



## Research Article

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# AKnowledge and Attitudes Regarding Cervical Cancer Screening among Women in Debre Markos Town, Amhara Region, Northwest Ethiopia: Community Based Cross-Sectional Study

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## Abstract

**Introduction:** Cervical cancer is the most common type of malignancy among all malignancies for women worldwide with 527,600 cases and 265,700 deaths every year. This research aimed to assess the knowledge of cervical cancer, attitude towards its screening, and associated factors among women at Debre Markos town, Northwest Ethiopia.

**Methods:** A community-based cross-sectional study was conducted among women from 30-49 years in Debre Markos town, from March 11 to May 31, 2020. Bivariable and multivariable logistic regression analyses were performed with SPSS version 25 and variables with a p-value of less than 0.05 were taken as significant variables.

**Result:** The study showed that 374 (59.4%) and 385 (61.1%) of respondents were knowledgeable and had a favorable attitude respectively. History of multiple sexual partners [AOR: 1.768 (95% CI: 1.227, 2.549)], and modern family planning method use [AOR: 2.238 (95% CI: 1.410, 3.554)] were significantly associated with knowledge of cervical cancer screening.

Again, education level ([AOR: 2.006, 95%CI: 1.147, 3.508]) marital status [AOR: 2.101 (95% CI: 1.219, 3.620)], and gravidity [AOR: 1.830 (95% CI: 1.125, 2.976)], were significantly associated with attitude towards cervical cancer screening.

**Conclusion:** This study showed the magnitude of knowledge and attitude towards cervical cancer screening was low even though the government recommended cervical cancer screening for eligible women.

## Keywords

Cervical cancer, Screening, Knowledge, Attitude

## List of Abbreviations

CC: Cervical cancer is Cancer; HPV: Human Papilloma Virus; LMICs: Low and Middle-Income Countries; MSPs: multiple sexual partners; STD: Sexually transmitted disease; WHO: World Health Organization

## Introduction

Cervical cancer is Cancer (CC) that starts in the cervix and occurs when cells in the cervix proliferate abnormally that have the chance to spread out to other parts of the body which is 70% of the case is caused by Human Papilloma Virus (HPV) [1,2]. CC screening is the use of different tests on individuals who have no signs and symptoms of a disease to identify those who probably have risk factors or are in the early stage of the disease [1,3]. CC is a global public health concern and a chronic non-communicable disease [4].

A global study reported 527,600 CC cases and 265,700 deaths occurred and 90% of cases occurred in Low and Middle-Income Countries (LMICs); the highest was occurred in

Sub-Saharan Africa (SSA) where CC is the leading killer among women [5]. Usually, women with CC do not observe symp-

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toms, especially in the early stages [6]. Therefore, the presentation of malignancy in the late-stage is vaginal bleeding, invasion, metastasis, and poor prognosis [7]. In addition to presenting a significant burden in terms of morbidity and mortality, CC also increases economic risk, which imposes very high direct costs on health systems, communities, households, and lost productivity of patients, premature death, and disability. The occurrence of CC related death is rare in high-income countries because of effective pre-invasive CC screening, and the risk of dying from CC is higher in resource-poor countries [8].

Cervical carcinoma is still the leading cause of morbidity and mortality among women on the African continent [9]. In Ethiopia, 7095 cases and 4732 death of CC occurs every year [10]. It is considered preventable because it has a long pre-invasive state to be changed from pre-cancer lesion to cancer and this gives a big chance to screen pre-cancer lesion and stop the existence of CC [2,11].

World Health Organization (WHO) recommended age for CC screening should be limited to women in the age of 30 to 50 years since there is evidence on younger age women with a milder degree of lesion spontaneously recover to normal [1]. As the WHO information Centre report showed there is a great difference in the level of CC coverage in different countries and the highest effective coverage was found in Ukraine (78%), the lowest was found in Ethiopia (1%) [12]. Having good knowledge and a positive attitude on CC screening is linked with the availability of health services [13,14].

Ethiopia adopted the WHO guideline and advised women to start CC screening at age of 30-49 years [1,7,15]. But CC utilization may be affected by women's knowledge and attitude towards CC screening [16]. Thus the purpose of this research is to assess the knowledge of cervical cancer, attitude towards its screening, and associated factors among women at Debremarkos town, Northwest Ethiopia.

## Methods

### Study area and period

This study was done in Debremarkos town, Amhara region, Northwest Ethiopia from March 11 to May 31, 2020. Debre Markos town is the capital city of East Gojjam Zone in Amhara regional state, Northwest Ethiopia, which is located at 300 km from Addis Ababa, the capital city of Ethiopia, and 265 km from Bihar Dar, the capital city of Amhara region. There are one referral hospital, three health centers, and five non-governmental clinics that give different reproductive health services in the town. Only the government referral hospital gives cervical cancer screening services.

### Study design

A community-based cross-sectional study design was used.

### Study participants

The source population was all women age 30-49 years-old who were residents of Debremarkos town. The study population was women age 30-49 years-old who were residents of Debremarkos town during the study period in the selected kebeles. We excluded women who are not permanent residents of the town and those who were critically ill during the data collection period.

### Sample size

The sample size for prevalence was determined based on a single population proportion formula assumption. The magnitude of knowledge and favorable attitude toward cervical cancer screening were 53.7% and 65.2% respectively from the previous study in Ethiopia at Hosanna town [17]. A 5% margin of error was used.

$$\text{initial sample size for knowledge} = \left( Z \frac{a}{2} \right)^2 * \frac{p(1-p)}{w^2} = 1.96^2 * \frac{0.537(1-0.537)}{(0.005)^2} = 382$$

With considering design effect 1.5 since it had two stages and the sample size was calculated as  $382 * 1.5 = 573$  then the non-response rate was also considered to be 10% and  $573 * 0.10 = 57$ . Then the final sample size was  $573 + 57 = 630$ .

The sample size for attitude was also calculated similarly.

$$\text{initial sample size for attitude} = \left( Z \frac{a}{2} \right)^2 * \frac{p(1-p)}{w^2} = 1.96^2 * \frac{0.652(1-0.652)}{(0.005)^2} = 349$$

Considering design effect 1.5 since it had two stages and the sample size was calculated as  $349 * 1.5 = 524$  then the non-response rate was also considered to be 10% and  $524 * 0.10 = 52$ . Then the final sample size was  $524 + 52 = 576$ . We took the larger sample size which was 630.

### Sampling techniques

A multistage sampling technique was used and firstly all the kebeles found in the Debremarkos town were listed in a frame.

Then three out of the seven kebeles were selected by the lottery method. Again the list of households found and coded in each kebele. The size of households consisting of the eligible population to be selected from each kebele was determined proportionally based on the size of the study units and the k<sup>th</sup> value was computed for each selected kebele. The women of the selected household were interviewed and if there was more than one woman in the household, the lottery method has been used to select only one. In the case of absenteeism, after three repeated visits the next eligible woman was included in the study.

### Study variables

**Dependent variables:** Knowledge and attitude of cervical cancer screening.

**Independent variables:** Socio-Demographic Characteristics, Reproductive and behavioral characteristics.

### Operational definitions

**Knowledgeable:** Women who answered knowledge questions score of mean value or above were considered as knowledgeable.

**Favorable attitude:** Women who answered attitude questions with a score of mean value or above were considered to have a favorable attitude.

**Multiple sexual partners:** Those women who have ever had penetrative sexual intercourse with more than one partner in their life serially or at the same time [18].

**Cigarette smoking:** The active smoking or ever had a smoking history of women one or more manufactured or hand-rolled tobacco cigarettes per day which excludes passive smokers [19].

### Data Collection and Data Quality Control

To assure the data quality, data were collected with face-to-face interviews by three trained diploma Midwives after two-day data collection training was given to them together with three BSc holder supervisors. The questionnaire was structured and pre-tested which was first prepared in English and translated to local (Amharic) language and then again translated back to English. A pretest was conducted on 32 women of the sample size in Dembecha town and the necessary correction on the tool was employed accordingly.

**Table 1:** Sociodemographic characteristics of women (n = 630) age 30-49 in Debremarkos town, Northwest Ethiopia, 2020.

Variable	Frequency	Percent
<b>Age of mothers</b>		
30-39	509	80.8
40-49	121	19.2
<b>Marital status</b>		
Married	504	80
Others*	126	20
<b>Religion</b>		
Christian	601	95.4
Muslim and protestant	29	4.6
<b>Educational status</b>		
No formal education	176	27.9
Primary education	149	23.7
Secondary education	168	26.7
College and above	137	21.7
<b>Ethnicity</b>		
Amhara	619	98.3
Others**	11	1.7
<b>Occupation</b>		
Housewife	119	18.9
Self-employee (doing own small business)	223	35.4
Private employee(salaried in the nongovernmental sector)	142	22.5
Government employee	146	23.2
<b>Household income ***</b>		
< 900	131	20.8
900-1600	129	20.5
1601-2699	239	37.9
> = 2700	131	20.8

\*Single, divorced and widowed; \*\*Oromo and Gurage; \*\*\* In Ethiopian Birr

## Data processing and analysis

Epi Info version 7 software was used for data entry and SPSS version 25 for used for analysis. Bivariate logistic regression was employed to identify an association between independent and dependent variables. Variables having a P-value of less than 0.25 in the bivariate logistic regression analysis were fitted into the multivariable logistic regression model. The 95% confidence interval of Adjusted Odds Ratio (AOR) was computed and a variable having P-value less than 0.05 in the multivariable logistic regression analysis was considered as statistically significant.

## Results

### Socio-demographic characteristics of the respondents

**Table 2:** Reproductive characteristics of women (n = 630) age 30-49 in Debre markos town, Northwest Ethiopia, 2020.

Variable	Frequency	Percent
<b>Age started sexual intercourse (in years)</b>		
< =16	138	21.9
> 16	492	78.1
<b>Multiple sexual partners</b>		
No	376	59.7
Yes	254	40.3
<b>History of smoking</b>		
No	617	97.9
Yes	13	2.1
<b>History of STD</b>		
No	542	86
Yes	88	14
<b>Ever use a modern FP method</b>		
No	102	16.2
Yes	528	83.8
<b>Duration of modern FP method use</b>		
1-3 years	425	80.6
> = 4 years	103	19.4
<b>Family history of cervical cancer</b>		
No	560	88.9
Yes	70	11.1
<b>Ever had got pregnant</b>		
No	105	16.7
Yes	525	83.3
<b>Gravidity</b>		
1-5	408	77.3
> 5	117	22.7
<b>Ever had given birth</b>		
No	123	19.6
Yes	507	80.4
<b>Parity</b>		
1-5	418	82.4
> 5	89	17.6

All 630 study participants responded to the questionnaire, giving a response rate of 100%. The majorities of women were Amhara 619 (98.3%), Christian religion 601 (95.4%), and married 504 (80%). Four hundred fifty-four (72.1%) of the women have attended formal education (Table 1).

### Reproductive and behavioral characteristics

One hundred thirty-eight (21.9%) women had first sexual intercourse at age 16 and below. Two hundred fifty-four (40.3%) women had a history of multiple sexual partners (MSPs). And 88 (14%) had a history of the sexually transmitted disease (STD). Around seventy (11.1%) of respondents had a family history of cervical cancer and 13 (2.1%) of the respondents had a smoking history (Table 2).

**Table 3:** Knowledge about cervical cancer screening among women (n = 630) in Debre markos town, Northwest Ethiopia, 2020.

Variable	Frequency	Percent
<b>Ever heard about cervical cancer</b>		
No	221	35.1
Yes	409	64.9
<b>Ever heard about cervical cancer screening</b>		
No	221	35.1
Yes	409	64.9
<b>Knew health institutions that give cervical cancer screening service</b>		
No	281	44.6
Yes	349	55.4
<b>Knew symptoms of cervical cancer</b>		
No	565	89.3
Yes	65	10.3
<b>Bleeding during sexual intercourse may be one of the signs of cervical cancer</b>		
No	569	90.3
Yes	61	9.7
<b>Cervical cancer is a killer disease</b>		
No	199	31.6
Yes	431	68.4
<b>Is cervical cancer a preventable disease</b>		
No	266	42.2
Yes	364	57.8
<b>Is cervical cancer a curable disease</b>		
No	257	40.8
Yes	373	59.2
<b>May have cervical cancer without any sign and symptom</b>		
No	342	54.3
Yes	288	45.7
<b>Overall knowledge</b>	<b>Frequency</b>	<b>Percent</b>
Knowledgeable	374	59.4
Not Knowledgeable	256	40.6

## Knowledge and attitude towards cervical cancer screening

About 374 (59.4%) of respondents were knowledgeable about cervical cancer screening [95% CI: 55.5, 63] (Table 3).

There hundred eighty-five (61.1 %) had a favorable attitude towards cervical cancer screening [95% CI: 57.4, 65] (Table 4).

## Factors associated with knowledge of cervical cancer screening

After controlling the effect of other variables with binary logistic regression, age, marital status, ethnicity, educational status, income, occupation, history of MSP, history of STD, modern FP method use, and smoking history were significantly associated with knowledge of cervical cancer screening (P-values < 0.25).

After controlling the effect of other variables with mul-

tivariable logistic regression analysis history of MSP [AOR: 1.768 (95% CI: 1.227, 2.549)], and modern FP method use [AOR: 2.238 (95% CI: 1.410, 3.554)] were significantly associated with knowledge of cervical cancer screening (Table 5).

## Factors associated with the attitude towards cervical cancer screening

Similarly, with controlling the effect of other variables in binary logistic regression, income, marital status, educational status, age at first sex, modern FP method use, duration of modern FP use, gravidity, and history of STDs were significantly associated with the attitude towards cervical cancer screening (P-values < 0.25).

And with controlling the effect of other variables in multivariable logistic regression analysis, an education level (College and above education level [AOR: 2.006, 95% CI: 1.147, 3.508])) marital status [AOR: 2.101 (95% CI: 1.219, 3.620)], and gravidity [AOR: 1.830 (95% CI: 1.125, 2.976)], were sig-

**Table 4:** Attitude towards cervical cancer and its screening among women (n = 630) in Debremarkos town, Northwest Ethiopia, 2020.

Variables	Level of agreement					
	Agree		Disagree		Indifferent	
	Number	Percent	Number	Percent	Number	Percent
Any reproductive age woman is susceptible to develop cervical cancer	320	47.5	148	23.5	162	25.7
Like any women, you are susceptible to develop cervical cancer	299	47.5	170	27	161	25.6
Cervical Cancer can be transmitted genetically	93	14.8	354	56.2	183	29
Cervical cancer may be dangerous	383	60.8	133	21.1	114	18.1
Precancerous cervical screening may be beneficial to health	387	61.4	112	17.8	131	20.8
Cervical cancer screening is painful	359	57	109	17.3	162	25.7
<b>Overall attitude</b>	<b>Frequency</b>			<b>percent</b>		
Favorable attitude	385			61.1		
Unfavorable attitude	245			38.9		

**Table 5:** Bivariable and Multivariable analysis of factors associated with knowledge about cervical cancer screening among women in Debremarkos town, Northwest Ethiopia, 2020.

Variable	Knowledge		Crude OR [95%CI]	AOR [95%CI]
	Knowledgeable	Not Knowledgeable		
<b>Age of mothers</b>				
40-49	65	56	1.331 (0.893, 1.984)	
30-39	309	200	1	
<b>Marital status</b>				
Others*	64	62	<b>1.55 (1.05, 2.29)</b>	0.746 (0.487, 1.141)
Married	310	194	<b>1</b>	<b>1</b>
<b>Religion</b>				
Muslim	19	10	0.76 (0.35, 1.66)	
Christian and protestant	355	246	1	

<b>Educational status</b>				
Primary education	103	46	0.68 (0.427, 1.07)	
Secondary education	91	77	1.28 (0.84, 1.97)	
College and above	74	66	1.35 (0.821, 2.03)	
No formal education	106	70	1	
<b>Ethnicity</b>				
Others**	9	2	0.319 (0.068, 1.49)	
Amhara	365	254	1	
<b>Occupation</b>				
Self-employee	122	101	1.36 (0.864, 2.15)	
Private employee	98	44	0.74 (0.442, 1.234)	
Government employee	80	66	1.357 (0.828, 3.430)	
Housewife	74	45	1	
<b>Household income ***</b>				
900-1600	62	67	1.24 (0.762, 2.018)	
1601-2699	144	95	0.757 (0.492, 1.164)	
> = 2700	98	33	0.386 (0.245, 2.22)	
< 900	70	61	1	
<b>Age started sexual intercourse for the first time</b>				
< =16		61		
>16	77	195	1.207 (0.824, 1.767)	
	297		1	
<b>Multiple sexual partners</b>				
Yes	178	76	<b>2.15 (1.54, 3.011)</b>	<b>1.768 (1.23, 2.55)</b>
No	196	180	<b>1</b>	<b>1</b>
<b>History of smoking</b>				
Yes	9	4	<b>3.37 (1.03, 11.07)</b>	3.057 (0.896, 10.429)
No	247	370	<b>1</b>	1
<b>History of STD</b>				
Yes	48	40	<b>1.926 (1.22, 3.034)</b>	1.446 (0.875, 2.389)
No	208	334	<b>1</b>	1
<b>Ever use a modern FP method</b>				
Yes	328	200	1.997 (1.30, 3.06)	<b>2.238 (1.41, 3.55)</b>
No	46	56	<b>1</b>	<b>1</b>
<b>Duration of modern FP method usage</b>				
> 3 years	65	37	1.08 (0.691, 1.695)	
1-3 years	263	162	1	
<b>Family history of cervical cancer</b>				
Yes	45	25	1.26 (1.54, 2.12)	
No	329	231	1	
<b>Ever had got pregnant</b>				
Yes	319	206	1.41 (0.924, 2.145)	
No	55	50	1	

<b>Gravidity</b>				
> 5	247	161	0.959 (0.629, 1.46)	
1-5	72	45	1	
<b>Ever had given birth</b>				
Yes	309	197	1.42 (0.959, 2.114)	
No	65	59	1	
<b>Parity</b>				
> 5	56	33	1.096 (0.683, 1.758)	
1-5	254	164	1	

\*single, divorced and widowed; \*\* Oromo and Gurage; \*\*\* In Ethiopian Birr

**Table 6:** Bivariable and Multivariable analysis of factors associated with an attitude towards cervical cancer screening among women in Debremarkos town, Northwest Ethiopia, 2019.

Variable	Attitude		Crude OR [95%CI]	AOR [95%CI]
	Favorable	Un Favorable		
<b>Marital status</b>				
Married	323	181	1	1
Others*	62	64	<b>1.842 (1.242, 2.73)</b>	<b>2.101 (1.22, 3.62)</b>
<b>Educational status</b>				
Primary education	99	50	0.862 (0.546, 1.363)	
Secondary education	100	68	1.161 (0.752, 1.793)	
College and above	75	52	1.412 (0.896, 2.225)	<b>2.01 (1.15, 3.51)</b>
No formal education	111	65	1	1
<b>Household income ***</b>				
900-1600	72	57	1.62 (0.979, 2.68)	
1601-2699	141	89	1.422 (0.910, 2.223)	
> = 2700	84	47	1.145 (0.687, 1.908)	
< 900	88	43	1	
<b>Age at first sex</b>				
< = 16	76	62	1.377 (0.940, 2.018)	
> 16	309	183	1	
<b>History of STD</b>				
Yes	44	44	<b>1.697 (1.08, 2.668)</b>	1.28 (0.719, 2.282)
No	201	341	1	1
<b>Ever use a modern FP method</b>				
Yes	336	192	1.893 (1.235, 2.90)	1.244 (0.709, 2.18)
No	49	53	1	1
<b>Duration of modern FP method usage</b>				
> 3 years	58	44	0.704 (0.454, 1.093)	
1-3 years	277	148	1	
<b>Gravidity</b>				
> 5	54	63	<b>1.659 (1.09, 0.517)</b>	<b>1.830 (1.125, 2.98)</b>
1-5	139	269	1	1

\*single, widowed, divorced; \*\*\* In Ethiopian Birr

nificantly associated \*\*\* with the attitude towards cervical cancer screening (Table 6).

## Discussion

This study was done to investigate knowledge and at-

titude towards cervical cancer screening among women in Debremarkos town, northwest Ethiopia. So, the study found that 59.4% [95% CI: 55.5, 63] and 61.1% [95% CI: 57.4, 65] of respondents were knowledgeable and had a favorable attitude towards CC screening respectively.

The finding of this research was lower than the studies done in Ethiopia (91%) [20]. The possible explanation for this might be the difference in the level of knowledge as evidenced by a study done in Ethiopia on health care providers.

The finding of this study was also higher than studies done in China (19.5%) [21], Kuwait (52.3%) [22], at Finote-Selam, Ethiopia (30.3%) [23], in Addis Ababa, Ethiopia (23.4%) [24], at Hadiya Zone (53.7%) [17], and Southern Ethiopia (77.1%) [25]. The possible explanation might be; the difference in the study area and study population as evidenced by a study done in Ethiopia on the both urban and rural population that was different from our study population and study area which was urban, and unavailability of screening center near the community as evidenced by a study done a Finote-Selam town.

As shown in this study, a woman who had a history of MSPs was an important factor for knowledge on cervical cancer screening. Women who have had a history of MSPs were 1.768 times more likely knowledgeable on cervical cancer screening as compared with those who did not MSP [AOR: 1.768 (95% CI: 1.227, 2.549)]. This study was supported by the result of a study done in China [21] and Kuwait [22]. The possible explanation might be women, who had MSP history, would have the chance to be infected with STIs with its signs and symptoms which increases health facility visits and availability of the screening service.

The current study result showed that a woman who had used the modern family planning method was another important factor for knowledge of cervical cancer screening. Women who have ever used the modern family planning method were 2.238 times more likely knowledgeable on cervical cancer screening as compared to those who did not use [AOR: 2.238 (95% CI: 1.410, 3.554)]. This result was supported by the finding from Malaysia [26] and China [21]. The above association might be explained by women who have used the modern family planning method, may have a chance of getting an education on CC screening.

The study finding of attitude towards cervical cancer screening (61.1%) was in-line with similar reports at Finote-Selam, Ethiopia (58.1%) [23]. The finding of this research was lower than the studies done in Zimbabwe (71.2%) [27]. The possible explanation might be the difference in the study area and study population which was done nationwide in religious areas.

The finding of this study was higher than studies done at Hadiya Zone, and South Ethiopia (53.7%) [17] and in Kuwait (30.6%) [22]. The possible explanation might be the difference in the study area and study population as evidenced by a study done in Ethiopia on the both urban and rural population that was different from our study population and study area which was urban; and unavailability of screening service near the community as evidenced b study done a Finote-Selam town.

As shown in this study, marital status was a significant predictor of attitude towards cervical cancer screening. This study showed that women who were single/divorced/widowed 2.101 times more likely had a favorable attitude to-

wards cervical cancer screening as compared with married women [AOR: 2.101 (95% CI: 1.219, 3.620)]. No study supported this finding. The possible explanation for this might be single, divorced, or widowed women may have MSP which causes sexually transmitted disease. His may lead the women to have more visit health facilities which increases the chance to have a good attitude towards CC screening.

Educational status was also the main significant factor for attitude towards CC screening. Women who took college & above education were 2.01 times more likely to have a favorable attitude towards CC screening as compared with women who did not take formal education [AOR: 2.01, 95%CI: 1.147, 3.508)]. This study was supported by the study done at Finote-Selam town in Ethiopia [23] and in Kuwait [22]. This might be explained with, as the level of education increases, the women will have the chance to know about cervical cancer screening which can change the attitude towards CC screening. The current study result also showed that women who had more than five pregnancies were 1.830 times more likely to have a favorable attitude towards CC screening as compared to those who had less than five pregnancies [AOR: 1.830 (95% CI: 1.125, 2.976)]. No study supported this finding. The above association might be explained by women who have had a large number of pregnancies, may have many health institution visits for antenatal care service or pregnancy-related complications. This may increase the chance of getting information on CC screening which may change their attitude.

## Conclusion

This study showed the magnitude of knowledge and attitude towards cervical cancer screening was low. Modern family planning method use and history of multiple sexual partners were significant factors for knowledge of cervical cancer screening. Similarly, education level, marital status, and gravidity were significant factors for attitude towards cervical cancer screening.

## Declarations

### Availability of data and materials

Data supporting this study can be obtained on request.

### Ethical clearance

Ethical clearance was obtained from the Ethical Review Committee of the Department of Midwifery, under the delegation of the institutional review board of the University of Gondar. Ethical clearance and formal letters were also obtained from the University Gondar School of Midwifery and were submitted to Debremarkos health office and permissions were obtained. Finally, written informed consent was also obtained from each study participant.

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## Consent for publication

All the authors have a copy of this manuscript. The authors would like to confirm that this article has not been submitted to any other journal and we fully agree to be published by this journal.

## Authors' contributions

BY: proposed the initial idea for the study; BY, KT, MM: Contributed to the study design; BY: Collected all the data; all authors analyzed and interpreted the data; BY: Drafted the manuscript; BY, KT and MM: Contributed to the writing of the manuscript. BY, KT, and MM: Prepared the manuscript for publication; all authors read and approved the final manuscript.

## Disclosure

The authors report no conflicts of interest in this work.

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