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Full Length Research Article

SURVIVAL ANALYSIS OF PROGNOSTIC FACTORS ASSOCIATED WITH CERVICAL CANCER

[*1]Abubakar Usman, [1]Fati Sayuti Yahaya, [1]Yisa Yakubu, [2]Abdullahi Abubakar Wuchin

[1]Department of Statistics, School of Physical Sciences, Federal University of Technology, Minna, Nigeria
[2]Department of Mathematics, Faculty of Science, Air Force Institute of Technology, Kaduna, Nigeria

*Corresponding Author Email Address: abu.usman@futminna.edu.ng

ABSTRACT
The paper aimed to present a survival analysis of prognostic factors associated with cervical cancer. This is a major public health menace to women of reproductive age. This study aimed to investigate the survival time and prognostic factors of patients diagnosed with cervical cancer from January 2010 to December 2020 at the National Hospital, Abuja (NHA), Nigeria. Survival function and median time were estimated using the Kaplan-Meier estimator. Results showed that out of 388 cervical cancer patients, 234 deaths (60%) were recorded. Each patient has a 50% chance of surviving at least 13 months and a minimum of 10 months, but not more than 17 months. The Log-rank test was used to test the differences in the survival curves. Result showed a significant difference in survival times for International Federation of Gynaecology and Obstetrics (FIGO) stages and recurrence, with a p-value of $5e^{-08}$ and 0.007, respectively. Accelerated failure time (AFT) was used to determine the prognostic factors associated with cervical cancer. AFT models considered were Exponential, Weibull, Log-normal, and Log-logistic. Based on the Akaike Information criterion (AIC), Log normal model with the minimum AIC value of 1821.70 was the best model for the data and was subsequently used for further analysis. Recurrence, histological type (adenosquamous (ADQ)) significantly prolonged the survival time of patients (Time ratio (TR) = 2.467; p: =0.00, TR= 2.78; p: = 0.05, respectively) compared to patients without recurrence and those with other histological types. Parity (TR=0.92; p: = 0.08), occupation (TR=0.49; p=0.00), tribe (TR=0.54; p=0.08), tumour grade (Well differentiated (WD)) (TR=0.65; p=0.05), treatment received (chemotherapy) (TR= 0.69; p=0.09) shortened the survival time of patients.

Keywords: Cervical cancer, Prognostic factors, Survival analysis, Survival time, Accelerated failure time

INTRODUCTION

Cancer is viewed as an unwelcome guest in every home, and it is often seen as the paper aimed at presenting a survival analysis of prognostic factors associated with cervical cancer. This is a major public health menace to women of reproductive age. The majority of all cervical cancer cases (99%) are linked to persistent infection with high-risk human papillomavirus (HPV), a virus transmitted through sexual contact. This study aimed to investigate the survival time and prognostic factors of patients diagnosed with cervical cancer from January 2010 to December 2020 at the National Hospital, Abuja (NHA), Nigeria. Survival function and median time were estimated using the Kaplan-Meier estimator. Results showed that out of 388 cervical cancer patients, 234 deaths (60%) were recorded. Each patient has a 50% chance of surviving at least 13 months and a minimum of 10 months, but not more than 17 months. The Log-rank test was used to test the differences in the survival curves. Result showed a significant difference in survival times for International Federation of Gynaecology and Obstetrics (FIGO) stages and recurrence, with a p-value of $5e^{-08}$ and 0.007, respectively. Accelerated failure time (AFT) was used to determine the prognostic factors associated with cervical cancer. AFT models considered were Exponential, Weibull, Log-normal, and Log-logistic. Based on the Akaike Information criterion (AIC), Log normal model with the minimum AIC value of 1821.70 was the best model for the data and was subsequently used for further analysis. Recurrence, histological type (adenosquamous (ADQ)) significantly prolonged the survival time of patients (Time ratio (TR) = 2.467; p: =0.00, TR= 2.78; p: = 0.05, respectively) compared to patients without recurrence and those with other histological types. Parity (TR=0.92; p:= 0.08), occupation (TR=0.49; p=0.00), tribe(Yoruba)(TR=0.54;p=0.08) tumour grade(Well differentiated(WD)) (TR=0.65; p=0.05), treatment received(chemotherapy) (TR= 0.69; p=0.09) shortened survival time of patients The paper aimed at presenting survival analysis of prognostic factors associated with cervical cancer. This is a major public health menace to women of reproductive age. The majority of all cervical cancer cases (99%) are linked to persistent infection with high-risk human papillomavirus (HPV), a virus transmitted through sexual contact. This study aimed at investigating the survival time and prognostic factors of the data of patients diagnosed with cervical cancer from January 2010 to December 2020 at National Hospital Abuja (NHA), Nigeria. Survival function and median time were estimated using the Kaplan-Meier estimator. Results showed that out of 388 cervical cancer patients, 234 deaths (60%) were recorded. Each patient has a 50% chance of surviving at least 13 months and a minimum of 10 months, but not more than 17 months. The Log-rank test was used to test the differences in the survival curves. Result showed a significant difference in survival times for International Federation of Gynaecology and Obstetrics (FIGO) stages and recurrence, with a p-value of $5e^{-08}$ and 0.007, respectively. Accelerated failure time (AFT) was used to determine the prognostic factors associated with cervical cancer. AFT models considered were Exponential, Weibull, Log-normal, and Log-logistic. Based on the Akaike Information criterion (AIC), Log normal model with the minimum AIC value of 1821.70 was the best model for the data and was subsequently used for further analysis.

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Cervical cancers are malignant proliferations that originate from the cervix, the lower cylindrical end ofthe uterus (Anfinan and Sait, 2020). It is a major cause ofmorbidity and mortality among women and continues to have a significant influence on women worldwide, particularly women in developing countries (Vishal *et al*., 2016). Akuna (2010) reported that one woman dies of cervical cancer every two minutes worldwide, and 80% of these deaths occur in developing nations. Studies have shown that the majority ofdeaths from gynaecological admissions were due to cancer, mostly cervical (Anorlu *et al*., 2010, and Anya *et al*., 2006). Nigeria is rated tenth in cervical cancer mortality worldwide (Okayed, 2014).

In Nigeria, 70,327 deaths in women have been attributed to cancer, with cervical cancer causing 14.89% of those deaths in 2018, making it the second most common cancer after breast cancer (Anyasi and Foss, 2021). A frequent occurrence and lower survival rate in Nigeria is a trend of late presentation and diagnosis at advanced stages of the disease, lack of awareness, inadequate screening facilities, inadequate treatment due to poor patient compliance, financial constraints, and inadequate treatment facilities leading to poor prognosis (Musa *et al.,* 2023). Thus, this study was conducted to determine the survival rates and prognostic factors in cervical cancer patients.

Survival analysis is a collection of statistical procedures for data analysis where the outcome variable of interest is time

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until the occurrence of an event (Clark *et al*., 2003; Bradbury *et al*., 2003; Gogra and Tate, 2017). Technically, survival analysis has a starting period, in which all the patients are recruited, and an observation period or follow-up, in which the patients are observed, and a final period in which all the data collected is analysed and the conclusions are drawn (Yu *et al*., 2021). It employs the use of the technique of "censoring," whereby each patient contributes data even if he/she does not achieve the desired outcome of interest or drop out during the course of the study for any reason (Gogra and Tate, 2017). The outcome of the survival analysis assesses his time of the outcome or 'event' in question (Prinja *et al.,* 2010, and Atlam *et al.,* 2021). In medical parlance, time to event could vary from time to fatal event that is, death, or time to metastases, onset of disease, time to tumour recurrence, time to discharge from the hospital, time to first exacerbation after a new drug treatment in patients with disease, time to dialysis in patients with renal dysfunction, attainment of a biochemical marker and bankruptcy (Prinja *teal*., 2010 and Seungyeoun and Heeju, 2019).

Investigating survival in cervical cancer studies helps to provide an in-depth knowledge and technical approach on the effective management of cervical cancer and also helps reflect the level of care given to the patients and the awareness among the population about screening and early diagnosis.

Previous studies on cervical cancer conducted by (Gurmu 2018) reported the potential risk factors affecting the survival time of women with cervical cancer, with death as the outcome variable. Findings from the study suggested that age, smoking, stage, family history, abortion history, living with HIV/AIDS, age at first marriage, and age at first birth had a major influence on the survival time of the patients. Mascarello *et al*. (2013) and Anfinan and Sait (2020) analysed survival data of women with cervical cancer and also described associated prognostic factors. Result revealed that early-stage diagnosis and treatment are key to reducing mortality from cervical cancer. Similarly, Musa *et al*. (2016) reported a retrospective study on 65 invasive cervical cancer cases with a prospective follow-up to ascertain the time from diagnosis to mortality among the subjects. Findings reveal that advanced-stage disease and baseline anaemia were independently associated with a higher death rate. In another study conducted by Wassie *et al*. (2019) to evaluate survival status and associated factors of deaths among cervical cancer patients, it was discovered that the overall survival rate was lower than in high and middle-income countries, and factors associated with death were advanced stage, advanced age, comorbidity, baseline anaemia, and treatment modality. Vishma *et al*. (2016) conducted a combined prospective and retrospective study to determine the survival rate and prognostic factors for 380 cervical cancer patients. The result showed five-year survival for cervical cancer to be 48%. The prognostic factors for the disease were age at diagnosis, performance status at presentation, staging, and treatment duration. Meanwhile, (Yagi *et al*., 2019) evaluated the trend of cervical cancer in Japan using the multiple imputation method to estimate age-adjusted incidence, relative survival, and conditional survival rates. Findings from the study reveal age to be an important predictor of radiotherapy resistance in cervical cancer.

Previous studies focused on the risk factors and associated factors of death using a semi-parametric model. A few studies that determine the prognostic factors of cervical cancer use cox proportional hazard model, among which are Gurmu (2018), Vishma *et al*. (2016), Anfinan & Sait (2020), and Marscarello *et al.* (2013). However, to the best of our knowledge, in all the studies, none was in Nigeria, and none employed the use of aparametric model. Consequently, this study intends to close the gaps by using a parametric model to determine the prognostic factors associated with cervical cancer.

MATERIALS AND METHODS

This study employs secondary data obtained from reviewed case folders of all women diagnosed with cervical cancer, treated, and followed up at the Oncology Department of the National Hospital Abuja (NHA), Nigeria, between January 2010 and December 2020. Prior to the commencement of the study, permission from hospital authorities was sought, and approval for the data used was granted. A total of 689 case folders were retrieved from the hospital libraries, and patient information was sorted and documented. The dataset has an identification for each patient, reporting date, summary, location, tribe, gender, age, hospital visit, death, and recovery. Only 388 subjects (patients) fulfilled the inclusion criteria (patients with complete information) and were included for further studies. All patients with missing follow-up data were excluded. Data collected for analysis include baseline demographic data (age, marital status, religion, tribe, occupation, parity), time variables including age at diagnosis, age at first birth, age at last birth, outcome data including events occurring during the follow-up period (recurrence, death) and 11-year status (alive with/without disease, deceased, censored), management data including radiotherapy, chemotherapy, combination of radiotherapy and chemotherapy and neither of the two, tumour characteristics including International Federation of Gynaecology and Obstetrics (FIGO) stage, tumour grade and histological type, comorbidity type (HIV, hypertension, diabetes and asthma.), family history, smoking status, menopause, alcohol consumption, menarche, coitarche and comorbidity.

The survival status of the patient was assessed at the end of eleven years after diagnosis. The data thus obtained were coded and entered into a Microsoft Excel worksheet and were analysed using R version 4.1.0.

Kaplan Meier Method

The Kaplan-Meier estimator is a nonparametric method that takes into account information from all subjects (censored and uncensored) and is calculated for each variable by taking the product of the proportion of patients at risk at that time minus the number of deaths divided by the number at risk (Etikan *et al*., 2017). Thus, it was used to visualize the survival curves and estimate the median survival time of the patients because the median is not affected by outliers, and since survival data are usually skewed. The Kaplan-Meier survival is given by equation (1).

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$$S_{KM}(t) = \prod_{1: t_i<t} \frac{n_i - d_i}{n_i} \quad (1)$$

Where
t_i = time point n_i = number at risk at time t
d_i = number of deaths at time t_i (Etikan *et al*., 2017)

Log-rank Test Statistic
The difference in survival among different groups was compared using the Log-rank test with the chi-square test statistic equation (2).

$$\chi^2 = \sum \frac{\left(\sum O_{jt} - \sum E_{jt}\right)^2}{\sum E_{jt}} \quad (2)$$

where
ΣO_{jt} is the sum of the observed number of events in the j^{th} group over time (t)
ΣE_{jt} is the sum of the expected number of events in the j^{th} group over time (t), with k-1 degree of freedom (df) where k represents the number of comparison groups.

Accelerated Failure Time (AFT) Model
An accelerated failure time (AFT) model, which is a parametric model, was used to find the prognostic factors associated with cervical cancer due to flexibility, accuracy, and simplicity in times of result interpretation. The AFT model defines the relationship between covariates and the survival time as a linear relation between the natural logarithm of survival time and the covariates X (Alfensi, 2018). This relationship is given by equation (3).

$$Y = \ln T = \mu + \theta^t X + \sigma W \quad (3)$$

Where
μ is the slope
σ > 0 is an unknown scale parameter
$\theta^t = (\theta_1, \theta_2, \ldots, \theta_p)$ is a vector of regression coefficients
θ = -β
σ is a scale parameter
W is a distribution error, which is a random variable and assumed to follow a certain parametric distribution.
The survival function of T_i, i = 1, 2,..., n, is given by equation (4).

$$S_i(t) = P_r\left(W_i \geq \frac{\ln t - (\mu + \theta^t X)}{\sigma}\right) \quad (4)$$

Weibull AFT model
The survival function of the multivariate Weibull AFT model is expressed by equation (5).

$$S(y|X) = \exp\left[-\exp\left(\frac{y - (\mu + \theta^t X)}{\sigma}\right)\right] \quad (5)$$

Exponential AFT model
The exponential AFT model is derived from the Weibull distribution by taking σ = 1 so that equation (5) becomes equation (6).

$$S(y|X) = \exp\left[-\exp\left(y - (\mu + \theta^t X)\right)\right] \quad (6)$$

Log-normal AFT model
If the random variable of the survival time T is assumed to follow a log-normal distribution, the baseline survival function $S_o(t)$ and baseline hazard function $h_o(t)$ are expressed by equations (7) and (8), respectively.

$$S_o(t) = 1 - \varphi\left(\frac{\ln t - \mu}{\sigma}\right) \quad (7)$$

$$h_o(t) = \frac{\varphi\left(\frac{\ln t}{\sigma}\right)}{1 - \Phi\left(\frac{\ln t}{\sigma}\right)} \quad (8)$$

Therefore, for a given set of covariates $X = (X_1, X_2, \ldots, X_p)^t$ the survival function is represented by equation (9).

$$S(t) = S_o[t \exp(\beta^t X)] = 1 - \varphi\left(\frac{(\ln t - (\mu + \theta' X))}{\sigma}\right) \quad (9)$$

Log-logistic AFT model
If the ε_i has the logistic distribution, then T_i follows the log-logistic distribution. The survival function of the logistic distribution is given by equation (10).

$$S_{\varepsilon_i}(\varepsilon) = \frac{1}{1 + e^{\varepsilon}} \quad (10)$$

Survival function of the log-logistic AFT model is represented by equation (11).

$$S_i(t) = \left\{\frac{1}{1 + e\left(\frac{\log t - \mu - \beta_1 X_1 - \cdots - \beta_p X_p}{\sigma}\right)}\right\} \quad (11)$$

Parameter Estimation of accelerated failure time model
AFT models are fitted by using maximum likelihood estimation (MLE) method. The likelihood of an n observed survival times $\{t_1, t_2, \ldots, t_n\}$ is given by equation (12) and the event indicator for the i^{th} individual δ_i is given by equation (13).

$$L = \prod_{i=1}^{n} \{f_i(t_i)\}^{\delta_i} \{S_i(t_i)\}^{1-\delta_i} \quad (12)$$

$$\delta_i = \begin{cases} 1, & \text{if the } i^{th} \text{ observation is event} \\ 0, & \text{if the } i^{th} \text{ observation is censored} \end{cases} \quad (13)$$

Now

$$S_i(t_i) = S_{\varepsilon_i}(W_i)$$

$$f_i(t_i) = \frac{1}{\sigma t_i} f_{\varepsilon_i}(W_i)$$

The log-likelihood function is given by equation (14)

$$\log L = \sum_{i=1}^{n} \sigma t_i^{-\delta_i} \{f_{\varepsilon_i}(W_i)\}^{\delta_i} \{S_{\varepsilon_i}(W_i)\}^{1-\delta_i} \quad (14)$$

$$\log L = \sum_{i=1}^{n} -\delta_i \log(\sigma t_i) + \delta_i \log\{f_{\varepsilon_i}(W_i)\} + (1 - \delta_i)\log\{S_{\varepsilon_i}(W_i)\} \quad (15)$$

Where

$$W_i = \log T - \mu - \beta_1 x_1 - \beta_2 - \cdots - \beta_p x_p \text{ and MLE of } (P + 2) \text{ unknown parameters}$$

μ, σ, and $\beta_1, \ldots, \beta_p$ are found by maximising the log-likelihood function using Newton Raphson procedure.

Model selection

The paper aimed to present a survival analysis of prognostic factors associated with cervical cancer. This is a major public health menace to women of reproductive age. The majority of all cervical cancer cases (99%) are linked to persistent infection with high-risk human papillomavirus (HPV), a virus transmitted through sexual contact. This study aimed to investigate the survival time and prognostic factors of patients diagnosed with cervical cancer from January 2010 to December 2020 at the National Hospital, Abuja (NHA), Nigeria. Survival function and median time were estimated using Kaplan-Meier estimator. Results showed that out of 388 cervical cancer patients, 234 deaths (60%) were recorded. Each patient has a 50% chance of surviving at least 13 months and a minimum of 10 months, but not more than 17 months. The Log-rank test was used to test the differences in the survival curves. Result showed a significant difference in survival times for International Federation of Gynaecology and Obstetrics (FIGO) stages and recurrence, with a p-value of $5e^{-08}$ and 0.007, respectively. Accelerated failure time (AFT) was used to determine the prognostic factors associated with cervical cancer. AFT models considered were Exponential, Weibull, Log-normal, and Log-logistic. Based on the Akaike Information criterion (AIC), Log normal model with the minimum AIC value of 1821.70 was the best model for the data and was subsequently used for further analysis. Recurrence, histological type (adenosquamous (ADQ)) significantly prolonged the survival time of patients (Time ratio (TR) = 2.467; p: =0.00, TR= 2.78; p: = 0.05 respectively) compared to patients without recurrence and those with other histological types. Parity (TR=0.92; p= 0.08), occupation (TR=0.49; p=0.00), tribe (Yoruba) (TR=0.54; p=0.08) tumour grade (Well differentiated (WD)) (TR=0.65; p=0.05), treatment received (chemotherapy) (TR= 0.69; p=0.09), and shortened survival time of patients were used. AIC was computed using equation (16).

$$\mathrm{AIC} = -2\mathrm{LL} + 2(\mathrm{P} + \mathrm{C}) \tag{16}$$

Where

P is the number of parameters

C is the number of coefficients (excluding the constant) in the model.

LL (log-likelihood) is the logarithm of the likelihood of the model.

RESULTS AND DISCUSSION

Table 1 shows summary statistics for quantitative variables. Both the average (mean) age and the median age of the patients are 54 years with a standard error of 0.62. Twenty-three (23) and ninety (90) years were the minimum and maximum ages of the patients. The skewness of 0.22 shows the age distribution is approximately symmetric, while a kurtosis of -0.37 is evidence that the age is light-tailed.

The total number (N) of patients' ages, age at first birth, age at last birth, menarche, coitarche, and parity is 388. Nineteen (19) years is the mean age at first birth, with the maximum age being 41 years. The mean age at last birth is 37 years, with a maximum of 53 years. Looking at the skewness, age at first birth is highly skewed, while age at last birth is moderately skewed. Kurtosis of 3.84 of age at first birth shows that it is heavily tailed, while that of age at last birth, which has a value of 0.11 indicate that the distribution is approximately normal.

Menopause has a total number (N) of 273 patients. This is due to the fact that not all patients attain menopause until the end of the study, while the mean menopause recorded is 49 years and the maximum is 62 years, with a skewness value of 0.09, which shows that it is fairly symmetric, and kurtosis of -0.45 indicates a light-tailed distribution

Table 1: Baseline characteristics of 388 cervical cancer patients for quantitative variables

Variables	N	Mean	StDev	Min	Med	Max	Skewness	Kurtosis
Age	388	54.43	0.62	29	54	90	0.22	-0.37
Age at first birth	388	19.12	0.19	5	18	41	1.20	3.84
Age at last birth	388	36.53	0.34	15	37	53	-0.41	0.11
Menarche	388	14.12	0.08	10	14	20	0.17	0.18
Coitarche	388	17.18	0.14	12	17	31	1.09	2.14
Parity	388	6.00	0.13	1	6	14	0.19	-0.42
Menopause	273	49.49	0.33	35	50	62	0.09	-0.4

From the result in Table 2 below, out of 388 cervical cancer patients, 234 experienced the event (death), the median survival time was 13 months, minimum and maximum survival times for patients were 10 and 17 months, respectively. Figure 1 depicts the Kaplan-Meier probability of the survival of the cervical cancer patients with a 95% confidence interval, where the vertical drop in the curve is an indication of an event (death), and the vertical thick mark on the curve means censored (alive or lost to follow-up). It shows that death was higher in the beginning of the follow-up months and it declined towards the end of the study, that is at later months of follow-up. At time zero, the survival probability is 1.0 (S (0) =1), (100% of the patients were alive). There was a drop in the curve within the first year (at 8 months), the probability of survival was approximately 0.80(80%) strict decrease in survival probability was observed till end of the study, follow-up of 132 months (11 years). This shows that as the time increases, the probability of survival decreases (S (∞) =0).

Table 2: Kaplan-Meier estimate of the overall survival function

No. of Patients	Events	Median	Std. Error	0.95LCL	0.95UCL
388	234	13	1.79	10	17

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Kaplan-Meier estimate of survival time is shown in (Figure 2 and Table 3 2). Patients who were diagnosed at an early stage had a better survival compared to those who were diagnosed at a later stage. Stage IA has a total number of two (2) patients, of which one (1) (50%) was event with a median survival time of 76 months. Stage IB has a total number of 30 patients, out of which 10 (33%) were events, with 66 months as the median survival time. Stage IIA and IIB had a total number of 44 and 101 patients, respectively, out of which 14 (32%) and 58 (57%) were events with median survival times of 30 and 12 months, respectively. Stage IIIA and IIIB had a total number of 63 and 102 patients, of which 44 (70%) and 81 (79%) were events with median survival times of9 and 5 months, respectively. Stage IV (A and B) had 33 and 13 patients in total, out ofwhich 18 (55%) and eight (8) (62%) with 15 and two (2) months median survival time, respectively. A decreasing trend in the 50% chance of survival as the tumour stage increases was observed. Patients in stage IA tumour had the highest median survival time, while those in stage IVB tumour had the least survival time. However, it is unclear why patients in stage IVA have a median survival time of 11 months. than those in stage IIIA and IIIB (9 and 5 months, respectively), although more deaths were observed between stage IIIA and I

Patients with business as an occupation have a total number of 134, out of which 74 (55%) were events with a median survival time of 13 months. Civil servant has a total number of 53, of which 32 (60%) have been events with a median survival time of 11 months. Farmers had a total number of 33, of which 16 (48%) been event with a median survival time of 25 months. Housewives have a total number of 136, of which 96 (71%) were events with nine (9) months as the median survival time of nine months, while others had a total of 32, of which 16 (49%) were events with a median survival time of 18 months. It was noted that farmers have a 50% chance of surviving 25 months, while housewives have the least median survival time. Excluding the other category, the farmers' category also experienced a smaller number of deaths.

Recurrence occurred among 35 patients, 23 (66%) deaths against a total number of 353 that did not reoccur with 211 (60%) deaths. However, the median survival time is higher (44 months) for patients whose cancer reoccurred after treatment than for those (11 months) who did not show symptoms of recurrence after treatment.

Fifty-three (53) patients had Adenocarcinoma, of which 35 (66%) were events with a median survival time of 12 months. Adenosquamous have 46 patients, of which eight 30 (65%) were events (deaths) with a median survival time of 25 months, and squamous cell carcinoma (SCC) had a total number of 360 patients, of which 217 (60%) were events with a median survival time of 13. Hence, those with Adenosquamous had the highest survival time and a lower proportion of deaths observed, while patients with Adenocarcinoma had the least survival time with a higher proportion of deaths observed. Patients with moderately differentiated (MD) tumour grade have a total number of 126, of which 74 (58%) have been event with 17 months median survival time. Patients with poorly differentiated (PD) tumour grade have a median survival time of 9 months, with 104 (65%) deaths observed, and patients with well differentiated tumour grade (WD) have a total of 102, with a median survival time of 12 months, with 56 (56%) deaths recorded. Thus, patients with moderately differentiated (MD) tumour grade have the highest median survival time, while poorly differentiated (PD) patients have the least median survival time, with a higher proportion of deaths, 66% observed.

Table 3: Kaplan-Meier estimate of survival time

Category	N	Events	%Events	Median	Std. Error	0.95LCL	0.95UCL
FIGO Stage							
Stage IA	2	1	50	76	-	NA	NA
Stage IB	30	10	33	66	24.29	18.39	113.61
Stage IIA	44	14	32	30	12.98	4.55	55.45
Stage IIB	101	58	57	12	2.98	6.17	17.83
Stage IIIA	63	44	70	9	5.31	0.00	19.40
Stage IIIB	102	81	79	5	0.74	3.55	6.45
Stage IVA	33	18	55	15	4.50	6.18	23.82
Stage IVB	14	8	62	2	1.07	10.00	4.11
Occupation							
Business	134	74	55	13	2.23	8.63	17.37
C/S	53	32	60	11	7.47	0.00	27.64
Farmers	33	16	48	25	12.93	0.00	50.34
H/W	136	96	71	9	3.22	2.69	15.31
Others	32	16	50	18	4.53	9.13	28.88
Recurrence							
Yes	35	23	66	43	7.92	27.48	58.53
No	353	211	60	12	1.51	9.04	14.96
Histology							
Adenocarcinoma	46	30	65	15	7.21	0.89	29.13

Adenosquamous	14	8	57	35	13.75	8.06	61.91
SCC	328	198	60	13	1.78	9.52	16.48
Tumour grade							
MD	126	74	58	18	2.50	13.09	22.91
PD	160	104	65	9	2.18	4.72	13.28
WD	102	56	55	12	2.31	7.47	16.53

Table 3 shows the log-rank test of the difference. P-value of less than 0.05 was used for the significant test of Log rank test. The p-values for FIGO (tumour stages) (5e-08) and recurrence (0.007) were less than 0.05, indicating statistical significance at 5%. It was therefore concluded that the survival times of patients significantly differ across groups of tumour stages and recurrence, while the survival times of patients based on occupation, tribe, histology, tumour grade, and treatment were not significantly different.

Table 3: Log Rank Test of Difference

Variables	Chi-square	P-value
FIGO Stage	47.4	5e-08
Occupation	5.9	0.2
Recurrence	7.2	0.007
Histology	2.5	0.3
Tumor Grade	1.5	0.5

The AFT models were compared using statistical criteria - the maximum likelihood (ML) test and AIC. The computed value of AIC for the Log-normal AFT model is 1821.70 with 95% predictive power (Table 4).

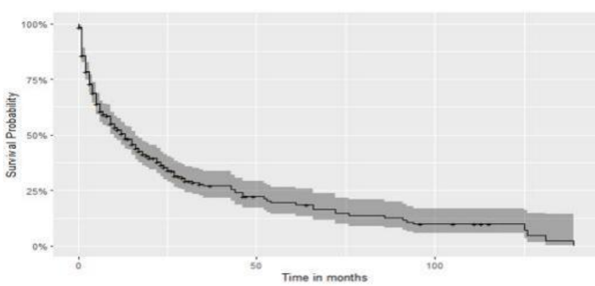
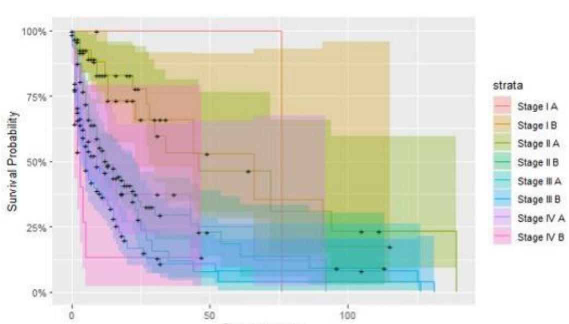
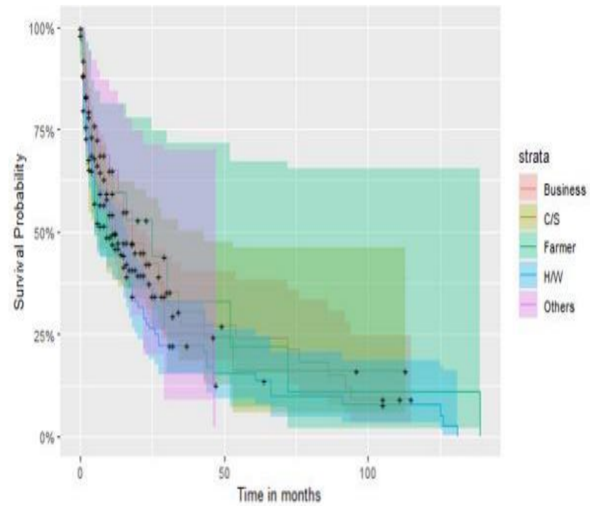


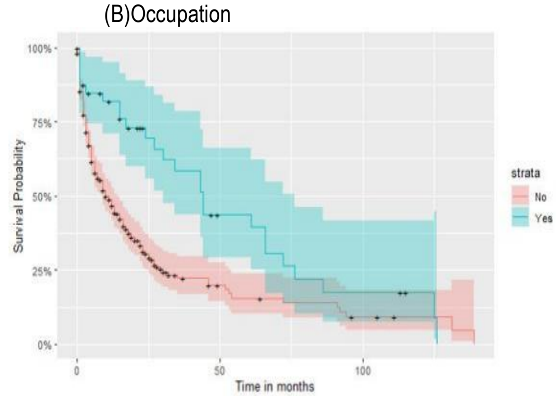
Figure 1: Kaplan-Meier estimates and 95% confidence limits of the survival function for the NHA Cervical Cancer data.



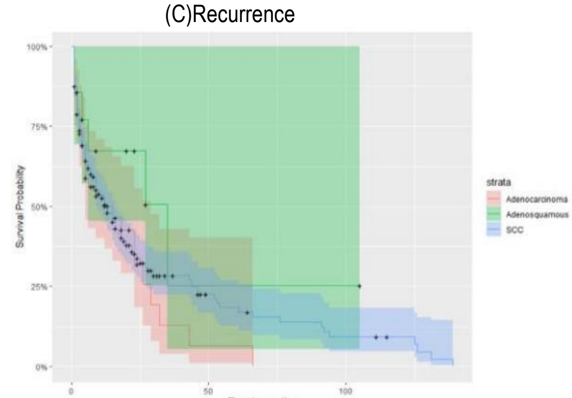
(A)Tumour stages



(B)Occupation



(C)Recurrence



(D)Histology

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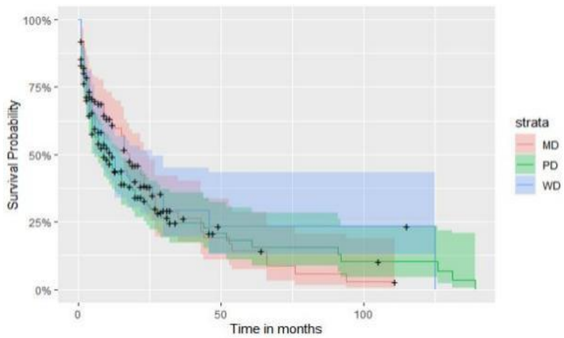

(E)Tumour grade

Figure 1: Kaplan-Meier estimates of the survival function for variables under study

Table 4: Log-likelihoods and Akaike Information Criterion (AIC) in the models

Distribution	K	AIC	AIC_Wt	LL
LogNormal	39	1821.70	0.95	-871.85
LogLogistic	39	1827.64	0.05	-874.82
Weibull	37	1843.01	0.00	-884.50
Exponential	38	1846.11	0.00	-885.05

Note: K is the number of parameters, AIC_Wt is the proportion of the total predictive power,

LL is the Log-likelihood of the model.

The effect of the covariate is to accelerate or decelerate the survival time of cervical cancer patients. The TR is the acceleration factor for a given covariate. A positive coefficient implies that the effect of the covariate is to prolong the survival time, while a negative coefficient is to shorten the time to event (death) (Majeed, 2020). Relatively, a TR greater than 1 implies the effect of the covariate increases the survival time and otherwise decreases ("speedup") the time to death. The TR of 0.92 for parity relative to nulliparous signifies a poor prognosis of cervical cancer, and it is slightly at higher risk compared to nulliparous patients; that is, the probability of a cervical cancer patient dying is 92% faster for parity. Occupation with an estimate of (-0.715) = 0.49, which is a 49% decrease in risk of death for patients in the housewife (H/W) category. This implies that the survival time for patients who are H/W is estimated to be 51% shorter than for patients in other categories of occupation. TR for recurrence 2.47 indicates that the survival time for cervical cancer patients who experience recurrence is longer than that of those without recurrence. This could be due to the fact that cervical cancer, if detected early, can be cured and may take longer before recurrence, that is, lengthen the survival time of the patients. Furthermore, those with cervical cancer from the Yoruba tribe have a chance of dying of 0.54, which indicates that the survival times for Yoruba patients are estimated to be 46% lower than those of patients in other categories of tribe. The estimated TR for the histologic group is 2.73, indicating that a longer time to death is more likely for the patients with adenosquamous cell type. This further implies that a patient diagnosed with adenosquamous will have a better chance of living in the following years. The survival time for a patient diagnosed with WD tumour grade is estimated to be 65% of that of patients diagnosed with PD or MD tumour grade. Patients exposed to chemotherapy treatment survived 0.69 years shorter than those exposed to radiotherapy or both. This implies that patients subjected to chemotherapy have 69% chance of dying, that is, they are at a higher risk of death (Table 5).

Table 5: Estimate of prognostic factors of cervical cancer based on NHA

Variables	Coefficient value	TR
SE	**Z value**	**P value**
(Intercept)	5.462	235.57
1.537	3.55	0.00
Parity	-0.081	0.92
0.046	-1.76	0.08
Occupation (H/W)	-0.715	0.49
0.219	-3.26	0.00
Recurrence (Yes)	0.904	2.47
0.86	3.16	0.00
Tribe (Yoruba)	-0.618	0.54
0.351	-1.76	0.08
Histology (ADQ)	1.005	2.73
0.507	1.98	0.05
Grade (WD)	-0.433	0.65
0.221	-1.96	0.05
Treatment (Chemo)	-0.377	0.69
0.224	-1.68	0.09
Log (scale)	0.290	1.34
0.047	6.17	0.00

SE = Standard error, TR = Time ratio

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Conclusion

Prognostic factors of cervical cancer patients were studied. The Kaplan Meier results reveal that each patient has an overall median survival time of a 50% chance of surviving at least 13 months but not more than 17 months. Survival times significantly differ between groups of Recurrence and Tumour stages. The Log-normal model is the best model for the study data. Parity, occupation, tribe, tumour grade, histological type, recurrence, and treatment received were found to be the significant prognostic factors of cervical cancer in the study.

Limitations in this study are the use of a retrospective design, which results in recall biases and missing values. As a result prospective data should be used in future cervical cancer studies, other medically attributed significant predictors such as performance status at presentation, history of reproductive tract and sexually transmitted infections, locoregional organ involvement (parametrium, pelvis, lymph node and vagina), distant metastasis and hydronephrosis should be included, and in other to cater for the problem of missing data, multiple imputation method should be adopted in future studies.

In an effort to reduce the burden of cervical cancer, emphasis should be on creating awareness among the public so that healthy lifestyles and early screening behaviours can be adopted by women. Cervical cancer diagnostic and treatment facilities should be made accessible and affordable to facilitate early detection. Its treatment should be included in the National Health Insurance Scheme (NHIS). Human papilloma virus (HPV) vaccine should be made available in primary health care centres due to the proximity of these centres to local communities.

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