Health and Quality of Life Outcomes

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The psychometric properties of the amharic version of EuroQoL five-dimensions-five level among Ethiopian cervical cancer patients

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Abstract

Background Despite being a widely used generic measure of health-related quality of life worldwide, there is limited evidence on the psychometric properties of the EuroQoL Five-dimensions five level (EQ-5D) among cervical cancer patients in Ethiopia.

Objective To evaluate psychometric properties of the Amharic version of EQ-5D among Ethiopian cervical cancer patients.

Methods A longitudinal survey of cervical cancer patients receiving treatment at two Ethiopian tertiary care facilities was conducted from March 2022 to July 2023. Participants completed the EQ-5D and the European Organization for Research and Therapy of Cancer (EORTC QLQ-C30) at baseline and after three months on treatment. Effect size and standardized response mean were used to assess responsiveness. Anchor-based and distribution-based methods were used to calculate the minimal clinically important difference (MCID). Minimal detectable change (MDC) ratios were computed at the individual and group levels. Statistical significance was determined at $p < 0.05$.

Results Three hundred seventy-one patients completed the survey at baseline and follow-up with a mean age of 49.72 (10.80) years. The majority (268,73%) of the patients had early-stage cancer. The EQ-5D index and EQ VAS scores respectively improved by 0.04 and 7.0 post-treatment.The physical domains of EORTC QLQ-C30 had showed high correlation with physical dimensions of EQ-5D ($r > 0.6$) and the instrument showed good discriminate validity between patients with different health states. The effect size ranged between −0.12 and 0.60 for the EQ-5D index value and −0.12 to 1.16 for the EQ VAS, indicating small to large responsiveness. The average (range) MCID value of the EQ-5D index was 0.10–0.15. The findings showed that MCID to MDC ratios at the group level were more clinically meaningful than the individual level.

Conclusion The EQ-5D effectively detected changes and discriminate patients with different levels of health. While group-level MCIDs were established in this study, further studies are recommended to prove its usefulness at the individual-level.

Keywords Cervical cancer, EQ-5D, Psychometric properties, HRQoL

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Introduction

Cervical cancer poses a significant global public health problem, particularly in low-and middle-income countries (LMICs) such as Ethiopia. With over 660,000 cases and 350,000 deaths annually worldwide, it ranks as the fourth most common cancer among women [1–4]. Cervical cancer is the second most common cancer type among women in Ethiopia, with an estimated 6294 new cases and more than 4000 deaths each year [5, 6]. The majority of patients in Ethiopia are diagnosed at an advanced stage, resulting in substantial decline in health-related quality of life (HRQoL), loss of productivity, and premature deaths [7].

Given the significance of the problem, expanding treatment interventions and evaluation of their success is important. Apart from objective clinical outcomes of the treatment, HRQoL has paramount importance in understanding changes in health status [8, 9]. HRQoL is a multidimensional construct comprising different health domains including physiological, psychological, and social functioning. It is affected by an individual's experiences, beliefs, expectations, and perceptions in addition to the disease conditions or treatment [10, 11]. Cervical cancer survivors have poorer HRQoL as they often experience adverse effects of the treatment for a longer period of time. This could directly affect the different domains of HRQoL measures such as physical functioning and emotional well-being [12, 13]. HRQoL in patients with cervical cancer can be quantified using generic or disease-specific instruments [14–16]. The European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) is among the most commonly used disease-specific tool in cancer survivors [17]. On the other hand, generic instruments such as SF-36 and EuroQoL 5 dimensions 5 level (EQ-5D) enable generation of a utility index that is used to calculate quality-adjusted life years (QALYs) [18].

The EQ-5D is a widely used generic measure of HRQoL that is used to measure health status across different diseases and the general population [18–24]. The EQ-5D has demonstrated good psychometric properties in previous studies that assessed its reliability, validity, and responsiveness across different population groups [21, 22, 25–30]. However, there is growing interest about its ability to discriminate small, clinically significant changes from the patient's perspective [31]. The minimal clinically important difference (MCID) and the minimal detectable change (MDC) are related to responsiveness, but they are more clinically oriented and focused at the individual level [32–34]. This change in HRQoL may reflect an improvement or deterioration from the patient side, which does not equate to meaningful changes in classical clinical outcomes [21, 35–38]. Previous studies have affirmed the small-to-moderate responsiveness of the EQ-5D in patients with chronic diseases [28, 39–41]. A study conducted by Hu et al. among patients with cervical cancer showed that the MCID for EQ-5D index and EQ VAS scores were 0.039 and 5.35, respectively [21]. Similarly, the estimated MCID of the index score was 0.0917 in a study of elderly patients with hypertension in Hong Kong [42]. All these studies illustrate the usability of EQ-5D in clinical settings to measure the MCID and MDC from patient's perspective. However, there is paucity of evidence on the EQ-5D responsiveness, MCID, and the relationship between MCID and MDC, particularly in the Ethiopian context. Hence, the current study aimed to assess the validity, and responsiveness of EQ-5D among Ethiopian cervical cancer patients. It also aimed to estimate the MCID of EQ-5D, and the relationship between MCID and MDC. The findings of this study could help to enhance the interpretability and clinical application of EQ-5D in measuring the effectiveness of treatment in routine clinical settings.

Methods

Study setting and design

A longitudinal study was conducted from March 2022 to July 2023 at two tertiary hospitals in Ethiopia: Tikur Anbessa Specialized Hospital (TASH) and Saint Paul's Hospital Millennium Medical College (SPHMMC). TASH is the largest tertiary care teaching hospital in the country with over 600 beds and serves over 800,000 patients per year. Besides, TASH is the largest referral clinical oncology center in the country rendering care to over 60,000 cancer patients annually. Likewise, SPHMMC is the second largest tertiary hospital in the country with 350 beds, and serves an average of 300,000 patients annually.

Patient recruitment and data collection procedure

All patients with cervical cancer who visited the study hospitals for oncology services comprised the source population while those who fulfilled the eligibility criteria during the data collection period comprised the study population. The sample size was estimated based on the single population proportion formula [43], considering a Z-value of 1.96 with a 95% level of confidence and a 5% margin of error with 10% contingency for attrition during the follow-up. Accordingly, 422 patients with cervical cancer were recruited consecutively from the two hospitals. All those who fulfilled the eligibility criteria were approached through face-to-face interview when they were admitted and 3 months post-treatment. The inclusion criteria were: [1] a newly confirmed diagnosis of cervical cancer; and [2] aged > 18 years. The exclusion criteria were: [1] a patient who already started treatment during data collection; [2] unwilling to provide

informed consent; and [3] with mental illness or cognitive impairment.

Before data collection, four nurses were trained on the purpose of the study, the EQ-5D instrument, other data collection tools, and how to conduct a face-to-face interview to maintain uniformity. The interviewer read the EQ-5D questions out loud to the patient and enter the response. Information on sociodemographic characteristics (age, marital status, age at marriage, number of children, occupational status, medical insurance status, household income, level of education, alcohol habit, smoking status, and chat habit) and medical record review was undertaken to gather information on clinical characteristics (diagnosis, comorbidity, cancer stage, treatment taken). The Amharic version of the interviewer administered EQ-5D, EORTC QLQ-C30, and Eastern Cooperative Oncology Group (ECOG) performance status were used to measure change in the health status of patients.

Instruments

EQ-5D

The tool has two parts: health state description and EQ VAS. For the description component, patients were asked to select the statement most reflective of their health state in the descriptive system that has five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) [23]. Under each dimension, there are five levels (no problem, slight problem, moderate problem, severe problem, and extreme problem), which represent the severity of problems. Following assessment, the scores from the descriptive component can be reported as a five-digit number ranging from 11,111 (perfect health) to 55,555 (worst health). To obtain EQ-5D index value, we used the Ethiopian value sets which ranged from −0.718 (representing the worst possible health state) to 1.0 (representing full health) [44]. Patients were asked to rate their present general health status using a visual analogue scale (EQ VAS). Each interviewee self-rated his/her health status on a vertical scale that ranges from zero (the worst health one can imagine) to 100 (the best health one can imagine) [44–46].

EORTC-QLQ-C30

It has 30 items that can be computed into multi-item scales and single-item measures. All items except for those referring to global health status have four response levels; the global health status items have seven. The scores are categorized to five functional (physical, role, cognitive, emotional, and social) and three symptom (fatigue, pain, and nausea/vomiting) domains, a global health status scale and a number of single items to assess symptoms (dyspnea, loss of appetite, sleep disturbances, constipation, and diarrhea) and perceived financial impact of the disease. Each functional scale is transformed to 0 to 100 where a higher scale score represents a higher level of functioning and therefore better HRQoL. The higher symptom scores represent a higher level of symptom, which in turn reflects poorer HRQoL [47, 48].

ECOG performance status

ECOG performance status was used to assess patients' disease progression and level of functioning on a scale of 0 (fully active) to 5 (dead). The levels 1,2,3, and 4 respectively indicate that the patient is restricted in physically strenuous activity, ambulatory and capable of all self-care, limited self-care and completely disabled [49].

Statistical analyses

Descriptive statistics (mean, standard deviation, median, interquartile range, and frequency) were used to describe the socio-demographic and clinical characteristics of the patients. The pre- and post-treatment EQ-5D index and EQ VAS scores were compared using the Wilcoxon signed-rank test as both were non-normally distributed (Shapiro–Wilk test < 0.05). We examined the convergent validity of the EQ-5D dimensions, EQ-5D index, and EQ VAS scores with the EORTC-QLQ-C30 dimensions using the Spearman correlation coefficient. It was hypothesized that physical domains EQ-5D (mobility, usual activity, and self-care) measuring the same construct and strongly correlated with EORTC-QLQ-C30 subscales. Similarly the anxiety/depression domain of the EQ-5D was assumed correlated with emotional functioning dimension of the EORTC-QLQ-C30.Therefore, a correlation coefficient between 0.1 and 0.29 was considered as weak, 0.30–0.49 as moderate, and above 0.5 as good [50]. For discriminate validity, the Kruskal Wallis U test was used to identify the varied health status of patients among patient subgroups based on cancer stage, ECOG performance status, age category, and treatment modality. Pre-treatment data was used to assess the discriminative ability and the convergent validity of the tool.

Responsiveness

The mean scores of the EQ-5D index and EQ VAS scores between baseline and 3 months post-treatment were compared using the Wilcoxon signed-rank test for each patient subgroup. To assess responsiveness, global health subscale of the EORTC-QLQ-C30 was used as an anchor to classify subgroups for clinical change (i.e. no change). Based on this, the health status of the patients was categorized into three: no change, improved, and worsened. The responsiveness of the EQ-5D and EQ VAS scores was evaluated by effect size (ES) and standardized response mean (SRM) between the pre-treatment and 3 months post-treatment. According to Cohen's d criteria, the ES

and SRM values were categorized into small (0.2 to 0.5), moderate (0.5 to 0.8), and large (≥0.8) [27, 51–53]. The reported increase in EQ-5D index and EQ VAS scores reflects the median difference observed between baseline and 3 months post-treatment and the Wilcoxon rank-sum test was used to determine statistical significance.

MCID

It is generally considered good practice to estimate the MCID using multiple approaches. In this regard, distribution-based, anchor-based, and instrument-defined methods are commonly used methods to estimate MCID [54, 55]. In our study, we used distribution-based and anchor-based methods to estimate the MCID of EQ-5D and EQ VAS scores. In the distribution-based method, the 0.5 SD for the baseline score and one-SEM were considered to approximate values of MCID [21, 28]. Therefore, we calculated 0.5 SD of the EQ-5D index and EQ VAS scores at baseline. Additionally, the one-SEM was calculated using the following formula: $SEM = SD\sqrt{(1-\mathrm{r})}$, where r is the test-retest reliability of the pre-treatment. The one-SEM was computed for no change, improve and worsen. The mean was calculated to provide an MCID estimate of both EQ-5D and EQ VAS scores.

For anchor-based method, we used global health status of domain of the EORTC-QLQ-C30 as the external criteria to anchor minimal but important change scores for the patients. Correlation ≥0.3 can be used as a threshold to assess the usefulness of the anchor [28]. The EORTC-QLQ-C30 global health subscale was selected as an anchor because it represents meaningful changes in patient health status not merely because it correlates with changes in the EQ-5D scores [56]. Therefore, Spearman's correlation coefficient was used to quantify the association between changes in the EQ-5D index score, EQ VAS, and global health status score of the EORTC-QLQ-C30 domain. We used the 0.5 SD of the anchor score at baseline as the lower cut-off for minimal change. The upper cut-off was set to be twice the value found at the 0.5 SD of the anchor score. We categorized the patients into five groups according to the change scores of the anchor: no change (<0.5 baseline SD), minimal improvement and deterioration (≥0.5 baseline SD and ≤1 baseline SD), and large improvement and deterioration (>1 baseline SD). To obtain the MCID for each group, the EQ-5D index and EQ VAS scores were subtracted from no change group and the average MCID estimation was calculated. For instance, the MCID for the improvement group was calculated by subtracting the score from the average change score for the no change group.

A receiver operating characteristic (ROC) curve was constructed to estimate the MCID in this study, and the area under the curve (AUC) was used to represent the ability of the instrument to distinguish patients who underwent a clinically meaningful change. The Youden index was calculated to determine MCID estimates with the highest sensitivity and specificity. The cut-off point corresponding to the maximum Youden index was the optimal cut-off value of the ROC curve and was the MCID.

MDC

To calculate the MDC after considering the measurement error and random variation using the following formula: $MDC = SEM * Z - score * \sqrt{2}$. A 95% confidence level was established, corresponding to a z-value of 1.96. This was considered the $MDC_{95\%(individual)}$, representing the smallest detectable change that is not due to measurement error or random variation. We used the same approach to calculate the MDC in a group of people ($MDC_{95\%group}$), by dividing the $MDC_{95\%individual}$ by $\sqrt{\mathrm{n}}$, where n is the sample size of the study. Finally, we compared the resulting MCID with the MDC at the individual and group levels, dividing the MCID by the MDC. If the ratio of MCID to MDC >1, the estimated MCID reflects the real minimal important change of health state among the patients and if the calculated MCID is below 1, it will represent the MCID is owning to measurement error of the questionnaire and is not a valid value.

Results

Participant characteristics

Four hundred twenty-two patients with cervical cancer were participated at the baseline. Of those patients, forty-six patients died during the follow-up time and five patients were lost to follow-up. Therefore, 371 patients who had completed data at both time points were included in the final analysis with mean (SD) age of 49.72 (10.80) years where most of them were married (277, 75%), lack formal education (225, 60.6%), unemployed (322, 86.8%), and resided outside Addis Ababa, the capital city (235,63.3%). Nearly three fourth (268, 73%) of the patients had early-stage tumor (stage I and stage II), and the majority of patients had taken surgery alone (127,34%). A total of 115 patients (31.0%) reported having comorbidities among which HIV/AIDS (67, 58.3%) accounted the largest proportion of comorbidity. Most of the patients (80%) had good performance status. Additionally, 39.4% of the patients reported an improved health status while 38% reported worsen health status post-treatment the various anticancer treatment modalities. Furthermore, n (22.6%) of the patients reported no change in their health status. The sociodemographic and clinical characteristics of the patients are depicted in Table 1.

Table 1 Sociodemographic and clinical characteristics for the pre-treatment

Characteristics	All (*n* = 371) *N* (%) or Median (IQR)	No change (*n* = 84) *N* (%) or Median (IQR)	Improved (*n* = 146) *N* (%) or Median (IQR)	Worsen (*n* = 141) *N* (%) or Median (IQR)
Age at diagnosis, mean (SD)	49.72 (10.80)	50 (40, 56)	50 (43, 57)	50 (43, 57)
Hospital				
TASH	168 (45)	52 (62)	106 (63)	30 (21)
SPMMC	203 (55)	32 (38)	40 (27)	111 (79)
Age at first marriage	18 (16, 20)	18 (16, 20)	18 (16, 20)	20 (16, 22)
Number of children	4 (3, 7)	4 (2, 6)	5 (2, 7)	4 (2, 6)
Level of educational				
Unable to read and write	157 (42.3)	34 (40.5)	77 (52.7)	46 (32.6)
Able to read and write	68 (18.3)	17 (20.2)	25 (17.3)	26 (18.4)
Primary school	86 (23.2)	19 (22.6)	31 (21.2)	36 (25.5)
Secondary school	45 (12.1)	11 (13.2)	11 (7.5)	23 (16.3)
Higher education	15 (4.1)	3 (3.50)	2 (1.4)	10 (7.1)
Marital status				
Single	8 (2.2)	4 (4.8)	2 (1.4)	2 (1.4)
Married	277 (74.7)	60 (71)	101 (69)	116 (82)
Divorced	36 (9.7)	8 (9.5)	24 (16)	9 (6.4)
Widowed	50 (13.4)	12 (14)		14 (9.9)
Employment status				
Employed	49 (13.2)	12 (14)	14 (9.6)	23 (16.3)
Unemployed	322 (86.8)	72 (86)	132 (90.4)	118 (83.7)
Place of residence				
Addis Ababa	136 (36.7)	26 (31)	47 (32.2)	63 (44.7)
Out of Addis Ababa	235 (63.3)	58 (69)	99 (76.8)	78 (55.3)
Monthly household income	2000 (1000–3000)	2000 (1000–3000)	2000 (1000–4000)	2000 (1500–3000)
Insurance type				
Not used	124 (33)	29 (35)	39 (26.7)	56 (39.7)
Private insurance	104 (28)	28 (33)	19 (13)	57 (40.4)
CBHI	143 (38)	27 (32)	87 (59.6)	28 (19.9)
Time since diagnosis	4 (3,7)	4 (3, 6)	4 (3, 8)	5 (3, 8)
Tumor stage				
Not staged	3 (0.8)		3 (2.1)	
Stage I	110 (29.6)	31 (37)	29 (20)	50 (35)
Stage II	158 (42.6)	28 (33)	64 (44)	66 (47)
Stage III	65 (17.5)	13 (15)	38 (26)	14 (9.9)
Stage IV	35 (9.4)	12 (14)	12 (8.2)	11 (7.8)
Treatment modalities				
Not take treatment	6 (1.6)			
Surgery alone	127 (34)	34 (40)	2 (1.4)	57 (40.7)
Chemotherapy	29 (7.8)	8 (9.5)	24 (16)	19 (13)
Radiotherapy	48 (13)	11 (13)	52 (36)	13 (9.2)
Chemoradiation	93 (25)	19 (23)		22 (16)
Surgery + adjuvant chemoradiation	5 (1.4)	-	-	4 (2.8)
Surgery + chemotherapy	69 (18. 6)	11 (13)	31 (21.7)	26 (18)
Chemotherapy regimen				
Carboplatin + Paclitaxel	65 (18)	15 (18)	34 (23)	16 (11)
Cisplatin + Paclitaxel	53 (14)	10 (12)	26 (18)	17 (12)
Chemotherapy cycle				
Cycle 1	143 (38)	32 (38)	62 (42)	47 (33)
Cycle 2	1 (0.3)			
Cycle 3	8 (2.2)	2 (2.4)	6 (4.1)	
Cycle 6	2 (0.5)		1 (0.7)	1 (0.7)
Comorbidity				

Table 1 (continued)

Characteristics	All (*n* = 371) *N* (%) or Median (IQR)	No change (*n* = 84) *N* (%) or Median (IQR)	Improved (*n* = 146) *N* (%) or Median (IQR)	Worsen (*n* = 141) *N* (%) or Median (IQR)
No	249 (67.1)	53 (63)	100 (68)	97 (69)
Yes	122 (32.9)	31 (37)		44 (31)
Type of comorbidity				
HTN	30 (8.1)	8 (9.5)	10 (6.8)	12 (8.5)
HIV/AIDS	67 (18.1)	18 (21)	24 (16)	25 (18)
Diabetes	5 (1.3)	1 (1.2)	3 (2.1)	2 (1.4)
Diabetes + HTN	5 (1.3)	1 (1.2)	3 (2.1)	-
HIV/AIDS + HTN	15 (12.5)	3 (3.6)	3 (2.1)	2 (1.4)
Number of comorbidities				
1	105 (28.3)	25 (30)	40 (27)	
2	14 (3.8)	5 (6.0)	5 (3.4)	40 (28)
4	3 (0.9)	1 (1.2)		4 (2.8)
ECOG-performance				
1	298 (80)	66 (79)	112 (77)	120 (85)
2	67 (18)	17 (20)	30 (21)	20 (14)
3	2 (0.5)	1 (1.2)	1 (0.7)	
Cigarette smoking				
No	371 (100)	84 (100)	146 (100)	141 (100)
Yes	-	-	-	
Alcohol habit				
No	363 (97.8)	83 (99)	140 (95.9)	140 (99.3)
Yes	8 (2.2)	1 (1)	6 (4.1)	1 (0.7)
Chat chewing habit				
No	366 (98.7)	84 (100)	142 (97.3)	140 (99.3)
Yes	5 (1.3)		4(2.7)	1 (0.7)

CBHI: Community based health insurance; *ECOG*: Eastern Cooperative Oncology Group; *HTN*: Hypertension; *SPMMC*: Saint Paul's Millennium Medical College; *TASH*: Tikur Anbessa Specialized Hospital

Convergent validity

Baseline data was used to calculate correlations between the dimensions of EORTC-QLQ-C30 and the EQ-5D index and EQ VAS scores. The physical, role, and emotional functioning dimensions of EORTC-QLQ-C30 had strong correlations with the mobility, usual activities and pain/dimensions of EQ-5D. Similarly, role functioning had high correlation with EQ-5D index (r=0.70) and EQ VAS score (r=0.64). The emotional domain of EORTC-QLQ-C30 was found to be moderate to strongly correlated with all EQ-5D dimensions, index and EQ VAS scores (Table 2).

Discriminate validity

It was found that the patients' health status decreased with an increase in disease severity and there were statistically significant differences in both EQ-5D index and EQ VAS scores based on tumor stage. On the other hand, patients with ECOG performance-I had better index score (0.91) than ECOG performance-III (0.38). Similarly, the EQ VAS score for patients with ECOG performance-III had significantly lower score (42.5; p-value < 0.01) than their counterpart. Overall, it was shown that both the index and EQ VAS scores were significantly different for different health status among the various treatment modalities (Table 3).

Responsiveness

The EQ-5D index and EQ VAS scores reflects the median difference observed between baseline and post-treatment. The paired-sample Wilcoxon rank test showed the EQ-5D index increased by 0.04 and EQ VAS score by 7.0 after three months of treatment (p < 0.001), indicating the tool was able to capture observed changes from the patient's point of view. After three months of treatment, 84 patients reported no change in total global health EORTC-30 score, 141 patients reported deterioration and 146 reported improvements on global health. It was found that only the EQ-5D index score moved in the expected direction corresponding with by, indicating worsen (deterioration) in the subgroups reporting deterioration on global health of the EORTC-QLQ-C-30 and positive changes (improvements) in the subgroups reporting improvements on global health. Nevertheless, only a minor change of EQ-5D index scores and EQ VAS were reported in the no change subgroup of

Table 2 Discriminatory validity of the EQ-5D index and EQ VAS scores with patient characteristics

Characteristics	EQ-5D index score				EQ VAS		
	N	Median (IQR)	Mean Rank	*p*-value	Median (IQR)	Mean Rank	*p*-value
Tumor stage							
Stage 1	110	0.91 (0.11)	236.0	**0.001**	80 (11.3)	249.6	**0.001**
Stage 2	158	0.88 (0.10)	180.6		65 (15.0)	177.4	
Stage 3	65	0.82 (0.37)	132.0		60 (20.0)	122.2	
Stage 4	35	0.81 (0.39)	138.1		55 (30.0)	127.8	
ECOG performance							
1	298	0.91 (0.10)	194.1	**0.001**	70 (20.0)	200.0	**0.001**
2	67	0.86 (0.26)	151.4		60 (20.0)	126.3	
3	4	0.38 (0.67)	69.3		42.5 (53.0)	49.80	
Age categories							
Less than 35	27	0.91 (0.14)	210.6	0.456	70 (10.0)	228.3	**0.001**
35–60	296	0.89 (0.13)	183.8		70 (20.0)	191.5	
Greater than 60	48	0.88 (0.13)	185.4		60 (20.0)	128.5	
Treatment modalities							
Surgery alone	127	0.91 (0.09)	227.5	**0.001**	80 (25.0)	243.6	**0.001**
Chemotherapy	29	0.91 (0.11)	205.8		65 (20.0)	186.0	
Radiotherapy	48	0.85 (0.31)	147.9		60 (23.8)	135.8	
Chemoradiation	93	0.85 (0.33)	149.5		60 (20.0)	136.5	
Surgery + chemotherapy	69	0.86 (0.09)	181.4		70 (10.0)	185.2	

ECOG: Eastern Cooperative Oncology Group; **IQR**: Interquartile range;

Table 3 Correlations of EQ-5D dimensions, index, and VAS scores with EORTC QLQ-C30 domain scores

EORTC QLQ- C-30	Pre-treatment						
	MO	SC	UA	PD	AD	EQ VAS	EQ-5D index
Physical functioning	-0.60	-0.48	-0.71	-0.63	-0.36	0.64	0.70
Role functioning	-0.61	-0.49	-0.68	-0.53	-0.34	0.58	0.64
Emotional functioning	-0.30	-0.23	-0.37	-0.35	-0.64	0.36	0.58
Cognitive functioning	-0.40	-0.29	-0.46	-0.32	-0.25	0.42	0.44
Social functioning	-0.33	-0.22	-0.38	-0.36	-0.31	0.36	0.45
Pain	0.48	0.36	0.53	0.63	0.44	-0.59	-0.66
Fatigue	0.44	0.35	0.53	0.60	0.46	-0.58	-0.66
Global health status/QoL	-0.31	-0.10	-0.26	-0.36	-0.37	0.51	0.42

MO: Mobility; **SC**: Self-care; **UA**: Usual activities; **PA**: Pain/Discomfort; **AD**: Anxiety/Depression; all statistically significant correlation; **QoL**: Quality of life

Table 4 Responsiveness of EQ-5D index and EQ VAS post treatment of cervical cancer

	EQ-5D index score				EQ VAS score			
	All (*n* = 371)	No change (*n* = 84)	Improvement (*n* = 146)	Worsen (*n* = 141)	All (*n* = 371)	No change (*n* = 84)	Improvement (*n* = 146)	Worsen (*n* = 141)
Pre-treatment score	0.81	0.86	0.72	0.89	65.31	68.5	59.5	69.6
Post-treatment score	0.85	0.86	0.89	0.82	72.31	73.5	75.8	67.9
Change in score	0.04	0.005	0.17	-0.07	7.00	5.02	16.39	-1.67
ES	0.20	0.03	0.60	-0.53	0.50	0.37	1.16	-0.12
SRM	0.16	0.03	0.59	-0.30	0.40	0.50	1.21	-0.12

the EORTC QLQ-C30. Our study revealed that the ES of EQ-5D index was 0.2, indicating small responsiveness in all patients. Among patients who responded to the anchor transition as "improvement" (including minimal improvement and much improvement), the ES and SRM were 0.60 and 0.59, respectively, suggesting a large responsiveness. The ES and SRM for worsen health status were 0.53 and 0.30, indicating moderate responsiveness. The ES and SRM showed no responsiveness among the no change group of EQ-5D index. Our study demonstrated that the ES and SRM were moderate to large for EQ VAS with the exception of the "worsen" health status (Table 4).

Table 5 Anchor-based MCID estimates

	EQ-5D index				EQ VAS			
Subgroups	**T0**	**T1**	**Change (SD)**	**MCID**	**T0**	**T1**	**Change (SD)**	**MCID**
No change ($n=84$)	0.86 (0.18)	0.86 (0.17)	0		68.51 (13.55)	73.54 (12.43)	5.02 (10.08)	
Small improvement ($n=84$)	0.76 (0.25)	0.88 (0.11)	0.12 (0.24)	0.02	62.80 (14.38)	75.98 (10.87)	13.18 (13.77)	2.44
Large improvement ($n=62$)	0.67 (0.32)	0.89 (0.09)	0.22 (0.31)	0.03	54.92 (12.53)	75.56 (9.76)	20.65 (12.06)	2.02
Small deterioration ($n=103$)	0.88 (0.11)	0.84 (0.16)	-0.04 (0.16)	0.02	67.52 (14.92)	68.16 (11.75)	0.63 (13.15)	5.38
Large deterioration ($n=38$)	0.89 (0.17)	0.77 (0.33)	-0.12 (0.34)	0.09	75.26 (10.39)	67.37 (15.32)	-7.89 (12.23)	6.17
Average MCID				**0.04**				**4.00**
MCID/MDC ratio								
Individual				0.095				0.191
Group				1.81				3.70

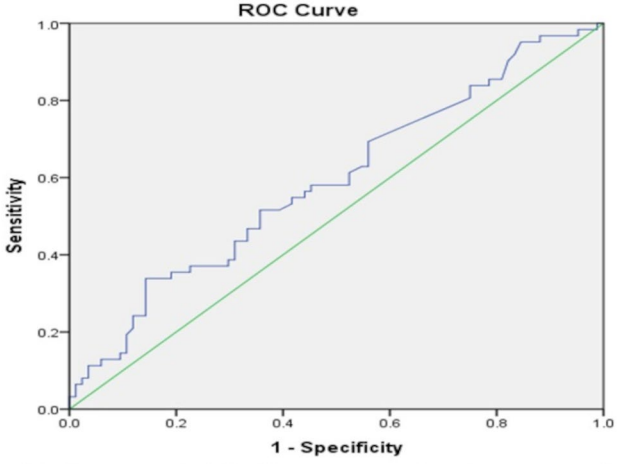

Fig. 1 ROC curve of the EQ-5D-5 L change score in patients whose health states improved from the baseline based on the anchor

MCID and MDC estimation

The MCID range of the EQ-5D index score obtained by the distribution-based method were 0.10 using half the SD of the anchor at baseline and 0.15 derived from the SEM value was 0.15 for the EQ-5D index score. Likewise, the MCID range of EQ VAS was 4.01 for 0.5SD and 7.56 for SEM, respectively. The MCID of EQ-5D index and EQ VAS was estimated based on the global health status of the EORTC-QLQ-C30. The minimal important change for patients with cervical patients ranges from 0.02 to 0.09 for EQ-5D index value while for EQ VAS it ranges from 2.02 to 6.17, respectively. The average MCID estimated by the anchor-based method had an EQ-5D index value of 0.04 and EQ VAS of 4.0 (Table 5). Receiver operating characteristic analysis was also performed to identify improved MCID only (Fig. 1). The MCID estimate derived from the ROC curve was 0.20, corresponding to a sensitivity of 34% and a specificity of 86%. The AUC anchored by the global health of EORTC-QLQ-C30 scale was 0.59 (95% CI: 0.50, 0.68), suggesting that EQ-5D can distinguish patients whose health states improved and those whose health states did not change.

MDC

Our study demonstrated that the EQ-5D index value and EQ VAS had $MDC_{95\%(individual)}$ of 0.064 and 16.44, and $MDC_{95\%(group)}$ of 0.42 and 20.95, respectively. The ratios of MCID to $MDC_{95\%(individual)}$ of index value and EQ VAS were all less than one. This illustrated that MCID cannot discriminate the score change of the EQ5D from the measurement error at the individual level. On the other hand, the ratios of MCID to $MDC_{95\%(group)}$ for EQ-5D index and EQ VAS scores were greater (Table 6).

Discussion

This longitudinal study established the psychometric properties of the EQ-5D instrument among patients with cervical cancer in Ethiopia. The study demonstrated

Table 6 MCID based on distribution-based method for EQ-5D index and EQ VAS scores

	EQ-5D index			EQ VAS score		
	Baseline SD	**0.5 SD**	**SEM**	**Baseline SD**	**0.5 SD**	**SEM**
No change	0.1772	0.089	0.13	12.43	6.22	8.80
Improved	0.2832	0.135	0.18	10.40	5.20	8.02
Worsen	0.1273	0.064	0.13	14.23	0.615	5.85
Mean MCID	-	**0.10**	**0.15**	**-**	**4.01**	**7.56**
$MDC_{95\%\ (individual)}$			0.42			20.95
$MDC_{95\%\ (group)}$			0.022			1.08
MCID/MDC ratio						
Individual		0.24	0.36		0.19	0.36
Group		4.55	6.82		3.71	7.0

that the instrument could distinguish small to moderate changes over time and detect both improvements and deteriorations in health status among patient subgroups. While the estimated MCID in this study detected significant changes in the scores at the group level, individual level changes were not identified.

This helped to demonstrate the usefulness of EQ-5D to measure HRQoL in patients with cervical cancer. Consistent with the findings of other studies, our study showed a moderate to high correlation between EORTC-QLQ-C30 subscales and EQ-5D dimensions, index, and EQ VAS scores [57]. Physical and role functioning dimensions of the EORTC-QLQ-C30 had good to excellent concurrent validity with index, mobility, usual activities, pain/discomfort, and EQ-VAS, indicating that the two tools measure the same construct [58]. Furthermore, it had a fair correlation between the cognitive and social functioning of EORTC-QLQ-C30 subscales, indicating that the EQ-5D emphasizes the general HRQoL whereas the EORTC-QLQ-C30 subscales focus on broad dimensions of disease-specific patient-reported outcome measures.

The EQ-5D index and EQ-VAS scores were high for patients with high ECOG performance status as well as for early-stage cancer. This indicates the discriminate ability of the instrument based on the different patient characteristics where patients with better performance and early cancer stage patients had perceived better health status [58]. These results indicated that EQ-5D is a valid measurement tool that can be applied to characterize HRQoL of patients based on the patient subgroups. This provides inputs for robust economic evaluations of interventions to improve the care of cervical cancer patients in the Ethiopian context.

Responsiveness has been suggested as an additional criterion for evaluating HRQoL instruments, which can reflect the ability of an instrument to respond to changes over time. In the current study, the Wilcoxon rank test showed significantly better post-treatment EQ-5D index and EQ-VAS scores of 0.04 and 7.0 compared to the baseline. According to Cohen's benchmarks for ES and SRM, the EQ-5D index and EQ-VAS scores showed small to moderate responsiveness [52]. In addition, this study illustrated relatively high changes in subgroups of patients with improvement and worsening on the EQ-5D index. This is in line with similar studies from other countries that reported moderate to high level of level of responsiveness [21, 28, 57, 59]. Therefore, we can be confident that post-treatment changes in HRQoL can reliably be evaluated by the change in the EQ-5D scores.

The MCID values calculated by the distribution-based method, the mean 0.5SD and SEM for index values were 0.10 and 0.15 while for EQ VAS scores were 4.0 and 7.56. Based on the distribution and anchor-based approaches, the MCID values ranged from 0.04 to 0.15 for index value and 4 to 7.56 on the EQ VAS. Our finding is in line with other studies that documented that EQ-5D can detect the minimal important meaningful change changes among patients [21, 22]. These highlight that the minimal change in scores were a result of changes in health status rather than measurement error and random variations. This indicates that the instrument is likely to detect a clinically important change. However, MCID of both index and EQ VAS values of EQ-5D was not able to detect the minimal change in health at the individual level at the 95% confidence level. This could possibly be because of the inclusion of patients with varied characteristics. Another possible explanation may be that, although we only included first-diagnosed patients, the HRQoL scores at baseline of some patients with a longer disease duration may have improved compared to those more recently diagnosed, resulting in the baseline score of the entire sample being raised. Consequently, future studies should be conducted among homogenous populations to examine whether the instrument can able to detect small meaningful changes.

The use of disease-specific questionnaire as an anchor to estimate the responsiveness and estimation of MCID using distribution, anchor-based, and instrument-defined methods were the major strengths of this study. However, this study followed patients for only three months and some were still on treatment. This could have influenced the ability of the study to establish MDC. Another limitation of our findings is that we have excluded 46 patients who died and 5 lost to follow-up from baseline analyses could introduced bias and affect responsiveness and MCID. As such, future evaluations should consider measurements after treatment completion to investigate whether the tool identified the MDC at the individual level. The responsiveness and MCID may differ depending on the research setting, including interventions and patients' characteristics. Therefore, the results of this study may not be applicable to other diseases.

Conclusion

Our findings demonstrated that the EQ-5D has a good psychometric propertiesy among patients with cervical cancer in Ethiopia. The EQ-5D instrument was able to detect changes in health and discriminate between patients with different levels of health. Furthermore, the study demonstrated that the instrument could distinguish small to moderate changes over time and detect both improvements and deteriorations in health status among patient subgroups. While group-level MCID were established in this study, further studies need to be done to prove its usefulness at the individual-level.

Abbreviations

ECOG-PS	European Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of life Questionnaires version 30
EQ-5D-5L	EuroQoL five-dimensional five-level instrument
HRQoL	Health-Related Quality of Life
MCID	Minimal clinically important difference
MDC	Minimal detectable change

Author contributions
GTG, GBG, AGW, and EEA: conceived the research idea, designed the research method, and wrote the proposal GTG, WT, BG, AM, and EEA: oversaw the patient recruitment and data collection process GTG, GBG, and AGW: performed data analysis and interpretation GTG : drafted the manuscript EEA, GBG, WT, AB, BG, AM,AG and EEA: reviewed and edited the manuscript. All authors critically evaluated the final manuscript for important intellectual content and approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Ethics Review Board of the School of Pharmacy, Addis Ababa University (Ref. No.: ERB/SOP/405/14/2022) and permission was received from the study hospital. Written informed consent was obtained from patients. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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