	1.02	0.92–1.13	0.62	–	–	–
36–45	1.22	1.10–1.35	**< 0.001**	1.02	0.91–1.15	0.65
46–55	1.06	0.95–1.18	0.26	–	–	–
56–65	1.05	0.93–1.18	0.35	–	–	–
> 65	0.98	0.86–1.12	0.79	–	–	–
Race						
Malay	1.17	1.07–1.29	**< 0.001**	1.10	0.91–1.32	0.31
Chinese	1.36	1.24–1.50	**< 0.001**	1.23	1.02–1.49	**0.02**
Indian	1.07	0.91–1.25	0.37	–	–	–
Indigenous Sarawak	0.65	0.57–0.75	**< 0.001**	0.74	0.58–0.95	**0.02**
Indigenous Sabah	0.77	0.69–0.86	**< 0.001**	1.01	0.83–1.23	0.91
Indonesian immigrants	0.79	0.67–0.94	**0.007**	0.91	0.72–1.16	0.47
Philippine immigrants	0.82	0.68–0.99	**0.04**	0.97	0.75–1.25	0.83
Others	1.39	1.00–1.93	**0.04**	1.30	0.89–1.90	0.16
Area						
Urban	1.47	1.35–1.60	**< 0.001**	1.46	1.33–1.61	**< 0.001**
Rural	1.00	–		1.00	–	
Marital status						
Single	1.14	1.04–1.24	**0.005**	0.97	0.88–1.07	0.63
Married	1.00	–		1.00	–	
Employment status						
Employed	1.33	1.22–1.46	**< 0.001**	1.21	1.09–1.34	**< 0.001**
Unemployed	1.00	–		1.00	–	
Alcohol drinkers						
Yes	8.02	6.67–9.66	**< 0.001**	4.91	4.04–5.96	**< 0.001**
No	1.00	–		1.00	–	
Intravenous drug user (IVDU)						
Yes	11.82	9.16–15.24	**< 0.001**	7.43	5.70–9.60	**< 0.001**
No	1.00	–		1.00	–	
TB type						
PTB	0.96	0.86–1.08	0.56	–	–	
EPTB	1.00	–		–	–	
Co-morbidity						
Yes	1.85	1.69–2.01	**< 0.001**	1.27	1.16–1.40	**< 0.001**
No	1.00	–		1.00	–	

Table 3 Clinical signs & symptoms among smokers and non-smokers patient groups

Symptoms	Total ***N*** = 9337	Never smoked ***N*** = 5024	Ever smoked ***N*** = 4313	***p***-Value
Night sweats				
Yes	2962 (31.7)	1500 (29.9)	1462 (33.9)	**< 0.001**
No	6164 (66)	3382 (67.3)	2782 (64.5)	
Unknown	211 (2.3)	142 (2.8)	69 (1.6)	
Cough				
Yes	7365 (78.9)	3786 (75.4)	3579 (83)	**< 0.001**
No	1944 (20.8)	1225 (24.4)	719 (16.7)	
Unknown	28 (0.3)	13 (0.3)	15 (0.3)	
Sputum				
Yes	5139 (55)	2947 (58.7)	2192 (50.8)	**< 0.001**
No	4035 (43.2)	2000 (39.8)	2035 (47.2)	
Unknown	163 (1.7)	77 (1.5)	86 (2)	
Shortening of breath				
Yes	3944 (42.2)	2033 (40.5)	1911 (44.3)	**0.001**
No	5298 (56.7)	2942 (58.6)	2356 (54.6)	
Unknown	95 (1)	49 (1)	46 (1.1)	
Fever				
Yes	5940 (63.6)	3146 (62.6)	2794 (64.8)	**0.002**
No	3377 (36.2)	1873 (37.3)	1504 (34.9)	
Unknown	20 (0.2)	5 (0.1)	15 (0.3)	
Weight loss				
Yes	6203 (66.4)	3234 (64.4)	2969 (68.8)	**< 0.001**
No	3037 (32.5)	1705 (33.9)	1332 (30.9)	
Unknown	97 (1)	85 (1.7)	12 (0.3)	
Loss of appetite				
Yes	6528 (69.9)	3347 (66.6)	3181 (73.8)	**< 0.001**
No	2694 (28.9)	1575 (31.3)	1119 (25.9)	
Unknown	115 (1.2)	102 (2)	13 (0.3)	
Hemoptysis				
Yes	2381 (25.5)	1295 (25.8)	1086 (25.2)	**< 0.001**
No	6842 (73.3)	3637 (72.4)	3205 (74.3)	
Unknown	114 (1.2)	92 (1.8)	22 (0.5)	

rate were less for smokers (aOR 0.76, 95% CI 0.69–0.84, $p < 0.001$), as shown in Table 4.

Discussion

Based on the National Health and Morbidity Surveys in 2006, the prevalence of smoking in Malaysia was 46.5%, as revised in 2015 [12]. The current study reported the same prevalence of smoking, i.e. 46.2%. Previously published studies conducted in Malaysia reported a higher prevalence of smokers than non-smokers among TB patients [11, 13]. The tobacco-tuberculosis association worldwide has been documented with different types of studies [1]. While the exact mechanism is not understood, nicotine may interfere with the host's immune reaction to *M. tuberculosis* [16].

The present study found that the male gender has a significant association with smoking habits. This could account for the observed differences in TB rates between men and women. A study from China reported that intravenous drug users (IVDUs) were found to be significantly associated with the smokers' group [17]. An additional study found that excessive intake of alcohol meant a greater chance of *M. tuberculosis* infection [18]. Chronic ethanol intake causes changes in the immune system and an increased risk of bacterial infections [19]. Consistent with the previous findings, the present study found that alcohol use and IVDUs were significantly associated with smoker TB patients.

If smoking is responsible for a decrease in cure rates and an increase in the risk of rapid disease progression and severity then there is a clear immunopathological association between smoking and TB [20, 21]. In the current study, the treatment success rate was low among the smokers' group. A person who smokes one packet of cigarettes daily inhales 1.12 μg of iron; iron-loading in the alveolar macrophages makes them more susceptible to the growth of *Mycobacterium tuberculosis* [22]. Cigarette smoke increases the threat of *Mycobacterium tuberculosis* infection in multiple ways: declined activity of alveolar macrophage, impairment of mucociliary clearance, decrease in the immune response of pulmonary lymphocytes, modified pulmonary dendritic cells activity, and reduction in the cytotoxic activity of natural killer cells [8]. Smoking also produces an alteration in both natural and acquired cell immunity, affecting macrophages and leukocytes. The effect of oxidative stress is important, as it induces apoptosis in both activated and non-activated macrophages, favoring the multiplication of the bacilli and making the process chronic [23, 24]. This is why tobacco smoking leads to severe clinical illness and eventually death. The current study showed that smokers were more likely to die. A previous study in China reported that the mortality rate was nine times higher among tuberculosis patients who smoked [25] while other studies from South Africa and India concluded that the higher odds of mortality were among smokers [26, 27]. Previous studies had also proved that tobacco smoking as one predictor and risk factors significantly associated with poor adherence and higher default rate in TB care settings [9, 28, 29]. A study from Hong Kong also showed that a smoking habit is a good indicator to evaluate the risk of defaulters from TB treatment under DOTS (OR = 3.00, 95% CI 1.41–6.39, $p = 0.004$) [9]. Patients who default treatment are at greatest risk of developing drug resistance and spreading TB in the community [30]. A recent study from Malaysia

Table 4 Unsuccessful treatment outcomes among smokers and non-smokers patients groups with Binary logistic regression

Treatment outcome	Total ***N*** = 9337	Never smoked ***N*** = 5024	Ever smoked ***N*** = 4313	Univariate analysis			Multivariate analysis		
				Crude OR	95% CI	***p***-Value	aOR	95% CI	***p***-Value
Cured									
Yes	5319 (57)	2900 (57.5)	2419 (56.1)	0.93	0.86–1.01	0.111	–	–	–
No	4018 (43)	2124 (42.3)	1894 (43.9)	1.00	–		–	–	
Treatment completed									
Yes	1924 (20.6)	1117 (22.2)	807 (18.7)	0.80	0.72–0.89	**< 0.001**	0.87	0.78–0.96	**0.01**
No	7413 (79.4)	3907 (77.8)	3506 (81.3)	1.00	–		1.00	–	
Expired									
Yes	500 (5.4)	217 (4.3)	283 (6.6)	1.55	1.29–1.86	**< 0.001**	1.57	1.31–1.89	**< 0.001**
No	8837 (94.6)	4807 (95.7)	4030 (93.4)	1.00	–		1.00	–	
Defaulters									
Yes	502 (5.4)	218 (4.3)	284 (6.6)	1.55	1.29–1.86	**< 0.001**	1.57	1.31–1.89	**< 0.001**
No	8835 (94.6)	4806 (95.7)	4029 (93.4)	1.00	–		1.00	–	
Treatment interrupted									
Yes	369 (4)	165 (3.3)	204 (4.7)	1.46	1.18–1.80	**< 0.001**	1.49	1.21–1.84	**< 0.001**
No	8968 (96)	4859 (96.7)	4109 (95.3)	1.00	–		1.00	–	
Treatment continued									
Yes	723 (7.7)	407 (8.1)	316 (7.3)	0.89	0.77–1.04	0.163	–	–	–
No	8614 (92.3)	4617 (91.9)	3997 (92.7)	1.00	–		–	–	
Overall treatment success									
Yes	7240 (77.5)	4004 (79.7)	3236 (75)	0.76	0.69–0.84	**< 0.001**	–	–	–
No	2097 (22.5)	1020 (20.3)	1077 (25)	1.00	–		–	–	–

recommends that interventions are necessary to improve treatment compliance in TB patients [11]. Improving compliance among smoking TB patients is a great challenge and should be addressed by securing support from families and social organizations as well as providing smoking cessation interventions [11]. Tachfounti et al. studied the association of smoking among TB patients and reported that the TB treatment failure rate was higher among smokers compared to non-smokers (9.1% vs 4.5%, $p < 0.01$) [31]. A few studies tested the effect of smoking on treatment outcomes and concluded that treatment failure was higher among current and ex-smokers, and smoking was significantly associated with low treatment success [2, 32, 33]. Fahrettin Talay et al. evaluated the treatment outcomes among TB patients and identified multiple patient factors that affect TB treatment outcomes [34]. The current study showed that patient mortality is higher among smokers [OR 1.57 (91.31–1.89); $p < 0.01$]. The reason might be due to drug addiction (OR 5.7) and co-morbidities (OR 1.27). The same picture can be drawn from the published articles [33, 35]. Smoking cessation seems to be an essential means of controlling TB epidemics, improving outcomes and drug resistance particularly in high-burden developing countries, as published elsewhere [33–35].

Conclusion

In conclusion, smoking is a risk factor for the occurrence of tuberculosis. Additionally, this study shows that the treatment effects are also poor. Tobacco also poses a strong risk factor in terms of poor adherence and higher mortality as well as defaulter rate. Therefore, proper public awareness campaigns and smoking cessation interventions should be presented to all smoking TB patients undergoing DOTS treatment to avoid the severity and progression of the disease and to avoid drug resistance.

Limitation of the study

A number of TB patients were excluded from the analysis due to a lack of / incomplete smoking-related data.

Abbreviations

TB: tuberculosis; WHO: World Health Organization; OR: odds ratio; CI: Confidence interval; MREC: Medical Research Ethics Committee; DOTS: Direct Observed Treatment Short course

Acknowledgments

We would like to thank the director general of Health Malaysia for his permission to publish this study. The researchers are grateful to all the paramedic staff who helped them out with data collection in the centers.

Authors' contributions

AHK: collected, analyzed, and interpreted the data. SASS, MOU and AHK: participated in conception and design of the study. MAH and AHK: drafted the manuscript. KUK: Article review, draft review & formatting. LCM: Revised the manuscript critically after analysis. OM: Analysis & Drafted the manuscript. MOU: Revised the manuscript critically after analysis and English editing. All the authors have read and approved the final manuscript.

Funding

This study received no funding from any organization.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available as institutional permission is required, but are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Ethical approval was granted from all relevant local authorities and obtained from the Medical Research Ethics Committee (MREC), registration number NMRR (National Medical Research Registration) # (2) KKM/NIHSEC/08/0804/P 67–177. Due to the study nature, patient consent was not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 21 July 2019 Accepted: 5 May 2020
Published online: 04 June 2020

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