Pharma Multidisciplinary Research Journal (PMRJ) **Open Access**
2024, Volume 1, Issue 1 **ISSN online: 3006-2896**
https://pmrj.epua.online/index.php/pmrj

Original Article

Predictors of time to death among cervical cancer patients at Hawassa University Comprehensive Specialized Hospital: Facility-based retrospective follow-up study

Afework Aklilu[1*], Akalewold Alemayehu[2], Temesgen Tafesse[2] and Anteneh Fikrie[3,4]

[1]Department of Nursing, Hawassa College of Health Sciences, P.O. Box 84, Hawassa, Ethiopia
[2]School of Public Health, College of Medicine and Health Sciences, Hawassa University, Ethiopia
[3] School of Public Health, Pharma College, Hawassa, Ethiopia, P.O.Box 67
[4] School of Public Health, Institute of Health, Bule Hora University, Bule Hora, PO. Box 144, Ethiopia.
*corresponding author: Afk.aklilu@gmail.com;

Abstract

Background: Cervical cancer is a significant global mortality issue, with less than 50% of women in developing countries surviving beyond 5 years, with survival and death predictors varying across studies. Hence, understanding predictors of time to death among cervical cancer patients is crucial for improving prognosis and to develop targeted interventions. The study aimed to determine the time to death from cervical cancer and predictors among cervical cancer patients at Hawassa University Comprehensive Specialized Hospital, Ethiopia, 2023.

Methods: This facility-based retrospective follow-up study used 212 medical records from cervical cancer patients at Hawassa University's Comprehensive Specialized Hospital from January 1, 2018 to December 31, 2022, using a simple random sampling method. Data were collected using a structured checklist and entered and analyzed using Epidata and Stata version 16 respectively. The Kaplan-Meier survival curve and log rank test were utilized for estimating survival time and comparing two groups statistically respectively. A Cox proportional hazard model was used to predict time to death. An adjusted hazard ratio with 95% confidence intervals (CI) and a p-value of less than 0.05 were considered to declare the statistical significance.

Results: The overall incidence density of death was 12.4 per 1000 person-years of Follow-up. The median (Interquartile range) time to death was 23 (2-36) months. The Cox proportional hazards regression analysis revealed that advanced Stage of cancer (AHR = 2.1; 95% CI: 1.068-4.068) and presence of co-morbidities (AHR=1.2; 95% CI: 1.065-1.233) were a significant predictors of time to death from cervical cancer.

Conclusion: The overall death rate was found to be low as compared to other studies conducted both nationally and globally. But Stages of cancer and co-morbidity status are critical predictors, emphasizing early detection and comprehensive care for improving survival outcomes in cervical cancer patients.

Keywords: Cervical Cancer, Survival Status, Hawassa University Comprehensive Specialized Hospital, Ethiopia

Introduction

Cancer is a disease characterized by abnormal blood cell or tumor formation, affecting various organs and parts of the body (1). In benign tumors, cells are confined to one area and cannot spread to other parts of the body, while malignant tumors consist of cancer cells that can spread through the bloodstream or lymphatic system (1).

Cervical cancer (CC) is a malignant tumor of the cervix that emerges at the junction between the outer squamous cell layer and inner columnar cell lining of the cervix (2,3). In the early Stages, it might not even cause any symptoms (4). However, in its advanced Stage, it may manifest symptoms such as chronic pelvic pain, inexplicable weight loss, unusual vaginal discharge, bleeding during and after sexual activity, and pain following sexual activity (5). Chronic infection with high-risk human papillomavirus (HPV) types is the primary cause of cervical pre-cancer and cancer (4,6). According to studies, more than 80% of women who engage in sexual activity may have genital HPV infection at some point in their lives (4).

Routine cervical screening has been shown to reduce both the incidence and mortality of the disease (7). However, over 80% of invasive cervical cancers globally occur in developing nations due to difficulties in implementing effective screening programs (8). The World Health Organization (WHO) reports that only 5% of women in resource-poor countries undergo CC screening, compared to 40-50% in developed countries (9). In Sub Saharan Africa the coverage still remains low (10), and the incidence and mortality rates associated with the disease are high in this region (11). The Catalan Institute of Oncology (CIO) information Centre on HPV and Cancer reports that in Ethiopia, cervical cancer screening coverage is less than 1% (12).

CC affects one in every 8,500 women globally each year (13). An approximate estimate of the number of cases and deaths worldwide from CC in 2018 is 570,000 cases and 311,000 deaths related to the disease (14). Less developed countries have a larger share of the global cancer burden, accounting for 57% of cases and 65% of deaths over the past three decades (15). The management of CC in Africa is hindered by inadequate pathology services, a shortage of diagnostic facilities, and a weak healthcare infrastructure along with a noticeable outflow of qualified healthcare workers (16). Estimates indicate that by 2030, CC will kill over 443,000 women annually, the majority

of whom will reside in sub-Saharan Africa (17). Sub-Saharan Africa's one-third of households are women-headed, and over half of grandchildren of departed parents living with their grandmothers are at risk for CC (18). Cancer-related deaths not only cause emotional distress but also have significant financial implications, including job loss for caregivers and high medical expenses for cancer patients (18).

According to available data, 7600 out of the approximately 22 million Ethiopian women aged 15 and older have been diagnosed with CC, and the disease claims the lives of about 6,000 of these women annually (19). These findings are perhaps significantly below the exact amount of cases, assumed the poor level of awareness, price, and inadequate access to screening services and absence of a countrywide cancer registry (19).

Thirty-five point nine (35.9%) new cases of CC are diagnosed and 22.6 die from it per 100,000 women annually and many factors associated with are HPV, cultural factors like early marriage, poverty, co-infection and lack of awareness (20). Due to sporadic and inconsistent CC screening as well as a lack of established policies and procedures, women usually seek cancer treatment when the disease is advanced and treatment is probably not effective. Likewise, it is anticipated that the qualifications of medical staff, enhanced health services, CC screening initiatives, and other relevant changes will impact the survival rate of patients with CC (20). For those all reasons, it is very significant to study the current predictors of time to death among CC patients. Therefore, the aim of this study was to identify predictors of time to death among cervical cancer patients at Hawassa University Comprehensive Specialized Hospital (HUCSH).

Methods and Materials

Study setting

This facility-based retrospective Follow-up study was conducted in H HUCSH Cancer Treatment Center. HUCSH Cancer Treatment Center is a specialized medical center located in Hawassa, which is located 275 km south of Addis Ababa, the capital of Ethiopia. It is a part of the HUCSH, which is one of the leading healthcare institutions in the region. It is the only cancer center in the southern parts of Ethiopia, which provides cancer treatment and management service for more than 18 million people living in the Sidama region, Southern Ethiopia region (21) and also serving as a referral for some Zones of Oromia regional state such as Arsi, Bale, Guji and Borena Zones. It has 18 beds

for chemotherapy and 4 beds for palliative cares. More than 800 new cancer patients receive chemotherapy from the treatment center annually (21).

Study design and Period

A facility-based retrospective Follow-up study was conducted from February 2023 to May 2023.

Study population

All medical records of CC patients who attended the Oncology center of HUCSH from January 1, 2018 to December 31, 2022 were considered as study participants.

Sample size determination

The required sample size was computed using the Freedman method of proportional event allocation as shown below (22).

$$\text{Sample size (n)} = \frac{\text{Number of events}}{\text{Probability of event}}$$

$$\text{Number of event} = \frac{(z_{\alpha/2} + z\beta)^2}{pq\,(\log HR)^2}$$

$$\text{Probability of the event} = 1 - (ps1(t) + qs2(t))$$

where n is the sample size; $z_{\alpha/2}$ is a significant level of α of 5%, which is 1.96; β is the power (90%), p is the proportion of population allocated for the first group, q proportion of population allocated for the second group, s1 (t) is survival function at time t1, s2 is survival function at time t2 and HR is the hazard ratio of each variable which are taken from similar previous studies.

In the freedman principle approach, the equal allocation between these groups assumed. That means p = q = 0.5. Stata version 14.0 was used to calculate the required sample size by using the "power" command (power log-rank 0.5, hratio (0.45) power (0.9) wdprob (0.1)) of Stata. The hazard ratios of five variables that are statistically significant from the previous articles were used in the calculation of the sample size for this study. The sample size obtained by the above command is 212.

Sampling technique and procedure

Simple random sampling was used to select study participants. First of all, the total number of Women with CC who was on follow-up from January1, 2018 to December 31, 2022 HUCSH was counted and recorded from the patient registration book. The total count of CC patients in the specified years of enrolment period was 371. The total unit of the Frame was thus from1 to 371. These recorded data were entered in to computer excel and made randomized. Then the randomized medical record numbers were sorted so that the desired number of subjects

(n=212) were taken top to down from the list.

Study variables

The dependent variable of the study was time to death and the independent variables were Socio demographic, Clinical predictors, reproductive related predictors and Treatment related predictors.

Operational definition

Event: Time to death from cervical cancer.

Censored: patients, who were lost, follow-up, not die up to the study period and those transfer to different care unit during the study.

Comorbidity: The presence of any conditions (mentioned in the Carlson comorbidity Index (23) other than CC at diagnosis which was designated as "yes**"** in the checklist.

Anemia: CC patient with hemoglobin levels below 12.0 g/dl was classified as anemic in this study (24).

Entry date and closing date to follow-up: The entry date was the starting date for calculation of survival status, and the first date of clear diagnosis of CC (January 1st, 2018 to December 31st, 2022). Closing dates were the ending date to Follow-up (December 31st, 2022).

Survival status: In this study, survival status was defined as the outcome of patients which has classified into censored or death from patient clinical data file from scheduled or unscheduled return visits.

Time to death: time to death was calculated at the time between the dates of clear diagnosis of CC to the date of death (in month).

Data collection procedures, and quality control

Data was extracted from patient's charts using pre-tested and structured data extraction checklist prepared in English. The checklist consisted three parts: (1) Sociodemographic predictors, (2) Clinical and reproductive related predictors and (3) Treatment related predictors.

Six Diploma HIT (Health Information Technician) for retrieving patient medical record from shelf of Medical record room, two supervisors first degree holder in Oncology Nursing and five data collectors having first degree in Nursing were involving in the data collection process. The quality of data was assured by proper designing and pre-testing of the checklists in

5% of patient's charts and by giving training to the data collectors and supervisors before the actual data collection. Appropriate modifications were made after viewing the pre-test result and overall supervision was made by the principal investigator.

After recruiting data collectors and supervisors, one-day intensive training techniques of data extraction process was given to them before the actual work begin regarding the aim of the study, procedures including ways of extraction the data and clarify about the checklist.

Data processing and analysis

Data were cleaned, coded and entered to EPI-data version 3.1 and exported to Stata version14.0 statistical software for analysis. Frequencies, proportions and descriptive statistics were used to explain the study population in relation to relevant variables and were presented using tables and graphs.

Kaplan Meier analyses with life table were used to identify the overall survival rates and median survival time. Differences in survival among different variables were compared using the log-rank test (25). Before running the Cox regression model, assumption of proportional hazard was performed. Cox-proportional hazard model assumption was checked using Schoenfeld residual test and variables having P-value > 0.05 were considered as fulfilling the assumption **(See Table S1 and Figure S2)**

Variables with a significance level below 0.2 in the bivariable Cox regression model were included in a multivariable Cox regression model analysis. Variables in multivariable Cox model with a p-value < 0.05 were considered to have actual interference with the survival of the patients with 95% confidence interval.

Results

Socio-demographic characteristics of the study participants

From 371 CC patients in the Oncology Center of HUCSH, about 212 were eligible samples for this study. The mean ± standard deviation (SD) of participants' age was 47.2 ± 12.2 years. The minimum and maximum ages of patients were 18 and 80 years, respectively, and majorities (58%) of the participants were rural dwellers. About more than two third 87.3 % were married and 85.4% have more than three children (Table 1).

Table 1. Socio-demographic characteristics of CC patients in HUCSH Oncology Center, Hawassa, Ethiopia, 2023 (n=212).

Covariates	Category of covariates/ response	Status at last contact		Total Frequency (%)
		Death No. (%)	Censored No. (%)	
Age at diagnosis	18-29 years	1(0.5)	19(9)	20(9.4)
	30-39 years	1(0.5)	37(17.5)	38(17.9)
	40-49 years	3(1.4)	56(26.4)	59(27.8)
	50-59 years	8(3.8)	44(20.8)	52(24.5)
	>=60 years	8(3.8)	35(16.5)	43(20.3)
Residence	Urban	9(4.2)	80(37.7)	89(42)
	Rural	12(5.7)	111(52.4)	123(58)
Marital status	Married	19(9)	166(78.3)	185(87.3)
	Single	0*	5(2.4)	5(2.4)
	Divorced	1(0.5)	9(4.2)	10(4.7)
	Widowed	1(0.5)	11(5.2)	12(5.7)
Number of children	No child	1(0.5)	11(5.2)	12(5.7)
	One child	0*	2(0.9)	2(0.9)
	Two children	1(0.5)	16(7.5)	17(8)
	≥Three	19(9)	162(76.4)	181(85.4)

***Values that hadn't death from the specific categorical variable in this research.**

Clinical and histopathological characteristics of the study participants

Among 212 CC patients, nearly one-fourth (21.7%) of them were presented at advanced Stages (IV), two hundred four (96.2%) had squamous cell carcinoma, one hundred thirty seven (64.6%) were anemic during the presentation. Nearly one-fifth (17.5%) had comorbidity and of those who had comorbidity, sixteen (43.2%) were HIV positives (Table 2).

Treatment related characteristics of study participants

Of a total of 212 study subjects, nearly two-thirds (67.9%) took chemotherapy treatment only. about thirty seven (17.5%) took treatments with combination. Fifty two (24.5%) of patients had four or more than four chemotherapy cycles (Table 3).

Table 2: Clinical and histopathological characteristics of CC patients in HUCSH Oncology center, Hawassa, Ethiopia, 2023 (n=212).

Covariates	Category of covariates/ response	Status at last contact		Total Frequency (%)
		Death No. (%)	Censored No. (%)	
FIGO Stage	Stage I (IA-IIA)	0*	12(5.7)	12(5.7)
	Stage II (IIB-IIIA)	2(0.9)	111(52.4)	113(53.3)
	Stage III (IIIB-IVA)	5(2.4)	36(17)	41(19.3)
	Stage IV (IVB)	14(6.6)	32(15.1)	46(21.7)
Histopathology	Squamous cell	20(9.4)	184(86.8)	204(96.2)
	Adenocarcinoma	1(0.5)	7(3.3)	8(3.8)
Baseline	Yes	20(9.4)	117(55.2)	137(64.6)
Anemic status	No	1(0.5)	74(34.9)	75(35.4)
Comorbidity	Yes	19(9)	18(8.5)	37(17.5)
	No	2(0.9)	173(81.6)	175(82.5)
Types of comorbidity	HIV	8(21.6)	8(21.6)	16(43.2)
	Hypertension	4(10.8)	9(24.3)	13(35.1)
	Others	7(18.9)	1(2.7)	8(21.6)

Values that hadn't death from the specific categorical variable in this research.

Table 3: Treatment-Related characteristics of CC patients in HUCSH Oncology Center, Hawassa, Ethiopia, 2023 (n=212)

Covariates	Category of covariates/ response	Status at last contact		Total Frequency (%)
		Death No. (%)	Censored No. (%)	
Treatment initiated	Chemotherapy	10(4.7)	134(63.2)	144(67.9)
	Surgery	6(2.8)	25(11.8)	31(14.6)
	Combination of treatments	5(2.4)	32(15.1)	37(17.5)
Chemotherapy cycles	No chemotherapy	5(2.4)	27(12.7)	32(15.1)
	First cycle	4(1.9)	42(19.8)	46(21.7)
	Second cycle	6(2.8)	45(21.2)	51(24.1)
	Third cycle	1(0.5)	30(14.2)	31(14.6)
	≥Fourth cycles	5(2.4)	47(22.2)	52(24.5)

Survival statuses of cervical cancer patients, at last, Follow-up

Of the total 212 eligible samples of CC patients in the oncology center of HUCSH who were followed for 58 months, about 191 (90.1%) were censored and 21 (9.9%) developed the event of interest, i.e. died. More than half 116 (60.73%) of the censoring were transferred out to other facilities up to the end of the study period. Those who was live up to end of study was 52 (27.23%) and lost to follow-up were 23 (12.04%) (Figure 1).

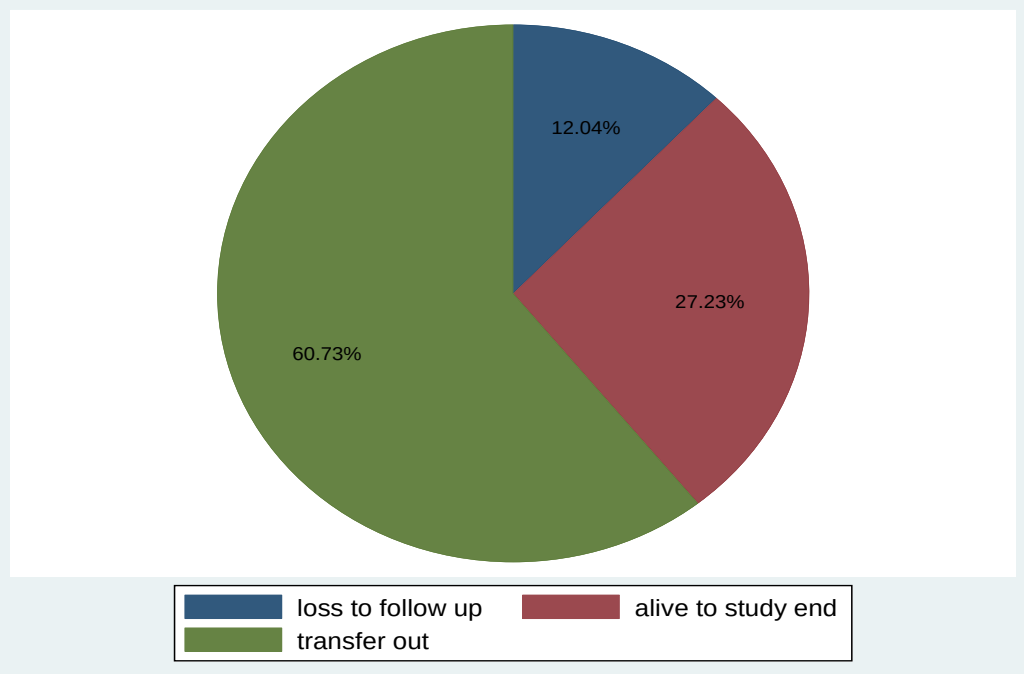

Figure 1: Censoring status of CC patients in HUCSH Oncology Center, Hawassa, Ethiopia, 2023 (n=212).

Incidence of death among cervical cancer patients during the follow-up time

A follow-up was conducted for 58 months on 212 CC patients yielding 1690 person years at risk. The median (Interquartile range) follows up time was 23 (2-36) months. Twenty one (9.9%) new death was observed in the total Follow-up time making the overall death incidence rate 12.4 per 1000 person-years.

Overall Survival of cervical cancer patients during the follow-up time

In this study, 212 CC patients were followed for 58 months. The median survival of this cohort was 23 months. The overall estimated survival rate after diagnosis of CC was 28.39% at 58 months of Follow-up. The estimated cumulative survival was 73.1%,

64.9%, 56.79 % and 28.39 % at 12, 24, 36, and 58 months respectively as shown in the following Kaplan Meir survival curve (Figure 2). The curve also indicates that the probability of survival decreases as the follow-up time increases which is the typical characteristics of survival data analysis. As it is also shown on the KM survival curve, the highest rate of mortality was observed between 20 to 40 months.

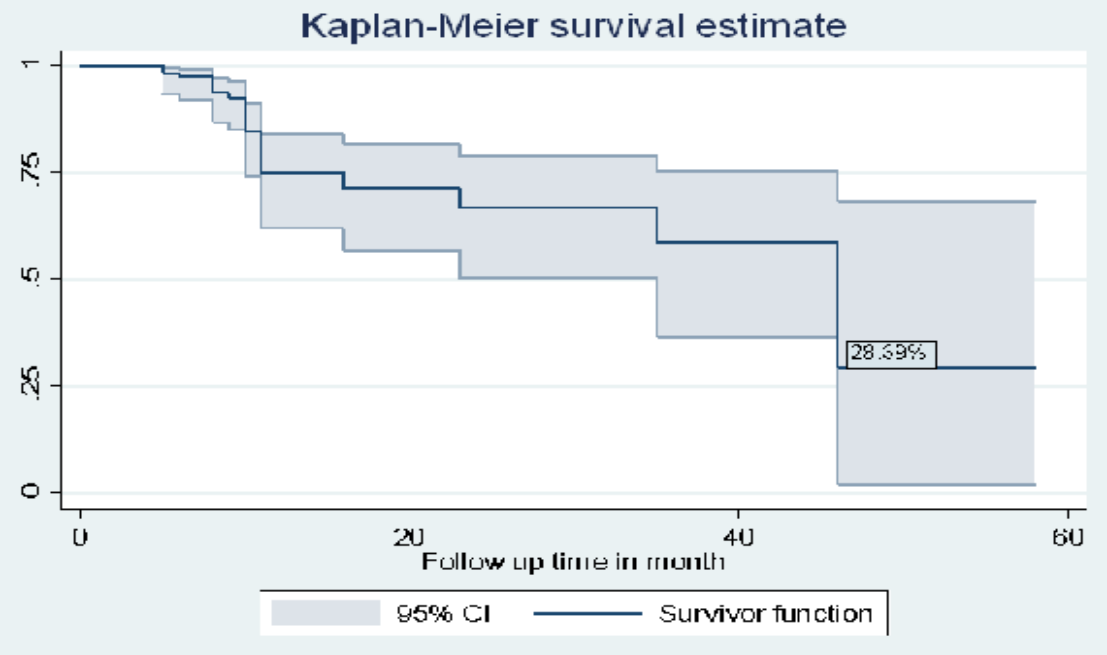

Figure 2. Overall Kaplan-Meier estimation of survival of CC patients followed at HUCSH from January 1st 2018 to December 31st 2022, Hawassa, Ethiopia, 2023 (n=212)

Survival experience among different groups of cervical cancer patients

Statistical difference in survival time between different categories of covariates was tested using the Log-rank test. It was found that there is a significant difference in survival experience among the categories of Age of patient, Stage of CC, level of anemia, co-morbidity and type of treatment initiated at p-value < 0.05.

The median survival time for those who had International Federation of Gynecology and Obstetrics (FIGO) Stage I, II or III at baseline had a longer survival time than those in Stage IV (11 months) (95% CI: 1.23-23.447) at p= 0.00. For CC cases diagnosed at early Stage (I and II), cumulative survival rate was 100% and 93.58% respectively. Patients who had Anemia had a shorter cumulative survival rate (21.80%) than those who did not anemic to CC (95.65%) and those cases diagnosed at advanced Stage (III and IV) was 41.65% and 18.36% respectively and for Patients

who had co-morbidity had a shorter cumulative survival rate (16.89%) than those who did not experience additional illness to CC (93.65%) (Table 4). It was found that there is a significant difference in survival experience among the categories of clinical Stage (Figure 3), anemic status (Figure 4) and comorbidity status (Figure 5).

Table 4. Median survival time, cumulative survival probability, and log rank test of CC patients at Hawassa University Comprehensive Specialized Hospital Oncology Center, Hawassa, Ethiopia, 2023 (n=212)

Covariate	Median survival time in month (95% CI)	Overall 58 months survival (%)	p-value with the log-rank test
Age at diagnosis			0.017
18-30 years	**	86.67	
30-39 years	**	93.94	
40-49 years	**	78.86	
50-59 years	23 (10.714-35.286)	33.45	
>=60 years	11 (1.2-24.939)	19.17	
FIGO Stage			0.000
Stage II	**	93.58	
Stage III	16(6.868-25.132)	41.65	
Stage IV	11(1.23-23.447)	18.36	
Presence of anemia			0.012
Yes	35(18.528-51.472)	21.80	
No	**	95.65	
Co-morbidity			0.000
Yes	11(9.841-12.159)	16.89	
No	**	93.65	
Initial treatment initiated			0.015
Chemotherapy	46(30.229-61.771)	32.58	
Surgery	**	59.33	
Combination of treatments	11(9.156-12.844)	22.62	

***** Values that hadn't median survival from the specific categorical variable in this research***

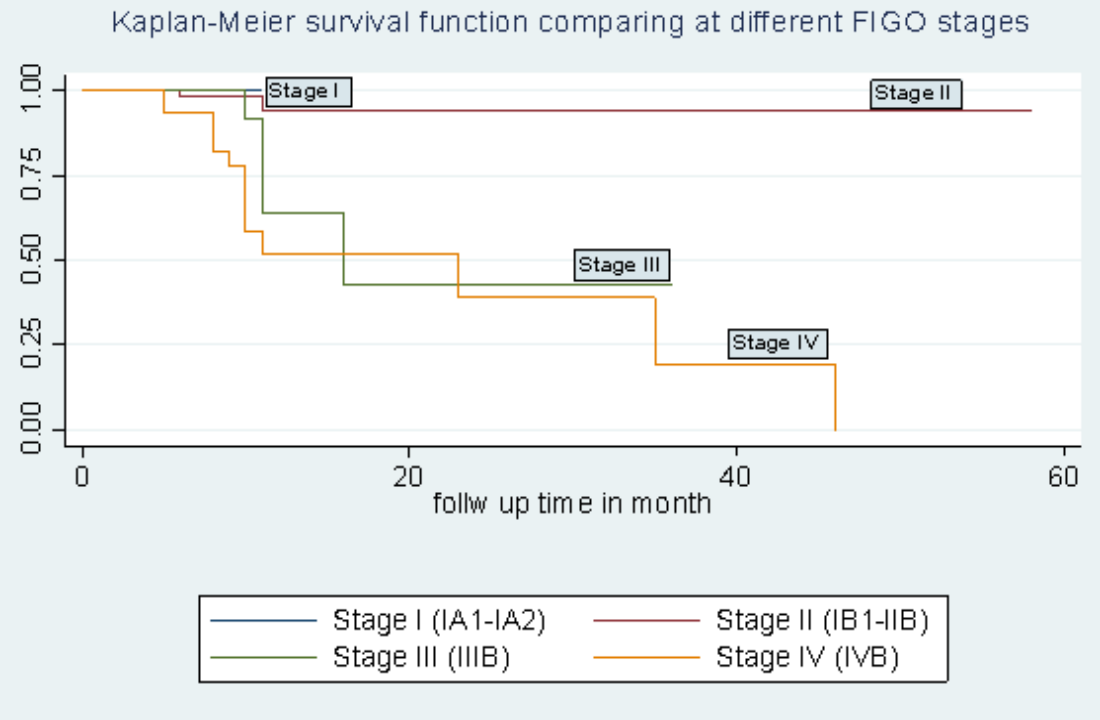

Figure 3: The Kaplan-Meier survival curves compare survival time of CC patients with different FIGO Stages from January 1st 2018 to December 31st 2022 in HUCSH, Hawassa, Ethiopia, 2023 (n=2012)

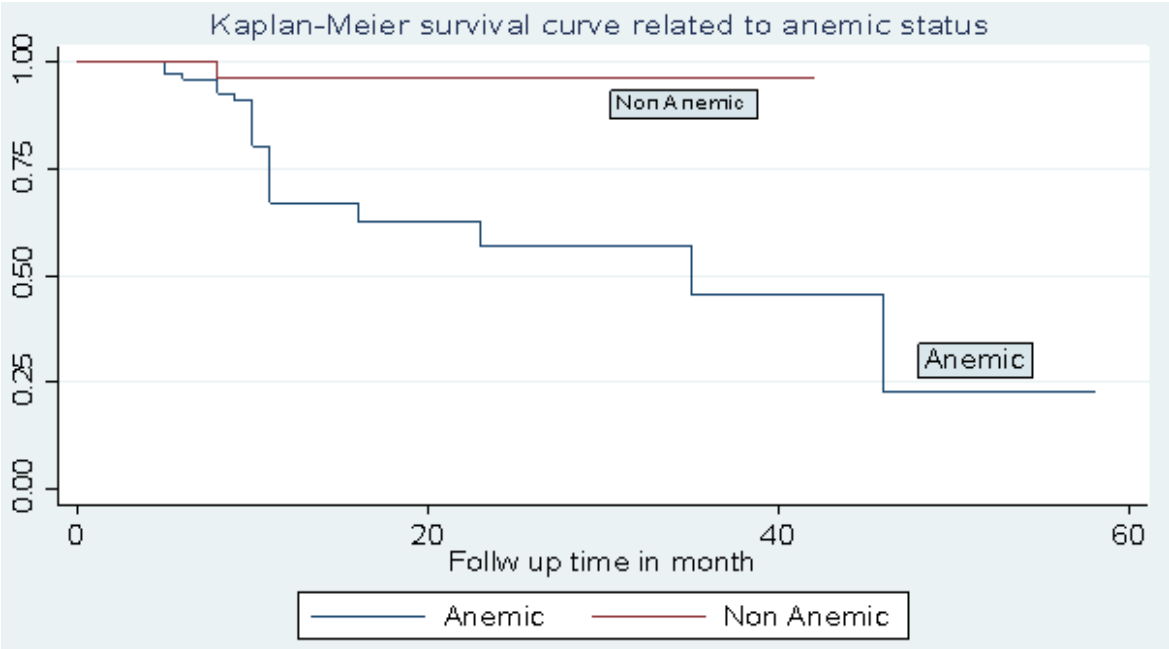

Figure 4. The Kaplan-Meier survival curves comparing survival time of CC patients related to anemic status in HUCSH from January 1st 2018 to December 31st 2022, Hawassa, Ethiopia, 2023 (n=212)

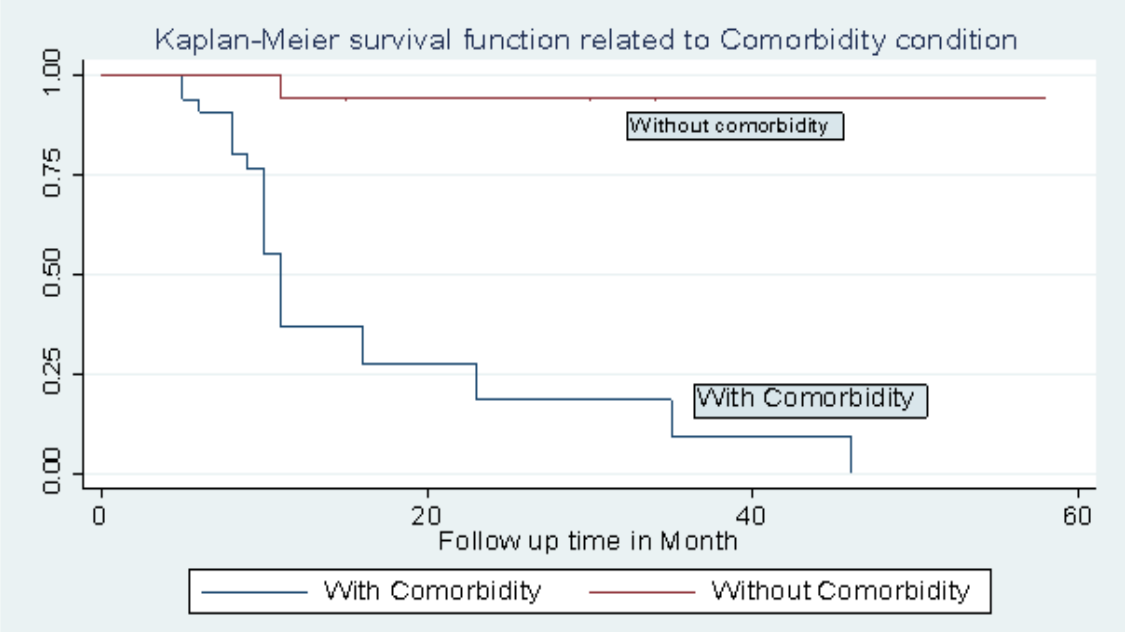

Figure 5: The Kaplan-Meier survival curves comparing survival time of CC patients related comorbidity status at HUSCH

Testing overall Cox model fitness

The figure below implies as Cox regression model fitted the data i.e. the estimated cumulative hazard for each individual at the time of their death or censoring is like a censored sample from a unit exponential. This is called the generalized or Cox Snell residual test. Hence, the output shows cox-Snell residuals satisfied the overall model fitness test **(Supplementary material_1).**

Testing proportional hazard assumption

A Cox regression model was used to examine the effects of Sociodemographic, clinical and treatment characteristics of patients on time to death. Schoenfeld residuals test were conducted to assess the proportional hazard (PH) assumptions of the Cox model for given factor variables. The findings indicated that all variables included in the model including global PH assumption test were satisfying PH assumptions (p value > 0.05).

Predictors of time death among cervical cancer patients

In multivariate analysis, FIGO Stage and comorbidity were significantly associated to the outcome variable. Women with advanced disease Stage (Stage IV) were 2.1 times [AHR = 2.08, 95% CI: 1.068-4.068)] at high risk to die as compared to those with early Stage of disease (FIGO Stage I). Those patients with co-morbidities have a 20% increase patients with co-morbidities in the likelihood of death compared to patients without co-morbidities [AHR =1.2, 95%CI: 1.065 - 1.335)] (Table 5).

Table 5. Results of the bivariable and multivariable Cox regression analysis of *CC* patients at HUCSH Oncology Center, Hawassa, Ethiopia, 2023 (n=212).

Covariates	Patient status, at last, Follow-up		Bivariable	Multivariable	
	Death No. (%)	Censored No. (%)	CHR (95% CI)	AHR (95% CI)	P-value
Age at diagnosis					
<30 years	1(0.5)	19(9)	0.329(0.0437- 2.474)	1.162(0.102- 13.15)	0.90
30-39 years	1(0.5)	37(17.5)	0.8989(0.0558-14.46)	2.814(0.112- 70.38)	0.52
40-49 years	3(1.4)	56(26.4)	1.2371(0.1276-11.993)	1.289(0.0835-19.90)	0.85
50-59 years	8(3.8)	44(20.8)	5.55(0.690-44.767)	2.075(0.119- 35.89)	0.61
>=60 years	8(3.8)	35(16.5)	5.187(0.634- 42.398)	0.336(0.021- 5.362)	0.44
FIGO Stage					
Stage I	*	12(5.7)	1	1	
Stage II	2(0.9)	111(52.4)	0.2149(0.0193- 2.388)	0.670(0.035-12.70	0.79
Stage III	5(2.4)	36(17)	1.599(.1853- 13.804)	2.50(0.203- 30.72	0.47
Stage IV	14(6.6)	32(15.1)	3.051(1.395- 23.564)	2.08(1.068-4.068)	**0.031***
Histopathology					
Squamous cell Carcinoma	20(9.8)	184(90.2)	0.2858(0.0364- 2.239)	0.483(0.0454-5.139)	0.54
Adenocarcinoma	1(0.5)	7(3.3)	1	1	
Comorbidity					
Yes	19(9)	18(8.5)	26.70(6.183-115.29)	1.2(1.065 - 1.335)	**0.000***
No	2(0.9)	173(81.6)	1		
Baseline anemia					
Yes	20(9.4)	117(55.2)	2.930(1.191- 7.205	2.352(0.238- 23.17)	0.464
No	1(0.5)	74(34.9)	1	1	
Contraceptive use					
Yes	6(2.8)	78(36.8)	0.5307(0.2032- 1.385	0.531(0.149- 1.896)	0.33
No	15(7.1)	113(53.3)	1	1	
Initial treatment					
Chemotherapy	10(4.7)	134(63.2)	0.3080(0.1236- .7677)	2.381(0.322-17.58)	0.39
Surgery	6(2.8)	25(11.8)	2.717(0.9306- 7.937)	0.507(0.044- 5.739)	0.58
Combination	5(2.4)	32(15.1)	4.138(1.355- 12.631)	0.0587(0.0032-1.07)	0.12
No. chemotherapy cycles					
No chemotherapy	5(2.4)	27(12.7)	2.372(.8394- 6.705)	.9368(.121- 7.19	0.95
Frist cycle	4(1.9)	42(19.8)	.4020(.1059- 1.525)	.710(.037- 13.52)	0.82
Second cycle	6(2.8)	45(21.2)	.4990(.1438- 1.731)	.586(.048- 7.012)	0.67
Third cycle	1(0.5)	30(14.2)	.1097(.0119- 1.006)	2.87(.0731-13.215)	0.57
Fourth & more cycles	5(2.4)	47(22.2)	.5678(.1604- 2.010)	2.47(.200- 30.69)	0.48

*Indicates the variables significantly associated with the outcome variable at < 0.05

Discussion

This study was undertaken to identify the time to death of CC patients and the predictors of death among CC patients in HUCSH, Hawassa Ethiopia, 2023. FIGO Stage and comorbidity were significant factors that influenced survival of CC patients. The median survival time of CC patients was estimated and found to be 23 months. The overall incidence of CC death from 212 CC patients in this study was 12.4 per 1000 woman-years. This finding is higher than CC mortality incidence rate reported Eastern, Western, and Southern part of the sub-Saharan African countries (25.3/100000, 24/100000 and 14.8/100000) (20). This difference could be due to variations in the study period, the cancer Stage at presentation, the waiting time for treatment after diagnosis, and the difference in quality of cancer care services (26, 27).

Ethiopia's poor CC treatment outcomes are a result of a number of factors, including inadequate pathology services, shortages in healthcare infrastructure, and a shortage of diagnostic and treatment facilities. Long wait times, a large number of potentially curable tumors that progress to incurable Stages, and premature death are the consequences of this outcome (7, 28). In this study, about 28.39% CC patients could survive at least 58 months after diagnosis of CC. This is significantly lower than the researchers conducted in Ethiopia Felegehiwot Specialized and Comprehensive Hospital 53.15% (25), black lion specialized hospital 38.6% (29). Brazil which were 84% (30), India 62% (31). The results may differ due to variations in participant sample size, CC policies, treatment modalities, and the availability of health-related infrastructure for early detection and treatment.

The estimated cumulative survival in this study was 73.1%, 64.9%, 56.79%, and 28.39% at 12, 24, 36, and 58 months respectively. These were lower than the overall survival rates in study conducted Ethiopia FHSCH (99.04%, 96.0%, 87.63%, and 53.15% at 12, 24, 36, and 46 months respectively) (25) and in SSA (76.5% and 64.2% at 12 and 36 months, respectively) (32,33). The discrepancy of the results might be due to difference in sample size of participants, difference in the study period as there could be changes in treatment modality, differences on health care policy related to CC, differences in treatment modalities and availability of health-related infrastructures that support early detection and treatment of the CC. The cumulative survival of CC patients at Stage IV in this study (18.9%) was relatively similar in previous studies in Ethiopia (20.03%) (29)

and SSA (20.05%) but, higher than in Nigeria (15%) and India (8.1%) (32,33). This may be due to the difference in study area and period. The cumulative survival rates for early and late Stages of disease in this study (93.5% and 24%, respectively, are comparable with a study conducted in Ethiopia FHSCH ((78.9% and 56.7%, respectively) (25) and with a study conducted in India (84% and 8.1%, respectively)(34). The difference may be due to the duration of follow-up time.

According to the findings of the current study, women with advanced disease Stage (Stage IV) were 2.1 times at high risk to die as compared to those with early Stage of disease (FIGO Stage I). This association holds but is lesser than a study conducted at FHSCH and adisAbaba black loin specilized hospital (25,29), higher than studies in SSA (32) and northwest Russia (35). The reason may be due to the study period, the overall condition of patients during the presentation, and other different predictors.

Comorbidity was another significant predictor contributing for lower survival of CC patients in the current study. In the lists of comorbidities, HIV/AIDS was most prevalent (21.6%). Therefore, HIV may contribute higher part of risks to die in this research. CC patients who had comorbidity were 1.2 times at high risk to die than those who haven't comorbid in this study. This is in agreement with the studies conducted in Ethiopia FHCSH [AHR=2.57, 95%CI:1.29, 5.11)] (27), Adis ababa (HR=2.02, 95%CI: 1.01-4.05) (29) and Australian (HR=4.6, 95% CI: 3.54-6.03) (21). this also strengthen the current study result. The rational of these similarities may be due to the fact of Carlson comorbidity index which states as the presence of comorbidity leads to shortening of the lives of patients based on the severity of each comorbidity (23).

Strength of study and Limitations

This study was carried out in a compressive specialized hospital, whose characteristics may represent the usual standard of care in most resource-limited settings, thus allowing generalizability. Since the study design was cohort, it is possible to see the temporal relationship between the risk factors since exposure precedes the outcome variable. As the sample size of this study is adequate, it provides ample statistical power to assess the time to death from CC, and predictors among CC patients are more broadly generalizable to other settings with consideration of their limitations.

This study has some limitations. First, cause-specific (relative) survival was not determined due to a lack of data on specific

causes of death; this may overestimate the CC-related mortality rate. Information on socio-demographic factors such as occupation, income, history of abortion, age at first marriage, age at first sex, history of CC recurrence, and family history of CC were not recorded and not included in this study. As well, this research did not include any information about HPV vaccination in Ethiopia due to the unavailability of documented sources. Moreover, the data were collected on patients registered from January 1, 2018 to December 31, 2022, which may not reflect the current utilization of advanced treatment modalities for CC treatment, which could affect the opportunity to improve the survival rate

Conclusion

This study documented the time to death and the predictors of mortality among CC patients. While the median survival time was undetermined in this study, it was 23 months. The death rate of CC patients was found to be high (12.4 per 1000 woman-years of follow-up). Advanced Stages of disease and the presence of co-morbidity were statistically significant predictors of CC mortality.

Abbreviations

AHR: Adjusted Hazard Ratio CC: Cervical Cancer CHR: Crude Hazard Ratio CI: Confidence Interval FIGO: International Federation of Gynecology and Obstetrics HPV: Human Papillomavirus HR: Hazards Ratio HCHS: Hawassa College of Health Sciences HUCSH: Hawassa University Comprehensive Specialized Hospital MPH: Master in Public Health OCP: Oral Contraceptive Pill WHO: World Health Organization

Declarations

Ethics approval and consent to participate

This study was carried out in accordance with the Declaration of Helsinki relevant guidelines and regulations. The ethical committee which approved informed consent waiver was HU-CMHS Institutional Review Board approved the study with a letter reference number of IRB/162/15. Then, additionally School of Public Health wrote a support (HUCSH /198/14) letter. After getting permission from HUCSH, data were collected from CC registry. The retrieved data kept strictly confidential and names of patients were not included and never disclosed to others without informed consent of hospital. Medical record number was recorded rather than the patient's name.

Consent for publication

"Not applicable"

Availability of data and materials

Data essential for the conclusion are included in this manuscript. Additional data can be obtained from the corresponding author on a reasonable request.

Conflict of interests

The authors declare that they have no conflict of interests

Funding

The financial aid of this thesis was obtained from Hawassa College of Health Sciences (HCHS) with specific grant numbers HCHS/257/1/2015. Afework Aklilu is author who received award. The funded agency did not take part in the thesis design, data collection, and manuscript preparation process.

Authors' contributions

AA: Designed the study, supervised the data collection, performed the analysis, interpretation of data and drafted the manuscript and approved the final manuscript. AA: Assisted in designing the study, data interpretation and critically reviewed the manuscript and approved the final manuscript**.** TT: Assisted in designing the study, data interpretation and critically reviewed the manuscript and approved the final manuscript**.** AF: Assisted in designing the study, data interpretation and critically reviewed the manuscript and approved the final manuscript

Acknowledgements

Authors acknowledge Hawassa College of Health Sciences (HCHS) for financial support.

Supplementary Materials: **S1.** Schoenfeld residual test to check the assumption of proportional hazard (PH), and S2. Cox-Snell residual model fitness

References

1. McGuire, S., World cancer report 2014. Geneva, Switzerland: World Health Organization, International Agency for research on cancer, WHO Press. 2015. Advance Nutr. 2016;**7**(2):418-19.
2. Mulugeta M, Kebede E, Mulualem E, Elias TB, Eshetu EC, Berhanu SD, Bikila T. Prevalence of Cervical cancer and associated factors among women attended cervical cancer screening center at Gahandi Memorial Hospital, Ethiopia. Cancer Inform. 2021;20(1):1-6.
3. Tariku S, Biruck G, Gedif T. Association between delayed initiation of treatment indications and survival in patients with cervical cancer: A systematic review and meta-analysis protocol. PloS One. 2022;**17**(7):e0271604.
4. Broutet N, Comprehensive cervical cancer control: a guide to essential practice. World Health Organization. 2014:p.1-378.
5. Debbie S, Diane Solomon S, Herschel WL, Maureen K, Shalini LK, Joanna C, Francisco AR, Ann TM, Alan GW,

David CW, Nicolas W, Levi SD, Mark S, Anna-Barbara M, Eduardo LF, Mark HS, Mark S, Philip EC, Evan RM. Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. Am J Clinical Pathol. 2012;137(4):516-42.

6. Organization, WHO. Noncommunicable diseases country profiles 2014. 2014.
7. Wondimu YT. *C*ervical cancer: assessment of diagnosis and treatment facilities in public health institutions in Addis Ababa, Ethiopia. Ethiop Med J. 2015; 53(2):65-74.
8. Marc A, Rengaswamy S, Richard M, Namory K, Amadou D, Charles GM, Hassan N, Boblewende S, Ramani Wesley, Thara S, Anjali S, Surendra S, Parthasarathy B, Pooled analysis of the accuracy of five cervical cancer screening tests assessed in eleven studies in Africa and India. Int J Cancer. 2008;123(1):153-160.
9. Duclos P. Human papillomavirus vaccines: WHO position paper. Biologicals, 2009.
10. Janice KL, Meileen A, Kathleen W, Cynthia J, Shilpa G, Robert S, Duc V, Kathleen H, Bela M, Carol AG, Michael CS, Jon R, John T, Douglas H. Factors associated with death or hospitalization due to pandemic 2009 influenza A (H1N1) infection in California. JAMA. 2009;302(17):1896-1902.
11. Torre, LA, , Rebecca LS, Elizabeth MW, Ahmedin J. *G*lobal cancer incidence and mortality rates and trends - an update. Cancer Epidemiol, Biomarkers Prevention. 2016:25(1):16-27.
12. Papillomavirus H. Related Cancers, Fact Sheet 2017. ICO Information Centre on HPV and Cancer, 2014.
13. Cunningham FG, Kenneth JL, Jodi SD, Barbara LH, Catherine YS, Brian MC. Williams obstetrics. Vol. 7. 2014: McGraw-Hill Medical New York.
14. Awoke D, Daniel M , Gizachew Y, Fantahun B, Xaveer VO, Tamrat A. Human Papilloma virus in Ethiopia. Virus Disease, 2019;30:171-79.
15. Denny L, Anorlu R. Cervical cancer in Africa. Cancer Epidemiol Biomarkers Prevention. 2012;21(9):1434-38.
16. Ralph-Sydney MB, Thierry P, Thérèse L, Mohammad-Ali J, Jean-François M, Laurent B. Cervical cancer in sub-Saharan Africa: a preventable noncommunicable disease. Expert Expert Rev Anti Infect Ther. 2017;15(6):613-27.
17. Melkamu G, Baye G, Abinet S, Eiman AM, Abate A. Prevalence and predictors of Pap smear cervical epithelial cell abnormality among HIV-positive and negative women attending gynecological examination in cervical cancer screening center at Debre Markos referral hospital, East Gojjam, Northwest Ethiopia. BMC Clinical Pathol. 2015;15(1):15:16.
18. Bewuketu T, Tewodros G, Masresha A, Chalachew A, Nega T, Getaneh M, Tadesse T, Addis B, Destaye G, Amare W, Bethelihem T, Mohammed S, Beletech F, Almaz T, Berhan T, Selam F, Bogale K, Amare D, Melkamu T, Kendalem A. Spatial distribution and associated factors of community based health insurance coverage in Ethiopia: further analysis of Ethiopian demography and health survey, 2019. BMC Public Health. 2022;22(1):1-13.
19. Mulugeta S, Tadele GA, Dereje M, Tamiru S. The burden of cancer in Ethiopia. 2000-2016: analysis of

evidence from the global burden of disease study and global health estimate. Medical Studies. 2020:36(2):83-89.
20. Asseffa NA. Cervical cancer: Ethiopia's outlook. J Gynecol Womens Health. 2017;5(2):555660;JGWH.MS.ID.55566
21. Bedilu D, Mohammed A, Dereje G, Lalisa G, Netsanet B, Kurabachew M, Anteneh G, Dubale D, Girma A, Achamyelesh G. Perceived Quality of nursing care among cancer patients attending Hawassa University Comprehensive Specialized Hospital Cancer Treatment Center; Hawassa Southern Ethiopia: Cross-Sectional Study. Dove Press 2021(13): 1225–1231.
22. Ryan TP. Sample size determination, and power. John Wiley & Sons, Inc. 2013.
23. Mary EC, Danilo C, Jenny G, Chiara P. Charlson Comorbidity Index. Karger, 2022;91(1):28.
24. The DHS Program ICF Demographic and Health Survey 2016 Central Statistical Agency Addis Ababa, Ethiopia, 2017.
25. Andamlak E, Nurilign A, Belsity T, Misganaw F. Time to death from cervical cancer and predictors among cervical cancer patients in Felege Hiwot Comprehensive Specialized Hospital, North West Ethiopia: Facility-based retrospective follow-up study. PLOS One, 2022;17(6):1-20.
26. Eva Johanna K, Ulrike M, Matthias B, Adamu A, Pietro T, Bekuretsion Y, Petros H, Andreas S, Christoph T, Dirk V, Tufa G, Yirgu G, Tigeneh W, Abreha A, Assefa M. Cervical cancer in Ethiopia: survival of 1,059 patients who received oncologic therapy. The oncologist, 2014;19(7):727-34.
27. Gurmu SE. Assessing survival time of women with cervical cancer using various parametric frailty models: a case study at Tikur anbessa specialized hospital, Addis Ababa, Ethiopia. Annals of Data Sci. 2018;**5**(4):513-527.--27
28. Federal Ministry of Health Ethiopia Disease Prevention and Control Directorate National Cancer Control Plan 2016-2020. October 2015.
29. Mulugeta W, Beletech F, Asefa, T. Determinants of mortality among cervical cancer patients attending in Tikur Anbessa Specialized Hospital, Ethiopia: Institutional-Based Retrospective Study. HIDAWI. J Oncology.2021;1(1):7.
30. Carneiro SR, Fagundes MdA, do Rosário PdJO, Neves LMT, Souza GdS, Pinheiro MdCN. Five-year survival and associated factors in women treated for cervical cancer at a reference hospital in the Brazilian Amazon. PLoS One 2017;12(11):e0187579. https://doi.org/10.1371/journal.pone.0187579,
31. Kasturi J, Rengaswamy S, Ranjit VT, Richard M, Sanjay JH, Nandkumar SP, Surendra SS, Sylla GM, Bhagwan N. Improved survival of cervical cancer patients in a screened population in Rural India. Asian Pac J Cancer Prev. 2017;17(11):4837-44.
32. Mazvita S, Walburga YJ, Adalberto M, Marcel E, Marie-TA, Guy N , Assefa M, Nathan B, Anne K, Shyam M, Cesaltina L, Carla C, Rolf H, Anne F, Nontuthuzelo I, Henry W, Tatenda C, Margaret B, Eric C, Biying L, Elvira S, Eva Johanna K, Donald M. Cervical cancer survival in sub-Saharan Africa by age, Stage at diagnosis and Human

Development Index: A population-based registry study. Int. J. Cancer, 2020;147(11):3037-3048.
33. Lin X, Ran C, Kai W, Xi Z, Jie L, Zhe Z, Shu Y, Zhiwen W, Taotao D, Xingsheng Y, Xuantao S, Xu Q, Kun S, Beihua K. Prognostic assessment of cervical cancer patients by clinical staging and surgical-pathological factor: A support vector machine-based approach. Front. Oncol. 2020;10(1353):11.
34. Andrej MG, Daria D, Shynar S, Gulmira Z, Gulzhakhan O, Gulnar S, Lyudmila V, Mikhail Y Valkov. Incidence, mortality and determinants of survival from cervical cancer in Northwest Russia: a registry-based cohort study. Int Health, 2018;10(1):8.
35. Abbey D, Peter DB, Patricia CV, Lisa JW, Suzanne PM , Joan C, Gail G, Julia MLB, Dianne LO, Karen C, Diana S, David R, Elizabeth B, John RC. Comorbidity and cervical cancer survival of Indigenous and non-Indigenous Australian women: A semi-national registry-based cohort study (2003-2012). PLoS One. 2018;13(5):e0196764.doi: