

## Compliance to Recommended Prevention and Management Practices among Type 2 Diabetes Patients in Morogoro Municipality, Tanzania

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### Abstract

**Introduction:** Diabetes-related complications are the significant causes of morbidity and mortality among type 2 diabetes patients. The complications can be reduced by practising and maintaining several preventive measures. The present study aimed to assess compliance and factors associated with recommended management practices and prevention of complications among type 2 diabetes patients in selected health facilities in Morogoro Municipality, Tanzania.

**Methods:** A hospital-based cross-sectional study was conducted from February to May 2023 among 140 patients diagnosed with diabetes for at least three months before the study. Data were collected through face-to-face interviews using a structured questionnaire, which included patients' characteristics and a previously validated Summary of Diabetes Self-care Activities questionnaire to assess patients' compliance with recommended practices. A multivariable regression analysis was employed to identify factors associated with compliance with recommended practices.

**Results:** The mean age of the respondents was 59 ±12.08 years and 65% were females. Among 140 patients, 91.4% (n=128) had poor or unsatisfactory self-care practices with an overall mean of 3.81± 2.08 days per week for diabetes management. The recommended practices with good or satisfactory performance were non-smoking, non-alcohol drinking and prescribed medication. In contrast, unsatisfactory performance was observed for self-monitoring blood glucose and physical activities. Multiple regression analysis showed that co-morbidity (AOR 4.5; 95% CI: 1.14-18.02) and being employed (AOR 4.4; 95% CI: 1.25-15.44) independently predict self-care practices.

**Conclusion and recommendation:** Compliance with self-monitoring of blood glucose, physical exercise and dietary practices were found to be low among type 2 diabetes patients, which could increase the risk of complications. Nutritional and lifestyle counselling and the use of peer groups should be emphasized to improve compliance with recommended practices.

**Keywords:** Type 2 diabetes, compliance, prevention and management practices, Tanzania.

### Introduction

Globally, type 2 diabetes mellitus (T2DM) is considered one of the major public health epidemics, with a considerable number of premature deaths, disabilities, and high morbidity and mortality rates (Khan *et al.*, 2020). The prevalence has been on the increase mainly due to the increasing prevalence of risk factors such as sedentary lifestyles and unhealthy eating habits resulting in overweight and obesity (Motala *et al.*, 2022). Tanzania is one of the top five Sub-Saharan African (SSA) countries where the high prevalence of T2DM has a significant effect (IDF, 2021). The International Diabetes Federation [IDF] (2021) reported that more than two million Tanzanian adults have diabetes, primarily found in urban areas.

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Complications of T2DM can be costly due to its chronic nature and multi-organ involvement which can cause damage to small blood vessels (micro-vascular) such as kidney diseases (nephropathy), eye damage (retinopathy) and nerve damage (neuropathy) and macro-vascular such as blood vessels which lead to heart attack, stroke, or leg amputation (WHO, 2019). People with diabetes are at risk of mental health, such as anxiety, that can result from the stress of managing their conditions (Kalra *et al.*, 2018). Furthermore, it tends to affect individual functional capacities and quality of life, leading to significant morbidity and premature mortality. This is associated with an economic burden to the patients, families, and national and health systems because of the frequent visits to the healthcare care providers and admission to health facilities (Riddle & Herman, 2018).

Even though diabetes can have several impacts on health, its early detection and adherence to a healthy lifestyle change can positively impact the course of the disease (American Diabetes Association [ADA], 2018). Secondary prevention aims to reduce disease impacts on those who already have diabetes or prevent the development of long-term complications (Bali *et al.*, 2018). The complications of the disease can be reduced by several preventive measures including maintaining body weight, limiting alcohol consumption, smoking cessation, and preventive medications (Alouki *et al.*, 2016). In addition, effective management of T2DM requires the patients to learn and practice healthy self-care and lifestyle behaviours like blood glucose monitoring, taking medications, diet and exercise, proper counselling and compliance to these self-care practices and healthy lifestyle behaviour to control blood glucose levels and other complications associated with diabetes (Aschner, 2017).

Numerous studies that assessed compliance and adherence to recommended practices reported varied results. The study done in Saudi Arabia reported that adherence to self-care activities, including diet, exercise, blood glucose monitoring and foot care, was relatively poor. However, medication intake was strictly followed (Alhaiti *et al.*, 2020). A study done by Bongor and Tariku (2018), revealed that the extent to which individuals adhere to the recommended management of T2DM is substantially low whereby about 80% of diabetes patients did not adhere to the recommended diet management and self-monitoring of blood glucose level, while a majority (96%) of the respondents adhere to the prescribed medications. A study done by Rijal *et al.* (2022), to assess compliance of diabetes patients to diet and exercise revealed that compliance on diet was reasonable compared to exercise aspects. Several studies indicated that demographic and socioeconomic, clinical, and health-related characteristics such as age, religion, employment status, sex, family support, duration of T2DM, presence of comorbidities and diabetes-related complications influence compliance to recommended management practices (Ayele *et al.*, 2018; Zarei *et al.*, 2022; Zewdie *et al.*, 2022).

In Tanzania, most studies on T2DM have focused on prevalence and risk factors, diabetes-related complications, knowledge, and awareness (Chiwanga *et al.*, 2016; Stanifer *et al.*, 2016; Damian *et al.*, 2017). However, more information is needed about compliance with recommended prevention and management practices (Rwegerera, 2014; Mwanri *et al.*, 2018). Thus, this study assessed compliance with the recommended management practice and identified factors associated with compliance among T2DM patients. The results will help plan interventions targeting secondary prevention among T2DM patients to improve their quality of life and reduce the burden on the health system.

## Methodology

### Study area, design, and population.

The cross-sectional study was carried out in urban areas of the Morogoro region between February and May 2023. Morogoro municipality was selected purposively due to limited information on diabetes and being a fast-growing area as it is a central connection to the Southern Highlands and central and

Lake zones. This study included patients diagnosed with T2DM within three months or more and receiving healthcare services in selected diabetes clinics. Type 2 diabetes patients who had hearing or speech problems and those who were critically ill to respond to the questions were excluded from the study.

#### **Sample size and sampling procedures.**

A sample was estimated using the formula adopted from Kothari (2004). Based on the prevalence of T2DM in Tanzania (STEP-SURVEY) of 9.1% (Mayige & Kagaruki, 2013), the standard normal distribution of 95% and absolute error of 5% were used to obtain the sample size of 127 T2DM and after adjusting the non-response rate of 10% the total sample size was 140. The two health facilities with diabetes clinics, Sabasaba Health Center, and Morogoro Regional Referral Hospital, were purposively selected to involve public health facilities with diabetes clinics and accommodate most patients. About 15 patients attended the diabetes clinic per day at Morogoro Regional Referral Hospital and about five patients at Sabasaba Health Center. Based on this, a simple random sampling technique was used to select participants from the register list. About 15 patients from the two hospitals who met inclusion criteria and consented to participate were interviewed daily. A proportionate sampling technique was applied to acquire a total sample of 140 T2DM patients in two hospitals. About 80% of the T2DM patients were selected from Morogoro Regional Referral Hospital and 20% from Sabasaba Health Center.

#### **Data collection tool and procedure**

Researchers visited the outpatient diabetes clinic weekly on Thursday. Patients were approached to introduce the study to them and seek their consent to participate while they waited for their consultation. Data were collected using a structured questionnaire, which took an average of 45 minutes to complete. Face-to-face interviews were done to collect information on the respondents' sociodemographic details, clinical characteristics, and a Summary of Diabetes Self-Care Activities (SDSCA) questionnaire (Toobert *et al.*, 2000). This questionnaire was adapted and modified to elicit information on patients' frequency to comply with recommended prevention and management practices. The questionnaire consisted of items on the general diet, specific diet, physical activity, blood-glucose testing, foot care and items for smoking. Also, items concerning alcohol consumption and medication were added to capture all recommended practices for the prevention and management of T2DM.

Each item in SDSCA asks the respondents to mark the number of days the patients performed and adhered to the indicated self-care behaviour related to diabetes care within the last week on an eight-point scale ranging from (0-7), with 0 being the least desirable. Therefore, to maintain this standardization in results interpretation, one item of the specific diet dimension, which asks about intake of fat-rich foods, had their score inverted (7=0, 6=1, 5=2, 4=3, 3=4, 2=5, 1=6, 0=7) and vice versa as recommended by the revised SDSCA. The overall mean score of adherence was generated for each item of recommended practices by summing the mean score for self-care practices of all items and dividing it by the sum of some questions on each scale of the items. Final classification was done as having satisfactory or good self-care practices if the score was above or equal to 5 and poor or unsatisfactory for scores below 5.

#### **Statistical analysis**

The Statistical Package for Social Science IBM (SPSS) for Windows version 25 was used for data analysis. Descriptive statistics such as means, and standard deviation (SD) were used for numerical or continuous variables to describe self-care practices. Univariate logistics regression (analysis of a single

variable) was used to determine the strength of association between the dependent (self-care practices) and independent variables (socio-demographic and clinical characteristics). All variables that were significant at a p-value of  $\leq 0.05$  in univariate analysis were selected for multivariate analysis (analysis of multiple variables) to adjust the effect of confounders. A backward stepwise procedure was used to ascertain the suitable variables whereby all variables with a p-value of  $\leq 0.05$  were retained in a model. Both crude odds ratio (COR) and adjusted odds ratio (AOR) with 95% CI were reported.

### Ethical approval

The study commenced upon ethical approval from the National Health Research Committee of the National Institute for Medical Research (NatHREC) with a reference number NIMR/HQ/R.8a/Vol.IX/4239. Also, permission to conduct this study was obtained from the President's Office of Regional Authority and Local Government (PORALG) and respective regional, district and health facility authorities. The aim, procedures, benefits and possible risks of the study were explained and all participants who agreed to participate in this study and met the eligibility criteria were enrolled. Informed written consent was sought from the respondents to ensure voluntary participation in the study. The participants were assured of confidentiality and anonymity concerning the collected information by using numbers to represent patients' names during data handling.

### Results

#### Socio-demographic characteristics of the respondents

The mean age of respondents was 59 years; 65% (n=91) were females, 60.7% (n=85) were married, 7.9% (n=11) had college or university education, and only 7.9% (n=11) were employed in the formal sector. The mean duration of diabetes was  $8 \pm 7.13$  years. About half of the respondents, 48% (n=67), had a family history of diabetes, and 42% (n=59) had comorbidities. Out of those with comorbidities, 35.7% (n=50) were hypertensive. About 66% (n=92) of respondents had diabetes-related complications. Of those with complications, 22.9% (n=32) had retinopathy (Table 1).

**Table: Socio-demographic and clinical characteristics of the respondents**

Variable	Frequency	Per cent	Mean (SD)
<b>Age</b>			58.84±12.08
18-49 years	35	25	
>50 years	105	75	
<b>Sex</b>			
Male	49	35	
Female	91	65	
<b>Marital status</b>			
Married	85	60.7	
Single (Separated/Divorced/Widowed)	55	39.3	
<b>Education level</b>			
No formal schooling	9	6.4	
Not completed primary school	16	11.4	
Primary school completed	85	60.7	
Not completed secondary school	2	1.4	
Completed secondary school	17	12.1	
College/university	11	7.9	
<b>Source of income</b>			
Formal employment	10	7.1	
Self-employed	44	31.4	

Retired officer	19	13.6	
Unemployed	52	37.1	
Farmer	15	10.7	
<b>Duration of T2DM</b>	140		8.18±7.13
<b>Family history of diabetes</b>			
Yes	67	47.9	
No	73	52.1	
<b>Presence of co-morbidity (Chronic disease)</b>			
Yes	59	42.1	
No	81	57.9	
<b>Type of comorbidity</b>			
Hypertension	50	35.7	
Heart disease	6	4.3	
Cancer	3	2.1	
<b>Presence of diabetes-related complications</b>			
Yes	92	65.7	
No	48	34.3	
<b>Type of complications</b>			
Retinopathy	32	22.9	
Hypertension	29	20.7	
Nephropathy	1	0.7	
Stroke	2	1.4	
Lower extremities amputation	6	4.3	
Retinopathy, Hypertension	14	10	
Hypertension, lower extremities amputation	2	1.4	
Lower extremities amputation and retinopathy	6	4.3	

### Frequency of Adherence to Recommended Practices

Table 2 presents the mean number of days participants performed self-care practices for the last seven days. Most participants (91.4%, n=128) reported poor compliance with an overall mean score of 3.81 ± 2.08 days. Only 8.6% of respondents (n=12) reported good compliance. The most performed self-care practice was non-smoking, where almost all respondents (98.6%, n=138) had never smoked, 95% (n=133) of participants had never taken a drink containing alcohol, and the least was self-monitoring of blood glucose with a mean of 2.22±2.05 days per week. About 22% (n=31) of respondents perform physical activities with a mean of 3.04 days per week in five days or more.

**Table 2: Frequency of Adherence to Recommended Practices**

Self-care behaviour	Poor < 5 days n (%)	Good ≥ 5 days n (%)	Mean (SD)
<b>Diet</b>	93 (66.4)	47 (33.6)	4.44 (1.81)
<b>General diet</b>			4.33 (1.67)
Follows a healthful eating plan	87 (62.1)	53 (37.8)	4.31 (1.62)
Follows eating plan	79 (56.4)	61 (43.6)	4.36 (1.72)
<b>Specific diet</b>			4.55 (1.95)
Eat five or more servings of fruits and vegetables.	74 (52.9)	66 (47.1)	4.42 (1.95)

Eats high-fat foods (red meat or full-fat dairy products)	60 (42.9)	80 (57.1)	4.68 (1.96)
<b>Exercise</b>	<b>109 (77.9)</b>	<b>31(22.1)</b>	<b>3.04 (2.44)</b>
Participate in at least 30 minutes of physical activity	85 (60.7)	55 (39.3)	3.79 (2.41)
Participate in specific exercise sessions	106 (75.7)	34 (24.3)	2.29 (2.47)
<b>Self-monitoring of blood glucose</b>	<b>121 (86.4)</b>	<b>19 (13.6)</b>	<b>2.22 (2.05)</b>
Tests blood sugar level	107 (76.4)	33 (23.6)	2.51 (2.09)
Tests blood sugar the number of times recommended by health care provider	121 (86.4)	19 (13.6)	1.94 (2.0)
<b>Foot Care</b>	<b>88 (62.9)</b>	<b>52 (37.1)</b>	<b>3.78 (2.41)</b>
Checks feet	84 (60)	56 (40)	3.83 (2.37)
Inspect inside of the shoes.	82 (58.6)	58 (41.4)	3.74 (2.45)
<b>Medication</b>	<b>15 (10.7)</b>	<b>125 (89.3)</b>	<b>6.09 (1.83)</b>
Took the prescribed medication			
<b>Total Mean</b>	<b>128 (91.4)</b>	<b>12 (8.6)</b>	<b>3.81 (2.08)</b>
	<b>Yes n (%)</b>	<b>No n (%)</b>	
<b>Smoking</b>	2 (1.4)	138 (98.6)	
<b>Alcohol</b>	7 (5.0)	133 (95)	

### Factors associated with compliance to recommended practices among Type 2 Diabetes Patients

Univariate analysis revealed that age, sex, education level, family history of diabetes and duration of diabetes were not significantly related to self-care practices and, therefore, were removed from the model. The selected factors, the primary source of income, co-morbidity, and complications, were analysed using multiple logistic regression with a stepwise backward selection procedure to determine their association with self-care practices. A significant association was observed in the presence of co-morbidity (AOR 4.5, 95% CI: 1.14-18.02) and primary source of income (employed patients) (AOR 4.4, 95% CI: 1.25-15.44) (Table 3).

**Table 3:** Odds ratio of select factors for recommended practices among T2DM Patients

Variables	Good self-care practices		Poor self-care practice		COR (95% CI)	P value
	n	%	n	%		
<b>Age (Years)</b>					0.98 (0.94-1.036)	0.581
<b>Sex</b>						
Male	6	4.3	43	30.7	1	0.262
Female	6	4.3	85	60.7	0.506 (0.154-1.662)	



Education level						
Primary or lower	8	5.7	104	74.3	1	0.3
Secondary or higher	4	2.9	24	17.1	0.51 (0.142-1.825)	
<b>Main source of income</b>	6	4.3	23	16.4	4.56 (1.35-15.436)	<b>0.015*</b>
Employed	6	4.3	105	7.5	1	
Unemployed						
<b>Family history of T2DM</b>	5	3.6	62	44.3	0.76 (0.229-2.522)	0.654
Yes	7	5.0	66		1	
No				47.1		
<b>Duration of T2DM</b>					0.98 (0.899-1.077)	0.727
<b>Presence of co-morbidity</b>						
No	3	2.1	78	55.7	1	
Yes	9	6.4	50	35.7	4.68 (1.208-18.126)	<b>0.025*</b>
<b>Presence of complications</b>						
No	8	5.7	41	29.3	1	
Yes	4	2.9	87	62.1	0.236 (0.067-0.828)	<b>0.024*</b>
					<b>Multivariate analysis</b>	
<b>Presence of co-morbidity</b>						
No	3	2.1	78	55.7	1	
Yes	9	6.4	50	35.7	4.5 (1.14-18.02)	<b>0.032*</b>
<b>Main source of income</b>						
Employed	6	4.3	23	16.4	4.4 (1.25-15.44)	<b>0.021*</b>
Unemployed	6	4.3	105	7.5	1	

**Note:** The abbreviation 95% CI =confidence interval, AOR=Adjusted odds ratio, COR =Crude odds ratio number 1 indicates reference in categorical variables at \*significance at  $p < 0.05$ ; multivariate analysis also includes the presence of complications with no significant association.

## Discussion

The present study aimed to determine the compliance of T2DM patients to recommended prevention and management practices in Morogoro municipality, Tanzania. The study results indicated that most patients performed poorly on recommended practices. This finding can be explained by the low level of education among study participants, as most of them had a primary level of education. It might also be due to a need for more health education regarding recommended self-care practices.

In Tanzania, there needs to be more information on adherence to self-care practices and the factors associated; however, the study done in Brazil supports the current findings that most respondents had poor adherence to self-care practices (Macedo *et al.*, 2022). This could be due to similarities between the standard tool and methodology. The findings of the current study are higher than those of the study conducted in Addis Ababa by Gemedo & Woldemariam, (2022) (52%) and in Northern Ethiopia (49.7%) (Zewdie *et al.*, 2022). The possible reason for this discrepancy could be the differences in methodology, study design, socio-economic and cultural factors, and variation in sample

size across the study. It might also be related to using different numbers of items in SDSCA to assess self-care practices.

In all diabetes domains, self-care practices, such as self-monitoring blood glucose (SMBG) and physical exercise, were the least practiced. Similar results have been reported in other hospital-based studies conducted in Ethiopia (Dedefo *et al.*, 2019; Katema *et al.*, 2020; Jemal *et al.*, 2022). The poor performance of SMBG practices is probably related to socio-economic variation. Some patients could not afford to undergo a checkup at a nearby health facility every day as recommended by healthcare providers or to purchase glucometer and strips for self-blood glucose tests. It might as well be related to discomfort from frequent finger pricking. Contrasting results have been shown by other studies with a very high rate of adhering to regular SMBG compared to other practices, for example, the study done by Al-Ozairi *et al.* (2023) in Arab population and a systematic review conducted by Paudel *et al.* (2022). The variation in knowledge and awareness of the importance of understanding the glycemic status, which helps to adopt appropriate action to cope with the glycemic status, may also explain the observed differences (Mercado, 2019).

In the current study, only 22% of participants adhered to physical activities, which is a higher rate than the findings from a study in South Africa. In contrast, only 9% reported good adherence to physical activity practices (Mutymbizi *et al.*, 2022). The possible reason for relatively low adherence to physical activities could be the presence of comorbidities or diabetes-related complications, which were relatively high in our study. A much better physical activity behaviour was reported in a study from Nepal (90%) (Adhikari & Baral, 2021) and (88%) from a study in Vietnam (Van Loi *et al.*, 2023). This variation may be due to methodological differences, and the tools used in the South African study are the Global Physical Activity Questionnaire (GPAQ) to assess adherence to physical activity.

Regarding recommended moderation of alcohol consumption and cessation of smoking, very few respondents reported having smoked or drunk alcohol in the previous week. The low rate of smoking status and alcohol consumption in the current study were attributed to the fact that after being diagnosed with T2DM, the individuals quit smoking and abstained from alcohol use to prevent the occurrence of diabetes-related complications (Wu *et al.*, 2021; Campagna, 2019). Contrary to the current findings, higher rates of smoking and alcohol status were observed in a systematic review conducted by Paudel *et al.* (2022) and a study from China (Hu *et al.*, 2022). Approximately, 95% of the respondents in the current study abstained from alcohol consumption. This finding is similar to a study at public healthcare facilities in Gauteng, South Africa, which found that 99% of T2DM patients abstained from alcohol consumption (Mutymbizi *et al.*, 2020).

Only one-third of respondents adhered to diet management practices regarding the diet dimension. It is always difficult to change established eating habits and social influence. This finding is consistent with a study in India which reported that 35.2% of participants had a satisfactory performance on dietary behaviours (Karthik *et al.*, 2020). The current study's findings are lower than those conducted in Ethiopia and South Africa, revealing that more than two-thirds of participants had good dietary practices (Gemeda & Woldemariam, 2022; Mutymbizi *et al.*, 2020). This discrepancy might be attributed to the differences in eating habits, availability of food options, socioeconomic and cultural factors, study population, and the study tool used as other studies used Diabetes Self-Management Questionnaire (DSMQ), 24-hour food recall and Dietary Diversity Score (DDS) whereas our study used SDSCA.

Considering the medication dimension, most patients behaved well when taking diabetes medications (insulin or pills) as recommended. The reason for higher compliance to medication could be a fear of worsening health conditions among patients with comorbidities and diabetes-related complications, which motivated them to adhere to their medication regimen. Another reason could be that patients might have perceived medication as more critical than other recommended ways to



control diabetes (Lim *et al.*, 2022). The findings of the current study are almost comparable to studies done in Ghana (84.5%) by Afaya *et al.* (2020), Ethiopia (82.3%) by Zewdie *et al.* (2022), India (81.6%) by Syed *et al.* (2022). This could be due to similarities between the standard tool and methodology.

According to the multivariate analysis, co-morbidities and being employed were strongly associated with compliance with recommended prevention and management practices. A possible reason for high compliance among those with comorbidities might be that other co-morbidities and their multiple burdens may encourage patients to improve their practices based on the recommendations. Also, it might be due to frequent visits to healthcare facilities, continued counselling and health education; hence, they tend to pay more attention to their health condition. This finding was supported by studies in Kakamega County, Kenya (Mbunya, 2022) and Adama town, Ethiopia (Gemedo & Woldemariam, 2022), which reported that the odds of being adherent to recommended practices were higher among patients with comorbidities. Nevertheless, patients with no comorbidities were less likely to adhere to the recommended practices than their counterparts because they might need to pay more attention to the importance of self-care practices. After all, they have not experienced the burden of managing multiple health conditions.

Furthermore, unemployment was also an essential factor affecting compliance with recommended prevention and management practices. This might be due to financial difficulties limiting a person's ability to engage in self-care practices such as healthy eating and medication. Also, unemployment can have a significant impact on mental health challenges such as stress and anxiety, which can make it difficult to prioritize self-care practices. A job can provide financial stability, improving access to healthcare services and diabetes management resources. Consistent with a study done in Addis Ababa, Ethiopia (Wolderufael & Dereje, 2021) and Debre Markos, Ethiopia (Bayable *et al.*, 2022), the present study revealed that being employed was four times more likely to practice self-care practice compared to their counterparts.

### **Conclusion and Recommendations**

The overall compliance rate with recommended prevention and management practices among T2DM patients was low, with self-monitoring of blood glucose, physical exercise, and dietary practices being the least performed, which could increase the risk of complications. Having diabetes-related comorbidities and being employed were significant variables associated with compliance with recommended prevention and management practices. Therefore, nutritional and lifestyle counselling and the use of peer groups should be emphasized to improve compliance with recommended practices.

### **Strengths and Limitations of the Study**

The major strength of this study is the use of standardized tools to measure frequency to comply with recommended practices, which allowed the findings to be comparable with previous studies. The main limitations of this study were the small sample size and the use of a self-report method to evaluate patients' compliance with recommended practices, which could have resulted in overestimation or underestimation of the level of compliance. The other limitation was that many variables had tiny observations during analysis, which caused low precision. Further research should incorporate qualitative methods to understand better patients' perspectives and experiences on adherence to recommended practices and explore contextual factors influencing compliance to recommended practices.

### Conflicts of Interest

The authors declared no conflicts of interest.

### Authors contribution

HB conceived the idea, developed the proposal, designed the study, participated in data collection, management, analysis and interpretation of the results, and drafted the manuscript. AWM and SSM assisted in the design and the proposal development, supervised the study procedures, and revised subsequent manuscript drafts. All authors read and approved the final version of the manuscript.

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