

The Impact of AC and AC-T Chemotherapy's Toxicities on Quality of Life Among Women with Breast Cancer in Ethiopia: A Prospective Patient-Reported Outcomes Study

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Purpose: The study aimed to evaluate the quality of life patterns and the effects of AC and AC-T chemotherapy's toxicities on QoL among Ethiopian women with breast cancer.

Methods: QoL was measured at baseline and at every end of two cycles, for the median of 8 cycles among 146 breast cancer women on AC and AC-T chemotherapy, using EORTC QLQ-C30 and BR23 instruments. The effect of QoL score, socio-demographic, and clinical variables at baseline were adjusted for the effect of chemotherapy's toxicities on QoL.

Results: Overall QoL, all functional scales (except cognitive functioning, body image, future perspectives, and sexual functioning) and symptom scales (except dyspnea, insomnia, pain score, arm, and breast symptoms) of EORTC QLQ-C30 and BR23 deteriorated significantly both clinically and statistically, in particular, during the first two cycles of chemotherapy. After the end of cycle 2 or 4, except for cognitive, social functioning, and financial difficulties of the patients, almost all other QoL dimensions were improved towards pretreatment score by the end of cycle 8. In addition to age, educational status, and tumor stage, the Global Health Status ($-10.55 \leq B \leq -7.71$, $P \leq 0.013$), and the functional scales ($-25.320 \leq B \leq -6.351$, $P \leq 0.033$) of EORTC QLQ-C30 and BR23 were significantly affected at least by one of the AC and AC-T chemotherapy's toxicity such as grade ≥ 2 fatigue, dysgeusia, constipation, dry mouth, vomiting, oral mucositis, skin hyperpigmentation and/or peripheral neuropathy than their lower grade. Grade ≥ 2 fatigue, dysgeusia, oral mucositis, constipation, peripheral neuropathy, anemia arthralgia/myalgia, dry mouth, diarrhea, constipation, and/or skin hyperpigmentation were positively predicted for the deterioration of symptoms scale of EORTC QLQ-C30 and BR23 ($4.819 \leq B \leq 26.451$, $P \leq 0.043$).

Conclusion: Quality of life among Ethiopian breast cancer patients on AC and AC-T regimens significantly deteriorated particularly during the first two cycles of chemotherapy. In addition to the age, tumor stage and educational status of the patients, grade ≥ 2 fatigue, dysgeusia, constipation, oral mucositis, dry mouth, peripheral neuropathy, and skin hyperpigmentation due to AC and AC-T chemotherapy were frequently associated with deterioration of different scales/items QoL. Hence, devising different strategies to improve the deteriorated QoL due to chemotherapy's toxicities particularly during the first two cycles has paramount importance.

Keywords: quality of life, deterioration, chemotherapy, toxicity, breast cancer, Ethiopia

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Introduction

In the era of an increasing number of breast cancer patients worldwide and the longer survival due to early detection programs and advancement in medical

technology, accurately assessing the quality of life (QoL) of breast cancer patients is becoming crucial.^{1,2} As such, there is a need to understand the impact of breast cancer treatment on quality of life (QoL) to help breast cancer patients cope with cancer and its treatment.³ It is due to the quality of life is frequently deteriorated during and after cancer chemotherapy, though the expected treatment outcome in chronic diseases like cancer is the improvement of quality of life.^{4,5}

Patient-reported outcomes measures (PROMs), especially QoL instruments, have increasingly been collected in randomized controlled trials (RCTs) to inform patient-centered care, clinical decision-making, and health policy or reimbursement decisions.^{6,7} QoL is increasingly being recognized as a valuable endpoint of cancer care for its prognostic value in clinical trials^{8,9} to serve as an endpoint, complementing traditional assessment measures, eg tumor response, freedom from relapse, survival, and the physician's opinion concerning patient status.^{10–13}

Breast cancer is probably the most feared by women, especially by the negative stigma and psychological distress brought by its diagnosis and treatments which eventually led them to reduced QoL.¹⁴ In addition to the disease itself, other socio-demographic characteristics like age, residence, educational level, employment status, and TNM stage were among the significant predictors for deterioration of QoL.⁸

Breast cancer chemotherapy has been known to cause deterioration of quality of life (QoL)^{15–17} as the greater treatment-related burden was associated with poorer QoL.¹⁸ That is why the impact of chemotherapy's toxicities on quality of life and patients' preferences gain particular relevance.^{10,19}

QoL assessment in women with breast cancer on therapy should address physical symptoms such as nausea, vomiting, fatigue (tiredness and pain), hair loss, functional ability, sexuality (intimacy and body perception), emotional symptoms such as worry (anxiety, depression, and insecurity); social function, work-life, family situation, hope for the future, future planning, spiritual aspects, and total QoL assessment, ie general life satisfaction.¹¹

More attention should be paid to improve patients' QoL through dealing with the particular impaired function or symptom.⁸ Unfortunately, evaluation of the impact of treatment modalities on QoL in patients with cancer is very limited.²⁰ In general, the AC and/or AC-T breast cancer chemotherapy poses physical, emotional, and financial burdens on the patients and families.²¹ Henceforth, it

affects almost all domains of quality of life to a greater or lesser degree.²² Hence, the present study aims to evaluate the quality of life patterns and the effects of AC and AC-T chemotherapy's toxicities on different domains of QoL among Ethiopian women with breast cancer.

Methods and Patients

The institutional-based longitudinal study was conducted from January 1 to February 30, 2017 GC at the only nationwide oncology center, Tikur Anbessa Specialized Hospital (TASH), Addis Ababa, Ethiopia. We enrolled all the 146 patients who visited the facility, with no missing quality of life data. A sample size of 100 patients is considered to have enough power to evaluate the quality of life study for each specific cancer site.¹⁴ Women age above 18 years with proven newly diagnosed breast cancer from stage I to IV and scheduled to receive the most commonly used neo/adjuvant or palliative first-line chemotherapy (ie, Adriamycin-Cyclophosphamide [AC] and Adriamycin-Cyclophosphamide followed by Paclitaxel [AC-T] regimen) were included.

We excluded patients who had a previous history of breast cancer treatment (ie currently on the second line for recurrent breast cancer). Patients with psychiatric disorders, other severe medical illnesses, and incomplete quality of life data were also excluded from the analysis. Overall, since this data was the part of the study previously described by Gadisa et al,^{23–25} the study participants in this finding share similarities with previously published articles of the same study project.

Treatment Modalities

The details of treatment modalities were also previously described by Gadisa et al.^{23–25} Moreover, seventy-one (71) women breast cancer patients on AC regimen received Doxorubicin (A) 60 mg/m² and Cyclophosphamide (C) 600 mg/m² as intravenous infusion repeated every 21 days for four or six cycles while 75 study participants on AC-T regimen received Doxorubicin (A) 60 mg/m² and Cyclophosphamide (C) 600 mg/m² for four cycles and followed by Paclitaxel (T) 175 mg/m² intravenous infusion repeated every 21 days for 4 cycles.

Besides, for every cycle of treatment, premedication with ondansetron 8 mg, dexamethasone 16 mg, cimetidine 400 mg, and metoclopramide 10 mg was given by intravenous infusion before the commencement of chemotherapy.

Study Outcomes

The primary endpoints of the study were patterns of QoL among women with breast cancer on chemotherapy. Secondary endpoints were toxicities of breast cancer chemotherapy that cause significant deterioration of QoL.

Assessment for Safety End-Point

Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAEs), Patient-Reported Outcome (PRO) version 4.03.²⁶ Each adverse event is graded as grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening), or grade 5 (death) according to an internationally agreed standard (Common Terminology Criteria for Adverse Events).²⁷ Accordingly, grade ≥ 2 leucopenia (white blood cells count $< 3000/\text{mm}^3$), grade ≥ 2 anemia (hemoglobin level $< 10.0 \text{ g/dl}$), grade ≥ 2 thrombocytopenia (platelets count $< 75,000/\text{mm}^3$), grade ≥ 2 neutropenia (absolute neutrophil count $< 1500/\text{mm}^3$); grade ≥ 1 alanine/aspartate aminotransferase increment ($>$ normal upper limit, U/L); grade ≥ 1 alkaline phosphatase (ALP) increment ($>$ normal upper limit, U/L); grade ≥ 1 serum creatinine increment ($>$ normal upper limit, mg/dL). The patients were personally interviewed for subjective toxicities such as nausea, vomiting, and the like and their toxicity grades were assessed based on the diary maintained during their revisits. The highest toxicity during any cycle was considered as the toxicity grade for that patient. We presented the detail of each adverse event used in our study, which was abstracted from NCI CTCAEs (version 4.03), in the [supplementary material 1](#). And, the detail of those toxicities experienced by our study participants was previously published²⁵ and/or available at <http://DOI.org/10.1177/1078155220907658>.

Assessment for Quality of Life Endpoints

Quality of life was assessed with the validated Amharic version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30, version 3.0) and the breast-cancer-specific QLQ-BR23 (version 1.0).²³ The QLQ-C30 includes nine multiple-item scales of symptoms (nausea and vomiting, diarrhea, constipation, appetite loss, pain, fatigue, insomnia, dyspnea, and financial problems), five to function [physical (PF), role (RF), emotional (EF), cognitive (CF) and social (CF)], and one to overall health—the global health

status (GHS) and quality-of-life scale. It also includes six single-item scales. The QLQ-BR23 includes 23 questions regarding disease symptoms, treatment-related side effects, body image, sexuality, and future perspective.²⁸ Patients were asked to complete both questionnaires at baseline and every two cycles of treatment.

For each of the multi-item scales, no item occurs in more than one scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems. And the scoring was fixed according to the procedures stated on the scoring manual of EORTC QLQ-C30 and BR23.²⁹ QoL deterioration was considered clinically meaningful using previously established thresholds for minimally important differences (MID) in QoL; for EORTC QLQ-C30 and BR23, the threshold for MID was a change of 10 points from baseline.³⁰

Statistical Analysis

The Statistical Package for Social Sciences v.25.0 (SPSS 25.0) software was used for analysis. Descriptive parameters were expressed as percentages and frequencies, continuous variables expressed as mean, standard deviation (SD). Repeated measure general linear model (GLM) and linear mixed model were used to determine the changes in quality of life score in terms of estimated marginal means from baseline and/or between cycles. Unstructured covariance structure was used and Bonferroni was also used for adjustment for multiple comparisons in linear mixed models.

The stepwise linear regression model was used to determine the effect of breast cancer chemotherapy's toxicities and sociodemographic variables or clinical variables on different domains of QoL. The linear regression model for different QoL domains' deterioration due to chemotherapy toxicities was corrected/adjusted for baseline QoL score, the statistically significant socio-demographic and clinical variables. The Probability of the variables to be entered into stepwise linear regression was ≤ 0.050 while the probability of the variable to be removed was ≥ 0.100 . All significance tests were 2-sided with a type I error of 5%. For identifying any outliers we used the outlier with ≥ 3 SD throughout the analysis. For the detail of variables entered into stepwise linear regression model for the effect of sociodemographic

and clinical variables on QoL see [supplementary material 2](#), and for the effect, each chemotherapy toxicity on QoL see [supplementary material 3](#).

Ethical Approval

The study was approved by the Institutional Review Board (IRB) of the school of pharmacy, College of Health Sciences, Addis Ababa University (Ref No: ERB/SOP/09/2016). Addis Ababa University approved the study since our site of data collection was Tikur Anbessa Specialized Hospital (the only oncology center at the national level) which was the part of College of Health sciences of Addis Ababa University.

Informed consent was obtained from all individual participants prior to participation in the study. Moreover, this study was conducted in accordance with the Declaration of Helsinki.³¹

Results

Socio-Demographic and Clinical Characteristics of Study Participants

The study participants had 42.2 years and 1.6 m² mean age and body surface area, respectively. The majority of the study participants had stage III 64 (43.8%) and ECOG performance I 135 (92.5%). The mean of all laboratory values was within the normal range. Averagely, study participants received 6.4 cycles or a median of 8 cycles of chemotherapy ([Table 1](#)). Since this data were part of the study previously described by Gadisa et al,^{23–25} the study participants in this finding share similarities with previously published articles of the same study project (see [Table 1](#)).

Quality of Life Pattern Among Breast Cancer Patients on AC and AC-T Regimen

The Pattern of Quality of Life (EORTC QLQ-C30 Scales) Scores Among Breast Cancer Patients on Chemotherapy

The results from GLM repeated measures in [Figure 1](#) and a linear mixed model in [Table 2](#) depicted, global health status was declined by 15.78 points from baseline to the end of cycle 2. Likewise, cognitive functioning, emotional functioning, social functioning, role functioning, and physical functioning of the patients were significantly ($P \leq 0.001$) decreased by 9.02, 12.21, 16.67, 17.63, and 28.99 points from baseline/pretreatment score to the end

of cycle 2 score respectively. After the end of cycle 2, GHS increased slowly to 6.85 ($P=0.02$) above baseline score at the end of the chemotherapy course whereas emotional functioning was also increased to 4.44 points ($P=0.155$) below the pretreatment score by the end of cycle 8. Moreover, role functioning (28.99 to 22.67 points below the baseline score) and physical functioning (17.63 to 18.58 points below the baseline score) subscales showed a kind stable pattern between cycle 2 and cycle 6, though they increased steeply (ie recovered) towards 11.39 ($P=0.000$) and 8.11 ($P=0.039$) points below pretreatment level by the end of cycle 8, respectively. However, the cognitive functioning of the patients was showed a decreasing pattern from baseline to the end of cycle 8 (ie, 17.24 points below baseline score, $P=0.000$) though social functioning started to recover from its lowest score (32.70 points below pretreatment score, $P=0.000$) at the end of cycle 6 to 22.80 points below pretreatment score ($P=0.000$) at the end of cycle 8 (see [Figure 1](#) and [Table 2](#)).

The symptom scales/items of EORTC QLQ-C30 such as constipation, diarrhea, fatigue, nausea and vomiting, and appetite loss scores were increased by 12.56, 14.16, 43.38, 50.23, and 53.42 points from baseline score to the end cycle 2 score, respectively (see [Table 3](#)). However, after a steep increment from baseline to the end of cycle 2, nausea and vomiting, fatigue, and appetite loss were started declining to 1.27 points ($P=0.295$) below pretreatment score, 18.09 ($P=0.000$) and 19.57 ($P=0.000$) points above pretreatment score, respectively, after the end cycle 4. Moreover, constipation, diarrhea, and dyspnea scores were started to decrease flatly from their higher score at cycle 2 to the end of chemotherapy cycles (ie, cycle 8) on contrary to insomnia which started to deteriorate again after cycle 6 (ie, from 2.43 to 4.70 points above pretreatment score). However, the financial difficulties of the patients were increased from baseline to the end of cycle 8 (17.13 points above pretreatment score, $P=0.000$) (for more please see [Figure 1](#) and [Table 3](#)).

In general, during the first two cycles of chemotherapy, the GHS and majority of functional scales and symptom scales/items of EORTC QLQ-C30 showed a steep decreasing and increasing pattern, respectively. Overall QoL, all functional scales (except cognitive functioning) and symptom scales/items (except dyspnea, insomnia, and pain score) of EORTC QLQ-C30 deteriorated significantly both clinically (ie change at least by 10 points from the baseline) and statistically (ie $P \leq 0.05$) at least during the first two cycles of chemotherapy ([Figure 1](#), and [Tables 2](#) and [3](#)).

Table I Socio-Demographic and Clinical Characteristics of Women with Breast Cancer on AC and AC-T Chemotherapy at TASH, N=146

	Category	N (%)	Mean ± Standard Deviation
Age (Year)	20–34	30(20.5)	42.2 ± 11.5
	35–49	76(52.1)	
	50–64	31(21.2)	
	≥65	9(6.2)	
Body Mass Index (BMI)(kgm ⁻²)	<18.5	14(9.6)	25.2±10.32
	18.5–24.99	74(50.7)	
	25–29.99	30(23.3)	
	≥30	24(16.4)	
Body Surface Area (BSA)(m ²)	1–1.49	31(21.2)	1.6±0.19
	1.5–1.99	110(75.3)	
	≥2	5(3.4)	
Chemotherapy cycles	4 cycles	46(31.5)	6.4±1.78 (median = 8 cycles)
	6 cycles	25(17.1)	
	8 cycles	75(51.4)	
Histological classification	Ductal	131(89.7)	
	Lobular	6(4.1)	
	Mixed	3(2.1)	
	Papillary	3(2.1)	
	Mucinous	2(1.4)	
	Metaplastic	1(0.7)	
Stage	I	6(4.1)	
	II	48(32.8)	
	III	64(43.8)	
	IV	28(19.2)	
Comorbidity	Yes	22(15.1)	
	No	124(84.9)	
Eastern Cooperative Oncology Group (ECOG) Performance	0	3(2.1)	
	I	135(92.5)	
	II	5(3.4)	
	III	3(2.1)	
Marital status	Having no spouse	48(32.9)	
	Having a spouse	98(67.1)	
Educational status	Illiterate	58(39.7)	
	Literate	88(60.3)	
Having children	Yes	115(78.80)	
	No	31(21.20)	
Baseline laboratory values (Mean ± Standard Deviation)	Serum Creatinine (mg/dl)		1.0(0.18)
	Aspartate Aminotransferase (U/L)		27.7 (21.87)
	Alanine Aminotransferase (U/L)		23.5(29.25)
	Alkaline Phosphatase (U/L)		227.9(212.11)
	White Blood Cell counts (10 ³ /mm ³)		7.3(2.40)
	Hemoglobin (gm/dL)		13.9(1.36)
	Platelet (10 ³ /mm ³)		314.1(110.58)
	Absolute Neutrophil Counts (10 ³ /mm ³)		4.1(1.97)
Lymphocyte Counts (10 ³ /mm ³)		2.4(0.80)	

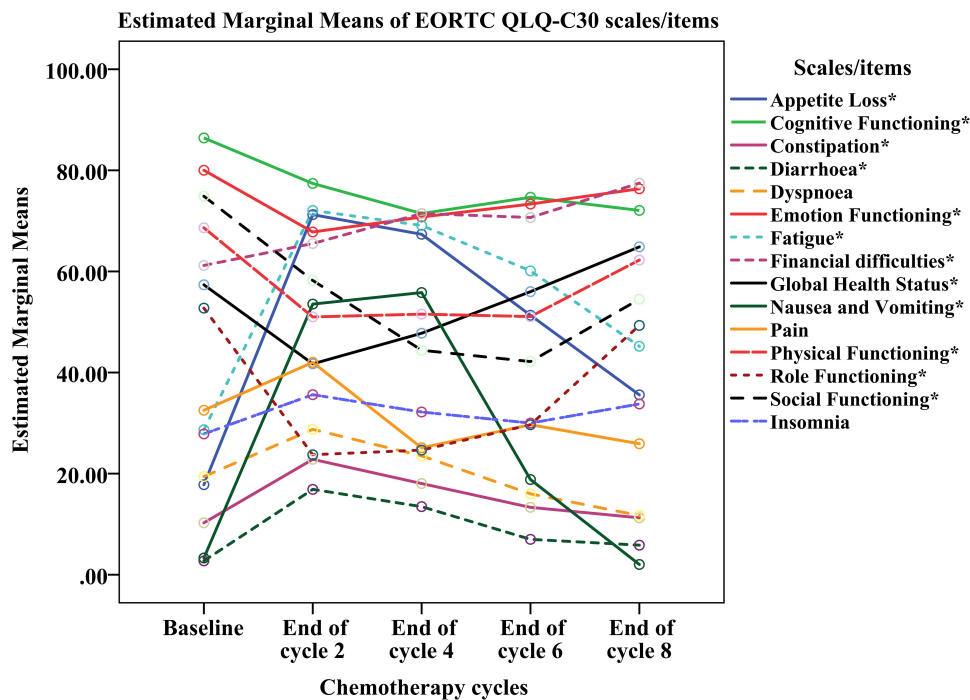


Figure 1 Patterns of quality of life (EORTC QLQ C-30 scales) score over time among women with breast cancer on chemotherapy, from January 1 to September 30, 2017 GC, N=146 (using GLM repeated measures). *Those quality of life domains score with both statistically and clinically significant deterioration at least once from baseline score.

The Pattern of Quality of Life (EORTC QLQ-BR23 Scales) Scores Among Breast Cancer Patients on Chemotherapy

As it is depicted in [Figure 2](#) (results from GLM repeated measures) and [Table 5](#) (results generated from the linear mixed model), systemic therapy side effects were increased by 37.83 ($P=0.000$) points above the pretreatment score by the end of the cycle 2 score. However, starting from the end of cycle 4 (38.88 points above pretreatment score, $P=0.000$), systemic therapy side effects were decreased (ie, recovered) towards 25.74 points above the pretreatment score ($P=0.000$). Also, the highest score for an upset by hair loss was detected at the end of cycle 2 (16.28 points above score at cycle 8, $P=0.000$) and the lowest score at the end of cycle 6 (10.90 points below the score at cycle 8, $P=0.000$) but it started to deteriorate afterward (see [Figure 2](#) and [Table 5](#)). On contrary to the systemic therapy side effects and upset by hair loss escalation during the first two cycles of chemotherapy, breast symptoms and arm symptoms were slowly decreased (ie, improved) to 14.85 ($P=0.000$) and 19.79 ($P=0.000$) points below the pretreatment score, respectively, by the end cycle 8.

Among the functional scales of EORTC QLQ-BR23, body image score was slightly increased from baseline to the end of cycle 8 (ie, 7.29 points above pretreatment

score, $P=0.031$). However, future perspectives and sexual functioning showed a decreasing pattern from pretreatment to the end of cycle 4 (ie, 6.62 points below the pretreatment score, $P=0.051$) and cycle 6 (ie, 9.59 points below the pretreatment score, $P=0.006$), respectively, even though they increased towards to pretreatment level afterward (for more please see [Figure 2](#) and [Table 4](#)).

Overall, except for body image, breast symptoms, arm symptoms, future perspectives, and sexual functioning, all EORTC QLQ-BR23 dimensions were deteriorated significantly (ie, both statistically and clinically) during chemotherapy ([Figure 2](#)).

Factors Affecting the Quality of Life of Study Participants

Socio-Demographic and Clinical-Pathological Factors

Literate patients had higher Global Health Status, physical, role, social functioning and sexual functioning scores ($6.927 \leq B \leq 14.705$, $P \leq 0.043$) than illiterate ones. Moreover, literate patients had lower fatigue, pain, dyspnea, appetite loss, diarrhea, and systemic therapy side effects scores ($-10.282 \leq B \leq -5.318$, $P \leq 0.028$) than their counterparts. Tumor stage $\frac{3}{4}$ significantly impairs GHS, role, emotional, social functioning, sexual functioning, and future perspectives score ($-4.763 \leq B \leq -2.590$, $P \leq 0.038$) of

Table 2 EORTC QLQ-C30 Global Health Status and Functional Scales Score Over Time Among Breast Cancer Patients on AC and AC-T Chemotherapy, from January 1 to September 30, 2017 GC (Using a Linear Mixed Model)

Global Health Status/Overall Quality of Life of EORTC QLQ C-30										
Parameters	B	SE	Sig.	95% CI						
				LB	UB					
Intercept	57.51	1.65	0.000	54.24	60.78					
Cycle 2	-15.78	2.02	0.000	-19.78	-11.79					
Cycle 4	-9.90	1.89	0.000	-13.66	-6.16					
Cycle 6	-1.75	2.16	0.420	-6.02	2.52					
Cycle 8	6.85	2.16	0.002	2.56	11.14					
Baseline	0 ^b	0.00								
Functional Scales EORTC QLQ C-30										
Role Functioning										
Parameters	B	SE	Sig.	95% CI		B	SE	Sig.	95% CI	
				LB	UB				LB	UB
Intercept	52.74	3.21	0.000	46.38	59.09	80.02	1.87	0.000	76.33	83.72
Cycle 2	-28.99	3.17	0.000	-35.26	-22.73	-12.21	2.20	0.000	-16.56	-7.87
Cycle 4	-28.08	3.46	0.000	-34.91	-21.24	-9.25	2.65	0.001	-14.49	-4.00
Cycle 6	-22.67	4.18	0.000	-30.94	-14.41	-6.58	2.81	0.021	-12.14	-1.02
Cycle 8	-8.11	3.88	0.039	-15.79	-4.43	-4.44	3.10	0.155	-10.59	1.71
Baseline	0 ^b	0.00				0 ^b	0.00			
Cognitive Functioning										
Parameters	B	SE	Sig.	95% CI		B	SE	Sig.	95% CI	
				LB	UB				LB	UB
Intercept	86.42	1.65	0.000	83.15	89.68	74.89	2.53	0.000	69.88	79.89
Cycle 2	-9.02	2.21	0.000	-13.39	-4.65	-16.67	2.58	0.000	-21.77	-11.56
Cycle 4	-14.95	4.41	0.001	-23.67	-6.24	-30.48	2.89	0.000	-36.19	-24.77
Cycle 6	-11.59	2.88	0.000	-17.29	-5.89	-32.70	3.36	0.000	-39.35	-26.04
Cycle 8	-17.24	3.67	0.000	-24.58	-9.91	-22.80	3.67	0.000	-30.09	-15.52
Baseline	0 ^b	0.00				0 ^b	0.00			

(Continued)

Table 2 (Continued).

Physical Functioning		95% CI		Sig.	SE	B
Parameters		LB	UB			
Intercept		64.37	72.89	0.000	2.16	68.63
Cycle 2		-21.64	-13.61	0.000	2.03	-17.63
Cycle 4		-21.15	-13.00	0.000	2.06	-17.08
Cycle 6		-24.24	-12.92	0.000	2.86	-18.58
Cycle 8		-17.08	-5.70	0.000	2.87	-11.39
Baseline					0.00	0 ^b

Note: 0^b = reference category.

Abbreviations: CI, confidence interval; B, estimated marginal means; LB, lower bound; SE, standard error; Sig, significance; UB, upper bound.

the patients than patients with tumor stage ½. Besides, it also causes deterioration (1.977≤B≤5.158, P≤0.023) of fatigue, constipation, and breast symptoms score.

Increasing age was also associated with increment (0.385≤B≤0.567, P≤0.033) in-body image, future perspectives, fatigue, insomnia, and constipation scores on contrary to its association with decrement (-0.529≤B≤-0.366, P≤0.033) in physical functioning, role functioning, and upset by hair loss score (Table 6).

Patients who received the AC-T regimen had lower (-18.46≤B≤-12.02, P≤0.001) nausea and vomiting, dyspnea, and appetite loss than those who received the AC regimen. Having children was among the contributing factor for having higher (9.45≤B≤9.87, P≤0.037) pain and financial problems score than those who had no children.

Moreover, baseline serum creatinine was a positive predictor (15.560≤B≤29.455, P≤0.007) for symptom scales such as pain, financial difficulties, systemic therapy side effects, and upset by hair loss scores on contrary to cognitive functioning (B=-27.234, P=0.009). Baseline alkaline phosphatase is also negatively associated (-0.018≤B≤-0.020, P≤0.046) with the role and social functioning scores. Having had higher baseline absolute neutrophil counts (B=1.81, P=0.000) and white blood cell counts (B=1.334, P=0.006) was associated with higher breast symptoms and arm symptoms score, respectively (see Table 6).

The Effect of AC and AC-T Chemotherapy’s Toxicities on Quality of Life Among Women with Breast Cancer in Ethiopia

Upon adjusting for baseline quality of life score, significant socio-demographic and clinical cofounding factors, grade 2 and above fatigue (-25.320≤B≤-7.709, P≤0.013) was significantly associated with deterioration of Global health status, physical functioning, emotional functioning, cognitive functioning, social functioning, sexual functioning and sexual enjoyment of the patients than those with lower grade fatigue. It is also significantly associated with the deterioration (9.620≤B≤14.914, P≤0.043) of symptom scales such as fatigue, insomnia, appetite loss, and financial difficulties (Table 7).

Grade 2 dysgeusia causes a significant impairment (-19.275≤B≤-10.544, P≤0.025) in global health status, role functioning, emotional functioning, social functioning, body image, future perspectives of the patients than grade 0/1 dysgeusia. It is also frequently associated with

Table 3 EORTC QLQ C-30 Items/Symptom Scales Score Over Time Among Breast Cancer Patients on AC and AC-T Chemotherapy, from January 1 to September 30, 2017 GC (Using a Linear Mixed Model)

Symptoms Scales/Items EORTC QLQ C-30															
Fatigue		Nausea and Vomiting				Dyspnea				Appetite Loss					
Parameters	B	SE	Sig.	95% CI		B	SE	Sig.	95% CI		B	SE	Sig.	95% CI	
				LB	UB				LB	UB				LB	UB
Intercept	28.69	2.52	0.000	23.72	33.66	3.31	0.98	0.001	1.37	5.25	19.41	2.46	0.000	14.54	24.27
Cycle 2	43.38	2.68	0.000	38.09	48.67	50.23	2.80	0.000	44.69	55.76	9.36	2.89	0.002	3.64	15.08
Cycle 4	40.41	3.05	0.000	34.38	46.44	52.51	2.94	0.000	46.71	58.31	4.11	3.11	0.188	-2.03	10.25
Cycle 6	30.81	3.38	0.000	24.14	37.49	15.46	3.02	0.000	9.48	21.44	-2.32	3.39	0.495	-9.01	4.38
Cycle 8	18.09	3.91	0.000	10.32	25.86	-1.27	1.21	0.295	-3.66	1.12	-5.36	2.67	0.047	-10.65	-0.06
Baseline	0 ^b	0.00				0 ^b	0.00				0 ^b	0.00			
Pain															
Parameters	B	SE	Sig.	95% CI		B	SE	Sig.	95% CI		B	SE	Sig.	95% CI	
				LB	UB				LB	UB				LB	UB
Intercept	32.53	2.53	0.000	27.54	37.53	19.41	2.46	0.000	14.54	24.27	9.36	2.89	0.002	3.64	15.08
Cycle 2	9.47	3.06	0.002	3.42	15.53	9.36	2.89	0.002	3.64	15.08	4.11	3.11	0.188	-2.03	10.25
Cycle 4	-7.42	3.13	0.019	-13.60	-1.24	4.11	3.11	0.188	-2.03	10.25	-2.32	3.39	0.495	-9.01	4.38
Cycle 6	-2.78	3.85	0.472	-10.40	4.84	-2.32	3.39	0.495	-9.01	4.38	-5.36	2.67	0.047	-10.65	-0.06
Cycle 8	-7.55	3.69	0.043	-14.86	-0.25	-5.36	2.67	0.047	-10.65	-0.06	0 ^b	0.00			
Baseline	0 ^b	0.00				0 ^b	0.00				0 ^b	0.00			
Insomnia															
Parameters	B	SE	Sig.	95% CI		B	SE	Sig.	95% CI		B	SE	Sig.	95% CI	
				LB	UB				LB	UB				LB	UB
Intercept	27.85	2.86	0.000	22.20	33.51	17.81	2.45	0.000	12.97	22.65	7.76	3.38	0.023	47.04	59.81
Cycle 2	7.76	3.38	0.023	1.08	14.45	53.42	3.23	0.000	47.04	59.81	4.34	3.51	0.218	42.97	56.11
Cycle 4	4.34	3.51	0.218	-2.60	11.27	49.54	3.32	0.000	42.97	56.11	2.43	4.30	0.573	26.45	39.66
Cycle 6	2.43	4.30	0.573	-6.08	10.93	33.05	3.34	0.000	26.45	39.66	4.70	4.83	0.333	11.45	27.69
Cycle 8	4.70	4.83	0.333	-4.88	14.27	19.57	4.09	0.000	11.45	27.69	0 ^b	0.00			
Baseline	0 ^b	0.00				0 ^b	0.00				0 ^b	0.00			

(Continued)

Table 3 (Continued).

Constipation		Diarrhea										
Parameters	B	SE	Sig.	95% CI		UB	B	SE	Sig.	95% CI		UB
				LB	UB					LB	UB	
Intercept	10.27	1.82	0.000	6.68	13.87	13.87	2.74	1.00	0.007	0.77	4.71	4.71
Cycle 2	12.56	2.73	0.000	7.16	17.96	17.96	14.16	2.49	0.000	9.24	19.07	19.07
Cycle 4	7.76	2.22	0.001	3.37	12.15	12.15	10.73	2.53	0.000	5.73	15.73	15.73
Cycle 6	3.07	2.43	0.210	-1.75	7.88	7.88	4.32	1.96	0.030	0.43	8.21	8.21
Cycle 8	1.16	2.56	0.651	-3.92	6.24	6.24	3.13	1.88	0.100	-0.61	6.86	6.86
Baseline	0 ^b	0.00					0 ^b	0.00				
Financial Difficulties												
Parameters	B	SE	Sig.	95% CI		UB						
				LB	UB		LB	UB	LB	UB	LB	UB
Intercept	61.19	3.04	0.000	55.18	67.20	67.20						
Cycle 2	4.34	2.77	0.120	-1.14	9.82	9.82						
Cycle 4	10.27	3.33	0.002	3.69	16.85	16.85						
Cycle 6	9.45	3.69	0.012	2.13	16.76	16.76						
Cycle 8	17.13	4.06	0.000	9.07	25.19	25.19						
Baseline	0 ^b	0.00										

Note: 0^b = reference category.

Abbreviations: CI, confidence interval; B, estimated marginal means; LB, lower bound; SE, standard error; Sig, significance; UB, upper bound.

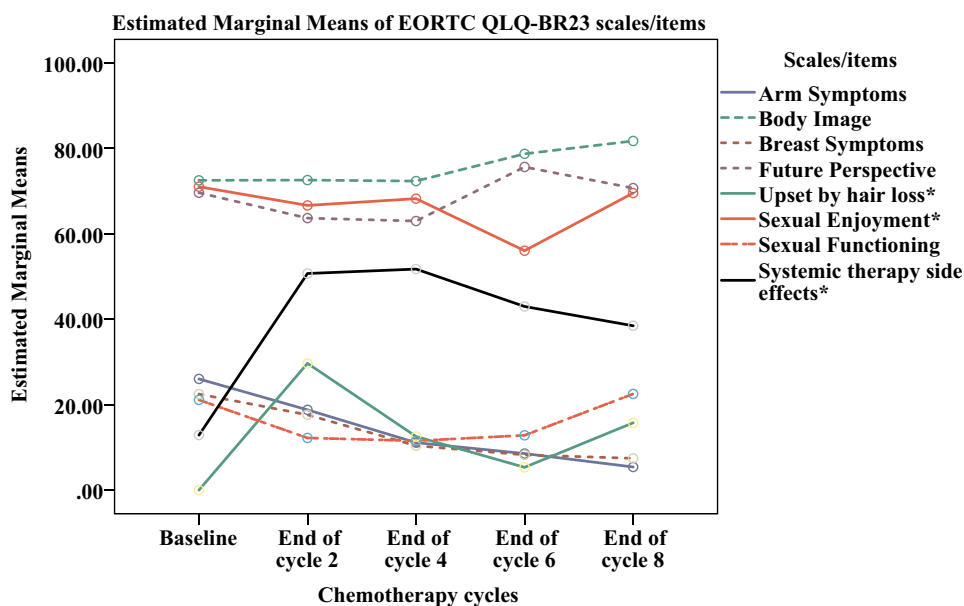


Figure 2 Patterns of quality of life score (EORTC QLQ-BR23 scales) over time among women with breast cancer on chemotherapy, from January 1 to September 30, 2017 GC, N=146 (using GLM repeated measures). *Those quality of life domains score with both statistically and clinically significant deterioration (ie except breast and arm symptoms) at least once from baseline score.

deterioration ($13.352 \leq B \leq 22.962$, $P \leq 0.003$) of symptom scales such as fatigue, pain, dyspnea, insomnia, appetite loss, systemic therapy side effects, and upset by hair loss scores.

Furthermore, grade 2 and above constipation ($8.355 \leq B \leq 26.451$, $P \leq 0.039$) was frequently associated with the deterioration of symptom scales like fatigue, pain, dyspnea, constipation, diarrhea, and systemic therapy side effects than its counterparts. Besides, it is also negatively ($-9.450 \leq B \leq -8.291$, $P \leq 0.033$) associated with the global health status and emotional functioning of the patients.

Grade 2 and above peripheral neuropathy was also the other non-hematological toxicity of AC and AC-T chemotherapy that causes the significant deterioration of physical functioning ($B = -10.482$, $P = 0.000$) and symptom scales ($4.819 \leq B \leq 9.557$, $P \leq 0.014$) such as fatigue, dyspnea, and systemic therapy side effect. Also, grade 2 and above oral mucositis was associated with significant impairment of physical and role functioning ($-7.661 \leq B \leq -6.351$, $P \leq 0.023$), and fatigue and financial difficulties of the patients ($7.963 \leq B \leq 8.067$, $P \leq 0.010$).

Some quality of life deteriorations were mirror images of their chemotherapy's toxicity. For examples, those suffering from grade ≥ 2 dry mouth and dysgeusia had significantly higher appetite loss score ($15.64 \leq B \leq 20.12$, $P \leq 0.002$); grade ≥ 2 constipation for higher constipation

score ($B = 26.45$, $P \leq 0.001$), grade ≥ 2 diarrhea for higher diarrheal score ($B = 19.55$, $P \leq 0.001$) and grade ≥ 2 myalgia and arthralgia for higher pain score ($B = 8.50$, $P = 0.011$), grade ≥ 2 skin hyperpigmentation for a higher upset by hair loss score ($B = 7.715$, $P = 0.033$) and lower body image ($B = -6.189$, $P = 0.05$). Moreover, some laboratory result based toxicities like grade 2 and above lymphopenia was associated with lower arm symptoms ($B = -6.607$, $P = 0.009$), grade ≥ 2 anemia associated with higher fatigue score ($B = 14.541$, $P = 0.003$), and grade ≥ 1 alkaline phosphatase increment was also associated with lower role functioning score ($B = -7.742$, $P = 0.027$) than their lower-grade toxicities. For more effect of AC and AC-T regimen's toxicities on quality of life please see [Table 7](#).

Discussion

Breast cancer chemotherapies harm the quality of life^{17,32} even though it increases overall survival (OS) and disease-free survival (DFS).³³⁻³⁶ As a result, understanding the effect of breast cancer treatment on patients' quality of life has been the central clinical and research question.³⁷ The trial of Hall and his coworker³⁸ showed that overall QoL/GHS and systemic therapy side effects significantly deteriorated clinically from baseline to throughout therapy. A minimum clinically meaningful difference/deterioration is considered to be 10 points, using an established method of interpretation for the EORTC QLQ-C30 scores.³⁹

Table 4 EORTC QLQ-BR23 Functional Scales Score Over Time Among Breast Cancer Patients on Chemotherapy, from January 1 to September 30, 2017 GC (Using a Linear Mixed Model)

Functional Scales of EORTC QLQ-BR23											
Body Image						Sexual Functioning					
Parameters	B	SE	Sig.	95% CI		B	SE	Sig.	95% CI		
				LB	UB				LB	UB	
Intercept	72.55	3.51	0.000	65.60	79.49	21.12	3.06	0.000	15.08	27.16	
Cycle 2	0.06	3.03	0.985	-5.94	6.05	-8.90	3.04	0.004	-14.92	-2.89	
Cycle 4	-0.17	3.57	0.962	-7.23	6.89	-9.59	3.41	0.006	-16.33	-2.84	
Cycle 6	5.57	3.83	0.150	-2.06	13.20	-8.15	3.55	0.023	-15.17	-1.13	
Cycle 8	7.29	3.29	0.031	0.69	13.89	-1.53	4.46	0.732	-10.38	7.31	
Baseline	0 ^b	0.00				0 ^b	0.00				
Future Perspectives											
Parameters	B	SE	Sig.	95% CI		B	SE	Sig.	95% CI		
				LB	UB				LB	UB	
Intercept	69.63	2.77	0.000	64.17	75.10	69.63	2.77	0.000	64.17	75.10	
Cycle 2	-5.94	2.96	0.047	-11.79	-0.08	-5.94	2.96	0.047	-11.79	-0.08	
Cycle 4	-6.62	3.36	0.051	-13.26	0.02	-6.62	3.36	0.051	-13.26	0.02	
Cycle 6	6.38	3.58	0.077	-0.70	13.46	6.38	3.58	0.077	-0.70	13.46	
Cycle 8	-0.47	4.35	0.915	-9.09	8.16	-0.47	4.35	0.915	-9.09	8.16	
Baseline	0 ^b	0.00				0 ^b	0.00				

Note: 0^b = reference category.

Abbreviations: CI, confidence interval; B, estimated marginal means; LB, lower bound; SE, standard error; Sig, significance; UB, upper bound.

Table 5 EORTC QLQ-BR23 Symptom Scales Score Over Time Among Breast Cancer Patients on Chemotherapy, from January 1 to September 30, 2017 GC (Using a Linear Mixed Model)

Symptom Scales of EORTC QLQ-BR23										
Systemic Therapy Side Effects					Upset by Hair Loss**					
Parameters	B	SE	Sig.	95% CI		B	SE	Sig.	95% CI	
				LB	UB				LB	UB
Intercept	12.88	1.25	0.000	10.42	15.35	16.28	3.18	0.000	9.97	22.59
Cycle 2	37.83	1.84	0.000	34.20	41.47	13.40	3.73	0.000	6.02	20.79
Cycle 4	38.88	1.77	0.000	35.37	42.38	-3.72	2.97	0.214	-9.63	2.19
Cycle 6	29.68	1.73	0.000	26.25	33.10	-10.90	3.19	0.001	-17.24	-4.55
Cycle 8	25.74	1.92	0.000	21.93	29.54	0 ^b	0.00			
Baseline	0 ^b	0.00								
Breast Symptoms										
Parameters	B	SE	Sig.	95% CI		B	SE	Sig.	95% CI	
				LB	UB				LB	UB
Intercept	22.49	1.85	0.000	18.83	26.14	26.03	2.16	0.000	21.76	30.29
Cycle 2	-4.85	1.34	0.000	-7.49	-2.21	-7.23	2.02	0.000	-11.22	-3.24
Cycle 4	-12.10	1.74	0.000	-15.55	-8.66	-14.69	1.99	0.000	-18.62	-10.76
Cycle 6	-13.48	1.83	0.000	-17.10	-9.87	-17.11	2.11	0.000	-21.28	-12.94
Cycle 8	-14.25	1.94	0.000	-18.10	-10.40	-19.79	2.26	0.000	-24.26	-15.33
Baseline	0 ^b	0.00				0 ^b	0.00			

Notes: **no hair loss score on the baseline. 0^b = reference category

Abbreviations: CI, confidence interval; B, estimated marginal means; LB, lower bound; SE, standard error; Sig, significance; UB, upper bound.

Table 6 Socio-Demographic and Clinical Factors Associated with Deterioration of Quality of Life on Stepwise Linear Regression, from January 1 to September 30, 2017 GC

EORTC QLQ-C30[#]					
Global Health Status/Overall QoL					
Socio-Demographic and Clinical Variables	Unstandardized Coefficients (B)	Standard Error	P-value	95% Confidence Interval for B	
				Lower Bound	Upper Bound
(Constant)	35.688	10.457	0.001	15.017	56.359
Tumor stage ($1/2_{ref.}$ vs $3/4$)	-2.590	1.081	0.018	-4.726	-.454
Illiterate $_{ref.}$ vs literate	7.157	2.434	0.004	2.346	11.969
Physical Functioning Score					
(Constant)	57.608	7.739	0.000	42.310	72.907
Age	-.529	0.133	0.000	-.792	-.267
Regimen (AC $_{ref.}$ vs AC-T)	8.255	2.994	0.007	2.336	14.173
Illiterate $_{ref.}$ vs literate	6.927	3.184	0.031	0.633	13.22
Role Functioning Score					
(Constant)	54.867	8.954	0.000	37.164	72.569
Illiterate $_{ref.}$ vs literate	14.705	3.888	0.000	7.018	22.391
Tumor stage ($1/2_{ref.}$ vs $3/4$)	-4.763	1.578	0.003	-7.883	-1.644
Age	-.475	0.166	0.005	-.803	-.147
Baseline Alkaline phosphatase	-.018	0.009	0.046	-.035	0.000
Emotional Functioning Score*					
(Constant)	80.116	3.897	0.000	72.414	87.818
Tumor stage ($1/2_{ref.}$ vs $3/4$)	-3.786	1.425	0.009	-6.602	-.969
Cognitive Functioning Score*					
(Constant)	100.929	9.975	0.000	81.212	120.646
Baseline Serum Creatinine	-27.234	10.284	0.009	-47.560	-6.907
Social Functioning Score					
(Constant)	54.358	5.319	0.000	43.844	64.872
Illiterate $_{ref.}$ vs literate	13.645	3.999	0.001	5.739	21.551
Baseline Alkaline phosphatase	-.020	0.009	0.037	-.039	-.001
Tumor stage ($1/2_{ref.}$ vs $3/4$)	-3.558	1.696	0.038	-6.909	-.206
Fatigue Score					
(Constant)	42.419	8.628	0.000	25.364	59.474
Illiterate vs literate	-10.282	3.726	0.007	-17.647	-2.917
Tumor stage ($1/2_{ref.}$ vs $3/4$)	5.158	1.480	0.001	2.232	8.084
Age	0.390	0.159	0.016	0.075	0.704
Nausea and Vomiting Score					
(Constant)	68.943	3.578	0.000	61.871	76.015
Regimen (AC $_{ref.}$ vs AC-T)	-18.435	2.244	0.000	-22.871	-13.998

(Continued)

Table 6 (Continued).

EORTC QLQ-C30[#]					
Global Health Status/Overall QoL					
Socio-Demographic and Clinical Variables	Unstandardized Coefficients (B)	Standard Error	P-value	95% Confidence Interval for B	
				Lower Bound	Upper Bound
Pain Score					
(Constant)	7.878	11.044	0.477	-13.954	29.709
Illiterate _{ref.} vs literate	-9.064	3.825	0.019	-16.626	-1.502
Baseline Serum Creatinine	22.560	10.153	0.028	2.490	42.630
Children (No _{ref.} vs Yes)	9.877	4.580	0.033	0.823	18.931
Dyspnea Score					
(Constant)	10.484	18.499	0.572	-26.086	47.054
Regimen (AC _{ref.} vs AC-T)	-12.021	3.645	0.001	-19.226	-4.816
Illiterate _{ref.} vs literate	-8.520	3.700	0.023	-15.833	-1.206
Baseline Hemoglobin	2.598	1.309	0.049	0.010	5.185
Insomnia Score*					
(Constant)	15.922	8.724	0.070	-1.321	33.166
Age	0.399	0.199	0.046	0.006	0.791
Appetite Loss Score					
(Constant)	88.783	5.740	0.000	77.436	100.130
Regimen (AC _{ref.} vs AC-T)	-14.541	3.630	0.000	-21.716	-7.367
Illiterate _{ref.} vs literate	-8.224	3.707	0.028	-15.552	-8.96
Constipation Score*					
(Constant)	-6.716	7.481	0.371	-21.504	8.072
Age	0.385	0.153	0.013	0.084	0.687
Tumor stage (½ _{ref.} vs ¾)	3.407	1.480	0.023	0.482	6.333
Diarrhea Score*					
(Constant)	-9.689	13.360	0.470	-36.098	16.721
Illiterate _{ref.} vs literate	-8.808	3.215	0.007	-15.164	-2.452
Body Surface Area	17.050	8.254	0.041	0.735	33.366
Financial Difficulties Score*					
(Constant)	39.448	10.619	0.000	18.457	60.440
Baseline Serum Creatinine	24.564	10.193	0.017	4.415	44.713
Children (No _{ref.} vs Yes)	9.445	4.490	0.037	0.570	18.320
EORTC QLQ-BR23[#]					
Body Image Score*					
(Constant)	75.916	10.768	0.000	54.632	97.201
Age	0.482	0.153	0.002	0.179	0.785
Baseline Serum Creatinine	-22.865	9.767	0.021	-42.171	-3.559

(Continued)

Table 6 (Continued).

EORTC QLQ-C30 [#]					
Global Health Status/Overall QoL					
Socio-Demographic and Clinical Variables	Unstandardized Coefficients (B)	Standard Error	P-value	95% Confidence Interval for B	
				Lower Bound	Upper Bound
Sexual Functioning Score					
(Constant)	10.964	5.100	0.033	0.881	21.047
Spouse (No _{ref.} vs Yes)	10.754	3.608	0.003	3.621	17.888
Tumor stage (1/2 _{ref.} vs 3/4)	-3.902	1.435	0.007	-6.740	-1.065
Illiterate _{ref.} vs literate	7.089	3.469	0.043	0.232	13.946
Sexual Enjoyment Score*					
(Constant)	31.608	16.036	0.055	-652	63.869
Baseline White Blood Cell Counts	4.720	2.268	0.043	0.158	9.282
Future Perspective Score					
(Constant)	64.884	28.591	0.025	8.361	121.406
Age	0.567	0.179	0.002	0.213	0.922
Body Surface Area	26.350	10.845	0.016	4.911	47.789
Baseline Hemoglobin	-3.933	1.531	0.011	-6.960	-906
Tumor stage (1/2 _{ref.} vs 3/4)	-4.354	1.768	0.015	-7.848	-859
Systemic Therapy Side Effects Score*					
(Constant)	35.985	6.304	0.000	23.525	48.445
Baseline Serum Creatinine	15.560	6.333	0.015	3.042	28.078
Illiterate _{ref.} vs literate	-5.318	2.331	0.024	-9.926	-710
Breast Symptoms Score					
(Constant)	8.428	4.784	0.080	-1.029	17.885
Baseline Absolute Neutrophil Counts	1.811	0.472	0.000	0.877	2.744
Regimen (AC _{ref.} vs AC-T)	-5.183	2.018	0.011	-9.173	-1.193
Tumor stage (1/2 _{ref.} vs 3/4)	1.977	0.858	0.023	0.280	3.673
Arm Symptoms Score					
(Constant)	14.384	5.021	0.005	4.459	24.310
Regimen (AC _{ref.} vs AC-T)	-7.224	2.277	0.002	-11.724	-2.723
Baseline White Blood Cells	1.334	0.476	0.006	0.393	2.275
Upset by Hair Loss Score					
(Constant)	17.842	12.903	0.169	-7.665	43.349
Baseline Serum Creatinine	29.455	10.752	0.007	8.199	50.710
Baseline lymphocytes	-5.523	2.429	0.024	-10.324	-722
Age	-366	0.170	0.033	-701	-031

Notes: *R² ≤ 10%; [#]for all others 10.5% ≤ R² ≤ 31.9%.

Abbreviation: ref, reference category.

Our study found that the global health status score, physical functioning, role functioning, and emotional functioning scores of the study participants were decreasing

steeply from baseline to the end of cycle 2 by more than 12 points and increasing slowly after the end of cycle 2 to the end of cycle 8. Different cross-sectional studies also

Table 7 The Effect of AC and AC-T Regimen's Toxicities on Quality of Life Among Women with Breast Cancer in Ethiopia, from January 1 to September 30, 2017 GC

EORTC QLQ-C30 #					
Global Health status/Overall QoL					
Chemotherapy Toxicity	Unstandardized Coefficients (B)	Standard Error	P-value	95% Confidence Interval for B	
				Lower Bound	Upper Bound
(Constant)	84.105	10.182	0.000	63.973	104.238
Fatigue (G0/I _{ref} .vs G≥2)	-7.709	3.070	0.013	-13.778	-1.640
Dysgeusia (G0/I _{ref} .vs G2)	-10.544	3.451	0.003	-17.366	-3.721
Constipation (G0/I _{ref} .vs G≥2)	-8.291	3.069	0.008	-14.360	-2.222
Physical Functioning Score					
(Constant)	85.039	10.918	0.000	63.446	106.632
Fatigue (G0/I _{ref} .vs G≥2)	-10.574	3.397	0.002	-17.292	-3.856
Peripheral neuropathy (G0/I _{ref} .vs G≥2)	-10.482	2.852	0.000	-16.123	-4.842
Vomiting (G0/I _{ref} .vs G≥2)	-6.853	2.282	0.003	-11.367	-2.339
Oral mucositis (G0/I _{ref} .vs G≥2)	-6.351	2.381	0.009	-11.061	-1.642
Role Functioning Score					
(Constant)	70.813	13.511	0.000	44.098	97.529
Dysgeusia (G0/I _{ref} .vs G2)	-19.275	5.324	0.000	-29.802	-8.748
Alkaline phosphatase increment (G0 _{ref} .vs G≥1)	-7.742	3.457	0.027	-14.577	-9.07
Oral mucositis (G0/I _{ref} .vs G≥2)	-7.661	3.338	0.023	-14.263	-1.060
Emotional Functioning Score*					
(Constant)	96.048	15.229	0.000	65.937	126.159
Fatigue (G0/I _{ref} .vs G≥2)	-14.635	4.381	0.001	-23.297	-5.973
Dysgeusia (G0/I _{ref} .vs G2)	-13.132	5.012	0.010	-23.042	-3.222
Constipation (G0/I _{ref} .vs G≥2)	-9.450	4.391	0.033	-18.132	-7.68
Cognitive Functioning Score*					
(Constant)	99.858	15.611	0.000	68.993	130.724
Fatigue (G0/I _{ref} .vs G≥2)	-20.385	4.846	0.000	-29.966	-10.803
Alkaline phosphatase increment (G0 _{ref} .vs G≥1)	7.709	3.584	0.033	0.623	14.795
Social Functioning Score					
(Constant)	64.558	13.898	0.000	37.081	92.035
Fatigue (G0/I _{ref} .vs G≥2)	-12.805	4.746	0.008	-22.188	-3.423
Dysgeusia (G0/I _{ref} .vs G2)	-14.533	5.289	0.007	-24.990	-4.076
Fatigue Score					
(Constant)	-28.929	15.012	0.056	-58.617	0.758
Fatigue (G0/I _{ref} .vs G≥2)	14.914	4.231	0.001	6.547	23.281
Dysgeusia (G0/I _{ref} .vs G2)	14.587	4.738	0.003	5.218	23.956
Oral mucositis (G0/I _{ref} .vs G≥2)	8.067	2.977	0.008	2.180	13.954
Constipation (G0/I _{ref} .vs G≥2)	8.598	4.120	0.039	0.450	16.745
Peripheral neuropathy (G0/I _{ref} .vs G≥2)	9.319	3.196	0.004	3.000	15.639

(Continued)

Table 7 (Continued).

EORTC QLQ-C30 #					
Global Health status/Overall QoL					
Chemotherapy Toxicity	Unstandardized Coefficients (B)	Standard Error	P-value	95% Confidence Interval for B	
				Lower Bound	Upper Bound
Anemia (G0/I _{ref.} Vs G≥2)	14.541	4.878	0.003	4.895	24.188
Pain Score					
(Constant)	-71.259	15.011	0.000	-100.943	-41.576
Skin hyperpigmentation (G0/I _{ref.} vs G2)	10.959	3.243	0.001	4.545	17.372
Dysgeusia (G0/I _{ref.} vs G2)	16.821	5.063	0.001	6.809	26.833
Constipation (G0/I _{ref.} vs G≥2)	14.477	4.491	0.002	5.596	23.358
Arthralgia/myalgia (G0/I _{ref.} vs G≥2)	8.502	3.313	0.011	1.951	15.052
Dyspnea Score					
(Constant)	-14.747	12.095	0.225	-38.665	9.171
Constipation (G0/I _{ref.} vs G≥2)	22.148	4.393	0.000	13.462	30.835
Dysgeusia (G0/I _{ref.} vs G2)	18.811	4.994	0.000	8.937	28.686
Peripheral neuropathy (G0/I _{ref.} vs G≥2)	9.557	3.832	0.014	1.979	17.134
Insomnia Score*					
(Constant)	-57.184	17.475	0.001	-91.731	-22.636
Dysgeusia (G0/I _{ref.} vs G2)	22.962	6.760	0.001	9.597	36.327
Fatigue (G0/I _{ref.} vs G≥2)	11.973	5.867	0.043	0.376	23.571
Appetite Loss Score					
(Constant)	25.482	14.679	0.085	-3.544	54.509
Dry mouth (G0/I _{ref.} vs G≥2)	20.016	3.869	0.000	12.365	27.668
Dysgeusia (G0/I _{ref.} vs G2)	15.642	4.911	0.002	5.930	25.353
Fatigue (G0/I _{ref.} vs G≥2)	9.620	4.421	0.031	0.878	18.361
Constipation Score*					
(Constant)	-34.838	7.578	0.000	-49.819	-19.857
Constipation (G0/I _{ref.} vs G≥2)	26.451	4.089	0.000	18.367	34.535
Diarrhea Score*					
(Constant)	-29.409	8.590	0.001	-46.392	-12.426
Diarrhea (G0/I _{ref.} vs G≥2)	19.552	3.775	0.000	12.089	27.015
Dry mouth (G0/I _{ref.} vs G≥2)	9.065	3.531	0.011	2.084	16.046
Constipation (G0/I _{ref.} vs G≥2)	8.917	4.097	0.031	0.818	17.016
Financial Difficulties Score					
(Constant)	-7.834	11.718	0.505	-31.003	15.336
Fatigue (G0/I _{ref.} vs G≥2)	11.572	4.182	0.006	3.303	19.841
Oral mucositis (G0/I _{ref.} vs G≥2)	7.963	3.032	0.010	1.967	13.958

(Continued)

Table 7 (Continued).

EORTC QLQ-C30 #					
Global Health status/Overall QoL					
Chemotherapy Toxicity	Unstandardized Coefficients (B)	Standard Error	P-value	95% Confidence Interval for B	
				Lower Bound	Upper Bound
EORTC QLQ-BR23#					
Body Image Score*					
(Constant)	79.548	15.459	0.000	48.983	110.113
Dysgeusia (G0/1 _{ref.} vs G2)	-11.406	5.050	0.025	-21.391	-1.421
Skin hyperpigmentation (G0/1 _{ref.} vs G2)	-6.189	3.124	0.050	-12.366	-0.13
Sexual Functioning Score					
(Constant)	19.504	10.878	0.075	-2.004	41.012
Fatigue (G0/1 _{ref.} vs G≥2)	-11.587	4.546	0.012	-20.576	-2.598
Gastritis (G0/1 _{ref.} vs G≥2)	10.909	3.602	0.003	3.787	18.030
Dry mouth (G0/1 _{ref.} vs G≥2)	-10.128	4.028	0.013	-18.093	-2.164
Sexual Enjoyment Score*					
(Constant)	49.739	20.740	0.021	7.966	91.512
Fatigue (G0/1 _{ref.} vs G≥2)	-25.320	8.346	0.004	-42.129	-8.512
Peripheral neuropathy (G0/1 _{ref.} vs G≥2)	16.231	7.286	0.031	1.556	30.906
Future Perspective Score					
(Constant)	32.397	26.130	0.217	-19.266	84.061
Dysgeusia (G0/1 _{ref.} vs G2)	-15.859	5.881	0.008	-27.487	-4.231
Systemic Therapy Side Effects Score*					
(Constant)	-21.726	8.765	0.014	-39.059	-4.392
Dry mouth (G0/1 _{ref.} vs G≥2)	11.789	2.254	0.000	7.332	16.246
Dysgeusia (G0/1 _{ref.} vs G2)	13.532	2.996	0.000	7.608	19.457
Constipation (G0/1 _{ref.} vs G≥2)	8.355	2.484	0.001	3.443	13.267
Vomiting ((G0/1 _{ref.} vs G≥2)	6.274	1.916	0.001	2.485	10.063
Peripheral neuropathy (G0/1 _{ref.} vs G≥2)	4.819	1.854	0.010	1.152	8.486
Diarrhea (G0/1 _{ref.} vs G≥2)	5.443	2.318	0.020	0.859	10.027
Nausea (G0/1 _{ref.} vs G≥2)	-6.199	2.696	0.023	-11.531	-0.867
Arm Symptoms Score					
(Constant)	19.313	5.053	0.000	9.323	29.303
Lymphopenia (G0/1 _{ref.} vs G≥2)	-6.607	2.507	0.009	-11.563	-1.652
Upset by Hair Loss Score					
(Constant)	-17.564	17.139	0.307	-51.455	16.327
Dysgeusia (G0/1 _{ref.} vs G2)	16.238	5.770	0.006	4.829	27.648
Skin hyperpigmentation (G0/1 _{ref.} vs G2)	7.715	3.589	0.033	0.617	14.813

Notes: *R² ≤ 10%; #for all others: 23.6% ≤ R² ≤ 55.6%. G0/1= Grade 0 or 1; G≥2=Grade 2 and above. The model was corrected/adjusted for baseline quality of life score, corresponding statistically significant sociodemographic and clinical variables.

Abbreviation: Ref, reference category.

revealed that different functional dimensions of QoL and GHS score were low among breast cancer patients chemotherapy.^{40–42} Despite the global health status was increased to 6.85 points above the pretreatment score by the end of cycle 8 ($P=0.020$), physical, role, and emotional functioning of the patients persisted below the pretreatment score by 11.39 ($P=0.000$), 8.11 ($P=0.039$) and 4.44 ($P=0.155$), respectively, by the end of cycle 8. Conversely, a study also reported that women who received chemotherapy will have worse QOL even at a 5-month follow-up.⁴³ However, the social and cognitive functioning of the patients were shown a persistent worsening pattern from baseline to the end of cycle 8. The psychological distress,⁴⁴ worsening of physical well-being⁴³ and social domain⁴⁵ were frequent among patients with breast cancer on chemotherapy. Cross-sectional studies in Ethiopia also indicated that social and psychological domains and social support were found to be poor in women with breast cancer.^{42,45} Therefore, implementing appropriate psychosocial support and social networks might improve the functional dimensions of QoL.^{42,46}

Even though different cross-sectional studies reported that the quality of life of breast cancer patients under chemotherapy treatment is poor,^{45,47} our prospective study found that the deterioration of quality of life among women with breast cancer depends on the domain/scales of quality of life and the cycle of chemotherapy. Likely, on contrary to the GHS and functional scales of scores, body image scores of the patients were slightly increased from baseline to the end of cycle 8 (ie, 7.29 points above pretreatment score, $P=0.031$). However, future perspectives and sexual functioning showed a decreasing pattern from pretreatment to the end of cycle 4 (ie, 6.62 points below the pretreatment score, $P=0.051$) and cycle 6 (ie, 9.59 points below the pretreatment score, $P=0.006$), respectively, even though they increased towards to pretreatment level afterward. The study by Horwitz et al.⁴³ supports our finding that chemotherapy harmed women's sexual functioning ($P=0.01$) and their physical well-being ($P=0.09$).

In addition to the functional scales, the symptom scales/items of the quality of life of the patients with cancer got worse (as shown by an increase in scores) during chemotherapy.^{45,47,48} Conversely, fatigue, appetite loss, and nausea and vomiting scores were increased (ie, deteriorated) from baseline to end of cycle 2 by more than 40 points while they started to decrease slowly from the end of cycle 2 to cycle 8. Nausea and vomiting score at the

end of cycle 8 was 1.27 points below the pretreatment score ($P=0.295$), whereas fatigue and appetite loss were decreased to 18.09 ($P=0.000$) and 19.57 ($P=0.000$) points above the pretreatment score. Therefore, these results indicated that there is a significant clinical and statistical worsening as compared to baseline for fatigue and appetite loss dimensions even by the end of all chemotherapy courses.

Shortness of breath/dyspnea, pain, and insomnia were also among the dimensions of quality of life that were impaired among breast cancer women who received chemotherapy.^{43,49} On contrary to fatigue, appetite loss, and nausea and vomiting subscale, maximum score difference observed for dyspnea, pain, and insomnia from baseline scores were 9.47 points which were less than 10 points to reach significant clinical deterioration despite their statistically significant impairment ($P\leq 0.023$) during the first two cycles of chemotherapy.

Except from financial difficulties in which its worsening were persistently increased from baseline to end of cycle 8 ($P=0.000$), pain, dyspnea, insomnia, constipation, and diarrhea scores among the study participants were recovered to scores that had no statistical and clinical significant worsening from baseline score by the end of cycle 8. Different cross-sectional studies in Ethiopia also indicated that financial difficulties were frequently reported, in addition to other dimensions, among patients with cancer.^{45,48,50}

The other dimensions of quality of life frequently affected during breast cancer chemotherapy were systemic therapy side effects.^{38,42,51} Our current finding also indicated that the systemic therapy side effects and upset by hair loss scores were increased steeply from baseline to the end of cycle 2 at least by 30 points. However, starting from the end of cycle 4, systemic therapy side effects were decreased (ie, recovered) towards 25.74 ($P=0.000$) points above the pretreatment score. This indicates that despite its significant decrements from the end of cycle 4, systemic therapy side effects remained statistically and clinically meaningful worsening even by the end of cycle 8. Moreover, the upset by hair loss score was started to worsening after it reached the pretreatment level in cycle 6. On contrary to the other symptom scales, breast symptoms and arm symptoms were decreasing (ie, improved) at least by 14 points from baseline to the end of cycle 8.

As it was demonstrated in our finding, different cross-sectional studies reported that the majority of the quality of life dimensions were deteriorated significantly (ie,

clinically and/or statistically) in the first two/three cycles of chemotherapy than higher cycles,^{9,39,47} and it improves once chemotherapy is completed or near to the end.^{52,53} Overall, our finding indicated that overall QoL/global health status and functional scales (ie physical, role, emotional, social, and sexual enjoyment), except for cognitive function significantly decreased both clinically (decreased at least by ten and more points) and statistically ($P \leq 0.05$) in particular from baseline score to the end of cycle 2. Except for cognitive and social functioning which persistently declined from baseline to the end of cycle 8, others were started to recover (ie, increased) after the end of cycle 2 and approached pre-treatment scores by the end of all treatment courses. However, despite their statistically significant deterioration ($P \leq 0.05$) from baseline, the other functional scales such as sexual functioning, body image, and future perspectives of the patients did not reach clinically meaningful deterioration during any course of chemotherapy.

On contrary to the functional scales above, the symptom scales such as nausea and vomiting, fatigue, appetite loss, constipation, diarrhea, systemic therapy side effects, and upset by hair loss of the patients were significantly deteriorated (ie, increased) both clinically and statistically from baseline score to the end of cycle 2, though they showed declining pattern afterward. However, dyspnea, insomnia, and pain did not reach clinically meaningful worsening even though their deterioration was statistically significant ($P \leq 0.05$) in particular during the first two cycles of chemotherapy. Fortunately, on opposite to all other symptom scales/items, breast symptoms, and arm symptoms of the patients were decreased even during the first two cycles to the end of cycle 8. As it was learned from our finding, the majority of the quality of life dimensions that were deteriorated during the first two cycles of chemotherapy were started to improve after the end of cycle 2 or cycle 4. This might be happened due to the so-called “response shift” characterized by an internal reframing of the patient concerning their perception of health.⁵⁴

Decreasing quality of life implicates that an increased dependence of the patients on family members or caregivers, and it might also cause an increased state of immunosuppression (ie, increased risk of infectious complications) and which ultimately affects the psychology of the cancer patient.⁵⁵

The deterioration of different dimensions of quality of life during chemotherapy and its improvements near and/

or after the end of chemotherapy indicates that it is obviously due to adverse events associated with chemotherapy.^{56–58} Unfortunately, on top of that, due to sociodemographic, clinical, and treatment-related factors, as well as behavioral and psychosocial factors,⁵⁹ the quality of life of Ethiopians with cancer was found below.⁵⁰

Multidimensional QoL assessment showed that breast cancer chemotherapy's toxicities mainly affect physical functioning and global quality of life.^{18,32,60} Likewise, among the AC and AC-T chemotherapy toxicities observed in our study,²⁵ grade 2 and above fatigue, dysgeusia, and constipation negatively affect the overall quality of life/Global Health Status of the patients ($-10.544 \leq B \leq -7.709$, $P \leq 0.013$). Furthermore, the functional subscales such as physical functioning, role functioning, social functioning, emotional functioning, cognitive functioning, sexual functioning, sexual enjoyment, body image, and future perspectives were also negatively affected ($-25.320 \leq B \leq -6.351$, $P \leq 0.033$) at least by one or more grade ≥ 2 AC and AC-T chemotherapy toxicities like fatigue, dysgeusia, constipation, vomiting, oral mucositis, and peripheral neuropathy. Conversely, a cross-sectional study in Spain found that nausea, dysgeusia, peripheral neuropathy, loss of appetite, myalgia, and peripheral edema due to cancer chemotherapy harmed the quality of life of those who did not experience these toxicities.⁵⁵

Studies elucidated that breast cancer chemotherapy impairs cognitive functions⁶¹ such as problems with memory, attention, processing speed, and executive functioning.³ And fatigue ($B = -20.385$, $P \leq 0.001$) was the only non-hematological toxicity that negatively associated with impairment of cognitive functioning among our study participants. As it was explained above, the social functioning of our study participants persistently decreased from baseline to the end of the chemotherapy course. Managing fatigue and dysgeusia in these patients could be a solution since grade ≥ 2 fatigue ($P = 0.008$) and dysgeusia ($P = 0.007$) were negatively associated with decrements in social functioning among our study participants. Our study also revealed that illiterate and patients with higher alkaline phosphatase and tumor stage $\frac{3}{4}$ had a lower social functioning status than their counterparts. Hence, they might need some fatigue and dysgeusia coping-up mechanisms in particular among illiterate and with tumor stage $\frac{3}{4}$ to overcome their social functioning problem.

The symptom scales were also frequently deteriorated due to breast cancer chemotherapy's toxicities in our study

participants. For example, the fatigue score was significantly increased ($8.067 \leq B \leq 14.914$, $P \leq 0.039$) due to grade ≥ 2 fatigue, dysgeusia, constipation, oral mucositis, and peripheral neuropathy. The systemic therapy side effects score was also significantly increased ($4.819 \leq B \leq 13.532$, $P \leq 0.020$) due to grade 2 to above dry mouth, dysgeusia, constipation, diarrhea, vomiting, and peripheral neuropathy.

As it was elucidated in our finding, different studies indicated that fatigue is the symptom that had, by far, the largest impact (ie, strong predictor) on limiting function and on overall QoL in breast cancer patients, unlike other toxicities.^{62–65} Conversely, in our study, in addition to its impact on GHS and functional scales, grade 2 and above fatigue was significantly associated with the worsening of different symptom scales/items of QoL. For example, it was associated with increased fatigue ($B=14.914$, $P=0.001$), appetite loss ($B=9.620$, $P=0.031$), insomnia ($B=11.973$, $P=0.043$) and financial problems ($B=11.572$, $P=0.006$) scores. Different studies in Ethiopia and elsewhere also indicated that cancer and treatment-related fatigue is common among cancer patients who have received chemotherapy and results in substantial adverse physical, psychosocial, and economic consequences for patients that significantly worsened QoL.^{44,47,66}

Henceforth, as the grade ≥ 2 fatigue was frequently associated with deterioration of multidimensional quality of life (ie, GHS, functional scales, and symptoms scales/items) of the patients with breast cancer on AC or AC-T chemotherapy, devising fatigue coping mechanism like yoga type physical exercise among the breast cancer patients have paramount importance for the improvement of overall quality of life.^{67–69}

Like that of fatigue, grade 2 dysgeusia was also frequently associated with impairment of multidimensional QoL among breast cancer patients who received AC or AC-T chemotherapy. Conversely, it was associated with the worsening of GHS ($P=0.003$), role functioning ($P=0.000$), emotional functioning ($P=0.010$), social functioning ($P=0.007$), body image ($P=0.025$), future perspectives ($P=0.008$), fatigue ($P=0.003$), pain ($P=0.001$), dyspnea ($P=0.000$), insomnia ($P=0.001$), appetite loss ($P=0.002$), systemic therapy side effects ($P=0.000$) and upset by hair loss ($P=0.006$). In line with our study, Ponticelli et al and other authors found that patients with dysgeusia have a higher probability of having a worse QoL.^{70,71}

Prieto-callejero et al.⁵⁵ reported that peripheral neuropathy as the toxicity of chemotherapy affects diverse aspects of quality of life in those patients who received taxane-containing regimen. Also, constipation is has a

highly significant effect on a patient's well-being.⁷² Likely, in our case, grade ≥ 2 peripheral neuropathy and constipation ($4.819 \leq B \leq 26.451$, $P \leq 0.039$) were also the other toxicities of AC and AC-T breast cancer chemotherapy that frequently associated with deterioration of symptom scales/items like fatigue, pain, dyspnea, constipation, diarrhea and/or systemic therapy side effects than their lower-grade counterparts. One preliminary finding reported that regional cooling of hands and feet might have good effectiveness and tolerability, in reducing the symptoms of chemotherapy-induced peripheral neuropathy, hence improving the different dimensions of quality of life affected by it.⁷³

The above finding of our study supported the evidence that all chemotherapy's toxicities do not equally deteriorate the quality of life.^{74,75} On the other hand, patients' self-reports quality of life domains mirrored those of their chemotherapy side effects.³⁸ For instance, in grade 2 and above, dry mouth and dysgeusia were associated with deterioration of appetite loss ($15.642 \leq B \leq 20.016$, $P \leq 0.031$). Likewise, grade 2 and above constipation ($B=26.451$, $P \leq 0.001$) and diarrhea ($B=19.52$, $P \leq 0.001$) were the positive predictor for constipation and diarrheal score, respectively. Grade ≥ 2 myalgia and arthralgia were also predicted for higher pain score ($B=8.50$, $P=0.011$), grade 2 skin hyperpigmentation was associated with lower body image ($B=-6.189$, $P=0.05$) and higher upset for hair loss score ($B=7.715$, $P=0.033$).

Nonetheless, diverse scales of both EORTC QLQ-C30 and EORTC QLQ-BR23 were deteriorated due to non-hematological AC and AC-T breast cancer chemotherapy's toxicities, its hematological toxicity like anemia was associated with worsening of QoL (ie fatigue dimension). On top of that, patients with lymphopenia experienced less deterioration of arm symptoms than those who did not report lymphopenia. Besides, alkaline phosphatase increment due to chemotherapy was among the contributing factors for deterioration of role functioning ($B=-7.742$, $P=0.027$) subscales. However, we did not find any association between neutropenia or leukopenia and deterioration of QoL. Likely, the study indicated that asymptomatic toxicities like granulocytopenia and leukopenia do not necessarily mean a decline in QoL unlike with symptomatic toxicities.^{32,52} Consequently, establishing supportive and peer groups such as psychiatrists, psychologists, physical therapists, and social workers,^{34,76} and providing educational sessions on the disease, and its treatment distressing toxicities can improve the QoL^{58,77} of patients of this group.

In general, besides grade ≥ 2 fatigue, dysgeusia, constipation, dry mouth, oral mucositis, peripheral neuropathy, and skin hyperpigmentation that frequently associated with deterioration QoL; anemia, lymphopenia, and ALP increment were non-subjective toxicities that predict fatigue, arm symptoms, and role functioning score, respectively.

In addition to the toxicities of the chemotherapy, the socio-demographic and clinical characteristics of the patients also contribute to the deteriorations of different quality of life domains. Conversely, educational status (literate vs illiterate), tumor stage ($\frac{1}{2}$ vs $\frac{3}{4}$), age (continuous), regimen (AC vs AC-T), having at least one child, marital status (having spouse vs having no spouse), body surface area and some baseline laboratory values such as hemoglobin, white blood cells, neutrophils, alkaline phosphatase, and serum creatinine affect diverse aspects of QoL among our study participants.

There was conflicting finding regarding the effect of sociodemographic and clinical characteristics on QoL among patients who received chemotherapy.^{63,64,78,79} However, in line with the studies conducted by Wondie et al and others,^{48,50} we found that the educational status (ie, illiteracy) and/or stage of the tumor (ie, stage $\frac{3}{4}$) were the most frequent sociodemographic factors associated with the deterioration of different subscales of EORTC QLQ-C30 and BR23. A possible explanation for this finding is the ability of educated women to understand the nature of the disease and to comply with the therapeutic recommendations better than the less educated.⁵⁹ Moreover, different studies identified sociodemographic predictors such as age, residence, marital status, educational level, employment status, and tumor stage for deterioration of QoL.^{8,47,79}

A holistic approach like combined diet, physical exercise, and psychosocial intervention during chemotherapy in patients with breast cancer led to positive changes in a range of psychological, physiological, and behavioral outcomes at the end of the intervention,^{61,69,80} that ultimately improve the overall quality of life of women on breast cancer chemotherapy.^{81,82}

Strength and Limitation of the Study

Even though the majority of studies conducted on QoL among patients with breast cancer so far were cross-section in nature, we reported the pattern of QoL prospectively among women with breast cancer particularly on AC or AC-T chemotherapy. Moreover, still, the majority

of QoL studies were reported from clinical trials, but importantly we reported this prospective patient-reported outcome study from the actual clinical practice (ie, real-world patients). To our knowledge, the current study is the first in design to answer the pattern QoL on a course of AC and AC-T chemotherapy cycles and in determining the impact of AC and AC-T chemotherapies' toxicities on QoL among women with breast cancer in Ethiopia. However, since we followed our cohorts only for the median of 8 cycles (ie, 6 months), we could not report the pattern of QoL and the factors that affect it long after the end of chemotherapy courses.

Conclusion

The majority of the quality of life dimensions among Ethiopian breast cancer patients on AC and AC-T chemotherapy were significantly deteriorated clinically and statistically particularly during the first two cycles of chemotherapy despite its improvements afterward. In addition to age, tumor stage and educational status of the patients, grade 2 and above AC and AC-T chemotherapy's toxicities such as fatigue, dysgeusia, constipation, oral mucositis, dry mouth, peripheral neuropathy, and skin hyperpigmentation were frequently associated with deterioration of different dimensions of quality of life. Devising different strategies to improve the deteriorated QoL due to chemotherapy's toxicities particularly during the first two cycles has paramount importance.

Data Sharing Statement

Please contact the corresponding author for data requests.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest.

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