BMJ Open Prevalence and associated factors of perceived stigma among medically ill patients on follow-up screened positive for depression in Ethiopia: facilitybased cross-sectional study

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ABSTRACT

Background Many people are familiar with the issues of stigma in mental health or HIV, but feeling stigma as an underlying factor for many medically ill-health conditions has not been examined.

Methods Institution-based cross-sectional study was conducted on patients followed for medical illnesses and having depression. We recruited 384 participants and who were interviewed by nurses using face-to-face interviews and a systematic random sampling technique applied. We used a perceived devaluation and discrimination, a 12-item tool that is used to measure outcome perceived stigma. Variables were coded and entered Epi Info V.3.5.3 and exported to SPSS V.20 for analysis. Statistical analysis parameters, such as descriptive and multivariate logistic regression, were used for data analysis. Adjusted ORs (AORs) with a 95% CI and p value <0.05 were declared significance.

Result The prevalence of perceived stigma on a patient who followed for medical illness screened positive for depression was found to be around 66.3%. In the multivariate logistic regression, patients with hypertension 61% less likely ((AOR=0.39, 95% CI (0.17 to 0.89)) to have perceived stigma than with asthma and cardiac patients, patients completed higher education 2.15 times ((AOR=2.15; 95% Cl 1.05 to 4.40)) more likely to have perceived stigma than which cannot read and write. Patients who had the previous admission with medical illness 1-2 times were 3.52 more likely (AOR=3.52, 95%) Cl (2.14 to 5.78)) perceived stigma than those who had no hospital admission. Patients who had the previous admission three times with medical illness were 6.1 more likely (AOR=6.1, 95% CI (2.32 to 16.07)) to have perceived stigma than those who had no previous hospital admission. **Conclusion** The prevalence of perceived stigma among patients who had on follow-up for medical illnesses was high. Educational status, history of previous hospital admission were considerably associated with higher perceived stigma.

INTRODUCTION

Stigma is when someone negatively views you because you have a distinguishing

Strengths and limitations of this study

- This study is the first of its kind in our context among patients with medical illness.
- It is founded on empirical data.
- Quick, inexpensive and simple to carry out.
- Possibility of determining prevalence of perceived stigma for independent variables under investigation.
- It does not show that perceived stigma is due to medical illness.

characteristic or personal trait that is thought to be, or is, a disadvantage (a negative stereotype).¹² It is generally a social process, characterised by exclusion, rejection and blame or devaluation by someone or a group.³ Perceived stigma is the internal feeling of fear that someone has of being discriminated by others or the fear of enacted stigma, which arises from society's behaviours.⁴ Stigmatised individuals may anticipate devaluation and discrimination, unwilling to seek services, social interaction and employment opportunities, leading them to adopt harmful coping mechanisms such as social withdrawal.^{5 6} Stigma has a negative impact or consequences on the life of patients with mental illness.⁷

When depression and non-communicable diseases combine, they result in a double burden. The inter-relationship between depression and chronic medical illnesses is bidirectional; for example, cardiovascular disease can lead to depression and vice versa.⁸ Its comorbid prevalence with a chronic medical illness, such as diabetes, hypertension and epilepsy, increases a patients' risk of disability and mortality,⁹ around 67% of depressed primary care patients have stigma related to depression, high among hypertension and diabetes.¹⁰

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People with mental illness experience stigma and discrimination, subject to a widely held misconception about the causes and nature of the mental illness.¹¹ A large number of epidemiological studies have reported that perceived stigma affects individual self-efficacy,¹² self-esteem,¹³¹⁴ recovery from illness, relationships,¹⁵ treatment adherence, help-seeking behaviour, persistent suffering, disability, economic loss¹⁶ and causes difficulty in accessing housing and employment.¹⁷ The prevalence of stigma among people with mental illness in Ethiopia was reported within the range of 32.1%-83.5%.18 19 People with mental illness are subjected to high levels of stigma and discrimination because of widely held misconceptions about the causes and nature of mental health situations.¹¹ When it occurs with medical illness, it causes non-adherence to healthcare provider recommendations, a risky lifestyle for chronic illness and perceptual and social inequality.

Several factors are significant indicators of perceived stigma among patients with depressive disorders, such as substance abuse, sex, age, educational status, unemployment and stress.^{20–24} Therefore, perceived stigma negatively affects patients with medical illness causing a double burden together with depression; thus, this study aims to assess the prevalence of perceived stigma and associated factors among patients with medical illness combined with depression in Ethiopia.

METHODS

An institution-based cross-sectional study conducted at the University of Gondar Comprehensive Specialized Hospital, Gondar, Ethiopia, from 1 May to 30 June 2020. Patients with chronic illness included in the sample were follow-ups from the outpatient department of the University of Gondar Specialized Hospital.

The sample size was determined by the single population proportion estimate using Epi-info V.7 with a 95% CI, a 5% margin of error and considering a prevalence of stigma of 47% from a previously published study of schizophrenia patients.²⁵ A total sample size of 384 was defined. We employed a systematic random sampling technique to pick a total sample size of 384 patients who had follow-up for the treatment of their chronic illness indicated below from a group of 1500 patients who had a monthly follow-up in our hospital, with a sample interval of three. Finally, 377 patients aged 18 and above were sampled, and those who had been followed up for at least 6 months were included in the study. Patients with a history of mental illness and treatment follow-up were excluded from the study. All consenting individuals who had a clinical diagnosis of medical illness (diabetes, hypertension, epilepsy, asthma and cardiac problems) were coming for follow-up. Patients who were unable to communicate were excluded from the study. Nurses applied a pretested interviewer-administered questionnaire, which contains the Patient Health Questionnaire nine (PHQ-9). Additional explanatory variables include

sociodemographic characteristics (age, sex, education, marital status and others), clinical factors (duration of illness, number of hospitalisations, duration of follow-up, history of discontinuation of follow-up, history of mental illness, family history of mental illness), social support and substance use (alcohol, cigarette, khat and drugs taken as injections).

INSTRUMENTS

Patient health questionnaire tool

First, depression among patients visiting the outpatient chronic illness clinic was assessed by the Amharic version of the PHQ-9. A PHQ-9 measurement ranges from 0 to 3. The sum of all questions has 0 to 27. The PHQ-9 has verified reliability, validity and has been established for use in Ethiopia. A PHQ-9 score ≥ 10 has a sensitivity of 88% and a specificity of 88% for major depression. The PHQ-9 contains the Diagnostic and statistical manual (DSM-5) for depression screening along with other leading depression symptoms in a brief self-report tool.²⁶

Oslo-3 social support scale

Social support was assessed by using the Oslo 3 social support scale (OSS-3) used in several studies. It provides a brief measure of social support and functioning and is considered one of the best predictors of mental health such as depression and anxiety. It covers different levels of social support by measuring the number of people the respondents feel close to, the interest and concern showed by others and the ease of obtaining practical help from others. In the OSS-3, total scores are calculated by adding up the raw scores for each item. The sum score ranges from 3 to 14 and it has three broad categories: 'poor social support' 3–8, 'moderate support' 9–11 and 'strong support' 12–14.²⁷

Substance use (current users) was considered when clients use a specified substance for non-medical purposes in the last 3 months.²⁸

Suicidal ideation was measured using a single question that addressed the previous history of suicidal ideation/ attempt with a 'yes' or 'no' answer.

Perceived Stigma scale

Perceived stigma was measured using the perceived devaluation and discrimination scale (PDD). PDD is a 12-item tool that measures the extent to which a person believes that most people will devalue or discriminate against someone with a mental illness. PDD was measured on a 4-point Likert scale with scores ranging from 1 to 4 (1=strongly disagree, 2=disagree, 3=agree and 4=strongly agree). A higher score indicates a higher level of perceived stigma. This scale has been widely used around the world, including in low-income countries.²⁹ A high level of PDD is indicated by agreement with six of the items and disagreements with six others and possible scores range from 1 to 4, thus, a higher score showed a higher level of perceived stigma, but items 1, 2, 3, 4, 8 and 10 were reverse directed.^{13 30} The prevalence of perceived stigma defined as an item mean score of 2.5 or a higher on the mean aggregated scale score represents the midpoint 1 to 4 item scale on the PDD scale. Then perceived stigma scores were dichotomised: participants scoring ≥ 2.5 on the PDD scale were considered as having 'high perceived stigma' and those scoring below the mean value were considered as having 'low perceived stigma'.³¹ This scale was used in different countries with different settings including Ethiopia.^{18 29 32 33} The questionnaires were translated into the Amharic language by an Amharicspeaking linguist. Back translations were performed by a psychiatrist in English and then a consensus version was developed in a group discussion by involving another psychiatrist and one Amharic-speaking linguist. This was compared with the original version and confirmed to be satisfactory for use. In this study, PDD had an internal consistency of Cronbach's alpha of 0.79.

Data processing and analysis

All data were checked, cleaned, coded and entered EPI-Info V.3.5.3 and imported to SPSS software V.20 for data analysis. Descriptive statistics, bivariate and multivariate binary logistic regression were done. Bivariate analysis was used to determine associations between dependent and independent variables and to estimate the strength of the association; an adjusted OR (AOR) at 95% CI was used. After bivariate analysis, variables with p value <0.2 were entered into a multivariate binary logistic regression to control confounding factors. Variables with p value less than 0.05 were considered significantly associated with *perceived stigma*.

Patient and public involvement

The study was prepared by WGA, SYT, EB, BE and HK. The study includes all patients who had followed in Gondar University's Comprehensive Specialized Hospital chronic illness. Five researchers (WGA, SYT, EB, BE and HK) were involved in analyses, interpretation of the results, editing, preparing the manuscript for publication as well as disseminating the findings to different academic and other concerned institutions. Furthermore, we would highly like to acknowledge them.

RESULTS

Sociodemographic characteristics

A total of 384 individuals were invited to participate in the study. Of the total respondents, 377 finished interviews appropriately with a 98% response rate. Two of the participants failed to complete the interviews and five questions were not fulfilled appropriately. The mean age of the respondents was 45 (\pm 15) years. More than half of the participants were women, 220 (58.4%). One hundred and ninety-one (50.7%) were 46 years old and above; most of the participants, 319 (84.6%), were orthodox and 231 (61.3%) were married. Of the participants, Table 1Sociodemographic characteristics of patientswith chronic illness with depression attending the medicaloutpatient clinic at the University of Gondar ComprehensiveSpecialized Hospital, Gondar, Ethiopia, 2020 (N=377)

Variables	Category	Frequency	Percentage
Sex	Male	157	41.6
	Female	220	58.4
Age	Below 41	150	39.8
	41 and above	277	62.2
Religion	Orthodox	319	84.6
	Muslim	49	13
	Protestant	9	2.4
Marital status	Single	84	22.3
	Married	231	61.3
	Divorced	24	6.4
	Widowed	38	10
Educational status	Cannot read and write	113	30
	Read-write	78	20.7
	Primary school	49	13
	Secondary school	48	12.7
	Higher education	89	23.6
Job	Government worker	111	29.4
	Merchant	30	8
	Farmer	66	17.5
	Housewife	125	33.2
	No job	45	11.9
Residence	Rural	117	31
	Urban	260	69

113 (30%) could not read and write. One hundred and twenty-five (33.2%) were housewives and over two-thirds of 260 (69%) were urban residents (table 1).

Clinical characteristics

Concerning clinical characteristics of respondents, 132 (35%) were followed for diabetes mellitus, two-thirds, 244 (64.7%), of the respondents had greater than 5 years of duration of chronic illness, and more than half, 219 (58.1%), were treated for more than 5 years; 205 (54.4%) participants had 1–2 hospital admissions. Nearly one-third, 107 (28.4%), had a history of stopping their medication. Regarding the clinical follow-up of clients, 144 (38.2%) had been followed every 2 months. Eighty-four (22.3%) clients had a comorbid illness with more than one medical illness. In this study, 34 (9%) had a history of previous mental illness and 33 (8.8%) had a family history of mental illness (table 2).

Table 2Clinical characteristics of chronic illness patientswith depression attending the medical outpatient clinicat the University of Gondar Comprehensive SpecializedHospital, Gondar, Ethiopia, 2020 (N=377)

Variables	Category	Frequency	Percentage
Dx. of the patient	Diabetes millets	132	35
	Hypertension	76	20.2
lollowed up	Epilepsy	117	31
	Asthma and cardiac problem	52	13.8
Duration of illness in years	<6 years	133	35.3
	Six and above	244	64.7
Duration of	Up to 5 years	158	41.9
Rx.	>5 years	219	58.1
Hx. of	No admission	117	31
admission	1–2 times	205	54.4
	3 times	35	9.3
	>3 times	20	5.3
Hx. of stopping a medication	Yes	107	28.4
	No	270	71.6
Frequency of follow-up	Every month	142	37.7
	Every 2 months	144	38.2
	Every 3 months	91	24.1
Dx. of comorbid illness	Yes	84	22.3
	No	293	77.7
Previous mental illness	Yes	34	9
	No	343	91
Family Hx of	Yes	33	8.8
mental illness	No	344	91.2

Dx., diagnosis; Hx., history.

Social support and substance-related factors

Among the participants, 33 (8.8%) lived alone, 81 (21.5%) had suicidal ideation; regarding social support, 41.6% and 55.7% of the participants had poor and moderate social supports, respectively. At the time, only a few participants, 41 (10.9%), consumed alcohol (table 3).

Predictors of perceived stigma

To determine the association of independent variables with perceived stigma, bivariate and multivariate binary logistic regression analyses were done. On the bivariate analysis, age 41 and above, a history of previous hospital admission and a previous history of mental illness were factors associated with perceived stigma.

In the bivariate analyses, factors including sex, age, educational status, residence, diagnosis of the patient, duration of disease, duration of treatment, admission history, history of stopping the medication, comorbid medical illness were factors with a p value less than 0.2 and entered the multivariate analysis. These factors were Table 3Social support and substance use characteristicof chronic illness patients with depression attendingthe medical outpatient clinic at the University of GondarComprehensive Specialized Hospital, Gondar, Ethiopia,2020 (N=377)

Variables	Category	Frequency	Percentage
Living condition	Living alone	33	8.8
	Living with family	344	91.2
Suicidal ideation	Yes	81	21.5
	No	296	78.5
Social support	Poor	157	41.6
	Moderate	210	55.7
	Strong	10	2.7
Tobacco use	No	370	98.1
	Yes	7	1.9
Alcohol use	No	336	89.1
	Yes	41	10.9
Khat use	No	364	96.6
	Yes	13	3.4
Cannabis use	No	374	99.2
	Yes	3	0.8

entered into the multivariate logistic regression model to control confounding effects. The result of the multivariate analysis showed that the diagnosis of the patient medical illness, with a history of previous hospital admission and had an association with high perceived stigma.

The model goodness-of-fit was assessed using the Hosmer and Lemeshow test and the p value was 0.87. Thus, the goodness-of-fit of the model was good. The multivariate analyses show that patients' follow-up for hypertension was 61% less likely ((AOR=0.39, 95% CI (0.17 to 0.89)) to develop perceived stigma compared with cardiac and asthma patients. The odds of developing perceived stigma among patients attending higher education were 2.15 times ((AOR=2.15, 95% CI (1.05 to 4.40)) more likely than those who cannot read and write. Furthermore, the odds of perceived stigma increased by 3.52 and 6 times (AOR=3.52, 95% CI (2.14 to 5.78), (AOR=6.1, 95% CI (2.32 to 16.07)) and was more likely among participants who had 1-2 and three hospital admissions than respondents who did not have hospital admissions, respectively (table 4).

DISCUSSION

The objective of this study was to assess the prevalence of perceived stigma and its possible association with different factors among patients with follow-ups with medical illnesses screened positive for depression at Gondar University Comprehensive Specialized Hospital. The results of this study showed that the prevalence of perceived stigma was 66.3%. This result is similar to
 Table 4
 Factors associated with perceived stigma (bivariate and multivariate) analysis at the University of Gondar

 Comprehensive Specialized Hospital, 2020

		Perceive	d stigma		
Explanatory variables		Low	High	COR (95% CI)	AOR (95% CI)
Sex	Male	59	98	1	1
	Female	68	152	1.34 (0.87 to 2.07)	1.52 (0.95 to 2.42)
Age	Below 41 years	62	88	1	1
	41 and above years	65	162	0.57 (0.37 to 0.88) *	1.60 (0.93 to 2.71)
Educational status	Cannot read and write	37	76	1	1
	Read and write	22	56	1.23 (0.66 to 2.32)	1.60 (0.79 to 3.22)
	Primary school	24	25	0.50 (0.25 to 1.00)	1.13 (0.50 to 2.54)
	Secondary school	17	31	0.88 (0.43 to 1.80)	1.83 (0.79 to 4.20)
	Higher education	27	62	1.11 (0.61 to 2.03)	2.15 (1.05 to 4.40) **
Residence	Rural	44	73	1	1
	Urban	83	177	1.28 (0.81 to 2.02)	1.11 (0.61 to 2.03)
Dx. patient followed	Diabetes mellitus	41	91	0.90 (0.44 to 1.82)	0.80 (0.37 to 1.72)
up	Hypertension	34	42	0.50 (0.23 to 1.06)	0.39 (0.17 to 0.89) **
	Epilepsy	37	80	0.87 (0.42 to 1.79)	0.79 (0.36 to 1.76)
	Asthma and cardiac	15	37	1	1
Duration of disease	<6 years	53	80	1	1
	Six and above	74	170	1.52 (0.97 to 2.36)	0.96 (0.57 to 1.61)
Duration of Rx.	Up to 5 years	62	96	1	1
	>5 years	65	154	1.53 (0.99 to 2.35)	1.11 (0.47 to 2.64)
Admission Hx	No admission	64	53	1	1
	1–2 times	51	154	3.64 (2.25 to 5.90) *	3.52 (2.14 to 5.78) **
	3 times	6	29	5.83 (2.25 to 15.11) *	6.1 (2.32 to 16.07) **
	4 and above	6	14	2.81 (1.01 to 7.84) *	2.60 (0.90 to 7.53)
Hx of stop medication	Yes	29	78	1.53 (0.93 to 2.51)	0.93 (0.52 to 1.68)
	No	98	172	1	1
Comorbid illness	Yes	22	62	1.57 (0.92 to 2.70)	1.09 (0.57 to 2.10)
	No	105	188	1	1
Family Hx of mental illness	Yes	7	26	1.99 (0.83 to 4.71)	0.96 (0.32 to 2.83)
	No	120	224	1	1
Living condition	Living alone	8	25	1.65 (0.72 to 3.78)	1.01 (0.38 to 2.71)
	Living with family	119	225	1	1
Social support	Poor	59	98	2.49 (0.67 to 3.78)	1.07 (0.22 to 5.31)
	Moderate	62	148	3.58 (0.97 to 13.13)	1.49 (0.30 to 7.24)
	Strong	6	4	1	1

AOR, adjusted OR.

the perceived stigma reported by research involving patients with schizophrenia and schizoaffective disorder in Austria. 66.9%;³⁴ a study conducted in 14 European countries. 69.4%;³² a systematic review of research carried out from 1994 to 2011 in the USA. 64.5%³⁵ and a study on patients with schizophrenia in the Czech Republic, 63.32%;³⁶ Global pattern of anticipated stigma.³⁷ The result also agrees with the findings of a workshop focusing on depressed patients in the USA¹⁰ and another study

that referred to people with schizophrenia in Ethiopia, 62.6%;.³³ However, our result is lower than those of other studies conducted in Ethiopia; one of them found the prevalence of perceived stigma to be higher than that in our work 83.5%,¹⁸ while another reported similarly higher results for epilepsy patients in Butajira, Ethiopia 81%.³⁸ The above differences in prevalence might be attributed to the varied timings of the studies as well as the differences in population and sample size.

The prevalence of perceived stigma in our study is higher compared with works conducted to explore high perceived stigma towards patients with TB in a rural community in southwest Ethiopia, 51.2%,³⁹ patients with mental illness,⁴⁰ patients with epilepsy in Ethiopia 31.2%,⁴¹ subjects with mental illness in Ethiopia,⁴² depressive patients in Ethiopia,⁴³ persons with epilepsy in Croatia 53%,⁴⁴ and those with reported chronic disease in Cambodia.⁴⁵ The varying magnitudes of these results could be attributed to the sample size differences, the different timelines of the studies, the use of different scales for assessing the levels of higher perceived stigma, the varying awareness levels for mental illness across countries and sociocultural differences among countries. For instance, the population in this study comprised only those with chronic illness having depression.

Regarding the determinant factors, participants who completed higher education were two times more likely to perceive stigma than those who cannot read and write. This finding is in line with that of a study conducted on chronically ill patients in Cambodia.⁴⁵ However, these results are inconsistent with those of a previous study conducted on patients with common mental disorders; those who reported lower education were more likely to perceive stigma.²³ Similar to a study conducted in China patients who received high school education or above had markedly higher scores in positive affect domain scores than those who received lower levels of education.⁴⁶ This is because participants who completed higher education could feel the effect of perceived stigma easily when discrimination exists rather than individuals who cannot read and write.

Patients who were followed up for hypertension were 61% less likely to develop a high perceived stigma than asthma and cardiac patients. These results are consistent with a previous study in the USA, which showed a higher stigma for those suffering from hypertension.¹⁰

The odds of developing high perceived stigma among participants with chronic illness having depression who was hospitalised once, two times or three times increased by 3.52 and 6.1 times compared with those who did not have a history of admission, respectively. These results are like the findings of other studies.^{33 36 47} The number of prior admissions showed high exposure to higher perceived stigma among chronically ill patients. This reasoning can be explained by the fact that patients with a higher number of admissions (more than one) might have been discriminated against by others due to the abnormal images associated with such subjects as well as negative attitudes of the community towards the illness. Another possible explanation for the association between perceived stigma and the number of hospitalisations is that the admitted patients could have likely harboured feelings of guilt and blamed themselves, thus leading to feelings of social isolation, compared with those with no history of hospitalisations. Another possible explanation for the association between the level of perceived stigma and the number of hospitalisations is that the more

stigmatised patients could have experienced recurrent illnesses. However, this statement could not be confirmed by the available studies. Thus, prospective observational studies are required to test the cause–effect relationships. But we measure factors like sex, age, residence, duration of disease, duration of treatment, history of stopping the medication, comorbid medical illness, which are important variables that have an effect of stigma on people with mental illness but, we did not get an association in our findings.

Strengths of the study

We used standardised instruments to measure perceived stigma. Moreover, this is the first study of its kind in Ethiopia to analyse perceived stigma among patients with the medical disease having depression.

Limitations of the study

The literature does not contain works that allow suitable comparisons and is difficult to know whether it is associated with depression or medical illness who had on follow-ups. Being on follow-up in the hospital every month or 3 months may cause and may perceive as stigmatised and increase the magnitude. Thus, we compared our findings with studies on perceived stigma for different populations. Moreover, some of the responses in the questionnaire may have been biased, and a few of the variables (eg, suicidal thoughts) were assessed with a single query.

CONCLUSION

In this study, the prevalence of high perceived stigma among patients following up with medical illness screened for depression was found to be 66.3%. Educational status, history of hospital admission, was considerably associated with higher perceived stigma. Measures are, thus, required to increase the awareness of the patients, their families and caregivers to prevent high perceived stigma. This research shows that the importance of including strategies for stigma reduction methods that increase the awareness of people with chronic medical illness comorbid with depression. Additional research with qualitative and quantitative types is necessary to explore the relationship among the determinant variables and perceived stigma.

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Contributors WGA critically reviewed the study proposal and conceived the study and was involved within the study method, reviewed the article, analysed, report writing and drafted the manuscript, and HK and SYT were participated in the study method, analysis and writing of the manuscript, EB and BE have participated in data collection and data entry. All authors see and approve the ultimate manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval Ethical approval was obtained from the Institutional Review Board of the University of Gondar with an ethical review number and grant award number (V/P/RCS//05/528/2019). All participants were given an information sheet and were exclusively enclosed within the study once providing written consent. Confidentiality was maintained by anonymous questionnaires. Those who had severe perceived stigma were brought up by a psychotherapist for further evaluation and treatment. Ethical approval was obtained from the ethical review board of the University of Gondar and the Comprehensive Specialized Hospital. A formal letter of permission was taken from the hospital and submitted to the respective outpatient department. Information about the study was provided to the participants. Verbal then written informed consent was obtained from each participant who agreed to participate in the study and fulfilled the inclusion criteria. Only anonymous data were collected in private rooms. The study was sponsored by the College of Medicine and Health Science University of Gondar RISE project with Grant number $\mathcal{P}^{\infty}C/\mathcal{U}\cdot\Omega/\lambda n/\mathcal{P}^{\nu}/T/05/2160/2012$, etc.

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Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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