



RESEARCH ARTICLE

REVISED Associated predictor covariates of cervical cancer stage and impact on survival at Khartoum oncology hospital, Sudan [version 2; peer review: 2 approved]

Previously titled: Associated predictor covariates of cervical cancer and impact on survival at Khartoum oncology hospital, Sudan

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V2 First published: 15 Feb 2021, 10:114
<https://doi.org/10.12688/f1000research.43590.1>
 Latest published: 07 Oct 2022, 10:114
<https://doi.org/10.12688/f1000research.43590.2>

Abstract

Background: Cervical cancer can be invasive and advanced at diagnosis causing devastating suffering and premature death. The cancer stage at presentation is related to survival evaluation and several factors determine stage. The aim of the study was to examine predictors covariates associated with cervical cancer stage at diagnosis and its impact on patient prognosis and survival.

Methods: This retrospective cross-sectional study was carried out at Khartoum oncology hospital, Sudan. Participants were 239 cervical cancer patients diagnosed and treated between 2011-2015. Patients' pathological and socio-demographic data were extracted from their medical files and survival times were calculated from follow-up. Chi-square, Kaplan-Meier, Log-rank test and Cox regression model were used to examine relationships between demographic and clinical variables and survival outcome.

Results: The mean age of the participants was 56.91 years and the majority were ≥ 45 years. Cancer survival analysis showed that the stage at diagnosis had limited association with socio-demographic factors, except where patients reside. Multivariate regression using the Cox proportional hazard model confirmed strongly that stage ($p=0.035$), chemotherapy ($p=0.000$) and radiotherapy ($p=0.001$) were the most likely predictor covariates of patient prognosis and survival time.

Conclusions: The results of this study suggest cancer stage at diagnosis and certain treatments are the most important factors impacting the prognosis and survival of patients with cervical cancer. Early detection and vaccination of women against HPV infection provide enormous opportunities for early diagnosis, more effective

Open Peer Review

Approval Status

	1	2
version 2 (revision) 07 Oct 2022		 view
version 1 15 Feb 2021	 view	 view

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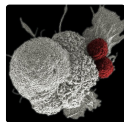
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Any reports and responses or comments on the article can be found at the end of the article.

treatment and better chances of survival.

Keywords

Cervical cancer, survival, stage, Cox model, Sudan



This article is included in the **Oncology** gateway.

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Author roles: **Elgoraish A:** Conceptualization, Formal Analysis, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Alnory A:** Conceptualization, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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How to cite this article: Elgoraish A and Alnory A. **Associated predictor covariates of cervical cancer stage and impact on survival at Khartoum oncology hospital, Sudan [version 2; peer review: 2 approved]** F1000Research 2022, 10:114 <https://doi.org/10.12688/f1000research.43590.2>

First published: 15 Feb 2021, 10:114 <https://doi.org/10.12688/f1000research.43590.1>

REVISED Amendments from Version 1

This new version of the article does not include any major changes in the shape and the contents of the original one. However, some small minor changes wording of the text have been made to meet clarifications of points raised by the peer-reviewers.

Any further responses from the reviewers can be found at the end of the article

Introduction

Cancer is a global public health problem, particularly in low- and middle-income countries, due to aging populations as well as broader social and environmental factors such as infectious diseases, education and ethnicity.¹ There are observed disparities in global cancer prognosis as mortality is higher among developing countries due to a lack of comprehensive early detection and effective medical care.² Cancer is a leading cause of death among women in both developing and developed countries and is increasing.³ Women in developing countries develop the disease during their prime reproductive period and face more suffering from the disease complications and risk of death.⁴ The most common cancers afflicting women are those of the breast and cervix. These cancers are closely related to sexual and reproductive behaviour in Woman.⁴

Cervical cancer is a considerable cause of death among women in developing countries though it is preventable. It is, also, potentially curable if detected early and treated effectively. It is the second most commonly diagnosed cancer in women in developing countries.⁴ In these countries, cancer mortality exceeds that of diseases related to death in pregnancy. However, there is clear diversity of trends among world regions, within regions and individual countries, in the incidence and mortality of cervical cancer. In Africa, there is a wide variation due to different exposure and disease susceptibility.¹ In Sub-Saharan Africa, the incidence is low but mortality rates are high due to advanced stage at presentation.⁵ In Sudan, cervical cancer represents more than 16% of all cancer in women and 85% of cases are diagnosed at an advanced stage.^{6,7} Cervical cancer is closely related to human papillomavirus (HPV) 16/18 infection and 78% of cases in the Sudan are diagnosed as invasive Lesions.⁸ Moreover, the incidence and mortality rates of this invasive cervical cancer have increased during the last decade, especially among relatively young women.³ This increase can be attributed to major changes in demography, economic and social factors, other disease risk factors and disease awareness.⁹

Cancer burden and disparity among countries and people can be explained by prevalence, incidence and mortality, but the most direct measure of disease severity can only be provided by survival rates.¹⁰ Early detection and prevention are the most effective ways to reduce premature death from cervical cancer; however, from a short-term perspective, immediate and effective treatment is the optimal solution.¹¹

Analysing cancer survival rates is an important way of discovering potential measures to be taken to improve the chances of better prognosis and survival. Cancer survival varies widely among different countries of the world due to differences in early detection and treatment modalities. By examining cancer survival from preventative measures and early detection, one can assess factors that have the greatest impact on cancer patient survival. Several studies have attempted to explain the relationships between patient survival and stage at diagnosis. These studies came to different conclusions about the strength and shape of these relationships and their impact. Researchers have found significant association between the stage of cancer at diagnosis and survival. Socio-demographic attributes such as age, education, gender and ethnicity have also been shown to have some effects.¹² On other hand, differences in the type of treatment and quality of medical services might have an important effect on survival outcome.¹¹

Previous literature has shown the complexity of determining the drivers of international differences in the incidence and mortality of cervical cancer. It is most likely that each step in a patient's journey to seek treatment contributes to some extent to these variations.¹² Many factors have been suggested to explain these variations; however, there is no complete agreement on potential predictor covariates that give overall explanations. Nevertheless, stage at diagnosis, tumor features and effective treatment have been postulated as the most widely accepted predictor covariates explaining degree and extent of their impact on prognosis and survival. For variations in cancer severity and survival, the stage at diagnosis remains the strongest predictor of cancer survival.¹³ One can conclude that stage at diagnosis is related to survival evaluation and assessment. Several factors determine stage at diagnosis, including age, education, occupation, location, tumor features, availability and accessibility of adequate diagnostic and treatment facilities.¹¹ The stage at diagnosis is crucial to disease treatment as treatment plans are usually based on the stage of the disease.¹⁴ The aim of this study was to examine predictor covariates associated with cervical cancer stage at diagnosis and its impact on cancer patient prognosis and survival.

Methods

Study design, setting and population

This was a retrospective cross-sectional hospital-based study. It was carried out at Khartoum oncology hospital, Sudan, which is the only medical institution providing complete diagnostic and cancer treatment services, where more than 80% of all Sudan cancer patients are registered.¹⁵ Available patient information was collected from the hospital's medical records during the study period from 2011-2015.

The target population of the study was patients with cervical cancer at Khartoum oncology hospital. To be included in the study, patients had to be between 18-79 years, be registered at the hospital, have complete medical records, have histopathologically confirmed cervical cancer and had received available treatment. Patients with incomplete medical records, unclear diagnosis and not treated at the hospital were excluded from the analysis. Written consent was obtained from the hospital to use participants' data. No direct contact was made with patients during this data collection level. However, consent was obtained from participants during the active follow-up period.

The total number of patients at the hospital during the study period who met inclusion criteria, and were included in the analysis, was 239. This sample size of randomly selected participants was calculated from the number of cervical cancer patients among all cancer patients at this hospital as follows:

The formula $n = 3.84 p(1-p)/(precision)^2$

Proportion = 0.044 (report of Federal Ministry of Health 2015), precision=0.026 with 95% CI

*$n = 3.84 * 0.044(1-0.044)/(0.026)^2 = 239$*

Data collection and sources

The study data collected from Khartoum oncology hospital patients' medical files were checked and rechecked for accuracy, duplication, completeness and consistency by the researcher with continuous assistance from the hospital medical staff. Active follow-up was carried out during the year 2016 by the researcher by contacting patients or next of kin to ensure collection of needed information concerning patients survival status data (dead or alive). Moreover, a checklist was prepared by the researcher from the literature on cancer patients' survival concerning socio-demographic and clinical factors affecting survival to assist in needed data collection.^{16,33} Data collected were tabulated and coded according to the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) TNM staging system for analysis.¹⁷

Variables

Data collected concerning socio-demographic characteristics and clinical status of patients included age at diagnosis, level of education, occupation, marital status, urban/rural residential area, tribe, menopausal status, cancer stage at diagnosis, tumor grade, tumor cell differentiation, histological subtype, treatment modalities, residence state and close family relation with previous disease experience. Dates of birth, death, loss to follow-up, diagnosis and survival times were checked by using other information provided by hospital medical and statistical staff. This information was clearly defined in medical terms concerning certificate of death, confirmation of diagnosis and calculation of survival time.

Statistical analysis

The statistical analysis is divided into two parts, descriptive statistics and regression analysis, using **Stata** version 11 (StataCorp, College Station, Texas) software. In the descriptive analysis, the visual presentation of data in tables and figures given, provides socio-demographic and clinical data in numbers, percentages, χ^2 and p-values and figures given provide clear indication of study population data distribution, relationships and associations. Then, important statistical conclusions were drawn. Statistical methods such as χ^2 , Kaplan-Meier, log-rank test and Cox regression were used to find out most prognostic factors associated with cancer patient survival. Socio-demographic variables and stage at diagnosis were tested by χ^2 . Stage, treatment, age and menopausal status were tested by log-rank test for equality. Socio-demographic variables, stage and treatment were tested by Cox regression. Stage was tested by Kaplan-Meier for survival rate between early and advanced levels. The analysis focuses on the stage at diagnosis as the most crucial prognostic predictor of cervical cancer patient survival.

Results

Descriptive statistics

The total number of patients included in the analysis was 239 (Table 1).³² The median age of participants was 56.91 years (SE=0.88, 95%CI=55.17-85.65). The majority of participants 82.9% were ≥ 45 years old. In total, 94.6% of participants

Table 1. Correlation between stage at diagnosis and socioeconomic variables among cervical cancer patients.

Variables	Total N(%)	Stage N(%)		Chi ² , P-value
		Early	Advanced	
Age group				
<30	4(1.7)	1(1.2)	3(1.9)	5.33, 0.255
30-44	37(15.5)	19(22.6)	18(11.6)	
45-59	81(33.9)	27(32.1)	54(34.8)	
60-74	91(38.1)	28(33.3)	63(40.6)	
≥75	26(10.9)	9(10.7)	17(11.0)	
Urban/Rural status				
Rural	60(25.1)	20(23.8)	40(25.8)	0.12, 0.734
Urban	179(74.9)	64(76.2)	115(74.2)	
Resident states				
Khartoum	49(20.5)	11(13.1)	38(24.5)	11.23, 0.047*
Central	28(11.7)	16(19.0)	12(7.7)	
Northern	11(4.6)	2(2.4)	9(5.8)	
Eastern	32(13.4)	13(15.5)	19(12.3)	
Western	93(38.9)	33(39.3)	60(38.7)	
Southern	26(10.9)	9(10.7)	17(11.0)	
Tribes				
Non Arab descent African	150(62.8)	54(64.3)	96(61.9)	0.41, 0.814
Arab descent African	62(25.9)	22(26.2)	40(25.8)	
Other tribes	27(11.3)	8(9.5)	19(12.3)	
Education				
Illiterate	195(81.6)	72(85.7)	123(79.4)	1.59, 0.450
Low education	39(16.3)	11(13.1)	28(18.1)	
High education	5(2.1)	1(1.2)	4(2.6)	
Marital status				
Un married	13(5.4)	4(4.8)	9(5.8)	0.12, 0.734
Married	226(94.6)	80(95.2)	146(94.2)	
Occupation				
Non-employed	221(92.5)	77(91.7)	144(92.9)	0.12, 0.729
Employed	18(7.5)	7(8.3)	11(7.1)	
Menopause status				
Premenopausal	66(27.6)	28(33.3)	38(24.5)	2.12, 0.149
Postmenopausal	173(72.4)	56(66.7)	117(75.5)	
Parent relationship				
First degree relation	200(83.7)	75(89.3)	125(80.6)	3.37, 0.186
Relatives	22(9.2)	6(7.1)	16(10.3)	
Non relatives	17(7.1)	3(3.6)	14(9.0)	
Total	239	84(35.1)	155(64.9)	

*P-value<0.05 statistically significant association.

were married, 92.5% were unemployed, and 97.9% were illiterate and/or had no formal education. Most participants resided in the western, Khartoum and eastern states of Sudan.

The distribution frequency of cervical cancer cases, according to the tumor, node and metastasis (TNM) staging classification system demonstrated that the majority 64.9% of participants were of advanced stage (III & IV), invasive

Table 2. Test of equality of survival distribution for predictor variables.

variable	no. of subjects (%)	Mean of survival time (months)	95% Confidence interval (CI)	log rank (chi ²)	P-value
Stage ^a					
I	9(3.8)	16.06	12.46 to 19.65	33.49	0.000**
II	75(31.4)	39.60	31.06 to 48.14		
III	110(46.0)	28.27	22.88 to 33.67		
IV	45(18.8)	13.09	6.55 to 19.62		
Early	84(35.1)	40.49	32.28 to 48.71	7.91	0.005*
Advanced	155(64.9)	23.77	19.32 to 28.23		
Treatment					
Surgery	15(6.3)	34.64	20.31 to 48.98	0.47	0.491
Chemotherapy	137(57.3)	40.13	33.45 to 46.80	19.12	0.000**
Radiotherapy	183(76.6)	33.86	28.4 to 39.31	3.63	0.057
Hormonal	25(10.5)	30.06	16.54 to 43.58	0.01	0.909
Age group					
<30	4(1.7)	29	28.9 to 29.01	10.13	0.038*
30-44	37(15.5)	27.22	17.31 to 37.17		
45-59	81(33.9)	33.85	27.72 to 39.98		
60-74	91(38.1)	29.26	21.83 to 36.68		
≥75	26(10.9)	11.92	7.01 to 16.82		
Menopause status					
Premenopausal	66(27.6)	30.16	22.44 to 37.89	0.26	0.611
Postmenopausal	173(72.4)	31.06	25.42 to 36.71		
Total	239	32.02	26.92 to 37.12		

^a% of invasive squamous cells carcinoma (98.0%), moderately to poorly differentiated cell (75.0%).

squamous cell carcinoma 98.0%, with a high probability of spreading to distant organs (Table 2). Most of these patients' tumors were of high grade and moderately to poorly differentiated cells. Furthermore, most of these patients had first-degree relations with previous disease history. Regarding treatment, 76.6% of these patients received radiotherapy, 57.3% chemotherapy, 10.5% hormone therapy and 6.3% surgery, alone or in combination with other therapies.

There was no significant correlation between age group of participants and stage (p -value>0.05), though the most frequent group among advanced stage was ≥45 years group. There was no significant correlation between cancer stage at diagnosis and other socio-demographic variables except state of residence ($\chi^2=11.23$, $df=5$, $p=0.047$). This could be explained by the fact that Khartoum and nearby states have diagnostic and treatment facilities.

Regression analysis

The overall mean survival time after 60 months of follow-up from time of diagnosis to the end of the study period was 32.0 months (95% CI=26.92 to 37.12). The lowest mean survival time according to stage levels was recorded at 13.1 months for stage IV(95% CI=6.55 to 19.62) (Table 2). Moreover, the log-rank test when performed to compare and explain survival distribution clearly showed highly statistically significant differences between various levels of the stage at diagnosis ($\chi^2=33.49$, $df=3$, $p=0.000$). Furthermore, the survival curve (Figure 1) gives a visual description of these differences in survival times of different stage levels. The Kaplan-Meier and log-rank tests were performed according to early and advanced stages and indicated clear differences in survival time means between the two groups. A low mean survival time of 23.77 months at the advanced stage was observed compared to 40.49 months at the early stage. The χ^2 was 7.91, $df=1$ with $p=0.005$ (Table 2). The graph of the two survival function curves was statistically different for the two groups. The lowest probability of 30% was recorded at the advanced stage (Figure 1).

The Kaplan-Meier method and log-rank test were performed on the main four treatment therapies and only chemotherapy showed a highly statistically significant impact of chemotherapy on survival time. The χ^2 was 19.12, $df=1$ with

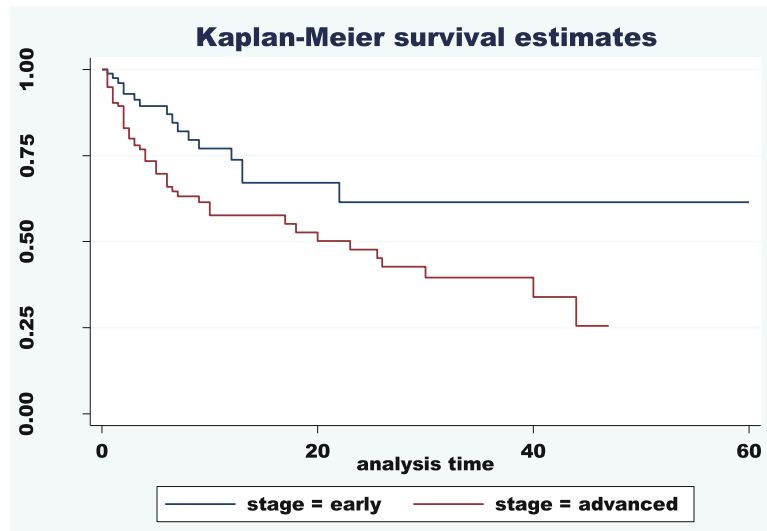


Figure 1. Survival rate according to early and advanced stage.

p=0.000. As for age groups and survival times, the analysis revealed there was a clear difference in the age group ≥ 75 years. The log-rank test equals 10.13, df=4 and p=0.038. However, when the comparison was made according to their menopausal status, the results showed the difference was not statistically significant (Table 2).

Cox proportional hazard model

The Cox proportional hazards model was performed in four phases.¹⁸ In the first univariate model, single predictor covariates; stage, treatment modality (chemotherapy) and age were statistically significantly associated with survival time (Table 3) while other factors were not. The hazard ratio of advanced stage at diagnosis was more than twice that at an earlier stage (HR=2.18 at 95% CI=1.24 to 3.83, p=0.007). This large difference was highly statistically significant with P-value <0.05. In the second multivariate (adjusted) model, all predictor covariates were included simultaneously which showed that advanced stage at diagnosis, treatment (chemotherapy and radiotherapy), state (eastern and western) and urban status were the only predictor covariates of survival time. Then, in the third model, all non-significant predictors, except age and surgery, were dropped from the model. The third model showed that stage and treatment (chemotherapy and radiotherapy) were statistically significant predictor covariates. The hazard ratio which measures the risk of dying from cervical cancer was nearly two times at the advanced stage compared to the early one (HR=1.84, at 95% CI=1.05 to 3.26, p=0.035). Other covariates were not statistically significant. However, the final multivariate model confirmed strongly stage, chemotherapy and radiotherapy, after age and surgery were dropped from the model, were the most likely predictor covariates of survival times and cervical cancer patient prognosis and survival outcome (Table 4).

Table 3. Univariate and multivariate regression models for association between survival time and predictor variables.

Factor	Univariate model		Multivariate model	
	HR(95%CI)	P-value	HR(95%CI)	P-value
Age	1.02(1.002 to 1.04)	0.027*	1.02(0.99 to 1.05)	0.131
Stage				
Early	1(reference)	-	1(reference)	-
Advanced	2.18(1.24 to 3.83)	0.007*	1.84(1.003 to 3.39)	0.049*
Treatment				
Surgery	0.75(0.32 to 1.74)	0.497	0.52(0.19 to 1.38)	0.187
Chemotherapy	0.35(0.21 to 0.57)	0.000**	0.23(0.13 to 0.43)	0.000**
Radiotherapy	0.57(0.32 to 1.03)	0.063	0.29(0.14 to 0.62)	0.001**
Hormonal	1.04(0.52 to 2.11)	0.910	1.14(0.48 to 2.71)	0.768

Table 3. *Continued*

Factor	Univariate model		Multivariate model	
	HR(95%CI)	P-value	HR(95%CI)	P-value
Residence state				
Khartoum	1(reference)	-	1(reference)	-
Central	0.51(0.19 to 1.30)	0.158	0.44(0.16 to 1.21)	0.111
Northern	1.44(0.59 to 3.53)	0.420	0.56(0.21 to 1.49)	0.243
Eastern	0.57(0.21 to 1.55)	0.267	0.23(0.06 to 0.82)	0.024*
Western	0.67(0.35 to 1.27)	0.221	0.46(0.22 to 0.99)	0.049*
Southern	0.97(0.44 to 2.14)	0.935	0.81(0.34 to 1.98)	0.649
Urban/Rural status				
Rural	1(reference)	-	1(reference)	-
Urban	0.78(0.46 to 1.32)	0.356	0.35(0.18 to 0.69)	0.002*
Education				
Illiterate	1(reference)	-	1(reference)	-
Low education	1.52(0.81 to 2.86)	0.189	1.67(0.82 to 3.40)	0.158
High education	1.55(0.38 to 6.39)	0.543	2.42(0.55 to 10.70)	0.246
Marital status				
Un married	1(reference)	-	1(reference)	-
Married	1.69(0.52 to 5.45)	0.383	1.38(0.42 to 4.60)	0.593
Tribe				
Non Arab descent African	1(reference)	-	1(reference)	-
Arab descent African	1.42(0.85 to 2.39)	0.183	1.67(0.76 to 2.71)	0.158
Others	0.91(0.39 to 2.16)	0.834	1.56(0.62 to 3.95)	0.343
Occupation				
Non employed	1(reference)	-	1(reference)	-
Employed	0.98(0.39 to 2.44)	0.961	1.40(0.49 to 3.97)	0.526
Menopause status				
Premenopausal	1(reference)	-	1(reference)	-
Postmenopausal	1.16(0.65 to 2.09)	0.615	0.65(0.25 to 1.73)	0.391

HR: Hazard ratio, CI: confident interval.
 *P-value<0.05 statistically significant association.
 **P-value<0.001 highly statistically significant association.

Table 4. The final multivariate Cox model for association between survival time and predictor variables.

Factor ^a	HR(95%CI)	P-value
Stage		
Early	1(reference)	
Advanced	1.84(1.05 to 3.26)	0.035*
Chemotherapy	0.28(0.16 to 0.49)	0.000**
Radiotherapy	0.33(0.17 to 0.64)	0.001**

prob>chi²=0.000, log likelihood=-293.99.
 *P-value<0.05 statistically significant association.
 **P-value<0.001 highly statistically significant association.
^aage, surgery and hormonal were dropped from the model.

Finally, one of the main assumptions of the non-parametric Cox proportional hazard model is proportionality upon which the Cox model and log-rank test procedure are based. This assumption is based on the requirement of the hazard ratios being constant over time or that the hazard for one individual is proportional to the hazard for any other individual. This proportionality constancy is independent of time. The test of proportionality showed clearly that the dependent covariate was statistically non-significant as the global test χ^2 was 1.23, $df=4$ and $p=0.873$, an indication of the constancy of hazard over time. This result indicated that the model did not violate the proportionality assumption. So, the appropriateness of the use of the model in the analysis was confirmed. Moreover, interaction in the model analysis showed that these interaction terms had no significant effects on the performance of the model.

Discussion

A range of factors contributes to global and regional differences in cervical cancer incidence and mortality. Determining the drivers of these variations is complicated and there have been no comprehensive studies looking at this to date. However, stage, clinical features and quality of treatment are the most likely accepted explanations for these international differences.¹² Cervical cancer survival mainly depends on early detection and effective treatment modalities. Thus, by examining this survival through the eyes of prevention and control of the disease at diagnosis, one can assess and evaluate potential covariates with the most impact on patient survival. This study focused on cancer stage at diagnosis as the most important potential predictor covariate of survival. The result showed that these patients were relatively old, married, unemployed, illiterate, urban and belonged to non-Arab descent African groups. Cervical cancer, in Sudan, is described as advanced at presentation and grade, aggressive and invasive squamous cell carcinoma and moderately to poorly differentiated cells leading to poor survival. Several previous studies reached the conclusion of the disease as being invasive and advanced at presentation.^{12,19-21} The stage at diagnosis is much related to survival and cancer survival analysis measures this relationship and the effectiveness of the health care system.

This study showed clearly that advanced cancer stage presentation at diagnosis had a significantly negative impact on survival outcomes compared to the early stage. This conclusion is in agreement with previous studies in different developed and developing countries.^{14,16,19,21-24} Cancer survival is measured as a proportion of cancer patients who remained alive after a specific period, usually 5-years. However, this cancer survival measure is fundamentally influenced by stage, age, treatment therapy and if it is preventable and curable. Cervical cancer is preventable and relatively curable if detected at an early stage though most cancer cases are diagnosed at a late-stage in low- and medium-income countries and Sudan as shown in this study.^{6,25-27} Late-stage diagnosis is correlated with low survival rates, as well as complicated treatment, poor prognosis and survival outcome.²⁸⁻³⁰

This study demonstrated not only that late-stage cancer diagnosis influences survival negatively but, also, how each predictor covariate affects the slope of the survival curve using Cox regression analysis. In a four step elimination process of confounding factors, the results confirmed strongly that stage, chemotherapy and radiotherapy were the most likely predictor covariates of survival times. This result was in agreement with a recent study in Saudia Arabia.³¹ Though the late cancer stage at diagnosis has proven to be closely related to poor survival, there are other factors associated with low survival rates such as socio-demographic, cultural, and economic characteristics of the patient, and histopathological features of the tumor.¹²

Aside from the impacted survival rate, diagnosis of cervical cancer at an advanced stage has been explained by delays in diagnosis at presentation and initiation of treatment.¹² For cervical cancer, effective control measures are generally available and affordable. This disease can be, to a large extent, prevented by vaccination against HPV infection and by screening and treating pre-cancerous lesions. Other than this, early detection of cervical cancer is imperative to improve treatment outcomes. Assessment of the study conclusion should be interpreted with caution since the study was based on retrospectively routinely collected data from one referral hospital with the largest registration of cancer patients in the country. It does not include all data of cervical cancer patients in the country and is limited by the type of available data. Due to the huge differences in settings, it is prudent not to extrapolate from one experience in developed countries to others in developing countries.

Conclusion and recommendations

The results of this study suggest that the cervical cancer stage at diagnosis and certain treatments are the most important factors impacting patient prognosis and survival outcome. The evidence presented has shown the complexity of determining what drives most variations in cancer outcomes between nations. It is most likely all steps the cancer patient takes when seeking medical care contribute to some degree to the differences in cervical cancer survival rates.

Cancer survival analysis can help in the diagnosis and treatment of cervical cancer and provide important information about where more effort should be directed. Early detection of cancer and vaccination of women against HPV infection

provide tremendous opportunities for prevention, early diagnosis, more effective treatment and a higher probability of better survival and outcomes.

Government intervention to reduce the suffering of cervical cancer treatment is of vital importance by providing diagnostic and oncological services in all general public hospitals and introduction of oncology units in all state capital's public hospitals. Early detection of cervical cancer should be the core of a proposed female cancer strategy through providing intensive and comprehensive vaccination, cervical cancer screening, and raising disease awareness among patients. This strategy needs to be closely linked to primary, secondary and tertiary care services.

Data availability

Underlying data

Zenodo: Elgoraish A. and Alnory A. cervical cancer dataset. <http://doi.org/10.5281/zenodo.4399441>³²

This project contains the following underlying data:

- Cervical cancer dataset

Extended data

Zenodo: Elgoraish A. Cervical cancer form. <https://doi.org/10.5281/zenodo.4469654>³³

This project contains the following extended data:

- checklist.pdf
- consent form.pdf

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

Acknowledgements

We are thankful to all people who participated in the study. We thank the medical and statistical staff of Khartoum oncology hospital for their help in collecting personal and clinical data of cancer patients.

Ethical approval

This study received ethical approval from the Sudan Federal Ministry of Health (number:3-10-2015, dated: 15/12/2015). The health ministry asked the participating hospital to provide the researchers with existing data of cervical cancer patients in accordance with the protection of the patients' personal information from improper use as required by law. The ethics board provided a waiver of consent for collecting participant's medical records before follow-up. When participants were called for follow-up, they or their next of kin were informed about the study and oral informed consent was obtained.

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Open Peer Review

Current Peer Review Status:  

Version 2

Reviewer Report 20 October 2022

<https://doi.org/10.5256/f1000research.139379.r152671>

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Elvynna Leong 

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Ong Sok King 

NCD Prevention Unit, Ministry of Health, Commonwealth Drive, Brunei

No further comments to make.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Statistics, Public Health

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 06 September 2022

<https://doi.org/10.5256/f1000research.46657.r147507>

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Elvynna Leong 

Faculty of Science, Universiti Brunei Darussalam, Jalan Tungku Link, Brunei

Ong Sok King 

NCD Prevention Unit, Ministry of Health, Commonwealth Drive, Brunei

This paper is very meaningful, especially for Sudan, as there are currently not many studies published from the Africa region or Sudan on cervical cancer survival. However, there are a few key components that require further clarification or analysis from the researchers.

Title

The researchers aimed to examine predictors associated with cervical cancer stage at diagnosis and its impact on cancer patient prognosis and survival. However, the title of the paper does not state the word "stage".

Methods

Data collection and sources

- The authors stated a study period of 2011-2015 in the study design and follow-up in 2016. What is the earliest year of diagnosis? Were the participants recruited diagnosed during the 2011-2015 period only? Also, please give more details on the follow-up period. How long was the follow-up period? Is it up to December 2016?

Statistical analysis

- The statement "*Statistical methods such as chi², Kaplan-Meier, log-rank test and Cox regression were used to find out most prognostic factors associated with cancer disease*" is not entirely correct. This needs to be revised. Explain why you used chi², Kaplan-Meier, log-rank test and Cox PH regression separately.
- "*Log-rank test for equality.*" We suggest adding more detail on 'equality'.

Results

Presentation of results needs to be improved, such as

- Paragraph 1 in Descriptive statistics: removing **at** in "*(SE=0.88, at 95%CI=55.17-85.65)*".
- Paragraph 1 in Descriptive statistics: rewriting "*majority 82.9% ≥45 years old*".
- Table 2: It is very important to keep the statistics consistent in tables, such as p-values of the log-rank test should be kept to 3 decimal places.
- Table 2: We suggest replacing 0.000 with <0.001, which is more commonly used in literature.
- Table 2: For Treatment, each p-value from the log-rank test is compared with no treatment?
- Table 2: On mean of survival time, to label months in the table.
- Regression analysis: "*(chi²=33.49, df=3, p=0.000)*". Is chi² =33.49 or 31.27, as indicated in Table 2?
- Regression analysis: "*The chi² was 7.91, df=1 with p=0.004 (Table 2).*" p-value is 0.005 (rounded up to 3 d.p).
- Regression analysis: "*The graph of the two survival functions curves were statistically equivalent*"

of the two groups". The p-value of 0.005 did not indicate statistical equivalence.

Table 1

- There were indications that geographical locations were significantly associated with stage of diagnosis, further discussion on this could be helpful.

For the survival analysis, was there a breakdown by 1-year or 3-years and 5-years survival rates? Was there any comparison or benchmarking of the findings or survival rates with other similar studies? It would also help to have some discussion on the potential explanations for these findings and to suggest for further studies. The researchers could identify the limitations of the study e.g. duration of treatment or any delay in treatment was not analyzed in the study.

Some grammar problems should also be paid attention.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Statistics, Public Health

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 04 Oct 2022

Amanda Elgoraish, Tropical Medicine Research Institute, National Centre for Research, Khartoum, Sudan

Some of your comments and suggestions have been taken care of in the text while others are clarified as below:

The study period is called 5-years survival, 2011-2015, starting from 1st Jan 2011 till 31st Dec 2015. The follow-up was passively collected from participants' medical records and active

follow-up during the year 2016 by contacting lost-to-follow-up participants to confirm their life status (dead or alive).

The log-rank test for equality was intended to compare between different groups of covariates and to confirm their statistical significance differences.

The survival tools of analysis were used to explain data analysis to suit descriptive and analytical sections and meet the requirement of each tool of analysis.

Table 2: all p-values of the log rank test are kept to 3 decimal places.

Table 2: for treatment each p-value of the log rank test basically is treatment and no treatment.

Table 1: the location result (east and west) included p-values which were insignificant in the univariate model, but significant in multivariate model. It was also insignificant in the final regression model. The study was intended to examine cases in a referral hospital in Khartoum State. So it is difficult to make final conclusion on a very small dataset of participants outside Khartoum State which was beyond the scope of the study objectives.

The study focused on 5-years survival (standard period for cancer survival analysis) and comparison with other short periods was not within the scope of the study.

The study discussed other explanations for survival of cervical cancer patients in developing countries despite the paucity of similar studies. It refers to most recent published studies. Delay was mentioned as one of the most plausible explanations for cervical cancer patients' stage at diagnosis. We are in the final stage of presenting our new article on associated predictor covariates at diagnosis focusing on the delay as the most important factor.

The study explained clearly its limitation based on availability and quality of data collected from participants' medical files and other sources.

Competing Interests: No competing interests were disclosed.

Reviewer Report 24 May 2021

<https://doi.org/10.5256/f1000research.46657.r84246>

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Nazik Hammad 

Department of Oncology, Queen's University, Kingston, ON, Canada

Overall, the work is presented well. Some minor details that could be addressed:

The introduction is too long and has number of repetitions. It needs to be shortened and made succinct.

I recommend replacing developing and developed countries with the more current terms: low-and-middle-income countries (**LMIC**) and high-income countries (HIC).

It is best to situate [this article](#) in the context of the WHO cervical cancer elimination strategy launched 2020; the 90-70-90 targets for 2030 especially in the recommendation section where Sudan should strive to achieve the WHO cervical cancer elimination targets by 2030. These are measurable targets for the Ministry of Health in Sudan and various stakeholders.

The last sentence in the discussion about the prudence of “not extrapolating from one experience in developed countries”, while correct, does not have relevance to the paragraph. I would suggest removing it.

The study design is appropriate. Outcome research is desperately needed in LMIC to inform policy and measure that need to be taken to improve access to cancer care across the continuum.

I have reviewed the methodology, the consent form and the follow-up and they have sufficient details. However, it would be of added benefit if the following could be addressed:

- Is there a different intake form that has the employment status and other sociodemographic variables?
- The authors may wish to explain what is the category “other tribes” that are neither non Arab descent Africans or Arab descent Africans mean. This constitutes 11% of the cohort.
- It would add to the value of the research if a sentence can be added about how consent was obtained from women who cannot read and write?

The statistical analysis is very well done; however, I have the following questions:

- Has the chemotherapy and radiotherapy use been defined by stage? e.g., how many patients with advanced stage received chemotherapy versus those with early stage?
- The data shows that 57% of patients received chemotherapy. Was there any correlation between receiving chemotherapy and residing in Khartoum versus peripheral areas, between receiving chemotherapy and education or ethnic origin?

The data supports that access to early diagnosis and treatment is needed to improve survival. As such the conclusion is supported by the results. While this is not surprising, it is important for future planning of health services to document this in Sudan.

The authors' use of employment data as an indicator of socioeconomic status (SE) should be listed as a limitation as not all unemployed women in Sudan are of similar SE status especially in this cohort of older women. Household income and area of residence are likely to be indicative of socioeconomic status which may influence access to care. This data might have been difficult to collect but this should also be acknowledged.

The data does not provide indications as to the reasons for lack of access to chemotherapy. Lack

of treatment details such as completion of a full course or radiotherapy and chemotherapy is also a limitation.

Health equity and cancer disparities should be highlighted. The data revealed that these patients are 62.2% non Arab descent African. Is this reflective of the general population in the area or is there more prevalence of cervical cancer among non Arab descent Africans? This is of relevance when planning prevention (vaccination), screening, treatment interventions by targeting the most vulnerable population.

The conclusion could be strengthened by calling further research looking into barriers to access to treatment. For example, this current cohort could be further interrogated in the future by investigating details of initiation and completion of treatment including chemotherapy and radiotherapy

Overall excellent effort in a much needed area of health services research. I believe the paper has academic merit, but I ask for a number of small changes to the article and response to some queries.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 30 Jun 2021

Amanda Elgoraish, Tropical Medicine Research Institute, National Centre for Research, Khartoum, Sudan

Your comments concerning length of introduction, using LIMC instead of developing and

developed countries and the last sentence of limitation paragraph have been taken notice of and appreciated.

The suggestion of outcome research is commended but it is beyond the purpose of this study. However, implementation research is more urgent to assess efficacy and effectiveness of intervention and early detection programmes.

Consent and follow-up was conducted by phone to collect vital status data (dead or alive) after explaining purpose of the interview and having verbal consent. Missing socio-demographic data were also, obtained during the interview to complete already collected data from patients medical files and diagnosis profiles. Other tribes indicate to participants who were Sudanese but did not belong to any of the known Sudanese tribes. They are most likely belong to non-Sudanese foreign ethnic groups.

Participant were classified as early or advanced stages at diagnosis and majority of them were at the advanced stage. Thus, most of participants who received chemo and radio therapies are most likely belong to this advanced stage. The study focus was on stage at diagnosis as the major determinant of survival. Other socio-demographic factors, residence state and rural/urban centres were considered insignificant confounding variables.

Household income and area of residence are proxy of socio-economic status and may influence access to care but the final conclusion of data analysis after removal of confounding variables and interaction terms affirmed that only stage at diagnosis and chemo and radio therapies are the effectors of cervical patient survival and outcome.

The majority of participants of cervical cancer disease were from the non-Arab decent African tribes is an indication which can be of great help in planning vaccination and screening programmes.

Suggested future research on barriers to treatment is commended but barriers to early detection is more urgent and appropriate in the short term future perspective.

Sufficient details of methods and analysis and source data are available and adequate for further reproducibility by looking into data availability section of the article.

Amanda Elgoraish
Corresponding author

Competing Interests: I have no competing interests

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